STAR-3D Clinical Trial Results: Improved performance and safety

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Abstract: Glycemic control (GC) has improved outcomes for intensive care unit (ICU) patients. However, the increased risk of hypoglycemia and glycemic variability due to inter- and intra- patient variability make safe, effective GC difficult. Stochastic TARgeted (STAR) GC framework is a unique, patient-specific, risk-based dosing protocol directly accounting for both inter- and intra- patient variability using a stochastic model of future patient variability. A new tri-variate (3D) stochastic model, developed and validated in virtual trials to provide more accurate future predictions of insulin sensitivity (SI), is clinically evaluated.

STAR-3D was implemented as standard care at the Christchurch Hospital ICU, New Zealand, between April 2019 and January 2021. In total, 567 patients (33276 hours) were treated. The overall median [IQR] BG achieved was 6.7 [6.0 7.8] mmol/L with 76% BG in the 4.4-8.0 mmol/L target band. Importantly, there were only 0.3% BG < 4.0 mmol/L (mild hypoglycemia) and no incidence of severe hypoglycemia (BG < 2.2 mmol/L). These outcomes were achieved with median [IQR] 4.0 [2.0 6.0] U/h insulin and median [IQR] nutrition delivery of 99 [80 100]% goal feed (GF). Similar safety and performance BG outcomes were obtained at a per-patient level, suggesting STAR-3D successfully provided safe, effective control for all patients, regardless of patient condition. Compared to the original version of STAR, STAR-3D provided improved safety and efficacy, while achieving higher nutrition delivery.

The new 3D stochastic model in STAR-3D provided higher safety and efficacy for all patients in this large clinical trial, despite using higher insulin rates than its predecessor to provide greater nutrition delivery. STAR-3D thus better captured patient-specific condition and variability to provide improved GC outcomes.

Keywords: Glycemic Control, Hyperglycemia, Hypoglycemia, Insulin, Clinical Trial, Intensive Care

1. INTRODUCTION

Patients admitted to critical care often experience stress-induced hyperglycemia (McCowen et al., 2001), associated with increased mortality and morbidity (Krinsley, 2003). It is mainly driven by increased insulin resistance and excessive endogenous glucose production (McCowen et al., 2001). Early studies showed glycemic control (GC) is associated with improved outcomes in critically ill patients (Chase et al., 2010a, Krinsley, 2004, Reed et al., 2007, Van den Berghe et al., 2001). However, other studies failed to replicate these results (Brunkhorst et al., 2008, Finfer et al., 2009, Finfer et al., 2012, Preiser et al., 2009), where the associated increased risk of hypoglycemia and glycemic variability, both associated with increased mortality and morbidity (Ali et al., 2008, Bagshaw et al., 2009, Egi et al., 2010, Krinsley et al., 2007), suggests GC is hard to achieve safely and effectively due to inter- and intra- patient variability (Chase et al., 2011a).

More specifically, recent studies have shown GC protocols failing to achieve safe control for nearly all patient could mainly be due to protocol design rather the GC itself (Uyttendaele et al., 2017, Uyttendaele et al., 2019c). Importantly, glycemic outcome and mortality is a function of the quality of control achieved and not patient condition, showing the importance to provide safe, and effective control to all patients (Penning et al., 2015, Uyttendaele et al., 2017).

GC protocols accounting for patient-specificity and ensuring high protocol compliance are thus needed (Chase et al., 2011b, Chase et al., 2011a, Chase et al., 2018a, Chase et al., 2018b, Chase et al., 2019, Uyttendaele et al., 2019c).

The Stochastic TARgeted (STAR) GC framework is a unique model-based, patient-specific, and risk-based insulin dosing approach accounting for both inter- and intra- patient variability (Evans et al., 2012, Fisk et al., 2012). STAR uses a validated physiological model together with stochastic predictions to evaluate patient-specific risk of hyper- and hypo- glycemia for any given treatment (Lin et al., 2008, Lin et al., 2011). Uniquely, STAR modulates both insulin and nutrition inputs for increased quality of control while optimizing nutrition also (Stewart et al., 2016, Stewart et al., 2018a, Uyttendaele et al., 2020a). STAR was independently proven safe and effective across cohorts and countries (Abu-Samah et al., 2019, Stewart et al., 2016, Uyttendaele et al., 2018a, Uyttendaele et al., 2019a, 2020a).

Currently, STAR uses hourly identified model-based insulin sensitivity (SI) to forecast future likely variations in patient-specific response to insulin, and mitigate risks accordingly (Lin et al., 2008). GC outcomes thus significantly rely on these predictions for control quality and outcomes. Previously, a more personalized 3D stochastic model using previous and current identified SI levels to forecast future SI was developed

and simulated using validated virtual trials (Uyttendaele et al., 2018b, Uyttendaele et al., 2019b). Results showed the potential ability of this new model to provide more personalized care by improving future SI forecasting and thus improved safety and efficacy in STAR compared to prior efforts using a lower dimensionality (Le Compte et al., 2010, Lin et al., 2006, Lin et al., 2008). Based on these encouraging results, a clinical trial using the new 3D stochastic model was implemented in the Christchurch Hospital Intensive Care Unit (ICU), New Zealand, where STAR is the standard of care. This study presents and compares preliminary results.

2. METHODS

2.1 STAR-3D protocol

STAR is a model-based GC framework developed to provide patient-specific, risk-based GC (Evans et al., 2012, Fisk et al., 2012, Lin et al., 2008, Lin et al., 2011). Time-varying, patient-specific SI levels are identified from clinical data using a clinically validated physiological model, accounting for inter-patient variability. SI characterizes patient-specific metabolic response to insulin, reflecting thus patient's current metabolic state, which can differ for each patient despite similar levels of glycemia, insulin, and carbohydrate intake (Chase et al., 2011a, Lin et al., 2011).

Intra-patient variability is assessed using a stochastic model (Uyttendaele et al., 2018b, Uyttendaele et al., 2019b). This model uses tri-variate kernel-density methods on large population data to provide a 90% confidence interval of future variation of future SI based on previous and current SI levels (Davidson et al., 2019, Uyttendaele et al., 2018b, Uyttendaele et al., 2019b). Based on these predictions, STAR evaluates the corresponding likelihood of future blood glucose (BG) levels for any insulin and nutrition inputs, as depicted in Figure 1. This new 3D stochastic model was developed, tested, and validated in virtual trials showing improved prediction accuracy in SI variability, and, thus, the potential to add precision to STAR GC control and improve clinical outcomes (Chase et al., 2010b, Dickson et al., 2017, Uyttendaele et al., 2018b, Uyttendaele et al., 2019b).

STAR treatment recommendations are thus suggested based on predicted risks. STAR determines what combination of insulin and nutrition results in the 90% CI of predicted BG best overlapping the 4.4-8.0 mmol/L (80-145 mg/dL) target band (Evans et al., 2012). This always ensures a maximum risk of 5% of predicted BG being below target, as safety is always ensured first. STAR currently offers up to three-hourly measurements option. However, 2- and 3- hourly interventions are not considered if no treatment option exists to ensure safety.

In this clinical trial, patients were included after 2 consecutive BG assays > 8.0 mmol/L (145 mg/dL). Insulin boluses of maximum 6U can be administered intra-venously, with a maximum of 2U increments between intervention, and possible 3U/h additional infusion for highly resistive patients. Nutrition can be temporarily decreased by maximum 30% steps between interventions, down to a minimum of 30% of the original 100% goal feed (GF). GF is determined based on typical 25kcal/kg/day recommendations (Singer et al., 2019) and adjusted based on age, sex and weight. Typically nutrition is reduced if insulin only is not sufficient to safely decrease BG levels in highly insulin resistant patients. STAR will always try to maximize nutrition. In the event of hypoglycemia (BG < 3.0mmol/L), a dextrose bolus (10ml of 50% glucose) is directly administered and insulin stopped. In case of hypoglycemia, a new BG measurement within 1 hour is required.

STAR is stopped if BG levels are stable (in target band) for at least 6 hours with total exogenous insulin rates ≤ 2U/h. It is important to note that patients can be included multiple times on STAR if their glycemia is dysregulated again after being stabilized. BG assays are taken using blood gas analyzer or glucometers, where typical reported measurement error in glucometers has minimal impact on decision making in the context of STAR (Uyttendaele et al., 2017).

STAR is fully computerized and used on Android™ Tablets at patient bedside. Medical staff can easily enter BG, insulin, and
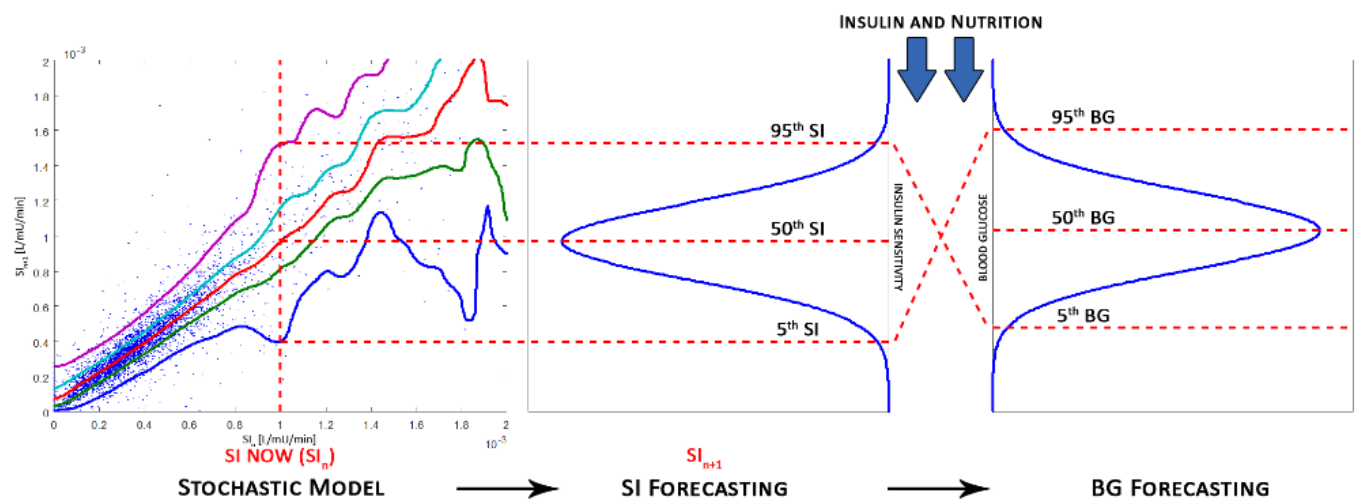

Figure 1 - STAR uses stochastic models to forecast change in SI based on current SI value, and determines BG outcomes for given insulin and nutrition intervention.

nutrition data directly in the tablet, and calculate a new treatment when required. Nurses are free to choose between the suggested 1-3 hour interval treatments and adapt rates according to their clinical judgment. This trial was implemented in the Christchurch Hospital ICU, New Zealand, as a clinical practice change and did not require ethics approval as the New Zealand Upper South Island Regional Ethics Committee approved the analysis and use of de-identified data as a clinical data audit.

2.2 Protocol performance analysis

Clinical trial data are analyzed to assess safety, efficacy, BG achieved, insulin and nutrition rates administered, and protocol workload. BG data is linearly interpolated and hourly resampled for each patient (Stewart et al., 2018b). Safety is assessed by percentage BG in mild hypoglycemia (% BG < 4.0 mmol/L), in severe hypoglycemia (% BG < 2.2 mmol/L), and the number of patients experiencing severe hypoglycemia. Safety from hyperglycemia is assessed by the percentage BG in mild hyperglycemia (%BG > 8.0 mmol/L), and severe hyperglycemia (%BG > 10.0 mmol/L). Severe hyper- and hypo- glycemia are associated with increased mortality in ICU patients (Dungan et al., 2009, Egi et al., 2009, Egi et al., 2010, Finfer et al., 2012, Krinsley, 2005).

Efficacy is assessed by %BG in target band (%BG in 4.4 – 8.0 mmol/L) and by the median [IQR] BG level achieved. More specifically, high %BG in 4.4 - 8.0 mmol/L is associated with improved outcome in ICU patients (Chase et al., 2010a, Krinsley et al., 2015, Penning et al., 2014, Signal et al., 2012).

Finally, workload is assessed by average BG measurements per day. Median insulin and nutrition rates are computed for each patient to assess patient-specific needs and how well they are met within glycemic control.

3. RESULTS

3.1 Patient Cohort

In total, 787 patients were included in this trial between April 2019 and January 2021. From these patients, 567 (72%) patients with GC episodes longer than 10 hours, average nutrition rates lower than 120% GF, and targeting the 4.4-8.0 mmol/L target band are included in this analysis. These criteria ensure the normal per-protocol use of STAR and discard too short GC episodes or some that might have been specifically biased by medical staff. These 567 patients correspond to 33276 hours of GC.

In this cohort, 72% of patients are male, while the median [IQR] age is 65 [52 73] years old. These numbers are close to those typically seen in general ICU setting patients. Demographics are summarised in Table 1.

3.2 Cohort Clinical results

Cohort clinical trial results are presented in Table 2 and Figure 2. In total, 19329 BG assays were taken, representing a workload of 14.0 measurements per day (one every 1.7 h). The median [IQR] BG achieved was 6.7 [6.0 7.8] mmol/L. STAR-

3D was highly effective, with more than 76% of hourly resampled BG within target band.

STAR also provided highly safe control, with only 0.3% mild hypoglycemia and, importantly, no incidence of severe hypoglycemia. There was only 13.7% BG in mild hyperglycemia, and 9.1% in severe hyperglycemia. This highly safe, effective control was achieved with median [IQR] insulin of 4.0 [2.0 6.0], and median [IQR] dextrose rates 99 [80 100] % GF. These carbohydrate intake rates do not consider 21.4% of unfed hours based on clinical choice.

Table 1 – Summary patient demographics

	STAR-3D
Number of patients	567
Control hours (h)	33276
Percent male (%)	72
Age (years)	65 [52 73]

Table 2 – Cohort clinical results.

	STAR-3D
Number of patients	567
Hours of control (h)	33276
Total BG measurements	19329
Workload (measurements/day)	14.0
BG (mmol/L)	6.7 [6.0 7.8]
% BG in 4.4-8.0 mmol/L (%)	76.3
% BG in 8.0 - 10.0 mmol/L (%)	13.7
%BG > 10.0 mmol/L (%)	9.1
% BG < 4.0 mmol/L (%)	0.3
% BG < 2.2 mmol/L (%)	0
Number of patient < 2.2 mmol/L	0
Insulin rates (U/h)	4.0 [2.0 6.0]
Total hours not fed (%)	21.4
Dextrose rates excl. not fed hours (%GF)	99 [80 100]

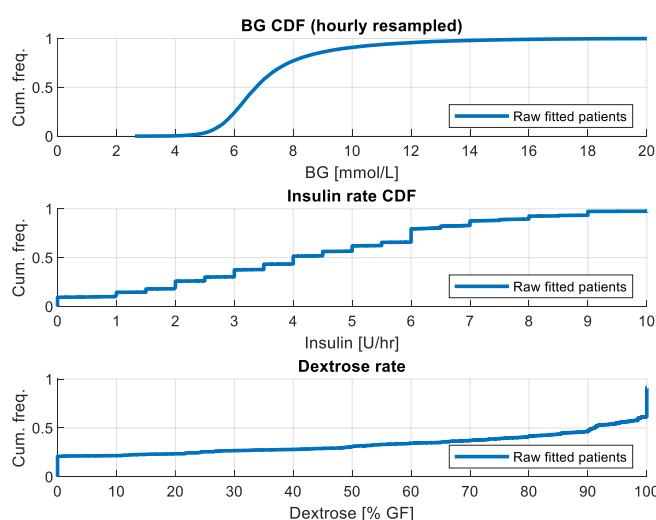*Data is given as median [IQR] where appropriate.*

Figure 2 – Cohort BG (top), insulin (middle), and dextrose (bottom) rates achieved cumulative distribution functions.

3.3 Per-patient clinical results

Per-patient results are presented in Table 3. Per-patient results are important, as high GC performance must also importantly be achieved for all patients, and not only be good at a cohort perspective. Median [IQR] GC episode length was 1.6 [0.7 3.1] days, and the median [IQR] starting BG was 10.9 [9.2 13.4] mmol/L. Median [IQR] per-patient workload was 14.9 [12.5 17.5] measurements per day. The median [IQR] median BG achieved was 6.7 [6.2 7.4] mmol/L, with 79 [60 89] %BG within target band.

Table 3 – Per-patient clinical results.

	STAR-3D
Number of patients	567
Episode length (days)	1.6 [0.7 3.1]
Starting BG (mmol/L)	10.9 [9.2 13.4]
Workload (measurements/day)	14.9 [12.5 17.5]
Median BG (mmol/L)	6.7 [6.2 7.4]
% BG in 4.4-8.0 mmol/L (%)	79 [60 89]
% BG in 8.0 - 10.0 mmol/L (%)	11 [6 19]
%BG > 10.0 mmol/L (%)	6 [0 18]
% BG < 4.0 mmol/L (%)	0 [0 0]
% BG < 2.2 mmol/L (%)	0 [0 0]
Number of patient < 2.2 mmol/L	0
Median insulin rates (U/h)	4.0 [2.5 5.0]
Patients with nutrition (%)	68
Median dextrose rates excl. patients not fed (%GF)	97 [71 100]

Data is given as median [IQR] where appropriate.

In terms of safety, median [IQR] %BG < 4.0 mmol/L as well as %BG < 2.2 mmol/L was 0 [0 0]%, with no patient experiencing severe hypoglycemia. The median [IQR] per-patient %BG in 8.0-10.0 mmol/L and % BG > 10.0 mmol/L was 11 [6 19]% and 6 [0 18]%, respectively.

These results were achieved with median [IQR] per-patient median insulin rates of 4.0 [2.5 5.0] U/h and median [IQR] 97 [71 100] %GF nutrition rates. Only 32% (180) of patients did not receive nutrition during GC.

4. DISCUSSION

This trial was implemented following encouraging results showing STAR-3D, using a new 3D, tri-variate stochastic model to better account for changes in identified patient-specific insulin sensitivity, could significantly improve GC outcomes (Uyttendaele et al., 2018b, Uyttendaele et al., 2019b). More specifically, improving prediction of future SI levels improves the assessment of hypoglycemic risk associated with any specific treatment, thus improving BG outcomes, GC, and, as a result, outcomes.

Overall, STAR-3D provided highly effective control (76.3% BG in band and 79 [60 89] per-patient %BG in band) and very high safety with no incidence of severe hypoglycemia (and very low 0.3% overall incidence of mild hyperglycemia). The 6.7 [6.0 7.8] mmol/L cohort BG and the per-patient 6.7 [6.2 7.4] mmol/L median BG show how STAR-3D successfully managed to control BG to beneficial ranges. Importantly,

while STAR-3D provided high quality control at a cohort perspective, these observations are all true at a per-patient perspective, showing STAR-3D provides high quality control to all patients, thanks to its patient-specific, risk-based dosing approach. Altogether, these outcomes are all associated with improved outcomes ICU patients (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).

In addition, STAR-3D was able to provide very high nutrition rates (99 [80 100] %GF for the overall cohort, 97 [71 100]%GF at per-patient level). These high, patient-specific nutrition rates achieved are close to best ICU settings in the world (Stewart et al., 2018a), despite remaining in safe BG ranges, and thus likely avoiding both over- and under- feeding.

The workload required to achieve these high performance and safety levels (14.0 measures per day, 14.9 [12.5 17.5] measures per day per-patient) may seem higher than most protocols only measuring every 4 hours. It is higher than the 12 measurements per day observed in the original version of STAR using a 2D stochastic model (Stewart et al., 2016). However, this trial shows similar to higher efficacy and higher safety, despite the higher insulin and nutrition rates achieved. This result thus suggests the 3D stochastic model, with improved prediction, better accounts for patient-specificity and provides safer, more effective control with more nutrition intake, but at the cost of slightly higher workload.

Finally, for context, it is very important to mention the starting BG in this trial is significantly higher than the value reported using the original version of STAR, which can clearly affects the slightly higher median BG achieved and the increased workload (Stewart et al., 2016). This issue is compounded by the reduced time on GC due to improved control. In a previous study, virtual trials showed workload could be reduced by increasing measurement intervals up to 6 hours, but would imply a trade-off between workload, safety, and nutrition intake (Uyttendaele et al., 2020b). However, overall, these results and slightly increased workload are likely anomalies of the reduced time on GC and improved control, where GC is halted when time in band is high and insulin is low.

5. CONCLUSIONS

The new 3D stochastic model used in STAR expectedly enabled greater patient-specific control, and provided highly safe, effective control to all patients. STAR-3D also provided higher nutrition delivery compared to its predecessor. These outcomes likely suggest improved patient outcome as the higher safety, efficacy, nutrition delivery achieved in this trial are all associated with improved outcome in ICU patients, but more analyses are needed to confirm this statement.

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