



Intensive Insulin Therapy and the Artificial Pancreas in Critical Care

Pitfalls, Practicalities, and Performance

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A (Now) Well Known Story

- **Hyperglycaemia is prevalent in critical care**
 - Impaired insulin production + Increased insulin resistance = High BG
 - Average blood glucose values **> 180mg/dL** are not uncommon
 - All due to the stress of the patient's condition
- **Tight control → better outcomes:**
 - Reduced mortality ~17-43% (6.1-7.75 mmol/L) [van den Berghe, Krinsley]
 - Costly treatments & tests (mech. ventilation, transfusions, ...) are also reduced
 - \$2000/day saved regardless of mortality outcome [van den Berghe, Krinsley]
- **However, how best to attack the problem?**
 - How to manage highly insulin resistant patients (usually high APACHE score)?
 - How to provide better safety from hypoglycaemia?
 - Initial results have been very hard to repeat to outcome
 - Model-based methods may offer an opportunity to better design and compare

Between a rock and a hard place: Pitfalls or just a hard problem?

- **Hypoglycaemia?**

- Risk of neurological damage?
- Fear of hypoglycaemia?
 - Lack of 'buy-in' by physicians and nursing staff

The “rock”

- **Hyperglycaemia?**

- Patients evolve rapidly
- High insulin resistance and insulin requirements
- Insulin effect saturation
- Infrequent measurement ← or → Burden

The “hard place”

- **Not doing anything ...? Too hard?**

There are actually very few “true” pitfalls of IIT

The Many Practicalities of IIT

- No standard protocols → variability of care
- Protocol **transparency** is usually minimal – big complex charts or mysterious computer programs
- No standard metrics to **assess safety & performance**
- Clinical **burden**?
 - Limited nursing resource?
 - Education, training
 - ICU layout?
- **Compliance** is thus an issue and can have the greater effect than a (good) protocol
- Who benefits? Which patients and which units?

How to satisfy or meet all these issues and still succeed?

Hypoglycaemia → ~0-32% Solution

Table 1. Studies Reporting Protocols and Practical Aspects of Intensive Insulin Therapy

Authors	Reference	Publication Year	Study Design	Number of Patients	Persons Involved in IIT	Threshold of IIT (BGC, mg/dl)	Incidence of Severe Hypoglycemia	Conclusions by Author Regarding Safety
Krinsley et al.	[6,41]	2004/2005	Before–after cohort	1,600		Less than 140	"Not changed"	Safe
Kanji et al	[21]	2004	Before–after cohort	100	Nurses	80–110	16%	
Grey et al.	[42]	2004	Randomized controlled trial	61		80–120	32%	
Zimmerman et al.	[43]	2004	Prospective cohort	342	Nurses	80–150	7%	
Laver et al.	[44]	2004	Prospective cohort					
Goldberg et al.	[45]	2004	Prospective cohort	118	Nurses	100–140	0.2%	Safe
Goldberg et al.	[46]	2004	Prospective cohort	52	Nurses	100–140	0.3%	Safe
Ku et al.	[47]	2005	Before–after cohort	156	Nurses			Safe
Thomas et al.	[48]	2005	Before–after cohort	891				Safe
Chant et al.	[49]	2005	Before–after cohort	86	Nurses	90–140	0.2%–0.4%	Safe
Bland et al.	[50]	2005	Randomized controlled trial	10	Nurses		"Rare"	Safe
Moeniralam et al.	[51]	2005	Before–after cohort	7,327	Nurses and physicians	80–140	3.3%–4.0%	Safe
Taylor et al.	[22]	2006	Before–after cohort	281	Physicians and nurses	120–150, 80–110	1.1%–3.4%	Safe

NB: VISEP sunk with 12% - van den Berghe et al 4-25%

Schultz MJ, Royackers AANM, Levi M, Moeniralam HS, Spronk PE (2006) Intensive insulin therapy in intensive care: An example of the struggle to implement evidence-based medicine. PLoS Med 3(12): e456. doi:10.1371/journal.pmed.0030456



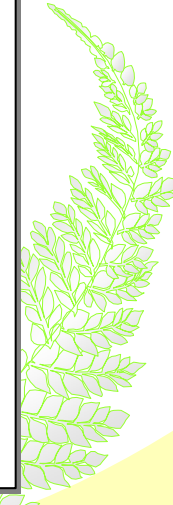
Hypoglycaemia?

Review

Hyperglycemia During Critical Illness

Stanley A. Nasraway, Jr, MD, FCCM

A universal concern with intensive insulin therapy has been that of the magnitude and consequences of hypoglycemia. A number of studies have conservatively defined hypoglycemia as a value of <40–60 mg/dL [2.2–3.3 mmol/L].^{2,16–18} Using this standard, the incidence of hypoglycemia using a protocol-driven continuous insulin regimen is reportedly in the range from 4.0% to 6.9%. In no trial has there been any reported observation of a hypoglycemic event that was severe or irreversible to the patient.



Compliance “... proved to be most difficult...”

A recurrent and concerning issue for protocol implementation was that glucose readings were not drawn every 30 mins when the blood glucose fell >20 mg/dL within the range of 80–150 mg/dL, responsible for 84.3% of protocol violations. This specification was added at the second revision in an attempt to prevent significant decreases in blood glucose that could be anticipated from trends in glucose.

Compliance

The most important element to the implementation of an intensive insulin regimen is the acceptance and cooperation of the nursing staff. This proved to

be most difficult from the results of nursing surveys (Table 5). The survey administered at 6 months exposed a loss of autonomy from patient care while gaining a labor-intensive, complex protocol that 50% deemed detrimental to their patients. Numerous meetings were held to enhance the protocol, and subsequent surveys are planned to ensure continuous quality improvement.

Burden

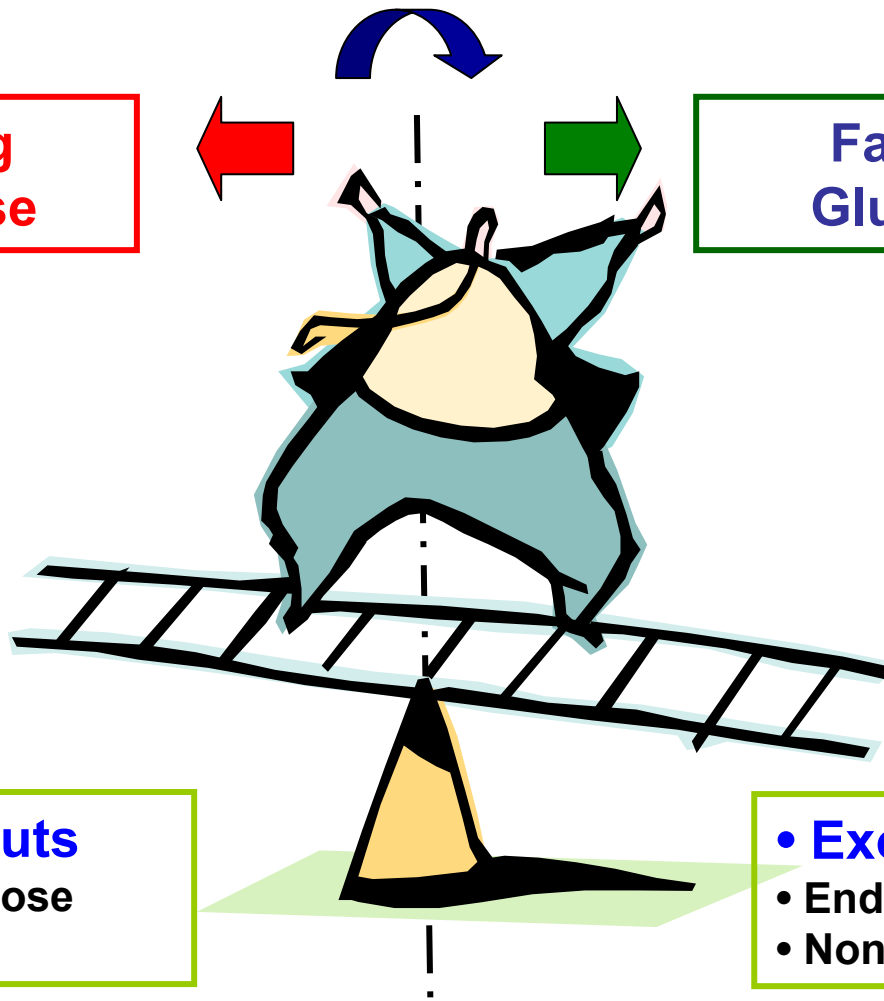
The limitation of this study by the implementation of intensive insulin therapy. This study did not seek to validate the efficacy of intensive insulin therapy. We studied only septic patients, with no data to generalize to an entire MICU population, and brittle hypoglycemia may be less a problem in other patient groups.

Transparency

Our Approach – Balance

**Rising
Glucose**

**Falling
Glucose**

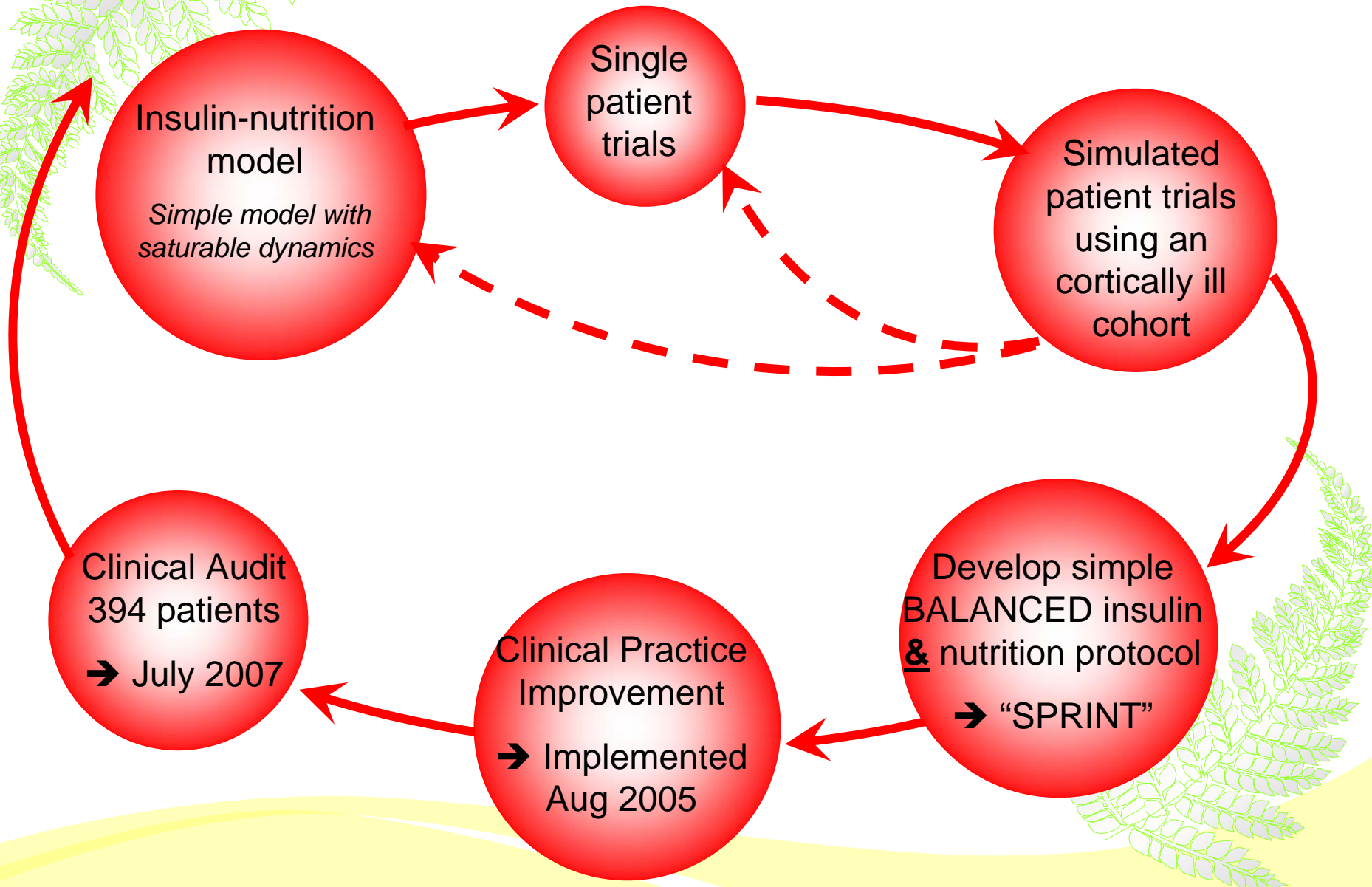


- **Nutritional Inputs**
- Endogenous Glucose Production

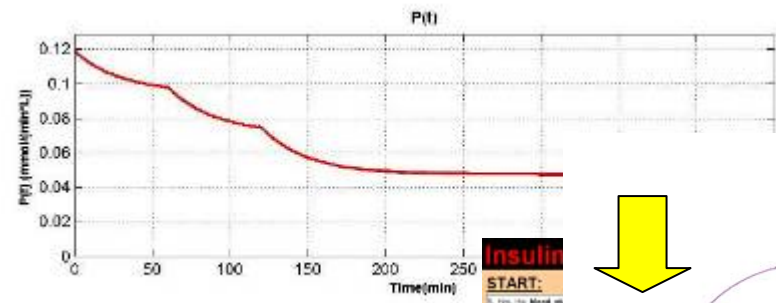
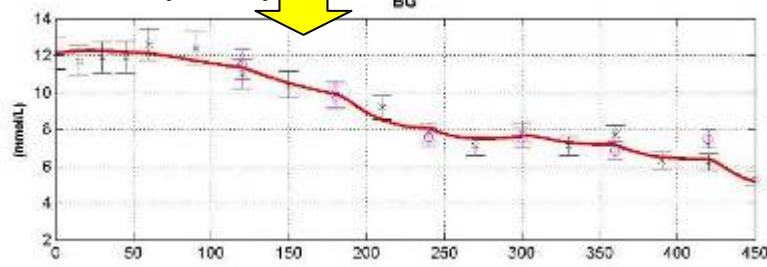
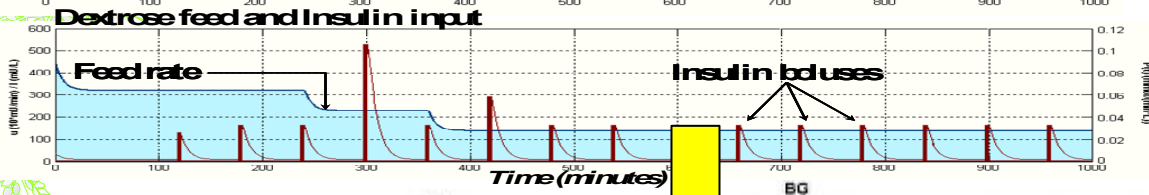
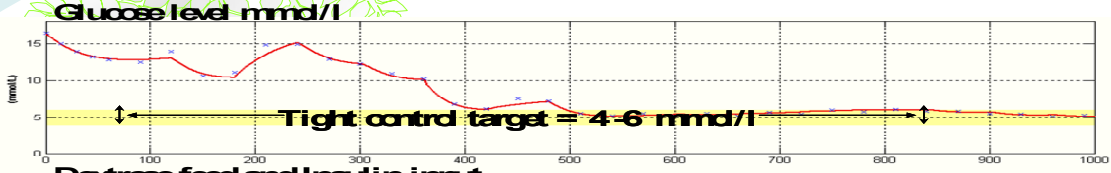
- **Exogenous Insulin**
- Endogenous Insulin
- Non-insulin Removal

- Measure as little as possible (1-2 hours for very critically ill cohort)
- Simple, transparent protocols/methods
- Do simple things, consistently and well, and in moderation

Basic Development



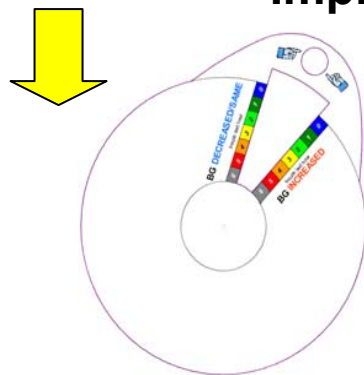
Basic Development



Insulin

START:

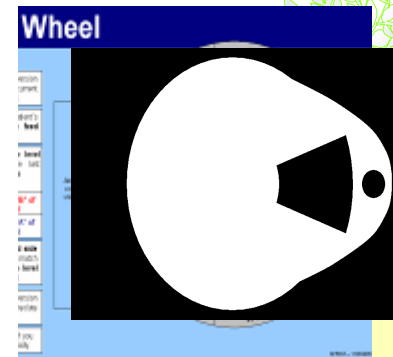
1. For the first 30 minutes, do not give any insulin.
2. From 30 to 60 minutes, give 0.025 units/kg/hr.
3. Estimate the glucose level and adjust the insulin rate.
4. Using the above information, give insulin boluses.
5. Administer the insulin boluses.
6. Use the feedback to adjust the insulin rate.



Virtual Trials

Short Proof of Concept
Computerised Trials

Implemented as SPRINT



Semi-Automated Feedback Control



Nursing Staff

Measured data



Decision Support System

The Decision Support System interface displays two main components: 'Insulin Wheel' and 'Feed Wheel'. Each wheel is a circular dial with a color-coded scale (red, orange, yellow, green, blue) representing different levels of therapy. The 'Insulin Wheel' is currently set to a yellow level. The 'Feed Wheel' is also set to a yellow level. Below the wheels are several line graphs showing trends over time for various parameters. The interface includes text boxes with instructions and a 'START' button.



Patient management



Standard infuser equipment

Identify and utilise patient specific parameters to optimise therapy



Control IV Insulin and Nutrition

Minimal time & training – Minimal interruption – Easy to understand
→ **Transparent**

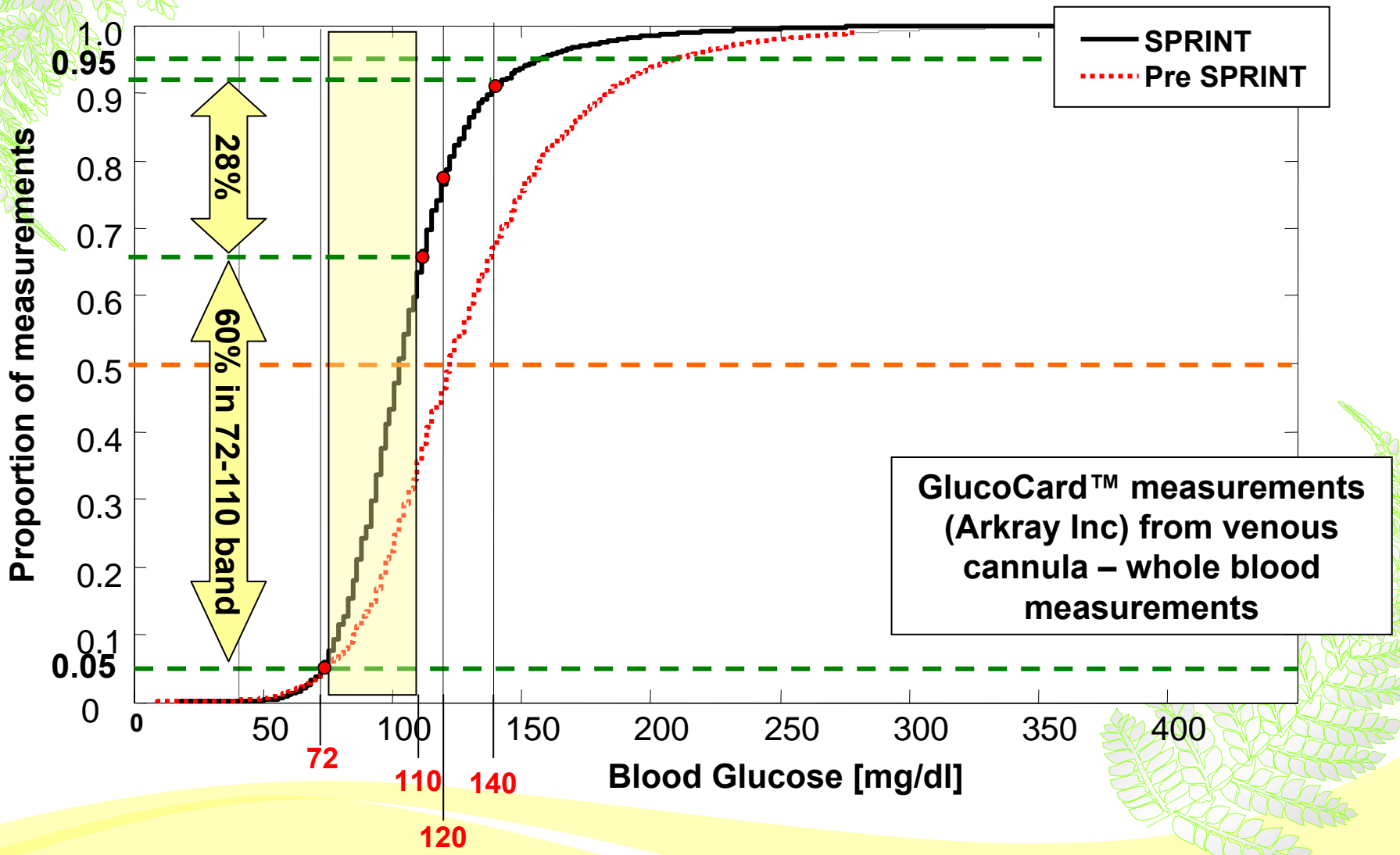
The Cohorts: Before/After Study

	<i>Overall</i>		
	<i>Retrospective</i>	<i>SPRINT</i>	
Total patients	516	394	
Age (years)	65 [53 - 74]	65 [50 - 74]	0.22
% Male	60.1%	62.9%	0.38
APACHE II score	19 [15 - 24]	18 [14 - 24]	0.06
APACHE II risk of death	24.1% [11.2% - 45.3%]	25.7% [13.3% - 48.1%]	0.19

Admission: 2 BG > 144 mg/dL or 1 BG > 180 mg/dL
No exclusions

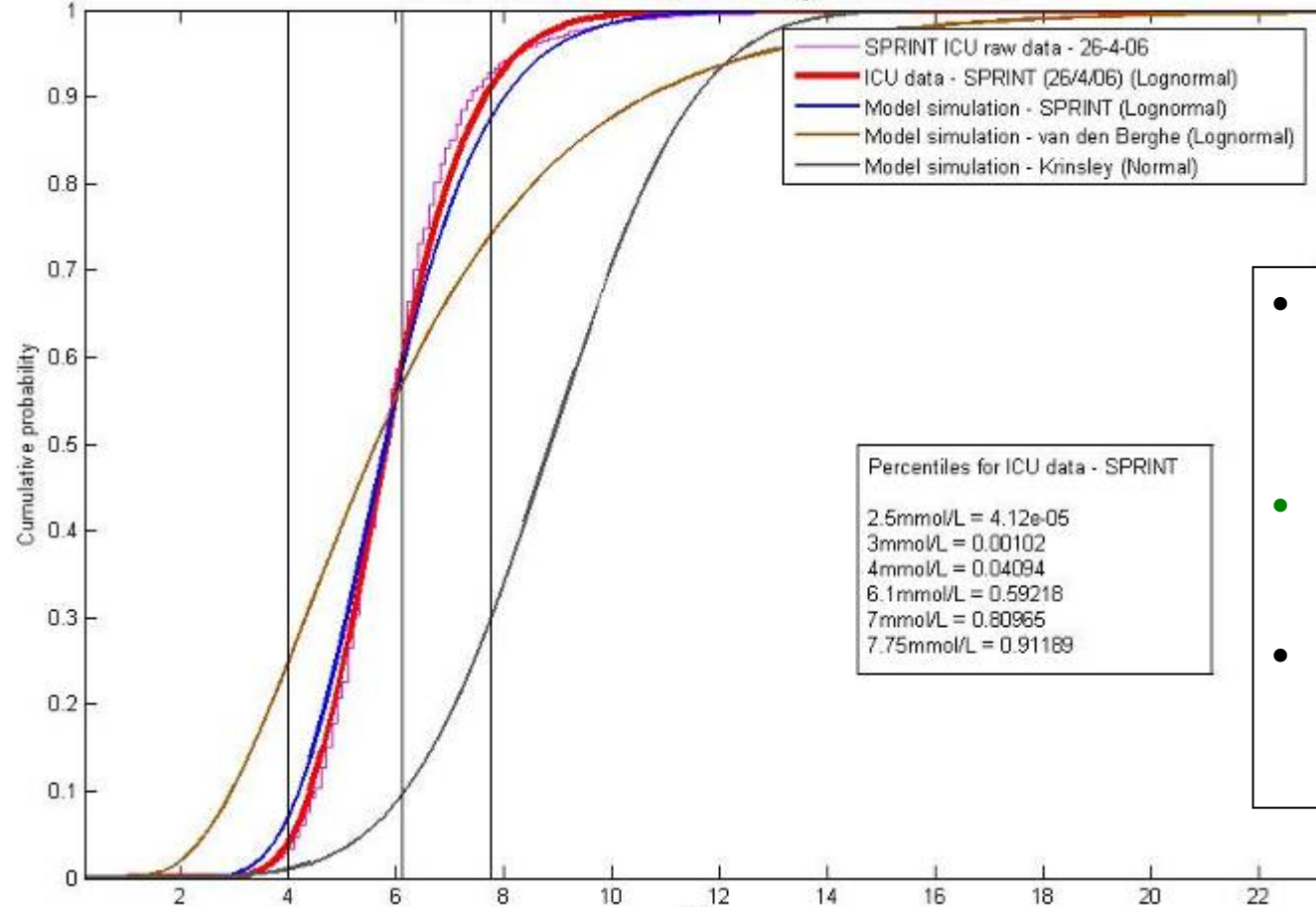
- **Retrospective before-after study – 1.2 yr SPRINT vs 2.5 yr past**
- **ROD is higher for SPRINT**
 - Different case mix with retrospective cohort having much more cardiovascular surgery than recently (non-clinical causes)
- **Otherwise statistically similar**
 - Retrospective more cardiovascular surgery so ROD likely lower again
 - More similar for LoS > 2 days

Cumulative Distribution of BG



Were Virtual Trials Effective?

Cumulative distribution function for all blood glucose measurements

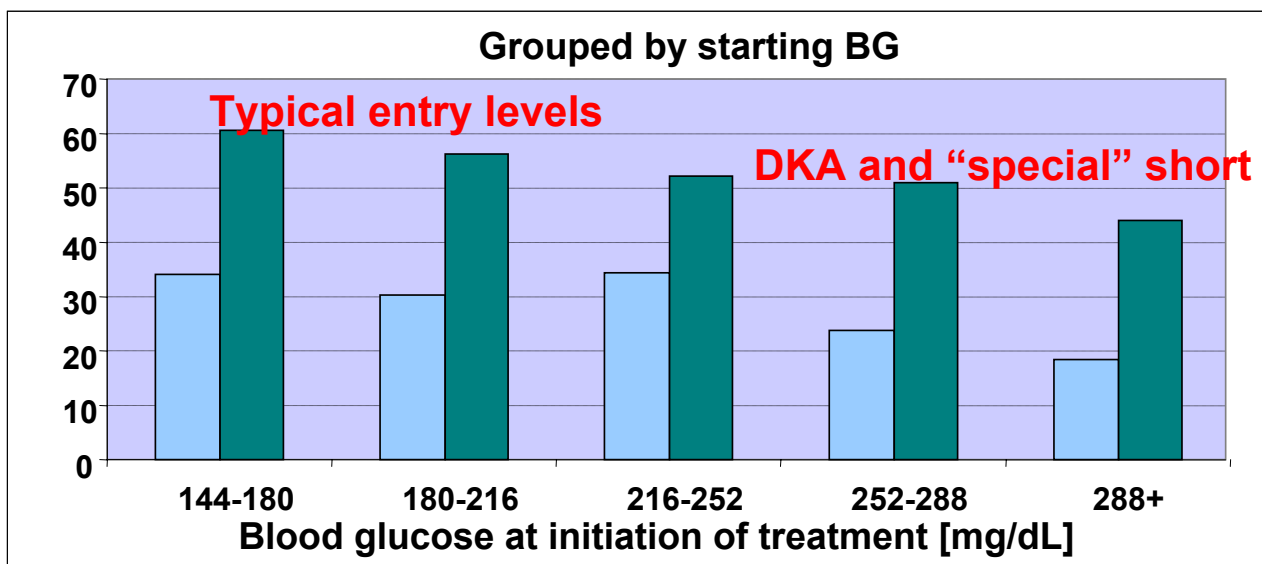
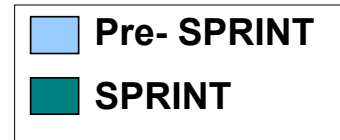
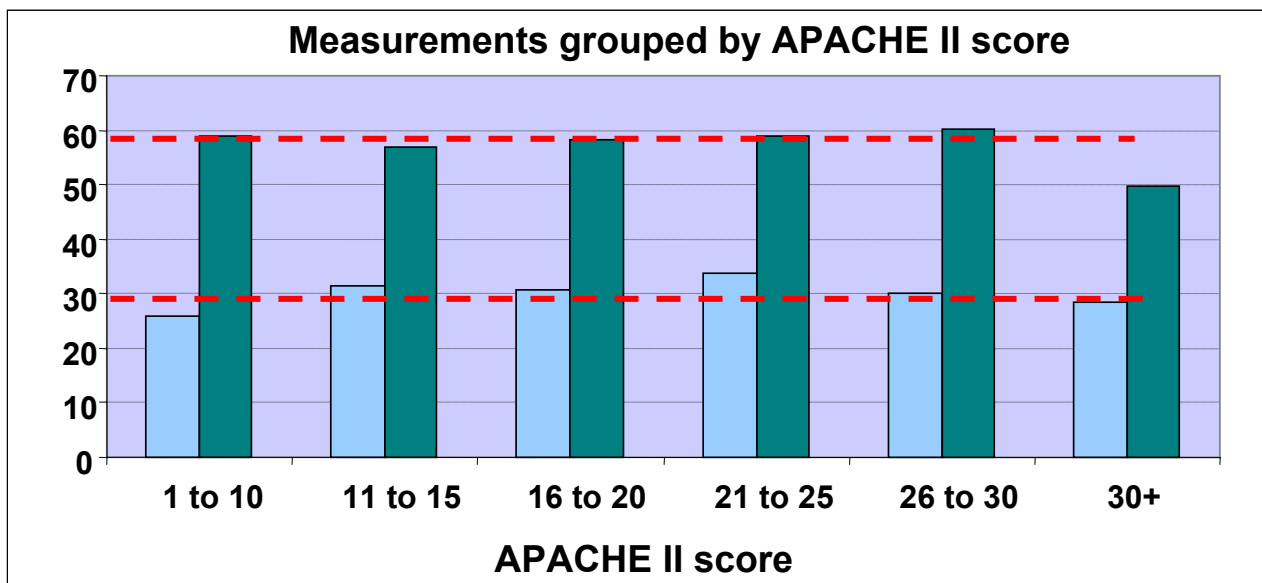


- **SPRINT was Monte Carlo simulated first in to show efficacy**
- **Clinical & virtual results are almost identical**
- **Other protocols were simulated and shown for comparison**

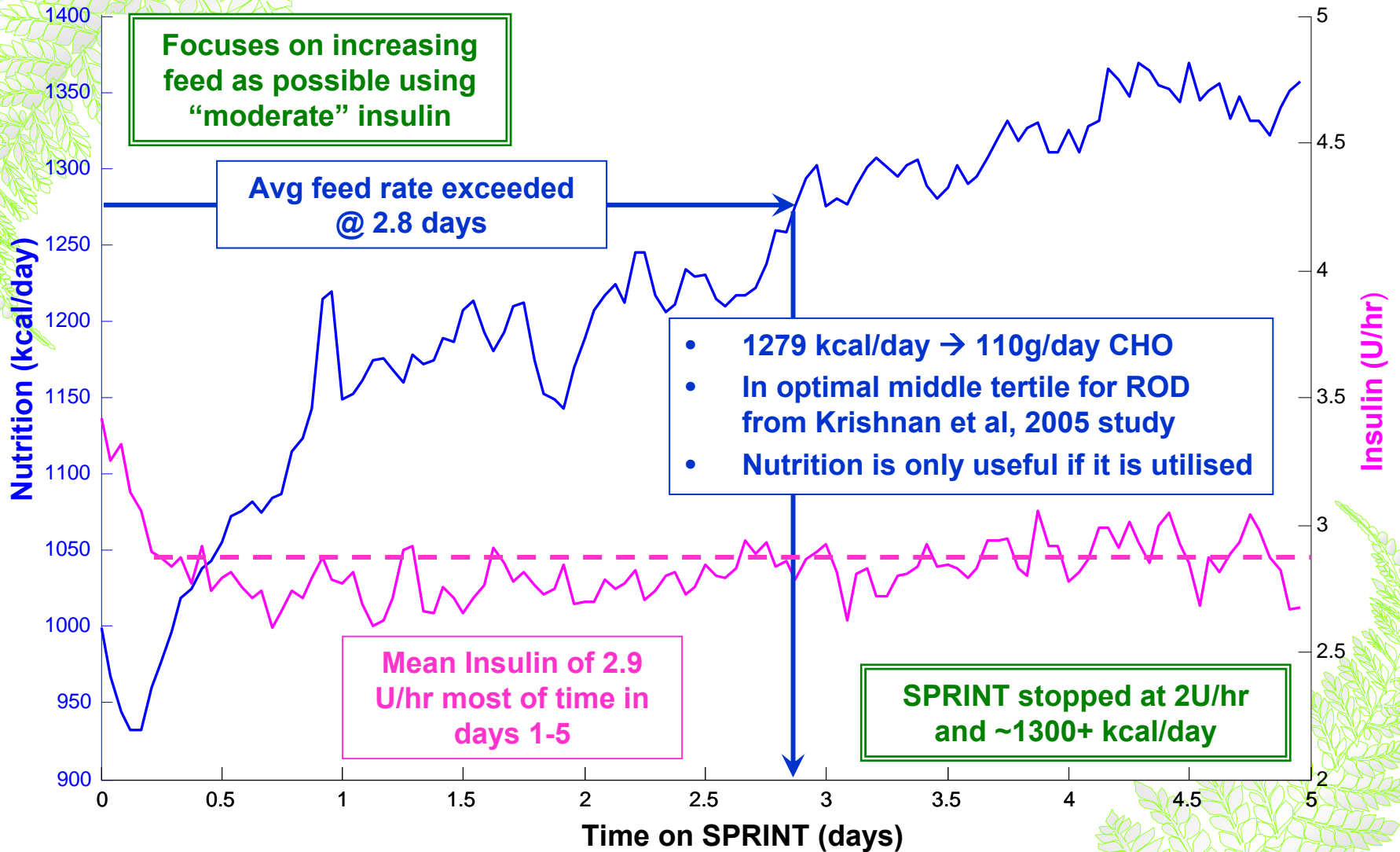
Virtual trials in a Monte Carlo format (for robustness to sensor and other errors) are useful to validate models and optimise protocols

Percentage time in 4-6.1 mmol/L band grouped by APACHE II score and starting BG

% of measurements in 72-110 mg/dL



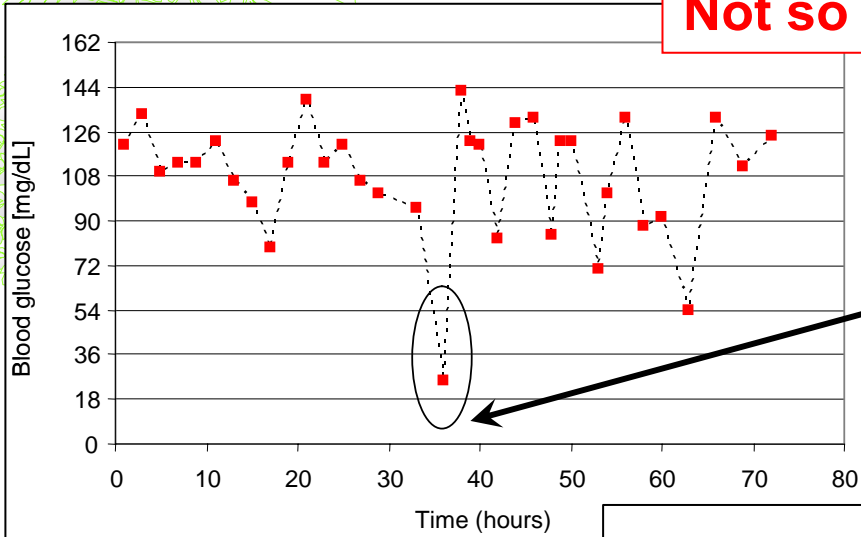
Nutrition and Insulin Concerns



Matches recent results where tight control via IIT decreased insulin required over days 2-7 and thus allows increased nutrition (Langouche et al, 2007)

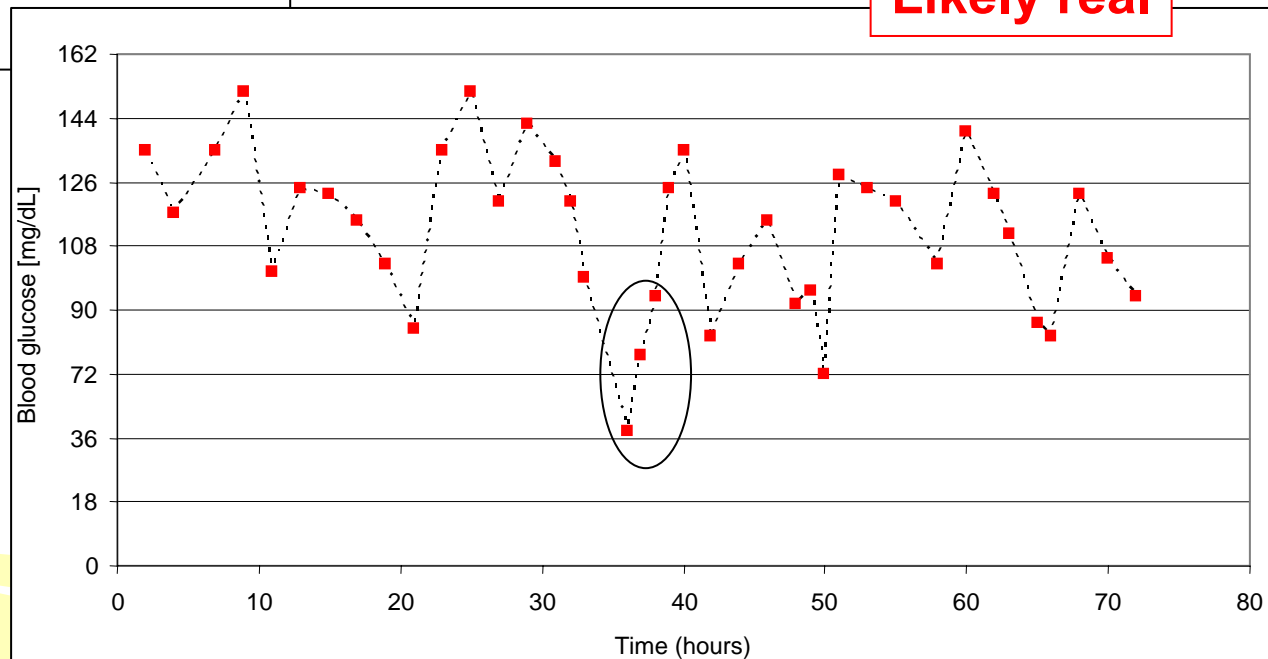
Lowest Recorded BG = 1.6 mmol/L

Not so real



Lowest of 28k measurements

Likely real



Of hypos and “funny” sensors ...

- **Approximately 1.5-2% of all measurements may be “funny”**
 - Sudden changes over 36 - 54 mg/dL/hour followed by reverse an hour later after a control input change by SPRINT
- **24 total hypo's \leq 40 mg/dL (Glucocard, Arkray Inc) and 14 (58%) have relatively very high rates of change**
- **Number where the average rate of change (down and up) was:**
 - > 36 mg/dL/hour = 14 (~48+% change per 1 hour)
 - > 54 mg/dL/hour = 8 (~58+% change per 1 hour)
 - > 72 mg/dL/hour = 2 (~65+% change per 1 hour)
- **Leaving 10 likely very real hypo's (0.036% of measures) on 8 patients (2%)**
- **Compare to 128 (0.44%) in ~30k measurements in Mackenzie et al (2006) and reported rates that are higher.**

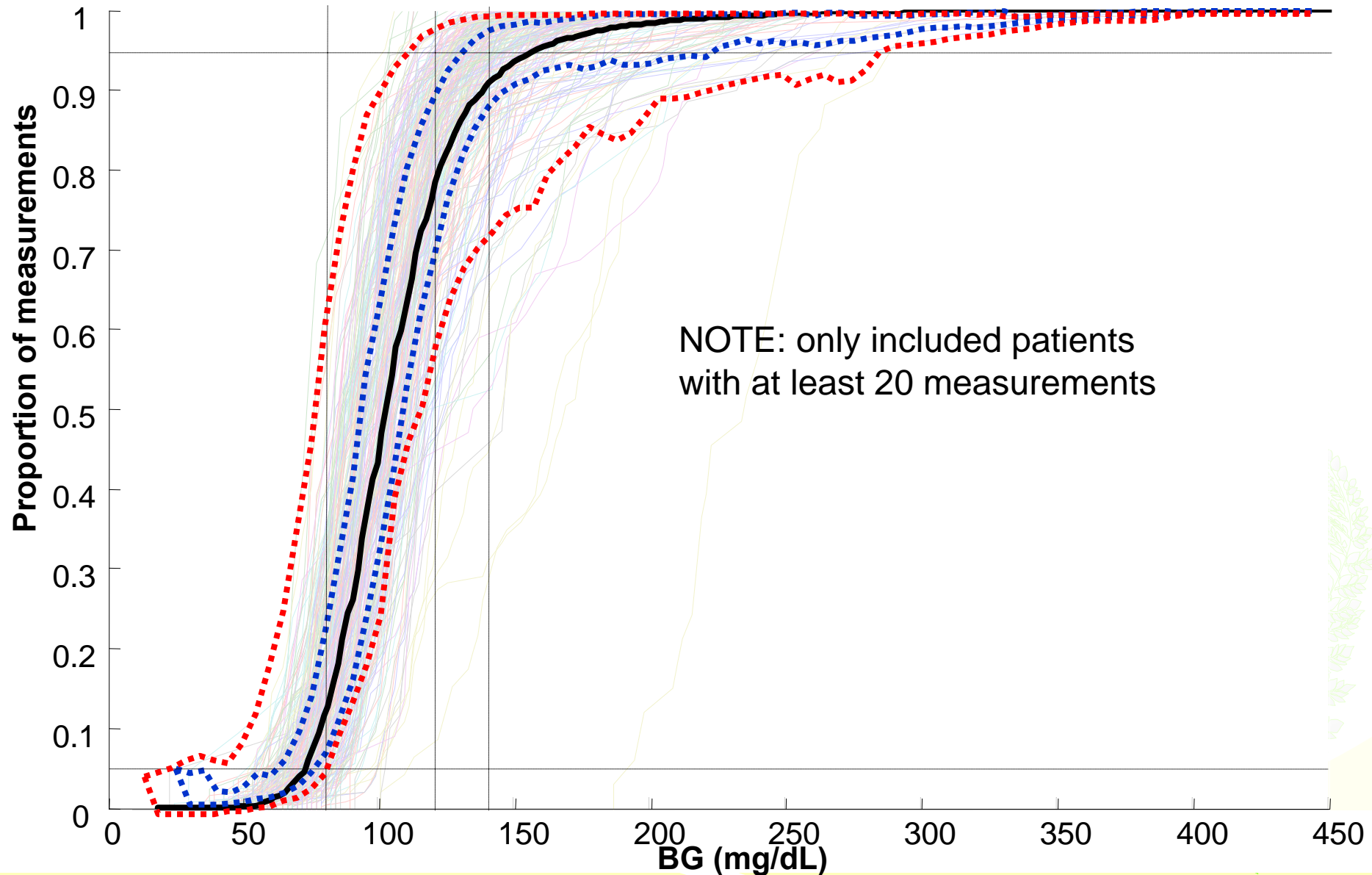
Overall SPRINT Glycaemic Control

Overall cohort data

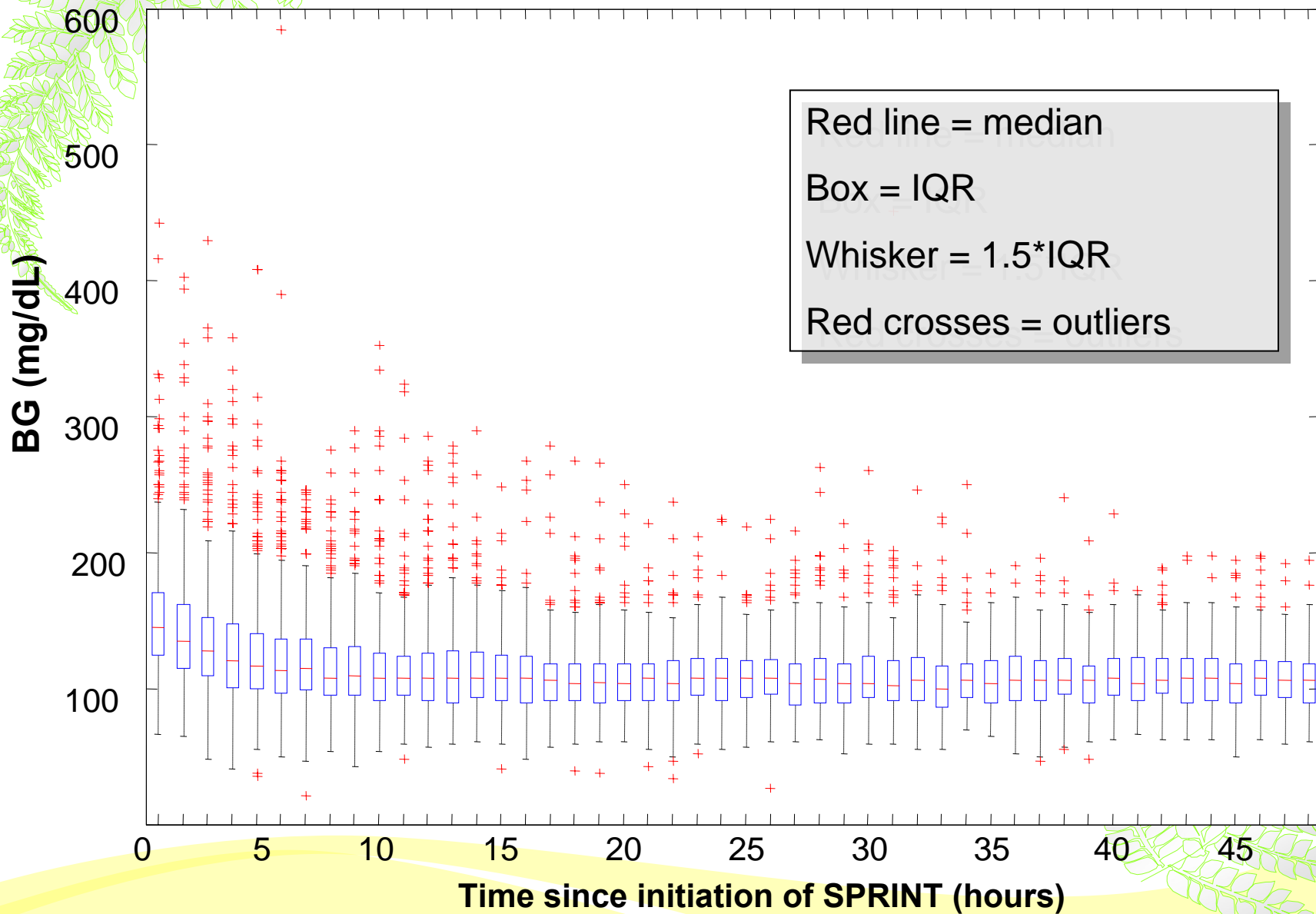
	<i>Retrospective</i>	<i>SPRINT</i>	
Number of patients	516	394	
Hours of control	62,769	47,290	hours
Total BG measurements	15,618	29,983	
BG mean (lognormal)	131	108	mg/dL
BG standard deviation (lognormal)	43	27	mg/dL
Percentage of measurements between:			
72 – 110 mg/dL	31.5%	59.2%	
72 – 126 mg/dL	50.3%	79.1%	
72 – 140 mg/dL	62.9%	86.5%	
Percentage of measurements less than:			
72 mg/dL	3.6%	3.9%	
40 mg/dL	0.2%	0.1%	
Mean insulin usage	1.0	2.9	U/hr
Mean nutrition rate			
During periods of feeding	1611	1279	kcal/day
Entire duration of SPRINT usage	-	1055	kcal/day
Mean % of goal feed	-	66%	

Per-Patient cumulative BG distribution: median, IQR & 90% CI

→ Each individual patient's BG cumulative distribution underneath



The First 48 Hours – All Patients



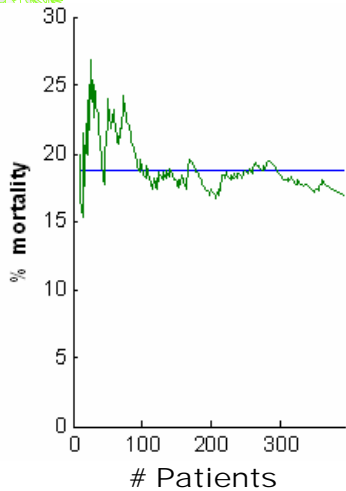
SPRINT Glycaemic Control Per Patient

<i>Per-patient data</i>	<i>Retrospective</i>	<i>SPRINT</i>	
Hours of control	57 [25 – 162]	53 [19 – 147]	hours
Number of BG measurements	17 [8 – 40]	37 [16 – 97]	
BG mean (lognormal)	135 [121 – 151]	108 [99 – 119]	mg/dL
BG standard deviation (lognormal)	29 [22 – 43]	23 [18 – 32]	mg/dL
Percentage of patients < 126 mmol/L	82%	99%	
Percentage of patients < 110 mmol/L	73%	96%	
Insulin usage	0.9 [0.1 – 1.6]	2.6 [2.1 – 3.3]	U/hr
Nutrition rate			
During periods of feeding	724 [0 – 1596]	938 [0 – 1304]	kcal/day
Entire duration of SPRINT usage	-	708 [0 – 1174]	kcal/day
% of goal feed	-	50% [0% - 71%]	

- **Tighter per patient std deviation – indicates each patient is tighter than the cohort to their patient specific mean**
- **Variability (std deviation) is 20% lower/tighter than retrospective**
- **Nutrition is actually higher (due to tighter control and less shutoff?)**
- **Feed shutoff for other clinical reasons can skew results**
- **Effectively all patients are brought under 7 mmol/L and 96% under 6.1 mmol/L**

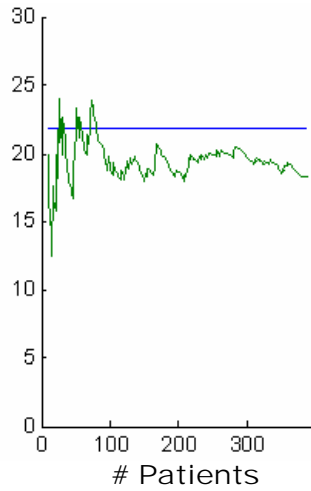
ICU Mortality: SPRINT/Pre-SPRINT

LOS \geq 1 day



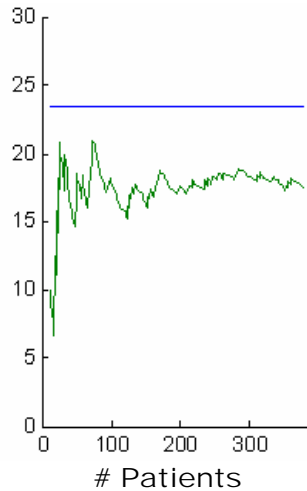
P=0.265

LOS \geq 2 days



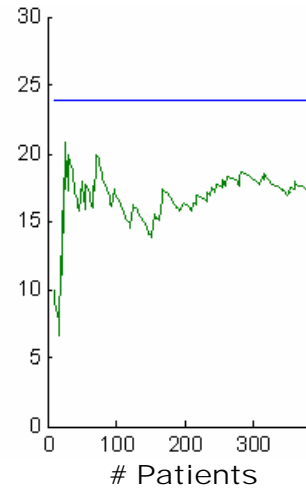
P=0.150

LOS \geq 3 days



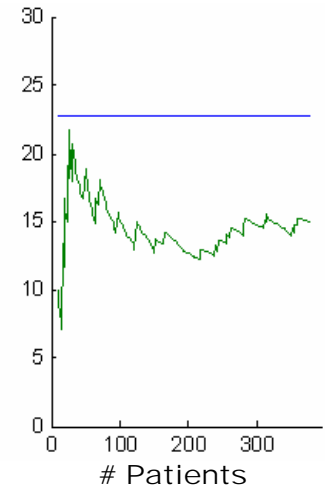
P=0.059

LOS \geq 4 days



P=0.058

LOS \geq 5 days



P=0.036

The horizontal line shows the mortality for the retro cohort. The green line is the total mortality of SPRINT patients against total number of patients treated on the protocol

NB: You likely survive or not in LOS < 2 days on merits of initial condition!

Hospital Mortality: SPRINT/Pre-SPRINT

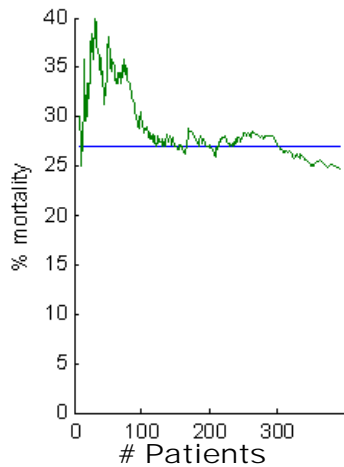
LOS \geq 1 day

LOS \geq 2 days

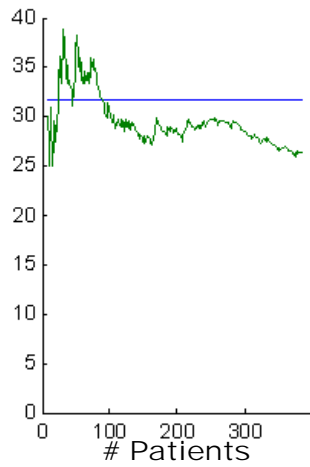
LOS \geq 3 days

LOS \geq 4 days

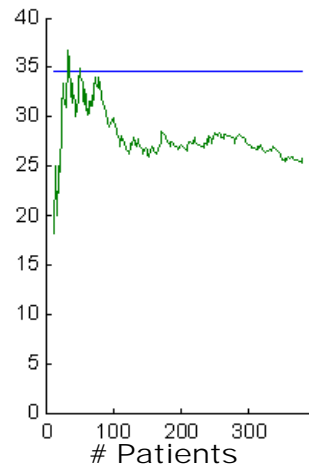
LOS \geq 5 days



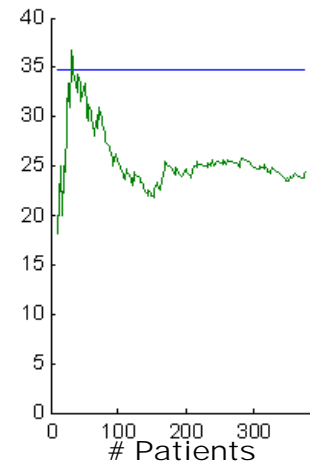
P=0.244



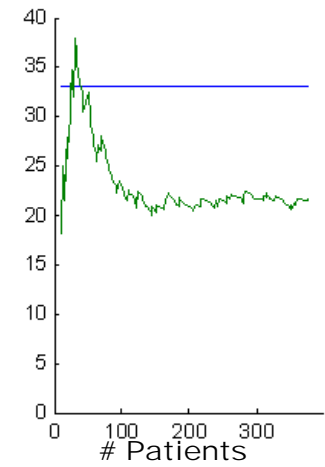
P=0.077



P=0.023



P=0.012

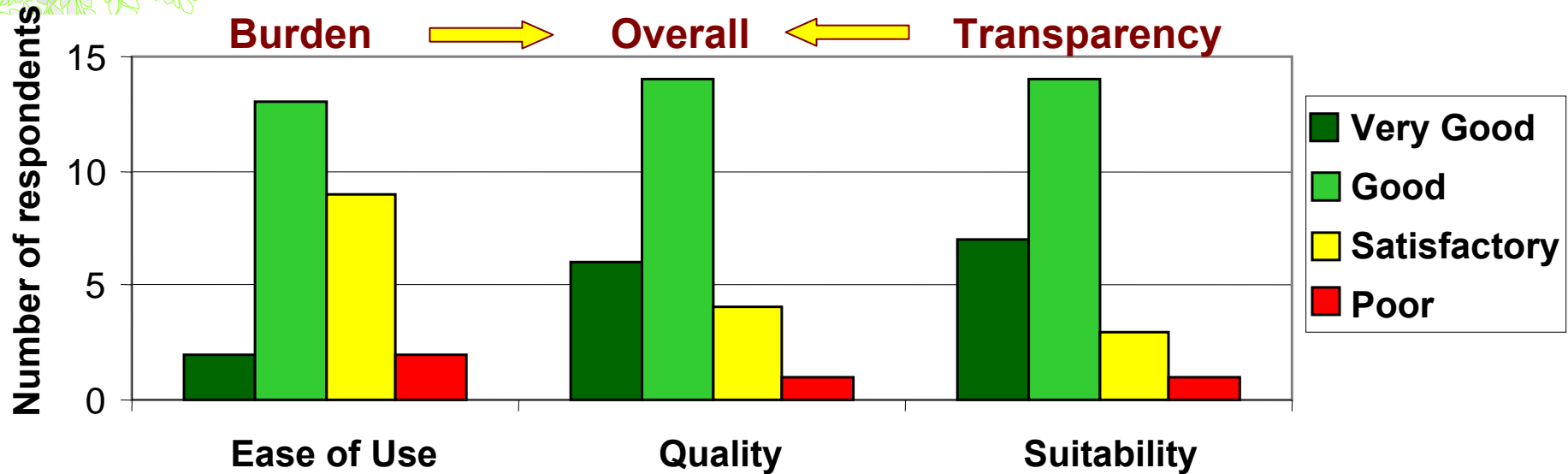


P=0.010

The horizontal line shows the mortality for the retro cohort. The green line is the total mortality of SPRINT patients against total number of patients treated on the protocol

NB: You likely survive or not in LOS < 2 days on merits of initial condition!

Nursing Feedback at 2 Months



Survey completed by 26 Christchurch Hospital ICU Nurses

Bottom line: Intuitive and easy for staff to use.
ICU staff workload reduced
Compliance over 97% (dose)

In Summary: There are no pitfalls...

- **It's just a problem with our expectations and the practicalities:**
 - Desired performance of IIT vs practicalities of implementation
 - Nutritional requirements in critical illness and cohort
 - Full reporting: per patient and cohort to allow better assessment of performance
- **It's a question of balance**
 - Of therapy choices, practicalities, workload, patient types
 - Matching utilisation to supply (in all these things!)

Acknowledgements



Intensive Care Nursing Staff, Christchurch Hospital

Questions for the QA?

