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ORIGINAL ARTICLE

Stochastic Targeted (STAR) Glycemic Control: Design, Safety, and Performance

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Abstract

Introduction:

Tight glycemic control (TGC) has shown benefits but has been difficult to achieve consistently. STAR (Stochastic TARgeted) is a flexible, model-based TGC approach that directly accounts for intra- and interpatient variability with a stochastically derived maximum 5% risk of blood glucose (BG) below 72 mg/dl. This research assesses the safety, efficacy, and clinical burden of a STAR TGC controller modulating both insulin and nutrition inputs in virtual and clinical pilot trials.

Methods:

Clinically validated virtual trials using data from 370 patients in the SPRINT (Specialized Relative Insulin and Nutrition Titration) study were used to design the STAR protocol and test its safety, performance, and required clinical effort prior to clinical pilot trials. Insulin and nutrition interventions were given every 1–3 h as chosen by the nurse to allow them to manage workload.

Interventions were designed to maximize the overlap of the model-predicted (5–95th percentile) range of BG outcomes with the 72–117 mg/dl band and thus provide a maximum 5% risk of BG <72 mg/dl. Interventions were calculated using clinically validated computer models of human metabolism and its variability in critical illness. Carbohydrate intake (all sources) was selected to maximize intake up to 100% of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) goal (25 kg/kcal/h). Insulin doses were limited (8 U/h maximum), with limited increases based on current rate (0.5–2.0 U/h). Initial clinical pilot trials involved 3 patients covering ~450 h. Approval was granted by the Upper South A Regional Ethics Committee.

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Abbreviations: (APACHE II) Acute Physiology and Chronic Health Evaluation II, (ACCP) American College of Chest Physicians, (CDF) cumulative distribution function, (EN) enteral, (ICU) intensive care unit, (IQR) interquartile range, (LoS) length of stay, (PN) parenteral, (SCCM) Society of Critical Care Medicine, (SPRINT) Specialized Relative Insulin Nutrition Titration, (STAR) Stochastic TARgeted, (TGC) tight glycemic control

Keywords: critical care, glycemic control, ICU, intensive care, intensive insulin therapy, SPRINT, STAR, stochastic, targeted, TGC

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Abstract cont.

Results:

Virtual trials indicate that STAR provides similar glycemic control performance to SPRINT with 2–3 h (maximum) measurement intervals. Time in the 72–126 mg/dl and 72–145 mg/dl bands was equivalent for all controllers, indicating that glycemic outcome differences between protocols were only shifted in this range. Safety from hypoglycemia was improved. Importantly, STAR using 2–3 h (maximum) intervention intervals reduced clinical burden up to 30%, which is clinically very significant. Initial clinical trials showed glycemic performance, safety, and management of inter- and intrapatient variability that matched or exceeded the virtual trial results.

Conclusions:

In virtual trials, STAR TGC provided tight control that maximized the likelihood of BG in a clinically specified glycemic band and reduced hypoglycemia with a maximum 5% (or lower) expected risk of light hypoglycemia (BG <72 mg/dl) via model-based management of intra- and interpatient variability. Clinical workload was self-managed and reduced up to 30% compared with SPRINT. Initial pilot clinical trials matched or exceeded these virtual results.

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Introduction

Critically ill patients often experience stress-induced hyperglycemia and high levels of insulin resistance.[1–7] The occurrence of hyperglycemia, particularly severe hyperglycemia, is associated with increased morbidity and mortality in this group of patients.[1,3] Glycemic variability, and thus poor control, are also independently associated with increased mortality.[8,9] It has been shown that tight glycemic control (TGC) can significantly reduce the rate of negative outcomes associated with poor control by modulating nutrition and/or insulin administration,[7,10,11] and can also reduce the rate and severity of organ failure[12] and cost.[13,14] However, consistent, effective TGC remains elusive with several studies achieving positive, negative, and inconclusive outcomes.[15–18] In addition, there is little agreement on what constitutes desirable glycemic performance,[19–21] particularly with regard to how TGC affects outcome.

The SPRINT protocol was successful at reducing organ failure and mortality[10,12] with a patient-specific approach that directly considered carbohydrate administration along with insulin. It provided the tightest control across all patients of several large studies[22,23] via its patient-specific approach to accounting for inter- and intrapatient variability. However, the protocol was also relatively inflexible, and the clinical burden, while acceptable, was higher than desired.

In particular, SPRINT had a fixed, implicit target glycemia of 90–110 mg/dl that could not be altered for specific clinical needs or more dynamic patients. Equally, the approach to control was fixed, titrating both insulin and nutrition with respect to the overall patient-specific insulin sensitivity evidenced in their glycemic response to the prior intervention. Thus, approaches that preferred greater or lesser carbohydrate or insulin administration than SPRINT would recommend, or different combinations of parenteral vs enteral nutrition administration routes, were not possible because of its model-derived, paper-based implementation.[24–26] In addition, its inability to forecast a range of outcomes to an intervention required more frequent 1–2 hour measurement intervals to ensure tight control when it was not always necessary.[24] The choice of measurement interval was not free and was specified as part of the protocol increasing perceived effort because of its inflexible approach.

This article presents a model-based TGC protocol that ameliorates or eliminates all these issues. Model-based uses stochastic models[27,28] to forecast the range of glycemic outcomes for a given intervention, providing greater certainty over longer measurement intervals. It can thus target a desired range and, unique to this Stochastic TARgeted (STAR) approach, provide a guaranteed, cohort-wide level of risk for hypo- or hyperglycemia to enhance

control and optimize risk. This risk level can be clinically set and thus provide a much better measure of clinical control over the risk of hypo- and/or hyperglycemia.[29] The STAR framework presented is also more flexible as glycemic target ranges and risk of hypo- or hyperglycemia can all be clinically specified to meet local criteria without adjusting the overall STAR approach. This research presents the (clinically validated)[30] virtual trials protocol design and optimization for an adult intensive care unit (ICU) cohort, its comparison with SPRINT clinical data, and three initial clinical pilot trial results covering ~450 h of TGC.

Methods

Model and Virtual Trials

Virtual trials enable testing of new TGC protocols before clinical implementation. It is a safe means of optimizing glycemic control performance, safety from hypoglycemia, clinical burden, and ability to handle dynamic changes in a patient's metabolic state or other unanticipated errors or effects prior to clinical implementation.[24,30,31]

The metabolic system model used is defined as follows:

$$\dot{G} = -p_G G - S_I G \frac{Q}{1 + \alpha_G Q} + \frac{p(t) + EGP - CNS}{V_G} \quad (1)$$

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u_{ex}(t)}{V_I} + 3e^{-(u_{ex}(t)*V_I)} \quad (3)$$

where

$$P(t) = \min\,(d_2 P_2, P_{max}) \quad (4)$$

$$\dot{P}_2 = -\min\,(d_2 P_2, P_{max}) + d_1 P_1 \quad (5)$$

$$\dot{P}_1 = -\,d_1 P_1 + D(t) \quad (6)$$

where all model parameters are described in **Table 1**, including values for the population constants employed.

Table 1.
Variable Definitions and Values for the Glucose-Insulin System Model of Equations (1)–(6)

Variable	Description	Values
G	Blood glucose level	(mmol/liter)
Q	Interstitial insulin concentration	(mU/liter)
I	Plasma insulin concentration	(mU/liter)
P_2	Glucose level in gut	(mmol)
P_1	Glucose level in stomach	(mmol)
Parameter	**Description**	**Values**
p_G	Insulin independent glucose removal (excluding central nervous system uptake) and the suppression of EGP from EGP_b with respect to G	0.006 (min^{-1})
α_G	Saturation parameter for insulin-mediated glucose removal	1/65 (liter/mU)
S_I	Insulin-mediated glucose removal and the suppression of EGP from EGP_b with respect to G and Q	(liter/mU/min)
$P(t)$	Glucose appearance in plasma from dextrose intake	(mmol/min)
EGP	Endogenous glucose production	1.16 (mmol/min)
CNS	Central nervous system glucose uptake	0.3 (mmol/min)
V_G	Plasma glucose distribution volume	13.3 (liter)
k	Interstitial insulin transport rate	- ln(0.5)/35 (min^{-1})
n	Plasma insulin decay rate	0.16 (min^{-1}) (min^{-1})
α_I	Saturation parameter for plasma insulin clearance	1.7 x 10^{-3} (liter/mU)
$u_{ex}(t)$	Exogenous insulin	(mU/min)
V_I	Plasma insulin distribution volume	3.15 (liter)
d_2	Glucose absorption rate from gut	-ln(0.5)/100 (min^{-1})
P_{max}	Maximal glucose flux from gut to plasma	6.11 (mmol/min)
d_1	Glucose absorption rate from stomach	-ln(0.5)/20 (min^{-1})
$D(t)$	Dextrose intake	(mmol/min)

Time-varying insulin sensitivity profiles [$S_I(t)$] created from patient data[32] are used as the critical marker of a patient's metabolic state[28,30,31] and identified hourly from clinical data.[32] This model-based insulin sensitivity metric has been shown to be independent of both the insulin and nutrition inputs used to derive it, and has been clinically validated in its ability to predict the median and variability of both cohorts and individual patients on matched cohorts treated with different TGC protocols.[30]

Hence, these virtual patients can be used to accurately predict the outcome of new protocol designs and intervention strategies prior to clinical implementation. This approach allows more robust protocols to be designed and rigorously tested, which can improve patient safety when implemented as well as minimize the need for protocol alterations after implementation to account for unforeseen uses or effects.

Virtual Patients and Clinical Data

Clinical data from 370 patients reported in SPRINT[10] were used to create virtual patients. They thus represented the SPRINT cohort, as reported, with which STAR protocol results were compared. **Table 2** summarizes these patients' clinical data; much more specific information is available in the studies by Chase and colleagues.[10,12]

Stochastic Model and Glycemic Control

The STAR TGC protocol recommends insulin and nutrition interventions based on recent patient data, and predicts blood glucose (BG) response to a particular intervention and a stochastic model[27,28] of the potential variability in $S_I(t)$ over the following 1–3 h. The stochastic models and their use in TGC are presented in detail in elsewhere.[27,28,33,34] However, these models capture the potential variation of (patient-specific) insulin sensitivity [$S_I(t)$] over the next 1, 2, or 3 h based on a cohort model. While the median and most likely variation is no significant change from the prior hour, the interquartile range (IQR) and (5^{th}, 95^{th}) percentile variations can result in significant changes in BG for a given insulin intervention. **Figure 1** shows this stochastic model and its impact, schematically, on BG outcome for a given intervention.

STAR Approach: Maximum Likelihood, Target to Range, and Maximum Risk

The STAR approach explicitly targets the (5^{th}–95^{th}) percentile outcomes shown in **Figure 1** to specific, clinically chosen target levels. Thus, it targets ranges rather than any specific value, a "target to range" approach. The 5^{th} percentile is never allowed to be lower than 72–80 mg/dl, providing a cohort-wide guaranteed (maximum) risk of 5% for BG below these values for any intervention. Importantly, this level can be clinically specified and be different for different measurement intervals.

For every intervention, the nurses have a free choice of measurement interval of 1, 2, or 3 h when BG is in the 72–117 mg/dl range, provided there is no forecasted risk of low BG. Outside this range, targeting and measurement interval are restricted to 1 h for patient safety. **Table 3** shows the target-to-range approach clinically specified in this case. The overall goal is a target range of 72–120 mg/dl with most measurements

Table 2.
SPRINT Patient Cohort Clinical Data and Glycemic Control Summary. Further Details Are in Chase and Colleagues[10,12]

Patient data[a]		
Total patients	370	
Age (years)	65 [49–74]	
% Male	63.6%	
APACHE II score	18 [15–24]	
APACHE II risk of death	25.7% [13.1–49.4%]	
Diabetic history	62 (16.7%)	
LoS [median, IQR] (days)	4.1 [1.7–10.4]	
APACHE III diagnosis		
Operative	Number of patients	%
Cardiovascular	76	20%
Respiratory	9	2%
Gastrointestinal	60	16%
Neurological	7	2%
Trauma	14	4%
Other (renal, metabolic, orthopaedic)	4	1%
Nonoperative	Number of patients	%
Cardiovascular	39	11%
Respiratory	66	18%
Gastrointestinal	10	3%
Neurological	20	5%
Trauma	32	9%
Sepsis	17	5%
Other (renal, metabolic, orthopaedic)	17	5%

[a] APACHE, Acute Physiology And Chronic Health Evaluation; LoS, length of stay; IQR, interquartile range.

desired in the 80–120 mg/dl range. Safety is preferred with a maximum expected risk of 5% for low BG rising from a threshold of 72 mg/dl at 1 h measurement to 80 mg/dl at 2–3 h intervals.

Specific insulin and nutrition interventions are optimized using the system model of **Equations (1)–(6)** and the stochastic models. More specifically, they are dosed in increments with a maximum allowed change from the prior intervention, defined as follows:

Insulin: 0.0–6.0 U/h in increments of 0.5 U excluding 0.5 U/h. Maximum change: +3 U/h or down to 0 U/h.

Nutrition: 30–100% of American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) goal feed of 25 kcal/kg/day[35,36] in increments of 5%, using a low carbohydrate enteral nutrition formula (local clinical standard) of 35–40% carbohydrate content. Nutrition may be turned off for other clinical reasons (0%) leaving only insulin as an intervention. Maximum change: ±20% for a given intervention interval, typically altered every 3–5 h to reduce workload.

The maximum changes of ±20% (of goal feed) in nutrition rate, and +3 U/h increase in insulin are set with an unlimited insulin decrease to 0 U/h allowed for any given intervention period. These limits provide robustness to clinically observed sensor assay errors or failure. Thus, any sudden hyperglycemia will only be gradually reduced. If parenteral nutrition is specified, the value is set by the clinician and taken into account during all calculations. Thus, nutrition is modulated in the same percentages based on all sources of administration.

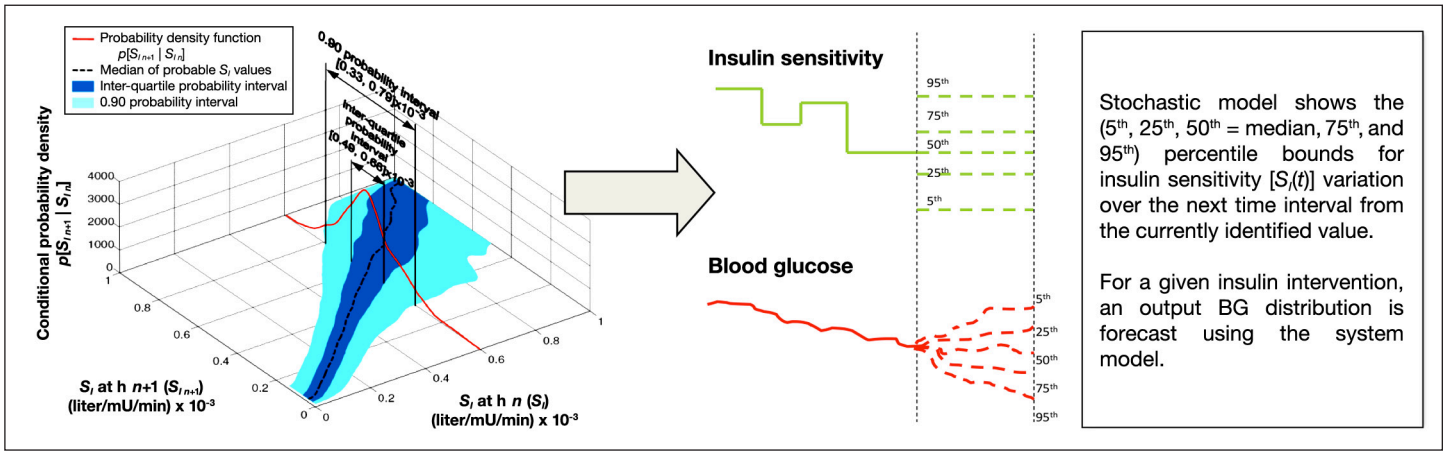

Figure 1. Stochastic model (left) can be used with an identified current level of $S_I(t)$ to provide a forecast range of SI(t) values over the next 1–3 h interval. This forecast range of values can be used with a given insulin intervention and the system model of **Equations (1)–(6)** to yield a range of BG outcomes of differing likelihood. Note that the stochastic model shown is for a 1 h interval; the 2–3 h interval models are very similar but not shown here. More details are in the studies by Lin and colleagues.[27,28]

Table 3.
STAR BG Target Ranges and Approach for BG in the 72–135 mg/dl Range

Measurement interval	BG percentile and target BG for that measurement interval	Goal and outcome
1 hour	95th percentile is targeted equal to 117 mg/dl unless 5th percentile BG <72 mg/dl Else 5th percentile targeted at 72 mg/dl	Ensures 95% of outcome BGs are in 72–117 mg/dl target range and risk of light hypoglycemia BG <72 mg/dl does not exceed 5%.
2 hour	5th percentile targeted at 80 mg/dl	Ensures most likely BG values are in 80–120 mg/dl range and a maximum risk of 5% for BG <80 mg/dl. It also accepts a potentially greater likelihood of exceeding 120 mg/dl at end of interval as preferable to being lower than 80 mg/dl.
3 hour	5th percentile targeted at 80 mg/dl	Ensures most likely BG values are in 80–120 mg/dl range and a maximum risk of 5% for BG <80 mg/dl. It also accepts a potentially greater likelihood of exceeding 120 mg/dl at end of interval as preferable to being lower than 80 mg/dl.

More specifically, at each measurement, the algorithm searches over all feasible solutions within these intervention constraints. If no feasible solution is available for a 2–3 h interval, the 5th percentile is set on a value over 80 mg/dl within these limits. If both interventions are changing, then the protocol selects the feasible option with greatest nutrition administration, a choice that was clinically specified.

An additional 1 U/h insulin infusion is recommended if the limits of nutrition and insulin are unable to adequately ensure avoidance of hyperglycemia, based on meeting the following conditions:

- Insulin was administered at a rate of ≥5 U/h for the past 3 h
- At least 4 h has elapsed since the last time the enteral feed was turned off.

The infusion is sustained for 6 h and accounted in all subsequent calculations unless enteral or parenteral feed is stopped or BG is decreasing rapidly.

Finally, there are three special cases for which measurement intervals are restricted to every 1 and/or 2 h and interventions modified, defined as follows:

Gradual reduction of hyperglycemia: BG >135 mg/dl (level set by clinician).

Rapid decrease in BG: BG is more than 18 mg/dl lower than the predicted 5th percentile BG output, signifying very rapid change outside of forecast ranges and toward hypoglycemia.

Nutrition suspension: When nutrition administration is turned off for clinical reasons, the risk of hypoglycemia can rise for a given insulin dose.

Each case represents a significant risk to patient safety where insulin can be dosed excessively in other protocols. The computerized system detects these situations automatically and offers only the relevant options. **Table 4** summarizes these cases and the resulting intervention and measurement interval.

Analyses

Results from virtual trials of STAR were compared with clinical data from patients treated with SPRINT in the Christchurch ICU. Statistics were collated for three versions or clinical uses of STAR:

Best case: Measurement interval limited to 1 h.

Intermediate case: Measurement interval limited to 2 h (when available).

Minimum clinical effort case: Measurement interval not limited (up to 3 h) and longest available selected.

The 2 h limited interval (intermediate) case is the best comparator to the clinical SPRINT data[10] given similar measurement intervals. **Table 5** defines the performance metrics used to assess performance, safety, and clinical effort.

In addition, SPRINT and STAR are compared by the distributions, across the same cohort, of insulin and nutrition interventions to assess how differently the outcomes are achieved by each protocol.

Clinical Implementation

Clinical implementation of STAR is straightforward and illustrated in **Figure 2**. In particular, a BG measurement is taken and that value is input into a table computer, laptop, or other device. The model then computes 1-, 2-, and 3-h interval treatment options as defined in earlier

Table 4.
Special Cases Definitions and Outcome Impact on Interventions and Measurement Interval

Case	Condition		Outcome		Maximum measurement interval (hours)
Gradual reduction of hyperglycemia	$BG_i > 135$		Percentile used for targeting	50th	1
			Target value	$0.85 \times BG_i$	
Rapid decrease in glucose levels	$BG_i < BG_{i-1\ (5th)} - 1$	$BG_i < 90$	Background insulin infusions stopped		1
		$BG_i \geq 90$	Background insulin infusions stopped		
Nutrition suspension	Feed turned off by clinician		Use only insulin intervention Stop all extra insulin infusions		2

Table 5.
Metrics to Assess Performance, Safety, and Clinical Effort

	Descriptions
Performance	Cohort: median and IQR of BG measurements Per-patient: median and IQR of BG measurements Percentage of BG measurements in desired target ranges Insulin and nutrition administration
Safety	Number of hypoglycemic events: light (<72 mg/dl) and severe (<40 mg/dl)
Clinical effort	Measurements per day

sections. Finally, the nurse must input the chosen recommendation to the insulin and nutrition pumps, as necessary. This semiautomated, human-in-the-loop approach improves safety, as advice can be examined or changed if desired and regulated equipment will not have to be modified for full automation. The user interface and human factors are described by Ward and colleagues.[37,38]

Clinical Pilot Trials

Initial pilot clinical trials results are presented from three initial patients (479 h) in a larger pilot trial as a proof of concept. These patients were recruited under informed consent based on treatment using SPRINT, the standard of care at Christchurch Hospital, Christchurch, New Zealand. Ethics approval for this pilot study was granted by the Upper South A Regional Ethics Committee.

Results

Performance

Table 6 shows STAR has similar or better performance than SPRINT. All BG results are resampled hourly with linear interpolation to provide a consistent timing basis across protocols with different prescribed measurement rates. The comparatively higher rate of measurements in the 90–117 mg/dl band reflects the higher range of 117 mg/dl versus 110 mg/dl in SPRINT. The percentage of measurements recorded in the target band (72–117 mg/dl) decreases with longer measurement intervals as more flexible control is permitted. Comparing the 2 h version of STAR with SPRINT shows that SPRINT achieves slightly higher percentages in the 72–117 mg/dl range but that the two protocols are similar across the other ranges. The 3 h interval case has slightly wider control toward slightly higher glycemia, as expected by design. Notably, in the 72–145 mg/dl range, all protocols are largely equivalent.

These glycemic outcomes in **Table 6** were obtained using wider ranges of per-patient insulin and nutrition administration rates. Higher enteral nutrition rates in STAR are directly proportional to the overall enteral nutrition given because a single, fixed composition (Glucerna, Abbott Labs, Colombus, OH) nutritional formula was used, and were offset in part by the virtual trials, such as SPRINT, providing no nutrition where clinically specified in the data. Hence, the 0% feeding over all patients includes several short-stay cardiovascular surgery patients (and others) who were not fed by clinical

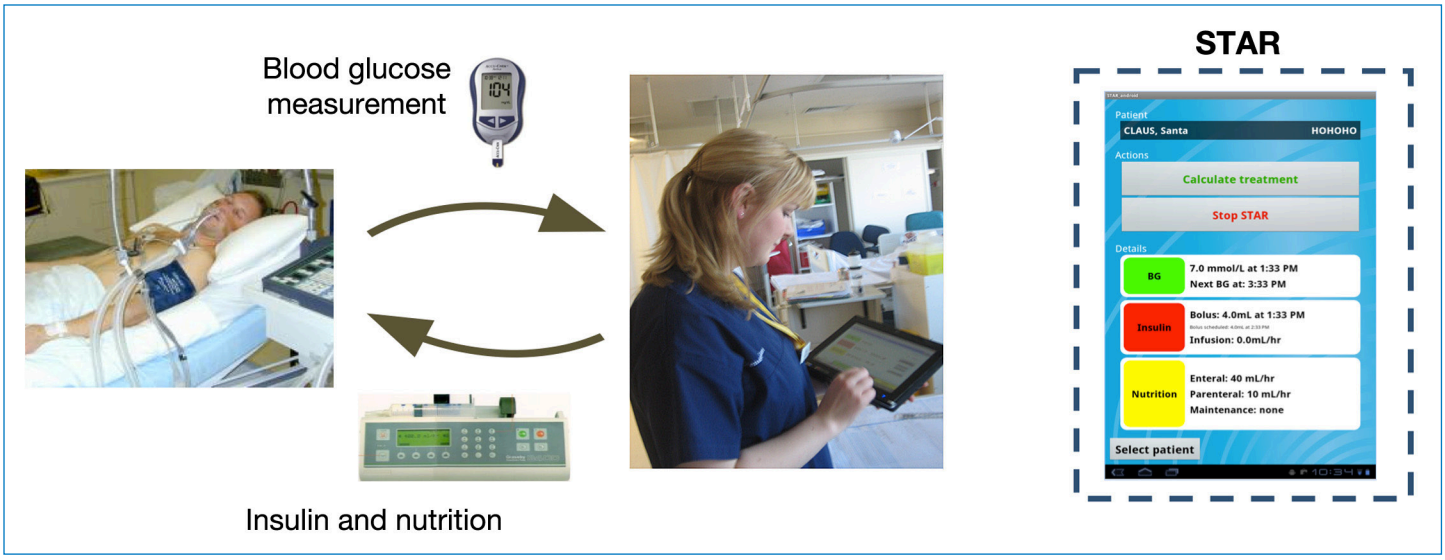

Figure 2. Schematic of clinical use of semiautomated and model-based STAR system on a tablet computer where the example screen shows the current STAR treatment and last BG measurement **(right side)**. The arrows indicate nursing staff interaction with sensors and pumps in semiautomated human-in-the-loop control.

decision. When only periods of feeding were included, the results were consistent. In particular, the lower quartile per-patient median dextrose administration rates (during nutrition administration) were 40–54% higher for STAR than for SPRINT, while the upper quartile value was similar to 20% higher. Note that SPRINT had a maximum nutrition rate of 80% of the goal ACCP/SCCM rate, whereas STAR was limited to 100%.

Figure 3 shows the per-patient BG cumulative distribution function (CDFs) for each case. STAR provided tighter control across all patients for each case than SPRINT. It did so using more insulin and a wider range of insulin administration rates, while also providing greater nutritional input. Hence, the model-based approach delivered better patient-specific management of intra- and interpatient variability.

Safety

Table 7 indicates that STAR effectively reduces hypoglycemia. Absolute (relative) reductions of 1.1% (41%), 0.7% (26%), and 0.7% (26%) can be seen in the percentage of light hypoglycemia assessed as percentage of BG <72mg/dl for STAR 1-, 2-, and 3 hmaximum measurement intervals, respectively. There are similar results for BG <80 mg/dl [range: 2.1–2.9% absolute (28–40% relative)]. Severe hypoglycemia (BG <40 mg/dl) was unchanged for the 3 h maximum interval but was significantly reduced by 5 patients for the best comparator 2 h case (35%) and to 6 for the 1 h best case (57%), which, despite improvement with STAR, still shows a (decreased) association between measurement interval and hypoglycemia.

Clinical Effort

Table 8 shows measurements per day, which are a main source of clinical effort. STAR reduces the average per day by 13.3% and 30.0% for the 2- and 3 h interval cases. These reductions are higher in longer-stay patients.

TGC Intervention Comparisons (SPRINT vs STAR)

Figure 4 compares the intervention choices made for STAR every 2 h and SPRINT, the most directly comparable protocols, as SPRINT only offered maximum measurements every 2 h based on a series of rules to determine patient stability.[10,24,25] It is clear that STAR provides significantly more hours at higher goal feed rates than SPRINT. Equally, STAR makes far wider use of the range of insulin interventions. This result occurs because STAR

Table 7.
Summary of Safety Results

	STAR 1 h intervals	STAR 2 h intervals	STAR 3 h intervals	SPRINT
%BG <80 mg/dl	5.1	5.2	4.4	7.3
%BG <72 mg/dl	1.6	2.0	2.0	2.7
Number of patients with BG measurements <40 mg/dl	6	9	14	14

Table 6.
Summary of Performance. Raw Data of SPRINT and Closest Comparator (STAR 2-Hour) Are Shaded to Show This Comparison[a]

	STAR 1 h intervals	STAR 2 h intervals	STAR 3 h intervals	SPRINT
BG median [IQR] (mg/dl)	97 [90–110]	99 [90–114]	106 [95–119]	104 [90–117]
%BG in 72–117 mg/dl	80.6	77.8	71.1	73.6
%BG in 72–126 mg/dl	86.0	84.4	81.2	82.4
%BG in 72–145 mg/dl	92.4	91.8	90.9	90.8
Median insulin rate [IQR] (U/h)	2.5 [1.3–4.0]	2.0 [1.0–3.3]	2.0 [1.0–3.0]	3.0 [2.0–3.0]
Nutrition over all patients:				
Median dextrose rate [IQR] (g/h)	3.3 [0.0–4.5]	3.1 [0.0–4.6]	3.6 [0.0–5.2]	2.3 [0.0–4.7]
Median glucose rate [IQR] (% goal)	51% [0–70%]	48% [0–72%]	56% [0–80%]	35% [0–72%]
Nutrition only during feeding:				
Median dextrose rate [IQR] (g/h)	4.0 [3.1–5.1]	3.9 [3.1–5.1]	4.7 [3.5–6.1]	3.9 [2.3–5.2]
Median glucose rate [IQR] (% goal)	63% [49–80%]	62% [48–80%]	73% [54–96%]	60% [35–80%]

[a] In virtual trials, patients were not given nutrition when clinically specified in the raw data to match the clinical situation in the SPRINT data. The nutrition is shown twice for all patients and hours and then only including times when nutrition was allowed.

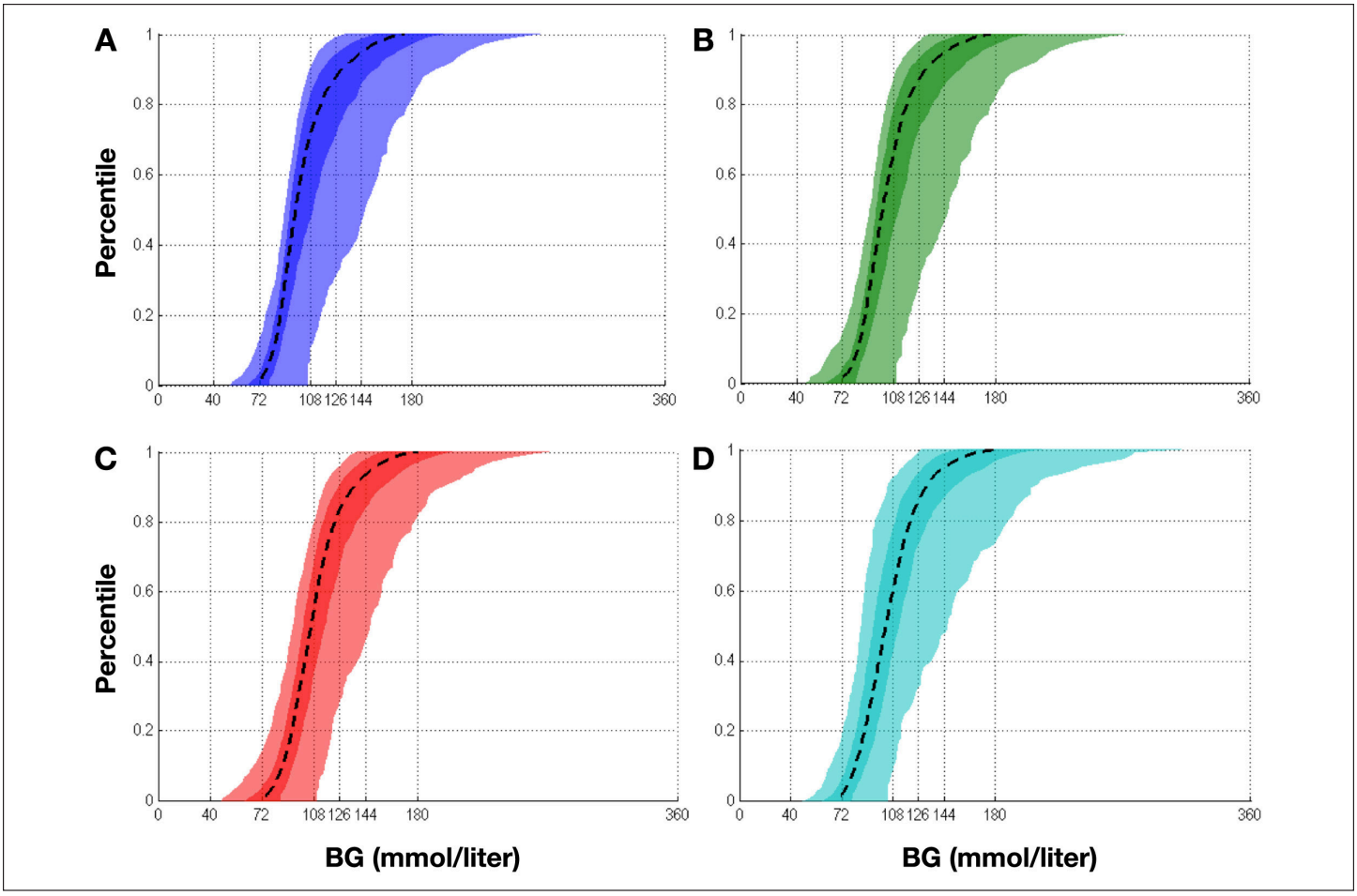

Figure 3. BG cumulative distribution functions (CDFs) of median, IQR, and 5th–95th percentile patients for the SPRINT and STAR protocols. **(A)** STAR 1-hour; **(B)** STAR 2-hour; **(C)** STAR 3-hour; and **(D)** SPRINT.

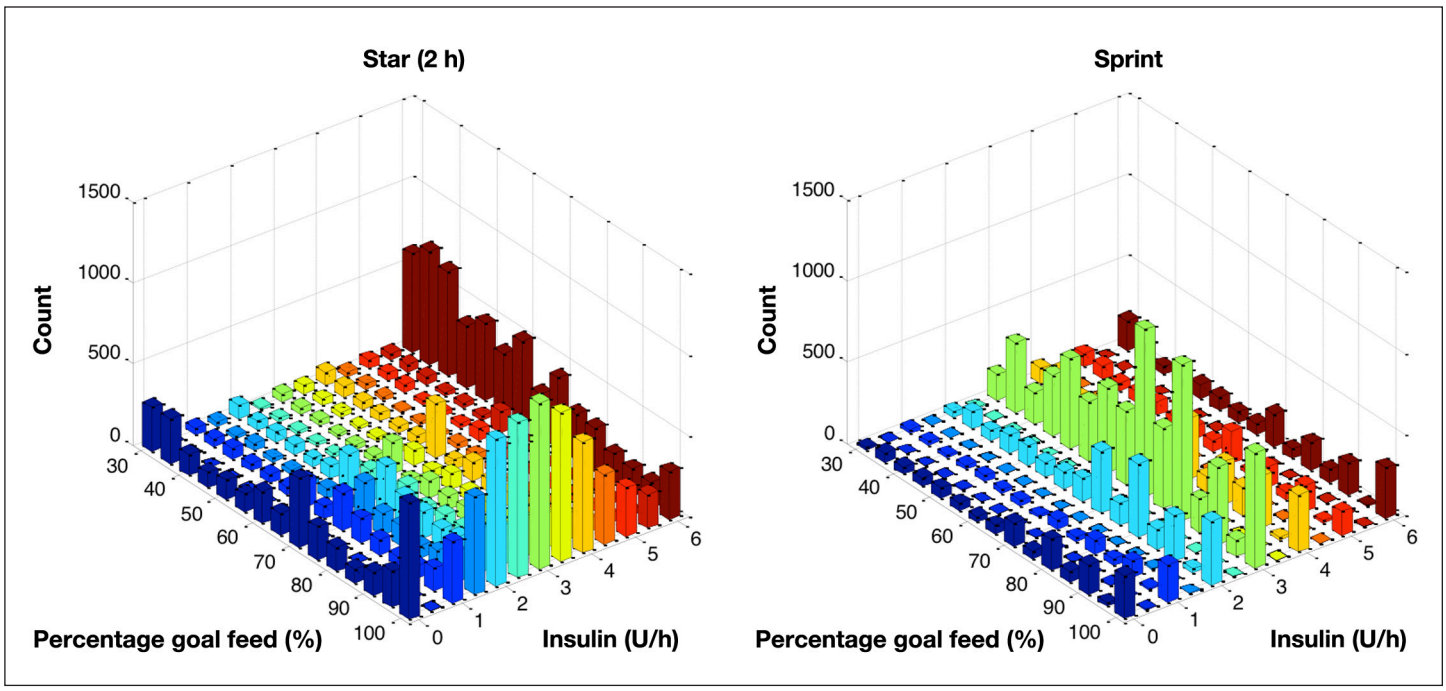

Figure 4. Distribution of insulin and nutrition interventions for STAR every 2 h (left) and SPRINT (right), where SPRINT does not offer 0.5 U/h interventions (e.g., 1.5, 2.5 ... 5.5 U/h), which are shown as having zero counts of occurrence.

tends to modulate insulin more dynamically around a narrower range of nutrition rates, where, in contrast, SPRINT tends to provide relatively constant insulin rates of 2–3 U/h and modulates nutrition rates more dynamically over the possible range. Thus, it is clear that STAR and SPRINT have very different approaches to TGC with respect to these two interventions, from which STAR achieves similar or improved performance, safety, and clinical burden outcomes as shown in **Tables 6–8**.

Pilot Clinical Trial Results

Figure 5 shows glycemic (top panel) and intervention (bottom panel) results for each of the three patients in the clinical pilot trial (patients A, B, and C), comprising 479 h of TGC. Overall median (IQR) BG is 104 (90–122) mg/dl. The percentage of clinical measurements in relevant bands are BG <72 mg/dl: 5.4%; BG in 72–117 mg/dl: 64%; and BG in 72–144 mg/dl: 88%. These results are comparable to or better than those in **Table 6**. The lowest BG was 52 mg/dl.

Discussion

STAR is a unique, model-based TGC protocol that uses clinically validated metabolic and stochastic models to optimize treatment recommendations in the context of possible future patient variation. It enables probabilistic forecasting to achieve adaptable and more optimized patient care. This forecasting capability in a computerized protocol enables increased protocol flexibility, increased safety, and reduced clinical effort by design.

In particular, the stochastic approach enables a unique targeting method. All interventions are designed based on maximizing the likelihood of BG in a clinically specified and desired range while guaranteeing a maximum (safety) cohort-wide risk of light hypoglycemia. The stochastic output range is thus overlaid with a clinically specified desired control range (72–117 mg/dl in this case) to maximize the likelihood of being in that range while also ensuring safety. Hence its control directly incorporates patient variability into control and selects treatments that are justified by their predicted effect on the full range of possible BG outcomes.

Use of stochastic forecasting and model-based control intrinsically avoids the risk of insulin saturation due to high insulin doses with minimum effect, thus minimizing excessive insulin dosing.[39,40] In particular, as insulin dose increases, the stochastic bounds become wider making it difficult to achieve the desired targets

Table 8.
Summary of Clinical Effort as Measurements per Day

	STAR 1 h intervals	STAR 2 h intervals	STAR 3 h intervals	SPRINT
Average measures/day	24	13	10.5	15

shown in **Table 3**. Equally, additional insulin infusion recommendations enable consistently high insulin resistance to be managed while avoiding overresponse. Hence, this approach can provide more flexible, patient-specific care as compared with SPRINT; part of the results are seen in **Figures 4** and **5**.

A further impact of stochastic forecasting is evident in the results shown in **Table 6** for insulin rates. In particular, while the BG levels achieved are similar, the median (IQR) insulin rates are slightly lower for STAR than for SPRINT despite similar or higher nutrition rates. In this case, the use of computer models and stochastic bounds allows STAR to be very aggressive with insulin when it is safe to do so. Hence, the stochastic forecasting available to STAR allows outlying (outside of the IQR or the outer 50%), aggressive insulin doses that SPRINT cannot use safely. This point of difference is evident also in **Figure 4**, where STAR clearly modulates insulin far more aggressively and frequently than SPRINT for both high (≥4 U/h) and low (≤1 U/h) doses that are rarely used in SPRINT. Therefore, similar BG outcomes are obtained for what appear to be, in terms of median and IQR, slightly lower insulin doses.

The STAR framework and approach presented allows (relatively) free choice of measurement interval to reduce real and perceived clinical burden through longer intervals between interventions.[41,42] While longer intervals used different targeting in **Table 3**, the overall glycemic performance was still comparable to or better than SPRINT. Equally, all degradation of control was toward moderate hyperglycemia (BG >126 mg/dl) by design and the use of stochastic maximum likelihood targeting. This approach reflects the greater opportunity for variation over a longer interval and thus maximizes safety while also keeping the glycemic outcome distribution centered on the desired range to maximize the likelihood of being in that range.

More specifically, the virtual patient simulations show that STAR is effective at reducing a primary source of

clinical effort and negative feedback about TGC, which has been a major drawback in earlier studies.[19] Staff perception of workload is influenced by the number of measurements per day, actual time spent at the bedside performing measurements and administering treatment, and accuracy of control obtained.[41] In particular, if a protocol is able to regulate glycemic levels effectively and achieve clinical outcomes, impressions of clinical staff are more positive, and perceived effort is (at least slightly) reduced. Although STAR is able to reduce the number of measurements per day, it is implemented through a computer, which requires time for data entry as well as calculation run-time. As a paper-based protocol, SPRINT is faster in this respect and may be

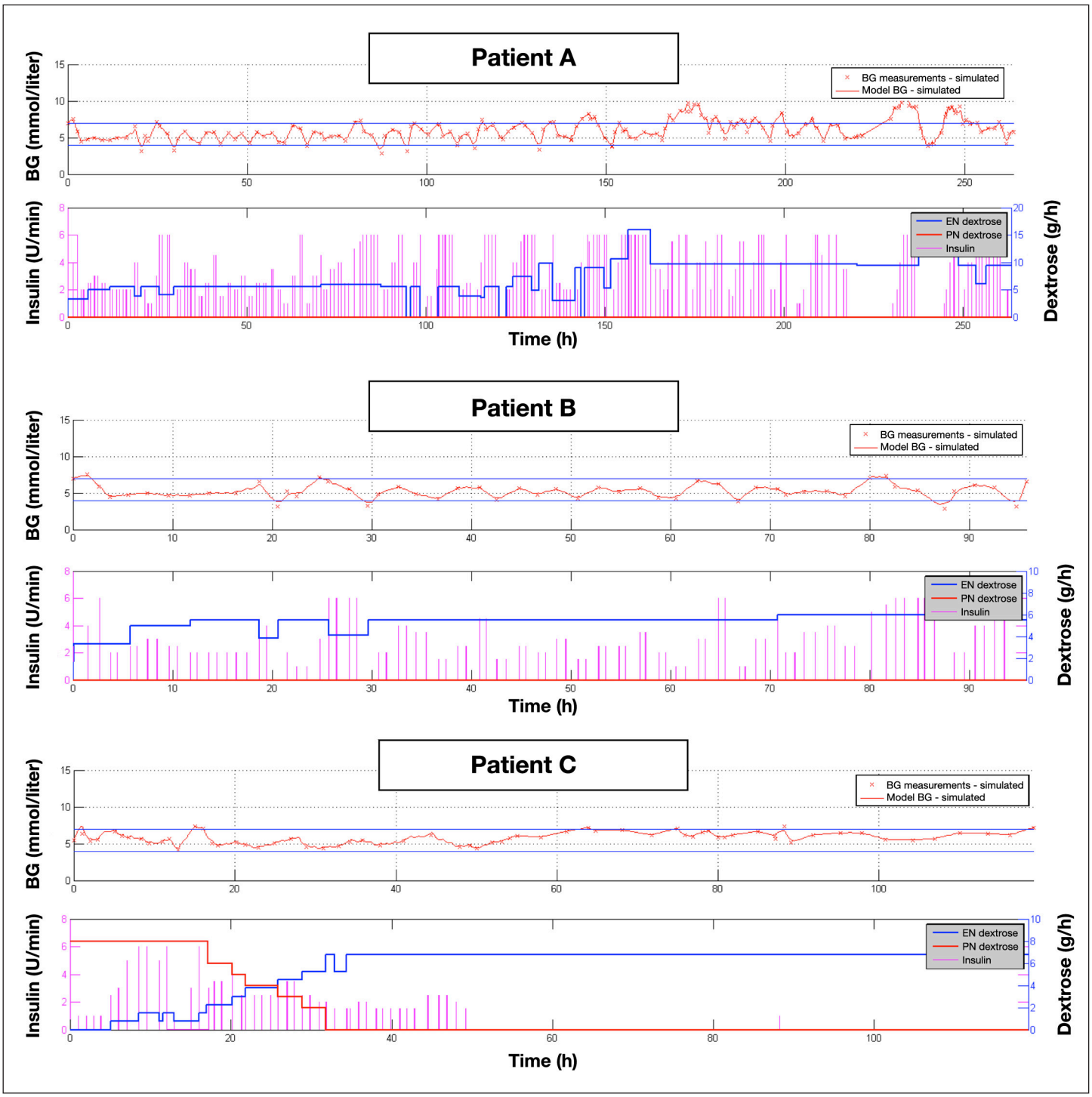

Figure 5. Patients A **(top)**, B **(middle)**, and C **(bottom)** showing BG (upper panel of each pair), and the insulin and nutrition interventions (lower panel of each pair) results on similar axes. The straight lines on the BG results are at 72 and 125 mg/dl. Vertical lines show insulin boluses (left axis, lower panels) and nutrition is on the right axis in (g/h) of those lower panels. EN, enteral; PN, parenteral.

more transparent in its operation to users,[41] which also affects perceived effort and compliance. Simulation results indicate that the accuracy of control for STAR is comparable to or exceeds clinical SPRINT results, so perceptions of effort will likely hinge on the outcome of clinical implementation.

Overall results highlight the trade-off between tight control and measurement rate (clinical effort). The clinical distribution functions (CDFs) of **Figure 3** show that the best control is achieved by the 1 hversion of STAR, as expected, but at a consequence of 24 measurements per day. When the maximum interval is set at every 2 or 3 h with lesser measurements and clinical effort, STAR outperforms SPRINT with respect to hypoglycemia (safety) with comparably tight control (performance). However, there is still some dependence, although weaker, between measurement interval, and safety and performance.

In contrast, there is little degradation in performance between the every 2 h and 3 h versions of STAR, which provide significant reductions in clinical effort. For a 17% (relative) reduction in measurements per day between the 2- and 3-h versions of STAR, there is a penalty of 9.5% (relative) reduction in measurements in the tightest (72–117 mg/dl) target band, which is not likely to be clinically significant as those measurements have only moved to very slightly higher BG, as seen in **Table 6** and **Figure 3**. Hence, STAR represents a potentially more optimal trade-off of clinical effort and performance.

Virtual trials are only a guideline. However, this *in silico* method has been extensively tested and validated for specific patients and in predicting both the median and variability of clinical trial outcomes. It is the only such model validated to this extent to date.[30] Hence, it is expected that initial clinical results, such as those shown here, will be consistent with the virtual trial, in line with earlier studies using this virtual trials method and approach.[30,31]

The STAR glycemic control approach presented is fully generalizable. The clinical targets and ranges can be set directly by clinical staff, as can the desired risk of hypo- or hyperglycemia (maximum 5% for BG <72 mg/dl here). Hence, this approach is entirely flexible. The ranges and risk values used here represent those chosen at Christchurch Hospital.

In contrast, while the glycemic ranges used here broadly match those in the design of SPRINT, SPRINT was fixed in its implementation, did not allow flexibility, and could not be adjusted directly by clinical staff for different patients or groups, as has been done for STAR in pilot trials in Belgium and Hungary that use only an insulin intervention with fixed nutrition rates and different glycemic target ranges.[43]

One possible limitation of this overall STAR framework and approach is the stochastic model. Its forecasting is at the center of all major advantages enabled by this approach. It is also a cohort-based model, which means that it will be too conservative for some patients but potentially not conservative enough for others.[34] Equally, there is no assurance that all ICU cohorts will have similar metabolic variability. However, these models can be readily created from existing clinical data for any reasonably similar metabolic system model.[27,28,34] Equally, and perhaps more importantly, there was a study that found similar metabolic variability between New Zealand and Belgian ICU cohorts,[23] although this specific result needs to be further generalized going forward.

Finally, the initial clinical results are positive. They do clearly show that the STAR controller implemented clinically for ~450 h has similar or better performance than the virtual trials. Equally, Patients A and B clearly showed different levels of metabolic variability, which was managed equally well with respect to glycemic performance and safety in both cases. Patient C showed a unique case worth noting, in which the controller recognized the relatively high insulin sensitivity of the patient after about half the patient's stay and was able to recommend that no insulin be given. This recommendation was correct given the resulting good glycemic control within the desired target band for over 50 subsequent hours. The correct recommendation of no insulin is one that many protocols find difficult to make as their design is implicitly based upon and biased toward active intervention. Hence, the STAR controller was able to avoid over-controlling the patient with insulin where necessary.

Conclusions

Clinically validated *in silico* virtual trials of the STAR TGC approach show that this approach can provide quality control performance while significantly reducing hypoglcycemia and clinical workload. The stochastic forecasting used is unique in this field and enables a maximum likelihood approach to targeting a desired glycemic range while also enabling the clinical risk of hypo- or hyperglycemia to be managed directly. It also

enables patients with very different metabolic (intra- and interpatient) variability to be managed directly and controlled within a single (STAR) framework. More specifically, the STAR approach presented is fully generalizable, and clinical targets and ranges can be set directly by clinical staff, with those used here representing those chosen at Christchurch Hospital. Initial clinical trials as part of a larger pilot trial matched or exceed these virtual results.

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References:

1. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355(9206):773–8.
2. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA. 2003;290(15):2041–7.
3. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78(12):1471–8.
4. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin. 2001;17(1):107–24.
5. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. Best Pract Res Clin Endocrinol Metab. 2001;15(4):533–51.
6. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87(3):978–82.
7. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359–67.
8. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006;105(2):244–52.
9. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med. 2008;36(11):3008–13.
10. Chase JG, Shaw G, Le Compte A, Lonergan T, Willacy M, Wong XW, Lin J, Lotz T, Lee D, Hann C. Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. Crit Care. 2008;12(2):R49.
11. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79(8):992–1000.
12. Chase JG, Pretty CG, Pfeifer L, Shaw GM, Preiser JC, Le Compte AJ, Lin J, Hewett D, Moorhead KT, Desaive T. Organ failure and tight glycemic control in the SPRINT study. Crit Care. 2010;14(4):R154.
13. Krinsley JS, Jones RL. Cost analysis of intensive glycemic control in critically ill adult patients. Chest. 2006;129(3):644–50.
14. Van den Berghe G, Wouters PJ, Kesteloot K, Hilleman DE. Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. Crit Care Med. 2006;34(3):612–6.
15. Preiser JC, Brunkhorst F. Tight glucose control and hypoglycemia. Crit Care Med. 2008;36(4):1391; author reply 1391–2.
16. Finfer S, Delaney A. Tight glycemic control in critically ill adults. JAMA. 2008;300(8):963–5.
17. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(2):125–39.
18. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180(8):821–7.
19. Mackenzie I, Ingle S, Zaidi S, Buczaski S. Tight glycaemic control: a survey of intensive care practice in large English hospitals. Intensive Care Med. 2005;31(8):1136.
20. Schultz MJ, Spronk PE, Moeniralam HS. Tight glycaemic control: a survey of intensive care practice in the Netherlands. Intensive Care Med. 2006;32(4):618–9.
21. Gale SC, Gracias VH. Glycemic control needs a standard reference point. Crit Care Med. 2006;34(6):1856–7.
22. Chase JG, Le Compte AJ, Suhaimi F, Shaw GM, Lynn A, Lin J, Pretty CG, Razak N, Parente JD, Hann CE, Preiser JC, Desaive T. Tight glycemic control in critical care--the leading role of insulin sensitivity and patient variability: a review and model-based analysis. Comput Methods Programs Biomed. 2011;102(2):156–71.
23. Suhaimi F, Le Compte A, Preiser JC, Shaw GM, Massion P, Radermecker R, Pretty C, Lin J, Desaive T, Chase JG. What makes tight glycemic control (TGC) tight? The impact of variability and nutrition in two clinical studies. J Diabetes Sci Technol. 2010;4(2):284–98.
24. Lonergan T, LeCompte A, Willacy M, Chase JG, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE. A simple insulin-nutrition protocol for tight glycemic control in critical illness: development and protocol comparison. Diabetes Technol Ther. 2006;8(2):191–206.
25. Lonergan T, Compte AL, Willacy M, Chase JG, Shaw GM, Hann CE, Lotz T, Lin J, Wong XW. A pilot study of the SPRINT protocol for tight glycemic control in critically Ill patients. Diabetes Technol Ther. 2006;8(4):449–62.
26. Chase J, Le Compte A, Preiser JC, Shaw G, Penning S, Desaive T. Physiological modelling, tight glycemic control, and the ICU clinician: what are models and how can they affect practice? Ann Intensive Care. 2011;1(1):11.

27. Lin J, Lee DS, Chase JG, Hann CE, Lotz T, Wong XW. Stochastic modelling of insulin sensitivity variability in critical care. Biomed Signal Process Control. 2006;1(3):229–42.

28. Lin J, Lee D, Chase JG, Shaw GM, Le Compte A, Lotz T, Wong J, Lonergan T, Hann CE. Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care. Comput Methods Programs. Biomed. 2008;89(2):141–52.

29. Bagshaw SM, Webb SA, Delaney A, George C, Pilcher D, Hart GK, Bellomo R. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. Crit Care. 2009;13(2):R45.

30. Chase JG, Suhaimi F, Penning S, Preiser JC, Le Compte AJ, Lin J, Pretty CG, Shaw GM, Moorhead KT, Desaive T. Validation of a model-based virtual trials method for tight glycemic control in intensive care. Biomed Eng Online. 2010;9:84.

31. Chase JG, Shaw GM, Lotz T, LeCompte A, Wong J, Lin J, Lonergan T, Willacy M, Hann CE. Model-based insulin and nutrition administration for tight glycaemic control in critical care. Curr Drug Deliv. 2007;4(4):283–96.

32. Hann CE, Chase JG, Lin J, Lotz T, Doran CV, Shaw GM. Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model. Comput Methods Programs Biomed. 2005;77(3):259–70.

33. Le Compte A, Chase JG, Lynn A, Hann C, Shaw G, Wong XW, Lin J. Blood glucose controller for neonatal intensive care: virtual trials development and first clinical trials. J Diabetes Sci Technol. 2009;3(5):1066–81.

34. Le Compte AJ, Lee DS, Chase JG, Lin J, Lynn A, Shaw GM. Blood glucose prediction using stochastic modeling in neonatal intensive care. IEEE Trans Biomed Eng. 2010;57(3):509–18.

35. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest. 2003;124(1):297–305.

36. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J; DGEM (German Society for Nutritional Medicine), Ebner C, Hartl W, Heymann C, Spies C; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr. 2006;25(2):210–23.

37. Ward L, Steel J, Le Compte A, Evans A, Tan CS, Penning S, Shaw GM, Desaive T, Chase JG. Interface design and human factors considerations for model-based tight glycemic control in critical care. J Diabetes Sci Technol. 2012;6(1):125–34.

38. Ward L, Steel J, Le Compte A, Evans A, Tan CS, Penning S, Shaw GM, Desaive T, Chase JG. Data entry errors and design for model-based tight glycemic control in critical care. J Diabetes Sci Technol. 2012;6(1):135–43.

39. Prigeon RL, Roder ME, Porte D Jr, Kahn SE. The effect of insulin dose on the measurement of insulin sensitivity by the minimal model technique. Evidence for saturable insulin transport in humans. J Clin Invest. 1996;97(2):501–7.

40. Natali A, Gastaldelli A, Camastra S, Sironi AM, Toschi E, Masoni A, Ferrannini E, Mari A. Dose-response characteristics of insulin action on glucose metabolism: a non-steady-state approach. Am J Physiol Endocrinol Metab. 2000;278(5):E794–801.

41. 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(3):409–16.

42. Aragon D. Evaluation of nursing work effort and perceptions about blood glucose testing in tight glycemic control. Am J Crit Care. 2006;15(4):370–7.

43. Penning S, Le Compte AJ, Moorhead KT, Desaive T, Massion P, Preiser JC, Shaw GM, Chase JG. First pilot trial of the STAR-liege protocol for tight glycemic control in critically ill patients. Comput Methods Programs Biomed. Forthcoming.