Assessment of the management of inpatient hyperglycaemia by physicians and intensivists in South African hospitals

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the department of Internal Medicine

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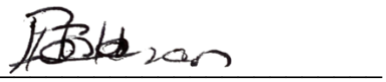
Declaration

I, Peter Llewellyn Blanshard Hewson, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the department of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Dr Peter Llewellyn Blanshard Hewson

12 June 2023

Date

Dedication

To Allayne, my loving wife, and my family, for all your support.

Publications and presentations arising from this research

1. Poster presentation to the Critical Care Society of Southern Africa Congress, Johannesburg, 13-16 October 2022
    - Poster details: Hewson PLB, Seedat F, Mohamed NA. The management of inpatient hyperglycaemia by intensivists in South African Hospitals

Ethics Committee Approval

Approval for this research was obtained from the Human Research Ethics Committee for Medical Sciences of the University of the Witwatersrand on 11 March 2020, Clearance certificate number M191052. Subsequent approval for continued investigation during the COVID-19 pandemic was obtained on 17 August 2020. Approval certificates may be found in Appendix F.

Abstract

Background: Hyperglycaemia is highly prevalent in patients admitted to hospital and is associated with prolonged hospital stay, increased costs, morbidity and mortality. As there is currently limited local data on the management of hyperglycaemia, this study aimed to investigate physician practices in the management of inpatient hyperglycaemia in South African hospitals.

Methods: A survey investigated the practices of 154 physicians in general medical wards and intensive care units (ICUs) in the state and private sectors. To validate these responses, an audit of 100 general medical and 111 ICU patient files was performed at three major Johannesburg academic hospitals. Patients with inpatient hyperglycaemia related to diabetes mellitus (DM) or hospital-associated factors were included, while patients admitted with diabetic emergencies were excluded.

Results: In the general medical wards, oral hypoglycaemic agents (OHAs) were used in the majority of survey respondents (94.5%) and audited files (64%). In the ICU, OHAs were used by 34.9% of survey respondents and 14.4% of audited patient files. Of the OHAs, metformin use was most frequently reported (93.8% in the survey) and used (64% in the audit) agent in the general medical wards, followed by sulfonylureas (SUs) (75.8% in the survey and 5% in the audit). In the critical care setting, the survey demonstrated frequent use of metformin followed by dipeptidyl peptidase-4 inhibitors (DPP4-i), while the audit showed that metformin and SU use was 14.4% and 0.9% respectively.

Surveyed clinicians in general medical wards report most frequently using the basal insulin plus sliding scale insulin (SSI) regimen (36.6%), while the audit showed that SSI alone (36%) or premix insulin-based regimens (34%) are used most often. In the critical care setting, more surveyed clinicians reported using an insulin infusion (34.9%) compared to other insulin regimens, while the audit demonstrated that the majority of patients (59.5%) were managed with SSI alone.

Four-to-six hourly glycaemic monitoring was noted as the standard of care in both surveys and audits. While the majority of clinicians reported daily review of their glycaemic management (91.7% and 87.3% of participants in the general medical wards and ICU, respectively), the audit revealed that this was noted in just 34% and 3.6% of participants in the general medical wards and ICU, respectively.

Conclusion: Both the survey and audit demonstrated significant discrepancies from current clinical guidelines. This highlights a significant impact on patient care, in particular, as OHAs have not been recommended for use in the ICU setting, one in every three critical care patients may be exposed to potential complications as a result of the use of such agents. The findings of this study suggest further investigations regarding inpatient hyperglycaemia practices as well as implementation of education and in-hospital protocols are needed in the South Africa healthcare context in order to improve clinical outcomes.

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Abbreviations

ADA	American Diabetes Association
ANOVA	Analysis of variance
CGM	Continuous glucose monitoring
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP4-i	Dipeptidyl peptidase-4 inhibitor
FDA	United States Food and Drug Administration
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HPCSA	Health Professions Council of South Africa
HJH	Helen Joseph Hospital
ICU	Intensive care unit
IDF	International Diabetes Federation
IQR	Interquartile range
OHA	Oral hyperglycaemic agent
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
SGLT2-i	Sodium-glucose cotransporter 2 inhibitor
SD	Standard deviation
SSI	Sliding scale insulin
SU	Sulfonylurea
TDD	Total daily dose
TZD	Thiazolidinedione
UK	United Kingdom
USA	United States of America

Chapter 1: Background literature analysis

1.1. Introduction

Hyperglycaemia is a highly prevalent and multifactorial condition which places a significant burden on the healthcare sector.[1-2] The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) defines inpatient hyperglycaemia as measured blood glucose levels above 7.8 mmol/L.[1] This definition is in line with other international associations such as the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists.[3] The diagnosis of inpatient hyperglycaemia can be classified into one of three categories: patients previously diagnosed with diabetes mellitus (DM); unrecognised DM where patients have documented inpatient hyperglycaemia which persists and meets the diagnostic criteria for DM following discharge; and patients who have hyperglycaemia which is hospital-related, is triggered by many factors including medications or the adrenergic stress response and resolves following discharge.[1]

1.2. Impact of inpatient hyperglycaemia on the healthcare sector

DM is a global pandemic with an increase in the combined prevalence of diagnosed and undiagnosed type 1 and type 2 DM of 16% in two years from 2019 to 2021 and a projected increase of 46% over 24 years from 2021.[2] According to the International Diabetes Federation (IDF), it is estimated that between 2000 and 2021 there was a global average increase in the prevalence of patients with DM aged 20-79 years of 12.2% per year.[2] Estimates in 2021 showed DM accounted for 10.5% of the global population, equivalent to 537 million cases.[2] Africa had 24 million cases of DM, of which 53.6% were predicted to be undiagnosed.[2] By 2045, 12.2% of the world's population is projected to have DM and Africa is forecasted to have a 134% increase in people living with DM from 2021 to 2045.[2] The latter equates to just under three times the global average.[2]

Hyperglycaemia is associated with an increased frequency, duration and cost of hospital admission as well as more frequent medical interventions during admission.[4-6] Records from the United Kingdom (UK) between 2006 and 2010 note that 97 689 patients with type 2 DM were registered on the general practice research database.[4] Of these, 59.4% were admitted with an average of 4.44 admissions per patient over the five year review.[4] In 2019, the prevalence of DM in the UK increased to 7% in the general population and 18.1% in UK hospitals, equating to almost one in six hospital beds being occupied by a patient with DM.[7]

Unfortunately there is a paucity of data on the prevalence of inpatient hyperglycaemia in South African hospitals.

Regarding duration of admission, a London study showed a longer hospital stay in patients with hyperglycaemia amongst a cohort with underlying chronic obstructive pulmonary disease (COPD) and a 15% greater chance of adverse outcomes including prolonged hospital stay per 1 mmol/L rise in glucose.[8] In 2010, the cost of extended hospital admission due to hyperglycaemia in the UK was estimated to be 129.2 million pounds per annum whilst the total excess costs associated with the management of inpatient hyperglycaemia amounted to 573-681 million pounds per annum.[9] A similar trend was described locally in a 2009 study comparing DM versus non-DM related hospital admissions in a tertiary-level hospital in Johannesburg, South Africa.[10] Amongst patients with DM, the duration of admission was 47% longer, and the total hospital cost was one and a half times greater than that of patients without DM.[10] However, it should be noted that patients were categorised into broad groups, based on organ systems, rather than matched according to demographics and specific conditions.[10] This could introduce an element of bias.

Patients with DM are at increased risk of morbidity and mortality, the aetiology of which is multifactorial.[11] Inpatient hyperglycaemia, in particular, is associated with poorer patient outcomes, including higher rates of infections, post-operative complications and mortality.[6,12-15] A Canadian study involving 2 471 inpatients with community-acquired pneumonia showed a 4% higher mortality rate and 7% higher complication rate in patients with admission glucose levels measuring above 11 mmol/L.[16] Furthermore, compared to patients with serum glucose levels under 6.1 mmol/L, the risk of complications and mortality was 52% and 73% higher, respectively.[16] This study illustrated that a rise in the serum glucose level of 1 mmol/L was associated with a 3% higher rate of inpatient complications.[16] This is supported by *Baker et al.*, who found that in patients with COPD, there was a 10% rise in mortality for every 1 mmol/L rise in serum glucose.[8] An additional study from Boston showed a 5.8 times higher rate of postoperative infection in patients with raised serum glucose levels.[17]

Patients with DM require more frequent and intensive monitoring, administration of medications, and ventilatory assistance compared to those without DM.[5] There is also a higher frequency of medication use, such as antimicrobials, corticosteroids, treatments for concomitant chronic illnesses and vasoactive medications in patients with DM.[5] This increase in medical intervention has been particularly pertinent during the Coronavirus Disease 2019 (COVID-19) pandemic where DM has been noted to be a frequent co-morbidity in patients

treated for SARS-CoV-2 infection and is also recognised as an independent risk factor for severe disease.[14]

An analysis of 1122 hospitalised patients with SARS-CoV-2 infection in the United States of America (USA) from March to April 2020 showed that 17.3% of all admissions had concomitant DM and a further 22.9% had uncontrolled hyperglycaemia on admission.[14] This at-risk group places a higher burden on the healthcare sector by increasing the duration of hospital admission[14] and required resources for staffing, glucose monitoring and treatment[11]. *Zhu et al.* demonstrated that patients with DM required higher administration of antibiotics, systemic corticosteroids, antihypertensive medications and various forms of oxygen support, from supplemental oxygen to invasive ventilation.[5] In the above-mentioned analysis from the USA, there was a 28.8% in-hospital mortality in patients with DM or uncontrolled hyperglycaemia compared to 6.2% in-hospital mortality in patients without hyperglycaemia.[14] Furthermore, it has been estimated that patients with DM have a two to four times increased risk of mortality from SARS-CoV-2 infection compared to patients without DM[18].

Hyperglycaemia may also be linked to hospital-related factors.[1,19-20] Up to 86% of inpatients managed with glucocorticoids above physiological doses are complicated by hyperglycaemia.[21] Additionally, many patients admitted to hospital experience a stress response characterised by physiological, hormonal and metabolic changes resulting in increased counterregulatory hormone release.[13,19-20] These hormones include endogenous glucocorticoids and catecholamines.[19-20] This may be triggered by many factors, including injury, systemic infections and inflammation.[1] The increased release of these hormones leads to insulin resistance, gluconeogenesis, and consequent hyperglycaemia.[13,19-20] Hyperglycaemia subsequently increases pro-inflammatory transcription factors, gene expression, and oxygen-free radicals.[13] This results in endothelial dysfunction, lipid breakdown releasing free fatty acids into the bloodstream, platelet aggregation, and vasoconstriction – all risk factors for vascular events.[13] Furthermore, inflammation leads to protein, cell and DNA damage.[13]

1.3. Benefits of glucose control

In contrast to the poor outcomes from uncontrolled hyperglycaemia during hospitalisation, good inpatient glycaemic control is associated with improved patient outcomes.[9,15,22] These include: reduced occurrence of severe infections and multi-organ failure; reduced risk of vascular events; improved wound healing; reduced hospital admission lengths and subsequent

admissions; improved short- and long-term survival; and reduced burden on healthcare systems and overall hospital expenditure.[13]

Van den Berghe et al. noted that good glycaemic control reduced complications by "prevention of immune dysfunction, reduction of systemic inflammation, and protection of the endothelium and of mitochondrial ultrastructure and function".[23(p.450)] This was demonstrated by comparing intensive glucose control (initiation of an insulin infusion for glucose levels above 6.1 mmol/L and titrated to maintain glucose levels between 4.4 and 6.1 mmol/L) to the conventional therapy at the time (initiation of an insulin infusion for glucose levels above 12 mmol/L and titrated to maintain glucose levels between 10 and 12 mmol/L) in patients admitted to a medical and surgical intensive care unit (ICU).[23-24] The study found similar mortality rates between the two treatment groups for patients with an ICU stay under five days ($p = 0.5$ in the medical ICU and $p = 0.9$ in the surgical ICU) but reduced mortality in patients treated with intensive glucose control for ICU stays longer than five days ($p = 0.03$ in the medical ICU and $p = 0.005$ in the surgical ICU).[23-24] They concluded that the reduced mortality was due to the prevention of complications in the intensively controlled group.[23-24]

Prevention of complications in both the medical and surgical cohorts resulted in shorter ICU stays (earlier discharge from the medical ICU, $p = 0.04$, and lower median number of patients admitted beyond five days in the surgical ICU, $p = 0.003$), shorter duration of ventilatory assistance (earlier weaning of ventilation in the medical ICU, $p = 0.03$, and lower median number of patients requiring ventilation longer than five days in the surgical ICU, $p = 0.006$), fewer events of renal replacement therapy in the surgical patients ($p = 0.007$) and reduced acute kidney injury in the medical cohort ($p = 0.04$).[23-24] In the surgical study, intensive glucose control was also associated with lower rates of septicaemia than conventional control ($p = 0.003$), shorter use of antibiotics ($p < 0.001$) and lower rates of mortality from multiorgan failure with sepsis.[24] In the study on medical patients, rates of septicaemia and antibiotic use were similar in both the intensive and conventional glucose control groups, which was thought to be a result of sepsis triggering ICU admission in these patients.[23] Furthermore, patients treated with intensive control were less likely to develop critical illness myopathy and were also found to recover more rapidly than those in the conventional group.[24] Interestingly, *Van den Berghe et al.* concluded in their 2001 study that inpatient morbidity was not affected by whether a patient was previously diagnosed with DM but rather by the control of hyperglycaemia during their ICU admission.[24] Although further research has failed to replicate

the benefit of intensive inpatient glycaemic control, the work by *Van den Berghe et al.* changed the standard of care as subsequent studies targeted glucose levels below 10 mmol/L.[27-28]

Recently, *Zhu et al.* found that even though patients with DM have a greater risk of severe SARS-CoV-2 disease, better outcomes were observed in hospitalised patients that maintained serum glucose levels below 10 mmol/L compared to those with levels greater than 10 mmol/L.[5] Furthermore, a reduction in the use of pharmacological therapy, major organ injury, ventilatory support, and mortality was observed compared to poorly controlled patients with DM.[5] In light of these benefits, guidelines recommend control of inpatient hyperglycaemia by maintaining glucose levels below 10 mmol/L.[1]

1.4. Approach to management

The management of inpatient hyperglycaemia is challenging due to the heterogeneity of this population of patients.[1,4,25] Some patients may be treatment-naïve, whilst others may already be using a variety of treatment regimens, including oral agents and insulin, either alone or in combination.[6] In addition, patients may be using similar therapeutic regimens but have different baseline levels of control.[25] Hence, the management of inpatient hyperglycaemia, both in the critical care and non–critical care setting, must be individualised to the particular patient and needs to balance glycaemic control with nutritional supply and contraindications to particular therapeutic agents.[1,26]

Meta-analyses have failed to demonstrate significant preferences or benefits of a specific treatment approach in managing inpatient hyperglycaemia.[6] This has led to variations amongst international guidelines concerning treatment targets and the use of non-insulin-based therapies.[6] However, insulin is the preferred drug for the management of inpatient hyperglycaemia in most guidelines.[1,3,9,15] In addition to reducing glucose levels, insulin potentially dampens inflammation induced by the physiological stress response.[13] Increased nitric oxide release produced by insulin may also reduce risk factors associated with atherosclerosis and vascular events through consequent vasodilation, decreased platelet aggregation, reductions in free fatty acids due to less lipid breakdown, reduced inflammation, and endothelial damage.[13]

1.5. Glucose monitoring

Regular glucose monitoring should be performed to monitor the response to glycaemic management and identify hypoglycaemic episodes.[1] The frequency of monitoring depends on patients' nutritional state.[1] Pre-prandial and bedtime measurements are recommended for

patients eating regular meals, while four to six hourly measurements are advised in those with a reduced or restricted intake.[11,15] It may be possible to reduce monitoring to daily or twice daily for patients who do not require insulin therapy and have maintained serum glucose levels below 10 mmol/L for the preceding 36 hours.[11] Regarding critically ill patients, those receiving an insulin infusion should have serum glucose levels monitored every 30-120 minutes.[15] Any hypoglycaemic event should prompt a review of potential triggers and a possible adjustment to the treatment regimen used.[15]

Point-of-care measurement devices are subject to artefact errors, and if there is concern about the reported measured glucose levels, these should be confirmed with laboratory glucose analysers.[15] Blood gas analysers using arterial samples are the preferred measurement for critically ill patients.[27]

Although the United States Food and Drug Administration (FDA) has not yet approved continuous glucose monitoring (CGM) devices for inpatient use, there is evidence supporting their potential benefit in the non-critical care setting, and some centres have permitted their use.[15] These devices may assist with earlier and more frequent detection of hypoglycaemia compared to point-of-care devices.[21] In light of this data, the 2022 *Endocrine Society* clinical practice guidelines suggest that CGM devices should be considered in the non-critical care setting for insulin-dependent patients at increased risk of hypoglycaemia.[21] This includes patients that are elderly, require a high total daily dose (TDD) of insulin, have major organ dysfunction, hypoglycaemic unawareness or recent hypoglycaemia.[21] Furthermore, these devices have been shown to achieve greater time within the therapeutic range as well as reduced mean glucose levels compared to patients managed with point-of-care devices.[21] Caution should, however, be applied to patients with haemodynamic compromise and other conditions impairing the device's accuracy.[21] Unfortunately, due to the cost of these devices, incorporating CGM devices into clinical practice is not feasible universally.[21]

1.6. Treatment targets

Following the positive findings by *Van den Berghe et al.* suggesting the use of intensive glucose control (blood glucose levels between 4.4 and 6.1 mmol/L) in critically ill patients, subsequent studies have failed to demonstrate safety in the use of intensive glucose control in the ICU setting.[27] Suggested reasons for this are differing glucose management and nutritional strategies in other studies and varying patient populations.[27] A large multicentre randomised control trial from 2009 compared the effect of intensive glucose control (maintaining glucose

levels between 4.5 and 6 mmol/L) and an updated conventional glucose control (initiating an insulin infusion for glucose levels above 10 mmol/L and titrating doses to maintain glucose levels between 8 and 10 mmol/L) on patient mortality in the ICU.[28] They found that patients who received intensive glucose control in the ICU had significantly higher rates of severe hypoglycaemia ($p < 0.001$) and mortality ($p = 0.04$) due primarily to cardiovascular deaths ($p = 0.02$).[28] Furthermore, the intensive and conventional glucose control groups noted similar durations of ICU admission and ventilation and similar rates of renal replacement therapy, bacteraemia and single- and multiorgan failure.[28] The authors concluded that aggressive glucose control in the critical care setting may be harmful and recommended a looser conventional glucose control goal (blood glucose targets of less than 10 mmol/L) compared to *Van den Berghe et al.* (maintaining glucose levels between 4.5 and 6 mmol/L).[28]

Challenges to obtaining tight control in the inpatient setting are the risk of hypoglycaemia, difficulty achieving normoglycaemia due to many physiological and pathological processes in critically ill patients, and intensive monitoring placing further demands on limited hospital resources.[27] As these challenges are patient and facility-dependent, treatments should be individualised to the patient and hospital facility.

It is clear that glucose levels above 10 mmol/L and below 3.9 mmol/L should be avoided.[27] Despite challenges with maintaining tight glycaemic control in hospitals, *Krinsley et al*. found a significant reduction in mortality in non-diabetic critically ill patients who maintained glucose levels between 3.9 and 7.8 mmol/L for more than 80% of their admission.[29] This range may be targeted in settings with adequate monitoring and validated protocols.[27] It may also be necessary to aim for lower targets in non-diabetics compared to diabetics in the critical care setting.[27]

Due to the lack of clear consensus on glycaemic targets, the ADA recommends maintaining blood glucose levels between 7.8 and 10 mmol/L in most critically and non-critically ill patients.[6,15] The UK recommendations endorse a broader range from 6 to 10 mmol/L and tolerate 4 to 12 mmol/L[9]. Finally, the *SEMDSA* guidelines recommend targets in non-critically ill patients of fasting and pre-meal glucose levels below 8 mmol/L and random glucose levels below 10 mmol/L[1].

To achieve these targets, the ADA recommends a conservative approach for glucose levels greater than 7.8 mmol/L, including dietary changes and a review of any hyperglycaemia-inducing medication, while suggesting that insulin therapy be initiated for levels above 10

mmol/L.[15] *SEMDSA* recommends insulin therapy as the mainstay for the management of inpatient hyperglycaemia. However, oral agents may be considered on a case-specific basis.[1] Despite differences, a common factor amongst all guidelines is that both basal and prandial insulin requirements need to be reviewed and adjusted as appropriate.[1,9,15]

In the critical care setting, patients have a more pronounced physiological response to stress than patients admitted to the general wards. This is due to multiple concurrent hyperglycaemic triggers as well as marked nutritional restrictions.[1] Studies investigating target glucose control in the critical care setting have shown mixed results, with the latest *SEMDSA* guidelines recommending maintaining a glucose range between 7.8 and 10 mmol/L.[1] As the risk of hypoglycaemia and mortality is increased by targeting euglycaemic levels in this setting, existing guidelines do not recommend targets lower than 6.1 mmol/L.[1,6]

1.7. Non-insulin glucose-lowering therapies

Guidelines frequently recommend against the use of oral hypoglycaemic agents (OHAs) to achieve glycaemic targets in both the critical and non-critical care setting.[1] This is due to the inability to rapidly adjust the effects of OHAs on glycaemic control and specific contraindications attributable to each agent.[1] Previous recommendations suggested interrupting the use of these agents and initiating insulin in lieu of OHAs.[26] However, there is growing support for the use of particular OHAs that may be considered in a select group of patients in the non-critical care setting, including patients who have mild hyperglycaemia, good pre-admission glycaemic control, obtain adequate nutritional intake and have no contraindications to their use.[1,6]

The COVID-19 pandemic has further enhanced the support for the use of OHAs as some centres have looked for alternatives to traditional insulin regimens in an attempt to simplify therapies by using OHAs or non-insulin injectable therapies.[11,15,30] Recent trials indicate potential benefits of dipeptidyl peptidase 4 inhibitors (DPP4-i) and the continued use of glucagon-like peptide-1 receptor agonists (GLP-1 RA) as they are effective in controlling glucose levels and reducing glycaemic variability while decreasing the risk of hypoglycaemia.[6,15,31-32] As a result, DPP4-is and GLP-1 RAs, along with insulin, have been suggested as preferred treatment agents in the non-critical care setting.[6,15,31]

DPP4-is are well tolerated, may be used in patients with varying renal function and can be used in conjunction with different insulin regimens.[31] In combination with basal insulin, DPP4-is are considered non-inferior to basal bolus insulin in non-critically ill patients[1] while offering

the patient a simpler treatment regimen[6]. These benefits have also been demonstrated in patients with SARS-CoV-2 infection for whom, although DPP4-is have not been linked to a direct reduction in poorer outcomes, they have been shown to have the glycaemic benefits listed above while also allowing treatment simplification.[30-31]

Similarly, GLP-1 RAs are highly effective in controlling glucose levels and decreasing the risk of hypoglycaemia.[32-33] Infusion forms are demonstrated to have a comparable effect to insulin and have been used for glycaemic control in normal and enteral feeding and the perioperative setting.[32] While other benefits of these agents include their significant cardiovascular effects, the initiation of these agents in hospitalised patients may be limited due to their gastrointestinal side effects.[32]

Other OHAs have not demonstrated sufficient benefit for their use in inpatient management.[32] Many factors that take place during a hospital admission are associated with an increased risk of lactic acidosis in patients treated with metformin.[32] These include major organ failure, sepsis, shock and the use of contrast media, among others.[32] As a result, the use of this agent requires high vigilance and correct patient selection to avoid this condition. In the setting of patients infected with SARS-CoV-2, while a limited number of retrospective observational studies have suggested a benefit of metformin in the reduction of mortality, potential confounders were not excluded and further randomised control trials are required to evaluate this benefit.[34]

Guidelines recommend against the use of sulfonylureas (SU) for the management of inpatient hyperglycaemia. Reasons include their long duration of action predisposing a patient to severe and persistent hypoglycaemia; multiple drug-drug interactions with fluoroquinolone antibiotics and drugs that affect the CYP2C9 enzyme; and a possible increased risk of cardiac and cerebral ischaemic events.[32] Hypoglycaemia is of particular concern in patients older than 65, those with severe renal (GFR < 30 mL/min/1.73m^2) or liver dysfunction[1] or in patients with inconsistent nutritional intake.[32]

There are concerns regarding the use of sodium-glucose cotransporter 2 inhibitors (SGLT2-is) for the management of inpatient hyperglycaemia as these agents are linked to an increased risk of euglycaemic diabetic ketoacidosis (DKA), dehydration and hypotension as well as an increased risk of urogenital infections.[32, 35] Thiazolidinediones (TZDs) may worsen heart failure while only having a delayed effect on glucose control.[32] These OHAs are, therefore, not recommended for use in the inpatient setting.[32]

If an OHA or non-insulin injectable is held during the hospital stay, guidelines recommend that they should be reintroduced within 48 hours prior to discharge, provided there are no contraindications to their use.[15]

1.8. Insulin therapy

Insulin is recommended as the preferred drug for the management of inpatient hyperglycaemia as it has a rapid onset of action and offers more precise glycaemic control than other agents.[1,6] To meet individual patients' glycaemic requirements, healthcare providers can easily adjust the choice of agent, rate of onset of action, duration of insulin effect, the dosage used, route and timing of administration.[1] As a result, insulin provides the healthcare provider with a wide range of treatment options, including its ability to be used in combination with non-insulin agents.[1,6]

A typical treatment regimen used locally and internationally is sliding scale insulin (SSI).[1,12] The sliding scale approach was introduced in 1934 by Elliot Joslin.[36] At the time, physicians relied on the indirect measure of glycosuria as serum glucose levels were not easily attainable.[36] Glycosuria was measured by observing the colour reaction of glucose in the urine with copper sulphate when boiled.[36] Insulin doses were then titrated according to the colour produced by the reaction to reduce the level of glycosuria.[36] This approach was later adapted to the use of blood glucose measurements.[36] Despite its origin being based on an antiquated practice and many studies showing poorer outcomes through the use of SSI compared to basal-bolus regimens, the regimen still retains significant popularity for the management of inpatient hyperglycaemia and is often the therapeutic mainstay used by physicians.[1,36]

A significant limitation of an SSI-based regimen is its reactive nature. In this approach, glucose levels are measured at fixed time points over 24 hours (usually four to six hourly) and insulin therapy is retrospectively administered in response to a hyperglycaemic episode rather than preventing its occurrence.[22] The predefined doses of rapid-acting insulin are administered irrespective of previous insulin administration, proximity to meals or a specific patient's response to insulin.[21-22] This prescription does not prevent hyperglycaemia, is frequently not reviewed by clinicians and leads to large glycaemic variability and hypoglycaemia due to insulin stacking (the accumulation of excess insulin due to narrow dosing intervals that do not allow for sufficient drug elimination).[1,22,32]

The popularity of this treatment is mainly due to convenience.[13] It is easily taught and communicated to colleagues, nursing staff find this easier to follow, and it reduces the concern

of hypoglycaemia as insulin is only given when the glucose level is raised.[13,20] It does not, however, address patients' basal insulin requirements, and it allows gluconeogenesis and ketogenesis to continue uninhibited, particularly during sleep.[22] It is for this reason that the SSI, as the sole therapy for inpatient hyperglycaemia, is ineffective and results in prolonged hospital admission and worse patient outcomes.[15,22]

The shortcomings of SSI were illustrated in a multicentre randomised trial in the USA investigating treatment regimens for control of inpatient hyperglycaemia in 375 patients with type 2 DM.[37] SSI resulted in a greater number of treatment failures, which was defined as three or more consecutive serum glucose readings measuring above 13.3 mmol/L compared to a basal bolus regimen ($p < 0.001$).[37] In addition, a prospective cohort from Boston involving 107 patients showed that the sole use of SSI, in the absence of basal or pre-prescribed prandial insulin, resulted in an average increase of 1.11 mmol/L in glucose level.[38] As a result, this method is not recommended for use in hospitals despite its popularity amongst clinicians.[6,15,22]

Pre-emptive treatment options addressing basal, nutritional and corrective insulin requirements are considered more physiological and are recommended in the inpatient setting.[1,22] These include continuous intravenous infusions and subcutaneous basal insulin with or without prandial or correction dose insulin in critical and non-critical care settings, respectively.[6,15,20,22] *SEMDSA* advises against using intravenous insulin in the non-critical care setting due to less frequent monitoring for hypoglycaemia.[1] Furthermore, SEMDSA recommends a period of at least four hours between correction doses to avoid hypoglycaemia from insulin stacking.[1]

Correction dose insulin regimens involve the use of rapid-acting insulin to adjust pre-prandial blood glucose levels or to correct levels measured four to six hourly in patients that are not eating.[21] These regimens may be considered in non-critically ill patients who were not previously managed for diabetes and maintain glucose levels below 10 mmol/L.[21] Basal insulin-based regimens should be used for patients previously treated with insulin or with more than one glucose reading above 10 mmol/L.[21] Diabetic patients previously managed with diet or non-insulin agents may be initially managed with correction or basal-based insulin regimens.[21]

On admission to non-critical care wards, it may be possible to continue a patient's preadmission insulin regimen. However, a reduction in the TDD of insulin is advised for patients with a reduced nutritional intake.[1,6] In addition, guidelines recommend against using premix insulins in the non-critical care setting as their use is associated with higher rates of hypoglycaemia

related to variations in type, quantity and timing of meals during a hospital stay.[1,6] Prehospital insulin pump use may be continued during a non-critical care hospital admission, provided the hospital staff have the adequate expertise to manage this form of insulin therapy.[21] If expertise is inadequate or the patient is too unwell to manage the device, then it is recommended that the patient be transitioned to a schedule-based insulin regimen.[21]

Basal insulin is associated with better glycaemic control without significantly increasing severe hypoglycaemia.[37] This results in fewer complications than SSI alone outside the ICU setting.[37] Furthermore, insulin requirements increased two to threefold when a basal regimen was administered compared to SSI alone.[37] This illustrates that the sole use of SSI results in insulin under-dosing and is likely insufficient to meet necessary insulin requirements.[37] This was supported by the *RABBIT 2 trial*, a multicentre randomised control trial comparing the use of basal bolus to SSI for control of inpatient hyperglycaemia in 130 patients with type 2 DM, in which two-thirds of patients were managed within the target range using a basal bolus regimen versus one-third in the SSI only regimen.[12]

Multiple illnesses and nutritional-related factors result in worse inpatient dysglycaemia, and their effect evolves during hospital admission.[22] As a result, insulin regimens may need to be modified, necessitating a precise, calculated and frequently reviewed approach to match basal, nutritional and correction dose insulin requirements.[22] Basal insulin is required to counteract gluconeogenesis as well as ketogenesis.[22] Furthermore, administration of prandial or nutritional insulin doses may vary due to changes in nutritional intake resulting from patient, disease and hospital-related factors.[6] This is a significant limitation of premix insulins which require consistency in nutritional intake.[1] Finally, correction dose insulin is required to control pre-prandial hyperglycaemia that the basal insulin has not adequately controlled.[1]

1.9. Specific nutritional circumstances

If nutritional intake during hospital admission is reduced, iatrogenic hypoglycaemia may result.[15] As a consequence, patients receiving alternative methods of nutrition, such as enteral and parenteral feeding, often require adjustments to their glycaemic management.[9] In this clinical scenario, insulin, rather than crushed OHAs, should be used in combination with DM-specific feed formulas, as its pharmacokinetics and pharmacodynamics are more predictable.[1,9]

Various insulin regimens, including basal, infusion, and bolus insulin, may be used.[1,9] Intermediate-acting insulin regimens may be preferred to long-acting insulin in patients receiving enteral feeding due to their shorter duration of action.[21] Although limited by an

increased risk of hypoglycaemia, premix insulin may be considered in patients receiving regular meals.[1,9]

Monitoring should be performed before and two hours after the feed, as well as four to six hourly during the feed and during prolonged periods of fasting.[1,9] It is essential that hypoglycaemia is avoided. The UK recommendations advise glycaemic targets of 5-8 mmol/L for fasting and 6-12 mmol/L while receiving the feeds.[9] *SEMDSA* suggests a review of glycaemic management for hypoglycaemic episodes and adjustment of any hypoglycaemic triggers.[1] Furthermore, *SEMDSA* recommends glycaemic targets above 6.1 mmol/L to avoid hypoglycaemia in the critically ill setting.[1]

Enteral feeding can be provided as either an infusion or as bolus doses.[1] Bolus feeds are more physiological and can be managed with basal-bolus insulin regimens.[1] Other feeding regimens should be treated with scheduled insulin bolus dosing.[1] When there is a break in the feeding, the patient should be given a dextrose-containing intravenous infusion, and insulin should be held.[1]

For parenteral feeding, *SEMDSA* recommends adding insulin to the solution with a starting dose of 1 unit per 10g of carbohydrate or using an insulin infusion.[1] Once the glucose levels are controlled, 50% of the TDD may be given as basal insulin.[1] Four to six hourly monitoring and bolus insulin is recommended to ensure that hyperglycaemia is corrected.[1]

1.10. Rationale for this research

Despite the direct adverse effects of hyperglycaemia, the perception amongst practising endocrinologists is that there is a lack of knowledge and significant physician inertia in the treatment of inpatient hyperglycaemia in South Africa. Well-identified reasons for the lack of response include: fear of hypoglycaemia which also has a high risk of morbidity and mortality; lack of expertise in managing the complexities of inpatient hyperglycaemia; lack of local protocols for the management of hyperglycaemia; glucose control often not being considered a significant priority to address during the course of inpatient admission; and SSI use being viewed as convenient and easy to use.[13] Mild hyperglycaemia is often regarded as non-harmful, with insulin frequently only given for glucose levels exceeding 10 mmol/L.[13] However, the significant risk of adverse effects and the need to prevent these effects outweigh the convenience of using SSIs. In addition, the reactive nature of this treatment method can lead to large fluctuations in glucose levels, which can be detrimental and result in iatrogenic DKA.[13] A USA multicentre trial showed that about two-thirds of patients with dysglycaemic recordings

had no adjustments to their therapy during the first week of admission.[38] This is likely due to a lack of awareness of the impact as well as the inertia of physicians towards the treatment of hyperglycaemia.[13]

A lack of knowledge among physicians regarding inpatient glycaemic management was identified by *Horton et al.*, who demonstrated a significant discrepancy between surveyed physicians' knowledge and guideline recommendations.[39] Physicians felt confident in their knowledge and practice, with 85.5% and 87.4% of respondents indicating they felt comfortable with glycaemic management and basal-bolus regimes, respectively.[39] 66.3% reported comfort in the level of training they received in managing inpatient hyperglycaemia.[39] However, glycaemic targets in critically ill and random and pre-prandial targets in non-critically ill patients were correctly identified in only 51.2%, 45.5% and 34.1%, respectively.[39] Furthermore, only 54.1% were able to define hypoglycaemia correctly.[39] Finally, insufficient training was identified as the second most common barrier towards effective glycaemic management.[39]

At present, little is known regarding the daily practice of managing inpatient hyperglycaemia amongst South African physicians and intensivists. To the knowledge of the author of this study, there are no current studies investigating physician practices in the management of inpatient hyperglycaemia in South Africa. Before any attempt to institute changes, it is of value to understand local practice. Hence this study aimed to investigate the current practices of physicians and intensivists in the management of inpatient hyperglycaemia in the critical care and ward setting in South African hospitals.

Chapter 2: Study Design

2.1. Study objectives

This study aimed to assess the following objectives among physicians and intensivists:

1. To describe the current treatments and trends used in inpatient glucose management.
2. To determine management approaches and the glucose-lowering agents utilised in everyday clinical practice.
3. To compare current clinical practice to evidence-based guidelines.
4. To validate the survey by reviewing inpatient glycaemic management based on patients' glucose monitoring charts.

2.2. Study design

This study was a questionnaire-based prospective observational cross-sectional study with descriptive and analytical elements. The questionnaire was administered in a paper-based format and via an online survey platform using RedCap. At the time of study design, due to the paucity of data in this area, there was no validated study on which the survey could be based. As a result, the second component of this study attempted to validate the responses from the participants in the state sector by conducting a prospective cross-sectional audit of inpatient glucose monitoring charts in the general medical wards and intensive care units at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH). However, due to COVID-19 restrictions, the audit was later changed to a retrospective audit of the hospital files of discharged patients.

2.3. Study population and data collection

Questionnaire

This multicentre study aimed to focus on clinicians in internal medicine and intensive care units in both the state and private sectors across South Africa. The study aimed to enrol at least 200 physicians representing the critical care and internal medicine disciplines. Only registrars and consultants were enrolled amongst the internal medicine physicians in the state sector. The questionnaire was subdivided into two parts, one specifically for internal medicine (29 questions) and the other for intensive care (30 questions). Study participants were required to

complete the section/s relating to the discipline in which they care for patients with hyperglycaemia. If the study participants' daily clinical practice encompassed both internal medicine and intensive care, they were asked to complete both sections. All questionnaires were completed anonymously with no personal identifiers linked to the answers.

At the time of initial approval for the study, it was anticipated that participants would be contacted via the following platforms:

1. Scheduled departmental meetings in the three major academic hospitals within the University of the Witwatersrand circuit (CMJAH, CHBAH and HJH).
2. Electronic communication methods such as email and online survey platforms.
3. Local conferences targeted at intensivists and/or physicians.

Due to the COVID-19 pandemic, there was a significant impact on the prospective aspects of this study. Restrictions on gatherings and in-person contact prevented participant enrolment at conferences and departmental meetings. As a result, re-approval was required from the Human Research and Ethics Committee at the University of the Witwatersrand for the prospective aspects of the study. Following this subsequent application, approval was granted for an online version of the questionnaire as the primary route of participant enrolment.

As a result, participants were enrolled solely via electronic forms disseminated via the following means:

- University of the Witwatersrand internal medicine department's email list.
- University of the Witwatersrand division of critical care email list.
- The Critical Care Society of South Africa.
- University of the Witwatersrand internal medicine registrar network.
- Personal emails sent to physicians and intensivists practising in private facilities that were listed on the Netcare and Life databases.

More than 1000 participants were contacted through these email lists. Given the various departments disseminating the questionnaire independently, the exact number of participants contacted is unclear.

Data were collated via RedCap and exported into an excel spreadsheet from which statistical analyses were performed. All study participants were assigned a study number and remained anonymous, whilst no identifiable parameters were recorded. Only the principal investigator,

supervisors and statistician had access to the data. Any incomplete questionnaires were discarded.

Variables measured

The questionnaire recorded participant demographics (age and gender), level of experience (assessed in terms of number of years in practice and level of training), area of expertise and whether the clinician was practising in the state or private sector. It also assessed current physician practices in the management of inpatient hyperglycaemia, which included: glucose-lowering therapeutic agents routinely used by physicians, therapeutic targets aimed for and barriers to utilising specific therapeutic agents. *(See appendix for questionnaire).*

Audit

A convenience sampling audit was performed reviewing data of patients admitted to the general medical wards and intensive care units at CMJAH, CHBAH and HJH. Initially, this was to take place prospectively, but due to COVID-19 restrictions, ethics approval was revised to review the files of discharged patients retrospectively. The glycaemic monitoring and treatment charts of 100 medical and 111 intensive care qualifying patients were reviewed. The data were compiled via RedCap and exported into an excel spreadsheet from which further statistical analyses were performed. All patients enrolled were assigned a study number, remained anonymous, and no identifiable parameters were recorded. Only the investigator, supervisors and statistician had access to the data.

Variables measured

The audit assessed which regimens of glucose-lowering agents were prescribed (insulin and/or non-insulin glucose-lowering-based regimens), whether chronic therapy was changed on hospital admission, the frequency at which therapy was reviewed, which insulin regimen was used (namely sliding scale, basal or basal bolus insulin) as well as episodes of hypo- and hyperglycaemia. Hypoglycaemia was defined as a measured glucose level below 4 mmol/L in both the general medical wards and ICU. Hyperglycaemia in the general medical wards was defined as a measured premeal glucose level above 7.8 mmol/L or a measured random glucose level above 10 mmol/L. In the ICU, hyperglycaemic events were defined as measured glucose levels above 7.8 mmol/L and 10 mmol/L irrespective of the proximity to meals. *(See appendix for audit data recording sheet).*

2.4. Inclusion criteria

Questionnaire
In order to be included in the study, participants needed to meet the below criteria: • Qualified medical doctors • Active members of the Health Professions Council of South Africa (HPCSA) registered for independent practice • Registrars or qualified physicians in the fields of internal medicine and/or intensive care
Audit
Patients from the medical wards or general intensive care units at CMJAH, CHBAH and HJH who had hyperglycaemia during their hospital admission were included in the audit.

2.5. Exclusion criteria

Questionnaire
Clinicians unwilling to participate or provide consent for the study were excluded from the study.
Audit
The following patients were excluded from the study: • Patients who were admitted for initiation of hyperglycaemic therapy • Patients who were admitted for hyperglycaemic emergencies (DKA or hyperosmolar hyperglycaemic state) • Patients admitted to dedicated endocrinology wards

2.6. Statistical analysis

Frequencies and proportions were used to describe categorical variables. Pearson's chi-square tests were used to compare proportions, and Fisher's exact tests were used instead where data were sparse (cells with n <5). Continuous variables were described using the mean and standard deviation (SD) or the median and interquartile range (IQR) for normal and non-normally distributed variables, respectively. The normality of continuous variables was assessed using the Shapiro-Wilk test. One-way analyses of variance (ANOVAs) were used to compare the means of continuous variables across three or more groups. The Wilcoxon rank sum test for comparison of medians for independent samples was used to compare continuous variables across two groups. Where there were more than two groups, the Kruskal-Wallis test was used. Analyses were done in Stata 15, and statistical significance was set at 5% (p-value < 0.05).

Chapter 3. Results

3.1. Population included in the survey

One hundred and fifty-four surveys were completed, with a response rate below 15%. Fifty-four respondents (35.1%) practised in both general wards and ICU, 91 (59.1%) only in the general wards and 9 (5.8%) in ICU alone (Figure 1).

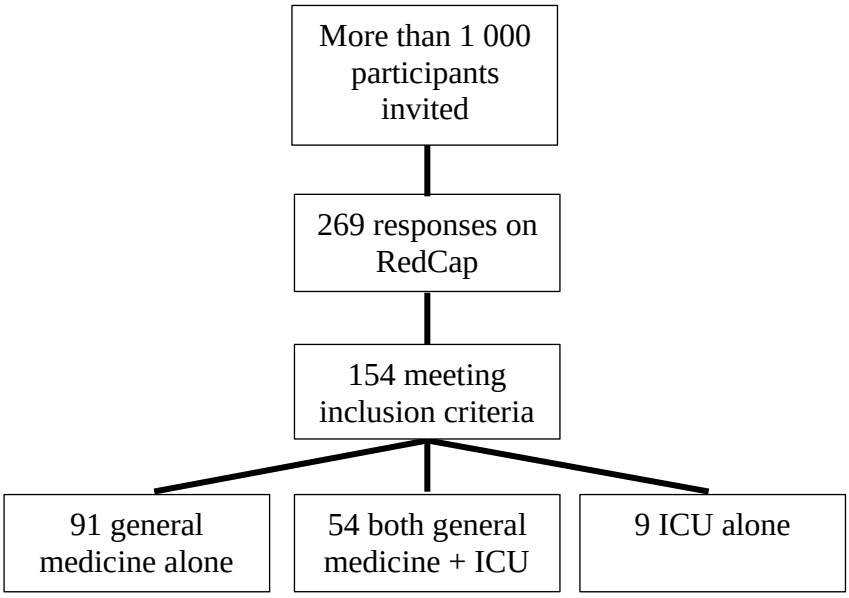


Figure 1. Summary of survey respondents.

The demographics of survey respondents are noted in Table 1. Most respondents practised in the public sector alone (73.4%), followed by 19.5% in private practice alone and 7.1% in both. Of those who worked in the public sector, two-thirds (66.9%) practised in one of the three major state hospitals in Johannesburg, with 36.3% based at CHBAH, 21% at CMJAH, 25.8% at HJH and 16.9% at other facilities. Of these, CHBAH had the highest number of respondents working only in the general wards (41.8%), followed by HJH (27.5%) and CMJAH (18.7%). Of the nine respondents working only in ICU, all were based in state practice exclusively.

Amongst the respondents, 57.1% were generalists, 5.8% were critical care specialists and 37.1% were other subspecialists. Among the 57 subspecialists, nephrology and pulmonology each accounted for 19.3%, followed by endocrinology (14%), cardiology, and rheumatology (10.5% each). Anaesthetics, gastroenterology, geriatrics, haematology, infectious diseases, neurology and oncology combined accounted for the remaining 26.4%. Registrars accounted for 52% of the total respondents.

Variable	Ward Type			
	State and Private (n=11)	**Private (n=30)**	**State (n=113)**	**Total**
Age				
Median(IQR)	45 (35-50)	47 (40-55)	32 (30-36)	-
<30	0 (0%)	0 (0%)	27 (23.9%)	27 (17.5%)
30-39	3 (27.3%)	5 (16.7%)	73 (64.6%)	81 (52.6%)
40-49	5 (45.5%)	11 (36.7%)	9 (8%)	25 (16.2%)
50+	3 (27.3%)	14 (46.7%)	4 (3.5%)	21 (13.6%)
Sex				
Female	4 (36.4%)	11 (36.7%)	57 (50.4%)	72 (46.8%)
Male	7 (63.6%)	19 (63.3%)	56 (49.6%)	82 (53.2%)
Rank				
Consultant	10 (90.9%)	30 (100%)	34 (30.1%)	74 (48.1%)
Registrar	1 (9.1%)	0 (0%)	79 (69.9%)	80 (51.9%)
Speciality				
Cardiology	0 (0%)	3 (10%)	3 (2.7%)	6 (3.9%)
Critical care	2 (18.2%)	1 (3.3%)	6 (5.3%)	9 (5.8%)
Endocrinology	0 (0%)	4 (13.3%)	4 (3.5%)	8 (5.2%)
Gastroenterology	1 (9.1%)	0 (0%)	1 (0.9%)	2 (1.3%)
Generalist	1 (9.1%)	8 (26.7%)	79 (69.9%)	88 (57.1%)
Geriatrics	1 (9.1%)	1 (3.3%)	2 (1.8%)	4 (2.6%)
Haematology	0 (0%)	1 (3.3%)	1 (0.9%)	2 (1.3%)
Infectious Diseases	0 (0%)	0 (0%)	1 (0.9%)	1 (0.6%)
Nephrology	3 (27.3%)	3 (10%)	5 (4.4%)	11 (7.1%)
Neurology	0 (0%)	1 (3.3%)	0 (0%)	1 (0.6%)
Oncology	1 (9.1%)	1 (3.3%)	1 (0.9%)	3 (1.9%)
Pulmonology	1 (9.1%)	4 (13.3%)	6 (5.3%)	11 (7.1%)
Rheumatology	1 (9.1%)	2 (6.7%)	3 (2.7%)	6 (3.9%)
Other	0 (0%)	1 (3.3%)	1 (0.9%)	2 (1.3%)

Table 1. Demographics stratified by health sector.

IQR = interquartile range.

In terms of years of experience, of the respondents in the general medical wards, 35.2% had up to 4 years, 33.1% had between 4 and 8 years, and 31.7% had more than eight years of experience. Respondents working in the ICU had more years of experience proportionally, with 30.2% having below four years, 20.6% between four and eight years, and 49.2% above eight years of experience.

Respondents working in the private sector were older, with a median age of 47 years (IQR: 40-55) compared to 32 years (IQR: 30-36). There were proportionally more consultants practising in the private sector compared to the state sector (100% vs 30.1% respectively). Conversely, registrars comprised the majority of respondents from the state sector (69.9%). No registrars practised in the private sector alone. There was a higher proportion of generalists in the public sector alone compared to the private sector alone (69.9% and 26.7%, respectively), as well as more critical care specialists in the public sector alone compared to the private sector alone (5.3% and 3.3%, respectively).

3.2. Hypoglycaemia and hyperglycaemia levels according to the survey

According to the survey, the median values used by clinicians to define hypoglycaemia were 3.9 mmol/L (IQR: 3.5-4) and 4 mmol/L (IQR: 3.5-4) for the general medical ward and ICU, respectively. The median value used to define hyperglycaemia was 10 mmol/L (IQR: 8-11) for both the general medical ward and ICU. In the general medical wards, hypoglycaemia was defined as glucose levels below 3 mmol/L in 16.6% of respondents and below 3.5 mmol/L in 24.8%. In the ICU, 19% of clinicians defined hypoglycaemia as glucose levels below 3 mmol/L, with the remainder using levels above 3.5 mmol/L. In terms of hyperglycaemia, 14.5% of respondents in the general medical wards and 12.7% of respondents in the ICU defined hyperglycaemia as glucose levels above 12 mmol/L.

3.3. Trends in the general medical wards, according to the survey

3.3.1. Use of non-insulin glucose-lowering agents

Of those surveyed, 87.6% would continue using previously prescribed non-insulin hypoglycaemic therapies on the admission of a patient to the general medical ward. There was no statistically significant difference in this finding according to years of experience ($p = 0.903$). Metformin was the most frequently continued of these agents (83.5%), followed by SUs (69%). DPP4-is and SGLT2-is were continued by 43.5% of respondents, while GLP-1 RAs and TZDs were used by 37.9% and 18.6% of the respondents, respectively. Years of working experience in the general medical wards had a positive association with continued use

of DPP4-is ($p < 0.001$), GLP-1 RAs ($p = 0.006$) and SGLT2-is ($p < 0.001$) with more than 50% of physicians above eight years of experience continuing use of these agents.

A similar relationship was observed regarding non-insulin glucose-lowering agents, with 89.7% of respondents reporting that they would initiate such agents on admission to hospital. Amongst these responses, years of physician experience was not associated with a significant difference in the general use of these agents ($p = 0.241$). The two most frequently initiated agents were metformin (87.6%) and SUs (63.5%). This was followed by SGLT2-is (33.1%), DPP4-is (31.4%), GLP-1 RAs (25.5%) and finally, TZDs (9.7%). More years of work experience in clinicians was only associated with a significant increase in the use of DPP4-is ($p = 0.006$), with more than 50% of physicians with 15-30 years of experience initiating these agents during hospital admission.

Table 2 compares the total use of non-insulin hypoglycaemic agents between registrars and state consultants as well as between consultants practising in the state and private sectors. Notably, a significantly higher proportion of state consultants indicated that they would use DPP4-is, GLP-1 RAs, SGLT2-is, and TZDs compared to registrars. Furthermore, a significantly higher proportion of consultants in private practice reported that they would use GLP-1 RAs when compared to consultants practising in state.

Non-insulin agent	State			Consultants		
	Registrar n = 79 (%)	Consultant n = 28 (%)	p-value	State n = 28 (%)	Private n = 38 (%)	p-value
Metformin	73 (92.4)	26 (92.9)	0.925	26 (92.9)	37 (97.4)	0.385
SU	56 (70.9)	23 (82.1)	0.281	23 (82.1)	31 (81.6)	0.953
DPP4-i	15 (19)	20 (71.4)	**< 0.001**	20 (71.4)	32 (84.2)	0.209
GLP-1 RA	15 (19)	14 (50)	**0.002**	14 (50)	29 (76.3)	**0.027**
SGLT2-i	23 (29.1)	17 (60.7)	**0.003**	17 (60.7)	30 (78.9)	0.106
TZD	4 (5.1)	10 (35.7)	**< 0.001**	10 (35.7)	15 (39.5)	0.756

Table 2. Comparison of non-insulin hypoglycaemic agent use between state registrars and consultants, and consultants in state and private.

SU = sulfonylurea; DPP4-i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2-i = sodium-glucose cotransporter 2 inhibitor; TZD = thiazolidinedione.

Of the 137 respondents that would either continue or initiate the use of non-insulin glucose-lowering agents during admission, 91.2% indicated that there were specific conditions that would prevent the use of these agents. This finding was consistent across years of experience. The five most frequent reasons for each agent are shown in Table 3, in which the percentage represents the proportion of physicians that would avoid using a non-insulin glucose-lowering agent for a particular condition. Renal failure was the most frequently reported reason for not using any of the non-insulin glucose-lowering agents as shown in Figure 2.

Condition	Metformin Rank (%)	SU Rank (%)	DPP4-i Rank (%)	GLP-1 RAs Rank (%)	SGLT2-i Rank (%)	TZD Rank (%)
Renal failure	**1** (87.2)	**1** (64.8)	**1** (47.2)	**1** (46.4)	**1** (53.6)	**1** (46.4)
Sepsis	**3** (12)	**4** (11.2)	**3** (8.8)	**3** (8.8)	**3** (8.8)	**3** (8.8)
Acute illness	**4** (10.4)	**5** (9.6)	**4** (8)	**4** (8)	**4** (8)	**4** (8)
Liver failure	**5** (9.6)	**3** (12.8)	**2** (10.4)	**2** (8.8)	**2** (8.8)	**2** (9.6)
NPO	-	-	**5** (5.6)	**5** (5.6)	**5** (5.6)	**5** (5.6)
Lactic acidosis	**2** (24.8)	-	-	-	-	-
Hypo-glycaemia	-	**2** (25.6)	-	-	-	-

Table 3. Top five conditions for which respondents would not use specific non-insulin glucose-lowering agents in the general wards.

NPO = nil per mouth; SU = sulfonylurea; DPP4-i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2-i = sodium-glucose cotransporter 2 inhibitor; TZD = thiazolidinedione.

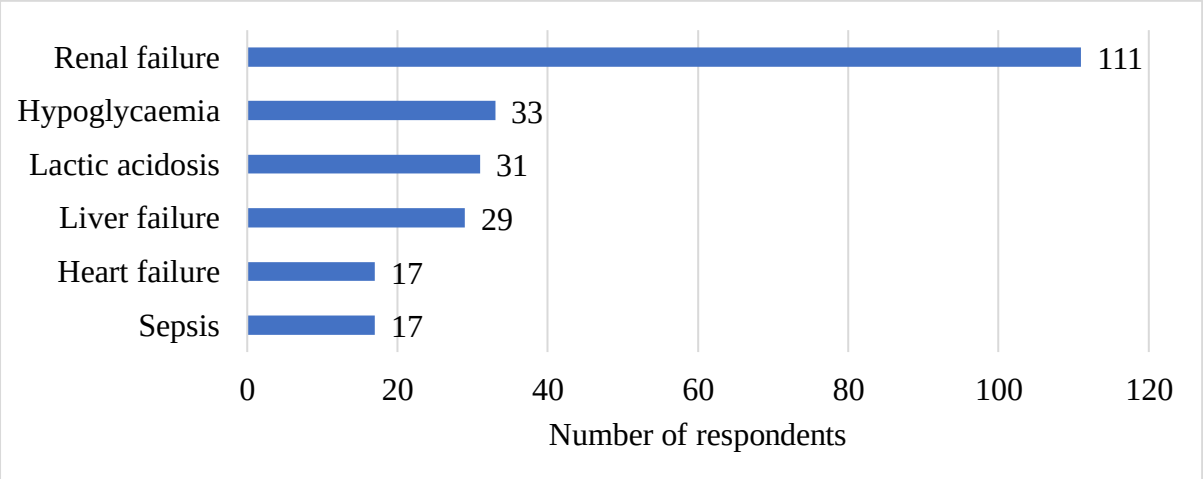


Figure 2. Top conditions for which non-insulin glucose-lowering agents were not used in general medicine wards.

3.3.2. Use of insulin

Regarding changes to the prehospital insulin regimen on admission, 60.7% of respondents reported that they would continue the prehospital TDD of insulin, 7.6% would reduce the TDD, 20.7% would increase the TDD, and 11% would stop the prehospital regimen altogether. These adjustments to prehospital insulin treatments were consistent across levels of experience (p = 0.127).

Figure 3 illustrates the frequency of use of insulin regimens in the general medical wards. The most frequently prescribed insulin regimen amongst respondents was basal insulin plus SSI (36.6%). Notably, the use of these regimens did not demonstrate significant variability with level of experience (p = 0.251).

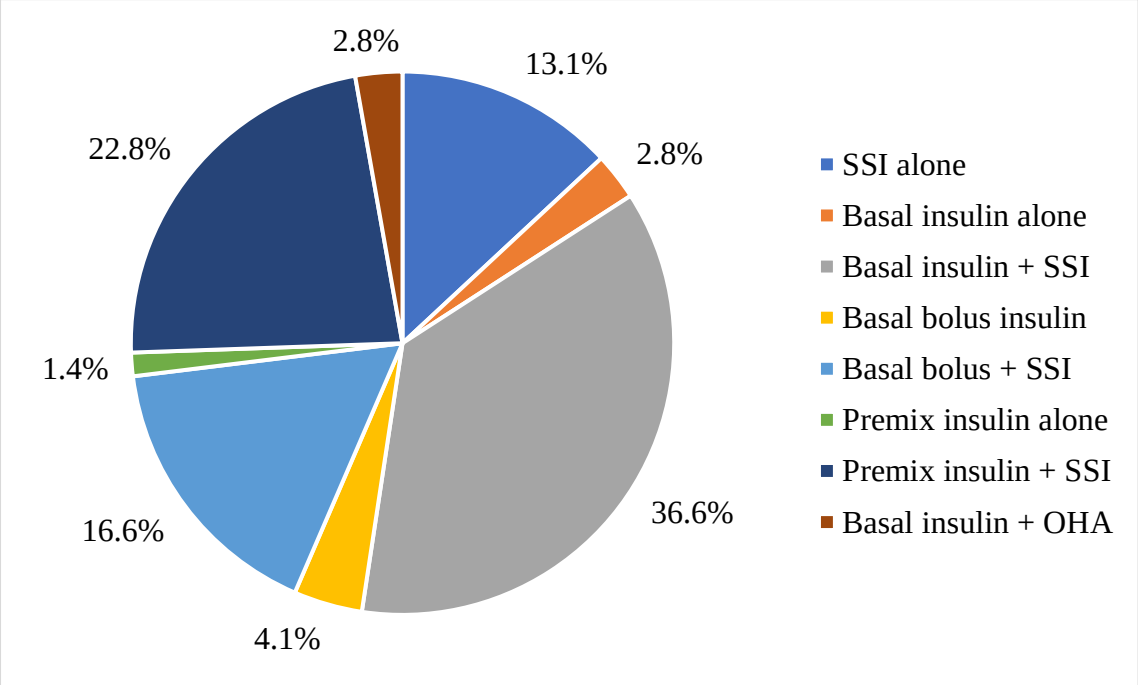


Figure 3. Frequency of prescribed insulin regimens in the general medical wards.
SSI = sliding scale insulin; OHA = oral hyperglycaemic agent.

Amongst those who prescribed SSI alone, the reasons offered for delaying basal insulin were concerns about the lack of inpatient glycaemic monitoring in 42.1% and uncertainty of the best insulin regimen to use in 26.3%. A further 21.1% would delay basal insulin for both fear of inpatient hypoglycaemia and the need to initially assess insulin requirements before initiating maintenance insulin. Lastly, 5% felt that SSI was as effective as pre-emptive strategies.

Monitoring of glucose levels in the general medical wards was reported to occur four to six hourly in 76.6% of respondents and in relation to meals in 18.6%. The remainder monitored

glucose at other scheduled intervals. Table 4 shows median glucose targets reported by clinicians for random, fasting, post-prandial and bedtime glucose recordings. Of note, there was a significant difference in the upper glycaemic target for random glucose measurements accepted according to years of experience, with those with more years of experience targeting tighter ranges (p = 0.003).

Variable	Median (IQR) or mean (SD)	Years of experience						
		0-2 (n=23)	2-4 (n=28)	4-8 (n=48)	8-15 (n=20)	15-30 (n=21)	30+ (n=5)	p-value
Random upper limit	10 (10-12)	12 (11-14)	11 (10-14)	10 (10-12)	10 (8.5-10)	10 (8-11)	9 (8-10)	**0.003**
Random lower limit	4 (4-5)	4 (4-5)	4 (4-6)	4 (4-5)	4 (4-5)	4 (4-5)	4 (4-4)	0.756
Fasting upper limit	7.8 (1.2)	7 (0)	7.3 (3.5)	8 (1.9)	8.4 (2.3)	8.2 (1.6)	7 (1)	0.911
Fasting lower limit	4 (4-5)	4.5 (4-5)	7 (4-7)	4 (4-5)	5.6 (4.5-7)	4 (4-6)	4 (3.2-4)	0.212
Post prandial upper limit	10.3 (2.2)	9.3 (1.1)	11 (3.0)	10.1 (2.8)	10.9 (4.4)	10.3 (1.4)	10.7 (1.2)	0.392
Post prandial lower limit	6 (5-7.8)	6 (5-7)	9 (5-11)	5 (5-6)	8 (6-10)	6 (4-7)	7.8 (4-8)	0.609
Bedtime upper limit	8.9 (1.8)	8.3 (0.4)	9 (1.7)	9.1 (2.1)	9.5 (3.5)	7.8 (1.6)	10 (0)	0.651
Bedtime lower limit	5.8 (5-6.5)	6 (5-7)	5 (5-7)	5.6 (5-6)	9.5 (5-14)	6 (4-6)	6 (4-8)	0.971

Table 4. Glycaemic targets in the general medical wards according to the survey represented as medians with interquartile range (IQR) or means with standard deviation (SD).

Daily review of glycaemic management was reported in 91.7% of participants, alternate daily in 5.5% and longer intervals in 2.8%. Based on these reviews, 41.4% of participants would change their glucose regimen for hypoglycaemia with glucose levels starting below 3 mmol/L, while the majority (54.5%) would adjust for levels starting below 4 mmol/L. Hyperglycaemic

adjustments were reported to be initiated for levels above 7.8 mmol/L in 8.3%, above 10 mmol/L in 45.5% and above 15 mmol/L in 37.2%. Adjustment for large glycaemic variability (measured glucose levels differing by more than 8 mmol/L) was reported in 50.3%. There was a significant difference in the reason to change management for hyperglycaemic levels according to years of experience, with more experienced clinicians altering the insulin regimen for glucose levels above 10 mmol/L ($p = 0.009$) compared to junior staff accepting higher levels of hyperglycaemia and only changing management for measured glucose levels above 15 mmol/L ($p < 0.001$).

Regarding SSI prescriptions, hypoglycaemic targets for SSI were reported as below 4 mmol/L in 91.2% of responses and below 3 and 3.5 mmol/L in 4.4% each. The glucose level for which insulin was started ranged between 8–20 mmol/L, with the most frequent glucose target for starting insulin measuring 10 mmol/L (35.3%). This was followed by 26.9% of respondents using a level of 12 mmol/L, 14.3% using a glucose target of 8 mmol/L and 10.9% accepting glucose levels up to 20 mmol/L. Very high doses of short-acting insulin (10 or more international units) were used most frequently (47.1%) for a measured glucose level of 20 mmol/L or greater, 37.3% used high doses for glucose measurements above 18 mmol/L and 9.8% for glucose levels of more than 16 mmol/L. This is further represented in Figure 4 below.

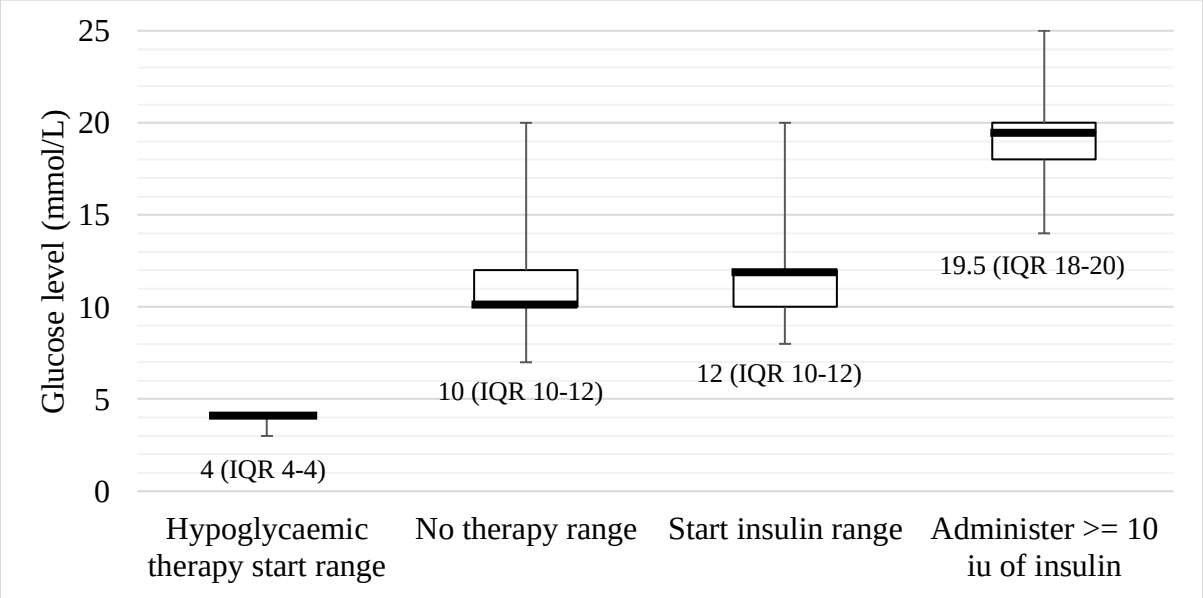


Figure 4. Medians and interquartile range (IQR) for sliding scale ranges used in the management of hyperglycaemia as reported by respondents.

3.4. Trends in the Intensive Care Units according to the survey

3.4.1. Use of non-insulin glucose-lowering agents

Amongst respondents practising in the ICU, just a quarter reported continued use of non-insulin therapies. This equates to a 62% lower rate of non-insulin glucose-lowering therapy use compared to the general medical wards. Metformin was continued by 22.2% of respondents, followed by SGLT2-is in 17.5% and DPP4-is in 15.9%. Continuation of both SUs and GLP-1 RAs was reported in 14.3% of respondents, while only 7.9% indicated that they would use TZDs. Regarding the initiation of new therapies, a similar proportion of ICU practitioners indicated that they would initiate metformin in the ICU (23.8%), followed by 14.3% each initiating SGLT2-is and DPP4-is. SUs, GLP-1 RAs and TZDs were again initiated less frequently (9.5%, 7.9% and 4.7%, respectively). These frequencies of use for non-insulin glucose-lowering agents did not vary significantly according to years of experience.

Of all respondents, 81.8% reported limiting the use of non-insulin agents in the ICU with consistency among varying levels of experience ($p = 0.713$). Table 5 lists the top five reported reasons why a practitioner would not use each non-insulin glucose-lowering agent in the ICU setting, where the percentage represents the proportion of physicians that would not use each non-insulin glucose-lowering agent for a particular condition. Renal failure was again the most frequently reported reason, as shown in Figure 5.

Condition	Metformin Rank (%)	SU Rank (%)	DPP4-i Rank (%)	GLP-1 RA Rank (%)	SGLT2-i Rank (%)	TZD Rank (%)
Renal failure	**1** (94.4)	**1** (94.4)	**1** (83.3)	**1** (83.3)	**1** (88.9)	**1** (83.3)
Liver failure	**3** (33.3)	**2** (38.9)	**2** (33.3)	**2** (33.3)	**2** (33.3)	**2** (33.3)
Sepsis	**4** (27.8)	**3** (22.2)	**3** (22.2)	**3** (22.2)	**3** (22.2)	**3** (22.2)
Hypoglycaemia	**5** (16.7)	**4** (16.7)	**4** (11.1)	**4** (11.1)	**4** (16.7)	**4** (11.1)
NPO	-	**5** (11.1)	**5** (11.1)	**5** (11.1)	**5** (11.1)	**5** (11.1)
Lactic acidosis	**2** (33.3)	-	-	-	-	-

Table 5. Top five conditions for which respondents would not use specific oral agents in intensive care wards.

NPO = nil per mouth; SU = sulfonylurea; DPP4-i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2-i = sodium-glucose cotransporter 2 inhibitor; TZD = thiazolidinedione.

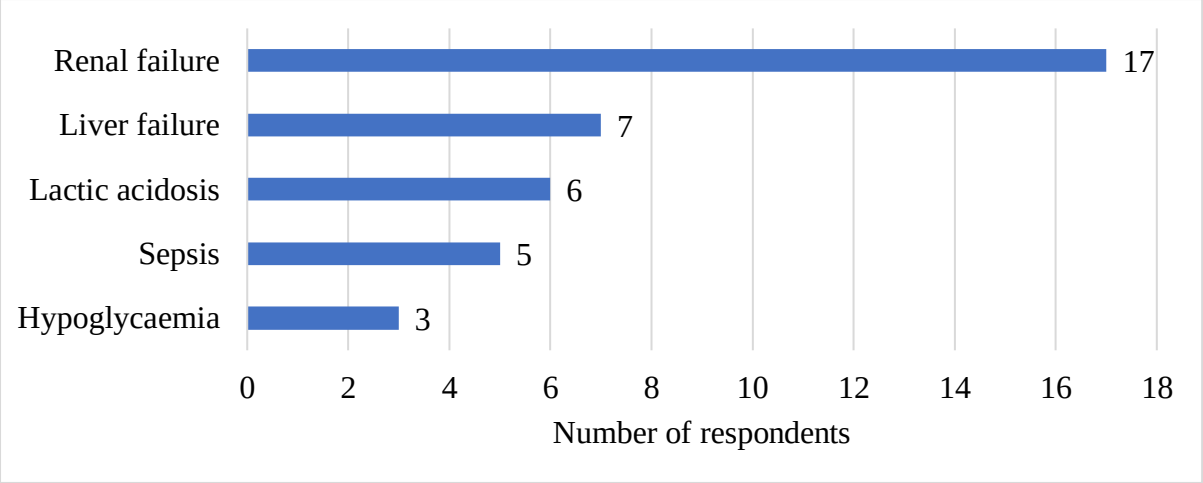


Figure 5. Top conditions for which oral hypoglycaemic agents were not used in the ICU

3.4.2. Use of insulin

Unlike in the general medical wards, there was a more varied approach to altering the prehospital insulin regimens on admission to the ICU. Thirty-nine point six percent of ICU practitioners would stop prehospital insulin, with the remainder either continuing (30.2%), reducing (15.9%) or increasing (14.3%) the TDD of insulin. No significant association was found between the type of approach and years of experience.

Figure 6 illustrates the frequency of use of insulin regimens in the ICU. The insulin infusion was the preferred insulin regimen in the ICU, reported in 34.9% of responses. Amongst those using SSI alone, reasons for delaying basal insulin included fear of inpatient hypoglycaemia (40% of respondents), concern about challenges with glucose monitoring (30% of respondents) and uncertainty about the best choice of regimen to use (20% respondents). A further 15% of respondents thought that basal insulin was not indicated in the ICU setting, while 10% believed a SSI is as effective as basal insulin.

In terms of glycaemic monitoring, respondents would use a glucometer more frequently than a blood gas analyser to process specimens (69.8% vs 30.2%). To obtain a sample, a finger prick technique was performed in most cases (50.8%), followed by an arterial blood draw (36.5%) and then a venous blood draw (12.7%). For each of these approaches, the median glucose limits identified by participants were an upper limit of 10 mmol/L (IQR 8-10) and a lower limit of 4 mmol/L (IQR 4-5).

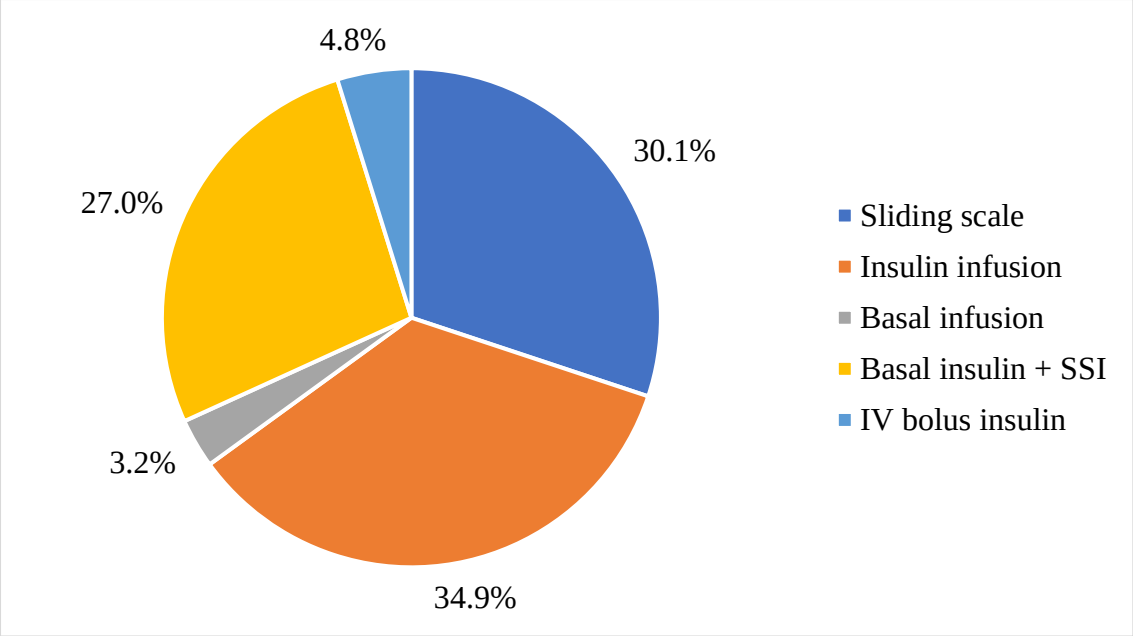


Figure 6. Frequency of prescribed insulin regimens in the ICU.

SSI = sliding scale insulin; IV = intravenous.

The frequency of reviewing patients' management was reported to be performed daily in 87.3% of participants and alternate daily in 3.2%, while 9.5% used longer intervals. In response to the review of management, 30.2% of participants indicated that they would change their glucose management for hypoglycaemia at levels below 3 mmol/L. In comparison, 69.8% of respondents noted that they would make changes for hypoglycaemia levels below 4 mmol/L. Hyperglycaemia management was initiated for levels above 7.8 mmol/L in 33.3% of participants, above 10 mmol/L in 44.4% of participants and above 15 mmol/L in 12.7% of participants. Finally, 33.3% of respondents would adjust their glucose management for a large glycaemic variability of more than 8 mmol/L.

3.5. Combined answers

Participants reported having learned about the SSI regimen at various times during their careers. In half of the respondents, the SSI was taught to them during internship (50%), in one-third as students (33.7%) and the remainder at more senior levels. Most respondents (55.2%) were taught the SSI regimen by their registrars, followed by a hospital facility protocol and consultants (15.6% and 13.6%, respectively), while 5.8% reported having been taught this regimen by a colleague at the same level.

In response to hypoglycaemia or hyperglycaemia when using SSI, 81.2% of participants reported that they would change their TDD of insulin, 7.1% would change the SSI regimen,

and 5.8% would change the frequency of insulin given. The remaining 5.8% would adopt other approaches depending on the individual patient.

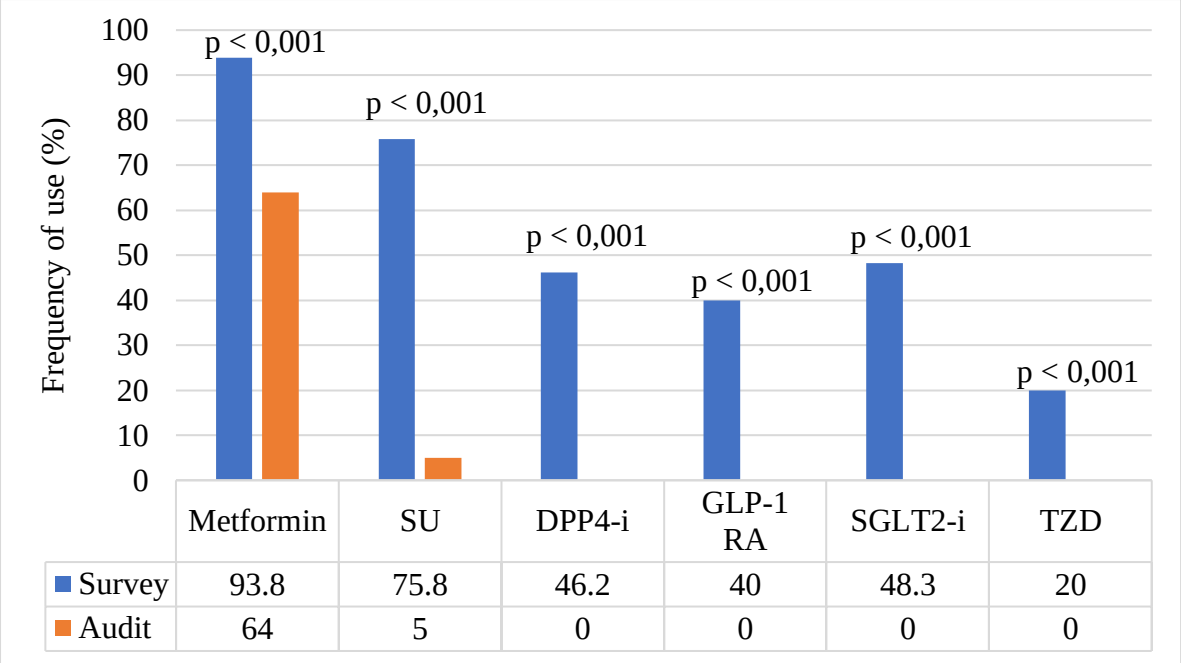
3.6. Validation with audit

The audit of both the general medical wards and ICUs found that the median target for hypoglycaemia was uniformly 4 mmol/L. For the upper limits before correction insulin was instituted, a median level of 10 mmol/L (IQR 10–10) and 10 mmol/L (IQR 10–12) was used for the general wards and ICUs, respectively. There was no statistically significant difference between the targets in the audit and the survey ($p = 0.153$ for general medical wards and 0.157 for ICU).

OHAs were used in 64% of audited patients in the general medical wards and 14.4% in the ICUs. This was significantly lower when compared to the reported use of such agents in the survey and accurate for both the general wards (94.5% survey vs 64% audit, $p < 0.001$) and for ICUs (34.9% survey vs 14.4% audit, $p = 0.002$). Compared to the survey, the audit was indicative of each OHA being used less frequently. This is reflected in Figures 7 and 8. DPP4-is, GLP-1 RAs, SGLT2-is and TZDs were not used during the audit in either the general wards or ICUs due to the lack of availability in the state sector.

There were significant differences in the insulin regimens used in the general wards compared to those reported in the survey. Greater use of the SSI alone was evident in the audit when compared with the survey (36% vs 13.1%, $p < 0.001$) and significantly lower use of basal insulin plus SSI (14% vs 36.6%, $p < 0.001$) as well as basal bolus plus SSI (7% vs 16.6%, $p = 0.027$) was observed when comparing the audit to the survey. There was no significant difference in the use of premix insulin with SSI (33% vs 22.8%, $p = 0.076$) nor premix insulin alone (1% vs 1.4%, $p = 1.000$) when comparing the audit to the survey. Basal insulin alone, basal bolus insulin and basal insulin with OHAs were not used in the general wards audit and were reflective of the frequencies reported in the survey.

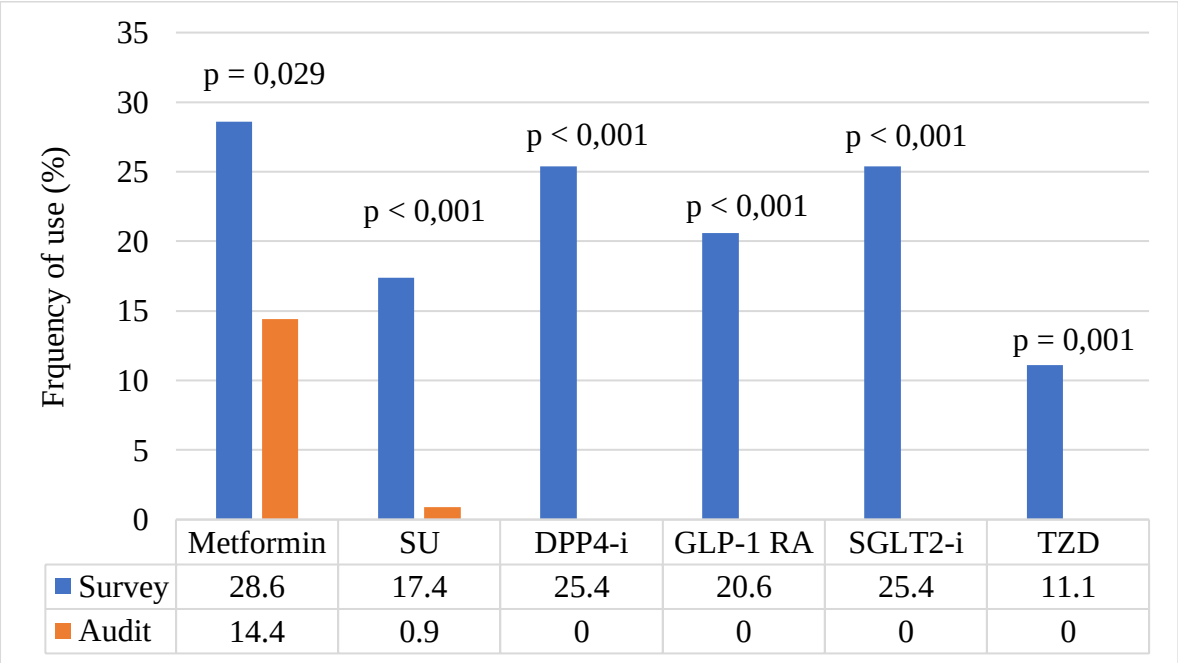
Similarly, in the ICUs, when comparing the audit to the survey, there was significantly greater use of the SSI alone (59.5% vs 30.1%, $p < 0.001$) but lower use of insulin infusion (14.4% vs 34.9%, $p = 0.002$) and intravenous bolus insulin (0% vs 4.8%, $p = 0.02$) when compared with the survey results. There was, however, a similarity between the audit and survey in the use of basal insulin with SSI (26.1% vs 27%, $p = 0.902$) and basal insulin alone (0% vs 3.2%, $p = 0.059$).



	Metformin	SU	DPP4-i	GLP-1 RA	SGLT2-i	TZD
Survey	93.8	75.8	46.2	40	48.3	20
Audit	64	5	0	0	0	0

Figure 7. Use of oral hypoglycaemic agents in the general medical wards.

SU = sulfonylurea; DPP4-i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2-i = sodium-glucose cotransporter 2 inhibitor; TZD = thiazolidinedione.



	Metformin	SU	DPP4-i	GLP-1 RA	SGLT2-i	TZD
Survey	28.6	17.4	25.4	20.6	25.4	11.1
Audit	14.4	0.9	0	0	0	0

Figure 8. Use of oral hypoglycaemic agents in the ICU

SU = sulfonylurea; DPP4-i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2-i = sodium-glucose cotransporter 2 inhibitor; TZD = thiazolidinedione.

Table 6 details the number of hypo- and hyperglycaemic episodes per insulin regimen observed during the audits of the general medical wards and ICUs.

	Total Use	**%**	**HGT < 4 (n)**	**%**	**HGT > 7.8 (n)**	**%**	**HGT > 10 (n)**	**%**	**p-value**
Insulin use in general medical wards									
SSI alone	36	36	26	32,9	322	28,7	273	17,6	**<0.001**
Basal insulin alone	0	0	0	0	0	0	0	0	-
Basal insulin + SSI	14	14	12	15,2	242	21,6	356	22,9	0.230
Basal bolus alone	0	0	0	0	0	0	0	0	-
Basal bolus + SSI	7	7	5	6,3	105	9,4	202	13	**0.005**
Premix insulin alone	1	1	0	0	4	0,4	9	0,6	0.710
Premix insulin + SSI	33	33	36	45,6	449	40	715	46	**0.008**
Basal insulin alone + OHA	0	0	0	0	0	0	0	0	-
None	9	9	0	0	0	0	0	0	-
Total	100	100	79	100	1122	100	1555	100	
Insulin use in ICU									
None	0	0	0	0	0	0	0	0	-
Correction insulin alone	82	73,9	123	54,4	3610	71,1	2158	68,6	**<0.001**
Basal insulin alone	0	0	0	0	0	0	0	0	-
Basal insulin + Correction insulin	16	14,4	72	31,9	981	19,3	631	20,1	**<0.001**
Basal bolus alone	0	0	0	0	0	0	0	0	-
Basal bolus + correction insulin	2	1,8	4	1,8	56	1,1	36	1,1	0.529
Premix insulin alone	0	0	0	0	0	0	0	0	-
Premix insulin + correction insulin	11	9,9	27	11,9	433	8,5	320	10,2	**0.015**
Total	111	100	226	100	5080	100	3145	100	

Table 6. Hypoglycaemic and hyperglycaemic events for each insulin regimen in general medical wards and ICU.

HGT = haemo glucose test; SSI = sliding scale insulin; OHA = oral hyperglycaemic agent; ICU = intensive care unit.

Table 7 compares the number of hypo- and hyperglycaemic events between basal-based insulin regimens, premix-based insulin regimens, SSI, and insulin infusion-based regimens in the general medical wards and ICU. To account for variations in patient numbers treated with each regimen as well as differences in the duration of admission, Tables 8 and 9 compare the average number of hypo- and hyperglycaemic events per hour admitted for every patient treated with each insulin regimen in the general medical wards and ICU, respectively.

In the general medical wards, there was a significantly higher average number of hyperglycaemic episodes per patient in the basal-based insulin regimens compared to SSI regimens for both premeal glucose recordings above 7.8 mmol/L ($p = 0.001$) and random glucose recordings above 10 mmol/L ($p < 0.001$). Similarly, a significantly higher frequency of events was noted in the premix-based insulin regimens compared to SSI regimens for both premeal ($p < 0.001$) and random hyperglycaemia ($p < 0.001$).

In the ICU, SSI was associated with a statistically significant reduction in the average number of hypo- and hyperglycaemic events compared to insulin infusion, basal, and premix insulin regimens. Furthermore, the insulin infusion was associated with a greater number of hyperglycaemic events above 7.8 mmol/L compared to basal and premix insulin and a higher number of events above 10 mmol/L when compared to basal insulin regimens.

	HGT Levels		
	< 4 mmol/L	**> 7.8 mmol/L**	**> 10 mmol/L**
General medical ward insulin			
SSI	26 (32.9%)	322 (28.7%)	273 (17.6%)
Basal	17 (21.5%)	347 (30.9%)	558 (35.9%)
Premix	36 (45.6%)	453 (40.4%)	724 (46.6%)
Total	79 (100%)	1122 (100%)	1555 (100%)
ICU insulin regimen			
SSI	98 (43.4%)	2726 53.7%)	1490 (47.4%)
Insulin infusion	25 (11.1%)	884 (17.4%)	668 (21.2%)
Basal	76 (33,6%)	1037 (20,4%)	667 (21,2%)
Premix	27 (11,9%)	433 (8,5%)	320 (10,2%)
Total	226 (100%)	5080 (100%)	3145 (100%)

Table 7 Frequency of hypoglycaemic and hyperglycaemic events for SSI, correction, basal and premix-based insulin regimens in the general medical wards and ICU.

HGT = haemo glucose test; SSI = sliding scale insulin; ICU = intensive care unit.

HGT levels	Regimen			p-value		
	SSI	Basal	Premix	SSI vs Basal	Basal vs Premix	SSI vs Premix
Average number of events per hour admitted per patient treated						
< 4 mmol/L	0.0028	0.0028	0.0048	0.114	0.451	0.107
> 7.8 mmol/L	0.0370	0.0664	0.0657	**0.001**	0.498	**< 0.001**
> 10 mmol/L	0.0311	0.1111	0.1130	**< 0.001**	0.485	**< 0.001**

Table 8. Average number of hypoglycaemic and hyperglycaemic events per hour admitted for patients treated with SSI, basal and premix-based insulin regimens in the general medical wards.

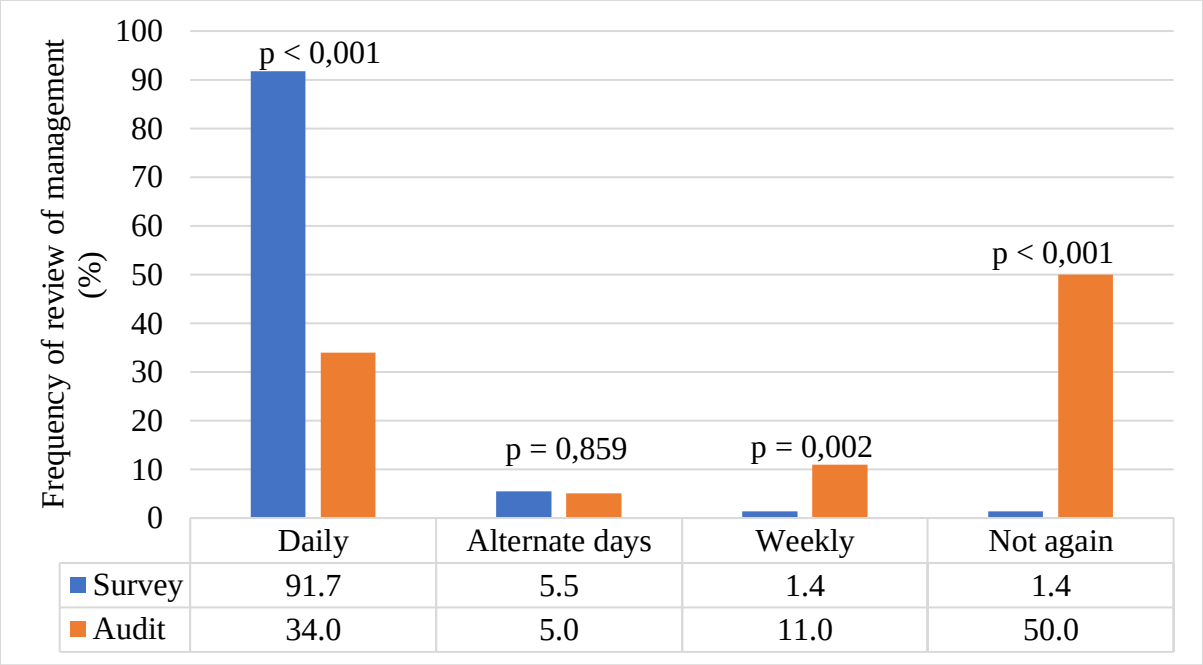
HGT = haemo glucose test; SSI = sliding scale insulin

	HGT Levels		
	< 4 mmol/L	**> 7.8 mmol/L**	**> 10 mmol/L**
Average number of events per hour admitted per patient treated			
SSI	0.0046	0.1632	0.0955
Insulin infusion	0.0122	0.4493	0.3485
Basal	0.0139	0.2580	0.1730
Premix	0.0137	0.2578	0.1883
p–values			
SSI vs Insulin infusion	**0.007**	**< 0.001**	**< 0.001**
SSI vs Basal	**0.005**	**0.006**	**0.007**
SSI vs Premix	**0.016**	**0.012**	**0.003**
Insulin infusion vs Basal	0.487	**0.008**	**0.005**
Insulin infusion vs Premix	0.480	**0.028**	0.050
Basal vs Premix	0.492	0.422	0.258

Table 9. Average number of hypoglycaemic and hyperglycaemic events per hour admitted for patients treated with SSI, insulin infusion, basal and premix-based insulin regimens in the ICU.

HGT = haemo glucose test; SSI = sliding scale insulin.

In terms of glycaemic monitoring, the audit of the general wards demonstrated an increased frequency of four hourly monitoring when compared to the survey (78% vs 41.4%, $p < 0.001$) and decreased frequency of six hourly (6% vs 35.2%, $p < 0.001$), pre-prandial (0% vs 11%, $p < 0.001$) and seven-point profile monitoring (0% vs 6.2%, $p = 0.012$). In the ICUs, glycaemic monitoring occurred more frequently in both the two hourly (18% vs 0%, $p < 0.001$) and four hourly (77.5% vs 23.8%, $p < 0.001$) schedules, with a lower frequency of six hourly (2.7% vs 36.5%, $p < 0.001$), pre-prandial (0% vs 14.3%, $p < 0.001$) and seven point profiles (0% vs 6.3%, $p = 0.016$) when compared to the survey. The frequency of the review of glycaemic management in the general medical wards and ICU is demonstrated in Figures 9 and 10.



	Daily	Alternate days	Weekly	Not again
Survey	91.7	5.5	1.4	1.4
Audit	34.0	5.0	11.0	50.0

Figure 9. Frequency of documented review of glycaemic management in the general medical wards.

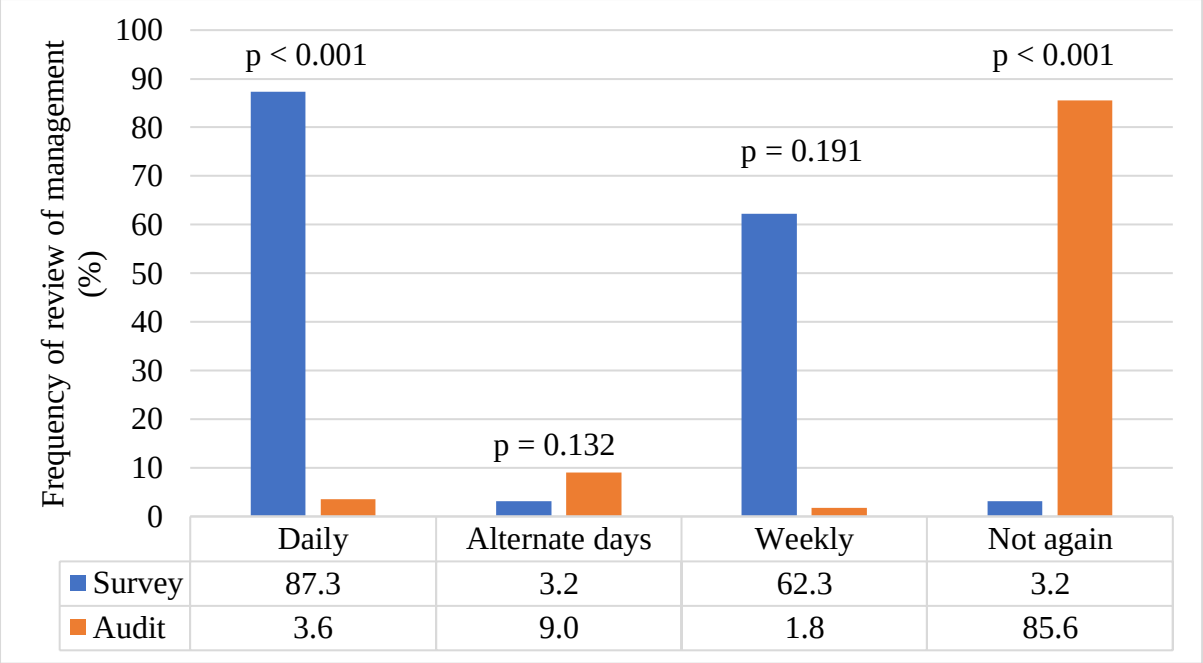


Figure 10. Frequency of documented review of glycaemic management in the ICU.

Chapter 4. Discussion

This study demonstrated significant differences in clinical practice amongst South African physicians and intensivists in the management of inpatient hyperglycaemia when compared to current guideline recommendations. Differences were observed in glycaemic limits and targets, use of OHAs, choice of insulin-based regimens, particularly the SSI, and monitoring of glycaemic levels.

According to the survey results, the majority of practitioners define hyperglycaemia as glucose levels that are significantly higher than those recommended by current guidelines. Physician tolerance of higher glucose levels exposes patients to more complications, with up to a 3% increase in complications[16] and a 10% increase in mortality[8] for every 1 mmol/L rise in glucose. Furthermore, both the survey and audit revealed that practitioners initiate insulin only in response to glucose levels exceeding recommended thresholds. This goes against current guidelines, which recommend actively maintaining levels within a conventional glucose range (7.8–10 mmol/L) rather than responding to levels outside these thresholds.[15] In addition, *Kinsley et al.* describe improved outcomes in patients who obtain a higher duration of time in their targeted glycaemic range, indicating that the duration of control significantly impacts patient outcomes.[29] Only initiating insulin at a measured serum glucose of 12 mmol/L (median level in the survey) exposes patients to higher glucose levels. Considering the associated complications, this should be avoided.

Despite the growing interest in the use of non-insulin glucose-lowering therapies in the inpatient setting[6], guidelines recommend against their use during hospital admission in both the critical and non-critical care settings and recommend reintroducing them 48 hours prior to discharge[1,15]. In contrast to these recommendations, a significant proportion of respondents in the general medical wards reported continuing or initiating non-insulin glucose-lowering therapies during hospital admission. This trend was not evident to the same extent in the ICU setting, where there was much lower use of these agents (34.9%). The audit observed similar patterns with markedly higher use of non-insulin glucose-lowering agents in the general medical wards compared to the ICU setting. However, the ICU findings have clinical significance as one in three critically ill patients may be exposed to potentially harmful therapy. As this study was not designed to investigate the impact of this discordance from guidelines, further research is required in this regard.

Regarding the use of specific OHAs or GLP-1 RAs, the survey of the general wards revealed a significant finding, showing that most respondents would use metformin, with the next most frequently used being SUs. A markedly lower proportion would use SGLT2-is followed by DPP4-is and GLP-1 RAs. This is despite substantial evidence against the use of SUs[32] and SGLT2-is for inpatient hyperglycemia[35]. Existing evidence does suggest a possible role for the use of DPP4-is and GLP-1 RAs[6,15,31] and cautions against the use of metformin in an inpatient setting[6].

The lower use of DPP4-is and GLP-1 RAs was due to registrars comprising the majority of respondents in the general medical ward survey. This was further supported by a significant increase in the use of DPP4-is, GLP-1 RAs and SGLT2-is associated with greater years of respondents' experience. As the private sector has a higher median age of respondents than the state sector, this increase in use is likely due to the greater availability of these agents and associated familiarity in the private sector. The survey further demonstrated this access to medications with significantly lower use of GLP-1 RAs in state consultants compared to those in private practice.

In the ICU survey, all OHAs were prescribed in under 30% of respondents, with metformin as the most frequently used agent, followed by SGLT2-is and DPP4-is. The higher use of metformin and SGLT2-is is of concern due to the increased risk of lactic acidosis and euglycaemic DKA, respectively, particularly in the critical care setting[32,35].

A lack of resources was observed in the audit of the state hospitals where metformin and SUs were the only OHAs prescribed. There was, however, markedly lower use of both of these agents in the audit compared to reported use in the survey, with a greater reduction in the use of SUs compared to metformin in both the general medical wards and ICU setting. Despite this, the high use of SUs amongst practitioners in both state and private practice and both the general medical wards and ICU, as well as the highly reported use of SGLT2-is, demonstrates a significant deviation of current practice from clinical guideline recommendations amongst physicians and intensivists in South African hospitals.[21]

In line with the current study, current literature shows that OHAs continue to be used for inpatient hyperglycaemia. *Bishay et al.* note that metformin was used in 62% of cardiac inpatients in western Sydney, followed by SU's in 29% of patients, DPP4-is in 13% of patients and SGLT2-is in 2% of patients.[40] Although clinical guidelines recommend against using OHAs, they are being used in practice because of their perceived benefits and ease of

administration. These agents have both glycaemic and non-glycaemic benefits. Due to the frequency of drug errors and hypoglycaemia, practitioners are reluctant to use insulin in the inpatient setting, with many opting instead for OHAs.[41] At times, these agents may be helpful in the control of mild to moderate inpatient hyperglycaemia in patients who are at low risk of hypoglycaemia and do not have contraindications to their use.[6] This is partly due to their longer duration of action and, therefore, their ability to reduce glycaemic variability.[42] To this end, the use of SU's has been recommended for managing steroid-induced hyperglycaemia in certain clinical scenarios.[9] Even metformin in a retrospective study was shown to obtain similar glycaemic control to insulin, with no hypoglycaemic episodes in enterally tube-fed patients compared to two hypoglycaemic episodes in the insulin group.[43]

The reasons for avoiding non-insulin glucose-lowering agents were not in line with the major concerns described in the literature. According to current literature, the use of metformin is limited by lactic acidosis and potential risk factors for this condition (cardiac, renal and pulmonary disease and hypoperfusion), as well as intravenous contrast media.[1] However, concern for lactic acidosis was only reported in 24.8% of participants in the general wards and 33.3% in the ICU setting. Renal failure, however, was reported as a concern in 87.2% and 94.4% in the general medical wards and ICUs, respectively. According to the literature, SU use is restricted by hypoglycaemia as well as its prolonged effect.[1] Responses from the survey, however, only report this concern in 25.6% in the general wards and 16.7% in the intensive care setting. The literature suggests that SGLT2-is are linked with an increased risk of euglycaemic DKA[35], and TZDs are linked with heart failure and delayed effect[32]. These conditions were not listed in the top five concerns from the survey. The most frequent reason against the use of DPP4-is, according to the survey, was renal failure. *Scheen*, however, describes that these agents remain useful despite varying renal function.[31] Therefore, concerns raised by practitioners for the use of certain OHAs appear to contrast with literature-supported reasons for concern. This may reflect a lack of understanding regarding the mechanisms of action of OHAs and a lack of knowledge of their specific contraindications among clinicians in the South African setting.

Regarding the use of insulin in the general medical wards, most survey responses were aligned with guideline recommendations which suggest continuing prehospital insulin regimens in stable patients or reducing the TDD in the case of nutritional limitations.[1] Furthermore, the choice of prescribing basal-based insulin regimens by the majority of general medical ward respondents paralleled guideline recommendations. However, in contrast to the survey, the

audit showed markedly higher use of premix-based insulin regimens and SSI by clinicians, which is against current guidelines due to concerns of hypoglycaemia and lack of efficacy.[1]

In the ICU, less than half of the survey respondents followed guideline-recommended adjustments to prehospital insulin regimens. Furthermore, under half of physicians reported using the guideline-recommended insulin infusion, while about a third of respondents indicated using the SSI. However, in the audit, there was a markedly higher rate of use of the SSI compared to the insulin infusion, which is against recommendations.[1] The insulin infusion allows the physician to rapidly manipulate glycaemic levels according to continually fluctuating insulin requirements.[44] However, due to this rapid control, insulin infusions require frequent detailed monitoring and adjustments by experienced clinicians and nursing staff to prevent hypoglycaemia.[44] Despite guideline recommendations, well-known limitations towards physicians' use of insulin infusions include fear of hypoglycaemia, insufficient resources in terms of staffing, expertise and glucose monitoring devices, as well as physician inertia.[1, 44] These limitations may have resulted in the use of SSI due to its convenience and simplicity.[36]

Regarding SSI, 85% of respondents reported being taught their SSI regimen in their basic training years. Considering that only 13.6% of all respondents were taught the SSI by their consultant (where only 5% of the total respondents were endocrinologists) and 15.6% from their facility protocol, most of the respondents were likely not taught inpatient glycaemic management according to guideline recommendations. This hypothesis was supported throughout the survey and audit. This indicates a deficiency in early training and general practice as trainees are taught an outdated approach instead of the recommended basal bolus with correction dosing regimen.

SSI use is associated with poorer glucose control, a greater number of treatment failure episodes[37], as well as an average increase of 1.11 mmol/L in glucose level[38]. The audit of the general wards, however, observed significantly higher numbers of hyperglycaemic episodes per patient in both the basal and premix insulin groups compared to SSI-only regimens. Similar control was achieved in the basal and premix insulin groups. This is contrary to previous research, which demonstrated worse control and poorer outcomes in those managed by SSI and premix insulin compared to basal insulin regimens.[1,6,15,37] A factor contributing to this difference is the infrequent and inadequate active management of glucose charts, as 50% of general medical files were not reviewed throughout admission after the initial prescription. In addition, patients with only mild to moderate elevations in glucose levels or those previously

controlled on OHAs may have been managed with SSI alone, whereas patients with severe hyperglycaemia and previously on insulin therapy may have been treated with basal-based regimens. This would lead to an imbalance in the direct comparison between patients treated with SSI alone and the basal insulin group. Other potential reasons may be insufficient knowledge among practitioners on how to use basal insulin based regimens adequately, insufficient basal insulin and insulin TDD prescribed and a greater familiarity with SSI regimens among nursing staff. Furthermore, these findings are limited by the study's sample size and retrospective design. To clarify the relationship between these insulin treatments and glycaemic control in the South African context, further studies, including randomised control trials, are needed.

Of those that would use SSI, the majority of respondents indicated that they would delay basal insulin use due to concerns around inadequate glucose monitoring during admission, followed by fear of hypoglycaemia and a desire to monitor insulin requirements prior to initiation of further treatment. This is in line with outcomes from previous research.[13] Concerningly, a quarter were unsure of which regimen to use. This demonstrates that there is a large gap in the knowledge of healthcare practitioners regarding the management of inpatient hyperglycaemia. The reasons for delaying basal insulin in the ICU were again in line with previous research.[13]

The audit of the ICU demonstrated better glycaemic control in patients managed by SSI compared to insulin infusion, basal and premix-based regimens. This is again contrary to guideline recommendations.[1] Potential reasons for this may be patient selection, in which patients with more severe hyperglycaemia may have been allocated to more intensive insulin regimens, as well as greater familiarity with SSI among ICU staff compared to other insulin regimens. Once again, the sample size and retrospective study design serve as limitations to this finding and further studies investigating glycaemic control with different insulin regimens in the ICU in the South African context are required.

SEMDSA recommends that there is insufficient evidence to support the use of specific devices for monitoring inpatient glucose levels.[1] Similarly, the *ADA* states that point-of-care devices may be used in the inpatient setting, but due to potential sampling errors, any measurement by a point-of-care device that is not in line with a patient's clinical picture should be confirmed using a more reliable measurement method.[15] *Mesotten et al.*, however, states that, due to the limitations of point-of-care devices - especially in critically ill patients - arterial blood samples and blood gas analysers should be the preferred method of monitoring in this setting.[27] In the current study, the predominant method of sampling was using capillary blood samples and

point-of-care devices. Although this is not against the recommendations by *SEMDSA* or the *ADA*, the concerns raised by *Mesotten et al.* should be considered particularly in the critical care setting.

Regarding the frequency of monitoring, the *ADA* advises monitoring every 30 minutes to two hours for patients on insulin infusions, four to six hourly in patients not eating, and pre-prandial in those taking regular meals.[15] Results from the survey and audit, however, show that the predominant monitoring frequency in both the ICU and general medical wards was four hourly regardless of mealtimes. Concerningly, more physiological monitoring schedules (monitoring in relation to meal times) in the general wards were reported to occur in less than one in five patients. The greater use of four hourly monitoring is likely due to convenience with nursing routines as well as monitoring in line with SSI prescriptions. However, this frequency of monitoring should not be the standard practice if patients in these settings are eating regular meals or are on insulin infusions. Considering that the latter was observed in 14.4% of cases in the audit and 44.4% of the responses in the survey, a revision of monitoring practices should be considered in both the ICU and general medical ward settings.

When compared to the audits, survey responses showed a higher frequency of practice in line with guideline recommendations in terms of choice of insulin regimen and glycaemic monitoring. This trend was not translated into clinical practice. While resource and staffing limitations may lead to a physician adapting their glycaemic management to their working environment, the greater concern is that this deviation could demonstrate significant physician inertia in the management of hyperglycaemia and a fear of implementing what is known to be recommended by clinical guidelines. Considering that registrars comprised the majority of survey respondents and were the primary physicians responsible for glycaemic control during the audit, there is a potential teaching opportunity to improve inpatient glycaemic management according to guideline recommendations.

Chapter 5. Conclusions

This study has identified significant differences between the reported and observed practice of physicians and intensivists in the management of inpatient hyperglycaemia, as well as between current practice and local and international guidelines. These differences include glycaemic targets, use of non-insulin glucose-lowering therapies and insulin regimens, contraindications and specific clinical settings preventing the use of agents, as well as the frequency of glycaemic monitoring.

The discrepancies between clinical practice and guideline recommendations that were identified support the perception that there is a lack of knowledge and significant physician inertia in the management of inpatient hyperglycaemia in South Africa. As a result, consideration should be taken to use this research as a basis for initiating institutional changes across all sectors in the management of inpatient hyperglycaemia. This would align clinician practices with guideline recommendations to improve inpatient glycaemic control and, consequently, patient outcomes. Methods to educate and assist clinicians should include further continued education, the development of updated protocols for healthcare practitioners to follow, and enhanced training and education of junior and senior clinicians.

As the outcome of comparing glycaemic control obtained by SSI, insulin infusion, basal, and premix based regimens was not a primary objective for this research, further studies investigating this relationship in the South African context are required.

Chapter 6. Limitations

The following limitations to the study were noted:

1. Study numbers: The study aimed to enrol at least 200 physicians in the state and private sectors. The author planned to contact participants during scheduled departmental meetings, local conferences and via an electronic platform. Due to restrictions imposed by the local government's response to the COVID 19 pandemic, contacting participants in these gatherings was not possible. As a result, participants were enrolled solely via electronic forms. Despite the widespread distribution of the electronic version of the survey, lower-than-expected participation of below 15% was obtained. Although the initial aim was to include participants across South Africa, the aforementioned restrictions resulted in the majority of participants being based in Johannesburg hospitals. After discussion with the study supervisors, data collection was terminated at the end of the study period granted by the ethics committee, having achieved 77% of the intended participants.
2. The audit only involved state hospitals: Although survey respondents were physicians and intensivists in both state and private hospitals, the audit only reviewed the management of patients in the three major state hospitals in Johannesburg. The scope of the current study did not include an investigation of practices in the private sector or other state hospitals. As a result, the audit would only be able to validate the responses of those practising in the three state hospitals involved by comparing the responses from the survey to the results observed in the audit. However, it should be noted that conclusions relating to the current practices of physicians and intensivists, in general, were made based on these findings.
3. Sixty-seven point six percent of respondents from the general medical wards practiced in the three major state hospitals in Johannesburg, and, of these, there was a higher proportion of registrars compared to consultants. As inpatient glycaemic charts were primarily managed by registrars, and registrars comprised most respondents in the general medical ward survey, the audit is representative of most responses from the survey. However, only 36.5% of respondents working in the ICU setting worked in these state hospitals, and, as a result, the audit is representative of the practices of the minority of respondents working in the ICU.
4. The audit was unable to validate the survey: There were significant differences in reported and observed practices in the use of OHAs, insulin regimens, frequency of

glycaemic monitoring and frequency of review of management in both the general medical wards and intensive care units. This reflects a disconnect between physician knowledge and clinical implementation in the management of inpatient hyperglycaemia and resulted in the audit being unable to validate the survey responses as an accurate representation of the current clinical practice in South African hospitals. Despite this, important trends in both the reported and observed practices can be noted from both the survey and the audit, particularly relating to current levels of knowledge in physicians and intensivists as well as glucose monitoring and control in the various facilities. It is also important to be aware of this disconnect when attempting to address any challenges affecting the implementation of clinical knowledge.

5. Convenience retrospective sampling for the audit: due to COVID-19 restrictions, a revision from the initial protocol was obtained from the University of the Witwatersrand ethics committee. This revision allowed for reviewing patient files following discharge instead of prospectively reviewing the charts during admission. As a result, files were frequently obtained from the general records departments in a convenience sampling manner. This sampling did not allow for auditing files of patients with similar levels of glucose control, demographics, or clinical factors. This is hypothesised to be a reason for the discrepancy between the current study's findings on glycaemic control of various insulin-based regimens compared to previous research, and may have had an impact on physicians' choice of glycaemic management.
6. Physician review of glycaemic management: Due to the revised retrospective nature of the audit, physician practices could only be observed if they were documented in the patients' files or ICU charts. Although a physician may have reviewed glycaemic charts more regularly, it was only possible to record this review if there was documentation of the glycaemic readings or a change in script.

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Appendix A: Paper-based Questionnaire Data Sheet

Study Number: S_____

SURVEY

Topic: Assessment of the management of inpatient hyperglycaemia by physicians and intensivists in South African hospitals

AIM OF THE STUDY

Hyperglycaemia is a highly prevalent multifactorial condition affecting inpatients in both the critical and non-critical care environments within a hospital. This places a large burden on the healthcare sector in South Africa as well as worldwide. Hyperglycaemia is also well documented to have a significant impact on the outcome of patients. The aim of this research is to investigate the knowledge and clinical practice of internists and intensivists in the management of inpatient hyperglycaemia in South African hospitals.

INSTRUCTIONS

Please answer the following questions based on how you would manage inpatient hyperglycaemia. This does not include patients that are admitted for:

- initiation of insulin therapy
- hyperglycaemic emergencies (Diabetic Ketoacidosis or Hyperosmolar Hyperglycaemic State)

but rather those who have pre – existing diabetes or develop hyperglycaemia in hospital when admitted for an unrelated problem such as but not limited to heart failure, pneumonia or surgery.

PARTICIPANT DETAILS

1. Age: _____
2. Gender (Please Circle): Male / Female
3. Rank (Please Circle): Registrar / Consultant
4. Area of subspecialty / generalist (Please Circle):

Cardiology	□	Critical Care	□	Gastroenterology	□
Generalist	□	Geriatrics	□	Haematology	□
Nephrology	□	Neurology	□	Pulmonology	□
Oncology	□	Rheumatology	□	Other: _____	

§

5. Which hospital are you currently working at?

CHBAH	□	HJH	□
CMJAH	□	Other	

6. Are you primarily working in: State / Private / Both?

State	□	Private	□	Both	□

7. Which wards do you work in?

General Wards	□	Intensive Care	□	Both	□

8. How long have you been working in these wards (years)?

8.1. General wards

0 – 2	□	8 – 15	□
2 – 4	□	15 – 30	□
4 – 8	□	> 30	□

8.2. ICU

0 – 2	□	8 – 15	□
2 – 4	□	15 – 30	□
4 – 8	□	> 30	□

MANAGEMENT IN THE GENERAL WARD

TARGETS

1. Below what level would you define as hypoglycaemia? _____ mmol/L
2. Above what level would you define as hyperglycaemia? _____ mmol/L

ORAL AND NON–INSULIN INJECTABLE AGENTS

3. If a patient was previously on an oral hyperglycaemic and or a non-insulin injectable agent/s, would you continue the use of the agent/s on admission? Yes / No

   3.1. If yes, please tick which agent/s you would continue? (You may choose one or more option)

Metformin	☐
Sulfonylureas (Glimepiride [Amaryl], Gliclazide [Diamicron])	☐
DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus])	☐
GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta])	☐
SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance])	☐
Thiazolidinediones (Pioglitazone [Actos])	☐
Other _____	

4. If a patient was not previously on an oral hyperglycaemia or non–insulin injectable agent, would you consider adding one while they are an inpatient? Yes / No

   4.1. If yes, please tick which agent/s you would add? (You may choose one or more option)

Metformin	☐
Sulfonylureas (Glimepiride [Amaryl], Gliclazide [Diamicron])	☐
DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus])	☐
GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta])	☐
SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance])	☐
Thiazolidinediones (Pioglitazone [Actos])	☐
Other _____	

5. If you answered yes to question 3 or 4, are there any conditions in which you would not use the above agent/s? Yes / No

   5.1. If yes, please name the agent and the conditions you would not use it in.

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

INSULIN

6. If a patient is already insulin requiring, on admission would you continue their current regimen or change it?

Continue as is	□	Stop current regimen	□
Increase cumulative dose	□	Decrease cumulative dose	□

7. Please select which one of the following insulin regimens you most often use for inpatient hyperglycemia?

Sliding scale alone (Novorapid/Apidra/Actrapid)	□
Basal insulin alone (Lantus/Optisulin/Levemir/Protophane)	□
Basal insulin PLUS sliding scale	□
Basal insulin PLUS premeal insulin	□
Basal insulin PLUS premeal insulin plus sliding scale	□
Premix insulin alone	□
Premix insulin PLUS sliding scale	□
Basal insulin PLUS oral agent	□

8. If you selected sliding scale insulin alone, is there any reason why you would delay basal insulin therapy in a patient? (You may choose one or more option)

Basal insulin is not indicated in inpatient management	□
Sliding scale insulin is effective as the only insulin	□
Fear of hypoglycaemia with basal insulin	□
Lack of local protocols on the use of basal insulin	□
Uncertainty of what regimen to use	□
Concern regarding inpatient glycaemic monitoring	□
Other: _____	

9. If you use a sliding scale at which point in your career did you learn your sliding scale?

Student	□	Registrar	□
Intern	□	Consultant	□
Community service / Medical officer	□	Other _____	

10. Who did you learn your sliding scale from?

Colleague at the same level	□	Registrar	□
Consultant	□	Facility protocol	□
Other _____			

11. Please provide an example of the sliding scale you mostly use.

_____

_____

_____

_____

_____

_____

MONITORING

12. How frequently do you usually monitor glucose levels? (Please tick one)

A) Hourly	□	E) Six hourly	□
B) Two hourly	□	F) Pre-prandial	□
C) Four hourly	□	G) 7-point profile	□
D) Other _____			

13. Based on your answer in question 12, please answer what therapeutic targets you aim for?

13.1. If you selected option A – F:

13.1.1. What upper limit do you aim for? _____

13.1.2. What lower limit do you aim for? _____

13.2. If you selected option G, what ranges do you aim for:

13.2.1. Fasting / Premeal: Upper Limit _____ Lower Limit _____

13.2.2. Post prandial: Upper Limit _____ Lower Limit _____

13.2.3. Bedtime: Upper Limit _____ Lower Limit _____

14. How often do you review your management for a specific patient? (Please tick one)

Daily	□	Weekly	□
On alternate days	□	Not again	□

15. When would you change your management in a specific patient? (You may choose one or more)

Glucose levels below 4.0 mmol/L	□	Glucose levels above 7.8 mmol/L	□
Glucose levels only below 3.0 mmol/L	□	Glucose levels above 10.0 mmolL	□
Large glycaemic variability (> 8 mmol/L)	□	Glucose levels above 15.0 mmol/L	□
Other: _____			

16. If the patient is hyper-/hypoglycaemic, what changes do you usually make? (Please choose one)

Change frequency of insulin given	□	Change your total daily dose	□
Change the type of insulin given	□	Change the sliding scale	□
Other: _____			

Thank you for your participation

CRITICAL CARE

TARGETS

1. Below what level would you define as hypoglycaemia? _____ mmol/L
2. Above what level would you define as hyperglycaemia? _____ mmol/L

ORAL AND NON–INSULIN INJECTABLE AGENTS

3. If a patient was previously on an oral hyperglycaemic and or a non-insulin injectable agent/s, would you continue the use of the agent/s on admission? Yes / No

   3.1. If yes, please tick which agent/s would you continue? (You may choose one or more option)

Metformin	☐
Sulfonylureas (Glimepiride [Amaryl], Gliclazide [Diamicron])	☐
DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus])	☐
GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta])	☐
SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance])	☐
Thiazolidinediones (Pioglitazone [Actos])	☐
Other _____	

4. If a patient was not previously on an oral hyperglycaemic or non–insulin injectable agent, would you consider adding one while they are an inpatient? Yes / No

   4.1. If yes, please tick which agent/s would you add? (You may choose one or more option)

Metformin	☐
Sulfonylureas (Glimepiride [Amaryl], Gliclazide [Diamicron])	☐
DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus])	☐
GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta])	☐
SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance])	☐
Thiazolidinediones (Pioglitazone [Actos])	☐
Other _____	

5. If you answered yes to question 3 or 4, are there any conditions in which you would not use the above agent/s? Yes / No

   5.1. If yes, please name the agent and the conditions you would not use it in.

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

INSULIN

6. If a patient is already insulin requiring, on admission would you continue their current regimen in the ICU or change it?

Continue as is	□	Stop current regimen	□
Increase cumulative dose	□	Decrease cumulative dose	□

7. If you were to stop a patient's prehospital insulin regimen, which of the following do you then use to manage your patient's hyperglycemia in the ICU?

Sliding scale	□	Insulin infusion	□
Basal insulin	□	Intravenous bolus insulin	□
Basal insulin plus sliding scale	□		

8. If you selected more than one option in question 7, in what percentage of patients do you use each of the insulin regimens that you selected?

   8.1. Regimen: _____ Percentage: _____

   8.2. Regimen: _____ Percentage: _____

   8.3. Regimen: _____ Percentage: _____

   8.4. Regimen: _____ Percentage: _____

   8.5. Regimen_____ Percentage: _____

9. If you selected sliding scale insulin alone in question 7, is there any reason why you would delay basal insulin therapy in a patient? (You may choose one or more option)

Basal insulin is not indicated in inpatient management	□
Sliding scale insulin is effective as the only insulin	□
Fear of hypoglycaemia with basal insulin	□
Lack of local protocols on the use of basal insulin	□
Uncertainty of what regimen to use	□
Concern regarding inpatient glycaemic monitoring	□
Other: _____	

10. If you use an insulin infusion in the ICU ;

10.1. Is the protocol:

Guideline recommended	□	Please specify the guideline	_____
Specific to a particular facility	□	From which facility:	_____

10.2. Could you please provide an example of your protocol?

_____
_____
_____
_____
_____
_____

11. Is there a time that you would use a different protocol? If so, please specify.

_____
_____
_____
_____

12. How often do you review the protocol used in a specific patient?

Daily	□	Weekly	□
On alternate days	□	Not again	□

MONITORING

13. Which of the following do you use to monitor glucose in the ICU? (Please choose one)

Glucometer	□	Blood gas analyser	□

14. Which sample do you usually use in the ICU? (Please choose one)

Finger prick	□	Venous sample (CVP / venesection)	□
Arterial sample	□		

15. What therapeutic targets do you aim for?

    15.1.1. Upper limit: _____

    15.1.2. Lower limit: _____

16. When would you change your management in a specific patient? (You may choose one or more)

Glucose levels below 4.0 mmol/L	□	Glucose levels above 7.8 mmol/L	□
Glucose levels only below 3.0 mmol/L.	□	Glucose levels above 10.0 mmolL	□
Large glycaemic variability (> 8 mmol/L)	□	Glucose levels above 15.0 mmol/L	□
Other: _____			

17. If the patient is hyper-/hypoglycaemic on your protocol what changes do you make?

Change frequency of insulin given	□	Change your total daily dose	□
Change the type of insulin given	□	Change the sliding scale	□
Other: _____			

Thank you for your participation.

COMBINED GENERAL WARD AND ICU

TARGETS

1. Below what level would you define as hypoglycaemia?
   General ward _____. ICU _____. mmol/L
2. Above what level would you define as hyperglycaemia?
   General ward _____. ICU _____. mmol/L

ORAL AND NON–INSULIN INJECTABLE AGENTS

3. If a patient was previously on an oral hyperglycaemic and or a non-insulin injectable agent/s, would you continue the use of the agent/s on admission?
   3.1. **General ward**? Yes / No
   3.2. **ICU**? Yes / No
   3.3. If yes, please tick which agent/s you would continue? (You may choose one or more option)

	General ward	ICU
Metformin	□	□
Sulfonylureas (Glimepiride [Amaryl], Gliclazide [Diamicron])	□	□
DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus])	□	□
GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta]).	□	□
SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance])	□	□
Thiazolidinediones (Pioglitazone [Actos])	□	□
Other _____		

4. If a patient was not previously on an oral hyperglycaemia or non–insulin injectable agent, would you consider adding one while they are an inpatient?
   4.1. **General ward?** Yes / No
   4.2. **ICU?** Yes / No

4.3. If yes, please tick which agent/s you would add? (You may choose one or more option)

	General ward	ICU
Metformin	□	□
Sulfonylureas (Glimepiride [Amaryl], Gliclazide [Diamicron])	□	□
DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus])	□	□
GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta])	□	□
SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance]).	□	□
Thiazolidinediones (Pioglitazone [Actos])	□	□
Other _____		

5. If you answered yes to question 3 or 4, are there any conditions in which you would not use the above agent/s? Yes / No

   5.1. If yes, please name the agent and the conditions you would not use it in.

   5.1.1. General ward.

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   5.1.2. ICU

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

   Agent _____ Condition _____

INSULIN

6. If a patient is already insulin requiring, on admission would you continue their current regimen or change it? (Please choose the most correct option)

	General Ward	ICU
Continue as is	□	□
Stop current regimen	□	□
Increase cumulative dose	□	□
Decrease cumulative dose	□	□

7. Please select which one of the following insulin regimens you most often use for inpatient hyperglycemia in the **general ward**?

Sliding scale alone (Novorapid/Apidra/Actrapid)	□
Basal insulin alone (Lantus/Optisulin/Levemir/Protophane)	□
Basal insulin PLUS sliding scale	□
Basal insulin PLUS premeal insulin	□
Basal insulin PLUS premeal insulin plus sliding scale	□
Premix insulin alone	□
Premix insulin PLUS sliding scale	□
Basal insulin PLUS oral agent	□

8. In the **ICU**, if you were to stop a patient's prehospital insulin regimen, which of the following do you then use to manage your patient's hyperglycemia?

Sliding scale	□	Insulin infusion	□
Basal insulin	□	Intravenous bolus insulin	□
Basal insulin plus sliding scale	□		

9. If you selected more than one option in question 8, in what percentage of patients do you use each of the insulin regimens that you selected?
   - 9.1. Regimen: _____ Percentage: _____
   - 9.2. Regimen: _____ Percentage: _____
   - 9.3. Regimen: _____ Percentage: _____
   - 9.4. Regimen: _____ Percentage: _____
   - 9.5. Regimen: _____ Percentage: _____
10. If you selected sliding scale insulin alone in question 7 or 8, is there any reason why you would delay basal insulin therapy in a patient? (You may choose one or more option)

	General ward	ICU
Basal insulin is not indicated in inpatient management	□	□
Sliding scale insulin is effective as the only insulin	□	□
Fear of hypoglycaemia with basal insulin	□	□
Lack of local protocols on the use of basal insulin	□	□
Uncertainty of what regimen to use	□	□
Concern regarding inpatient glycaemic monitoring	□	□

Other: _____

11. If you use a sliding scale at which point in your career did you learn your sliding scale?

Student	□	Registrar	□
Intern	□	Consultant	□
Community service / Medical officer	□	Other _____	

12. Who did you learn your sliding scale from?

Colleague	□	Registrar	□
Consultant	□	Facility protocol	□
Other _____			

13. Please provide an example of the sliding scale you mostly use.

_____

_____

_____

_____

_____

14. If you use an insulin infusion in the **ICU**;

14.1. Is the protocol:

Guideline recommended	□	Please specify the guideline _____
Specific to a particular facility	□	From which facility: _____

14.2. Could you please provide an example of your protocol?

_____

_____

_____

_____

_____

15. Is there a time that you would use a different protocol? If so, please specify.

_____

_____

_____

_____

MONITORING

16. In the **General ward,** how frequently do you usually monitor glucose levels? (Please tick one)

A) Hourly	□	E) Six hourly	□
B) Two hourly	□	F) Pre-prandial	□
C) Four hourly	□	G) 7-point profile	□
D) Other _____			

17. Based on your answer in question 16, please answer what therapeutic targets you aim for?

17.1. If you selected option A – F:

17.1.1. What upper limit do you aim for? _____

17.1.2. What lower limit do you aim for? _____

17.2. If you selected option G, what ranges do you aim for:

17.2.1. Fasting / Premeal: Upper Limit _____ Lower Limit _____

17.2.2. Post prandial: Upper Limit _____ Lower Limit _____

17.2.3. Bedtime: Upper Limit _____ Lower Limit _____

18. In the **ICU,** which of the following do you use to monitor glucose? (Please choose one)

Glucometer	□	Blood gas analyser	□

19. In the **ICU,** which sample do you usually use? (Please choose one)

Finger prick	□	Venous sample (CVP / venesection)	□
Arterial sample	□		

20. In the **ICU,** what therapeutic targets do you aim for?

20.1.1. Upper limit: _____

20.1.2. Lower limit: _____

21. How often do you review your management / protocol for a specific patient? (Please tick one)

	General Ward	ICU
Daily	□	□
On alternate days	□	□
Weekly	□	□
Not again	□	□

22. When would you change your management in a specific patient? (You may choose one or more)

	General Ward	ICU
Glucose levels below 4.0 mmol/L	□	□
Glucose levels only below 3.0 mmol/L	□	□
Glucose levels above 7.8 mmol/L	□	□
Glucose levels above 10.0 mmolL	□	□
Glucose levels above 15.0 mmol/L	□	□
Large glycaemic variability (> 8 mmol/L)	□	□

Other: _____

23. If the patient is hyper-/hypoglycaemic, what changes do you make? (Please choose most correct option)

Change frequency of insulin given	□	Change your total daily dose	□
Change the type of insulin given	□	Change the sliding scale	□

Other: _____

Thank you for your participation

Appendix B: RedCap Questionnaire Data Sheet

Confidential

Assessment of the management of inpatient hyperglycaemia by physicians and intensivists in South African hospitals

Dear colleague, I would like to invite you to participate in this research into the management of inpatient hyperglycaemia. Your participation is entirely voluntary and your responses will be handled confidentially. You will not be negatively affected in any way if you withdraw at any point or choose not to participate in the survey. Please note: completion of this survey implies consent to participation and the use of the results obtained.

AIM OF THE STUDY

Hyperglycaemia is a highly prevalent multifactorial condition affecting inpatients in both the critical and non-critical care environments. This places a large burden on the healthcare sector both in South Africa and worldwide. Hyperglycaemia is also well documented to have a significant impact on the outcome of patients. The aim of this research is to investigate the knowledge and clinical practice of internists and intensivists in the management of inpatient hyperglycaemia in South African hospitals.

INSTRUCTIONS

Please answer the following questions based on how you would manage inpatient hyperglycaemia. This does not include patients that are admitted for

initiation of insulin therapy orhyperglycaemic emergencies (Diabetic Ketoacidosis or Hyperosmolar Hyperglycaemic State)but rather those who have pre-existing diabetes or develop hyperglycemia in hospital when admitted for an unrelated problem such as but not limited to heart failure, pneumonia or surgery.

If you have any questions or would like to clarify any information please contact the principle investigator at: plbhewson@gmail.com.

Informed consent
I confirm that:

I have read and understood the information provided above.I have been given enough time to understand the aim of this research and what is required from me through my participation in this study.I have been able to ask any questions that I may have related to the research in order to clarify my understanding.I have not been pressured into participation in this research against my will.I understand participation is entirely voluntary.I may refuse to participate or withdraw at any stage.

Do you consent to participate in this study?

- ◯ I consent to participate in this study
- ◯ I do not consent to participate in this study

Demographics	
Please enter your age:	_____
Please select your gender	◯ Female ◯ Male
Please select your rank:	◯ Registrar ◯ Consultant ◯ Other (Complete other option)
Other	_____
Please select your area of speciality:	◯ Cardiology ◯ Critical Care ◯ Endocrinology ◯ Gastroenterology ◯ Generalist ◯ Geriatrics ◯ Haematology ◯ Nephrology ◯ Neurology ◯ Oncology ◯ Pulmonology ◯ Rheumatology ◯ Other
Please enter your other subspecialty:	_____
Which hospital are you currently working at?	◯ CHBAH ◯ CMJAH ◯ HJH ◯ Other
Please enter which hospital you work at:	_____
Which sector are you primarily working in?	◯ State ◯ Private ◯ Both
Which wards do you work in?	◯ General Wards ◯ Intensive Care ◯ Both
How long have you been working in the general wards? (Years)	◯ 0 - 2 ◯ 2 - 4 ◯ 4 - 8 ◯ 8 - 15 ◯ 15 - 30 ◯ > 30

How long have you been working in the Intensive Care	◯ 0 - 2 ◯ 2 - 4 ◯ 4 - 8 ◯ 8 - 15 ◯ 15 - 30 ◯ > 30

Targets	
Below what level would you define as hypoglycaemia in the general ward? (mmol/L)	_____
Below what level would you define as hypoglycaemia in the ICU? (mmol/L)	_____
Above what level would you define as hyperglycaemia in the general ward? (mmol/L)	_____
Above what level would you define as hyperglycaemia in the ICU? (mmol/L)	_____

Oral and non-insulin injectable agents	
If a patient was previously on an oral hypoglycaemic and or a non-insulin injectable agent/s, would you continue the use of the agent/s on admission to the general ward?	◯ Yes ◯ No
If a patient was previously on an oral hypoglycaemic and or a non-insulin injectable agent/s, would you continue the use of the agent/s on admission to the ICU?	◯ Yes ◯ No
If a patient was previously on an oral hypoglycaemic and or a non-insulin injectable agent/s, would you continue the use of the agent/s on admission?	☐ Yes, in the General Ward ☐ Yes, in the ICU ☐ No, I would not continue the agent/s
Please tick which agent/s you would continue in the general wards. (You may choose one or more option)	☐ Metformin ☐ Sulfonylureas (Glimepiride [Amayl], Gliclazide [Diamicron]) ☐ DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus]) ☐ GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta]) ☐ SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance]) ☐ Thiazolidinediones (Pioglitazone [Actos]) ☐ Other
Please enter the name of the non-listed agent that you would use in the general ward.	_____
Please tick which agent/s you would continue in the ICU. (You may choose one or more option)	☐ Metformin ☐ Sulfonylureas (Glimepiride [Amayl], Gliclazide [Diamicron]) ☐ DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus]) ☐ GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta]) ☐ SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance]) ☐ Thiazolidinediones (Pioglitazone [Actos]) ☐ Other
Please enter the name of the non-listed agent that you would use in the ICU:	_____
If a patient was not previously on an oral hypoglycaemic or non-insulin injectable agent, would you consider adding one while they are an inpatient in the general ward?	◯ Yes ◯ No
If a patient was not previously on an oral hypoglycaemic or non-insulin injectable agent, would you consider adding one while they are an inpatient in the ICU?	◯ Yes ◯ No
If a patient was not previously on an oral hypoglycaemic or non-insulin injectable agent, would you consider adding one while they are an inpatient?	☐ Yes, in the General Ward ☐ Yes, in the ICU ☐ No, I would not continue the agent/s

Please tick which agent/s you would add in the general ward. (You may choose one or more option)	☐ Metformin ☐ Sulfonylureas (Glimepiride [Amayl], Gliclazide [Diamicron]) ☐ DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus]) ☐ GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta]) ☐ SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance]) ☐ Thiazolidinediones (Pioglitazone [Actos]) ☐ Other
Please enter the name of the non-listed agent that you would use in the general ward.	_____
Please tick which agent/s you would add in the ICU. (You may choose one or more option)	☐ Metformin ☐ Sulfonylureas (Glimepiride [Amayl], Gliclazide [Diamicron]) ☐ DPP4-inhibitors (Sitagliptin [Januvia], Vildagliptin [Galvus]) ☐ GLP-1 receptor agonists (Liraglutide [Victoza], Exenatide [Byetta]) ☐ SGLT2 inhibitors (Dapagliflozin [Farxiga], Empagliflozin [Jardiance]) ☐ Thiazolidinediones (Pioglitazone [Actos]) ☐ Other
Please enter the name of the non-listed agent that you would use in the ICU:	_____
Are there any conditions in which you would not use the agents selected above in the general ward?	◯ Yes ◯ No
Please list the agent/s that you selected and which conditions you would not use each agent for.	_____
Are there any conditions in which you would not use the agents selected above in the ICU?	◯ Yes ◯ No
Please list the agent/s that you selected and which conditions you would not use each agent for:	_____

Insulin	
If a patient is already insulin requiring, on admission would you continue their current regimen or change it in the general ward?	◯ Continue as is ◯ Stop current regimen ◯ Increase cumulative dose ◯ Decrease cumulative dose
If a patient is already insulin requiring, on admission would you continue their current regimen or change it in the ICU?	◯ Continue as is ◯ Stop current regimen ◯ Increase cumulative dose ◯ Decrease cumulative dose
Please select which one of the following insulin regimens you most often use for inpatient hyperglycaemia in the general ward.	◯ Sliding scale alone (Novorapic/Apidra/Actrapid) ◯ Basal insulin alone (Lantus/Optisulin/Levemir/Protophane) ◯ Basal insulin PLUS sliding scale ◯ Basal insulin PLUS premeal insulin ◯ Basal insulin PLUS premeal insulin PLUS sliding scale ◯ Premix insulin alone ◯ Premix insulin PLUS sliding scale ◯ Basal insulin PLUS oral agent
If you were to stop a patient's prehospital insulin regimen, which of the following do you then use to manage your patient's hyperglycaemia in the ICU?	☐ Sliding scale ☐ Insulin infusion ☐ Basal insulin ☐ Basal insulin PLUS sliding scale ☐ Intravenous bolus infusion
In what percentage of patients do you use Sliding Scale?	0 50 100 *(Place a mark on the scale above)*
In what percentage of patients do you use Insulin Infusion?	0 50 100 *(Place a mark on the scale above)*
In what percentage of patients do you use Basal Insulin?	0 50 100 *(Place a mark on the scale above)*
In what percentage of patients do you use Basal insulin PLUS Sliding Scale?	0 50 100 *(Place a mark on the scale above)*
In what percentage of patients do you use Intravenous bolus insulin?	0 50 100 *(Place a mark on the scale above)*

Since you selected sliding scale insulin alone, is there any reason why you would delay basal insulin therapy in a patient in the general ward? (You may choose one or more options)	☐ Basal insulin is not indicated in inpatient management ☐ Sliding scale insulin is effective as the only insulin ☐ Fear of hypoglycaemia with basal insulin ☐ Lack of local protocols on the use of basal insulin ☐ Uncertainty of what regimen to use ☐ Concern regarding inpatient glycaemic monitoring ☐ Other
Please list your other reasons for delaying Basal Insulin	_____
Since you selected sliding scale insulin alone, is there any reason why you would delay basal insulin therapy in a patient in the ICU (You may choose one or more options)	☐ Basal insulin is not indicated in inpatient management ☐ Sliding scale insulin is effective as the only insulin ☐ Fear of hypoglycaemia with basal insulin ☐ Lack of local protocols on the use of basal insulin ☐ Uncertainty of what regimen to use ☐ Concern regarding inpatient glycaemic monitoring ☐ Other
Please list your other reasons for delaying Basal Insulin:	_____
If you use a sliding scale, at which point in your career did you learn your sliding scale?	☐ Student ☐ Intern ☐ Community service / Medical officer ☐ Registrar ☐ Consultant ☐ Other
At what stage did you learn your sliding scale?	_____
Who did you learn your sliding scale from?	◯ Colleague at the same level ◯ Registrar ◯ Consultant ◯ Facility protocol ◯ Other
Who did you learn you sliding scale from?	_____
Please provide an example of the sliding scale that you mostly use:	_____
Is the protocol for the Insulin Infusion that you use in the ICU:	☐ Guideline recommended ☐ Specific to a particular facility
Please specify the guideline:	_____
Please specify the facility:	_____

Please can you either upload or type an example of your protocol.	◯ Upload ◯ Type
Click here to upload your protocol	
Please provide an example of your protocol:	_____
Is there a time that you would use a different protocol?	◯ Yes ◯ No
Please specify when you would use a different protocol:	_____

Monitoring	
How frequently do you usually monitor glucose levels in the general ward?	◯ Hourly ◯ Two hourly ◯ Four hourly ◯ Six hourly ◯ Preprandial ◯ 7-point profile ◯ Other
Please specify how frequently you monitor glucose levels in the general ward:	_____
What upper limit do you aim for in the general ward? (mmol/L)	_____
What lower limit do you aim for in the general ward? (mmol/L)	_____
What fasting/premeal upper limit do you aim for in the general ward? (mmol/L)	_____
What fasting/premeal lower limit do you aim for in the general ward? (mmol/L)	_____
What post prandial upper limit do you aim for in the general ward? (mmol/L)	_____
What post prandial lower limit do you aim for in the general ward? (mmol/L)	_____
What bedtime upper limit do you aim for in the general ward? (mmol/L)	_____
What bedtime lower limit do you aim for in the general ward? (mmol/L)	_____
Which of the following do you use to monitor glucose in the ICU? (Please choose one)	◯ Glucometer ◯ Blood gas analyzer
Which sample do you usually use in the ICU? (Please choose one)	◯ Finger prick ◯ Arterial sample ◯ Venous sample (CVP / Venesection)
What lower limit do you aim for in the ICU? (mmol/L)	_____
What upper limit do you aim for in the ICU? (mmol/L)	_____
How often do you review your management for a specific patient in the general ward?	◯ Daily ◯ On alternate days ◯ Weekly ◯ Not again ◯ Other

Please specify how often you review your management:	_____
How often do you review the protocol used in a specific patient in the ICU?	◯ Daily ◯ On alternate days ◯ Weekly ◯ Not again ◯ Other
Please specify how often you review you management in the ICU	_____
When would you change your management in a specific patient in the general ward? (You may choose one or more)	☐ Glucose levels below 3.0 mmol/L ☐ Glucose levels below 4.0 mmol/L ☐ Glucose levels above 7.8 mmol/L ☐ Glucose levels above 10.0 mmol/L ☐ Glucose levels above 15.0 mmol/L ☐ Large glycemic variability (> 8 mmol/L) ☐ Other
Please detail the conditions for which you would change your management:	_____
When would you change your management in a specific patient in the ICU? (You may choose one or more)	☐ Glucose levels below 3.0 mmol/L ☐ Glucose levels below 4.0 mmol/L ☐ Glucose levels above 7.8 mmol/L ☐ Glucose levels above 10.0 mmol/L ☐ Glucose levels above 15.0 mmol/L ☐ Large glycemic variability (> 8 mmol/L) ☐ Other
Please detail the conditions for which you would change your management:	_____
If the patient is hyper-/hypoglycaemic, what changes do you usually make? (Please choose one)	◯ Change frequency of insulin given ◯ Change the type of insulin given ◯ Change your total daily dose ◯ Change the sliding scale ◯ Other
Please specify the other change that you make:	_____

You have selected not to participate in this research.
If this is correct please click submit.
However, if you would like to participate, please kindly click previous page.

Appendix C: Paper-based Audit Data Sheet

Study Number: AG_____

Audit Rubric General Ward

Hyperglycaemia	Hospital associated		Dx DM in hospital		Known DM			
Hypoglycaemia	< 2.0	< 2.5	< 3.0	< 3.5	< 4.0	< 4.5	Value =	
Hyperglycaemia	< 10.0	> 10.0	> 10.5	> 11.0	> 11.5	> 12.0	Value =	
Pre-admission								
Treatment	None	OHA/NI only	OHA/NI + BI	OHA/NI + BB	BI only	BB only	PI only	PI + OHA/NI
OHA/NI	None	Metformin	SU	DPP4-I	GLP-1	SGLT2	TZD	Other
Targets (mean)								
Random	< 4.0 mmol/L	4.1-7.0	7.1-10.0	10.1 – 14.0	> 14.0	Range:		
Fasting/Premeal	< 4.0 mmol/L	4.1-7.0	7.1-10.0	10.1 – 14.0	> 14.0	Range:		
Post prandial	< 4.0 mmol/L	4.1-7.0	7.1-10.0	10.1 – 14.0	> 14.0	Range:		
Bed time	< 4.0 mmol/L	4.1-7.0	7.1-10.0	10.1 – 14.0	> 14.0	Range:		
Admission								
Δ Treatment	N/A or None	Stop OHA/NI	Add OHA/NI	Started insulin	↑ Insulin dose	↓ Insulin dose	Stop insulin	Δ Insulin type
OHA/NI use	None	Metformin	SU	DPP4-I	GLP1	SGLT 2	TZD	Other
Insulin use	II	SSI	BI alone	BI + SSI	BB alone	BB + SSI	PI alone	PI + SSI
SSI starting HGT	Not used	< 10.0	>= 10.0	>= 12.0	>= 14.0	>= 16.0	>= 18.0	Value =
HGT monitoring	Hourly	Two hourly	Four hourly	Six hourly	12 hourly	Pre-prandial	7 point profile	Other
Script review	Daily	Alternate days	Weekly	None				
Script adjusted	If HGT < hypoglycaemic limit		None	HGT > hyperglycaemic limit		Large glycaemic variation (> 8mmol/L)		
Adjustment	None	Change frequency		Change insulin type		Change MI dose		Change SSI
No. events	Below 4.0		>=7.8(Premeal)		>=10.0(Random)		Inpatient days	
Events/24 hrs	< 4.0 mmol/L		>=7.8(Premeal)		>=10.0(Random)			
HGT correction	None	SSI	Adjusted MI dose		Changed MI			
Time to start MI	<24 hours	24-48 hours	48-72 hours	> 72 hours				

Study Number: AI_____

Audit Rubric Intensive Care Unit

Hyperglycaemia	Hospital associated		Dx DM in hospital		Known DM			
Hypoglycaemia	< 2.0	< 2.5	< 3.0	< 3.5	< 4.0	< 4.5	Value =	
Hyperglycaemia	< 10.0	> 10.0	> 10.5	> 11.0	> 11.5	> 12.0	Value =	
Pre-admission								
Treatment	None	OHA/NI only	OHA/NI + BI	OHA/NI + BB	BI only	BB only	PI only	PI + OHA/NI
OHA/NI	None	Metformin	SU	DPP4-I	GLP-1	SGLT2	TZD	Other
Targets (mean)								
Upper Limit	< 7.0 mmol/L	7.0 - 7.9	8.0 - 8.9	9.0 – 9.9	10.0 – 10.9	11.0 – 11.9	>= 12.0	Value =
Lower Limit	< 3.0	3.0 – 3.9	4.0 – 4.9	5.0 – 5.9	6.0 – 6.9	7.0 – 7.9	>= 8.0	Value =
Admission								
Δ Treatment	N/A or None	Stop OHA/NI	Add OHA/NI	Started insulin	↑ Insulin dose	↓ Insulin dose	Stop insulin	Δ Insulin type
OHA/NI use	None	Metformin	SU	DPP4-I	GLP1	SGLT 2	TZD	Other
Insulin use	None	CI	BI alone	BI + CI	BB alone	BB + CI	PI alone	PI + CI
CI	ICD bolus	S/C bolus	II	SSI				
CI starting HGT	Not used	< 7.0	7.1 – 7.9	8.0 – 8.9	9.0 – 9.9	10.0 – 10.9	>= 11.0	Value =
HGT monitoring	Hourly	Two hourly	Four hourly	Six hourly	12 hourly	Pre-prandial	7 point profile	Other
Script review	Daily	Alternate days	Weekly	None				
Monitor method	Glucometer		Blood gas analyser					
Sample	Finger prick		Venous	Arterial				
Script adjusted	If HGT < hypoglycaemic limit		None	HGT > hyperglycaemic limit		Large glycaemic variation (> 8mmol/L)		
Adjustment	None	Change frequency		Change insulin type		Change MI dose		Change SSI
No. events	Below 4.0		>= 7.8 mmol/L		>= 10.0 mmol/L		Inpatient days	
Events/24 hrs	< 4.0 mmol/L		>= 7.8 mmol/L		>= 10.0 mmol/L			
HGT correction	None	SSI	Adjusted MI dose		Changed MI			
Time to start MI	<24 hours	24-48 hours	48-72 hours	> 72 hours				
Protocol	No	Yes	If Yes, origin:					

Glossary

BI – Basal insulin	**CI** – Correction insulin	**ICD** – Infusion correction doses	**IV** – Intravenous insulin	**MI** – Maintenance insulin	**PI** – Premix insulin
BB – Basal bolus	Δ - Change	**II** – Insulin infusion	**OHA** – Oral hyperglycaemic agent	**NI** – Non-insulin	**SSI** – Sliding Scale insulin

SSI Protocol

Facility Protocol

Appendix D: RedCap Audit General Medicine Data Sheet

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Audit
Page 1

General Medicine Audit

Record ID	_____
Hospital	_____
Ward	○ General ward ○ ICU
Study number	_____
Hyperglycaemia	○ Hospital Associated ○ Diagnosed in Hospital ○ Known Diabetic ○ Not diabetic
Pre-admission treatment	○ None ○ OHA/NI only ○ OHA/NI + BI ○ OHA/NI + BB ○ BI only ○ BB only ○ PI only ○ PI + OHA/NI ○ Unknown
Pre-admission OHA/NI	☐ None ☐ Metformin ☐ SU ☐ DPP4-I ☐ GLP-1 ☐ SGLT2 ☐ TZD ☐ Other
Change of treatment on admission	☐ N/A or None ☐ Stop OHA/NI ☐ Add OHA/NI ☐ Started insulin ☐ Increased insulin dose ☐ Decreased insulin dose ☐ Stop Insulin ☐ Change insulin type
OHA/NI use during admission	☐ None ☐ Metformin ☐ SU ☐ DPP4-I ☐ GLP1 ☐ SGLT2 ☐ TZD ☐ Other

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Insulin use during admission	◯ Insulin infusion ◯ Sliding scale insulin ◯ Basal insulin alone ◯ Basal insulin + Sliding scale insulin ◯ Basal bolus alone ◯ Basal bolus + sliding scale ◯ Premix insulin alone ◯ Premix insulin + sliding scale
Insulin use while in ICU	◯ None ◯ Correction insulin ◯ Basal insulin alone ◯ Basal insulin + Correction insulin ◯ Basal bolus alone ◯ Basal bolus + correction insulin ◯ Premix insulin alone ◯ Premix insulin + correction insulin
Hypoglycaemia limit	◯ < 2.0 ◯ < 2.5 ◯ < 3.0 ◯ < 3.5 ◯ < 4.0 ◯ < 4.5 ◯ Other
Hypoglycaemia value	_____
Hyperglycaemia limit	◯ < 10.0 ◯ > 10.0 ◯ > 10.5 ◯ > 11.0 ◯ > 11.5 ◯ > 12.0 ◯ Other
Hyperglycaemia value	_____
Target - Random HGT	◯ < 4.0 mmol/L ◯ 4.1-7.0 mmol/L ◯ 7.1 - 10.0 mmol/L ◯ 10.1 - 14.0 mmol/L ◯ > 14.0 mmol/L ◯ Not recorded
Target - Random HGT Range	_____
Target -Fasting/Premeal HGT	◯ < 4.0 mmol/L ◯ 4.1-7.0 mmol/L ◯ 7.1 - 10.0 mmol/L ◯ 10.1 - 14.0 mmol/L ◯ > 14.0 mmol/L ◯ Not recorded
Target - Fasting/Premeal HGT Range	_____

Target - Post Prandial HGT	◯ < 4.0 mmol/L ◯ 4.1-7.0 mmol/L ◯ 7.1 - 10.0 mmol/L ◯ 10.1 - 14.0 mmol/L ◯ > 14.0 mmol/L ◯ Not recorded
Target - Post prandial HGT Range	_____
Target - Bed time HGT	◯ < 4.0 mmol/L ◯ 4.1-7.0 mmol/L ◯ 7.1 - 10.0 mmol/L ◯ 10.1 - 14.0 mmol/L ◯ > 14.0 mmol/L ◯ Not recorded
Target - Bed time HGT Range	_____
Upper limit target	◯ < 7.0 mmol/L ◯ 7.0-7.9 mmol/L ◯ 8.0-8.9 mmol/L ◯ 9.0-9.9 mmol/L ◯ 10.0-10.9 mmol/L ◯ 11.0-11.9 mmol/L ◯ >= 12mmol/L
Upper limit value	_____
Lower limit target	◯ < 3.0 mmol/L ◯ 3.0-3.9 mmol/L ◯ 4.0-4.9 mmol/L ◯ 5.0-5.9 mmol/L ◯ 6.0-6.9 mmol/L ◯ 7.0-7.9 mmol/L ◯ >= 8.0 mmol/L
Lower limit value	_____
Correction insulin type	◯ Infusion correction doses ◯ Subcutaneous bolus ◯ Insulin infusion ◯ Sliding scale insulin
Correction insulin starting HGT	◯ Not used ◯ < 7.0 ◯ 7.1-7.9 ◯ 8.0-8.9 ◯ 9.0-9.9 ◯ 10.0-10.9 ◯ >= 11.0
Correction insulin start HGT value	_____

Admission Sliding scale insulin starting HGT	◯ Not used ◯ < 10.0 ◯ >= 10.0 ◯ >= 12.0 ◯ >= 14.0 ◯ >= 16.0 ◯ >= 18.0
Admission SSI starting HGT value	_____
HGT monitoring	◯ Hourly ◯ Two hourly ◯ Four hourly ◯ Six hourly ◯ Twelve hourly ◯ Preprandial ◯ 7 point profile ◯ Other
Monitoring method	◯ Glucometer ◯ Blood gas analyser
Blood sample	◯ Finger prick ◯ Venous ◯ Arterial
Script review	◯ Daily ◯ Alternate days ◯ Weekly ◯ None
Script adjusted	☐ HGT < hypoglycaemic limit ☐ None ☐ HGT > hyperglycaemic limit ☐ Large glycemic variation (>8 mmol/L)
Script Adjustment	☐ None ☐ Change frequency ☐ Change insulin type ☐ Change maintenance insulin dose ☐ Change SSI
Number of HGTs below 4	_____
Number of HGTs premeal above 7.8 mmol/L	_____
Number of HGT >= 10.0 random	_____
HGT correction	☐ None ☐ SSI ☐ Adjusted MI dose ☐ Changed MI

Time to start Maintenance insulin	☐ < 24 hrs ☐ 24-48 hrs ☐ 48-72 hrs ☐ > 72 hrs
Protocol (Yes/No/Origin)	_____
SSI insulin Protocol	_____
Facility protocol	_____

Appendix E: RedCap Audit ICU Data Sheet

Confidential

ICU Audit

Record ID	_____
Hospital	_____
Ward	◯ General ward ◯ ICU
Study Number	_____
Hyperglycaemia	◯ Hospital Associated ◯ Diagnosed in Hospital ◯ Known Diabetic ◯ Not diabetic
Pre-admission treatment	◯ None ◯ OHA/NI only ◯ OHA/NI + BI ◯ OHA/NI + BB ◯ BI only ◯ BB only ◯ PI only ◯ PI + OHA/NI ◯ Unknown
Pre-admission OHA/NI	☐ None ☐ Metformin ☐ SU ☐ DPP4-I ☐ GLP-1 ☐ SGLT2 ☐ TZD ☐ Other
Change of treatment on admission	☐ N/A or None ☐ Stop OHA/NI ☐ Add OHA/NI ☐ Started insulin ☐ Increased insulin dose ☐ Decreased insulin dose ☐ Stop Insulin ☐ Change insulin type
OHA/NI use during admission	☐ None ☐ Metformin ☐ SU ☐ DPP4-I ☐ GLP1 ☐ SGLT2 ☐ TZD ☐ Other

Insulin use during admission	◯ Insulin infusion ◯ Sliding scale insulin ◯ Basal insulin alone ◯ Basal insulin + Sliding scale insulin ◯ Basal bolus alone ◯ Basal bolus + sliding scale ◯ Premix insulin alone ◯ Premix insulin + sliding scale
Insulin use while in ICU	◯ None ◯ Correction insulin ◯ Basal insulin alone ◯ Basal insulin + Correction insulin ◯ Basal bolus alone ◯ Basal bolus + correction insulin ◯ Premix insulin alone ◯ Premix insulin + correction insulin
Hypoglycaemia limit	◯ < 2.0 ◯ < 2.5 ◯ < 3.0 ◯ < 3.5 ◯ < 4.0 ◯ < 4.5 ◯ Other
Hypoglycaemia value	_____
Hyperglycaemia limit	◯ < 10.0 ◯ >= 10.0 ◯ >= 10.5 ◯ >= 11.0 ◯ >= 11.5 ◯ >= 12.0 ◯ Other
Hyperglycaemia value	_____
Target - Random HGT	◯ < 4.0 mmol/L ◯ 4.1-7.0 mmol/L ◯ 7.1 - 10.0 mmol/L ◯ 10.1 - 14.0 mmol/L ◯ > 14.0 mmol/L ◯ Not recorded
Target - Random HGT Range	_____
Target -Fasting/Premeal HGT	◯ < 4.0 mmol/L ◯ 4.1-7.0 mmol/L ◯ 7.1 - 10.0 mmol/L ◯ 10.1 - 14.0 mmol/L ◯ > 14.0 mmol/L ◯ Not recorded
Target - Fasting/Premeal HGT Range	_____

Target - Post Prandial HGT	◯ < 4.0 mmol/L ◯ 4.1-7.0 mmol/L ◯ 7.1 - 10.0 mmol/L ◯ 10.1 - 14.0 mmol/L ◯ > 14.0 mmol/L ◯ Not recorded
Target - Post prandial HGT Range	_____
Target - Bed time HGT	◯ < 4.0 mmol/L ◯ 4.1-7.0 mmol/L ◯ 7.1 - 10.0 mmol/L ◯ 10.1 - 14.0 mmol/L ◯ > 14.0 mmol/L ◯ Not recorded
Target - Bed time HGT Range	_____
Upper limit target	◯ < 7.0 mmol/L ◯ 7.0-7.9 mmol/L ◯ 8.0-8.9 mmol/L ◯ 9.0-9.9 mmol/L ◯ 10.0-10.9 mmol/L ◯ 11.0-11.9 mmol/L ◯ >= 12mmol/L ◯ Not recorded
Upper limit value	_____
Lower limit target	◯ < 3.0 mmol/L ◯ 3.0-3.9 mmol/L ◯ 4.0-4.9 mmol/L ◯ 5.0-5.9 mmol/L ◯ 6.0-6.9 mmol/L ◯ 7.0-7.9 mmol/L ◯ >= 8.0 mmol/L ◯ Not recorded
Lower limit value	_____
Correction insulin type	◯ Infusion correction doses ◯ Subcutaneous bolus ◯ Insulin infusion ◯ Sliding scale insulin
Correction insulin starting HGT	◯ Not used ◯ < 7.0 ◯ 7.1-7.9 ◯ 8.0-8.9 ◯ 9.0-9.9 ◯ 10.0-10.9 ◯ 11.0-11.9 ◯ >= 12.0

Correction insulin start HGT value	_____
Admission Sliding scale insulin starting HGT	◯ Not used ◯ < 10.0 ◯ >= 10.0 ◯ >= 12.0 ◯ >= 14.0 ◯ >= 16.0 ◯ >= 18.0
Admission SSI starting HGT value	_____
HGT monitoring	☐ Hourly ☐ Two hourly ☐ Four hourly ☐ Six hourly ☐ Twelve hourly ☐ Preprandial ☐ 7 point profile ☐ Other
Monitoring method	◯ Glucometer ◯ Blood gas analyser
Blood sample	◯ Finger prick ◯ Venous ◯ Arterial
Script review	◯ Daily ◯ Alternate days ◯ Weekly ◯ None
Script adjusted	☐ HGT < hypoglycaemic limit ☐ None ☐ HGT > hyperglycaemic limit ☐ Large glycemic variation (>8 mmol/L)
Script Adjustment	☐ None ☐ Change frequency ☐ Change insulin type ☐ Change maintenance insulin dose ☐ Change SSI
Number of HGTs below 4	_____
Hgt below 4 timing	◯ Within 24 hrs ◯ Within 48 hrs ◯ Not the above
Number of HGTs above 7.8 mmol/L	_____

Hgt above 7.8 timing	◯ Within 24 hrs ◯ Within 48 hrs ◯ Not the above
Number of HGT >= 10.0 random	_____
Hgt above 10 timing	◯ Within 24 hrs ◯ Within 48 hrs ◯ Not the above
HGT correction	☐ None ☐ SSI ☐ Adjusted MI dose ☐ Changed MI
Time to start Maintenance insulin	☐ < 24 hrs ☐ 24-48 hrs ☐ 48-72 hrs ☐ > 72 hrs ☐ Nil use
Protocol (Yes/No/Origin)	_____
SSI insulin Protocol	_____
Facility protocol	_____

Appendix F: Ethics approval certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr PLB Hewson

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M191052

NAME: (Principal Investigator)	Dr PLB Hewson
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	Assessment of the management of inpatient hyperglycaemia by physicians and internists in South African hospitals
DATE CONSIDERED:	2019/10/25
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr F Seedat
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/03/11

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore reports and re-certification will be due early in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

15.03.2020
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2020/08/29

Dr PLB Hewson
School of Clinical Medicine
Department of Medicine
Division of Internal Medicine
Medical School
University

Sent by e-mail to: plbhewson@gmail.com

Dear Dr Hewson

Re: **Protocol Ref No: M191052**
Protocol Title: *Assessment of the management of inpatient hyperglycaemia by physicians and internists in South African hospitals*
Principal Investigator: Dr PLB Hewson

Thank you for your e-mail of 2020/08/17.

We have noted and approve of your intention to:

1. use online survey procedures whenever possible
2. review patient files only in retrospect, after hospital discharge

Thank you for keeping us informed.

Yours Sincerely

I. Burns

.....

Mr I Burns
For the Human Research Ethics Committee (Medical)

C.B. Penny

.....

Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Appendix G: Turn it in report and Supervisor's letter of the percentage similarity

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File size:	3.88M
Page count:	105
Word count:	19,355
Character count:	111,393
Submission date:	23-Feb-2023 11:51AM (UTC+0200)
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Assessment of the management of inpatient hyperglycaemia by physicians and intensivists in South African hospitals

Peter Llewellyn Blanshard Hewson

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the department of Internal Medicine

Johannesburg 2023

The Chair

Postgraduate Studies Committee

Faculty of Health Sciences

University of Witwatersrand

Re: Turn – it – in report: Dr Peter Hewson MMed: "Assessment of the management of inpatient hyperglycaemia by physicians and intensivists in South African hospitals"

I have reviewed the Turn – it – in report of Dr P. Hewson's MMed dissertation. The report identifies a similarity index of 13%. Much of this relates to the use of standardised definitions; furthermore, the other information that bears a similarity has been appropriately referenced

Yours sincerely,

Dr NA Mohamed
Endocrinologist and Specialist Physician
Internal Medicine
Chris Hani Baragwanath Academic Hospital
Supervisor

Dr F Seedat
Endocrinologist and Specialist Physician
Nuffield Department of Medicine
University of Oxford

Supervisor