What Makes Tight Glycemic Control (TGC) Tight?
The impact of variability and nutrition in 2 clinical studies

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List of Abbreviations / Acronyms:

- Acute Physiology and Chronic Health Evaluation II (APACHE II)
- American College of Chest Physicians (ACCP)
- Centre Hospitale Universitaire (CHU)
- Cumulative Distribution Function (CDF)
- Intensive Care Unit (ICU)
- Inter-Quartile Range (IQR)
- Length of Stay (LoS)
- Specialised Relative Insulin Nutrition Titration (SPRINT)
- Tight Glycemic Control (TGC)
- Type 2 Diabetes Mellitus (T2DM)

ABSTRACT:

Introduction: Tight glycemic control (TGC) remains controversial, and successful, consistent and effective protocols elusive. This research analyses data from 2 TGC trials for root causes of the differences achieved in control and thus potentially in glycemic and other outcomes. The goal is to uncover aspects of successful TGC and delineate the impact of differences in cohorts.

Methods: A retrospective analysis using records from a 211 patient subset of the Glucontrol trial taken in Liege, Belgium and 393 patients from SPRINT in New Zealand. SPRINT targeted 4.0-6.0 mmol/L similar to the Glucontrol-A (N = 142) target of 4.4-6.1 mmol/L. The Glucontrol-B (N = 69) target was 7.8-10.0 mmol/L. Cohorts were matched by APACHE II score and percentage males (p > 0.35), however the Glucontrol cohort was slightly older (p = 0.011). Overall cohort and per-patient comparisons (median [IQR]) are shown for: a) glycemic levels achieved; b) nutrition from carbohydrate (all sources); c) insulin dosing for this analysis. Intra- and Inter- patient variability are examined using clinically validated model-based insulin sensitivity metric and its hour-to-hour variation

Results: Cohort blood glucose was: SPRINT: 5.7 [5.0 – 6.6], Glucontrol-A: 6.3 [5.3 – 7.6], Glucontrol-B: 8.2 [6.9 – 9.4] mmol/L. Insulin dosing was: 3.0 [1.0 – 3.0], 1.5 [0.5 – 3] and 0.7 [0.0 – 1.7] U/hr, respectively. Nutrition from carbohydrate (all sources) was: 435.5 [259.2 – 539.1], 311.0 [0.0 – 933.1], and 622.1 [103.7 – 1036.8] kcal/day, respectively.

Median per-patient results for blood glucose are: 5.8 [5.3 – 6.4], 6.4 [5.9 – 6.9], and 8.3 [7.6 – 8.8] mmol/L. For insulin dose: 3.0 [2.0 – 3.0], 1.5 [0.8 – 2.0], and 0.5 [0.0 – 1.0] U/hr. For carbohydrate administration: 383.6 [207.4 – 497.7], 103.7 [0.0 – 829.4], and 207.4 [0.0 – 725.8] kcal/day. Overall, SPRINT gave ~2x more insulin with a 3-4x narrower, but generally non-zero, range of nutritional input to achieve equally tight TGC with less hypoglycemia.

SPRINT had much less hypoglycemia (<2.2 mmol/L) with 2% of patients, compared to Glucontrol-A (7.7%) and Glucontrol-B (2.9%), indicating much lower variability, with similar results for glucose levels <3.0 mmol/L. SPRINT also had less hyperglycemia (> 8.0 mmol/L) than Groups A and B.

Glucontrol patients (A+B) had a ~2x wider range of insulin sensitivity than SPRINT. Hour-to-hour variation was similar. Hence, Glucontrol had greater inter-patient variability, but similar intra-patient variability.

Conclusions: Protocols that dose insulin blind to carbohydrate administration can suffer greater outcome glycemic variability, even if average cohort glycemic targets are met. While the cohorts varied significantly in model-assessed insulin resistance, their variability was similar. Such significant intra- and inter- patient variability is a further significant cause and marker of glycemic variability in TGC. The results strongly recommended that TGC protocols be explicitly designed to account for significant intra- and inter- patient variability in insulin resistance, as well as specifying or having knowledge of carbohydrate administration to minimise variability in glycemic outcomes across diverse cohorts and/or centres.

1.0 Introduction

Critically ill patients often experience stress-induced hyperglycemia and high levels of insulin resistance [1-7]. Hyperglycemia worsens outcomes, increasing the risk of severe infection [8], myocardial infarction [1], and critical illness such as polyneuropathy and multiple organ failure [7]. The occurrence of hyperglycemia, particularly severe hyperglycemia, is associated with increased morbidity and mortality in this group of patients [1, 3]. Glycemic variability, and thus poor control, are also independently associated with increased mortality [9, 10].

Some studies have shown that tight glucose control (TGC) reduced intensive care unit patient mortality up to 45% with glycemic targets from 6.1 to 7.75 mmol/L [7, 11-13]. However, there is a little agreement on what constitutes desirable glycemic performance [14-16], particularly with regard to how TGC affects outcome. Despite the potential, many intensive care units do not used fixed protocols [4, 14, 15, 17, 18].

In general, any glycemic control protocol must reduce elevated blood glucose levels with minimal hypoglycaemia, while accounting for inter-patient variability, conflicting drug therapies and dynamically evolving physiological condition. As patient condition evolves, particularly acutely, TGC and intensive insulin therapy can prove difficult. Protocols or clinical practises that utilize large insulin doses can thus suffer from high glycemic variability and excessive hypoglycemia [19]. As a result, several clinical trials have not achieved any benefit from TGC [19-22].

However, for comparison, any TGC result has to be viewed in the context of the following clinical aspects:

- Patient condition and cohort (diagnostic codes, age, sex, etc).

- Insulin dosing and carbohydrate administration from all sources, relative to the resulting blood glucose.

- Intra-patient variability and adaptability of the protocol to acute changes in patient condition and resulting acute changes in metabolic response.

- Inter-patient variability and/or adaptability of a protocol across patients with very different condition and thus different levels of insulin resistance.

Thus, how TGC protocols are designed and implemented with respect to these clinical aspects will affect results.

In particular, only 2 reported protocols explicitly considered carbohydrate intake in protocol design or implementation [13, 23-25]. Of these, only SPRINT was implemented long enough to show an impact on mortality. Importantly, carbohydrate input has been shown to be an independent marker of mortality in ICU patients [26], and thus worthy of consideration in designing overall metabolic management.

More specifically, both cohorts and clinical practice varies between hospitals and countries. These differences may be physiological, part of different clinical practice standard or culture, or have other causes. In particular, nutritional standards and practice can vary substantially across countries and practices [26-28], and were thus potentially one cause of the high variability in nutritional intake and resulting glycemic outcome (the insulin protocols being equivalent) seen in the recent, initial NICE-SUGAR results [20], as well as in other results that have not yielded a

mortality outcome [22]. Hence, to design protocols that will consistently yield any potential benefit of TGC these differences need to be assessed and/or quantified.

This paper examines data from SPRINT [13] and a subset of the patients from one centre (CHU Liege, Belgium) of the Glucontrol [29] study. The analysis examines:

- Association between carbohydrate administration, insulin dosing and glycemic outcome with respect to benefit (tight control) and risk (hypoglycemia).

- Differences between cohorts in terms of insulin resistance, using a model-based measure, and thus differences in inter-patient variability that might affect results.

- Differences in the evolution of patient insulin resistance or insulin sensitivity between cohorts, and thus differences in intra-patient variability that also might affect results.

In particular, while SPRINT was successful in achieving tight control, and reducing both hypoglycemia and mortality, the overall 7-country and 21-centre Glucontrol study was stopped early for reasons of compliance [29]. Thus, this evaluation will compare these results to determine if the differences in control and glycemic outcomes were due to differences in the patient cohorts or their evolution, or if they were due to aspects of the control protocol itself and/or its implementation in the context of the single Glucontrol centre studied. The results should provide insight and clearer guidance into the design and implementation of clinical TGC protocols.

2.0 Methods

2.1 SPRINT Protocol:

SPRINT is a model-derived [24, 30, 31] protocol that controls both insulin and (carbohydrate) nutrition inputs. It was implemented at the Christchurch Hospital Department of Intensive Care on August 2005 [13] and has now been used on over 1,000 patients. Interventions consider current and previous blood glucose measurements, current nutrition feed rate relative to a patient specific goal feed rate, and the prior hourly insulin dose to determine a new nutrition and insulin intervention for the coming 1-2 hour measurement interval defined in the protocol [13].

More specifically, SPRINT titrates its insulin and nutrition inputs to achieve a target range of 4-6 mmol/L based on the patient's current insulin sensitivity, determined in response to the insulin and nutrition interventions. More resistant patients receive more insulin and less nutrition (relative to their 100% goal feed rate). Stability and stopping criteria were also based on patient-specific insulin sensitivity. Hence, the protocol explicitly considers glycemic response in the context of both insulin and carbohydrate intake and is thus not blind to carbohydrate intake, which is unique, to the best of the authors' knowledge. Virtually all other studies leave nutritional intake to local clinical standards and are thus "blind" to this critical parameter.

A low carbohydrate enteral nutrition formula was also specified for all SPRINT patients per protocol, reducing the percentage of carbohydrate calories as a percentage of the total (specified) caloric intake. Minimum and maximum nutrition rates are 7.5

and 25 kcal/kg/day respectively, with 2.7 to 9 kcal/kg/day (35-40%) from carbohydrates, which matches ACCP guidelines at the maximum level [27].

A further difference is that SPRINT uses insulin boluses, limited to 6U per hour to minimise insulin saturation [32-35]. Boluses also avoid high rates of insulin infusion being left running when clinical staff are occupied, increasing potential safety, which is an important aspect in situations where high insulin infusion rates combined with infrequent measurement can lead to significantly increased hypoglycemic events and variability resulting from acute changes in patient condition and metabolic response.

2.2 Glucontrol:

In the Glucontrol trial [29], patients were randomised in each centre to intensive (Group A, target: 4.4-6.1 mmol/L) and conventional (Group B, target: 7.8-10 mmol/L) insulin therapy. Insulin was administered as a continuous IV infusion. Hourly measurement was used when the glycemic level was not within the target range. Otherwise, 2-hourly measurement was used in the case of limited variation of glycemia, defined as less than a 50% change from the previous glycaemia in 2-hour range. Finally, 4-hourly measurement was used when the glycemic level was less than 50% of the highest glycemia of the four last hours. The insulin infusion rates are defined as shown in Tables 1-2 for the Intensive (Table 1) and Conventional (Table 2) protocols. Nutritional input was left to local and/or clinician standards, and was not explicitly considered in the design or implementation of the protocol.

Table 1: Glucontrol protocol for intensive insulin therapy (Group A). (a) Starting insulin infusion rate. (b) Maintenance insulin infusion rates and increments.

(a)

Glycemia	Insulin infusion rate
< 110 mg/dl	On hold
110 - 140 mg/dl	1 U/H
140 - 180 mg/dl	2 U/H
> 180 mg/dl	4 U/H

(b)

Glycemia	Incremental insulin infusion rate
> 300 mg/dl	+ 3 U/H
180 - 300 mg/dl	+ 2 U/H
140 - 180 mg/dl	+ 1 U/H
110 - 140 mg/dl	+ 0.5 U/H
80 - 110 mg/dl	+ 0 U/H (target range)
40 - 80 mg/dl	Stop insulin, Hourly control of glycemia until > 80mg/dl
< 40 mg/dl	Stop insulin, 10gr glucose IVD, Call immediately physician, Hourly control of glycemia until > 80 mg/dl

Table 2: Details of the Glucontrol protocol for conventional insulin therapy group (Group B). (a) Starting insulin infusion rate. (b) Maintenance insulin infusion rates and increments.

(a)

Glycemia	Insulin infusion rate
< 180 mg/dl	On hold
180 - 250 mg/dl	1 UI/H
250 - 300 mg/dl	2 UI/H
> 300 mg/dl	4 UI/H

(b)

Glycemia	Incremental insulin infusion rate
> 300 mg/dl	+ 3 UI/H
250 - 300 mg/dl	+ 2 UI/H
180 - 250 mg/dl	+ 1 UI/H
140 - 180 mg/dl	+ 0 UI/H (target range)
80 - 140 mg/dl	Decrease 50% rate insulin
40 - 80 mg/dl	Stop insulin, Hourly control of glycemia until > 80mg/dl
< 40 mg/dl	Stop insulin, 10gr glucose IVD, Call immediately physician, Hourly control of glycemia until > 80 mg/dl

2.3 Patient Data:

In this study, data was used from 350 patients treated using the Glucontrol protocol at CHU de Liege, Belgium, between March 2004 and April 2005. Thus, the Glucontrol data is from only one centre out of the full study [29]. <mark>However, the other 21 centres were reported to be generally similar in behaviour. Hence, individual centres did not fail, but the overall trial did not achieve a clinical mortality outcome.</mark> Figure 1 shows the selection of patients used in this analysis. Patients were eliminated from the analysis if they received no insulin for their entire stay (per protocol), had less than 5 BG measurements over their time in the study or received little or no (recorded) carbohydrate administration (in any form) for more than 48 hours of their stay. All 393 SPRINT patients study met these criteria.
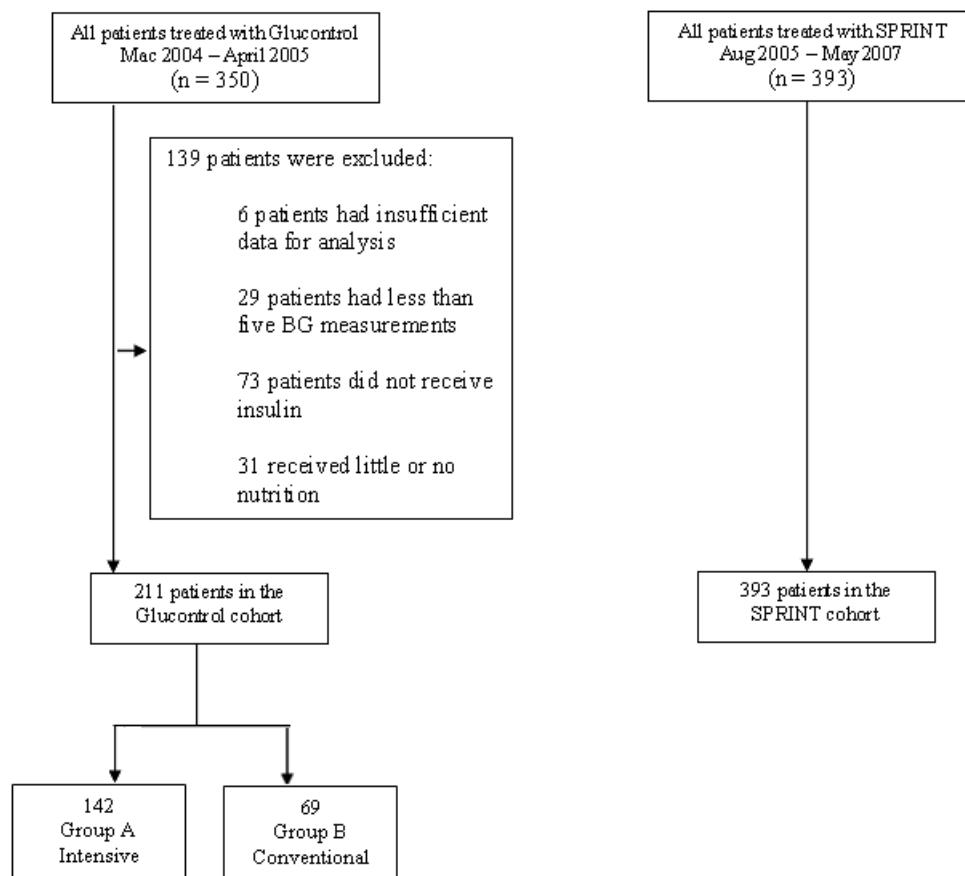
Figure 1: Cohort selection for SPRINT and Glucontrol A (Intensive) and B (Conventional) insulin therapy groups, resulting in 211 total Glucontrol patients being retained from the original 350.

2.4 Glucose-Insulin System Model:

The analysis of patient-specific insulin sensitivity uses a glucose insulin system model clinically validated in several studies [30, 31, 33, 36-42], defined:

$$\dot{G} = -p_G G - S_I G \frac{Q}{1 + \alpha_G Q} + \frac{P(t) + EGP_{max} - CNS}{V_G(t)} \tag{1}$$

$$\dot{Q} = -kQ + kI \tag{2}$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u_{ex}(t)}{V_I} + e^{-k_I U_{ex}(t)} I_B \tag{3}$$

In this model, $G(t)$ is the total plasma glucose, $I(t)$ is the plasma insulin, and $Q(t)$ is the effect of previously infused insulin being utilized over time. EGP_{max} is the theoretical maximum endogenous glucose production (EGP) for a patient, which is suppressed with increasing glucose concentrations. This suppression, independent of non-insulin mediated glucose uptake by the central nervous system (CNS) is captured by the term with p_G. In contrast, patient-specific insulin mediated glucose removal is captured with, S_I, insulin sensitivity, which is identified from clinical data as a time varying value that reflects evolving patient condition [37-39]. Exogenous inputs are from the carbohydrate content of nutrition infusions that appear ($P(t)$) in plasma blood glucose via a two compartment model leading to $P(t)$ [30, 36], and intravenous insulin administration $u_{ex}(t)$. The remaining parameters are physiologically defined

population constants for transport rates (n, k), saturation parameters (α_G, α_I), or volumes (V_G, V_I) that have been validated over several studies.

The essential parameter that drives the observed patient-specific glycemic response to insulin and nutrition inputs is insulin sensitivity, S_I. With this model, patient specific profiles can be generated for time-varying S_I and its hour-to-hour variation as patient condition evolves. This task is achieved by fitting the model to retrospective clinical data for blood glucose measurements, and insulin and carbohydrate administration input data from the protocols [39]. The resulting insulin sensitivity profile has been validated in correlation to gold standard euglycemic clamp and IVGTT data [43-45], as well as in in-silico virtual trials [24, 31, 37, 38, 42].

2.5 Stochastic Model:

Insulin sensitivity can evolve both gradually and acutely over time in ICU patients [36-38]. Stochastic models based on the hour-to-hour variation of this model variable yield distributions of the potential change in insulin sensitivity over 1-4 hours. These distributions then allow the creation of outcome blood glucose confidence bands for a given insulin and nutrition intervention (using the model). Thus, these models also quantify the potential affect on glycemic control of both minor (frequent) and acute (rare) evolutions in patient condition, as a function of current metabolic state and the clinical interventions. As a result, a model-based or adaptive TGC system can optimise interventions to minimise the risk of unexpected glycemic excursion and provide better decision making [37, 38, 42].

Knowledge of these dynamic changes provides further metrics of how metabolically dynamic and insulin resistant a given cohort may be. Therefore, they are another means of comparing cohorts for similarities or differences relevant to the quality of glycemic control achieved. While details are left to the references, a more dynamic and/or insulin resistant cohort would expect to have different bounds on this variability, and thus, all else equal, more variable glycemic control. Similarly, a more insulin resistant cohort would be expected to require more insulin to achieve equal glycemic outcomes. Thus, this model-based parameter and its variation can be used to quantify inter-patient and intra-patient variability for different cohorts, also enabling comparison of metabolic variability (over time and across patients) between cohorts.

3.0 Results

Table 3 compares the SPRINT and Glucontrol patients, where the latter are separated by TGC therapy (Groups A and B). Severity of illness over all Glucontrol (A+B) patients (via APACHE II) and percentage of male patients were similar (p > 0.35). The total Glucontrol cohort (A + B) was slightly older (p = 0.011).

Median blood glucose for Groups A and B were 6.3 and 8.2 mmol/L respectively, as expected, and SPRINT was 5.7 mmol/L, which is similar to the Group A value due to their similar glycemic targets. However, variability is much different across these protocols. Median inter-quartile range (IQR) spread (75th – 25th percentile) was 1.6 mmol/L for SPRINT, but 2.3 mmol/L for Group A and 2.5 mmol/L for Group B over the entire cohort(s).

To achieve these results, SPRINT used approximately 2x as much insulin (median: 2.8 U/hour) as Group A (median: 1.5 U/hour), which had a similar glycemic target, and 4x more than Group B (0.7 U/hour) with the higher glycemic target. It is important to recall that this analysis does not include patients from Glucontrol who did not receive insulin so the comparison is per protocol patient treated with insulin. Median nutrition, reported as appearance rate of carbohydrate in the nutritional formulas used, were broadly similar with median rates of 0.3, 0.6 and 0.42 mmol/min for Group A, Group B and SPRINT, respectively. However, it is also clear in Table 3 that the spread of carbohydrate administration rates is much more tightly controlled by SPRINT with an IQR range of 0.27 mmol/min for SPRINT versus 0.9 mmol/min for Glucontrol Groups A and B.

With respect to variability and safety from hypoglycemia, SPRINT had increasingly less percentage of measurements below 4.0, 3.0 and 2.2 mmol/L compared to the similarly targeted Group A. Surprisingly, it also had less percentage of measurements below 3.0 and 2.2 mmol/L than Group B which had a much higher glycemic target indicating that this protocol had significant variability in glycemic response. As a percentage of patients, SPRINT thus had a much lower rate of hypoglycemia below 2.2 mmol/L with 2% compared to Group A with 7.7% and the higher targeted Group B with 2.9%. The results for hyperglycemic measurements (percentage > 8.0 mmol/L) follow similar trends with expected differences for the higher targeted Group B.

On a per-patient basis, the median patient's median glucose was 6.4 mmol/L for Group A, 8.3 mmol/L for Group B, and 5.8 mmol/L for SPRINT, similar to those results for each overall cohort. However, the spread of median glucose levels across patients in each cohort was comparable for SPRINT with 1.1 mmol/L separating the 25th and 75th percentile patient's median blood glucose value, and Glucontrol with 1.0 and 1.2 mmol/L spreads for Groups A and B, respectively.

All of these results indicate that SPRINT maintained far tighter control on a cohort wide basis, but was comparable for intra-patient glycemic variability when analysing on a per-patient basis. Figure 2 provides cumulative distribution functions (CDFs) for each protocol's entire cohort, where the steeper SPRINT CDF clearly shows the lower variability compared to Glucontrol. The Glucontrol CDFs are similar in slope, but shifted, indicating similar behaviour around each glycemic target for each cohort. The

crossover of the Group A and SPRINT CDFs (at ~0.1 y-axis likelihood value) shows the higher hypoglycemia risk in the similarly targeted Group A cohort.

Figure 3, shows the same cohort CDFs for insulin delivered and Figure 4 for nutritional carbohydrate (all sources) delivery rate. It is clear in Figures 3-4 that SPRINT provides insulin and nutrition far more consistently across the cohort (steeper and less zero valued CDFs). Thus, SPRINT provided a more constant nutrition rate in terms of carbohydrate appearance from all sources to balance the insulin given with far less variation in glycemic outcome. Importantly, nutrition rate was not a controlled variable and specified only to local standards in the Glucontrol study, which likely resulted in the greater variability in this input, even in the single center studied here, and thus the greater resulting glycemic variability.

Figures 5 and 6 show empirical per-patient CDFs of model-based insulin sensitivity, S_I, for each protocol. The shaded areas show the 90% confidence interval (90%CI) range and IQR, with the median patient noted by a line. It is clear that the Glucontrol cohort has higher insulin sensitivity at all likelihoods (y-axis) and for all observed percentile patients compared to the SPRINT cohort. It is also clear that the spread or range of insulin sensitivity across the cohort is ~2x wider for Glucontrol indicating a cohort with far greater inter-patient variability in insulin sensitivity / resistance, and thus one potential reason for its greater outcome glycemic variability.

Figure 7 shows the distribution and hour-to-hour variation of fitted S_I over time for all Glucontrol protocol patients where measurements were 1-2 hours apart enabling the use of the stochastic model of Lin et al [37, 38]. The x-axis shows the S_I value at hour

'*t*' and a vertical line shows the distribution of possible S_I values in the next hour, *t+1* based on the entire cohort's data. The median, IQR and 90% confidence interval lines provide context and indicate the potential variability and the shape of its distribution over the next hour. This plot thus shows the hour to hour distribution and likelihood of metabolic intra-patient glycemic variability in response to an insulin dose for the Glucontrol cohorts. Hence, it might be hypothesized that the greater the intra-patient variability in response to insulin interventions, the greater the resulting glycemic variability in response.

Figure 8 provides the same data for SPRINT on a different y-axis scale for clarity. Figure 9 shows the combination of IQR, median and 90% CI from Figures 7-8 for both protocols. Figure 9 clearly shows very similar trends of median, IQR and 90% CI, indicating very similar metabolic intra-patient variability as assessed by this clinically validated parameter. Thus, despite the different inter-patient variation between SPRINT and Glucontrol in Figures 5-6, the hour to hour intra-patient variation between cohorts is very similar.

Figure 10 summarises the control and metabolic balance delivered by the protocols between carbohydrate administration, insulin administration and resulting glucose levels. It uses three dimensional plots of median blood glucose, median insulin dose, and median carbohydrate administration rates for every patient in all 3 cohorts. For clarity, Figures 11-13 show the decomposition of this 3D plot into two of the dimensions for each parameter. It is clear in all three of Figures 11-13 that the SPRINT data and glycemic outcomes are far less variable and/or more tightly controlled. This result is particularly valid with respect to the median nutrition rate

and carbohydrate content versus outcome median blood glucose. In Figure 11, both groups had zero feed rates at some portions for very short staying patients. In SPRINT, some patients were not fed, which corresponds to ~1-2% of hours with no feed rate as shown in Figure 4. Overall, these plots show the metabolic balance achieved for each patient between insulin and carbohydrate inputs and the resulting glycemic outcome. They also clearly show the outlying patients with unbalanced and/or extreme insulin and nutrition inputs resulting in poor(er) glycemic control to the desired target.

While this study does not directly examine mortality outcomes, the range of carbohydrate administration between all of Glucontrol and SPRINT was examined. Median carbohydrate administration rate (per-patient) was not associated with mortality in SPRINT ($p = 0.82$). However, there was a strong association with mortality in the overall Glucontrol cohort ($p = 0.03$).

Finally, Figure 14 illustrates the inter-patient variability in the resulting glycemic outcome(s). The per-patient CDFs shown reveal a tighter result across patients, particularly over the 25th to 75th percentile inter-quartile range patients, for the SPRINT protocol despite the differences or variability noted in prior results. The same lower variability seen for SPRINT over the cohort (steeper CDF in Figure 2) is also evident for all percentile patients in Figure 14, in comparison to the Glucontrol cohorts shown in Figure 14.

4.0 Discussion

SPRINT achieved tighter control than Glucontrol A or B (for the one centre examined) around their respective target glycemic levels, as clearly seen in Figure 5. The steeper CDFs indicate the lower, by cohort, glycemic variability. Importantly, the Glucontrol CDFs are very similar, but (primarily) shifted to their respective target glucose levels, resulting in higher hypoglycemia for the Group A cohort with the lower target. This result is reinforced by the steeper and less variable per-patient CDFs for the middle 50% of patients (IQR) in each cohort shown in Figures 14, which thus indicates the ability of each protocol to manage inter-patient variability.

The higher incidence of hypoglycemia for lower percentile patients is clearer in Figure 14. In particular, it indicates that the intensive Glucontrol A protocol could not effectively account for the inter- and intra- patient variability in metabolic behaviour seen in Figures 5-8, despite the wider range of (median) insulin and nutrition inputs used, as shown in Figures 10-13. Hence, some Glucontrol-A patients were simply controlled by the protocol to too low of a glycemic level, resulting in increased risk of hypoglycemia, which has been commonly reported in other studies (e.g. [19, 22, 46]).

This outcome clearly indicates that the Group A Glucontrol protocol was not able to fully account for differences between patients or/and intra-patient variability. This outcome was reinforced by the cohort and per patient results in Table 3, which show cohort IQR ranges for glycemic outcomes are much wider in this group than in the similarly targeted SPRINT case. As a result, SPRINT also had far less hypoglycemia.

In terms of providing nutrition and insulin, SPRINT has a higher proportion of patients receiving, on average, more insulin than Group A, and more consistently as well for Group B (less zero values on the CDF in Figure 3). In current thinking [22, 46-48], this increased insulin usage should have resulted in similar or greater hypoglycemia, which was not the case here. However, SPRINT patients also received a more consistent input of carbohydrate administration from all sources compared to Glucontrol Groups A and B, as seen in the relatively very steep CDFs for SPRINT in Figure 4 with virtually no zero values. Considering the carbohydrate intake, noted that all sources of carbohydrate includes enteral and parenteral nutrition an iv dextrose. This difference in CDFs is critical given that the median and average values are similar across all 3 cohorts. However, per-patient results for all 3 cohorts show that the spread of carbohydrate administration rates was much tighter for SPRINT than for either Group A or Group B by a factor of almost 4x for median rates across patients, as seen in Table 2.

Importantly, while Figure 11 shows that some SPRINT patients did have median zero feed rates, the work of Krishnan et al [26] shows that 33-66% of the ACCP guidelines is a more optimal rate of carbohydrate administration with respect to mortality outcome. The SPRINT data are thus clustered almost entirely in this range in Figure 4. In contrast, the greater spread in Glucontrol data is due to not controlling this variable and local clinical practice for that patient cohort. Hence, it may not be unexpected that there was no correlation between mortality and median per-patient carbohydrate administration in SPRINT, but that it was significant considering all Glucontrol patients.

These results indicate that the higher insulin usage combined with consistent, tightly managed carbohydrate input was balanced in the SPRINT protocol resulting in less glycemic variation and, for similar target glucose, less hypoglycemia. More specifically, the SPRINT protocol interventions were both more consistent and, within their tighter range, better able to manage the inter- and intra- patient variation in their cohort. Overall, hypoglycemia and tight control are, as might be expected, explicit functions of the nutrition and insulin dosing, leading to the conclusion that explicit knowledge of carbohydrate intake must be accounted for (if not explicitly controlled) in successful TGC, which is a result reported in independent studies [49]. In particular, without this information, it will be far more difficult to strike a safe, long-term and consistently achieved glycemic balance.

Thus, variability and/or inconsistency in insulin and nutritional carbohydrate inputs are one source of glycemic variability. A second major source would be the metabolic inter- and intra- patient variability, all else equal, of the cohort, where a more variable cohort would potentially be expected to have a more variable glycemic outcome. Figures 5-6 clearly shows that the Glucontrol cohorts span a wider range of insulin sensitivity than the SPRINT cohort with more inter-patient variability. However, their hour-to-hour variation can significantly affect the level of glycemic control, especially in cases with less frequent measurement where small evolutions over several hours can result in large changes in metabolic status and glycemic outcome for a constant infusion of insulin and nutrition. Hourly changes are the same for both Glucontrol and SPRINT given the similar plots in Figure 9 where 1 hour variations may be considered significant with respect to glycemic control and interventions when outside a 15% change from the prior hour [38, 50]. However, interestingly, Figures 7-

9 show very similar results between the cohorts for this intra-patient variability. Note that, while not shown, recreating Figure 9 separating Groups A and B yields the same result. Hence, while insulin sensitivity distributions were different between the SPRINT and Glucontrol cohorts, their hour-to-hour variability is very similar, which is an unexpected result and indicates a more universal behaviour may be evident.

Two conclusions may be drawn from this result. First, any protocol must be able to adapt to a given patient's specific level of insulin resistance and its changes over time, thus accounting for inter- and intra- patient variability. It is clear that Glucontrol was potentially unable to manage one or both of these aspects, as per-patient glycemic outcomes in Figure 14 were similar shaped (in CDF) across Group A and Group B with a simple shift due to the different glycemic targets. Second, to better control glycemic levels carbohydrate administration must be explicitly accounted for in the protocol design and implementation, which enables assessment or estimation of effective insulin sensitivity in real-time in response to interventions. In particular, this data would allow protocols to adapt their inputs to match gradual or acute changes in a patient's metabolic status (insulin resistance or insulin sensitivity S_I), which is what SPRINT effectively does [13, 24], and thus to provide potentially tighter control and more consistent care.

This last point may be critical when considering Glucontrol and other multi-centre trials. Glucontrol, NICE-SUGAR and VISEP [20, 29, 51] were all multi-centre trials that reported increased hypoglycemia with tighter/lower glycemic target groups, as well as failing to show benefit from TGC. In these recent studies, nutritional inputs were (largely) left to local standards of care, which can be quite variable both between

centres and between clinicians in a centre. As seen in these results, the level of hypoglycemia for Glucontrol Group A at CHU of Liege was still lower than the ~12% by patient level that stopped the multi-centre VISEP trial. Thus, it might be concluded that the variation of nutrition across centres in that trial resulted in even further variation in glycemic outcome for the fixed insulin delivery protocols used (all else equal). Hence, the result for the intensively controlled Group A would have been even further hypoglycemia and even more variable control around the target level when run over multiple centres, as was indeed the case in the final multi-centre report [29] with 8.7% of patients experiencing hypoglycemia for Group A versus 7.7% in the insulin treated Group A cohort examined here from the single Glucontrol pilot study centre. Certainly, this variability in nutrition input (alone) is evident in Figure 11 where median input rates span a very wide range. In contrast, explicit protocol knowledge of carbohydrate administration has, in both cases it has been used [13, 23], resulted in tighter control with minimal hypoglycemia.

One potential limitation of this study is that it uses a model-based metric of insulin sensitivity (S_I) to assess inter- and intra- patient variability. Thus, it should be noted that all cohorts studied here have measurable numbers of patients with diagnosed and/or undiagnosed type 2 diabetes mellitus (T2DM). However, the difference in insulin resistance between T2DM individuals and otherwise normal individuals are small in hyperglycemic critical care patients. In particular, non-critically ill T2DM individuals have an insulin sensitivity of S_I = 1.0-2.0e-3 (L/mU/min) in insulin sensitivity tests using this model [44, 45]. This range of values covers only a very few patients or hours in Figures 5-7 for the least resistant (most sensitive). The typical critically ill patient, with or without T2DM, has a significantly counter-regulated

metabolic system that drives effective insulin resistance, as measured by this clinically validated model, to values well below an otherwise healthy T2DM individual. Thus, there is little impact expected on the overall glycemic outcomes and this analysis due to a subset of patients with this diagnosis. In SPRINT in particular, there were no differences in glycemic or mortality outcome for diabetic individuals.

Finally, it should be noted that the Glucontrol data examined here was only from one centre (CHU de Liege, Belgium) where the protocol was piloted. While the glycemic outcomes of the two protocols in this subset are similar to those over the study, it should be noted that these results could potentially differ if the full 21 centre study data set were considered. However, the overall goal of this article was to examine differences in glycemic control outcomes and the associated control inputs to define aspects that can result in greater success or difficulty in obtaining tight glycemic control. In that context, the study presented is valid, and a further analysis using the full data set, when available, might better define these results as well as characterise where variability across centres, within a given protocol, had positive and negative effects on TGC.

More importantly, from this study, it can be evaluated that clear guidelines for nutrition intake of carbohydrate are essential in TGC protocol regardless of the nutritional standards and practises across different countries. In addition, considering frequent and convenient measurement, future protocols should also consider bedside glucose monitoring systems for reduced clinical effort and better control. For future studies, comparison of protocols that achieve high level of compliance should be evaluated.

5.0 Conclusions

Three main conclusions may be drawn from this analysis:

1. Successful TGC protocols must be able to account for the significant inter- and intra- patient variability in insulin resistance (sensitivity) that can be observed in critically ill cohorts.

2. a)   Explicit knowledge of, and potentially control of, carbohydrate administration within reasonable limits reported in the literature, appears to be a mandatory component in reducing outcome glycemic variability and thus, potentially, in achieving all of the benefits of TGC with minimal risk. It is a factor that is missing from many of the published protocols to date.

   b)   Limits to non-saturable ranges of insulin infusion or intervention of 0-8 U/hour would also limit the changes seen in glycemia when intra-patient variability is high.

3. While inter-patient variability in insulin sensitivity can be quite different between cohorts that are otherwise similar in severity of illness, the evolution and dynamic change or intra-patient variability of this parameter appears to be very similar across (at least) the cohorts studied here.

All of these main conclusions remain to be prospectively tested. However, this analysis highlights key aspects of TGC trials and data that can be used in developing improved protocols, as well as used for retrospective analysis and comparisons that may have been previously overlooked.

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Table 3: Comparison of Glucontrol and SPRINT cohorts. The p-values are for comparing the Glucontrol A+B cohorts together versus SPRINT

| | SPRINT | Glucontrol | | *P* value |
		A	B	
Number of patients	393	142	69	
Percentage of males (%)	62.8	64.8	56.5	0.8531
Age [IQR]	65 [50 – 74]	71 [61 – 80]	69 [53 – 77]	0.0011
Apache II score median [IQR]	18 [14 – 24]	17 [14 – 22]	17 [14 – 21]	0.3894
Hours of control	49,008	16831	12946	
Total BG measurement	29,919	4571	2820	
Cohorts				
BG median [IQR] (mmol/L)	5.7 [5.0 – 6.6]	6.3 [5.3 – 7.6]	8.2 [6.9 – 9.4]	
Insulin rate median [IQR] (mU/min)	50.0 [16.7 – 50.0]	25.0 [8.3 – 50.0]	11.7 [0.0 – 28.3]	
Feed rate of carbohydrate median [IQR] (mmol/min)	0.42 [0.25 – 0.52]	0.30 [0.00 – 0.90]	0.60 [0.10 – 1.00]	
No. of patient with BG less than 2.2 mmol/L	8 (2.0%)	11 (7.7%)	2 (2.9%)	
Percentage of measurement less than 2.2 mmol/L (%)	0.05	0.4	0.1	
Percentage of measurement less than 3.0 mmol/L (%)	0.28	1.3	0.4	
Percentage of measurement less than 4.0 mmol/L (%)	3.9	5.3	0.8	
Percentage of measurement less than 4.4 mmol/L (%)	9.4	9.4	1.7	
Percentage of measurement between 4.4 and 6.1 mmol/L (%)	48.2	35.8	10.4	
Percentage of measurement between 7.8 and 10.0 mmol/L (%)	6.2	15.6	40.6	
Percentage of measurement greater than 8.0 mmol/L (%)	8.0	20.3	52.5	

	SPRINT	A	B	
Per Patient Results				
Hours of control median [IQR]	53 [19 – 149]	61 [38 – 138]	89 [43 – 229]	
Number of BG measurements taken: median [IQR]	37 [16 – 97]	19 [11 – 37]	22 [11 – 47]	
BG median [IQR] (mmol/L)	5.8 [5.3 – 6.4]	6.4 [5.9 – 6.9]	8.3 [7.6 – 8.8]	
Insulin rate median [IQR] (mU/min)	50.0 [33.3 – 50.0]	25.0 [13.3 – 33.3]	8.3 [0.0 – 16.7]	
Feed rate median [IQR] (mmol/min)	0.37 [0.20 – 0.48]	0.1 [0.0 – 0.8]	0.2 [0.0 – 0.7]	
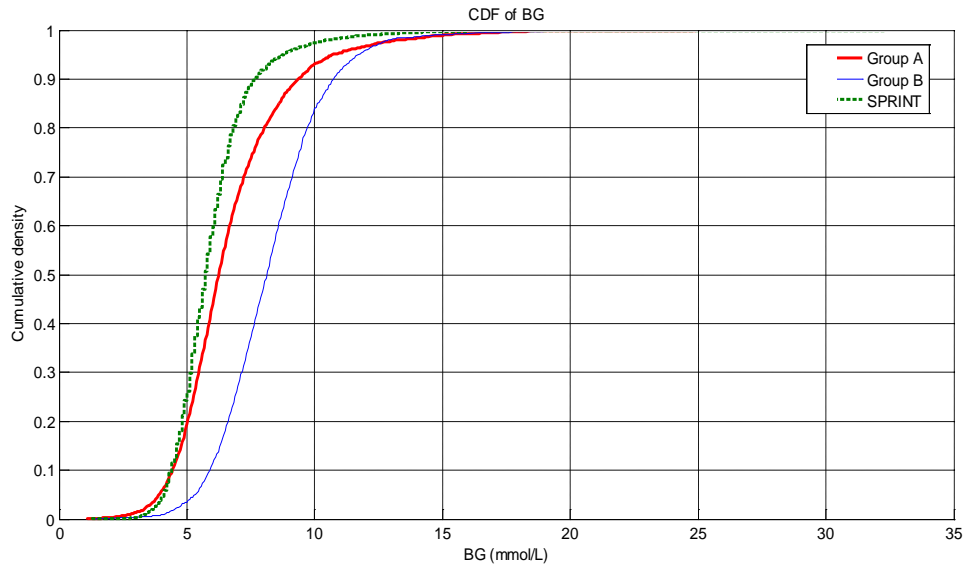
Figure 2: CDF of measured blood glucose on cohort basis for SPRINT, Group A and Group B (Glucontrol).
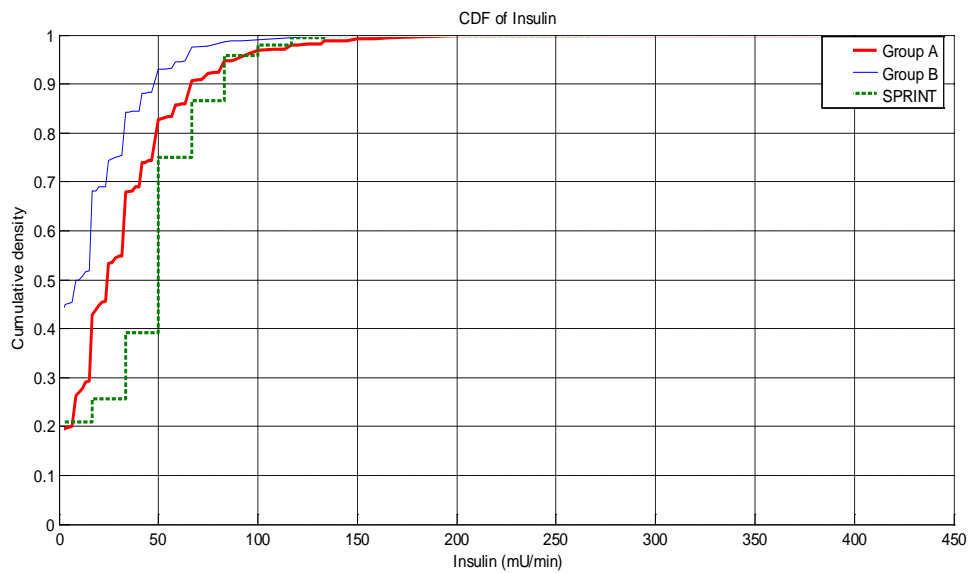
Figure 3: CDF for hourly insulin infusion rate on cohort basis for SPRINT, Group A and Group B (Glucontrol).
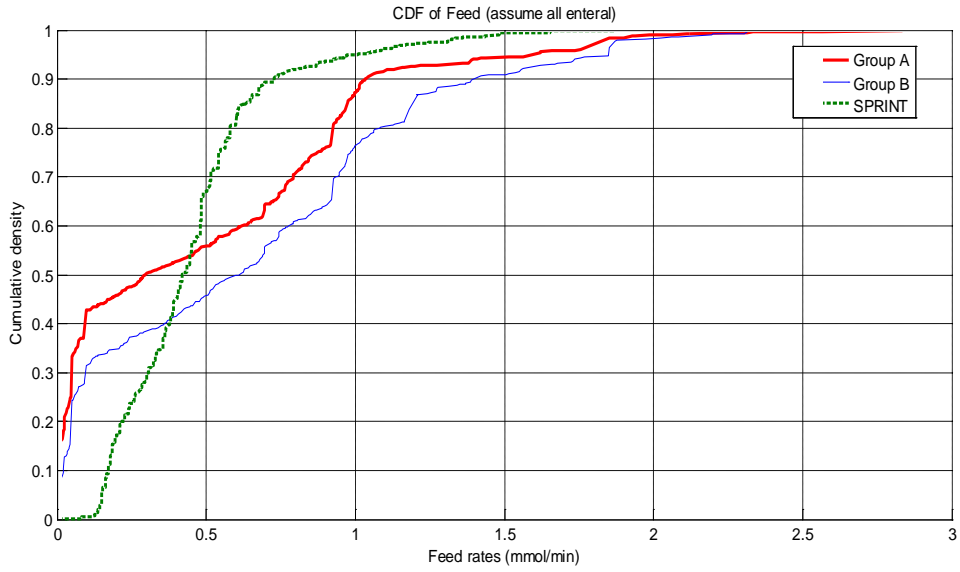
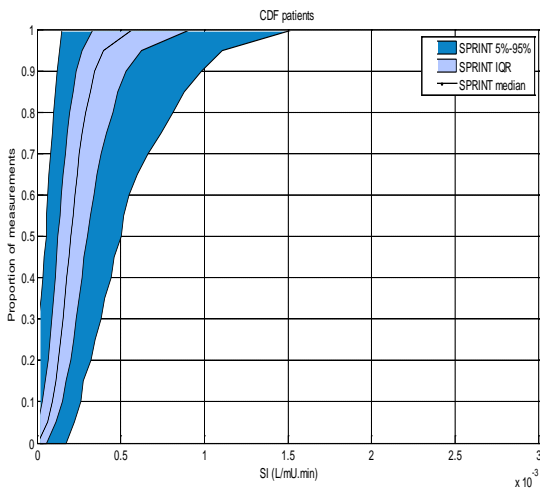Figure 4: CDF of nutrition rate on cohort basis for SPRINT, Group A and Group B (Glucontrol).

Figure 5: Empirical cumulative distribution functions per patient of insulin sensitivity on SPRINT.
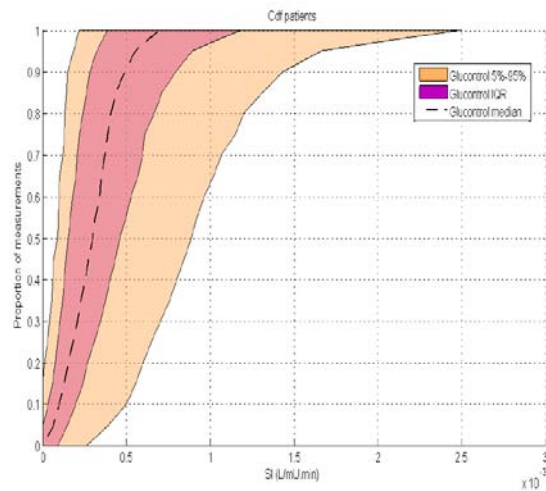

Figure 6: Empirical cumulative distribution functions per patient of insulin sensitivity on Glucontrol.
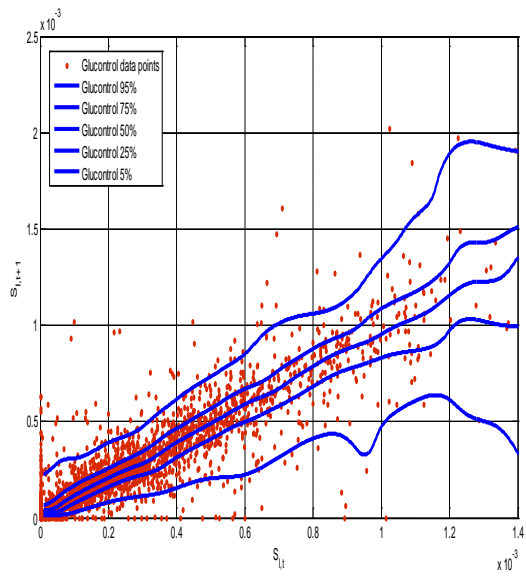
Figure 7: Fitted hourly S_I variation and probability distribution function of Glucontrol (1-2 hours interval).
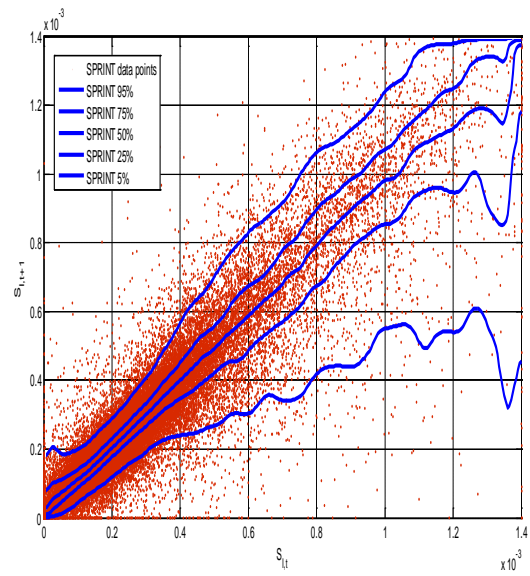
Figure 8: Fitted hourly S_I variation and probability distribution function of SPRINT.
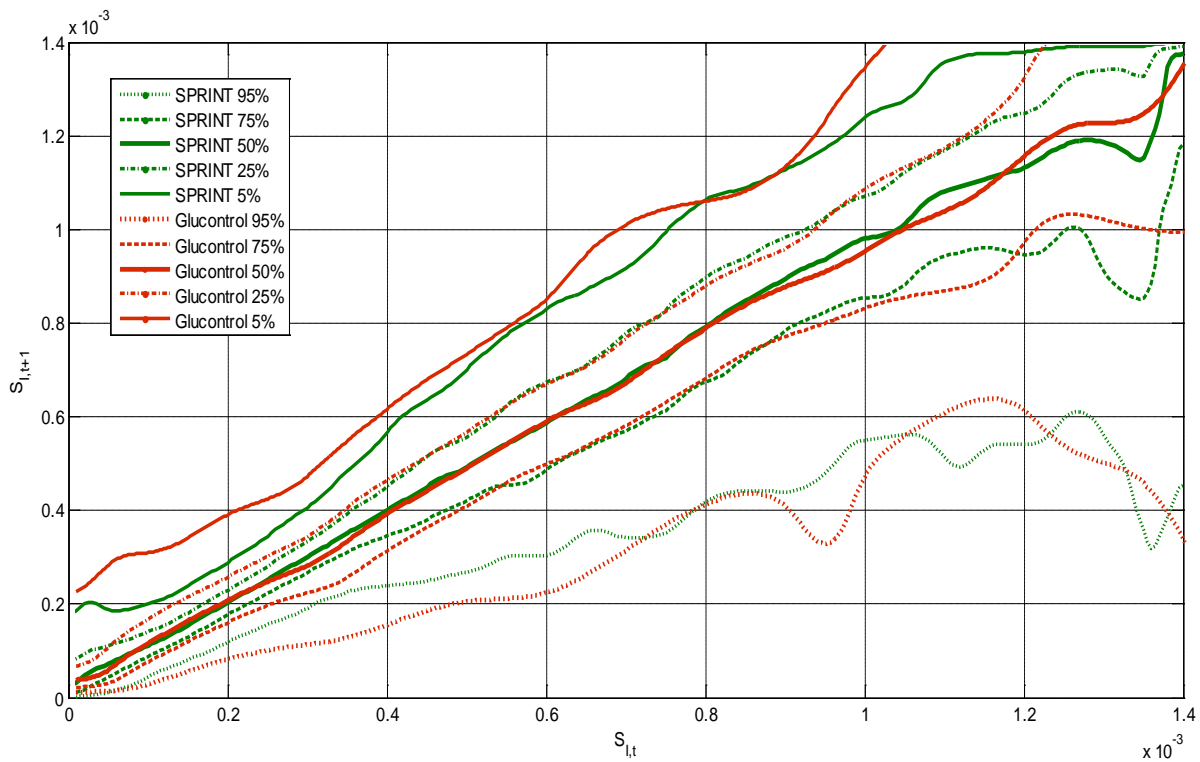
Figure 9: Fitted hourly S_I variation and probability distribution function of SPRINT and Glucontrol with 1-2 hours measurement interval. The trends are very similar at most S_I values with differences at very low insulin sensitivity (S_I) due to lower numbers of data points in the Glucontrol cohort, per Figures 5-6.
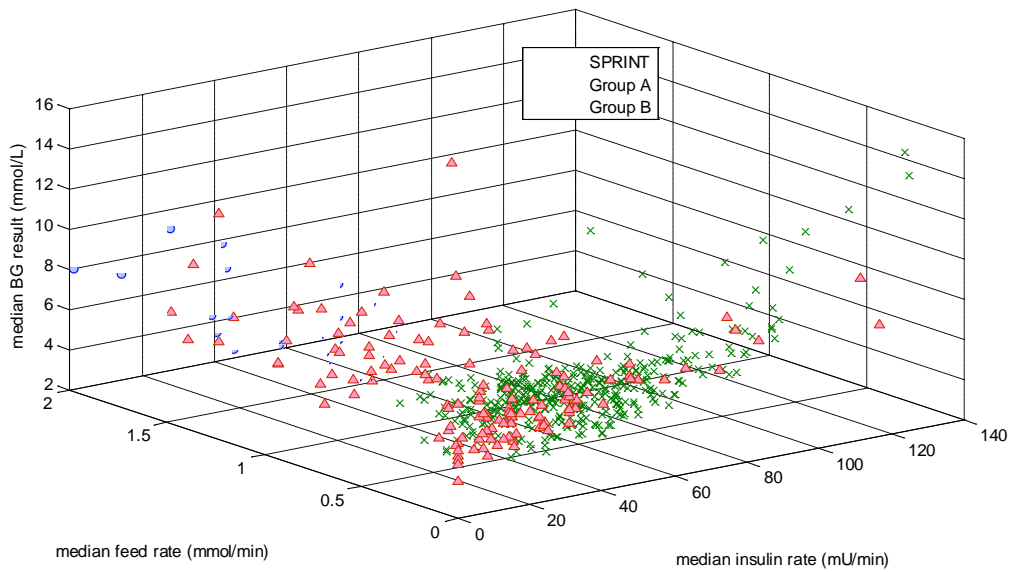
Figure 10: Three dimensional plot of median insulin rate, median feed rates and median

BG for SPRINT and Glucontrol (Group A and Group B).
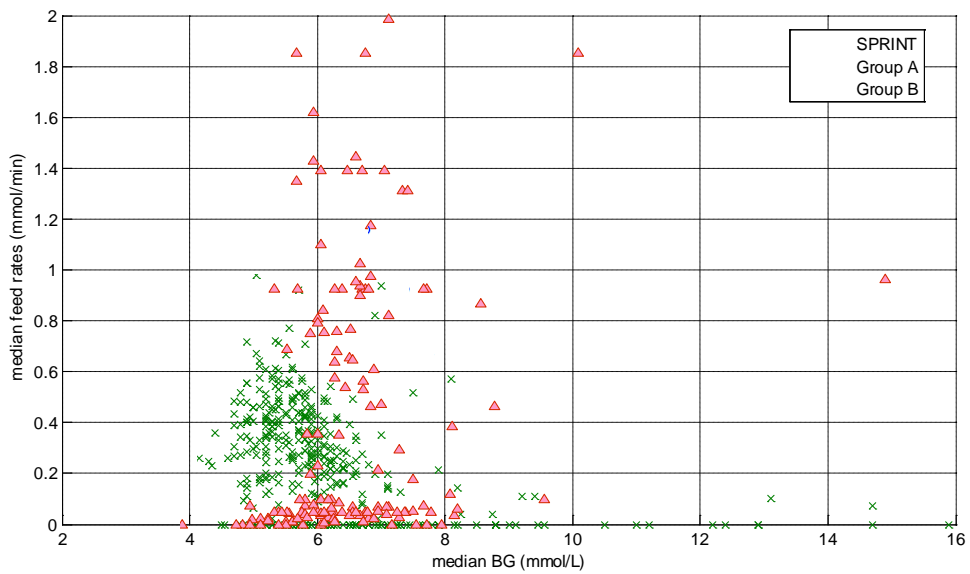
Figure 11: Distribution of median feed rates (all sources) versus median blood glucose

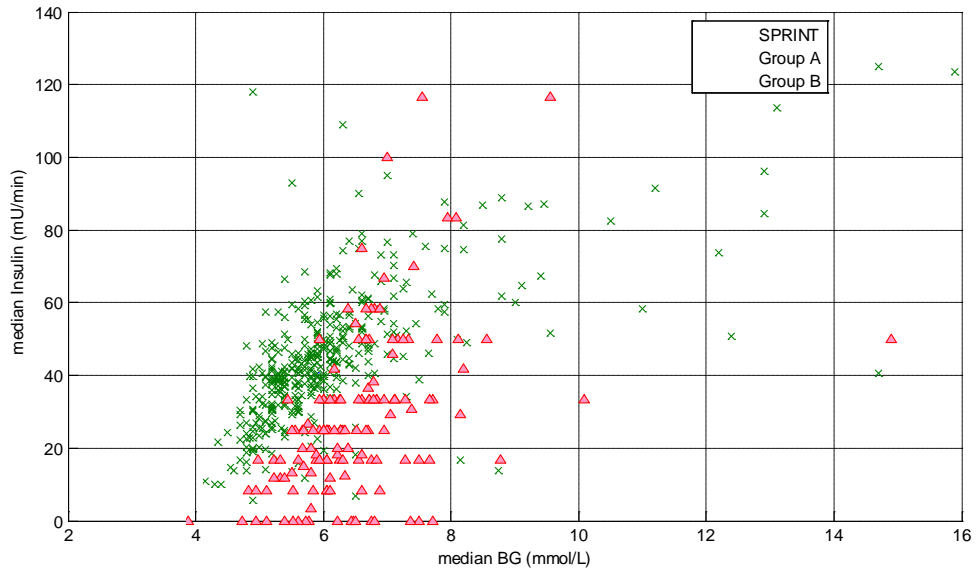measured for SPRINT and Glucontrol (Group A and Group B).

Figure 12: Distribution of median insulin versus median blood glucose measured for SPRINT and Glucontrol (Group A and Group B).
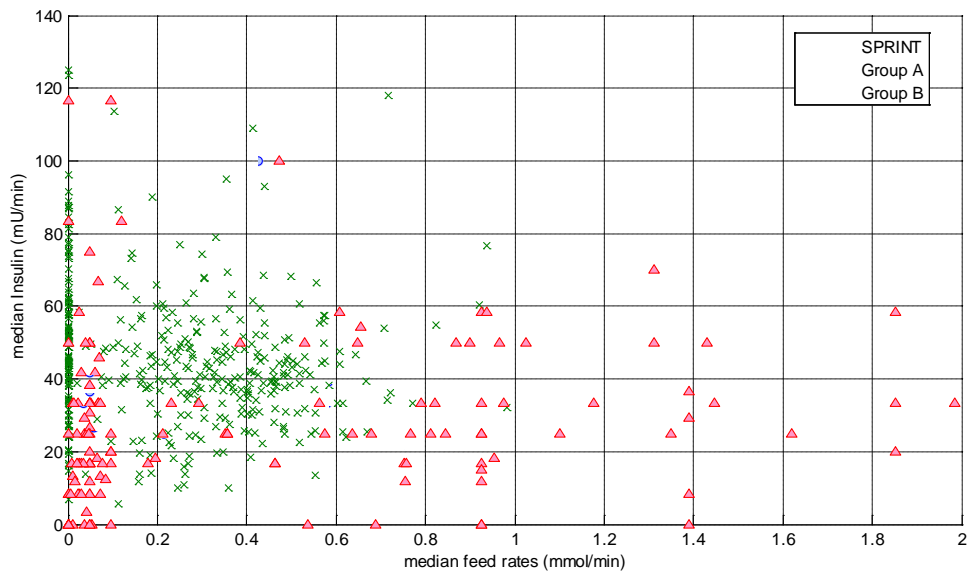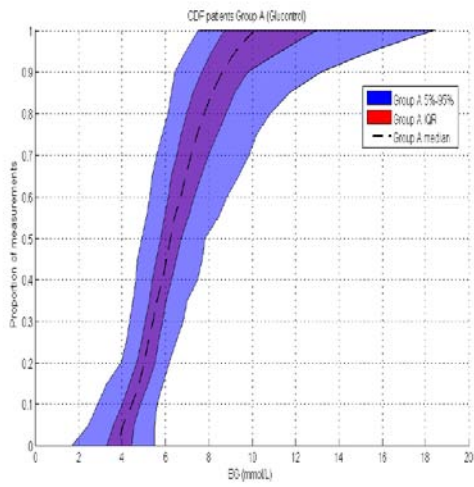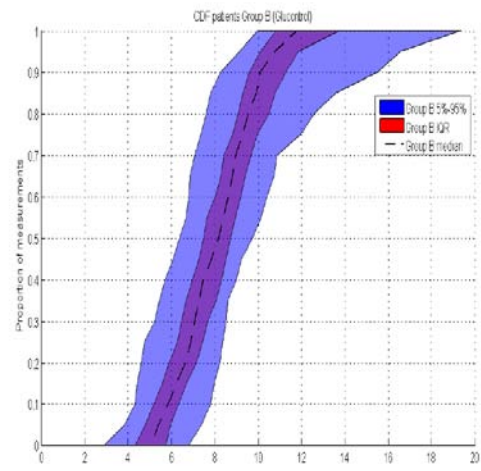

Figure 13: Distribution of median insulin against median feed rates (all sources) for SPRINT and Glucontrol (Group A and Group B).

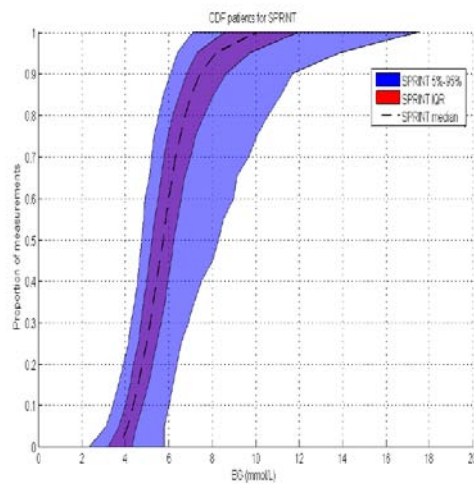(a)   (b)

(c)

Figure 14: Empirical cumulative distribution functions per patient of measured blood glucose on: a) Group A of Glucontrol, b) Group B of Glucontrol and c) SPRINT. Lines show the 5th, 25th, 50th (median), 75th and 95th percentile patient responses and shaded

areas show the resulting inter-quartile and 90% CI ranges. All x and y axes have the same scale.