Translating A Risk-Based Glycaemic Control Framework for Critically Ill Patients: STAR-Liège

Vincent Uyttendaele*, **, Jennifer L. Knopp, Marc Pirotte***, Philippe Morimont***, Bernard Lambermont***, Geoffrey M. Shaw****, Thomas Desaive*, and J. Geoffrey Chase****

** GIGA – In silico Medicine, University of Liège, Belgium*
(email: Vincent.Uyttendaele@uliege.be, Vincent.Uyttendaele@pg.canterbury.ac.nz)
***Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand*
**** Department of Medical Intensive Care, University Hospital of Liège, Belgium*
***** Department of Intensive Care, Christchurch Hospital, New Zealand*

Abstract: Glycaemic control (GC) in the intensive care unit (ICU) has been widely debated over the last 20 years. While many studies showed benefits, many others failed to replicate the results, blaming the increased related risk of hypoglycaemia. Current ICU guidelines thus often suggest higher glycaemic target ranges, led by the fear of hypoglycaemia – permissive hyperglycaemia. However, recent studies have shown improved safety and performance in GC outcome, using model-based computerised methods. The Stochastic-Targeted (STAR) framework is a patient-specific risk-based dosing protocol modulating insulin and nutrition. This study presents recent intermediate results of the STAR-Liège clinical trial, targeting 4.4-8.0 mmol/L glycaemic band. Clinical data from patients controlled under STAR and STAR insulin only (STAR-IO) are compared to retrospective data under the standard protocol (SP), targeting higher 5.6-8.3 mmol/L glycaemic ranges.

Overall, STAR performance was significantly higher (88% blood glucose measurements in the 4.4-8.0 mmol/L or 80-145 mg/dL target band) compared to STAR-IO (78%) and SP (55%). Incidence of hypoglycaemia was similar (1% below target), while hyperglycaemia was much higher for SP (31% above target) compared to STAR (9%) and STAR-IO (11%). The resulting lower median blood glucose (BG) levels in STAR (6.5 mmol/L), compared to STAR-IO (6.7 mmol/L) and SP (7.7 mmol/L), was achieved with less variability, but required higher clinical workload for STAR (12 measurements per day) compared to SP (7 measurements per day). Compliance to protocol was higher for STAR (98%) compared to STAR-IO (90%) and SP (79%).

Although targeting lower glycaemic ranges, STAR provided better GC compared to the SP. Typically, the full version of STAR also modulating nutrition, was able to better control extremely insulin resistant patients, further improving glycaemic control results. The results of this clinical trial indicate the capability to provide the safe, effective control for all patients required to improve outcomes.

Keywords: Glycaemic control, Hyperglycaemia, Hypoglycaemia, Insulin, Insulin therapy

1. INTRODUCTION

Stress-induced hyperglycaemia is a common complication in critically ill patients resulting from stress and inflammatory metabolic response to injury (McCowen *et al.*, 2001), and is associated with increased morbidity and mortality (Krinsley, 2003). Glycaemic control (GC) for these patients has been associated with improved outcomes (Chase *et al.*, 2010a; Krinsley, 2004; Reed *et al.*, 2007; Van den Berghe *et al.*, 2001). However, the associated increased risk of hypoglycaemia (Brunkhorst *et al.*, 2008; Finfer *et al.*, 2009; Finfer *et al.*, 2012; Preiser *et al.*, 2009) has been the heart of a debate on what appropriate glycaemic target band to choose in intensive care units (ICUs) (Gunst *et al.*, 2016; Krinsley, 2018; Preiser *et al.*, 2016a; Preiser *et al.*, 2016b). To date, guidelines often suggest a higher target band due to fear of harm (Krinsley, 2018; Singer *et al.*, 2019), hypoglycaemia being potentially more harmful than the potential benefit (Penning *et al.*, 2014a; Penning *et al.*, 2015).

However, these recommendations are often based studies failing to achieve safe and effective control for all patients. Most importantly, recent analyses suggest increased hypoglycaemia could mainly be due to protocol compliance and protocol design rather than GC itself (Uyttendaele *et al.*, 2019b). Additionally, another study shows glycaemic outcomes and mortality is a function of the quality of control achieved and not patient condition (Uyttendaele *et al.*, 2017). These results overall suggest safe, effective control for all must be achieved for all patients before potentially assessing its impact on clinical outcomes (Chase *et al.*, 2017).

The STAR (Stochastic Targeted) GC framework is a personalised risk-based dosing approach (Evans *et al.*, 2012; Fisk *et al.*, 2012). It uses a validated physiological model and

stochastic predictions to evaluate the risk of hypo- and hyperglycaemia for any given treatment (Lin *et al.*, 2008; Lin *et al.*, 2011). STAR has shown positive results in New Zealand and Hungary, providing safe control for nearly all patients (Stewart *et al.*, 2016). While STAR is not the only successful model-based protocol (Chase *et al.*, 2008; Mesotten *et al.*, 2017; Van Herpe *et al.*, 2013), it is the only controller also modulating nutrition for increased quality of control, while optimising carbohydrate intake.

This study presents intermediate results of the STAR-Liège clinical trial, currently ongoing at the University Hospital of Liège, Belgium. STAR-Liège aims to assess safety and performance of STAR in a general ICU environment, and compare results to local standards. This trial includes patients on a STAR Insulin-Only version (STAR-IO), leaving nutrition at clinician discretion, or on full STAR modulating both insulin and nutrition inputs. This study thus also analyses the impact of modulating nutrition on glycaemic control outcomes, in the context of a proven GC framework.

2. METHODS

2.1 STAR-Liège protocol (STAR & STAR-IO)

STAR is a model-based GC framework developed in Christchurch, New Zealand (Evans, *et al.*, 2012). It uses a clinically validated physiological model to identify insulin sensitivity (SI) from clinical data (Chase *et al.*, 2010b; McAuley *et al.*, 2011). This parameter represents patient-specific response to insulin, and is identified from clinical data, using integral based methods (Docherty *et al.*, 2012). A stochastic model is then used to evaluate future potential metabolic variability (Davidson *et al.*, 2019; Davidson *et al.*, 2020; Lin *et al.*, 2006; Lin, *et al.*, 2008; Uyttendaele *et al.*, 2018a; Uyttendaele *et al.*, 2019a). This probabilistic model forecasts the 90% likelihood range of future SI. STAR can thus evaluate the corresponding 90% confidence interval (CI) of likely future BG for any specific insulin and nutrition intervention.

STAR computes recommendations based on predicted risks, by determining what combination results in the 90% CI of predicted BG best overlapping the clinically specified target band (Fig. 1). This approach minimises to 5% the risk of being below the lower limit of the target band. This risk-based dosing approach is unique in GC, and extensively explained in the literature (Evans, *et al.*, 2012). STAR always maximizes safety first, and suggests 1-3 hourly blood glucose (BG) measurements. Overall, STAR accounts for inter- and intra- patient variability, offering a unique risk-based dosing approach and modulating both insulin and nutrition inputs.

STAR is fully computerised and used on Android Operating System Tablets. STAR easily adjusts to local ICU practises and has shown encouraging results in different ICUs across different countries. Nurses enter BG, insulin, and nutrition data directly in the tablet. STAR then operates using the patient data to compute the new treatment. The University Hospital of Liège Ethics Committee approved this trial (#**B707201733994**) and the use of this data.

STAR-Liège is started if two consecutive BG measurements > 8.0 mmol/L (145 mg/dL). The target band is 4.4-8.0 mmol/L (80-145 mg/dL). Insulin is continuously administered through intra-venous catheter. The maximum insulin rate is 9U/h. Increments of maximum 2U/h are allowed between successive interventions. Nutrition, in the full STAR version, can be temporarily decreased down to a minimum of 30% of the original clinically set 100% goal feed (GF). Typically, nutrition is reduced if insulin alone is not sufficient to decrease persistent elevated BG levels. Nutrition can only be reduced by a maximum 30% between consecutive measurements. In STAR-IO, nutrition is left at clinician discretion. In the case of hypoglycaemia, a dextrose bolus (20ml of 30% glucose) is administered intravenously while insulin is stopped, and a new BG measurement will be needed within one hour.

STAR stopping criteria are BG levels stable (in target band) for 6 hours at low insulin rates (≤2U/h), or after 72 hours of control. BG measurements are taken using a blood gas analyser. This clinical trial aims to include 20 patients in each arm.

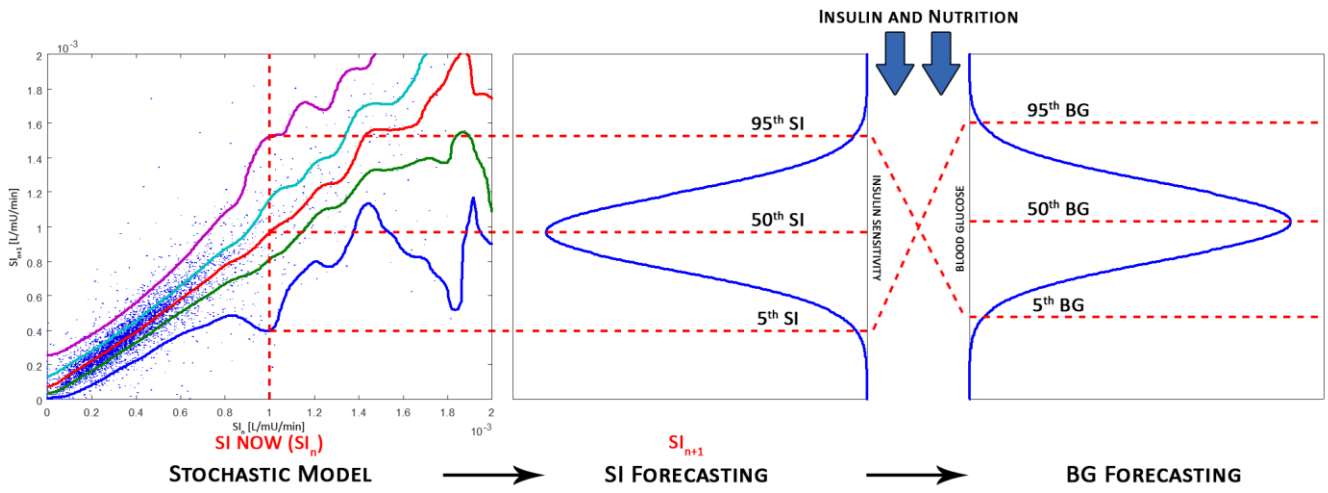

Fig. 1. STAR uses stochastic models to forecast change in SI based on current SI value, and determines BG outcomes for given insulin and nutrition intervention

2.2 Local Standard Protocol (SP)

Clinical trial results are compared to retrospective data from the local standard GC protocol (SP). SP is a table-based protocol targeting 5.6-8.3 mmol/L (100-150mg/dL). BG measurements are typically taken 4-hourly when 5.6 mmol/L < BG < 10.0 mmol/L (100 mg/dL < BG < 180 mg/dL), 1-hourly otherwise. There is no specified maximum insulin infusion rate. Starting criteria is BG > 10.0 mmol/L (180 mg/dL). BG measurements are made using glucometers or blood gas analyser. In the case of nutrition stoppage, insulin is automatically stopped. Insulin administration is stopped only when BG is below 3.3 mmol/L (60 mg/dL), and a 20ml of 30% glucose bolus is administered for severe hypoglycaemia (BG < 2.2 mmol/L).

2.3 Protocol comparison and analysis

To date, 12 patients were included under STAR-IO and 10 patients under STAR. Results from 20 retrospective patients under SP are used for comparison. Statistics and details on these patients can be found in (Dickson *et al.*, 2017) and (Penning *et al.*, 2014b).

Safety, performance, nutrition, workload, and compliance are compared. Safety is assessed by the percentage BG in mild and severe hypoglycaemic (BG ≤ 4.0 mmol/L and BG ≤ 2.2 mmol/L respectively), and in severe hyperglycaemia (BG > 10.0 mmol/L). Performance is evaluated by the percentage BG in target band (4.4-8.0 mmol/L or 5.6-8.3 mmol/L), and per-patient median BG achieved. Workload considers the number of measurements per day. Nutrition comparisons are made using the per-patient dextrose rates achieved in g/h and in % of the original GF. Compliance is analysed by the % of interventions unchanged from the original protocol recommendations. Only changes in insulin rate (and/or nutrition for STAR) occurring within 15 minutes after recommendation time are considered, unless it resulted from clinical stoppage. BG measurements are resampled hourly to allow fair comparison of the data, using linear interpolation (Stewart *et al.*, 2018b).

3. RESULTS

Clinical results for STAR-IO, STAR, and retrospective results for SP are presented in Table 1. Resampled BG, insulin, and nutrition cumulative distribution functions (CDFs) are shown in Fig. 2.

Performance is significantly higher for STAR. Lower (6.5 [6.1, 7.2] mmol/L) BG levels were achieved compared to STAR-IO (6.7 [5.9, 7.6] mmol/L) and SP (7.7 [6.5, 8.9] mmol/L), with less variability for STAR compared to STAR-IO (overall median [IQR] hour-to-hour BG measurements difference of 0.3 [0.1, 0.5] mmol/L vs. 0.4 [0.2, 0.8] mmol/L). Time in target band (4.4-8.0 mmol/L) was much higher for STAR (88%) compared to STAR-IO (78%). SP %BG in that range was only 55%. Considering the SP target band (5.6-8.3 mmol/L), STAR outperformed both STAR-IO and SP (84%, 67%, and 54%).

Table 1. Clinical results for STAR-IO, STAR, and SP.

	STAR	***STAR-IO***	***SP***
# Patients	10	12	20
Total hours	455	674	5006
Workload (meas/day)	12	16	7
Median BG (mg/dL)	6.5 [6.1, 7.2]	6.7 [5.9, 7.6]	7.7 [6.5, 8.9]
Median ΔBG (mg/dL)	0.3 [0.1, 0.5]	0.4 [0.2, 0.8]	N/A
Per-patient median insulin (U/h)	3.0 [2.0, 4.0]	3.5 [2.0, 4.5]	2.5 [2.0, 3.0]
Per-patient median dextrose (g/h)	7.3 [5.0, 8.4]	7.8 [6.5, 8.8]	9.8 [8.6, 11.5]
Per-patient median dextrose (%GF)	90 [61, 100]	90 [55, 130]	N/A
% BG in 4.4-6.5 mmol/L	47	42	N/A
% BG in 4.4-8.0 mmol/L	88	78	55
% BG in 5.6-8.3 mmol/L	84	67	54
% BG in 8.0-10.0 mmol/L	9	11	31
% BG > 10.0 mmol/L	2	10	12
% BG < 4.4 mmol/L	1	1	1
% BG < 4.0 mmol/L	1	0.5	0.5
% BG < 2.2 mmol/L	0	0	0
# Patients < 2.2 mmol/L	0	0	0
% intervention unchanged	98	90	79

Data given as median [IQR] as appropriate, multiply by 18 for mg/dL.

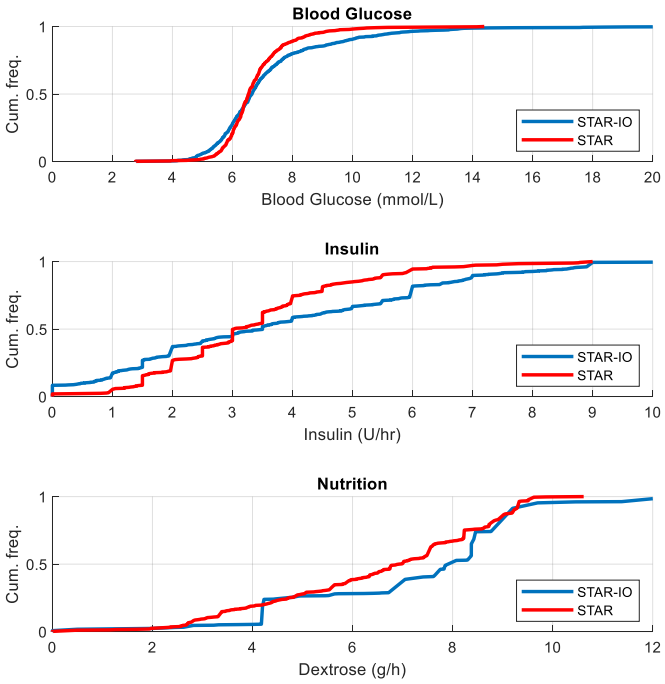

Fig. 2. BG, Insulin, and Nutrition cumulative distribution functions for STAR and STAR-IO.

Safety was high and similar across all protocols, but STAR had slightly higher mild hypoglycaemia (1% BG < 4.0 mmol/L) compared to STAR-IO and SP (0.5%). No patients in any arms experienced severe hypoglycaemia. On the other extreme, severe hyperglycaemia (BG > 10.0 mmol/L) was significantly lower for STAR (2%), compared to STAR-IO (10%) and SP (12%). Mild hyperglycaemia (8.0-10.0 mmol/L) for STAR and STAR-IO were similar (9% and 11%), and significantly lower than SP (31%).

Higher per-patient median insulin rates were administered for STAR-IO (3.5 [2.0, 4.5] U/h) compared to STAR (3.0 [2.0, 4.0] U/h) and SP (2.5 [2.0, 3.0]), while the per-patient median dextrose rate was higher for SP (9.8 [8.6, 11.5] g/h) compared to STAR-IO (7.8 [6.5, 8.8] g/h) and STAR (7.3 [5.0, 8.4] g/h). However, this difference between STAR and STAR-IO becomes smaller when considering the %GF (90 [61, 100] vs. 90 [55, 130] %GF).

Overall, these results were achieved with higher workload for STAR-IO (16 measures per day) and STAR (12 measures per day) compared to SP (7 measures per day). However, these outcomes are expected from protocol design.

Finally, compliance to protocol was high for all protocols, but, interestingly, much higher for STAR (98%) and STAR-IO (90%) compared to the standard protocol (79%).

4. DISCUSSION

Clinical results from this ongoing trial are encouraging, and suggest key observations. Overall, STAR (and STAR-IO) achieved safe and effective control for all patients, despite targeting a lower target band than SP or those usually recommended in ICU guidelines. This result suggests intensive GC to lower target bands is possible without increasing hypoglycaemic risks. Furthermore, it reinforces the idea that GC has been wrongly blamed for hypoglycaemia (Uyttendaele, *et al.*, 2019b), while protocol design is the primary concern to safely achieve high quality GC outcomes. This goal is essential before assessing potential clinical outcome, and failing to do so would suggest poor protocol design (Uyttendaele, *et al.*, 2017).

The difference in %BG in the 4.4-8.0 mmol/L range using STAR (~80-90%) compared to SP (55%) is significant, and these ranges have been associated with improved outcomes in numerous studies (Krinsley *et al.*, 2015; Penning, *et al.*, 2014a; Signal *et al.*, 2012). While this result could be explained from the modestly different target band, SP only managed to have 54 %BG within target (5.6-8.3 mmol/L), where STAR (84%) and STAR-IO (67%) performed better in this range also.

SP %BG in mild hyperglycaemia is high compared to STAR and STAR-IO (31% vs. ~10%). The higher target could somewhat explain this result, or the higher BG level starting criteria (10.0 mmol/L compared to 8.0 mmol/L with STAR). However, it is likely a consequence of clinical judgement considering BG in 8.0-10.0 mmol/L as acceptable. The lower compliance to protocol for SP (79%) could also explain this result (Penning, *et al.*, 2014b).

A previous analysis showed that 68% of the 21% total interventions changed from original protocol recommendations were made when BG was above target band. For those 68%, nurses (unexpectedly) decreased insulin in 62% of the deviations. While in band, 18% of the 21% total intervention changes were made, from which 78% were a decreased in insulin rate. In STAR and STAR-IO, compliance to protocol was high, and even higher for STAR. Typically, nurses increased insulin for very resistant patients. However, insulin effect saturates insulin at 9U/h. Two changes were made to reduce insulin, while close to 4.4 mmol/L, by fear of hypoglycaemia.

STAR's lower incidence of mild and severe hyperglycaemia compared to STAR-IO is a consequence of nutrition modulation. This result is also reflected in the overall nutrition rates achieved, and insulin requirements (Fig. 2). While being somewhat lower in STAR, the gain in performance is significant. In fact, nutrition below GF for STAR is minimal, because nutrition is mainly temporarily decreased for very resistant patients, where BG remains high while receiving the maximum insulin rate. These patients BG levels can only be lowered if glucose intake is lowered.

A recent study analysed the nutrition delivery of STAR compared to other ICUs in the world, and showed STAR performs equal to the best ICUs in the world (Stewart *et al.*, 2018a). Therefore, despite modulating nutrition, STAR does not underfeed patients, and still manages to improve GC outcomes.

The main trade-off using STAR is the increased workload. Workload for STAR (12 measures per day) compared to SP (7 measures per day). However, the increased safety and performance explain the increased clinical burden. Additionally, in a previous study, virtual trials of SP on virtual patients created using this cohort data suggested, despite similar GC outcomes, a likely low compliance to protocol (Uyttendaele *et al.*, 2018b). Simulations show SP needed an average of 11 measurements per day when exactly following the protocol, much higher than the 7 observed here, and, more importantly, very close to the 12 measurements per day required by STAR.

This model-based GC protocol identifies and directly uses inter- and intra- patient variability to improve safety and efficacy of GC, avoiding reliance on clinical judgment (Chase *et al.*, 2018). Altogether, the improved safety, improved performance, and lower glycaemic variability, all associated with lower mortality, lower morbidity and lower ICU length of stay (Ali *et al.*, 2008; Chase, *et al.*, 2010a; Egi *et al.*, 2006; Egi *et al.*, 2010; Krinsley, 2005; Mesotten *et al.*, 2009; Van den Berghe *et al.*, 2006), might be worth the slightly increased workload.

This study compares clinical data to retrospective patients and has some limitations. The number of patients in each arm are not identical, and the results are not based on the exact same underlying cohorts. However, these patients are from the same general medical ICU, and the cohorts are believed to be representative of the overall population. More work is needed to generalise STAR to other population.

5. CONCLUSIONS

STAR was able to achieve safe and effective GC, while targeting lower intermediate glycaemic ranges, associated with improved outcomes. The full STAR version is also able to tailor nutrition needs for the patient, by temporarily reducing caloric intake for persistent hyperglycaemia. This approach significantly improves GC performance compared

to the insulin-only version, STAR-IO. These intermediate results of the STAR-Liège clinical trial are encouraging, and suggest the continuation of this trial.

GC needs to be safe and effective for all patients, regardless of patient condition. Computerised model-based methods using key physiological parameters to identify patient-specific needs have recently proven positive results in GC targeting lower glycaemic ranges. It is thus maybe time to reopen the debate on GC, and avoid to be guided by fear of hypoglycaemia.

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