First Pilot Trial of the STAR-Liege Protocol for Tight Glycemic Control in Critically Ill Patients

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ABSTRACT: Tight glycemic control (TGC) has shown benefits in ICU patients, but been difficult to achieve consistently due to inter- and intra- patient variability that requires more adaptive, patient-specific solutions. STAR (Stochastic TARgeted) is a flexible model-based TGC framework accounting for patient variability with a stochastically derived maximum 5% risk of blood glucose (BG) below 72mg/dL. This research describes the first clinical pilot trial of the STAR approach and the post-trial analysis of the models and methods that underpin the protocol.

The STAR framework works with clinically specified targets and intervention guidelines. The clinically specified glycemic target was 125mg/dL. Each trial was 24 hours with BG measured 1-2 hourly. Two-hourly measurement was used when BG was between 110-135mg/dL for 3 hours. In the STAR approach, each intervention leads to a predicted BG level and outcome range (5-95th percentile) based on a stochastic model of metabolic patient variability. Carbohydrate intake (all sources) was monitored, but not changed from clinical settings except to prevent BG < 100mg/dL when no insulin was given. Insulin infusion rates were limited (6U/hour maximum), with limited increases based on current infusion rate (0.5-2.0U/hour), making this use of the STAR framework an insulin-only TGC approach. Approval was granted by the Ethics Committee of the Medical Faculty of the University of Liege (Liege, Belgium).

Nine patient trials were undertaken after obtaining informed consent. There were 205 measurements over all 9 trials. Median [IQR] per-patient results were: BG: 138.5 [130.6 - 146.0] mg/dL; Carbohydrate Administered: 2-11 g/hour; Median Insulin: 1.3 [0.9 – 2.4] U/hour with a maximum of 6.0 [4.7 – 6.0] U/hour. Median [IQR] time in the desired 110-140 mg/dL band was: 50.0 [31.2 - 54.2]%. Median model prediction errors ranged: 10-18%, with larger errors due to small meals and other clinical events. The minimum BG was 63mg/dL and no other measurement was below 72 mg/dL, so only 1 measurement (0.5%) was below the 5% guaranteed minimum risk level.

Post-trial analysis showed that patients were more variable than predicted by the stochastic model used for control, resulting in some of the prediction errors seen. Analysis and (validated) virtual trial re-simulating the clinical trial using stochastic models relevant to the patient's particular day of ICU stay were seen to be more accurate in capturing the observed variability. This analysis indicated that equivalent control and safety could be obtained with similar or lower glycemic variability in control using more specific stochastic models.

STAR effectively controlled all patients to target. Observed patient variability in response to insulin and thus prediction errors were higher than expected, likely due to the recent insult of cardiac surgery or a major cardiac event, and their immediate recovery. STAR effectively managed this variability with no hypoglycemia. Improved stochastic models will be used to prospectively test these outcomes in further ongoing clinical pilot trials in this and other units.

1. INTRODUCTION

Critically ill patients often present stress-induced hyperglycemia due to significant stress-induced insulin resistance. Hyperglycemia worsens outcomes and increases mortality [1-4]. Effective glycemic control should reduce blood glucose (BG) levels, reduce variability and account for inter- and intra-patient variability and evolving physiological patient condition [5-7]. Some studies have shown that tight glycemic control (TGC) can reduce mortality up to 45% and significantly reduce negative outcomes linked to hyperglycemia [8-10]. However, achieving these outcomes has been difficult to reproduce [11-13] in the variable and dynamic critical care patient.

Hypoglycemia is a major risk associated with TGC [3, 14, 15]. Limiting hypoglycemia and ensuring safety is critical for any TGC protocol. However, its occurrence is exacerbated by patient variability and only one study reduced hypoglycemia with TGC [10]. BG measurement frequency also varies significantly across reported studies, from 1 to 4 hours, where longer intervals can lead to greater glycemic variability and hypoglycemia [16, 17]. Model-based controllers using computer models of patient physiology can enable a TGC protocol to capture the patient-specific response to insulin and nutrition inputs and account for patient-specific dynamics to optimize interventions and BG levels [7, 17-20].

The STAR (Stochastic TARgeted) model-based controller presented in this paper is a framework that enables adaptive, patient-specific TGC. The STAR protocol directly accounts for evolving physiological patient condition and intra-patient variability by identifying insulin sensitivity (SI) changes at each intervention and using a stochastic model of its future potential variability [6, 7] to optimize control and maximize safety. Because STAR is a model-based approach it can be customized for clinically specified glycemic targets, control approaches (e.g. insulin only, insulin and nutrition, *etc*.) and clinical resources (measurement frequency). This paper presents a STAR protocol modulating insulin infusions only towards a target glycemia of 125 mg/dL per clinical practice in the trial ICU, and the initial pilot trial results of the protocol.

This pilot trial also tested the ability to adapt the model-based STAR TGC framework from its development environment at Christchurch Hospital in New Zealand to a completely separate institute in Liege, Belgium. Specifically, the following areas of control design and performance were explored:

- Control of BG in post-surgical patients by modulating insulin infusions only. This is a departure from previous use of this model in a heterogeneous ICU cohort, using primarily the bolus route to introduce exogenous insulin, while also explicitly modulating nutritional inputs for glycemic control.
- Real-time model prediction performance in clinical trial in an ICU with different clinical practices and patient populations from Christchurch, NZ.
- Suitability of the applied stochastic model to this Belgian group of patients. In particular, were the stochastic models generated from a heterogeneous ICU population over all patient days applicable, or were more specialized stochastic models required?

2. METHOD

2.1. STAR-Liege Protocol

The STAR-Liege protocol presented is customized in glycemic target (125 mg/dL) and control interventions (insulin-only via infusions) to match clinical standards at CHU of Liege (Belgium). If necessary, it raises nutrition rates to avoid hypoglycemia when no exogenous insulin is being given. The time interval between BG measurements is also determined by the protocol, with intervals of 1 and 2 hours for this pilot study. The step-by-step description of this protocol is illustrated in Figure 1 and the insulin rate is calculated as follows:

1. Previous and current blood glucose measurements are used to identify a patient-specific current SI parameter value for the prior time interval [21]. This step accounts for inter-patient variability [17, 22, 23].
2. For a given patient, insulin sensitivity is quite variable over time (even hour to hour variation of SI parameter value can be important). The stochastic model [6, 7] provides a distribution of possible SI parameter values for the next 1-2 hours and accounts for intra-patient variability. This New Zealand patient-based stochastic model was assumed to be broadly applicable to Belgian patients as hour-to-hour insulin sensitivity variability in retrospective comparison is similar [5].
3. The target BG value for the next 1-2 hour interval is defined from the current BG levels (BG_{now}) by:

$$BG_{target,\mathrm{t+1h/+2h}} = \max(0.85 * BG_{now}, 125)$$

where reductions of 15% per interval are targeted until the target of 125 mg/dL is achieved.

4. The insulin rate required to achieve this BG target is computed with a bisection method using a clinically validated insulin-glucose system model [23-25] and the median (50^{th} percentile) expected SI value over the next 1-2 hours, obtained from the stochastic model distribution [6, 7]. Note that the median value is the same as the current SI (no change) at all levels [6, 7].

5. Once an insulin intervention is found, the BG outcome predictions are calculated for the 5th, 25th, 75th and 95th percentile SI values from the stochastic model in Step 2 over the next 1-2 hours. These results show the possible BG spread due to intra-patient variability typically observed in critical care patients.
6. The predicted outcome BG range in Step 5 is checked to ensure the lowest possible BG (5th percentile) is not < 72 mg/dL, ensuring a guaranteed maximum risk of 5% for BG < 72 mg/dL, for safety from moderate (< 60 mg/dL) or severe (< 40 mg/dL) hypoglycemia.
7. If the lowest BG is < 72 mg/dL, the insulin rate is reduced to ensure the maximum risk of BG < 72 mg/dL remains 5%, which effectively raises the target BG level defined in Step 3, so that the 5th percentile outcome is equal to 72 mg/dL. If this step is necessary it effectively raises the BG target in recognition that the original target cannot be safely attained due to the insulin resistance of the patient requiring large insulin doses making the stochastic (5th – 95th percentile) band too wide.

These steps define the STAR-Liege protocol used in this research and are illustrated in Figure 1. The overall, basic model-based STAR framework was adapted to local clinical conditions in glycemic targets (Step 3), interventions (Step 4) and/or limits (Step 6).

A maximum insulin rate of 6 U/h is prescribed for safety and to avoid insulin saturation effects [26, 27]. Similarly, the insulin rate rise per intervention is limited to +1U/h if the previous insulin rate is < 1U/h and to +2U/h otherwise to avoid over responding to sudden changes or larger sensor errors. To reduce nursing staff workload associated with making small and frequent changes in insulin rates and thus improve clinical implementation, insulin rates were limited to specific values of (0.0, 0.5, 1.0, 1.3, 1.5, 1.8, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0) U/hour.

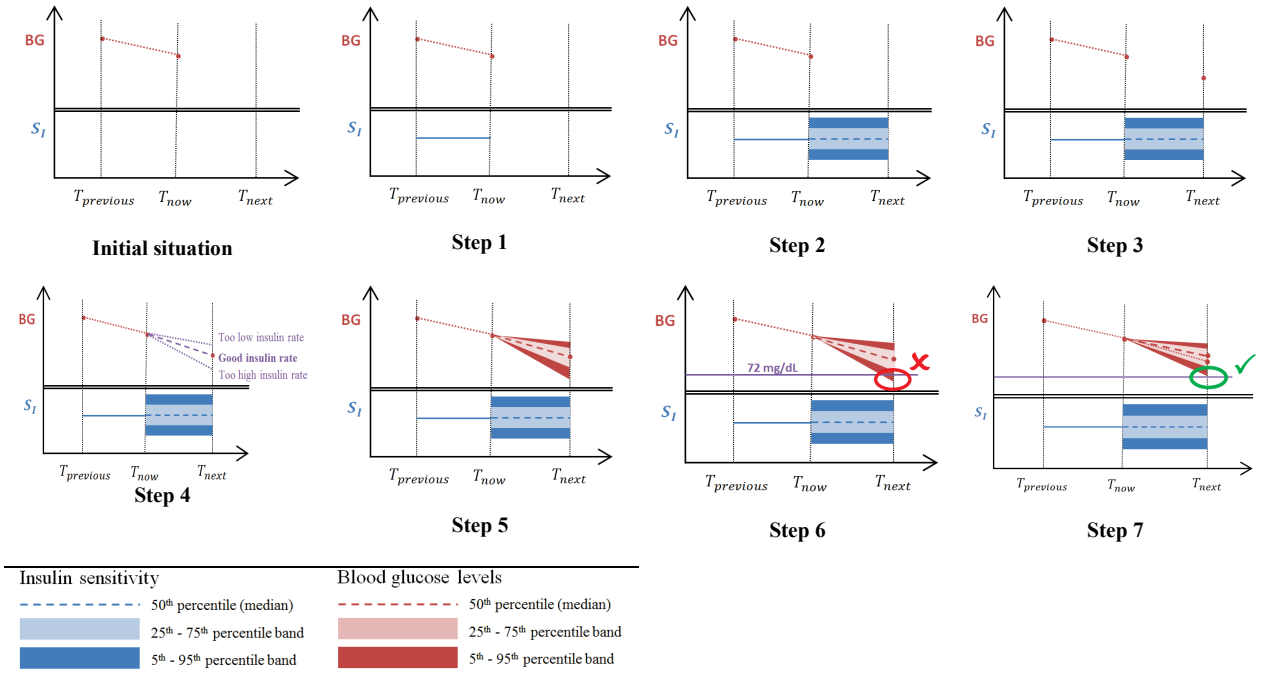

Figure 1 – STAR-Liege protocol. Initial situation: BG measurement. Step 1: SI parameter value calculation and patient-specific model adaptation to inter-patient variability (Integral Fitting Method [21]). Step 2: Distribution of possible SI parameter values (Stochastic Model [6, 7]). Step 3: Definition of the target BG value for the next 1-2 hours. Step 4: Insulin rate calculation to meet the target with same SI (Bisection Method). Step 5: Stochastic model analysis of intra-patient variability and range of glycemic outcomes. Step 6: Hypoglycemia prevention for 5th percentile outcome, $BG_{5\%} \geq 72$ mg/dL. Step 7: Insulin rate adjustment (if necessary) to ensure $BG_{5\%} \geq 72$ mg/dL.

A desired 6.25 g/hour default enteral nutrition rate is requested, based on [28], but nutrition administration is left to the attending clinician. There is typically no parenteral nutrition, unless clinically specified otherwise. To prevent unintended hypoglycemia, enteral and parenteral nutrition rates can be increased by 10% when BG ≤ 108 mg/dL and no insulin has been given or recommended. In this case, the nutrition rates are increased only until the next blood glucose measurement, but can be maintained if required.

The protocol specifies hourly BG measurement, but measurement frequency is decreased by going to a 120-minute interval when the patient is glycemically stable. Stability is defined here as occurring when the current and last three BG measurements are between 90 mg/dl and 139.5 mg/dl. These relatively short 1-2 hour intervals are used to avoid drift during longer intervals [16]. They also match those used in all or part of other protocols (e.g. [10, 11, 19]), as well as ensuring safety in this proof-of-concept pilot trial.

2.2. Pilot Trial and Patients

The STAR-Liege protocol was tested in July 2010 at the Centre Hospitalier Universitaire (CHU) in Liège, Belgium. The pilot trial was 24 hours long and included 9 primarily cardiovascular or cardiac surgery (7) patients from the hospital's intensive care units, 3 patients (Patients 2, 3 and 6) were in the first 24 hours post-surgery. Patients were recruited when they had initial blood glucose levels > 145 mg/dL. Table 1 shows the patient details. Ethical consent was granted by the Comité d'éthique hospitalo-facultaire de l'Universitaire de Liège (B70720108843) for the performance of this trial and the audit, analysis and publication of these data.

For each patient, the trial started with a BG measurement made by nursing staff. BG measurements were made using Accu-Chek Inform (Roche Diagnostics, Mannheim, Germany) glucometers. The protocol then calculated a new insulin infusion rate, which was then given by the nurse. The time interval until the next BG measurement is also specified. This clinical procedure is shown in Figure 2.

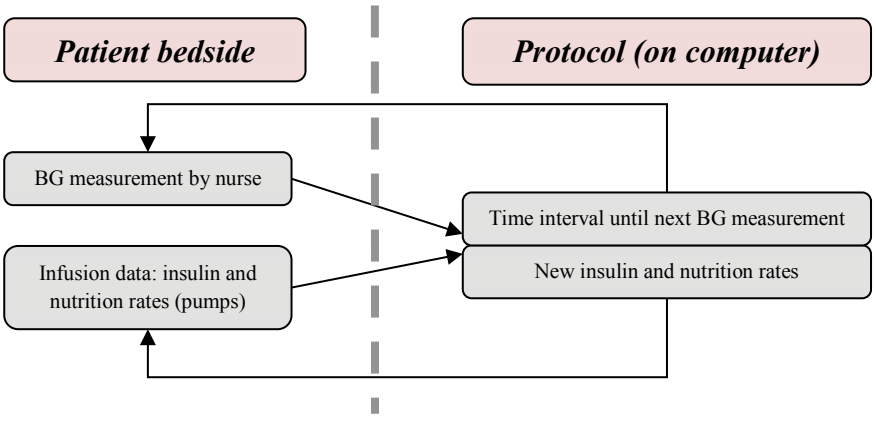

Figure 2 - Pilot trial clinical implementation. The dashed line shows the boundary between the computerised protocol elements (right) and the measurements or clinical actions (left).

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
General information	**Date of birth**	30/01/1931	8/03/1932	12/06/1941	13/04/1931	11/07/1928	19/12/1938	13/05/1949	14/03/1936	7/12/1965
	Sex	M	F	M	M	F	F	M	M	M
	Diagnosis	Hypercapnia, Coma	Aortic valve re-placement	Triple coronary artery bypass surgery	Cerebral aneurysm	Gastro-Intestinal surgery	Post-RVA	Myocardial infrac-tion + Cardiac arrest + ECMO	Mitral valve re-placement	Post-RVA
	Diabetic	No	No	Yes (type II) Non insulin-dependent	No	Yes (type II) Insulin-dependent	Yes (type II) Non insulin-dependent	Yes (type II) Non insulin-dependent	No	No
	Post-surgical days in ICU	5	1	1	4	14	0	16	3	7
Control details	**Initial BG (mg/dL)**	199	159	147	166	150	152	168	184	160
	Did nurses override recommended insulin rate?	Yes, 2 times	Yes, 2 times	Yes, 1 time	No	No	No	No	Yes, 4 times	No
	Meals	/	/	Pudding : 1 spoon-ful	/	/	Pudding	/	/	/
	Additional drugs?	4 mg of MethylPrednisone	/	/	/	/	/	/	Antibiotic	/
	Vomiting?	No	No	No	No	Yes, after 1530 minutes (trial stopped for 4 hours)	No	No	Yes, after 810 minutes (trial stopped for 1 hour)	No
	Notes	Hypoxic episode during trial	/	/	/	/	/	/	/	/

Table 1 - Clinical details for recruited patients, where RVA = Right Ventricular Aneurysm

2.3. Stochastic Models

The goal of a stochastic model is to describe the hourly variations of the insulin sensitivity. A stochastic model is based on clinically observed insulin sensitivity variations in ICU population data (for more information, refer to appendix). These clinical data can come from a specific type of patients and can be selected in function of the patient days of stay.

The stochastic model initially used in the trial was that of Lin *et al.* [6, 7] based on all types of patients included in the SPRINT[1] glucose control study and all patient days of stay. However, post-operative cardiac surgery patients in the first few post-operative days have recently been found, based on the results of this pilot study, to potentially be as much as two times more variable in their insulin sensitivity than this broader cohort [unpublished]. Hence, new stochastic models using data from cardiac-surgery patients were generated to better account for this variability and for post-trial assessment of its impact on the clinical results.

Eight new stochastic models are defined, as shown in Table 2. Each new stochastic model is based on different clinical data sets characterized by three features:

1. the study group: clinical data can come from patients included in the SPRINT study or in the Glucontrol study [2] (or both);
2. the type of patients: clinical data can come from all patients included in the previous selected study(ies), or from a specific type of patients (cardiac-surgery or not cardiac surgery patients);
3. the days of stay: clinical data can come from all days or specific day(s) of patient's ICU stay.

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[1] SPRINT refers to specialized relative insulin nutrition tables. It's a model-based clinical protocol for glycemic control that modulates both insulin and nutrition inputs. 29. Chase, J.G., G. Shaw, A. Le Compte, T. Lonergan, M. Willacy, X.W. Wong, J. Lin, T. Lotz, D. Lee, and C. Hann, *Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change.* Crit Care, 2008. **12**(2): p. R49.

[2] Glucontrol refers to a prospective randomized controlled trial that compares the effects on ICU mortality of intensive insulin therapy (IIT) with an intermediate glucose control. 11. Preiser, J.C., P. Devos, S. Ruiz-Santana, C. Melot, D. Annane, J. Groeneveld, G. Iapichino, X. Leverve, G. Nitenberg, P. Singer, J. Wernerman, M. Joannidis, A. Stecher, and R. Chiolero, *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**(10): p. 1738-48.

Models 1 to 6 use data from specific days and cohorts to better match the enhanced variability observed clinically in these specific pilot trial cardiac-surgery patients. Models 7 and 8 are based on a parameter modification in the generation of the original stochastic model [30]. More precisely, the variance of each data point of the hourly changes in S_I distribution (each couple $(S_{I,n} = x_i, S_{I,n+1} = y_i)$) is modified compared with the original model. Patient data from the SPRINT and Glucontrol databases were used to create these new models. SPRINT patients were treated at Christchurch hospital in New Zealand between August 2005 and April 2007 [29] and Glucontrol was a multi-center study with data from 21 participating ICUs in 7 countries across Europe during the period November 2004 – May 2006 [11]. However, only Glucontrol data from the CHU of Liege site was used here.

Stochastic model	Study group	Type of patients	Patient days of stay	N
Original (used in pilot trials [6, 7])	SPRINT	All patients	All days of stay	/
Model 1	SPRINT	Cardiac surgery patients	Day 1	1361
Model 2	SPRINT	Cardiac surgery patients	Day 2	701
Model 3	SPRINT	Non- cardiac surgery patients	Day 1	6442
Model 4	Glucontrol	All patients	Day 1	991
Model 5 (Models 1 + 4)	SPRINT Glucontrol	Cardiac surgery patients All patients	Day 1	2352
Model 6 (Models 1 + 2)	SPRINT	Cardiac surgery patients	Days 1 and 2	2062
Model 7 (original model with 1.5x variance modifier)	SPRINT	All patients	All days of stay	/
Model 8 (original model with 1.5x variance modifier)	SPRINT	All patients	All days of stay	/

Table 2 - New stochastic model definitions for assessing variability and results observed in pilot clinical trial (N refers to the number of hours used to create the stochastic model)

These models are assessed using the clinical data from this trial. Forecasting performance is assessed by the number of clinical results falling in an interquartile range (denoted as IQR, 50% confidence interval band) and 90% confidence interval band (expect ~50% and ~90%). The different stochastic models are also assessed in clinically validated virtual trial re-simulations [23] of the trial to determine the potential impact on interventions given and glycemic outcomes.

3. RESULTS

3.1. Clinical Trial Results - Blood Glucose Control Performance

Clinical results are summarized by whole cohort and per-patient statistics in Table 3. There were 205 BG measurements taken during 215 hours of control. Hence, primarily 1-hour measurements were specified by the STAR-Liege protocol. This result can also be seen in the individual patient results in Table 4. Overall, these results indicate that patients were particularly resistant to glycemic stability. This outcome is likely due, in part, to the fact that they were recently out of cardiac surgery and thus more variable in their insulin sensitivity.

Whole cohort statistics		**Per-patient statistics (presented as median [IQR])**	
Number of patients:	9	Initial BG (mg/dL):	160.0 [151.5 - 172.0]
Total hours:	215 hours	Hours of control:	24.0 [23.0 - 24.3]
Number of BG measurements:	205	Number of BG measurements:	24.0 [22.0 - 24.0]
BG median [IQR] (mg/dL):	136.0 [122.5 - 158.0]	BG median (mg/dL)	138.5 [130.6 - 146.0]
% BG within 80-110 mg/dL	8.8	Median %BG within 80-110 mg/dL [IQR]:	8.3 [4.2 – 9.9]
% BG within 110-140 mg/dL	45.4	Median %BG within 110-140 mg/dL [IQR]:	50.0 [31.2 - 54.2]
% BG within 140-180 mg/dL	37.1	Median %BG within 140-180 mg/dL [IQR]:	40.9 [28.4 – 41.7]
% BG ≥ 180 mg/dL	8.3	Median %BG ≥ 180 mg/dL [IQR]:	8.3 [0.0 – 17.0]
% BG < 80 mg/dL	0.5	Time to < 125 mg/dL (hours):	4.0 [2.1 – 5.0]
% BG < 72 mg/dL	0.5	% patients to < 125 mg/dL:	100
% BG < 40 mg/dL	0.0	Time to < 140 mg/dL (hours):	2.1 [2.0 – 4.0]
Number of patients < 40 mg/dL	0	% patients to < 140 mg/dL:	100
Median insulin rate [IQR] (U/hour):	1.5 [0.5 – 3.4]	Median insulin rate [IQR] (U/hour):	1.3 [0.9 – 2.4]
		Max insulin rate [IQR] (U/hour):	6.0 [4.7 – 6.0]
Median glucose rate [IQR] (g/hour):	7.4 [2.0 – 11.2]	Median glucose rate [IQR] (g/hour):	4.2 [2.0 – 11.1]

Table 3 – Clinical results for the whole cohort (left column) and per-patient statistics (right column) for glucose control performance and interventions (insulin, glucose administration) given.

Patient	Total hours	Num. measurements	Initial BG (mg/dL):	BG median [IQR] (mg/dL):	% BG within 80-110 mg/dL	% BG within 110-140 mg/dL	% BG within 140-180 mg/dL	% BG ≥ 180 mg/dL	% BG < 80 mg/dL	% BG < 72 mg/dL	% BG < 40 mg/dL	Min BG level (mg/dL)	Median insulin rate [IQR] (U/hour):	Max insulin rate (U/hour):	Median dextrose rate [IQR] (g/hour):
1	24	22	199	134.0 [121.0 - 167.0]	9.1	50.0	18.2	18.2	4.5	4.5	0	63	1.3 [0.7 - 2.0]	6.0	11.0 [11.0 - 11.0]
2	23	19	159	115.0 [102.3 - 130.0]	31.6	52.6	15.8	0.0	0.0	0.0	0	82	0.2 [0.0 - 1.0]	3.8	2.0 [2.0 - 2.0]
3	23	22	147	128.0 [123.0 - 147.0]	4.5	63.6	31.8	0.0	0.0	0.0	0	105	0.8 [0.0 - 1.6]	4.0	2.0 [2.0 - 2.0]
4	23	24	166	145.5 [124.0 - 167.5]	12.5	29.2	41.7	16.7	0.0	0.0	0	98	2.0 [0.8 - 4.0]	6.0	10.5 [9.5 - 10.5]
5	26	24	150	138.5 [129.5 - 150.0]	0.0	54.2	41.7	4.2	0.0	0.0	0	110	1.0 [0.0 - 2.0]	5.0	3.7 [1.4 - 7.4]
6	24	24	152	149.0 [133.0 - 159.5]	4.2	29.2	58.3	8.3	0.0	0.0	0	109	1.0 [0.0 - 4.0]	5.8	2.0 [2.0 - 2.0]
7	23	24	168	140.5 [127.0 - 165.0]	4.2	45.8	41.7	8.3	0.0	0.0	0	108	3.8 [2.8 - 5.7]	6.0	11.2 [11.2 - 11.2]
8	24	22	184	147.5 [130.0 - 161.0]	9.1	31.8	40.9	18.2	0.0	0.0	0	105	1.8 [0.1 - 5.8]	6.0	4.2 [4.2 - 14.9]
9	25	24	160	131.5 [120.5 - 152.0]	8.3	54.2	37.5	0.0	0.0	0.0	0	108	3.5 [1.9 - 4.8]	6.0	17.6 [12.0 - 17.6]

Table 4 - Clinical results for each individual patient

BG median values in Tables 3 and 4 are higher than the BG target of 125 mg/dL, except for Patient 2. BG levels are relatively distributed, as evidenced by the IQR range (75^{th} – 25^{th} percentile value) of 35.5 mg/dL in Table 3 for the cohort, and the 25%-75% confidence interval across patients in Figure 3. Note that the slope of the per-patient BG cumulative distribution function (CDF) median is slightly steeper at low BG, so that BG levels are skewed toward higher values as expected with this stochastic model driven approach, as well as for short pilot trial with high initial BG values.

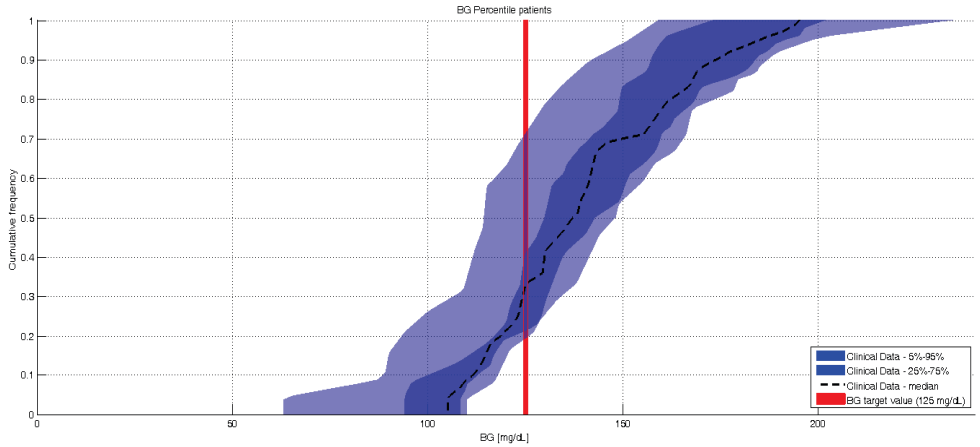

Figure 3 - Median, 25-75% and 5-95% intervals of per-patient BG CDFs defined on whole cohort, where the solid line shows the target BG = 125 mg/dL.

Table 3 shows that 45.4% of BG measurements are between 110 and 140 mg/dL and the control is tight in this band, as illustrated by the steep slope of BG CDF for the whole cohort in Figure 4 and similar per-patient CDFs in Figure 3. A total of 70% of measurements are between 110 and 160 mg/dL, which is largely due to the short length of trial where 8-17 % of total trial time was spent reducing initial BG levels to 140 mg/dL (Table 3). Thus, the pilot trial length wasn't sufficient to achieve consistently high percentages of BG levels in a tight band around the target. In addition, patient variability played a role in the further time spent with BG > 140 mg/dL.

Importantly for safety, Tables 3 and 4 show that there was no severe hypoglycemic measurement (BG < 40 mg/dL). The minimum value reached was 63 mg/dL (Patient 1). Hence, the STAR approach reduced BG levels safely without hypoglycemia. More specifically, STAR guarantees a maximum risk of 5% for BG < 72 mg/dL by design, where these initial results show 1 out of 205 measurements (0.5%).

Finally, nurses only overrode 9 (4.4 %) of the 205 interventions recommended, usually to give a slightly lower insulin dose, indicating good overall compliance.

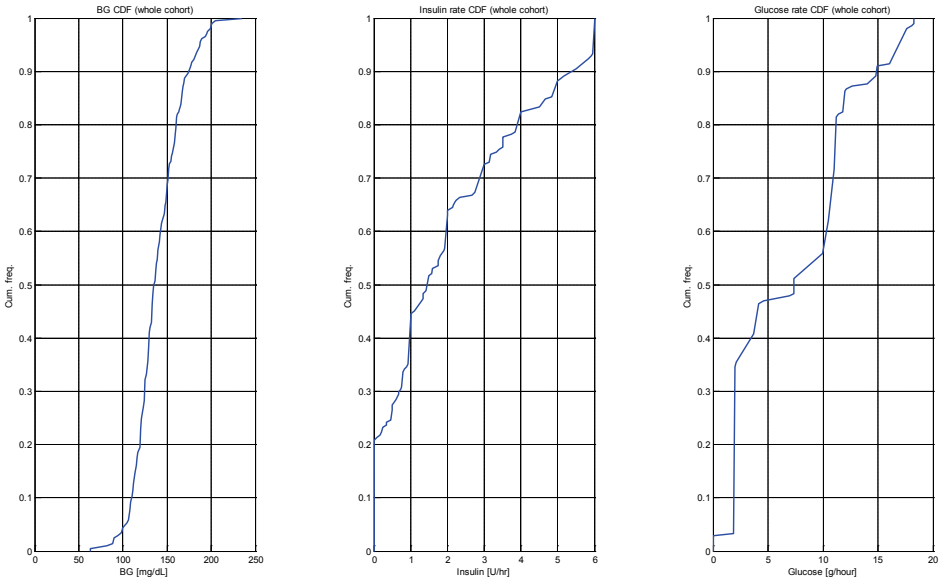

Figure 4 - BG, insulin rate and dextrose rate CDF's defined for the whole cohort

The CDF in Figure 4 shows that no insulin is given in 25% of controller interventions, and that insulin rates varied over the full range allowed. Only 25% of insulin rates are higher than 3.2 U/hour, but more than half of the patients received the maximum allowable insulin rate of 6 U/hour at least once during the 24-hour trial (Patients 1, 4, 7, 8 and 9, Table 4). These results indicate the significant intra- and inter- patient variability in insulin sensitivity encountered, which was initially unexpected from the cohort-based stochastic model. They might also be expected in part, as 3 of the patients were in an acute post-surgical (first day) phase (Table 1).They also indicate the adaptability of the model-based TGC protocol in responding to these changes.

Similarly, 25% of clinically specified exogenous glucose rates are between 2.0 and 7.4 g/hour. More than a quarter of dextrose rates are equal to 2.0 g/hour and approximately 40% of dextrose rates are between 10.0 and 12.0 g/hour. These results indicate patients were fed very differently, due to specific clinical orders given. Patient 8 in particular received highly variable nutrition rates during the trial for (unspecified) clinical reasons, which would have been a further factor in the variable insulin rates observed as the model-based controller responded to these changes.

3.2. Clinical Results - Model Control Performance

Control performance relies directly on the model's prediction ability. Table 5 shows that the average prediction error is 13.9 mg/dl (10.5%). To reduce this error, the system model has to be improved by revisiting the fundamental model structure or the population parameters. However, forecasts within stochastically defined prediction ranges (5%-95% and 25%-75%) are lower than expected (71.6% and 26.1%, instead of 90% and 50%, respectively). This result shows that this group of patients had significantly increased variability in insulin sensitivity compared to the stochastic model used to guide control [7], which was also similar to a prior analysis over 200 CHU patients over all days of stay [5]. Therefore, to make improvements about forecasting, the original stochastic model needs to be more specific.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Average
Median prediction error (mg/dL)	13.9	13.2	12.9	18.0	15.3	17.3	11.6	11.8	10.9	13.9
25th percentile error (mg/dL)	6.8	5.0	4.2	9.4	5.7	10.4	6.7	5.5	4.0	6.5
75th percentile error (mg/dL)	39.1	25.9	33.7	28.1	41.5	31.0	17.1	22.5	16.0	28.3
Median prediction error (%)	12.5	11.7	10.5	12.7	11.5	12.9	6.8	8.5	7.9	10.5
25th percentile error (%)	5.0	4.8	3.4	7.0	4.2	6.7	5.3	3.5	3.3	4.8
75th percentile error (%)	27.9	21.9	23.5	17.4	29.1	18.3	14.2	17.4	12.5	20.2
Total Forecasts	20	16	20	23	22	22	22	21	25	21.2
Predictions within 90% confidence interval (%)	65	44	65	74	64	68	91	86	88	71.6
Predictions within IQR (%)	35	19	20	22	23	14	23	29	52	26.1

Table 5 - Statistics on model prediction performance

3.3. Stochastic Model Assessment – Virtual Trial Results

This section analyses the changes due to the incorporation of different stochastic models representing cardiac-surgery post-operative patients (Table 2). Virtual trial [16, 17, 23] was performed using the eight new stochastic models of Table 2 to better assess the increased variability in insulin sensitivity observed.

The original stochastic model, based on all SPRINT patients over their entire ICU stay and used during clinical pilot trial, had only 71.6% of forecasts within 5%-95% and 26.1% within 25%-75% (Table 5). Among the proposed models in Table 2, Model 5 yielded 85.1% and 43.8%, respectively. These values are acceptable [7] given the relatively low number (205) of predictions. Therefore, this new model generated solely from SPRINT and Glucontrol cardiac-surgery patient data on only day 1 of their stay, better accounts for the variability in insulin sensitivity observed in this trial with similar patients. Models 1, 2, 4 and 6 are similar in results, and, notably use only the first 1-2 days of stay for cardiovascular surgery or cardiac care patients, similar to the cohort in this ICU.

Comparison of the model control performance for these new stochastic models is shown in Table 6.

	Original Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Median prediction error (mg/dL)	13.9	15.8	13.9	13.9	13.3	14.8	14.4	13.9	13.9
25th percentile error (mg/dL)	6.5	7.9	6.7	6.1	6.3	6.7	7.0	6.3	6.3
75th percentile error (mg/dL)	28.3	30.1	27.7	27.9	28.8	29.2	29.2	28.3	28.3
Median prediction error (%)	10.5	11.6	10.5	10.4	10.2	11.2	11.1	10.2	10.2
25th percentile error (%)	4.8	5.8	4.8	4.5	4.6	5.0	4.9	4.7	4.7
75th percentile error (%)	20.2	20.7	20.1	20.3	20.9	20.6	20.3	20.3	20.3
Predictions within 90% confidence interval (%)	71.6	84.3	78.0	79.3	82.5	85.1	83.1	67.4	69.5
Predictions within IQR (%)	26.1	46.5	41.2	40.0	44.2	43.8	41.3	26.9	27.4

Table 6 - Model control performance for new stochastic models

The potential impact of control performance of using a more specialized stochastic model was investigated in virtual trial re-simulations of the clinical trial. Tables 7 and 8 present whole cohort and per-patient statistics of the clinical and (re-simulated) virtual trial, respectively. The first column refers to the actual clinical results. The second and third columns refer to virtual trial using the original stochastic model and the new Model 5, respectively. Differences, particularly in columns 2 and 3, assess possible outcomes from using a stochastic model more specific to this patient group.

	Clinical data	Clinical trial re-simulated as per-protocol	Simulations with new stochastic model (Model 5)
Number of patients:	9	9	9
Total hours:	215 hours	208 hours	208 hours
Number of BG measurements:	205	198	198
BG median [IQR] (mg/dL):	136.0 [122.5 - 158.0]	135.8 [122.9 - 153.3]	131.7 [118.8 - 150.8]
% BG within 80-110 mg/dL	8.8	7.1	10.6
% BG within 110-140 mg/dL	45.4	49.5	48.0
% BG within 140-180 mg/dL	37.1	36.4	32.8
% BG ≥ 180 mg/dL	8.3	6.6	7.1
% BG < 80 mg/dL	0.5	0.5	1.5
% BG < 72 mg/dL	0.5	0.0	1.0
% BG < 40 mg/dL	0.0	0.0	0.0
Number of patients < 40 mg/dL	0	0	0
Median insulin rate [IQR] (U/hour):	1.5 [0.5 - 3.4]	1.5 [0.5 - 3.9]	2.0 [0.8 - 4.7]
Median glucose rate [IQR] (g/hour):	7.4 [2.0 - 11.2]	7.4 [2.0 - 11.2]	7.4 [2.0 - 11.2]

Table 7 - Re-run virtual trial analysis results: whole cohort statistics

	Clinical data	Clinical trial re-simulated as per protocol	Simulations with new stochastic model (Model 5)
Initial BG (mg/dL):	160.0 [151.5 - 172.0]	160.0 [151.5 - 172.0]	160.0 [151.5 - 172.0]
Hours of control:	24.0 [23.0 - 24.3]	23.0 [22.0 - 23.5]	23.0 [22.0 - 23.5]
Number of BG measurements:	24.0 [22.0 - 24.0]	23.0 [21.0 - 23.3]	23.0 [21.0 - 23.3]
BG median (mg/dL)	138.5 [130.6 - 146.0]	136.3 [130.2 - 142.8]	131.4 [126.9 - 141.0]
Median %BG within 80-110 mg/dL [IQR]:	8.3 [4.2 – 9.9]	4.8 [3.3 - 8.9]	13.0 [3.6 - 14.9]
Median %BG within 110-140 mg/dL [IQR]:	50.0 [31.2 – 54.2]	54.2 [34.8 - 57.1]	45.8 [34.8 - 54.8]
Median %BG within 140-180 mg/dL [IQR]:	40.9 [28.4 – 41.7]	37.5 [28.6 – 44.1]	33.3 [22.3 – 39.0]
Median %BG ≥ 180 mg/dL [IQR]:	8.3 [0.0 - 17]	4.3 [0.0 - 13.4]	4.3 [0.0 - 13.4]
Time to < 125 mg/dL (hours):	4.0 [2.1 - 5.0]	4.0 [3.8 - 6.4]	4.0 [3.8 - 6.1]
% patients to < 125 mg/dL:	100	100	100
Time to < 140 mg/dL (hours):	2.1 [2.0 - 4.0]	3.0 [2.0 - 4.3]	3.0 [2.0 - 4.3]
% patients to < 140 mg/dL:	100	100	100
Median insulin rate [IQR] (U/hr):	1.3 [0.9 - 2.4]	1.4 [1.0 - 3.4]	1.7 [1.0 - 4.3]
Max insulin rate [IQR] (U/hr):	6.0 [4.7 - 6.0]	6.0 [5.1 - 6.0]	6.0 [5.8 - 6.0]
Median glucose rate [IQR] (g/hour):	4.2 [2.0 - 11.1]	4.2 [2.0 - 11.1]	4.2 [2.0 - 11.1]

Table 8 - Re-run virtual trial analysis results: per-patient statistics (presented as median [IQR])

Differences between the clinical data and simulations using the original stochastic model arise from different nursing interventions and ability of the simulation environment to replicate the clinical trial [23]. During the pilot trial, slightly less insulin than specified by the controller was administered to patients in some cases if the nurses chose to override the recommendations (9 of 205, 4.4%), which explains the slightly higher BG levels for the clinical data. The difference in trial length and number of BG measurements in the simulated trial can be attributed to delays in BG measurements in the clinical environment and subsequent rounding of intervention times (where the simulated controller would take measurements on the hour). However, with respect to glycemic outcome, these differences are not clinically significant.

	Total hours		Number of measurements	
Patient	**Clinical data**	**Clinical trial re-simulated as per-protocol**	**Clinical data**	**Clinical trial re-simulated as per-protocol**
1	24	23	22	21
2	23	22	19	18
3	23	22	22	21
4	23	22	24	23
5	26	26	24	24
6	24	23	24	23
7	23	22	24	23
8	24	23	22	21
9	25	25	24	24

Table 9 - Comparison between clinical data and clinical virtual trials re-simulated as per-protocol in terms of number of measurements and trial length

It is observed in Tables 7-9 that there is no real difference in measurement frequency using the new Model 5 stochastic model. It is also seen that patients received more insulin (~ 30%) in re-simulated trial, especially with Model 5. This result explains the lower BG levels associated with Model 5 in Table 8 and in the BG CDFs shifting to slightly lower BG values in Figure 5 with a steeper slope at intermediate values. Nutrition rates are the same as they were kept at the clinically specified levels.

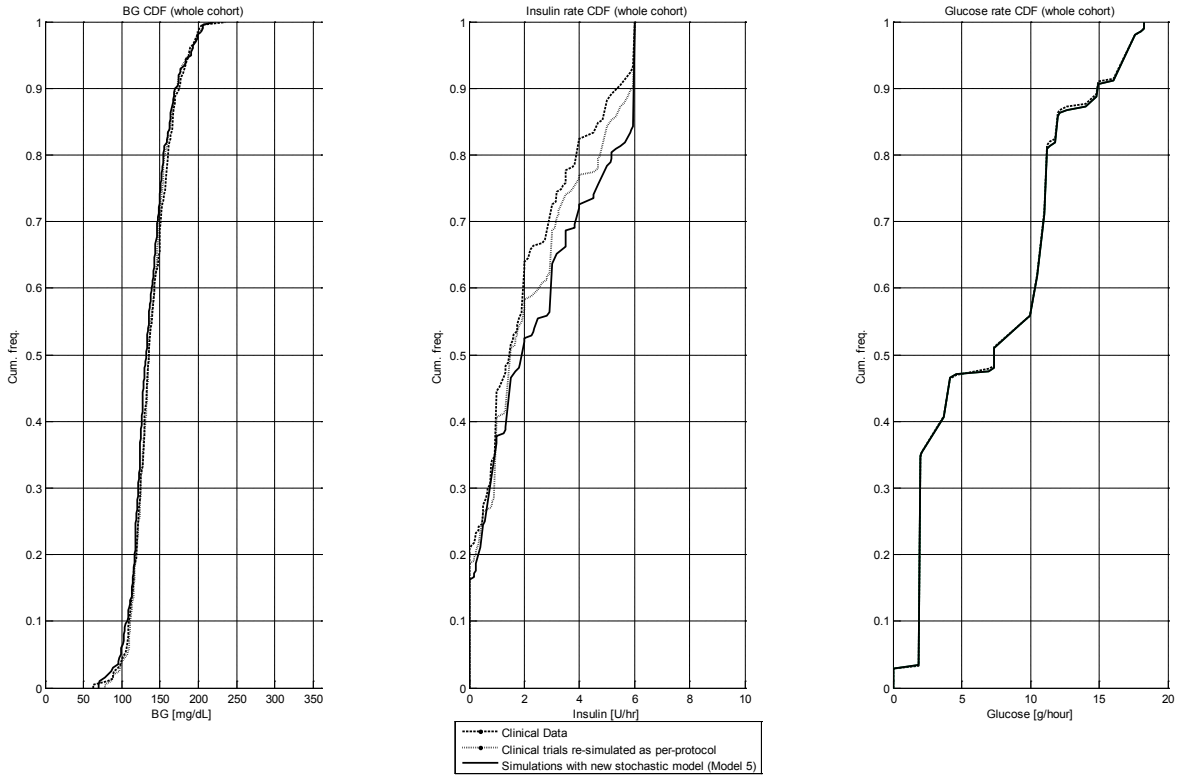

Figure 5 – Comparison of CDF's defined on whole cohort between clinical data and virtual trial. From top to bottom: BG, insulin rate and dextrose rate CDF's

Table 10 shows the p-values comparing the CDFs in Figure 5. The clinical data to STAR rerun (column 1) shows the impact of timing or delayed/missed clinical measurements, as well as any rounding of the insulin interventions given. The second column indicates that using a more relevant stochastic model (Model 5) would have yielded a different set of insulin interventions, as seen in Table 8, with lesser impact on BG likely due to trial length. The p –value of 0.91 between clinical data and re-simulation results results from small increases in nutrition in re-simulations, based on increases in nutrition rates at lower BG values with no insulin being given, and is thus not 1.0.

P-values	**Clinical Data/STAR rerun**	**Clinical Data/Model 5**
BG	0.78	0.12
Insulin rate	0.13	*0.01*
Nutrition rate	0.91	0.91

Table 10 - p-values using Wilcoxon rank sum test for equal medians. The p-value is the probability of observing a difference between the two data set medians as large as the difference observed here, or larger, assuming the hypothesis that the medians are equal.

4. DISCUSSION

This proof-of-concept trial is the first attempt to use the STAR approach outside the neonatal ICU (NICU) [25] and initial STAR trials ongoing in Christchurch ICU. One important result is that no severe hypoglycemia (BG < 40 mg/dL) occurred during this 24-hour clinical pilot trial. The minimum BG recorded was 63 mg/dL for Patient 1, with the next lowest at 82 mg/dL for Patient 2. Hence, there was no apparent risk of hypoglycemia, despite the unexpected high metabolic variability in SI observed.

The control was generally consistent across different, highly variable patients, as seen in Figure 3. However, the time spent at the 125 mg/dL target was relatively low due primarily to patient variability, high initial BG levels, and the short 24-hour total trial length. The fact that relatively long times in the desired glycemic bands (110-140 mg/dL in particular) were achieved supports the overall efficacy of this approach.

During the pilot trial, several patients displayed relatively large variability in insulin sensitivity, as shown by example for Patient 3 in Figure 6. This variability exceeded the predictions of the cohort-based stochastic model and made accurate model-based forecasting, prediction and TGC more difficult. As a result, forecasts within prediction ranges were lower than expected (Table 5). New stochastic models using clinical data specific to cardiac-surgery patients and for specific days post-surgery were much more effective in capturing this variability. It should also be noted that Patient 3 was immediate post-surgery, and this greater variability should perhaps be expected based on the re-analysis done with modified stochastic models. The improved forecasting in Table 6 for models using only 1-2 days of stay indicates that the greater variability seen here may be reflective of patients early in their stay being more variable. Earlier analyses [5] showed similar variability for a similar cohort over all days, but did not examine specific patients or days of stay. Equally, these 9 patients may simply have been more variable.

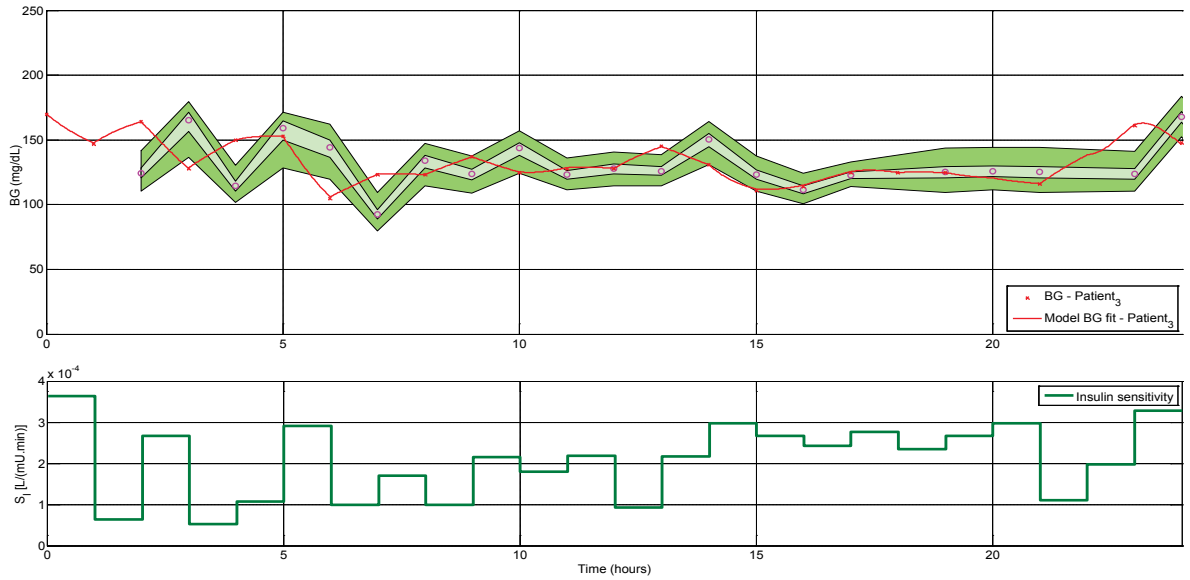

Figure 6 - STAR trial progression for Patient 3, BG (top) and model-based SI (bottom). The SI variation observed is very large, particularly over hours 0-12.

The main goal of this pilot trial was to assess performance, safety and implementation issues. In particular, several features were adapted for clinical implementation and to reduce nursing effort, which was higher than desired. Three-hour measurement periods would be desirable to further reduce nursing staff effort. However, as patients were not glycemically stable in this pilot trial such an improvement would not have been effective here. Longer trials over more patients would see improvements if variability declined over time or if patients were less variable than the small subset in this pilot trial.

Equally, longer intervals can be implemented using improved stochastic models and accepting a lower level of control than targeted in this study. In particular, stochastic bounds can be used to maximize the likelihood of BG in a desired range, as opposed to a specific target, as has been done in NICU STAR studies [25]. This approach and other changes will be implemented and tested going forward.

In addition, when insulin infusions are used with hourly measurement, a measurable fraction of the administered insulin has no time to act before the end of the hour, and insulin "cycling" may occur. Insulin "cycling" is defined here as periodic insulin rate evolution characterized by a progressive increase followed by a sudden decrease. This behavior is illustrated by Patient 6 in Figure 7. These cycles occur in part due to clinically imposed limits in increasing insulin infusion rates (for safety) in

response to increasing BG. However, because a given infusion rate's full effect is not seen before the end of one hour (~55%) the controller using a model for hour-to-hour control may underestimate its effect and thus increase the infusion rate further. This effect is exacerbated at the relatively low (or zero) insulin infusion rates seen in this study. The presence of higher rates of insulin infusion may allow the model to make a more accurate estimation of patient state by reducing the impact of endogenous insulin production, for which the model must assume a population constant [23] as it is currently not measurable in clinical real-time. Hence, longer time intervals might be better when using infusions of insulin compared to bolus administration in SPRINT [16].

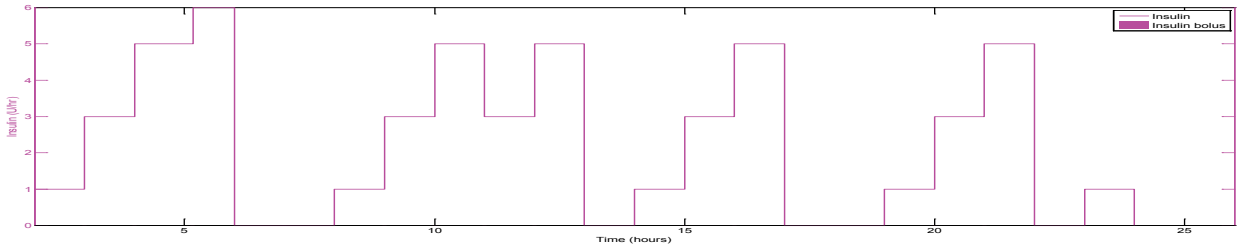

Figure 7 - STAR trial progression for Patient 6: evolution of insulin rates with a constant nutritional administration rates

Protocol application in the clinical environment was not perfect. Some situations were not managed automatically by the controller, such as when the patient vomited or was given meals. Such events were managed on a case-by-case basis by stopping the dextrose input to the controller, or assuming an equivalent dextrose infusion, for vomiting and meals, respectively. These events are important for TGC because BG levels are directly linked to carbohydrate administration and appearance. The resulting estimations made on how much carbohydrate might appear, and at what time, also affected the quality of control obtained. These issues affected Patients 3, 5, 6 and 8 on one occasion each. Future work will involve revising the control scheme to take better account of such possible scenarios to improve the clinical implementation and make it more autonomous.

5. CONCLUSIONS

This paper presents a new model-based stochastic targeted (STAR) controller. The controller method is flexible for a wide range of clinical approaches. This research presents initial results from a trial in a Belgian ICU (STAR-Liege).

Clinical results show that the controller is effective and safe, resulting in no hypoglycemic event (BG < 40 mg/dL) for the nine patients included in the pilot trial. Among the 205 BG measurements, only one was below 72 mg/dL (63 mg/dL). Controlled BG levels were tightly distributed. However, the pilot trial length of 24-hours was not designed to show long-term steady state control. Thus, despite every patient reaching 125 mg/dL, median BG values were slightly higher than the 125 mg/dL target.

An important result was the observation that some patients were significantly more variable in their insulin sensitivity (SI) than expected from stochastic cohort models using all patient days of stay. New stochastic models were created to better account for this variability. The application of a stochastic model using only the initial 1-2 days of stay would have resulted in different, more continuous insulin interventions and better forecasting. Ongoing next-generation pilot trials are thus expected to account for this variability directly and should thus reduce the measurement rate seen here as a result.

The overall results show tight, very safe control for post-cardiac surgery patients who exhibit significantly enhanced variability. Thus, the fundamental stochastic targeted (STAR) concept has been shown to be safe and effective when adapted, within its control framework, for an insulin-only approach in this Belgian ICU. Specific issues to be modified to enhance performance and usability were identified in this short, proof-of-concept trial, and will be implemented in a next generation pilot trial.

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Abbreviations:

BG: blood glucose

CDF: cumulative density function

CHU: centre hospitalier universitaire

ICU: intensive care units

IQR: interquartile range

NICU: neonatal intensive care units

SI: insulin sensitivity

SPRINT: specialized relative insulin and nutrition tables

STAR: stochastic targeted

TGC: tight glycemic control

Conflicts of Interest: The authors declare no financial or other conflicts of interest.

Appendix

A-1: Definition of the glucose-insulin system model.

Equations (1) to (3) define the clinically validated model of the glucose-insulin system [31].

$$\dot{G} = -p_G.G - \mathrm{SI(t)} * G.\frac{Q}{1+\alpha_G Q} + \frac{P(t) + \left(P_{END} * m_{body}\right) - \left(CNS * m_{brain}\right)}{\left(V_{G,frac}(t) * m_{body}\right)} \quad (1)$$

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

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{\left(V_{I,frac} * m_{body}\right)} + e^{-(k_I \frac{u_{ex}(t)}{V_i})} I_B \quad (3)$$

Where *G(t)* [mmol/L] is plasma glucose *I(t)* [mmol/L] is plasma insulin, $u_{ex}(t)$ [mU/min] is exogenous insulin input, basal endogenous insulin secretion is I_B [mU/L/min], with k_I representing suppression of basal secretion by exogenous insulin. Interstitial insulin is *Q(t)* [mU/L], with *k* [1/min] accounting for losses and transport. Body and brain weight are denoted by m_{body} [kg] and m_{brain} [kg]. Endogenous glucose clearance is p_G [1/min] and time-varying insulin sensitivity is SI or (formally) SI(t) in Equation (1) [L/(mU.min)]. Finally, $V_{I,frac}$ [L/kg] is the insulin distribution volume per kg body weight and V_I the resulting volume [L], and *n* [1/min] is the transport rate of insulin from plasma. Total plasma glucose input is *P(t)* [mmol/min], endogenous glucose production is P_{END} [mmol/kg/min] and $V_{G,frac}$ [L/kg] represents the glucose distribution volume per kg body weight. *CNS* [mmol/kg/min] captures non-insulin mediated glucose uptake by the central nervous system. Michaelis-Menten functions model saturation, with α_I [L/mU] for the saturation of plasma insulin disappearance, and α_G [L/mU] for insulin-dependent glucose clearance saturation.

A-2: The stochastic model for insulin sensitivity.

The insulin sensitivity is the critical parameter in predicting the outcome of an insulin intervention. As insulin sensitivity is relatively variable hourly, modeling the changes in insulin sensitivity is quite important to improve assessment of the patient's insulin response, and thus to allow more accurately targeted control.

The goal of the stochastic model is to describe the hourly variations of the insulin sensitivity, based on clinically observed insulin sensitivity variations in ICU population data. First, clinical data (blood glucose, insulin and nutrition inputs) are used to identify hourly insulin sensitivity values using the glucose-insulin system model (A-1) [21]. If insulin sensitivity at hour n+1 and at hour n are denoted respectively by $S_{I,n+1}$ and $S_{I,n}$, the distribution of the hourly changes in S_I, $(S_{I,n} = x_i, S_{I,n+1} = y_i)$, can be assessed (Figure 8, left panel). Finally, a probability density of insulin sensitivity at hour n+1 $(S_{I,n+1})$ taking on a value y can be calculated by knowing insulin sensitivity at hour n $(S_{I,n})$, using identified variations from clinical data. This probability density function, $p(S_{I,n+1} = y|S_{I,n} = x)$, defined the stochastic model. An example is illustrated on the right panel in Figure 8.

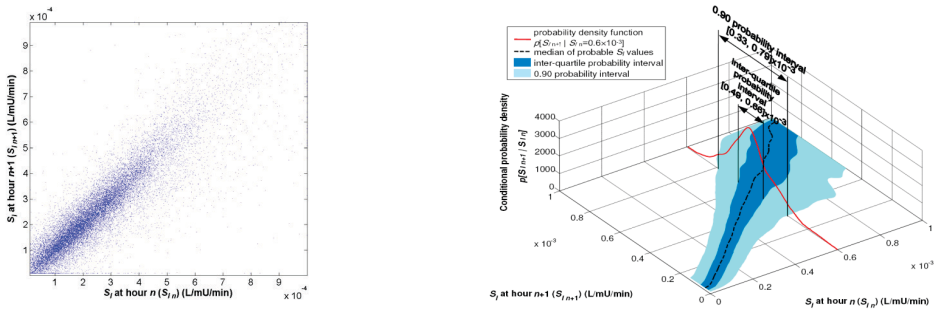

Figure 8 – On the left panel: hourly SI variation (dots). On the right panel: stochastic model of S_I variation, probability density function of S_I

The stochastic insulin model can then be used to forecast likely blood glucose outcomes for a given intervention (a given insulin infusion), using the model defined by Equations (1) to (3). This approach, illustrated in Figure 9, allows the optimization of prediction and ensures safety, especially from hypoglycemia.

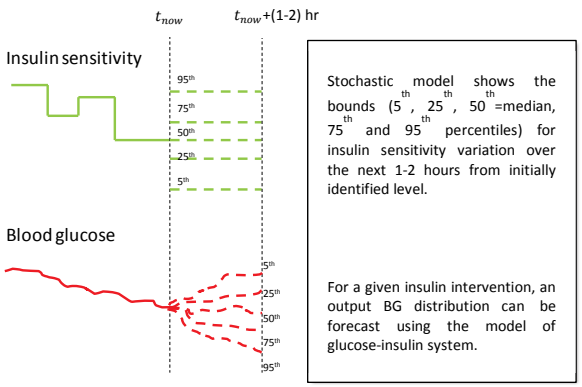

Figure 9 - Distribution of BG outcomes based on the stochastic model for insulin sensitivity variations

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