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Early intervention models of diabetes care to address adverse glycaemia in hospital

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Abstract

Diabetes affects one quarter of individuals in hospital and contributes to worse clinical and economic outcomes. Acute hyperglycaemia causes immune dysfunction, proinflammatory and prothrombotic changes, and endothelial dysfunction, leading to increased risk of hospital-acquired infections, and cardiovascular and renal complications. Acute hypoglycaemia also causes proinflammatory and prothrombotic changes, endothelial dysfunction, and neuroglycopaenia-related complications. 'Adverse glycaemia' describes both extremes of hypoglycaemia and hyperglycaemia (defined as glucose <4 or >15 mmol/L), that are associated with adverse pathophysiology and adverse outcomes in hospital. Adverse glycaemia remains common in hospital patients due to various barriers including clinical inertia. This thesis aimed to develop and investigate a strategy of proactive care and early diabetes intervention to address adverse glycaemia in hospital.

A glucose alert system, comprising a novel clinical escalation tool coupled with alert-capable networked glucose meters, was developed to decrease clinical inertia (Chapter 3). In a 14-week, pre- and post-implementation study, the glucose alert system increased nursing and medical staff actions in response to adverse glycaemia, and this translated to a reduction in the incidence of hyperglycaemia.

Networked glucose meter technology was then implemented on eight noncritical medical and surgical care wards at the Royal Melbourne Hospital, enabling detailed baseline assessment of inpatient glycaemia (Chapter 4). In this first detailed glucometric analysis of an Australian hospital, our cohort was found to have a higher incidence of hyperglycaemia but a lower incidence of hypoglycaemia compared to benchmarks in the United States hospitals. A novel glucometric measure of 'adverse glycaemic days', defined as patient-days with glucose <4 or >15 mmol/L, was proposed as a useful metric for benchmarking, and as a tangible concept for educating health professionals about safe glycaemic control in hospital.

A comprehensive early intervention model of diabetes care was developed and investigated in the Randomised study of a Proactive Inpatient Diabetes Service (RAPIDS) (Chapter 5). The early intervention model included remote glycaemic surveillance and proactive management of all diabetes patients, by an inpatient diabetes team within 24 hours of admission. RAPIDS, a 24-week cluster randomised trial with a baseline period, involving 1002 consecutive patients, is amongst the largest randomised trials of inpatient diabetes care to date. Early intervention decreased the incidence of adverse glycaemic days by 28%, and decreased severe hyperglycaemia (patient-days with mean glucose >15 mmol/L) by 55%. This intervention was associated with an 80% relative risk reduction (and 4% absolute risk reduction) of developing hospital-acquired infection.

Lastly, a prediction tool to enable early identification of diabetes inpatients at high risk for persistent adverse glycaemia was developed (Chapter 6). A prediction tool based on four clinical factors available at

admission (glucose at admission, glucose-lowering treatment regimen, glycosylated haemoglobin and glucocorticoid medication), accurately identified high-risk patients, and may assist delivery of targeted management.

The studies describe models of clinical care which may be implemented as stand-alone or as a bundle of interventions. The findings support the strategy of proactive care to improve inpatient glucose. Proactive and early intervention models of care which improve glycaemia may improve the care of individuals with diabetes in hospital.

Declaration

This is to certify that:

1) This thesis is of my own composition and that it is a record of original work towards the degree of Doctor of Philosophy, except where described in the preface.

2) Due acknowledgements have been made in the text to all other material used

3) This thesis is fewer than 100,000 words in length, exclusive of tables, figures, the bibliography and appendices

Dr Mervyn Kyi

Nov 2019

Preface

This work presented in this thesis was performed under the joint supervision of Associate Professor Spiros Fourlanos, Professor Peter Colman and Associate Professor Paul Wraight, in the Department of Diabetes and Endocrinology, Royal Melbourne Hospital. With guidance from my supervisors, I performed all aspects of the studies including development of study design, ethics submission, study implementation, data collection, statistical analysis, and interpretation of the results. I received additional guidance from Ms Alexandra Gorelik for statistical analysis.

Conduct of large-scale clinical studies in hospital requires enthusiastic assistance from a multidisciplinary team. I received great assistance from various members of the Diabetes and Endocrinology team during the setup and implementation of the studies. Ms Lois Rowan, Ms Katie Marley and the Diabetes Education Service contributed to the implementation of networked glucose meters and glucose alert pathway, and provided education for nursing staff. Ms Emma Farrugia, Mr Hari Chandra and Mr Martin Rocliffe (Australasian Medical and Scientific Limited), assisted with implementation of networked glucose meters and provided ongoing technical support. Dr Anna Galligan, Dr Shanal Kumar and Ms Lois Rowan delivered the proactive inpatient diabetes team clinical service during the RAPIDS trial. Associate Professor Spiros Fourlanos, Professor Peter Colman, Associate Professor Paul Wraight and Associate Professor Alison Nankervis provided endocrinologist supervision for the inpatient diabetes team. Ms Jane Reid significantly contributed to data collection. Dr Sidha Sreedharan performed blinded adjudication of clinical outcomes.

For each manuscript contained in this thesis (Chapters 3 to 6), I wrote the initial manuscript and received guidance and editorial support from my supervisors, especially A/Prof Spiros Fourlanos. All authors contributed to revision of the manuscript. Manuscripts comprising chapters 3, 4 and 5 have been published in peer-reviewed journals. Manuscript for chapter 6 is ready for submission to a peer-reviewed journal.

Acknowledgements

First and foremost, I would like to thank my primary supervisor Associate Professor Spiros Fourlanos for his enthusiastic and dedicated mentorship throughout every step of my PhD journey. Spiros and I have spent countless hours planning, drafting, executing and philosophising in the last four years, and I have learnt much about all aspects of life in addition to research and clinical practice. His passion and strive to improve the care of people with diabetes is inspiring. Additionally, I was privileged to be mentored by someone with the similar family values as my own. I will forever be grateful for every aspect of Spiros' guidance and I look forward to a lifetime of learning throughout my career.

I wish to thank my co-supervisors Professor Peter Colman and Associate Professor Paul Wraight. I thank Peter for his constant wisdom, guidance and meticulous drafting throughout my PhD journey. He has been an inspiration for us all, particularly his devotion to clinical research and patient-centred care in diabetes and endocrinology. I thank Paul for his guidance and experience, particularly on the approach to implementing change in a hospital setting. I would like to thank Ms Alexandra Gorelik for her assistance on statistical methods and study design.

Large-scale clinical research in a busy tertiary hospital setting would not have been possible without kind and dedicated support from a whole team of people. I wish to thank every member of the Department of Diabetes and Endocrinology and Diabetes Education Service for their assistance in the study set up, staff education, maintenance of networked glucose meters and providing excellent patient care throughout my doctoral studies. I wish to particularly thank Ms Lois Rowan for her enthusiasm in providing Inpatient Diabetes Team service, and Ms Katie Marley for her support and leadership as the manager of the Diabetes Education Service. I thank endocrinology registrars Dr Anna Galligan and Dr Shanal Kumar for providing the Inpatient Diabetes Team service, as well as all the medical registrars who backfilled the clinical duties of the endocrinology registrars. I am grateful for the invaluable assistance I received from Ms Emma Farrugia, Mr Hari Chandra and Mr Martin Rocliffe (Australasian Medical and Scientific Limited), and the team from Abbott Diabetes Care for implementation of the networked glucose meters and technical assistance. I would like to thank the nursing managers and nursing staff from the study wards at the Royal Melbourne Hospital for their support and enthusiasm during our studies.

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I wish to thank my family for their support in my academic research endeavours. I am grateful for my parents Winston and Stella for giving me the opportunity to become a health professional, and inspiring me to peruse academic studies. When I started my doctoral study, our first child was only a few weeks old, but as I am submitting my thesis, our daughters Clara and Audrey are almost starting primary school and kindergarten, respectively. An African proverb, "It takes a village to raise a child", is no less true in Modern Australia, and we were greatly assisted by my parents, parents-in-law, and brothers and sisters in raising our children during my PhD journey.

Last but not least, I wish to thank my wife Jenny for her unwavering support in my pursuit of academic research and for her steadfast devotion to our family. I cannot express adequately, my sincere gratitude for being the most caring and supportive person she is, and I look forward to a lifetime of companionship and building our family together.

Publications

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Kyi M, Colman PG, Marley KA, Rowan LM, Wraight PR, Fourlanos S: Glucometric benchmarking in an Australian hospital enabled by networked glucose meter technology. *Med J Aust* 2019;(in press) accepted 29th March 2019

Kyi M, Colman PG, Wraight PR, Reid J, Gorelik A, Galligan A, Kumar S, Rowan LM, Marley KA, Nankervis AJ, Russell DM, Fourlanos S: Early Intervention for Diabetes in Medical and Surgical Inpatients Decreases Hyperglycemia and Hospital-Acquired Infections: A Cluster Randomized Trial. *Diabetes Care* 2019;42:832-840

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Kyi M, Colman PG, Wraight PR, Reid J, Galligan A, Kumar S, Rowan LM, Nankervis A, Gorelik A, Marley K, Russell DM, Fourlanos S: A Randomized trial of a Proactive Inpatient Diabetes Service (RAPIDS) demonstrates decreased adverse glycaemia and hospital-acquired infections. *American Diabetes Association scientific meeting*, San Diego, June 2017

Kyi M, Reid J, Galligan A, Kumar S, Rowan LM, Nankervis A, Gorelik A, Marley K, Russell DM, Wraight PR, Colman PG, Fourlanos S. Randomised trial of a Proactive Inpatient Diabetes Service (RAPIDS) demonstrates decreased adverse glycaemia and hospital-acquired infections. *Australian Diabetes Society scientific meeting*, Perth, August 2017

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Poster discussion presentations

Kyi M, Reid J, Galligan A, Kumar S, Rowan LM, Gorelik A, Nankervis A, Marley KA, Russell DM, Wraight PR, Colman PG, Fourlanos S. Adverse Glycaemic Days in the RAPIDS study: assessing the performance & safety of an inpatient glycaemic management program. *American Diabetes Association scientific meeting*, San Diego, June 2017

Kyi M, Rowan LM, Marley KA, Wraight PR, Colman PG, Fourlanos S. Early admission glycaemia predicts subsequent glycaemic extremes in hospitalised patients with diabetes. *Australian Diabetes Society scientific meeting*, Gold Coast, August 2016

Kyi M, Italiano S, Colman PG, Fourlanos S. Glycaemic variability and diabetes inpatient outcomes. *Australian Diabetes Society scientific meeting*, Adelaide, August 2015

Abbreviations

ADA	American Diabetes Association
ADS	Australian Diabetes Society
AG	Adverse Glycaemia
AGD	Adverse Glycaemic Days
AUC	Area Under Curve
BBI	Basal-Bolus Insulin
BG	Blood Glucose
BPI	Basal-Plus Insulin
CAGS	Coronary Artery Graft Surgery
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CIII	Continuous Intravenous Insulin Infusion
CSII	Continuous Subcutaneous Insulin Infusion
CKD	Chronic Kidney Disease
CV	Coefficient of Variation
CVD	Cardiovascular Disease
DKA	Diabetic Ketoacidosis
DNE	Diabetes Nurse Educator
DNP	Diabetes Nurse Practitioner
DPP-4	Dipeptidyl Peptidase-4
DSWI	Deep Sternal Wound Infection
EMR	Electronic Medical Record
FPG	Fasting Plasma Glucose
GHb	Glycosylated Haemoglobin (also HbA1c)
GIK	Glucose Insulin Potassium
GLM	Glucose-Lowering Medication
GLP1	Glucagon-Like Peptide-1
GMT	Glucose Management Team
GV	Glycaemic Variability
HbA1c	Haemoglobin A1c
HL7-ADT	Health Level-7: Admission Discharge Transfer (data system)
HHS	Hyperosmolar Hyperglycaemic State
ICU	Intensive Care Unit
IDT	Inpatient Diabetes Team
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IIT	Intensive Insulin Therapy

IT	Information Technology
LOS	Length of Stay
MI	Myocardial Infarct
NaDIA	National Diabetes Inpatient Audit
NPH	Neutral Protamine Hagedorn
OR	Odds Ratio
POC	Point-of-Care
RCT	Randomised Controlled Trial
RMH	Royal Melbourne Hospital
ROC	Receiver Operating Characteristics
SD	Standard Deviation
SSI	Sliding-Scale Insulin
SGLT	Sodium-Glucose Cotransporter
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
UK	United Kingdom
US	United States (of America)

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CHAPTER ONE: LITERATURE REVIEW

1.1 Diabetes Mellitus

Diabetes mellitus is a group of metabolic conditions characterised by a defect in insulin secretion, insulin action, or a combination of both, leading to hyperglycaemia. Insulin, produced by β cells in the islets of Langerhans in the endocrine pancreas, is secreted in response to hyperglycaemia, or in response to other pancreatic and incretin hormones. Insulin acts at the peripheral tissues and liver to promote glucose uptake, glycogen synthesis, and lipogenesis. In diabetes, lack of insulin action causes impairment in glucose uptake in the peripheral tissues, and causes gluconeogenesis and glycogenolysis in the hepatocytes, leading to hyperglycaemia. Extreme insulin deficiency promotes lipolysis and ketogenesis, leading to ketoacidosis.

The acute sequelae of hyperglycaemia include osmotic diuresis which causes polyuria, polydipsia, and dehydration, leading to metabolic disturbances. With extreme insulin deficiency, glycaemic emergencies such as Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycaemic State (HHS) may develop. Other acute sequelae of hyperglycaemia include impaired immunity, endothelial dysfunction, as well as prothrombotic and pro-inflammatory changes [1], leading to acute cardiovascular and renal pathology, and increased risk of infection.

Chronic sequelae of hyperglycaemia include microvascular complications (chronic kidney disease, retinopathy, peripheral neuropathy and autonomic neuropathy), and macrovascular complications (ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, diabetic foot ulcers and lower limb amputations). Cardiovascular disease is the leading cause of death in Australia; diabetic kidney disease is the leading cause of end stage kidney disease; diabetic retinopathy is the most common cause of blindness in working-age adults [2-4]. Other emerging chronic complications of diabetes include cognitive impairment, and increased risk of fractures.

Although more than 60 subtypes of diabetes have been described [5], the predominant subtypes encountered in routine hospital practice include: type 1, type 2, type 3c, drug-induced, and gestational diabetes. Type 1 diabetes (T1D) accounts for 5-10% of individuals with diabetes, and occurs due to destruction of β cells via immune-mediated mechanisms, leading to absolute insulin deficiency. Individuals with T1D are dependent on exogenous insulin therapy and can develop life-threatening DKA in the absence of insulin. Individuals with T1D are also more prone to hypoglycaemia compared to those with other types of diabetes [6].

Type 2 diabetes (T2D) accounts for approximately 90% of diabetes worldwide, and its aetiology relates to insulin resistance and relative (rather than absolute) insulin deficiency. Although treatment of T2D includes diet, lifestyle measures and glucose lowering medications (GLM), some individuals will become insulin dependent. Although it was traditionally believed that people with T2D had low risk of DKA, some individuals can develop this complication with severe illness and/or during treatment with sodium glucose cotransporter (SGLT) inhibitors [7].

Diseases of exocrine pancreas (e.g. recurrent pancreatitis, pancreatic cancer, pancreatectomy and cystic fibrosis) can lead to type 3c diabetes due to β cell deficiency or due to paracrine effects of pancreatic inflammation. Individuals with type 3c diabetes are more likely to be insulin dependent, and at risk of hypoglycaemia due to concurrent defects in glucagon-producing α cells and nutrient malabsorption due to exocrine pancreatic deficiency [8]. Diabetes can also develop due to medications such as glucocorticoids [9], immunomodulators (e.g. tacrolimus, cyclosporine, and sirolimus) and antipsychotic medications (e.g. olanzapine, clozapine). Lastly, gestational diabetes mellitus may be encountered in hospitals with maternity services, but is not a focus of this thesis and will not be explored further.

Accurate identification and classification of diabetes subtypes is critical for provision of appropriate treatment, particularly during hospitalisation where treatment adjustments are often necessary. It is particularly important to determine if an individual is likely to be insulin deficient, so as to ensure insulin treatment is not withheld to avoid iatrogenic in-hospital DKA.

In 2017, global estimates suggest that approximately 425 million (or 9% of people aged 20 to 79 years) are living with diabetes and it is estimated one in two are undiagnosed. Additionally, 1.1 million children and adolescents (aged 0 to 19 years) has type 1 diabetes [10]. It has been quoted that "If diabetes were a country, it would be the third largest country in the world" [11]. The global epidemic of diabetes is unprecedented; tripling in the last 20 years and projected to further increase by 50% in the next 25 years. By 2045, an estimated 630 million adults will be living with diabetes, with four out of five living in a low or medium income country [10]. Additionally, 325 million adults (or 7% of people aged 20 to 79 years) are estimated to have impaired glucose tolerance, a prediabetes condition. Therefore, 16% of the adult population have a disorder of glucose metabolism (diabetes or prediabetes). In the United States (US) of America where the prevalence is particularly high, diabetes and prediabetes are estimated to be present in 14.3% and 38.0% respectively [12].

In Australia the prevalence of diabetes mirrors the global trend. An estimated 1.1 million people are living with diabetes and 2.5 million are living with prediabetes [13, 14]. In 2011, diabetes was the underlying cause of death in 3% of the Australian population, and underlying or associated cause of death in 10% [15]. The co-related chronic diseases comprising diabetes, cardiovascular disease (CVD), and chronic kidney disease (CKD), were responsible for 36% of all deaths. The economic burden of diabetes is estimated to be AU $1.7 billion in direct costs and over $14 billion including indirect costs [16].

Individuals with diabetes are more likely to require hospital treatment and amongst those who were hospitalised, 30% had two or more hospital stays each year [17]. Hence, inpatient care is the biggest component of diabetes related-costs [18].

In summary, diabetes is a chronic condition with both acute and chronic sequelae, and one of the biggest contributors to chronic disease morbidity and mortality. The epidemic of diabetes is one of the greatest health priorities of the 21st century, both in Australia and globally.

1.2 The modern hospital in Australia

Various examples of institutions to care for the ill can be found in ancient Greece, the Roman Empire, and in the Indian and Sri Lankan civilisations. During medieval times in Europe, infirmaries were established by religious orders with care provided by monks and nuns. In the 18th century, 'voluntary hospitals' began to appear, evolving from basic places to care for the ill, to becoming complex institutions for provision of medicine, surgery, and conduct of research and education [19]. In the 19th century, Florence Nightingale was instrumental in developing the modern nursing profession and reforming the hospitals by changing the image from places for the sick to go to die, to places for recuperation and healing.

Today, modern hospitals are complex health care institutions providing patient treatment with medical, surgical, nursing care and specialised medical equipment. They are supported by various allied health professionals and ancillary departments such as radiology, pathology and pharmacy. Hospitals vary in size from rural and regional hospitals to tertiary and quaternary referral centres. Specialised hospitals, such as paediatric, obstetric, psychiatric, rehabilitation, aged care and palliative care hospitals may coexist in addition to the general hospitals. Although hospitals traditionally care for inpatients, ambulatory care departments provide treatment to patients who do not require inpatient treatment. Many hospitals are publicly funded; however, some are privately funded or supported by religious institutions.

Hospital wards are generally classified as critical care or noncritical care and provide different levels of medical and physiological support, and different intensity of monitoring, depending on the acuity of patient illness. Operating theatres and procedure units provide equipment and staff for surgical or other interventional procedures. Some hospitals provide day procedure units, where an individual may be admitted for a procedure or minor surgery and discharged on the same day without the need for overnight admission. Many teaching hospitals are affiliated with a university and provide education and vocational training for undergraduate, postgraduate and specialist trainees in medicine, nursing and other disciplines.

Treating doctors of various specialities provide specialised care for inpatients. In secondary and tertiary hospitals, treating medical teams generally comprise of specialist consultants, registrars (or fellows) who are specialists in training, and residents or house staff. Treating medical teams typically manage

inpatients admitted under their care, but additionally provide consultations and advice to inpatients admitted under other treating teams when requested.

A hospital inpatient's journey can commence in the emergency department for those with an emergency presentation, or in the day procedure or perioperative unit for those with an elective admission. Patients are typically admitted under a treating general or specialist medical (or surgical) team depending on the reason for admission, and admitted in a ward where nursing care is provided by the nursing unit of the ward. During the hospital stay, medical care is mostly delivered by the treating team's doctors, but other specialists may provide consultation advice if requested. As most clinicians work in shifts, patients are managed by different clinicians depending on the time: during business hours vs. after hours. In addition, many other health professionals, including pharmacists and allied health staff provide care. A patient may undergo investigations or procedures, some of which require interruption to nutrition (or fasting). With pressure on hospital bed occupancy, patients may be transferred between wards either due to clinical need, or due to nursing workload distribution. Upon convalescence, an inpatient may be discharged directly home, transferred to a subacute care hospital, or to a residential care facility.

Compared to early Nightingale-era hospitals, modern hospitals have evolved to be dynamic institutions where there is a constant interplay between various clinicians, hospital wards and departments. Medical treatment, surgical techniques and nursing care have developed to improve patient comfort and safety. However, this is paralleled by a rise in the cost of health care and consequently there is pressure to improve efficiency, such as to decrease hospital length of stay (LOS). Although modern hospitals have improved patient care, they are often operating under financial constraints and constantly striving to improve efficiency, minimise cost, decrease LOS and utilise ambulatory treatment modalities.

1.3 Diabetes in hospital

1.3.1 Prevalence of diabetes in hospital

Given the prevalence of diabetes, and its acute and chronic sequelae, it is not surprising that diabetes is a significant comorbidity in hospitals. The prevalence of diabetes in hospital varies depending on the methodology of measurement. Based on discharge diagnostic codes, 8.9% of all hospitalisations in Australia had diabetes as a diagnosis (principal or additional) [20]. However, this is probably a gross underestimate as diabetes is often omitted in discharge summaries [21]. More accurate estimates are obtained by point-prevalence studies using manual surveys, blood glucose (BG) screening, or glycosylated haemoglobin (HbA1c) measurements.

In the United Kingdom (UK), the National Diabetes Inpatient Audit (NaDIA) is conducted annually. It includes over 200 hospitals in England and Wales, and uses a one-day 'snap-shot' survey. In 2016, NaDIA reported 17.3% of inpatients had diabetes, and this has progressively increased each year [22].

There was wide variability between hospitals, with a quarter of hospitals reporting prevalence greater than 20%, and a few hospitals reporting prevalence greater than 33%. Hospitals in continental Europe reported similar prevalence of diabetes (Table 1).

In Australia, the prevalence of diabetes appears to be higher than in UK or Europe. Point-prevalence surveys on 11 hospitals in Melbourne in 2011 reported that overall 25% of inpatients had diabetes, ranging from 16% to 35% across different hospitals [23]. At the Royal Melbourne Hospital (RMH), the prevalence was 30% in 2012, with the rate doubling in the preceding decade [24]. Other Australian hospitals have reported similar prevalence rates (Table 1).

Within each hospital, the prevalence of diabetes varies between different medical and surgical units. Traditionally, medical units such as cardiology, nephrology, stroke, and general medicine, and surgical units such as vascular surgery and cardiothoracic surgery have higher prevalence rates of diabetes, reflecting the burden of diabetes-related cardiovascular and renal pathology. A study based on discharge codes at RMH, reported the prevalence of diabetes in nephrology, general medicine and cardiology units was 36%, 29% and 24%, respectively. In cardiothoracic and vascular surgery units, the prevalence was 29% and 28%, respectively. In comparison, trauma, neurosurgery and orthopaedic surgery units had prevalence of 6%, 10% and 11% respectively [25].

Despite the significant prevalence of inpatients with diabetes, only a minority (3% to 8%) of individuals are admitted with diabetes as a primary diagnosis (such as DKA, HHS, or hypoglycaemia) [22, 26]. The majority are admitted with diabetes as a secondary diagnosis; most admissions are due to CVD, renal disease and infectious diseases [27]. Accordingly, the majority of inpatients with diabetes are admitted under different medical and surgical units and managed by treating teams who are not diabetes specialists.

1.3.2 Prevalence of new hyperglycaemia in hospital

Many individuals are discovered to have hyperglycaemia while in hospital, without previously recognised as having diabetes. New hyperglycaemia in hospital is generally defined as random BG >7.8 mmol/L in the absence of previously known diabetes [28]. Alternative thresholds such as fasting BG ≥7.0 mmol/L or random BG ≥11.1 mmol/L are occasionally used [29].

New hyperglycaemia in hospital can occur as a first detection of hyperglycaemia in a patient with undiagnosed diabetes. It can also occur due to the physiological stress of acute illness in an individual with previously normal glucose tolerance, an entity called ‘stress hyperglycaemia’. To distinguish between these two scenarios, assessment of Glycosylated haemoglobin (HbA1c) may be helpful; HbA1c ≥6.5% suggests pre-existing but undiagnosed diabetes. However, HbA1c does not reflect chronic hyperglycaemia in the setting of anaemia, acute blood loss or transfusion; therefore, the utility of HbA1c can be limited in the acute hospital setting. Hence, an oral glucose tolerance test after discharge from

hospital and resolution of acute physiological stress is recommended to distinguish between stress hyperglycaemia and undiagnosed diabetes [30]. Regardless of the aetiology, new hyperglycaemia in hospital is associated with adverse outcomes; therefore, this group of people should be identified and managed.

The prevalence of new hyperglycaemia in hospital depends on the definition used and the method of case finding. Screening for new hyperglycaemia using plasma glucose testing detects new hyperglycaemia in 10 to 15% of inpatients [31, 32]. Routine HbA1c testing reports 5% of all inpatients [33], and 11% of inpatients with BG ≥5.5 mmol/L have undiagnosed diabetes [34]. However, routine HbA1c screening is not able to detect individuals with stress hyperglycaemia, as it requires assessment of BG levels. Table 1 summarises published prevalence of new hyperglycaemia and undiagnosed diabetes.

Table 1: Point-prevalence of diabetes in hospitalised patients

Study	Location	Year	Hospitals (n)	Patients (n)	Method	Known diabetes	New Hyper-glycaemia	Un-diagnosed diabetes
Umpierrez 2002 [31]	USA (Atlanta)	1998	1	2030	Fasting and Random BG	26%	12%	-
Wexler 2008 [35]	USA (Boston)	2006	1	695	Universal screening using HbA1c	18%	-	5% (HbA1c >6.5%)
Feldman-Billard 2013 [36]	France	2009	9	2141	Point-prevalence using FPG	17%	7%	-
Ena 2015 [27]	Spain	2014	111	1000	Point-prevalence manual survey	17%	9%	1%
NaDIA 2016 [22]	UK (England & Wales)	2016	209	15744	Point-prevalence Manual survey	17.3%	-	-
Baker 2008 [32]	Australia (Melbourne)	2004	1	903	FPG and Random glucose	22%	9%	-
Valentine [34]	Australia (Adelaide)	2009	1	2360	HbA1c test if random BG ≥5.5 mmol/L	12%*	-	10%*
Bach 2014 [23]	Australia (Melbourne)	2011	11	2273	Point-prevalence manual survey	25%	-	-
Nanaya-karra 2015 [33]	Australia (Melbourne)	2014	1	5082	Universal screening using HbA1c (age >54y)	29%	-	5%
Russell 2012 [24]	Australia (Melbourne)	2012	1	310	Point-prevalence manual survey	30%	-	-
Taylor [37]	Australia (Sydney)	2016	1	1143	Point-prevalence manual survey	25%	-	6%
Kyi 2018 [38]	Australia (Melbourne)	2018	1	351	Point-prevalence random BG	36%	15%	1%

* Of patients with random BG ≥ 5.5 mmol/L (not out of all inpatients). Abbreviations, FPG = Fasting Plasma Glucose, BG = blood glucose,

1.3.3 The significance of diabetes and new hyperglycaemia in hospital

It is well-established that diabetes is associated with poor outcomes in hospital. A wealth of observational studies consistently report that individuals with diabetes have increased risk of adverse hospital outcomes, including infection, poor wound healing, cardiac complications, renal failure, increased mortality and LOS. This association is consistent across various settings including critical care and noncritical care, as well as medical and surgical disciplines. In addition, regardless of the aetiology, new hyperglycaemia is also associated with poor outcomes, particularly with increased risk of mortality. In this section, the association between diabetes and new hyperglycaemia with adverse outcomes is discussed. In the next section (Section 1.4) the mechanistic link between the severity of hyperglycaemia and adverse outcomes will be discussed.

1.3.3.1 Mortality

Diabetes is consistently associated with greater inpatient mortality across various patient populations (Table 2). In a UK study of 10 million admissions, patients with known diabetes had 6.5% higher risk of inpatient mortality compared to patients without diabetes, even after adjusting for comorbidities and severity of disease [39]. In individuals admitted with myocardial infarction (MI), diabetes increases the risk of inpatient and 180-day mortality [40-42], and is an important prognostic factor for poor outcomes [43]. It is of concern that the higher rates of diabetes-associated mortality in MI has not diminished over time [40]. In individuals hospitalised with respiratory illnesses (e.g. community acquired pneumonia, pulmonary embolism), neurological diseases (e.g. ischaemic and haemorrhagic stroke), and infectious diseases (e.g. pandemic influenza, infective endocarditis), diabetes is consistently associated with higher inpatient mortality (Table 2). Following cardiothoracic surgery, diabetes is a well-established prognostic factor for post-operative mortality [44, 45].

Although the majority of published research in cardiothoracic surgery demonstrated increased mortality with diabetes, two studies reported a lack of association [46, 47], but this may be related to perioperative intensive insulin infusion treatment that has been in routine practice since the early 2000s. Diabetes does not appear to be associated with inpatient mortality in individuals with hip fractures [48, 49]. Intriguingly, diabetes appeared to be associated with a lower rate of inpatient mortality in patients admitted with acute pancreatitis [50].

Table 2: Inpatient mortality in patients with pre-existing diabetes vs. no diabetes

Study (Year)	Country	Population (n)	Inpatient mortality: Diabetes vs. no diabetes.
General Inpatients			
Umpierrez 2002 [31]	USA	All inpatients (n=2030)	OR = 2.7
Papazafiropoulou 2010 [51]	Greece	All inpatients (n=16100)	OR = 1.32 (1.14-1.53)
Holman 2013 [39]	UK	All inpatients (n=10 million)	Adjusted OR = 1.065 (1.052-1.079)
Patients with cardiac illness			
Maier 2006 [52]	Germany	AMI females only (n=921)	Adjusted OR = 2.92 (1.75-4.87)
Canto 2012 [42]	USA	AMI (n=540,000)	Adjusted OR = 1.23 (1.20-1.26)
Parissis 2013 [53]	Multinational	Acute heart failure (n=4950)	Adjusted OR = 1.9 (1.1-3.1)
Ahmed 2014 [40]	USA	AMI (n=1.5 million)	Adjusted OR = 1.069 (1.051-1.087)
Patients with respiratory illness			
Lepper 2012 [54]	Germany	Community acquired pneumonia (n=6891)	Hazard Ratio = 2.5
Valent 2017 [55]	Italy	Community acquired pneumonia (n=458)	OR = 1.94
Fabbian 2013 [56]	Italy	Pulmonary embolism (n= 24690)	Adjusted OR = 1.12 (1.001-1.253)
Patients with neurological disease			
Arboix 2000 [57]	Spain	Haemorrhagic stroke (n=229)	Adjusted OR = 6.1 (2.0-18.3)
Koennecke 2011 [58]	USA	Stroke (n=16500)	Adjusted OR = 1.37 (1.00-1.89)
Patients with infectious disease			
Delahaye 2007 [59]	France	Infective endocarditis (n=560)	Adjusted OR = 7.8 (2.7-23.1)
Xi 2010 [60]	China	H1N1 Pandemic Influenza (n=155)	Adjusted OR = 8.8 (2.0-38.2)
Patients with surgical admissions			
Rosenthal 2003 [44]	USA	Coronary Artery Bypass Graft (n=19200)	Adjusted OR = 1.29 (1.17-1.41)
Nowicki 2004 [61]	USA	Mitral valve surgery (n=8900)	Adjusted OR = 1.47

OR = odds ratio (95% confidence interval). 95% CI are presented where reported in the original study.

New hyperglycaemia is also strongly associated with inpatient mortality (Table 3). A seminal study by Umpierrez et al., evaluated the hospital outcomes of over 2000 inpatients depending on their glycaemic status, and found inpatient mortality in patients with normoglycaemia, with pre-existing diabetes, and with new hyperglycaemia were 1.7%, 3.0% and 16.0% respectively. After adjustment for covariates, compared to the normoglycaemia group, patients with pre-existing diabetes had a 2.7 fold increase, and new hyperglycaemia had a 18.3 fold increase in mortality [31]. A similar Australian study of consecutive general medical inpatients, reported individuals with pre-existing diabetes had a modest (but non-significant) increase in mortality compared to the normoglycaemic group, with odds ratio of 1.4 (95% CI 0.6-3.2). However, individuals with new hyperglycaemia had a significantly higher risk of inpatient mortality compared to the normoglycaemic group: odds ratio 2.9 (1.2-7.0) [32].

In summary, studies consistently report individuals with new hyperglycaemia have higher rates of inpatient mortality, followed by patients with pre-existing diabetes when compared to normoglycaemic individuals.

Table 3: Inpatient mortality in patients with normoglycaemia vs. pre-existing diabetes vs. new hyperglycaemia

Study (Year)	Country	Population (n)	Inpatient mortality	
			New hyperglycaemia vs. no diabetes.	Pre-existing diabetes vs. no diabetes
Umpierrez 2002 [31]	USA	All inpatients (n=2030)	Adjusted OR = 18.3	Adjusted OR = 2.7
Baker 2008 [32]	Australia	General medicine (n=903)	Adjusted OR = 2.9 (1.2-7.0)	Adjusted OR = 1.4 (0.6-3.2)
Scheutz 2014 [62]	Germany	Community acquired pneumonia (n=880)	Adjusted OR = 2.9 (0.8-9.9)	Adjusted OR = 0.9 (0.1-9.9)
Capes 2001 [63]	Multi-national	Stroke (n=21 studies)	Adjusted OR = 3.1 (2.5-3.8)	NA
Di Bonito 2003 [64]	Italy	Ischaemic stroke (n=286)	OR = 5.9 (2.7-13.0)	OR = 1.3 (0.6-2.8)

OR= odds ratio, (95% confidence interval)

1.3.3.2 Infection

Diabetes and new hyperglycaemia are well-established risk factors for hospital-acquired (also called nosocomial), or health-care associated infections. The strongest association is reported with post-operative surgical site infections (SSI) and deep sternal wound infections (DSWI) after cardiothoracic surgery [65-69]. For example, in a prospective cohort of 1040 patients undergoing coronary artery graft surgery (CAGS), patients with diabetes had adjusted odds ratio of 2.7 (95% CI: 1.4-5.8) and patients with new hyperglycaemia (post-operative BG >11.1 mmol/L without known diabetes) had adjusted odds ratio of 2.2 (1.2-3.4) for developing SSI [70]. A similar association between diabetes and infection is found in non-cardiac surgery. In a prospective study of 3000 individuals undergoing non-cardiac surgery, those with diabetes had a 2.2 fold increase risk of pneumonia, 2.2 fold increase risk of SSI, and 3.2 fold increase risk of urinary tract infection compared to patients without diabetes [71]. In a meta-analysis of 94 studies comprising over 860,000 surgical procedures, diabetes had an odds ratio of 1.5 (95% predictive interval 1.1-2.1) for SSI. The association was present across different types of surgery but was strongest in cardiac, spinal, orthopaedic and gynaecological surgeries [72].

Aside from SSI, other hospital-acquired infections are more common in individuals with diabetes. Diabetes is a risk factor for Staphylococcus aureus bloodstream infection: relative risk 10.6 (95% CI: 9.3-11.9) in one study [73] and 4.4 times more prevalent in another study [74]. Diabetes is also associated with urinary tract infections [75], and peri-prosthetic joint infection [76]. In addition, diabetes is a risk factor for infections with more resistant or virulent microorganisms. Individuals with diabetes were 4 times more likely to develop methicillin-resistant, rather than methicillin-sensitive, Staphylococcus aureus blood stream infection [77]; and more likely to develop Gram-negative rather than Gram-positive central line associated infections [78].

1.3.3.3 Length of stay and readmissions

Patients with diabetes have longer hospital LOS than patients without diabetes. According to the Australian Institute of Health and Welfare data in 2012-2013, the mean LOS in public hospitals for all patients was 5.8 days, but 6.4 and 7.4 days for in patients with T1D and T2D, respectively [20, 79]. In the UK hospitals in 2011, median LOS was 6 nights for all inpatients, but 8 nights for patients with diabetes [80]. In the US, patients with diabetes had almost one day longer LOS (5.3 vs. 4.4 days) than patients without diabetes, based on 35 million admission episodes in 2008 [81]. In Japan, the difference in LOS was even greater: 14 vs. 10 days [82]. Locally at the Royal Melbourne Hospital, inpatients with diabetes had 1 day longer median LOS compared to patients without diabetes (6 days vs. 5 day) [25]. Inpatients with new hyperglycaemia have even longer LOS compared to individuals with normoglycaemia or pre-existing diabetes. In the aforementioned seminal study by Umpierrez et al., LOS in new hyperglycaemia, known diabetes and normoglycaemia were 9.0, 5.5 and 4.5 days, respectively [31]. Patients with new hyperglycaemia have disproportionately higher LOS, possibly related to the severity of illness rather than due to hyperglycaemia itself.

LOS outcomes are generally based on hospital discharges data registries. Outcomes are often not adjusted for demographics or severity of illness. To overcome this limitation, one UK study analysed the mean 'excess bed days' attributable to diabetes after matching for age and admission unit. This study reported patients with diabetes had 1.9 days in excess compared to patients without diabetes, which contributed to 17.8% excess bed-day use [83]. Hence, inpatients with diabetes remains 1-2 days longer in hospital compared to patients without diabetes, even after adjusting for covariates.

A small proportion of patients experience recurrent hospitalisations and this is a significant burden of inpatient care. Unplanned hospital readmission within 30 days of discharge is an important quality measure of hospital care. Similar to other chronic conditions, diabetes is associated with an increased risk of hospital readmissions. Compared to the 30-day readmission rate of between 9 to 14% in the overall hospital population, the readmission rate is between 15 to 23% in patients with diabetes [17, 84], which represents a 40% higher readmission rate [85]. The 3-month and 1-year readmission rates for diabetes patients are approximately 26% and 30%, respectively [86].

Identified risk factors for readmission in diabetes patients include medical factors (e.g. number of comorbidities, history of recent hospitalisations, low serum sodium, and high serum creatinine), and socioeconomic factors (e.g. socioeconomic status, ethnic minority, insurance status, and lack of carer or social supports) [84]. Prediction models for readmission have been developed [87] and approximately one quarter of readmissions were considered to be preventable [88]. The majority of readmissions were for reasons other than diabetes. In a cohort of older Australian veterans with diabetes, 25% were re-hospitalised within 30 days of discharge, but only 24% were readmitted for diabetes-related reasons [89]. Another recent study evaluated readmission in people following an index admission with hypoglycaemia or hyperglycaemia. Following the index admission with hypoglycaemia, 10% were readmitted within 30 days, comprising 1.2% for recurrent hypoglycaemia, 0.2% for hyperglycaemia, and 8.6% for non-diabetes reasons. Following the index admission for hyperglycaemia, 9.8% were readmitted within 30 days, comprising 4.0% for recurrent hyperglycaemia, 0.4% for hypoglycaemia, and 5.4% for non-diabetes related reasons [90]. Thus, although diabetes confers a 40% increased risk of early readmission; the majority of readmissions were not related to diabetes.

1.3.4 Mechanisms for diabetes-related adverse outcomes in hospital

Conceptually, there are three potential mechanism that link diabetes (and hyperglycaemia) with adverse outcomes (Figure 1). Firstly, *long-term microvascular and macrovascular complications* of diabetes may be responsible for adverse hospital outcomes. For example, patients with established CKD are more likely to experience acute kidney injury, and patients with established CVD are more likely to experience acute cardiac complications during acute illness in hospital. Secondly, *chronic hyperglycaemia* and its associated pathophysiology may be responsible for adverse hospital outcomes. Chronic hyperglycaemia causes endothelial and vascular dysfunction which impairs adaptive response to blood pressure changes of acute physiological stress. Chronic hyperglycaemia causes immune dysfunction and impaired wound

healing potentially accounting for increased risk of infection. Thirdly, the *acute metabolic effects of dysglycaemia* that occurs *during* hospitalisation may contribute to adverse hospital outcomes. Metabolic changes include acute hyperglycaemia, acute hypoglycaemia, and glycaemic variability, all of which are associated with pathophysiological changes which may contribute to adverse outcomes.

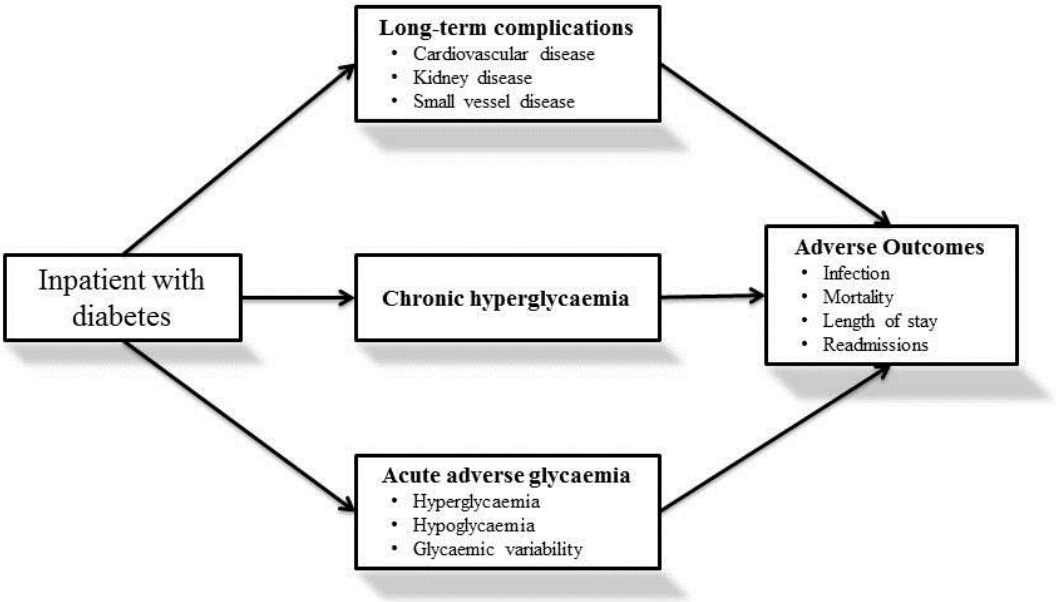

Figure 1: Potential mechanisms of diabetes leading to adverse outcomes in hospitalised patients

The relative importance of each mechanistic link between diabetes and adverse outcomes are unclear; however, it is likely that all three mechanisms are involved. The finding that patients with stress hyperglycaemia have worse adverse outcomes implies the importance of the third mechanism, acute metabolic effects of dysglycaemia. Patients with stress hyperglycaemia have normal glucose tolerance prior to illness; therefore, would not be expected to have vascular complications or physiological changes of chronic hyperglycaemia. Furthermore, for the patient who is already admitted to hospital, only the third mechanism is modifiable. By improving glycaemic control in hospital, the negative effect of acute dysglycaemia may be mitigated. To explore this concept, the following section reviews the acute effects of hyperglycaemia and hypoglycaemia, and the effects of improving glycaemia in hospital.

1.4 Adverse glycaemia in hospital

Both acute hyperglycaemia and acute hypoglycaemia are associated with adverse pathophysiology and adverse clinical outcomes in hospital. The term *adverse glycaemia* is used to encompass both extremes of hyperglycaemia and hypoglycaemia in this thesis.

1.4.1 Acute hyperglycaemia

The definition of acute hyperglycaemia in hospital is understandably different across different studies and has varied over time. Most individuals with normal glucose tolerance maintain BG in a narrow range and rarely exceed 8.0 mmol/L. In hospital, BG >7.8 mmol/L is defined as inpatient hyperglycaemia, and BG >10.0 mmol/L is defined as a threshold to commence treatment [91]. BG is a continuous measure and adverse pathophysiological changes may occur at different thresholds in different individuals; thus, individualised targets may be necessary in specific situations.

Many observational studies report a dose-dependent relationship between the severity of acute hyperglycaemia and adverse patient outcomes. The association is found in different clinical settings but has been most extensively studied in the following subgroups: coronary care, stroke care, critical care and noncritical care. The strength of the association between hyperglycaemia and adverse outcomes is modified by the presence of pre-existing diabetes. Therefore, there is debate whether hyperglycaemia causes adverse outcomes, or whether it is simply a marker of illness severity. To clarify this debate, intervention studies treating hyperglycaemia were performed aiming to decrease adverse clinical outcomes; however, results were mixed and differed between clinical settings.

1.4.1.1 Pathophysiology

The pathophysiological consequences of acute hyperglycaemia is summarised in a comprehensive review by Clement et al [1]. Acute hyperglycaemia affects the immune, cardiovascular and endothelial systems, which result in increased risk of infection, thrombosis, myocardial injury and renal failure.

The effects of hyperglycaemia on immune function are well known. Prior to the discovery of insulin, infection was the major cause of death in people with diabetes. On the innate immune system, hyperglycaemia induces polymorphonuclear neutrophil and macrophage dysfunction [92]. Hyperglycaemia causes decreased mobilisation of neutrophils across the endothelial barrier, decreased chemotaxis, decreased superoxide radical production, and decreased neutrophil degranulation [93, 94] ultimately leading to decreased microbial killing. Hyperglycaemia impairs macrophage ability to secrete IL-1 and perform phagocytosis [95]. On the adaptive immune system, hyperglycaemia appears to cause increased glycosylation of B lymphocyte immunoglobulin, which may impair immunoglobulin-mediated immune response [1]. Hence, hyperglycaemia increases the risk of SSI and other hospital-acquired infection due to its effect on the innate and adaptive immune systems.

On the cardiovascular system, hyperglycaemia causes numerous changes in haemostasis favouring thrombosis. Hyperglycaemia has been shown to increase platelet hyperactivity, increase platelet activation, and elevate plasma fibrinogen levels, all of which may increase the risk of thrombotic events. Hyperglycaemia increases production of IL-6 and tumour necrosis factor-α; inflammatory responses that further contribute to vascular changes [1]. Hyperglycaemia at various thresholds between 8.0 and 16.7 mmol/L causes endothelial dysfunction in human in vivo studies [96]. Endothelial dysfunction is linked to inflammation, thrombosis and decreased ability for maintenance of vascular homeostasis. Hyperglycaemia also induces reactive oxygen species causing oxidative stress [97], which leads to direct tissue injury and further inflammation. Ultimately hyperglycaemia increases the risk of cardiovascular complications including myocardial injury and renal complications [1]. Acute hyperglycaemia also causes osmotic diuresis which may lead to dehydration, metabolic disturbance, acute kidney injury and further cardiovascular stress.

Pathophysiological changes of hyperglycaemia can occur even after exposure to a short duration (between 2 to 6 hours) of moderate levels of hyperglycaemia (BG 15.0 mmol/L) [98]. Reversal of hyperglycaemia leads to a rapid resolution of these changes [1]. Much of the evidence comes from animal studies, and human studies in both normoglycaemic individuals and those with diabetes. It is unclear if pathophysiological changes occur to the same extent in an individual with pre-existing chronic hyperglycaemia. It could be speculated in individuals with chronic hyperglycaemia, the adverse effects of acute hyperglycaemia may be somewhat blunted possibly due to adaptive changes. Conversely, individuals with stress hyperglycaemia may experience marked pathophysiological changes in response to acute hyperglycaemia.

It is unclear whether the pathophysiological changes occur to the same extent in the hospitalised individuals who are already exposed to acute physiological stresses due to illness. Hospitalised patients have additional challenges from counter-regulatory hormones which cause increased insulin resistance leading to further hyperglycaemia and increased free fatty acid. Hyperglycaemia then causes glucotoxicity and β-cell dysfunction which further leads to a vicious cycle of hyperglycaemia and insulin deficiency [99]. Hyperglycaemia through immune, vascular and endothelial dysfunction further leads to tissue injury, inflammation and ischaemia which lead to increased stress response, perpetuating another vicious cycle. Ultimately, the combination of hyperglycaemia, insulin deficiency, tissue injury and stress response are postulated to be the mechanisms relating acute hyperglycaemia to organ dysfunction and poor hospital outcomes [1].

1.4.1.2 Adverse outcomes in different hospital settings

1.4.1.2.1 Acute myocardial infarction

The prognostic importance of hyperglycaemia in MI has been recognised since the 1970s [100]. A meta-analysis of 15 observational studies reported that in individuals *without* pre-existing diabetes, *admission*

glucose greater than the range of 6.1-8.0 mmol/L was associated with 3.9 fold (95% CI 2.9-5.4) greater risk of death compared to those with normoglycaemia [101]. In people with *pre-existing diabetes*, admission BG greater than the range of 10.0-11.0 mmol/L was associated with 1.7 fold (95% CI 1.2-2.4) increased risk of mortality. Admission hyperglycaemia is additionally associated with longer term adverse outcomes such as 30-day and 1-year mortality [102]. *Fasting BG* as a continuous measure is associated with poor outcomes including congestive cardiac failure, post-thrombolysis bleeding and mortality [103]. *Persisting hyperglycaemia* during the admission is reportedly a stronger predictor of poor outcomes than admission hyperglycaemia [104].

Intervention studies where insulin is utilised to manage hyperglycaemia following a MI demonstrated conflicting results. Two different approaches to insulin therapy in MI have been tried: the insulin-based approach and the glycaemic-based approach. The insulin-based approach used a glucose, insulin and potassium (GIK) infusion as a cardio-protective, therapeutic measure to potentially limit myocardial necrosis. Although several smaller studies in the 1990s showed some benefit, a large-scale definitive randomised controlled trial (RCT) reported no benefit of GIK infusion in patients with ST-elevation acute MI [105].

The glycaemic-based approach focused on using intensive insulin therapy (IIT) to achieve BG targets. The DIGAMI RCT recruited 620 acute MI patients with admission hyperglycaemia (BG >11.0 mmol/L), regardless of underlying diabetes status [106]. Participants randomised to the IIT group were treated with glucose and insulin to maintain BG between 7 and 10 mmol/L for 24 hours, and then followed by a basal-bolus subcutaneous insulin therapy for at least 3 months. The IIT group had lower mean BG at 24 hours (9.6 vs. 11.7 mmol/L), 29% lower 1-year mortality, and 11% lower mortality at 3.5 years; however, it was unclear if the benefit was due to the reduction in acute hyperglycaemia or due to the subsequent improvement in glycaemic control in the months following MI. The subsequent DIGAMI-2 [107] and Hi-5 [108] studies failed to show the same benefits of IIT following MI. In the Hi-5 study, there was only a modest difference in mean 24-hour glucose (8.3 vs. 9.0 mmol/L) achieved between the two treatment groups. Furthermore, compared to the original DIGAMI study, participants in DIGAMI-2 and HI-5 had substantially better glycaemic control prior to admission, and less severe hyperglycaemia at admission; therefore, the possible benefits of improved glycaemic control could have been diminished [109, 110]. In a post-hoc analysis of the Hi-5 study, participants who achieved a mean BG ≤8 mmol/L in the first 24 hours had a lower 6 month mortality rate than patients with mean BG >8 mmol/L, leading to the speculation that reducing acute hyperglycaemia could still be beneficial following an acute MI.

1.4.1.2.2 Stroke

In patients admitted with stroke, admission hyperglycaemia is associated with increased mortality and morbidity. A meta-analysis of 26 studies reported amongst patients without known diabetes with ischaemic stroke, admission hyperglycaemia greater than the range of 6.1–8.0 mmol/L had 3.3 (95% CI 2.3-4.6) fold increase in mortality [63], and greater risk of poor functional outcomes. In contrast, amongst

patients with known diabetes, admission hyperglycaemia was not associated with increased mortality (odds ratio 2.0 [95%CI: 0.04-90.1]). Hyperglycaemia is common following stroke. Using continuous glucose monitoring technology, 50% of individuals without diabetes and 100% of individuals with diabetes were observed to develop hyperglycaemia following acute stroke [111]. Mean glucose levels post stroke was also independently associated with expansion of infarct size and worse clinical outcomes [112].

Intervention studies using insulin to treat hyperglycaemia following stroke reported conflicting results. A Cochrane meta-analysis reported a lack of benefit of IIT on mortality, disability or dependence following a stroke [113]. A more recent cluster randomised study named Quality in Acute Stroke Care (QASC), investigating a bundle of interventions including management of hyperglycaemia, fever, and swallowing dysfunction, reported a 15.7% absolute risk reduction in death or dependency at 3 months [114]. Although hyperglycaemia management was one component of the bundle of interventions, the QASC study suggested improving glycaemic control may contribute to improving outcomes following stroke.

1.4.1.2.3 Cardiac Surgery

An observational study in patients undergoing cardiac surgery demonstrated that pre-existing diabetes (OR 2.7) and peri-operative hyperglycaemia (OR 2.0) were both independently associated with SSI and Deep Sternal Wound Infection (DWSI) [70]. Interestingly, among patients with known diabetes, perioperative hyperglycaemia (but not admission HbA1c) was associated with SSI; suggesting that perioperative hyperglycaemia may be more detrimental than chronic hyperglycaemia [70].

In the early to mid-1990s, there was a shift in cardiac surgery glycaemic management approach to more aggressively treat perioperative hyperglycaemia with continuous intravenous insulin infusion (CIII), rather than subcutaneous insulin injections [115]. CIII was commenced intraoperatively or immediately postoperatively to achieve BG target between 8.3 and 11.1 mmol/L. This approach resulted in a significant decrease in the rate of DSWI (from 2.0% down to 0.8%), to similar rates as normoglycaemic individuals [116], as well as decreased mortality [117]. A meta-analysis confirmed the improved outcomes with ‘tight glycaemic control’ in the perioperative setting in cardiac surgery [118]. It is now routine clinical practice to use CIII targeting a BG target of <11.1 mmol/L in cardiac surgery and following this approach, diabetes is no longer believed to be a risk factor for in-hospital mortality in this setting [47]. Hence, studies in cardiac surgery have provided some of the strongest evidence that treating hyperglycaemia decreases wound infection and mortality.

1.4.1.2.4 Critical Care

In patients admitted to the intensive care unit (ICU), there is a clear continuous relationship between severity of hyperglycaemia and mortality, across various conditions and severity of illness [119]. Falciglia et al., evaluated a retrospective cohort of 260,000 ICU admissions, reporting a dose-dependent

relationship between mean glucose and mortality, even after adjustment for age, diagnosis, comorbidities and severity of illness [120]. This association exists regardless of pre-admission diabetes status; however, it was strongest in patients without pre-existing diabetes (Figure 2). Several other ICU studies have reported similar findings [121-123]

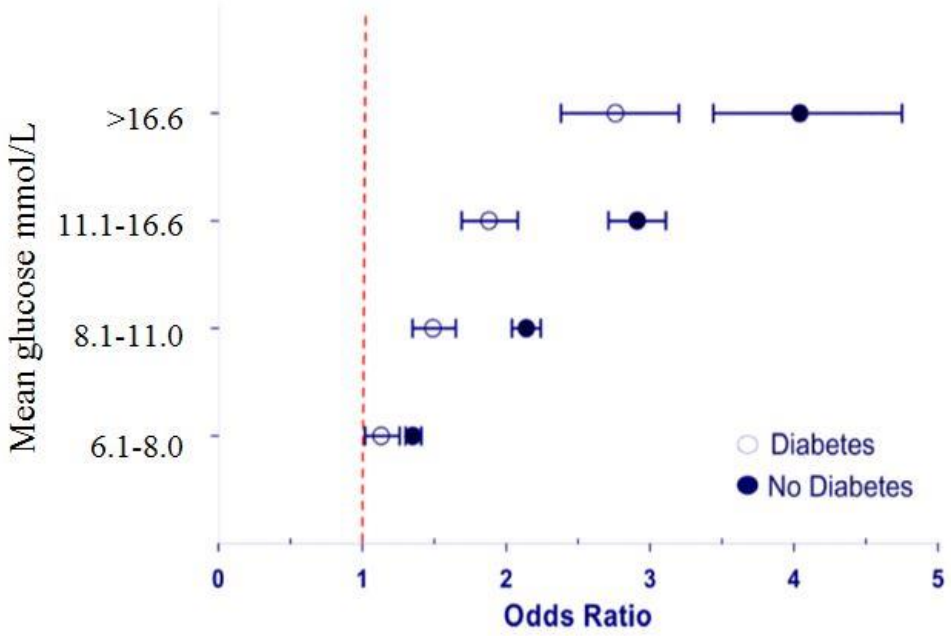

Figure 2: Mortality risk in patients with and without diabetes, depending on mean glucose in the intensive care. Odds ratios and 95% confidence intervals are presented compared to group with mean glucose ≤ 6.0mmol/L. Adapted from Falciglia, Crit Care Med 2009 [120]

A number of large RCTs investigating intensive glycaemic control using IIT were performed in the critical care setting. The first study (Leuven-I), recruited patients admitted to a surgical ICU and randomised to IIT (target BG: 4.4 to 6.1 mmol/L) vs. conventional care (target BG: 10.0 to 11.1 mmol/L) [124]. The IIT group had 42% risk reduction in ICU mortality, 34% reduction in hospital mortality, and 34% reduction in blood stream infections. The second study (Leuven-II) in a medical ICU, IIT did not show improvements in mortality, but there were reductions in secondary outcomes including kidney injury [125]. Although the Leuven studies sparked a worldwide interest in IIT, concerns were raised about the generalisability of these single-centre studies, with particular reference to a more aggressive provision of enteral and total parenteral nutrition, and high baseline mortality rate in this centre compared to many other ICUs worldwide.

Subsequent multicentre trials on IIT in critical care did not reproduce the Leuven results [126-128]. In contrast, the multicentre NICE-SUGAR study involving more than 6000 patients reported increased mortality with IIT compared to conventional therapy (OR 1.14 [95% CI 1.02 to 1.28]) [129]. It has been speculated that excess mortality could be related to cardiovascular events associated with severe

hypoglycaemia, which were more prevalent with IIT (6.8% vs. 0.5%). A meta-analysis of intensive glycemic control (target BG 4.4 to 6.1 mmol/L) using IIT in critical care reported no difference in-hospital mortality (pooled relative risk 0.98 [95% CI: 0.89 to 1.09] or long-term mortality (pooled relative risk 1.07 [CI: 1.00 to 1.14]), but caused more hypoglycaemia (pooled relative risk 6.00 [CI: 4.06 to 8.87]) [130]. This meta-analysis however, found that intensive glycaemic control was associated with a lower risk of hospital-acquired infection (pooled relative risk 0.78 [CI: 0.62 to 0.97]), suggesting lowering infection could be the standout benefit of intensive glycaemic control.

1.4.1.2.5 Noncritical care

Observational studies in noncritical care also report a dose-dependent relationship between hyperglycaemia and adverse outcomes, irrespective of the glycaemic measure (e.g. admission glucose, or mean glucose in hospital). The association exists regardless of diabetes status, although it is strongest in patients without pre-existing diabetes. For example, admission hyperglycaemia was reported as an independent marker of mortality with a threshold at ≥8.0 mmol/L, and each 1.0 mmol/L increase in BG conferred a hazard ratio of 1.04 [95% CI: 1.02-1.06] [131]. This association was strongest amongst patients with new hyperglycaemia, although a similar trend was observed (but did not reach statistical significance) in patients with pre-existing diabetes. In a more contemporary cohort, a similar relationship was reported between admission hyperglycaemia and in-hospital mortality after adjusting for covariates [132].

In patients admitted with community acquired pneumonia, a continuous relationship exists between admission glucose and risk of complications and mortality [54, 133]; the severity of hyperglycaemia correlates with markers of inflammation [62]. In patients with exacerbation of chronic obstructive pulmonary disease, each 1 mmol/L increase in mean BG during hospital-stay is associated with 15% increased risk of adverse outcomes after adjustment for covariates [134]. In bone marrow transplant patients, mean laboratory glucose during admission correlates with LOS [135]. The mechanistic link between glucose levels and LOS is not entirely clear. Hyperglycaemia may reflect a greater severity of illness, affect clinical decision to discharge a patient, or delay discharge due patient education required for diabetes self-management.

In non-cardiac surgery, hyperglycaemia during the pre-operative, intraoperative, and post-operative periods are all associated with adverse outcomes. Hyperglycaemia during the post-operative period is considered to be particularly detrimental due to the presence of a surgical wound which is vulnerable to infection and poor would healing. In a prospective cohort of 3100 individuals undergoing non-cardiac surgery, perioperative hyperglycaemia >10 mmol/L was associated with a higher risk of post-operative pneumonia, bacteraemia, urinary tract infection, acute renal failure, acute myocardial infarction and longer LOS [71]. In patients without pre-existing diabetes, 30-day mortality increased exponentially with degree of hyperglycaemia; however, in patients with pre-existing diabetes, this association was less strong. Table 4 summarises the association between perioperative hyperglycaemia and poor outcomes.

Table 4: Association between perioperative hyperglycaemia and adverse outcomes, non-cardiac surgery

Study, Year, Country	Population (n)	Threshold of hyperglycaemia	Adverse outcomes
Pomposelli 1998 Boston, USA [69]	Non-cardiac surgery (n=100)	>12.2 mmol/L	Infection
Noordzij 2007, Netherlands [136]	Non-cardiac surgery (n=2100)	>5.6 mmol/L	Mortality, Cardiovascular mortality
Ramos 2008 Boston, USA [137]	General & vascular surgery (n=990)	>6.1 mmol/L	Infection
Frisch 2010 Atlanta, USA [71]	Non-cardiac surgery (n=3100)	>10.0 mmol/L	Infection, AMI, AKI, Mortality
Jackson 2012 Washington, USA [138]	Colorectal surgery (n=9600)	>9.0 mmol/L	SSI, Mortality
Kwon 2013 Washington, USA [139]	General & bariatric surgery (n=11600)	> 10.0 mmol/L	Infection, Reoperation, Mortality
Kotagal 2015 Washington, US [140]	General, bariatric, vascular & spinal surgery (n=40800)	> 7.0 mmol/L	Composite (AMI, stroke, Arrhythmia, unplanned ICU, fall w injury, infection, AKI, unplanned reoperation, mortality)
Buehler 2015 Atlanta, USA[141]	General surgery (n=2100)	>7.8 mmol/L	Composite (AMI, wound, respiratory infection, bacteraemia, AKI, mortality)

Abbreviations: AKI, acute kidney injury; AMI, acute myocardial infarct; ICU, intensive care unit; SSI, surgical site infection

A recent study analysed over 6600 non-cardiac surgeries at a large tertiary hospital network to investigate the relationship between pre-surgery glucose control (as determined by HbA1c), perioperative glucose control (as determined by median glucose from day 0 to day 3 following surgery) and 30-day mortality [142]. This analysis reported a linear relationship between perioperative glucose and mortality after adjustment for HbA1c. This relationship did not interact with the presence of pre-existing diabetes, suggesting perioperative hyperglycaemia is critically more important than chronic hyperglycaemia.

Despite the wealth of observational studies, there have not been any RCTs of various glycaemic targets in noncritical care; therefore, the ideal BG target has not been subject to empirical research. However, the importance of glycaemic control in noncritical care was demonstrated by studies of different insulin regimens in hospital. In the RABBIT-2 Surgery study, surgical inpatients with hyperglycaemia were randomised to a basal-bolus regimen vs. sliding scale regimen [143]. The basal-bolus treated group achieved a lower mean glucose (8.1 mmol/L vs. 9.6 mmol/L), and had a lower rate of composite outcomes comprising: wound infection, pneumonia, acute respiratory failure, acute renal failure, bacteraemia and mortality (8.7% vs. 24.3% p=0.003). There were fewer wound infections, pneumonia and acute renal failure in the basal-bolus group. LOS in the intensive care unit was shorter but overall

hospital LOS was not different. This study was the first to demonstrate in noncritical care, basal-bolus insulin decreased hyperglycaemia and adverse clinical outcomes.

Subsequent studies of intensive insulin treatment in noncritical care demonstrated improvements in glycaemic control but were not powered to investigate improvements in clinical outcomes [144-146]. A meta-analysis of 9 RCTs and 10 observational studies in noncritical care patients found intensive glycaemic control did not significantly affect risk of death, MI, or stroke. However, intensive glycaemic control demonstrated decreased risk of infection (relative risk 0.41 [95% CI 0.21-0.77]), mainly based on observational studies in surgical patients [147].

1.4.1.3 Summary

Acute hyperglycaemia results in altered pathophysiology including immunosuppression, endothelial dysfunction, and pro-thrombotic and pro-inflammatory changes. These changes lead to increased risk of infection, myocardial infarct, kidney injury, and ultimately higher mortality and longer LOS. These pathophysiological changes occur at moderate degrees of hyperglycaemia that is routinely encountered in hospital practice. Different thresholds may apply to individuals without diabetes vs. those with pre-existing diabetes. There is a wealth of observational data in various clinical settings (including critical care and noncritical care) reporting associations between acute hyperglycaemia and adverse outcomes. Intervention studies in myocardial infarction and critical care have yielded mixed results on the effectiveness of intensive glycaemic control to improve outcomes. Current evidence suggests modest glycaemic control (aiming BG <10 mmol/L) is safer than tight glycaemic control (BG target 4.4 to 6.1 mmol/L), at least in the critical care setting. In noncritical care, there is a lack of large prospective trials of glycaemic targets powered for clinical outcomes. Extrapolating the RABBIT-2 surgery study and the QASC study in stroke care, modest glycaemic control may improve outcomes in noncritical care, particularly in decreasing infectious complications.

1.4.2 Acute hypoglycaemia

The glycaemic threshold that defines hypoglycaemia of clinical and pathophysiological significance has been subject to debate. In ambulatory care, hypoglycaemia can be defined by the onset of sympathoadrenal or neuroglycopenic symptoms, and severity can be defined by whether third-party assistance is required for treatment. However, in the inpatient setting, it is inappropriate to define hypoglycaemia by symptoms because individuals may have counter-regulatory responses associated with illness; may have impaired conscious state; or may be treated with medications (such as beta adrenergic blockers) that interfere with symptoms. The individual may be unable to self-treat hypoglycaemia due to lack of mobility or access to carbohydrate supply. Hence, in the inpatient setting, absolute BG thresholds are used to define hypoglycaemia [148].

There are minor differences in BG thresholds that define hypoglycaemia across different health systems. In the US, BG <70 mg/dL (<3.9 mmol/L) is commonly used to define hypoglycaemia. However, in the UK, Australia and European countries where mmol/L is the standard unit of glucose measurement, the whole number cut-off <4.0 mmol/L (<72 mg/dL) is commonly used. Furthermore, different BG thresholds have been proposed to define severe hypoglycaemia such as <3.0 mmol/L (<54 mg/dL), or <2.8 mmol/L (<50 mg/dL), or <2.2 mmol/L (<40 mg/dL) [148]. The American Diabetes Association (ADA) now recommends reporting inpatient hypoglycaemia at three different levels: Level 1, BG <3.9 mmol/L (<70 mg/dL) but ≥3.0 mmol/L (≥54 mg/dL); Level 2, BG <3.0 mmol/L (<54 mg/dL); and Level 3, a severe event characterised by altered mental and/or physical status requiring assistance [28].

1.4.2.1 Pathophysiology

Hypoglycaemia can independently cause adverse pathophysiological changes in the immunological, cardiovascular and neurological systems. Hypoglycaemia causes a counter-regulatory response, comprising catecholamine release, inflammation and endothelial dysfunction. Hypoglycaemia causes expression of vascular adhesion molecules [149], leucocyte mobilisation [150], inflammation and platelet adhesion [151], which lead to a pro-inflammatory and pro-thrombotic state. These changes are observed in all individuals experiencing hypoglycaemia, regardless of whether the individual has pre-existing diabetes.

Hypoglycaemia additionally causes ischaemic and arrhythmogenic changes. In rats, increasing duration of severe hypoglycaemia causes increasingly lethal changes on the electrocardiogram, including prolonged QT interval, heart block, atrioventricular dissociation, and finally malignant arrhythmia [152]. Blockade of the beta adrenergic receptor attenuates arrhythmias, supporting the critical importance of adrenergic system. In humans, similar ischaemic and QT interval changes have been observed on electrocardiograms during hypoglycaemia [153]. Hypoglycaemia-induced arrhythmia is the purported mechanism of the ‘dead in bed syndrome’, of unexplained sudden death in young individuals with type 1 diabetes [154]. Most evidence is derived from ambulatory patients and it is unclear if pathophysiological

changes occur in hospitalised patients, who may have underlying adrenergic responses due to illness. On the other hand, hospitalised patients may be more vulnerable to hypoglycaemia as they are more likely to have CVD or electrolyte abnormalities.

Severe hypoglycaemia causes neuroglycopenia which can result in temporary or permanent neurological deficit, seizure and coma, as well as indirect effects such as falls and injuries. As the human brain can utilise alternative fuels during hypoglycaemia, permanent neurological damage is thought to be rare [155], and the mechanisms of hypoglycaemia-related death is believed more likely to be secondary to cardiac arrhythmias. Furthermore, although an episode of hypoglycaemia may be transient with appropriate treatment, it could destabilise glycaemic control for many hours due to changes in counter-regulatory hormone responses, resulting in hyperglycaemia or recurrent hypoglycaemia.

1.4.2.2 Adverse outcomes

Inpatient hypoglycaemia is associated with increased mortality, although a causal relationship has not been established. In critical care, a study including over 66000 admissions reported hypoglycaemia (<4.5 mmol/L) due to any cause, within the first 24 hours of admission, was associated with increased mortality (adjusted OR 1.41 [95% CI, 1.31-1.54]) [156]. In noncritical care, amongst 4300 patients with diabetes, each additional day with hypoglycaemia (BG <2.8 mmol/L) increased the odds of inpatient mortality by 83%; and increased LOS by 2.5 days [157]. Both studies demonstrated a correlation between severity of hypoglycaemia and subsequent risk of death.

In hospital, spontaneous vs. treatment-related hypoglycaemia must be distinguished. *Spontaneous hypoglycaemia* occurs in the absence of diabetes or glucose-lowering agents, typically in the setting of severe organ failure. Hence, spontaneous hypoglycaemia is strongly associated with mortality; however, hypoglycaemia is usually not the cause of death. *Treatment-related hypoglycaemia* occurs in people treated with GLM and/or insulin; therefore, adverse outcomes could be caused by glycaemic management in hospital. Table 5 summarises studies evaluating the association between mortality and spontaneous vs. treatment-related hypoglycaemia. Two studies demonstrated mortality is associated with spontaneous hypoglycaemia only [158, 159], whilst two other studies reported mortality is associated with *both* spontaneous and treatment-related hypoglycaemia [160, 161].

Studies evaluating mortality and morbidity associated with hypoglycaemia are summarised on Table 6 and Table 7. Studies in Table 6 evaluated all patients (with and without diabetes), and did not differentiate between spontaneous vs. treatment-related hypoglycaemia. Studies in Table 7 included subsets of patients with pre-existing diabetes; hence, focussed on treatment-related hypoglycaemia. Studies consistently report increased risk of mortality, LOS, and other adverse outcomes with inpatient hypoglycaemia. Although cardiac complications of hypoglycaemia can occur, it is often difficult to attribute an episode of cardiac ischaemia solely to the hypoglycaemic event in patients who are subject to multiple sources of physiological stresses. In contrast, neurological sequelae, including transient altered

mental state, can often be attributed to inpatient hypoglycaemia. In a study of 500 episodes of hypoglycaemia, serious neurological sequelae, including seizures, occurred in 4% of individuals [162]. A survey of UK hospital endocrinology services compiled 12 serious hypoglycaemia-related adverse events including three deaths, two cases of permanent cerebral damage, two cardiac arrests and three seizures; a finding which is likely to be the 'tip of the iceberg' [163].

For treating clinicians, each episode of inpatient hypoglycaemia demands increased clinical resources for treatment of hypoglycaemia and increased frequency of BG monitoring. Occasionally a medical emergency team (MET) response may be required to treat a patient in a hypoglycaemia-induced depressed conscious state. Even in the absence of cardiac or neurological sequelae, an episode of symptomatic hypoglycaemia is an unpleasant event for the individual and could affect the physical and psychological wellbeing during hospitalisation. Hence, avoidance of hypoglycaemia is a major priority for safe hospital care.

Table 5: Association between in-hospital hypoglycaemia and mortality risk, categorised between spontaneous vs. treatment-related hypoglycaemia

Study, Year Country	Patient population	Hypoglycaemia threshold	Risk of mortality (compared to patients without hypoglycaemia)	
			Spontaneous hypoglycaemia	Treatment-related hypoglycaemia
Kosiborod 2009, USA [159]	AMI patients with hyperglycaemia (n=7800)	<3.3 mmol/L	OR: 2.3	Nil association
Boucai 2011 New York, USA [158]	Noncritical care (n=31 900)	<3.9 mmol/L	HR: 2.6	Nil association
Garg 2013 Boston, USA [161]	All hospital patients (n=2800)	≤2.8 mmol/L	OR 20	OR 7.0
Akirov, 2017 Israel [160]	Medical inpatients (n=33 600)	<3.9 mmol/L	OR 2.2	OR 2.5

Table 6: In-hospital hypoglycaemia and adverse outcomes, diabetes and non-diabetes patients (spontaneous vs. treatment-related hypoglycaemia not defined)

Study, Year, Country	Patient population	Threshold Hypoglycaemia	Associated Adverse Outcomes
D'Ancona 2011, Italy [164]	Cardiac surgery (n=590)	<3.9 mmol/L	Mortality Respiratory failure
Stamou 2011, North Carolina, USA [165]	Cardiac surgery (n=2500)	<3.3 mmol/L	Pneumonia Respiratory failure Longer length of stay
Brodovicz 2013, USA [166]	All inpatients (n=107,000)	<3.9 mmol/L	Mortality Longer length of stay
Gomez-Huelgas 2013, Spain [167]	All inpatients (n=154,000)	Discharge code	Mortality
Kim 2014, Chicago, USA [168]	Medical inpatients (n=1276)	<3.9 mmol/L	Composite (infection, acute renal failure, critical care admission)
Merrill 2018, Ohio, USA [169]	Patients with heart failure (n=13400)	<3.9 mmol/L	Mortality

Table 7: In-hospital hypoglycaemia and adverse outcomes, patients with pre-existing diabetes

Study, Year, Country	Patient population	Threshold Hypoglycaemia	Associated Adverse Outcomes
Turchin 2009, Boston, USA [157]	Diabetes inpatients in noncritical care (n=4300)	≤2.8 mmol/L	Mortality Longer length of stay
Curkendall 2009, USA [170]	Diabetes patients (n=100 000)	<3.9 mmol/L	Mortality Longer length of stay Greater cost
Nirantharakumar 2012, UK [171]	Diabetes inpatients (n=7300)	<3.9 mmol/L	Mortality Longer length of stay
Zapatero 2014, Spain [172]	Diabetes inpatients (n=921300)	Discharge code	Mortality Longer length of stay Readmissions
Kuan 2014, Singapore [173]	Diabetes inpatients in noncritical care (n=8900)	<3.5 mmol/L	Mortality Longer length of stay Readmission

1.4.3 Glycaemic variability

Glycaemic variability (GV) refers to the glucose excursions from the mean value. In the short-term, GV is characterised by within-day glucose fluctuations (peaks to nadirs). As two individuals with diabetes with the same mean glucose and HbA1c can have different glucose profiles, GV can be significantly different between individuals. Various measures of GV have been developed particularly for reporting continuous glucose monitoring data, but in the hospital setting, standard deviation (SD) or coefficient of variation (CV) are most practical and commonly used [174].

In addition to hyperglycaemia and hypoglycaemia, GV is postulated to contribute to adverse short-term and long-term complications. In vitro human and animal studies report intermittent exposure to high glucose stimulate greater production of reactive oxygen species than constant exposure to high glucose [174]. However, in-vivo studies in humans have not been consistent. One study in individuals with type 2 reported a strong correlation between degree of GV and oxidative stress [175], whilst another study in individuals with type 1 diabetes reported no correlation [176].

In ambulatory care, long-term GV is emerging as an independent risk factor for mortality from cardiovascular disease and mortality from any cause in people with diabetes [177]. In hospital, short-term GV is associated with adverse outcomes in all inpatients, but the association is stronger in people without diabetes [178]. However, a recent study reported that GV remained a risk factor for longer hospital LOS and increased mortality in patients with and without diabetes, even after adjustment for several potential confounders [179]. As there are no intervention studies specifically targeting GV, it is unclear whether improving GV provides additional benefit than improving rates of hyperglycaemia and hypoglycaemia in hospital.

1.4.4 Glycaemic targets

As prospective studies of BG targets in noncritical care are not available, inpatient glucose targets are extrapolated from critical care. Based on RCTs in critical care, glycaemic control to avoid hyperglycaemia-related adverse effects is recommended. However, tight glycaemic control (BG 4.4-6.1 mmol/L) may be deleterious and therefore is not recommended. As the comparator arms in critical care RCTs aimed for BG <10 mmol/L, this has become the recommended target for most critically ill patients [180]. In addition, observational data suggest thresholds of hyperglycaemia differ depending on the presence of diabetes. In individuals with pre-existing diabetes, adverse outcomes increase above a threshold of 10-11 mmol/L, whereas in those without diabetes, the threshold is around 6-8 mmol/L. Therefore, a more stringent glycaemic target may be more appropriate in individuals with new hyperglycaemia.

Accordingly, the ADA and the US Endocrine Society recommend BG target of 7.8-10.0 mmol/L (140-180mg/dL) in critical illness, and “a more stringent goal, such as 6.1-7.8 mmol/L (110-140 mg/dL) may

be appropriate for selected patients, if this can be achieved without significant hypoglycaemia" [28]. In some European ICUs, a more stringent target of 5.6-7.8 mmol/L is recommended [181], and following the Leuven studies, many Belgian ICUs target a BG range of 5.0-8.0 mmol/L [182].

In noncritical care, the ADA and US Endocrine Society recommend a target of fasting BG <7.8 mmol/L and random BG <10.0 mmol/L [28, 183]. A lower limit of BG target was not specified, but guidelines recommend adjusting anti-diabetic therapy when BG falls <5.6 mmol/L (<100mg/dL) to avoid hypoglycaemia. The Australian Diabetes Society recommend similar targets stating "most patients in general hospital wards with hyperglycaemia should be treated to achieve and maintain glucose level less than 10 mmol/L", and to "avoid treatment which lowers the glucose below 5.0 mmol/L" [30]. Of note, although hypoglycaemia is defined as <4.0 mmol/L, guidelines recommend avoiding BG <5.0 mmol/L to leave a buffer in place, and to de-intensify treatment appropriately to avoid hypoglycaemia. The Joint British Diabetes Societies for Inpatient Care has not recommended a specific BG target in critical or noncritical care, but in patients undergoing surgery, BG target of 6.0-10.0 mmol/L is recommended, but that BG 6.0-12.0 mmol/L "could be acceptable in most people" [184]. Conversely, patients with multiple comorbidities and frailty may not benefit from stringent control and hypoglycaemia could be more harmful; hence, all guidelines unanimously recommend higher BG targets with the main aims of avoiding symptomatic hyperglycaemia and hypoglycaemia.

In summary, national and international guidelines recommended most individuals in critical and noncritical care should target BG <10 mmol/L. For some patients (with new hyperglycaemia), a more stringent target (such as <7.8 mmol/L) may be appropriate if this is able to be achieved without hypoglycaemia. Conversely, a less stringent and individualised target may be appropriate in individuals with severe comorbidities and life-limiting illness.

1.4.5 Definition of adverse glycaemia

Recommendations to target inpatient BG <10 mmol/L were not based on strong experimental data as there are no definitive studies comparing BG target <10 mmol/L vs. a higher cut-off, although a pilot study [185], and a phase 2 study comparing BG target <10 vs. <14 mmol/L for type 2 diabetes patients in critical care is currently underway (LUCID, ANZCTR 12616001135404). In people with severe comorbidities, a higher cut off is appropriate, although severe hyperglycaemia must be avoided to avoid symptoms such as thirst, polyuria and dehydration. In most people, adverse pathophysiological changes including immune and endothelial dysfunction, pro-inflammatory and pro-thrombotic changes occur after a few hours of exposure to glucose levels approximately 15 mmol/L (section 1.4.1.1). Therefore, the glucose level of 15 mmol/L was chosen as the upper cut-off for adverse glycaemia, a level of hyperglycaemia that should be avoided in most inpatients regardless of comorbidities.

At the other extreme, any degree of hypoglycaemia in hospital is undesirable and should be avoided. Adverse outcomes occur with a threshold of BG <4.0 mmol/L (section 1.4.2.2); therefore, this threshold was chosen as the lower cut-off of adverse glycaemia.

Hence, *adverse glycaemia in this thesis is defined as BG <4.0 or >15.0 mmol/L*, a composite of hypoglycaemic and hyperglycaemic extremes at which there are adverse changes in pathophysiology, and thresholds which are associated with adverse clinical outcomes. Adverse glycaemia describes unsafe glucose level that should be avoided in virtually all hospital patients regardless of clinical context or comorbidities.

1.5 Diabetes management in critical care

Diabetes management practice differs between critical care and noncritical care settings. In critical care, glucose-lowering treatment is often initiated when BG exceeds 10 mmol/L over two consecutive measurements [123]. Typically, most ICUs follow the ADA guidelines aiming for BG target of <10 mmol/L. Intravenous insulin infusion is often used in preference to subcutaneous insulin as it allows for frequent dose titration in combination with intensive glucose monitoring. Central laboratory measurement or blood gas analysis on venous or arterial blood is often used in preference to capillary blood, which may be inaccurate in patients with hypotension and increased oxygen utilisation. Point-of-care (POC) glucose meters may have variable accuracy in the critically ill patient, particularly due to anaemia or drugs that interfere with enzymatic reactions of BG measurement [186]. However, improvements in technology have increased the accuracy of POC glucose meters. Recently, one POC glucose monitoring system was approved by the US Food and Drug Authority for capillary glucose measurements in critically ill patients [187], raising the possibility of less invasive methods of glucose monitoring.

Most ICUs have established algorithms for initiation and titration of intravenous insulin infusion. In some centres, computerised alert systems and decision support tools assist insulin dosing and administration. Upon recovery from critical illness, insulin infusion is transitioned to subcutaneous insulin treatment at the time of transfer to noncritical care wards. Given the relatively confined environment and greater clinical resources available in ICUs, glucose management practice is often more protocolised and easier to implement than in the noncritical care settings.

1.6 Diabetes management in noncritical care

Given the lower acuity of illness and absence of evidence in noncritical care, diabetes management is more variable, less intensive and less protocol-driven than in critical care. There is also variation in glycaemic management practices between health systems in Australia and abroad. In general, most patients have capillary BG monitoring using POC glucose meters several times each day depending on clinical need. Adherence to glycaemic target guidelines is also more variable; therefore, there is generally a higher prevalence of adverse glycaemia in noncritical care wards than critical care wards [188, 189]. Although the ADA guidelines recommend subcutaneous insulin for treatment of hyperglycaemia in hospital, in practice, inpatients are treated with a variety of insulin regimens and GLM, especially in the UK, Europe and Australia. As the focus of this thesis is diabetes care in the noncritical care setting, the remainder of the literature review focuses on the incidence of adverse glycaemia, barriers to glucose control and strategies to improve glycaemia in noncritical care.

1.6.1 Traditional 'reactive' model of diabetes care

Individuals admitted to hospital receive all aspects of medical care from the admitting (or parent) unit, which is determined by the primary reason for admission. In some countries, individuals are admitted under the care of 'hospitalists' who specialise in inpatient care. Therefore, comorbidities including diabetes are generally managed by the hospitalists or admitting team's medical officers. Some larger hospitals have endocrinologists, diabetes specialists or physicians with an interest in diabetes who manage individuals admitted with diabetes-related illnesses (e.g. an individual presenting with DKA). As diabetes is seldom the primary reason for admission, the majority of inpatients with diabetes are admitted under the care of non-diabetes specialists. Diabetes specialists may provide a referrals service that can assist in management of patients admitted under other treating teams. Although various models of diabetes care exist, the majority consist of a diabetes or endocrinology advanced trainees (registrars) supervised by an endocrinologist or diabetologist, who provide a consultation service in response to a referral from the treating team.

Many hospitals have also established a diabetes education service to assist inpatient and ambulatory diabetes care. These services are delivered by diabetes nurse educators who educate patients and assist in self-management of diabetes, including self-monitoring of glucose, self-administration of insulin, and insulin dose titration. Diabetes education services play an invaluable role in inpatient management, discharge planning, and follow up. Most diabetes education services provide a consultation service in response to referrals from the treating teams.

The traditional model of diabetes care can be described as a 'reactive' service, which responds to formal referrals from the treating teams. However, in the absence of appropriate referrals, many patients do not receive care by diabetes specialists with this model of care.

1.6.2 Prevalence and incidence of adverse glycaemia in hospitals globally

1.6.2.1 Hyperglycaemia

Despite recommended glycaemic targets, hyperglycaemia remains common in hospital. A glycaemic survey of diabetes inpatients in 44 US hospitals reported 77% of patients had at least one episode of hyperglycaemia >11.1 mmol/L; 60% had at least one episode of hyperglycaemia >13.8 mmol/L; and 38% had persistent hyperglycaemia (three consecutive days with BG >11.1 mmol/L) [190]. Rates of hyperglycaemia were similar in two other cohorts. In one study, 76% of patients had at least one episode of BG >10 mmol/L [191]. In another study, 40% of patients had at least one episode of BG >16.5 mmol/L [192].

Networked BG meters, which automate collection of glucose measurements, facilitate hospital-wide assessment of inpatient glucose at many hospitals (see section 1.7.5). Cook et al., reported a glycaemic survey of 126 US hospitals which included over 9 million BG measurements from almost 1 million patient-admissions over a 1-year period [188]. Over 46% of noncritical care inpatients had hyperglycaemia >10 mmol/L. Of note, hospital-wide glucometric studies typically include all inpatients who had capillary glucose monitoring, including non-diabetes indications. This potentially explains a lower rate of hyperglycaemia compared to the aforementioned studies which included only individuals with pre-existing diabetes.

Hyperglycaemia incidence can also be reported using standardised glucometric analyses and expressed as rates per patient-day (see section 1.7.6). In the study by Cook et al., patient-days with mean glucose >10.0 mmol/L, >13.8 mmol/L, and >16.7 mmol/L occurred in 30%, 11% and 5% of patient-days respectively [188]. A subsequent larger hospital-wide glucometric study (involving 635 hospitals, 51 million BG measurements from 2.4 million patients), reported patient-days with mean glucose >10.0 mmol/L, >13.8 mmol/L and >16.7 mmol/L occurred in 32%, 7% and 2% of patient-days respectively [189]. Outside the US, there is a paucity of published data on hyperglycaemia incidence. The annual NaDIA in the UK does not audit the incidence of hyperglycaemia. The available published data at other countries reported similar rates of hyperglycaemia (proportion of diabetes inpatients with at least one BG >10.0 mmol/L: 57% in Puerto Rico [193], 90% in Brazil [194], and 81% in Singapore [195]).

1.6.2.2 In-hospital diabetic ketoacidosis and hyperglycaemic hyperosmolar state

DKA and HHS are life threatening hyperglycaemic emergencies that can occur due to lack of insulin treatment, failure to increase insulin dose to meet increased physiological demands, or in the presence of an SGLT-inhibitor therapy. Regardless of the precipitating cause, DKA and HHS occurring in hospital are severe adverse clinical outcomes that potentially reflect inappropriate diabetes management.

NaDIA formally audits hyperglycaemic emergencies in hospital and in 2016 reported that 4.4% of inpatients with type 1 diabetes developed DKA during their inpatient stay [22]. Based on a survey of UK

diabetes services, 8% of DKAs developed in hospitalised patients [196]. NaDIA also reported that 0.2% of inpatients with type 2 diabetes developed HHS in hospital. Therefore, a significant number of patients experience life-threatening severe adverse clinical outcomes related to hyperglycaemia.

1.6.2.3 Hypoglycaemia

The reported prevalence of hypoglycaemia depends on the glucose definition and method of data collection. Using hospital discharge codes may underestimate the prevalence of hypoglycaemia because of inconsistencies in coding. For example, in a study of all diabetes inpatients admitted to internal medicine wards in Spain, 5% had documented hypoglycaemia on discharge code [167]. More accurate incidence of hypoglycaemia may be obtained using manual or automated glycaemic surveys. In 2016, NaDIA reported 20% and 8.4% of patients had at least one episode of hypoglycaemia <4 mmol/L, and severe hypoglycaemia <3 mmol/L respectively, in the preceding 7 days [22]. This finding is comparable to the glycaemic survey in US hospitals where 16% of patients had hypoglycaemia <3.3 mmol/L and 10% had severe hypoglycaemia <2.8 mmol/L [190]. In other countries, glycaemic surveys report the proportion of patients with hypoglycaemia (<3.9 mmol/L) varies between 10% in Spain [27], 19% in Singapore [195], and up to 30% in Brazil [194]. In the networked glucose meter assisted large glycaemic survey of US hospitals, hypoglycaemia <3.9 mmol/L occurred in 21% of patients [188]. Analysis by patient-day reported glucose <3.9 mmol/L and <2.8 mmol/L occurred in 6.1% and 1.7% of patient-days respectively.

1.6.2.4 'Good diabetes day'

Thus far, the prevalence of hyperglycaemia and hypoglycaemia has been reported as two separate figures, but a metric that combines both glycaemic extremes can be useful. NaDIA uses the metric 'good diabetes day', defined as a patient-day with no BG in the hypoglycaemic range (<4.0 mmol/L), and no more than one BG >11.0 mmol/L. Therefore, a 'good diabetes day' represents a patient-day with relatively stable glucose. In 2017, amongst all inpatients with diabetes, 4.6 out of 7.0 (66%) of patient-days were 'good diabetes days', therefore 34% of patient-days had glucose in the 'unstable' range. As would be expected, inpatients with T1D and insulin-requiring T2D had a lower proportions of 'good diabetes days'; 2.6 out of 7.0 (37%), and 3.5 out of 7.0 (50%) respectively [22].

1.6.3 Prevalence and incidence of adverse glycaemia in Australian hospitals

In Australia, there is scarcity of inpatient glycaemic data or benchmarking, largely due to a lack of automated technologies to capture inpatient glucose data. Glycaemic assessment typically required resource-intensive manual chart reviews of inpatient glucose measurements from paper-based clinical records or scanned electronic clinical records. Only one Australia study included glucometric data. Cheung at al., evaluated the impact of a standardised glucose observation and insulin prescription chart at Westmead hospital in Western Sydney [197]. In a cohort of 205 inpatients with pre-existing diabetes,

patient-days with mean BG >10 mmol/L and >16 mmol/L occurred in 40% and 4% respectively; both of which were higher than the US hospital cohort [189]. Hypoglycaemia (<4.0 mmol/L) occurred in 44% of inpatients during their admission. On patient-day analysis, 14% of patient-days had hypoglycaemia. Although both hyperglycaemia and hypoglycaemia rates were higher than the US glucometric studies, the Australian cohort included only patients with pre-existing diabetes.

In summary, adverse glycaemia remains common in noncritical care. Globally, hyperglycaemia occurs in approximately 50 to 80% of patients, or 30 to 40% of patient-days. Hypoglycaemia occurs in 20% of inpatients or 6 to 10% of patient-days. There is a lack of hospital glycaemic data in Australia. As auditing and benchmarking is important to improve clinical care, there is a pressing need to audit and report glycaemic control in Australian hospitals.

1.6.4 Barriers to optimal glucose control in hospital

Multiple factors contribute to the ongoing high incidence of adverse glycaemia in hospital. Blood glucose concentrations are highly dynamic and affected by many factors: patient and illness-related, treatment-related, health professional-related, and hospital systems-related factors.

1.6.4.1 Patient and illness factors

An individual's diabetes and glucose control prior to admission influences glycaemic control in hospital. An individual with chronic hyperglycaemia prior to admission may experience ongoing hyperglycaemia in hospital. Conversely, an individual with stable glucose prior to admission can become hyperglycaemic in hospital due increased insulin resistance related to counter-regulatory response of illness or surgery. The severity of hyperglycaemia reflects the interplay between the intensity of counter-regulatory responses and β-cell reserve; however, anecdotally there is wide inter-individual variability. Hyperglycaemia may also be exacerbated by deceased skeletal muscle glucose uptake due to decreased physical activity when an individual is confined to bed rest.

Conversely, in individuals treated with GLM or insulin, decreased carbohydrate intake due to illness can cause hypoglycaemia. Hypoglycaemia can also occur with impaired renal gluconeogenesis and insulin-clearance due to kidney injury, and with impaired hepatic gluconeogenesis due to liver failure. Both kidney and liver dysfunction cause altered metabolism and clearance of diabetes medications which can promote hypoglycaemia. Patients with multiple comorbidities, multi-organ dysfunction, frailty, and polypharmacy are particularly at risk. Therefore, the severity of illness, burden of comorbidities, and alterations in pathophysiology contribute to the occurrence of adverse glycaemia.

1.6.4.2 Nutrition and medication treatment

Treatments in hospital, including nutrition and medications can contribute to adverse glycaemia. Nutritional interruption due to the requirement for fasting prior to procedures or surgery, can predispose an individual to hypoglycaemia. Conversely, the provision of nutritional supports, such as oral carbohydrate-containing supplements, often exacerbates hyperglycaemia. Enteral nutrition (which delivers carbohydrate and nutrient rich liquid into the gastrointestinal system) and total parenteral nutrition (which delivers carbohydrate, protein and lipids directly into the systemic circulation) can cause hyperglycaemia and other metabolic disturbances. Many inpatients can develop adverse glycaemia due to a loss of self-management routine due to altered meal times, delays in medication administration and a lack of direction from treating clinicians.

Medications administered or altered in hospital contribute to glycaemic instability. GLMs are often withheld in periods of altered nutritional intake. Some GLMs including metformin, become contraindicated due to sepsis, impaired renal function or liver failure. Without appropriate substitution with alternative treatments, hyperglycaemia could ensue. Glucocorticoid medications, calcineurin inhibitors and tyrosine kinase inhibitors are potent inducers of hyperglycaemia [198] and adverse glycaemia can develop during treatment with these medications in the absence of an appropriate escalation in glucose-lowering therapy.

1.6.4.3 Health professional factors

Adverse glycaemia in hospital can occur as a result of decisions and actions performed by the treating health professionals. Firstly, health professionals may not recognise that the individual has diabetes and therefore may not commence appropriate glucose observation or GLM treatment. The clinician may misclassify the type of diabetes (e.g. attribute an individual with pancreatogenic diabetes as type 2 diabetes), an error which can result in inappropriate withholding or cessation of insulin. The clinician may not perform BG monitoring at the appropriate timing or frequency for clinical need. For example, infrequent BG monitoring during fasting can lead to a failure to detect falling glucose levels prior to developing hypoglycaemia.

Medication errors (which include recommendation, prescription and administration errors) are common causes of adverse glycaemia. Medication recommendation errors include inappropriate treatment or withholding of GLM or insulin. Prescription errors include prescription of an incorrect medication, dose, timing, or ambiguous handwriting (including the practice of writing ‘U’ instead of ‘unit’, which could be mistaken with a zero, potentially causing a ten-fold increased dosing error). Administration errors include inappropriate withholding, or incorrect timing of administration (such as administering prandial insulin separated in time from a meal).

A significant clinician-related barrier is the ongoing widespread use of sliding-scale insulin (SSI) alone. SSI refers to boluses of short acting insulin dose dependent on BG at the time of administration. Multiple

studies reported SSI is ineffective at controlling hyperglycaemia, causes excessive hypoglycaemia, and could potentially cause DKA [199]. RCTs demonstrate the superiority of scheduled insulin over SSI in controlling hyperglycaemia (section 1.7.2). However, there is continued widespread practice of SSI treatment which may contribute to the ongoing high incidence of adverse glycaemia [27, 191, 192, 194] An underpinning contributor is the lack of knowledge and confidence in initiating or titrating insulin treatment contributing to clinical inertia (section 1.6.4.5).

Collectively, audits demonstrate health professional factors remain significant barriers. NaDIA reported 38% of patients have at least one diabetes-related medication error; half of which were due to prescription or administration error and the remaining half were due to a lack of escalation or de-escalation of diabetes medication despite hyperglycaemia or hypoglycaemia [22].

1.6.4.4 Hospital system factors

As discussed in section 1.2, modern hospitals are dynamic institutions where a patient's clinical care may be managed by multiple health professionals, even during a relatively short hospital stay. As treating medical and nursing teams work in rotating shifts, a patient's clinical care is 'handed over' between clinicians multiple times per day resulting in a lack of continuity of care. At each handover, many clinical observations and clinical tasks are communicated between clinicians, and during each interaction there is a potential for error or omission. As most treating team doctors work business hours (8 am to 5 pm Monday to Friday), after business hours and on weekends (which comprises 123 hours or 73% of the week), an individual's management is the responsibility of doctors that are not part of the treating team. An audit of barriers contributing to hyperglycaemia reported that being the weekend was the 4th most common reason for suboptimal glycaemic control [200].

Due to the pressure on bed occupancy in modern hospitals, the patients' journey through the hospital admission can involve multiple ward and bed changes. With pressures on expediting discharge, there are pressures to focus only on the presenting problem with a less focus or scope to manage comorbidities including diabetes. A large study in the Veteran's association hospitals in the US demonstrated in a cohort of inpatients with pre-existing poor glycaemic control (average HbA1c 9.6%), only 22% had intensification of therapy at discharge [201].

The structure of medical teams is also a barrier, because the most junior medical staff (intern or resident staff) are often tasked with inpatient diabetes management, so clinicians experienced in managing diabetes are seldom involved in patient care. Although the doctors' clinical skills, knowledge and experience improve over time, due to rotating medical officer training system, several new groups of junior staff rotate through treating teams several times each year, necessitating retraining and relearning of clinical skills. Lastly, clinical systems to streamline diabetes care, such as dedicated glucose observation and insulin prescription charts, insulin order sets or protocols, are not universally available. Electronic medical records, alerts or glycaemic auditing systems which can facilitate inpatient glucose

control are not yet universally available especially outside the US. Hence, a lack of infrastructure and resources contribute to ongoing high prevalence of adverse glycaemia.

1.6.4.5 Clinical inertia

A common overarching theme that contributes to adverse glycaemia is clinical inertia. Defined as a failure to optimise therapy when indicated, the term clinical inertia was first used in ambulatory care [202]. In acute inpatient care, clinical inertia describes a lack of health professional action in response to adverse glycaemia. This was first demonstrated in a cohort of inpatients with diabetes where only 34% of those with hyperglycaemia had any change in therapy [203]. In a subsequent large cohort of 2900 inpatients, despite persistent hyperglycaemia, 42% had no change in insulin therapy and more than 50% remained on SSI insulin therapy alone [204]. Clinical inertia is demonstrated in various settings, including perioperative care, and surgical and medical noncritical care wards [205-207]. Without appropriate intensification of therapy, individuals may experience persistent hyperglycaemia. Without treatment de-escalation in response to hypoglycaemia, individuals may experience recurrent episodes of hypoglycaemia.

Clinical inertia was also demonstrated at RMH in during a prospective audit of 200 inpatients with diabetes. This audit surveyed capillary BG measurements in the first 72 hours of admission and found 150 episodes of acute hyperglycaemia (BG >10 mmol/L on two occasions over 24 hours) and 65 episodes of acute hypoglycaemia (BG <4.0 mmol/L). In 43% of acute hyperglycaemic and 58% of acute hypoglycaemic events, there was no clinical escalation from nursing staff to medical officers and there was no change in diabetes therapy [208].

Clinical inertia is the result of multiple barriers discussed above. Most diabetes inpatients are managed by admitting units who are focussed on delivering optimal care in their respective specialist fields, but may not be well-equipped to deal with the complex issues of diabetes. Often diabetes management is the responsibility of the junior medical staff who may lack the knowledge, clinical experience or confidence to adjust therapy to achieve optimal glycaemia. Adverse glycaemia often occurs after hours and the covering medical officer (who is not part of the treating team) may not feel empowered to make appropriate adjustment to treatment; instead temporary (or 'Band-Aid') solutions are often prescribed. Due to frequent ward and staff changes, diabetes treatment plans may not be appropriately or completely handed over between clinicians. With the pressures of expediting discharge, adverse glycaemia may be overlooked, in fear of slowing down the patient's journey through the hospital system. Although diabetes specialists and diabetes education services are available, the majority rely on referrals from the treating team. With the competing clinical tasks and increasing prevalence of inpatients with diabetes, treating teams often do not refer or delay referring to the diabetes specialists for assistance. Ultimately, the diabetes specialist expertise is not utilised effectively resulting in ongoing clinical inertia and adverse glycaemia. Hence, multifaceted interventions are likely to be required to address clinical inertia and improve clinical outcomes.

1.7 Strategies to improve hospital diabetes care

From the early 2000s, with accumulating evidence on the adverse effects of hyperglycaemia in hospital, various strategies to optimise glucose control have been investigated. In noncritical care, strategies for improving glucose can be categorised into methods to promote medication treatment (e.g. more intensive insulin regimens, insulin order sets, non-insulin GLMs); methods for glucose surveillance (e.g. glucometrics and benchmarking); and methods to increase diabetes specialist management (e.g. inpatient diabetes teams).

1.7.1 Insulin regimens

Sliding scale insulin (SSI) was the predominant hospital insulin regimen in the 1990s. SSI therapy consisted of a variable dose of insulin administered according to the BG measurement at the time of administration. However, due to the reactive nature of insulin dosing, SSI resulted in wide BG variability, was ineffective at controlling hyperglycaemia [199, 209], and was associated with worse clinical outcomes. There was a risk of DKA in insulin-dependent patients because insulin was not consistently administered.

The superiority of basal-bolus insulin (BBI) regimen over SSI regimen was demonstrated in the RABBIT-2 RCTs. In the first study, a BBI regimen was compared against SSI regimen in a cohort of insulin-naïve general medical patients with type 2 diabetes. BBI was initiated at a weight-based calculated dose (0.5 units/kg), half administered as basal and half administered as bolus (or prandial) insulin in separate doses with each meal. Both treatment arms had daily insulin titration according to a pre-specified protocol. The group treated with BBI had a significantly lower mean BG compared to the group receiving SSI (9.2 vs 10.7 mmol/L), and resulted in a higher proportion of patients at target mean BG of <7.8 mmol/l (65% vs 14%) [210]. In a subsequent RABBIT-2 surgery study, BBI treated surgical patients had a lower inpatient mean glucose, but additionally had a significantly lower rate of composite adverse clinical outcome (see also section 1.4.1.2.5) [143]. However, BBI-treated patients had a higher proportion of hypoglycaemia (BG <3.9 mmol/L: 23% vs. 5%), but no difference in severe hypoglycaemia (BG <2.2 mmol/L).

Other studies investigated optimal initial insulin doses for BBI. A case-control study reported insulin doses exceeding 0.6 units/kg/day was associated with an increased risk of inpatient hypoglycaemia [211], and an RCT reported initiating dose of 0.25 units/kg caused fewer episodes of hypoglycaemia than 0.50 units/kg in patients with renal impairment (estimated glomerular filtration rate: eGFR ≤45 ml/min/1.73m^2) [212].

Subsequent studies compared BBI with basal-plus insulin (BPI) therapy. In contrast to BBI regimen where prandial insulin is administered with each meal, in BPI regimen, prandial insulin is administered with meals only if pre-meal BG was above a certain threshold (>7.8 mmol/L in the study). A RCT

reported BPI was equally efficacious as BBI in controlling hyperglycaemia, but hypoglycaemia rates were lower [143], therefore was safer. A post-hoc analysis concluded outcomes were consistent between medical and surgical patients [213]. Based on these RCTs, the ADA guidelines recommend treating inpatients with an insulin regimen that contained basal insulin: specifically, BPI for patients with poor nutritional intake or nil by mouth; BBI for patients with adequate nutritional intake; and SSI monotherapy was strongly discouraged [28].

In ambulatory care setting, people with type 2 diabetes may be treated with a variety of insulin regimens. BBI treatment is common in the US, but pre-mixed insulin (fixed combination of rapid and intermediate acting insulin) treatment is more common in Europe, Asia and Australia. The efficacy and safety of pre-mixed insulin in hospital was evaluated in several studies. In one RCT, an insulin regimen consisting of 30% human insulin and 70% neutral protamine Hagedorn (NPH) given twice daily, was comparable to BBI regimen in efficacy and safety [214]. Another RCT compared pre-mixed insulin (Mixtard 30/70 ®) twice daily vs. BBI. Both regimens achieved similar glycaemic control, but the trial was terminated early due to excess hypoglycaemia with pre-mixed regimen compared to SSI (64% vs. 24%) [215]. Excess hypoglycaemia occurred pre-lunch and pre-dinner in the context of an aggressive insulin titration protocol aiming for BG target of 4.4-7.8 mmol/L. Resultantly, the ADA guidelines recommend against the routine use of pre-mixed insulin in hospital [28]. In contrast, another similarly designed, albeit smaller, RCT comparing pre-mixed analogue insulin (lispro mix 25/75 ®) vs. BBI reported similar efficacy in glucose control and incidence of hypoglycaemia [216]. Anecdotal clinical experience suggests pre-mixed insulin may be efficacious and safe in certain scenarios. For example, hyperglycaemia exacerbated by glucocorticoid mediations, or in patients with significant renal impairment, a higher dose of premixed insulin in the morning can be efficacious and minimise hypoglycaemia. Therefore, although discouraged by the ADA guidelines, pre-mixed insulin regimens in hospital may be appropriate in selected clinical scenarios.

1.7.2 Insulin protocols and order sets

Given the importance of insulin treatment in controlling hyperglycaemia in hospital, various strategies have been developed to facilitate appropriate insulin prescription and administration. One such strategy is a chart that combined documentation of glucose observations and insulin prescription. In an Australian hospital, the implementation of a dedicated hospital insulin prescription chart decreased the rate of hypoglycaemia and increased the proportion of BG measurements within the ideal range [197]. A more recent and updated chart improved clarity of insulin prescription and increased the number of BG measurements within the target range [217].

Insulin order sets and protocols that facilitate insulin prescription were evaluated in many studies. Order sets involve pre-printed prescription forms, often incorporating insulin protocols and dosing guidelines [218-221]. Implementation of order sets were usually accompanied by educational campaigns. Electronic

insulin order sets were evaluated in hospitals with an electronic medical record (EMR). Such systems have the advantage of electronically incorporating patient's weight and patient's eGFR to aid calculation of insulin doses [218, 222, 223].

Most studies investigating insulin order sets utilised a pre- and post-implementation observational study design, and most reported improved rates of BBI prescription, and decreased rates of hyperglycaemia (Table 8 and Table 9). However, rates of hypoglycaemia largely remained unchanged, although several studies reported higher rates of hypoglycaemia. There is one cluster randomised study comparing a computerised order set vs. a paper order set in a cohort of general medical inpatients. This study demonstrated the superiority of computerised order set over paper-based order set in increasing the proportion of patients treated with scheduled insulin (42% vs 75%), decreasing patient-day mean glucose (8.8 mmol/L vs. 8.2 mmol/L), and increasing proportion of BG measurements within ideal range (71% vs. 75%) [224]. Although significant improvements in glycaemic control were reported, these studies did not (and were not powered to) evaluate differences in clinical outcomes. Furthermore, pre- and post-intervention observational studies are subject to unmeasured confounders and a Hawthorne effect. None-the-less insulin order sets generally increased insulin treatment in hospital.

Table 8: Paper-based insulin protocol and order sets

Study, Year, Location	Study Design, Subjects	Intervention	Hyper-glycaemia	Hypo-glycaemia	Notes
Theilen 2008 Missouri, USA [225]	Pre-/post-Vascular surgery (n=52)	Basal-bolus protocol	Decreased	Decreased	BG in target: 61% to 75% Hypoglycaemia: 3.4% to 2.1%
Trujillo 2008 Boston, USA [221]	Pre-/post-General medicine (n=180)	Basal-bolus protocol	Nil change	Nil change	Improved basal-bolus prescription
Ena 2009 Spain [226]	Pre-/post-General medicine (n=138)	Basal-bolus protocol	Decreased	Increased	Mean glucose 10.2 to 9.0 mmol/L Hypoglycaemia 0.3% to 1.1%
Roberts 2012 Adelaide, Australia [220]	Pre-/post-Medical, surgical (n=220)	Basal-bolus protocol	Decreased	Increased	Mean glucose 11.3 to 10.6 mmol/L Hypoglycaemia 1.4% to 3.3%
Moraes 2013 Brazil [227]	Sequential Pre-/post-Cardiology (n=182)	Insulin & GLM protocol	NA	NA	Nil differences in outcomes 75% excluded from analysis
Michaelian 2011 Pennsylvania, USA [219]	Pre-/post-Perioperative (n=1100)	Perioperative insulin protocol	Decreased	NA	Decreased hyperglycaemia
Schnipper 2009 Boston, USA [218]	Pre-/post-General medicine (n=171)	Basal-bolus protocol & paper order set	Decreased	Nil change	BG in range 59% to 64%
Noschese 2008 Pittsburgh, USA [228]	Pre-/post-(n=70)	Paper order set	NA	NA	Increased basal-bolus prescription
Schroeder 2012 Israel [229]	Cluster-RCT Diabetic foot patients (n=65)	Basal-bolus protocol	Decreased	Nil change	Increased insulin prescription Patients with average BG <10mmol/L higher 71% vs. 57%

Table 9: Electronic insulin protocol and order set

Study, Year, Location	Study Design, Subjects	Intervention	Hyper-glycaemia	Hypo-glycaemia	Notes
Maynard 2009 San Diego, USA [222]	Pre-/post-Medical/ surgical (n=931)	Electronic order set, basal bolus protocol	Decreased	Decreased	Increased basal-bolus prescription Hyperglycaemic patient-days decreased 38% to 34% Hypoglycaemic patient-days decreased 3.8% to 2.6%
Schnipper 2010 Boston, USA [224]	Cluster RCT General medicine (n=179)	Electronic vs. paper order set	Decreased	Nil change	BG in range increased 71% to 75%
Mulla 2014 Virginia, USA [223]	Pre-/post-Medical/Surgical (n=NA)	Electronic order set & Basal-bolus protocol	Decreased	Decreased	Decreased hyperglycaemia and hypoglycaemia. Large rebound after cessation of education program

1.7.3 Glucose-lowering medications

GLM treatment in hospitalised patients is somewhat controversial and is an active area of research. Metformin is contraindicated in renal failure, sepsis or shock due to the risk of lactic acidosis. Sulphonylureas can cause hypoglycaemia in individuals with decreased carbohydrate intake. SGLT-inhibitors can cause dehydration, electrolyte imbalance, ketone production and increases the risk of DKA and should be withheld in ill patients or those undergoing surgery [230]. Glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors can cause gastrointestinal symptoms and can interfere with nutritional intake. The ADA guidelines recommend that all GLM be withheld and subcutaneous insulin therapy initiated in all individuals with diabetes admitted to hospital [183]. As a result, US hospital cohort studies report low rates of GLM treatment in hospital (10 to 30% of inpatients) [191, 193]. Outside the US, GLMs continue to be used in hospital with rates varying between 38% in Brazil [194], 45% in UK [22], 50% in Australia [197] and 80% in Singapore [195].

A recent RCT randomised inpatients with type 2 diabetes to sitagliptin plus basal insulin vs BBI in order to formally evaluate the safety and efficacy of DPP-4 inhibitors in hospital [146]. Sitagliptin-plus-basal insulin had similar efficacy in glucose control to BBI with no difference in hypoglycaemia or clinical complications. Another recent pilot study evaluated the efficacy and safety of a GLP-1 agonist in an RCT comparing exenatide vs. exenatide plus basal insulin vs. BBI. This study reported exenatide plus basal insulin and BBI had comparable efficacy in glucose control and both were superior to exenatide alone. Hypoglycaemia rates were similar but exenatide-containing treatment regimens caused more nausea and vomiting with 6% of participants discontinuing treatment due to adverse events [231].

Hence, recent studies suggest inpatient treatment regimens containing DPP-4 inhibitors and/or GLP1 agonists may decrease the necessity of more intense subcutaneous insulin regimens, and can provide alternative methods to achieve optimal glucose control. However, these agents were used in addition to basal insulin, further strengthening the importance of basal insulin treatment in hospital.

1.7.4 Staff education programs

Educating and upskilling treating team clinicians is an obvious strategy to improve glucose control. Various staff education programs have been implemented ranging from short duration (e.g. 1 hour) [232] to more comprehensive (e.g. 8 hour) education sessions [233]. Some interventions consisted of face-to-face small group sessions [233-236], whilst others involved computerised learning packages [237]. Training programs mostly aimed at upskilling medical officers and hospitalists. These interventions generally reported increased clinician knowledge and confidence [232, 235], increased use of BBI [226, 237-239], and reduction in medication errors [232-234]. In the subset of studies that evaluated glycaemic outcomes, results were heterogeneous with some interventions decreasing hyperglycaemia [226, 236, 239, 240], some did not change glucose control [235, 241], and of concern, some interventions increased

hypoglycaemia [236, 238, 239]. Studies of education programs have not evaluated patient or economic outcomes.

The main disadvantage of education interventions is the frequent rotations of resident medical staff between clinical services, necessitating programs to be repeated regularly. It is not surprising some studies reported initial improvements in clinical care that were not sustained upon reassessment at a later time [242, 243]. Hence, a successful education program should provide repeated or 'refresher' education sessions [236, 240]. With improving information technology, online education resources are more likely to be sustainable and may be incorporated as regular mandatory training requirements to achieve long-term improvements in clinical care.

Anecdotally, some inpatients with diabetes are highly complex and optimising their glucose challenges even the most experienced diabetes specialists. For these individuals, general education of treating staff may not be sufficient to ensure optimal management and diabetes specialist management remains essential. Thus, an effective educating program and upskilling resident medical officers may improve general diabetes management but will not completely replace expert management by diabetes specialists altogether.

1.7.5 Networked glucose meter technology

Point-of-care capillary glucose meters are essential for inpatient diabetes care. Using a small volume of blood, capillary BG testing allows immediate determination of glucose levels facilitating rapid treatment decisions. The alternative methods of determining BG (formal laboratory glucose or blood gas analysers testing) are slower, more complex, and require more invasive procedures to acquire a larger blood volume [244]. However, POC technology has disadvantages, including the potential for assay interference in the presence of non-glucose sugars (such as maltose and xylose), and with extremes of low or high haematocrit or blood oxygen levels [244-246]. New advances in POC glucose meter chemistry can overcome some of these limitations [187].

An important new development in POC glucose testing is the connectivity or networked technology. Prior to this technology, hospital BG monitoring practice involved a health professional (most often a nurse) who performed a capillary BG measurement using a non-connected BG meter and manually recording the result on a glucose observation chart into an EMR. In contrast, networked BG meters are connected to the hospital information system via docking stations and cables, or using wireless fidelity (WIFI) network. With each BG measurement, the patient unique identifier is also recorded so that each measurement is linked to an individual patient and the time of measurement. This data is then electronically transferred into a database, clinical result system or EMR, eliminating transcription errors and administrative time required to enter in the glucose data [247].

A major advantage of networked BG meter technology is automated capture of hospital-wide capillary BG data which allows institution-wide analysis of glucose and benchmarking against other hospitals. It also enables evaluation of glycaemic management programs by analysing glycaemic outcomes for groups of patients or time periods of interest. In addition, remote surveillance of glucose is now possible, whereby diabetes specialist teams can monitor glucose measurements and identify individuals with adverse glycaemia, allowing targeted management strategies. Hence, networked BG meters are becoming an essential component of glycaemic improvement programs [248].

Although networked BG technology has been available in the US since the early 2000s, and in the UK and Europe since mid-late 2000s, it has not been available in Australia until recently. Accordingly, Australian hospitals were limited in auditing and benchmarking inpatient glucometric data. In 2015, two different networked BG meter systems, (Statstrip ®, Australasian Medical and Scientific Limited and Freestyle Precision Pro ®, Abbott Diabetes Care) gained approval from the Australian Therapeutic Goods Administration to be used for capillary BG measurement in hospital.

1.7.6 Glucometric reporting and benchmarking

Hospital 'glucometrics' was developed to systematically analyse and report inpatient glucose control from the large amount of capillary glucose data captured by networked BG meters. The fundamental issues in reporting inpatient glucose data are: 1) the variability in frequency and timing of BG measurements between patients; 2) the variability in LOS between patients. As a routine, an inpatient with diabetes may have four BG measurements performed each day in hospital. However, another patient with unstable glucose may have BG measurements performed every 2 hours (e.g. 12 measurements each day), and a patient on an intravenous insulin infusion routinely have BG measurements performed every hour. Furthermore, while one patient may be admitted for 2 days (e.g. 8 measurements performed), another patient may be admitted for 30 days (e.g. 120 measurements performed) during hospital-stay. Traditional analytical methods of determining mean and variance of all BG measurements do not reflect the variability in number of tests per day and the number of tests per patient during hospital-stay. Glucometric reporting techniques overcome these issues.

Although various glucometric reporting techniques are described, the most widely used was first described by Goldberg et al., [249]. Briefly, inpatient glucose data can be presented in three separate models:

1) Per-population model, where all BG measurements for the entire cohort are considered and weighted equally.
2) Per-patient-stay model, where BG measurements for the entire hospital-stay for each patient are aggregated, and weighted equally irrespective of their length of stay.
3) Per-patient-day model, where BG measurements are grouped by each calendar day for each patient.

Although each model can be useful in certain situations, the per-patient-day model is the most balanced and useful model to analyse and present glucometric data. As glucose outcomes are aggregated by each calendar day for each patient, an individual with a longer LOS is given more weight than an individual with a shorter LOS. The key glucometric measure is the patient-day mean glucose obtained by calculating the mean of glucose measurements per-patient, per-calendar day. Other key glucometric outcomes include the proportion of patient-days with various thresholds of hypoglycaemia or hyperglycaemia.

Additional glucometric techniques have been developed to account for multiple repeated BG measurements following a clinical episode of hypoglycaemia or hyperglycaemia. For example, if a patient's BG measurement is abnormal, a clinician may perform another measurement immediately to confirm the result. Similarly, after treating an episode of hypoglycaemia, repeated measurements are usually performed in close succession to ensure resolution. Repeated measurements unequally weigh the glucose aggregates towards the extremes. Therefore, glucometric reports are recommended to exclude repeated BG measurements from a single clinical episode of hypo- or hyperglycaemia [250]. Other recommendations have been developed pertaining to accurate selection, analysis and presentation of glucometric outcomes to ensure standardised reporting [251].

With widespread use of networked BG meters, health systems in the US have developed central repositories of capillary BG data from multiple hospitals and developed benchmarking of glycaemic control [188, 189, 252]. Hospitals can submit local glucometric data and receive feedback on their performance compared to similar hospitals. As benchmarking is essential to improve the quality of care and patient safety, further development of inpatient glucose benchmarking in other countries, including in Australia, can lead to improvements in diabetes care.

1.7.7 Glycaemic alert systems

Alert systems are designed to elicit an appropriate action from users to prevent an adverse event. In ambulatory care, continuous glucose monitors often function as alert systems to warn the individual of impending hypoglycaemia. Similarly, alerts systems have been used to improve clinicians' awareness of adverse glycaemia in the inpatient care setting. In critical care, computerised alert systems can notify bedside nurses about glucose abnormalities and aid treatment with insulin infusion. In Leuven, Belgium (where tight glycaemic control is routinely practiced), a computerised alert system which aid adjustment of insulin infusion decreased mean glucose and decreased hypoglycaemia [253]. A similar alert system at another Belgian ICU which generated an audio-visual alert when BG was out of target range, resulted in increased BG in target range whilst decreasing hyperglycaemia and hypoglycaemia [254].

In perioperative care, two studies of glycaemic alert systems have been reported. In a study by Satishkumar et al., a computerised alert system incorporated patient information, laboratory results and

physiological data into standardised display and generated an audio-visual alert when intraoperative BG measurement exceeded 11.1 mmol/L [255]. The alert was 'silenced' when insulin prescription was initiated, but a subsequent alert was then generated 90 minutes later if a follow up BG measurement was not performed. This system was associated with 55% increased insulin treatment in patients with intraoperative hyperglycaemia. A similar intraoperative glucose alert system was studied by Ehrenfeld et al., demonstrating increased intraoperative glucose monitoring, decreased post-operative hyperglycaemia, and decreased rate of surgical site infections [256].

In noncritical care, alert systems vary widely in function and complexity. A manual alert system was studied by Roman et al., [257] consisting of colour-coded BG observation charts which provided a visual alert when BG measurements were out of range, coupled with a management algorithm. Use of this system was associated with 41% decrease in the frequency of prolonged hyperglycaemia (three consecutive BG measurements >13.9 mmol/L). Electronic alert systems can monitor POC BG measurement and generate alerts on EMR. Electronic alert systems can be classified as retrospective or real-time. A retrospective alert system generates alerts when clinicians interact with the system (e.g. when a clinician 'logs on' to computer system or generates a report). A real-time alert system generates alerts without input from the clinician (e.g. a pop-up alert is generated on a computer as soon as a glucose trigger is reached). Some electronic alert systems use an algorithm to integrate other available clinical information such as age, weight, laboratory results (e.g. GFR), and current treatment (e.g. insulin treatment) to generate alerts [258]. Such alert systems require fully-integrated hospital electronic clinical information systems.

Most alert systems target treating medical and nursing staff at the point-of-care, but some systems directly target a specialist diabetes team. Donihi et al., studied a glucose alert system that alerted an inpatient diabetes team (IDT) when an inpatient had severe hyperglycaemia (BG >16.7 mmol/L). The IDT then provided a consultation and advice to the treating team to intensify glycaemic management. In a 3-month pre- and post- intervention study, this service improved the treating team's response to hyperglycaemia by 50% and decreased occurrence of subsequent severe hyperglycaemia by 55% [243]. Two subsequent observational studies evaluated electronic systems that generated an automated referral to IDTs [259, 260]. These alert systems facilitated more IDT consultations and decreased mean glucose by 0.7 mmol/L in one study [259] and achieved a 20% reduction in proportion of patient-days with mean BG >15mmol/L in another study [260]. Both alert systems required complex integrated hospital EMRs and demanded greater resources.

In summary, glycaemic alert systems improve health professional response to adverse glycaemia. However, in noncritical care glycaemic alert systems are heterogeneous in design and complexity. A few observational studies of complex electronic alert systems which alert IDTs report improvement in glucose control. There are few studies of simple alert systems aiming to improve clinician response at the point-of-care, and there are no studies evaluating clinical outcomes.

1.7.8 Specialist Inpatient Diabetes Teams

Although endocrinologists and diabetes specialist physicians practice at many hospitals, the traditional model of inpatient diabetes care is a referral-based consultative service (section 1.6.1). With this model, inpatient diabetes management is primarily performed by the treating team's medical staff and at their discretion, diabetes specialists are invited to assist with management. However, due to rising prevalence of diabetes, the majority of diabetes inpatients do not receive diabetes specialist management. In addition, referrals to the diabetes specialists typically occur after the occurrence of adverse glycaemia and often after many days of persistent adverse glycaemia. Therefore, new approaches to inpatient diabetes care have been developed.

Inpatient Diabetes Teams (IDTs) (also known as Glycaemic Management Teams) were introduced in some hospitals particularly in the UK and US since the early 2000s. The roles of IDTs are to improve diabetes management expertise throughout the hospital. IDTs develop and implement diabetes management protocols, deliver education programs, perform clinical audits, and directly assist in diabetes management of patients admitted under various treating medical and surgical teams. Various models of IDTs have been described (Table 10 and Table 11). Although models of IDT vary, the essential features can be summarised into the following four components.

1. **Team composition:** Members of IDT generally include nursing and medical staff but can also include other members such as pharmacist and dietitians. The IDTs in the UK generally consist of Diabetes Inpatient Specialist Nurse, with oversight by a consultant diabetes physician. The IDTs in US generally consist of diabetes nurse consultants, diabetes nurse practitioner (DNP) and diabetes fellow (i.e. registrar), led by a diabetologist. DNPs with prescribing rights are particularly suited for this role.

2. **Patient identification:** IDTs require an efficient method of identifying inpatients with diabetes or adverse glycaemia. Patient identification can be performed manually (e.g. physical ward rounds), or remotely (e.g. using electronic referrals or alerts). Some IDTs identify patients using protocolised referrals from treating medical or nursing staff. For example, hospitals in the UK use a clinical triage tool ('Think Glucose' program) to identify diabetes inpatients who should be referred to the IDT. In some UK hospitals this triage tool is incorporated into an EMR to generate an automated referral to the IDT [261]. A subsequent improved referral tool (Diabetes Patient At Risk score), incorporating the clinical indication and urgency of referral further refined referrals to the IDT [262]. At hospitals with networked glucose meter systems and EMRs, IDT can perform remote surveillance of POC BG measurements to identify inpatients for management. Remote surveillance has the advantage of bypassing referrals from the ward staff; however, demands greater resources in infrastructure and staffing.

3. **Model of care:** IDT models of care can be classified as *reactive* or *proactive*. A *reactive* IDT provides care in response to referrals from the treating teams. A reactive model is less resource intensive and care can be delivered to individuals who were identified by the treating teams to require care. However, the reactive model can miss patients who may benefit from care due to inappropriate recognition or assessment by the treating teams. Consultations may occur later in the admission course, often after multiple episodes of adverse glycaemia. A *proactive* IDT provides management autonomously, without referral from the treating teams. As proactive care bypasses the need for referrals, more patients can receive specialist care. However, proactive models are resource-intensive. Additionally, from clinical experience, some treating teams may not prefer IDT involvement due to potential loss of autonomy.

4. **Model of management:** IDT can provide *consultative* or *direct* management. In a *consultative* management model, the IDT provides management advice (e.g. suggesting commencing or titrating insulin) to the treating teams. The treating team clinicians can then consider the recommendations (e.g. prescribing insulin or adjusting doses). In a *direct* management model, the IDT directly prescribes the medication treatment (e.g. directly prescribing insulin or adjusting doses). The direct management model ensures treatment is administered promptly; however, this approach may not be acceptable to some treating teams due to the potential for confusion and loss of clinician autonomy.

There are twenty-nine studies on various models of IDTs. Twelve studies evaluated an IDT with a reactive model of care (Table 10), and seventeen studies evaluated an IDT with a proactive model of care (Table 11). Only two were prospective randomised studies whist the remainder were observational studies. The first RCT conducted in 1997 aimed to evaluate the impact of a proactive IDT, but the study was inconclusive and was stopped early due to poor recruitment [263]. In 2001, in a Welsh hospital, a diabetes nurse educator (DNE) service was studied in a prospective RCT. The DNE service operated on a reactive model of care in response to referrals from the treating nurses. Inpatients randomised to receive DNE care had 3 day shorter median LOS than patients who did not receive DNE care (8 vs. 11 days) [264]. This study provided the first prospective RCT evidence that inpatient care delivered by a DNE service improved hospital LOS, possibly related to provision of diabetes self-management which facilitated earlier discharge from hospital. Glycaemic or clinical outcomes were not evaluated. Of note, baseline LOS was 11 days in this study, much longer than the median LOS in UK hospitals in contemporary years (8 days in NaDIA 2013) [265].

The remaining twenty-seven studies all employed an observational design consisting of a pre- and post-intervention analyses, retrospective cohort analyses, or time-series analyses. In pre- and post- intervention studies, outcomes before and after implementation of an IDT intervention were compared; some studies used a retrospective pre-intervention group as a comparator. The primary outcomes usually consisted of glycaemic outcomes (i.e. various indices of hyperglycaemia and hypoglycaemia) or LOS. Only four

studies reported both glycaemic and LOS outcomes concurrently [266-269], whereas the remainder reported either outcome. Studies in the UK mainly focussed on LOS, whilst studies from the US generally focused on glucometric outcomes captured by networked BG meter systems.

Several studies reported time-series analyses of hospital LOS data or glucometric data to evaluate trends in outcomes after implementation of an IDT. Flanagan et al, published two a proactive IDT intervention studies. The first study was in general inpatients, and a subsequent study was in elective surgical patients [270, 271]. The primary outcomes in these studies were the difference in LOS between diabetes and non-diabetes inpatients. The time-series analyses reported: 1) diabetes patients had longer LOS than non-diabetes patients; 2) there were gradual reductions in LOS in both groups of patients; but 3) the LOS reductions in diabetes patients were greater than in non-diabetes patients, concluding that proactive IDT was associated with a reduction in excess LOS experienced by diabetes patients. Other studies using LOS as primary outcome reported reductions in LOS between 0.3 and 3 days, depending on cohorts studied.

In the seventeen IDT studies reporting glycaemic outcomes, reduction in hyperglycaemia was a consistent finding. Although various glucometric parameters were reported, IDT interventions were generally associated with a 0.5 to 2.0 mmol/L decrease in population, or patient-day mean glucose. Hypoglycaemia outcomes were variable, with 8 studies reporting improvement, 8 studies reporting no significant change, and one study reported increase in hypoglycaemia [238].

Several studies evaluated multifaceted hospital-wide glycaemic management interventions in addition to an IDT [267, 272-275]. The various interventions included a combination of insulin protocols, electronic order sets, glycaemic alerts, and education campaigns in addition to implementation of an IDT. These studies reported improvement in glycaemic outcomes but it is difficult to ascertain the proportion of improvement attributable to the IDT amongst the bundle of interventions.

From the available literature it is difficult to compare the efficacy of reactive vs. proactive models of IDT. Most studies reported similar magnitude of hyperglycaemia or LOS reduction. Given the heterogeneity of IDT models and study designs, a pooled analysis was not possible and there were no head-to-head studies.

Table 10: Inpatient Diabetes Teams operating with a reactive model of care

Study, Location, Year	Design	n	IDT model				Outcomes			Comments
			Team composition	Patient identification	Model of care	Model of management	Hyper-glycaemia	Hypo-glycaemia	Length of stay	
Levetan, New York, 1995 [278]	Retrospective cohort	104	DNE, Dietitian, Fellow	Medical Referral	Reactive	Consultative	NA	NA	↓	Patients who received IDT consultation had 56% shorter mean LOS than patients who did not receive IDT. (3.6 vs 8.2 days)
Davies, Wales, UK, 2001 [264]	RCT	300	DNE	Consecutive patients	Reactive	Consultative	NA	NA	↓	Randomised Controlled Trial of DNE vs. no DNE. Median LOS 11 vs. 8 days
Cavan, Bournemouth, UK 2001 [279]	Pre-Post	1611	DNE	Nursing Referral	Reactive	Consultative	NA	NA	↓	Median LOS decreased: 11 to 8 days
DeSantis, Chicago, USA 2006 [273]	Pre-Post	922	DNE, Fellow, Consultant	Nursing Referral	Reactive	Consultative	↓	↔	NA	Multi-faceted hospital-wide glycaemic management program including IDT. Population mean BG decreased 9.1 to 8.0 mmol/l
Sampson, Norwich, UK 2006 [83]	Time Series	14722	DNE	Nursing Referral	Reactive	Consultative	NA	NA	↓	Time series analysis. LOS (excess bed days for diabetes patients) decreased 1.9 to 1.2 days
Piug, Barcelona, Spain, 2007 [280]	Pre-Post	435	DNE Consultant	Medical Referral	Reactive	Consultative	NA	NA	↓	Mean LOS in diabetes patients decreased: 5.5 to 4.9 days.
Pietras, Boston, USA 2010 [267]	Time Series	NA	DNP, DNE, Fellow, Consultant	Medical or Nursing Referral	Reactive	Consultative	↓	↔	↓	Multi-faceted hospital-wide glycaemic management program (insulin protocol, electronic order sets, education) and reactive IDT. Population BG decreased 9.4 to 8.6 mmol/L. LOS reduction in diabetes patients 40% greater than in non-diabetes patients.

Bar-Dayan, Israel 2014 [272]	Pre-Post	NA	DNE	Unclear	Reactive	Consultative	↓	↓	NA	Multi-faceted hospital-wide glycaemic management program. Pop mean BG decreased: 10.8 to 9.7 mmol/l; Hypoglycaemic decreased: 2 → 1.3%
Wong, Sydney, Australia, 2014 [269]	Retrospective cohort	74	DNE. Medical Registrar, Consultant	Medical Referral	Reactive	Direct	↓	↔	↓	Patients who had treatment with enteral nutrition (EN). Mean BG during EN lower 11.1 vs. 8.6 mmol/L LOS shorter: 37 vs 27days. **Mortality** lower: 32% vs 11%.
Rajendran, Ipswich, UK 2015 [275]	Pre-Post	3848	DNE	Diabetes Patient at Risk Score (DPAR)	Reactive	Consultative	NA	↓	NA	Comprehensive diabetes assessment by treating nurse at admission. Risk score dictated referral to diabetes nurse. Patients with hypoglycaemia decreased: 15% to 10%. Medication errors decreased: 57% to 21%.
Lin, Taiwan, 2015 [259]	Controlled Pre-post	1644	DNP, Consultant	Glucose alert system-automated IDT referral	Reactive	Consultative	↓	↓	NA	Patient-day mean glucose decreased 10.0 to 9.4 mmol/L Patient-day with hypoglycaemia decreased 4.8 to 3.8%
Wang, Colorado, USA, 2016 [276]	Retrospective cohort	440	Unclear	Medical Referral	Reactive	Unclear	NA	NA	NA	Retrospective RV of patients with 'cardiac' or 'infection' discharge code. **Clinical:** In patients with mean BG >10 during admission, those seen by IDT had 50% fewer complications than those not seen by IDT (26% vs 48%)

Abbreviations: IDT: Inpatient diabetes team; DNP: Diabetes Nurse Practitioner; DNE: Diabetes Nurse Educator; Consultant: endocrinologist or diabetologist; Fellow: diabetes fellow or endocrinology registrar; NA: not assessed; LOS: length of stay; BG: blood glucose. ↓: decreased; ↑: increased; ↔: no change. See text for explanation on model of care and management

Table 11: Inpatient Diabetes Teams operating with a <u>proactive</u> model of care

Study, Location, Year	Design	n	IDT model				Outcomes			Comments
			Team composition	Patient Identification	Model of care	Model of management	Hyper-glycaemia	Hypo-glycaemia	Length of stay	
<u>Koproski</u>, New York, USA, 1997 [263]	RCT	179	DNE, Consultant	Unclear	Proactive	Direct	↔	↔	↔	Inconclusive RCT stopped due to poor recruitment.
<u>Baldwin,</u> Chicago, USA, 2005 [238]	Pre-Post	186	Consultant	Ward Round	Proactive	Direct	↓	↑	NA	Population mean BG decreased: 11.1 to 8.3 mmol/l Hypoglycaemia increased 1.4 to 3.6%
<u>Newton,</u> North Carolina, USA, 2006 [266]	Pre-Post	NA	DNP	Ward Round	Proactive	Consultative	↓	↔	↓	Population mean BG decreased: 9.8 to 8.9 mmol/l LOS decreased 0.1 day more with intervention. **Clinical**: Central line associated blood stream reduction
<u>Courtenay,</u> Reading, UK, 2007 [281]	Pre-Post	452	DNP	Unclear	Proactive	Direct	NA	NA	↓	Medication errors decreased by 50% LOS: decreased from 9 to 7 days
<u>Flanagan,</u> Plymouth, UK, 2008 [270]	Time Series	28016	DNP Consultant	Ward Round	Proactive	Consultative	NA	NA	↓	LOS decreased by 0.3 days more for diabetes patients compared to hospital population (over 5 years)
<u>Flanagan,</u> Plymouth, UK, 2010 [271]	Time Series	2287	DNP Consultant	Pre-admission Clinic	Proactive	Consultative	NA	NA	↓	LOS decreased by 0.26 days more for diabetes patients compared to hospital population (over 2 years)
<u>Donihi,</u> Pittsburgh, USA, 2011 [243]	Pre-Post	147	DNP, DNE, pharmacist, dietitian	Glycaemic surveillance	Proactive	Consultative	↓	↓	NA	Proportion of patients with glucose in range increased from 49% to 73%.
<u>Brooks,</u> Winchester, UK, 2011 [282]	Pre-Post	1695	DNP, consultant	Ward Round	Proactive	Unclear	NA	NA	↓	LOS for diabetes patients decreased from 9 to 4 days (over 5 years).
<u>van Noord,</u> Netherlands, 2012. [283]	Pre-Post	350	DNP, Consultant	Blanket referral	Proactive	Direct	↓	↔	NA	Proportion of patients with hyperglycaemia (BG >15 mmol/L) during admission decreased from 28% to 20%.

Apsey, Arizona, USA, 2014 [284]	Pre-Post	560	DNP	Pre-admission & theatre recovery	Proactive	Consultative	↓	↔	NA	Patient-stay mean glucose decreased: 9.1 to 7.8 mmol/l
Amor, Barcelona, Spain, 2014 [285]	Pre-Post	NA	Consultant	Glycaemic surveillance	Proactive	Direct	↓	↔	NA	Pop mean glucose decreased: 8.9 to 7.9 mmol/l
Maynard, San Diego, USA, 2015 [274]	Pre-Post	NA	DNE, Consultant	Glycaemic surveillance	Proactive	Consultative	↓	↓	NA	Multi-faceted glycaemic management program Patients with hypoglycaemia decreased 13.7 to 9.8% Patient-day with hyperglycaemia decreased: 37 to 35%
Mendez, New York, USA, 2014 [286]	Pre-Post	7133	DNP Consultant	Glycaemic Surveillance	Proactive	Consultative (virtual electronic consultation)	↓	↓	NA	Patient-day mean BG decreased 9.9 to 9.6 mmol/L Adjusted risk of hypoglycaemia Odds ratio 0.53
Seheult, Dublin, Ireland, 2015 [260]	Pre-Post & Time Series	NA	Registrar	Glycaemic surveillance	Proactive	Consultative	↓	↔	NA	Patient-days with mean BG >15 mmol/L decreased: 5.3 to 4.1%
Swee, Singapore, 2017 [268]	Pre-Post	603	DNE, Fellow, Consultant, Dietitian, Pharmacist	Glycaemic surveillance	Proactive	Consultative	↓	↓	↓	Patient-day mean BG decreased: 11.2 to 10.0 mmol/L LOS mean decreased 15 to 12 days.
Rushakoff, San Francisco, USA, 2017 [287]	Pre-Post & Time Series	12535	Consultant	Glycaemic surveillance	Proactive	Consultative (virtual electronic consultations)	↓	↓	NA	Patient-days with hyperglycaemia (2 or more BG ≥12.5 mmol/L) decreased 6.6 to 4.0% Patient-days with hypoglycaemia decreased by 36%
Bansal, Boston, USA, 2018 [288]	Retrospective matched cohort	262	DNP, DNE, Consultant	Medical referral	Reactive	Unclear	NA	NA	↓	Amongst surgical patients, those seen by IDT had lower LOS. Amongst medical patients those seen by IDT had lower 30 day readmission.

Abbreviations: IDT: Inpatient diabetes team; DNP: Diabetes Nurse Practitioner; DNE: Diabetes Nurse Educator; Consultant: endocrinologist or diabetologist; Fellow: diabetes fellow or endocrinology registrar; NA: not assessed; LOS: length of stay; BG: blood glucose. ↓: decreased; ↑: increased; ↔: no change. See text for explanation on model of care and management

In addition to glycaemic and LOS outcomes, three studies also reported clinical outcomes. Newton et al., reported the impact of a proactive IDT service in a community hospital in a pre- and post-implementation comparison. A reduction in population mean glucose of 0.9 mmol/L, and a 33% reduction in central line associated blood stream infections was reported suggesting improvements in glucose control contributed to decreased infections [266]. Wong et al., analysed a retrospective cohort of 74 individuals who had enteral nutrition treatment, and compared those that received IDT intervention vs. those that did not [269]. The group that received IDT intervention had a lower mean glucose (11.1 vs. 8.6 mmol/L), shorter mean LOS (37 vs 27 days), but also lower proportion with in-hospital mortality (32% vs 11%). Lastly, Wang et al., retrospectively analysed 440 patients with diabetes discharged with a 'cardiac' or 'infection' diagnostic codes and compared patients who had IDT treatment vs. those who were managed by the treating team alone. In the analysis of the entire cohort, there were no differences in clinical outcomes. However, in a subgroup of people who had a mean BG >10 mmol/L during admission, the group managed by an IDT had a 50% reduction in complications (a composite outcome comprising nine items including mortality, infection, renal failure, ICU admission and readmission) [276]. Therefore, there is published data suggesting that IDT intervention improved clinical outcomes in addition to glucose control; however, evidence is based on observational and retrospective studies only and generalisability may be limited.

A major limitation in this area of research is the abundance of observational, rather than prospective randomised studies, reflecting the difficulty in performing prospective trials of clinical care in hospitals. With a lack of a parallel control group, these observational studies are subject to confounding such as variation in hospital processes and outcomes over time. For example, many aspects of hospital care are becoming more efficient, and outcomes such as LOS are decreasing year on year. Therefore, reduction in LOS associated with IDT intervention maybe partially related to these measured and unmeasured confounders. In addition, some studies used retrospective 'pre-intervention' cohorts as the control group, which are subject to selection biases. Hence, changes in glycaemic and LOS outcomes are associated with an IDT intervention, rather than proving a definitive causal link. Lack of prospective randomised trials of IDTs is a significant gap in research evidence, prompting the ADA's 'Planning Research in Inpatient Diabetes' interest group to send out a 'call to arms' for more high level research in this area [277].

1.7.9 Risk stratification and prediction models

With the rising number of inpatients with diabetes, there is an increasing need for efficient allocation of management resources. Specialist IDTs improve glucose control but providing management to every diabetes inpatients is resource intensive, as it can be up to 25 to 30% of the hospital population. There are efforts to develop risk stratification or prediction models to identify inpatients who are more likely to require IDT management. Studies on risk stratification either focus on those who develop adverse outcomes, or who develop adverse glycaemia.

Nirantharakumar et al., reported a prediction model for adverse outcomes in inpatients with diabetes [289]. Adverse outcomes in this study were defined as inpatient mortality or LOS that was above the 75th centile of LOS for patients with diabetes. Analysis of 25,000 inpatient episodes from a UK hospital database found multiple clinical factors (including age, gender, admission type, foot disease, insulin use, critical care admission), and biochemical factors (low albumin, low GFR, low haemoglobin, low potassium, high inflammatory markers, and either low or high sodium) were associated with adverse outcomes. A regression model based on these variables was accurate at predicting adverse outcome, with receiver-operating characteristic, area under curve (ROC-AUC) of 0.802. A subsequent external validation study reported a similar accuracy of this prediction model in other UK cohorts, supporting its clinically utility [290]. However, this model did not include glycaemic variables as it was not reliably available in the discharge databases; therefore, it is unclear if adverse outcomes were linked to adverse glycaemia or whether targeted intervention by an IDT can improve outcomes.

Several studies developed risk stratification strategies for adverse glycaemia; however, these only focussed on hypoglycaemia. Known risk factors for inpatient hypoglycaemia include greater comorbidities, greater duration of diabetes, lower HbA1c, insulin or sulphonylurea treatment, kidney and liver impairment and longer LOS [162, 291-293]. Four prediction models for hypoglycaemia have been described (Table 12).

Despite hyperglycaemia being significantly more common, there are relatively few studies formally addressing risk factors. From clinical experience, many variables are known to cause exacerbation of hyperglycaemia including patient variables (pre-existing hyperglycaemia, counter-regulatory stress response, severity of illness), and hospital treatment factors (glucocorticoid treatment, provision of enteral and parenteral nutrition and withheld glucose-lowering treatment). There are two studies reporting that admission HbA1c predicted inpatient hyperglycaemia [294, 295] but there are no prediction tools for hyperglycaemia.

Table 12: Prediction models for inpatient hypoglycaemia

Study, Location, Year	Cohort (n)	Methods (hypoglycaemia threshold)	Predictive variables	Performance (ROC-AUC)
Elliot, Missouri, US, 2012 [296]	All inpatients (n=172 hypo episodes) (n=3028 patients for validation)	Logistic regression Internal validation (BG <2.2 mmol/L)	Insulin regimen Insulin dose Sulphonylurea Weight eGFR	0.700
Stuart, Birmingham, UK, 2017 [297]	Diabetes inpatients (n=9,584)	Logistic regression Internal validation (BG<4.0 mmol/L)	Insulin regimen Sulphonylurea Age Ethnicity Emergency admission eGFR C-reactive protein Sodium Albumin	0.731
Shah, Toronto, Canada, 2018 [298]	Medical inpatients (n=300) (n=300 validation)	Logistic regression. External validation. (BG <3.9 mmol/L)	Insulin regimen Age CKD History of ED visits Non-sulphonylurea GLM (protective)	0.642
Mathioudakis, Maryland, US, 2018 [299]	Noncritical care inpatients (n=128,657 patient-days)	Logistic regression Internal validation (BG <3.0 mmol/L)	Insulin dose Type 1 diabetes Type 2 diabetes Mean BG Nadir BG CV of BG Sex Weight Diet CKD stage Glucocorticoid treatment	0.80

Abbreviations: BG: blood glucose; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; CV: coefficient of variation. ROC-AUC: receiver operating characteristic-area under curve

1.7.10 Continuous glucose monitoring and automated insulin delivery systems

Diabetes technology in ambulatory care has rapidly evolved and many individuals (especially those with type 1 diabetes) now use subcutaneous insulin infusion (CSII) pumps with or without continuous glucose monitoring (CGM) systems to optimise diabetes management. Some individuals use stand-alone CMG systems with multi-dose insulin injections (i.e. not insulin pump) to closely monitor glucose and make treatment decisions. Strategies and protocols have been developed to deal with such technology when individuals using these systems are admitted to hospital. In addition, the possibilities of using these new technologies de novo in hospital to optimise inpatient diabetes management have been explored.

Current guidelines recommend individuals using an insulin pump prior to hospitalisation should remain on the pump in hospital, when safe to do so [30, 300]. This requires the individual to self- monitor BG and self-manage the insulin pump. There are also established contraindications to insulin pump therapy in hospital including critical illness, psychiatric or cognitive conditions and hyperglycaemic emergencies.

Real-time CGM in the hospital has potential advantages due to the ability to rapidly detect increasing or decreasing BG and enable rapid treatment decisions aiming to prevent adverse glycaemia. CGM systems in hospital can be invasive and intravascular (used in the intensive care) or less invasive and subcutaneous (similar to systems used in ambulatory care). However, the limitation of subcutaneous interstitial CGM in the inpatient setting include: 1) the need for regular calibration; 2) the time-lag for capillary glucose measure to be reflected in interstitial glucose measure; 3) interference with substances such as mannitol, maltose ,and paracetamol; and 4) a lack of evidence of accuracy during hypotension, hypothermia and hypoxia. Use of CGM in hospital remains experimental at present although a number of small studies evaluating device accuracy have been performed in critical care and noncritical care [300]. Currently there is only one subcutaneous CGM system approved for inpatient use in Europe, but there are no approved systems in US or Australia. There are no studies to date evaluating if CGM improves inpatient glycaemia in the noncritical care arena.

Another new technology that has the potential to revolutionise diabetes management in ambulatory care is automated insulin delivery systems (or a closed-loop pumps). Utilising a CGM and a computer algorithm, a closed-loop pump constantly adjusts insulin infusion rate to achieve optimal glycaemic control. This technology has been tested in the hospital in a RCT of 136 inpatients with type 2 diabetes, who were randomised to a closed-loop system or a conventional subcutaneous BBI regimen [301]. The group randomised to closed-loop had a significantly higher percentage of time in target range (66% vs. 42%), lower proportion of patients with BG above target range (23% vs. 50%), and lower mean glucose (8.5 vs. 10.4 mmol/L). Automated insulin delivery systems have the potential to significantly improve BG control for individuals, however their use in the hospital setting remains technically and financially challenging.

1.8 Summary

The prevalence of diabetes in hospital has increased rapidly in the last few decades and diabetes now affects one in four inpatients. Most diabetes inpatients are admitted under the care of non-diabetes specialists. Individuals with diabetes and those who are discovered to have hyperglycaemia in hospital have worse outcomes, including increased risk of hospital-acquired infections, longer LOS, greater readmissions and higher inpatient mortality. Adverse outcomes are (at least partially) attributable to metabolic and physiological changes resulting from acute hyperglycaemia and hypoglycaemia; collectively termed adverse glycaemia.

There are well-established cellular and pathophysiological mechanisms linking adverse glycaemia with adverse clinical outcomes. Acute hyperglycaemia causes immune dysfunction, pro-inflammatory and pro-thrombotic changes, and endothelial dysfunction. These changes occur even after a short duration of exposure to moderate levels of hyperglycaemia, situations that are routinely encountered in hospitalised patients. Treatment of hyperglycaemia improves outcomes, especially decreasing the risk of hospital-acquired infections, but aggressive 'tight glycaemic control' is not warranted and may be harmful, possibly due to increased incidence of hypoglycaemia. Acute hypoglycaemia is linked to cardiac arrhythmia, cardiac ischaemia, endothelial dysfunction, neurological sequelae and injuries. Therefore, adverse glycaemia (defined as blood glucose <4.0 or >15.0 mmol/L in this thesis) should be avoided in hospitalised patients. Despite the importance of glucose control, adverse glycaemia remains common in noncritical care, with more than 50% of inpatients with diabetes experiencing hyperglycaemia and 20% experiencing hypoglycaemia. There are multiple barriers interfering with optimal glucose control including patient-related, illness-related, treatment-related, health professional-related, and hospital-system-related factors all contributing to clinical inertia.

Various strategies to improve hospital diabetes care have been studied. Several RCTs demonstrated the superiority of basal-insulin containing insulin regimens over sliding-scale insulin. Insulin protocols and order sets improve appropriate insulin prescription in hospital. Although staff education programs improve clinician knowledge and glucose control in the short term, improvements are often unsustained. Glucometric reporting and benchmarking are essential aspects of auditing and improving inpatient glucose control; however, due to the lack of automated technologies to capture glucose data, there is a lack of glucometric data or benchmarking in Australian hospitals. Glycaemic alert systems may improve clinician response to adverse glycaemia; however, many alert systems require integrated electronic medical records and information systems.

Ultimately, the significant barrier in current diabetes management practice is a lack of diabetes clinical expertise for the majority of inpatients with diabetes. Specialist IDTs have been implemented to provide specialist diabetes management aimed at improving glycaemic control and clinical outcomes. However, evidence of the effectiveness of IDTs are based on observational studies, and randomised trials are

lacking. Furthermore, studies have focused on glycaemic or LOS outcomes; very few studies evaluated clinical outcomes.

Alert systems and IDTs that foster a more proactive model of diabetes care can theoretically be more effective at decreasing clinical inertia. A proactive IDT would also benefit from a system to risk-stratify and identify subgroups of inpatients who are most at risk of developing adverse glycaemia to enable targeted management. Above all, a successful inpatient diabetes management approach should increase insulin use, decrease adverse glycaemia, and improve clinical outcomes for individuals with diabetes and hyperglycaemia in hospital. The term 'proactive' originates from a Greek word 'Pro' (meaning 'before' or 'early'), and the Latin word 'Activus' (meaning 'to act'). Hence, to be proactive is to provide an 'early action' or an 'early intervention' for people with diabetes.

1.9 Research aims

The aims of this thesis are to develop and evaluate *early intervention* models of inpatient diabetes care to address adverse glycaemia in hospital. The specific aims are:

- To develop and evaluate a glucose alert system designed to improve health professional responses to adverse glycaemia
- To implement networked glucose meter technology and describe baseline glucometric outcomes at Royal Melbourne Hospital compared to international benchmarks.
- To develop a comprehensive early intervention model of inpatient diabetes care and investigate its effects on glycaemic and clinical outcomes, in a prospective randomised controlled trial
- To develop a prediction tool for early identification of inpatients at high-risk for adverse glycaemia.

1.10 Hypotheses

- A glucose alert system, comprising of a clinical escalation pathway and alert-capable networked glucose meters, will improve health professional responses to adverse glycaemia and improve inpatient glycaemia
- Inpatients with diabetes at the Royal Melbourne Hospital have similar glucose control as hospitals in the United States and United Kingdom.
- A comprehensive early intervention model of inpatient diabetes care will increase insulin treatment, as well as improve glycaemia and clinical outcomes.
- Clinical factors available early in admission can predict the development of adverse glycaemia during hospital stay

CHAPTER TWO: MATERIAL AND METHODS

General materials and methods are outlined in this chapter. Specific details of methods for each study are outlined in the respective chapters.

2.1 Study design overview

Two separate clinical studies were conducted at the Royal Melbourne Hospital (RMH), a tertiary teaching hospital affiliated with the University of Melbourne. Study 1 was a prospective, pre- and post-implementation, observational study on two wards over 16 weeks investigating the efficacy of a glucose alert system (**Chapter 3**). This study also provided invaluable insights into the performance of networked glucose meters at our hospital. Following this, networked glucose meters were implemented on eight noncritical care wards for the subsequent study. Study 2, was the **Ra**ndomised study of a **P**roactive **I**npatient **D**iabetes **S**ervice (RAPIDS) which was prospectively registered with the Australia New Zealand Clinical Trials registry (ANZCTR.org.au: number: 12616000265471). RAPIDS was a cluster randomised trial with a baseline period, conducted on eight wards over 24 weeks and formed the basis of **Chapters 4, 5 and 6**. Both studies were approved by the Melbourne Health Humans Research and Ethics committee (QA2013.189 and HREC 2015.127) with a waiver of the need for individual consent.

2.2 Setting

Located in Parkville, 2 kilometres from Melbourne's central business district, the RMH comprises a 480-bed acute care campus, and a 100-bed subacute care campus. The studies were conducted at the acute care campus. The RMH is co-located with the Peter MacCallum Cancer Institute and the Royal Women's Hospital, in addition to a number of medical and scientific research facilities comprising the Parkville medical and research precinct. The RMH provides acute medical and surgical care for adult patients in most disciplines, as well as serving as one of two dedicated trauma centres for the State of Victoria. It does not provide paediatric, maternity or gynaecology services as these are provided by co-located specialist hospitals. As a university teaching hospital, the RMH has a full array of students including medical, nursing and allied health, across a range of education including undergraduate, postgraduate and specialist training.

The wards included in the studies are acute, noncritical care, general and specialist medical and surgical wards. In study 1, a specialty surgical ward (vascular and urology surgery) and a specialty medical ward (rheumatology and infectious diseases) were included. In study 2 (RAPIDS), eight wards (half medical and half surgical) were included, and were different to the wards in study 1. The eight wards included

were two general medical, two general surgical, and one each of cardiology, neurology, neurosurgery and orthopaedic/trauma surgery wards. These wards were chosen to be representative of patients admitted to the hospital. The wards range from 20 to 32 beds and with the exception of two general medical wards which are considered symmetrical wards, the remaining wards are considered specialist wards with unique medical or surgical services.

The RMH does not have a fully-integrated EMR for inpatient care. Therefore, documentation of patient observations, clinical progress notes and medication prescription are performed on paper charts at the patient bedside. Pathology, radiology, patient administration, scanned medical records and various other clinical systems are available in separate electronic programs.

Inpatient diabetes care is generally provided by the treating team's medical officers but the Department of Diabetes and Endocrinology provides a referral-based diabetes consultation service. The inpatient diabetes referrals service consists of an advanced endocrinology trainee and a diabetes nurse practitioner who are supervised by the ward service endocrinologist. Various inpatient diabetes guidelines, including hypoglycaemia management and perioperative diabetes management, are available to assist with clinical care. Twice yearly education sessions are conducted for junior medical staff and nursing staff. The diabetes education department also provides a referral-based service in response to requests from ward nursing staff and treating medical teams.

2.3 Networked glucose meter implementation

In study 1, two different networked glucose and ketone meter systems (Precision Pro ®, Abbott Diabetes; and Statstrip ®, Nova Biomedical – distributed by Australasian Medical and Scientific Limited [AMSL]) were used as part of the glucose alert system. Subsequently, Statstrip ® glucose meter system was implemented for the RAPIDS study. The Statstrip was chosen as the preferred system for the RAPIDS study after an evaluation of both systems by a multidisciplinary team, as it was found to be superior in functionality and connectivity, in addition to superior accuracy in the setting of critical illness and extremes of haemoglobin. Both systems comply with the International Organisation for Standardisation (ISO) 15197 and Clinical and Laboratory Standards Institute standards for accuracy [186] and both are approved by the Therapeutics Goods Administration for use in Australian hospitals.

Networked glucose meter systems were installed on participating wards using a Local Area Network (LAN) cable which connected the meter docking stations to the hospital's information technology (IT) network. Each meter was configured and administered using associated data management software (POCcelerator ®, Siemens Healthineers for Precision Pro; and Novanet ®, Nova Biomedicals for Statstrip). Meters communicated to the hospital IT system using Health Level-7: Admission, Discharge and Transfer (HL7-ADT) data transfer system, enabling real-time transfer of patient information and

glucose measurement results. During the studies, electronic glucose measurement data was not available for routine clinical care, but available only to the research team for delivery of proactive interventions and data collection. BioViewer (© Bio-Asia Diagnostics) data manager was used to extract capillary glucose data from the database.

Implementation of networked glucose meters was accompanied by an extensive staff training program, consisting of small group 30-minute nursing 'in-service' sessions. At least five sessions were provided for each participating ward with more than 90% of staff receiving face-to-face training. In addition, train-the-trainer sessions were held for nursing educators who continued to educate new staff members. For study 1, implementation of networked BG meters (which was a component of the glucose alert pathway) was completed during the two-week implementation phase. For study 2, implementation of networked BG meters was completed one month prior to the beginning of the study to ensure adequate staff familiarity with this technology. Quality control testing of the meters was performed as per hospital policy (daily for glucose strips and weekly for ketone strips) The pre-existing simple glucose meters (Freestyle Optium ®, Abbott Diabetes) were removed from the wards to ensure all BG measurements were performed using the networked meters in the participating wards.

2.4 Participants

For both studies, consecutive inpatients who were admitted to a study ward, during the study period, were included. Study 1 included inpatients with pre-existing diabetes. Study 2 included inpatients with pre-existing diabetes and new hyperglycaemia (random capillary BG >11.1 mmol/L). Exclusion criteria comprised of inpatients admitted under the care of the diabetes and endocrinology unit, those admitted with hyperglycaemic crises (DKA or HHS), and those admitted for palliative care. Inpatients admitted for day procedures and those with hospital LOS less than 1 day were also excluded.

To ensure inclusion of all consecutive eligible inpatients, the ward patient list was generated each calendar day and screened for the presence of patients with diabetes or new hyperglycaemia. All inpatients meeting inclusion criteria were identified and included prospectively, without the need for individual patient consent for recruitment based on the waiver approved by the ethics committee. For patients with multiple admissions during the study period, each inpatient episode was included and data collected.

2.5 Data collection

Patient clinical information was collected from the inpatient clinical notes from the time of admission. Data collection was subsequently completed after patient discharge from hospital, to ensure accurate collection of clinical outcome data. To determine patient outcomes, clinical progress notes, discharge summaries, pathology and radiology result systems were assessed. Patient identification and initial data collection was performed on a paper data collection forms, but later the information was entered into a Microsoft Access ® database. In study 2, patient clinical outcomes were adjudicated by an independent clinician who was blinded to the treatment allocation.

Glycaemic data collection was performed by manual audit of glucose observation charts for study 1. In study 2, glycaemic data collection was performed by extracting electronically captured glucose measurements, and additionally verified by cross-referencing all glucose measurements with the paper glucose observation charts. In the event of discordance between electronic data and paper observation chart data (estimated to be present in less than 5% of measurements), the BG measurements documented on the observation charts were used.

For each included patient an HbA1c measurement was requested if it was not already requested by the treating teams. HbA1c results were available to all clinicians regardless of whether it was ordered by the treating clinical team or the research team. HbA1c was performed using high performance liquid chromatography. Creatinine and eGFR results were requested at the discretion of treating teams and were performed in the hospital pathology department using Abbott Architect analyser.

2.6 Data analysis

Data analysis was performed using a variety of statistical software. Minitab Version 17.2.1 (Minitab Inc., State College, PA, USA) was used to perform glucometric analyses and comparative analyses for Chapters 3 and 4. STATA version 15 (StataCorp LLC, College station, TX, USA) was used to perform complex analyses including logistic and Poissons regression (including mixed-level regression), and creation of ROC curves in Chapters 5 and 6. GraphPad Prism version 7.00 for Windows, (La Jolla California USA) was used to create charts and figures. For continuous variables, parametric or non-parametric tests were used to compare between groups as appropriate. Categorical variables were compared using Fisher's exact test or X^2 tests as appropriate.

CHAPTER THREE:

GLUCOSE ALERT SYSTEM TO IMPROVE HEALTH PROFESSIONAL RESPONSES TO ADVERSE GLYCAEMIA

3.1 Introduction

Clinical inertia is a common barrier to attaining optimal glycaemia in hospital. Clinical inertia in inpatient diabetes care describes a lack of health professional action in response to adverse glycaemia. A lack of appropriate treatment adjustment often leads to persistent adverse glycaemia. Alert systems to notify the occurrence of adverse glycaemia can prompt health professionals to make appropriate remedial actions. Studies of glucose alert systems in noncritical care have been heterogeneous and mostly required complex integrated electronic systems.

We sought to develop a simple glucose alert system that incorporated a novel clinical escalation pathway coupled with alert-capable networked glucose meters. The alert system provided a visual alert when BG was out of range, and prompted clinicians to respond according to the 'Melbourne glucose alert pathway'. The alert system was aimed at both nursing and medical staff at the point of care. It is an example of a proactive intervention, as it aims to increase early treatment. The efficacy of the alert system was investigated in a pre- and post- implementation observational study. Additionally, this study provided invaluable experience with the two available networked glucose meter systems, as well as generating pilot data on the incidence of adverse glycaemic days at our institution. The design and conduct of the subsequent RAPIDS cluster-randomised trial was based on the experience and results obtained from this present study.

3.2 Manuscript

The work described in this chapter has been published in the peer-reviewed journal Diabetic Medicine. The citation is:

M. Kyi, P.R. Wraight, L.M. Rowan, K.A. Marley, P.G. Colman, S. Fourlanos, Glucose alert system improves health professional responses to adverse glycaemia and reduces the number of hyperglycaemic episodes in non-critical care inpatients. *Diabetic Medicine*. 2018;35(6):816-23. DOI: 10.1111/dme.13623

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Research: Care Delivery

Glucose alert system improves health professional responses to adverse glycaemia and reduces the number of hyperglycaemic episodes in non-critical care inpatients

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Abstract

Aim To investigate the effect of a novel glucose alert system, comprising the Melbourne Glucose Alert Pathway and glucose-alert-capable networked blood glucose meters, on nursing and hospital medical officer responses to adverse glycaemia.

Methods A prospective, pre- and post-observational study was undertaken in non-critical care wards of a tertiary hospital over 4 months (n=148 or 660 patient-days). The intervention consisted of two components designed to promote a consistent staff response to blood glucose measurements: (1) a clinical escalation pathway, the Melbourne Glucose Alert Pathway, and (2) networked blood glucose meters, which provide a visual alert for out-of-range blood glucose measurement. All consecutive inpatients with diabetes were assessed for diabetes management and capillary blood glucose. The primary outcome was documented nursing and medical staff action in response to episodes of adverse glycaemia (blood glucose >15 mmol/l or <4 mmol/l). Secondary outcomes consisted of glycaemic measures.

Results In response to episodes of adverse glycaemia, nursing action increased (proportion with nursing action: 45% to 73%; P<0.001), and medical action increased (proportion with medical action: 49% to 67%; P=0.011) with the glucose alert system in place. Patient-days with hyperglycaemia (any blood glucose value >15 mmol/l: 24% vs 16%; P=0.012) and patient-days with mean blood glucose >15 mmol/l (7.4% vs 2.6%; P=0.005) decreased. There was no difference in hypoglycaemia incidence.

Conclusions Use of a novel glucose alert system improved health professional responses to adverse glycaemia and decreased hyperglycaemia in the hospital setting.

Diabet. Med. 00: 1–8 (2018)

Introduction

In hospitalized individuals, both hyper- and hypoglycaemia are associated with worse outcomes [1–4]. The term 'adverse glycaemia' can be used to describe both extremes of hyperglycaemia and hypoglycaemia, which should be avoided. Despite established glycaemic targets in the non-critical care setting [5,6], glycaemic control remains suboptimal with hyperglycaemia occurring in up to 80% of inpatient diabetes admissions [7,8], and hypoglycaemia occurring in 20% of admissions [7,9].

Clinical inertia in acute diabetes care can be defined as a lack of health professional action in response to adverse glycaemia and is a significant barrier to optimizing glycaemia in hospital. Despite hyperglycaemia being common in diabetes inpatients, capillary blood glucose (BG) measurements are often overlooked and appropriate intensification of therapy does not occur [10]. Persistent hyperglycaemia or recurrent hypoglycaemia on multiple consecutive days may occur without appropriate adjustment in therapy [11]. Clinical inertia is evident in both nursing and hospital medical officer practice. Nursing staff who perform point-of-care BG observations may not escalate a case to medical staff for assistance with managing out-of-range BG measurements, and hospital medical officers may not review BG observation charts daily, make appropriate therapy adjustment, or refer to specialist diabetes services for assistance.

Glucose alert systems have been shown to improve staff action in response to adverse glycaemia. In the intensive care setting, real-time computer-generated glucose alert systems (which provide audio-visual alerts when BG measurements are out of range) have been used to facilitate insulin infusion

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What's new?

- Lack of health professional response (clinical inertia) to adverse glycaemia is a major barrier to improving diabetes care in the hospital setting.
- To improve health professional responses, a novel glucose alert system, comprising the Melbourne Glucose Alert Pathway (a clinical escalation and management guide) and glucose alert-capable networked blood glucose meters, was implemented and evaluated.
- The glucose alert system improved health professional responses and decreased the number of hyperglycaemic episodes and could be a component of various strategies to improve the care of hospitalized people with diabetes.

adjustment by the treating nurse, and can improve glucose control [12,13]. In the non-critical care setting, structured glucose observation charts (with a coloured background to indicate when BG measurements are out of range), accompanied by hyperglycaemia and hypoglycaemia management guidelines have been used to encourage staff response to adverse glycaemia [14]. The efficacy of this approach to address clinical inertia has not been studied in detail, although one study observed a decrease in hyperglycaemia after the introduction of a structured BG observation chart [15].

Networked BG meters are point-of-care devices that link BG measurements to patient identifiers and store this information in a central database. Hospital-wide implementation of networked BG meters enables collection of electronic point-of-care BG data for research, quality improvement and benchmarking of glycaemic control between hospitals [16,17]. In addition, networked BG meters can be programmed to display visual cues when BG measurements are outside a predefined range and therefore could function as an alert device for adverse glycaemia.

Experts have suggested that system-based solutions are required to overcome obstacles for glycaemic control in hospital [18]. In an attempt to decrease clinical inertia and improve glycaemic control, we developed a glucose alert system designed to escalate health professional responses to adverse glycaemia. The glucose alert system comprised the Melbourne Glucose Alert Pathway (GAP), along with glucose-alert-capable networked BG meters. We hypothesized that this glucose alert system would increase nursing and hospital medical officer responses to adverse glycaemia.

Methods

This was a prospective observational study conducted over a 4-month period in 2015. It was performed on two wards at the Royal Melbourne Hospital, a tertiary teaching hospital affiliated with the University of Melbourne, and approved by the local Human Research Ethics Committee.

Population

Consecutive inpatients with diabetes who were admitted to one of two study wards were recruited. One surgical ward (predominantly vascular and urology surgery) and one medical ward (predominantly general medicine) were included in the present study because of the relatively high prevalence of diabetes in these wards. We excluded people with hyperglycaemia without a history of diabetes, and those admitted under endocrinology or palliative care units, or admitted for <1 day. Participant information, capillary BG measurements and diabetes management during hospitalization were collected prospectively from progress notes and bedside charts. For people with a prolonged hospital stay, only the first 14 days of admission were collected and analysed.

Baseline: routine care

At our hospital, diabetes management is primarily the responsibility of the hospital medical officers of the admitting unit. The specialist diabetes referral team (diabetes nurse and endocrinologist) is available for assistance on a formal referral basis. Documentation and management of acute inpatient care is performed via written medication orders, glucose observation charts and progress notes at the bedside. In accordance with local practices, there is no standardized algorithm of routinely withholding all antidiabetic medications and commencing regular and/or supplemental subcutaneous insulin on all patients admitted to hospital. A hypoglycaemia management algorithm has been in routine use, but a hyperglycaemia management algorithm has not been used.

During the baseline period, there was no formal glucose-based alert system and non-networked (and not alert-capable) point-of-care capillary BG meters (Freestyle optium®; Abbott Diabetes, Alameda, CA, USA) were in use. Baseline 2-month data collection was performed prior to implementation of the glucose alert system.

Intervention

The glucose alert system consisted of two components: (1) the GAP and (2) glucose-alert-capable networked BG meters.

The first component, the GAP, was a structured clinical escalation pathway to be used by nursing and medical staff in response to BG measurements (Fig. 1). The GAP was developed by a multidisciplinary team of nursing and medical staff in conjunction with the Department of Diabetes and Endocrinology at the Royal Melbourne Hospital. The GAP is a colour-coded guide attached to the bedside glucose observation charts consisting of four different BG ranges

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with corresponding action responses for nursing and medical staff. The four BG ranges are hypoglycaemia (BG <4.0 mmol/l, red), safe glycaemia (BG 4.0–10.0 mmol/l, green), acute hyperglycaemia (one BG 15.1–20.0 mmol/l or two consecutive BG 10.1–15.0 mmol/l, yellow) or critical hyperglycaemia (BG >20.0 mmol/l, red). Within each range, recommended nursing actions are summarized as follows: manage the situation, monitor BG more intensively and notify medical officer. The recommended medical officer actions are summarized as follows: review BG, revise diabetes treatment and refer to diabetes team for assistance. In addition to glucose measurements, the GAP also provided recommendations in response to clinical changes that may affect BG (such as fasting, provision of enteral nutrition, or glucocorticoid treatment).

The second component was the glucose-alert-capable networked BG meters, which enabled a visual alert for out-of-range BG measurements and facilitated electronic transfer and storage of BG data linked to a unique identifier. Two networked BG meter systems [Nova StatStrip® (Australasian Medical and Scientific Ltd, Chatswood, NSW, Australia) and Freestyle Precision Pro® (Abbott Diabetes)] were introduced to our hospital and used in the present study. Networked BG meters were programmed to display visual alerts when BG was outside the optimal range defined in the GAP. The visual alerts consisted of a yellow highlight or single arrow for moderately out-of-range measurements (BG 3.1–3.9 mmol/l or 10.1–20.0 mmol/l) and a red highlight or double arrows for critically out-of-range measurements (BG <3.0 mmol/l or >20.0 mmol/l). Nursing staff continued to record BG measurements manually on the bedside glucose observation charts, as per routine clinical care.

All nursing staff and medical officers underwent group education sessions on both components of the glucose alert system. A 2-month intervention period and data collection was undertaken with the glucose alert system in place.

Outcomes

The primary outcome was staff response to adverse glycaemia. An episode of adverse glycaemia was defined as a patient-day with capillary BG in the severe hyperglycaemia range (BG >15 mmol/l) or hypoglycaemia range (BG <4 mmol/l). These thresholds were chosen because severe hyperglycaemia is associated with adverse physiology (neutrophil dysfunction, osmotic diuresis) [19] and hypoglycaemia <4 mmol/l is associated with counter-regulatory hormone responses and adverse events [20]. Adverse glycaemia indicated unsafe glycaemic extremes that should be avoided and should prompt a review of diabetes management and adjustment of therapy [9].

Nursing and medical staff responses (<24 hours after an episode of adverse glycaemia) were assessed. Nursing response was defined as documented evidence of notifying

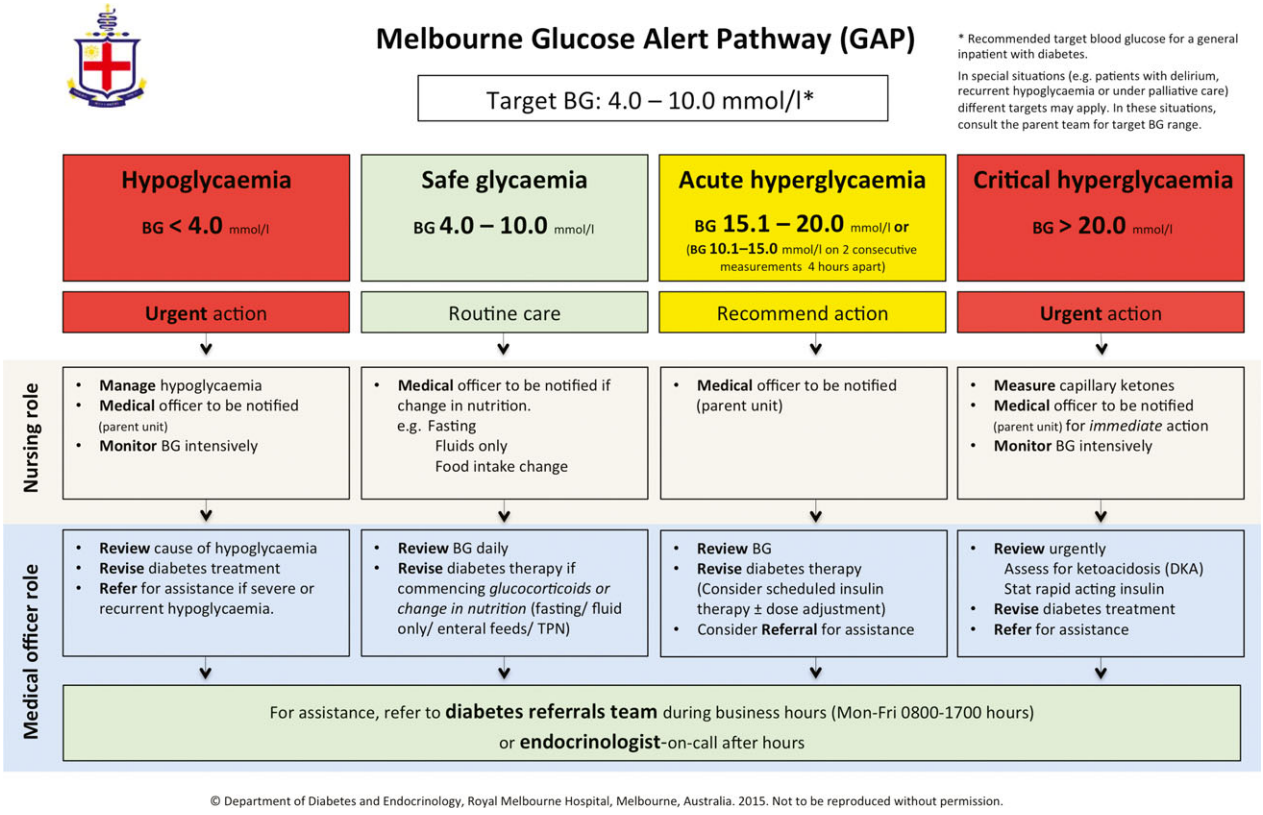

FIG. 1 Melbourne Glucose Alert Pathway (GAP). BG, blood glucose.

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(or escalating to) medical officers about adverse glycaemia. Medical officer response was defined as documented evidence of one or more of the following: reviewing BG observations; revising diabetes treatment (adjustment of diabetes medication or insulin, including prescription of correctional dose of insulin, as per the medication prescription chart); or escalating by referral to the specialist diabetes team. To account for potential confounders that may affect staff action, a logistic regression analysis was also performed to evaluate staff response to hyperglycaemia, adjusting for the peak BG (severity of hyperglycaemia), insulin treatment, admission unit and day of occurrence (weekday vs weekend).

Secondary outcomes were measures of glycaemic control (patient-days with hyperglycaemia or hypoglycaemia and patient-day mean glucose). To ensure BG measurement assessment was consistent across the entire study, capillary BG measurements that were documented in writing by the nursing staff in the BG observation charts were used, rather than electronically extracting data from networked BG meters. In addition, we excluded repeated BG measurements from a single episode of hypo- or hyperglycaemia as previously described [21]. Despite differences in chemical methods, all the BG meters in the study comply with the 2013 ISO: 15197:2013 standards and therefore we anticipated minimal difference in BG measurements in this non-critically ill population. Outcomes were compared between the baseline and intervention periods using Fisher's exact test, a *t*-test or a rank-sum test, as appropriate, using Minitab® version 17.2.1 (Minitab Inc., State College, PA, USA). At the conclusion of the study, nursing staff were asked to complete a survey evaluating satisfaction with both components of the glucose alert system.

Results

In the present study, we observed a total of 148 inpatients (660 patient-days), including 70 patients (349 patient-days) in the baseline period and 78 patients (311 patient-days) in the intervention period. The groups were well matched between baseline and intervention periods (Table 1). The majority had Type 2 diabetes, a third were receiving insulin treatment prior to admission and the mean HbA_{1c} was 57 mmol/mol (7.4%). This cohort consisted of largely surgical admissions (80%), with half admitted for elective procedures. The median length of stay was 4 days per person.

During the study there were 168 episodes of adverse glycaemia, with severe hyperglycaemia (>15 mmol/l) and hypoglycaemia (<4 mmol/l) occurring in 24% and 7% of

Table 1 Summary of participant characteristics

	Baseline (n = 70)	Intervention (n = 78)	P
Mean ± SD age, years	70±14	68±14	0.90
Men, *n* (%)	48 (69)	52 (68)	0.99
Mean ± SD BMI	29 ± 7	30 ± 7	0.58
Median (IQR) modified* Charlson comorbidity index	2 (0, 4)	2 (1, 4)	0.89
Diabetes type, *n* (%)			0.40
Type 2 diabetes	60 (86)	72 (92)	
Type 1 diabetes	4 (6)	3 (4)	
Other (e.g. steroid-induced, pancreatic)	6 (8)	3 (4)	
Diabetes treatment prior to admission, *n* (%)			0.33
Diet only	16 (23)	11 (14)	
Oral and glucagon-like peptide-1	31 (44)	42 (54)	
Insulin-requiring	23 (33)	25 (32)	
Mean ± SD HbA_{1c}, mmol/mol	54 ± 15	60 ±17	0.06
Mean ± SD HbA_{1c}, %	7.1 ± 1.4	7.6 ± 1.6	
Mean ± SD admission eGFR, ml/min/1.73m^2	71 ± 19	69 ± 22	0.53
Elective admission, *n* (%)	34 (49)	36 (46)	0.87
Admission unit, *n* (%)			0.35
Surgical	52 (74)	64 (82)	
Vascular surgery	21 (30)	21 (27)	
Urology surgery	20 (29)	26 (33)	
Other surgery	11 (16)	17 (22)	
Medical	18 (26)	14 (18)	
Median (IQR) observed patient-days per patient	3.8 (2.1, 7.8)	3.2 (1.8, 6.3)	0.18
Median (IQR) BG measurements per patient-day	4 (2, 5)	4 (2, 5)	0.10
Insulin regimen on admission to ward, *n* (%)			0.99
No insulin treatment	43 (61)	48 (62)	
Insulin treatment: basal ± bolus	10 (14)	11 (14)	
Insulin treatment: pre-mixed	11 (16)	12 (15)	
Insulin treatment: supplemental only	6 (9)	7 (9)	

BG, blood glucose; eGFR, estimated GFR; IQR, interquartile range.
*Excludes items related to diabetes.

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patient-days, respectively. In the baseline period there were 101 episodes of adverse glycaemia compared with 67 episodes in the intervention period. In response to adverse glycaemia, nursing responses increased from 45% during the baseline period to 73% during the intervention period ($P<0.001$). Medical responses increased from 49% during the baseline period to 67% during the intervention periods ($P=0.011$). The medical responses consisted mostly of reviewing BG measurements and revision of diabetes treatment (Table 2). After multivariable adjustment, staff response to hyperglycaemia was much more likely during the intervention than the baseline period [nursing action: adjusted odds ratio 6.7 (95% CI 2.5, 18.1); medical action 4.9 (95% CI 1.9, 12.7); Appendix S1].

On glucometric analyses, 1331 and 1077 BG measurements were observed in the baseline and intervention periods, respectively. Frequency of BG monitoring was as per local guidelines (median 4 measurements per person-day) and was consistent throughout the entire study. Patient-days with severe hyperglycaemia (>15 mmol/l) decreased (24% vs 16%; $P=0.012$), and patient-days with critical hyperglycaemia (>20 mmol/l) decreased (9% vs 2%; $P<0.001$). Patient-days with mean BG >15 mmol/l decreased [7.4% vs 2.6%; $P=0.005$ (Fig. 2)]. There was no difference in patient-days with hypoglycaemia (BG <4 mmol/l; 7% vs 6%; $P=0.9$) or severe hypoglycaemia (BG <3 mmol/l; 3.4% vs 2.8%; $P=0.8$). The proportion of patients with severe hypoglycaemia during hospitalization was not different (11% vs 5%; $P=0.2$). Patient-day mean glucose was not different (although showed a trend to decrease) between baseline and intervention periods (9.5±3.2 vs 9.1±2.5 mmol/l; $P=0.082$).

Satisfaction surveys were returned by 24 nurses (40% of eligible nurses). Twenty respondents (83%) were satisfied with the GAP, and 18 respondents (75%) were satisfied with networked BG meters; however, 25% indicated that the alert system placed increased demands on their time. The majority responded that both components improved patient safety (Appendix S2).

Discussion

In keeping with previous literature, the present study identified frequent episodes of adverse glycaemia in non-critical care inpatients with diabetes. In the baseline period of this study, more than half of adverse glycaemic episodes did not lead to documented action by nursing or medical staff, highlighting significant clinical inertia. Adjustment of diabetes treatment occurred in only one-third of episodes, similar to findings in a previous study in which only 22% of patient-days with hyperglycaemia led to treatment intensification [22].

Intervention with an instructive visual glucose alert system aiming to escalate health professional responses resulted in significant improvement in responses to adverse glycaemia. Increased staff responses were most evident in nursing staff, where a 62% increase in notification of adverse glycaemia to hospital medical officers was observed. Similarly, medical staff reviewed BG measurements and made adjustment to diabetes treatment more often. The two components of the glucose alert system were designed to work in concert, as networked BG meters provided a visual alert for an out-of-range BG measurement, prompting staff to refer to the GAP, which then provided the clinical escalation and management guideline. In addition, treating staff were aware that patient-identifiable BG data were electronically recorded with the theoretical potential for remote electronic surveillance (which was not performed in this study), which may have encouraged a greater sense of accountability for BG management. Improved accountability is an important aspect of improving inpatient diabetes management, which can be facilitated by networked BG meters [23]. In the present study

Table 2 Staff response to adverse glycaemia episodes

	Baseline	Intervention	*P* *
1.1.1 Number of episodes of adverse glycaemia (BG >15 or <4 mmol/l)	**101**	**67**	
Nursing response, % (*n*)	45 (45)	73 (49)	<0.001
Medical response, % (*n*)	49 (49)	67 (46)	0.011
Types of medical responses, % (*n*)			
Review of BG measurements	41 (41)	63 (42)	
Revision of diabetes treatment (adjustment of medications or insulin and prescription of correctional insulin)	32 (32)	45 (30)	
Referral to specialist inpatient diabetes team	19 (19)	16 (11)	
1.1.2 Number of episodes of severe hyperglycaemia (BG> 15.0 mmol/l)	**85**	**51**	
Nursing response, % (*n*)	47 (40)	75 (38)	0.002
Medical response, % (*n*)	49 (42)	69 (35)	0.032
1.1.3 Number of episodes of hypoglycaemia (BG <4.0 mmol/l)	**24**	**20**	
Nursing response, % (*n*)	50 (12)	70 (14)	0.227
Medical response, % (*n*)	46 (11)	70 (14)	0.135

BG, blood glucose.
*Fisher's exact test.

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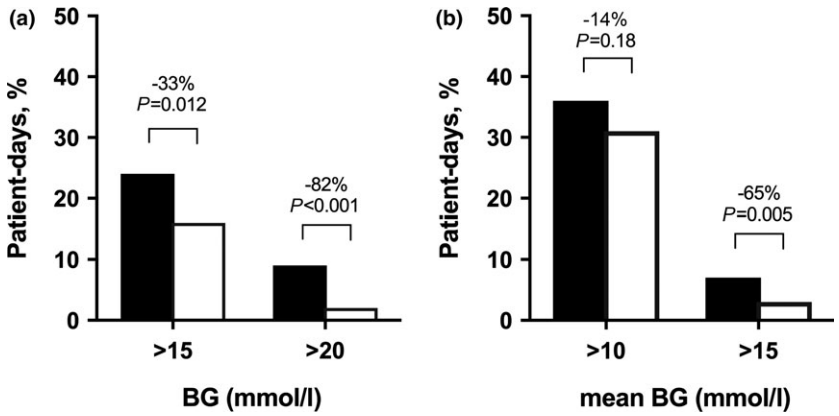

FIG. 2 (a) Patient-days with any blood glucose (BG) value in the severe hyperglycaemia (>15 mmol/l), or critical hyperglycaemia (>20 mmol/l) range. (b) Patient-days with mean BG >10 or >15 mmol/l. Baseline period represented with filled bars and intervention period represented as open bars.

it was not possible to determine the relative contributions of the two components to modification of staff action.

Increase in the proportion of adverse glycaemic episodes with staff action resulted in significant improvements in glycaemia. A 33% decrease in patient-days with severe hyperglycaemia (BG >15 mmol/l), and a 65% decrease in patient-days with mean glucose levels >15 mmol/l were observed. Other studies have shown similar improvements in glycaemic control using alternative glucose alert interventions aimed at increasing staff responses. Roman *et al.* [15] devised a colour-coded BG monitoring chart that provided visual alerts for out-of-range BG trends, coupled with a management algorithm. This intervention resulted in a 41% decrease in the frequency of prolonged hyperglycaemia (three consecutive BG measurements >13.9 mmol/l) [15]. Donihi *et al.* [24] studied a glycaemic management team who remotely monitored BG measurements and alerted treating teams of the occurrence of severe hyperglycaemia (BG >16.7 mmol/l). This approach improved treating team staff response by 50%, and decreased the occurrence of subsequent severe hyperglycaemia by 55% [24]. Our study supports the evidence that increasing health professional action (and decreasing clinical inertia) in response to adverse glycaemia may improve glycaemic control in hospital.

Glucose alert systems in the non-critical care setting can vary greatly in function and complexity, as evident in a relatively small number of heterogeneous studies [15,24–28]. A manual alert system may be a simple colour-coded BG monitoring chart, whilst an electronic alert system uses point-of-care BG data and generates computerized alerts when predefined BG criteria are met. An alert may be generated electively by a user (e.g. when the user logs on to a computer system or generates a report) or in real time (e.g. when an alert is generated without input from the user). The alerts may be based on BG measurements alone or on integration of various clinical variables such as age, weight, laboratory results and current treatment [25], but such systems necessitate fully integrated hospital electronic clinical information systems. Although most systems alert the treating staff at the point of care, some electronic alert systems directly alert a specialist diabetes team. Two studies have evaluated an electronic alert system that generated an automated referral and subsequent consultation by a specialist diabetes team. There was a modest decrease in mean BG (0.7 mmol/l) in one study [26], and a 20% decrease in the proportion of patient-days with mean BG >15 mmol/l in another [27]. These alert systems require complex integrated hospital electronic systems, and demand greater resources and staffing. In contrast, the simple glucose alert system investigated in the present study provides real-time electronic visual alerts and structured recommendations to the treating staff at the point of care. This is an example of a less resource-intensive alert system, which is more likely to be applicable in a wider variety of hospital settings.

Our glucose alert system did not decrease the incidence of hypoglycaemia, similar to other systems which alerted the treating team [15,24]. Hypoglycaemia is less common than hyperglycaemia; therefore a longer duration of study may be required to detect improvements in hypoglycaemia. Nevertheless, it is reassuring that this intervention, which intensified staff responses to hyperglycaemia, did not concomitantly increase hypoglycaemia. A larger study by Rajendran *et al.* [29] showed that a comprehensive diabetes care pathway, significantly decreased the proportion of patients with severe hypoglycaemia (BG <3 mmol/l) from 15.4% to 9.7%, but that intervention was multi-faceted; it included an extensive education campaign, new subcutaneous insulin prescription and BG observation charts, as well as increased staffing levels [29]. Similarly, Rushakoff *et al.* [28] implemented a comprehensive glycaemic management service where a specialist inpatient diabetes team remotely identified patients with adverse glycaemia, and provided a consultation note, effectively acting as a glucose alert system. This service was associated with a 36% decrease in patient-days with hypoglycaemia, along with a decrease in hyperglycaemia. These studies suggest more resources and staffing may be required to decrease hypoglycaemia [28].

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A limitation of the present study is its observational format, which may be more susceptible to a 'Hawthorne effect' on clinical practice because staff were more likely to take action whilst aware that a clinical study was being undertaken. Nevertheless the changes in staff responses observed were associated with a decrease in the number of hyperglycaemic episodes. This study was of relatively short duration and thus less susceptible to any influence from hospital-wide changes in staff or hospital processes.

To fully address the problem of managing diabetes in the hospital it is important to appreciate and address each step required to identify and treat adverse glycaemia. Recognizing clinical inertia and alerting adverse glycaemia to health professionals is the first step and cornerstone for improving diabetes care in the hospital. Implementing a practical and novel glucose alert system, the GAP with glucose-alert-capable networked BG meters, can address clinical inertia in the management of inpatients with diabetes in the non-critical care setting. The glucose alert system improved both nursing and medical staff responses to adverse glycaemia and decreased number of episodes of hyperglycaemia. Glucose alert systems could become important components of larger hospital-wide intensive management strategies required to improve the care of persons with diabetes admitted to hospital.

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Conflict of interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Staff action: logistic regression analysis.
Appendix S2. Staff survey and results.

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3.3 Supplemental material

Appendix 1: Staff action in response to episodes of hyperglycaemia (BG > 15 mmol/L)

Nursing staff action

Clinical factor	Adjusted OR	95% CI	p-value
Intervention period (vs. baseline)	**6.7**	**2.5, 18.1**	**<0.001**
Peak BG: (each mmol/L increase)	1.4	1.2, 1.7	<0.001
Insulin treatment	0.7	0.3, 1.6	0.360
Surgical admission (vs. medical)	2.6	1.0, 5.7	0.061
Weekend (vs. weekday)	1.0	0.4, 2.6	0.928

Medical staff action

Clinical factor	Adjusted OR	95% CI	p-value
Intervention period (vs. baseline)	**4.9**	**1.9, 12.7**	**0.001**
Peak BG: (each mmol/L increase)	1.4	1.2, 1.6	<0.001
Insulin treatment	1.8	0.8, 4.1	0.171
Surgical unit (vs. medical)	1.5	0.6, 3.4	0.370
Weekend (vs. weekday)	0.4	0.2, 0.9	0.035

Logistic regression models were constructed to determine if improvement in nursing and medical staff action were independent of potential confounders. The potential confounders used were selected due its association with staff action on statistical analysis and consisted of:

1) Peak BG (severity of hyperglycaemia)
2) Insulin treatment (whether insulin treatment was in place at the time of hyperglycaemia)
3) Admission unit (surgical vs. medical)
4) Day of occurrence of hyperglycaemia (weekend vs. weekday)

Appendix 2: Staff Survey

Regarding the Glucose Alert Pathway (GAP)

1) To what extent do you agree or disagree with the following statements?

	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
The GAP was easy to follow.	○	○	○	○	○
The GAP was helpful.	○	○	○	○	○
The GAP placed excessive demands on my time.	○	○	○	○	○
The GAP improved patient safety.	○	○	○	○	○
Overall, I am happy with the GAP.	○	○	○	○	○

2) Please write down any other comments:

_____

_____

Regarding the Networked Blood Glucose Meters (NGBM)

1) To what extent do you agree or disagree with the following statements?

	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
The NBGM were easy to use.	○	○	○	○	○
Out-of-range indicators were helpful.	○	○	○	○	○
The NBGM placed excessive demands on my time.	○	○	○	○	○
The NGBM improved patient safety.	○	○	○	○	○
Overall, I am happy to continue using the NBGM.	○	○	○	○	○

2) Please write down any other comments:

_____

_____

Thank you for your time in completing this survey.

Results of staff satisfaction survey. Responses: n (%)

	Disagree or Strongly Disagree	Neutral	Agree or Strongly Agree
The GAP was easy to follow.	1 (4%)	1 (4%)	22 (92%)
The GAP was helpful.	0	4 (17%)	20 (83%)
The GAP placed excessive demands on my time.	11 (50%)	6 (27%)	5 (23%)
The GAP improved patient safety.	0	4 (17%)	20 (83%)
Overall, I am happy with the GAP.	0	4 (17%)	19 (83%)
The NBGM were easy to use.	2 (8%)	2 (8%)	20 (83%)
Out-of-range indicators were helpful.	0	6 (25%)	18 (75%)
The NBGM placed excessive demands on my time.	12 (50%)	6 (17%)	6 (24%)
The NGBM improved patient safety.	4 (17%)	6 (25%)	14 (58%)
Overall, I am happy to continue using the NBGM.	3 (13%)	3 (13%)	18 (75%)

CHAPTER FOUR:

GLUCOMETRIC BENCHMARKING IN AN AUSTRALIAN HOSPITAL ENABLED BY NETWORKED GLUCOSE METER TECHNOLOGY

4.1 Introduction

Glucometric assessment, reporting and benchmarking are important strategies in improving inpatient glucose control but this approach has been deficient in Australian hospitals due to a lack of automated technologies to capture glucose data. As part of the RAPIDS cluster randomised trial, we implemented networked glucose meters on eight medical and surgical wards, representative of patients admitted to the Royal Melbourne Hospital. Applying well-established glucometric reporting techniques, we provided first ever detailed glucometric analysis in noncritical care wards at an Australian hospital. This study enabled assessment of baseline glycaemia for the RAPIDS study.

4.2 Manuscript

The work described in this chapter has been published in the peer-reviewed journal, Medical Journal of Australia. The citation is:

M. Kyi, P.G. Colman, K.A. Marley, L.M. Rowan, P.R. Wraight, S. Fourlanos, Glucometric benchmarking in an Australian hospital enabled by networked glucose meter technology, *Medical Journal of Australia*, 2019;211(4):175-180. DOI: 10.5694/mja2.50247

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Glucometric benchmarking in an Australian hospital enabled by networked glucose meter technology

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The known: Despite the importance of glucose control for people admitted to hospital, inpatient glucose levels have not been systematically audited or benchmarked in Australia.

The new: We report the first detailed glucometric analysis for inpatients in a major Australian hospital, an analysis facilitated by networked glucose meter technology. For 260 of every 1000 patient-days, blood glucose levels were outside the safe range for hospital patients. The incidence of hyperglycaemia was higher and that of hypoglycaemia lower than in an American hospital benchmark.

The implications: Glucometric benchmarking in Australian hospitals is important for ensuring the safe care of patients with diabetes.

Abstract

Objective: To assess glucometric outcomes and to estimate the incidence of hypo- and hyperglycaemia among non-critical care inpatients in a major Australian hospital.

Design, setting and participants: A prospective 10-week observational study (7 March – 22 May 2016) of consecutive inpatients with diabetes or newly detected hyperglycaemia admitted to eight medical and surgical wards at the Royal Melbourne Hospital. Point-of-care blood glucose (BG) data were collected with networked glucose meters.

Main outcome measures: Glycaemic control, as assessed with three glucometric models (by population, by patient, by patient-day); incidence of adverse glycaemic days (AGDs; patient-days with BG levels below 4 mmol/L or above 15 mmol/L).

Results: During the study period, there were 465 consecutive admissions of 441 patients with diabetes or newly detected hyperglycaemia, and 9817 BG measurements over 2953 patient-days. The mean patient-day BG level was 9.5 mmol/L (SD, 3.3 mmol/L). The incidence of hyperglycaemia was higher than for a United States hospital benchmark (patient-days with mean BG level above 10 mmol/L, 37% *v* 32), and that of hypoglycaemia lower (proportion of patient-days with mean BG level below 3.9 mmol/L, 4.1% *v* 6.1%). There were 260 (95% CI, 245–277) AGDs per 1000 patient-days; the incidence was higher in medical than surgical ward patients (290 [CI, 270–310] *v* 206 [CI, 181–230] per 1000 patient-days). 604 AGDs (79%) were linked with 116 patients (25%). Episodes of hyperglycaemia (BG above 15 mmol/L) were more frequent before lunch, dinner, and bedtime; 94 of 187 episodes of hypoglycaemia (BG below 4 mmol/L) occurred between 11 pm and 8 am.

Discussion: Glucometric analysis supported by networked glucose meter technology provides detailed inpatient data that could enable local benchmarking for promoting safe diabetes care in Australian hospitals.

Diabetes is emerging as one of the greatest health care challenges of the 21st century. In 2014, more than 1.2 million Australians had been diagnosed with diabetes,[1] and the number was expected to double during the following decade.[2] Diabetes increases the likelihood of needing hospital care;[3] 25–30% of inpatients have diabetes,[4] and a further 5–10% have undiagnosed diabetes.[5,6] The direct and indirect costs of diabetes in Australian adults were nearly $11 billion in 2005;[7] inpatient care is a major contributor to the overall costs of diabetes in the United States.[8]

Although the importance of long term glycaemic control is recognised, that of acute glycaemic control during a hospital stay is often underappreciated. Acute hyperglycaemia in hospital is linked with hospital-acquired infections because of the associated neutrophil and macrophage dysfunction, as well as with cardiovascular and renal disease secondary to pro-thrombotic changes, osmotic diuresis, and endothelial dysfunction.[9,10] Similarly, acute hypoglycaemia in hospital can lead to neuroglycopenia, causing seizures, falls, and neurological injury, as well as cardiac ischaemia and arrhythmia.[11] Adverse glycaemia is a term used to describe both hyperglycaemia and hypoglycaemia; both are associated with pathophysiology and adverse clinical outcomes,[12] and optimising glycaemic control in hospital patients is essential.[13] Glucometric reporting and benchmarking standards for optimal diabetes care, however, have not been standardised in Australian hospitals.

The National Safety and Quality Health Service (NSQHS) has published standards for Australian hospitals for reporting and benchmarking important adverse outcomes in hospital, including staphylococcal blood stream infections, falls, and pressure injuries.[14] A key recommendation in the Australian National Diabetes Strategy 2016–2020[15] was that the NSQHS standards be expanded to encompass diabetes care for hospital patients. Auditing and benchmarking of glucose control in inpatients is receiving increasing attention around the world,[16] and hospital glucometrics have been developed for systematically analysing and reporting inpatient glucose data[17] and assessing diabetes management programs.[18]

Efficient acquisition of point-of-care blood glucose (BG) measurements is essential for glucometric assessment, but has been limited in Australia by the lack of automated technologies for capturing patient-level glucose data. Glucose monitoring in Australian hospitals typically involves nurses performing bedside capillary glucose measurements with point-of-care glucose meters and manually recording the results on paper observation charts or in electronic clinical records. Although data from glucose meters can be downloaded manually, BG measurements are not linked with unique patient identifiers, making patient-level analysis impossible. Investigations of inpatient glucose control have therefore required labour-intensive manual auditing of clinical records.[19]

Networked glucose meters have recently become available in Australia, enabling electronic capture of patient BG measurements, with the data readily available in searchable databases. Networked meters have facilitated hospital-wide glycaemic management programs[18] and inter-hospital benchmarking of glucose control in the US.[20] As this approach will be important

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for establishing standards of diabetes care in Australian hospitals, we undertook detailed glucometric assessments of consecutive inpatients at a major metropolitan hospital, with the aim of reporting glucometric outcomes and the incidence of hypo- and hyperglycaemia.

Methods

We undertook an observational study in the non-critical care wards of a tertiary referral hospital, the Royal Melbourne Hospital. We installed thirty networked blood glucose meters (StatStrip, Australasian Medical and Scientific [AMSL]) in eight wards during January 2016; the installation was accompanied by a comprehensive staff education program. The meters were connected to the hospital information system and the Health Level 7: Admission, Discharge and Transfer (HL7-ADT) messaging system for instant transfer of patient information and glucose data. The patient unique record number and time of measurement were recorded with each point-of-care BG measurement, allowing analysis of patient-level glucose data.

Inpatient diabetes care in our hospital is primarily the responsibility of the medical officers of the admitting unit; a diabetes referrals team is available for consultations on a formal referral basis. Patients are treated with various combinations of glucose-lowering medications and insulin as appropriate. At the time of the study, the hospital had guidelines for inpatient diabetes management, but no dedicated insulin prescription charts or order sets. Patients with diabetes routinely had four capillary BG measurements each day (before each meal and before going to bed).

Participants

We included consecutive inpatients with pre-existing diabetes or newly detected hyperglycaemia (patients with random capillary BG levels exceeding 11.1 mmol/L but without a history of diabetes) admitted to a study ward during the 10-week study period (7 March – 22 May 2016). The eight study wards included two general medical, two general surgical, and single cardiology, neurology, neurosurgery, and orthopaedic surgery wards (a total of 220 beds, or 50% of all acute non-critical care beds); the patients were thus representative of the non-critical care hospital population. We excluded patients hospitalised for less than 24 hours and those receiving palliative care. Patients were identified and included prospectively at admission, and patient- and admission-related data were extracted from progress notes, discharge summaries, and pathology systems after their discharge.

Glucometric outcomes

We analysed point-of-care BG measurements for each patient from ward admission until discharge. We excluded BG measurements after admission day 14 (to avoid skewing by data from the few patients with prolonged hospital stays), BG measurements during intensive care admissions or intravenous insulin infusions, and closely repeated measurements following episodes of hypoglycaemia or hyperglycaemia, as previously described.[21]

We assessed glycaemic control with the glucometric models described by Goldberg and colleagues:[17]

- by population: all BG measurements for all patients were included and equally weighted;
- by patient stay: all BG measurements during the hospital stay of a patient were aggregated and weighted equally, irrespective of length of stay;

1 Characteristics of the 441 patients with pre-existing diabetes or newly detected hyperglycaemia admitted to the eight study wards

Characteristics: patients	
Total number of patients	441
Age (years), mean (SD)	70 (15)
Sex (men)	247 (56%)
Modified Charlson comorbidity score,* median (IQR)	2 (0–3)
Diabetes type	
Type 2 diabetes	383 (87%)
Type 1 diabetes	19 (4%)
Other (including pancreatogenic and steroid-induced)	15 (3%)
Newly detected hyperglycaemia	24 (5%)
Diabetes treatment prior to admission	
Diet only	99 (23%)
Glucose-lowering medications only†	212 (48%)
Insulin	130 (29%)
Glycated haemoglobin (HbA_{1c}) (mmol/mol), median (IQR)	54 (45–65)
Estimated glomerular filtration rate (mL/min/1.73 m^2) (admission)	
≤ 30	49 (11%)
31–59	139 (32%)
60–89	139 (32%)
≥ 90	104 (24%)
Missing data	10 (2%)
Characteristics: admissions	
Total number of admissions	465
Admission to medical unit	293 (63%)
General medicine	117 (25%)
Cardiology	71 (15%)
Neurology and stroke	49 (11%)
Respiratory	21 (4%)
Gastroenterology	22 (5%)
Other medical	13 (3%)
Surgical unit	172 (37%)
General surgery	70 (15%)
Neurosurgery	49 (11%)
Orthopaedic and trauma	47 (10%)
Other surgical	6 (1%)
Elective admission	59 (13%)
Length of stay (days), median (IQR)	5 (3–9)
Insulin treatment during hospital admission	
No insulin	216 (46%)
Basal (with or without prandial insulin)	105 (23%)
Pre-mixed insulin	59 (13%)
Supplemental insulin only	85 (18%)
Glucocorticoid treatment‡	74 (16%)
Managed by inpatient diabetes team	48 (10%)

IQR = interquartile range; SD = standard deviation. * Items related to diabetes excluded. † Including glucagon-like peptide-1 agonists. ‡ Treatment with glucocorticoid medications (dose equivalent: at least 7.5 mg prednisolone) for at least 24 hours. ◆

- by patient-day: BG measurements were grouped by each calendar day for each patient, and the key glucometric measure is the patient-day mean glucose level (mean glucose measurement per patient per calendar day).

We compared the glucometric outcomes with a US benchmark based on all BG measurements for the more than 2.4 million people admitted to 635 hospitals during the 2012 calendar year,[20] and with United Kingdom National Diabetes Inpatient Audit (NaDIA) data for 15 774 people with diabetes admitted to 209 hospitals during a single day in 2016.[16]

In addition, we evaluated a novel measure of inpatient glucose control: the adverse glycaemic day (AGD), defined as a patient-day for which the BG level was below 4.0 mmol/L or above 15.0 mmol/L, extremes that should be avoided in hospital patients.[22] The incidence of AGDs (per 1000 patient-days) is reported, and is the converse of the "good diabetes day" (patient-day without hypoglycaemia and no more than one measurement exceeding 11 mmol/L) used by NaDIA.[16] We compared AGD incidence for medical and surgical patients, and evaluated the temporal distribution of hypoglycaemia or severe hyperglycaemia across the day. Differences between groups were assessed in non-parametric tests, Fisher exact tests, or χ^2 tests, conducted in Minitab 17.2.1 (Minitab).

Ethics approval

The investigation was approved by the Melbourne Health Human Research Ethics Committee (reference, 2015.126), with a waiver of the requirement for individual patient consent.

Results

During the 10-week study period, there were 465 consecutive admissions of 441 patients with diabetes or newly detected hyperglycaemia; 22 people were admitted twice, one person was admitted three times. Most patients had type 2 diabetes (383, 87%); 130 (29%) had been treated with insulin prior to admission. Patients were treated with insulin during 249 admissions (54%) and with glucocorticoid medications during 74 admissions (16%). The median length of hospital stay was 5 days (interquartile range, 3–9 days) (Box 1).

Primary glucometric outcomes

A total of 9817 BG measurements were made over 2953 patient-days; the mean number of BG observations was 21 (standard deviation [SD], 16) per patient stay, and 3.3 (SD, 1.7) per patient-day. A total of 394 patients (85%) had at least one measurement exceeding 10 mmol/L and 206 (44%) had at least one exceeding 15 mmol/L during their stay; 75 people (16%) had at least one episode of hypoglycaemia (BG < 4 mmol/L) and 27 (5.8%) episodes of severe hypoglycaemia (BG < 3 mmol/L). The mean BG level by patient stay was 9.5 mmol/L (SD, 2.8 mmol/L) (Box 2).

In the patient-day analysis, the mean patient-day glucose level was 9.5 mmol/L (SD, 3.3 mmol/L). The mean BG level exceeded 10 mmol/L for 1083 (37%) and 15 mmol/L for 216 patient-days (7.3%); hypoglycaemia and severe hypoglycaemia were respectively recorded for 136 (4.6%) and 38 (1.3%) patient-days (Box 2).

Adverse glucometric days

The overall incidence of AGDs was 260 per 1000 patient-days (95% confidence interval [CI], 245–277 per 1000 patient-days); of the 769 AGDs, 633 (82%) were related to hyperglycaemia, 113 (15%) to hypoglycaemia, and 23 (3%) to both. There were no AGDs for half the patient admissions (228 of 465); the 121 patients (26%) with one or two AGDs accounted for 165 (21%) of all AGDs, while the 116 patients (25%) who had three or more AGDs accounted for 604 (79%). AGDs were more frequent among medical than surgical ward patients (290 [95% CI, 270–310] *v* 205 [95% CI, 181–230] AGDs per 1000 patient-days) (Box 3, A).

The patient-day mean BG level was also higher for medical than surgical patients (9.7 mmol/L [SD, 3.5 mmol/L] *v.* 9.2 mmol/L [SD, 3.0 mmol/L] (Box 3, B). The median number of comorbid conditions was higher for medical than surgical patients, and the distribution of estimated glomerular filtration rates at admission was shifted to lower values; glucocorticoid treatment during admission was more frequent among medical ward patients (20% *v* 9%) (Box 4).

Diurnal distribution of episodes of hypo- and hyperglycaemia

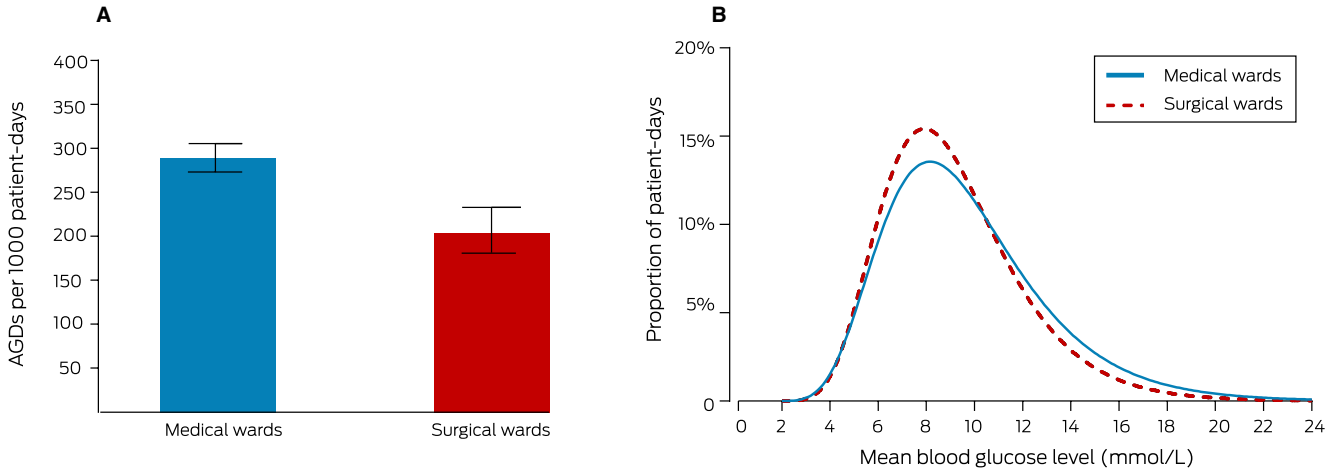
Hyperglycaemia was most frequent during the day, with three peaks before lunch, dinner, and bedtime, coinciding with three

2 Glucometric data for 441 patients (465 admissions) with pre-existing diabetes or newly detected hyperglycaemia admitted to the eight study wards

	Model		
	By population	By patient stay	By patient-day
Number of samples	9817	465	2953
Blood glucose observations per unit, mean (SD)	9817	21 (16)	3.3 (1.7)
Blood glucose level (mmol/L), mean (SD)	9.9 (4.3)	9.5 (2.8)	9.5 (3.3)
Mean blood glucose level > 10 mmol/L	NA	171 (37%)	1083 (37%)
Mean blood glucose level > 15 mmol/L	NA	27 (5.8%)	216 (7.3%)
Any measurement < 4 mmol/L	187 (1.9%)	75 (16%)	136 (4.6%)
Any measurement < 3 mmol/L	47 (0.5%)	27 (5.8%)	38 (1.3%)
Any measurement > 10 mmol/L	3945 (40%)	394 (85%)	1672 (57%)
Any measurement > 15 mmol/L	1254 (13%)	206 (44%)	656 (22%)
Adverse glycaemia (< 4 mmol/L or > 15 mmol/L)	1441 (15%)	237 (51%)	769 (26%)

NA = not applicable; SD = standard deviation. ◆

3 Glycaemic control in patients admitted to medical and surgical units. A. Patient-days with any blood glucose measurement below 4 mmol/L or above 15 mmol/L), with 95% confidence intervals. B. Distribution of patient-day mean blood glucose level measurements



of the peak times for BG measurements. Hypoglycaemia was most frequent overnight, before breakfast, and before dinner (Box 5). BG measurements were performed between 11 pm and 8 am on 2217 (75%) of patient-days; 94 of 187 hypoglycaemic episodes (50%) were during this period.

Discussion

Benchmarking of key hospital clinical outcomes is essential for improving the quality of care and patient safety. We anticipate that our detailed study of glucometric outcomes in an Australian hospital will initiate a systematic approach to auditing and benchmarking glycaemic control in Australia.

Our patient-day mean glucose level was marginally higher than for the US hospital benchmark[20] (9.5 mmol/L *v* 9.3 mmol/L); the incidence of hyperglycaemia was higher (37% *v* 32%), but that of hypoglycaemia lower (4.1% *v* 6.1%) in our sample (Box 6). The patients in the British NaDIA had similar characteristics to our patients (90% with type 2 diabetes, 29% treated with insulin prior to admission);[16] the incidence of hypoglycaemia was, however, lower in our group: BG level under 4 mmol/L, 16% *v* 20%; BG level below 3 mmol/L, 5.8% *v* 8.4%. As NaDIA does not collect detailed glucometric data, comparing the incidence of hyperglycaemia with our findings was not possible.

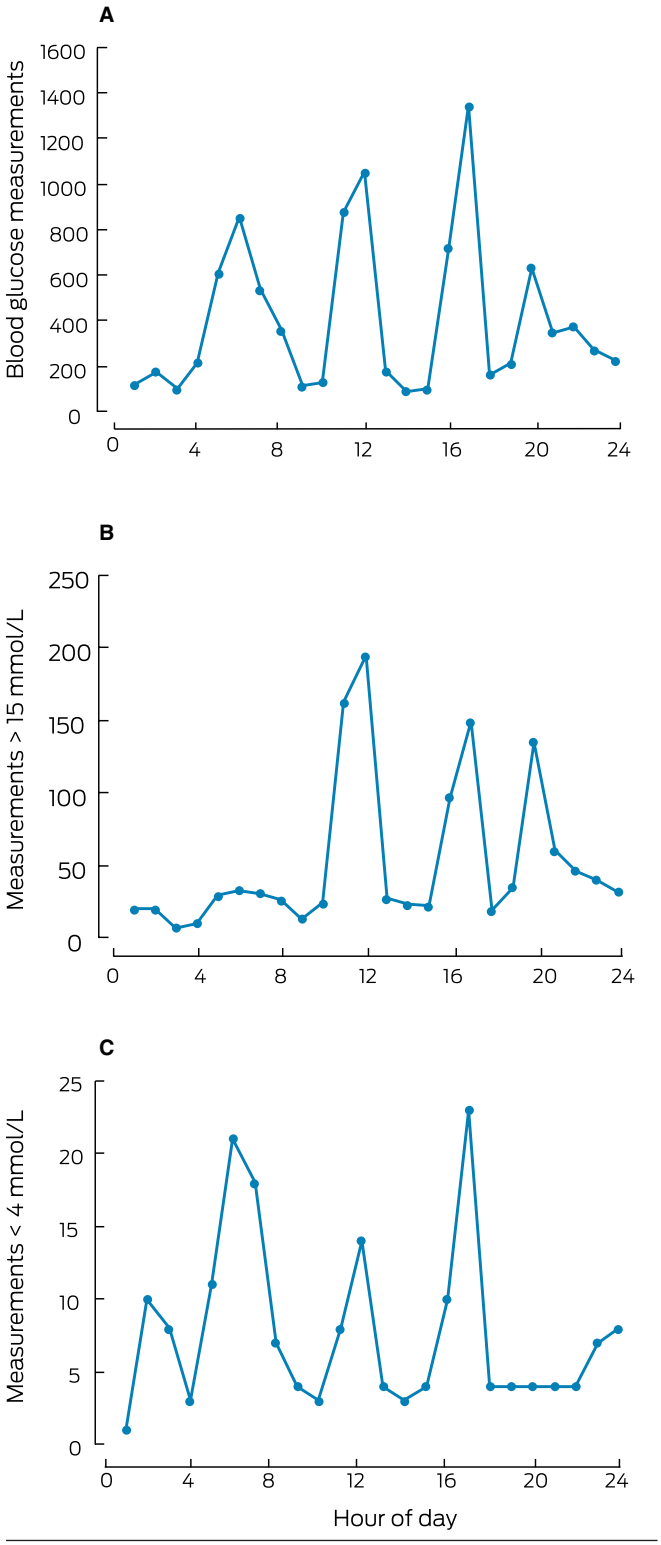
Comparisons with the American benchmark may be limited by differences in patient selection and hospital management practices. The US benchmarking study, despite comprehensive glucose data, did not include patient-level clinical information,[20] so it was not possible to ascertain whether the characteristics of the Australian and American cohorts were similar. We included patients with diabetes or newly detected hyperglycaemia, whereas the US benchmarking study included all patients whose blood glucose levels were monitored, including for reasons unrelated to diabetes. Further, we did not include all patients with diabetes in our study, excluding, for example, those admitted as nephrology or cardiothoracic surgery patients. These differences may restrict the direct comparison of glucose outcomes. Further, like most Australian hospitals, our hospital has not adopted basal–bolus insulin treatment for all inpatients with diabetes, an approach that is widely promoted in the US. The incidence of hyperglycaemia among our patients was similar to that found by a study in western Sydney,[19] but the glucometric outcomes in Australian hospitals that regularly employ basal–bolus insulin treatment[23,24] may be more comparable with those of American hospitals. In the absence of standardised glucometric analyses by Australian hospitals, this question remains open, but we have shown that glucometric analysis and benchmarking is possible in an Australian hospital.

4 Patient and treatment characteristics for medical and surgical ward patients

	Medical wards	Surgical wards	*P**
Number of patients	282	159	
Age (years), mean (SD)	72 (15)	68 (14)	0.008
Sex (men)	155 (55%)	92 (58%)	0.62
Modified Charlson comorbidity score,† median (IQR)	2 (1–4)	1 (0–2)	< 0.001
Patients with type 2 diabetes	246 (87%)	137 (86%)	0.77
Insulin treatment prior to admission	89 (32%)	41 (26%)	0.23
Glycated haemoglobin (HbA_{1c}) level (mmol/mol), median (IQR)	54 (45–67)	52 (44–61)	0.12
Estimated glomerular filtration rate (mL/min/1.73 m^2) (admission)			< 0.001
≤ 30	39 (14%)	9 (6%)	
31–59	98 (36%)	41 (26%)	
60–89	88 (32%)	51 (33%)	
≥ 90	49 (18%)	55 (35%)	
Glucocorticoid treatment‡	55 (20%)	14 (9%)	0.002
Managed by inpatient diabetes team	26 (9%)	20 (13%)	0.33

IQR = interquartile range; SD = standard deviation. * Kruskal–Wallis test for continuous variables, Fisher exact or χ^2 tests for categorical variables. † Items related to diabetes excluded. ‡ Treatment with glucocorticoid medications (dose equivalent: at least 7.5 mg prednisolone) for at least 24 hours. ◆

5 The diurnal distribution of blood glucose measurements (A), blood glucose measurements exceeding 15 mmol/L (B), and blood glucose measurements below 4 mmol/L (C)*



* Meals are routinely provided at 8 am (breakfast), noon (lunch), and 5 pm (dinner); bedtime is usually at 9 pm. ◆

6 Glucometric data (patient-day model) for our sample of patients and for the United States hospitals benchmark[19]

	Our sample*	US hospital benchmark†	P‡
Number of patient admissions	465	2.4 million	
Number of patient-days	2953	about 17 million	
Blood glucose (mmol/L), mean (SD)	9.5 (3.3)	9.3 (0.8)	0.001
Hyperglycaemia			
Mean glucose > 10.0 mmol/L (> 180 mg/dL), patient-days	1083 (37%)	32.3%	< 0.001
Mean glucose > 13.9 mmol/L (> 250 mg/dL), patient-days	314 (11%)	7.4%	< 0.001
Mean glucose > 16.7 mmol/L (> 300 mg/dL), patient-days	110 (3.7%)	2.3%	< 0.001
Hypoglycaemia			
Glucose < 3.9 mmol/L (< 70 mg/dL), patient-days	120 (4.1%)	6.1%	< 0.001
Glucose < 2.8 mmol/L (< 50 mg/dL), patient-days	26 (0.9%)	1.7%	< 0.001

SD = standard deviation. * Consecutive patients with diabetes admitted to non-critical care wards over 10 weeks. † Consecutive patients admitted to non-critical care wards (635 hospitals) over one calendar year. ‡ Kruskal–Wallis test for continuous variables, Fisher exact test for categorical variables. ◆

Optimal glycaemic management requires a balance between reducing hyperglycaemia and avoiding hypoglycaemia, and a complete glucometric analysis therefore concurrently assesses and reports both conditions. The traditional glucometric outcome of patient-day mean BG level does not reflect the two extremes; further, a lower mean BG level may not reflect safer glycaemic control if the hospital rate of hypoglycaemia is also high. Accordingly, the AGD, encompassing both hyperglycaemia and hypoglycaemia, could become an important index of glycaemic control and a useful concept for educating health professionals about unsafe glycaemia in hospital patients. Guidelines for inpatients recommend avoiding BG levels below 4 mmol/L or above 10 mmol/L, but the level of the upper threshold depends on the clinical context.[13] We chose 15 mmol/L because it pragmatically defined an unsafe hyperglycaemic extreme that should generally be avoided, regardless of clinical context, but does not require aggressive treatment that could increase the risk of hypoglycaemia. The impact of hospital diabetes care quality improvement programs can be assessed with the AGD concept; a recent cluster randomised trial found that AGD incidence, as a primary outcome measure, was reduced by an early intervention model of inpatient diabetes care.[25]

The incidence rate of 260 AGDs per 1000 patient-days indicates excursions of BG levels into the unsafe extreme ranges for a substantial proportion of patient-days. The incidence was higher for medical than surgical patients, perhaps reflecting greater complexity of their diabetes and hospital treatment. The peak periods for hyperglycaemia were before lunch, dinner and bedtime, suggesting that the prandial insulin regimen was inadequate; more standardised insulin treatment at meal times could reduce the incidence of hyperglycaemia. In contrast, hypoglycaemia was more frequent overnight, as also reported by another study.[26] This suggests that insulin and sulphonylurea treatment should be employed at night with caution, and that carbohydrate snacks at bedtime might be helpful, especially for people with risk factors for hypoglycaemia. Further, as one-quarter of patients contributed 81% of AGDs, management strategies should

focus on identifying and targeting this subset of individuals at greater risk of glycaemic extremes.

Networked glucose meter technology was fundamental to our study, as it facilitated the automated collection of complete patient-level, point-of-care BG data. Its implementation required multidisciplinary cooperation between nursing, medical, diabetes education, information technology, and biomedical engineering teams. Glucometric assessment might be possible without networked meter technology, but it would require more resources, and incomplete or inaccurate data would be more likely. Most importantly, networked meters contribute to improved glycaemic and clinical outcomes by enabling remote surveillance of BG measurements and proactive glycaemic management programs.[12,18,25]

Conclusion

Auditing and benchmarking BG outcomes in hospital patients is essential for improving glycaemic control and ultimately for improving patient outcomes. We undertook a detailed glucometric study of consecutive inpatients in an Australian hospital that was supported by point-of-care networked glucose meter technology. We propose that AGD incidence is a suitable measure of safe glucose control in hospital patients for future benchmarking. With the increasing availability of networked glucose meters, more health services in Australia will be able to implement this technology for local auditing and benchmarking of safe diabetes care for hospital patients.

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CHAPTER FIVE:

EARLY INTERVENTION FOR DIABETES IN MEDICAL AND SURGICAL INPATIENTS: A CLUSTER RANDOMIZED TRIAL (RAPIDS)

5.1 Introduction

To overcome clinical inertia and increase diabetes specialist management for noncritical care inpatients, a comprehensive early intervention model of diabetes care was developed. Termed "Proactive Inpatient Diabetes Service", this early intervention model of diabetes care comprised three components:

1) Networked glucose meters enabling remote electronic surveillance of capillary glucose meter
2) Glucose alert system to increase health professional response to adverse glycaemia and facilitate escalation to inpatient diabetes team (chapter 3);
3) Proactive inpatient diabetes team which identified all patients with diabetes and hyperglycaemia and provided proactive model of care, and direct management within 24 hour of admission to hospital

This model was investigated in a prospective cluster randomised trial to address the gap prospective randomised evidence on models of inpatient diabetes care. The study was designed to evaluate various levels of outcomes including processes of care, glycaemia and clinical outcomes. This study was named **Ra**ndomised study of a **P**roactive **I**npatient **D**iabetes **S**ervice (RAPIDS), and was prospective registered with the Australia New Zealand Clinical Trials Registry (ANZCTR).

5.2 Manuscript

The work presented in this chapter has been published in the peer-reviewed journal Diabetes Care. The citation is:

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Early intervention for diabetes in medical and surgical inpatients decreases hyperglycemia and hospital-acquired infections: a cluster randomized trial

Running title: early intervention for diabetes in hospital

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Abstract

Objective: To investigate if early electronic identification and bedside management of inpatients with diabetes improves glycemic control in non-critical care.

Research Design and methods: We investigated a proactive or early intervention model of care (whereby an inpatient diabetes team electronically identified individuals with diabetes and aimed to provide bedside management within 24-hours of admission), compared to usual care (a referral-based consultation service). We conducted a cluster randomized trial on eight wards, consisting of a 10-week baseline period (all clusters received usual care) followed by a 12-week active period (clusters randomized to early intervention or usual care). Outcomes were adverse glycemic days (AGD: patient-days with glucose <4or>15mmol/L [<72or>270mg/dL]) and adverse patient outcomes.

Results: We included 1002 consecutive adult inpatients with diabetes or new hyperglycemia. More patients received specialist diabetes management (92% vs. 15%, p<0.001), and new insulin treatment (57% vs. 34%, p=0.001) with early intervention. At the cluster level, incidence of AGD decreased by 24%, from 243 to 186 per 1000 patient-days in the intervention arm (p<0.001), with no change in the control arm. At the individual level, adjusted number of AGD per-person decreased from mean 1.4(sd. 1.6) to 1.0(0.9) days (-28% change, 95%CI -45 to -11%, p=0.001) in the intervention arm, but did not change in the control arm [1.8(2.0) to 1.5(1.8), -9% change, CI -25 to +6%, p=0.23]. Early intervention reduced overt hyperglycemia (55% decrease in patient-days with mean glucose >15mmol/L, p<0.001), and hospital-acquired infections (odds ratio 0.20 [CI 0.07 to 0.58], p=0.003).

Conclusions: Early identification and management of diabetes inpatients decreased hyperglycemia and hospital-acquired infections.

Hyperglycemia and hypoglycemia are common events in hospital and are associated with adverse patient outcomes (1; 2). Acute hyperglycemia is independently associated with hospital-acquired infections, longer length of stay and greater mortality (1; 3). Multiple cellular and physiological mechanisms are implicated, particularly neutrophil and endothelial dysfunction, osmotic diuresis and pro-inflammatory changes (4). Treating hyperglycemia may improve clinical outcomes in the critical care (5), stroke care (6), and non-critical care settings (7). However, aggressive treatment of hyperglycemia can lead to hypoglycemia (7-9), which causes undesirable symptoms and adverse outcomes. Thus, a key target of inpatient diabetes care should be to avoid the glycemic extremes of both hyperglycemia and hypoglycemia, also described as adverse glycemia (10). Despite published guidelines on ideal blood glucose (BG) targets (11-13), glycemic control remains challenging due to multiple obstacles, and system-based solutions are needed (14).

As most inpatients with diabetes are managed by hospitalists or parent (admitting) teams, diabetes specialists are seldom involved in their care. Many hospitals have implemented specialized inpatient diabetes teams (or glycemic management teams) to develop protocols, deliver education programs, and perform clinical audits, in addition to directly assisting in diabetes management. These teams usually consist of specialized diabetes nurses and diabetologists who provide management advice in response (or reactive) to referrals from the parent team (15-18). However, referrals to inpatient diabetes teams may be inconsistent due to clinical inertia (19).

A more proactive model of diabetes care can be delivered by a diabetes team which autonomously provides early assessment and management without referral from the admitting team (20). Availability of networked BG meters (which electronically capture capillary BG measurements) has enabled remote electronic surveillance of glycemic control. Proactive models of care utilizing networked BG meters have demonstrated improved glycemic control in observational studies (21-23), but randomized studies are lacking (14). Therefore, we investigated the effect of early intervention, using a proactive model of inpatient diabetes care, on glycemic and clinical outcomes in a prospective cluster-randomized study.

Methods

Study design and participants

Randomized study of a Proactive Inpatient Diabetes Service (RAPIDS) is an open-label, cluster-randomized controlled study with a baseline period, conducted over six months at the Royal Melbourne Hospital (tertiary-referral hospital affiliated with the University of Melbourne). The intervention was implemented at the cluster level. Outcomes were assessed at both the cluster and individual levels.

There were eight wards (clusters) involved in the study, comprising four medical wards (cardiology, neurology and two general medicine) and four surgical wards (orthopedic surgery, neurosurgery, abdominal surgery and emergency surgery). The two general medical wards contained patients with similar characteristics and can be considered as sister (symmetrical) wards, however the remaining six wards had unique parent teams and patient characteristics.

We included consecutive adult inpatients admitted over the study period, with pre-existing diabetes or new hyperglycemia (random capillary BG>11.1mmol/L [>200mg/dL] without a history of diabetes), with more than

one day length of stay. Individuals admitted with glycemic emergencies, or those admitted under Endocrinology or Palliative Care teams were excluded. For individuals who were admitted more than once during the study period, only the first admission was included. The study was approved by Melbourne Health Human Research Ethics Committee with the waiver of individual consent and registered prospectively with Australian New Zealand Clinical Trials Registry (ACTRN12616000265471).

Procedures, randomisation and masking

Prior to the commencement of the study, we implemented networked BG meters (StatStrip®, Australasian Medical and Scientific Limited) on the study wards. These devices have recently become available in Australia, and facilitated accurate collection of capillary BG data and remote identification of inpatients with diabetes.

At commencement of the study, and prior to randomisation, there was a 10-week baseline period where all eight clusters received usual care. The clusters were then randomized 1:1 into control and intervention arms, stratified by type of ward (medical or surgical) using a random number generator by a blinded statistician. A 12-week active period then followed, where the four clusters randomized to the intervention arm received the proactive, early management model of care, and the four clusters randomized into the control arm continued with usual care (Supplemental figure 1). Treating staff and patients were not masked to the allocation of clusters to intervention or control arms.

Usual inpatient diabetes management (usual care)

Diabetes management is performed primarily by the hospital medical officers of the parent team. A specialist inpatient diabetes team (IDT), consisting of a diabetes nurse and endocrinology fellow supervised by a diabetologist, provided a consultation service in response (or reactive) to referrals from the parent unit. Our institution had guidelines and protocols on inpatient diabetes management, but did not have insulin order sets or an electronic medical record for delivering inpatient care; therefore, written BG observation charts and medication orders at the bed-side were used. In accordance with local practice in Australia, United Kingdom and Europe, there is no standardized algorithm of discontinuing oral antidiabetic medications and routine prescription of a subcutaneous basal-bolus insulin regimen in all individuals with diabetes admitted to hospital.

Early intervention (proactive model of care)

The specialist IDT identified all consecutive inpatients with diabetes or hyperglycemia, and aimed to provide diabetes management within 24 hour of admission, without referral from the parent team. The IDT performed electronic surveillance of capillary BG measurements captured by networked BG meters which enabled early identification of inpatients with diabetes and ongoing electronic surveillance of glucose control. In addition, a structured clinical escalation pathway (Melbourne Glucose Alert Pathway) (10) was implemented on the intervention wards to encourage clinical escalation of patients with dysglycemia to the IDT.

Prior to the intervention, the IDT undertook four training modules delivered by a senior diabetologist. Aimed at upskilling the team, training modules included insulin initiation guidelines and case-based discussions focussed on optimizing glycemic control. During consultations, the IDT prescribed subcutaneous insulin and glucose lowering medications in an individualized manner, aiming to achieve safe glycemic control and avoiding glycemic extremes. The IDT consultations occurred daily, with insulin dose titration depending on clinical need. The IDT

optimized long-term diabetes control by intensifying or de-escalating diabetes treatment at the time of discharge, depending on admission HbA1c (24). The IDT regularly interacted with the parent teams' medical and nursing staff providing an opportunity for ward-based education on inpatient diabetes management. A weekly audit meeting was led by a senior diabetologist, to discuss patient care and monitor outcomes. The proactive IDT operated during weekdays with an on-call endocrinologist available for advice after hours and on weekends. During the active period, the same IDT provided proactive care in the intervention wards and consultation service in response to referrals (usual care) in the control wards.

Data collection

A researcher independent of the IDT performed surveillance of capillary BG measurements to identify eligible patients. Patient information and clinical outcomes were collected from inpatient progress notes, pathology results system, and the patient administration database. Point-of-care BG measurements were collected by networked BG meters. BioViewer (© Bio-Asia Diagnostics) data manager was used to obtain BG measurements from day 1 of admission until discharge. BG measurements from day 0 were excluded, as glycemic control on the day of admission is influenced by treatment prior to admission, or in the emergency department, rather than ward management. BG measurements were excluded after day 14 of admission to avoid skewing of BG data by the few individuals with prolonged hospital stay. In addition, we applied the glucometric technique to exclude repeated measurements from a single episode of hypo- or hyperglycemia as described by Weinberg et al (25).

Outcomes measures

The primary outcome was Adverse Glycemic Day (AGD) defined as a patient-day with any BG <4 or >15mmol/L (<72 or >270mg/dL). These pragmatic BG cut off points were used to define AGD as the aim of this trial was for 'safe' glycemic control rather than 'tight' glycemic control. Although a target random BG <10mmol/L (<180mg/dL) is recommended in the non-critical care, this target is not based on strong experimental evidence and the target may vary depending on the individual's comorbidities (13). However, BG >15mmol/l (>270mg/dL) may be associated with adverse pathophysiology (4), and should be avoided in most inpatients. Similarly, any degree of hypoglycemia (even BG <4mmol/L [<72 mg/dL]) in inpatients with complex comorbidities and concurrent illness is undesirable and should be avoided. Therefore, the AGD outcome reflects glycemic extremes that should be avoided for safe diabetes management in hospital (26). At the cluster level, the incidence of AGD is reported per 1000 observed patient-days; and at the individual level, the number of AGD per person is reported. As BG measurements were excluded after day 14 of admission, each individual contributed to a maximum of 14 observed patient-days.

The pre-specified secondary outcomes were process-of-care measures, glucometric measures, adverse patient outcomes, and length of stay. Adverse outcomes were analysed individually and as a composite of five items and included: hospital-acquired infections, acute kidney injury, acute myocardial infarct, unplanned critical care admission and in-hospital mortality. These outcomes were included as they were commonly associated with poor glycemic control (27). Hospital-acquired infection was defined as clinical or microbiological evidence of skin wound or surgical site infection, urinary tract infection, bacteremia or pneumonia that developed at least 48 hours after admission. Acute kidney injury was defined as rise in serum creatinine by more than 50% from admission, or the need for acute renal replacement therapy. Myocardial infarction was defined as new ischemic changes on

electrocardiogram and a rise in troponin that developed at least 48 hours after admission. The adverse patient outcomes were adjudicated by an independent assessor who was blinded to the treatment group allocation.

Statistical analysis

The primary outcome of AGD was analysed at the cluster level (proportion of the total number of AGD divided by the total number of observed days and reported as a rate per 1000 patient-days); and at the individual level (the number of AGD per patient). The number of AGD per patient was adjusted for patient covariates (age, gender, modified Charlson comorbidity index, creatinine, HbA1c, diabetes type, insulin treatment prior to admission); and hospital treatment covariates (number of days observed, admission unit, type of admission, type of ward) as fixed effects, and wards (clusters) as random effect using a mixed-effect Poisson regression model (supplemental table S1). The adjusted number of AGD per patient was then calculated using the predict function from the regression. We expected differences in patient characteristics between control and intervention arms due to enrolling clusters with unique clinical services. However, we expected well-matched patient characteristics between baseline and active periods within each treatment arm. Therefore, we planned to analyse the outcomes between treatment arms, and as a change from baseline within each treatment arm. To enable this analysis, we created four distinct groups depending on treatment arm (control vs. intervention) and time period (baseline period vs. active period). The four groups (control-baseline period, control-active period, intervention-baseline period, and intervention-active period) were used as a factor in the mixed-effect regression model to allow simultaneous comparison between treatment arms, and as a change between baseline and active periods within each treatment arm.

Hospital-acquired infections were analysed using a mixed effects logistic regression model adjusting for covariates (post-hoc analysis). All analyses were performed using intention-to-treat approach, therefore if an individual crossed over treatment arms due to ward transfers, they were analysed in the initial treatment arm that was in place when first admitted. If an individual was transferred out of the study wards to a non-study ward in the hospital, subsequent BG measurements from the time of transfer were excluded, but clinical outcomes and hospital length of stay for the entire hospitalisation were analysed.

This study was designed as a 24-week trial (the feasible duration of the study), recruiting consecutive inpatients. The power calculation was performed prospectively and estimated the minimum difference in AGD that can be detected, given the expected number of patient recruitment. A previous pilot study showed that the incidence of AGD was 300 per 1000 patient-days at our institution (10). On the eight wards, we expected to recruit 600 individuals during baseline and 600 individual during active periods with a median of 3.5 observed days per patient. This entailed 300 patients and 1050 patient-days per treatment arm during the active period. For four clusters in each arm, using 0.01 intraclass correlation, and two-sided alpha of 0.05, this study had over 80% power to detect a 33% change in AGD. Analyses were performed using STATA15 (StataCorp LLC, College station, TX, USA).

Results

There were 1019 unique patient admissions to the eight study wards between March and August 2016. After exclusion, the final sample comprised of 1002 individuals equally distributed across the study arms (Figure 1). Overall, 87% of the cohort had type 2 diabetes, mean HbA1c 58 (sd 18) mmol/mol [7.5 (1.7)%], and 30% were treated with insulin prior to admission. Patients were observed for a median of 4 (IQR: 2 to 8) days and had 3.5 (1.7) capillary BG measurements per patient-day.

There were differences in patient characteristics between control and intervention arms. Compared to the control arm, the intervention arm had a higher proportion of individuals with surgical and emergency admissions. The intervention arm had a lower proportion of patients with insulin treatment prior to admission, and a lower mean HbA1c (Table 1). However, patient characteristics were well-matched between the baseline and active periods within each treatment arm. There were more emergency admissions during the active period compared to the baseline period in the intervention arm.

Early identification and management improved process of care outcomes (Figure 2). In the intervention arm, (1) the proportion of patients managed by the IDT increased from 8% during the baseline to 92% during the active period ($p<0.001$); (2) the proportion of patients managed within 24 hour of admission increased from 4% to 64%, ($p<0.001$); and (3) insulin treatment in insulin-naïve patients increased from 34% to 57%, ($p<0.001$). No changes were observed in the control arm.

Over the study period, 5447 patient-days were observed. At the cluster level, there was a 24% decrease in the incidence of AGD (243 vs. 186 per 1000 patient-days, $p<0.001$) in the intervention arm with a non-significant 9% decrease observed in the control arm (291 vs. 261 per 1000 patient-days, $p=0.09$). The decrease in incidence in the intervention arm (57 per 1000 patient-days) was significantly higher than decrease in the control arm (30 per 1000 patient-day), ($p=0.004$).

At the individual level, the adjusted number of AGD per patient decreased from mean 1.4 (sd 1.6) to 1.0 (0.9) days [-28% change, 95%CI (-45 to -11%), $p=0.001$] in the intervention arm, with a non-significant change in the control arm [1.8 (2.0) to 1.5 (1.8) days, -9% change, CI (-25 to +6%), $p=0.23$] (Table 2). Comparing parallel treatment groups during the active period, the number of AGD per patient was 23% lower (CI: 6 to 40%, $p=0.008$) in the intervention arm compared to control arm (supplemental table S1). Comparison between the two symmetrical general medical clusters demonstrated that the cluster randomized to the intervention arm had a significant reduction in AGD per patient [2.2(2.3) to 1.4(1.3) days, $p=0.010$], while the cluster randomized to the control arm had no significant change [2.0(2.5) to 2.1(2.6) days, $p=0.96$)] (Supplementary table S2).

On glucometric analyses, 19060 capillary BG measurements were observed during the study period. The patient-day mean glucose decreased from 9.4(sd 3.3) to 9.0(2.7) mmol/L [169(59) to 162(49)mg/dL], $p=0.003$, in the intervention arm but remained stable in the control arm, 9.6(3.2) to 9.5(3.2)mmol/L [173(58) to 171(58) mg/dL], $p=0.235$. The proportion of patient-days with mean BG >10 and >15mmol/L (>180 and >270 mg/dL), decreased by 14% and 55%, respectively in the intervention arm, with no change in the control arm (Table 2 and Figure 2). The proportion of 'good diabetes days' (patient-day with no BG <4 mmol/L[<72 mg/dL] and no more than one

BG >11mmol/L [198mg/dL]), a United Kingdom metric, (28) increased in the intervention arm (70% to 74%, p=0.020), but did not change in the control arm (65% to 66%, p=0.61). There was no change in the incidence of hypoglycemia in either of the treatment arms.

The proportion of individuals with hospital-acquired infections decreased from 6.4% to 2.4% (p=0.035) in the intervention arm but did not change significantly in the control arm (8.6% to 7.0%, p=0.61). Post-hoc analyses using mixed-effect logistic regression adjusting for covariates (supplemental table S3) demonstrated that early diabetes management conferred a lower risk of developing hospital-acquired infection (adjusted odds ratio: 0.20 (95% CI 0.07 to 0.58), p=0.003). Number needed to treat to prevent one hospital-acquired infection was 25. There was a strong correlation between number of AGD and hospital-acquired infection (each day increase in AGD conferred an odds ratio of 1.35 (95% CI 1.20, 1.51) for hospital-acquired infection). The reduction in infection rate remained consistent on subgroup analysis of only individuals with type 2 diabetes (supplemental table S4-S7). There was a higher baseline incidence of infections (hence greater reduction in infections) in medical compared to surgical patients (supplementary table S8). There were no differences in the remaining individual or composite clinical outcomes in either arm (Table 2).

Conclusions

RAPIDS is the first randomized trial to investigate the effect of comprehensive early intervention for all consecutive patients with diabetes to non-critical care wards, consisting of early electronic identification and bedside specialist IDT management. The RAPIDS study achieved its primary outcome of reducing adverse glycemic days, with no concomitant increase in hypoglycemia.

This study used the primary outcome of AGD (with a more liberal glycemic target), as an index of safe glycemic control in hospital, to achieve the balance of decreasing overt hyperglycemia, whilst minimising hypoglycemia. This is similar to the concept of ‘good diabetes day’ used in the annual National Inpatient Diabetes Audit in the United Kingdom (28). Although there is no published data investigating AGD and clinical outcomes, we propose AGD is a clinical index of both hyperglycemia and hypoglycemia events, as well as being a tangible concept for educating health professionals about safe glycemic control in hospital.

Early identification and management for diabetes decreased the number of AGD per patient by 28% in the intervention arm. There was a slight (but non-significant) 9% decrease in the control arm possibly related to contamination or a Hawthorne effect, but even after adjusting for this change, the intervention arm had a 23% lower number of AGD per person compared to control arm. In addition to AGD outcomes, traditional glucometric analyses also demonstrated improved glycemic control. With early identification and management, patient-day glucose was lower in both the mean (decreased by 0.4mmol/L [7.2mg/dL]), and the variance (standard deviation decreased by 0.6mmol/L [10.8mg/dL]). There was a 55% decrease in patient-days with mean glucose >15mmol/L. These findings are comparable to an observational study by Seheult et al, where a proactive diabetes team achieved 0.13mmol/L(2.3mg/dL) decrease in patient-day mean glucose and a 20% reduction in patient-days with mean glucose >15mmol/L (22). Similarly, Rushakoff et al, provided a virtual glucose monitoring service with proactive electronic consultation notes on patients with unstable diabetes, decreasing patient-day mean glucose by

0.24mmol/L(4.3mg/dL) and achieving 40% reduction in patient-days with hyperglycemia (2 or more BG measures >12.5mmol/L[>225mg/dL]) (21).

In RAPIDS, early identification and management did not decrease hypoglycemia, in contrast to Rushakoff et al (21). The baseline incidence of hypoglycemia in our cohort (4.7% of patient-days), was lower than the mean incidence in 635 USA hospitals (6.1% of patient-days) (29). A more extensive multifaceted intervention including dedicated insulin prescription order sets, protocols and education campaigns (16), may be required to further decrease hypoglycemia from the current relatively low rates at our institution. Nevertheless, it is encouraging that early intervention and increased tailored insulin treatment did not increase hypoglycemia and thus did not pose any safety risk for inpatients.

With early identification and management of diabetes, a 4% absolute risk reduction in hospital-acquired infection was observed. It is well known that poor glycemic control in the community (30) and in hospital (31; 32) is associated with increased risk for infection. There is strong evidence that intensive glycemic control decreases infections in cardiac and general surgery (33; 34), critical care (35), and non-critical care (7; 36). In a non-critical care study, basal-bolus insulin therapy improved a composite outcome but especially, decreased wound infections and hospital-acquired pneumonia (7). A meta-analysis of non-critical care studies also demonstrated that intensive glycemic control was associated with 60% decreased risk of hospital-acquired infections (37). We found AGDs were strongly correlated with hospital-acquired infection, and that the decrease in hospital-acquired infections paralleled a decrease in AGD, despite a modest change in mean glucose. This suggests that eliminating glycemic extremes may be most effective at improving clinical outcomes. In addition, the RAPIDS study adds further evidence to support the notion that improving inpatient glycemic control decreases hospital-acquired infection; however, as one of several pre-specified secondary outcomes, this finding requires further confirmatory randomized studies.

Of various models of inpatient diabetes care (16; 20-22; 38-40), the strengths of our intervention included remote surveillance and identification of hyperglycemia, and bedside consultations by a specialist IDT who directly prescribed insulin. The IDT used individualized treatment (rather than protocolized intensive insulin treatment), with the practical aim of decreasing both extremes of glycemia, rather than aiming for 'tight glycemic control'. This approach successfully decreased hyperglycemia without increasing hypoglycemia. By providing bed-side management it was also possible to recognize and address any other relevant aspects of patient care in addition to diabetes management, which may have contributed to improved clinical outcomes.

The RAPIDS study used a parallel cluster-randomized design with a baseline period, which was necessitated by several factors. It was only practical to deliver the proactive intervention at the ward level rather than individual patient level. Contamination was possible due to movement of patients and staff across wards, although the active period occurred during one resident staff rotation. In addition, increased presence of the IDT could result in increased awareness and upskilling of inpatient diabetes care. The study design which included baseline and active periods, allowed for comparison of the intervention against its own baseline, whilst a parallel control arm accounted for any other potential variations within the over the study period.

Limitations of this study include the relatively few clusters and some differences in patient characteristics between clusters due to our hospital structure with non-symmetrical specialist medical and surgical wards. We used a mixed effects model, which accounted for clustering and adjusted for baseline patient characteristics, but it is possible that there are residual confounders that are unaccounted for. The Hawthorne effect may also have contributed to improved glycemic outcomes. This study was relatively short; therefore, the sustainability of the improvements is yet to be determined. A longer duration study was not feasible with the available resources and would be susceptible to further contamination.

There are also limitations on the generalizability of our findings. Our hospital did not have a comprehensive electronic medical record including electronic medication prescription and order sets to assist with delivering inpatient care. The baseline proportion of inpatients managed by an IDT was modest. Therefore, the early intervention model may have less impact in a hospital with 'state of the art' hospital systems already in place. Furthermore, the IDT identified and provided consultation on all consecutive individuals with diabetes or new hyperglycemia (as a proof of concept of this model of care), but this was resource-intensive. However, we have since developed a risk-stratification tool to identify individuals at high-risk for adverse glycemia to enable a more sustainable model of care, and plan to evaluate the cost-effectiveness of targeted proactive intervention models.

RAPIDS is the first cluster-randomized trial of an early intervention model of diabetes care in the non-critical setting. RAPIDS demonstrated early electronic identification of inpatients with diabetes and treatment by a specialist inpatient diabetes team decreased hyperglycemia without increasing hypoglycemia. In addition, early management of diabetes was associated with decreased hospital-acquired infection, but this important observation requires further confirmatory studies. This study provides evidence that early intervention models of diabetes care in hospital improve glycemia and patient outcomes. With the increasing prevalence of diabetes and complexity of hospital care, hospital clinicians should concentrate on early identification and management to improve the care of people with diabetes.

Author Contributions

MK, PC and SF conceived the study and wrote the initial research proposal. MK and SF wrote the initial manuscript. PC, PW, AGo, AN, DR reviewed and edited the manuscript and contributed to the discussion. AGo contributed to the study design and generated the random allocation of clusters to treatment arms. MK and AGo performed the statistical analysis. AGa, SK, LR and KM provided the inpatient diabetes team clinical service. JR, AGa, SK, LR and KM recruited patients and collected research data. All authors reviewed the final manuscript and approved for submission.

SF had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Conflicts of interest

All authors report no relevant disclosures or conflicts of interest.

Data from this trial were presented as an oral presentation at the American Diabetes Association meeting (San Diego, CA, USA) in June, 2017 and a poster presentation at European Association for the study of Diabetes (Lisbon, Portugal) in September 2017.

Abbreviations

AGD: adverse glycemic days

BG: blood glucose

IDT: inpatient diabetes team

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Table 1: Patient characteristics

	Control arm (4 clusters)			Intervention arm (4 clusters)			
	Baseline Period (n=221)	**Active Period** (n=270)	**P‡**	**Baseline Period** (n=220)	**Active Period** (n=291)	**P‡**	**P (4 groups) §**
Age (years)	70±14	70±14	0.726	70±15	71±16	0.292	0.124
Male	135 (61)	166 (61)	0.929	112 (51)	156 (54)	0.545	**0.039**
Modified Charlson* score	2 (1, 3.5)	2 (0, 3)	0.476	1 (0, 3)	1(0, 3)	0.525	0.066
Admission creatinine (µmol/l)	111±57	107±59	0.430	102±59	104±68	0.742	0.477
Type of Diabetes:			0.799			0.190	0.071
Type 2 diabetes	193 (87)	241 (89)		190 (86)	251 (86)		
Type 1 diabetes	18 (8)	19 (7)		16 (7)	12 (4)		
New hyperglycemia	10 (5)	10 (4)		14 (6)	28 (10)		
HbA1c:							
mmol/mol	60±18	62±19	0.158	57±19	57±18	0.590	**0.049**
%	7.6±1.7	7.8±1.8		7.4±1.8	7.4±1.7		
Diabetes treatment prior to admission			0.960			0.843	**0.007**
No treatment	43 (19)	55 (20)		56 (25)	79 (27)		
Oral agents & GLP1	99 (45)	121 (45)		113 (51)	142 (49)		
Insulin (+/-oral agents & GLP1)	79 (36)	94 (35)		51 (23)	70 (24)		
Hospital stay (days)	5 (3, 5)	4 (2, 4)	0.064	4 (2, 7)	4 (2, 8)	0.964	0.335
BG measurements/day	3.6±1.9	3.5±1.7	0.543	3.4±1.5	3.5±1.6	0.469	0.990
Capillary glucose at admission							
mmol/L	10.3±4.4	10.3±4.3	0.986	9.3±4.0	9.2±3.8	0.620	**0.001**
mg/dL	182±79	182±77		167±72	165±68		
Glucocorticoid treatment during admission †	41 (19)	38 (14)	0.179	28 (13)	30 (10)	0.395	0.062
Type of admission							
Elective	31 (14)	35 (13)	0.731	26 (12)	15 (5)	**0.006**	**0.003**
Emergency	190 (86)	235 (87)		194 (88)	276 (95)		
Admission Parent Unit			0.294			0.159	**<0.001**
Medicine	168 (76)	194 (72)		106 (48)	122 (42)		
Surgery	53 (24)	76 (28)		114 (52)	169 (58)		
Medical admissions by parent unit							
General medicine	54 (24)	55 (20)		56 (25)	89 (31)		
Cardiology	70 (32)	95 (35)		0	2 (1)		
Neurology	0	3 (1)		49 (23)	71 (24)		
Respiratory	21 (10)	22 (8)		0	1		
Gastroenterology	15 (6)	9 (3)		5 (2)	5 (2)		
Other medical	8 (4)	11 (5)		4 (2)	2 (1)		
Surgical admission by parent unit							
Abdominal & emergency general surgery	16 (7)	21 (8)		47 (21)	68 (23)		
Neurosurgery	0	0		43 (19)	41 (14)		
Orthopedics & Trauma	37 (17)	50 (19)		10 (5)	8 (3)		
Other surgery	0	4 (1)		6 (3)	4 (1)		

Data presented as mean±sd, median (IQR), or n (%) or as appropriate. ***** modified Charlson index excluded items related to diabetes. † Glucocorticoid treatment was defined as treatment with a supra-physiological dose of glucocorticoid medication (dose equivalent >7.5 mg of prednisolone) for 24 hours or more during admission. ‡ p-value of difference between baseline and active periods within each treatment arm. § p-value of difference between 4 groups.

Table 2: Primary and secondary outcomes

	Control arm (4 clusters)			**Intervention arm (4 clusters)**		
	Baseline Period	Active Period	p	Baseline Period	Active Period	p
	(usual care)	(usual care)		(usual care)	(**Early/pro-active intervention**)	
Primary outcome: Adverse Glycemic Days						
Cluster level: Incidence of AGD (per 1000 patient-days)	291	261	0.090	243	186	**<0.001**
Individual level: Adjusted* number of AGD per patient: mean±sd,	1.8±2.0	1.5±1.8	0.23†	1.4±1.6	1.0±0.9	**0.001**†
median (Q1, Q3)	1.2 (0.7,1.9)	1.0 (0.6,1.7)		0.9 (0.5,1.7)	0.7 (0.4, 1.3)	
Secondary: Glucometric outcomes						
Patient-days	**n=1271**	**n=1394**		**n=1200**	**n=1582**	
Patient-day mean BG (mean±sd)	9.6±3.2	9.5±3.2	0.23	9.4±3.3	9.0±2.7	**0.003**
mean BG > 10 mmol/L [>180 mg/dL]	37%	37%	0.88	35%	30%	**0.010**
mean BG > 15 mmol/L [>270 mg/dL]	6.9%	6.1%	0.39	7.3%	3.3%	**<0.001**
BG <4 mmol/L [<72 mg/dL]	5.6%	5.0%	0.52	3.8%	4.0%	0.69
BG <3 mmol/L [<54 mg/dL]	1.6%	1.4%	0.75	1.0%	0.7%	0.40
Secondary: Clinical outcomes						
Patients	**n=221**	**n=270**		**n=220**	**n=291**	
Any hospital-acquired infection	19 (8.6)	19 (7.0)	0.52	**14 (6.4)**	**7 (2.4)**	**0.035**
Skin wound & surgical site	5 (2.3)	8 (3.0)		2 (0.9)	2 (0.7)	
Urinary tract	5 (2.3)	4 (1.5)		4 (1.8)	3 (1.0)	
Bacteremia	1 (0.5)	0		1 (0.5)	0	
Pneumonia	9 (4.1)	10 (3.7)		9 (4.1)	4 (1.4)	
Acute kidney injury	15 (6.8)	22 (8.1)	0.56	11 (5.0)	11 (3.8)	0.50
Acute myocardial infarct	4 (1.8)	5 (1.9)	0.97	2 (0.9)	1(0.3)	0.40
Unplanned critical care admission	12 (5.4)	12 (4.4)	0.61	2 (0.9)	3 (1.0)	0.89
Hospital mortality	5 (2.3)	8 (3.0)	0.63	6 (2.7)	6 (2.1)	0.63
Composite outcome (hospital acquired infection, acute kidney injury, acute myocardial infarct, unplanned critical care admission and mortality)	39 (17.6)	51 (18.9)	0.72	28 (12.7)	26 (8.9)	0.17
Length of stay (days)	6 (3, 11)	6 (3, 11)	0.60	6 (3, 10)	6 (3, 10)	0.19

*adjusted for age, gender, modified Charlson index, creatinine, HbA1c, insulin treatment prior to admission, admission unit, admission type, ward type, days observed (fixed effects), and ward (random effect) †mixed model Poisson regression. Data expressed as mean±sd, median (Q1, Q3), or n (%).

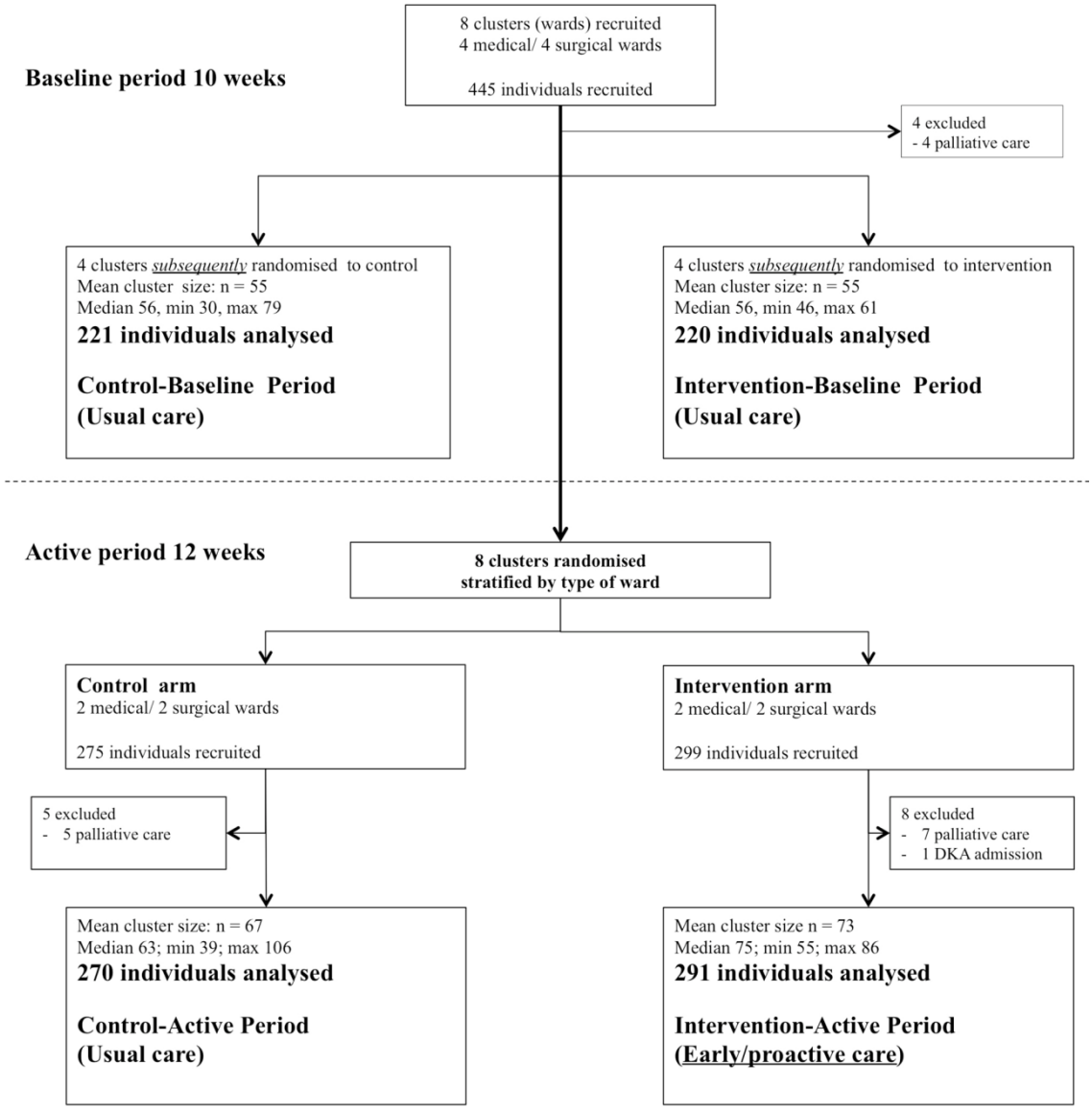


Figure 1: Patient recruitment

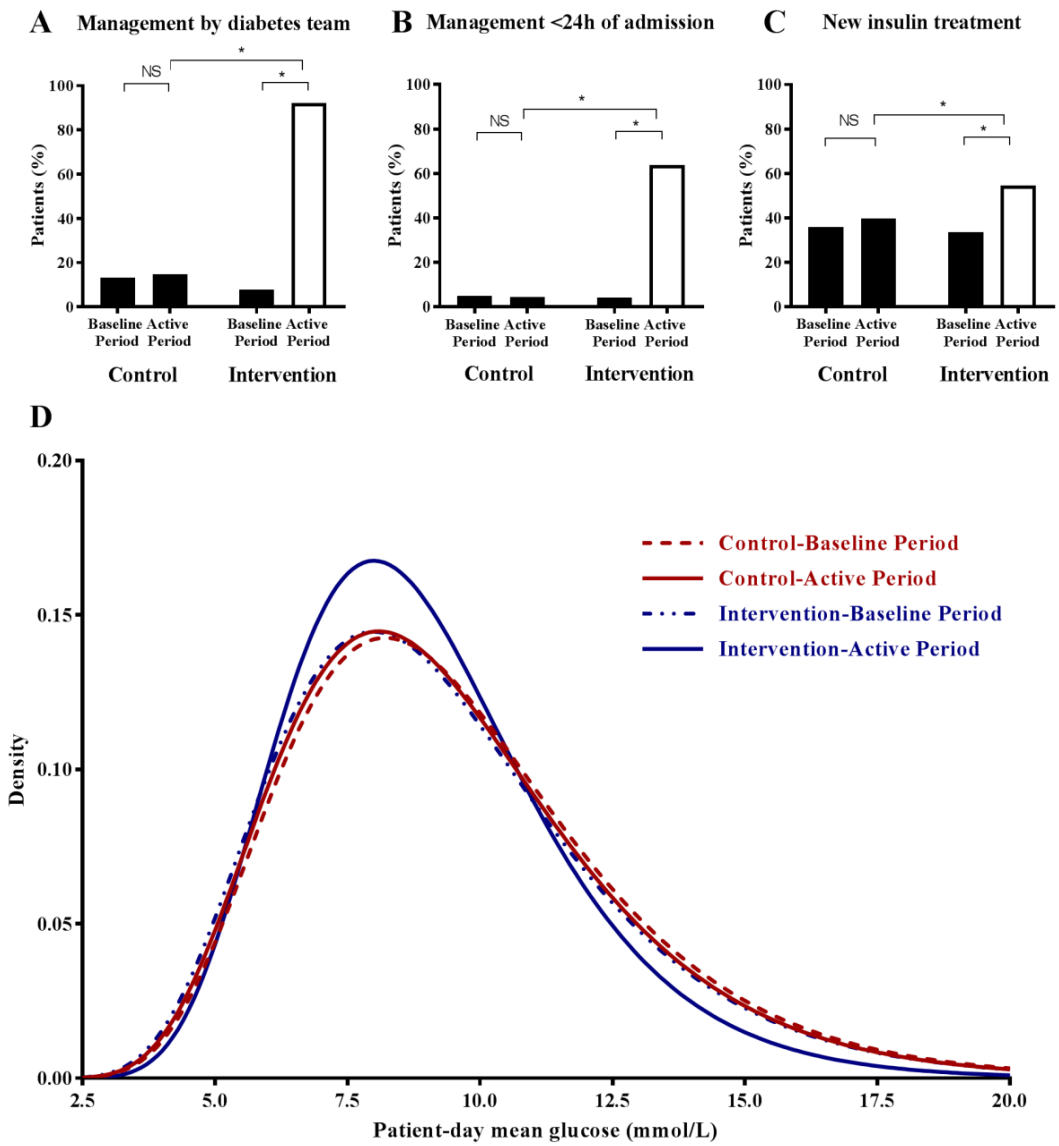
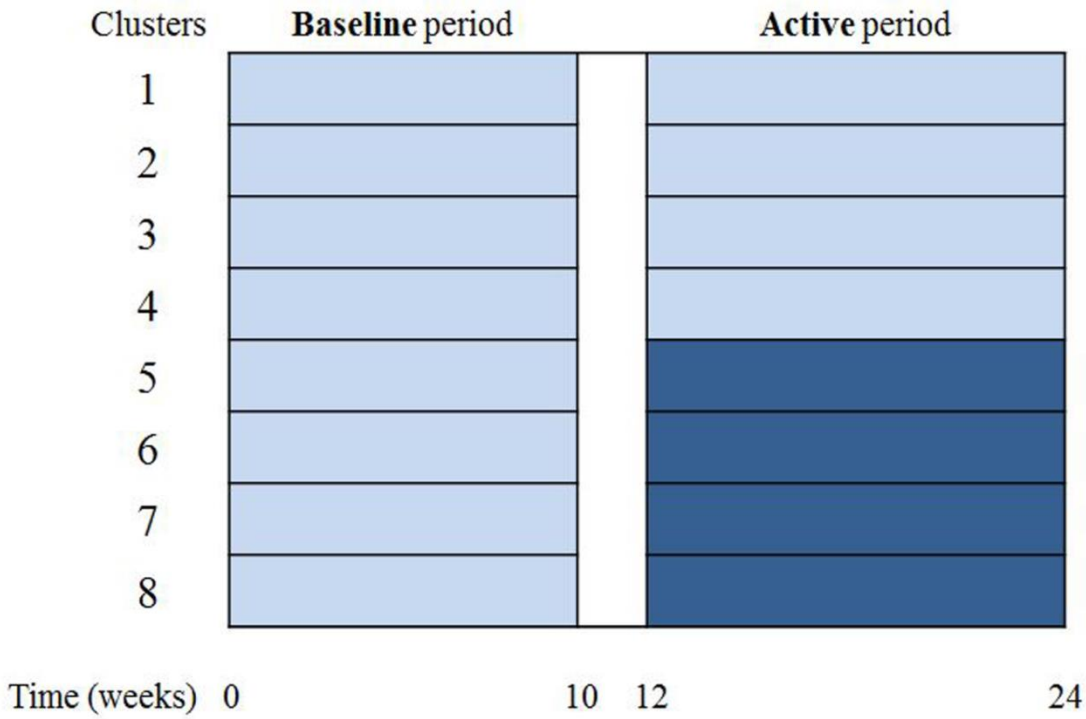


Figure2: Process of care & glucometric outcomes. **(a)** Proportion of patients who received management by the inpatient diabetes team during admission. **(b)** Proportion of patients who had diabetes team management within 24 hours of admission. **(c)** Proportion of insulin-naïve patients who had treatment with subcutaneous insulin during admission. X-axis represents the control and intervention arms during the baseline and active periods. Filled bars represent usual care, open bar represents proactive/early intervention model of care. * $p<0.001$. **(d)** Distribution of patient-day mean glucose. Patient-day mean glucose fit a lognormal distribution. There was no difference in the distribution in the groups that received usual care (interrupted lines and solid red line). The group that received early intervention (solid blue line) had a lower mean and variance in the distribution, therefore lower proportion of days with severe hyperglycemia.

5.3 Supplementary material



Supplementary Figure 5**:** RAPIDS study design: Parallel cluster-randomized study with a baseline period. There was a 10-week baseline period, and 12-weeks active period. Light shading represents clusters unexposed to the intervention (i.e. usual care). Dark shading represents clusters exposed to the intervention (i.e. early identification and management). Between weeks 10 to 12 constituted the transition period where implementation of the intervention occurred and no patient recruitment was conducted.

Supplementary Table S1:

Primary analysis Individual level: Number of Adjusted AGD per-patient. Mixed model Poisson regression where ward (cluster) was included as random variable. Group (control-baseline period, control-active period, intervention-baseline period, and intervention-active period) was included as a factor to allow simultaneous comparison across treatment arms and between baseline and active periods within each treatment arm. IRR = incidence rate ratio.

	β-Coefficient (95%CI)	**IRR (95% CI)**	**p-value**
Age	0.009 (0.004, 0.013)	1.009 (1.004, 1.013)	<0.001
Male	0.102 (-0.017, 0.221)	1.107 (0.983, 1.248)	0.094
Modified Charlson Index *	0.062 (0.029, 0.094)	1.063 (1.029, 1.098)	<0.001
Creatinine	0.000 (0.000, 0.001)	1.000 (0.999, 1.001)	0.553
HbA1c (each % increase)	0.203 (0.174, 0.232)	1.225 (1.190, 1.261)	<0.001
Diabetes Type	-0.252 (-0.368, -0.137)	0.777 (0.692, 0.872)	<0.001
Insulin treatment prior to admission	0.601 (0.475, 0.727)	1.823 (1.607, 2.068)	<0.001
Surgical unit admission	-0.111 (-0.336, 0.133)	0.895 (0.701, 1.143)	0.372
Elective admission	-0.246 (-0.500, 0.008)	0.782 (0.606, 1.008)	0.057
Surgical ward	0.038 (-0.203, 0.278)	1.038 (0.817, 1.320)	0.759
Number of observed days	0.148 (0.134, 0.163)	1.160 (1.143, 1.177)	<0.001
Constant	-2.536 (-3.057, -2.014)	0.079 (0.047, 0.133)	<0.001
Ward (random variable)	9.37^{-33}	0.000	
Group			
Control-baseline (usual care)	0.038 (-0.122, 0.199)	1.039 (0.885, 1.220)	0.640
Control-active (usual care)	-0.056 (-0.217, 0.106)	0.946 (0.805, 1.112)	0.501
Intervention-baseline (usual care)	Ref	Ref	
Intervention-active (proactive care)	**-0.283 (-0.453, -0.112)**	**0.754 (0.636, 0.894)**	**0.001**

* modified Charlson index excludes items related to diabetes

Comparison between groups	**β-coef (95%CI)**	**IRR (95%CI)**	**p**
Control-baseline period vs. Control-active period (change in control arm)	-0.094 (-0.248, +0.060)	0.910 (0.780, 1.062)	0.233
Intervention-baseline period vs. Intervention-active period (change in intervention arm)	**-0.283 (-0.453, -0.112)**	**0.754 (0.636, 0.894)**	**0.001**
Control-active period vs. Intervention-active period (comparison of early intervention against parallel control group)	**-0.227 (-0.395, -0.059)**	**0.797 (0.674, 0.942)**	**0.008**

Supplementary Table S2:

Adjusted* Adverse Glycaemic Days per patient during baseline and active periods by clusters

Control Clusters	Baseline	Active	P#	**Intervention** Clusters	Baseline	Active	P#
C1-General medicine	2.0±2.5	2.1±2.6	0.96	I1-General Medicine	2.2±2.3	1.4±1.3	0.01
C2-General surgery	1.8±1.9	1.0±0.6	0.05	I2-General Surgery	0.8±0.8	0.7±0.5	0.40
C3-Cardiology	1.6±1.7	1.4±1.2	0.53	I3-Neurology	1.6±1.4	1.1±0.9	0.02
C4-Orthopaedic	1.6±1.4	1.3±1.4	0.20	I4-Neurosurgery	0.9±0.8	0.8±0.7	0.43

*adjusted for age, gender, modified Charlson index, creatinine, HbA1c, insulin treatment prior to admission, admission unit, admission type, ward type, days observed (fixed effects), and ward (random effect) # Kruskal-Wallis rank-sum test

Supplementary Table S3:

Post-hoc analysis: Hospital-acquired infections. Mixed model logistic regression where ward (cluster) was included as random variable. Group (control-baseline period, control-active period, intervention-baseline period, and intervention-active period) was included as a factor to allow simultaneous comparison across treatment arms and between baseline and active periods within each treatment arm.

	Adj OR	**95% CI**	**p-value**
Age (each 1 year increase)	1.03	1.00, 1.06	0.033
Male	1.65	0.84, 3.25	0.143
Modified Charlson Index # (each 1 point increase)	1.08	0.90, 1.29	0.427
Creatinine (each 10 umol/L increase)	1.00	1.00, 1.00	0.898
HbA1c (each % increase)	1.13	0.92, 1.38	0.239
Diabetes Type			
- Type 2 diabetes	1.00	ref	ref
- Type 1 diabetes	0.35	0.04, 3.03	0.343
- New hyperglycaemia	3.79	1.12, 12.76	0.032
Insulin treatment prior to admission	0.55	0.23, 1.34	0.188
Surgical unit admission	0.76	0.19, 3.12	0.708
Elective admission	1.50	0.47, 4.76	0.490
Surgical ward	1.52	0.35, 6.52	0.577
Number of observed days (each 1 day increase)	1.40	1.28, 1.54	<0.001
Constant	0.00	0.000, 0.003	<0.001
Ward (random variable)	0.08		
Group			
Control-baseline (usual care)	1.24	0.48, 3.14	0.654
Control-active (usual care)	0.89	0.34, 2.28	0.792
Intervention-baseline (usual care)	Ref	Ref	
Intervention-active (proactive care)	**0.20**	**0.07, 0.58**	**0.003**

modified Charlson index excludes items related to diabetes

Comparison between groups	**Adj OR [95%CI]**	**p**
Control-baseline period vs. Control-active period (change in control arm)	0.71 [0.31, 1.63]	0.420
Intervention-baseline period vs. Intervention-active period (change in intervention arm)	**0.20 [0.07, 0.58]**	**0.003**
Control-active period vs. Intervention-active period (comparison of early intervention against parallel control group)	**0.23 [0.07, 0.73]**	**0.013**

Supplementary Table S4:

Post-hoc analysis: Hospital-acquired infections (subgroup of <u>patients with type 2 diabetes</u>). Mixed model logistic regression where ward (cluster) was included as random variable. Group (control-baseline period, control-active period, intervention-baseline period, and intervention-active period) was included as a factor to allow simultaneous comparison across treatment arms and between baseline and active periods within each treatment arm.

	Adj OR	95% CI	p-value
Age (each 1 year increase)	1.04	1.01, 1.08	0.016
Male	1.71	0.83, 3.52	0.144
Modified Charlson Index # (each 1 point increase)	1.08	0.90, 1.31	0.409
Creatinine (each 10 umol/L increase)	1.00	0.99, 1.00	0.680
HbA1c (each % increase)	1.18	0.95, 1.46	0.138
Insulin treatment prior to admission	0.47	0.18, 1.21	0.117
Surgical unit admission	0.77	0.18, 3.33	0.729
Elective admission	1.34	0.39, 4.67	0.643
Surgical ward	1.95	0.44, 8.62	0.378
Number of observed days (each 1 day increase)	1.42	1.28, 1.56	<0.001
Constant	0.00	0.000, 0.002	<0.001
Ward (random variable)	0.04		
Group			
Control-baseline (usual care)	1.37	0.55, 3.39	0.497
Control-active (usual care)	0.67	0.25, 1.78	0.420
Intervention-baseline (usual care)	Ref	Ref	
Intervention-active (proactive care)	**0.17**	**0.05, 0.56**	**0.003**

modified Charlson index excludes items related to diabetes

Comparison between groups	Adj OR [95%CI]	p
Control-baseline period vs. Control-active period (change in control arm)	0.49 [0.20, 1.19]	0.114
Intervention-baseline period vs. Intervention-active period (change in intervention arm)	**0.17 [0.05, 0.56]**	**0.003**
Control-active period vs. Intervention-active period (comparison of early intervention against parallel control group)	**0.26 [0.08, 0.89]**	**0.033**

Supplementary Table S5: Glycaemic and Clinical outcomes, patients with Type 2 diabetes

	Control arm (4 clusters)			Intervention arm (4 clusters)		
	Baseline Period	Active Period	p	Baseline Period	Active Period	p
	(usual care)	(usual care)		(usual care)	(**Early/proactive intervention**)	
Glucometric outcomes						
Patient-days	**n=1131**	**n=1264**		**n=1053**	**n=1396**	
Patient-day mean BG (mean±sd)	9.6±3.3	9.4±3.1	0.10	9.2±3.2	9.0±2.7	0.296
mean BG > 10 mmol/L [>180 mg/dL]	36%	36%	0.90	32%	30%	0.370
mean BG > 15 mmol/L [>270 mg/dL]	7.0%	5.6%	0.18	**6.6%**	**3.2%**	**<0.001**
BG <4 mmol/L [<72 mg/dL]	4.3%	4.1%	0.79	3.0%	3.9%	0.27
BG <3 mmol/L [<54 mg/dL]	1.0%	1.0%	0.89	0.7%	0.4%	0.42
Clinical outcomes						
Patients	**n=193**	**n=241**		**n=190**	**n=247**	
Any hospital-acquired infection	18 (9.3)	16 (6.4)	0.37	**13 (6.8)**	**6 (2.4)**	**0.032**
Acute kidney injury	14 (7.3)	19 (7.9)	0.86	11 (5.8)	9 (3.7)	0.36
Acute myocardial infarct	3 (1.6)	4 (1.7)	0.99	2 (1.1)	1 (0.4)	0.58
Unplanned critical care admission	10 (5.1)	9 (3.7)	0.49	2 (1.1)	2 (0.8)	0.99
Hospital mortality	3 (1.6)	7 (2.9)	0.52	5 (2.6)	4 (1.6)	0.51
Composite outcome	35 (18.1)	43 (17.8)	0.99	26 (13.7)	21 (8.5)	0.09
Length of stay (days)	6 (3, 11)	6 (3, 10)	0.47	5 (3, 10)	6 (3, 11)	0.14

Data expressed as mean±sd, median (Q1, Q3), or n (%). P-values using t-test or Fisher's exact test as appropriate

Supplementary Table S6: Glycaemic and clinical outcomes, patients with Type 1 diabetes

	Control arm (4 clusters)			Intervention arm (4 clusters)		
	Baseline Period	Active Period	p	Baseline Period	Active Period	p
	(usual care)	(usual care)		(usual care)	(**Early/proactive intervention**)	
Glucometric outcomes						
Patient-days	**n=55**	**n=53**		**n=34**	**n=28**	
Patient-day mean BG (mean±sd)	10.6±3.1	10.5±3.0	0.88	**10.3±3.2**	**10.7±3.3**	**0.64**
mean BG > 10 mmol/L [>180 mg/dL]	60%	57%	0.72	44%	54%	0.61
mean BG > 15 mmol/L [>270 mg/dL]	9.1%	7.6%	0.99	15%	14%	0.99
BG <4 mmol/L [<72 mg/dL]	22%	13%	0.31	29%	32%	0.82
BG <3 mmol/L [<54 mg/dL]	11%	4%	0.27	12%	17%	0.72
Clinical outcomes						
Patients	**n=18**	**n=19**		**n=16**	**n=12**	
Any hospital-acquired infection	0	0		1 (6)	0	0.99
Acute kidney injury	0	2 (11)	0.49	0	0	
Acute myocardial infarct	1 (6)	0	0.49	0	0	
Unplanned critical care admission	2 (11)	1 (5)	0.60	0	0	
Hospital mortality	0	1 (5)	0.99	0	0	
Composite outcome	2 (11)	4 (21)	0.66	1 (6)	0	0.99
Length of stay (days)	5 (3, 13)	4 (3, 9)	0.64	4 (2, 14)	5 (3, 5)	0.59

Data expressed as mean±sd, median (Q1, Q3), or n (%). P-values using t-test or Fisher's exact test as appropriate

Supplementary Table S7: Glycaemic and clinical outcomes, patients with <u>New Hyperglycaemia</u>

	Control arm (4 clusters)			**Intervention arm (4 clusters)**		
	Baseline Period	Active Period	p	Baseline Period	Active Period	p
	(usual care)	(usual care)		(usual care)	(**Early/proactive intervention**)	
Glucometric outcomes						
Patient-days	**n=53**	**n=48**		**n=46**	**n=139**	
Patient-day mean BG (mean±sd)	9.3±2.5	9.9±3.9	0.35	**11.3±4.1**	**8.7±2.5**	**<0.001**
mean BG > 10 mmol/L [>180 mg/dL]	32%	38%	0.57	**48%**	**22%**	**0.001**
mean BG > 15 mmol/L [>270 mg/dL]	**1.9%**	**14.6%**	**0.03**	**17.4%**	**2.2%**	**0.001**
BG <4 mmol/L [<72 mg/dL]	0	2.1%	0.47	0	0	
BG <3 mmol/L [<54 mg/dL]	0	0		0	0	
Clinical outcomes						
Patients	**n=10**	**n=10**		**n=14**	**n=28**	
Any hospital-acquired infection	1 (10)	3 (30)	0.59	0	1 (4)	0.99
Acute kidney injury	1 (10)	1 (10)	0.99	0	2 (7)	0.55
Acute myocardial infarct	0	1 (10)	0.99	0	0	
Unplanned critical care admission	0	2 (20)	0.47	0	1 (4)	0.99
Hospital mortality	2 (20)	0	0.47	1 (7)	2 (7)	0.99
Composite outcome	2 (20)	4 (40)	0.63	1 (7)	5 (18)	0.65
Length of stay (days)	5 (3, 7)	11 (4, 18)	0.31	7 (4, 11)	7 (3, 10)	0.97

Data expressed as mean±sd, median (Q1, Q3), or n (%). P-values using t-test or Fisher's exact test as appropriate

Supplementary Table S8: Clinical outcomes: medical vs. surgical patients

	Control arm (4 clusters)			Intervention arm (4 clusters)		
	Baseline Period	Active Period	p	Baseline Period	Active Period	p
	(usual care)	(usual care)		(usual care)	(**Early/proactive intervention**)	
Medical Patients	**n=168**	**n=194**	**p***	**n=114**	**n=169**	**p***
Any hospital-acquired infection	12 (7.1)	9 (4.6)	0.37	**12 (10.5)**	**6 (3.6)**	**0.025**
Acute kidney injury	12 (7.1)	12 (8.3)	0.84	9 (7.9)	7 (4.1)	0.20
Acute myocardial infarct	2 (1.9)	4 (2.1)	0.69	1 (0.9)	1 (0.6)	0.99
Unplanned critical care admission	9 (5.4)	9 (4.6)	0.81	1 (0.9)	2 (1.2)	0.99
Hospital mortality	5 (3.0)	8 (4.1)	0.59	5 (4.4)	6 (3.6)	0.76
Composite outcome	28 (16.7)	38 (19.6)	0.50	24 (21.1)	21 (12.4)	0.07
Length of stay (days)	5 (3, 10)	6 (3, 12)	0.54	8 (4, 12)	8 (4, 14)	0.44
Surgical Patients	**n=53**	**n=76**		**n=106**	**n=122**	
Any hospital-acquired infection	7 (13.2)	10 (13.2)	0.99	2 (1.9)	1 (0.8)	0.60
Acute kidney injury	3 (5.7)	6 (7.9)	0.73	2 (1.9)	4 (3.3)	0.69
Acute myocardial infarct	2 (3.8)	1 (1.3)	0.57	1 (0.9)	0	0.46
Unplanned critical care admission	3 (5.7)	3 (4.0)	0.69	1 (0.9	1 (0.8)	0.99
Hospital mortality	0	0		1 (9.4)	0	0.46
Composite outcome	11 (20.8)	13 (17.1)	0.65	4 (3.8)	5 (4.1)	0.99
Length of stay (days)	9 (4, 14)	5 (4, 9)	0.03	4 (2, 7)	5 (2, 7)	0.51

Data expressed as mean±sd, median (Q1, Q3), or n (%). P-values using Fisher's exact test.

Supplementary Table S9: Insulin-naïve patients that received insulin treatment in hospital

	Control arm (4 clusters)		Intervention arm (4 clusters)	
	Baseline Period **(Usual care)**	Active Period **(Usual care)**	Baseline Period **(Usual care)**	Active Period **(Early/ proactive intervention)**
Medical units				
- General medicine	12/34 (35)	17/40 (43)	18/42 (43)	47/67 (70)
- Cardiology	13/41 (32)	25/61 (41)	0/0	1/1 (100)
- Neurology	0/0	1/3 (33)	15/39 (39)	30/56 (54)
- Respiratory	11/19 (58)	7/14 (50)	0/0	0/1 (0)
- Gastroenterology	4/10 (40)	3/6 (50)	1/2 (50)	0/4 (0)
- Other medical	1/3 (33)	1/1 (100)	1/3 (33)	0/0
Surgical units				
- Abdominal & emergency surgery	3/11 (27)	9/16 (56)	8/36 (22)	28/52 (50)
- Neurosurgery	0/0	0/0	11/34 (32)	17/32 (53)
- Orthopedics & Trauma	7/24 (29)	7/33 (21)	2/7 (29)	3/5 (60)
- Other surgery	0/0	0/2 (0)	1/6 (17)	1/3 (33)
TOTAL	**51/142 (36)**	**70/176 (40)**	**57/169 (34)**	**127/221 (57)**

Data presented as: number that received insulin / total number of patients (percentage)

CHAPTER SIX:

EARLY IDENTIFICATION OF HIGH-RISK DIABETES INPATIENTS

6.1 Introduction

With increasing prevalence of diabetes in hospitalised patients, specialist management of every diabetes inpatient is resource-intensive and impractical. Risk-stratification and targeted management of high-risk inpatients is becoming an important strategy for sustainable diabetes programs. Ideally, a risk-stratification tool should aim to identify inpatients who develop adverse glycaemia to enable targeted management by inpatient diabetes services. In addition, a risk-stratification tool that predicts high-risk patients early in their admission could enable early and targeted intervention.

Although prediction tools for inpatient hypoglycaemia have been developed, there are no prediction tools for the more common glycaemic extreme of inpatient hyperglycaemia. To address this gap in literature, we sought to develop a prediction tool for adverse glycaemia (which includes both hyperglycaemia and hypoglycaemia), using the patient cohort recruited in the RAPIDS trial. The prediction tool was designed to identify early in admission, inpatients who subsequently developed adverse glycaemia in hospital. The prediction tool can assist inpatient diabetes programs, and refine the proactive inpatient diabetes service developed in Chapter 5.

6.2 Manuscript

The material presented in this chapter has been submitted as a manuscript to the *Journal of Diabetes* and is currently under peer-review.

A clinical prediction tool identifies patients with diabetes at risk for persistent adverse glycaemia in hospital

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Abstract

Aims: Given the high incidence of hyperglycaemia and hypoglycaemia in hospital and lack of prediction tools for this problem, we developed a clinical tool to assist early identification of individuals at risk for persistent adverse glycaemia (AG) in hospital.

Methods: We analysed a cohort of 594 consecutive adult inpatients with type 2 diabetes. We identified clinical factors available early in the admission course that were associated with persistent AG (defined as two or more days with capillary glucose <4 or >15 mmol/L during admission). A prediction model for persistent AG was constructed using logistic regression and internal validation was performed using a split-sample approach.

Results: Persistent AG occurred in 153 (26%) of inpatients, and was associated with dysglycaemia at admission (Odds Ratio 3.65); glycosylated haemoglobin ≥64 mmol/mol (≥8.1%) (OR 5.08); glucose-lowering treatment regimen containing sulphonylurea (OR 3.50), or insulin (OR 4.22); glucocorticoid medication treatment (OR 2.27); Charlson comorbidity index; and the number of observed-days. An early-identification prediction tool, based on clinical factors reliably available at admission (dysglycaemia at admission, glycosylated haemoglobin, glucose-lowering regimen and glucocorticoid treatment), could accurately predict persistent AG (receiver operating characteristic area under curve: 0.806), and at the optimal cut off, the sensitivity, specificity and positive predictive value were 84%, 66% and 53% respectively.

Conclusions: A clinical prediction tool based on clinical risk factors available at admission to hospital identified patients at increased risk for persistent adverse glycaemia and could assist early targeted management by inpatient diabetes teams.

Keywords

hospital care; hyperglycaemia; hypoglycaemia; clinical prediction models; proactive care; risk factors

Abbreviations

AG	adverse glycaemia (composite of hyper- and hypoglycaemia)
AUC	area under curve
BG	blood glucose
IDT	inpatient diabetes team
ROC	receiver-operating characteristics

What's new?

- Despite the high incidence of hyperglycaemia in hospitalised individuals with diabetes, clinical tools to predict those at risk for hyperglycaemia are lacking.
- We developed a practical clinical prediction model that identifies individuals at high risk for developing persistent hyperglycaemia and/or hypoglycaemia during their admission.
- This clinical prediction tool allows early identification of the high-risk individual with diabetes, and can assist targeted management by inpatient diabetes teams.

Introduction

In many hospitals of developed nations, more than one in four individuals have diabetes and most are admitted under the care of hospitalists or non-diabetes specialist medical and surgical teams [1, 2]. Hyperglycaemia in hospital is associated with adverse outcomes, such as healthcare-associated infection due to impaired immunity from neutrophil and macrophage dysfunction; and increased cardiovascular and renal pathology due to pro-thrombotic changes, endothelial dysfunction and oxidative stress [3]. Treatment of hyperglycaemia with glucose-lowering treatment can cause hypoglycaemia, which can also be associated with adverse outcomes, such as brain injury and cardiac arrhythmia [4]. The term Adverse Glycaemia (AG) can be used to encompass these glycaemic extremes of hyperglycaemia and hypoglycaemia [5]. Although ideal blood glucose (BG) targets in non-critical care have been published these targets are not based on high level evidence and may vary between guidelines [6, 7]. However, it is well-accepted that hypoglycaemia (<4 mmol/L) and severe hyperglycaemia (>15 mmol/L) should be avoided for the safe management of diabetes in hospital.

Hyperglycaemia in hospital is common and affects up to 50% of inpatients [8]. Based on clinical experience, many factors are known to cause perturbation of glycaemia including patient factors (pre-existing hyperglycaemia, counter-regulatory hormone 'stress' response, and the severity of illness); and hospital treatment factors (glucocorticoids, enteral and parenteral nutrition, and inappropriately withheld insulin). However, aside from glycosylated haemoglobin [9], and glucocorticoid treatment [10], risk factors for inpatient hyperglycaemia have not been formally investigated and there are no published clinical prediction tools for determining the risk of inpatient hyperglycaemia.

Hypoglycaemia affects up to 20% of inpatients [1]. Risk factors for inpatient hypoglycaemia have been investigated and include: greater age and comorbidities, longer duration of diabetes, lower glycosylated haemoglobin, sulphonylurea or insulin treatment, renal or liver impairment, and longer length of stay [11]. In addition, hospital treatment factors such as interruption in nutrition, medication errors and inadequate blood glucose monitoring contribute to inpatient hypoglycaemia [4]. Several prediction models for inpatient hypoglycaemia have been reported utilising combinations of these risk factors [12-15].

Early treatment of inpatient hyperglycaemia improves clinical outcomes [16-18] and many hospitals have implemented inpatient diabetes teams (IDT) to optimise glycaemic control. IDTs generally provide diabetes management in response to referrals from the treating teams [19, 20] or in response to the occurrence of AG during surveillance of capillary glucose measurements [21-23]. Therefore, IDT management typically occurs after the occurrence of AG, often later in the admission course. We previously reported an early intervention model of care whereby an IDT identified all patients with diabetes and provided bedside management within 24 hours of admission, even prior to occurrence of AG. In a cluster randomised study, this proactive model of care decreased hyperglycaemia and hospital-acquired infections [18]. However, as not every inpatient with diabetes develops AG, we sought to develop a refined approach for early identification of patients who are at high-risk of AG, to enable early

and targeted management by IDTs. We investigated clinical risk factors that were associated with development of persistent AG, and subsequently developed a clinical prediction tool to assist early identification of high-risk patients, as part of ongoing efforts to optimise systematic approaches to inpatient diabetes care [24].

Materials and Methods

This study is based on the patient cohort recruited in the Randomised study of a Proactive Inpatient Diabetes Service (RAPIDS): a cluster-randomised trial conducted between March and August 2016 at the Royal Melbourne Hospital, an acute care tertiary referral hospital (ANZCTR number 12616000265471) [18]. RAPIDS recruited consecutive adult inpatients with known diabetes or new hyperglycaemia (random capillary BG >11.1 mmol/L) admitted to one of eight medical and surgical wards. The intervention consisted of remote identification of diabetes inpatients and early bedside management by a specialist diabetes team. This analysis is based on patients who had the comparator of usual care (hence did not receive the intervention). Full details of the RAPIDS study have been previously reported [18].

Participants and data collection

For this analysis we included individuals with type 2 diabetes who had a length of stay of two or more days. Although RAPIDS recruited individuals with all diabetes types, we excluded patients with type 1 diabetes or type 3c (exocrine pancreatic disease) diabetes because these forms of diabetes are already known to have glycaemic instability and thus considered at high-risk for AG in hospital. The inpatient diabetes management was mostly performed by the treating team's medical officers. As per usual practice in Australia, United Kingdom and Europe, there was no standardized algorithm recommending cessation of all glucose-lowering medications and prescription of subcutaneous basal-bolus insulin in all patients with diabetes. Therefore, inpatients were treated with an individualized approach using a variety of glucose-lowering medications and/or insulin regimens. Individuals with diabetes had BG measurements performed at least four times per day or 4-hourly while fasting.

Recruitment and data collection was conducted prospectively. Capillary BG measurements from the time of admission until discharge were collected electronically using networked BG meters (Statstrip ®, Australasian Medical and Scientific Limited) and extracted for analysis using BioViewer (© Bio-Asia Diagnostics) data manager. We excluded BG measurements after day 14 of admission in patients with prolonged stay and excluded repeated BG measurements from a single clinical episode of hypo- or hyperglycaemia [25].

Outcome and risk factors

The outcome of interest was persistent AG, defined as the occurrence of two or more days with capillary BG <4 or >15 mmol/L, as a composite measure of hypoglycaemia and hyperglycaemia that was persistent during admission. We used BG measurements from day 2 onwards to define persistent AG, as glycaemic

control in the first 24 hours is influenced by treatment before admission or in the emergency department rather than ward management.

Putative clinical risk factors were investigated based on clinical experience and included patient factors (age, gender, modified Charlson Comorbidity Index), diabetes factors (glucose-lowering regimen prior to admission), hospital treatment factors (admission unit, admission type, glucocorticoid treatment), laboratory results (glycosylated haemoglobin and eGFR at admission), and the number of observed-days (calendar days that an individual had glucose observations performed). The modified Charlson Comorbidity Index excluded items related to diabetes. Glucose-lowering regimen prior to admission was categorised into four groups: 1) diet-controlled; 2) glucose-lowering medications excluding sulphonylurea; 3) glucose-lowering medications including sulphonylurea; and 4) insulin treatment. Glucocorticoid treatment was defined as oral or intravenous treatment with a glucocorticoid medication (equivalent to ≥7.5 mg of prednisolone) that was commenced within 24 hours of hospital admission and continued for at least 24 hours. We also evaluated dysglycaemia at admission (BG <4 or >15 mmol/L in the first 24 hours) as a putative risk factor for AG. Admission hyperglycaemia is a known risk factor for adverse clinical outcomes [26]. From clinical experience, dysglycaemia early in admission is an antecedent for subsequent AG, but surprisingly this has not been formally studied.

Some potential clinical risk factors including duration of diabetes, patient weight, and sepsis were not included in the analyses as this clinical information were not collected or reliably available. Treatment with enteral or total parenteral nutrition was not included as only a few individuals received this treatment.

Prediction models for persistent adverse glycaemia

We constructed two logistic regression models to predict persistent adverse glycaemia. The first (hospital-stay) model used all clinical risk factors that were independently associated with persistent AG on multivariable analysis. The second (early-identification) model used clinical risk factors that were reliably and accurately available within 24 hours of admission. The early identification model excluded Charlson Comorbidity Index (a research tool which is difficult to accurately determine in routine clinical practice at admission), and observed-days (which depends on length of stay and difficult to predict at the time of admission). The early-identification model was used to develop a clinical prediction tool, based on clinical features available within 24 hours of admission, thus assisting early identification of patients at increased risk of persistent AG.

Statistical approach

Patient demographic, diabetes and treatment variables, and laboratory results were summarised using mean (SD), or median (inter quartile range) for continuous measures, and proportions for categorical measures. Odds ratios (ORs) (95% CI) were estimated using logistic regression models. For multivariable models, all putative clinical factors were initially included as independent variables with stepwise

elimination performed for variables with p >0.1. As the prospectively collected data formed near-complete data set, no imputations were performed. A 50/50 split cohort approach was used for model construction and internal validation. Therefore, the models were derived using a randomly selected subgroup of the half the cohort, and their performance tested on the remaining half of the cohort. Model performance was assessed by calculating the area under the curve (AUC) of a receiver operating characteristic (ROC) curve. *C*-statistics were compared between the hospital-stay and early identification models. Sensitivity, specificity, positive and negative predictive values, and likelihood ratios were reported at various predicted probability cut-offs. All analyses were performed using STATA 15 (StataCorp LLC, College station, TX, USA).

Results

This analysis consisted of 594 consecutive individuals with type 2 diabetes admitted for a median of 4 (2 to 7) days. In this cohort glucose-lowering regimen prior to admission consisted of: diet-controlled (21%), glucose-lowering medications excluding sulphonylurea (27%), glucose-lowering medications including sulphonylurea (24%), and insulin treatment (28%). Mean glycosylated haemoglobin (SD) at admission was 58 (19) mmol/mol or 7.5 (1.7) %. 216 (37%) individuals had dysglycaemia at admission, and 88 (15%) were treated with glucocorticoid medications.

In this cohort, 210 (35%) had at least one episode of hyperglycaemia (>15.0 mmol/L), 62 (10%) had at least one episode of hypoglycaemia (<4.0mmol/L), and 25 (4%) had both. Persistent AG occurred in 153 (26%) individuals. Patient characteristics and clinical variables for individuals with and without persistent AG are presented in Table 1.

Risk factors for persistent adverse glycaemia

Coefficients and the ORs for the clinical risk factors that were independently associated with persistent AG are presented in Table 2. Persistent AG was associated with dysglycaemia at admission (OR 3.65); admission glycosylated haemoglobin 7.1-8.0% (OR 2.15); >8.0% (OR 5.08); Glucocorticoid treatment (OR 2.27); pre-admission treatment with insulin (OR 4.22), and sulphonylurea (OR 3.50); observed-days; and modified Charlson Comorbidity index. Interestingly, treatment with non-sulphonylurea glucose-lowering medications was not associated with persistent AG. Age, gender, admission unit, admission type and admission eGFR were not associated with persistent AG. Risk factors independently associated with hyperglycaemia hypoglycaemia as separate outcomes are presented in supplemental tables 1 and 2.

Prediction models for persistent adverse glycaemia

The hospital-stay model for predicting persistent AG using six associated clinical variables (dysglycaemia at admission, glycosylated haemoglobin, glucose-lowering regimen, glucocorticoid treatment, modified Charlson Index and observed-days) had a ROC-curve AUC of 0.872 (95% CI 0.828-0.916) (Fig. 1). The early-identification model using four clinical variables reliably and accurately available within 24 hours

of admission (dysglycaemia at admission, glycosylated haemoglobin, glucose-lowering regimen, glucocorticoid treatment) had a ROC-curve AUC of 0.806 (0.751-0.861) (Fig. 1 and supplementary table 3). At the optimal cut-off point where the combined sensitivity and specificity total was maximal, early-identification model had a sensitivity of 84%, specificity of 66%, positive predictive value of 53% and likelihood ratio of 2.5 (supplementary table 4). Although the early-intervention model had a slightly lower AUC than the hospital-stay model (C-statistic p=0.006), the early-intervention model was practical and relatively accurate (AUC >0.8) as a clinical tool to predict persistent AG.

Figure 2 depicts an example of a clinical algorithm based on the early identification model which categorises individuals as low or high risk for persistent AG. Individuals not on sulphonylurea or insulin treatment and not dysglycaemic at admission are classified as low-risk. Individuals on sulphonylurea or insulin treatment, and dysglycaemic at admission are classified as high risk. For the remaining individuals, glucocorticoid treatment and admission glycosylated haemoglobin further categorise between low and high risk of persistent AG.

Discussion

Early treatment of hyperglycaemia improves glycaemic control and may improve clinical outcomes [16, 18], thus there is a need for early identification and targeted management of individuals at high-risk for adverse glycaemia in hospital. Clinical prediction models in hospital diabetes patients have focussed on risk factors for adverse clinical outcomes [27], but there has been less focus on predicting *adverse glycaemic* outcomes. Although a few studies have developed prediction tools for inpatient hypoglycaemia [12-15], there are no published prediction tools for the more common glycaemic extreme of inpatient hyperglycaemia. To our knowledge this is the first prediction tool for both hyperglycaemia and/or hypoglycaemia which could practically assist to identify high-risk patients, early in the admission course. As hyperglycaemia was three times more prevalent than hypoglycaemia, this early prediction tool is particularly useful for predicting hyperglycaemia in hospital.

In this well-characterized prospective cohort of consecutive inpatients with type 2 diabetes, 26% of individuals had two or more days of hyperglycaemia and/or hypoglycaemia. Variables that were independently associated with persistent AG (dysglycaemia at admission, glycosylated haemoglobin, glucose-lowering regimen, glucocorticoid treatment, modified Charlson Comorbidity Index and the number of observed-days) were consistent with anecdotal clinical experience, but only glycosylated haemoglobin, glucocorticoid treatment have been previously reported as risk factors for hyperglycaemia [9, 10].

Although the hospital-stay model was more accurate at predicting persistent AG, it included clinical variables that were difficult to obtain early in the admission. Determining the Charlson Comorbidity Index is difficult given it requires accurate documentation of seventeen diagnostic codes, and it is also not possible to determine observed-days (length of stay) from the outset at admission to hospital. Hence, the early identification model, using clinical factors reliably available at the beginning of the admission

course, was developed as a practical clinical prediction tool to identify high-risk individuals. The early-identification model confirmed four factors that predicted persistent AG, a biologically plausible finding as each factor either directly reflects glycaemia (Dysglycaemia at admission and glycosylated haemoglobin) or influence glycaemia (glucose-lowering regimen and glucocorticoid treatment). The early-identification model could be incorporated into an electronic medical record as a tool to flag individual at risk for persistent AG using variables from point-of-care glucose measurements, electronic prescription system, and pathology systems. Alternatively, in the absence of a fully-integrated electronic medical record, a clinical algorithm based on this model (such as depicted in Fig. 2) could be another tool used to identify high-risk individuals.

Importantly, this clinical prediction tool also identifies individuals at low-risk for persistent AG. We observed that individuals who had pre-admission glucose-lowering regimens which did not contain sulphonylurea or insulin (e.g. metformin monotherapy, or dual metformin and dipeptidylpeptidase-4 inhibitor therapy), and were not dysglycaemic at admission, were at low-risk of persistent AG. Hence, these individuals may not require aggressive and more expensive subcutaneous insulin treatment and this may decrease the risk of treatment-related hypoglycaemia in hospital.

The standard of hospital diabetes care is to treat hyperglycaemia with insulin [6], and various models of IDTs have been developed to increase insulin use and optimise glycaemic control, but the majority provide specialist management after the occurrence of hyperglycaemia or hypoglycaemia [21-23]. In the UK, the 'Think Glucose' project and 'Diabetes patient at risk' (DPAR) score system use patient clinical factors to guide treating teams to make appropriate and early referrals to the IDTs [28, 29]. Similar to the DPAR score, we found admission hypoglycaemia <4 mmol/L or hyperglycaemia >15 mmol/L to be important variables that should trigger IDT management. A strength of our early prediction tool is that it allows an IDT to remotely identify at-risk patients and provide early specialist management without referrals from treating teams. The tool can help predict at risk patients, thereby allowing very early intervention prior to the development, and hence even prevent adverse glycaemic from occurring. As the tool identifies patients at risk of either hyperglycaemia or hypoglycaemia, early specialist management may decrease both glycaemic extremes and could assist an early intervention model of inpatient diabetes care that we previously described [18], or other targeted inpatient diabetes management strategies. Another strength of this study is the use of a prospectively recruited cohort of consecutive inpatients who underwent detailed clinical characterisation and glucometric analysis.

A study limitation is that some potentially predictive clinical variables were not included, such as duration of diabetes, weight or sepsis. However, this reflects the 'real world' hospital clinical practice where these variables are often incompletely characterised and difficult to document electronically early in the admission course. We did not evaluate subsequent inpatient diabetes management such as changes in glucose-lowering medications, insulin, or nutrition, as the clinical prediction tool was designed to be used early in the admission course, and these variables can vary on a daily basis throughout the hospital stay. In this cohort, almost all glucocorticoid treatment was commenced within 24 hours of admission (e.g. used to treat conditions such as acute gout or exacerbation of chronic obstructive pulmonary

disease). However, in routine clinical practice, some individuals who have glucocorticoid treatment commenced later in the admission course may not be accurately categorised by the prediction tool. We used laboratory results including glycosylated haemoglobin in the prediction tool which may not be available in a rapid manner at every hospital, however recent glycosylated haemoglobin results from the community prior to hospital admission will be useful if this information can be obtained in a timely manner. In addition, glycosylated haemoglobin testing is recommended in all inpatients with diabetes [6], routine testing is performed for all inpatients at some hospitals [30], and rapid glycosylated haemoglobin measurement with point-of-care technology is also possible. A prediction model excluding glycosylated haemoglobin was found to be inferior and hence not pursued further. Lastly, this analysis included only patients with type 2 diabetes, to help identify high-risk patients out of this prevalent cohort. Individuals with type 1 and type 3c diabetes were not included in the prediction tool and could be considered already high-risk from a pathophysiological basis and from clinical experience.

In conclusion, we describe an easily implementable clinical prediction tool which may assist early identification of inpatients with diabetes at high-risk of persistent hyperglycaemia and hypoglycaemia. Our findings confirm clinician experience that dysglycaemia at admission, glycosylated haemoglobin, pre-admission glucose-lowering treatment regimen, and glucocorticoid medication treatment best predicted persistent adverse glycaemia in hospital. Further studies should aim to externally validate this tool and demonstrate if case-finding and early intervention in high-risk patients improves glycaemic and clinical outcomes. Clinical prediction tools could become essential for early identification and targeted management of individuals at risk for adverse glycaemia in hospital, and ultimately improve the care and outcomes of people with diabetes.

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Author Contributions

MK and SF conceived the study, contributed to collection of data, interpreted the results, and wrote the initial manuscript. JR and LR contributed to collection of data. MK and AG performed the statistical analyses. AG, PW and PC contributed to the study design, contributed to the discussion, and reviewed and edited the manuscript. All authors reviewed the final manuscript and approved for submission. SF had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Data availability

De-identified patient-level data set analysed in this study are available from the corresponding author on reasonable request.

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Conflicts of interest

All authors report no relevant disclosures or conflicts of interest.

Prior Presentation

Data from this study were presented as a poster presentation at the 78th American Diabetes Association meeting (Orlando, Florida, USA) in June, 2018

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Table 1 – Patient characteristics and clinical variables for all individuals; individuals without persistent glycaemia; and individuals with persistent adverse glycaemia

	All patients	No persistent AG [c]	Persistent AG [c]	p-value
Putative clinical risk factors	**n = 594**	**n = 441**	**n = 153**	
Age (years) mean (SD)	72 (13)	71 (13)	73 (13)	0.04
Men	341 (57)	253 (57)	88 (58)	0.99
Glucose-lowering treatment regimen prior to admission				<0.001
Diet controlled	124 (21)	109 (25)	15 (10)	
Glucose-lowering medications excluding sulphonylurea	161 (27)	136 (31)	25 (16)	
Glucose-lowering medications including sulphonylurea	141 (24)	96 (22)	45 (29)	
Insulin treatment	168 (28)	100 (22)	68 (45)	
Glycosylated haemoglobin				<0.001
≤ 7.0% (≤53 mmol/mol)	265 (49)	228 (58)	37 (25)	
7.1-8.0% (54-64 mmol/mol)	130 (24)	94 (24)	36 (25)	
≥ 8.1% (≥65 mmol/mol)	145 (27)	71 (18)	74 (50)	
Comorbidities				
Modified Charlson Comorbidity Index [a]				<0.001
0 to 1 points	263 (44)	221 (50)	42 (27)	
2 to 3 points	190 (32)	126 (29)	64 (42)	
4 to 5 points	105 (18)	73 (16)	32 (21)	
6 or more points	39 (6)	21 (5)	15 (10)	
Admission eGFR (ml/min/1.73m^2)				<0.001
≥ 90	129 (25)	106 (25)	23 (15)	
60 - 89	190 (33)	151 (35)	39 (26)	
31 - 59	194 (34)	134 (32)	60 (40)	
≤ 30	64 (11)	35 (8)	29 (19)	
Dysglycaemia at admission [b]				
Hypoglycaemia BG < 4 mmol/L	62 (10)	24 (5)	38 (25)	<0.001
Hyperglycaemia BG > 15 mmol/L	210 (35)	72 (16)	138 (90)	<0.001
Dysglycaemia BG <4 or >15 mmol/L	216 (37)	116 (26)	100 (65)	<0.001
Hospital Treatment				
Glucocorticoid medication	88 (15)	52 (12)	36 (24)	0.001
Admission Unit				
Medical units	398 (67)	214 (62)	117 (76)	0.004
- cardiology	133	77	28	
- general medicine	150	72	56	
- other medical	115	65	33	
Surgical	196 (33)	133 (38)	36 (23)	
- trauma/ orthopedic	83	49	19	
- general surgery	69	49	13	
- other surgical	44	35	4	
Admission Type				0.006
Elective admission	72 (12)	63 (14)	9 (6)	
Emergency admission	522 (88)	378 (86)	144 (94)	
Observed-days				<0.001
3 to 4 days	186 (31)	179 (41)	7 (5)	
5 to 7 days	189 (32)	138 (31)	51 (33)	
8 to 10 days	104 (18)	66 (15)	38 (25)	
11 or more days	115 (19)	58 (13)	57 (37)	

[a] Modified Charlson Comorbidity Index excludes items related to diabetes. [b] Dysglycaemia at admission (In the first 24h of admission). [c] Persistent Adverse Glycaemia to or more days with BG<4 or >15 mmol/L. Data presented as mean (SD) for age, and n (%) for all other variables.

Table 2– Regression coefficients and odds ratios for Persistent Adverse Glycaemia

	Persistent Adverse Glycaemia (≥2days)		
Putative clinical risk factor	**Coefficient**	**OR (95% CI)**	**p**
Dysglycaemia at admission [a]			
No	0	1	1
Yes	1.293	3.65 (2.09, 6.37)	<0.001
Glycosylated Haemoglobin			
≤ 7.0% (≤53 mmol/mol)	0	1	
7.1-8.0% (54-64 mmol/mol)	0.765	2.15 (1.13, 4.10)	0.020
≥ 8.1% (≥65 mmol/mol)	1.627	5.08 (2.63, 9.87)	<0.001
Glucose-lowering treatment regimen prior to admission			
Diet controlled	0	1	
Glucose-lowering medications excluding sulphonylurea	0.196	1.22 (0.52, 2.85)	0.652
Glucose-lowering medications including sulphonylurea	1.252	3.50 (1.57, 7.77)	0.002
Insulin treatment	1.440	4.22 (1.84, 9.70)	0.001
Glucocorticoid medication treatment			
No	0	1	
Yes	0.819	2.27 (1.17, 4.40)	0.015
Modified Charlson Comorbidity Index [b]			
0 to 1 points	0	1	
2 to 3 points	0.671	1.96 (1.09, 3.53)	0.026
4 to 5 points	0.725	2.06 (0.98, 4.34)	0.056
6 or more points	1.069	2.91 (1.02, 8.33)	0.046
Observed-days			
3 to 4 days	0	1	
5 to 7 days	2.363	10.6 (4.33, 26.1)	<0.001
8 to 10 days	3.276	26.5 (9.84, 71.2)	<0.001
11 or more days	3.980	53.5 (19.6, 146.3)	<0.001

[a] BG <4 or >15 mmol/L in the first 24h of admission. [b] Modified Charlson score excludes items related to diabetes.

Figures

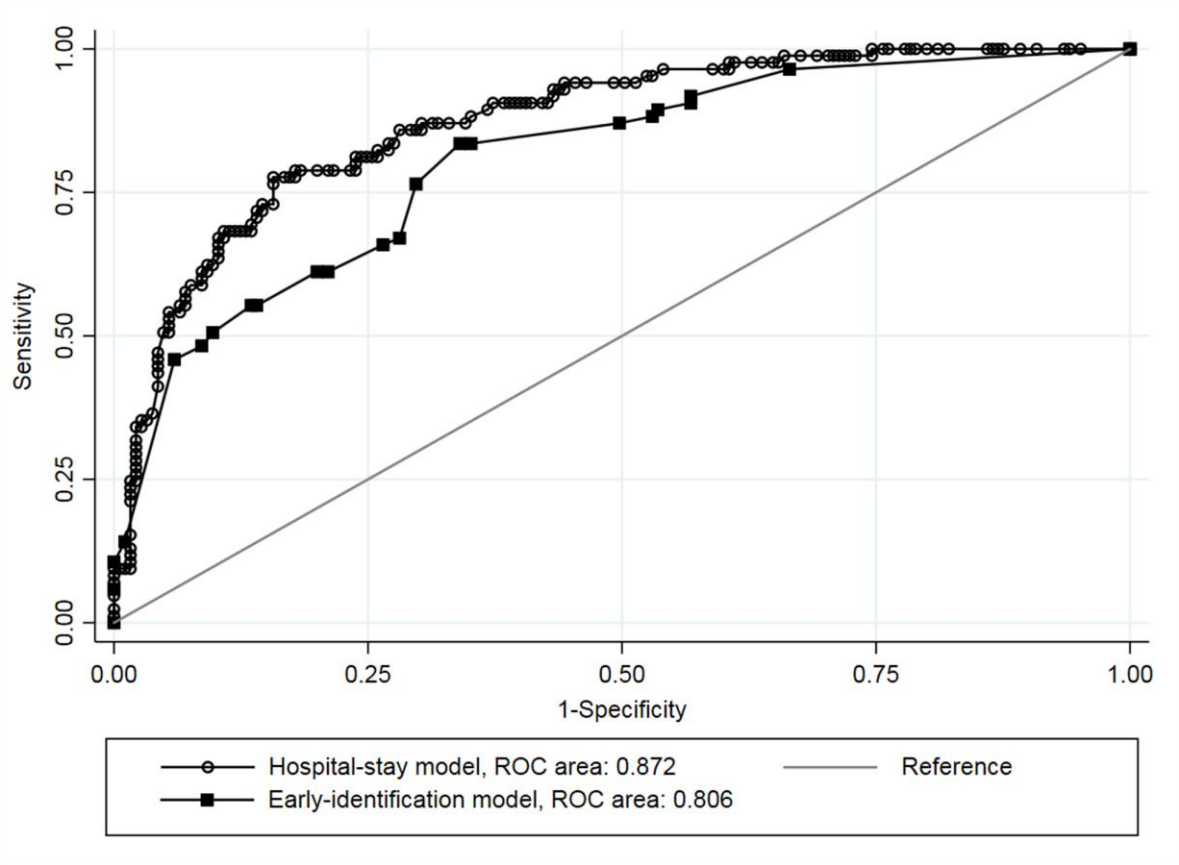


Fig. 1: Receiver operating characteristic (ROC) curves of models for predicting persistent adverse glycaemia. Hospital-stay model used six putative factors (dysglycaemia at admission, glycosylated haemoglobin, glucose-lowering treatment regimen prior to admission, glucocorticoid medication treatment, modified Charlson score and observed-days). Early identification model used four factors reliably available within 24 hours of admission (dysglycaemia at admission, glycosylated haemoglobin, glucose-lowering treatment regimen and glucocorticoid medication)

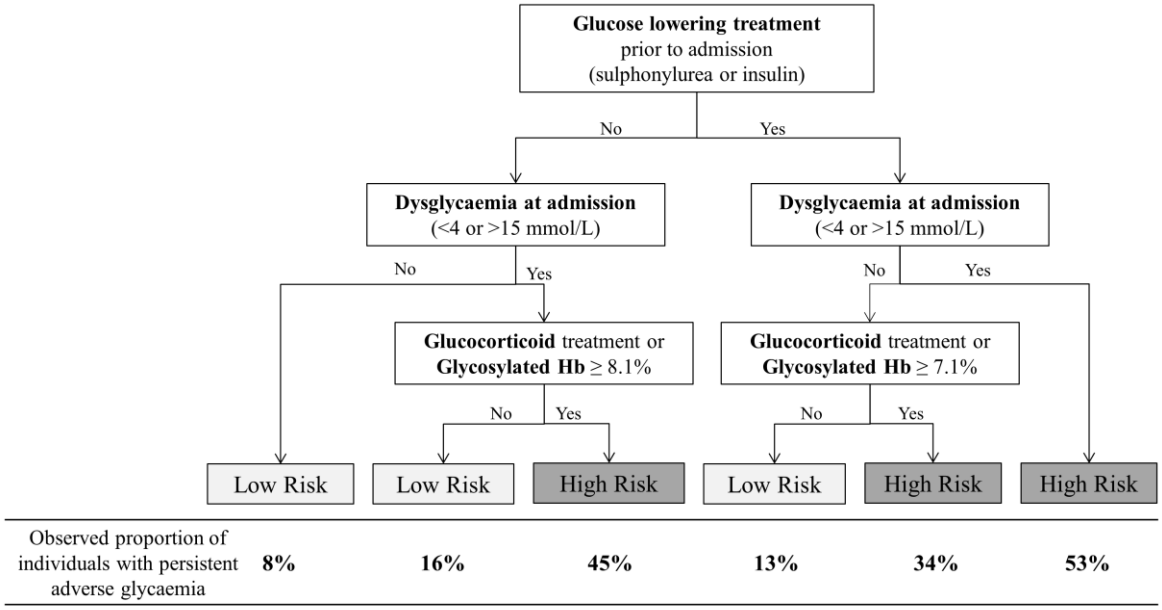
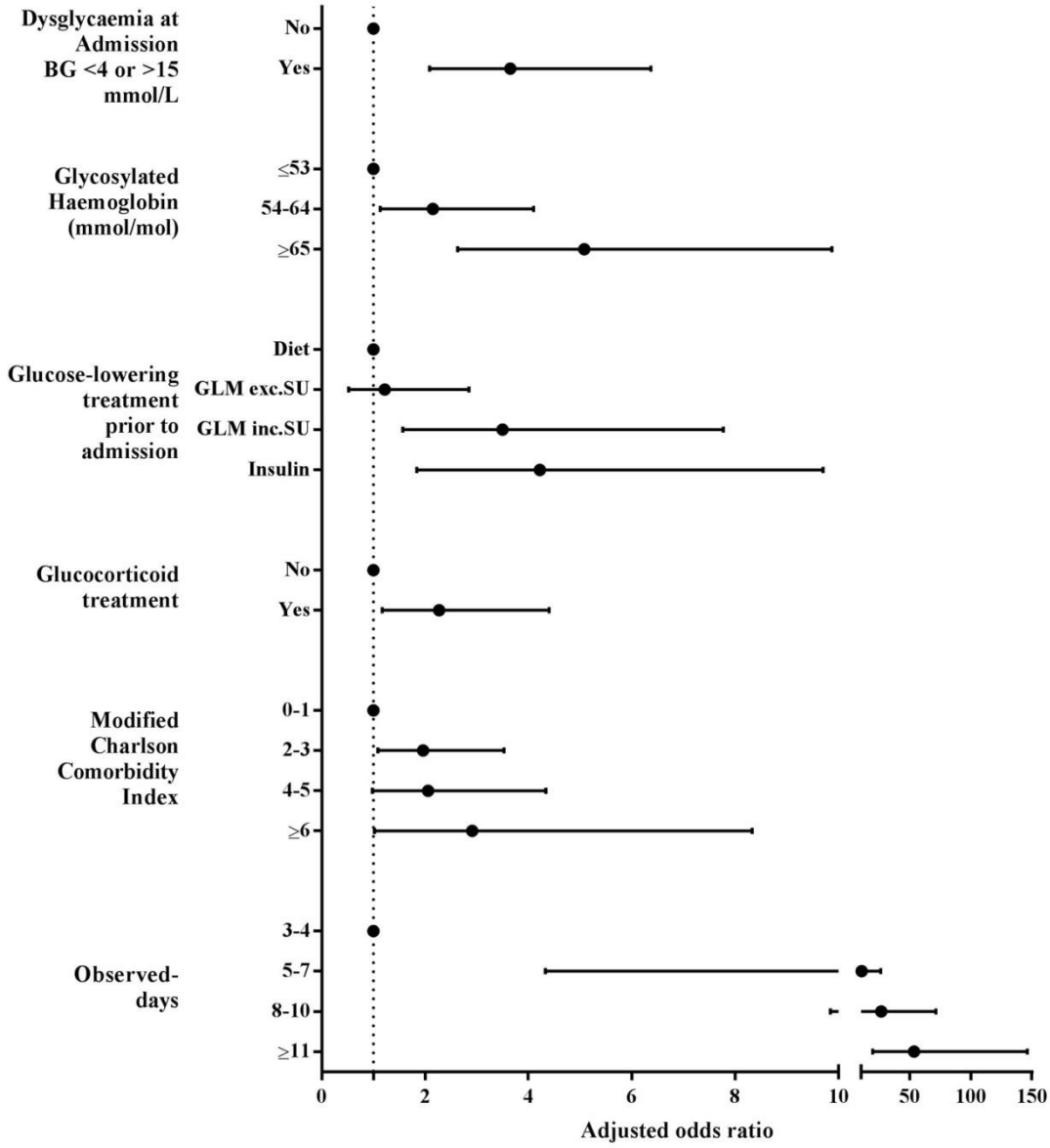


Fig.2: An algorithm based on the Melbourne Clinical Prediction Tool for predicting inpatients at high-risk for persistent adverse glycaemia during hospitalisation. Actual observed proportions of patients with persistent AG in the cohort are displayed beneath each corresponding category. Hb = haemoglobin

6.3 Supplemental material



Supplementary Figure 2: Adjusted odds ratio for **Persistent Adverse Glycemia**.
(2 or more days with adverse glycemia)

Supplementary table 1:

Regression coefficients and odds ratios for developing hyperglycaemia (BG >15.0 mmol/L)

	Hyperglycaemia (>15.0 mmol/L)		
Putative clinical risk factor	**Coefficient**	**OR (95% CI)**	**P value**
Dysglycaemia at admission *			
>15.0 mmol/L			
No	0	1	
Yes	1.308	3.70 (2.27, 6.02)	<0.001
Glycosylated hemoglobin			
≤ 7.0% (≤53 mmol/mol)	0	1	
7.1-8.0% (54-64 mmol/mol)	1.067	2.91 (1.71, 4.94)	<0.001
≥ 8.1% (≥65 mmol/mol)	1.607	4.99 (2.83, 8.80)	<0.001
Glucose-lowering treatment regimen prior to admission			
Diet controlled	0	1	
Glucose-lowering medications excluding sulphonylurea	0.155	1.17 (0.60, 2.29)	0.650
Glucose-lowering medications including sulphonylurea	0.994	2.70 (1.39, 5.25)	0.003
Insulin treatment	0.801	2.23 (1.14, 4.35)	0.019
Observed-days			
3 to 4 days	0	1	
5 to 7 days	1.117	3.06 (1.72, 5.43)	<0.001
8 to 10 days	1.920	6.82 (3.49, 13.3)	<0.001
11 or more days	2.002	7.41 (3.84, 14.3)	<0.001

* In the first 24h of admission

Supplementary table 2

Regression coefficients and odds ratios for developing hypoglycaemia (BG <4.0 mmol/L)

	Hypoglycemia (<4.0 mmol/L)		
Putative clinical risk factor	**Coefficient**	**OR (95% CI)**	**P value**
Dysglycaemia at admission*			
<4.0 mmol/L			
No	0	1	
Yes	1.775	5.90 (2.45, 14.3)	<0.001
Glucose-lowering treatment regimen prior to admission			
Diet controlled	0	1	
Glucose-lowering medications excluding sulphonylurea	-0.629	0.53 (0.15, 1.92)	0.336
Glucose-lowering medications including sulphonylurea	0.526	1.69 (0.63, 4.54)	0.296
Insulin treatment	1.565	4.78 (1.96, 11.7)	0.001
Modified Charlson Comorbidity Index †			
0 to 1 points	0	1	
2 to 3 points	0.934	2.54 (1.11, 5.83)	0.028
4 to 5 points	0.801	2.23 (0.88, 5.65)	0.091
6 or more points	2.061	7.86 (2.77, 22.3)	<0.001
Observed-days			
3 to 4 days	0	1	
5 to 7 days	0.898	2.45 (0.99, 60.7)	0.052
8 to 10 days	1.100	3.00 (1.11, 8.11)	0.030
11 or more days	1.829	6.23 (2.46, 15.8)	<0.001

* In the first 24h of admission. † Modified Charlson Comorbidity Index excludes items related to diabetes.

Supplementary table 3

Early identification model for persistent Adverse Glycaemia

	Persistent Adverse Glycaemia		
Clinical risk factor	**Coefficient**	**OR (95% CI)**	**P value**
Dysglycaemia at admission*			
<4.0 or >15.0 mmol/L			
No	0	1	
Yes	0.982	2.67 (1.69, 4.22)	<0.001
Glycosylated haemoglobin			
≤ 7.0% (≤53 mmol/mol)	0	1	
7.1-8.0% (54-64 mmol/mol)	0.618	1.85 (1.07, 3.23)	0.029
≥ 8.1% (≥65 mmol/mol)	1.219	3.38 (2.00, 5.73)	<0.001
Glucose-lowering treatment prior to admission (sulphonylurea or insulin)			
No	0	1	
Yes	1.043	2.84 (1.76, 4.57)	<0.001
Glucocorticoid treatment			
No	0	1	
Yes	0.835	2.31 (1.32, 4.04)	0.003
Constant	-2.776		

* BG<72 mg/dL in the first 24h of admission.

Regression equation:

Pr (persistent AG) = $\frac{e^{(y)}}{(1+e^{y})}$ where

$$y = -2.776 + 0.982(if\ dysglycaemia\ at\ admission) + 0.618(if\ GHb = 7.1 - 8.0\%) + 1.219(if\ GHb \geq 8.1\%) + 1.043(if\ on\ sulfonylurea\ or\ insulin\ \ treatment) + 0.835\ (if\ glucocorticoid\ treatment)$$

Supplementary table 4:

Discriminating ability of the early-identification model

Cut off point for the probability of persistent AG	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Correctly classified
0.05	1	0	0.31	-	1	-	0.31
0.10	0.92	0.43	0.43	0.92	1.61	0.19	0.59
0.15	0.88	0.47	0.43	0.90	1.66	0.26	0.60
0.20	**0.84**	**0.66**	**0.53**	**0.90**	**2.47**	**0.24**	**0.72**
0.25	0.67	0.72	0.52	0.83	2.39	0.46	0.70
0.30	0.61	0.79	0.57	0.82	2.90	0.49	0.73
0.35	0.55	0.86	0.65	0.81	3.93	0.52	0.76
0.40	0.48	0.91	0.72	0.79	5.33	0.57	0.78
0.45	0.48	0.91	0.72	0.79	5.33	0.57	0.78
0.50	0.14	0.99	0.86	0.71	14.00	0.87	0.72
0.55	0.14	0.99	0.86	0.71	14.00	0.87	0.72
0.60	0.11	1.00	1.00	0.71	-	0.89	0.72
0.65	0.06	1.00	1.00	0.70	-	0.94	0.70
0.70	0.06	1.00	1.00	0.70	-	0.94	0.70
0.75	0.00	1.00	-	0.69	-	1.00	0.69
0.80	0.00	1.00	-	0.69	-	1.00	0.67
0.85	0.00	1.00	-	0.69	-	1.00	0.67
0.90	0.00	1.00	-	0.69	-	1.00	0.67
0.95	0.00	1.00	-	0.69	-	1.00	0.67
1.00	0.00	1.00	-	0.69	-	1.00	0.67

PPV – Positive predictive value

NPV – Negative predictive value

LR+ positive likelihood ratio

LR- negative likelihood ratio

CHAPTER SEVEN: DISCUSSION AND CONCLUSIONS

7.1 Synopsis

Diabetes affects approximately one quarter of individuals in hospital, and contributes to worse clinical and economic outcomes. Hyperglycaemia causes adverse pathophysiological changes, including immune dysfunction, proinflammatory and prothrombotic changes and endothelial dysfunction, leading to increased risk of hospital-acquired infections, cardiovascular complications, longer length of stay and increased mortality. Hypoglycaemia also causes proinflammatory, prothrombotic, proarrhythmic and neuroglycopenic changes leading to adverse outcomes and increased mortality. The term 'adverse glycaemia' is used to describe both hypoglycaemia and hyperglycaemic extremes (defined as BG <4 or >15 mmol/L) that should be avoided for safe management of individuals in hospital.

Despite the importance of safe glycaemic control, adverse glycaemia continues to be common, particularly in noncritical care wards. Hyperglycaemia occurs in 50% of patients or 30% of patient-days, while hypoglycaemia occurs in 20% of patients or 10% of patient-days. Multiple barriers contribute to ongoing high rates of adverse glycaemia, including patient and illness-related factors, treatment-related factors, health professional-related factors and hospital system-related factors. A significant common barrier is clinical inertia in diabetes management, largely due to a lack of diabetes specialist involvement or guidance. To overcome clinical inertia, the aims of this thesis were to develop and investigate proactive or early intervention models of inpatient diabetes care to address adverse glycaemia.

This thesis investigated three different proactive interventions: a glucose alert system, a comprehensive proactive inpatient diabetes service, and a prediction tool for early identification of high-risk inpatients. The studies utilised networked blood glucose meter technology to develop the glucose alert system, to enable remote identification of inpatients with diabetes, and to ensure comprehensive glucometric data collection and analyses. In addition, this thesis presents the first detailed glucometric outcomes and benchmarking at an Australian hospital. The main results of this thesis are summarised below.

7.1.1 Early intervention using a glucose alert system decreases clinical inertia

A glucose alert system designed to increase health professional responses to adverse glycaemia (i.e. to decrease clinical inertia) was described in Chapter 3. The alert system consisted of a novel clinical escalation tool (Melbourne Glucose Alert Pathway), coupled with alert-capable networked glucose meters which provided visual alerts for adverse glycaemia. In a pre- and post-implementation study (n=148 patients), the use of this alert system demonstrated improvement in recognition and management of adverse glycaemia by health professionals. In response to episodes of adverse glycaemia, nursing staff increased notification to medical officers, and medical officers increased actions to address glucose control. The Hawthorne effect may have contributed to improvement in action, as the ward staff were aware that a clinical study was taking place. Indeed, the Hawthorne effect is an important aspect of remote glucose monitoring offered by networked glucose meters. Clinicians are more likely to be accountable for glucose measurements and subsequent actions if they are aware remote surveillance of glucose measurements could be taking place. Increased action led to decreased hyperglycaemia. Specifically, patient-days with BG >15 mmol/L decreased from 24% to 16%, and patient-days with mean BG >15 mmol/L decreased from 7.4% to 2.5%. There was no change in the incidence of hypoglycaemia. Adverse glycaemic days (patient-days with BG <4 or >15 mmol/L) decreased from 290 per 1000 patient-days to 215 per 1000 patient-days.

The glucose alert system is an example of a proactive intervention for inpatient diabetes care, as it encourages earlier recognition and treatment of adverse glycaemia. Although there was improved medical staff action, most actions were temporary or 'Band-Aid' solutions, such as prescription of correctional (or once off, stat dose) insulin. Referrals to the inpatient diabetes team did not increase. Furthermore, the cohort consisted of predominantly elective surgical patients with relatively uncomplicated diabetes, and it is unclear if the same efficacy of glycaemic improvement would be observed in more complex diabetes patients. This study did not evaluate the relative impact of glucose alert pathway vs. alert capable networked glucose meters in improving clinical care. A clinical study comparing glucose alert pathway with and without networked glucose meters could be performed to address this question. None-the-less this study demonstrates the importance of alert systems in decreasing clinical inertia. Both the networked glucose meters and Glucose Alert Pathway are essential components of the early intervention model developed for the RAPIDS trial.

7.1.2 Glucometric assessment demonstrated high incidence of adverse glycaemia at the Royal Melbourne Hospital

Detailed glucometric analysis of a cohort of consecutive noncritical care patients (n=465 admissions) was described during the baseline period of the RAPIDS trial (Chapter 4). Well-established glucometric reporting techniques were applied to capillary glucose data obtained by the networked glucose meters. This was also the first report of detailed glucometric outcomes at an Australian hospital. Compared to the largest published glucometric benchmarking study in US hospitals, the RMH patient cohort had a higher

incidence of hyperglycaemia (e.g. patient-days with mean BG >10 mmol/L: 37.0% vs. 32.3%, p<0.001), but a lower incidence of hypoglycaemia (e.g. patient-days with BG<3.9 mmol/L: 4.1% vs. 6.1%, p<0.001). The findings were potentially influenced by the differences in routine clinical practice between US and Australian hospitals. In particular, the practice of cessation of all GLM and prescription of subcutaneous insulin in all patients with diabetes admitted to hospital is widely promoted in the US but not in Australia. Our cohort has relatively fewer patients with type 1 diabetes (4%) compared to 8% in the UK which may account for lower rates of hypoglycaemia. In addition, other differences in patient characteristics including number of comorbidities, glucocorticoid treatment and readmissions may account for the differences in the rates of hypoglycaemia and hyperglycaemia.

We propose the concept of adverse glycaemic day (AGD), as novel metric of unsafe levels of hypoglycaemia and hyperglycaemia, which can be used for future benchmarking. The metric of AGD has advantages over traditional metrics as it encompasses both hyperglycaemic and hypoglycaemic extremes. AGD is a tangible concept that can help educate health professionals about glucose extremes that should be avoided in hospital. The incidence of AGD was 260 per 1000 patient-days in the cohort of medical and surgical patients, slightly lower than observed in the cohort of mostly surgical patients in Chapter 3. Accordingly, AGD formed the primary outcome measure used to investigate the proactive model of care in the RAPIDS study. Finally, Chapter 4 also demonstrated that the majority (80%) of observed AGDs occurred in a subgroup (25%) of individuals, suggesting a strategy of identifying and targeting high-risk individuals may be possible.

7.1.3 Early intervention (RAPIDS) model of inpatient diabetes care decreased adverse glycaemia

A comprehensive early intervention model of inpatient diabetes care was developed (Chapter 5) and investigated in the large-scale prospective cluster randomised (RAPIDS) trial. The RAPIDS model comprised a bundle of three interventions: 1) glucose alert system developed in chapter 3; 2) networked BG meters which enabled remote surveillance and identification of patients with diabetes; and 3) proactive IDT which delivered proactive care (without referral from treating teams) and direct management (directly prescribed medication and insulin). The proactive IDT aimed to provide management within 24 hours of admission to <u>all</u> patients with diabetes and hyperglycaemia, as a proof of concept for this model of care. As the IDT operated during business hours on weekdays, not all patients had management within 24 hours, particularly those that were admitted over the weekend.

This model of care was investigated in an open-label cluster randomised study with a baseline period. This complex study design was necessitated by the nature of the intervention which could only be delivered at the cluster level, and due to enrolment of eight hospital wards with unique medical and surgical services within a hospital. Analysis was performed using mixed-model multivariable regression

to account for baseline clinical differences and effects of clustering, and included assessment of outcomes as change from baseline within each treatment arm.

With the early intervention model of care, almost all individuals with diabetes received specialist management (two thirds of patients receiving specialist management within 24 hours of admission), and more individuals received insulin treatment. The intervention decreased the incidence of AGD from 240 to 190 per 1000 patient-days at the cluster level and by 28% at the individual patient level. There was a decrease in patient-day mean BG from 9.4±3.3 to 9.0±2.7 mmol/L, and a 55% reduction in severe hyperglycaemia (patient-days with mean BG >15mmol/L) from 7.3% to 3.3%. The intervention was particularly effective at decreasing extremes of hyperglycaemia despite a modest reduction in patient-day mean glucose. There was no difference in the incidence of hypoglycaemia; however, this is in the context of relatively low incidence of hypoglycaemia at baseline compared to US and UK hospitals as demonstrated in Chapter 4.

RAPIDS is one of only two completed prospective randomised trials of an IDT published to date. Almost two decades ago, Davies et al., reported a RCT (n=300 patients) of a diabetes nurse education service which resulted in a reduction in median hospital LOS from 11 to 8 days [264]. Other subsequent studies of IDTs were observational studies with only a few reporting glycaemic, clinical and LOS outcomes concurrently. Compared to RCTs of insulin regimens, which enrolled between 50 and 400 participants, RAPIDS included 1002 participants and is one of the largest randomised trials of diabetes care in the noncritical care setting.

RAPIDS provided prospective RCT evidence on the efficacy of IDTs, particularly an early intervention model of care, at improving glycaemic control and decreasing adverse glycaemia. AGD reduction was driven by improvement in hyperglycaemia as a result of increased insulin treatment, without a concurrent increase in hypoglycaemia. Chapter 3 demonstrated the glucose alert system decreased AGD from 290 to 215 per 1000 patient days. RAPIDS was conducted on different wards and included a different patient cohort to chapter 3; therefore, the baseline incidence of AGD cannot be directly compared. Nonetheless, the comprehensive intervention in RAPIDS appeared to decrease AGD even further (from 240 to 190 per 1000 patient-days). This reduction was both statistically and clinically significant compared to the parallel control group. As a proof-of-concept of proactive care, the IDT provided management to all inpatients with diabetes but this was resource intensive. Further refinement of the intervention will be required to ensure a sustainable model of care. None-the-less, RAPIDS clearly demonstrated the efficacy of diabetes specialist management in decreasing clinical inertia, increasing insulin treatment, and subsequently improving glycaemic control.

7.1.4 Early intervention (RAPIDS) model of inpatient diabetes care decreased hospital-acquired infections

In the RAPIDS cohort, the baseline incidence of hospital-acquired infection (7.5%) is consistent with published incidence in Australian hospitals [302]. RAPIDS demonstrated a significant reduction in hospital-acquired infections with early intervention, which was a secondary outcome verified by blinded adjudication. The magnitude of change was an 80% relative risk reduction (adjusted odds ratio 0.20 after adjustment for covariates), and a 4% absolute risk reduction, equating to a number needed to treat of 25 for preventing one hospital-acquired infection. Reduction in hospital-acquired infection was observed with a modest decrease in mean glucose, but a marked decrease in severe hyperglycaemia. This suggests that targeting extremes of hyperglycaemia may be more efficacious than achieving reductions in mean glucose.

There is a strong biological basis which supports the link between decreased hyperglycaemia and decreased infections. Acute hyperglycaemia causes impaired immunity due to neutrophil and phagocyte dysfunction, which increases vulnerability to bacterial infections. Immune dysfunction appears to occur at a threshold of 12 to 14 mmol/L, although different thresholds exist in people with and without pre-existing diabetes (section 1.4.1.1). Immune dysfunction can be reversed upon resolution of hyperglycaemia [303]. Therefore, it is biologically plausible that early intervention, which decreased episodes of severe hyperglycaemia, resulted in decreased hospital-acquired infections. The findings are also in concordance with previous results in noncritical care. In RABBIT2-surgery study, a reduction in hyperglycaemia led to a decrease in hospital-acquired pneumonia and wound infections [143]. A meta-analysis in noncritical care inpatients demonstrated decreased infection with intensive insulin treatment [147]. Reducing perioperative hyperglycaemia using a glycaemic alert system also demonstrated improvement in post-operative wound infections [256]. RAPIDS study adds to the growing evidence that reduction in infection may be a standout benefit of treating inpatient hyperglycaemia.

RAPIDS included inpatients with all diabetes types but it could be postulated that acute hyperglycaemia during hospitalisation has different biological consequences between patients with T1D, T2D and new hyperglycaemia. Therefore, clinical outcomes including hospital-acquired infections were subjected to exploratory subgroup analyses (chapter 5 supplementary materials) to delineate outcomes in a more homogenous group containing only type 2 diabetes patients. Indeed, improvement in hospital-acquired infections was confirmed in a pure cohort of individuals with type 2 diabetes. Furthermore, subgroup analyses between medical and surgical patients demonstrated hospital-acquired infections were more prevalent in medical patients at baseline, and the greatest reduction in hospital-acquired infections occurred in medical patients. This is contrary to the observations that hyperglycaemia is a risk factor for wound and surgical site infections, and contrary to the previous meta-analysis demonstrating benefit in mainly surgical patients [147]. However, given that hospital-acquired infection was one of a number of secondary outcomes, results should be regarded as hypothesis generating, and should be subjected to further prospective clinical studies.

7.1.5 Generalisability of early intervention (RAPIDS) model of inpatient diabetes care

Although early intervention decreased adverse glycaemia and hospital-acquired infections, there are limitations to the generalisability of the RAPIDS early intervention model. It was a single centre study performed in a hospital without a pre-existing comprehensive EMR or insulin order sets. As a result, our findings may not be generalisable to all health systems. The early intervention model of care may have less efficacy in some large US academic hospitals with fully integrated electronic systems, insulin order sets and pre-existing glycaemic management teams. However, many other hospitals in Australia, Asia, Europe and the United Kingdom possess similar clinical systems, infrastructure and approach to inpatient diabetes care.

The RAPIDS model of care was resource-intensive as the proactive IDT provided management to all inpatients with diabetes or hyperglycaemia. Further refinement of this model of care will be necessary for a sustainable proactive inpatient service. One approach is to selectively target the subgroups of patients who had persistent AGDs or those who were at high-risk of adverse outcomes. In addition, it will be important to perform health economic analyses to inform the costs vs. benefits of a refined model of early intervention. Nonetheless, RAPIDS demonstrated that early intervention and proactive management by a specialist diabetes teams improve glycaemic control and clinical outcomes.

7.1.6 A prediction tool can facilitate targeted and early management of high-risk inpatients with diabetes

The clinical characteristics of high-risk patients, defined as those who developed persistent adverse glycaemia during hospitalisation was investigated in Chapter 6. In addition, we investigated whether it was possible to identify these high-risk patients at the time of admission. The analysis was based on the cohort of patients who received usual care during the RAPIDs trial. It identified four clinical variables, which were readily available early in admission, that were associated with subsequent development of persistent adverse glycaemia. These four variables were glucose at admission (BG <4 or >15 mmol/L in the first 24 hours); glucose-lowering treatment regimen containing insulin or sulphonylurea; glycosylated haemoglobin; and glucocorticoid treatment. Based on these four factors, a clinical prediction model accurately identified patients who subsequently developed persistent adverse glycaemia with a ROC-AUC of 0.806. This prediction tool can be built into an EMR which can generate an alert system to identify high-risk patients. Alternatively, these patients can be identified using a flowchart algorithm as described in Chapter 6 figure 2.

Although prediction tools for hypoglycaemia have been described, this is the first description of a clinical tool to predict the more common glycaemic extreme of hyperglycaemia. Additional novelty of this tool is the ability to identify high-risk inpatients early (within 24 hours) of admission; therefore, it is well-placed to refine the RAPIDS early intervention model of care. For example, using the optimal cut-off of 0.20 probability, the tool would classify 46% of inpatients as potentially high risk. The proactive IDT can

focus management on this cohort with a sensitivity of 84% and specificity of 66% for identifying patients with persistent hyperglycaemia. Depending on available resources the threshold probability can be shifted to select a smaller or larger subgroup for proactive intervention. Conversely, the clinical prediction tool also identifies the patients who are at low-risk of developing adverse glycaemia (i.e. patients who may not need glycaemic intervention), and this may decrease aggressive insulin therapy in this cohort which may decrease the risk of treatment-related hypoglycaemia. The prediction tool can facilitate any number of inpatient diabetes interventions which aims to provide early targeted management. With increasing prevalence of diabetes in hospital, identification and targeted management is expected to become an essential strategy for sustainable inpatient diabetes services.

7.2 Clinical implications

The findings described in this thesis have immediate and practical clinical utility, and have the potential to transform clinical practice. Firstly, diabetes inpatients at our Australian hospital had a high incidence of adverse glycaemia. Indeed, our incidence of hyperglycaemia was significantly higher than US hospital benchmarks, although this was partially offset by our lower incidence of hypoglycaemia. Nonetheless, it confirmed the need to improve glycaemic control, and also highlighted the need to establish local benchmarking of glycaemic control in Australian hospitals.

Secondly, our findings demonstrated proactive care interventions can decrease clinical inertia, decrease adverse glycaemia and improve clinical outcomes. Each of the three examples of proactive interventions can be implemented either as stand-alone systems or as a bundle of interventions to help decrease adverse glycaemia. The Melbourne Glucose Alert Pathway and the glucose alert system are simple interventions that can be implemented at many hospital systems with or without electronic clinical systems. Implementation of such an alert system has the potential to decrease clinical inertia and increase health professional action to address adverse glycaemia. The prediction tool for high-risk diabetes inpatients is another readily implementable tool which can assist a variety of glycaemic interventions to provide targeted management.

Thirdly, the RAPIDS early intervention model of inpatient diabetes care, consisting of remote surveillance and proactive management by an IDT, can be implemented in many hospitals. Although the IDT in RAPIDS managed every patient with diabetes or hyperglycaemia, a targeted management approach on the high-risk subgroup will be less resource intensive and more sustainable. Indeed, the Department of Diabetes and Endocrinology at RMH now provides a targeted clinical service of proactive management in high-risk individuals in the cardiology wards following the completion of RAPIDS.

Early or ‘proactive’ intervention is a common theme in this thesis. This approach is particularly important as blood glucose is a highly dynamic variable, and can be affected by many clinical factors, often early in the admission course. For this reason, it is believed that early specialist management can have greatest efficacy at improving clinical outcomes. This is in contrast to the traditional ‘reactive’ model of care which relies on referrals from treating teams, which often occur many days into the admission course, often after many days of persistent adverse glycaemia. Although several models of early intervention are presented in this thesis, other alternative approaches of proactive care may be efficacious at improving glycaemic control. None-the-less proactive models developed in this thesis provide tangible and practical interventions, which can be implemented in a variety of hospital settings to assist improving inpatient glycaemia.

From a conceptual point of view, our findings suggest addressing adverse glycaemia, potentially with any effective approach, may improve clinical outcomes. Reduction in hospital-acquired infection

demonstrated in this thesis was consistent with the literature in cardiac surgery [116], perioperative services [256], critical care [130] and noncritical care [147]. Any clinical improvement programs or models of care which decrease hyperglycaemia may decrease the risk of infection. A benefit of the RAPIDS model of care, which provides autonomous proactive management of patients, is the ability for the IDT to incorporate latest glycaemic management practices and emerging technologies in diabetes treatment.

7.3 Future research suggestions

Suggested future research to build on our findings can be summarised into the following six themes.

1. To investigate the efficacy of early identification and targeted management of high-risk inpatients using the clinical prediction tool to refine the RAPIDS model of care. Chapter 6 described a practical clinical prediction tool which can be used to risk categorise inpatients between low and high risk of persistent adverse glycaemia. An early intervention model of proactive care can be delivered by an IDT to the subgroup of 'high-risk' patients to improve glycaemic outcomes. Targeted management is expected to be less resource intensive and more sustainable than universal management of all diabetes inpatients. Indeed, as part of ongoing clinical research programme, an observational study evaluating proactive care in high-risk patients in cardiology wards has been conducted.

2. To investigate long-term outcomes of the RAPIDS intervention at the patient level and at the ward level. To evaluate long-term outcomes for patients included in RAPIDS, a follow-up study will evaluate readmission and mortality at 30-days and at 1-year post discharge from hospital. Data linkage with state-wide hospital admission database and with the national death registry will be conducted to assess these outcomes. HbA1c at 3 months following discharge from hospital will be evaluated to assess longer term glycaemic outcomes for patients who received proactive care vs. usual care. At the ward level, an observational extension study has been underway assessing ward glucometrics to assess whether improvements in glycaemic outcomes are sustained following the cessation of proactive care.

3. To analyse the health economics of a targeted proactive model of care. Decreased incidence of hospital-acquired infection translates to cost savings for the health system. Cost savings will need to be balanced against salary costs of IDT staff members and capital costs of networked glucose meters.

4. To refine the clinical practice of hospital glycaemic control. Although different insulin regimens have been compared in pre-existing literature, further studies are required to optimise insulin dose initiation and dose adjustment in various settings. For example, there is a need to investigate insulin adjustment protocols in situations such as: 1) glucocorticoids commencement or dose adjustment; 2) GLMs (especially metformin) cessation or recommencement. These clinical studies can be pre- and post- implementation studies, or randomised trials of different algorithms. These studies should inform clinical practice to optimise guidelines and algorithms, in addition to upskilling IDTs

5. To investigate the biological and clinical link between adverse glycaemia and adverse clinical outcomes, especially hospital-acquired infections. This can consist of an observational study of inpatients with or without diabetes or new hyperglycaemia; and inpatients with or without hospital-acquired infections. The aim of such a study would be to identify the specific patient cohorts that are particularly susceptible to hyperglycaemia-related hospital-acquired infection and those who are most likely to benefit from improved glycaemic control. This will enable a definitive study to confirm improvements in clinical outcomes observed in RAPIDS.

6. To perform a large-scale intervention study aimed at early intervention to improve glycaemic control with the primary outcome of decreasing infection complications. To confirm RAPIDS findings, a prospective multi-centre randomised controlled trial of early intervention by a proactive inpatient diabetes service should be conducted. This trial would ideally involve a parallel or stepped wedged, cluster randomised design involving multiple clusters at multiple hospitals. Indeed, our research group continues to seek funding from the National Health and Medical Research Council for such a large-scale RCT.

7.4 Concluding remarks

Despite the importance of glycaemic control in hospital inpatients, adverse glycaemia and associated clinical complications remain common. This thesis aimed to better understand glycaemic landscape in hospital and to develop proactive or early intervention models of diabetes care to address adverse glycaemia. Networked glucose meter technology was used to perform detailed glucometric assessment, and to develop proactive interventions to overcome clinical inertia and improve inpatient glycaemia.

Three examples of proactive diabetes interventions were developed and investigated. A glucose system improved health professional action to address adverse glycaemia. A comprehensive early intervention model of diabetes care, comprising remote glucose surveillance and proactive management by an inpatient diabetes team, was investigated in a large-scale cluster randomised trial. This model of care decreased extremes of hyperglycaemia, and demonstrated a reduction in hospital-acquired infections. A practical clinical tool was then developed for early identification of high-risk patients to assist early and targeted management for sustainable proactive interventions.

This thesis demonstrates early intervention for diabetes care improves inpatient glycaemic control. It suggests that reducing adverse glycaemia may decrease hospital-acquired infection and improve clinical outcomes. The findings are clinically relevant and may assist transforming the approach to hospital diabetes management. Proactive and early intervention approaches to diabetes care in hospital should be implemented to improve the care of inpatients with diabetes.

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