Improving Safety of Glucose Control in Intensive Care using Virtual Patients and Simulated Clinical Trials

Liam M. Fisk[1], B.Eng, Aaron J. Le Compte[1], PhD, Geoffrey M. Shaw[2], MBChB, J. Geoffrey Chase[1*], PhD,

[1]Department of Mechanical Engineering, Centre for Bio-Engineering, University of Canterbury, Christchurch, New Zealand

[2]Department of Intensive Care, Christchurch Hospital, Christchurch School of Medicine, University of Otago, Christchurch, New Zealand

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ABSTRACT

Despite the potential clinical benefits of normalizing blood glucose in critically ill patients, the risk of hypoglycemia is a major barrier to widespread clinical adoption of accurate glycemic control. To compare five glucose control protocols, a validated insulin-glucose system model was employed to perform simulated clinical trials. STAR, SPRINT, UNC, Yale and Glucontrol protocols were assessed over a medical-surgical intensive care unit patient cohort. Results were interpreted separately for patients with low to high sensitivity to insulin, and low to high variability in metabolic state. STAR and SPRINT provided good glucose control with risk of severe hypoglycemia less than 0.05% across all patient groups. UNC also achieved good control for patients with low and medium levels of insulin sensitivity (SI), but risk of severe hypoglycemia was raised for patients with high SI. Glucontrol showed degradation of performance for patients with high metabolic variability.

Keywords: critical care, glycemic control, virtual trials

1. INTRODUCTION

Stress-induced hyperglycemia (high blood sugar levels) affects 30–50% of intensive care patients [1]. Treatment to normalize blood glucose (BG) concentration with conventional insulin dosing schemes has proved difficult without excessive risk of hypoglycemia [2]. Extreme BG and glycemic variability have been independently linked to increased morbidity and mortality [1, 3–5]. Protocols that have successfully

*Corresponding author: J. Geoffrey Chase, Dept. of Mechanical Engineering, University of Canterbury, New Zealand. Phone: +64 21 342 743. E-mail: Geoff.chase@canterbury.ac.nz Other authors: liam.fisk@pg.canterbury.ac.nz, aaron.lecompte@canterbury.ac.nz, geoff.shaw@cdhb.govt.nz

managed BG to within normal ranges have been shown to reduce ICU mortality by 18–45% [6–8], resulted in faster resolution of organ failure [9], and reduced overall healthcare costs [10, 11]. However, despite these potential benefits, the risk of hypoglycemia and worsened outcome [2, 12] is seen as a major barrier to widespread adoption of accurate glycemic control, with higher BG preferred due to reduced risk of iatrogenic hypoglycemia [13].

Management of BG in intensive care patients presents a significant challenge. Insulin is a potent regulator of carbohydrate metabolism and is routinely administered to combat hyperglycemia. However, a patient's glycemic response to insulin can vary rapidly as a consequence of the initial physiological insult and evolution of condition over time, and predicting such changes in response can be challenging [14]. Medical ICUs typically house a heterogeneous patient population, and control systems that initially work well on a homogenous population can exhibit poorer performance when applied to a broader group of patients [15, 16].

In general, ICU patients are less sensitive to insulin than healthy adults, and their insulin sensitivity (SI) varies over time. Only one study [7] has demonstrated both reduction in the incidence of hypoglycemia and improved patient outcomes, with BG controlled effectively by tracking the patient-specific insulin sensitivity, as well as adjusting insulin and nutrition administration [17]. Moreover, the pharmaco-dynamic effect of insulin on the rate of glucose uptake can saturate at high doses [18], suggesting that an account of carbohydrate load may also be an important component of glycemic control [19].

Accurate glycemic control requires balancing insulin and nutrition inputs within clinical guidelines, while also managing changes in patient-specific response to insulin over time. More aggressive insulin dosing can reduce hyperglycemia faster, but increases the risk of hypoglycemia if the patient's insulin sensitivity were to increase suddenly [20]. Responding too slowly or ignoring changes in patient state can allow variability in insulin response to flow through to increase variability in patient's BG levels [17]. Finally, BG measurement devices, especially those used at the point of care, may be prone to inaccuracy and interference, where the response to a falsely high BG measurement may result in clinically significant iatrogenic hypoglycemia [21].

Glucose control protocols in current clinical practice, or used in research studies, range in complexity from (1) simple tables of insulin dosages prescribed in response to current BG levels (e.g., UNC [22], Yale [23], Glucontrol [24]), (2) paper-based adaptive protocols that manage both insulin and carbohydrate inputs [7], to (3) full computerized model-based control systems with glucose prediction capabilities [25, 26]. Metrics describing the behavior of glycemic control protocols vary between studies, making direct comparison difficult, with performance often simply measured by the degree of hypoglycemia and/or mean BG.

A number of protocols have been trialed clinically with varying levels of success. The UNC protocol [22] achieved 36–47% of BG measurements within the target 70–110 mg/dL range, with 2.0–2.4% BG < 70 mg/dL. Yale protocols have undergone several revisions with different target ranges, where the 2005 version [23] achieved 60% within the target 90 – 119 mg/dL range once glycemia had crossed the 119 mg/dL

threshold. The Glucontrol study [24] was a multi-center prospective randomized control trial with two arms 'A' and 'B' that targeted 80–110 mg/dL and 140–180 mg/dL, respectively. This study was stopped because of excessive protocol violations. Patients in the 'A' arm only spent 39.5% of their time in the target range, and 8.7% experienced severe hypoglycemia (BG < 40 mg/dL). SPRINT [7] is an insulin-nutrition control protocol that achieved 54% of measurements in the 80–110 mg/dL range with a reduction in hypoglycemia compared to retrospective patients. STAR [25] is a new model-based insulin-nutrition control system currently in pilot trials with 63% of BG measurements in the 72–117 mg/dL range and reduced hypoglycemia.

Virtual trials offer the ability to design protocols *in-silico* by testing on virtual patients to optimize protocol performance and safety without risk to real patients. This system has been validated to reproduce the results of clinical trials on equivalent patient cohorts [27], and can be used to comprehensively evaluate the performance of any desired glucose control system. STAR and SPRINT used virtual trials to assess performance before clinical implementation. In contrast, UNC, Yale, and Glucontrol were first tested clinically.

This study used virtual patients to conduct a simulated clinical trial comparing the UNC, Yale, Glucontrol, SPRINT and STAR glucose control systems. The overall goal was to assess protocol safety and performance across different patient types, allowing aspects of safe, high performance protocols to be defined.

2. METHODS

2.1. Virtual Patients and Simulation Environment

Clinically validated virtual trials [27] were carried out using the SPRINT cohort clinical data [7] (371 patients, 39,841 hours, 26,646 measurements) to create virtual patients. Patient demographics are given in Table 1. The Upper South Regional Ethics Committee, New Zealand, granted ethics approval for the audit, analysis, and publication of this data. Virtual patients were generated from the hourly treatment-independent insulin sensitivity profile of real patients [28] using the ICING model [30], allowing virtual trials to realistically simulate patient response to modified treatments administered by different protocols. This approach has been validated on independent matched cohort data [27] and in several clinical trials [25, 31–33].

Patients were considered to require glucose control once BG > 125 mg/dL, and this value was used to determine the beginning of a virtual trial using the patient data. Interruptions in nutrition are common for some patients in clinical practice, and were incorporated by setting nutrition administration to zero over the same periods they occurred in the clinical data. Equally, parenteral nutrition was included in the simulations where it was given clinically.

2.2. Control Protocols Comparison

Five different protocols were assessed in simulation on this virtual cohort: STAR [25], SPRINT [7] and three other published protocols: UNC [22], Yale [23] and Glucontrol A [24]. STAR and SPRINT use IV insulin boluses, while the other 3 protocols deliver IV insulin infusions. All protocols take the form of dynamic sliding scales, apart from

Table 1. Patient demographics

	SPRINT Cohort
Total patients	371
Age (years)	65 [49 – 74]
Male (%)	63.6
APACHE II score [29]	18 [15 – 24]
APACHE II risk of death (%)	25.7 [13.1 – 49.4]
Diabetes history	62 (16.7%)
APACHE III Category	
Operative	**Number of patients**
Cardiovascular	76 (20%)
Respiratory	9 (2%)
Gastrointestinal	60 (16%)
Neurological	7 (2%)
Trauma	14 (4%)
Other (Renal, metabolic, orthopedic)	4 (1%)
Non-Operative	**Number of patients**
Cardiovascular	39 (11%)
Respiratory	66 (18%)
Gastrointestinal	10 (3%)
Neurological	20 (5%)
Trauma	32 (9%)
Sepsis (Renal, metabolic, orthopedic)	17 (5%)

STAR (computerized stochastic forecasting). The rules for each protocol were programmed into the simulation software. Patients were divided into tertiles by their median within-patient model-based insulin sensitivity to divide the cohort by insulin resistance. To further group the patients by metabolic variability, they were divided into tertiles by their within-patient SI variability, defined as the normalized interquartile range (IQR) of SI. Results were analyzed in terms of safety, performance, and workload for each tertile:

- Hypoglycemia safety
  - %BG in severe hypoglycemic range (%BG below 40 mg/dL)
  - %BG in moderate hypoglycemic range (%BG in the range of 40–60 mg/dL)
  - Number of patients with BG in sever hypoglycemic range
  - Number of patients with BG in moderate hypoglycemic range

- Glucose control performance
  - %BG within target range (80–145 mg/dL)
  - Hyperglycemic index. This quantifies the relative area of BG above a specific level [34], defined as 145 mg/dL in this study.
  - Spread of BG (IQR)
  - Glycemic lability index (GLI). GLI measures hour-to-hour changes in BG [35].
  - Mean amplitude of glycemic excursions (MAGE). MAGE quantifies variability by calculating the relative size of BG decreases [36].

- Clinical workload
  - Number of BG measurements per day

Clinical workload was evaluated using BG measurement frequency as a surrogate [37, 38], and BG data was resampled hourly to provide a consistent time-basis for comparison across protocols with different measurement and intervention intervals. Global insulin dosing behavior was investigated by isolating the insulin dose and relative change in insulin dose (±0.5U) at glycemic levels between 40 and 145 mg/dL.

Two-way ANOVA was used to compare the effect of protocol choice and patient category (by tertiles of SI or SI variability) on each aspect of performance.

3. RESULTS

Figure 1 presents results grouped by tertiles of median within-patient SI and indicate that high SI corresponds to the highest risk of hypoglycemia, and low SI corresponds to increased spread of glycemic levels and decreased performance. Of note, the incidence of severe hypoglycemia (BG < 40 mg/dL) is relatively consistent across SI levels for the STAR, SPRINT and Yale protocols, but increases with SI for UNC and Glucontrol A. Glucose control performance is generally better in patients with higher SI. It is likely that this trend is caused by the ability to regulate glycemia with insulin doses below insulin effect saturation, which reduces performance for patients with very low SI. Statistical analysis indicates that protocol choice has a significant effect on hypoglycemia, but overall incidence of mild and severe hypoglycemia does not vary significantly between SI tertiles. Both protocol choice and SI tertile have a significant effect on performance and spread of BG.

Per-patient results in Table 2 present trends similar to Figure 1, with incidence of moderate hypoglycemia increasing with SI, and median hyperglycemic index significantly increased for patients with low SI. Wider spread of BG at low SI was supported by raised median GLI and MAGE scores, further suggesting increased BG variability.

Similarly, the results grouped by variability in SI as presented in Figure 2 and Table 3 show consistently increased hypoglycemia risk and decreased glucose control performance in patients with higher SI variability. In particular, Glucontrol showed

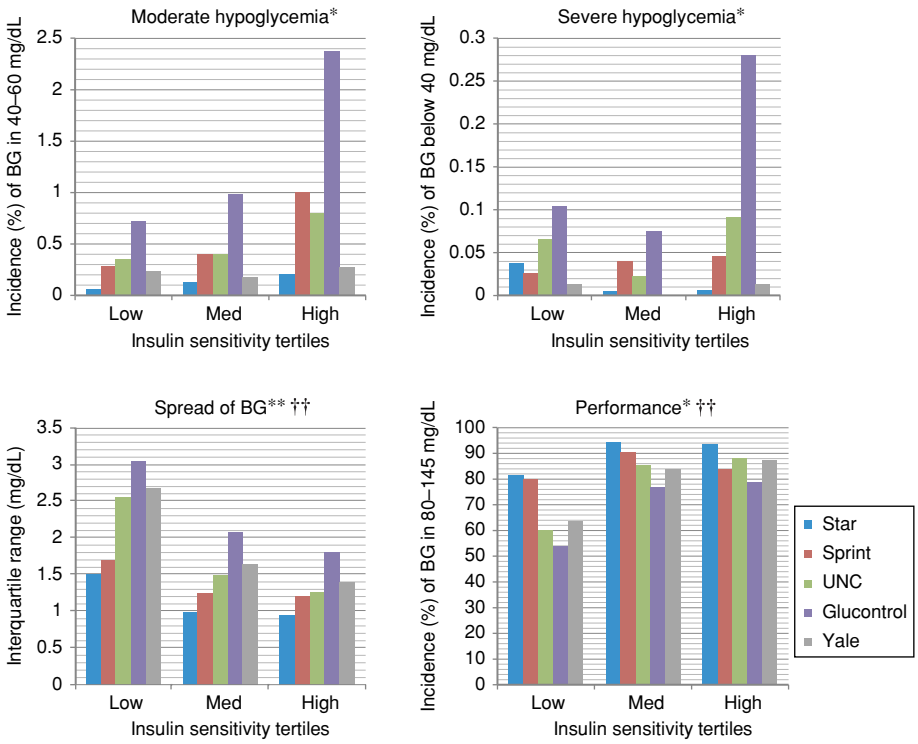


Figure 1. Hypoglycemia safety, BG variability, and glucose control performance metrics across assessed protocols grouped by insulin sensitivity level tertiles. Incidence of moderate hypoglycemia increased for all protocols for patients with higher sensitivity to insulin. Marked increases in severe hypoglycemia were evident with the Glucontrol A protocol. Variability of BG reduced and time in target ranges increased for patients with higher insulin sensitivity. Statistical significance of protocol choice was denoted by * ($p < 0.05$) and ** ($p < 0.01$), while statistical significance of different patient category tertiles was denoted by † ($p < 0.05$) and †† ($p < 0.01$).

the highest incidence of severe hypoglycemia (> 0.25% of the 26,646 BG measurements) for patients with high SI variability, whilst STAR and SPRINT which track SI were able to limit severe hypoglycemia to less than 0.07% across all insulin sensitivity and SI variability tertiles. Yale also showed extremely low hypoglycemia rates. Glucose control performance of each protocol deteriorated as patients' metabolic (SI) variability increased. Grouping patients by SI variability tertile also showed higher statistical significance than SI tertiles, across all performance and safety metrics.

Table 2. Additional per-patient markers for performance and safety by insulin sensitivity tertile

	Insulin Sensitivity Tertiles		
	Low	**Med**	**High**
Hypoglycemia safety			
Number of patients in			
40 – 60 *mg/dL** †			
STAR	8	23	32
SPRINT	22	69	154
UNC	27	68	122
Glucontrol	55	169	364
Yale	18	31	42
Number of patients			
< 40 *mg/dL**			
STAR	2	1	1
SPRINT	2	5	4
UNC	1	2	6
Glucontrol	6	9	19
Yale	1	1	2
Glucose control performance			
Median Hyperglycemic			
Index [*IQR*], *mmol/L*††			
STAR	2.99 [0.95 – 8.68]	0.40 [0.06 – 1.40]	0.16 [0.00 – 0.99]
SPRINT	2.65 [0.60 – 10.10]	0.28 [0.03 – 1.22]	0.11 [0.00 – 1.17]
UNC	8.13 [2.74 – 15.37]	1.80 [0.41 – 4.13]	0.48 [0.02 – 1.70]
Glucontrol	8.33 [2.92 – 17.44]	2.49 [0.90 – 4.94]	1.01 [0.26 – 2.80]
Yale	7.61 [2.84 – 14.20]	1.98 [0.59 – 4.13]	0.96 [0.40 – 2.35]
GLI [*IQR*],			
$mmol^2.hr^{-1}.wk^{-1}$††			
STAR	3.3 [1.1 – 10.9]	0.7 [0.3 – 2.6]	1.1 [0.4 – 3.7]
SPRINT	6.3 [2.2 – 20.3]	1.2 [0.4 – 4.4]	1.5 [0.5 – 5.3]
UNC	3.5 [1.5 – 11.7]	0.9 [0.4 – 3.8]	1.4 [0.5 – 3.7]
Glucontrol	5.0 [2.0 – 12.8]	1.1 [0.5 – 3.6]	1.4 [0.7 – 4.2]
Yale	6.8 [2.5 – 14.8]	1.6 [0.6 – 5.6]	2.2 [0.8 – 7.6]
MAGE [*IQR*],			
*mmol/L*** ††			
STAR	2.24 [1.60 – 3.55]	1.87 [1.48 – 2.48]	1.99 [1.53 – 2.57]
SPRINT	2.36 [1.63 – 3.23]	1.95 [1.48 – 2.51]	1.85 [1.39 – 2.57]
UNC	2.70 [2.04 – 3.91]	2.12 [1.61 – 2.73]	2.16 [1.67 – 2.61]
Glucontrol	3.00 [2.30 – 4.80]	2.80 [1.96 – 3.81]	2.93 [2.33 – 3.79]
Yale	2.95 [2.12 – 4.43]	2.29 [1.86 – 3.12]	2.24 [1.77 – 3.15]

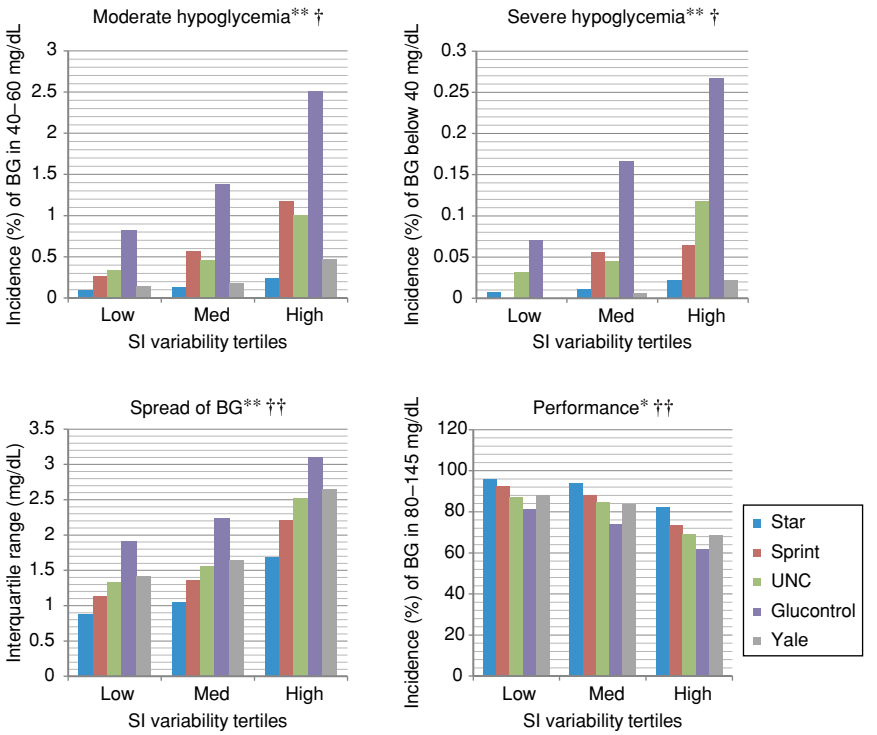


Figure 2. Hypoglycemia safety, BG variability, and glucose control performance metrics across assessed protocols grouped by insulin sensitivity variability tertiles. Highly variable patients tended to have a higher risk of hypoglycemia, particularly if treated with the Glucontrol A protocol. STAR and SPRINT contained severe hypoglycemia to less than 0.1% across patients. BG spread increased and glucose control performance decreased consistently with insulin sensitivity variability. Statistical significance of protocol choice was denoted by * ($p < 0.05$) and ** ($p < 0.01$), while statistical significance of different patient category tertiles was denoted by † ($p < 0.05$) and †† ($p < 0.01$).

Figures 1 and 2 demonstrate that glucose control performance did not differ significantly between protocols across the range of SI (Figure 1) or SI variability (Figure 2). The key difference between protocols was the ability to maintain safety across each patient category. The highest incidence of mild and severe hypoglycemia for all protocols occurred under conditions of high SI and/or high SI variability. SPRINT, STAR and Yale were the least likely to cause severe hypoglycemia, limiting it to below 0.07% hourly BG. However, only STAR was able to consistently limit moderate hypoglycemia to below 0.3% hourly BG. In contrast, Glucontrol A caused more hypoglycemia than all the other protocols across each category.

Table 3. Additional per-patient markers for performance and safety by SI variability tertile

	SI Variability Tertiles		
	Low	**Med**	**High**
Hypoglycemia safety			
Number of patients in			
40–60 *mg/dL*** †			
STAR	13	25	25
SPRINT	33	102	110
UNC	42	81	94
Glucontrol	105	248	235
Yale	17	31	43
Number of patients			
< 40 *mg/dL*** †			
STAR	1	1	2
SPRINT	0	6	5
UNC	2	2	5
Glucontrol	6	15	13
Yale	0	1	3
Glucose control performance			
Median Hyperglycemic Index [*IQR*], *mmol/L*** ††			
STAR	0.18 [0.00 – 0.98]	0.59 [0.06 – 1.83]	2.80 [0.64 – 7.83]
SPRINT	0.07 [0.00 – 0.81]	0.41 [0.04 – 1.58]	2.76 [0.50 – 9.34]
UNC	0.84 [0.15 – 3.08]	1.75 [0.41 – 4.78]	4.17 [1.10 – 11.81]
Glucontrol	1.38 [0.52 – 3.64]	2.50 [0.80 – 5.60]	4.25 [1.75 – 13.17]
Yale	0.92 [0.41 – 2.65]	2.02 [0.61 – 4.60]	4.32 [1.88 – 11.98]
GLI [IQR], $mmol^2.hr^{-1}.wk^{-1}$††			
STAR	0.9 [0.3 – 4.3]	0.9 [0.3 – 3.0]	2.7 [0.9 – 8.5]
SPRINT	1.4 [0.5 – 6.4]	1.3 [0.4 – 4.8]	5.8 [1.6 – 20.1]
UNC	1.2 [0.5 – 4.7]	1.2 [0.4 – 3.4]	3.4 [1.2 – 9.9]
Glucontrol	1.5 [0.6 – 6.6]	1.4 [0.6 – 4.5]	4.2 [1.4 – 10.5]
Yale	1.7 [0.6 – 5.3]	1.8 [0.8 – 6.0]	7.3 [3.2 – 14.8]
MAGE [*IQR*], *mmol/L*** ††			
STAR	1.62 [1.36 – 2.23]	1.95 [1.58 – 2.49]	2.50 [1.86 – 3.56]
SPRINT	1.72 [1.30 – 2.16]	1.86 [1.46 – 2.55]	2.55 [1.88 – 3.58]
UNC	1.85 [1.40 – 2.23]	2.16 [1.69 – 2.73]	2.78 [2.22 – 3.85]
Glucontrol	2.38 [1.83 – 3.25]	2.81 [2.19 – 3.92]	3.48 [2.91 – 4.79]
Yale	1.94 [1.63 – 2.37]	2.29 [1.90 – 3.33]	3.30 [2.51 – 4.33]

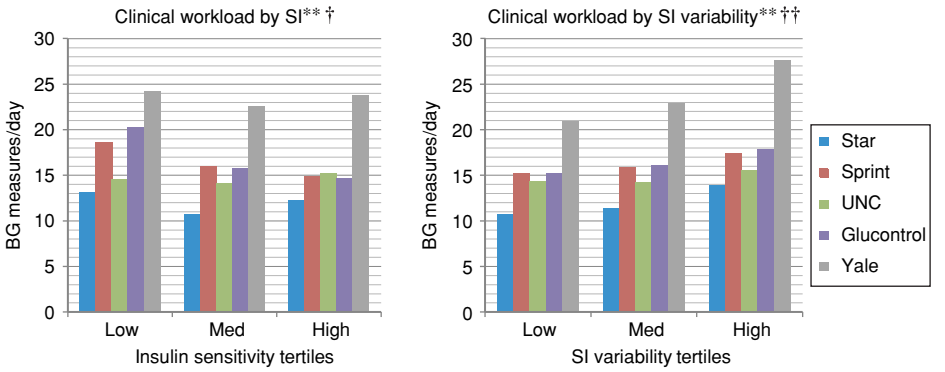
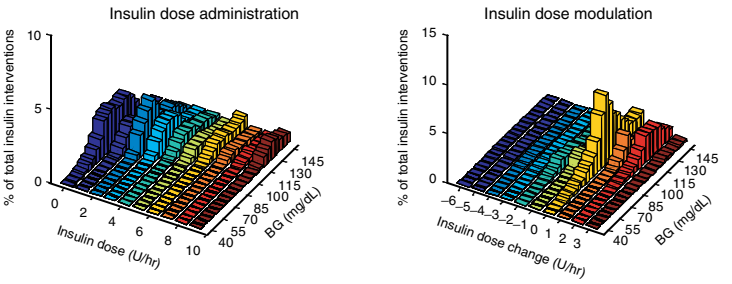


Figure 3. Clinical workload by patient category.

Figure 4 indicates that Glucontrol A demonstrates a limited ability to respond dynamically, with little change in insulin dose being a much more common response compared to similar protocols such as UNC. This behavior is particularly detrimental to patient safety for patients with high SI variability as shown in Figure 2, where Glucontrol A resulted in heightened severe hypoglycemia. STAR and SPRINT appear to be more dynamic insulin-dosing protocols, providing much greater variation in insulin doses in the displayed range. SPRINT was designed with a preference for moderate insulin levels, and this is clearly seen with the high incidence of 3U insulin dose selection in Figure 4.

Clinical workload by category (Figure 3) indicates similar behavior across protocols, with high SI variability or low SI corresponding to increased clinical workload, though UNC remains relatively consistent across both SI and SI variability tertiles. Finally, the clinical workload required by Yale was significantly higher than any of the other protocols, with high SI variability patients requiring more than 27 measures per day. Many of these extra measurements were triggered by the relatively conservative limits for hypoglycemia requiring intensive BG monitoring as per protocol and may



(a) Star

Figure 4. (*Continued*)

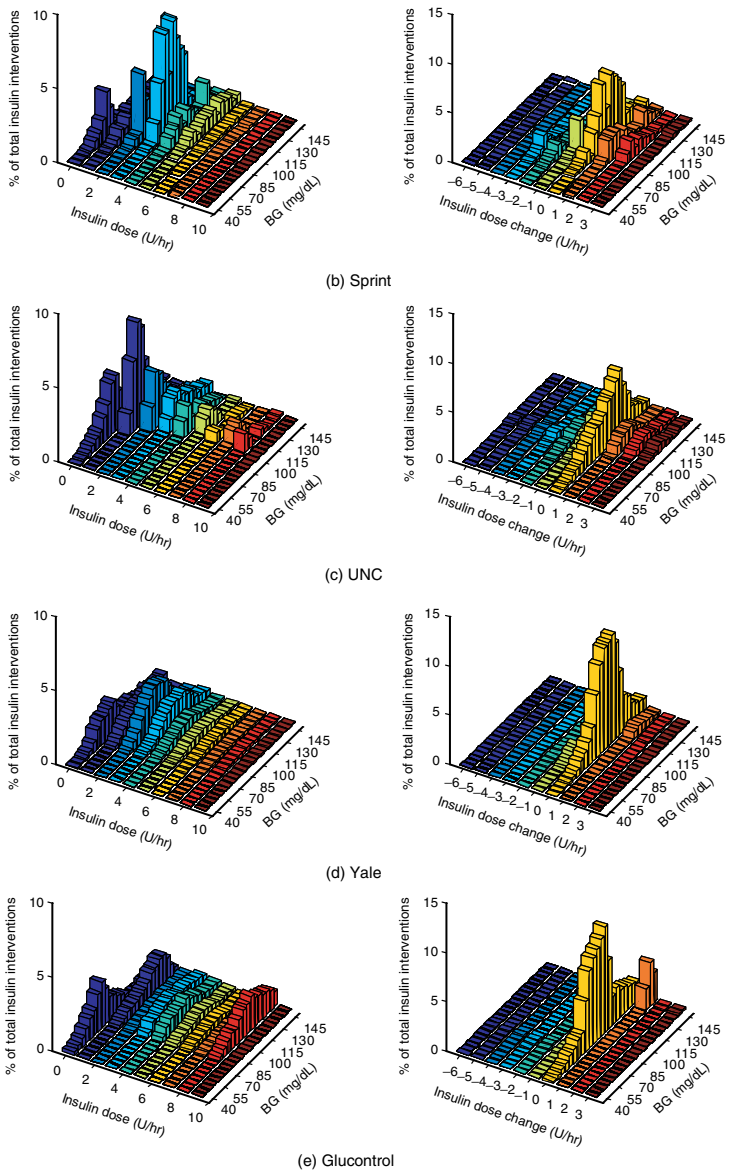


Figure 4. Insulin dosing at glycemic levels between 40 and 145 mg/dL. Insulin dose administration plots the insulin rate chosen at each BG level during virtual trials, and insulin dose modulation shows the change in insulin dose. UNC modulates insulin the most from the insulin-only protocols, whereas Glucontrol uses relatively high rates of insulin with little adjustment of the rate. STAR and SPRINT also modulate nutrition in addition to insulin.

potentially be a source of non-compliance in clinical practice. Thus, Yale performance comes at a cost in workload compared to SPRINT and STAR which achieve performance via their adaptive tracking of SI.

4. DISCUSSION

High SI and high SI variability were clearly identified as the major factors discriminating the degree of safety between glucose control protocols. The trends in Figures 1–3 suggest that to provide protection from moderate and severe hypoglycemia across a wide range of patient types, a clinically applied protocol must be able to recognize and respond to patients with high SI and large changes in patient condition. The comparison between STAR (a highly dynamic, computerized, risk-based framework that directly identifies SI) and Glucontrol A (a relatively static tabular protocol, responding to changes in BG) illustrates the two extremes, indicated by both insulin dosing behavior and glycemic outcome. Yale, SPRINT, and UNC demonstrate the suitability of a tabular protocol, with the benefits of SPRINT over UNC, likely due to SPRINT's design aiming to directly identify the underlying SI changes that lead to a BG response. Additionally, SPRINT and STAR modulate nutrition in addition to insulin as a means to obtain a stronger, more dynamic glycemic response without increasing the risk due to changes in SI and insulin effect saturation at high doses.

Clinical trial simulation using virtual patients is a valuable tool to analyze and characterize performance of glucose control protocols. In particular, it can be employed to identify areas of weakness in a protocol design that would otherwise only appear after detrimental clinical incidents in real patients. The tabular form of the UNC, Yale and Glucontrol A protocols makes it difficult to assess how they will perform from simply reading the protocols. Virtual trials directly communicate the expected performance and implementation issues implicit in each system, and validation ensures that the results are representative of likely clinical outcomes over specific BG ranges and nutrition/insulin inputs.

Virtual patients can also be used directly for protocol design, as performed with SPRINT [39] and STAR [25]. Designing a glucose control protocol for clinical implementation requires balancing clinical workload, performance, and safety. Being able to quantify each trade-off is a powerful tool, and simulation allows for investigation of possible effects without placing patients at risk. Protecting the patient at each step of the process is an important concern, particularly after the discouraging outcomes of several protocol trials that resulted in increased hypoglycemia [2].

Compliance in the clinical unit with a specified glucose control protocol plays a major role in the success of a clinical trial. The Glucontrol study was stopped early due to excessive protocol violations [24], and subsequent analysis indicated that BG measurement frequency was often not compliant with protocol instructions [27]. The rate of change of insulin dosage in the Glucontrol protocol depends upon BG measurement frequency by design, thus altering the rate of BG measurement will alter control response and subsequently protocol dynamics, directly affecting safety and performance. Optimizing BG measurement frequency requires balancing improved performance and safety with increased nursing workload, and thus requires further analysis.

The Yale protocol showed high BG measurement rate, up to 53% higher than other protocols and often triggered by the relatively conservative threshold for intensive BG monitoring around hypoglycemic events. It is possible that nurses will override protocol rules and measure BG less frequently to match typical clinical practice [37]. These changes too may directly impact safety as they occur at lower BG levels.

Finally, protocols such as Yale and UNC could recommend relatively high insulin rates of up to 10–30 U/hr, which may also be capped or curtailed if applied clinically. Simulations will perform protocols as instructed and in these analyses, such non-compliance issues were not implemented, although they may be readily added. However, whenever non-compliance occurs, it triggers deviations from intended safe, effective performance, and thus these situations should be avoided by design.

Utilizing simulations over clinical trials isolates the development process from application on patients in a clinical setting. Virtual trials can easily be extended to investigate factors such as the influences of nutrition on glucose control, methods of insulin delivery, and differences in clinical practices between units that may provide safety or performance benefits or insights that would not otherwise be realized without large-scale clinical trials. Virtual trials are limited to applications where sufficient clinical data have been gathered, and a suitable treatment-independent parameter such as SI must exist. Validity of this approach for glycemic control has previously been established by Chase et al. [27]. Use of a non-linear model, coupled with an adaptive control system and a data-driven stochastic forecasting approach such as STAR, introduces a level of complexity that means trade-offs between factors such as performance and safety can only be adequately and safely explored through virtual trials.

5. CONCLUSIONS

Achieving accurate glycemic control in intensive care patients has proven difficult in practice. Performance of systems from a variety of institutes resulted in a variety of clinical outcomes, likely due to the different ability of each protocol to cope with highly insulin sensitive and/or variable patients. Virtual trials can be used to investigate why some protocols impacted on patient safety from hypoglycemia. In particular, increases in hypoglycemia were observed for protocols that failed to respond dynamically to changing patient condition. Identifying such areas of concern highlights how virtual patients and simulated trials protocols can be used to investigate and refine clinical practice long before patient lives hinge on the outcomes.

CONFLICT OF INTEREST:

The authors indicated no potential conflicts of interest.

NOMENCLATURE

APACHE	Acute Physiology and Chronic Health Evaluation
BG	Blood glucose concentration, mg/dL
GLI	Glycemic lability index, $mmol^2.hr^{-1}.wk^{-1}$
IQR	Interquartile range, mg/dL
MAGE	Mean amplitude of glycemic excursions, mmol/L

SI	Insulin sensitivity
SPRINT	Specialized Relative Insulin and Nutrition Tables
STAR	Stochastic TARgeted
UNC	University of North Carolina

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