Glucose control in the ICU using continuous glucose monitoring: What level of the measurement error is acceptable?

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Running title

CGM and glucose control

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Key words

glucose control, critical care, insulin titration protocol, continuous glucose monitoring

Abbreviations

ICU Intensive Care Unit, **CGM** Continuous Glucose Monitoring, **BG** Blood Glucose, **MARD** Mean Absolute Relative Difference, **POC** Point of Care

Abstract

Background

Accuracy and frequency of glucose measurement is essential to achieve safe and efficacious glucose control in the ICU. Emerging continuous glucose monitors provide frequent measurements, trending information and alarms. The objective of this study was to establish the level of accuracy of continuous glucose monitoring (CGM) associated with safe and efficacious glucose control in the intensive care unit.

Methods

Three established glucose control protocols (Yale, University of Washington, and NICE-SUGAR) underwent evaluation using computer simulations. Insulin delivery was informed by intermittent blood glucose (BG) measurements or CGM levels with an increasing level of the measurement error. Measures of glucose control included mean glucose, glucose variability, time glucose was in target range, and hypoglycemia episodes.

Results

Apart from Washington protocol, CGM with mean absolute relative deviation (MARD) up to 15% resulted in similar mean glucose as with the use of intermittent BG measurements. Glucose variability was also similar between CGM and BG-informed protocols. Frequency and duration of hypoglycemia were not worse using CGM with MARD at or below 10%. Measures of glucose control varied more between protocols than at different levels of the CGM error.

Conclusions

The efficacy of CGM-informed and BG-informed commonly used glucose protocols is similar but the risk of hypoglycemia may be reduced using CGM with MARD at or below 10%. Protocol choice has greater influence on glucose control measures than the glucose measurement method.

INTRODUCTION

Accurate measurement of blood glucose concentration is essential for achieving safe and efficacious glucose control in the intensive care unit [1,2]. Accuracy standards to determine adequacy of intermittent and continuous glucose monitoring devices are subject of an ongoing debate informed by consensus but lacking convincing evidence [3].

Various types of glucose measuring devices are currently used in the ICU setting. A limited number of studies report the use of subcutaneous continuous glucose monitors (CGM) [4-9] and majority of glucose measurements are currently performed intermittently using either blood gas analyzers or point-of-care (POC) glucose meters. Although blood gas analyzers have been shown to be accurate [10], the use of POC meters raised many concerns [11-13]. The point-of-care devices which measure glucose concentration in either arterial or capillary blood were not designed for use in the critically ill patients who are prone to frequent and often large changes in hematocrit, pH and blood oxygenation. Intermittent measurements are also limited by the heavy workload at the ICU and could lead to missing important events such as hypoglycemia episodes.

In response to these concerns and also to increase the frequency of blood glucose measurements without affecting staff workload, CGM devices are being developed for use in the critically ill. Intravenous and subcutaneous CGM systems are now available for clinical use and have undergone early clinical testing [14-17]. CGM technologies offer frequent automated glucose measurements, a glucose rate of change assessment, and threshold or predictive alarm functionality. These properties may positively impact the safety of current glucose control protocols and improve clinical outcomes [18].

Potential benefits may be substantial but should be evaluated and documented to attain regulatory approvals, reimbursement, and clinical acceptance. To date, no studies have assessed glucose control measures obtained from using continuous glucose monitoring compared to intermittent glucose measurements. Such direct comparison could provide valuable data to help inform the debate on accuracy guidelines.

Two approaches to perform comparison studies are feasible. Clinical trials may be conducted but these are costly, time-consuming and bounded by ethical constraints. Computer simulations offer a resource efficient alternative [19,20]. In the present study, we utilized a validated virtual population of 56 critically ill patients [21] to simulate clinical experiments and compare glucose control measures using three commonly used glucose control protocols informed by either intermittent or continuous glucose measurements.

MATERIALS AND METHODS

We used computer simulations to contrast the ability of continuous and intermittent glucose measurements to achieve desirable glucose levels in combination with common glucose protocols in the critically ill. This allowed direct comparison, similar to that offered by crossover clinical trials, among glucose measurement methods (continuous vs. intermittent) and glycemic control protocols. The simulated experiments utilized a virtual population of critically ill patients, developed from data collected in multicentre multinational clinical trials [22-26], and validated against independent clinical data [21].

Virtual patients

The virtual patients were created from clinical database collected in 56 critically ill patients, 29 patients treated in the medical ICU [M 25; age 66.7(11.7)yrs; weight 76.5(14.6)kg, diabetes 5; APACHE II 19(16-24); total CHO intake 7.2(3.8)g/h; mean(SD) or mean(range)] and 27 in the surgical ICU [M 16; age 62.6(13.7)yrs; weight 83.5(18.4)kg, diabetes 7; APACHE II 22(19-25); total CHO intake 7.5(3.5)g/h; mean(SD) or mean(range)] at Charles University, Prague [22,23] Medical University, Graz [23,24], Katholieke Universiteit, Leuven [25,26], and Royal Brompton Hospital, London [23,25].

From the clinical data, 56 virtual patients were created, one virtual patient per one real patient, through a process termed experimental *in silico* cloning [19]. A physiologically-based compartment model was fit to glucose measurements capturing the between-person and temporal variability in insulin sensitivity as well as institutional differences in nutritional and other treatment protocols [19].

Validity of the virtual population was assessed by replicating two open-label randomized clinical trials evaluating glucose control protocols [25,27]. One study compared performance of the enhanced model predictive control algorithm at two ICUs in the UK and Belgium [25]. The other study compared three algorithms for insulin delivery in a single intensive care unit in Prague [27]. Principal findings of the two studies were reproduced [21].

Simulations design

We simulated a 48-hour stay in the ICU. When evaluating intermittent glucose measurements, insulin delivery was adjusted according to the glucose measurement pertinent at the protocol-defined time points, i.e. hourly or less frequently. When evaluating continuous glucose measurements, available every 5 minutes, insulin delivery was adjusted at the protocol-defined time points as for the intermittent measurements, and additionally at hypoglycemia and hyperglycemia alarm thresholds set at 70mg/dL (3.9mmol/L) ~~(70mg/dL)~~ and 300mg/dL (16.7mmol/L) ~~(300mg/dL)~~. Once activated, alarms were disabled over the following 30minutes. Protocol-specific hypoglycemia and hyperglycemia treatment guidelines were applied.

Further simulated experiments assessed sensitivity and specificity of CGM-triggered hypoglycemia alarms. An alarm was considered true positive if it occurred within ±30min from the start of BG-confirmed hypoglycemia event. If hypoglycemia did not occur within ±30min of the start of the alarm, the alarm was considered false positive. In these simulations, hypoglycemia treatment was not administered as it confounded the assessment of alarm sensitivity and specificity.

Glucose protocols

Three common glucose protocols were simulated, Yale [28] (target range 100-140 mg/dL or 5.6-7.8mmol/L or; hypoglycemia thresholds 75 and 60 mg/dL or 4.2 and 3.3mmol/L), University of Washington [13] (target range 80-180 mg/dL or 4.4-10mmol/L; hypoglycemia threshold 60 mg/dL or 3.3mmol/L) and NICE-SUGAR [29] (target range 80-180 mg/dL or 4.4-10mmol/L); hypoglycemia thresholds 72 and 40 mg/dL or 4.0 and 2.2mmol/L). The same unmodified protocols were used when evaluating intermittent and continuous glucose measurements.

CGM measurement error

The CGM measurement error combined *scale*, *bias* and *residual* error components. The scale was expressed as a proportional error pivoted around blood glucose of 5.55mmol/l (100mg/dl). The constant bias was applied across the entire glucose range. The residual error was assumed to be autocorrelated with zero mean, normally distributed, and absolute at blood glucose values below 100mg/dL (5.55mmol/L) and proportional otherwise.

Seven levels of the scale component (range 0.8 to 1.2 in steps of 0.1) were considered. The constant bias ranged from -15 mg/dL (-0.84mmol/L) to +15 mg/dL (+0.84mmol/L) in seven steps of 5 mg/dL (0.28mmol/L). The residual error was assumed to have a standard deviation ranging from 0 to 15 mg/dL (0.84mmol/L) for blood glucose below 100 mg/dL (5.55mmol/L), and a coefficient of variation from 0 to 15% for other glucose values. Seven steps with resolution of 2.5 mg/dL (0.14mmol/L) of SD and 2.5% of CV were considered. Three levels of the autocorrelation coefficient, 0.97, 0.98 and 0.99, were applied to

glucose values sampled every minute. Overall, 735 combinations of the three error components were simulated. The total error obtained in the simulations was stratified according to the mean absolute relative deviation (MARD) into ranges 0-5%, 5-10% and 10-15%. Sixty error combinations per virtual subject were randomly selected, twenty for each MARD range, and used in subsequent simulated experiments. Different error combinations could be selected for different subjects.

Additional analyses were carried out to assess the effect of CGM imprecision and bias on glucose control and rate and duration of hypoglycemia. CGM imprecision was varied between 0% and 15% in 5% steps in the absence of bias. Similarly, CGM bias varied from -15% to +15% in 5% steps in the absence of imprecision.

Intermittent glucose measurement error

Three intermittent glucose measurement methods were simulated, the arterial blood gas measurement (ABG), a point-of-care device using capillary blood (POC capillary) and a point-of-care device using arterial blood (POC arterial). The measurement error was assumed to be uncorrelated, normally distributed with zero mean and with characteristics reported by a systematic review by Inoue *et al* [10]; ABG, POC arterial and POC capillary measurement errors were assumed absolute below 75mg/dL (4.2mmol/L) with a constant SD of 2.3mg/dl (0.13mmol/L), 5.8mg/dL (0.32mmol/L) and 8.0mg/dL (0.44mmol/L), respectively. For glucose values above 75 mg/dL (4.2mmol/L) the measurement error was assumed to be proportional with a coefficient of variation at 3.2%, 6.0% and 7.8% for ABG, POC arterial and POC capillary measurements.

Implementation

The Simulation Environment version 5.8 (University of Cambridge, Cambridge) was implemented under Matlab® (The Mathworks, Natick, MA, USA) [21].

Statistics

Glycemia control measures were based on the blood glucose concentration. Hypoglycemia measures included the percentage of simulated patients experiencing at least one episode of hypoglycemia (<70 and <40 mg/dL or <3.9mmol/l and <2.2mmol/l) and the median duration of such episodes across simulated studies. Values shown are mean ± standard deviation or median (interquartile range).

RESULTS

In total, 20,160 forty-eight-hour long simulated experiments were generated, a result of multiplication of 20 error combinations, 56 virtual subjects, 6 measurement methods (3 ranges of CGM error plus 3 intermittent methods) and 3 ICU protocols. Three quarters of the simulated experiments (15,120) were used in the data analysis providing 560 simulated experiments per ICU protocol and per measurement method. Further selection was carried out to obtain an equal representation of virtual ICU subjects in each MARD range and to assure an equal number of simulated experiments in each MARD range. The selection process adopted random sampling from allowable subsets (see details in **Supplemental Information**).

Table 1~~Table 1~~ shows glucose control measures stratified according to the glucose measurement method and the glucose control protocol. Apart from the Washington protocol, CGM with MARD up to 15% resulted in similar mean glucose as with the use of intermittent BG measurements. Adopting the University of Washington protocol, the mean glucose was higher when CGM was used but this was offset by lower rates of hypoglycemia. Glucose variability was similar across all measurement methods and protocols. The time spent in target glucose range improved with increased CGM accuracy applying the Yale and Washington protocols reaching similar values as with the use of intermittent BG measurement methods when CGM MARD was below 10%. Applying NICE-SUGAR protocol, the time spent in target glucose range was largely unaffected by the glucose measurement method.

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Hypoglycemia measures are shown in Table 2~~Table 2~~. The frequency and duration of hypoglycemia episodes was reduced or similar for CGM measurements with MARD at or

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below 10% across all protocols. For CGM measurements with MARD in the upper 10-15% range the frequency and duration of hypoglycemia less than ~~<~~40 mg/dL (<2.2mmol/L) was also reduced but hypoglyc~~a~~emia less than ~~<~~70mg/dL (3.9mmol/L) was only reduced whilst applying Washington and NICE-SUGAR protocols.

Supplemental Table1 shows sensitivity and specificity of CGM-based hypoglycemia alarms. Sensitivity was reduced with CGM measurements with MARD above 10%. Specificity was also reduced above 10% MARD apart from the Yale protocol where it remained similar across the investigated MARD range.

Table 3~~**Table 3**~~ shows glycemic control measures stratified according to CGM imprecision. Apart from the Yale protocol, CGM with imprecision up to 15% resulted in a similar mean glucose and glucose standard deviation. With the Yale protocol, CGM imprecision of 15% resulted in a higher mean glucose and higher glucose variability leading to a reduction of time spent in target glucose range. The effect of CGM imprecision on frequency and duration of hypoglycemia is shown in **Table 4**~~**Table 4**~~**.** An increase in the number of hypoglycemia episodes, but not the duration, was seen with the increasing imprecision in all three protocols.

Table 5~~**Table 5**~~ shows the effect of CGM bias on glucose control. As expected, a reduction in mean glucose with increasing bias was observed in all protocols. A marked reduction in time spent in target glucose range was present in all protocols with negative bias at or below 10%. With the Yale protocol, both positive and negative bias exceeding 10% resulted in reduced time spent in the target glucose range. With the Washington protocol time spent in target range was least affected by positive bias whereas with NICE-SUGAR protocol the time spent in target range increased with increasing positive bias.

The effect of CGM bias on frequency and duration of hypoglycemia is shown in **Table** ~~**6Table 6**~~. An increase in the number of hypoglycemia episodes below 70mg/dL (3.9mmol/l) with increasing bias was evident with all protocols, although at a different bias threshold. The Yale protocol was sensitive to positive CGM bias with the number of hypoglycemic episodes steadily increasing with increasing positive bias. The NICE-SUGAR protocol was the least sensitive. A marked increase in the number of hypoglycemia episodes below 70 and 40 mg/dL (3.9 and 2.2mmol/L) was observed at bias 10% and above.

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DISCUSSION

The present study assessed the level of accuracy of continuous glucose monitoring required for safe and efficacious glycemic control in the intensive care unit by contrasting glucose control measures obtained with three common insulin titrating protocols. Experiments using intermittent and continuous glucose measurements demonstrated comparable efficacy of CGM-informed and BG-informed ICU insulin protocols in terms of mean glucose and glucose variability across all levels of the CGM error and protocols. The time spent in target glucose range was similar for CGM error up to 10% but decreased thereafter. Hypoglycemia rates were maintained or improved with CGM error up to 10% MARD. The frequency and duration of severe hypoglycemia below 40 mg/dL (2.2mmol/L) was reduced across the investigated MARD range.

Unlike Yale and NICE-SUGAR protocols which provided similar mean glucose across all measurement methods, mean glucose associated with CGM-driven Washington protocol was higher and was offset by a considerably reduced frequency of hypoglycemia (Table 2~~Table 2~~). A reduction in hypoglycemia frequency was also observed in the CGM-driven Yale protocol but only with MARD less than 10%. With MARD values above 10% both frequency and duration of hypoglycemia events were higher than using intermittent BG measurements. In contrast, the CGM informed NICE-SUGAR protocol resulted in a similar frequency of hypoglycemia less than 70 mg/dL (3.9mmol/L) as with intermittent BG measurements.

Glucose control measures were protocol dependent so that the type of protocol had a larger effect on endpoints than the glucose measurement method. This applied to mean glucose, glucose variability, and hypoglycemia rates and duration.

The efficacy of the CGM-driven Washington protocol measured as a percentage of time glucose was in target range was offset by the high frequency of hypoglycemia episodes compared to the other two ICU protocols. In contrast, the NICE-SUGAR protocol had fewer hypoglycemia episodes but also the lowest percentage of time spent with glucose in the target range. Of the three ICU protocols, the Yale protocol appeared to be the safest with the lowest rates of hypoglycemia while attaining the mean glucose similar to the Washington protocol.

CGM-triggered alarms are designed to facilitate timely detection of hypo- and hyperglycemia and may improve the safety of existing protocols. We documented acceptable sensitivity and specificity of hypoglycemia alarms at MARD up to 10% and then gradual deterioration in sensitivity and specificity. This finding was consistent across all protocols.

The insulin titrating protocols achieved different balances between safety, as measured by hypoglycemia exposure, and efficacy as assessed by time spent in the target range. The NICE-SUGAR protocol emphasized hypoglycemia avoidance at the expense of higher glucose concentrations whereas with the Washington protocol the emphases were reversed. The Yale protocol was most balanced with 50% of time spent in a tight glucose range and a low risk of hypoglycemia.

Additional analyses contrasted CGM imprecision and bias. In agreement with Boyd and Bruns [20], we observed a smaller effect of imprecision on mean glucose and time spent in the target range compared to bias. This observation extended to frequency and duration of

hypoglycemia in the case of the Yale and NICE-SUGAR protocols but not with the Washington protocol. In the latter protocol the effect of increasing CGM imprecision on the number of hypoglycemia events was more pronounced than the effect of bias. The results from this additional analysis support our main finding that glucose control measures are protocol dependent.

The partial difference between our observations and those by Boyd and Bruns [20] on the effect of imprecision can be explained by the different ways CGM levels informed glucose protocols. In the present study, a single CGM level pertinent to the protocol-directed control time was used. Boyd and Bruns used the linear regression analysis to interpolate CGM measurements between two control times, and in case of hourly sampling 12 CGM measurements (one every 5 minutes) were used to derive the glucose level informing the protocol and mitigating the effect of imprecision. Authors of this recent study [20] indicated that when CGM was used to raise alarms between algorithm-defined time points the commonly used glucose control metrics remained unchanged. The results of our study confirm this finding for some of the studied protocols but not for others adding an emphasis on protocol dependence.

Originally, the three protocols were designed for the use with intermittent glucose measurements. Apart from the benefit of any-time display of glucose concentration, additional information provided by continuous glucose measurement devices such as glucose trending, hypo/hyper and predictive alarms could lead to further refinements of existing protocols or may stimulate the development of novel protocols with enhanced performance but this is outside the scope of the present work.

Simulations have limitations but offer the only practical approach given the prohibitive cost and ethical dilemmas associated with conducting similar evaluations as large scale clinical trials. It is important that virtual populations represented by a simulation model of glucose regulation are validated and predictions confirmed. In our previous work we carefully considered these aspects and apart from developing our virtual population from clinical data and applying it on a one-to-one basis (one virtual subject per one critically ill patient) we validated predictions by replicating glucose control measures of comparative clinical studies [21]. Others used simulations to evaluate the effect of measurement error on glucose control in the ICU [13,30-31] using intermittent BG measurements. Our study expands these findings by contrasting intermittent and continuous glucose measurements and simulating an intended use of CGM with currently available ICU protocols, i.e. advising on insulin delivery at protocol time points and, additionally, at times of CGM-triggered alarms. Validation of our observations in an appropriately designed clinical study is desirable but is logistically and ethically challenging.

Accuracy of glucose meters in the ICU has been studied extensively [10-13] although accuracy guidelines and standards are being debated. Existing standards such as ISO 15197:2003/2013 may not be fully applicable to the ICU environment as their purpose is to regulate glucose meters for self-monitoring at home setting. Recent recommendations for the ICU were set out in a consensus document [3] suggesting that 98% of intermittent BG readings should fall within 12.5% of a reference standard (or within 10 mg/dL or 0.55mmol/L for glucose < 100 mg/dL or < 5.5mmol/l) and the remaining 2% of readings should be within 20% of reference standard [3]. It was also suggested that for CGM MARD values should not exceed 14% and that MARD values above 18% demonstrate poor

accuracy. Our study is in a broad agreement with these CGM guidelines but we would suggest that MARD of a single CGM sensor and not across a large number of sensors should be below 10% as averaging results may mask individual sensors with poor accuracy.

In conclusion, the efficacy of CGM-informed and BG-informed common glucose protocols is similar with MARD up to 15% but the risk of hypoglycemia may be reduced using CGM with MARD at or below 10%. Protocol choice has greater influence on glucose control measures than the glucose measurement method. Continuous glucose monitoring may stimulate the development of novel more efficacious and safer glucose control protocols than those currently available.

Authors' contributions

RH and MEW conceptualized the study. RH is the guarantor and had full access to all the data in the study. RH and MEW co-designed the study. MEW carried out the simulation work, performed the data and statistical analyses. MEW drafted the manuscript. Both authors critically revised the manuscript, and have seen and approved the final version of the report.

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Table 1[a]: Glucose control measures based on simulated blood glucose (without error component) and stratified according to the glucose measurement method (continuous glucose monitoring vs. intermittent BG) and ICU glucose protocol (Yale, Washington and NICE-SUGAR).

		Continuous glucose measurement			BG intermittent		
					ABG[c]	POC[c] arterial	POC[c] capillary
		0–5% MARD[b]	5–10% MARD[b]	10–15% MARD[b]	2.6%[d] MARD[b]	4.8%[d] MARD[b]	6.2%[d] MARD[b]
Yale	Mean glucose (mg/dL)	137 (126,151)	137 (126,151)	137 (123,157)	135 (126,150)	137 (128,151)	139 (128,155)
	SD glucose (mg/dL)	29 (22,41)	31 (22,45)	31 (22,45)	29 (22,45)	31 (22,45)	31 (22,490)
	Time in target[e] (%)	50 (33,66)	47 (31,61)	41 (28,57)	51 (33,68)	48 (31,68)	47 (30,66)
Washington	Mean glucose (mg/dL)	139 (132,150)	141 (130,153)	142 (123,157)	119 (108,133)	119 (108,133)	119 (108, 135)
	SD glucose (mg/dL)	20 (16, 29)	22 (16, 29)	22 (18,31)	18 (14,25)	20 (16,25)	20 (16,27)
	Time in target[f] (%)	94 (88,98)	92 (85,98)	91 (81,98)	95 (88,99)	94 (87,99)	94 (87,98)
NICE-SUGAR	Mean glucose (mg/dL)	171 (162,178)	173 162,182)	166 (153,193)	171 (164,178)	171 (164,178)	173 (164,180)
	SD glucose (mg/dL)	25 (18,36)	25 (18,36)	25 (18,36)	25 (18,38)	27 (20,38)	27 (22,38)
	Time in target[f] (%)	68 (56,81)	62 (49,79)	66 (37,87)	66 (54,79)	65 (54,78)	63 (53,76)

[a] SI unit version of this table can be found in Supplemental Data (Supplemental Table 2)

[b] Mean absolute relative deviation

[c] Measurement error obtained from meta-analysis evaluating blood gas analyzer (ABG) and point-of-care (POC) glucose meters [10];

[d] Calculated from the data; [e] Target range 100 to 140mg/dL; [f] Target range 80 to 180mg/dL

Table 2: Frequency and duration of hypoglycaemia <70mg/dL (< 3.9mmol/L) and <40mg/dL (< 2.2mmol/L) stratified according to the glucose measurement method (continuous glucose monitoring vs. intermittent BG) and ICU glucose protocol (Yale, Washington and NICE-SUGAR).

			Continuous glucose measurement			BG intermittent		
						ABG[b]	POC[b] arterial	POC[b] capillary
			0–5% MARD[a]	5–10% MARD[a]	10–15% MARD[a]	2.6%[c] MARD[a]	4.8%[c] MARD[a]	6.2%[c] MARD[a]
Yale	<70 mg/dL	Frequency (%subjects)	12	22	31	21	25	29
		Duration (min)	21(14,38)	31(17,64)	43 (23,82)	28 (18,32)	31 (19,46)	34 (21,52)
	<40 mg/dL	Frequency (%subjects)	0	0	0.7	1.4	1.8	2.4
		Duration (min)	-	-	14 (13,17)	16 (13,47)	17 (11,51)	22 (15,36)
Washington	<70 mg/dL	Frequency (%subjects)	11	12	15	36	39	41
		Duration (min)	38 (30,49)	39 (31,53)	38 (29,62)	52 (35,57)	54 (39,69)	51 (30,70)
	<40 mg/dL	Frequency (%subjects)	2.5	3.0	3.2	3.2	5.0	5.0
		Duration (min)	20 (15,24)	22 (17,25)	19 (14,26)	14 (12,22)	15 (13,23)	17 (12,28)
NICE-SUGAR	<70 mg/dL	Frequency (%subjects)	6	7	7	8	8	7
		Duration (min)	30 (19,55)	30 (21,75)	32 (21,75)	36 (26,69)	44 (23,74)	31 (23,69)
	<40 mg/dL	Frequency (%subjects)	0.4	1.3	1.3	1.4	0.8	0.8
		Duration (min)	13 (12,14)	12 (11,16)	17 (16,21)	31 (24,32)	29 (25,41)	25 (17,33)

[a] Mean absolute relative deviation [b] Measurement error obtained from meta-analysis evaluating blood gas analyzer (ABG) and point-of-care (POC) glucose meters [10] [c] Calculated from the data

Table 3[a]: Glucose control measures based on simulated blood glucose (without error component) stratified according to CGM imprecision expressed as CV and ICU protocols (Yale, Washington and NICE-SUGAR) in the absence of bias.

		Imprecision (%)			
		Baseline	5%	10%	15%
Yale	Mean glucose (mg/dL)	132 (124,146)	133 (124,148)	137 (130, 153)	150 (137,166)
	SD glucose (mg/dL)	25 (20,38)	27 (20,38)	29 (22,43)	34 (25,45)
	Time in target [b] (%)	56 (37,68)	55 (36,69)	48 (30,63)	37 (23,50)
Washington	Mean glucose (mg/dL)	137 (130,150)	137 (130,148)	135 (128,144)	135 (128,144)
	SD glucose (mg/dL)	20 (9,34)	22 (18,27)	23 (18, 3129)	25(20,34)
	Time in target [c] (%)	94 (89,98)	94 (89,98)	93 (87,98)	91 (84,97)
NICE-SUGAR	Mean glucose (mg/dL)	169 (162,177)	169 (162,177)	171 (162,178)	171 (162,182)
	SD glucose (mg/dL)	25 (18,36)	25 (20,36)	29 (22,40)	32 (23,43)
	Time in target [c] (%)	70 (57,80)	68 (57,79)	63 (53,75)	60 (50,73)

[a] SI unit version of this table can be found in Supplemental Data (Supplemental Table 3)~~;~~

[b] Target range 100 to 140mg/dL

[c] Target range 80 to 180mg/dL

Table 4: Frequency and duration of hypoglycemia < 70 mg/dL (<3.9mmol/l) and < 40 mg/dL (<2.2mmol/L) stratified according to CGM imprecision expressed as CV and ICU glucose protocol (Yale, Washington and NICE-SUGAR) in the absence of bias.

			Imprecision (%)			
			baseline	5%	10%	15%
Yale	<70 mg/dL	Frequency (%subjects)	8.3	10.1	15.9	12.8
		Duration (min)	18(14,24)	21(13,31)	22 (13,33)	25 (16,36)
	<40 mg/dL	Frequency (%subjects)	0	0	0	0.2
		Duration (min)	-	-	-	22[a]
Washington	<70 mg/dL	Frequency (%subjects)	7.8	9.1	17.5	26.6
		Duration (min)	38 (33,51)	37 (30,46)	39 (30,58)	40(31,53)
	<40 mg/dL	Frequency (%subjects)	1.9	1.5	2.6	4.8
		Duration (min)	20 (18,22)	18 (13,21)	24 (19,27)	22(19,27)
NICE-SUGAR	<70 mg/dL	Frequency (%subjects)	6.6	6.1	6.9	10.1
		Duration (min)	32 (19,58)	30 (20,48)	36 (21,53)	34 (20,57)
	<40 mg/dL	Frequency (%subjects)	0.9	0.3	0.6	1.4
		Duration (min)	14 (12,16)	20[a]	19 (15,23)	11 (10,16)

[a] Single hypoglycemia episode

Table 5[a]: Glucose control measures based on simulated blood glucose (without error component) stratified according to CGM bias expressed as CV and ICU glucose protocols (Yale, Washington and NICE-SUGAR) in the absence of imprecision.

		Bias (%)						
		Baseline	-15%	-10%	-5%	5%	10%	15%
Yale	Mean glucose (mg/dL)	132 (124,146)	151 (144,164)	144 (137,1598.8)	137 (130,155)	128 (119, 139)	123 (115,137)	119 (110, 132)
	SD glucose (mg/dL))	25 (20,38)	25 (20,38)	25 (20,40)	27 (20,38)	27 (22,40)	27 (22,40)	27 (22,40)
	Time in target[b] (%)	56 (37,68)	36 (24,48)	44 (29,56)	51 (35,65)	56 (39,70)	54 (37,66)	49 (36,60)
Washington	Mean glucose (mg/dL)	137 (130,150)	159 (150,173)	151 (142,164)	144 (137,157)	132 (124,142)	126 (119,137)	121 (115,132)
	SD glucose (mg/dL)	20 (9,34)	23 (16,31)	22 (16, 29)	22 (16,27)	20 (16,25)	20 (18,25)	20 (18,25)
	Time in target[c] (%)	94 (89,98)	81 (61,91)	87 (77,93)	91 (85,96)	97 (91,100)	97 (92,100)	97 (92,100)
NICE-SUGAR	Mean glucose (mg/dL)	169 (162,177)	195 (184,204123)	184 (177,193)	177 (169,184)	162 (155,169)	155 (150, 162)	148 (144,155)
	SD glucose (mg/dL)	25 (18,36)	25 (18,34)	25 (18,34)	25 (18,36)	25 (18,34)	25 (18,34)	23 (18,34)
	Time in target[c] (%)	70 (57,80)	34 (19,48)	46 (36,60)	58 (47,71)	79 (67,88)	85 (75,92)	89 (80,95)

[a] SI unit version of this table can be found in Supplemental Data (Supplemental Table 4)~~;~~

[b] Target range 100 to 140mg/dL

[c] Target range 80 to 180mg/dL

Table 6: Frequency and duration of hypoglycemia < 70 mg/dL (<3.9mmol/L) and < 40 mg/dL (<2.2mmol/L) stratified according to CGM bias expressed as CV and ICU glucose protocol (Yale, Washington and NICE-SUGAR) in the absence of imprecision.

			Bias (%)						
			baseline	-15%	-10%	-5%	5%	10%	15%
Yale	<70 mg/dL	Frequency (%subjects)	8.3	0.9	0.4	2.9	17.0	34.8	42.2
		Duration (min)	18 (14,24)	16 (14,21)	29 (28,29)	14 (10,29)	20 (13,33)	26 (16,46)	33 (20,61)
	<40 mg/dL	Frequency (%subjects)	0	0	0	0	0	0	0
		Duration (min)	-	-	-	-	-	-	-
Washington	<70 mg/dL	Frequency (%subjects)	7.8	3.9	6.0	6.3	10.2	12.5	15.6
		Duration (min)	38 (33,51)	23 (18,30)	32 (23,37)	33 (25,38)	41 (32,54)	46 (36,56)	53 (42,84)
	<40 mg/dL	Frequency (%subjects)	1.9	0.6	1.5	1.9	1.5	1.9	2.4
		Duration (min)	20 (18,22)	17 (13,18)	14 (13,17)	15 (14,19)	18 (17,23)	22 (17,24)	23 (18,26)
NICE-SUGAR	<70 mg/dL	Frequency (%subjects)	6.6	3.5	4.3	5.5	6.9	11.0	12.7
		Duration (min)	32 (19,58)	23 (16,30)	26 (20,34)	25 (18,35)	32 (19,47)	28 (17,57)	34 (19,64)
	<40 mg/dL	Frequency (%subjects)	0.9	0	1.2	0.3	0.9	1.7	1.7
		Duration (min)	14 (12,16)	-	11 (10,13)	17[a]	18(15,18)	17(14,20)	19(17,20)

[a] Single hypoglycemia episode