Increasing Blood Glucose Variability Heralds Hypoglycemia in the Critically Ill Surgical Patient

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Introduction

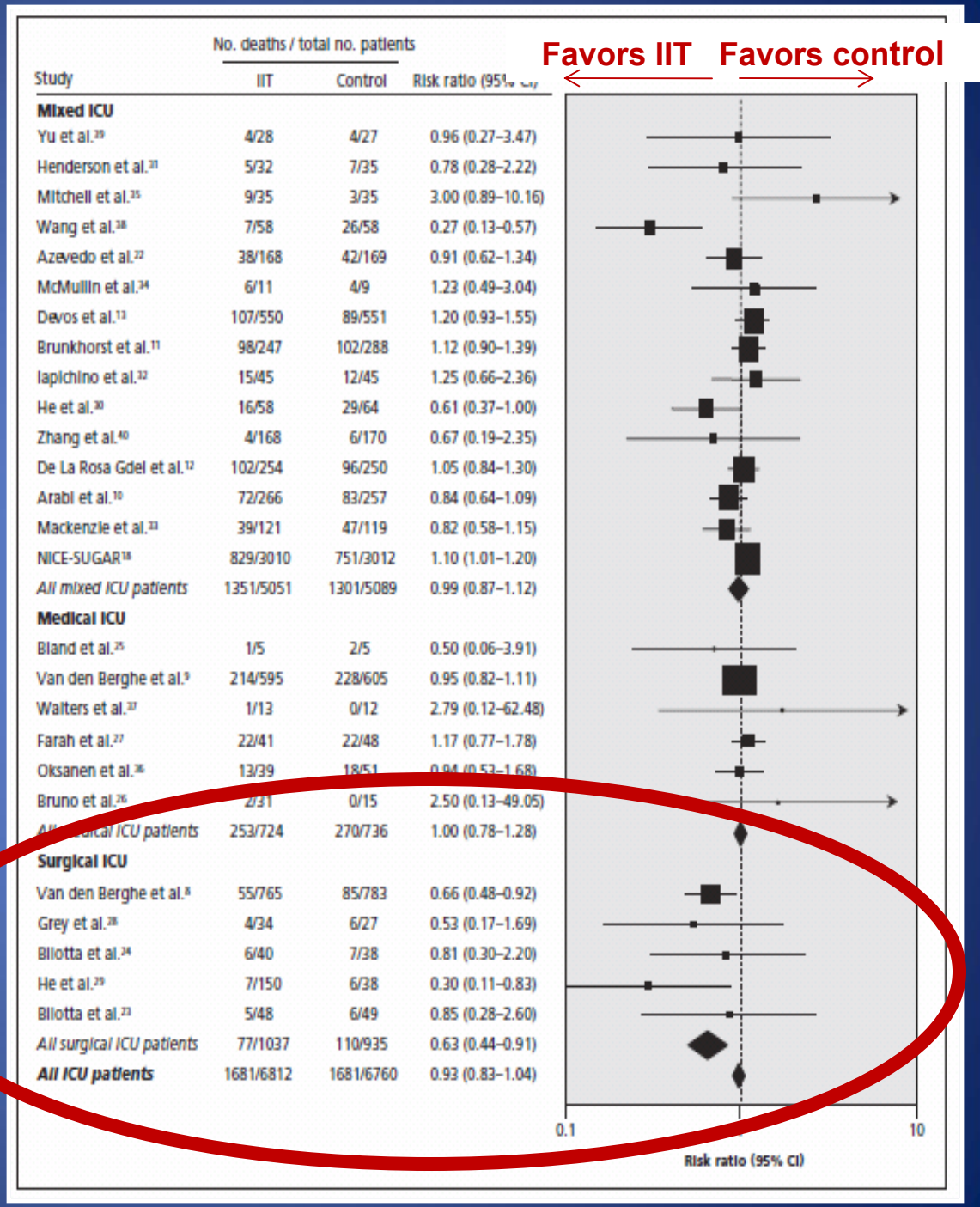
- Hyperglycemia is common in critically ill patients and is associated with increased morbidity and mortality
- Intensive Insulin Therapy (IIT) has been widely adopted
- Concerns persist over rates of hypoglycemia in patients on IIT
- There is emerging evidence that blood glucose variability is a better predictor of adverse outcomes

Summary of IIT Literature

Summary Data from Randomized Clinical Trials of Intensive Insulin Therapy in Critically Ill Patients						
Trial Name (Source)†	Leuven 1	Leuven 2	Glucontrol	VISEP	NICE-SUGAR7	Arabi
Author	Van den Berghe	Van den Berghe	Devos	Brunkhorst	Finfer	Arabi
No. of Patients	1548	1200	1101	537	6104	523
Type of ICU	Surgical	Medical	General	General	general	general
Target Glucose: Intensive	80-110	80-110	80-110	80-110	81-108	80-110
Target Glucose: Conventional	180-200	180-200	140-180	180-200	144-180	180-200
Primary Outcome	Death in ICU	Death in hospital	Death in ICU	Death @ 28d	Death @ 90d	Death in ICU
Rate of Outcome; Intensive	4.6	37.3	16.7	24.7	27.5	13.5
Rate of Outcome: Conventional	8.0	40.0	15.2	26.0	24.9	17.1 (0.3)
Morbidity measures	IIT: < ICU LOS, Vent d, RRT, septicemia, neuropathy	IIT < renal failure, vent days, ICU d, Hosp d.	?	No differences LOS, vent days, dialysis	No difference in MSOF, ICU LOS, Hosp LOS, Vent days, renal failure	ITT < % mort in APACHE II < 22 & BMI < 26 < sepsis 20.7 vs 27.2 (0.08)

Meta-analysis of IIT in critical illness

- All studies combined:
  - no significant benefit
- Surgical ICU studies:
  - significant benefit



Griesdale D, CMAJ 2009;180(8):821-827

Factors Associated with Hypoglycemia

- Time on IIT
- Severity of illness
- Previous diagnosis of diabetes mellitus
- BMI
- Time between BG measurements
- Blood glucose variability

Glycemic variability is associated with mortality in the critically ill

- Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients.
  - *Crit Care Med*. 2008;36:3008-3013

- Al Dorzi HM - Glycaemic fluctuation predicts mortality in critically ill patients.
  - *Anaesth Intensive Care*. 2010;38:695-70

Hypothesis

- Individual differences in blood glucose variability over time are associated with hypoglycemia (<50 mg/dL)

- Blood glucose variability can be utilized to estimate a patient's risk of hypoglycemia

Methods

Study Design	• Retrospective cohort; 1392 patients
Setting	• SICU of Academic Level I Trauma Center • June 1, 2006- September 1, 2009
Subjects	• Age ≥ 18 • Admitted to SICU, treated with IIT for at least 12 hours with 5 subsequent BG measurements • Survived >24 hours after SICU admission
Data Collection	• Age, gender, weight, APACHE II scores, preexisting diabetes, pressor use • BG values, insulin dose, test times
Outcome of Interest	• Hypoglycemia (<50 mg/dL) at next BG measurement
Measures of BG variability	• SD of BG over the entire SICU stay • Successive change in BG values and temporal relationship to hypoglycemia

Intensive Insulin Therapy Protocol

A Computerized Insulin Infusion Titration Protocol Improves Glucose Control With Less Hypoglycemia Compared to a Manual Titration Protocol in a Trauma Intensive Care Unit

Marcus J. Dortch, PharmD*; Nathan T. Mowery, MD†; Asli Ozdas, PhD‡; Lesly Dossett, MD†; Hanqing Cao, PhD†; Bryan Collier, DO†; Gwen Holder, RN, MSN§; Randolph A. Miller, MD‡; and Addison K. May, MD†

Journal of Parenteral and Enteral Nutrition 2008; 32:18–27

- Goal range= 80-110 mg/dL
- Insulin Dose= (BG-60) X multiplier {start at 0.03}
- Serum BG measured Q2 hours

Results

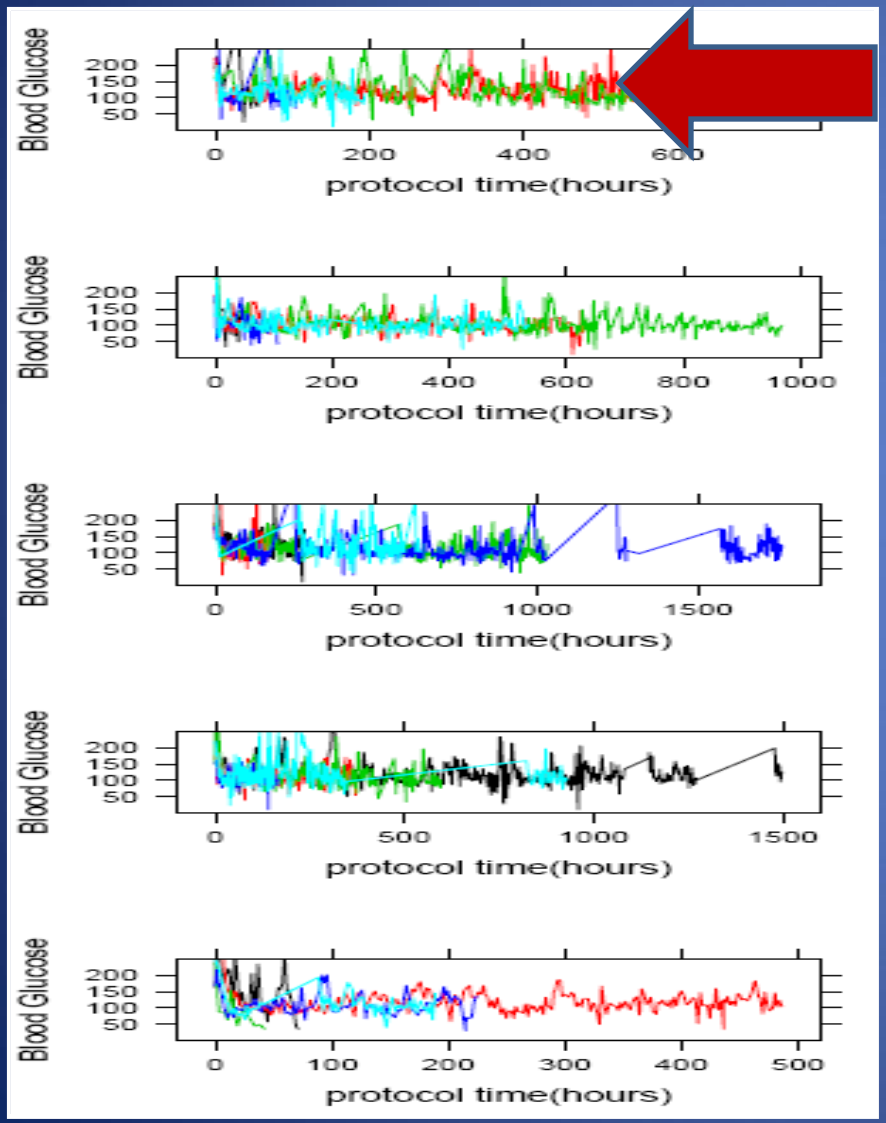
- 66, 592 BG measurements on 1392 patients
- 45% of BG measurements were in target range (80-110 mg/dL)
- 84.3% of BG measurements were between 80-150 mg/dL
- Hypoglycemia (<50 mg/dL) occurred in 154/1392 patients (11.1%)

Demographics and Clinical Characteristics

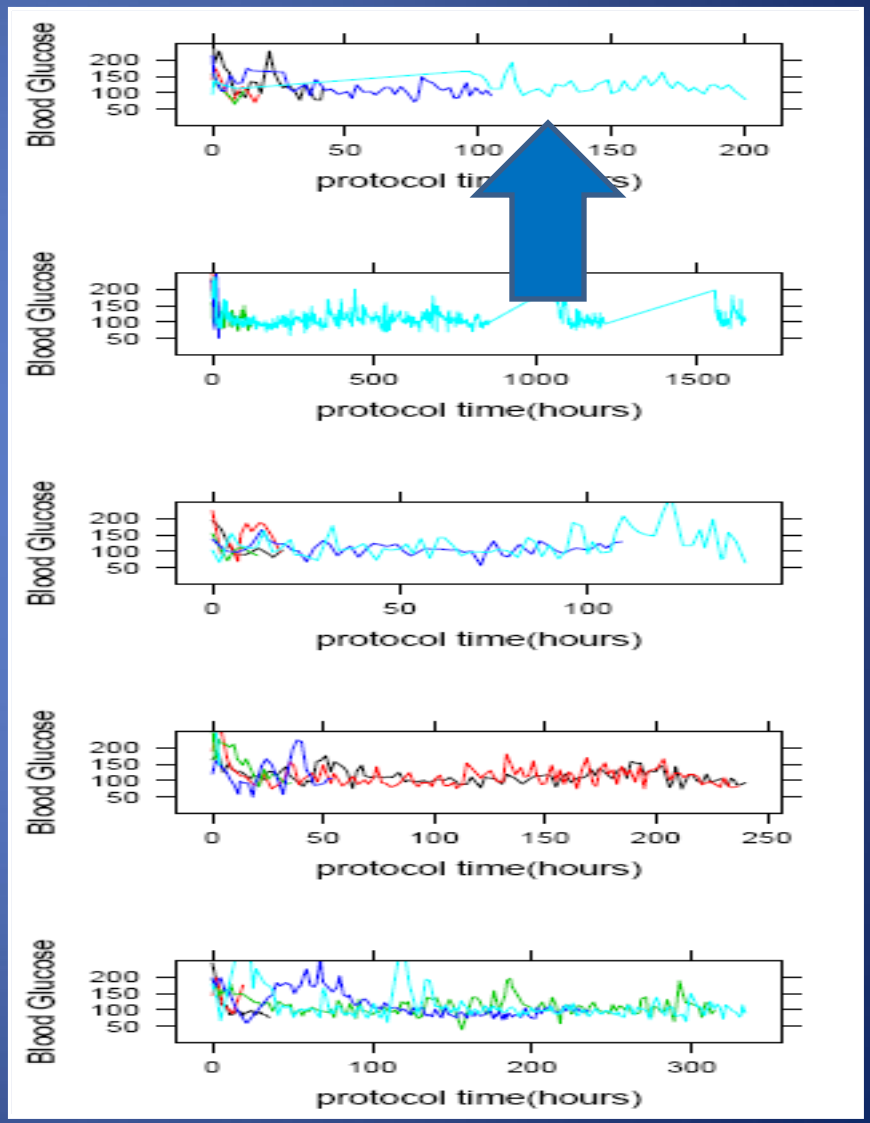
	Ever Hypoglycemic (<50 mg/dL) n= 154	Never Hypoglycemic (<50 mg/dL) n= 1,238	p-value
Age (yrs)	60.7	58.2	0.04
Males (%)	58.4	59.7	0.8
Patient weight (Kg)	81.3	87.4	0.01
History of diabetes (%)	26.6	33.4	0.11
APACHE II	21	19	0.001
ICU LOS	14.8	5	<0.001
Average blood glucose	109	108	0.9
Max glucose	197	150	<0.001
SD blood glucose	35.5	24.3	<0.001
Mortality (%)	24.7	12.5	<0.001

Blood Glucose Variability by Patient over Time

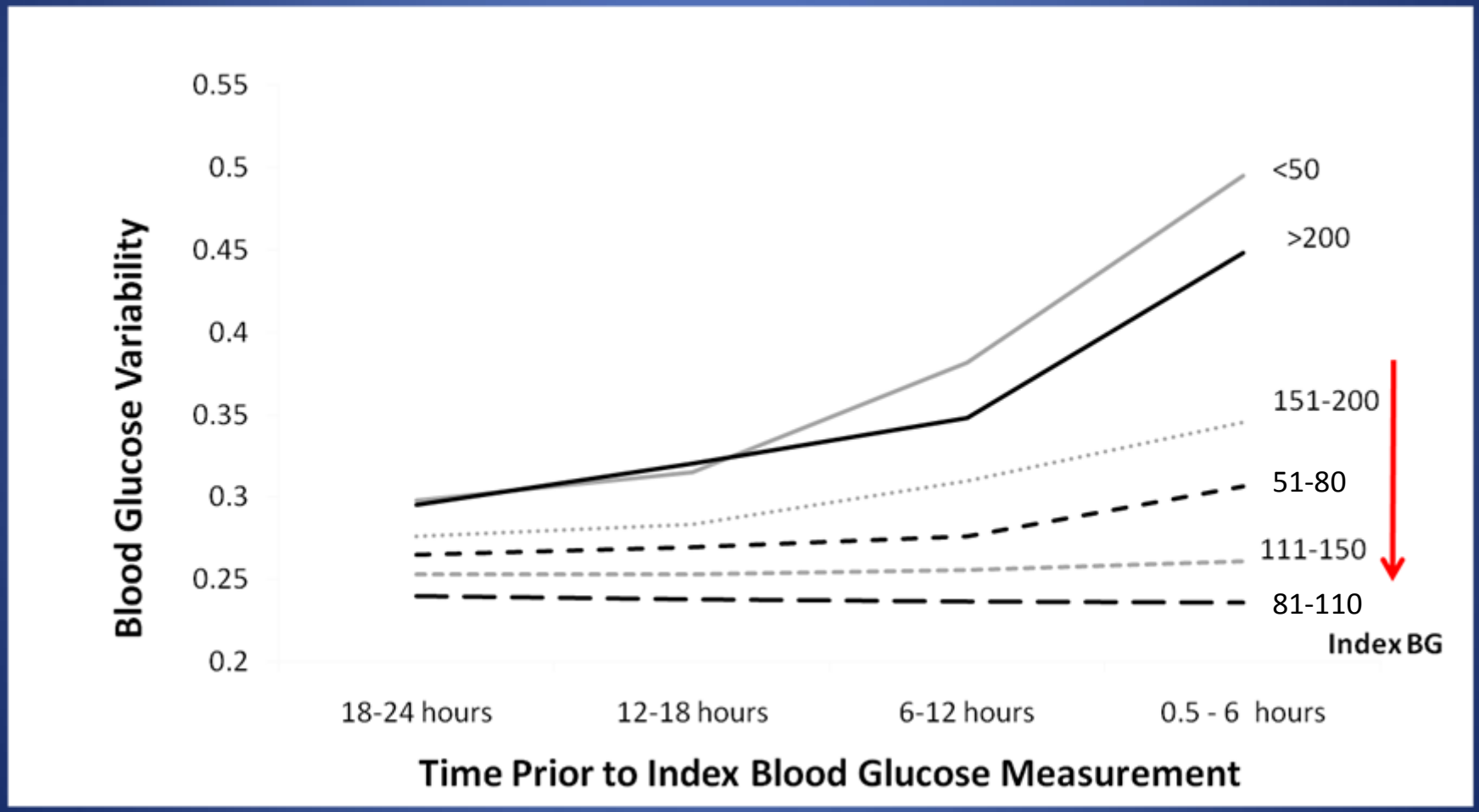
Hypoglycemics



Non-Hypoglycemics



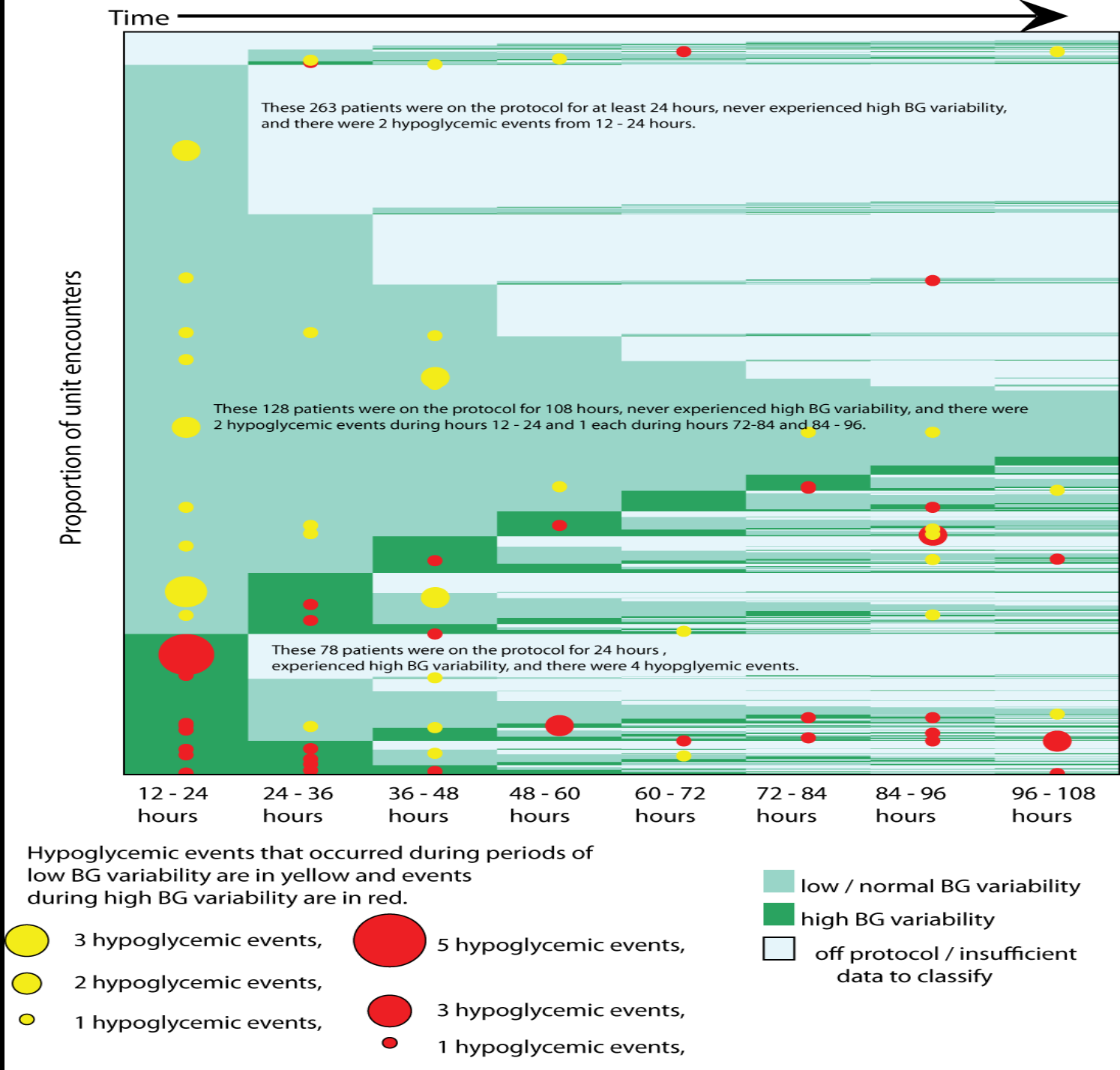
Blood glucose variability increases in 24 hours preceding hypoglycemic event



- Row = 1 patient over time

- 3.3 events/1000 hrs high BGV

- 1 event/1000 hrs low BGV



Predictors Independently Associated with Hypoglycemia

Variables in multivariable regression model	Exposure	OR	95% CI
Most recent absolute change in BG	IQR (4-34)	1.42*	1.29 – 1.57
Previous hypoglycemic episodes (count) (<60 mg/dL)	0	Reference	
	1	1.69	1.12 – 2.53
	2	1.45	0.94 – 1.90
	3 or more	4.14	2.56 – 6.70
Weight (kg)	IQR (70.1-103)	0.72*	0.56 – 0.93
Time since previous BG measurement (hours)	IQR (1.7-2.3)	1.45*	1.33 – 1.58

*OR for risk associated with 75th percentile compared to 25th percentile is shown

Predictors Not Independently Associated with Hypoglycemia

Variables in multivariable regression model	Exposure	OR	95% CI
Diagnosed diabetes	Y/N	0.88	0.63– 1.22
Female sex	Y/N	0.96	0.75 – 1.37
Current vasopressors	Y/N	1.19	0.86 – 1.64
Patient age (years)	IQR (50.6-70)	1.39*	0.92-2.12
Volume of 5% dextrose infused in 2 hours (ml)	IQR (0-73)	0.98*	0.87-1.12
Baseline APACHE II score	IQR (16-26)	0.95*	0.75-1.21
Hours on Protocol	IQR (49-247)	0.91*	0.82-1.02

*OR for risk associated with 75th percentile compared to 25th percentile is shown

Conclusions

- Patients who experience hypoglycemia are characterized by higher BG variability prior to the event
- BG variability increases in the 8 hours preceding a hypoglycemic event
- Patients with high BG variability are at increased risk for hypoglycemia during the period their BG variability remains high
- Prospective measuring of BG variability may provide means for early identification of patients at high risk for hypoglycemia, and provide an opportunity to mitigate this risk

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