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Original Article

Subcutaneous continuous glucose monitoring in critically ill patients during insulin therapy: a meta-analysis

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Abstract: Background: Using continuous glucose monitoring (CGM) in critically ill adult patients requiring insulin therapy has increased with inconsistent results. Thus, we conducted a meta-analysis to assess the effect of CGM and frequent point-of-care (POC) measurements in such a patient population. Methods: We searched PubMed, Embase, Cochrane Library, China national knowledge infrastructure, and Wanfang for relevant articles from inception to Jan 15, 2022. Randomized controlled trials (RCTs) were considered if they focused on critically ill patients who required insulin and were treated with CGM or any POC measurements. We used the Cochrane risk evaluating tool to assess study quality. Subgroup analysis and publication bias were also conducted. Results: We finally included 19 RCTs with 1,852 participants. The quality of the included studies were at a low to moderate levels. Overall, CGM devices significantly reduced hypoglycemia incidence (Risk ratio (RR) 0.35; 95% CI, 0.25-0.49; P<0.00001) than the POC measurement. Further subgroup and sensitivity analyses confirmed this result. The CGM group also had lower overall mortality (RR 0.54; 95% CI, 0.34-0.86; P=0.01), lower glucose variability, and nosocomial infection. The time in, below, or above target blood glucose range, insulin use, and length of stay in the ICU were comparable between the two groups. In addition, few studies provided data in favor of decreased nursing workload and medical costs in the CGM group. Conclusions: The CGM technique could significantly reduce hypoglycemia incidence, overall mortality, and glucose variability compared to POC measurement in critically ill patients. However, further large, well-designed RCTs are required to confirm our results.

Keywords: Subcutaneous continuous glucose monitoring, intensive care, hypoglycemia, meta-analysis, mortality

Introduction

Dysglycemia, including hypoglycemia, hyperglycemia, and high hyperglycemic variability, is a typical concition in intensive care unit (ICU) settings, whether patients have prior diabetes or not [1, 2]. It is associated with an increased poor prognosis in these patients [1]. Based on the available evidence, maintaining blood glucose (BG) levels around 8.0 mmoL/L seems preferable for most critically ill patients [3]. However, there is an inherent risk of insulin-induced hypoglycemia in BG regulation, which is related to higher mortality [4]. Therefore, precise BG control is essential.

In most ICU settings, several frequent point-of-care (POC) measurements, including fingertip, venous blood, and blood gas analysis, are commonly used to guide insulin therapy. However, intermittent measurement can detect only one instant BG and does not reflect long-term day-to-week glucose levels [5]. Thus, frequent blood collection is essential, leading to inevitable labor-intensive, time-consuming, and cost-increasing [5, 6]. Furthermore, intermittent BG measurement may still overlook the hypoglycemia episodes between two measures [7]. Therefore, continuous glucose monitoring (CGM), which can continuously and automatically provide instant BG values, has become more attractive [8].

Subcutaneous CGM is the most established clinical use among the CGM technologies [5]. CGM can measure glucose in interstitial fluid

through minimally invasive subcutaneous sensors [9]. Conceptually, CGM can automatically provide BG values every few minutes, thus making it more readily to identify trends in glucose concentrations. On the other hand, CGM help to reduce the incidence of severe hyperglycemia and hypoglycemia by more rapidly and appropriately adjusting insulin infusions [10]. CGM-derived glucose values have shown higher accuracy than BG measurements in diabetic patients [11]. Recently, CGM has been gradually applied to critically ill patients. Numerous studies have demonstrated that the subcutaneous CGM devices have relatively good accuracy in measuring interstitial glucose levels and are not affected by electrolyte and acid-base imbalance, the severity of illness, and BMI in critically ill patients [12]. In addition, CGM is less invasive with a lower risk of infection, reduced blood loss, and is popular among ICU members for its ease to use [9, 13]. However, whether these advantages of CGM translate into improved patient prognosis remains unclear. Several randomized controlled trials (RCTs) compared CGM with POC measurement to guide insulin use in ICU patients with inconsistent results [6, 12, 14]. This might be related to the different studies' BG control strategies and the small sample sizes of the RCTs.

Several RCTs on this topic have recently been published [15-18], with some of these studies having a small sample size and inconsistent conclusions. As a result, we aimed to conduct a systematic review and meta-analysis of available RCTs to address the above limitations using the increased power of meta-analytic techniques. We hypothesized that CGM devices might benefit more for glucose control and the prognosis than any POC measurements in critically ill patients requiring insulin therapy.

Methods

This study protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols database (INPLASY2021120102), and is available at inplasy.com (https://inplasy.com/inplasy-2021-12-0102). We present our results following the Preferred Reporting Items of Systematic reviews and Meta-Analyses guidance [19] (**Appendix File 1**). This work did not require ethical approval.

Search strategy and selection criteria

Two investigators (YY and Y-HZ) ran a systematic search without language restrictions in the PubMed, Embase, Cochrane Library, Wanfang, and China national knowledge infrastructure, from inception through Jan 15, 2022, the date of our most recent search. We searched for potentially relevant RCTs using CGM in critically ill patients using Medical Subject Headings and keywords. Our full-search strategy is attached in **Appendix File 2**. There were no restrictions based on language. We screened titles and abstracts for eligibility and assessed full texts of the potentially eligible articles for final eligibility. We also reviewed the reference lists of related papers to find relevant studies. Disagreements were solved through discussion by the two review authors.

RCTs were eligible if they compared insulin treatment guided by subcutaneous CGM devices to any frequent point-of-care (POC) measurements in critically ill adult (≥18 years old) patients. We excluded trials enrolling children, breastfeeding women, or pregnant. Studies that reported microdialysis for detecting glucose concentration in the interstitial fluid were excluded since they were techniques that preceded the CGM devices of today. We also removed papers that were only available in abstract form, meeting reports, or included less than ten patients. Disagreements were reviewed by a third author (H-BH), who had a deciding vote.

Data extraction and quality assessment

The aforementioned independent investigators (YY and Y-HZ) undertaken data extraction from included trials on study design, first author, published year, patient characteristics, study interventions, and clinical outcomes of interest.

We used the Cochrane risk-of-bias method to examine RCTs for evidence of bias [20]. We assigned high, unclear, or low values to the following items: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. We determined that if there was a high risk of bias in any area, the overall risk of bias in the study was high. As caregivers blinding was difficult in these studies, we evalu-

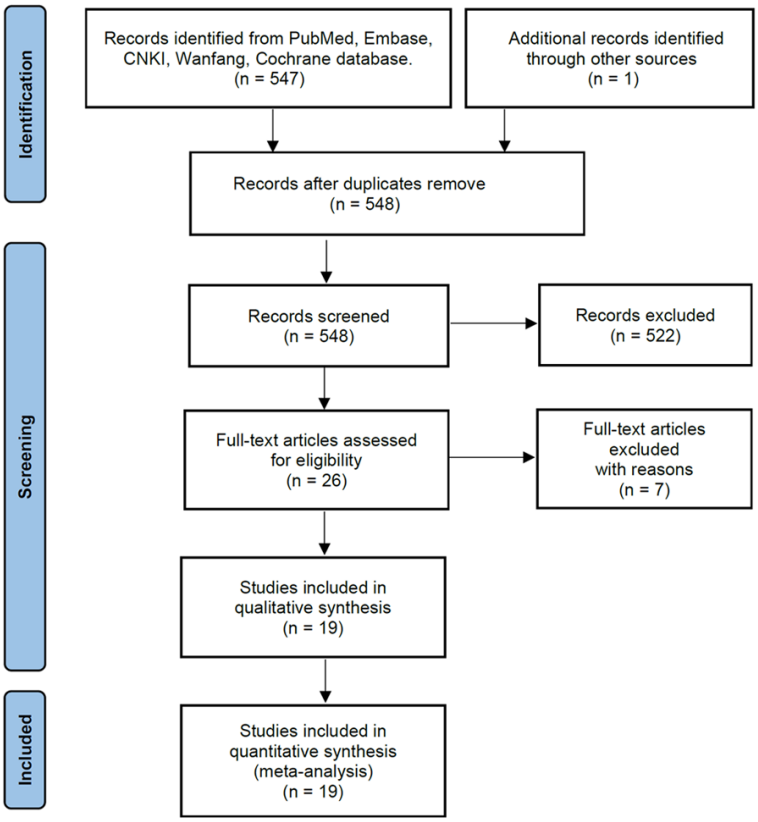

Figure 1. Selection process for studies included in the meta-analysis.

ated blinding solely at the outcome assessment. Disagreements were recognized and resolved through discussion between the two authors.

Data analysis

The primary outcome was the incidence of hypoglycemia (defined by the author of included RCTs, respectively). Secondary outcomes included time in, below, or above the target BG range (%), glucose variability parameters (i.e., coefficient of variation [CV], or mean amplitude of glucose excursions [MAGE], as defined by authors), length of stay (LOS) in ICU or hospital, mortality (28 days or ICU or hospital), nosocomial infection, nursing workload and medical cost.

Testing the potential influencing factors of our primary outcome, we conducted sensitivity analyses by pooled studies with the following: (1) type of CGM devices; (2) study design (blinding or non-blinding); (3) POC measurement; (4) low limitation of target BG range >6.1 mmol/L or <6.1 mmol/L; and (5) hypoglycemia definition (<2.2 mmol/L, <3.5 mmol/L, or <4 mmol/L), (6) geographic location (China or the other countries) and glucose management protocol (with or without intensive glucose control management), if available.

For dichotomous outcomes, we combined the results to calculate the pooled risk ratio (RR) and associated 95% confidence intervals (CI). Mean differences (MD) and 95% CI were calculated for continuous outcomes. Some studies reported treatment effects measured in the median with interquartile range (IQR). Thus, we calculated the mean from the median and the standard deviations (SD) from IQR [21]. To evaluate heterogeneity, we employed the I^2 statistics. In situations with inconsiderable heterogeneity (I^2<50%), a fixed-effect model was employed, whereas a random-effect model was used in cases of significant heterogeneity (I^2>50%) [22]. Whenever there was heterogeneity, sensitivity analyses were conducted, eliminating one trial in each turn to examine the impact of a single study on the total pooled estimate. Furthermore, where data from at least two RCTs were available, we conducted statistical analyses. Visual inspection of funnel plots was used to determine Publication bias. We performed all used Review Manager (Version 5.3) to conduct all of our analyses.

Results

Trial identification and characteristics

Our electronic search revealed 1689 citations after database searching, 1345 were selected for full-text review, and 19 RCTs were eligible for final analysis (**Figure 1**) [6, 12, 14-18, 23-34]. The excluded studies based on the full-text review with exclusion reasons were summarized in **Appendix File 2**.

Table 1 describes the key characteristics of the included RCTs, whereas **Appendix File 3**

Table 1. Characteristics of the included studies

Study	Country	Design	Type of patients	APACHEII	% Diabetes	Sample size (CGM/C)	CGM system	Control BG measurement	Study duration (Hour)	Mean age (CGM/C), Year	Male (CGM/C) %
Holzinger 2010 [12]	Austria	RCT; SC; SB	MICU	NA	NA	63/61	Medtronic MiniMed	Selective arterial BG	72	58/62	68/57
Huang 2011 [27]	China	RCT; SC; NB	Mixed ICU	NA	100	40/80	Medtronic MiniMed	Fingertip BG	168	31-72	57
Leelarathna 2013 [23]	United Kingdom	RCT; SC; NB	NICU	12.9 SC 11.2 SC	100	12/12	FreeStyle Navigator	Arterial BG	48	63/58	75/75
Kopecky 2013 [24]	Prague	RCT; SC; NB	Cardiac ICU	NA	33	12/12	Medtronic MiniMed	Arterial BG	24	68/68	50/67
Boom 2014 [6]	Netherlands	RCT; SC; SB	Mixed ICU	NA	100	78/78	FreeStyle Navigator I, Abbott	Indwelling arterial catheter BG	24	66/67	48/61
De Block 2015 [26]	Belgium	RCT; MC; SB	Mixed ICU	29xed 28xe	22.8	16/19	GlucoDay, A. Menarini Diagnostics	Arterial BG	96	64/68	50/48
Qi 2016 [28]	China	RCT; SC; NB	Mixed ICU	NA	81.2	48	NA	Fingertip BG	NA	47-85	54
Sun 2017 [25]	China	RCT; SC; NB	Mixed ICU	NA	100	135	NA	Fingertip BG	168	59/59	51
Preiser 2018 [14]	Belgium	RCT; SC; SB	Mixed ICU	≥10	100	39/38	Gluco Clear	Peripheral venous catheter BG	72	62/60	80/66
Lu 2018 [15]	China	RCT; SC; SB	Mixed ICU	22xed 22xe	27	74/70	DGMS, San MediTech	Fingertip BG	120	50/49	50/48
Zhang 2020 [16]	China	RCT; SC; NB	Mixed ICU	20.1d ICU 28.9d IC	0	32/32	Medtronic MiniMed	Fingertip BG	NA	69/68	59/63
Guan 2017 [30]	China	RCT; SC; NB	Mixed ICU	15-25	0	60/70	CGM-2009	Fingertip BG	72	52	58
Li 2019 [17]	China	RCT; SC; NB	Mixed ICU	16.2±3.2/16.9±3.8	0	37/35	Medtronic MiniMed	Fingertip BG	168	59/62	NA
LV 2012 [31]	China	RCT; SC; SB	NICU	≥15	0	59/58	DGMS, San MediTech	Fingertip BG	72	61	52
Tian 2019 [32]	China	RCT; SC; SB	Mixed ICU	NA	19.2	81/80	RGMS-III	Fingertip BG	72	61/65	69/65
Wang 2015 [33]	China	RCT; SC; NB	Mixed ICU	NA	100	32/64	Medtronic MiniMed	Fingertip BG	72	58	44
Yuan 2008 [34]	China	RCT; SC; NB	NICU	16.6±6.8/15.3±6.9	16.1	36/32	Medtronic MiniMed	Fingertip BG	168	65/66	72/69
Fan 2013 [29]	China	RCT; SC; NB	Mixed ICU	>15	0	69/79	CGMS-2009	Fingertip BG	72	58/60	56/53
Zhang 2018 [18]	China	RCT; SC; NB	Mixed ICU	NA	NA	58/58	TouchRulteaTM	Fingertip BG	NA	45/44	60/62

APACHEII = Acute Physiology, Age and Chronic Health Evaluation II; BG = blood glucose; C = control group; CGM = continuous glucose monitoring; M = male; MC = multiple-center; MICU = medical ICU; NA = not available; NB = not blind; NICU = Neurosciences ICU; RCT = randomized controlled trial; SB = single blind; SC = single-center.

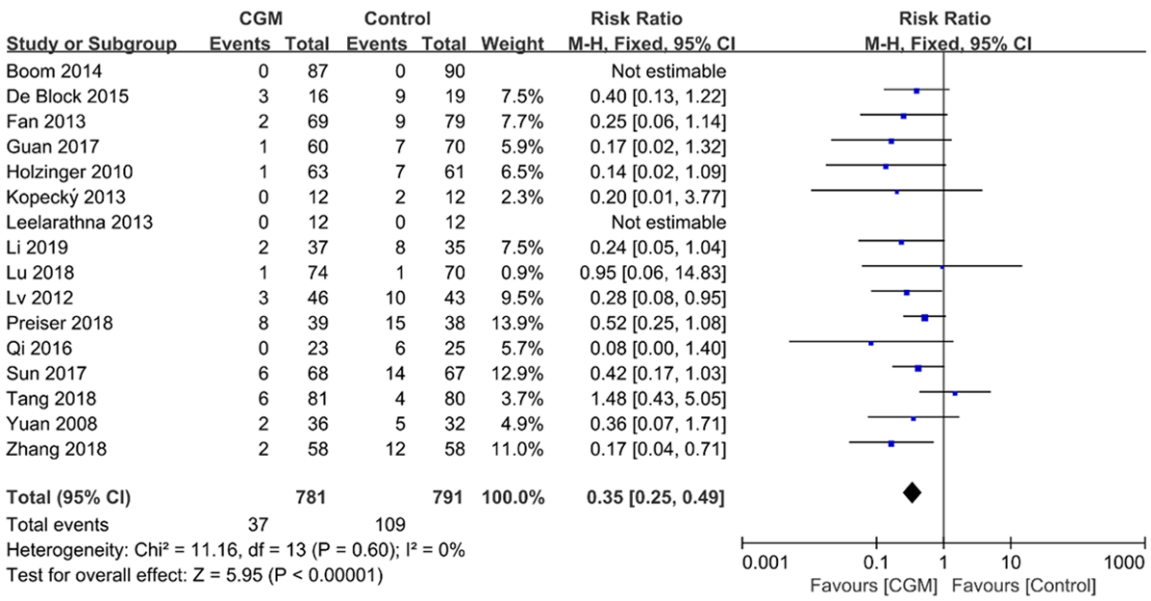

Figure 2. Forest plot showing the incidence of hypoglycemia.

describes the BG parameters and outcome data. The final analysis comprised 1852 participants (sample sizes ranging from 24 to 177 individuals), including 885 in the CGM group and 967 in the POC group. These studies were published from 2008 onwards. Most studies enrolled mixed-ICU patients, except five from neurosciences [23, 31, 34], medical [12], or cardiosurgical ICU patients [24]. Studies varied concerning the target BG range and severe hypoglycemia criteria. As to the POC measurements used, fingertip BG, arterial BG, and peripheral venous BG were used in 17, 5, and 1 studies. CGM system application varied among the included trials, with the Medtronic MiniMed of the most used. The risk of bias was low across the included RCTs (**Appendix File 4**). A visual examination of a funnel plot revealed no evidence of publication bias (**Appendix File 5**: Figure S5).

Primary outcome

Data on the incidence of hypoglycemia were available in the 19 RCTs. In the pooled analysis, the use of CGM devices significantly reduced hypoglycemia incidence (19 trials, 1,572 patients; RR 0.35, 95% CI 0.25 to 0.49, P<0.00001; I^2=0%) (**Figure 2**). Despite the absence of considerable heterogeneity, we conducted stratified analyses based on predefined major research features and clinical variables. In general, all the subgroup studies indicated that the occurrences of hypoglycemia among groups were similar. Sensitivity analyses were then performed, revealing that the results were constant when the analyses were limited to studies that defined hypoglycemia as <2.2 mmol/L or <3.3 mmol/L, or <4 mmol/L. **Table 2** shows the findings of subgroup and sensitivity analyses in detail.

Secondary outcomes

The CGM group had a lower overall mortality rate (12 trials, n=1,294; RR 0.54; 95% CI, 0.34 to 0.86; I^2=56%; P=0.01) (**Figure 3**). The time in target BG range (7 trials, n=584, MD 7.58%; 95% CI, -0.18 to 15.34, I^2=85%; P=0.06), time below target BG range (4 trials, n=422, MD 1.31%; 95% CI, -3.63 to 1.00, I^2=82%; P=0.27) and time above target BG range (3 trials, n=345, MD -7.86%; 95% CI, -20.54 to 4.83, I^2=88%; P=0.22) were also similar. In addition, there was no significantly difference in insulin use (6 trials, n=516, MD 0.01; 95% CI, -0.17 to 0.18, I^2=0%; P=0.93) and the length of stay in ICU between the two groups (9 trials, n=863; MD -2.28 days; 95% CI, -5.99 to 1.39; I^2=98%; P=0.22). As to glucose variability parameters, six trials provided outcome of MAGE and pooled data showed lower MAGE in CGM group (n=767; MD -1.41 mmoL/L; 95% CI, -2.24 to -0.58; I^2=95%; P=0.0009); while four used CV

Table 2. Subgroup analyses on primary outcome of Incidence of hypoglycemia

	Subgroup analyses	Study number	Patient number	Hypoglycemia event in CGM croup	Hypoglycemia event in control croup	Risk ratio (95% CI)	I^2, %	P
CGM devices	Medtronic	[12, 17, 24, 34]	244	5 of 148	22 of 140	0.23 [0.09, 0.57]	0	0.001
	Others*	[6, 14, 15, 18, 23, 26, 29-32]	1,101	26 of 542	67 of 559	0.40 [0.26, 0.61]	13	<0.0001
	Not reported	[25, 28]	183	6 of 91	20 of 92	0.32 [0.14, 0.74]	20	0.008
Study design	Blinded	[6], 12, 14, 15, 31, 32],	730	14 of 367	31 of 363	0.46 [0.25, 0.83]	31	0.01
	Unblinded	[17, 18, 23-25, 28-30, 34]	842	23 of 414	78 of 428	0.30 [0.20, 0.47]	0	<0.00001
Control BG measurement	Fingertip	[15, 17, 18, 25, 28-32, 34]	992	25 of 552	76 of 559	0.33 [0.22, 0.51]	2	<0.00001
	Arterial	[6, 12, 23, 24, 26]	384	4 of 190	18 of 194	0.27 [0.10, 0.68]	0	0.006
	Venous	[14]	77	8 of 39	15 of 38	0.52 [0.25, 1.08]	-	-
Low limitation of target BG range	≥6.1 mmol/L	[12, 15, 25, 28, 29, 31]	688	13 of 342	47 of 345	0.29 [0.16, 0.51]	0	<0.0001
	<6.1 mmol/L	[6, 14, 17, 23-26]	461	13 of 203	34 of 206	0.40 [0.23, 0.70]	0	0.001
	Not reported	[18, 30, 32, 34]	409	11 of 235	28 of 240	0.39 [0.20, 0.78]	34	0.006
Average APACHEII score	>20	[15, 26, 29, 31]	475	9 of 205	29 of 211	0.33 [0.16, 0.67]	4	0.002
	<20	[17, 23, 34]	164	4 of 85	13 of 79	0.28 [0.10, 0.83]	0	0.02
	Others	[6, 10, 12, 18, 24, 25, 28, 30, 32]	992	4 of 85	13 of 79	0.37 [0.24, 0.57]	28	<0.00001
Country	China	[15, 17, 18, 25, 28, 29, 31, 32, 34]	1,111	25 of 552	76 of 559	0.33 [0.22, 0.51]	2	<0.0001
	Others	[6, 12, 14, 23, 24, 26, 30]	461	12 of 229	33 of 232	0.38 [0.21, 0.68]	0	0.001
% Diabetes	>50%	[6, 14, 23, 25, 33]	461	14 of 229	35 of 232	0.40 [0.23, 0.70]	0	0.001
	<50%	[15, 17, 24, 26, 29, 30-32, 34]	871	20 of 431	55 of 440	0.38 [0.23, 0.41]	0	<0.0001
	Not reported	[12, 18]	240	3 of 121	19 of 119	0.16 [0.05, 0.51]	0	0.002

BG = blood glucose; CGM = continuous glucose monitoring. *FreeStyle Navigator, GlucoDay, Gluco Clear, DGMS, San MediTech, CGM-2009, RGMS-III, and TouchRulteaTM.

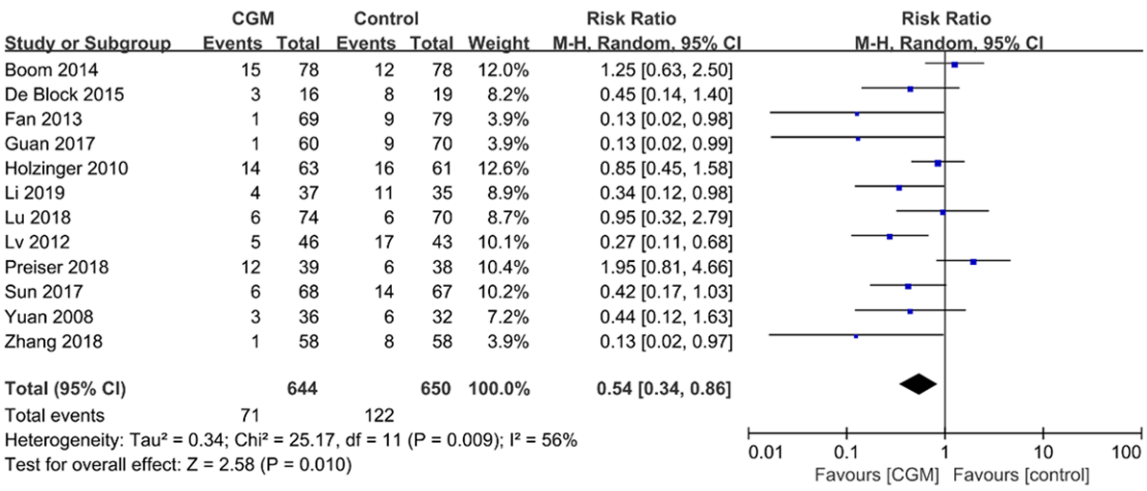

Figure 3. Forest plot showing the overall mortality rate.

as interest and the pooled data tended to be lower during CGM therapy (n=404; MD -1.41%; 95% CI, -3.50 to 0.46; I^2=88%; P=0.08). Four trials reported outcome of nosocomial infection [16, 18, 32, 34] and the pooled data showed that CGM group had a significantly lower infections (n=378; RR 0.21; 95% CI, 0.10 to 0.44; I^2=9%; P<0.0001). Only two RCTs described the costs between the two strategies, with one [6] showing the CGM group had lower mean daily costs per patient while the other [28] reported no difference between groups. (See **Appendix File 6**: Figures S6, S7, S8, S9, S10, S11, S12 and S13).

Discussion

In the current meta-analysis, we compared the use of CGM devices with any frequent POC measurements in critically ill adult patients requiring insulin treatment for ICU dysglycemia. We found that CGM technique could significantly reduce hypoglycemia incidence during insulin treatment. Further subgroup and sensitivity analyses confirmed this finding. CGM-guided insulin treatment was associated with lower overall mortality, nosocomial infection, and glucose variability than the POC measurement. In addition, time in, below, or above the targeted glucose range, insulin use, and ICU LOS were comparable between the two groups.

Our findings are consistent with those of a recent meta-analysis published in Chinese [35], which showed that the use of CGM decreased hypoglycemia incidence in critically ill patients. However, the pooled data from ICU and non-ICU research may have contributed to the high heterogeneity of included RCTs. Moreover, the authors included only seven trials of 531 patients and mainly focused on patients receiving intensive insulin therapy, a glucose control strategy that preceded the CGM devices of today and had already not been recommended to apply in critically ill patients. To overcome these limitations, we enlarged the prior meta-analysis to include 19 RCTs with more than 1,800 patients [6, 12, 14-18, 23-34]. Thus, with larger sample size, we had more power to evaluate the effect of CGM in the ICU setting and conducted the subgroup and sensitivity analyses based on various clinical characteristics to confirm our primary outcome. Moreover, we also assessed other important clinical outcomes (e.g., time in, below, above target glucose time, overall mortality, insulin use, and ICU LOS). These findings provided effect and safety evidence of the robustness of our primary outcome.

Our results suggest some important clinical implications of CGM. First, the CGM-guided glucose control strategy significantly reduced the occurrence of hypoglycemia by 67%, suggesting that CGM could help ICU members detect hyperglycemia and hypoglycemia, thus reducing potential complications in critically ill patients. Second, CGM devices help reduce the need for regular blood glucose monitoring. This is a time-consuming and labor-intensive procedure in the ICU setting, especially for high glucose fluctuation, such as steroid-induced

hyperglycemia, diabetic ketoacidosis, or hyperglycemic hyperosmolar syndrome. Most CGM devices only require calibration 2-3 times per day and reduce the workload of medical staff in the ICU. In the study by Boom and colleagues [6], the authors found the CGM significantly reduced the daily nursing workload for glucose control (17 versus 36 minutes; P<0.001) compared to the intermittent POC glucose measurements. In two COVID-19 studies, CGM devices were associated with a reduction in POC testing by 60% [36] and 63% [37] in critically ill patients who required continuous insulin infusions. In addition, using CGM can shorten the time the caregivers contact the critically ill patients, thereby reducing the risk of transmission of infectious microorganisms to ICU medical staff, especially from the COVID-19 patients [36, 37].

Our results showed that the CGM-guided strategy significantly reduced mortality in critically ill patients. It is consistent with other improved outcomes in the present meta-analysis, such as decreasing the incidence of hypoglycemia and improved glycemic variability. Several studies have demonstrated that more significant glycemic variability in ICU patients was related to higher in-hospital mortality, independent of mean BG levels and hypoglycemia [38, 39]. However, we should interpret the mortality outcome with caution since this result has significant heterogeneity. As a secondary outcome, we did not further explore the potential factors for the heterogeneity. However, explaining the heterogeneity is very difficult because the heterogeneity might be due to the different etiologic distributions of the ICU population, disease severity, glycemic control strategies, and organ function supports among the included studies. In addition, most included RCTs with a small sample size are more likely to conclude an overestimation of the treatment effect. Therefore, further clarification of the results by high-quality RCT studies is required.

We found that CGM did not show an advantage in time in the target glucose range, which might be related to the development of glucose management and experienced nursing teams in the ICU. The control group maintained glycemic control well among the included studies, possibly offering little space for improvement by CGM [12]. In addition, patients with varied difficulty in glycemic control, e.g., in the study by Lu et al. [15], about 50% of recruited patients were SAP, which made controlling blood glucose levels and getting them into the target range more challenging than in other studies.

Although our results are encouraging. However, CGM still needs some improvement. First, in the future, more designs and applications of closed-loop systems integrating CGM and automatic insulin infusion systems will be required and ultimately achieve the goal of fully closed-loop blood glucose management. Second, the life span of the biosensor is relatively short, about seven days. Third, the Mean Absolute Relative Difference (MARD), an indicator to quantify the deviation from the reference measurement, was 12.5% in the present meta-analysis, which complied with the clinical application criteria of CGM [40]. However, we should pay more attention to the accuracy of CGM in some situations in the ICU setting. For example, CGM has a lag time due to glucose transport from the blood to the subcutaneous interstitium, which takes approximately 15-20 minutes [9]. Thus, if the patient's blood glucose level fluctuates widely, the lag time should be considered. There is currently a lack of adequate data to correlate glucose levels in the blood with interstitial fluids in some individuals with severe generalized edema, such as hypoalbuminemia and hepatic failure. In addition, critically ill patients often require high doses of pressors, leading to peripheral vasoconstriction. In such patients, blood circulation to the skin where the CGM is placed may decrease, thus affecting CGM readings' accuracy. Although a small prospective study focusing on intraoperative CABG showed good accuracy in patients receiving CGM and large amounts of vasoactive drugs (MARD of 12.9 and Clarke error grid analysis showed 98.6% of glucose values falling into zones A and B) [41]. More data from the ICU population are still needed to confirm this.

There are some limitations to our meta-analysis. (1) Few studies provide data related to the accuracy of CGM, such as MARD, Clarke Error Grid (CEG), and ISO criteria. (2) Several secondary outcomes, including the costs, workload, and infections during the glucose management guided by CGM, were reported in only a few studies. (3) Significant heterogeneity was

found among the included studies. However, we did not explore the heterogeneity due to fewer related studies. (4) Most included studies were single-center designs, and there may be differences in the underlying treatment among the centers. Also, most included studies were small samples, which could amplify its effect. (5) CGM requires calibration with fingerstick glucose, usually 2-3 times per day. However, only about half of the studies provide data on CGM calibration. Enhanced calibration leads to a decreased MARD, more points in CEG zone A, and better conformity with ISO criteria [42].

Conclusion

More and more physicians focus on CGM during glucose management in the ICU. Generally, our meta-analysis of aggregate data shows that using the CGM technique significantly reduces hypoglycemia incidence, overall mortality, nosocomial infection, and glucose variability compared to POC measurement in critically ill patients. However, further large, well-designed RCTs will be needed to confirm our results.

Disclosure of conflict of interest

None.

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Appendix File 1. PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 and **Appendix File 2**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 **Figure 1**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 **Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Appendix File 4**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health-care providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

Appendix File 2-1. Search strategy: (database: PubMed Embase Cochrane library; search completed 15th Jan 2022).

PubMed

1. (("Critical Care"[Mesh]) OR ((((critical care[Title/Abstract]) OR (critically ill[Title/Abstract])) OR (intensive care[Title/Abstract])) OR ((((((((((((((Critical Illness[Title/Abstract]) OR (Critical Care[Title/Abstract])) OR (intensive care units[Title/Abstract])) OR (Burn units[Title/Abstract])) OR (coronary care units[Title/Abstract])) OR (respiration, artificial[Title/Abstract]))) OR (ventilators, mechanical[Title/Abstract])) OR (pulmonary ventilation[Title/Abstract])) OR (respiratory insufficiency[Title/Abstract])) OR (multiple organ failure[Title/Abstract])) OR (systemic inflammatory response syndrome[Title/Abstract])) OR (respiratory distress syndrome, adult[Title/Abstract])) OR (sepsis[Title/Abstract])) OR (shock, septic[Title/Abstract]))))

2. ("glucose monitoring"[Title/Abstract] OR "tissue glucose"[Title/Abstract] OR "glucose management"[Title/Abstract] OR "glucose monitor"[Title/Abstract] OR "bg monitoring"[Title/Abstract] OR "bg management"[Title/Abstract] OR "subcutaneous glucose"[Title/Abstract] OR "glucose analysis"[Title/Abstract] OR "interstitial glucose"[Title/Abstract] OR "subcutaneous glucose sensor"[Title/Abstract]) AND "continuous"[Title/Abstract]

3. ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

4. ("glucose monitoring"[Title/Abstract] OR "tissue glucose"[Title/Abstract] OR "glucose management"[Title/Abstract] OR "glucose monitor"[Title/Abstract] OR "bg monitoring"[Title/Abstract] OR "bg management"[Title/Abstract] OR "subcutaneous glucose"[Title/Abstract] OR "glucose analysis"[Title/Abstract] OR "interstitial glucose"[Title/Abstract] OR "subcutaneous glucose sensor"[Title/Abstract]) AND "continuous"[Title/Abstract] AND ("Critical Care"[MeSH Terms] OR ("Critical Care"[Title/Abstract] OR "critically ill"[Title/Abstract] OR "intensive care"[Title/Abstract] OR ("critical illness"[Title/Abstract] OR "Critical Care"[Title/Abstract] OR "intensive care units"[Title/Abstract] OR "burn units"[Title/Abstract] OR "coronary care units"[Title/Abstract] OR "respiration artificial"[Title/Abstract] OR "ventilators mechanical"[Title/Abstract] OR "pulmonary ventilation"[Title/Abstract] OR "respiratory insufficiency"[Title/Abstract] OR "multiple organ failure"[Title/Abstract] OR "systemic inflammatory response syndrome"[Title/Abstract] OR "respiratory distress syndrome adult"[Title/Abstract] OR "sepsis"[Title/Abstract] OR "shock septic"[Title/Abstract]))) AND (("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))

Embase

No. Query

#22. #12 AND #13 AND #20 AND #21

#21. 'continuous':ab,ti AND [embase]/lim

#20. #14 OR #15 OR #16 OR #17 OR #18 OR #19

#19. 'glucose monitoring':ab,ti AND [embase]/lim

#18. 'tissue glucose':ab,ti AND [embase]/lim

#17. 'glucose management':ab,ti AND [embase]/lim

#16. 'glucose monitor':ab,ti AND [embase]/lim

#15. ‘subcutaneous glucose’:ab,ti AND [embase]/lim

#14. ‘interstitial glucose’:ab,ti AND [embase]/lim

#13. ‘clinical trial’/exp OR ‘randomization’/exp OR’single blind procedure’/exp OR ‘double blind procedure’/exp OR ‘randomized controlled trial’/exp OR ‘crossover procedure’/exp OR ‘placebo’/exp OR ‘prospective studies’/exp OR (‘randomi?ed controlled’ NEXT/1 trial*) OR rct OR ‘randomly allocated’ OR ‘allocated randomly’ OR ‘random allocation’ OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*

#12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#11. ‘sepsis’:ab,ti AND [embase]/lim

#10. ‘wound’:ab,ti AND [embase]/lim

#9. ‘trauma’:ab,ti AND [embase]/lim

#8. ‘icu’:ab,ti AND [embase]/lim

#7. ‘critical illness’:ab,ti AND [embase]/lim

#6. ‘intensive care’:ab,ti AND [embase]/lim

#5. ‘critically ill’:ab,ti AND [embase]/lim

#4. ‘critical care’:ab,ti AND [embase]/lim

#3. ‘septic shock’:ab,ti AND [embase]/lim

#2. ‘bacteremia’:ab,ti AND [embase]/lim

#1. ‘intensive care’/exp

Cochrane library

ID→Search

#1→(“intensive care”):ti,ab,kw (Word variations have been searched)

#2→(“critically ill”):ti,ab,kw (Word variations have been searched)

#3→(“critical care”):ti,ab,kw (Word variations have been searched)

#4→(“critical illness”):ti,ab,kw (Word variations have been searched)

#5→(“Burn”):ti,ab,kw (Word variations have been searched)

#6→(“acute respiratory distress syndrom”):ti,ab,kw (Word variations have been searched)

#7→(“truma”):ti,ab,kw (Word variations have been searched)

#8→(“septic shock”):ti,ab,kw (Word variations have been searched)

#9→#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#10→(glucose monitoring):ti,ab,kw (Word variations have been searched)

#11→(tissue glucose):ti,ab,kw (Word variations have been searched)

#12→(glucose management):ti,ab,kw (Word variations have been searched)

#13→(glucose monitor):ti,ab,kw (Word variations have been searched)

#14→(subcutaneous glucose):ti,ab,kw (Word variations have been searched)

#15→(interstitial glucose):ti,ab,kw (Word variations have been searched)

#16→#10 OR #11 OR #12 OR #13 OR #14 OR #15

#17→(continuous):ti,ab,kw (Word variations have been searched)

#18→#16 AND #17

#19→(randomized controlled trial):pt (Word variations have been searched)

#20→#9 AND #18 AND #19

Wanfang database

Subject: (Critical Care or Intensive Care or critically ill or ICU or Sepsis or Trauma or Burns) and Subject: (Continuous Glucose Monitoring or Continuous Real Time Glucose Monitoring or Doynamic Glucose Monitoring System) and Subject: (Randomized Control or Randomized or RCT)

China National Knowledge Infrastructure database

TKA = ("continuous glucose monitoring" + "continuous real-time glucose monitoring" + "dynamic glucose monitoring system") and TKA = ("critical care" + "intensive care" + "critically ill" + "critical care measurement system" + "sepsis" + "toxicity" + "trauma" + "injury" + "burn") and TKA = ("randomized control" + "randomized" + "RCT")

Appendix File 2-2. Studies needed for full-reviewed but not included in the current meta-analysis (n=7 trials)

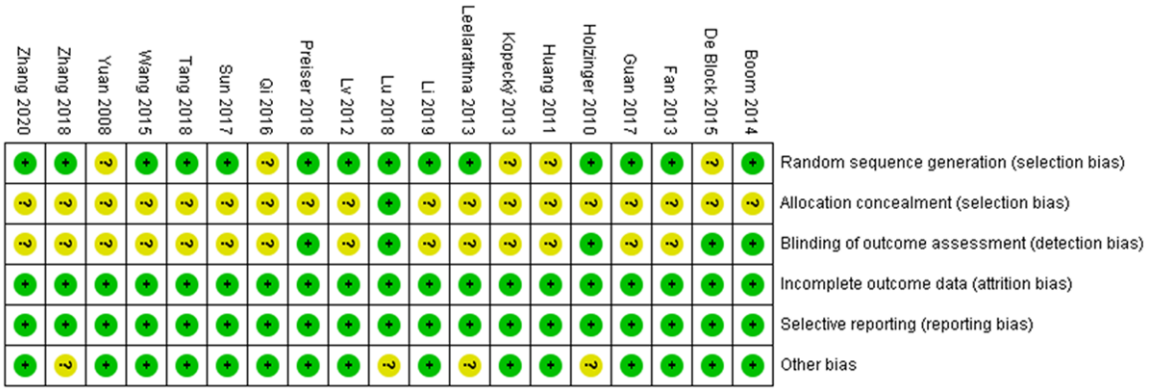
No	Study	Reason of exclusion
1	Rodríguez-Quintanilla KA, Lavalle-González FJ, Mancillas-Adame LG, Zapata-Garrido AJ, Villarreal-Pérez JZ, Tamez-Pérez HE. Continuous glucose monitoring in acute coronary syndrome. Arch Cardiol Mex. 2013 Oct-Dec;83(4):237-43.	Non RCT
2	Sampaio CR, Franco DR, Goldberg DJ, Baptista J, Eliaschewitz FG. Glucose control in acute myocardial infarction: a pilot randomized study controlled by continuous glucose monitoring system comparing the use of insulin glargine with standard of care. Diabetes Technol Ther. 2012 Feb;14(2):117-24.	Inappropriate control group
3	Li FF, Zhang WL, Liu BL, Zhang DF, Chen W, Yuan L, Chen MY, Zhai XF, Wu JD, Su XF, Ye L, Cao HY, Ma JH. Management of glycemic variation in diabetic patients receiving parenteral nutrition by continuous subcutaneous insulin infusion (CSII) therapy. Sci Rep. 2018 Apr 12;8(1):5888.	Reported without ICU admission
4	T van den Boorn M, Lagerburg V, van Steen SCJ, Wedzinga R, Bosman RJ, van der Voort PHJ. The development of a glucose prediction model in critically ill patients. Comput Methods Programs Biomed. 2021 Jul;206:106105.	Inappropriate control group
5	Steil GM, Langer M, Jaeger K, Alexander J, Gaies M, Agus MS. Value of continuous glucose monitoring for minimizing severe hypoglycemia during tight glycemic control. Pediatr Crit Care Med. 2011 Nov;12(6):643-8.	Non RCT
6	Chang Ning, Pei Yinghao. The Correlation Between Serum Glucose Variability and Prognosis in Patients with Chronic Critical Illness by Continuous Glucose Monitoring System. Journal of Chengdu Medical College, 2018, 13(1):54-58	Non RCT
7	Zhu W, Jiang L, Jiang S, Ma Y, Zhang M. Real-time continuous glucose monitoring versus conventional glucose monitoring in critically ill patients: a systematic review study protocol. BMJ Open. 2015 Jan 23;5(1):e006579.	Study protocol

Appendix File 3. Glucose measurement parameters between continuous glucose monitoring and control groups

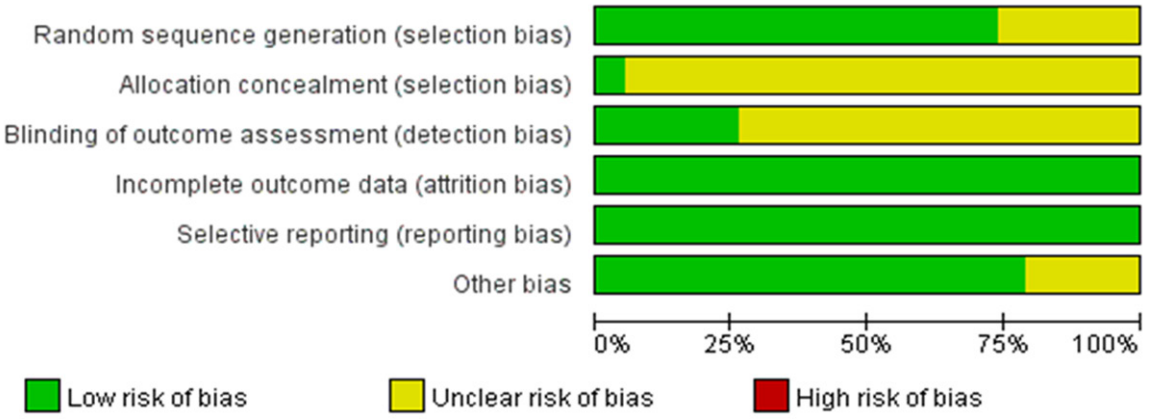
Study	Average BG	Calibration	Target BG mmol/L	Defined hyperglycemia	Defined hypoglycemia	Time in range	Target above range	Target below range	MAGE	Insulin used
Holzinger 2010 [12]	6.2±0.7/ 6.3±0.6	QID	6.1	NA	<2.2	59.0±20.4/ 55.0±18.0	NA	NA	NA	104±78/ 110±52
Huang 2011 [27]	7.4±1.7/ 8.9±2.0	NA	7.0	NA	<2.8	NA	NA	NA	8.9±1.8/ 12.0±2.9	NA
Leelarathna 2013 [23]	7.9±0.5/ 9.1±3.4	NA	6.0-8.0	≥15	<4	54.3±20.6/ 18.5±29.4	NA	NA	NA	40.9±49.2/ 57.4±53.4
Kopecky 2013 [24]	6.2±0.1/ 6.1±0.6	BID	4.4-6.1	NA	<2.9	46.3±5.5/ 46.2±6.5	40.6±5.9/ 38.4±5.1	13.1±2.6/ 15.4±2.4	NA	NA
Boom 2014 [6]	8.2/8.3	5 times/d	5.0-9.0	>9	<2.2	66±19.2/ 69±19.2	28±19.2/ 34±20	5±5.1/ 3±3.7	0.3±0.2/ 0.3±0.1	NA
De Block 2015 [26]	6.6±0.9/ 6.7±0.6	QD	4.4-6.7	NA	<3.3	37±12/ 34±10	20±18/ 17±10	0.6±1.6/ 2.4±4.3	3.1±1.4/ 3.2±1.3	57±49/ 52±23
Qi 2016 [28]	NA	QID	6.1-8.3	NA	<3.9	NA	NA	NA	NA	NA
Sun 2017 [25]	NA	NA	7.0	NA	NA	NA	NA	NA	NA	NA
Preiser 2018 [14]	6.7±1.4/ 6.8±1.3	NA	5.0-8.3	>8.3	<2.2	70±27/ 73±23	NA	0.4±0.9/ 1.6±3.4	NA	NA
Lu 2018 [15]	9.6/10.3	NA	8.0-10	NA	<2.2	51.5±27.2/ 29±10.9	27.5±32.3/ 50±26.3	10±12.5/ 15.5±12.4	NA	186±98.5/ 158±70.3
Zhang 2020 [16]	NA	NA	4.4-8.3	NA	<3.3	NA	NA	NA	NA	NA
Guan 2017 [30]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Li 2019 [17]	NA	NA	3.9-8.3	NA	≤3.9	NA	NA	NA	NA	90.6±15.7/ 130±20.6
LV 2012 [31]	NA	QID	7.8-11.1	NA	<3.9	NA	NA	NA	4.9±1.0/ 5.9±1.4	NA
Tian 2019 [32]	9.4±1.9/ 8.8±1.2	QD	NA	NA	NA	NA	NA	NA	NA	NA
Wang 2015 [33]	7.2±1.5/ 8.6±1.9	NA	7-10	NA	NA	NA	NA	NA	8.7±1.7/ 11.8±2.5	NA
Yuan 2008 [34]	6.8±5.1/ 7.3±6.9	NA	NA	NA	<2.8	NA	NA	NA	NA	46.2±4.3/ 58.5±5.1
Fan 2013 [29]	NA	NA	10.0-11.1	NA	<3.9	NA	NA	NA	?	NA
Zhang 2018 [18]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

BG = blood glucose; CGM = continuous glucose monitoring; MAGE = mean amplitude of glycemic excursion; NA = not available.

Appendix File 4. Quality assessment and overall risk of bias of included studies.



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Appendix File 5. Figure: Publication bias.

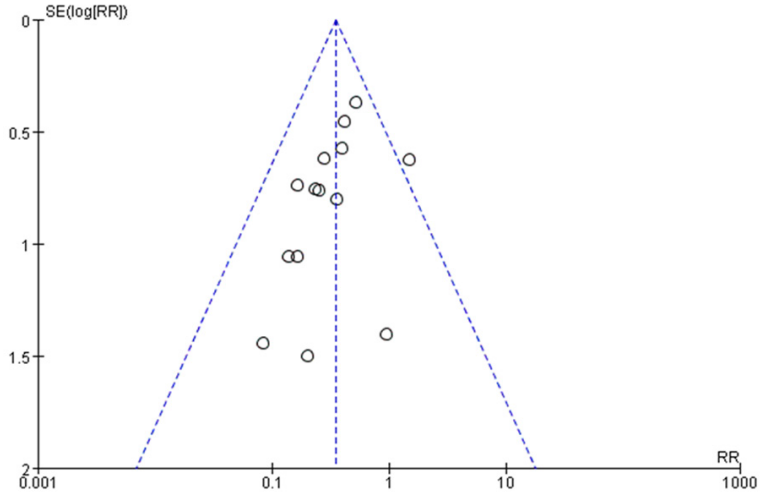


Figure S5. Publication bias (outcome of incidence of hypoglycemia, 19 RCTs).

Appendix File 6. Figure: Secondary outcomes.

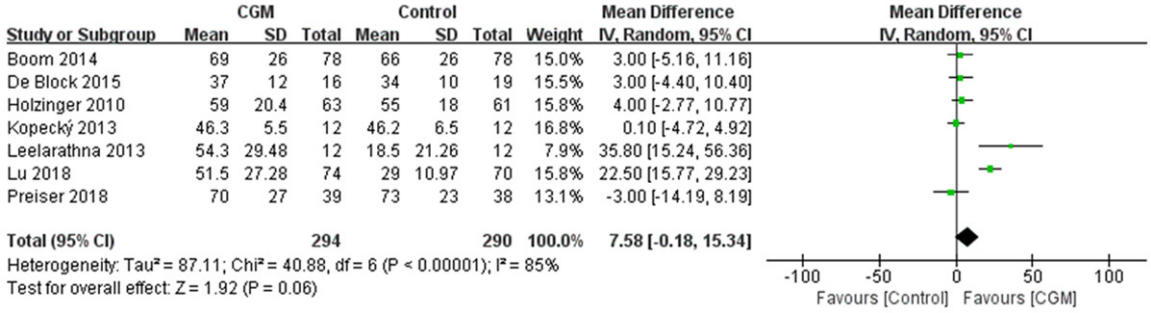


Figure S6. Plot of outcome of the time in target BG range.

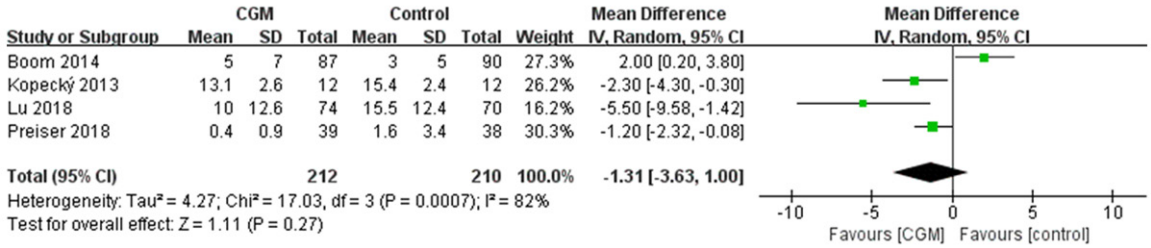


Figure S7. Plot of outcome of the time below target BG range.

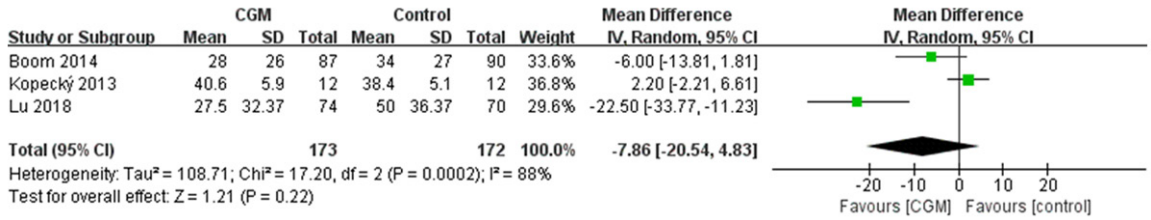


Figure S8. Plot of outcome of the time above target BG range.

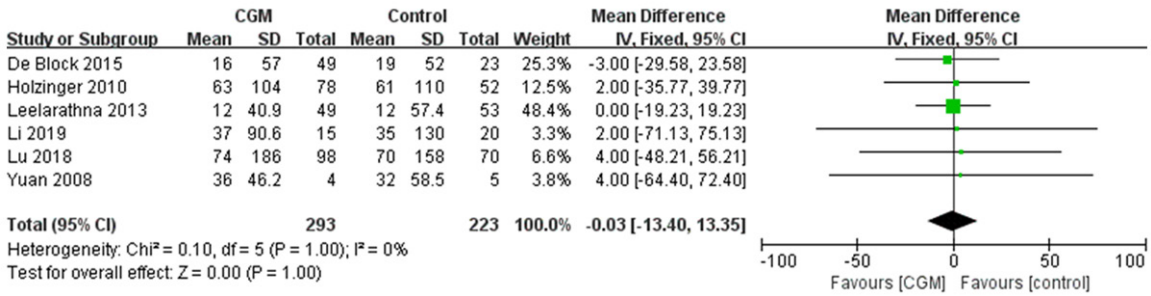


Figure S9. Plot of outcome of the insulin use.

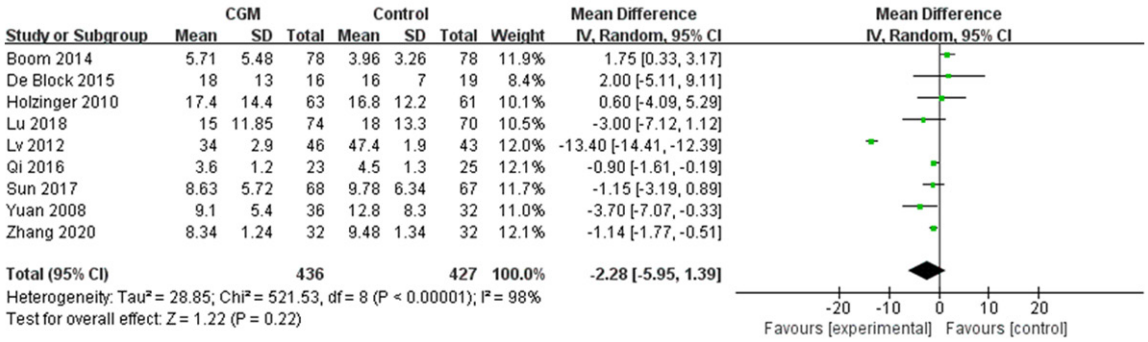


Figure S10. Plot of outcome of the length of stay in ICU.

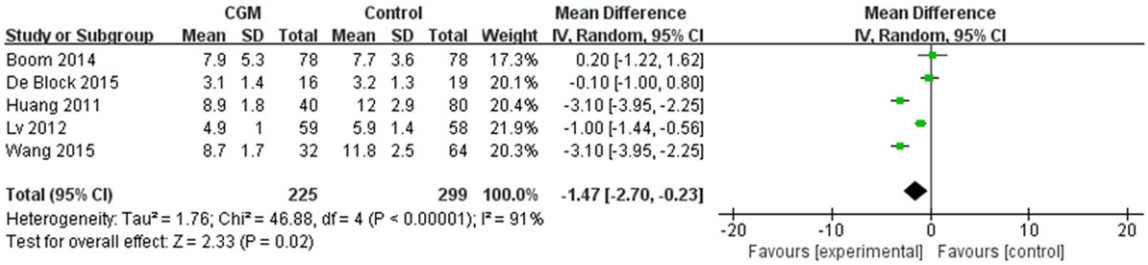


Figure S11. Plot of outcome of the MAGE.

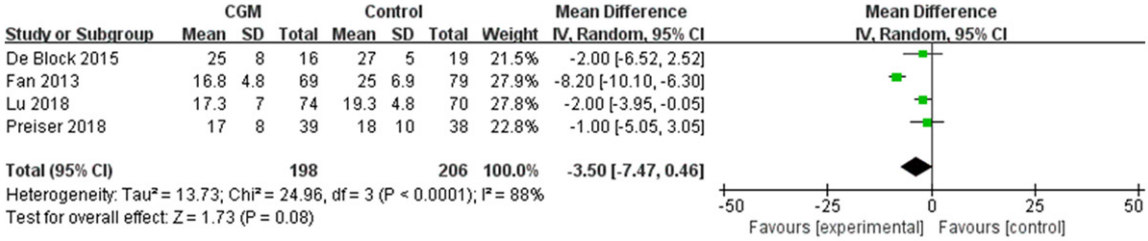


Figure S12. Plot of outcome of the CV.

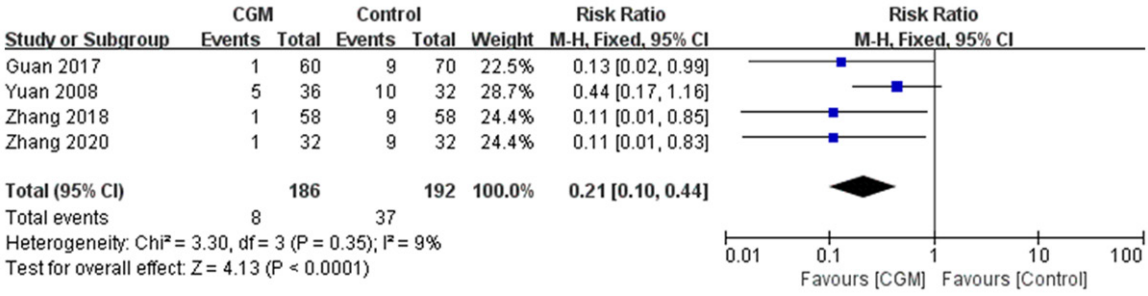


Figure S13. Plot of outcome of the incidence of infection.