Title: Tight glycemic control can be achieved in adult ICU patients safely: Results from a 5-year single-center observational study using the STAR Glycemic Control Framework

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Abbreviations: (AI) Artificial intelligence, (BG) blood glucose, (GC) glucose control, (GF) goal feed, (ICU) intensive care unit, (IQR) interquartile range, (RCT) randomized controlled trial, (SI) insulin sensitivity, (SIH) stress-induced hyperglycemia, STAR (Stochastic TARgeted)

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Abstract

Background: Glycemic control (GC) is hard to implement safely in intensive care due to patient variability. GC has been wrongly blamed for increased hypoglycemic risk instead of protocol design, limiting its adoption. STAR is a model-based, patient-specific, risk-based GC framework modulating intravenous (IV) insulin and nutrition, accounting for both inter- and intra-patient variability. This study assesses STAR GC's ability to provide safe and effective control across a large cohort.

Methods: This study was performed in Christchurch Hospital Intensive Care Unit, New Zealand. Patients were treated with STAR GC between April 2019 and December 2024. STAR GC episodes not complying with filtering criteria were excluded. Results are analyzed in terms of performance, safety and workload.

Results: Of 1340 adult ICU patients totaling 1958 STAR GC episodes, 1085 patients and 1430 episodes (86,010 hours of control) remained after filtering. 71% of blood glucose (BG) measurements were in the target band for a median [IQR] BG of 124 [110 – 148] mg/dL. Only three (0.21%) severe hypoglycemia events (BG < 40 mg/dL) occurred, two unrelated to the control design. High median [IQR] nutrition delivery (89.0 [17.2 – 100.0]) %goal feed was achieved with median [IQR] insulin rate of 4.5 [2.0 – 6.0] U/h. Results were consistent per-patient and improved once in the target band.

Conclusions: STAR provides safe, effective control for all patients in this large cohort, with minimal hypoglycemia and high nutrition rates. The protocol adapts to patients' specific needs and tolerances encouraging STAR's adoption

in other ICUs. The quality of control also enables prospective assessment in the future of GC's impact on patient outcomes.

1. Introduction

Stress-induced hyperglycemia (SIH) and insulin resistance affects 30-50% of patients admitted to intensive care units (ICU) [1]. SIH results from stress-related hormonal responses, systemic inflammation, and insulin resistance. Safely normalizing glycemia for all patients using glycemic control (GC) is essential [1], as hyperglycemia and glycemic variability are associated with increased mortality, morbidity, and ICU length of stay [1,2].

Studies have shown GC benefits patients by providing safe and effective control with reduced mortality, morbidity, and, thus, indirect care costs [3-5]. However, achieving consistent GC remains challenging due to inter- and intra-patient variability [6]. Importantly, this variability, not GC strategies themselves [7], is the primary contributor to poor GC outcomes and increased risks of hypoglycemia. Many studies, including the landmark NICE-SUGAR, and GLUCONTROL have revealed the limitations of traditional approaches, failing to provide safe and effective control to all patients [8-11]. While intensive insulin therapy could improve patient outcomes, it can significantly increase the risk of hypoglycemia, associated with severe brain damage and increased mortality [12,13].

The clinical implementation of GC protocols is impeded by fear of hypoglycemia and the associated workload, especially in ICUs with low nurse-to-patient ratio [14,15]. Recent results have been confounded by poor protocol designs, and a lack of consensus has led many ICUs worldwide to adopt permissive hyperglycemia strategies [16,17], mainly guided by studies showing the inability to provide safe intensive GC. However, the limitations of traditional GC protocols are often rooted in poor clinical and human factors design [18]. Most protocols lack patient-specific adaptability, leading to suboptimal control outcomes, including increased hypoglycemia and glucose variability [19]. Additionally, ICU workload results in low compliance and increased human errors with non-automated, highly demanding protocols [20]. There is thus a need for patient-specific, safe and effective solution addressing the challenges of GC and balancing control quality with clinical workload [20,21].

Recent advancements in model-based and predictive artificial intelligence (AI) driven GC protocols offer unique new approaches to these challenges. By explicitly accounting for inter- and intra- patient variability, some protocols enable personalized and adaptive glucose management [22]. Model-based approaches use patient-specific physiological data and real-time computational models to create a digital twin of the patient. This digital twin can be used to simulate glucose-insulin dynamics and identify patient-specific response to treatment through insulin sensitivity identification. Combined with predictive AI technology, it allows to tailor treatment to each individual patient by forecasting variability and risk, and thus, patient-specific response to treatment. [22,23] This way, the risks of hyper- and hypo- glycemia can be balanced based on predicted risks, and the optimal treatment can be recommended to clinical staff [24]. Unlike conventional table-based or clinically-derived protocols, computerized model-based protocols can deliver safe, effective, and consistent GC across diverse ICU populations, despite targeting lower glycemic ranges [3,6].

In addition, the role of nutrition in managing SIH should be emphasized. Nutrition interacts directly with insulin therapy and metabolic regulation, necessitating an integrated approach for optimal GC outcomes [25]. The adequate amount of nutrition is patient-specific and depends on patient's metabolism and tolerance [26,27]. Very few GC protocols modulate nutrition in addition to insulin. Current studies emphasize the urgent need for personalized nutrition therapy solutions based on important metabolic factors, such as insulin sensitivity [25,27]. An automated, model-based protocol optimizing GC outcomes, workload, and nutrition could significantly improve outcomes in ICU patients.

This study presents the results of a 5-year observational trial involving 1085 patients treated with the STAR (Stochastic TARgeted) GC protocol framework implemented at the Christchurch Hospital Intensive Care Unit, New Zealand. The objective is to demonstrate it is possible to control BG levels in a safe (low rates of severe hypoglycaemia, BG <40mg/dL) and effective (high time in the target band, BG in 80-145 mg/dL) way for all ICU patients.

2. Methods

2.1. STAR GC protocol

STAR is a model-based, patient-specific, and risk-based dosing GC approach accounting for both inter- and intra- patient variability [22,23]. Using a validated physiological model and a 3D stochastic model, it identifies and predicts patient-specific insulin sensitivity evolution in the next three hours [23,28] to simulate patient-spectific treatment impact on BG and assess hypo- and hyper- glycemic risk. These predicted risks are balanced to offer clinicians optimal treatment recommendations to safely maintain BG in the 80-145 mg/dL (4.4-8.0 mmol/L) target band [23]. Uniquely, STAR GC and its predecessor SPRINT are the first protocols modulating both IV insulin and enteral/parenteral nutrition to control glycemia [22,29], accounting for the significant interplay between glycemia, nutrition, and clinical outcomes [25]. The STAR GC protocol and its implementation are further presented in detail in [22,23].

STAR GC is implemented on Android™ tablets at the patient's bedside. Nurses input BG level, insulin and nutrition data in the tablet, allowing STAR GC to compute a treatment suggestion. Nurses can choose the suggested treatments or adapt rates according to their clinical judgment. This occurs when nurse believe the treatment suggested by STAR GC may be unsafe. Typical concerns include hyperglycemia following a high nutrition rate or a low insulin dose, hypoglycaemia following a high insulin dose or when suggested treatment interval is considered too long. BG is measured using either blood gas analyzer or glucometers as continuous glucose monitors have not yet been fully validated for use in ICU patients. STAR GC is initiated after two consecutive BG measurements over 145 mg/dL (8.0 mmol/L) within a 4-hour period and stopped after 6 hours of BG levels in the target band at low insulin rates (≤ 2U/h). Insulin and nutrition are dosed in increments. A maximum 6 U/h insulin bolus is administered in increments between 0.5 and 2.0 U. An additional 3 U/h background insulin infusion can be administered to highly insulin resistant patients. Nutrition is delivered in rates between 30% and 100% goal feed (GF) and can be adjusted by up to ±30% at each intervention [22]. GF is determined for each patient based on age, sex and weight, and on the recommended 25 kcal/kg/day [22,30]. In case of hypoglycemia, insulin is stopped, and a dextrose bolus (10 mL of 50% glucose) is administered.

2.2. Cohort

This study considered adult patients treated with STAR GC between April 2019 and December 2024 at the Christchurch Hospital ICU, New Zealand. All patient STAR GC episodes were included. Multiple episodes can arise from interruptions due to clinical procedures, re-admission, or reinitiation of STAR GC after stability and/or stoppage of IV insulin. Thus, a patient refers to a single ICU admission and an episode is a period of uninterrupted STAR GC [29]. STAR GC episodes lasting less than 10 hours, with >120%GF nutrition, and those targeting different band were excluded as they are not representative of long-term glycemic control or the STAR GC guidelines, respectively.

All adult ICU patients receiving IV inulin and meeting the inclusion criteria were included. There are no additional filtering criteria based on patient condition or demographic. Patients received either enteral, parenteral, combined, or no nutrition when clinically indicated.

2.3. Ethic approval and consent

STAR GC is implemented as standard of care in the Christchurch Hospital ICU, New Zealand. This study is implemented as a clinical practice change and did not require ethics approval as the New Zealand Health and Disability Ethics Committee Upper South Regional Ethics Committee B (Ref: URB/07/15/EXP) approved the analysis and use of de-identified data as a clinical data audit.

2.4. Analysis

Outcomes are analyzed using typical GC metrics [31-33]. BG data is linearly interpolated and hourly resampled for better outcomes assessment and comparison [34]. The different outcomes are assessed at cohort and per-episode level to check if a high-quality control is achieved for all patients and not only at a cohort perspective. Both approaches ensure full coverage of the actual results. Results are also analyzed once in the target band to assess STAR GC ability to maintain patients stable once in the band.

Primary outcomes include safety, performance and workload indicators. Safety is assessed by incidence of severe hypoglycemia. Severe hypoglycemia is characterized by the percentage below 40 mg/dL or 2.2mmol/L and by the number of STAR GC episodes presenting severe hypoglycemia. Performance is characterized by the %BG in the normoglycemic target band (145-180 mg/dL). Workload is represented by the number of BG measurements performed per day.

Secondary outcomes include time spent in moderate and severe hyperglycemia (%BG in 145-180 mg/dL or 8.0-10.0 mmol/L and %BG > 180 mg/dL or 10 mmol/L) and below the target band and in moderate hypoglycemia (hypoglycemia (%BG < 80 mg/dL or 4.4 mmol/L and %BG < 72mg/dL or 4.0 mmol/L) They also include median [IQR] nutrition (%GF), insulin (U/h) rates and summary glycemia statistics (median [IQR] BG levels). Time to reach the target band is also reported as this time is not predefined by STAR GC and is specific to each patient.

3. Results

In total, there were 1958 STAR GC episodes from 1340 patients between April 2019 and December 2024. After applying the filtering criteria, 1430 (73%) STAR GC episodes from 1085 patients (81%) were considered in the study. The number of episodes excluded per criterion is shown in **Figure 1**.

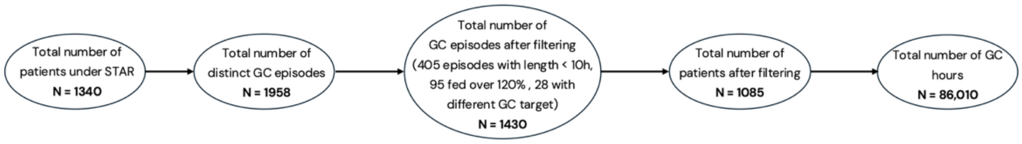

Fig.1 GC episode filtering from the original 1340 patients.

Cohort demographics are presented in **Table 1**. From the 1085 patients, 67% were male, with a median [IQR] age of 65 [54 – 72] years. The median [IQR] ICU stay under STAR GC was 1.7 [0.8 – 3.1] days. Among the 30.8% of patients with diabetic history, 5.5% patients had type 1 diabetes, and 25.3% patients had type 2 diabetes. These demographics reflect typical ICU populations.

Table 1. Patient demographics

Cohort demographics	STAR
Number of patients	1085
Age (years)	65 [54 – 72]
% (#) Male / Female	67% (729) / 33% (356)
Episode length (days)	1.7 [0.8 – 3.1]
Diagnosed Type 1 Diabetes	5.5 (60)
Diagnosed Type 2 Diabetes	25.3 (275)

Data is given as median [25th – 75th percentiles] where appropriate.

Results for the whole cohort are presented in **Table 2** and **3**. Those results represent mean across the entire cohort giving a general view of the control performance. In total, 53,584 BG measurements were made for 86,010 hours of control resulting in 14.9 measurements/day or one measurement every 1.6 hours. Once in target band, the workload decreased to 14.2 measurements/day, where some workload is due to nursing choice rather than protocol.

71.2 %BG were in target band for a median BG of 124 [110 – 148] mg/dL. In total, 1398 episodes (97.8%) reached the target band, for which the %BG in target increased to 79.1% for a median BG of 121 [108 – 139] mg/dL.

Table 2. Cohort clinical results

	STAR
Number of patients	1085
Number of GC episodes	1430
Hours of control (h)	86010
Total BG measurements	53584
BG measurements/day	14.9
Median BG (mg/dL)	124 [110 – 148]
Median insulin (U/h)	4.5 [2.0 – 6.0]
Median nutrition (%GF)	89.0 [17.2 – 100.0]
%BG in 80-145 mg/dL	71.2
%BG in 145-180 mg/dL	16.3
%BG > 180 mg/dL	11.7
%BG < 80 mg/dL	0.9
%BG < 72 mg/dL	0.3
%BG < 40 mg/dL	<0.01
Episodes with min. BG < 40 mg/dL (%)	3 (0.21)

Data is given as median [25^{th} – 75^{th} percentiles] where appropriate.

Table 3. Cohort clinical results once target band reached

	STAR
Number of patients	1065
Number of GC episodes	1398
Hours of control (h)	77245
Total BG measurements	45819
BG measurements/day	14.2
Median BG (mg/dL)	121 [108 – 139]
Median insulin (U/h)	4.0 [2.0 – 6.0]
Median nutrition (%GF)	90.9 [31.7 – 100.0]
%BG in 80-145 mg/dL	79.1
%BG in 145-180 mg/dL	14.1
%BG > 180 mg/dL	5.9
%BG < 80 mg/dL	1.0
%BG < 72 mg/dL	0.4
%BG < 40 mg/dL	<0.01
Episodes with min. BG < 40 mg/dL (%)	3 (0.21)

Data is given as median [25th – 75th percentiles] where appropriate.

In addition, very low incidence of BG below the target band and light and severe hypoglycemia (1 %BG < 80 mg/dL, 0.3 %BG < 72 mg/dL and <0.01 %BG < 40 mg/dL) was observed. Out of the 1430 episodes, only 3 severe hypoglycemia events occurred in 3 episodes (0.21% of episodes). The incidence of mild and severe hyperglycemia was 16.3% and 11.7% respectively, which dropped to 14.1% and 5.9% once the target band was reached **Table 3**.

Those results were achieved with a median nutrition of 89.0 [17.2 – 100.0] %GF and 90.9 [31.7 – 100.0] %GF once target band is reached showing higher nutrition delivery rates when in target. Finally, the median [IQR] insulin was 4.0 [2.0 – 6.0] U/h over the entire cohort. **Figure 2** shows the blood glucose, the total amount of nutrition administered in %GF and kcal/day, and the number of patients under STAR GC as a function of episode length.

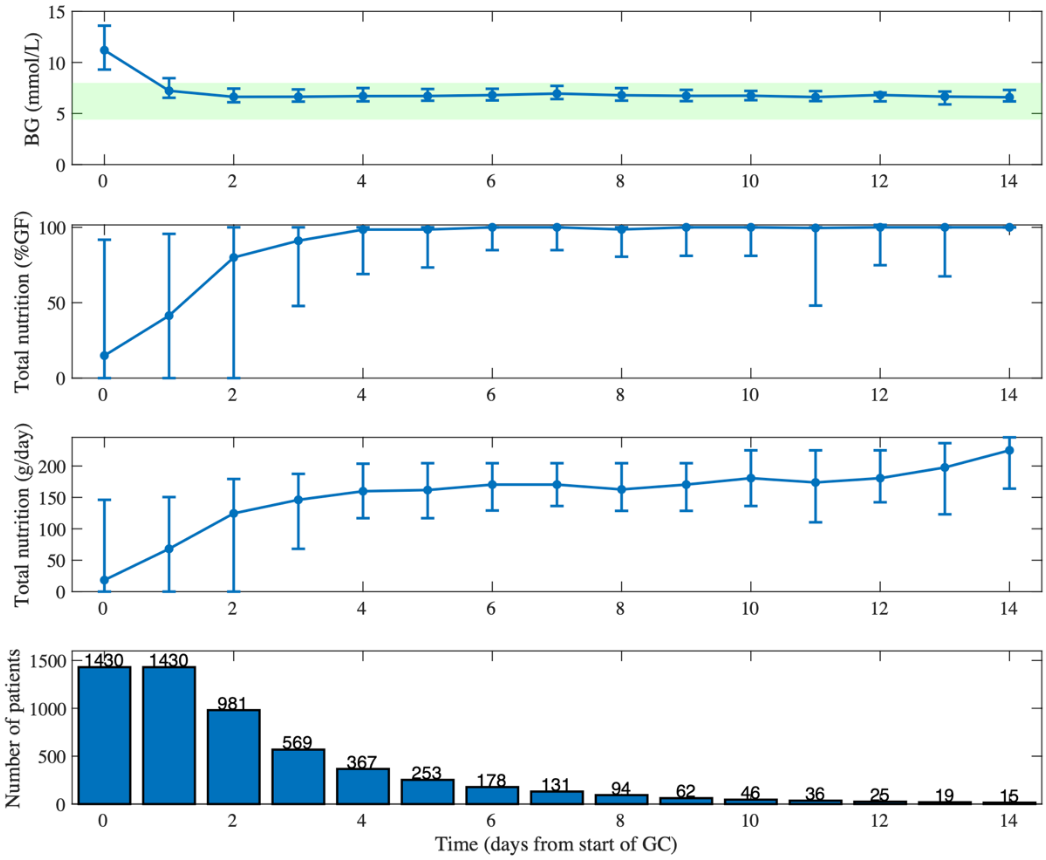

Fig.2 BG level, nutrition and patients under STAR GC over time during GC. BG level (top), total amount of nutrition administered in %GF (second to top) and in kcal/day (third to top), and number of patients under STAR GC (bottom) are shown as a function of the number of days under GC. The first three panels are expressed as median (IQR). The shaded band in the top panel represents the target range (80-145 mg/dL)

Per-episode results for the whole episodes and once target band is reached are presented in **Table 4** and **5**. Those results give information on how the control framework adapts to each episode and possibly detects subgroups of patients. The median workload was 15.7 [13.3 – 18.0] measurements/day and 14.7 [12.4 – 16.9] measurements/day once in target band. The median STAR GC episodes length was 1.7 [0.8 – 3.1] days and the median time to reach the target was 4.0 [1.9 – 8.0] hours. Median starting BG was 202 [167 – 245] mg/dL.

Results considering performance showed a median per-episode BG of 130 [119 – 146] mg/dL with 72.7 [54.0 – 86.7] %BG in target. This result shows that 75% of patients had at least 50% of their BG levels within the target band. Once target band is reached, median BG decreased with 121 [112 – 131] mg/dL and %BG in the different band increased with 88.0 [70.4 – 98.5] %BG in 80-145 mg/dL target band (75% of patients remained at least 70% of the time in the target band).

Table 4. Per-episode clinical results

	STAR
Number of GC episodes	1430
Episode length (days)	1.7 [0.8 – 3.1]
Starting BG (mg/dL)	202 [167 – 245]
BG measurements/day	15.7 [13.3 – 18.0]
Median BG (mg/dL)	130 [119 – 146]
Median insulin (U/h)	4.0 [3.0 – 5.8]
Median nutrition for those fed (%GF)	95.0 [67.9 – 100.0]
%BG in 80-145 mg/dL	72.7 [54.0 – 86.7]
%BG in 145-180 mg/dL	13.6 [7.1 – 23.1]
%BG > 180 mg/dL	7.7 [1.3 – 21.0]
%BG < 80 mg/dL	0.0 [0.0 – 0.0]
%BG < 72 mg/dL	0.0 [0.0 – 0.0]
%BG < 40 mg/dL	0.0 [0.0 – 0.0]
Episodes with min. BG < 40 mg/dL (%)	3 (0.21)

Data is given as median [25th – 75th percentiles] where appropriate.

Regarding safety, there was virtually no hypoglycemia, with only 3 (0.21%) of 1085 patients experiencing severe hypoglycemia (BG < 40 mg/dL). For two of these patients (0.18%), no insulin was being administered when the hypoglycemic event occurred. For hyperglycemia, the incidence of moderate and severe hyperglycemia was 13.6 [7.1 – 23.1] % and 7.7 [1.3 – 21.0] % respectively, significantly reduced once target band is reached (7.4 [0.0 – 18.8] % and 0.0 [0.0 – 0.0] %).

Table 5. Per-episode clinical results once target band reached

	STAR
Number of GC episodes	1398
Time to target (hours)	4.0 [1.9 – 8.0]
Starting BG (mg/dL)	131 [121 – 139]
BG measurements/day	14.7 [12.4 – 16.9]
Median BG (mg/dL)	121 [112 – 131]
Median insulin (U/h)	3.5 [2.5 – 5.0]
Median nutrition for those fed (%GF)	97.9 [74.1 – 100.0]
%BG in 80-145 mg/dL	88.0 [70.4 – 98.5]
%BG in 145-180 mg/dL	7.4 [0.0 – 18.8]
%BG > 180 mg/dL	0.0 [0.0 – 2.8]
%BG < 80 mg/dL	0.0 [0.0 – 0.6]
%BG < 72 mg/dL	0.0 [0.0 – 0.0]
%BG < 40 mg/dL	0.0 [0.0 – 0.0]
Episodes with min. BG < 40 mg/dL (%)	3 (0.21)

Data is given as median [25th – 75th percentiles] where appropriate.

Finally, these outcomes were achieved with per-episode median insulin rates of 4.0 [3.0 – 5.8] U/h for the whole cohort and 3.5 [2.5 – 5.0] U/h once target band is reached. Median nutrition rates achieved were high 95.0 [67.9 – 100.0] %GF and 97.9 [74.1 – 100.0] %GF once in the target band, based only on episodes where patients were fed.

4. Discussion

This large cohort study shows the ability of STAR GC to provide safe, effective, control with long time in target band (71.2% BG in 80-145 mg/dL) and low hypoglycemia (0.9% BG < 80 mg/dL; <0.01% BG < 40 mg/dL). These results outperform most GC studies and are consistent at both cohort and per-patient levels (**Tables 2** and **4**).

There were only three episodes of severe hypoglycemia (0.21% of patients), exceeding other protocols (1-7%) [4,8,29]. STAR GC ability to provide consistently safe control to virtually all patients suggests the association of GC with increased hypoglycemia reported in many recent landmark studies, including NICE-SUGAR, is likely a result of poor control protocol design rather than GC itself. Hence, the benefits of intensive GC on patient outcomes may finally be assessed without the bias from avoidable hypoglycemia due to using protocols with less safety, performance, and personalization, and could thus show improved outcomes for these patients [12,18].

When analyzing the three adverse events (0.21% of episodes), two (0.18%) occurred without the patient receiving any insulin at the time the hypoglycaemia occurred and for the immediate hours before and after the event, and are thus not a result of the STAR GC recommendation. The last occurred from a sudden extreme rise in insulin sensitivity, and is influenced by many different factors [35]. However, the low incidence of hypoglycemia demonstrates safety suitable for regular clinical use.

STAR GC also achieved high nutrition rates at cohort (89.0 [17.2 – 100.0] %GF) and per-episode (95.0 [67.9 – 100.0] %GF), corresponding to 1440 [240 – 1800] kcal/day and 1584 [1200 – 1810] kcal/day. Those rates match the best worldwide [26] due to the digital-twin enabled personalized care. As a result, while some patients remain at low feed rates for the first days, others can assimilate nutrition much earlier. Feeding patients according to their specific tolerance and need is associated with improved outcomes [26,27].

The workload required to achieve the results is relatively high clinically (14.9 measurements/day, 1.6/hour) and may be challenging in ICUs with lower nurse-to-patient ratios [14,33]. However, STAR GC allows choices of 1-3 hourly intervals and protocol compliance studied during STAR GC validation study was 96-99% with some measurements taken more frequently by choice [29, 36]. Equally, longer measurements intervals are being investigated to reduce workload with good control [33], and validated virtual trials [37] have already shown STAR GC can deliver safe, effective control with 8-10 measurements/day. A trade-off can thus be considered to further reduce workload while maintaining high BG safety and efficacy.

Only 32 episodes (2.2%) did not reach the target band, with median (IQR) episode of 13.6 [11.5 – 16.5] hours. Once in target band, STAR GC maintained BG within range for ~80% of time and 88 [70.4 98.5] % per-patient. Nutrition also increased when considering only data once in target band, while workload decreased (14.9 vs. 14.2 measurements/day). The hours before reaching target band are hyperglycemic with hourly measurements and often where nutrition has typically not been started.

The high quality of control achieved is directly attributed to the more recent and complex 3D stochastic models implemented in STAR GC, which incorporate more date to forecast insulin sensitivity [28]. These models provide tighter prediction inducing more aggressive insulin dosing for stable glycemia. When there is a higher risk of glycemic variability, they provide wider predictions inducing more conservative insulin dosing to limit the risk of hypoglycemia. Considering more data allowing a better representation of the metabolic state of the patient positively impacts future insulin sensitivity and the control, consequently improving patient outcomes. The high efficacy and safety observed in this study reflects this high-quality control with greater patient-specificity. In this case, the increased incidence of hypoglycemia associated with glucose control would be seen as a question of protocol design rather than control or target range [18]. Finally, it could help to assess the impact of GC on patients' outcomes without the concern of higher hypoglycemia risk seen in large recent RCTs such as NICE-SUGAR or others [8,9].

The performance of STAR GC can be compared with that of other validated computerized glycemic control systems used in intensive care, such as the

LOGIC-Insulin and Glucommander algorithms. While such protocols provide safe and effective control [38-40], STAR GC has been shown to achieve more stable glycemic regulation and reduce the occurrence of hyper and hypoglycemia. The better performance of STAR GC can be attributed to its unique design. Unlike other protocols, STAR GC modulates both insulin and nutrition to control blood glucose, rather than adjusting insulin alone. Moreover, it uses a predictive stochastic model simulating patient glycemic trajectories and allowing personalized and risk-based recommendations which is not present in other GC protocols.

Considering all the elements discussed above, STAR GC framework provides safe and effective control with patient-specific care. High quality control is achieved for all patients regardless of their condition. This automated, computerized protocol easily adapts to different ICU guidelines and practices, and can be integrated with electronic health record to further facilitate its use. In addition, the data collected for this study represent five years of use of the protocol and more than 1000 patients adding confidence in the results obtained. This large cohort shows the protocol is effective on large populations with potentially large variations between patients.

A key limitation of this study is its results originate from a single-center observational study, rather than a large multi-center, international RCT. RCTs are the gold standard to validate such protocol but they often suffer from variability between the different centers in the way patients are treated, data reported, and often lack the full picture where nutrition is typically left to local clinical practice and often not analyzed despite its impact on control [3,8,41,42]. While the variability between practices is real, the benefit from a computerized system, such as STAR GC, thus provides a mean to standardize control (across ICUs, nurse shifts, etc.) and compensate for variability seen. STAR GC has been consistently tested in different ICUs from Belgium, Hungary, Malaysia, and New Zealand, and has always shown its ability to provide safe and effective control [14,29,43]. Multi-center RCT could be conducted to further validate STAR GC, but each center included has to ensure its ability to provide a safe and effective control before assessing the impacts of STAR GC on patients outcomes [6,7,21].

In this study, patient outcomes (such as mortality, complications, etc.) are not assessed and analyzed. The primary objective of this work is to demonstrate safe and precise control can be achieved as soon as the protocol used is well-designed. Therefore, the focus was placed on the control performance and the risks directly associated with it. An analysis of the patient outcomes could be considered as part of future work since some studies suggest safe and effective GC improves outcomes in critically ill patients [12,32,44].

5. Conclusions

STAR GC provided safe and effective control for nearly all the 1085 patients in this 5-year study, with almost no incidence of hypoglycemia despite targeting normoglycemic ranges. These results thus suggest tight GC control can be achieved safely for all patient when using computerized, patient-specific protocols accounting for inter- and intra- patient variability. Therefore, the associated risk of hypoglycemia with tight GC reported in many GC studies is a causality from poor protocol design.

Low incidence of hypoglycemia, high time in normoglycemic ranges, and tailored nutrition are all associated with improved outcomes in ICU patients. While this study did not directly investigate association with patient outcomes, it proves tight GC does not necessarily imply increased hypoglycemia, often affecting the potential benefit from reduced hyperglycemia.

It is also important to note that with such computerized and automated protocols, even ICUs with limited financial and nursing staff resources can provide safe and effective GC protocols to patients, overall reducing the costs of care from high quality control. Future work will investigate potential benefit from unbiased tight GC on patient outcomes.

6. Declarations

6.1. Acknowledgements

Not applicable.

6.2. Ethics approval and consent to participate

This study was implemented in the Christchurch Hospital ICU, New Zealand, as a clinical practice change and did not require ethics approval as the New Zealand Health and Disability Ethics Committee Upper South Regional Ethics Committee B (Ref: URB/07/15/EXP) approved the analysis, use and publication of de-identified data as a clinical data audit.

6.3. Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

6.4. Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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6.6. Authors' contributions

VU, JGC, GMS and TD contributed to conception and design of the presented study. MS carried out the main analysis, results interpretation and drafted the manuscript. VU, JGC and TD had input in interpretation, manuscript formulation and into redaction process. GMS assisted in implementing the protocol in Christchurch ICU. All authors read and approved the final manuscript.

7. References

1 Plummer MP, Bellomo R, Cousins CE, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. *Intensive Care Med* 2014; **40**: 973-80.

2 Ali NA, O'Brien JM, Jr., Dungan K, et al. Glucose variability and mortality in patients with sepsis. *Crit Care Med* 2008; **36**: 2316-21. https://doi.org/10.1097/CCM.0b013e3181810378.

3 Dubois J, Van Herpe T, van Hooijdonk RT, et al. Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multicenter randomized controlled clinical trial. *Crit Care* 2017; **21**: 212. https://doi.org/10.1186/s13054-017-1799-6.

4 Gunst J, Debaveye Y, Guiza F, et al. Tight Blood-Glucose Control without Early Parenteral Nutrition in the ICU. *N Engl J Med* 2023; **389**: 1180-90. https://doi.org/10.1056/NEJMoa2304855.

5 Van den Berghe G, Wouters PJ, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359-67. https://doi.org/10.1056/nejmoa011300.

6 Chase JG, Desaive T, Bohe J, et al. Improving glycemic control in critically ill patients: personalized care to mimic the endocrine pancreas. *Crit Care* 2018; **22**: 1-10. https://doi.org/10.1186/s13054-018-2110-1.

7 Uyttendaele V, Knopp JL, Shaw G, Desaive T, Chase JG. Is intensive insulin therapy the scapegoat for or cause of hypoglycaemia and poor

outcome? *IFAC J Syst Control* 2019; **9**: 100063. https://doi.org/10.1016/j.ifacsc.2019.100063.

8 Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283-97. https://doi.org/10.1056/NEJMoa0810625.

9 Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009; **35**: 1738-48. https://doi.org/10.1007/s00134-009-1585-2.

10 Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125-39. https://doi.org/10.1056/NEJMoa070716.

11 De La Rosa C, Donado JH, Restrepo AH, et al. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Crit Care* 2008; **12**: R120. https://doi.org/10.1186/cc7017.

12 Egi M, Bellomo R, Stachowski E, et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc* 2010; **85**: 217-24. https://doi.org/10.4065/mcp.2009.0394.

13 Lacherade JC, Jacqueminet S, Preiser JC. An overview of hypoglycemia in the critically ill. *J Diabetes Sci Technol* 2009; **3**: 1242-9. https://doi.org/10.1177/193229680900300603.

14 Uyttendaele V, Knopp JL, Pirotte M, et al. Translating A Risk-Based Glycaemic Control Framework for Critically Ill Patients: STAR-Liège. *IFAC-PapersOnLine* 2020.

15 Anger KE, Szumita PM. Barriers to glucose control in the intensive care unit. *Pharmacotherapy* 2006; **26**: 214-28. https://doi.org/10.1592/phco.26.2.214.

16 Honarmand K, Sirimaturos M, Hirshberg EL, et al. Society of Critical Care Medicine Guidelines on Glycemic Control for Critically Ill Children and Adults 2024. *Crit Care Med* 2024; **52**: e161-e81. https://doi.org/10.1097/CCM.0000000000006174.

17 Adigbli DK, Hammond NE, Finfer S. Managing blood glucose in the intensive care unit. *Intensive Care Med* 2024. https://doi.org/10.1007/s00134-024-07754-4.

18 Gunst J, Van den Berghe G. Blood glucose control in the intensive care unit: the context does matter-author's reply. *Intensive Care Med* 2025. https://doi.org/10.1007/s00134-025-07795-3.

19 Uyttendaele V, Dickson JL, Shaw GM, Desaive T, Chase JG. Untangling glycaemia and mortality in critical care. *Crit Care* 2017; **21**: 152. https://doi.org/10.1186/s13054-017-1725-y.

20 Chase JG, Andreassen S, Jensen K, Shaw GM. Impact of human factors on clinical protocol performance: a proposed assessment framework and case examples. *J Diabetes Sci Technol* 2008; **2**: 409-16. https://doi.org/10.1177/193229680800200310.

21 Chase JG, Benyo B, Desaive T. Glycemic control in the intensive care unit: a control systems perspective. *Annu Rev Control* 2019; **48**: 359-68. https://doi.org/10.1016/j.arcontrol.2019.03.007.

22 Evans A, Le Compte A, Tan CS, et al. Stochastic targeted (STAR) glycemic control: design, safety, and performance. *J Diabetes Sci Technol* 2012; **6**: 102-15. https://doi.org/10.1177/193229681200600113.

23 Fisk LM, Le Compte AJ, Shaw GM, Penning S, Desaive T, Chase JG. STAR development and protocol comparison. *IEEE Trans Biomed Eng* 2012; **59**: 3357-64. https://doi.org/10.1109/TBME.2012.2214384.

24 Chase JG, Shaw GM, Preiser JC, Knopp JL, Desaive T. Risk-Based Care: Let's Think Outside the Box. *Front Med (Lausanne)* 2021; **8**: 535244. https://doi.org/10.3389/fmed.2021.535244.

25 Doola R, Dupuis C, Preiser JC. Nutrition support, carbohydrate feeding and insulin sensitivity in the critically ill patient: a complex relationship. *Curr Opin Clin Nutr Metab Care* 2024; **27**: 350-4. https://doi.org/10.1097/MCO.0000000000001039.

26 Stewart KW, Chase JG, Pretty CG, Shaw GM. Nutrition delivery of a model-based ICU glycaemic control system. *Ann Intensive Care* 2018; **8**: 4. https://doi.org/10.1186/s13613-017-0351-9.

27 Wischmeyer PE, Bear DE, Berger MM, et al. Personalized nutrition therapy in critical care: 10 expert recommendations. *Crit Care* 2023; **27**: 261. https://doi.org/10.1186/s13054-023-04539-x.

28 Uyttendaele V, Knopp JL, Davidson S, et al. 3D kernel-density stochastic model for more personalized glycaemic control: development and in-silico validation. *Biomed Eng Online* 2019; **18**: 1-18. https://doi.org/10.1186/s12938-019-0720-8.

29 Stewart KW, Pretty CG, Tomlinson H, et al. Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis. *Ann Intensive Care* 2016; **6**: 24. https://doi.org/10.1186/s13613-016-0125-9.

30 Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019; **38**: 48-79. https://doi.org/10.1016/j.clnu.2018.08.037.

31 Finfer S, Wernerman J, Preiser JC, et al. Clinical review: Consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. *Crit Care* 2013; **17**: 229. https://doi.org/10.1186/cc12537.

32 Krinsley JS, Preiser JC. Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults. *Crit Care* 2015; **19**: 179. https://doi.org/10.1186/s13054-015-0908-7.

33 Uyttendaele V, Knopp JL, Shaw GM, Desaive T, Chase JG. Risk and reward: extending stochastic glycaemic control intervals to reduce workload. *Biomed Eng Online* 2020; **19**: 26. https://doi.org/10.1186/s12938-020-00771-6.

34 Stewart KW, Pretty CG, Shaw GM, Chase JG. Interpretation of Retrospective BG Measurements. *J Diabetes Sci Technol* 2018; **12**: 967-75. https://doi.org/10.1177/1932296818786518.

35 Greabu M, Badoiu SC, Stanescu S, II, et al. Drugs Interfering with Insulin Resistance and Their Influence on the Associated Hypermetabolic State in Severe Burns: A Narrative Review. *Int J Mol Sci* 2021; **22**: 9782. https://doi.org/10.3390/ijms22189782.

36 Razak AA, Abu-Samah A, Abdul Razak NN, et al. Assessment of Glycemic Control Protocol (STAR) Through Compliance Analysis Amongst Malaysian ICU Patients. *Med Devices (Auckl)* 2020; **13**: 139-49. https://doi.org/10.2147/MDER.S231856.

37 Dickson JL, Stewart KW, Pretty CG, et al. Generalisability of a Virtual Trials Method for Glycaemic Control in Intensive Care. *IEEE Trans Biomed Eng* 2018; **65**: 1543-53. https://doi.org/10.1109/TBME.2017.2686432.

38 Dubois J, Van Herpe T, Van Hooijdonk RT, et al. Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multicenter randomized controlled clinical trial. *Crit Care* 2017; **21**: 212. https://doi.org/10.1186/s13054-017-1799-6.

39 Yamashita S, NG E, Brommecker F, Silverberg J, Adhikari N KJ. Implementation of the Glucommander Method of Adjusting Insulin Infusions in Critically Ill Patients. *Can J Hosp Pharm* 2011; **64**: 333-39. https://doi.org/10.4212/cjhp.v64i5.1068.

40 John SM, Waters KL, Jivani K. Evaluating the Implementation of the EndoTool Glycemic Control Software System. *Diabetes Spectr* 2018; **31**: 26-30. https://doi.org/10.2337/ds16-0061.

41 Vincent JL. Improved survival in critically ill patients: are large RCTs more useful than personalized medicine? No. *Intensive Care Med* 2016; **42**: 1778-80. https://doi.org/10.1007/s00134-016-4482-5.

42 Vincent JL. We should abandon randomized controlled trials in the intensive care unit. *Crit Care Med* 2010; **38**: S534-8. https://doi.org/10.1097/CCM.0b013e3181f208ac.

43 Abu-Samah A, Knopp JL, Abdul Razak NN, et al. Model-based glycemic control in a Malaysian intensive care unit: performance and safety study. *Med Devices (Auckl)* 2019; **12**: 215-26. https://doi.org/10.2147/MDER.S187840.

44 Chase JG, Pretty CG, Pfeifer L, et al. Organ failure and tight glycemic control in the SPRINT study. *Crit Care* 2010; **14**: R154. https://doi.org/10.1186/cc9224.