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In silico assessment of a computerized model-based glycaemic control approach in a Belgian medical intensive care unit

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Abstract: Glycaemic control can be used to enhance critically ill patient outcome. This paper presents the *in-silico* design of a computerized model-based controller for a Belgian medical intensive care unit (CHU of Liege, Belgium). *In silico* trials are used to assess the current clinical protocol efficiency and safety and to compare this protocol with the existing Stochastic Targeted (STAR) control approach. The objective of this research is to optimize a glycaemic controller for its future clinical implementation and clinical workflow requirements. Results suggest that the currently used, paper-based sliding scale protocol is too general to achieve safe and effective glycaemic control. The computerized model-based protocol STAR leads to better glycaemic outcomes associated with increased safety. In particular, time in target band is higher than 80% with STAR targeting 90-150 mg/dL and 100-160 mg/dL. Time in the desired 100-150 mg/dL band is improved using STAR, and BG < 80 mg/dL is reduced. Results suggest that control targeting 100-160 mg/dL is associated with increased time in band and increased safety.

1. INTRODUCTION

Critically ill patients often present stress-induced hyperglycaemia and high glycaemic variability that worsen patient outcome (Egi *et al.*, 2006, Krinsley, 2003). Effective glycaemic control (GC) should reduce patient glycaemic levels and variability and should also account for inter-patient variability, evolving physiological patient conditions and minimizing hypoglycaemic risk (Suhaimi *et al.*, 2010, Krinsley and Keegan, 2010). During glycaemic control, protocols are used to specify insulin and nutrition rates, and control frequency (time interval between glycaemia measurements). Protocols must also be designed to meet clinician expectations, fit into clinical practice of a unit, and provide patient-specific, safe and effective GC.

The STAR (Stochastic Targeted) model-based controller enables adaptive, patient-specific and computerized GC (Evans *et al.*, 2012, Fisk *et al.*, 2012). STAR accounts for evolving patient condition by identifying patient insulin sensitivity (SI) and by forecasting patient SI until the next glycaemia measurement using a stochastic model of SI future potential variability (Lin *et al.*, 2006, Lin *et al.*, 2008). The STAR protocol framework can be customized in terms of its glycaemic target, control approach (insulin and nutrition, insulin-only, enteral and/or parenteral nutrition…), and clinical resources (control frequency) to best fit clinical practice.

This research presents a STAR protocol customized for the clinical practice needs of a Belgian medical intensive care unit (ICU) at the University Hospital of Liege, Belgium. This particular ICU currently uses a sliding scale GC protocol but are interested in performance improvements that may arise from adopting STAR. The main objective of this study is the development and the clinical implementation of a computerized controller using the STAR framework. First, this research assesses the current clinical protocol for efficiency, safety and GC compliance *in silico*. Then, these results are compared with the STAR protocol to optimize control and assess potential improvements. The work is based on a retrospective and comparative analysis of GC protocols using retrospective clinical data and a clinically validated virtual trial approach (Chase *et al.*, 2010).

2. METHODS

2.1 Clinical protocol

The current clinical protocol follows an experimental sliding scale and targets patient glycaemia to be between 100 and 150 mg/dL. The protocol is characterized by an insulin infusion-only approach with a 1-4 hour time interval between blood glucose (BG) measurements. Insulin rate is adjusted depending on current BG level and previous insulin infusion rate (Table 1). The nutrition rate is left to attending clinicians, but is increased (12 g bolus of exogenous glucose) when BG becomes lower than 40 mg/dL for severe hypoglycaemia.

2.2 STAR protocol

The glycaemic target of STAR is customizable to different targets. This study examines 3 target bands (80-140 md/dL, 90-150 mg/dL and 100-160 mg/dL) to determine the best option of the mix of patients in this medical ICU. An insulin infusion-only approach is used and the nutrition rate corresponds to the clinical one as it was left to attending

clinicians, but nutrition rate is increased to avoid hypoglycaemia the same way it is done by the clinical protocol. Measurement frequency during the GC varies from 1 hour to 3 hours.

Table 1: Current sliding scale clinical protocol.

Calculation of time interval		
If two consecutive BG measurements are within 100-180 mg/dL: 2 hours; otherwise 1 hour.		
Calculation of insulin rate adjustment		
Based on current blood glucose level (BG) [mg/dL] and previous insulin rate (u) [U/h]		
Conditions		Insulin rate adjustment
180 < BG and		
	u ≤ 2 U/h	+ 0.5 U/h
	2 U/h < u ≤ 10 U/h	+ 1 U/h
	10 U/h < u ≤ 20 U/h	+ 2 U/h
	20 U/h < u	+ 4 U/h
80 < BG ≤ 180		+ 0 U/h
60 < BG ≤ 80 or BG reduction higher than 50 mg/dL per hour and		
	u ≤ 2 U/h	- 0.5 U/h
	2 U/h < u ≤ 10 U/h	- 1 U/h
	10 U/h < u ≤ 20 U/h	- 2 U/h
	20 U/h < u	- 4 U/h
40 < BG ≤ 60		0 U/h
BG ≤ 40		0 U/h +12 g exogenous glucose (bolus)
Then, once BG > 80 mg/dL, set u to half the rate applied before BG ≤ 40 mg/dL and stop bolus of exogenous glucose.		
Specific case 1:		
When BG decreases below 100 mg/dL whereas during previous 24 hours BG was within 100-180 mg/dL and insulin was unchanged → reduce insulin rate by 20 % and set time interval to 1 hour.		
Specific case 2:		
When nutrition is stopped, stop insulin and when nutrition starts again, administrate the same insulin rate than before stop.		

The insulin rate and time interval are adjusted based on glycaemic levels and previous insulin and nutrition rates. This adjustment process is composed of four steps. This step-by-step process is partly illustrated in Figure 1.

Step 1. Previous and current BG measurements are used to identify a patient-specific SI value for the prior time interval (Hann *et al.*, 2005). This step accounts for inter-patient variability (Lonergan *et al.*, 2006, Chase *et al.*, 2007, Chase *et al.*, 2011).

Step 2. Insulin rates are limited to the range 0 - 8 U/h, in 0.5 U/h increments, except between 0 U/h and 1 U/h. Thus, allowable insulin rates are 0, 1, 1.5, 2, 2.5, 3, 3.5…8 U/h. The increment is defined to reduce nurse workload associated with making small and frequent changes in insulin rates. The maximum insulin rate of 8 U/h is defined for safety and to avoid insulin saturation effects (Rizza *et al.*, 1981, Black *et al.*, 1982). Possible time intervals are limited to 1 hour, 2 hours and 3 hours.

However, in two specific cases, no insulin and hourly measurement are required. First, when the current BG value is more than 18 mg/dL below the 5th percentile expected from the last protocol intervention; second, when the current BG level is lower than a hypoglycaemic threshold value (40 mg/dL). In this case, nutrition is increased (12g bolus of exogenous glucose).

Moreover, time interval is limited to only 1 hour when current BG level is lower than the low bound of the target band and when there is a hyperglycaemia (BG > 180 mg/dL).

Step 3. For each possible time interval defined is Step 2 (1 hour or 1-3 hours), insulin rate resulting in the forecast 5th percentile BG value closest to the lower bound of the target range (80 mg/dL, 90 mg/dL or 100 mg/dL), but above 80 mg/dL, is selected among the possible insulin rates defined in Step 2. The step is composed of three phases that are repeated for each possible time interval (1 hour or 1, 2 and 3 hours).

- Phase a. The stochastic model (Lin *et al.*, 2006, Lin *et al.*, 2008) provides the distribution of likely SI values for the next time interval based on current SI value (Step 1). This phase accounts for intra-patient variability, as SI can be quite variable over time for a patient.
- Phase b. Based on SI distribution and for each possible insulin rate defined in Step 2, the associated glycaemic outcome predictions (the 95th and the 5th percentile values) are calculated using the 5th and 95th percentile SI values (calculated in Phase a), respectively. This accounts for the glycaemic variability due to intra-patient variability.
- Phase c. For the given time interval, the selected insulin rate is the one resulting in the forecast 5th percentile BG value closest to the lower bound of the target range (80 mg/dL, 90 mg/dL or 100 mg/dL), but above 80 mg/dL. For 3 hour forecasts, an additional constraint of the median BG ≤ central value of the target band (110 mg/dL, 120 mg/dL or 130 mg/dL) is also implemented.

This step leads to one selected insulin rate per allowable time interval. Note that there is always at least one recommendation for the 1-hour interval and a maximum of three recommendations when hourly measurement are not required.

Step 4. Among selected insulin rates from Step 3, the insulin rate associated with the longest possible time interval is selected to minimize nurse workload. The time interval is set to that longest possible time interval.

During the *in silico* trials, the insulin adjustment cannot be calculated using this method for the first BG measurement as the previous BG is needed. Hence, the first STAR controller intervention is based on the clinical protocol (Section 2.1) and time interval is set to 1 hour.

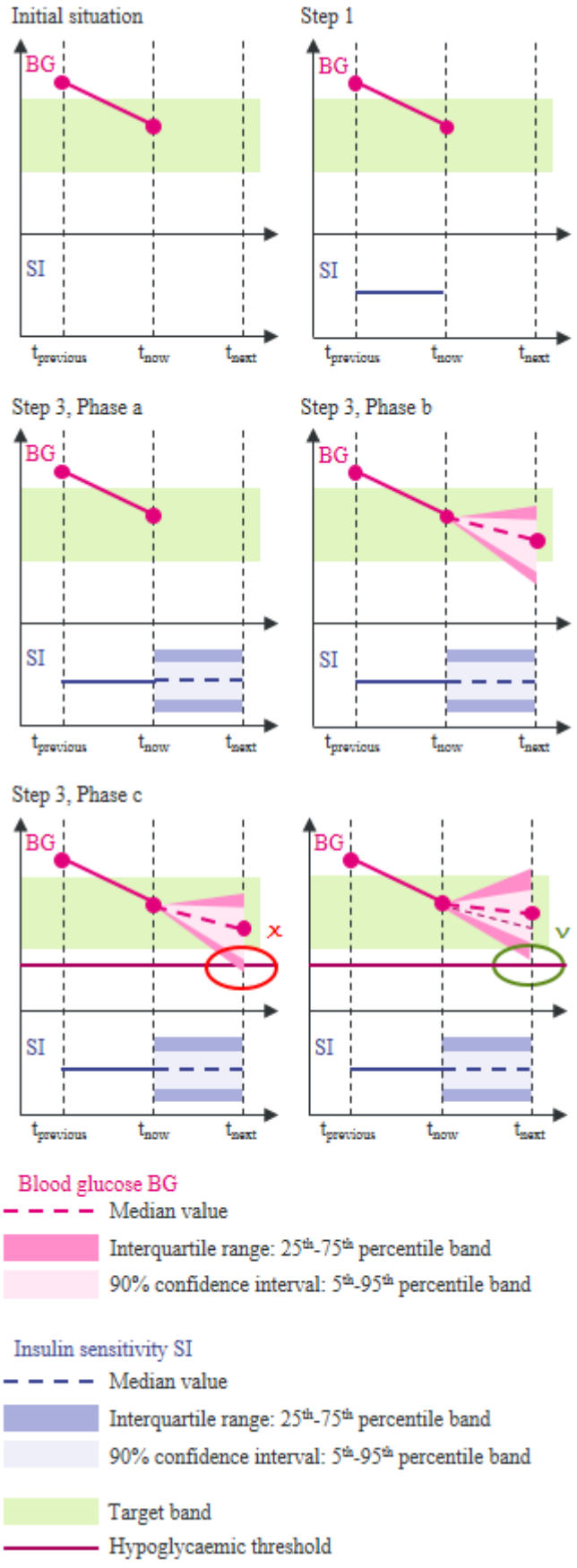

Figure1: Step-by-step description of STAR framework.

2.3 Stochastic model of insulin sensitivity variability

The objective of a stochastic model of insulin sensitivity variability is to forecast a likely distribution of patient SI based on current condition and current SI. Such stochastic model is based on historical SI variations in ICU population data. 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 used in this research was based on all types of patients included in the SPRINT GC study (Chase et al., 2008b) and all patient days of stay (Lin et al., 2006; Lin et al., 2008). It used clinical data from 393 critically ill patients (Christchurch Hospital, New Zealand) (Lin et al., 2008). This large number of patients and data is critical to reliably capture stochastic variation of insulin sensitivity.

Based on a current, identified SI value, SI_n, the stochastic model returns the probability density function for future insulin sensitivity values, SI_{n+1} where n+1 represents a time step of 1-3 hours.

2.4 Patient data

In this research, we have used retrospective clinical data from 20 non-diabetic patients whose glycaemia was controlled during their stay in a medical ICU at the University Hospital of Liege, Belgium. All patients were admitted in 2011. The selection criteria for patients were: (1) GC for at least 60 hours; (2) insulin administration at the beginning of the control; (3) clinical data clarity; and (4) at least 10 BG measurements during control. Diabetic patients were excluded as they received subcutaneous insulin and clinicians wished to analyse an insulin-infusion approach. Patient characteristics are summarized in Table 2 and clinical data in Table 3 (first column).

Table 2: Patient characteristics. Data is presented as median [IQR] when it is appropriate.

Number of patients	20
Age (years)	68 [54-76]
SAPS(*) II	67 [51-76]
Number of women (%)	11 (55%)
Length of ICU stay (days)	18.5 [12.8-25.8]
Initial BG (mg/dL)	153.5 [131.8-175.8]

(*)SAPS refers to Simplified Acute Physiology Score (Le Gall et al., 1993).

2.5 Virtual trials

Virtual trials are a safe, rapid, and efficient method to analyse, develop, and optimise or validate GC protocols. Virtual trials could be divided into two phases: the fitting and the simulation (Fig.2). During the fitting, clinical data are used to identify hourly SI values and create a SI profile over ICU stay (Hann *et al.*, 2006). This profile reflects the patient state evolution and its glycaemic response to insulin and nutrition inputs (Chase *et al.*, 2007, Chase *et al.*, 2010). This SI profile can then be used to simulate glycaemic response to different insulin and nutrition inputs, associated with

different control protocols (Chase *et al.*, 2010). This second phase is the simulation phase and allows *in silico* assessment of protocol performance and safety.

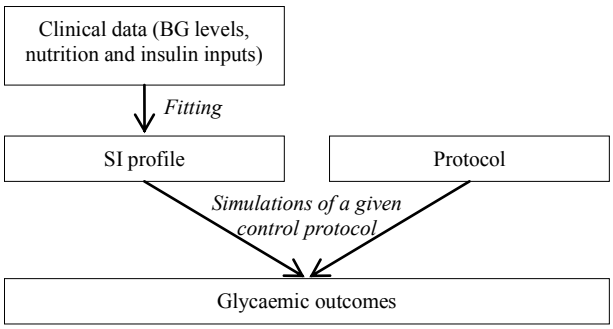

Figure 2: Virtual trial process.

2.6 Analysis

Control efficiency is assessed by median BG levels and interquartile range (IQR), by percentage of BG levels in different glycaemic bands. Number of patients with severe hypoglycaemic event (BG < 40 mg/dL), and the percentage of BG below 80 mg/dL, and below 60 mg/dL are used to evaluate control safety (Finfer *et al.*, 2013). GC compliance is assessed by comparing clinical data and *in silico* trial of the clinical protocol. P-values are calculated using the Mann-Whitney U-test. Analysis is performed using glycaemic data resampled hourly from modelled or interpolated data to provide a consistent measurement frequency for fair comparison between different protocols.

3. RESULTS

Tables 3 and 4 present the clinical data and *in silico* trial glycaemic outcome. Insulin inputs given the GC approach are shown in Figure 3.

Table 3: Whole cohort glycaemic statistics for clinical data and results of *in silico* clinical protocol virtual trials.

	Clinical data 100-150 mg/dL	Clinical protocol 100-150 mg/dL	P-values
Total hours of control	5006	5009	
Number of BG measurements	1391	2125	
BG median [IQR] (mg/dL)	137.8 [117.8 - 160.9]	127.1 [109.3 - 149.4]	0.00
% BG ≥ 180 mg/dL	12.01	7.95	
% BG in 150-180 mg/dL	24.71	16.33	
% BG in 100-150 mg/dL	55.42	60.43	
% BG in 100-160 mg/dL	66.43	68.50	
% BG in 90-150 mg/dL	59.93	67.67	
% BG in 80-140 mg/dL	50.70	62.46	
% BG < 100 mg/dL	7.86	15.29	
% BG < 90 mg/dL	3.35	8.05	
% BG < 80 mg/dL	1.42	3.44	
% BG < 60 mg/dL	0.12	0.26	
% BG < 40 mg/dL	0.00	0.00	
Median [IQR] insulin rate (U/hour)	2.5 [2.0 - 3.0]	3.0 [2.0 - 6.5]	0.00
Median [IQR] exogenous glucose rate (g/hour)	9.7 [8.8 - 11.7]	9.7 [8.8 - 11.7]	

Table 4: Whole cohort glycaemic statistics for results of *in silico* STAR protocol virtual trials with three different glycaemic target bands.

	STAR 80-140 mg/dL	STAR 90-150 mg/dL	STAR 100-160 mg/dL
Total hours of control	5006	5007	5014
Number of BG measurements	2186	2112	2051
BG median [IQR] (mg/dL)	109.6 [102.1 - 128.0]	116.3 [109.6 - 130.0]	125.7 [119.5 - 135.4]
% BG ≥ 180 mg/dL	4.76	4.97	5.15
% BG in 150-180 mg/dL	6.80	7.24	8.20
% BG in 100-150 mg/dL	69.18	81.46	84.64
% BG in 100-160 mg/dL	72.62	84.98	88.54
% BG in 90-150 mg/dL	84.50	86.23	85.90
% BG in 80-140 mg/dL	82.73	82.71	79.86
% BG < 100 mg/dL	19.26	6.33	2.01
% BG < 90 mg/dL	3.94	1.55	0.75
% BG < 80 mg/dL	1.05	0.46	0.24
% BG < 60 mg/dL	0.14	0.04	0.02
% BG < 40 mg/dL	0.00	0.00	0.00
Median [IQR] insulin rate (U/hour)	6.5 [3.5 - 8.0]	4.5 [2.5 - 8.0]	3.0 [2.0 - 7.5]
Median [IQR] exogenous glucose rate (g/hour)	9.7 [8.8 - 11.6]	9.7 [8.8 - 11.6]	9.7 [8.8 - 11.6]

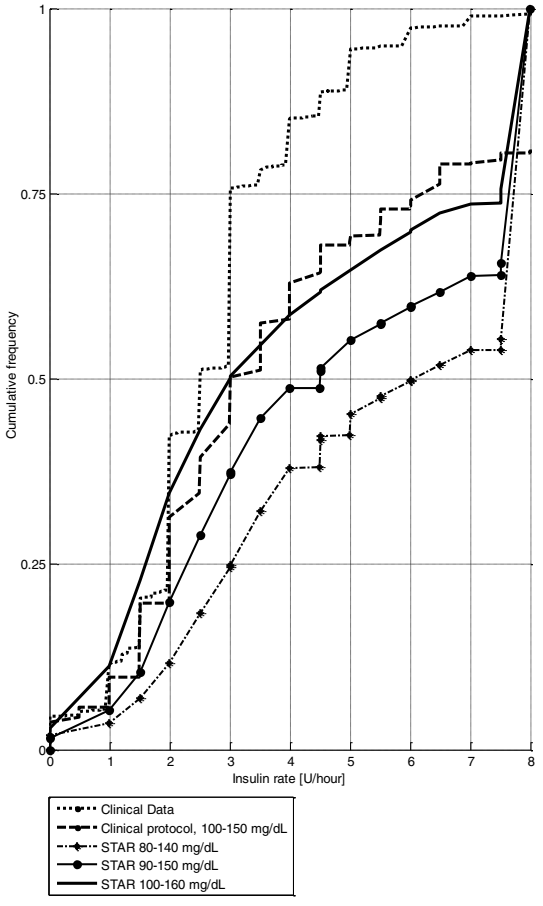

Figure 3: Cumulative density functions for exogenous insulin input, given the control protocol used.

4. DISCUSSION

This research aims to develop and assess a computerized glycaemic controller for clinical implementation in an ICU using the STAR framework. Current clinical protocol performance is assessed in Table 3 where *in silico* results for retrospective patients show: 24.28 % of the BG are above the target band (≥ 150 mg/dL), 60.43 % of the BG are within the target glycaemic band (100-150 mg/dL) and 15.29 % of the BG are below 100 mg/dL, with 3.44 % < 80 mg/dL.

The comparison between clinical data and results of the clinical protocol simulation provides information about the nurse compliance, in clinical practice, to this protocol as differences in BG outcomes result from difference in insulin rates and measurement frequency. In particular, results in Table 3 show that the clinical protocol was not fully followed during clinical implementation. Clinical data are associated with higher patient glycaemic levels ($p < 0.01$), reduced low BG and thus increased safety with reduced number of BG measurements. These results are associated with significantly reduced insulin administration during clinical practice (Table 3 and Fig.3), probably due to fear of hypoglycaemia.

STAR is patient-specific and accounts for evolving patient condition. Results show that the STAR protocol enhances control performance and safety compared with clinical data and clinical control protocol. As shown in Table 4, STAR is associated with the best percentages of BG within the desired 100-150 mg/dL glycaemic band and within the specified band, and with reduced low BG (< 80 mg/dL). More precisely, time within 100-150 mg/dL was increased from 60.43 % with the clinical protocol to 84.64 % with the STAR framework targeting 100-160 mg/dL.

As expected given the insulin rate calculation used by STAR (Section 2.2), less than 5 %, of BG are below 80 mg/dL (Table 4). STAR is also associated with tighter GC as IQR is reduced from 40.1 mg/dL (clinical protocol) to 25.9 mg/dL, 20.4 mg/dL and 15.9 mg/dL with STAR targeting 80-140 mg/dL, 90-150 mg/dL and 100-160 mg/dL, respectively.

Better glycaemic outcomes are associated with more dynamically changing exogenous insulin inputs and higher insulin rates, except for the 100-160 mg/dL target band (Table 4 and Fig.3). These improvements of glycaemic outcomes could be explained by a GC protocol, STAR, that can account for patient dynamics and evolving conditions, while paper-based clinical protocol cannot. A more patient-specific protocol could lead to enhance patient glycaemic outcomes. As control efficiency could be associated with higher and more dynamic exogenous insulin inputs than those usually administrated in this ICU, simulations of protocols have also been performed with a 30 % reduction of total nutrition inputs. The results (not shown) suggest that reduced nutrition should facilitate tighter control of glycaemic levels. Reduced nutrition associated with the STAR protocol leads to better glycaemic outcomes. Clinically, it should be noted that the nutrition rules used correspond to 100 % of ACCP guidelines (Cerra *et al.*, 1997).

The glycaemic target of STAR is customized to different ranges (80-140 mg/dL, 90-150 mg/dL and 100-160 mg/dL) to assess the effect of a glycaemic target shift. Results in Table 4 show that a 10 mg/dL increase in target bounds to shift from 80-140 mg/dL to 90-150 mg/dL is associated with a reduction BG under 100 mg/dL (12.93 %), an increase of BG within the 100-150 mg/dL desired band (12.28 %) and a slight increase of BG over 150 mg/dL (0.65 %). But, the shift between the 90-150 mg/dL and the 100-160 mg/dL target band is associated with a reduction of BG under 100 mg/dL (4.32 %), a small increase of BG within the 100-150 mg/dL desired band (3.18 %) and a slight increase of BG over 150 mg/dL (1.14 %). These results suggest that the 100-160 mg/dL is the best target band as it's associated with an increased time in the desired band and a reduced low BG, and thus increased safety; compared with the other assessed target bands.

Considering the clinical implementation of STAR control approach, we should pay attention to higher insulin inputs associated with this approach compared with clinical data. Nursing staff could be reluctant to make such practice changes. We should simulate STAR with reduced maximum insulin rate of 4 U/h and 6 U/h to assess impact of maximum insulin rate on GC efficiency.

5. CONCLUSIONS

This research presents the assessment of a clinical protocol performance using STAR framework in virtual trials. This research shows that the STAR computerized model-based glycaemic controller is associated with improved glycaemic outcomes and increased safety compared to the existing sliding scale protocol and could thus potentially improve patient outcome. The 100-160 mg/dL glycaemic range seems to be the target band best achieving the control objective: maximizing time in the 100-150 mg/dL and ensuring safety. STAR should be now implemented in a Belgian ICU to assess its efficiency in real clinical conditions. This pilot clinical trials should include 10 critically ill patients whose glycaemia will be controlled during at least 24 hours.

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