

When NICE is Not Nice: Performance of Two ICU Glycaemic Control Protocols

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Objectives

Glycaemic control using insulin therapy has shown clinical benefits and improved outcomes in critical care. However, the international multi-centered NICE-SUGAR trial have failed to reproduce these results.

This study compares the table-based NICE-SUGAR and model-based STAR protocols and assess their relative capability to achieve safe, effective control for all patients. The level of compliance is also tested using NICE-SUGAR published results.

Methods

Clinical Data:

Validated virtual patients (n=443) are used to simulate glycaemic outcomes from the NICE-SUGAR and STAR protocols, and are compared with reported clinical data [1].

Protocols:

- NICE-SUGAR is a table-based protocol targeting 4.5-6.0 mmol/L (intensive therapy). There are no guidelines regarding nutrition. The original protocol measures hourly.
- STAR is a model-based protocol modulating both insulin and nutrition. The STAR target band is 4.4-8.0 mmol/L, and enteral feed is modulated between 30-100% goal feed.
- NICE-SUGAR 3-hours (NS-3H) was created to approximate the number of measurements reported clinically, using 3 hourly measurements if BG is within the 4.5-10 mmol/L band, unless BG decreased rapidly.

As NICE-SUGAR does not modulate nutrition, 100% STAR goal feed was used for all patients.

Performance and safety analysis:

- Performance is assessed by:
 - % time in the 4.4-8.0mmol/L
 - Per-patient mean blood glucose (BG) level.
- Safety is evaluated by:
 - Number of severe hypoglycaemic events (BG < 2.2 mmol/L)
 - % BG < 4.0 mmol/L

STAR vs. NICE-SUGAR (per protocol):

- STAR provides better performance than NICE-SUGAR, with higher % BG in 4.4-8.0mmol/L range (90.7% vs. 78.3%), and tighter median [IQR] per-patient BG (6.2 [5.9, 6.6] vs. 6.5 [5.9, 7.6]).
- STAR is safer with 5 (1%) vs. 10 (2.5%) patients experiencing severe hypoglycaemia, and 1.2% vs 3.1% BG < 4.0 mmol/L
- STAR has lower workload, with ~12 measurements per day where NICE-SUGAR averages ~25.

NICE-SUGAR clinically reported vs. NS-3H:

- NS-3H resulted in a mean ~10.5 measurements per day, matching better the reported value of 9.4.
- NS-3H safety and per-patient performance were similar to that reported clinically (mean BG (SD) 6.6 (1.9) vs. 6.4 (1.0) mmol/L with 6% of patient experiencing severe hypoglycaemia.

Compliance:

- The reported 9.4 measurements per day does not match the expected ~25 as per protocol, showing clearly the poor compliance of the original NICE-SUGAR study.

Results

Simulation results are summarised in Table 1 and Figure 1.

Table 1 – Simulation results summary and recorded clinical outcome NICE-SUGAR

	NICE-SUGAR		NS-3H	STAR
	Clinical	Sim	Sim	Sim
% Patient receiving insulin	97.2	100	100	100
Average measurement per day	~9.4	~25	~10.5	~12
Mean insulin dose (SD) U/day	50.2 (38.1)	138 (100)	105.5 (64.7)	70.4 (53.5)
Mean resampled BG (SD) [mmol/L]	6.4 (1.0)	6.4 (1.9)	6.6 (1.9)	6.2 (1.2)
Median [IQR] per-patient mean BG [mmol/L]	/	6.5 [5.9, 7.6]	6.8 [6.1, 7.8]	6.2 [5.9, 6.6]
5th-95th per-patient BG [mmol/L]		[5.4 - 10.3]	[5.6 - 10.4]	[5.4 - 8.1]
% BG in 4.4-8.0 [mmol/L]	/	78.3	77.5	90.7
% BG < 4.0 [mmol/L]	/	3.1	2.5	1.2
% BG < 2.2 [mmol/L]	/	0.04	0.11	0.02
Number of patient with min(BG) <= 2.2 (%)	207 (6)	10 (2.5)	24 (6)	5 (1)
Median [IQR] glucose rate (g/hr)	/	6.1 [6.1, 6.1]	6.1 [6.1, 6.1]	6.1 [6.1, 6.1]

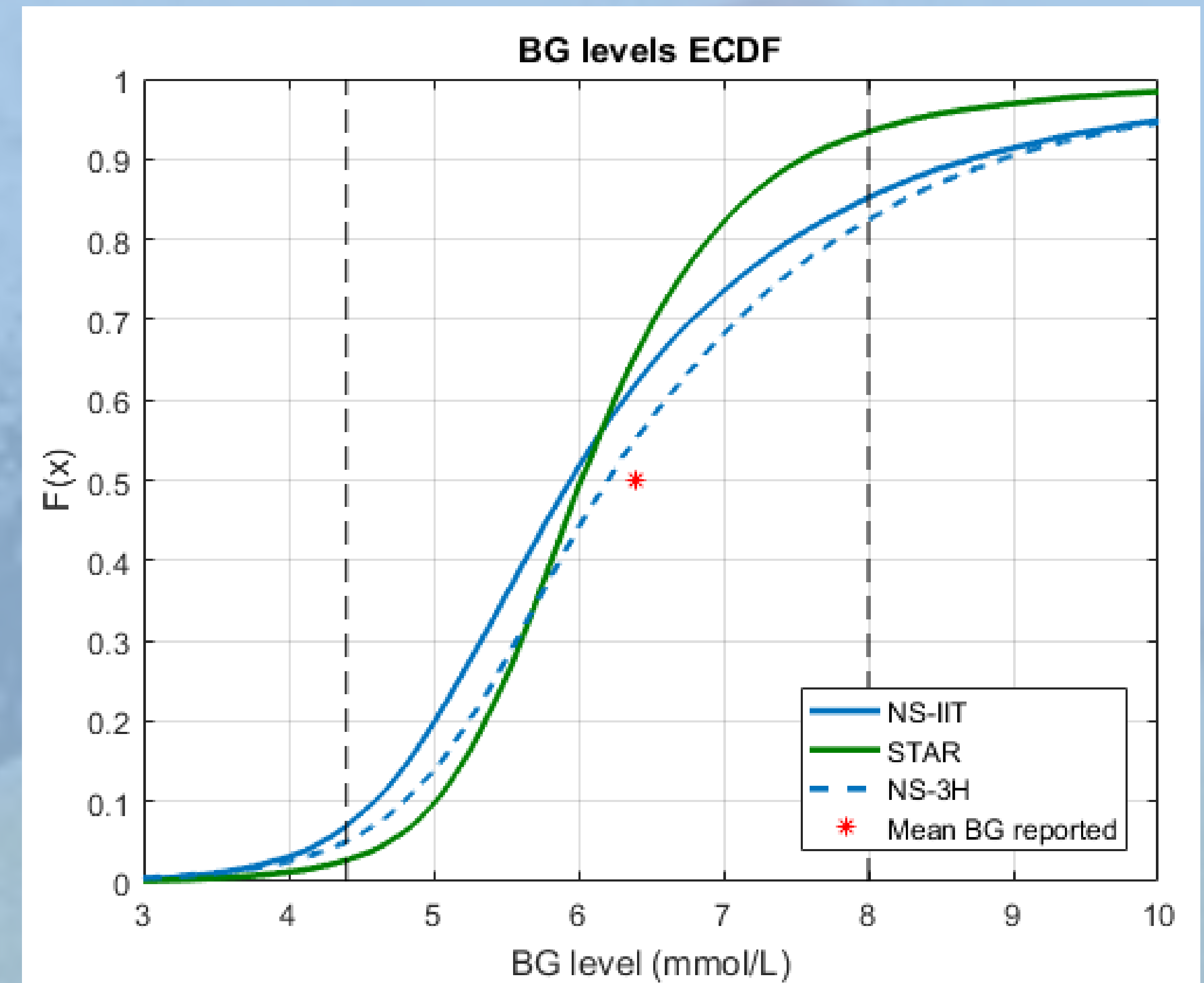


Figure 1 – BG empirical cumulative distribution level reported clinically (NICE-SUGAR), for STAR simulations (STAR) and NICE-SUGAR simulations (NS-IIT), and NICE-SUGAR 3-hourly protocol (NS-3H).

Conclusion

Glycaemic control protocols need to be both safe and effective for all patients before potential clinical benefits can be assessed. NICE-SUGAR clinical results do not match results expected from their protocol, and show reduced safety and performance in comparison to STAR.