Sliding-Scale Insulin Used for Blood Glucose Control: A Meta-analysis of Randomized Controlled Trials

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Abstract

**Background:** Sliding-scale insulin has been widely used in treating inpatient hyperglycemia. A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to evaluate the efficacy and possible adverse effects of sliding-scale insulin in hospitalized patients.

**Methods:** PubMed, EMBASE, Cochrane Library, Scopus, and ClinicalTrials.gov registry were searched for studies published up to February 2014. Individual effect sizes were standardized, and a meta-analysis was performed to calculate a pooled effect size using random effects models.

**Results:** Twelve RCTs containing a total of 1372 patients were identified. Among eight studies in which the RISS was compared with other regimens, no significant difference was observed in the percentage of patients who achieved the mean blood glucose level between the two groups, which was determined according to the numbers of blood samples (RR: 2.84; 95% CI: 0.94 to 8.59) and patients (RR: 1.75; 95% CI: 0.86 to 3.55). The mean blood glucose level (weighted mean difference = 27.33, 95% CI: 14.74 to 39.92) and incidence of hyperglycemic events were significantly higher in the RISS group than in the non-sliding-scale group. No significant difference in the incidence of severe hypoglycemia and length of hospitalization between the groups was identified.
Conclusions: The overall results of the meta-analysis indicated that applying the RISS alone or in combination with other antidiabetic medications did not provide any benefits in blood glucose control, but was accompanied by an increased incidence of hyperglycemic events. Therefore, we suggest that the use of sliding-scale insulin be discontinued in hospitals.

Keywords: diabetes, hyperglycemia, hypoglycemia, meta-analysis, sliding scale insulin
Background

Diabetes mellitus is common in hospitalized patients. Inpatient glycemic control has been addressed over the past several years because evidence that uncontrolled hyperglycemia is associated with poor outcomes, such as increased mortality, infections, or slow wound healing, was reported. Therefore, managing hyperglycemia in a hospital setting, which involves medical, surgical, and intraoperative care, is crucial but extremely challenging.

The optimal inpatient glycemic goals have been the subject of controversy over the past few years. According to the American Diabetes Association guidelines, the glucose level should be maintained between 140 and 180 mg/dL for critically ill patients. For patients who are not critically ill, premeal glucose is recommended to be maintained at less than 140 mg/dL, and the random glucose level should be maintained at less than 180 mg/dL. Numerous insulin regimens have been developed for managing inpatient hyperglycemia, including intravenous insulin infusion, the automatic closed-loop infusion of regular insulin or glucose (artificial pancreas system), multiple daily subcutaneous insulin that consists of basal and bolus or preprandial components, and sliding-scale insulin with or without regularly scheduled insulin. However, controlling glucose levels within the target range without inducing any hypoglycemic events remains difficult because an acute disease state or
stress, various medications used during hospitalization, and nutritional intake may influence the blood glucose levels of inpatients.\textsuperscript{11}

Sliding-scale insulin is defined as a set of various insulin doses that are administered based on the patient’s glucose reading at the time. Generally, a small amount of short-acting insulin is subcutaneously administered when hyperglycemia occurs. Sliding-scale insulin has been widely used in treating inpatient hyperglycemia for several decades. Prescribing sliding-scale insulin to patients with uncontrolled blood glucose levels has become an established habit for physicians and medical students.\textsuperscript{12,13} However, the sliding-scale regimen can provide only short-acting insulin to patients when the blood glucose level is over a certain threshold, potentially leaving the patient without insulin coverage for several hours. Therefore, the sole use of sliding-scale insulin can lead to fluctuating glucose levels.\textsuperscript{14,15} Both prospective and retrospective studies have reported that patients who received sliding-scale insulin therapy experienced unsatisfactory glycemic control and other adverse outcomes, such as hypoglycemia or infection.\textsuperscript{16,17} Nevertheless, most people still consider sliding-scale insulin therapy to be a convenient and simple treatment despite the high degree of uncertainty regarding outcomes. Therefore, we conducted this systematic literature review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effectiveness of regular insulin sliding-scale (RISS) compared with that of other
insulin regimens in hospitalized patients.

**Materials and Methods**

**Literature Search**

Relevant studies published before the end of February 2014 were identified by conducting a computer search of the PubMed, EMBASE, Scopus, and Cochrane databases. The following Medical Subject Headings search headings were used: *diabetes* or *diabetes mellitus* or *DM*, *glycemia* or *glycemic control* or *hypoglycemia* or *hyperglycemia*, *sliding scale*, *insulin*. These terms and the associated combinations were also searched as text words. The “related articles” search feature provided by PubMed was used to broaden the search, and all of the retrieved abstracts, studies, and citations were reviewed. In addition, we identified additional studies by searching the reference sections of the accessed papers by hand and contacting known experts in the field. Finally, unpublished studies were sought using the ClinicalTrials.gov registry (http://clinicaltrials.gov/). No language restrictions were applied. The systematic review described herein was accepted by the online PROSPERO international prospective register of systematic reviews of the National Institute for Health Research (CRD42014006967).
Study Selection

The following types of study were included in the analysis: RCTs that evaluate the efficacy and safety of using sliding-scale insulin for blood glucose control in hospitalized patients; that clearly state the inclusion and exclusion criteria used for patient selection; and that adequately describe the procedures used for administering the experimental drugs. Studies were excluded from the analysis if one or both of the following conditions applied: the outcomes of interest were not clearly reported for each of the two methods used for blood glucose control; or the extraction or calculation of the appropriate data from the published results was not possible even contacted with the authors of the studies. When duplicate papers using overlapping data sets were published, the study with the larger population was included.

Data Extraction and Quality Assessment

Two reviewers (K.W. Tam and M.Y. Wu) independently extracted the following information from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, drug administration methods, mean blood glucose level, and complications including hypoglycemia, hyperglycemia, infections, and days of hospitalization. The retrieved studies were assessed for eligibility by the two reviewers according to the inclusion criteria.
specified. The individually recorded decisions of the two reviewers were compared, and any disagreements were resolved by a third reviewer (Y.Y. Lee). The authors of the studies were contacted for additional information when necessary.

**Study Quality Assessment**

The quality of the studies was assessed using the “risk of bias” method recommended by The Cochrane Collaboration.\(^\text{18}\) Several domains were assessed: allocation generation; allocation concealment; the blinding of participants, personnel, and outcome assessors; the completeness of outcome data; freedom from selective reporting; and freedom from other biases.

**Data Synthesis and Analysis**

We used the following outcomes to evaluate the efficacy and safety of using sliding-scale insulin for maintaining the blood glucose levels of inpatients: (1) percentage of patients who achieved the average blood glucose target; (2) incidence of hypoglycemia; (3) incidence of hyperglycemia; (4) mean blood glucose level; (5) complications, including wound infections and all-cause mortality; and (6) the duration of hospitalization.

Blood glucose levels (mg/dL) were measured in either capillary blood, collected
using a finger stick method, or venous blood. The average blood glucose targets were based on definitions stated in the articles included in this analysis. The definitions of hypoglycemia and hyperglycemia were determined by the study investigators. The incidence of hypoglycemia in each study was calculated by dividing the number of patients with low glucose levels by the total number of patients included in the study. The incidence of hyperglycemia was measured as either the percentage of patients with high blood glucose levels or the proportion of hyperglycemic episodes that occurred in all of the samples.

We conducted the analysis using the Review Manager, Version 5 statistical package (Cochrane Collaboration, Oxford, England). Meta-analysis was performed according to the recommendations reported in the PRISMA guidelines.\textsuperscript{19} When necessary, standard deviations were estimated using either the provided confidence interval (CI) limits, standard error, or range values.\textsuperscript{20}

We statistically analysed the dichotomous outcomes using risk ratios (RRs) as the summary statistic. Continuous outcomes were analysed using the weighted mean difference (WMD). Both of these summary statistics were reported with 95\% CIs. Data were pooled only for studies that reported sufficiently similar clinical and methodological variables. A pooled estimate of the RR and WMD was computed using the DerSimonian and Laird random-effect model.\textsuperscript{21} This calculation method
provides an appropriate estimate of the average treatment effect when studies are statistically heterogeneous; furthermore, it yields wide CIs, resulting in conservative statistical claims. Heterogeneity among the studies was assessed using the $I^2$ test and a null hypothesis test, in which $P < .1$ was considered to indicate significant outcome heterogeneity. Sensitivity analyses were performed to assess any effect of study quality on the effect estimates. Subgroups analyses were performed by pooling estimates for similar subsets of patients across trials when available.

**Results**

**Study characteristics**

Figure 1 shows a flowchart for the study selection process. The initial search strategy used yielded 864 citations, 757 of which were ineligible based on the criteria used in screening the titles and abstracts; thus, we retrieved the full text of 107 studies. Of these studies, four were study protocols, 13 investigated the efficacy and safety of using the insulin regimens other than sliding scale; 4 studied the effects of the RISS, but no glycemic control outcomes provided; and 74 compared the outcomes of RISS and non-sliding-scale regimens, but were not randomized. Thus, the final number of eligible studies was 12.4-10,22-26

The included studies were published between 2002 and 2013, and had sample
sizes ranging from 30 to 351 participants. Eight studies evaluated the effects of blood glucose management involving the use of either the RISS or non-sliding-scale regimens. All of the eight studies, except for Umpierrez (2007), recruited patients who had received surgery. One study investigated the effects of implementing the RISS in routine diabetes medication administered to inpatients with a concurrent diagnosis of type 2 diabetes. Two studies compared the outcomes of the RISS and the RISS combined with routine glargine in controlling blood glucose. One study evaluated approaches to glucose management for diabetic patients who had undergone cardiopulmonary bypass. The definition of glycemic events varied across studies. The inclusion criteria used to select patients, the baseline characteristics of the studies, and the intervention method used for blood glucose management are reported in Table 1.

The results of the methodological quality assessment of the 12 RCTs are illustrated in Table 2. Three studies clearly documented the use of random allocation. Two studies described whether or how patient allocation to different treatment groups was concealed from the participants. Four studies reported no blinding of the participating patients or personnel. No studies reported the blinding of the researchers who assessed the outcomes. All of the included studies, except for one study by Okabayashi et al., based their analyses on the
intention-to-treat principle. The number of patients lost to follow up was acceptable (< 20%) in all of the studies. None of the studies reported relevant information that could be used for determining the risk of incomplete data bias. Other biases that existed in the studies included an unbalanced patient number between groups;\(^4\) differences in the routine diabetes medications administered between groups;\(^22\) and differences in the cardioplegic solutions used between groups.\(^{24}\)

The regular insulin sliding scale versus non-sliding-scale regimens

Eight of the included studies compared the RISS with others regimens (Table 1).\(^{4-9,25}\) The results of the meta-analysis are presented as follows:

**Percentage of patients with average blood glucose achieved the target range**

We analyzed five of the RCTs that reported blood glucose targets and percentages within the desired range.\(^4,5,7,9\) Two studies maintained blood glucose levels at less than 140 mg/dL,\(^5,8\) one study maintained blood glucose levels between 100 to 140 mg/dL,\(^9\) one maintained blood glucose levels between 100 to 150 mg/dL,\(^4\) and the final study maintained the blood glucose levels at less than 180 mg/dL.\(^7\) Although Datta (2007) and Umpierrez (2013) investigated the results for blood glucose levels at various ranges, we did not include that study in the results of this
meta-analysis because of insufficient data.\textsuperscript{25,26} We conducted subgroup analysis by dividing the studies into two groups based on the calculated percentage of patients that achieved the target blood glucose level according to the either the number of patients\textsuperscript{4,7,8} or number of blood samples\textsuperscript{5,9}. After calculating the percentage of blood glucose levels achieved the target range according to the number of blood samples, we observed a nonsignificant difference between the two groups, but identified a trend favoring the non-sliding-scale group (RR: 2.84; 95% CI: 0.94 to 8.59).

Regarding the percentage of patients with average glucose level achieved the target range according to the number of patients, we also observed no significant difference between the 2 groups, but identified a trend favoring the non-sliding-scale group (RR: 1.75; 95% CI: 0.86 to 3.55). Significant heterogeneity existed across the studies for the percentage calculated according to the number of blood glucose sampling times ($I^2 = 99\%, P < .00001$), and for the percentage calculated according to the number of patients ($I^2 = 78\%, P = .01$) (Fig. 2).

We performed a sensitivity analysis of the percentage calculated for the patient number subgroup by excluding one study with an extremely wide confidence interval.\textsuperscript{4} The heterogeneity decreased ($I^2 = 30\%, P = .23$) and the difference between the two groups became significant, favoring the non-sliding-scale group (RR: 1.48; 95% CI: 1.09 to 2.02).
**Incidence of hypoglycemia**

Six studies evaluated the incidence of hypoglycemia.\textsuperscript{4,6,8,9,26} Hypoglycemia was defined differently among the included studies; generally, all of the studies defined blood glucose levels below 70 mg/dL as indicative of hypoglycemia. The incidence of hypoglycemia was significantly higher in the non-sliding-scale than RISS group (RR: 3.96; 95% CI: 1.70 to 9.21). We determined that no hypoglycemic events occurred in three of the studies, which had established a strict cut point indicating hypoglycemia (< 50 mg/dL\textsuperscript{3} or < 40 mg/dL\textsuperscript{5,6}). We also observed mild heterogeneity across the studies ($I^2 = 20\%; P = .29$) (Fig. 3).

Datta (2007) reported on the frequency of hypoglycemia. In this study, the occurrence of hypoglycemic episodes was rare. Among all of the 926 blood glucose measurements taken, only two patients in the insulin glargine group and one patient in the RISS group exhibited blood glucose levels that were less than 60 mg/dL.\textsuperscript{25} Moreover, Schroeder (2012) observed no significant difference in the number of hypoglycemic events ($P = 0.6$).\textsuperscript{7}

**Incidence of hyperglycemia**

The target blood glucose levels varied among the included studies. We evaluated
the incidence of hyperglycemia in only two of the included studies because the other trials provided insufficient data.\textsuperscript{8,9} Hyperglycemia was defined as blood glucose levels $> 240$ mg/dL\textsuperscript{7} and $> 180$ mg/dL.\textsuperscript{9} Umpierrez (2007) evaluated the incidence of hyperglycemia according to the number of patients: 9 of 65 patients in the RISS group and zero of 65 patients in the basal-bolus regimen group experienced hyperglycemic events (RR: 19.0, 95\% CI: 1.13 to 319.8).\textsuperscript{8} In Umpierrez (2011), the incidence of hyperglycemia was investigated by using the number of blood samples: hyperglycemic events occurred 645 out of 1826 times in the RISS group and 400 out of 1952 times in the basal-bolus group (RR: 1.72, 95\% CI: 1.55 to 1.92) (9). The results indicated that the incidence of hyperglycemia was significantly higher in the RISS group than in the basal-bolus group.

\textit{Mean blood glucose level}

Seven of the included studies reported the mean blood glucose level (mg/dL).\textsuperscript{4,6-9,25,26} We combined the results for mean blood glucose levels reported in only five studies because insufficient data for pooling in two trials was provided by the other studies.\textsuperscript{6,25} Significantly lower mean blood glucose levels were observed in the non-sliding-scale group than in the RISS group, as well as the total effect (WMD $= 27.33$, 95\% CI: 14.74 to 39.92). Significant heterogeneity was observed across the
studies ($I^2 = 89\%; P < .00001$) (Fig.4). Therefore, we performed sensitivity analysis by excluding one study that reported an extremely low standard deviation for both groups. The mean blood glucose level was significantly lower in the non-sliding-scale group than in the RISS group (WMD = 31.58, 95% CI: 15.28 to 17.89). Heterogeneity decreased after conducting sensitivity testing ($I^2 = 84\%; P = .0001$).

The mean blood glucose level was $154 \pm 33$ mg/dL in the RISS group and $134 \pm 30$ mg/dL in the insulin glargine group ($P < .01$) in Datta (2007). In Okabayashi-2 (2009), the postoperative blood glucose levels were significantly higher in the RISS group than in the artificial pancreas group during the first 18 hours after pancreatic resection ($P < .05$).

**Duration of hospitalization**

Five studies reported the duration of hospitalization stay. We excluded two studies when conducting data pooling because of the lack of standard deviation values provided. No significant difference in the duration of stay between the non-sliding-scale and RISS groups was observed (WMD = 0.47; 95% CI: -1.60 to 2.53). The heterogeneity was not significant across the studies ($I^2 = 56\%; P = .1$) (Fig.5).
Routine medication combined with the regular insulin sliding scale versus routine medication alone

Dickerson et al. (2003) conducted a randomized open-label study comparing the effects of routine antidiabetic medications with those of routine diabetes medications combined with the RISS in type 2 diabetic inpatients. They observed that the addition of the RISS to routine diabetes medications did not affect the hyperglycemic rate (33.3% versus 34.6%, $P = .87$), hypoglycemic rate (8% versus 9%, $P = .83$), or the length of stay (5 ± 4.2 versus 5.3 ± 5.4, $P = .86$) compared with administering routine diabetes medications alone.\textsuperscript{22}

The regular insulin sliding scale versus the regular insulin sliding scale combined with routine glargine

Korytkowski et al. (2009) compared the efficacy of subcutaneous RISS alone with that of combining RISS and glargine in controlling the glucose levels of diabetic patients receiving enteral nutrition therapy. Patients in the RISS group received additional neutral protamine Hagedorn (NPH) to maintain blood glucose levels above 180 mg/dL. The mean glucose level was similar in both groups ($P = .71$). However, additional NPH was administered to 48% of the patients in the RISS group. No
differences in the total number of adverse events and the duration of stay between the groups were observed.\textsuperscript{10}

One study investigated the effect of glycemic control after coronary artery bypass grafting (CABG) in patients randomly receiving either subcutaneous RISS alone or daily glargine combined with the RISS as needed for maintaining the preprandial glucose levels of the patients above 180 mg/dL. The percentages of patients with blood glucose levels within the target range were 61\% and 30\% in the glargine group and RISS group, respectively ($P < .001$). The postoperative glucose levels were significantly lower in the glargine group ($P < .001$). The study demonstrated that the routine administration of glargine can substantially improve glycemic control with a low incidence of hypoglycemia.\textsuperscript{23}

**Intraoperative Glucose Control**

One study evaluated intraoperative glucose management for patients with diabetes undergoing cardiopulmonary bypass (CPB). Fifty patients were randomly divided into two groups and received either a 5\% dextrose-based cardioplegic solution and a continous infusion of insulin, or a normal saline-based cardioplegic solution and the RISS. The mean blood glucose levels pre- and postCPB at each measurement time were all significantly higher in the patients receiving dextrose-based cardioplegia and
continual insulin infusion than in the patients in the second group. Blood glucose levels were within the acceptable range (< 200 mg/dL) for patients who were administered a saline-based cardioplegic solution and the RISS.²⁴

**Complications**

Three studies investigated the incidence of complications between the non-sliding-scale and RISS groups.⁴,⁹,¹⁰ No significant difference in the incidence of wound infection between the non-sliding-scale (4/209) and RISS groups (16/172) was observed (RR = 0.30; 95% CI: 0.05 to 1.86) (Fig.6).

**Discussion**

The results of our review suggested that no potential advantage was provided by using the RISS alone or in combination with routine antidiabetic agents to maintain the blood glucose level. The mean blood glucose level and incidence of hyperglycemic events were significantly higher in the RISS group than in the non-sliding-scale group. Moreover, the RISS group exhibited a trend in that they repeatedly failed to achieve the blood glucose target range. Although the incidence of hypoglycemia was significantly higher in the non-sliding-scale group, there was no difference among the groups in the frequency of severe hypoglycemia (<40 mg/dL),
and no symptomatic hypoglycemic event was reported. The duration of hospital stay was similar between the RISS and non-sliding-scale groups.

The results of this analysis are consistent with those of other studies. One retrospective study that evaluated hyperglycemia management for patients with pneumonia indicated that the patients in the sliding-scale group exhibited significantly higher mean blood glucose values than did patients who received non-sliding-scale treatments \( (P < .0001) \).\(^{27}\) One cross-sectional study comparing the effects of inpatient glycemic control between a basal-bolus insulin group and an RISS group reported that the mean daily glucose level was significantly lower in the patients receiving basal-bolus insulin \( (P < .001) \), and the percentage of patients whose blood glucose levels were in the target range was significantly higher in the basal-bolus group than in the RISS group \( (P < .001) \). The incidence of severe hypoglycemia was not significantly different between the two groups.\(^ {28}\)

Several insulin regimens were applied for managing hyperglycemia in the studies included. Basal-bolus subcutaneous insulin therapy was commonly used and proven effective in controlling blood glucose levels.\(^ {7,9,25}\) It was designed to mimic normal physiologic pancreatic insulin secretion, which was combined with meal-stimulated insulin peaks and basal insulin constantly produced throughout the day. Conducting continuous intravenous insulin infusion according to the standardized protocol is an
option for treating uncontrolled hyperglycemia in inpatients, especially for those who
do not respond to the subcutaneous basal-bolus treatment. Establishing a strict blood
glucose goal (80–110 mg/dL) is no longer recommended because the Normoglycemia
in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation trial
suggested that intensive glucose control may increase the incidence of hypoglycemia
and mortality.\textsuperscript{29} One study included in this review compared intravenous insulin
infusion with the RISS set a high target blood glucose level (100–150 mg/dL), and the
risks of hypoglycemia were similar between the two groups compared.\textsuperscript{4} A closed-loop
artificial pancreas system was also used in several of the studies. The automatic
infusion of insulin and glucose based on continually monitored glucose levels can
provide more effective glucose control than the RISS can.\textsuperscript{5,6} The successful
implementation of an effective and safe insulin regimen may involve the medical
staff’s correct perception of the required glucose control and intensive nursing care
regimens. Therefore, reeducating inpatient health care professionals on appropriate
insulin strategies is crucial.\textsuperscript{13}

Scheduled subcutaneous basal and nutritional (bolus) insulin combined with
correction components, sliding-scale insulin, is suggested by the American Diabetic
Association for treating hyperglycemia in patients who are not critically ill.\textsuperscript{3} This
recommendation was based on a study that evaluated the efficacy of applying
basal-bolus regimens involving weight-based dosing. Correctional insulin, which resembles sliding-scale insulin, was also prescribed for all the patients included in Baldwin (2012). Consequently, the recommendation of adding correctional insulin to scheduled insulin is not based on a randomized-controlled comparison. In the present review, the RCT conducted by Dickerson (2003) did not reveal any benefits of adding the RISS to a routine antidiabetic regimen. However, this study was possibly biased by the use of open-label and various routine antidiabetic medications between the two groups. Additional well-designed RCTs are required to examine the effect of adding the RISS to routine diabetes medications.

One study compared the effects of continuous insulin infusion combined with the RISS on glucose management during CABG. This is the only study that indicated that the RISS can improve glycemic control. Nonetheless, the results should be interpreted with caution because the two groups received different cardioplegic solutions: a 5% dextrose solution was used in the group that was administered insulin intravenously, whereas a normal saline solution was used in the RISS group. Because dextrose can cause iatrogenic hyperglycemia, the use of dextrose-based solutions may have contributed to high glucose levels and inadequate blood glucose control in the non-RISS group. Consequently, we were not able to conclude that the RISS can provide benefits in intraoperative blood glucose control.
The significant heterogeneity observed among the selected studies was attributable to various factors. First, the characteristics of the participants varied. Among the 12 studies, nine studies that evaluated the RISS efficacy in surgical patients involved the use of various types of surgery, including CABG and orthopedic, bariatric, hepatic, and pancreatic surgeries. Second, the antidiabetic strategies used were not identical across all of the studies. Third, clinical factors such as the definition of glycemic events, the target blood glucose levels, and blood glucose sampling time and methods also exaggerated the heterogeneity observed in this study. Finally, the methodological quality also played a role in the existence of heterogeneity. Sensitivity analysis revealed that the values of $I^2$ decreased from 78% to 30% for the patients in the patient number subgroup who achieved the average blood glucose target by excluding one study with an extremely wide confidence interval.\textsuperscript{4}

Despite the improvements made in the current review, this research was subject to certain limitations. Population characteristics, low patient numbers, unbalanced patient numbers between groups, differing antidiabetic agents and dosages, the use of concomitant drugs, various outcome analyses, and the methodological weaknesses inherent in several of the studies we reviewed may have resulted in a slightly speculative interpretation of the subgroup analysis results. These differences may have contributed to the observed heterogeneity. Furthermore, the concomitant use of
various types of cardioplegia solution might have altered the efficacy of blood glucose
control in individual patients.\textsuperscript{24}

Presently, the RISS is still commonly prescribed in hospitals. Based on the limited
available RCT data, neither the RISS alone nor the RISS combined with other
antidiabetic medications provided any benefits in blood glucose control. Contrary to
facilitating control of the ideal blood glucose level for surgical and medical patients,
the use of RISS caused more hyperglycemic events to occur compared with other
insulin regimens. Our results indicate that the use of sliding-scale insulin should be
discontinued in hospitals.
Contributors: Ka-Wai Tam and Mei-Yi Wu devised and designed the study; Yen-Ying Lee, You-Meei Lin, Wuan-Jin Leu, Ju-Huei Tseng, Meng-Ting Hsu, and Chia-Shan Tsai extracted data; Yen-Ying Lee, You-Meei Lin, An-Tsz Hsieh, Ka-Wai Tam and Mei-Yi Wu analyzed and interpreted data; Yen-Ying Lee, Ka-Wai Tam and Mei-Yi Wu wrote the first draft; all authors contributed to subsequent versions and approved the final article; Ka-Wai Tam and Mei-Yi Wu are guarantor.

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Competing interests: The authors have no conflicts of interest or financial ties to disclose.
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20. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the


**Figure Legends**

Figure 1. Flowchart of the study selection process.

Figure 2. Forest plot of comparison: the RISS versus non insulin sliding-scale. 
Outcome: Percentage of patients with average blood glucose achieved the target range.
2.1.1. Calculated according to the number of blood samples. 2.1.2. Calculated according to the number of patients.

Figure 3. Forest plot of comparison: the RISS versus non insulin sliding-scale. 
Outcome: The incidence of hypoglycemia.

Figure 4. Forest plot of comparison: the RISS versus non insulin sliding-scale. 
Outcome: The mean blood glucose level, mg/dL.

Figure 5. Forest plot of comparison: the RISS versus non insulin sliding-scale. 
Outcome: Duration of hospitalization.

Figure 6. Forest plot of comparison: the RISS versus other regimens. Outcome: The incidence of wound infection.
### Table 1. Characteristics of Studies that Fulfilled the Inclusion Criteria Used in the Meta-analysis

<table>
<thead>
<tr>
<th>Study [year]</th>
<th>Inclusion criteria</th>
<th>No. of patient (% of male)</th>
<th>Age, y, mean ± SD</th>
<th>Intervention</th>
<th>Definition of glycemic Events (mg/dL)</th>
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<tbody>
<tr>
<td><strong>RISS vs. Other Regimens</strong></td>
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<tr>
<td>Datta [2007]</td>
<td>Gastric bypass surgery BS &gt; 144 mg/dL with or without history of diabetes</td>
<td>S: 39 (18)  N: 42 (14)</td>
<td>S: 44.5  N: 45.4</td>
<td>S: RISS  N: Glargine plus regular insulin for BS &gt; 200 mg/dL</td>
<td>Hypoglycemia: BS &lt; 60</td>
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<tr>
<td>Schroeder [2012]</td>
<td>Diabetes or recurrent hyperglycemia (≥2 BS levels &gt; 180 mg/dL) patients underwent emergent orthopedic surgery</td>
<td>S: 30 (50)  N: 35 (50)</td>
<td>S: 71  N: 70</td>
<td>S: RISS  N: Routine medications plus basal-bolus for BS &gt; 200 mg/dL</td>
<td>Hyperglycemia: BS &gt; 400</td>
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<tr>
<td>Umpierrez [2011]</td>
<td>Surgical patients with diabetes, BS between 140 and 400 mg/dL</td>
<td>S: 107 (49.5)  N: 104 (51.9)</td>
<td>S: 57±10  N: 58±12</td>
<td>S: RISS  N: Basal-bolus regimen (glargine + glulisine)</td>
<td>Hyperglycemia: BS &gt; 180</td>
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<td><strong>Routine + RISS vs Routine</strong></td>
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<td><strong>RISS vs RISS + Routine glargine</strong></td>
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<tr>
<td>Korytkowski [2009]</td>
<td>Diabetes with ≥2 BS levels &gt; 130mg/dL during enteral nutrition therapy</td>
<td>S: 25 (56)  G: 25 (64)</td>
<td>S: 63±10  G: 67±10</td>
<td>S: RISS (NPH added for persistent BS &gt; 180 mg/dL)  G: Glargine + RISS</td>
<td>Hyperglycemia: BS &lt; 70  Hyperglycemia: BS &gt; 180</td>
</tr>
<tr>
<td>Hagelberg [2008]</td>
<td>Diabetes or impaired glucose intolerance patients underwent primary CABG</td>
<td>S: 22 (82)  G: 21 (86)</td>
<td>S: 64.9±10.4  G: 64.3±9.1</td>
<td>Regular insulin infusion at the start of surgery until 6AM postoperatively, then  S: RISS  G: Glargine + RISS</td>
<td>Hypoglycemia: BS &lt; 90</td>
</tr>
<tr>
<td><strong>Intraoperative Sugar Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BS: blood sugar; D5W: Dextrose 5%; G: glargine-based regimen; N: non-sliding scale group; NS: normal saline; RISS: regular insulin sliding scale; S: sliding scale group
Table 2  Assessment of the Methodological Quality of Included Studies

<table>
<thead>
<tr>
<th>Study [year]</th>
<th>Country</th>
<th>Allocation generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Data analysis</th>
<th>Loss to follow up</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emam [2010]</td>
<td>Saudi Arabia</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Unbalanced patient number between groups</td>
</tr>
<tr>
<td>Okabayashi-1 [2009]</td>
<td>Japan</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Schroeder [2012]</td>
<td>Israel</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Umpierrez [2007]</td>
<td>USA</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Umpierrez [2011]</td>
<td>USA</td>
<td>Computer generated</td>
<td>Adequate</td>
<td>Unclear</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Umpierrez [2013]</td>
<td>USA</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Open-label</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Dickerson [2003]</td>
<td>USA</td>
<td>Sealed envelopes</td>
<td>Adequate</td>
<td>Open-label</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Routine diabetes medications different between groups</td>
</tr>
<tr>
<td>Korytkowski [2009]</td>
<td>USA</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Open-label</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Hagelberg [2008]</td>
<td>Sweden</td>
<td>Sealed envelopes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Gustafson [2002]</td>
<td>USA</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>ITT</td>
<td>0</td>
<td>Low risk</td>
<td>Different cardioplegic solution between groups</td>
</tr>
</tbody>
</table>

Risk of bias was assessed with the method recommended by the Cochrane Collaboration.

Abbreviations: ITT, Intention-to-treat; PP, Per-protocol.
Figure 1

Flowchart of the Study Selection Process

Studies identified using the PubMed, EMBASE, and Cochrane, databases (n = 858)  

Search for potentially relevant trials (n = 864)

Studies retrieved for further evaluation (n = 107)

Additional studies identified using SCOPUS and searching references by hand (n = 6)

Studies excluded after reading titles and abstracts
  - Not relevant (n = 696)
  - Review (n = 47)
  - Comment (n=14)

Included studies (n = 12)

Studies excluded
  - Different comparison (n = 13)
  - Not randomised (n = 74)
  - Protocol (n=4)
  - No glycemic control outcome (n = 4)
### 2.1.1 Percentage of achieving of average sugar target: Blood sampling numbers

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Non-sliding scale Events</th>
<th>Sliding scale Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M.H. Random, 95% CI</td>
<td>M.H. Random, 95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okabayashi 2009</td>
<td>403 440</td>
<td>91 440</td>
<td>494</td>
<td>43.7%</td>
<td>4.66 (4.06, 6.07)</td>
<td></td>
</tr>
<tr>
<td>Urgueix 2011</td>
<td>1011 1952</td>
<td>579 1528</td>
<td>1651</td>
<td>50.3%</td>
<td>1.03 (0.91, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2392 2266</td>
<td>100%</td>
<td>2.84 (0.84, 8.59)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1441
Heterogeneity: Tau^2 = 3.53; CH^2 = 165.77, df = 1 (P = 0.00001); I^2 = 99%

Test for overall effect: Z = 1.85 (P = 0.06)

### 2.1.2 Percentage of achieving of average sugar target: Patient numbers

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Non-sliding scale Events</th>
<th>Sliding scale Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M.H. Random, 95% CI</td>
<td>M.H. Random, 95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ehrin 2016</td>
<td>29 60 0</td>
<td>40 5.3%</td>
<td>26.05 (1.01, 466.74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmaier 2012</td>
<td>25 35 17</td>
<td>30 46.7%</td>
<td>1.26 (0.36, 4.94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urquieix 2017</td>
<td>43 85 20</td>
<td>65 47.6%</td>
<td>1.12 (0.21, 5.49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>180 135 100%</td>
<td>1.75 (0.88, 3.55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 96
Heterogeneity: Tau^2 = 0.24; CH^2 = 8.10, df = 2 (P = 0.01), I^2 = 76%

Test for overall effect: Z = 1.55 (P = 0.12)

Total for subgroups difference: Chi^2 = 0.43, df = 1 (P = 0.47), I^2 = 0%
Figure 3

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Non-sliding Scale</th>
<th>Sliding Scale</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Emam 2010</td>
<td>0</td>
<td>88</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Okubawashi 2009</td>
<td>0</td>
<td>44</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>Umpierrez 2007</td>
<td>2</td>
<td>65</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>Umpierrez 2011</td>
<td>23</td>
<td>144</td>
<td>5</td>
<td>167</td>
</tr>
<tr>
<td>Umpierrez 2013</td>
<td>20</td>
<td>144</td>
<td>2</td>
<td>74</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>454</td>
<td>343</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>49</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.12; Chi² = 5.49; df = 2 (P = 0.26); I² = 26%

Test for overall effect Z = 3.20 (P = 0.001)
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sliding scale Mean</th>
<th>SD</th>
<th>Total</th>
<th>Non-sliding scale Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enwani 2010</td>
<td>211.1</td>
<td>36.6</td>
<td>24</td>
<td>151.8</td>
<td>28.8</td>
<td>52</td>
<td>17.1%</td>
<td>59.50 [43.05, 75.95]</td>
<td>59.50 [43.05, 75.95]</td>
</tr>
<tr>
<td>Umpierrez 2007</td>
<td>192</td>
<td>54</td>
<td>86</td>
<td>165</td>
<td>32</td>
<td>95</td>
<td>17.0%</td>
<td>27.90 [11.74, 42.26]</td>
<td>27.90 [11.74, 42.26]</td>
</tr>
<tr>
<td>Umpierrez 2013</td>
<td>172</td>
<td>41</td>
<td>74</td>
<td>155</td>
<td>38</td>
<td>144</td>
<td>20.4%</td>
<td>10.00 [6.59, 13.41]</td>
<td>10.00 [6.59, 13.41]</td>
</tr>
<tr>
<td>Schnecker 2012</td>
<td>175.8</td>
<td>2.3</td>
<td>36</td>
<td>161.2</td>
<td>3.2</td>
<td>35</td>
<td>24.1%</td>
<td>14.80 [13.26, 15.94]</td>
<td>14.80 [13.26, 15.94]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>398</td>
<td>480</td>
<td>100.9%</td>
<td>398</td>
<td>100.9%</td>
<td>27.33 [14.74, 39.92]</td>
<td>27.33 [14.74, 39.92]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 170.54; I² = 55.83; # = 4 ($P = 0.0001$); $I^2 = 88%$.
Test for overall effect: $Z = 4.28$ ($P = 0.0001$).

Figure 4
Figure 5

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sliding scale</th>
<th>Non-sliding scale</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Einam 2010</td>
<td>12.3</td>
<td>7.8</td>
<td>24</td>
<td>9.1</td>
</tr>
<tr>
<td>Umeda 2011</td>
<td>9.3</td>
<td>5.5</td>
<td>107</td>
<td>7.23</td>
</tr>
<tr>
<td>Umeda 2007</td>
<td>5.1</td>
<td>4.5</td>
<td>85</td>
<td>5.2</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>196</td>
<td></td>
<td>221</td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.05; CH² = 4.63, df = 2 (p = 0.10); R² = 58%.
Test for overall effect Z = 4.44 (p = 0.64)

Favours sliding scale Favours non-sliding scale
Figure 6