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Safe and Effective Glycaemic Control for Minimal Workload in Critically Ill Patients: Virtual trials analysis on performance and safety

Marie Seret*, Vincent Uyttendaele*, Thomas Desaive*, and J. Geoffrey Chase**

** GIGA – In silico Medicine, University of Liège, Belgium*
(email: Vincent.Uyttendaele@uliege.be)

***Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand*

Abstract: STAR is a glycaemic control (GC) framework using a unique model-based and risk-based dosing approach. STAR modulates both insulin and nutrition inputs to mitigate the risk of hypo- and hyperglycaemia. This protocol, accounting for both inter- and intra- patient variability successfully manages to provide safe, effective control to all patients, regardless of their condition. In a recent clinical trial in Belgium, workload was pointed as a potential barrier for clinical adoption despite clear benefit for patients. Clinical burden is a key factor in compliance and uptake. This study assesses the impact on GC outcomes when increasing measurement intervals from 1-3 hourly to 1-6 hourly in the STAR GC framework.

Retrospective data from 606 critically ill patients totalling over 59,000 hours of control are used to create virtual patients. Insulin sensitivity is identified for each patient using a validated physiological model, and new stochastic predictive models are built to forecast variability up to 6-hourly. Five-fold cross validation is used to build the models on 80% of data and simulate virtual trials on the remaining 20%. Safety, performance, nutrition intake and workload are compared and analysed.

Results showed similar, very high safety and performance regardless of the measurement intervals, showing STAR GC framework robustness in controlling patients. However, there was a clear risk and reward trade-off between the increased risk of hypoglycaemic event (from 12 to 23 patients between 1-3 hourly and 1-6 hourly protocols) and reduced nutrition intake (from 100 [85 - 100] to 85 [70 - 95] % GF) for the benefit of significant lower workload (from 12.1 to 8.3 measurement per day), closer to clinical practice. These promising results should be confirmed in clinical trials but offer possibilities to adapt measurement strategy based on local ICU practice and clinical burden.

Keywords: Glycaemic Control, Insulin Therapy, Intensive Care, Stochastic Modelling, Hyperglycaemia

1. INTRODUCTION

Stress-induced hyperglycaemia is common in critically ill patients. Hyperglycaemia is associated with worse outcome and mortality. Glucose control (GC) using insulin therapy is thus necessary to reduce blood glucose (BG) levels to safe ranges, and has been associated with improved outcomes (Chase et al., 2010a, Krinsley, 2004, Reed et al., 2007, Van den Berghe et al., 2001). However, patient metabolic variability during critical illness increases the risk of hypoglycaemia, also associated with severe outcomes and mortality (Ali et al., 2008, Bagshaw et al., 2009, Brunkhorst et al., 2008, Chase et al., 2011, Egi et al., 2010, Finfer et al., 2009, Finfer et al., 2012, Krinsley et al., 2007, Preiser et al., 2009).

The lack of safe, effective GC protocols and fear of hypoglycaemia has led to permissive hyperglycaemia (Honarmand et al., 2024), a clear control design failure. In addition, typical protocols currently used in intensive care units (ICU) often lack patient specificity and do not account for patient variability (Chase et al., 2011). Such one size fits all solutions are unable to provide safe control to all patients due to poor protocol design, and often require high clinical effort and variable results (Uyttendaele et al., 2017, Uyttendaele et al., 2019a) . However, recent technologies offer the opportunity to use more complex, model-based, and personalised GC treatment based on patient data. Such computerised solution enables to provide tailored treatment and significantly improve GC outcomes while reducing hypoglycaemic risks (Chase et al., 2010a, Krinsley et al., 2015).

The STAR (Stochastic Targeted) GC control framework is a computerized clinical decision support system using digital twin technology and risk-based artificial-intelligence (AI) to control patients safely and effectively (Evans et al., 2012, Fisk et al., 2012). A digital twin is a real-time digital copy of the patient. This digital twin enables to identify patient-specific response to insulin over time. Predictive AI is then used to assess future patient variability based on patient-specific response history (Le Compte et al., 2010, Lin et al., 2008)., and to optimize insulin and nutrition treatment minimizing the risk of hyper- and hypo- glycaemia while reducing glycaemic variability, all associated with improved outcomes in the ICU (Chase et al., 2010a, Dungan et al., 2009, Egi et al., 2009, Egi et al., 2010, Finfer et al., 2012, Krinsley, 2004, 2005, Reed et al., 2007, Van den Berghe et al., 2001). STAR has been extensively used and shown to provide safe, effective control for nearly all patient despite targeting lower BG ranges, ultimately improving patient outcomes (Abu-Samah et al.,

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2019, Chase et al., 2010a, Krinsley et al., 2015, Stewart et al., 2016, Uyttendaele et al., 2019b).

While the algorithm logic is crucial for good control, protocol compliance is key. Indeed, the ICU is a stressful environment, where resources are limited. The recent COVID-19 pandemic has further emphasized the clinical burden of care. Thus, other factors like excessive workload, double encoding, protocol accessibility and clarity are key factors in the uptake of new digital solutions for GC.

In a recent clinical trial of STAR in a Belgian ICU (Uyttendaele et al., 2020a), where the nurse per patient ratio is low, workload has been clearly pointed as a potential barrier for clinical adoption of STAR. More specifically, retrospective analyses in this specific ICU have shown typical interval measurement was around 4-5 hours, compared to 2.5 hours on average with STAR. Hence, this study aims at extending measurement intervals from 1-3 hourly to 1-6 hourly in the context of STAR to better match clinical practice, and assess the impact of longer measurement intervals on GC outcomes in virtual trials prior potential clinical implementation. Previous work using an older version of STAR already showed the risk and reward trade-off of such an increased interval (Uyttendaele et al., 2020b), but this study aims at confirming the promising results with a focus on a new version of STAR, currently used as a standard of care in some ICUs, using a novel 3D stochastic model for variability prediction.

2. METHODS

2.1 STAR GC framework

STAR is a unique GC framework using a clinically validated digital twins of patients to identify insulin sensitivity (SI). SI characterises patient-specific response to insulin and can be evaluate using clinical data. This parameter varies over time and differs across patients. Its patient-specific evolution over time is then used to predict future variability as confidence intervals using a 3D stochastic model built on population data (Uyttendaele et al., 2018, Uyttendaele et al., 2019c). These confidence intervals can be used to simulate and predict confidence intervals for patient-specific BG evolution for a given treatment. The predicted risk of hypo- and hyper-glycaemia are thus mitigated and minimised by optimizing and recommending insulin and nutrition treatment to nursing staff.

STAR has been extensively shown safe for all patients, despite targeting normoglycaemia ranges (80-145 mg/dL) as it accounts for both inter- and intra- patient variability. SI variability prediction is the key to assess the risk associated with a given treatment. The stochastic model used to predict future patient-specific SI evolution was recently extended to a more complex, 3D models and have shown improved predictions, resulting in improved GC outcomes (Davidson et al., 2019, Davidson et al., 2020, Uyttendaele et al., 2018, Uyttendaele et al., 2019c). Currently, STAR offers 1-3 hourly treatment options if the measurement interval considered result in safe predicted BG outcomes.

To increase STAR treatment options up to 1-6 hourly and simulate the STAR protocol using virtual trials, new 3D-stochastic models must be built and validated first.

2.2 Stochastic modelling

Stochastic models are built on population data using three variate Gaussian kernel density methods. Two inputs (SI_{t-1}, SI_t) are used to estimate the conditional probability of future SI_{t+i} (i=1:6). Each data point is given a gaussian estimator function weighted according to local data density. Gaussian distributions are then normalised in the positive domain ensuring a total conditional probability of 1 for each combination (SI, SI). More details can be found in (Uyttendaele et al., 2018, Uyttendaele et al., 2019c).

Five-fold validation is used to validate the models and its impact on GC outcomes using STAR. Virtual patient data are randomly split in 5 similar groups and new stochastic models are built using 4 groups (80% of data), and tested on the remaining group (20% of data). Each virtual patient will thus be simulated once for each protocol, but using a stochastic model that was built without its own data. This approach provides unbiased and robust analysis from the training and test sets.

2.3 Virtual trials

Virtual trials enable to assess the impact of a GC protocol by simulating the protocol on virtual patients. Virtual patients are anonymised digital copies of high-quality real patient data from which SI traces have been identified and original BG and nutrition rates are used as starting point for the simulation (Chase et al., 2010b). In this study, the new built stochastic models and longer treatment intervals options are integrated and simulated to assess their impact on GC outcomes. It is thus possible to compare GC safety and performance using the different time intervals on the same underlying virtual patient cohort.

Virtual trials represent simulation of protocols in ideal condition. It is thus important to note that the selected treatment is always the longest possible, and BG measurements are considered exactly at the time suggested, reflecting perfect compliance to protocol. These trials are thus not influence by any potential external factors that could affect nurse judgement.

2.4 Comparison analysis

Different metrics are used to analyse safety, performance, and workload on resulting GC outcomes obtained from the simulated virtual trials. These metrics have been chosen based on typically used metrics in GC studies.

Performance is assessed by the median [25^{th} – 75^{th} percentiles] BG levels achieved as well as the %BG in target band. Safety is assessed by both the %BG in moderate (145-180 mg/dL) and severe (>180mg/dL) hyperglycaemia, but more importantly by the %BG in moderate (72-80 mg/dL) and severe (<72 mg/dL) hypoglycaemia. The number of patients experiencing severe hypoglycaemia is also reported. Workload for each protocol is calculated by the number of measurements per day required to control patients. Finally, nutrition rates achieved are also analysed as higher nutrition delivery is associated with improved outcomes in ICU patients. Data are analysed at a cohort level.

Hypothesis testing is used to examine differences, with a statistical significance threshold of $p \leq 0.05$. The Kolmogorov-Smirnov (KS) test was used to identify bias and shape difference in distributions between groups where possible and relevant. BG data is linearly interpolated and hourly resampled to provide more robust representation and comparison between the groups (Stewart et al., 2018).

3. RESULTS

3.1 Patient Cohorts

A total of 606 retrospective patient clinical data was collected. These patients received insulin therapy between July 2005 and May 2015 at the Christchurch Hospital, New Zealand (292 and 267 patients with the SPRINT and the STAR protocols respectively) and the Kalman Pandy Hospital, Hungary (47 patients with STAR). These patients represent a total of 819 GC episodes, corresponding to more than 68,000 hours of control. The number of episodes is greater as patients can have multiple episodes of control during their ICU stay.

From these episodes, only those lasting more than 10 hours and with an initial BG level >125 mg/dL are used. This ensure episodes to be representative of typical GC patients. This results in 681 GC episodes and 59,439 hours of control used in this study. **Table 1** presents cohort demographics. A cohort of 681 independent virtual patients was thus created and used to create the stochastic models and simulate the virtual trials.

3.2 Virtual trial results

Virtual trial results are presented in **Table 2**. All simulated episodes from the five-fold cross-validation are gathered in each column, where each column represents simulations of different time intervals considered. The slight increased number of hours is due to the greater time interval considered for each protocol, adding some hours at the end of a simulated episode.

As expected, the number of measurements required by each protocol is reduced as the maximum time interval considered increases. In STAR 1-3 hourly, 12.1 measurements per day are required while this drops to 8.3 measures per day for STAR 1-6 hourly. The time interval between measurement drops thus from one measure every 2 hours to one measure every 3 hours on average.

Performance in all scenarios was high, with a slight reduction from 83.8 to 81.4 %BG in target for STAR 1-3 hourly and STAR 1-6 hourly, respectively. The median BG achieved shifted upward, but still in well accepted safe ranges (6.4 [5.8 – 7.2 mmol/L] for STAR 1-3 hourly vs. 6.8 [6.2 7.5] mmol/L for STAR 1-6 hourly. Slightly less patients spent at least 50% time in the target band as time interval increased (86.8% to 85.7%).

Interestingly, safety was extremely high and stable regardless of the measurement intervals. While more %BG>8.0mmol/L is observed for higher intervals (14.5 to 16.9%), there is lower %BG<4.4mmol/L (1.7 to 1.6%). However, and more importantly, despite being low, the %BG<2.2mmol/L increased from 0.03% in STAR 1-3 hourly to 0.05% in STAR 1-6 hourly, with a significant increase in patients experiencing hypoglycaemia (12 vs. 23 patients respectively).

The median nutrition achieved as the total % of patient-specific goal feed, was consistently reduced as time interval increased (from 100 [85 100] to 85 [70 95] % GF for STAR 1-3 hourly to STAR 1-6 hourly. Finally, the median insulin rates administered decrease with time intervals (3.5 [2.0 5.0] vs. 2.5 [1.5 3.0] U/h for STAR 1-3 hourly and STAR 1-6 hourly).

4. DISCUSSION

These virtual trial results of STAR using different, increasing measurement intervals showed, surprisingly, outstanding, constant, and robust results regardless the measurement interval considered. This personalised, risk-based approach is able to provide safe, effective GC to nearly all patients, despite targeting lower, often debated, glycaemic target. These virtual trial results once again emphasize the importance of protocol design assessing patient variability and tailoring treatment to each patient for optimised outcomes.

In STAR, treatment options are based on predicted variability. The predicted variability confidence intervals increase with measurement intervals (there is more confidence in predicting 1 hours ahead compared to 6 hours ahead and more extreme changes may occur). This thus typically implies greater predicted risks of both hyper- and hypo- glycaemia, which is reflected in the lower resulting nutrition and insulin delivery rates. Lower nutrition reduces excessive hyperglycaemia, while lower insulin reduces the risk of hypoglycaemia. However, nutrition delivery is important in ICU patients, and associated with improved outcomes. This is thus a first trade-off in using longer measurement intervals, where the risk of severe hyperglycaemia induces lower nutrition intake.

While performance in stable across simulation, the number of severe hypoglycaemias has significantly increased, doubling from 12 to 23 patients for STAR 1-3 hourly and STAR 1-6 hourly, a clear safety concern in the context of GC. This can be explained as 3-hourly measurement interval enables to detect earlier any potential rapid change in SI and, thus, BG compared to 6-hourly interval. An example is depicted in **Figure 1**. The ideal would be to take measurements every hour, or less using continuous glucose monitoring, but is currently clinically not feasible. Clearly, this reflects a direct risk and reward trade-off balancing significant reduced workload achieved from 12.1 to 8.3 measurements per day, closer to what is typically observed clinically.

Table 1 – Cohort demographics summary

	SPRINT Christchurch	**STAR Christchurch**	**STAR Hungary**
Episodes	**442**	**330**	**47**
Patients	292	267	47
Hours	39,838	22,523	6,268
% Male	62.7	65.5	61.7
Age	63 [48 73]	65 [55 72]	66 [58 71]

Data is given as median [25th – 75th percentiles] where appropriate.

Table 2 – Virtual trial results summary

	STAR 1-3hourly	STAR 1-4hourly	STAR 1-5hourly	STAR 1-6hourly
#episodes	681	681	681	681
#hours	59209	59522	59701	60054
#BG measurements	29903	25471	22951	20696
Workload (meas/day)	12.1	10.3	9.2	8.3
Median BG (mmol/L)	6.4 [5.8 - 7.2]	6.6 [6.0 - 7.4]	6.7 [6.1 - 7.5]	6.8 [6.2 - 7.5]
Median Nutrition (%GF)	100% [85% - 100%]	95% [79% - 100%]	90% [75% - 97%]	85% [70% - 95%]
Median Insulin (U/hr)	3.5 [2.0 - 5.0]	3.0 [2.0 - 4.0]	2.5 [2.0 - 3.5]	2.5 [1.5 - 3.0]
%BG in target	83.8	82.9	82.0	81.4
#patients ≥50%BG in 4.4-8.0 mmol/L	591 (86.8)	592 (86.9)	586 (86.0)	584 (85.7)
%BG>8.0mmol/L	14.5	15.5	16.4	16.9
%BG<4.4mmol/L	1.7	1.7	1.6	1.6
%BG<2.2mmol/L	0.03	003	0.05	0.05
#patients BG<2.2mmol/L	12 (1.8)	14 (2.0)	19 (2.8)	23 (3.4)

Data is given as median [25th – 75th percentiles] where appropriate.

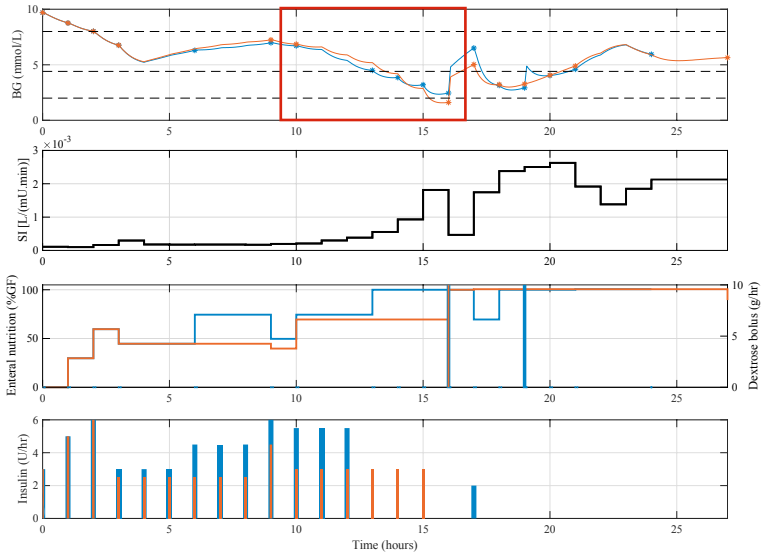

Figure 1 – Comparison of STAR 1-3hourly (blue) and 1-6 hourly (red) simulated GC episode for the same patient. STAR 1-3 hourly earlier detects sudden drop in BG and compensates to avoid severe hypoglycaemia seen at T=16h in STAR 1-6 hourly.

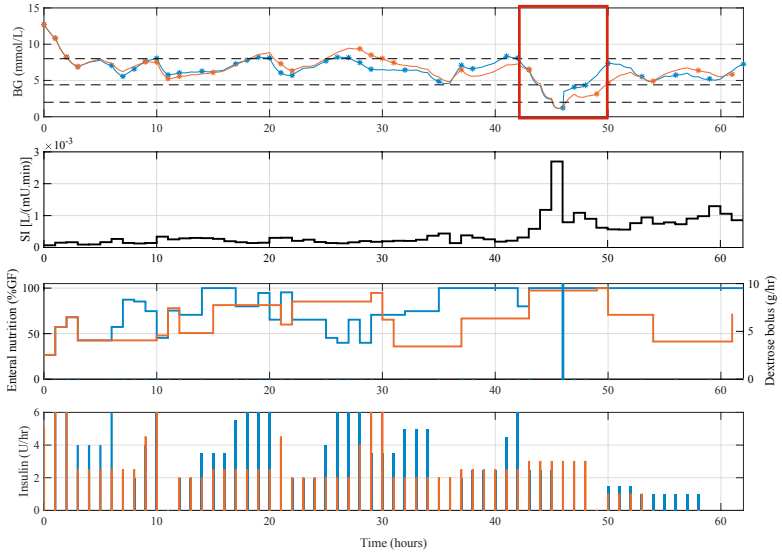

Figure 2 – Comparison of STAR 1-3hourly (blue) and 1-6 hourly (red) simulated GC episode for the same patient. STAR 1-6 hourly fails to detect a severe hypoglycaemic event seen at T=46h. This is a consequence of the different measurement intervals but also the actual timing in the measurements, but reflect how longer treatment intervals may miss hypoglycaemic event, ultimately biasing real (clinical) safety results compared with virtual trial simulations.

It is also important to note that, while it is possible in simulation, some hypoglycaemic event may not even be measured or seen clinically when using longer measurement intervals. Indeed, patient variability is such that, some short hypoglycaemic event may occur and resolve without insulin or nutrition adjustment due to endogenous insulin secretion and glucose production, or even change in SI over time. This observation is important to mention as it can bias judgement when considering increasing the time interval between measurements. An example is shown in **Figure 2**, where the severe hypoglycaemia is detected and a dextrose bolus is administered to the patient at T=46h in the STAR 1-3 hourly protocol, but not in the STAR 1-6 hourly.

Overall, increasing measurement intervals have shown promising results in these virtual trials, with high safety and performance for reduced workload. While a trade-off exists, these positive outcomes suggest confirming the results clinically. A possible trade-off considering the discussion above could be to limit the measurement interval somewhere between 1-3hourly to 1-6 hourly based on local ICU nurse per patient ratio, clinical practice, and clinical acceptance of risks (hypoglycaemia and lower nutrition).

One important limitation in this study is that virtual trial reflects ideal condition and, while they have been validated, other external factors may impact results. The results in terms of safety, efficacy, and protocol compliance may thus be slightly biased compared to clinically.

5. CONCLUSIONS

Virtual trials of STAR comparing measurement intervals from 1-3 hourly up to 1-6 hourly showed STAR robustness in providing very safe, effective control to nearly all patients, regardless of measurement interval considered. However, there are clear considerations regarding the significant increased risk of severe hypoglycaemic event and reduced nutrition intake when opting for longer measurement intervals. These promising results should be confirmed in a clinical trial to consider adopting longer measurement intervals in the STAR GC framework, and respond to the need for reduced workload in ICU settings where clinical burden is extreme.

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REFERENCES

Abu-Samah, A., Knopp, J. L., Abdul Razak, N. N., Razak, A. A., Jamaludin, U. K., Mohamad Suhaimi, F., Md Ralib, A., Mat Nor, M. B., Chase, J. G. and Pretty, C. G. 2019. Model-based glycemic control in a Malaysian intensive care unit: performance and safety study. *Med Devices (Auckl),* 12**,** 215-226.

Ali, N. A., O'brien, J. M., Dungan, K., Phillips, G., Marsh, C. B., Lemeshow, S., Connors, A. F. and Preiser, J. C. 2008. Glucose variability and mortality in patients with sepsis. *Crit Care Med,* 36**,** 2316-21.

Bagshaw, S. M., Bellomo, R., Jacka, M. J., Egi, M., Hart, G. K. and George, C. 2009. The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Crit Care,* 13.

Brunkhorst, F. M., 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. and German Competence Network, S. 2008. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med,* 358**,** 125-39.

Chase, J. G., Pretty, C. G., Pfeifer, L., Shaw, G. M., Preiser, J. C., Le Compte, A. J., Lin, J., Hewett, D., Moorhead, K. T. and Desaive, T. 2010a. Organ failure and tight glycemic control in the SPRINT study. *Crit Care,* 14**,** R154.

Chase, J. G., Suhaimi, F., Penning, S., Preiser, J. C., Le Compte, A. J., Lin, J., Pretty, C. G., Shaw, G. M., Moorhead, K. T. and Desaive, T. 2010b. Validation of a model-based virtual trials method for tight glycemic control in intensive care. *Biomed Eng Online,* 9**,** 84.

Chase, J. G., Le Compte, A. J., Suhaimi, F., Shaw, G. M., Lynn, A., Lin, J., Pretty, C. G., Razak, N., Parente, J. D., Hann, C. E., Preiser, J. C. and Desaive, T. 2011. 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,* 102**,** 156-71.

Davidson, S., Pretty, C., Uyttendaele, V., Knopp, J. L., Desaive, T. and Chase, J. G. 2019. Multi-input stochastic prediction of insulin sensitivity for tight glycaemic control using insulin sensitivity and blood glucose data. *Comput Methods Programs Biomed,* 182.

Davidson, S., Uyttendaele, V., Pretty, C., Knopp, J. L., Desaive, T. and Chase, J. G. 2020. Virtual patient trials of a multi-input stochastic model for tight glycaemic control using insulin sensitivity and blood glucose data. *Biomedical Signal Processing and Control*.

Dungan, K. M., Braithwaite, S. S. and Preiser, J. C. 2009. Stress hyperglycaemia. *Lancet,* 373**,** 1798-807.

Egi, M. and Bellomo, R. 2009. Reducing glycemic variability in intensive care unit patients: a new therapeutic target? *J Diabetes Sci Technol,* 3**,** 1302-8.

Egi, M., Bellomo, R., Stachowski, E., French, C. J., Hart, G. K., Taori, G., Hegarty, C. and Bailey, M. 2010. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc,* 85**,** 217-24.

Evans, A., Le Compte, A., Tan, C. S., Ward, L., Steel, J., Pretty, C. G., Penning, S., Suhaimi, F., Shaw, G. M., Desaive, T. and Chase, J. G. 2012. Stochastic targeted (STAR) glycemic control: design, safety, and performance. *J Diabetes Sci Technol,* 6**,** 102-15.

Finfer, S., Chittock, D. R., Su, S. Y., Blair, D., Foster, D., Dhingra, V., Bellomo, R., Cook, D., Dodek, P., Henderson, W. R., Hebert, P. C., Heritier, S., Heyland, D. K., Mcarthur, C., Mcdonald, E., Mitchell, I., Myburgh, J. A., Norton, R., Potter, J., Robinson, B. G. and Ronco, J. J. 2009. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med,* 360**,** 1283-97.

Finfer, S., Liu, B., Chittock, D. R., Norton, R., Myburgh, J. A., Mcarthur, C., Mitchell, I., Foster, D., Dhingra, V., Henderson, W. R., Ronco, J. J., Bellomo, R., Cook, D., Mcdonald, E., Dodek, P., Hebert, P. C., Heyland, D. K. and Robinson, B. G. 2012. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med,* 367**,** 1108-18.

Fisk, L. M., Le Compte, A. J., Shaw, G. M., Penning, S., Desaive, T. and Chase, J. G. 2012. STAR development and protocol comparison. *IEEE Trans Biomed Eng,* 59**,** 3357-64.

Honarmand, K., Sirimaturos, M., Hirshberg, E. L., Bircher, N. G., Agus, M. S. D., Carpenter, D. L., Downs, C. R., Farrington, E. A., Freire, A. X., Grow, A., Irving, S. Y., Krinsley, J. S., Lanspa, M. J., Long, M. T., Nagpal, D., Preiser, J. C., Srinivasan, V., Umpierrez, G. E. and Jacobi, J. 2024. Society of Critical Care Medicine Guidelines on Glycemic Control for Critically Ill Children and Adults 2024. *Crit Care Med*.

Krinsley, J. S. 2004. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc,* 79**,** 992-1000.

Krinsley, J. S. 2005. Glucose control reduces ICU stay and mortality. *Perform Improv Advis,* 9**,** 4-6, 1.

Krinsley, J. S. and Grover, A. 2007. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med,* 35**,** 2262-7.

Krinsley, J. S. and Preiser, J. C. 2015. Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults. *Crit Care,* 19**,** 179.

Le Compte, A. J., Lee, D. S., Chase, J. G., Lin, J., Lynn, A. and Shaw, G. M. 2010. Blood glucose prediction using stochastic modeling in neonatal intensive care. *IEEE Trans Biomed Eng,* 57**,** 509-18.

Lin, J., Lee, D., Chase, J. G., Shaw, G. M., Le Compte, A., Lotz, T., Wong, J., Lonergan, T. and Hann, C. E. 2008. Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care. *Comput Methods Programs Biomed,* 89**,** 141-52.

Preiser, J. C., Devos, P., Ruiz-Santana, S., Melot, C., Annane, D., Groeneveld, J., Iapichino, G., Leverve, X., Nitenberg, G., Singer, P., Wernerman, J., Joannidis, M., Stecher, A. and Chiolero, R. 2009. 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,* 35**,** 1738-48.

Reed, C. C., Stewart, R. M., Sherman, M., Myers, J. G., Corneille, M. G., Larson, N., Gerhardt, S., Beadle, R., Gamboa, C., Dent, D., Cohn, S. M. and Pruitt, B. A., Jr. 2007. Intensive insulin protocol improves glucose control and is associated with a reduction in intensive care unit mortality. *J Am Coll Surg,* 204**,** 1048-54; discussion 1054-5.

Stewart, K. W., Pretty, C. G., Tomlinson, H., Thomas, F. L., Homlok, J., Noemi, S. N., Illyes, A., Shaw, G. M., Benyo, B. and Chase, J. G. 2016. Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis. *Ann Intensive Care,* 6**,** 24.

Stewart, K. W., Pretty, C. G., Shaw, G. M. and Chase, J. G. 2018. Interpretation of Retrospective BG Measurements. *J Diabetes Sci Technol,* 12**,** 967-975.

Uyttendaele, V., Dickson, J. L., Shaw, G. M., Desaive, T. and Chase, J. G. 2017. Untangling glycaemia and mortality in critical care. *Crit Care,* 21**,** 152.

Uyttendaele, V., Dickson, J., Stewart, K., Desaive, T., Benyo, B., Szabo-Nemedi, N., Illyes, A., Shaw, G. and Chase, G. 2018. A 3D insulin sensitivity prediction model enables more patient-specific prediction and model-based glycaemic control. *Biomed Signal Process Control,* 46**,** 192-200.

Uyttendaele, V., Knopp, J. L., Shaw, G. M., Desaive, T. and Chase, J. G. 2019a. Is intensive insulin therapy the scapegoat for or cause of hypoglycaemia and poor outcome? *IFAC Journal of Systems and Control,* 9.

Uyttendaele, V., Knopp, J. L., Pirotte, M., Morimont, P., Lambermont, B., Shaw, G. M., Desaive, T. and Chase, J. G. 2019b. STAR-Liège Clinical Trial Interim Results: Safe and Effective Glycemic Control for All. *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC).* Berlin, Germany: IEEE.

Uyttendaele, V., Knopp, J. L., Davidson, S., Desaive, T., Benyo, B., Shaw, G. M. and Chase, J. G. 2019c. 3D kernel-density stochastic model for more personalized glycaemic control: development and in-silico validation. *BioMedical Engineering OnLine,* 18**,** 102.

Uyttendaele, V., Knopp, J. L., Pirotte, M., Morimont, P., Lambermont, B., Shaw, G. M., Desaive, T. and Chase, J. G. 2020a. Translating A Risk-Based Glycaemic Control Framework for Critically Ill Patients: STAR-Liège. *IFAC-PapersOnline***,** 6-pages.

Uyttendaele, V., Knopp, J. L., Shaw, G. M., Desaive, T. and Chase, J. G. 2020b. Risk and Reward: Extending stochastic glycaemic control intervals to reduce workload. *Biomed Eng Online*.

Van Den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P. and Bouillon, R. 2001. Intensive insulin therapy in critically ill patients. *N Engl J Med,* 345**,** 1359-67.