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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	6
OBJECTIVES	6
METHODS	6
RESULTS	10
Figure 1.	11
Figure 2.	13
Figure 3.	14
DISCUSSION	16
AUTHORS' CONCLUSIONS	17
ACKNOWLEDGEMENTS	17
REFERENCES	18
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	49
Analysis 1.1. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 1 All-cause mortality.	50
Analysis 1.2. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 2 Non-severe hypoglycaemic episodes.	50
Analysis 1.3. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 3 Severe hypoglycaemic episodes.	51
Analysis 1.4. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 4 Length of hospital stay.	52
Analysis 1.5. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 5 Adverse events other than hypoglycaemic episodes (infectious complications).	52
Analysis 1.6. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 6 Mean glucose levels.	53
Analysis 2.1. Comparison 2 Sliding scale insulin versus basal insulin regimen, Outcome 1 Non-severe hypoglycaemic episodes.	54
Analysis 2.2. Comparison 2 Sliding scale insulin versus basal insulin regimen, Outcome 2 Length of hospital stay.	54
Analysis 2.3. Comparison 2 Sliding scale insulin versus basal insulin regimen, Outcome 3 Adverse events other than hypoglycaemic episodes.	54
Analysis 2.4. Comparison 2 Sliding scale insulin versus basal insulin regimen, Outcome 4 Mean glucose levels.	54
Analysis 3.1. Comparison 3 Sliding scale insulin versus continuous insulin infusion, Outcome 1 Mean glucose levels.	55
ADDITIONAL TABLES	56
APPENDICES	59
CONTRIBUTIONS OF AUTHORS	89
DECLARATIONS OF INTEREST	89
SOURCES OF SUPPORT	89
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	89
NOTES	89
INDEX TERMS	90

[Intervention Review]

Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus

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ABSTRACT

Background

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, function, or both. Hyperglycaemia in non-critically ill hospitalised people is associated with poor clinical outcomes (infections, prolonged hospital stay, poor wound healing, higher morbidity and mortality). In the hospital setting people diagnosed with diabetes receive insulin therapy as part of their treatment in order to achieve metabolic control. However, insulin therapy can be provided by different strategies (sliding scale insulin (SSI), basal-bolus insulin, and other modalities). Sliding scale insulin is currently the most commonly used method, however there is uncertainty about which strategy provides the best patient outcomes.

Objectives

To assess the effects of SSI for non-critically ill hospitalised adults with diabetes mellitus.

Search methods

We identified eligible trials by searching MEDLINE, Embase, LILACS, and the Cochrane Library. We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov trial registers. The date of the last search for all databases was December 2017. We also examined reference lists of identified randomised controlled trials (RCTs) and systematic reviews, and contacted trial authors.

Selection criteria

We included RCTs comparing SSI with other strategies for glycaemic control in non-critically ill hospitalised adult participants of any sex with diabetes mellitus.

Data collection and analysis

Two review authors independently extracted data, assessed trials for risk of bias, and evaluated the overall certainty of evidence utilising the GRADE instrument. We synthesised data using a random-effects model meta-analysis with 95% prediction intervals, if possible, or descriptive analysis, as appropriate.

Main results

Of 720 records screened, we included eight trials that randomised 1048 participants with type 2 diabetes (387 SSI participants and 615 participants in comparator groups were available for final analysis). We included non-critically ill medical and surgical adults with the diagnosis of diabetes mellitus. The mean follow-up time was measured by the mean length of hospital stay and ranged between five and 24 days. The mean age of participants was 44.5 years to 71 years.

Overall, we judged the risk of bias on the trial level as unclear for selection bias, high for outcome-related performance and detection bias with regard to hypoglycaemic episodes, other adverse events, and mean glucose levels, and low for all-cause mortality and length of hospital stay. Attrition bias was low for all outcome measures.

Six trials compared SSI with a basal-bolus insulin scheme, three of which investigating 64% of all participants in this category also applying an SSI approach in the bolus comparator part. One trial had a basal insulin-only comparator arm, and the remaining trial used continuous insulin infusion as the comparator. For our main comparison of SSI versus basal-bolus insulin, the results were as follows. Four trials reported mortality data. One out of 268 participants in the SSI group (0.3%) compared with two out of 334 participants in the basal-bolus group (0.6%) died (low-certainty evidence). Severe hypoglycaemic episodes, defined as blood glucose levels below 40 mg/dL (2.2 mmol/L), showed a risk ratio (RR) of 0.22, 95% confidence interval (CI) 0.05 to 1.00; $P = 0.05$; 5 trials; 667 participants; very low-certainty evidence. The 95% prediction interval ranged between 0.02 and 2.57. All nine severe hypoglycaemic episodes were observed among the 369 participants on basal-bolus insulin (2.4%). The mean length of hospital stay was 0.5 days longer for the SSI group, 95% CI -0.5 to 1.4; $P = 0.32$; 6 trials; 717 participants; very low-certainty evidence. The 95% prediction interval ranged between -1.7 days and 2.7 days. Adverse events other than hypoglycaemic episodes, such as postoperative infections, showed a RR of 1.16, 95% CI 0.25 to 5.37; $P = 0.85$; 3 trials; 481 participants; very low-certainty evidence. The mean blood glucose levels ranged across basal-bolus groups from 156 mg/dL (8.7 mmol/L) to 221 mg/dL (12.3 mmol/L). The mean blood glucose level in the SSI groups was 14.8 mg/dL (0.8 mmol/L) higher (95% CI 7.8 (0.4) to 21.8 (1.2); $P < 0.001$; 6 trials; 717 participants; low-certainty evidence). The 95% prediction interval ranged between -3.6 mg/dL (-0.2 mmol/L) and 33.2 mg/dL (1.8 mmol/L). No trial reported on diabetes-related mortality or socioeconomic effects.

Authors' conclusions

We are uncertain which insulin strategy (SSI or basal-bolus insulin) is best for non-critically hospitalised adults with diabetes mellitus. A basal-bolus insulin strategy in these patients might result in better short-term glycaemic control but could increase the risk for severe hypoglycaemic episodes. The certainty of the body of evidence comparing SSI with basal-bolus insulin was low to very low and needs to be improved by adequately performed, well-powered RCTs in different hospital environments with well-educated medical staff using identical short-acting insulins in both intervention and comparator arms to compare the rigid SSI approach with flexible insulin application strategies.

PLAIN LANGUAGE SUMMARY

Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus

Review question

What are the effects of sliding scale insulin compared with other insulin therapies for non-critically ill hospitalised adults with diabetes mellitus?

Background

There are several options to treat people with diabetes who have been admitted to the hospital. Both low glucose levels (hypoglycaemia) and high glucose levels (hyperglycaemia) might increase the risk of death and complications such as infections and longer hospital stay and therefore should be avoided. The most common method to treat hospitalised people with diabetes is sliding scale insulin therapy. The term 'sliding scale' refers to the increasing administration of the pre-meal insulin dose based on the blood sugar level before the meal. For example, if a person has a blood glucose level between 140 mg/dL to 180 mg/dL, a short-acting usual insulin dose could be 4 units insulin, and for a blood glucose level between 181 mg/dL and 220 mg/dL, it could be 6 units insulin. This kind of rigid insulin application usually fixes the amount of carbohydrate to be eaten at each meal but does not deliver insulin in a physiologic manner. It is therefore doubtful whether good glycaemic control (satisfactory blood glucose levels) can be achieved by sliding scale insulin in hospitalised diabetic people and whether this approach results in better outcomes in the long term. There are other insulin strategies like background (basal) insulin doses combined with flexible pre-meal insulin (bolus insulin) according to what and how much people want to eat. Sliding scale insulin means strict adherence to a regular schedule of meals and physical activity, and people must follow a prescribed diet. Intensified insulin therapy (basal-bolus strategy) allows flexible insulin doses according to physical activity, stress, and meal preferences, and under hospital

conditions demands well-trained medical staff. Sliding scale insulin is still widely used, and it remains unclear which insulin strategy is best to treat hospitalised diabetic people.

Study characteristics

We found eight randomised controlled trials (studies in which participants are assigned to one of two or more treatment groups in a random manner) where 387 people on sliding scale insulin therapy and 615 on mainly basal-bolus insulin treatment with type 2 diabetes could be analysed. The average length of hospital stay was between five and 24 days. Six studies compared sliding scale insulin with basal-bolus insulin; one study compared sliding scale insulin with basal insulin only; and the remaining study used continuous insulin infusion as the control group. The average age of participants was 44.5 years to 71 years.

The evidence is up to date as of December 2017.

Key results

The main comparison was between sliding scale insulin and basal-bolus insulin therapy with the following results. Of the four studies reporting deaths, one out of 268 participants in the SSI group compared with two out of 334 participants in the basal-bolus group died. Severe hypoglycaemic episodes, defined as blood glucose levels below 40 mg/dL, occurred in 5 per 1000 people in the sliding scale insulin groups compared with 24 per 1000 people in the basal-bolus insulin groups. These data are uncertain because further analyses showed neither a positive nor a negative effect comparing both insulin strategies. The length of hospital stay in the sliding scale insulin groups compared with the basal-bolus insulin groups was 0.5 days longer, again with further analyses indicating that this information is uncertain. The results for adverse events other than hypoglycaemic episodes, such as postoperative infections, did not indicate an advantage or disadvantage of either strategy. The average blood glucose level during hospital stay in the sliding scale groups was 14.8 mg/dL higher compared with the basal-bolus groups. We are uncertain about these data because analyses showed neither a positive nor a negative effect comparing both insulin strategies. No trial reported on deaths caused by diabetes as such or socioeconomic effects like costs of the interventions or absence from work.

Certainty of the evidence

Overall, our confidence in the results for all analysed outcomes was low or very low mainly due to the low number of studies and participants and because the results were not precise, that is they could change in any direction once new studies are published.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Sliding scale insulin compared to basal-bolus insulin for non-critically ill hospitalised adults with diabetes mellitus

Sliding scale insulin compared to basal-bolus insulin for non-critically ill hospitalised adults with diabetes mellitus

Patient or population: non-critically ill hospitalised adults with diabetes mellitus

Setting: medical and surgical inpatients

Intervention: sliding scale insulin

Comparison: basal-bolus insulin

Outcomes	Risk with basal-bolus insulin	Risk with sliding scale insulin	Relative effect (95% CI)	No. of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality (N) Follow-up: 5 to 9 days	6 per 1000	3 per 1000 (0 to 29)	Peto OR 0.50 (0.05 to 4.85)	602 (4)	⊕⊕⊕⊕ low^a	4/8 trials reported data (very low number of events)
Diabetes-related morbidity	Not reported					
Severe hypoglycaemic episodes (N) Follow-up: 5 to 9 days	24 per 1000	5 per 1000 (1 to 24)	RR 0.22 (0.05 to 1.00)	667 (5)	⊕⊕⊕⊕ very low^b	The 95% prediction interval ranged between 0.02 and 2.57 All 9 severe hypoglycaemic episodes were observed among 369 participants (2.4%) in the basal-bolus insulin groups
Length of hospital stay (days) Follow-up: 5 to 24 days	The mean length of hospital stay ranged across control groups from 5.3 days to 24.2 days	The mean length of hospital stay in the intervention groups was 0.5 days longer (0.5 days shorter to 1.4 days longer)	-	717 (6)	⊕⊕⊕⊕ very low^c	The 95% prediction interval ranged between -1.7 days and 2.7 days
Adverse events other than hypoglycaemic episodes (postoperative complications, mainly infectious) (N)	62 per 1000	72 per 1000 (15 to 332)	RR 1.16 (0.25 to 5.37)	481 (3)	⊕⊕⊕⊕ very low^d	

Follow-up: 6 to 24 days					
Mean glucose level (mg/dL (mmol/L))	The mean glucose level ranged across control groups from 156 mg/dL (8.7 mmol/L) to 221 mg/dL (12.3 mmol/L)	The mean glucose level in the intervention groups was 14.8 mg/dL (0.8 mmol/L) higher (7.8 mg/dL (0.4 mmol/L) higher to 21.8 mg/dL (1.2 mmol/L) higher)	-	717 (6)	⊕⊕⊕⊖ low^e
Follow-up: 5 to 24 days					The 95% prediction interval ranged between -3.6 mg/dL (-0.2 mmol/L) and 33.2 mg/dL (1.8 mmol/L)
Socioeconomic effects	Not reported				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by two levels because of serious imprecision (small number of participants, small number of trials, uncommon event) (see [Appendix 14](#)).

^bDowngraded by one level because of trial limitations (risk of performance and detection bias) and by two levels because of serious imprecision (small number of participants, confidence interval consistent with benefit and harm) (see [Appendix 14](#)).

^cDowngraded by one level because of inconsistency (non-consistent direction of effects) and by two levels because of serious imprecision (small median number of participants, confidence interval consistent with benefit and harm) (see [Appendix 14](#)).

^dDowngraded by one level because of trial limitations (risk of performance and detection bias); by one level because of inconsistency (non-consistent direction of effects); and by one level because of imprecision (small number of trials and participants, confidence interval consistent with benefit and harm) (see [Appendix 14](#)).

^eDowngraded by one level because of trial limitations (risk of performance and detection bias) and by one level because of imprecision (small median number of participants) (see [Appendix 14](#)).

BACKGROUND

Description of the condition

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, function, or both. The consequence of DM is chronic hyperglycaemia, with subsequent effects on carbohydrate, fat, and protein metabolism. Long-term DM complications include retinopathy, nephropathy, neuropathy, and an increased risk of cardiovascular disease (e.g. myocardial infarction, cerebrovascular events). Adequate glycaemic control in hospitalised people with DM represents a clinical challenge due to the wide range of treatment strategies and the morbidity/mortality risk that these participants present (Umpierrez 2002).

Diabetes mellitus is the most common chronic disease in low-, middle-, and high-income countries. In 2000, the worldwide diabetes prevalence was 2.8% (for all age groups); in 2011, the global prevalence in the adult population was 8.3%. It is estimated that in 2030 diabetes prevalence will be 4.4% (for all age groups), affecting approximately 366 million people worldwide (Whiting 2011; Wild 2004).

People diagnosed with DM are frequently admitted for hospital care, with an estimated admission rate by year of about 25% to 30% (Moss 1999). At hospital admission, glycaemic control becomes a priority; there is an expected increase in serum glucose because of the metabolic stress (caused by the present illness or procedures) resulting in hyperglycaemia, increased infection risk, and poor wound healing. Insulin therapy regimens are currently under discussion (Braithwaite 2008; Buchleitner 2012). Most of the data comes from people with critical care illness; however, even in these patients the best treatment regimens are unclear (Farrokhi 2012; Friedrich 2010; Griesdale 2009; Klonoff 2011).

Description of the intervention

Four strategies are used to achieve glycaemic control in hospitalised diabetic people: basal insulin, prandial insulin, correction-dose insulin, and sliding scale insulin (SSI). These strategies are used to maintain optimal glucose levels (fasting and postprandial). The main difference between these strategies is the intervention purpose: basal insulin administration inhibits hepatic glucose production and is mainly responsible for controlling fasting glucose; prandial (bolus or mealtime) insulin aims to control postprandial glucose levels by promoting glucose disposal into the muscles; and correction dose insulin is administered in addition to prandial insulin using an algorithm-based treatment to provide an adjustment to carbohydrate intake (Lien 2011).

Sliding scale insulin (sometimes called correctional insulin) is poorly defined and is used in different ways: traditionally, the insulin prescription is administered according to the measured blood glucose levels and therefore constitutes a reactive response to hyperglycaemia; SSI is an intervention usually characterised by a subcutaneous administration (regular insulin or rapid-acting insulin analogues), regardless of the timing of food intake, presence or absence of pre-existing insulin administration, and sensitivity to insulin, without the acute illness consideration. The SSI scheme aims to maintain the glucose levels between 7.7 mmol/L (140 mg/dL) and 10 mmol/L (180 mg/dL) (Lien 2011; Umpierrez 2012). Some physicians even employ this approach using long-acting insulin analogues or neutral protamine Hagedorn (NPH) insulin.

Sliding scale insulin is regularly prescribed as part of the medical treatment in hospitalised diabetic people, despite the lack of physiological congruence and strong evidence to support it.

Adverse effects of the intervention

There are many considerations regarding the use of SSI in the treatment of diabetic inpatients. This strategy has been widely criticised when used to obtain glycaemic control. Previous studies have revealed longer days to achieve metabolic control, greater variability of glucose levels (hypoglycaemia and hyperglycaemia), higher infection rate, and increased mortality (Baldwin 2005; Childs 2003; Umpierrez 2012).

Why it is important to do this review

Sliding scale insulin is one of the most frequently used therapies in the metabolic control of diabetic inpatients. However, this strategy may be associated with poor glycaemic control causing more complications (higher infection rate, increased mortality, prolonged hospital stay). Several non-systematic review articles have addressed the SSI scheme (Miller 2011; Umpierrez 2007b). Given the potential public health relevance, we have systematically collected and examined all randomised controlled trials on SSI treatments for non-critical diabetic hospitalised people in order to establish the risk and benefits of this therapy.

OBJECTIVES

To assess the effects of sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled clinical trials (RCTs).

Types of participants

Non-critically ill hospitalised adult (18 years or older) diabetic people. We expected that most of the trials would have type 2 diabetes participants, because people with type 1 diabetes mellitus require a basal-bolus insulin treatment. We excluded nursing home residents and people treated in intensive care units.

Diagnostic criteria

In order to be consistent with changes in the classification of and diagnostic criteria for diabetes over the years, the diagnosis had to be established using the standard criteria valid at the time of the trial commencing (e.g. ADA 1999; ADA 2008; WHO 1998). Ideally, the diagnostic criteria should have been described. Where necessary, we used the trial authors' definition of diabetes mellitus and planned to subject diagnostic criteria to a subgroup analysis.

Types of interventions

We planned to investigate the following comparisons of intervention versus comparator.

Intervention

- Sliding scale insulin.

Comparators

- Basal insulin only.
- Basal-bolus insulin (delivered by multiple subcutaneous injections or an insulin pump).
- Correction dose insulin.

Other concomitant interventions had to be the same in the intervention and comparator groups to establish fair comparisons.

Minimum duration of intervention and follow-up

We accepted any duration of intervention and follow-up.

We defined extended follow-up periods (also called open-label extension studies) as follow up of participants once the original trial, as specified in the trial protocol, has been terminated. However, such studies are frequently of an observational nature, and we only planned to evaluate them for adverse events ([Buch 2011](#); [Megan 2012](#)).

Summary of specific exclusion criteria

- Nursing home residents and people treated in intensive care units.
- Children and adolescents up to 18 years of age.

We did not exclude trials because one or several of our primary or secondary outcome measures were not reported in the publication. If no additional data were available, we planned to provide some basic information in a supplementary table.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Diabetes-related mortality.
- Hypoglycaemic episodes.

Secondary outcomes

- Length of hospital stay.
- Adverse events other than hypoglycaemic episodes.
- Mean blood glucose.
- Socioeconomic effects.

Method and timing of outcome measurement

- All-cause mortality: defined as the total number of deaths from any cause, measured as in-hospital mortality and as 30-day all-cause mortality.
- Diabetes-related mortality: defined as the total number of deaths due to myocardial infarction, ischaemic heart disease, stroke or sequelae of stroke, heart failure, cardiac arrest, peripheral vascular disease, kidney disease, hyperglycaemia, and hypoglycaemia, measured as in-hospital mortality and as 30-day mortality.
- Hypoglycaemic episodes: defined as the number of blood glucose values less than 70 mg/dL or according to trial authors' definitions.
- Length of hospital stay: defined as the duration of a single episode of hospitalisation and measured by subtracting the day of admission from the day of discharge.

- Adverse events other than hypoglycaemia, e.g. hypokalaemia defined as a serum potassium concentration less than 3.5 mEq/L or injection site reactions, measured at any time during the hospital stay.
- Mean blood glucose: as measured during participant hospital stay.
- Socioeconomic effects, e.g. costs of the intervention, absence from work, medication consumption.

Search methods for identification of studies

Electronic searches

We searched the following sources from the inception of each database to the date given, placing no restrictions on language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library (Issue 11 of 12, November 2017; searched on 22 December 2017).
- MEDLINE Ovid SP (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE; 1946 to present; searched on 22 December 2017).
- Embase Ovid SP (1974 to 21 December 2017; searched on 22 December 2017).
- LILACS (Latin American and Caribbean Health Science Information database; last update 8 December 2017; searched on 22 December 2017).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (searched on 22 December 2017).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/trialsearch/); searched on 22 December 2017).

We applied a continuous MEDLINE (via Ovid SP) email alert service to identify newly published trials using the same search strategy as described for MEDLINE ([Appendix 1](#)).

Searching other resources

We attempted to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, (systematic) reviews, meta-analyses, and health technology assessment reports.

Data collection and analysis

Selection of studies

Two review authors (LECL, NDF) independently scanned the abstract, title, or both, of every record retrieved to determine which trials should be assessed further. We evaluated the full texts of all potentially relevant articles for inclusion in the review. Any discrepancies were resolved through consensus or by recourse to a third review author (AVH). We prepared a flow diagram of the number of trials identified and excluded at each stage in accordance with the PRISMA flow diagram of trial selection ([Liberati 2009](#)).

Data extraction and management

Two review authors (LECL, DGP) independently extracted key participant and intervention characteristics from the included

trials. We reported data on efficacy outcomes and adverse events using standard data extraction forms from Cochrane Metabolic and Endocrine Disorders. Any disagreements were resolved by discussion or by consultation with a third review author (AVH) where necessary (for details see [Table 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#); [Appendix 6](#); [Appendix 7](#); [Appendix 8](#); [Appendix 9](#); [Appendix 10](#); [Appendix 11](#); [Appendix 12](#)).

We provided information about potentially relevant ongoing trials, including trial identifier, in the [Characteristics of ongoing studies](#) table and in 'Matrix of study endpoints (publications and trial documents)' ([Appendix 6](#)). We attempted to retrieve the protocol for each included trial and planned to report in [Appendix 6](#) primary, secondary, and other outcomes in comparison with data in publications.

We emailed the authors of all included trials to enquire as to whether they would be willing to answer questions regarding their trials. We presented the results of this survey in [Appendix 13](#). We sought relevant missing information on the trial from the primary author(s) of the article, if possible.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary trial, we maximised the information yield by collating all available data, and used the most complete data set aggregated across all known publications. We listed duplicate publications, companion documents, multiple reports of a primary trial, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included trial. Furthermore, we listed duplicate publications, companion documents, multiple reports of a trial, and trial documents of excluded trials (such as trials registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trials registers

If data from included trials were available as study results in clinical trials registers such as ClinicalTrials.gov or similar sources, we made full use of this information and extracted the data. If there was also a full publication of the trial, we collated and critically appraised all available data. If an included trial was marked as a completed study in a clinical trials register but no additional information (study results, publication, or both) was available, we added this trial to the [Characteristics of studies awaiting classification](#) table.

Assessment of risk of bias in included studies

Two review authors (LECL, DGP) independently assessed the risk of bias of each included trial. Any disagreements were resolved by consensus or by consultation with a third review author (AVH) where necessary. If adequate information was unavailable from the trials, trial protocols, or both, we contacted the trial authors for missing data on 'Risk of bias' items.

We used the Cochrane 'Risk of bias' assessment tool to assess each 'Risk of bias' domain as low, high, or unclear risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (for details see [Appendix 2](#)) ([Higgins 2011a](#); [Higgins 2017](#)).

Summary assessment of risk of bias

We presented a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We distinguished between self reported, investigator assessed, and adjudicated outcome measures.

We considered the following self reported outcomes.

- Adverse events other than hypoglycaemia.
- Hypoglycaemic episodes.

We considered the following investigator-assessed outcomes.

- Adverse events other than hypoglycaemia.
- All-cause mortality.
- Diabetes-related mortality.
- Hypoglycaemic episodes.
- Length of hospital stay.
- Mean blood glucose.
- Socioeconomic effects.

Risk of bias for a trial across outcomes

Some 'Risk of bias' domains such as selection bias (sequence generation and allocation sequence concealment) affect the risk of bias across all outcome measures in a trial. In case of high risk of selection bias, we marked all endpoints investigated in the associated trial as being at high risk. Otherwise, we did not performed a summary assessment of the risk of bias across all outcomes for a trial.

Risk of bias for an outcome within a trial and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We considered a judgement of low risk of bias to denote a low risk of bias for all key domains; unclear risk of bias to denote an unclear risk of bias for one or more key domains; and high risk of bias to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains

These are the main summary assessments that we incorporated into our judgements about the certainty of evidence in the 'Summary of findings' tables. We defined outcomes as at low risk of bias when most information came from trials at low risk of bias; unclear risk of bias when most information came from trials at low or unclear risk of bias; and high risk of bias when a sufficient proportion of information came from trials at high risk of bias.

Measures of treatment effect

When at least two trials were available for a comparison of a given outcome, we expressed dichotomous data as risk ratio (RR) with 95% confidence intervals (CIs). We planned to calculate time-to-event data as hazard ratio (HR) with 95% CI with the generic inverse variance method. We expressed continuous data reported on the same scale as mean difference (MD) with 95% CIs. For trials addressing the same outcome but using different outcome measure scales, we planned to use standardised mean differences (SMD) with 95% CI.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome. If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we either combined groups to create a single, pairwise comparison, or we appropriately reduced the sample size so that the same participants did not contribute multiply times (splitting the 'shared' group into two or more groups). Although the latter approach offers some solution for adjusting the precision of the comparison, it does not account for correlation arising from inclusion of the same set of participants in multiple comparisons (Higgins 2011b).

We planned to re-analyse cluster-randomised trials that did not appropriately adjust for potential clustering of participants in their analysis. Variance of the intervention effects would have been inflated by a design effect (DEFF). Calculation of a DEFF involves estimation of an intracluster correlation (ICC). We planned to obtain estimates of ICCs through contact with trial authors, or by imputing ICC values using either estimates from other included trials that reported ICCs or external estimates from empirical research (e.g. Bell 2013). We planned to examine the impact of clustering by performing sensitivity analyses.

Dealing with missing data

We attempted to obtain missing data from the authors of included trials. We carefully evaluated important numerical data such as screened, randomly assigned participants, as well as intention-to-treat and as-treated and per-protocol populations. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we critically appraised issues concerning missing data and imputation methods (e.g. last observation carried forward).

When included trials did not report means and standard deviations for outcomes and we were unable to obtain the requested information from trial authors, we imputed these values by estimating the mean and the variance from the median, the range, and the size of the sample (Hozo 2005).

We planned to investigate the impact of imputation on meta-analyses by performing sensitivity analyses.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we planned not to report trial results as the pooled effect estimate in a meta-analysis.

We identified heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard χ^2 test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across trials, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

Assessment of reporting biases

If we included 10 or more trials investigating a particular outcome, we used funnel plots to assess small-trial effects. Several explanations can account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and

publication bias (Sterne 2017). We therefore interpreted results carefully (Sterne 2011).

Data synthesis

We planned to undertake (or display) a meta-analysis only if we judged the participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that would be clinically meaningful. Unless good evidence showed homogeneous effects across trials of different methodological quality, we primarily summarised data judged as at low risk of bias using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects and presented a 95% prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval requires at least three trials to be calculated and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1%, we planned to use the Peto odds ratio (OR) method, provided there was no substantial imbalance between intervention and comparator group sizes, and intervention effects were not exceptionally large. In addition, we performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity and performed subgroup analyses to investigate interactions (Altman 2003).

- Medical or surgical intervention.
- Comorbid conditions.
- Age, depending on data.
- Time of follow-up.
- Type of insulin used.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting the analysis to the following.

- Published trials.
- Taking into account risk of bias, as specified in the [Assessment of risk of bias in included studies](#) section.
- Use of the following filters: imputation, language of publication, source of funding (industry versus other), or country.

We planned to test the robustness of results by repeating analysis using different measures of effect size (i.e. RR, OR, etc.) and different statistical models (fixed-effect and random-effects models).

Certainty of evidence

We presented the overall certainty of the evidence for each outcome specified below according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. Two review authors (LECL, DGP) independently rated the certainty of evidence for each outcome. Differences in assessment were solved by discussion or by consultation with a third review author (AVH).

[Appendix 14](#) 'Checklist to aid consistency and reproducibility of GRADE assessments' helps with standardisation of the 'Summary of findings' tables ([Meader 2014](#)). Alternatively, we planned to use GRADEpro GDT software and wanted to present evidence profile tables as an appendix ([GRADEpro GDT 2015](#)). We presented results for outcomes as described in the [Types of outcome measures](#) section. If meta-analysis was not possible, we presented the results in a narrative format in the 'Summary of findings' table. We justified all decisions to downgrade the certainty of the evidence with footnotes, and made comments to aid the reader's understanding where necessary.

'Summary of findings' table

We presented a summary of the evidence in the [Summary of findings for the main comparison](#). This provides key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the [Summary of findings for the main comparison](#) according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* and using the Review Manager 5 table editor ([RevMan 2014](#); [Schünemann 2017](#)). We reported the following outcomes, listed according to priority.

- All-cause mortality.
- Diabetes-related mortality.
- Severe hypoglycaemic episodes.
- Length of hospital stay.
- Adverse events other than hypoglycaemia.
- Mean blood glucose.
- Socioeconomic effects.

RESULTS

Description of studies

For a detailed description of trials, see [Table 1](#) and [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); and [Characteristics of ongoing studies](#) sections.

Results of the search

The electronic search strategies retrieved a total of 939 articles. After exclusion of duplicates, two review authors (LECL, DGP) independently assessed 720 titles, abstracts, or both. We obtained the full text of 45 articles/records, of which eight completed trials were included in our review. One potentially relevant trial is ongoing ([NCT01143948](#)), and two trials are awaiting classification ([IRCT201311118307N2](#); [ISRCTN55845280](#)). An adapted PRISMA flow diagram of trial selection is presented in [Figure 1](#).

Figure 1. Trial flow diagram.

Figure 1. (Continued)

Included studies

For a detailed description of the characteristics of the included trials, see [Characteristics of included studies](#) and [Appendix 3](#); [Appendix 4](#); [Appendix 5](#); [Appendix 6](#); [Appendix 7](#); [Appendix 8](#); [Appendix 9](#); [Appendix 10](#); [Appendix 11](#); [Appendix 12](#)). The following is a succinct overview.

Source of data

Eight trials met our inclusion criteria. These were published as peer-reviewed articles in English.

Comparisons

All included trials investigated SSI therapy against other strategies for glycaemic control. Six trials used a basal-bolus regimen ([Korytkowski 2009](#); [Said 2013](#); [Schroeder 2012](#); [Umpierrez 2007a](#); [Umpierrez 2011](#); [Umpierrez 2013](#)). Two were three-arm trials ([Said 2013](#); [Umpierrez 2013](#)). [Umpierrez 2013](#) also employed a basal-bolus correction regimen, and [Said 2013](#) also used a mixed correction regimen (70/30 regular insulin plus neutral protamine Hagedorn (NPH) by means of SSI). One trial employed a basal insulin regimen by means of glargine plus regular insulin in 6% of cases ([Datta 2007](#)), and another trial used a continuous insulin infusion strategy ([Gustafson 2002](#)).

Overview of trial population

A total of 1048 participants with type 2 diabetes were randomised to SSI intervention and comparators; 387 participants in the SSI groups and 615 in the comparator groups were finally analysed. The sample size of randomised individuals per trial ranged from 50 to 375 participants.

Trial design

Seven trials had a parallel RCT design, and one trial was a cluster RCT ([Schroeder 2012](#)). The trials were published between 2002 and 2013. One trial was self funded ([Said 2013](#)), and five trials were partly or entirely sponsored by the pharmaceutical industry ([Datta 2007](#); [Korytkowski 2009](#); [Umpierrez 2007a](#); [Umpierrez 2011](#); [Umpierrez 2013](#)).

Settings

Six trials were conducted in the USA ([Datta 2007](#); [Gustafson 2002](#); [Korytkowski 2009](#); [Umpierrez 2007a](#); [Umpierrez 2011](#); [Umpierrez 2013](#)), one trial in Israel ([Schroeder 2012](#)), and one in Egypt ([Said 2013](#)). Four trials evaluated surgical participants ([Datta 2007](#); [Gustafson 2002](#); [Schroeder 2012](#); [Umpierrez 2011](#)); three trials evaluated medical inpatients ([Korytkowski 2009](#); [Said 2013](#);

[Umpierrez 2007a](#)); and one trial evaluated both surgical and medical participants ([Umpierrez 2013](#)).

Participants

Two trials specified the ethnic background of their participants ([Umpierrez 2007a](#); [Umpierrez 2011](#)). Two trials reported the duration of diabetes mellitus ([Umpierrez 2011](#); [Umpierrez 2013](#)). The percentage of female participants per intervention/comparator group ranged between 26% and 86%. The mean age of participants ranged between 44.5 years and 71 years. The mean participants' glycated haemoglobin ranged between 7.4% and 8.9%. The mean body mass index (BMI) ranged between 26.9 kg/m² and 55 kg/m². Major exclusion criteria within the included trials were no history of diabetes, type 1 DM, corticosteroid therapy during hospitalisation, hyperglycaemic crisis, admission to an intensive care unit, severe heart failure or cardiogenic shock, clinically relevant hepatic disease, impaired renal function, gastrointestinal bleeding, pregnancy, inability to give informed consent, and any mental condition.

Interventions

The average daily insulin dose of SSI ranged between 8 units and 28 units. The average daily dose of basal-bolus insulin ranged between 12 units and 44 units, and the average daily dose of basal-plus insulin was 27 units. The mean duration of hospital stay ranged between 5 and 24 days.

Outcomes

Five trials explicitly stated a primary endpoint in the publication ([Said 2013](#); [Schroeder 2012](#); [Umpierrez 2007a](#); [Umpierrez 2011](#); [Umpierrez 2013](#)). The most commonly defined primary outcomes in the publications were differences in glycaemic control, as measured by mean daily blood glucose concentration. Five trials were registered in ClinicalTrials.gov ([Korytkowski 2009](#); [Said 2013](#); [Umpierrez 2007a](#); [Umpierrez 2011](#); [Umpierrez 2013](#)).

Excluded studies

We excluded 29 of 45 articles/records after evaluation of the full publication/record. The main reasons for exclusion were wrong trial design, wrong population, wrong setting, and wrong comparison (for further details see [Characteristics of excluded studies](#)).

Risk of bias in included studies

For an overview of review authors' judgements about each 'Risk of bias' item for individual trials and across all trials, see [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials (blank cells indicate that the particular outcome was not investigated in some trials).

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial (blank cells indicate that the trial did not report that particular outcome).

		Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All-cause mortality	Blinding of participants and personnel (performance bias): Diabetes-related mortality	Blinding of participants and personnel (performance bias): Non-severe hypoglycaemic episodes	Blinding of participants and personnel (performance bias): Length of hospital stay	Blinding of participants and personnel (performance bias): Adverse events other than hypoglycaemic episodes	Blinding of participants and personnel (performance bias): Mean glucose level	Blinding of participants and personnel (performance bias): Socioeconomic effects	Blinding of participants and personnel (performance bias): Severe hypoglycaemic episodes	Blinding of outcome assessment (detection bias): Severe hypoglycaemic episodes	Blinding of outcome assessment (detection bias): All-cause mortality	Blinding of outcome assessment (detection bias): Diabetes-related mortality	Blinding of outcome assessment (detection bias): Non-severe hypoglycaemic episodes	Blinding of outcome assessment (detection bias): Length of hospital stay	Blinding of outcome assessment (detection bias): Adverse events other than hypoglycaemia	Blinding of outcome assessment (detection bias): Mean glucose level	Blinding of outcome assessment (detection bias): Socioeconomic effects	Incomplete outcome data (attrition bias): Severe hypoglycaemic episodes	Incomplete outcome data (attrition bias): All-cause mortality	Incomplete outcome data (attrition bias): Diabetes-related mortality	Incomplete outcome data (attrition bias): Non-severe hypoglycaemic episodes	Incomplete outcome data (attrition bias): Length of hospital stay	Incomplete outcome data (attrition bias): Adverse events other than hypoglycaemic episodes	Incomplete outcome data (attrition bias): Mean glucose level	Incomplete outcome data (attrition bias): Socioeconomic effects	Selective reporting (reporting bias)	Other bias	
Datta 2007	?	?			+	+	+	+			+	+								+				+	+	+	+	+	+	+
Gustafson 2002	?																													
Korytkowski 2009	?	?			+	+	+	+			+	+			?	+	?			+			+	+	+	+	+	+	+	+
Said 2013	?	?	+		+	+	+	+			+	+	+			+				+	+			+	+	+	+	+	+	+
Schroeder 2012	?	?			+	+	+	+			+	+				+				+			+	+	+	+	+	+	+	+
Umpierrez 2007a	?	?	+		+	+	+	+			+	+	+		+	+	+	+		+	+			+	+	+	+	+	+	+
Umpierrez 2011	+	+	+		+	+	+	+			+	+	+		+	+	+	+		+	+			+	+	+	+	+	+	+
Umpierrez 2013	+	+	+		+	+	+	+			+	+	+		+	+	+	+		+	+			+	+	+	+	+	+	+

Allocation

Two trials had a low risk of selection bias (Umpierrez 2011; Umpierrez 2013), and six trials did not provide enough information to adequately judge selection bias (Datta 2007; Gustafson 2002; Korytkowski 2009; Said 2013; Schroeder 2012; Umpierrez 2007a).

Blinding

The majority of trials showed a high risk of performance and detection bias for the outcome measures hypoglycaemic episodes, adverse events other than hypoglycaemic episodes, and mean glucose levels.

Incomplete outcome data

We rated all trials as at low risk of attrition bias if all data for the associated outcome measures were reported. Umpierrez 2011 excluded 10% of randomised participants from the analysis, and

Umpierrez 2013 excluded 6% of randomised participants from the analysis (for details see Table 1).

Selective reporting

We rated one trial as at high risk of reporting bias (Schroeder 2012).

Other potential sources of bias

We rated one trial as at unclear risk of other bias because it did not use adequate statistical analyses for its cluster-randomised design (Schroeder 2012).

Effects of interventions

See: [Summary of findings for the main comparison Sliding scale insulin compared to basal-bolus insulin for non-critically ill hospitalised adults with diabetes mellitus](#)

Most trials compared an SSI regimen with a basal-bolus insulin regimen (Korytkowski 2009; Said 2013; Schroeder 2012; Umpierrez 2007a; Umpierrez 2011; Umpierrez 2013). Three of these trials, investigating 64% of all participants for this comparison, also applied the SSI approach in the bolus comparator part (Korytkowski 2009; Umpierrez 2007a; Umpierrez 2013), thus essentially reducing the comparison to the evaluation of additional basal insulin administration. Umpierrez 2013 had a second comparator arm ("basal-plus"), which did not differ in a clinically relevant way from the basal-bolus arm of the trial. We used only the results of the basal-bolus comparator part of this trial in our review.

Baseline characteristics

For details of baseline characteristics, see Appendix 4 and Appendix 5.

SSI versus basal-bolus insulin

Primary outcomes

All-cause mortality

Four trials reported data on death (Said 2013; Umpierrez 2007a; Umpierrez 2011; Umpierrez 2013). One of 268 participants in the SSI group (0.3%) compared with two of 334 participants in the basal-bolus group (0.6%) died (Peto odds ratio 0.50, 95% confidence interval (CI) 0.05 to 4.85; 4 trials; 602 participants; low-certainty evidence; Analysis 1.1).

Diabetes-related mortality

No trial reported on diabetes-related mortality.

Hypoglycaemic episodes

Non-severe hypoglycaemia

Non-severe hypoglycaemia was usually defined by trial authors as a blood glucose level below 60 mg/dL (3.3 mmol/L) or 70 mg/dL (3.9 mmol/L). Schroeder 2012 reported that "no significant difference was noted in hypoglycaemic rates (blood glucose level below 70 mg/dL) between the two groups ($P = 0.6$)". Korytkowski 2009 reported hypoglycaemia frequency as the percentage of patient-days with one or more event (SSI compared with basal-bolus insulin: 4.8 days versus 2.7 days, with $P = 0.34$) and percentage of all glucose values less than 3.9 mmol/L (70 mg/dL) (SSI compared with basal-bolus insulin: 1.1 blood glucose measures versus 1.3 blood glucose measures, $P = 0.35$).

The risk ratio (RR) for non-severe hypoglycaemic episodes comparing SSI with basal-bolus insulin was 0.25 (95% CI 0.11 to 0.59 in favour of SSI; $P = 0.001$; 3 trials; 561 participants; Analysis 1.2). Overall, nine non-severe hypoglycaemic episodes occurred in 246 participants on SSI (3.7%) compared with 49 non-severe hypoglycaemic episodes in 315 participants on basal-bolus insulin (15.6%). Calculation of the 95% prediction interval did not reveal a meaningful interval. Performance bias and detection bias were high in the majority of the included trials reporting this outcome.

Comparing the subgroup of medical with surgical inpatients did not show a statistically significant interaction effect of subgroup differences. There were not enough data to analyse the other prespecified subgroups.

Severe hypoglycaemia

Five trials reported on severe hypoglycaemic episodes (Said 2013; Schroeder 2012; Umpierrez 2007a; Umpierrez 2011; Umpierrez 2013). Severe hypoglycaemia was defined by trial authors as blood glucose levels below 40 mg/dL (2.2 mmol/L), Said 2013; Umpierrez 2007a; Umpierrez 2011; Umpierrez 2013, or as hypoglycaemia requiring intravenous glucose administration (Schroeder 2012). The RR for severe hypoglycaemic episodes comparing SSI with basal-bolus insulin was 0.22 (95% CI 0.05 to 1.00; $P = 0.05$; 5 trials; 667 participants; very low-certainty evidence; Analysis 1.3). All nine severe hypoglycaemic episodes were observed among the 369 participants on basal-bolus insulin (2.4%). The 95% prediction interval ranged between 0.02 and 2.57. The fixed-effect model showed a RR of 0.20 (95% CI 0.05 to 0.87). Elimination of the cluster RCT, Schroeder 2012, showed a statistically non-significant effect estimate for both the random-effects and the fixed-effect model (RR 0.22, 95% CI 0.04 to 1.24 and RR 0.20, 95% CI 0.04 to 1.03, respectively). Performance bias and detection bias were high in the majority of the included trials reporting this outcome.

Secondary outcomes

Length of hospital stay

Six trials reported data on length of hospital stay (Korytkowski 2009; Said 2013; Schroeder 2012; Umpierrez 2007a; Umpierrez 2011; Umpierrez 2013). The mean length of hospital stay ranged across basal-bolus groups from 5.3 days to 24.2 days. The mean length of hospital stay in the SSI groups was 0.5 days longer (95% CI -0.5 to 1.4; $P = 0.32$; 6 trials; 717 participants; very low-certainty evidence; Analysis 1.4). The 95% prediction interval ranged between -1.7 days and 2.7 days. Elimination of the cluster RCT, Schroeder 2012, showed a mean difference between intervention and comparator groups of -0.06 days (95% CI -0.91 to 0.80).

Comparing the subgroup of medical with surgical inpatients did not show a statistically significant interaction effect of subgroup differences. There were not enough data to analyse the other prespecified subgroups.

Adverse events other than hypoglycaemic episodes (such as postoperative infections)

Four trials reported on adverse events other than hypoglycaemic episodes (Korytkowski 2009; Schroeder 2012; Umpierrez 2011; Umpierrez 2013).

Schroeder 2012 reported that "there was no difference in the postoperative complications between the groups. No difference in operative-related and unrelated complications between groups was noted".

The RR for postoperative complications comparing SSI with basal-bolus insulin was 1.16 (95% CI 0.25 to 5.37; $P = 0.85$; 3 trials; 481 participants; very low-certainty evidence; Analysis 1.5). Overall, 20 complications among 206 participants on SSI (9.7%) occurred compared with 17 complications among 275 participants on basal-bolus insulin (6.2%). Calculation of the 95% prediction interval did not reveal a meaningful interval. Performance bias and detection bias were high in the majority of the included trials reporting this outcome, and selection bias was high for Schroeder 2012.

Mean blood glucose levels

Six trials reported on mean glucose level during hospital stay (Korytkowski 2009; Said 2013; Schroeder 2012; Umpierrez 2007a; Umpierrez 2011; Umpierrez 2013). The mean blood glucose level ranged across basal-bolus groups from 156 mg/dL (8.7 mmol/L) to 221 mg/dL (12.3 mmol/L). The mean blood glucose level in the SSI groups was 14.8 mg/dL (0.8 mmol/L) higher (95% CI 7.8 (0.4) to 21.8 (1.2); $P < 0.001$; 6 trials; 717 participants; low-certainty evidence; Analysis 1.6). The 95% prediction interval ranged between -3.6 mg/dL (-0.2 mmol/L) and 33.2 mg/dL (1.8 mmol/L). The cluster RCT, Schroeder 2012, did not have a substantial impact on the effect size (data not shown).

Comparing the subgroup of medical with surgical inpatients did not show a statistically significant interaction effect of subgroup differences. There were not enough data to analyse the other prespecified subgroups.

Four trials reported on hyperglycaemia, which was variably defined (Datta 2007; Said 2013; Umpierrez 2007a; Umpierrez 2011). Datta 2007 reported that 16% of SSI-treated participants compared with 6% of basal-bolus insulin-treated participants had blood glucose levels greater than 200 mg/dL. Said 2013 reported that 68% of SSI-treated participants compared to 53% of basal-bolus insulin-treated participants had blood glucose levels greater than 300 mg/dL. Blood glucose levels greater than 240 mg/dL were reported in 9% of SSI-treated participants in Umpierrez 2007a and in 12% of SSI-treated participants in Umpierrez 2011.

All trials reported that the mean total daily dose of insulin in the basal-bolus group was greater than in the SSI group.

Socioeconomic effects

No trial reported on socioeconomic effects.

SSI versus basal insulin

Only one trial compared an SSI regimen with a basal insulin regimen (Datta 2007). This trial, which involved 81 participants, did not provide information on all-cause mortality, diabetes-related mortality, or socioeconomic effects. One of 39 participants in the SSI group (2.6%) compared with two of 42 participants in the basal insulin group (4.8%) reported a non-severe hypoglycaemic episode (Analysis 2.1). Mean length of hospital stay was the same in both the intervention and the comparator group (3.8 days; Analysis 2.2). Adverse events other than hypoglycaemic episodes (postoperative infections) were reported in two participants in both the intervention and the comparator group (Analysis 2.3). The mean blood glucose level in the SSI group was 20 mg/dL higher than in the basal insulin group (Analysis 2.4).

One trial compared SSI with a continuous insulin infusion during coronary artery bypass surgery in 50 participants (Gustafson 2002). The only outcome measure of relevance for this review was mean blood glucose levels, which were 110 mg/dL less in the post-cardiopulmonary bypass period in the SSI group compared with the continuous insulin infusion group (Analysis 3.1). There was also a difference in the cardioplegic solution between the groups: the continuous insulin infusion group received a dextrose 5%-based cardioplegic solution, and the SSI group received normal 0.9% saline, limiting the interpretation of the results of this trial.

Subgroup analyses

With the exception of medical versus surgical inpatients for some outcome measures, we did not perform subgroup analyses as data were insufficient to estimate effects in various subgroups.

Sensitivity analyses

With the exception of comparing the random-effects model with the fixed-effect model for some outcome measures, we did not perform sensitivity analyses due to insufficient data.

Assessment of reporting bias

We did not draw funnel plots due to the limited number of trials ($N = 8$).

Ongoing studies

We found one ongoing trial, NCT01143948, and two trials awaiting classification, IRCT201311118307N2; ISRCTN55845280 (for details see Characteristics of ongoing studies and Characteristics of studies awaiting classification sections).

The ongoing trial is investigating an SSI regimen compared with a basal-bolus insulin regimen in approximately 45 participants with type 2 diabetes and liver cirrhosis.

Two trials awaiting classification, with a total of approximately 320 participants, compared an SSI regimen with a basal-bolus insulin regimen in diabetic people with cardiovascular diseases and diabetic people with acute medical and surgical conditions.

DISCUSSION

Summary of main results

This systematic review analysed the evidence from published RCTs of SSI therapy for the treatment of non-critically ill adults with diabetes mellitus. We included eight trials randomising 1048 participants with type 2 diabetes. The main comparison with SSI was basal-bolus insulin therapy. A basal-bolus insulin strategy might result in better short-term glycaemic control, but might also result in an increase in severe hypoglycaemic episodes. We are uncertain about the effects of SSI and basal-bolus insulin on length of hospital stay, postoperative complications, and mean blood glucose levels. No studies reported on diabetes-related mortality or socioeconomic effects.

Overall completeness and applicability of evidence

Most trials analysed in our review were conducted in the USA, and younger adult diabetic participants were underrepresented in the trials. Our inclusion criteria specified surgical and medical patients, and both were represented, reflecting the general practice in the non-critical hospital environment. However, most trials did not include people with newly diagnosed diabetes, people who were treated with insulin before hospitalisation, or people on corticosteroid therapy, who all form an important part of the hospitalised population with hyperglycaemia. The total daily dose of insulin was lower in the SSI groups compared with the basal-bolus insulin groups, probably reflecting that the SSI regimen on admission remained unchanged throughout the hospitalisation period. It is therefore unclear whether the results of this review are associated with the SSI regimen per se or a suboptimal insulin

dosing in the SSI intervention groups, which might be an attribute of the rigid SSI treatment approach.

Quality of the evidence

We assessed the certainty of the evidence as low to very low mainly because of trial limitations (especially performance bias and detection bias), imprecision (low number of participants and trials, wide prediction intervals), and inconsistency (non-consistent direction of effects) for most of the outcome measures.

Potential biases in the review process

We attempted to contact the trial authors to obtain additional information ([Appendix 13](#)), as well as information about potential admissions of non-critically ill participants to intensive care units, but did not receive an answer from the authors of three included trials. We therefore cannot exclude the possibility that in some trials some participants were also treated in critical care. Furthermore, we did not systematically search the grey literature.

Agreements and disagreements with other studies or reviews

Lee 2015 published a meta-analysis of SSI treatment for blood glucose control. The review authors included 11 trials in their meta-analysis but did not discriminate between critical and non-critical care participants. [Gómez Cuervo 2016](#) published a meta-analysis of adverse events related to basal-bolus insulin therapy compared with SSI. The review authors included five trials combining observational studies and RCTs in their meta-analysis. [Christensen 2017](#) published a meta-analysis of basal-bolus insulin regimens compared to other insulin regimens. The review authors included five trials using basal-bolus insulin as the main intervention in their meta-analysis. The overall results of these reviews were similar to our results, indicating that SSI therapy resulted in lower hypoglycaemia rates and higher mean glucose levels compared with non-SSI therapies.

AUTHORS' CONCLUSIONS

Implications for practice

Based on low- to very low-certainty evidence, our results for non-critically ill hospitalised adults with diabetes mellitus in the medical and surgical in-hospital setting showed that a basal-bolus insulin strategy that applied higher total daily doses of insulin than the sliding scale insulin regimen might result in better short-term glycaemic control but might also cause an increase in severe hypoglycaemic episodes. We are uncertain whether sliding scale insulin increases or decreases mortality, length of hospital stay, and adverse events other than hypoglycaemic episodes (such as infectious complications).

Implications for research

Future randomised controlled trials should adequately define the clinical conditions of hospitalised people with diabetes mellitus and the associated appropriate treatment choice. Multinational trials would improve the external validity of trial results. There is a need for adequately performed, well-powered randomised controlled trials in different hospital environments with well-educated medical staff. Identical short-acting insulins in both intervention and comparator arms should be used to compare the rigid sliding scale insulin approach with flexible insulin application strategies.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Datta 2007

Methods	Parallel randomised controlled trial

Datta 2007 (Continued)

Participants	<p>Inclusion criteria: patients who underwent bariatric surgical procedure, Roux-en-Y gastric bypass, between 21 to 60 years old, glucose level of more than 144 mg/dL, measured postoperatively in the recovery unit</p> <p>Exclusion criteria: not described</p> <p>Diagnostic criteria: medical history of diabetes and blood glucose levels exceeding 144 mg/dL, measured postoperatively in the recovery unit</p> <p>Setting: hospital</p> <p>Age group: adults</p> <p>Gender distribution: females and males</p> <p>Country where trial was performed: USA</p>
Interventions	<p>Treatment before study: insulin, sulphonylurea, metformin, and thiazolidinedione</p> <p>Titration period: none</p> <p>Intervention: sliding scale insulin: BG level measured every 6 hours, and participants were given a pre-determined SC dose of regular insulin based on the current BG level, as follows: less than 140 mg/dL, no insulin; between 140 and 160 mg/dL, 4 U; between 161 and 180 mg/dL, 6 U; between 181 and 200 mg/dL, 8 U; between 201 and 220 mg/dL, 10 U; and 221 mg/dL or more, 12 U.</p> <p>Comparator: basal insulin, initial dose of 0.3 U of insulin glargine per kg of body weight. Blood glucose was monitored every 6 hours thereafter by point-of-care reflectance meters. The initial dose of insulin glargine was repeated every 24 hours as long as the BG level remained between 80 and 140 mg/dL. If the BG level was between 140 and 180 mg/dL, the next dose of insulin glargine was increased by 30%; if the glucose level was more than 180 mg/dL, the next dose of insulin glargine was increased by 60%. All BG values greater than 200 mg/dL were also treated with an additional compensatory dose of SC regular insulin equal to 25% of the previous dose of insulin glargine.</p> <p>Duration of intervention: 4 days</p> <p>Duration of follow-up: 30 days</p> <p>Number of study centres: 1</p> <p>Run-in period: no description</p>
Outcomes	<p>Outcomes reported in abstract of publication: mean blood glucose levels (postoperative hyperglycaemia)</p>
Study registration	<p>Trial identifier: N/T</p> <p>Trial terminated early: no</p>
Publication details	<p>Language of publication: English</p> <p>Commercial funding: Sanofi-Aventis</p> <p>Publication status: peer review journal</p>
Stated aim for study	<p>Quote from publication: "We hypothesized that once-daily insulin glargine may be more effective than SSRI in achieving glycaemic control and also may be safer (that is, associated with less chance of occurrence of hypoglycaemia)"</p>
Notes	-
Risk of bias	

Datta 2007 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "Patients were randomised to receive insulin glargine or SSRI" Comment: no further description, page 226, "study protocol" and no more information provided by the authors
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) Non-severe hypoglycaemic episodes	High risk	Quote from publication: "Treatment was not blinded" Comment: treatment was not blinded, outcome likely affected by lack of blinding techniques
Blinding of participants and personnel (performance bias) Length of hospital stay	Low risk	Comment: treatment was not blinded, outcome unlikely to be affected by lack of blinding
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemic episodes	High risk	Quote from publication: "Treatment was not blinded" Comment: treatment was not blinded, outcome likely affected by lack of blinding techniques
Blinding of participants and personnel (performance bias) Mean glucose level	High risk	Quote from publication: "Treatment was not blinded" Comment: treatment was not blinded, outcome likely affected by lack of blinding techniques
Blinding of participants and personnel (performance bias) Severe hypoglycaemic episodes	High risk	Quote from publication: "Treatment was not blinded" Comment: treatment was not blinded, outcome likely affected by lack of blinding techniques
Blinding of outcome assessment (detection bias) Severe hypoglycaemic episodes	High risk	Comment: outcome assessor not reported, treatment was not blinded, outcome likely affected by lack of blinding techniques
Blinding of outcome assessment (detection bias) Non-severe hypoglycaemic episodes	High risk	Comment: outcome assessor not reported, treatment was not blinded, outcome likely affected by lack of blinding techniques
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Comment: outcome not reported, outcome not likely to have been influenced by blinding
Blinding of outcome assessment (detection bias) Adverse events other than hypoglycaemia	High risk	Comment: outcome assessor not reported, treatment was not blinded, outcome likely affected by lack of blinding techniques
Blinding of outcome assessment (detection bias)	High risk	Comment: outcome assessor not reported, treatment was not blinded, outcome likely affected by lack of blinding techniques

Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus (Review)

24

Datta 2007 (Continued)

Mean glucose level

Incomplete outcome data (attrition bias) Severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Non-severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Mean glucose level	Low risk	Comment: no missing data
Selective reporting (reporting bias)	Low risk	Comment: the study protocol was not available, no ORBIT criteria detected
Other bias	Low risk	Comment: none detected

Gustafson 2002

Methods	Parallel randomised controlled trial
Participants	<p>Inclusion criteria: patients diagnosed with diabetes mellitus type 2 undergoing coronary artery bypass surgery</p> <p>Exclusion criteria: not described</p> <p>Diagnostic criteria: medical history of diabetes</p> <p>Setting: hospital</p> <p>Age group: elderly people</p> <p>Gender distribution: females and males</p> <p>Country where trial was performed: USA</p>
Interventions	<p>Intervention: sliding scale insulin plus saline-based cardioplegic solution. Mix 50 U of regular human insulin in 100 cm³ of normal saline (concentration is 0.5 U = 1 cm³) 200 to 250 mg/dL 10 IU insulin, 251 to 300 mg/dL 15 IU insulin, 301 to 350 mg/dL 20 IU insulin, 351 to 400 mg/dL 25 IU insulin, 401 to 500 mg/dL 30 IU insulin, > 501 mg/dL 35 IU insulin</p> <p>Comparator: continuous insulin infusion plus 5% dextrose-based cardioplegic solution</p> <p>Maintenance of the insulin infusion:</p>

Gustafson 2002 (Continued)

1. For glucose < 80 mg/dL give 25 cm³ 50% dextrose IV. ii. Reduce infusion by 1 U/h (= 2 cm³); for glucose < 80 mg/dL x 2 consecutive times, reduce by 1/2 current rate. iii. Check glucose every 15 min until glucose 80 mg/dL then resume hourly monitoring. iv. Resume infusion when glucose is > 180 mg/dL. Begin at 0.5 U/h and check glucose in 1 hour
2. For glucoses 80 to 120 mg/dL reduce infusion by 0.5 U and check glucose hourly
3. For glucoses 121 to 180 mg/dL keep infusion rate the same and check glucose hourly: i. If glucose remains in this range x 2 then check glucose every 2 hours. ii. If again glucose remains in this range x 2, then check glucose in 4 hours
4. For glucose > 180 mg/dL. i. Glucose did not decrease since last checked, increase infusion by 0.5 U/h (= 1 cm³). ii. Glucose did decrease since last checked, keep infusion rate the same. iii. Check glucose hourly
5. For glucose > 250 mg/dL during open-heart surgery, adjust insulin infusion rate to 0.1 U/kg per hour and continue to maintain as in steps iii 1-4
6. Stop infusion if tube feeding or meal is stopped at any time and check glucose hourly, then resume insulin infusion when glucose is > 180 mg/dL. Begin infusion at 0.5 U/h (= 1 cm³) and follow maintenance of the insulin infusion (step iii)

Duration of intervention: 1 day

Duration of follow-up: 1 day

Run-in period: not reported

Number of study centres: 1

Treatment before study: not reported

Outcomes	Outcomes reported in abstract of publication: blood glucose levels
Study registration	Trial identifier: N/T Study terminated early: no
Publication details	Language of publication: English Funding: not reported Publication status: peer review journal
Stated aim for study	"Continuous insulin infusion was not an effective mode of treatment in maintaining safe blood glucose levels (< 200 mg/dL) during the intraoperative period of diabetic patients requiring open-heart surgery. The two modifications investigated to gain better control of the blood glucose were a change in the base solution of the cardioplegia and the use of a sliding insulin scale"
Notes	Trial was conducted in a coronary unit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "The patients were then randomly divided into two groups" (abstract section) Comment: insufficient detail
Incomplete outcome data (attrition bias) Mean glucose level	Low risk	Comment: no missing data

Gustafson 2002 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: the study protocol was not available, no ORBIT criteria detected
Other bias	Low risk	Comment: none detected

Korytkowski 2009

Methods	Parallel randomised controlled trial
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Type 2 diabetes defined according to ADA criteria • Enterally nutrition therapy • 2 blood glucose readings > 130 mg/dL within 48 hours prior to or within a 48-hour period during enterally nutrition therapy • Men and women age 18 years or older • Ability for patient or legally authorised representative to understand and sign an informed consent document <p>Exclusion criteria</p> <ul style="list-style-type: none"> • People who are anticipated to have short term (i.e. < 2 months) survival based on discussions with the treatment team and attending physician • People admitted to the cardiothoracic intensive care unit or any unit with pre-established protocols for glycaemic management • People with known type 1 diabetes (who will absolutely require a long- or intermediate-acting insulin preparation) • People with known type 2 diabetes who currently receive 30 units or more of an intermediate- or long-acting insulin • Pregnancy <p>Diagnostic criteria: medical history of diabetes (2 or more blood glucose measurements > 7.2 mmol/L during enteral nutrition therapy)</p> <p>Setting: hospital</p> <p>Age group: adults/elderly people</p> <p>Gender distribution: females and males</p> <p>Country where trial was performed: USA</p>
Interventions	<p>Information provided in the online appendix</p> <p>Regular insulin sliding scale - standard orders</p> <p><u>Recommended indications:</u></p> <ul style="list-style-type: none"> • As a <u>supplement</u> to a participant's usual diabetes medications (long-acting insulin or oral agents) to treat uncontrolled high blood sugars • For short-term use (24 to 48 hours) in a participant admitted with an unknown insulin requirement <p><u>Regimens:</u></p> <ul style="list-style-type: none"> • Low-dose scale: suggested starting point for thin and elderly, or those being initiated on TPN. Insulin dose starts with 2 IU from 130 mg/dL BG, with a change in dose by 50 mg/dL BG increase, max dose 12 IU.

Korytkowski 2009 (Continued)

- **Moderate-dose scale:** suggested starting point for average patient. Insulin dose starts with 4 IU from 130 mg/dL BG, with a change in dose by 50 mg/dL BG increase, exchanging from 4 IU to 2 IU, max dose 20 IU.
- **High-dose scale:** suggested for patients with infections or those receiving therapy with high-dose corticosteroids. Insulin dose starts with 8 IU from 130 mg/dL BG, with a change in dose by 50 mg/dL BG increase of 4 IU, max dose 28 IU.

Intervention: treatment algorithm (Appendix C) glargine group: BG > 7.2 mmol/L (130 mg/dL) x 1:

Start glargine 10 units once a day with SSRI

If ≥ 2 BG > 10 mmol/L (180 mg/dL) add 50% of SSRI given in previous 24 hours to glargine dose; or if ≤ 1 BG > 10 mmol/L (180 mg/dL) or all BG 3.9 to 10 mmol/L (70 to 180 mg/dL) with ≤ 20 units SSRI per day continue current regimen

Comparator: treatment algorithm (Appendix B) if BG > 7.2 mmol/L (130 mg/dL) x 2:

Start low-dose SSRI, then participants were divided into the following 2 strategies

- If > 2 BG > 10 mmol/L (180 mg/dL) (low-dose SSRI from every 6 to every 4 hours for 24 to 36 hours); if ≥ 2 BG > 10 mmol/L (180 mg/dL) advance to moderate-dose SSRI for 24 to 36 hours; if > 2 BG > 10 mmol/L (180 mg/dL) advance to high-dose SSRI for 24 to 36 hours; and if > 2 BG > 10 mmol/L (180 mg/dL) start NPH insulin every 12 hours continuously or once daily; calculate total daily dose as 50% prior day total regular insulin dose. If > 2 BG > 10 mmol/L (180 mg/dL) increase NPH by adding 50% of SSRI required in prior 24 hours or if ≤ 1 BG > 10 mmol/L (180 mg/dL) or all BG 3.9 to 10 mmol/L (70 to 180 mg/dL) continue current regimen.
- If ≤ 1 BG > 10 mmol/L (180 mg/dL) or all BG 3.9 to 10 mmol/L (70 to 180 mg/dL), decision was to continue current regimen

Duration of intervention: 8 days

Duration of follow-up: 23 days

Run-in period: February 2005 to August 2006

Number of study centres: 1

Treatment before study: not reported

Titration period: none

Outcomes	Outcomes reported in abstract of publication: glycaemic control (mean glucose levels), frequency of hypoglycaemia, total adverse events, length of stay
Study registration	Trial identifier: ClinicalTrials.gov: NCT00177398 Study terminated early: no
Publication details	Language of publication: English (Commercial and non-commercial) funding: Sanofi-Aventis, University of Pittsburgh Publication status: peer review journal
Stated aim for study	Quote from publication: "The purpose of this study is to determine if the early initiation of a long acting insulin (i.e. glargine) with supplemental doses of short acting regular (SSR) insulin in hospitalised people with diabetes who are fed using tube feedings reduces the frequency of high and low blood sugar levels when compared to use of SSR insulin alone"
Notes	Some data were extracted from ClinicalTrials.gov
Risk of bias	

Korytkowski 2009 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "Randomized clinical trial" Comment: insufficient detail
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient detail
Blinding of participants and personnel (performance bias) Non-severe hypoglycaemic episodes	High risk	Quote from publication: "open label" Comment: outcome likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Length of hospital stay	Low risk	Comment: open-label trial, outcome unlikely to be influenced by blinding
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemic episodes	High risk	Quote from publication: "open label" Comment: outcome likely influenced by lack of blinding techniques
Blinding of participants and personnel (performance bias) Mean glucose level	High risk	Quote from publication: "open label" Comment: outcome influenced by lack of blinding techniques
Blinding of participants and personnel (performance bias) Severe hypoglycaemic episodes	High risk	Quote from publication: "open label" Comment: outcome likely influenced by lack of blinding techniques
Blinding of outcome assessment (detection bias) Severe hypoglycaemic episodes	High risk	Quote from publication: "open label" Comment: outcome likely influenced by lack of blinding techniques
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Comment: outcome assessor not reported, outcome unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) Severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Non-severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	Comment: no missing data

Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus (Review)

Korytkowski 2009 (Continued)

Incomplete outcome data (attrition bias) Adverse events other than hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Mean glucose level	Low risk	Comment: no missing data
Selective reporting (reporting bias)	Low risk	Comment: not detected by ORBIT criteria
Other bias	Low risk	Comment: not detected

Said 2013

Methods	Parallel randomised controlled trial
Participants	<p>Inclusion criteria: non-surgical patients, 18 to 64 years old with a known history of type 2 DM for longer than 3 months admitted to general medicine wards</p> <p>Exclusion criteria: hyperglycaemia without any known history of DM, presence of diabetic ketoacidosis, patients admitted to intensive care unit or undergoing surgery during their hospitalisation, patients with relevant hepatic disease, impaired renal function (serum creatinine > 3.0 mg/dL), systemic infections, or pregnancy, and patients on medication known to interfere with blood glucose level</p> <p>Diagnostic criteria: known history of type 2 DM</p> <p>Setting: hospital</p> <p>Age group: adults</p> <p>Gender distribution: females and males</p> <p>Country where trial was performed: Egypt</p>
Interventions	<p>Intervention: Basal-bolus scheme</p> <p>Glargine</p> <ul style="list-style-type: none"> Patients treated with diet or oral agents before admission: hold oral antidiabetic drugs on admission, starting glargine insulin dose: 0.2 U/kg/day for admission BG ≤ 200 mg/dL or 0.3 U/kg/day for BG exceeding 200 mg/dL Patients treated with insulin before admission: glargine/glulisine-treated patients should be started at half amount of the total outpatient insulin dose as glargine <p>Glulisine</p> <ul style="list-style-type: none"> Give glulisine 3 times before each meal for BG ≥ 150 mg/dL according to scale provided as SSI. Hold glulisine if a patient is not able to eat to prevent hypoglycaemia. Premixed 70/30 + regular scheme Patients treated with diet or oral agents before admission: hold oral antidiabetic drugs on admission. Starting premixed 70/30 insulin dose: 0.2 U/kg/day for admission BG ≤ 200 mg/dL or 0.4 U/kg/day for BG exceeding 200 mg/dL Patients treated with insulin before admission: premixed 70/30 insulin-treated patients should be started at the same outpatient insulin dose and schedule <p>In both cases: give 2/3 of TDD before breakfast and 1/3 of TDD before dinner</p>

Said 2013 (Continued)

Supplemental insulin (regular insulin) given as SSI protocol

Insulin adjustment

- If fasting and pre-meal blood glucose is < 150 mg/dL (in the absence of hypoglycaemia): no change
- If fasting and pre-meal blood glucose is between 150 and 180 mg/dL (in the absence of hypoglycaemia): increase the TDD of 70/30 insulin or glargine by 10% every day
- If fasting and pre-meal blood glucose is > 180 mg/dL (in the absence of hypoglycaemia): increase the TDD of 70/30 insulin or glargine dose by 20%
- If a patient develops hypoglycaemia (< 60 mg/dL): decrease the TDD of 70/30 insulin or glargine insulin dose by 20%
- The distribution of 70/30 insulin doses followed the 2/3 a.m. and 1/3 p.m. scheme

Comparator: sliding scale insulin protocol: BG (mg/dL) < 150 mg/dL = no insulin, 151 to 200 mg/dL = 5 IU, 201 to 250 mg/dL = 10 IU, 251 to 300 mg/dL = 15 IU, 301 to 350 mg/dL = 20 IU, 351 to 400 mg/dL = 25 IU, and > 400 mg/dL = 30 IU and call the internal medicine resident

Duration of intervention: 6 days, 4 days, 5 days

Duration of follow-up: 8 days, 62 days, 72 days

Run-in period: March 2010 to May 2013

Number of study centres: 1

Treatment before study: insulin plus oral antidiabetic agents, oral antidiabetic agent as monotherapy, multiple oral antidiabetic agents and non-pharmacological agent

Titration period: none

Outcomes	<p>Primary outcome: glycaemic control by mean daily BG concentration during participant hospital stay</p> <p>Secondary outcomes: hypoglycaemic events, length of hospital stay, and mortality rate</p>
Study registration	<p>Trial identifier: NCT01855243</p> <p>Study terminated early: no</p>
Publication details	<p>Language of publication: English</p> <p>Funding: Cairo University</p> <p>Publication status: peer review journal</p>
Stated aim for study	To compare efficacy and safety of traditional sliding scale insulin versus modified 70/30 insulin versus modified basal-plus supplemental scale/bolus insulin regimens for glycaemic control in hospitalised diabetic patients
Notes	Some data were extracted from ClinicalTrials.gov

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote from publication: "open-label parallel, randomized study"</p> <p>Comment: insufficient detail</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no description</p>

Said 2013 (Continued)

Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	Comment: no events, outcome unlikely to be affected by lack of blinding
Blinding of participants and personnel (performance bias) Non-severe hypoglycaemic episodes	High risk	Comment: open-label, outcome likely affected by lack of blinding techniques
Blinding of participants and personnel (performance bias) Length of hospital stay	Low risk	Comment: outcome unlikely to be affected by lack of blinding
Blinding of participants and personnel (performance bias) Mean glucose level	High risk	Comment: open-label, outcome likely affected by lack of blinding techniques
Blinding of participants and personnel (performance bias) Severe hypoglycaemic episodes	High risk	Comment: open-label, outcome likely affected by lack of blinding techniques
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Comment: no events, outcome not likely to be affected by potential lack of blinding
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Comment: not reported, outcome unlikely to be affected by potential lack of blinding
Incomplete outcome data (attrition bias) Severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	Comment: no events
Incomplete outcome data (attrition bias) Non-severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Mean glucose level	Low risk	Comment: no missing data

Said 2013 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: not detected
Other bias	Low risk	Comment: not detected

Schroeder 2012

Methods	Cluster-randomised controlled trial (2 orthopaedic wards)
Participants	<p>Inclusion criteria: diabetes or hyperglycaemia, admitted to the orthopaedic surgery department</p> <p>Exclusion criteria: no description</p> <p>Diagnostic criteria: all individuals with previously diagnosed diabetes or suffering from recurrent hyperglycaemia (2 or more measurements of blood glucose levels > 180 mg/dL)</p> <p>Setting: hospital</p> <p>Age group: adults</p> <p>Gender distribution: females and males</p> <p>Country where trial was performed: Israel</p>
Interventions	<p>Intervention(s): sliding scale insulin (Actrapid)</p> <p>Regular insulin was given according to participant's blood glucose level (i.e. for levels between 150 mg and 200 mg of blood glucose, 4 units of short-acting human insulin (Actrapid) were given; for each 50 mg increase in blood glucose levels, 2 more units of insulin were added).</p> <p>Comparator(s): basal-bolus insulin</p> <p>The initial total daily dose of insulin was 0.25 U/kg body weight divided equally between 4 doses, unless the participant was on a higher insulin dose prior to admission. Regular insulin was administered 3 times per day before each meal, and NPH was given once daily at 10:00 p.m.</p> <p>Duration of intervention: 7 days</p> <p>Duration of follow-up: 7 days</p> <p>Run-in period: October 2007 to March 2008</p> <p>Number of study centres: 1</p> <p>Treatment before study: not reported</p> <p>Titration period: none</p>
Outcomes	Outcomes reported in abstract of publication: mean blood glucose levels during hospitalisation, percentage of glucose measurements > 400 mg/dL, the daily difference between the mean levels in both departments, and the frequency of hypoglycaemic episodes (blood glucose level < 70 mg/dL)
Study registration	<p>Trial identifier: N/T</p> <p>Study terminated before regular end: no</p>
Publication details	<p>Language of publication: English</p> <p>Funding: none stated</p>

Schroeder 2012 (Continued)

Publication status: peer review journal

Stated aim for study	Quote from publication: "We performed a randomised controlled prospective study to test the efficacy and safety of this intervention and the ability to maintain glucose levels in the desired range as a result of the treatment protocol"
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "We performed a randomized controlled prospective study" Comment: insufficient detail
Allocation concealment (selection bias)	Unclear risk	Comment: no details
Blinding of participants and personnel (performance bias) Non-severe hypoglycaemic episodes	High risk	Quote from publication: "The first two steps were to introduce the concept of intensive glucose monitoring to both the physicians and nurses in the orthopaedic department and appoint one of the nurses as a 'diabetes' nurse; the third step was to implement a scheduled predetermined basal bolus insulin regimen for all uncontrolled diabetic patients (blood glucose levels > 200 mg/dL on two or more tests)." Comment: no description, cluster design (possible recruitment bias), outcome likely affected by lack of blinding
Blinding of participants and personnel (performance bias) Length of hospital stay	Low risk	Comment: outcome unlikely to be affected by lack of blinding
Blinding of participants and personnel (performance bias) Mean glucose level	High risk	Comment: no description, cluster design (personnel not blinded - training session about the intervention), outcome likely affected by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemic episodes	High risk	Comment: no description, cluster design (possible recruitment bias), outcome likely affected by lack of blinding
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Comment: not reported, outcome unlikely to be influenced by potential lack of blinding
Incomplete outcome data (attrition bias) Severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Non-severe hypoglycaemic episodes	Low risk	Comment: no missing data

Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus (Review)

34

Schroeder 2012 (Continued)

Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Mean glucose level	Low risk	Comment: no missing data
Selective reporting (reporting bias)	High risk	Quote from publication: "There was no difference in the postoperative complications between the groups". No difference in operative-related and -unrelated complications between groups was noted. Comment: clear that outcome was measured and analysed; trial report states that outcome was analysed, but reports only that result was not significant
Other bias	Unclear risk	Comment: lack of detail related to the cluster design (possibility of incorrect analysis)

Umpierrez 2007a

Methods	Parallel randomised controlled trial
Participants	<p>Inclusion criteria: non-surgical, insulin-naïve people with a known history of diabetes for 3 months, aged 18 to 80 years, and admitted to medical general services with a blood glucose level between 140 mg/dL and 400 mg/dL. Diabetes treatment with either diet alone or any combination of oral antidiabetic agents and the absence of diabetic ketoacidosis</p> <p>Exclusion criteria: people without a known history of diabetes, intensive care unit patients, the use of corticosteroid therapy, patients expected to undergo surgery during the hospitalisation course, people with clinically relevant hepatic disease, serum creatinine 3.0 mg/dL, pregnancy, and any mental condition rendering the person unable to understand the scope and possible consequences of the study</p> <p>Diagnostic criteria: medical history of diabetes and with a blood glucose level between 140 and 400 mg/dL</p> <p>Setting: hospital</p> <p>Age group: 18 to 80 years</p> <p>Gender distribution: females and males</p> <p>Country where trial was performed: USA</p>
Interventions	<p>Intervention(s): sliding scale insulin</p> <p>Discontinue oral antidiabetic drugs on admission</p> <ul style="list-style-type: none"> • If a participant is able and expected to eat all or most of his/her meals, give regular insulin before each meal and at bedtime, following the "usual" column • If a participant is not able to eat, give regular insulin every 6 hours (6–12–6–12), following the "insulin sensitive" column. Insulin adjustment • If fasting and pre-meal plasma glucose are persistently 140 mg/dL in the absence of hypoglycaemia, increase insulin scale from the "insulin sensitive" to the "usual" column or from the "usual" to the "insulin-resistant" column • If a participant develops hypoglycaemia (blood glucose 70 mg/dL), decrease regular insulin from "insulin-resistant" to "usual" column or from the "usual" to "insulin-sensitive" column. Blood glucose monitoring: measure blood glucose before each meal and at bedtime (or every 6 hours if nothing by mouth)

Umpierrez 2007a (Continued)

Comparator(s): basal bolus insulin (glargine and glulisine)

Discontinue oral antidiabetic drugs on admission

Start total daily insulin dose: 0.4 units/kg body weight day 1 when the admission blood glucose concentration is 140 to 200 mg/dL; 0.5 units/kg body weight day 1 when the admission blood glucose concentration is between 201 and 400 mg/dL.

Give 1/2 of total daily dose as insulin glargine and 1/2 as insulin glulisine

Give insulin glargine once daily at the same time of day

Give insulin glulisine in 3 equally divided doses before each meal. Hold insulin glulisine if participant is not able to eat. Supplemental insulin: give supplemental insulin glulisine following the "sliding-scale" protocol for blood glucose 140 mg/dL

- If a participant is able and expected to eat all or most of his/her meals, give supplemental glulisine insulin before each meal and at bedtime following the "usual" column.
- If a participant is not able to eat, give supplemental glulisine insulin every 6 hours (6–12–6–12), following the "insulin-sensitive" column.
- If the fasting or mean blood glucose during the day is 140 mg/dL in the absence of hypoglycaemia, increase insulin glargine dose by 20% every day.
- If participant develops hypoglycaemia (70 mg/dL), decrease glargine daily dose by 20%. Blood glucose monitoring: measure blood glucose before each meal and at bedtime (or every 6 hours if nothing by mouth).

Duration of intervention: 5 days

Duration of follow-up: 5 days

Run-in period: September 2005 to June 2006

Number of study centres: 1

Treatment before study: no description

Titration period: no description

Outcomes	Outcomes reported: the primary endpoint was to determine differences in glycaemic control between treatment groups as measured by the mean daily blood glucose concentration. Secondary outcomes included differences between treatment groups in number of hypoglycaemic events, number of episodes of severe hyperglycaemia, length of hospital stay, and mortality rate
Study registration	Trial identifier: NCT00394407 Study terminated early: no
Publication details	Language of publication: English (Commercial and non-commercial) funding: Sanofi-Aventis, American Heart Association (0555306B), the National Institutes of Health (R03 DK07319001), and the General Clinical Research Center (M01 RR-00039) Publication status: peer review journal
Stated aim for study	Quote from publication: "This study will compare how well regular insulin will compare to glargine (Lantus) once daily plus glulisine (Apidra) insulin before meals in hospitalised people with type 2 diabetes and elevated blood glucose (sugar) levels. Lantus is a long-acting insulin which is given subcutaneously (under the skin) once daily. Apidra is a rapid-acting insulin which is given subcutaneously several times a day and frequently before meals. Regular insulin is a short-acting insulin in clinical use for more than 20 years that is also given subcutaneously several times per day. Lantus, Apidra and regular insulins are approved for use in the treatment of individuals with diabetes by the FDA"
Notes	-

Umpierrez 2007a (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "In this multicenter, prospective, open-label, randomized study ..." Comment: insufficient detail
Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	Quote from publication: "open-label" Comment: outcome unlikely to be affected by lack of blinding
Blinding of participants and personnel (performance bias) Non-severe hypoglycaemic episodes	High risk	Comment: open-label, outcome likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Length of hospital stay	Low risk	Comment: open-label, outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) Mean glucose level	High risk	Comment: open-label, outcome measure likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemic episodes	High risk	Comment: open-label, outcome likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) Severe hypoglycaemic episodes	High risk	Comment: author reply: "We did not have an independent adjudication board or member in our studies"; outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Comment: author reply: "We did not have an independent adjudication board or member in our studies"; outcome measure unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Non-severe hypoglycaemic episodes	High risk	Comment: author reply: "We did not have an independent adjudication board or member in our studies"; outcome measure likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Comment: author reply: "We did not have an independent adjudication board or member in our studies"; outcome measure unlikely to be influenced by lack of blinding

Umpierrez 2007a (Continued)

Blinding of outcome assessment (detection bias) Mean glucose level	High risk	Comment: author reply: "We did not have an independent adjudication board or member in our studies"; outcome measure likely influenced by lack of blinding
Incomplete outcome data (attrition bias) Severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Non-severe hypoglycaemic episodes	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) Mean glucose level	Low risk	Comment: no missing data
Selective reporting (reporting bias)	Low risk	Comment: none detected by ORBIT criteria
Other bias	Low risk	Comment: none detected.

Umpierrez 2011

Methods	Parallel randomised controlled trial
Participants	<p>Inclusion criteria: general elective or emergency surgery and not expected to require ICU admission were eligible for inclusion. Glucose (BG) level between 140 mg/dL and 400 mg/dL, had a history of diabetes for more than 3 months, aged 18 to 80 years old, treated with diet alone, any combination of oral antidiabetic agents, or low-dose insulin therapy at a daily dose of 0.4 units/kg before admission</p> <p>Exclusion criteria: hyperglycaemia without a known history of diabetes, cardiac surgery, clinically relevant hepatic disease or impaired renal function (serum creatinine > 3.0 mg/dL), history of diabetic ketoacidosis (21), pregnancy, or any mental condition rendering the participant unable to give informed consent</p> <p>Diagnostic criteria: people with a BG level between 140 mg/dL and 400 mg/dL with a history of diabetes mellitus for more than 3 months</p> <p>Setting: hospital</p> <p>Age group: adults</p> <p>Gender distribution: females and males</p> <p>Country where trial was performed: USA</p>
Interventions	Intervention(s): sliding scale insulin

Umpierrez 2011 (Continued)

Participants received 4 times daily for BG 140 mg/dL. The doses of insulin were adjusted according to a prespecified protocol. For participants receiving SSI, if the mean daily BG level was > 240 mg/dL, or if 3 consecutive values were 240 mg/dL on the maximal sliding scale dose, participants were switched to basal-bolus regimen starting at a TDD of 0.5 units/kg

Comparator(s): basal bolus insulin

Participants treated with basal-bolus therapy were started at a TDD of 0.5 units/kg divided half as insulin glargine once daily and the other half as insulin glulisine given before meals. The insulin TDD was reduced to 0.3 units/kg in participants ≥ 70 years of age and/or with a serum creatinine ≥ 2.0 mg/dL

Duration of intervention: 9 days

Duration of follow-up: 9 days

Run-in period: February 2008 to October 2009

Number of study centres: 3

Treatment before study: diet alone, oral agents, insulin alone, insulin plus oral agents

Titration period: none

Outcomes	Outcomes reported: differences between treatment groups in mean daily blood glucose concentration, composite of postoperative complications including wound infection, pneumonia, bacteraemia, respiratory failure, and acute renal failure, differences between treatment groups in any of the following measures: occurrence of mild and severe hypoglycaemia (70 mg/dL and 40 mg/dL, respectively), length of hospital stay, surgical complications (wound infection and dehiscence, bacteraemia, pneumonia, and acute renal failure defined as an increase in serum creatinine 50% of baseline or a serum creatinine 2.5 mg/dL, or both), admission to the ICU, death
Study registration	Trial identifier: NCT00596687 Study terminated early: no
Publication details	Language of publication: English (Commercial and non-commercial) funding: Sanofi-Aventis, Research Grant 7-03-CR-35, National Institutes of Health (NIH) Grant R03-DK-073190-01 and General Clinical Research Center Grant M01 RR-00039. DS is supported by NIH Research Grant K12-RR-017643 Publication status: peer review journal
Stated aim for study	To evaluate the optimal management of hyperglycaemia in patients undergoing general surgery
Notes	The primary outcomes in the protocol from ClinicalTrials.gov and in the published article were not the same, and 13 participants failed treatment with SSI and were switched to the basal-bolus scheme

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "Computer generated block randomisation table"
Allocation concealment (selection bias)	Low risk	Quote from publication: "Treatment assignment was coordinated by a research pharmacist at each institution"
Blinding of participants and personnel (performance bias)	Low risk	Comment: open-label, outcome unlikely to be influenced by blinding

Umpierrez 2011 (Continued)

All-cause mortality

Blinding of participants and personnel (performance bias) Non-severe hypoglycaemic episodes	High risk	Quote from ClinicalTrials.gov: "masking: none (open label)" Comment: outcome likely affected by lack of blinding techniques
Blinding of participants and personnel (performance bias) Length of hospital stay	Low risk	Comment: outcome unlikely to be influenced by blinding
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemic episodes	High risk	Comment: outcome likely affected by lack of blinding techniques
Blinding of participants and personnel (performance bias) Mean glucose level	High risk	Comment: outcome likely affected by lack of blinding techniques
Blinding of participants and personnel (performance bias) Severe hypoglycaemic episodes	High risk	Comment: outcome likely affected by lack of blinding techniques
Blinding of outcome assessment (detection bias) Severe hypoglycaemic episodes	High risk	Quote from ClinicalTrials.gov: "masking: none (open label)" Quote from author survey: "We did not have an independent adjudication board or member in our studies" Comment: outcome likely affected by lack of blinding techniques
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Quote from ClinicalTrials.gov: "masking: none (open label)" Quote from author survey: "We did not have an independent adjudication board or member in our studies" Comment: outcome unlikely to be affected by lack of blinding technique
Blinding of outcome assessment (detection bias) Non-severe hypoglycaemic episodes	High risk	Quote from ClinicalTrials.gov: "masking: none (open label)" Quote from author survey: "We did not have an independent adjudication board or member in our studies" Comment: outcome likely affected by lack of blinding technique
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Quote from ClinicalTrials.gov: "masking: none (open label)" Quote from author survey: "We did not have an independent adjudication board or member in our studies" Comment: outcome unlikely to be affected by lack of blinding technique
Blinding of outcome assessment (detection bias)	High risk	Quote from ClinicalTrials.gov: "masking: none (open label)"

Umpierrez 2011 (Continued)

Adverse events other than
hypoglycaemia

Quote from author survey: "We did not have an independent adjudication board or member in our studies"

Comment: outcome likely affected by lack of blinding technique

Blinding of outcome as-
sessment (detection bias)
Mean glucose level

High risk

Quote from ClinicalTrials.gov: "masking: none (open label)"

Quote from author survey: "We did not have an independent adjudication board or member in our studies"

Comment: outcome likely affected by lack of blinding technique

Incomplete outcome data
(attrition bias)
Severe hypoglycaemic
episodes

Low risk

Comment: low attrition rate not likely to have influenced outcome measure

Incomplete outcome data
(attrition bias)
All-cause mortality

Low risk

Comment: low attrition rate not likely to have influenced outcome measure

Incomplete outcome data
(attrition bias)
Non-severe hypogly-
caemic episodes

Low risk

Comment: low attrition rate not likely to have influenced outcome measure

Incomplete outcome data
(attrition bias)
Length of hospital stay

Low risk

Comment: low attrition rate not likely to have influenced outcome measure

Incomplete outcome data
(attrition bias)
Adverse events other than
hypoglycaemic episodes

Low risk

Comment: low attrition rate not likely to have influenced outcome measure

Incomplete outcome data
(attrition bias)
Mean glucose level

Low risk

Comment: low attrition rate not likely to have influenced outcome measure

Selective reporting (re-
porting bias)

Low risk

Comment: none detected by ORBIT criteria

Other bias

Low risk

Comment: none detected

Umpierrez 2013

Methods

Parallel randomised controlled trial, non-inferiority design

2:2:1 ratio to 1 of 3 regimens: a basal-bolus regimen with insulin glargine given once daily and glulisine before meals plus corrective doses of glulisine by sliding scale for BG > 140 mg/dL; a basal-plus regimen with a daily dose of glargine and corrective doses of glulisine by sliding scale before meals for BG > 140 mg/dL; and SSI for BG > 140 mg/dL

Participants

Inclusion criteria: people with a known history of type 2 diabetes (T2DM) and with a BG before randomisation between 140 mg/dL and 400 mg/dL, a known history of T2DM for > 3 months, age between 18 and 80 years, and treatment at home with diet alone, any combination of oral antidiabetic agents, or low-dose insulin therapy at a daily dose of 0.4 units/kg before admission to general medicine and surgery services

Umpierrez 2013 (Continued)

Exclusion criteria: individuals with any BG > 400 mg/dL before randomisation or with a history of hyperglycaemic crises; individuals with hyperglycaemia without a known history of diabetes; people admitted to or expected to require ICU admission, undergoing cardiac surgery, receiving corticosteroid therapy, clinically relevant hepatic disease, impaired renal function (serum creatinine > 3.0 mg/dL), history of diabetic ketoacidosis, pregnant women, or with any mental condition rendering them unable to give informed consent

Diagnostic criteria: medical history of diabetes mellitus for 3 months or more and with a blood glucose before randomisation between 140 and 400 mg/dL

Setting: hospital

Age group: adults

Gender distribution: females and males

Country where trial was performed: USA

Interventions	<p>Intervention: sliding scale insulin, 4 times daily</p> <p>Comparator(s):</p> <ul style="list-style-type: none"> Basal-bolus insulin: glargine once daily plus glulisine before meals (plus corrective doses of glulisine as needed). Participants were started at a TDD of 0.5 units/kg (half as insulin glargine once daily and half as insulin glulisine before meals). Basal-plus insulin: glargine once daily plus corrective doses of glulisine before meals and bedtime as needed. Participants received 0.25 units/kg of glargine plus corrective doses of glulisine before meals. <p>Duration of intervention: 6 days</p> <p>Duration of follow-up: 6 days</p> <p>Run-in period: January 2010 to June 2012</p> <p>Number of study centres: 5</p> <p>Treatment before study: diet alone, oral agents, insulin alone, insulin with oral agents</p> <p>Titration period: none</p>
Outcomes	<p>Outcomes reported in abstract of publication: difference in glycaemic control, as measured by mean daily blood glucose concentration, differences between treatment groups in any of the following measures: number of hypoglycaemic events (BG 70 and 40 mg/dL) after the first day of treatment, number of episodes of hyperglycaemia (BG 200 mg/dL) after the first day of treatment, TDD of insulin, hospital stay, hospital complications</p>
Study registration	<p>Trial identifier: NCT00979628</p> <p>Study terminated early: no</p>
Publication details	<p>Language of publication: English</p> <p>Commercial funding: Sanofi-Aventis</p> <p>Publication status: peer review journal</p>
Stated aim for study	<p>Quote from publication: "The present study aims to determine which insulin treatment is best for glucose control in hospitalised people with diabetes admitted to general medicine wards"</p>
Notes	<p>The number of participants reported in ClinicalTrials.gov differs from the number of participants reported in the publication</p>

Umpierrez 2013 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "Computed-generated randomization table to coordinate the randomization and treatment assignment"
Allocation concealment (selection bias)	Low risk	Quote from publication: "A research pharmacist at each institution followed a computer-generated randomization..."
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	Quote from publication: "Open label" Comment: outcome unlikely to be influenced by blinding
Blinding of participants and personnel (performance bias) Non-severe hypoglycaemic episodes	High risk	Comment: outcome likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Length of hospital stay	Low risk	Comment: outcome unlikely to be influenced by blinding
Blinding of participants and personnel (performance bias) Adverse events other than hypoglycaemic episodes	High risk	Comment: outcome likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Mean glucose level	High risk	Comment: outcome likely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Severe hypoglycaemic episodes	High risk	Comment: outcome likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) Severe hypoglycaemic episodes	High risk	Quote from ClinicalTrials.gov: "masking: none (open label)" Author survey: "Trial authors did not have an independent adjudication board" Comment: outcome likely influenced by lack of blinding
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Quote from ClinicalTrials.gov: "masking: none (open label)" Author survey: "Trial authors did not have an independent adjudication board" Comment: outcome unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	High risk	Quote from ClinicalTrials.gov: "masking: none (open label)"

Umpierrez 2013 (Continued)

Non-severe hypoglycaemic episodes

Author survey: "Trial authors did not have an independent adjudication board"

Comment: outcome likely influenced by lack of blinding

Blinding of outcome assessment (detection bias)
Length of hospital stay

Low risk

Quote from ClinicalTrials.gov: "masking: none (open label)"

Author survey: "Trial authors did not have an independent adjudication board"

Comment: outcome unlikely to be influenced by lack of blinding

Blinding of outcome assessment (detection bias)
Adverse events other than hypoglycaemia

High risk

Quote from ClinicalTrials.gov: "masking: none (open label)"

Author survey: "Trial authors did not have an independent adjudication board"

Comment: outcome likely influenced by lack of blinding

Blinding of outcome assessment (detection bias)
Mean glucose level

High risk

Quote from ClinicalTrials.gov: "masking: none (open label)"

Author survey: "Trial authors did not have an independent adjudication board"

Comment: outcome likely influenced by lack of blinding

Incomplete outcome data (attrition bias)
Severe hypoglycaemic episodes

Low risk

Quote from publication: "A total of 375 patients with T2D gave consent (210 medical and 165 surgical patients); of them, 22 patients were excluded from further analysis because they received 24 h of insulin treatment, were transferred to the ICU, or received corticosteroid therapy"

Comment: low attrition rate unlikely to have influenced outcome measure

Incomplete outcome data (attrition bias)
All-cause mortality

Low risk

Comment: low attrition rate unlikely to have influenced outcome measure

Incomplete outcome data (attrition bias)
Non-severe hypoglycaemic episodes

Low risk

Comment: low attrition rate unlikely to have influenced outcome measure

Incomplete outcome data (attrition bias)
Length of hospital stay

Low risk

Comment: low attrition rate unlikely to have influenced outcome measure

Incomplete outcome data (attrition bias)
Adverse events other than hypoglycaemic episodes

Low risk

Comment: low attrition rate unlikely to have influenced outcome measure

Incomplete outcome data (attrition bias)
Mean glucose level

Low risk

Comment: low attrition rate unlikely to have influenced outcome measure

Selective reporting (reporting bias)

Low risk

Comment: none detected

Other bias

Low risk

Comment: none detected

:- denotes not reported

Note: where the judgement is 'unclear' and the description is blank, the trial did not report that particular outcome.

ADA: American Diabetes Association; **BG:** blood glucose; **DM:** diabetes mellitus; **ICU:** intensive care unit; **IU:** international units; **IV:** intravenous; **NPH:** neutral protamine Hagedorn insulin; **N/T:** no trial document available; **ORBIT:** Outcome Reporting Bias In Trials; **SC:** subcutaneous; **SSI:** sliding scale insulin; **SSRI:** sliding scale regular insulin; **TDD:** total daily dose; **TPN:** total parenteral nutrition; **U:** units

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alfonso 2006	Wrong study design: quasi-randomised trial (participants were randomised to receive lispro or regular insulin based on whether the last digit of their Social Security number was odd or even); both groups were treated by the sliding scale scheme
Attia 1998	Wrong population: individuals with ketoacidosis
Choi 2016	Wrong study design: modelling study
Christensen 2017	Wrong study design: systematic review
Connor 2015	Wrong population: not diabetic participants
Dickerson 2003	Wrong comparator: the trial compared insulin plus routine medications versus routine medications
Emam 2010	Wrong setting: critical care setting
Fiore 2011	Data not extractable. Bayesian model study
Furnary 1999	Wrong study design: cohort study
Gerards 2016	Wrong comparator: sliding scale plus other treatment
Gómez Cuervo 2016	Wrong study design: systematic review
Hagelberg 2008	Wrong population: critical care setting
Hakeam 2017	Wrong comparator: no sliding scale in 1 of the intervention arms
Jackson 2014	Wrong study design: systematic review
Lee 2015	Wrong study design: systematic review
Mader 2014	Wrong comparator: the trial compared insulin plus routine medications versus routine medications (combination of oral agents, insulin, or both)
NCT00700362	Withdrawn trial
NCT01081938	Wrong comparator: the trial compared SSI versus SSI plus basal insulin
NCT01594060	Wrong study design: non-randomised trial
NCT00670228	Wrong population: only 39% of participants had diabetes at baseline, no subgroup analysis available for diabetic participants
Okabayashi 2009a	Wrong comparator: artificial pancreas trial
Okabayashi 2009b	Wrong comparator: artificial pancreas trial

Study	Reason for exclusion
Perera 2011	Wrong comparator: the trial evaluated routine oral medications
Sabouhi 2015	Wrong setting: critical care unit
Schnipper 2010	Wrong study design: trial authors randomised the team work, not the intervention
Schoeffler 2005	Wrong study design: cohort study
Vellanki 2015	Wrong comparator: no sliding scale insulin
Walters 2006	Wrong comparator: no comparison with sliding scale insulin
Zaman Huri 2014	Wrong study design: non-randomised trial

SSi: sliding scale insulin

Characteristics of studies awaiting assessment *[ordered by study ID]*

[IRCT201311118307N2](#)

Methods	<p>Type of study: interventional</p> <p>Allocation: randomised using permuted block</p> <p>Intervention model: parallel assignment</p> <p>Masking: not blinded</p> <p>Primary purpose: treatment</p>
Participants	<p>Condition: diabetic people with cardiovascular diseases</p> <p>Enrolment: 70</p> <p>Inclusion criteria: people with cardiovascular diseases, with a history of diabetes of more than 3 months, blood glucose 140 to 400 mg/dL, glycated haemoglobin 6.5%, aged 18 to 80 years, who can eat, receiving oral hypoglycaemic agent and insulin with doses of 0.4 IU/kg/day or lower</p> <p>Exclusion criteria: hyperglycaemia without known diabetes, coronary artery bypass surgery, severe liver diseases, renal dysfunction (creatinine > 3 mg/dL), history of diabetic ketoacidosis, pregnancy, inability to fill and understand the consent form, consented patients who want to discontinue the study at any time</p>
Interventions	<p>Intervention(s): sliding scale insulin</p> <p>Comparator(s): basal-bolus insulin</p>
Outcomes	<p>Primary outcome(s): fasting blood level of glucose in each group, blood glucose level before each meal, intensive care unit admission, mortality rate, severe hypoglycaemic episodes, recurrent myocardial infarction, heart failure</p> <p>Secondary outcome(s): coronary care unit admission, mild hypoglycaemic episodes, length of hospitalisation</p> <p>Other outcome(s): -</p>
Study details	IRCT201311118307N2

IRCT201311118307N2 (Continued)

Publication details

-

Stated aim of study

This study will be performed to compare basal-bolus insulin with sliding scale insulin in glycaemic control of diabetic patients with cardiovascular diseases.

Notes

Recruitment status: complete

Investigator: Dr Taher Entezari-maleki, Tabriz University of Medical Science, sDanezhgah Street Tabriz (Islamic Republic of Iran), tentezari@gmail.com

We contacted the authors but have received no response.

ISRCTN55845280

Methods

Type of study: interventional

Allocation: single-centre randomised

Intervention model: parallel assignment

Masking: open trial

Primary purpose: treatment

Participants

Condition: acute medical or surgical condition

Enrolment: 250 (target sample size)

Inclusion criteria: adult inpatients (aged > 18 years, men and women) with an acute medical or surgical condition, and any of the following criteria:

- in participants known to have diabetes: capillary blood glucose level > 180 mg/dL, in consecutive measurements separated by 2 hours, or just 1 measurement if insulin was administered after the first
- in participants without previous diagnosis of diabetes: capillary blood glucose level > 200 mg/dL, in consecutive measurements separated by 2 hours, or just 1 measurement if insulin was administered after the first

Exclusion criteria:

- Pregnancy
- Acute complications of diabetes
- Terminal illness (expected survival of less than a month)
- Elective hospitalisation
- Hospitalisation predicted to last < 72 hours
- Haemodialysis initiated during hospitalisation
- Peritoneal dialysis
- Corticosteroids (prednisone) dose over 30 mg/day
- Parenteral nutrition
- Inability to receive carbohydrates by mouth for > 8 hours
- Patients with an unresolved surgical condition

Interventions

Group 1: intensive insulin therapy with basal NPH and nutritional regular insulin consisting of:

- 2 doses of basal NPH insulin, standardised according to weight and insulin resistance
- regular insulin (short-acting) prior to meals ("nutritional") both in fixed dose and through a sliding scale

ISRCTN55845280 (Continued)

Group 2: intensive insulin therapy with basal glargine and nutritional regular insulin consisting of:

- 1 dose of basal glargine insulin, standardised according to weight and insulin resistance
- regular insulin (short-acting) prior to meals ("nutritional") both in fixed dose and through a sliding scale

Group 3: standard care consisting of regular insulin 4 times a day or NPH twice daily, according to a sliding scale

Outcomes	<p>Primary outcome measures: number of measurements of blood glucose levels between 70 and 130 mg/dL; all measurements will be recorded at day 7 and at the moment of discharge</p> <p>Secondary outcome measures: mean blood glucose level, length of hospitalisation, health-care-associated infections, number of measurements of blood glucose levels < 70 mg/dL, time to achieve good glycaemic control (≥ 2 measurements between 70 and 130 mg/dL)</p>
Study details	ISRCTN55845280
Publication details	-
Stated aim of study	This trial will assess whether an adjustable insulin scheme which simulates the physiological secretion of this hormone is superior to standard treatment in medical inpatients with hyperglycaemia
Notes	<p>Overall trial status: completed</p> <p>Investigator: Dr Luis Rojas, Marcoleta 367, Quinto Piso, Santiago, Chile, lrojas@med.puc.cl</p> <p>We contacted the authors but have received no response</p>

NPH: neutral protamine Hagedorn insulin

Characteristics of ongoing studies [ordered by study ID]

NCT01143948

Trial name or title	Acronym: VIRDICT (Various Insulin Regimens for Diabetic Inpatients with Cirrhosis Trial)
Methods	<p>Type of study: interventional</p> <p>Allocation: randomised</p> <p>Intervention model: parallel assignment</p> <p>Masking: open-label</p> <p>Primary purpose: treatment</p>
Participants	<p>Condition: type 2 diabetes, liver cirrhosis</p> <p>Enrolment: 45</p> <p>Inclusion criteria: hospitalised type 2 diabetes mellitus with liver cirrhosis and entry blood glucose (fasting or random) > 180 mg/dL</p> <p>Exclusion criteria: type 1 diabetes mellitus, pregnancy, steroids: prednisone > 7.5 mg/day or equivalent, serum creatinine > 3 mg/dL, people in intensive care units</p>
Interventions	<p>Intervention(s): regular insulin</p> <p>Comparator(s): NPH and bolus regular insulin and basal glargine and bolus glulisine</p>

NCT01143948 (Continued)

Outcomes	<p>Primary outcome(s): optimal glycaemic control in inpatients with cirrhosis (time frame: 3 to 7 days)</p> <p>Secondary outcome(s): incidence of hypoglycaemic episodes (time frame: 3 to 7 days)</p> <p>Other outcome(s): -</p>
Starting date	<p>Study start date: January 2011</p> <p>Estimated study completion date: May 2011</p>
Contact information	Responsible party/principal investigator: Mostafa M Alfishawy, MB BCh; mostafa.alfishawy@yahoo.com
Study identifier	NCT01143948
Official title	Insulin therapy in the inpatient management of cirrhotic patients with type 2 diabetes
Stated purpose of study	Best management of hyperglycaemia in non-intensive care unit cirrhotic patients with type 2 diabetes by different insulin regimens: either sliding scale regular insulin or basal-bolus insulin using NPH and regular insulin or glargine and glulisine
Notes	<p>Recruitment status: unknown</p> <p>Investigators: Ibtisam Z Eissa, MD, Mary N Rizk, MD, Ahmad A Khairy, MD; all Cairo University</p> <p>We contacted the authors but have received no response</p>

NPH: neutral protamine Hagedorn (isophane) insulin

DATA AND ANALYSES

Comparison 1. Sliding scale insulin versus basal-bolus insulin regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	4	602	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.05, 4.85]
2 Non-severe hypoglycaemic episodes	3	561	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.11, 0.59]
2.1 Medical participants	1	130	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.15, 6.89]
2.2 Surgical participants	1	211	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.08, 0.51]
2.3 Medical/surgical participants	1	220	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.04, 0.71]
3 Severe hypoglycaemic episodes	5	667	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 1.00]
4 Length of hospital stay	6	717	Mean Difference (IV, Random, 95% CI)	0.47 [-0.46, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Medical participants	3	221	Mean Difference (IV, Random, 95% CI)	0.23 [-0.94, 1.39]
4.2 Surgical participants	2	276	Mean Difference (IV, Random, 95% CI)	1.18 [-0.97, 3.34]
4.3 Medical/surgical participants	1	220	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.80, 1.00]
5 Adverse events other than hypoglycaemic episodes (infectious complications)	3	481	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.25, 5.37]
6 Mean glucose levels	6	717	Mean Difference (IV, Random, 95% CI)	14.79 [7.75, 21.82]
6.1 Medical participants	3	221	Mean Difference (IV, Random, 95% CI)	9.52 [-14.38, 33.43]
6.2 Surgical participants	2	276	Mean Difference (IV, Random, 95% CI)	16.20 [9.95, 22.44]
6.3 Medical/surgical participants	1	220	Mean Difference (IV, Random, 95% CI)	16.0 [4.98, 27.02]

Analysis 1.1. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 1 All-cause mortality.

Analysis 1.2. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 2 Non-severe hypoglycaemic episodes.

Analysis 1.3. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 3 Severe hypoglycaemic episodes.

Analysis 1.4. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 4 Length of hospital stay. **Analysis 1.5. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 5 Adverse events other than hypoglycaemic episodes (infectious complications).**

Analysis 1.6. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 6 Mean glucose levels.

Comparison 2. Sliding scale insulin versus basal insulin regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-severe hypoglycaemic episodes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Length of hospital stay	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Adverse events other than hypoglycaemic episodes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Mean glucose levels	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Sliding scale insulin versus basal insulin regimen, Outcome 1 Non-severe hypoglycaemic episodes.

Analysis 2.2. Comparison 2 Sliding scale insulin versus basal insulin regimen, Outcome 2 Length of hospital stay.

Analysis 2.3. Comparison 2 Sliding scale insulin versus basal insulin regimen, Outcome 3 Adverse events other than hypoglycaemic episodes.

Analysis 2.4. Comparison 2 Sliding scale insulin versus basal insulin regimen, Outcome 4 Mean glucose levels.

Comparison 3. Sliding scale insulin versus continuous insulin infusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean glucose levels	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Sliding scale insulin versus continuous insulin infusion, Outcome 1 Mean glucose levels.

Study or subgroup	Sliding scale insulin		Continuous in- sulin infusion		Mean Difference	
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Gustafson 2002	25	182 (35)	25	292 (64)		-110[-138.59,-81.41]
Favours sliding scale insulin					-200 -100 0 100 200	Favours continuous in- sulin infusion

ADDITIONAL TABLES

Table 1. Overview of trial populations

Trial ID (trial design)	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/ eligible (N)	Ran- domised (N)	Analysed (N)	Finishing trial (N)	Ran- domised finishing trial (%)	Follow-up
Said 2013 (parallel RCT)	I: SSI (regular insulin)	-	-/63	22	22	22	100	6 days
	C1: 70/30 insulin SSI (regular insulin + NPH)			21	21	21	100	
	C2: basal-bolus regimen (glargine + glulisine)			20	19	19	95	
	Total:			63	62	62	98	
Umpierrez 2013 (parallel non-inferiority RCT)	I: SSI (regular insulin)	"...reasonable to assume that the SD of mean daily BG is bounded by 50 mg/dL. On the basis of two-sample t-test or Wilcoxon test (one sided, $\alpha = 0.05$), 147 subjects were required for both the basal plus and the basal-bolus groups to ensure 80% power to reject the non-inferiority hypothesis, with Bonferroni correction applied to adjust for multiple comparisons across four time points"	375 (210 medical and 165 surgical patients)	-	74	-	N/A	6 days
	C1: basal-bolus regimen (glargine once daily + glulisine before meals + corrective doses of glulisine by SSI)			-	146 ^a	-	N/A	
	C2: basal-plus regimen (daily glargine + corrective doses of glulisine by SSI before meals)			-	133	-	N/A	
	Total:			375^b	353	-	N/A	
Schroeder 2012 (cluster RCT)	I: SSI (short-acting human insulin)	-	65	30	30	30	100	7 days

Table 1. Overview of trial populations (Continued)

	C: basal-bolus regimen (NPH and regular insulin)		35	35	35	100		
	Total:		65	65	65	100		
Umpierrez 2011	I: SSI (regular insulin)	"Assuming a with-in-group standard deviation of 40 mg/dL and a-error rate of 5% and a <10% attrition rate, we estimated that 104 subjects per group were needed to achieve 90% power"	1405/297	116	107	107	92	9 days
(parallel RCT)	C: basal-bolus regimen (glargine + glulisine)			118	104	104	88	
	Total:		297/234^c	211	211	90		
Korytkowski 2009	I: SSI (regular insulin) + NPH for persistent glucose levels > 10 mmol/L	-	50	25	25	25	100	24 days
(parallel RCT)	C: basal-bolus regimen (glargine + SSI regular insulin)			25	25	25	100	
	Total:		50	50	50	100		
Umpierrez 2007a	I: SSI (regular insulin)	-	130	65	65	65	100	5 days
(parallel RCT)	C: basal-bolus regimen (glargine + glulisine + SSI glulisine)			65	65	65	100	
	Total:		130	130	130	100		
Datta 2007	I: SSI (regular insulin)	-	81	39	39	39	100	5 days
(parallel RCT)	C: basal regimen (glargine) + regular insulin if BG > 200 mg/dL			42	42	42	100	
	Total:		81	81	81	100		
Gustafson 2002^d	I: SSI (regular insulin)	-	50	25	25	25	100	1 day

Table 1. Overview of trial populations (Continued)

(parallel RCT)	C: continuous insulin infusion (regular insulin)	25	25	25	100
	Total:	50	50	50	100
Grand total	All interventions	N/A	387		
	All comparators	N/A	615		
	All interventions and comparators	1048	1002		

-: denotes not reported

^aAccording to table 1 (clinical characteristics of study patients) N = 144 participants.

^b22/375 (5.9%) participants were excluded from further analysis because they received < 24 hours of insulin treatment, were transferred to the intensive care unit, or received corticosteroid therapy.

^c23/234 (9.8%) participants were excluded after randomisation because they received < 24 hours of insulin treatment (N = 14); were treated with continuous insulin infusion during parenteral nutrition (N = 3); consent was withdrawn (N = 3); or surgery was cancelled (N = 3). 63/297 participants refused to participate at or after randomisation (information from trial flow diagram).

^dParticipants were subdivided into two groups categorised by the type of cardioplegia administration and mode of insulin treatment. Group I participants received a 5% dextrose-based cardioplegic solution and continuous insulin infusion for glucose management. Group II participants received normal saline-based cardioplegia and sliding scale insulin for glucose management.

BG: blood glucose; **C:** comparator; **I:** intervention; **N/A:** not applicable; **NPH:** neutral protamine Hagedorn insulin; **RCT:** randomised controlled trial; **SD:** standard deviation; **SSI:** sliding scale insulin

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library)

1. [mh "Diabetes Mellitus"]
 2. diabet*:ti,ab,kw
 3. ("IDDM" or "NIDDM" or "MODY" or T1D* or T2D*):ti,ab,kw
 4. (((("non insulin*" or noninsulin*) next depend*) or "non insulindepend*" or noninsulindepend*):ti,ab,kw
 5. ((insulin* next depend*) or insulindepend*):ti,ab,kw
 6. [mh "Diabetes Insipidus"]
 7. (diabet* next "insipidus"):ti,ab,kw
 8. {or #1-#5}
 9. #6 or #7
 10. #8 not #9
 11. (correct* near/4 insulin*):ti,ab,kw
 12. ("sliding" near/4 scale*):ti,ab,kw
 13. #11 or #12
 14. #10 and #13
-

MEDLINE (Ovid SP)

1. exp Diabetes Mellitus/
 2. diabet*.tw.
 3. (IDDM or NIDDM or MODY or T1D* or T2D*).tw.
 4. (non insulin* depend* or noninsulin* depend* or non insulindepend* or noninsulindepend*).tw.
 5. (insulin* depend* or insulindepend*).tw.
 6. exp Diabetes Insipidus/
 7. diabet* insipidus.tw.
 8. or/1-5
 9. 6 or 7
 10. 8 not 9
 11. (correct* adj3 insulin*).tw.
 12. (sliding adj3 scale*).tw.
 13. 11 or 12
 14. 10 and 13
-

(Continued)

[15-25: Cochrane Handbook 2008 RCT filter - sensitivity maximizing version]

15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomi?ed.ab.
18. placebo.ab.
19. drug therapy.fs.
20. randomly.ab.
21. trial.ab.
22. groups.ab.
23. or/15-22
24. exp animals/ not humans/
25. 23 not 24
26. 14 and 25

Embase (Ovid SP)

1. exp Diabetes Mellitus/
2. diabet*.tw.
3. (IDDM or NIDDM or MODY or T1D* or T2D*).tw.
4. (non insulin* depend* or noninsulin* depend* or non insulindepend* or noninsulindepend*).tw.
5. (insulin* depend* or insulindepend*).tw.
6. exp Diabetes Insipidus/
7. diabet* insipidus.tw.
8. or/1-5
9. 6 or 7
10. 8 not 9
11. (correct* adj3 insulin*).tw.
12. (sliding adj3 scale*).tw.
13. 11 or 12
14. 10 and 13

[15: [Wong 2006](#) "sound treatment studies" filter – BS version]

15. random*.tw. or clinical trial*.mp. or exp health care quality/
16. 14 and 15
17. limit 16 to embase

LILACS (IAHx)

(Continued)

((diabet\$ OR insulin\$) AND (scale\$ OR esquema\$ OR escala\$) AND (movil\$ OR deslizante\$ OR sliding))

+ Filter "Controlled Clinical Trial"

WHO ICTRP (standard search)

diabet* AND sliding

ClinicalTrials.gov (advanced search)

Search terms: (diabetes OR diabetic) AND sliding

Age Group: Adult (18-65), Senior (66+)

Appendix 2. Assessment of risk of bias

'Risk of bias' domains

Random sequence generation

Selection bias due to inadequate generation of a randomised sequence - assessment at trial level

We described for each included trial the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if performed by an independent person not otherwise involved in the trial. We considered use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random (e.g. sequence generated by odd or even date of birth or some rule based on date (or day) of admission or hospital or clinic record number; allocation by judgement of the clinician, by preference of the participant, based on the results of a laboratory test or a series of tests, or by availability of the intervention). We excluded such trials.

Allocation concealment

Selection bias due to inadequate concealment of allocations prior to assignment - assessment at trial level

We described for each included trial the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: using an open random allocation schedule (e.g. a list of random numbers); using assignment envelopes without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure. We excluded such trials.

Blinding of participants and study personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the trial - assessment at outcome level

We evaluated the risk of performance bias separately for each outcome ([Hróbjartsson 2013](#)). We noted whether outcomes were self reported, investigator assessed, or adjudicated outcome measures (see below).

(Continued)

- Low risk of bias: blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial did not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessment - assessment at outcome level

We evaluated the risk of detection bias separately for each outcome ([Hróbjartsson 2013](#)). We noted whether outcomes were self reported, investigator assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

Attrition bias due to amount, nature, or handling of incomplete outcome data - assessment at outcome level

We described for each included trial, and for each outcome, the completeness of data including attrition and exclusions from the analysis. We investigated whether attrition and exclusions were reported and the number included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups), if reasons for attrition or exclusion were reported, and whether missing data were balanced across groups or were related to outcomes. We considered the implications of missing outcome data per outcome, such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the trial did not address this outcome.
- High risk of bias: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting

Reporting bias due to selective outcome reporting - assessment at trial level

We assessed outcome reporting bias by integrating the results of [Appendix 7](#), 'Matrix of trial endpoints (publications and trial documents)' ([Mathieu 2009](#)), with those of [Appendix 8](#), 'High risk of outcome reporting bias according to ORBIT classification' ([Kirkham 2010](#)). This analysis formed the basis for the judgement of selective reporting.

- Low risk of bias: the trial protocol was available and all of the trial's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way; the study protocol was not available but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all of the trial's prespecified primary outcomes were reported; one or more primary outcomes was reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that had not been prespecified; one or more reported

(Continued)

primary outcomes had not been prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the trial report failed to include results for a key outcome that would be expected to have been reported for such a trial (ORBIT classification).

Other bias

Bias due to problems not covered elsewhere - assessment at trial level

Other risk of bias reflects other circumstances that may threaten the validity of the trials, e.g. funding bias and academic bias.

- Low risk of bias: the trial appeared to be free of other sources of bias.
- Unclear risk of bias: insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: had a potential source of bias related to the specific trial design used; has been claimed to have been fraudulent; had some other serious problem.

Summary assessment of risk of bias

Risk of bias for a trial across outcomes

Some 'Risk of bias' domains like selection bias (sequence generation and allocation sequence concealment) affected the risk of bias across all outcome measures in a trial. Otherwise, we did not perform a summary assessment of the risk of bias across all outcomes for a trial. In case of high risk of selection bias, we excluded the trial.

Risk of bias for an outcome within a trial and across domains

We assessed the risk of bias for an outcome measure including all of the entries relevant to that outcome, i.e. both trial-level entries and outcome-specific entries. We defined low risk of bias as low risk of bias for all key domains; unclear risk of bias as unclear risk of bias for one or more key domains; and high risk of bias as high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains

These were our main summary assessments that were to be incorporated in our judgements about the certainty of evidence in the 'Summary of finding' table(s). We defined low risk of bias as most information coming from trials at low risk of bias; unclear risk of bias as most information coming from trials at low or unclear risk of bias; and high risk of bias as a sufficient proportion of information coming from trials at high risk of bias.

Abbreviation: ORBIT: Outcome Reporting Bias In Trials

Appendix 3. Description of interventions

Trial ID	Sliding scale insulin	Comparator(s)
Said 2013	<p>Sliding scale insulin</p> <p>Regular insulin 3 times daily SC approx. 30 min before meal for BG > 150 mg/dL (or every 8 hours if a participant was not eating)</p> <p>If BG < 150 mg/dL give no insulin</p> <p>If BG 151 to 200 mg/dL give 5 IU insulin</p> <p>If BG 201 to 250 mg/dL give 10 IU insulin</p>	<p>C1 - basal-bolus regimen:</p> <p><i>Glargine once every night</i></p> <ul style="list-style-type: none"> • Participants treated with diet or oral agents before admission: hold oral antidiabetic drugs on admission, start glargine insulin dose: 0.2 U/kg/day for admission BG ≤ 200 mg/dL or 0.3 U/kg/day for BG > 200 mg/dL • Participants treated with insulin before admission: glargine/glulisine-treated patients should be started at half amount of the total outpatient insulin dose as glargine. <p>+ <i>Glulisine</i>: give glulisine 3 times before each meal for BG ≥ 150 mg/dL according to scale provided as SSI, hold glulisine if a participant is not able to eat to prevent hypoglycaemia.</p>

(Continued)

If BG 251 to 300 mg/dL give 15 IU insulin

If BG 301 to 350 mg/dL give 20 IU insulin

If BG 351 to 400 mg/dL give 25 IU insulin

If BG > 400 mg/dL give 30 IU insulin and call the internal medicine resident

C2 - premixed 70/30 insulin regimen (30% regular insulin and 70% isophane NPH insulin):

premixed 70/30 + supplemental regular insulin at lunch time according to SSI

- Participants treated with diet or oral agents before admission: hold oral antidiabetic drugs on admission. Starting premixed 70/30 insulin dose: 0.2 U/kg/day for admission BG ≤ 200 mg/dL or 0.4 U/kg/day for BG > 200 mg/dL
- Participants treated with insulin before admission: premixed 70/30 insulin-treated patients should be started at the same outpatient insulin dose and schedule.

In both cases: give 2/3 of TDD before breakfast and 1/3 of TDD before dinner.

Insulin adjustment:

- If fasting and pre-meal BG < 150 mg/dL (in the absence of hypoglycaemia): no change
- If fasting and pre-meal BG 150 to 180 mg/dL (in the absence of hypoglycaemia): increase the TDD of 70/30 insulin or glargine by 10% every day
- If fasting and pre-meal BG is > 180 mg/dL (in the absence of hypoglycaemia): increase the TDD of 70/30 insulin or glargine dose by 20%
- If participant develops hypoglycaemia (< 60 mg/dL): decrease the TDD of 70/30 insulin or glargine insulin dose by 20
- The distribution of 70/30 insulin doses followed the 2/3 a.m. and 1/3 p.m. scheme

Umpierrez 2013

Sliding scale insulin for BG > 140 mg/dL

In participants who were not eating or with intermittent nutritional intake, regular insulin was administered every 6 hours according to the recommended dose from the protocol.

In participants who were eating, regular insulin was administered before each meal and at bedtime, following the "usual" according to the dose of the sliding scale protocol.

If fasting and pre-meal glucose was > 140 mg/dL, the SSI with regular insulin could be increased; if participant developed hypoglycaemia, the SSI was decreased; glucose was measured before each meal and at bedtime.

C1 - basal-bolus regimen: glargine once daily and glulisine before meals plus corrective doses of glulisine as SSI for BG > 140 mg/dL (TDD of 0.5 units/kg, half as glargine once daily and half as glulisine before meals)

C2 - basal-plus regimen: daily dose of glargine and corrective doses of glulisine as SSI before meals for BG > 140 mg/dL (0.25 units/kg of glargine plus corrective doses of glulisine before meals)

In participants > 70 years of age and/or with creatinine > 2 mg/dL, starting TDD in the basal-bolus group was reduced to 0.3 units/kg, and to 0.15 units/kg in the basal-plus group.

Schroeder 2012

Glucose levels were monitored 4 times a day (before each meal and once at 10 p.m.); short-acting human insulin was administered SC according to the participant's blood glucose

Basal-bolus regimen: subcutaneous insulin was administered for all uncontrolled diabetic participants (glucose > 200 mg/dL 2 or more times); after the initial dose, insulin doses were changed daily based on previous measurements; initial TDD was 0.25 U/kg divided equally in 4 doses; regular insulin was administered

Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus (Review)

(Continued)

level: between 150 and 200 mg/dL, 4 units were administered; for each 50 mg/dL increase in glucose levels, 2 more units of insulin were added.

3 times per day before each meal and NPH only at 10 p.m.; modified pre-meal regular insulin based on pre-meal glucose levels, increasing dose as needed by 2 to 4 units/injection; NPH doses were modified based on the previous morning fasting levels.

Participants were educated regarding the importance of a proper diet and glucose control.

Umpierrez 2011

Participants received regular insulin 4 times daily if BG > 140 mg/dL; doses were adjusted according to a pre-specified protocol; if the mean daily BG level was 240 mg/dL, or if 3 consecutive values were > 240 mg/dL on the maximal SSI dose, participants were switched to basal-bolus regimen starting TDD of 0.5 units/kg.

Basal-bolus regimen: started at a TDD of 0.5 units/kg divided half as glargine once daily and the other half as glulisine given before meals; if a participant was not able to eat, glargine was given but glulisine was held until meals were resumed; the TDD was reduced to 0.3 units/kg in participants > 70 years of age and/or with a creatinine > 2.0 mg/dL.

Korytkowski 2009

Sliding scale insulin (regular insulin) was administered SC every 4 to 6 h according to results of bedside blood glucose; if > 130 mg/dL twice, SSI started at doses of 2, 4, or 6 units depending on participant's characteristics; if $\geq$ 180 mg/dL, low-dose SSI every 4 to 6 h for 24 to 36 h; if continued > 180 mg/dL, moderate-dose SSI every 4 to 6 h for 24 to 36 h; if $2x > 180$ mg/dL, high-dose SSI for 24 to 36 h; if $2x > 180$ mg/dL, NPH every 12 h for enteral nutrition or once daily in fasting participants.

Basal-bolus regimen: if blood glucose > 130 mg/dL, insulin glargine 10 units SC once a day and SSI regular insulin; if $\geq$ 180 mg/dL, NPH dose was increased by adding 50% of SSI insulin required in prior 24 h

Umpierrez 2007a

Regular insulin 4 times daily for BG > 140 mg/dL

If participant was eating, regular insulin was given before each meal and at bedtime, beginning with 4 U if > 140 to 180 mg/dL and adding 2 U for each "level cohort" 181 to 220 mg/dL, 221 to 260 mg/dL, 261 to 300 mg/dL, 351 to 400 mg/dL, > 400 mg/dL ("usual" column of the sliding-scale protocol); if participant was not eating, regular insulin was given every 6 h, beginning with 2 U if > 140 mg/dL and adding 2 U for each "level cohort" ("insulin-sensitive" column of the sliding scale protocol); if fasting and pre-meal glucose were persistently > 140 mg/dL, SSI was increased, beginning with 6 U if > 140 mg/dL and adding 2 U for each "level cohort" (insulin resistant); if a participant developed hypoglycaemia, regular insulin dose was decreased in order of 2 U for each "level cohort".

Basal-bolus regimen: total daily dose of 0.4 U/kg/day if admission blood glucose was 140 to 200 mg/dL or 0.5 U/kg/day if 201 to 400 mg/dL; 1/2 of TDD was given as glargine once daily and 1/2 as glulisine; glulisine was given in 3 divided doses before each meal; glulisine was stopped if participant was not able to eat.

Supplementary glulisine following the SSI protocol if BG > 140 mg/dL: if a participant was eating, glulisine was given before each meal and at bedtime following the "usual" scheme; if a participant was not eating, supplemental glulisine was given every 6 h following the "insulin-sensitive" scheme. If fasting and pre-meal BG > 140 mg/dL, glargine was increased by 20%; if participant developed hypoglycaemia (< 70 mg/dL), glargine dose was decreased by 20%.

Datta 2007

Glucose was measured every 6 h, and participants were given a SC dose of

Basal regimen: subcutaneous insulin glargine dose was given at dose of 0.3 U/kg; if glucose 140 to 180 mg/dL, glargine was

(Continued)

regular insulin based on glucose levels as follows: 140 to 160 mg/dL, 4 U; 161 to 180 mg/dL, 6 U; 181 to 200 mg/dL, 8 U; 201 to 220 mg/dL, 10 U; and 221 mg/dL or more, 12 U.

increased by 30%; if glucose was > 180 mg/dL, glargine was increased by 60%; if glucose > 200 mg/dL, participants were treated with an additional dose of regular insulin equal to 25% of the previous glargine dose (this was the case in 6% of blood glucose measurements only).

Gustafson 2002

SSI with regular insulin as follows: 200 to 250 mg/dL, 10 U; 251 to 300 mg/dL, 15 U; 301 to 350 mg/dL, 20 U; 351 to 400 mg/dL, 25 U; 401 to 500 mg/dL, 30 U; > 501 mg/dL, 35 U

Continuous insulin infusion with regular insulin:

on the day of surgery, obtain glucose level 5:30 p.m. and 8 p.m.; for glucose < 180 mg/dL, check every 2 h; for glucose > 180 mg/dL, begin infusion at 0.5 U/h and check hourly.

Infusion maintenance: for glucose < 80 mg/dL, give 25 cm³ 50% dextrose IV, reduce infusion by 1 U/h; for glucose < 80 mg/dL 2 consecutive times, reduce by 1/2 current rate, check every 15 min until glucose > 80 mg/dL, then resume hourly monitoring; resume infusion when glucose is > 180 mg/dL, begin at 0.5 U/h and check glucose in 1 h; for glucose 80 to 120 mg/dL, reduce infusion by 0.5 U and check hourly; for glucose 121 to 180 mg/dL, keep infusion rate and check hourly, if glucose remains check every 2 h, if level remains in this range check in 4 h, for glucose > 180 mg/dL, if glucose has not decreased since last checked, increase infusion by 0.5 U/h, if glucose decreased since last checked, keep infusion rate the same.

For glucose > 250 mg/dL during open-heart surgery, adjust infusion rate to 0.1 U/kg/h; stop infusion if tube feeding or meal is stopped at any time and check hourly, resume infusion when glucose is > 180 mg/dL, begin infusion at 0.5 U/h and follow maintenance of the infusion.

BG: blood glucose; **IU:** international units; **IV:** intravenous; **NPH:** neutral protamine Hagedorn insulin; **SC:** subcutaneous; **SSI:** sliding scale insulin; **TDD:** total daily dose; **U:** units

Appendix 4. Baseline characteristics (I)

Trial ID	Intervention(s) and comparator(s)	Duration of intervention (follow-up)	Description of participants	Trial period (year to year)	Country	Setting	Ethnic groups (%)	Duration of diabetes (mean years (SD))
Said 2013	I: SSI (regular insulin)	6 days (8 days)	Non-surgical patients with a known history of type 2 diabetes mellitus for > 3 months admitted to general medicine wards	2010 to 2014	Egypt	Medical unit	-	-
	C1: 70/30 insulin SSI (regular insulin + NPH)	4 days (62 days)					-	-
	C2: basal-bolus regimen (glargine + glulisine)	5 days (72 days)					-	-
Umpierrez 2013	I: SSI (regular insulin)	6 days (6 days)	People with known history of type 2 diabetes and a blood glucose before randomisation of 140 to 400 mg/dL or with a known history of type 2 diabetes for > 3 months, admitted to general medicine and surgery services	2010 to 2012	USA	Medical and surgical units	-	8.4 (7)
	C1: basal-bolus regimen (glargine + glulisine + SSI glulisine)						-	9.9 (8)
	C2: basal-plus regimen (glargine + SSI glulisine)						-	7.6 (7)
Schroeder 2012	I: SSI (short-acting human insulin)	7 days (7 days)	All individuals with previously diagnosed diabetes or suffering from recurrent hyperglycaemia (≥ 2 measurements of blood glucose levels > 180 mg/dL) admitted to an orthopaedic surgery department	2007 to 2008	Israel	Orthopaedic unit	-	-
	C: basal-bolus regimen (NPH + regular insulin)						-	-
Umpierrez 2011	I: SSI (regular insulin)	9 days (9 days)	People with a blood glucose level of 140 to 400 mg/dL with a history of diabetes for > 3 months, admitted to general elective or emergency surgery and not expected to require intensive care unit admission	2008 to 2009	USA	Surgical unit	Other: 7 Black: 55 White: 38	6.8 (6.3)
	C: basal-bolus regimen (glargine + glulisine)						Other: 10 Black: 41 White: 49	6.3 (6.2)

(Continued)

Korytkowski 2009	I: SSI (regular insulin) + NPH	8 days (24 days)	People diagnosed with diabetes (≥ 2 blood glucose measures > 7.2 mmol/L (139 mg/dL) during enteral nutrition therapy)	2005 to 2006	USA	Surgical and medical unit	-	-
	C: basal-bolus regimen (glargine + SSI regular insulin)						-	-
Umpierrez 2007a	I: SSI (regular insulin)	5 days (5 days)	Non-surgical, insulin-naive individuals with a known history of type 2 diabetes for 3 months, with a blood glucose level of 140 to 400 mg/dL admitted to medical general services	2005 to 2006	USA	Medical unit	Hispanic: 21 Black: 74 White: 5	-
	C: basal-bolus regimen (glargine and glulisine + SSI glulisine)						Hispanic: 27 Black: 66 White: 7	-
Datta 2007	I: SSI (regular insulin)	4 days (30 days)	People with a bariatric surgical procedure and blood glucose levels > 144 mg/dL measured postoperatively in the recovery unit (67% in the sliding scale group and 62% in the glargine group had a history of diabetes).	2006	USA	Surgical unit	-	-
	C: basal regimen (glargine) + regular insulin		32/81 participants had an open abdominal operation and were admitted to the surgical intensive care unit; when they were ready for transfer to the general surgical ward they were randomised. 49/81 participants underwent a laparoscopic procedure and were admitted to a general surgical unit; they were randomised on admission.				-	-
Gustafson 2002	I: SSI (regular insulin)	1 day (1 day)	Participants with type 2 diabetes undergoing coronary artery bypass surgery	2001	USA	Coronary care unit	-	-
	C: continuous insulin infusion (regular insulin)						-	-

-: denotes not reported

C: comparator; **I:** intervention; **NPH:** neutral protamine Hagedorn insulin; **SD:** standard deviation; **SSI:** sliding scale insulin

Appendix 5. Baseline characteristics (II)

Trial ID	Intervention(s) and comparator(s)	Sex (female %)	Age (mean years (SD))	Glycated haemoglobin (% (SD))	BMI (mean kg/m ² (SD))	Comedications/Cointerventions (% of participants)
Said 2013	I: SSI (regular insulin)	31.8	55 (7)	8.8 (2.6)	31 (5)	-
	C1: 70/30 insulin SSI (regular insulin + NPH)	42.9	55 (7)	9.4 (2.3)	31 (5)	-
	C2: basal-bolus regimen (glargine + glulisine)	26.3	54 (11)	9.1 (3.0)	31 (6)	-
Umpierrez 2013	I: SSI (regular insulin)	41	58.7 (12)	8.0 (2.1)	32.6 (9)	-
	C1: basal-bolus regimen (glargine + glulisine + SSI glulisine)	40	58.7 (11)	8.7 (2.5)	32.6 (8)	-
	C2: basal-plus regimen (glargine + SSI glulisine)	41	58.6 (13)	8.3 (2.3)	33 (9)	-
Schroeder 2012	I: SSI (short-acting human insulin)	50	71 (-)	-	-	-
	C: basal-bolus regimen (NPH + regular insulin)	50	70 (-)	-	-	-
Umpierrez 2011	I: SSI (regular insulin)	50	57 (10)	7.4 (1.9)	32.2 (8.5)	-
	C: basal-bolus regimen (glargine + glulisine)	48	58 (11)	8.1 (2.4)	30.3 (7.4)	-
Korytkowski 2009	I: SSI (regular insulin) + NPH	44	63 (10)	-	26.9 (1.7)	-
	C: basal-bolus regimen (glargine + SSI regular insulin)	36	67 (10)	-	29.1 (5.8)	-
Umpierrez 2007a	I: SSI (regular insulin)	67	56 (11)	8.7 (2.5)	32 (9)	-
	C: basal-bolus regimen (glargine and glulisine + SSI glulisine)	35	56 (13)	8.9 (2)	32 (8)	-
Datta 2007	I: SSI (regular insulin)	82	44.5 (-)	8.3 (-)	53 (12)	Bariatric surgery: 100
	C: basal regimen (glargine) + regular insulin	86	45.4 (-)	7.7 (-)	55 (16)	Bariatric surgery: 100
Gustafson 2002	I: SSI (regular insulin)	40	69.6 (8.2)	-	-	CABG: 100
	C: continuous insulin infusion (regular insulin)	44	67.4 (7.4)	-	-	CABG: 100

(Continued)

-: denotes not reported

BMI: body mass index; **C:** comparator; **CABG:** coronary artery bypass graft; **I:** intervention; **NPH:** neutral protamine Hagedorn insulin; **SD:** standard deviation; **SSI:** sliding scale insulin

Appendix 6. Matrix of trial endpoints (publications and trial documents)

Trial ID	Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper) ^a	Trial results available in trial register	Endpoints quoted in publication(s) ^{b,c}	Endpoints quoted in abstract of publication(s) ^{b,c}
Said 2013	Source: NCT01855243	Unclear ^d	Primary outcome measure: differences in glycaemic control as measured by mean daily BG concentration during hospital stay	Primary outcome measures: -
	Primary outcome measures: differences in glycaemic control as measured by mean daily BG concentration during hospital stay (time frame: during hospital stay, which was expected to be on average 3 weeks); the results of BG values were measured as pre-meal glucose and mean daily BG during the hospital stay from the day of admission			
	Secondary outcome measures: number of hypoglycaemic events, hypoglycaemic episodes classified as major (BG ≤ 40 mg/dL or associated with impaired mental status or loss of consciousness) or minor (BG 40 to 59 mg/dL), severe hyperglycaemia episodes defined as BG > 300 mg/dL, mortality rate (time frame for all outcomes: during hospital stay, which was expected to be on average 3 weeks)		Secondary outcome measures: number of hypoglycaemic events, number of episodes of severe hyperglycaemia, length of hospital stay, mortality rate	Secondary outcome measures: -
	Other outcome measures: -		Other outcome measures: -	Other outcome measures: mean daily BG after first day of hospitalisation
Umpierrez 2013	Source: NCT00979628 Primary outcome measure: mean BG levels after first day of treatment	Yes	Primary outcome measure: difference in glycaemic control, as measured by mean daily BG concentration	Primary outcome measures: -

(Continued)

	<p>Secondary outcome measures: number of participants with hypoglycaemic events (BG < 70 mg/dL) during hospital stay (time frame: up to 12 days)</p>	<p>Secondary outcome measures: differences in any of the following measures: number of hypoglycaemic events (BG < 70 mg/dL and < 40 mg/dL) after the first day of treatment, number of episodes of hyperglycaemia (BG > 200 mg/dL) after the first day of treatment, total daily dose of insulin, hospital stay, hospital complications</p>	<p>Secondary outcome measures: -</p>
	<p>Other outcome measures: -</p>	<p>Other outcome measures: differences in glycaemic control between medical and surgical participants</p>	<p>Other outcome measures: improvement in mean daily BG after the first day of therapy, mean daily BG, treatment failure (defined as > 2 consecutive BG > 240 mg/dL or a mean daily BG > 240 mg/dL)</p>
<p>Schroeder 2012</p>	<p>Source: N/T</p>	<p>Primary outcome measure: mean blood glucose levels during hospitalisation</p> <p>Secondary outcome measures: -</p> <p>Other outcome measures: % glucose measurements > 400 mg/dL, daily difference between the mean levels in both departments, frequency of hypoglycaemic episodes (BG < 70 mg/dL)</p>	<p>Primary outcome measure: -</p> <p>Secondary outcome measures: -</p> <p>Other outcome measures: mean BG throughout hospitalisation, number of severe hyperglycaemic events (BG > 400 mg/dL), number of hypoglycaemic events</p>
<p>Umpierrez 2011</p>	<p>Source: NCT00596687</p> <p>Yes</p> <p>Primary outcome measure: mean BG concentration (time frame: hospital stay days 2 to 10)</p> <p>Secondary outcome measures: number of participants with hypoglycaemic events (< 70 mg/dL) (time frame: hospital stay days 2 to 10)</p>	<p>Primary outcome measures: differences in mean daily BG concentration and a composite of post-operative complications including wound infection, pneumonia, bacteraemia, respiratory failure and acute renal failure</p> <p>Secondary outcome measures: differences in any of the following measures: occurrence of mild and severe hypoglycaemia (< 70 mg/dL and < 40 mg/dL), length of hospital stay, surgical complications (wound infection and dehiscence, bacteraemia, pneumonia, acute renal failure (defined as an increase in serum creatinine > 50%</p>	<p>Primary outcome measure: -</p> <p>Secondary outcome measures: -</p>

(Continued)

			of baseline or a serum creatinine > 2.5 mg/dL, or both), admission to the ICU, death	
	Other outcome measures: -		Other outcome measures: -	Other outcome measures: differences in daily BG, composite of postoperative complications including wound infection, pneumonia, bacteraemia, respiratory and acute renal failure
Korytkowski 2009	Source: NCT00177398 Primary outcome measures: frequency and severity of hyperglycaemia and hypoglycaemia; time to mean 24-hour plasma glucose < 180 mg/dL Secondary outcome measures: triglyceride level at study entry and conclusion; hospital length of stay; inpatient mortality; number of days of antibiotic therapy; number of days with recorded temperature ≥ 100.4 °F; occurrence of any of the following: myocardial infarction, heart failure, cerebrovascular accident, pneumonia, renal impairment (defined as serum creatinine > 2 mg/dL); quality of life measures; outpatient glycaemic control and self management practices Other outcome measures: -	No	Primary outcome measure: - Secondary outcome measures: - Other outcome measures: BG levels during all postoperative days: mean BG, % BG 80 to 140 mg/dL, % BG 141 to 200 mg/dL; total doses of insulin administered; frequency of hypoglycaemia (BG < 60 mg/dL); total inpatient length of stay; frequency of postoperative infections	Primary outcome measure: - Secondary outcome measures: - Other outcome measures: mean BG levels, frequency of hypoglycaemia, total adverse events, length of hospital stay
Umpierrez 2007a	Source: NCT00394407 Primary outcome measure: BG control (time frame: during hospitalisation) Secondary outcome measures: frequency of hypogly-	No	Primary outcome measures: differences in glycaemic control as measured by mean daily BG concentration Secondary outcome measures: number of hypoglycaemic events,	Primary outcome measure: - Secondary outcome measures: -

(Continued)

caemia, frequency of severe hyperglycaemia (BG > 400 mg/dL), length of hospital stay, inflammatory markers (C-reactive protein, interleukin-6, tumour necrosis factor)

Time frame for all outcomes: during hospitalisation

Other outcome measures: -

number of episodes of severe hyperglycaemia, length of stay, mortality rate

Other outcome measures: -

Other outcome measures: BG target < 140 mg/dL, mean daily BG, rate of hypoglycaemia, length of hospital stay

Datta 2007

Source: N/T

Primary outcome measure: -

Primary outcome measure: -

Secondary outcome measures: -

Secondary outcome measures: -

Other outcome measures: mean BG levels, % of BG values between 80 and 140 mg/dL, % of BG values between 141 and 200 mg/dL, % of BG values > 200 mg/dL, total doses of insulin administered, frequency of hypoglycaemia (BG < 60 mg/dL), total inpatient length of hospital stay, frequency of postoperative infections

Other outcome measures: mean BG levels

Gustafson 2002

Source: N/T

Primary outcome measure: -

Primary outcome measure: -

Secondary outcome measures: -

Secondary outcome measures: -

Other outcome measures: maintenance of BG within 180 and 200 mg/dL (intraoperative BG levels)

Other outcome measures: BG levels

-: denotes not reported

^aTrial document(s) refer to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers).

^bPublication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents, or multiple reports of a primary trial).

^cOther outcome measures refer to all outcomes not specified as primary or secondary outcome measures.

^dResults information has been submitted to ClinicalTrials.gov by the sponsor or investigator, but is not yet publicly available (or 'posted') on ClinicalTrials.gov.

BG: blood glucose; **EMA:** European Medicines Agency; **FDA:** US Food and Drug Administration; **ICU:** intensive care unit; **N/T:** no trial document available

Appendix 7. High risk of outcome reporting bias according to ORBIT classification

Trial ID	Outcome	High risk of bias (category A) ^a	High risk of bias (category D) ^b	High risk of bias (category E) ^c	High risk of bias (category G) ^d
Said 2013	N/D				
Umpierrez 2013	N/D				
Schroeder 2012	Hypoglycaemic events, other adverse events	Yes	Yes	No	No
Umpierrez 2011	N/D				
Korytkowski 2009	N/D				
Umpierrez 2007a	N/D				
Datta 2007	N/D				
Gustafson 2002	N/D				

^aClear that outcome was measured and analysed; trial report states that outcome was analysed but reports only that result was not significant (Classification 'A', table 2, [Kirkham 2010](#)).

^bClear that outcome was measured and analysed; trial report states that outcome was analysed but reports no results (Classification 'D', table 2, [Kirkham 2010](#)).

^cClear that outcome was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported due to non-significant results (Classification 'E', table 2, [Kirkham 2010](#)).

^dUnclear whether outcome was measured; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported due to non-significant results (Classification 'G', table 2, [Kirkham 2010](#)).

N/D: none detected; **ORBIT:** Outcome Reporting Bias In Trials

Appendix 8. Definition of endpoint measurements^a

Trial ID	All-cause mortality	Diabetes-related mortality	Length of hospital stay	Glycated haemoglobin (%)	Socioeconomic effects	All hypoglycaemic events	Severe/serious hypoglycaemia	Severe/serious adverse events other than hypoglycaemic episodes
Said 2013	Mortality rate (IO)	N/R	Mean hospital stay (days) (IO)	NR	NR	Hypoglycaemic episodes were classified as major (BG ≤ 40 mg/dL or associated with impaired mental status or loss of consciousness) or minor (BG between 40 and 59 mg/dL) events (IO).	Hypoglycaemic episodes were classified as major (BG ≤ 40 mg/dL or associated with impaired mental status or loss of consciousness) (IO).	NR
Umpierrez 2013	Mortality rate (IO)	N/R	Mean hospital stay (days) (IO)	Mean admission glycated haemoglobin (IO)	N/R	BG < 70 mg/dL (IO)	BG < 40 mg/dL (IO)	Postoperative wound infection, pneumonia, bacteraemia, acute renal and respiratory failure (IO)
Schroeder 2012	N/R	N/R	In-hospital length of stay (days) (IO)	N/R	N/R	BG < 70 mg/dL (IO)	Requiring intravenous glucose administration	Postoperative complications (IO)
Umpierrez 2011	Mortality rate (IO)	N/R	Mean hospital stay (days) (IO)	N/R	N/R	"Mild": BG < 70 mg/dL (IO)	BG < 40 mg/dL (IO)	Postoperative complications, wound infection, pneumonia, bacteraemia, respiratory failure, acute renal failure (IO)
Korytkowski 2009	N/R	N/R	Mean hospital stay (days) during enteral nutrition therapy (IO)	N/R	N/R	% of patient-days with ≥ 1 event and % of all glucose values < 3.9 mmol/L (IO)	N/R	Body temperature 100.4 °F, antibiotic use, arrhythmias, pulmonary emboli, deep venous thrombosis, wound infection, respiratory symptoms, cardiac arrest, liver abscess (IO)

(Continued)

Umpierrez 2007a	Mortality rate (IO)	N/R	Mean hospital stay (days) (IO)	Mean admission glycated haemoglobin	N/R	BG < 60 mg/dL or < 70 mg/dL (IO)	BG < 40 mg/dL (IO)	N/R
Datta 2007	N/R	N/R	Mean hospital stay (days) (IO)	Mean admission glycated haemoglobin (IO)	N/R	BG < 60 mg/dL (IO)	N/R	Postoperative infections (IO)
Gustafson 2002	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R

^aIn addition to definition of endpoint measurement, description of who measured the outcome (AO: adjudicated outcome measurement; IO: investigator-assessed outcome measurement; SO: self reported outcome measurement).

BG: blood glucose; **N/D:** not defined; **N/R:** not reported

Appendix 9. Adverse events (I)

Trial ID	Intervention(s) and comparator(s)	Partici- pants in- cluded in analysis (N)	Deaths (N)	Deaths (% of par- ticipants)	Partici- pants with at least 1 adverse event (N)	Partici- pants with at least 1 adverse event (%)	Partici- pants with at least 1 severe/seri- ous adverse event (N)	Partici- pants with at least 1 severe/seri- ous adverse event (%)
Said 2013	I: SSI (regular insulin)	22	0	-	0	-	0	-
	C1: 70/30 insulin SSI (regular insulin + NPH)	21	0	-	0	-	0	-
	C2: basal-bolus regimen (glargine + glulisine)	19	0	-	0	-	0	-
Umpierrez 2013	I: SSI (regular insulin)	74	0	0	7	9.4	6	8.1
	C1: basal-bolus regimen (glargine + glulisine + SSI glulisine)	144	0	0	21	14.5	17	11.8
	C2: basal-plus regimen (glargine + SSI glulisine)	133	3	2	20	15	17	12.7
Schroeder 2012	I: SSI (short-acting human insulin)	30	-	-	-	-	-	-
	C: basal-bolus regimen (NPH + regular insulin)	35	-	-	-	-	-	-
Umpierrez 2011	I: SSI (regular insulin)	107	1	0.9	26	24.2	19	17.7
	C: basal-bolus regimen (glargine + glulisine)	104	1	0.9	9	8.6	7	6.7
Korytkows- ki 2009	I: SSI (regular insulin) + NPH	25	-	-	11	44	4	16
	C: basal-bolus regimen (glargine + SSI regular insulin)	25	-	-	6	24	3	12
Umpierrez 2007a	I: SSI (regular insulin)	65	0	0	2	3	0	-
	C: basal-bolus regimen (glargine and glulisine + SSI glulisine)	65	1	1.5	2	3	1	1.5
Datta 2007	I: SSI (regular insulin)	39	-	-	2	5.1	0	-

(Continued)

	C: basal regimen (glargine) + regular insulin	42	-	-	2	4.7	0	-
Gustafson 2002	I: SSI (regular insulin)	25	-	-	-	-	-	-
	C: continuous insulin infusion (regular insulin)	25	-	-	-	-	-	-

-: denotes not reported

C: comparator; **I:** intervention; **NPH:** neutral protamine Hagedorn insulin; **SSI:** sliding scale insulin

Appendix 10. Adverse events (II)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants discontinuing trial due to an adverse event (N)	Participants discontinuing trial due to an adverse event (%)
Said 2013	I: SSI (regular insulin)	22	0	-
	C1: 70/30 insulin SSI (regular insulin + NPH)	21	0	-
	C2: basal-bolus regimen (glargine + glulisine)	19	0	-
Umpierrez 2013	I: SSI (regular insulin)	74	0	-
	C1: basal-bolus regimen (glargine + glulisine + SSI glulisine)	144	0	-
	C2: basal-plus regimen (glargine + SSI glulisine)	133	0	-
Schroeder 2012	I: SSI (short-acting human insulin)	30	0	-
	C: basal-bolus regimen (NPH + regular insulin)	35	0	-
Umpierrez 2011	I: SSI (regular insulin)	107	-	-
	C: basal-bolus regimen (glargine + glulisine)	104	-	-
Korytkowski 2009	I: SSI (regular insulin) + NPH	25	0	-
	C: basal-bolus regimen (glargine + SSI regular insulin)	25	0	-
Umpierrez 2007a	I: SSI (regular insulin)	65	0	-
	C: basal-bolus regimen (glargine and glulisine + SSI glulisine)	65	0	-
Datta 2007	I: SSI (regular insulin)	39	0	-
	C: basal regimen (glargine) + regular insulin	42	0	-
Gustafson 2002	I: SSI (regular insulin)	25	0	-
	C: continuous insulin infusion (regular insulin)	25	0	-

-: denotes not reported

C: comparator; **I:** intervention; **NPH:** neutral protamine Hagedorn insulin; **SSI:** sliding scale insulin

Appendix 11. Adverse events (III)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants with a specific adverse event (description)	Participants with at least 1 specific adverse event (N)	Participants with at least 1 specific adverse event (%)
Said 2013	I: SSI (regular insulin)	22	-	-	-
	C1: 70/30 insulin SSI (regular insulin + NPH)	21	-	-	-
	C2: basal-bolus regimen (glargine + glulisine)	19	-	-	-
Umpierrez 2013	I: SSI (regular insulin)	74	(1) Wound infections (2) Acute renal failure (3) Bacteraemia	(1) 1 (2) 3 (3) 3	(1) 1.3 (2) 4 (3) 4
	C1: basal-bolus regimen (glargine + glulisine + SSI glulisine)	144	(1) Wound infections (2) Pneumonia (3) Acute respiratory failure (4) Acute renal failure (5) Bacteraemia	(1) 1 (2) 3 (3) 1 (4) 9 (5) 7	(1) 0.6 (2) 2 (3) 0.6 (4) 6.2 (5) 4.8
	C2: basal-plus regimen (glargine + SSI glulisine)	133	(1) Wound infections (2) Acute respiratory failure (3) Acute renal failure (4) Bacteraemia (5) Mortality	(1) 3 (2) 2 (3) 8 (4) 4 (5) 3	(1) 2.2 (2) 1.5 (3) 6 (4) 3 (5) 2.2
Schroeder 2012	I: SSI (short-acting human insulin)	30	-	-	-
	C: basal-bolus regimen (NPH + regular insulin)	35	-	-	-
Umpierrez 2011	I: SSI (regular insulin)	107	(1) Wound infections (2) Pneumonia (3) Acute respiratory failure (4) Acute renal failure (5) Bacteraemia	(1) 11 (2) 3 (3) 5 (4) 11 (5) 2	(1) 10.2 (2) 2.8 (3) 4.6 (4) 10.2 (5) 1.8
	C: basal-bolus regimen (glargine + glulisine)	104	(1) Wound infections (2) Acute respiratory failure (3) Acute renal failure (4) Bacteraemia	(1) 3 (2) 1 (3) 4 (4) 1	(1) 2.8 (2) 0.9 (3) 3.8 (4) 0.9
Korytkowski 2009	I: SSI (regular insulin) + NPH	25	(1) Body temperature 100.4 °F (2) Arrhythmias (3) Pulmonary emboli (4) Respiratory symptoms (5) Cardiac arrest	(1) 8 (2) 2 (3) 1 (4) 2 (5) 1	(1) 32 (2) 8 (3) 4 (4) 8 (5) 4
	C: basal-bolus regimen (glargine + SSI regular insulin)	25	(1) Arrhythmias (2) Pulmonary emboli (3) Deep venous thrombosis (4) Wound infection (5) Respiratory symptoms	(1) 1 (2) 2 (3) 2 (4) 1 (5) 2	(1) 4 (2) 8 (3) 8 (4) 4 (5) 8

(Continued)

			(6) Liver abscess	(6) 1	(6) 4
Umpierrez 2007a	I: SSI (regular insulin)	65	-	-	-
	C: basal-bolus regimen (glargine and glulisine + SSI glulisine)	65	-	-	-
Datta 2007	I: SSI (regular insulin)	39	Postoperative infections	2	5.1
	C: basal regimen (glargine) + regular insulin	42	Postoperative infections	2	4.7
Gustafson 2002	I: SSI (regular insulin)	25	-	-	-
	C: continuous insulin infusion (regular insulin)	25	-	-	-

-: denotes not reported

C: comparator; **I:** intervention; **NPH:** neutral protamine Hagedorn insulin; **SSI:** sliding scale insulin

Appendix 12. Adverse events (IV)

Trial ID	Intervention(s) and comparator(s)	Partici- pants in- cluded in analysis (N)	Partici- pants with at least 1 hypogly- caemic episode (N)	Partici- pants with at least 1 hypogly- caemic episode (%)	Partici- pants with at least 1 noctur- nal hypo- glycaemic episode (N)	Partici- pants with at least 1 noctur- nal hypo- glycaemic episode (% partici- pants)	Partici- pants with at least 1 severe/se- rious hypo- glycaemic episode (N)	Partici- pants with at least 1 severe/se- rious hypo- glycaemic episode (%)
Said 2013	I: SSI (regular insulin)	22	1	4.5	-	-	-	-
	C1: 70/30 insulin SSI (regular insulin + NPH)	21	0	0	-	-	-	-
	C2: basal-bolus regimen (glargine + glulisine)	19	2	10.5	-	-	2	10.5
Umpierrez 2013	I: SSI (regular insulin)	74	2	2.7	-	-	0	0
	C1: basal-bolus regimen (glargine + glulisine + SSI glulisine)	74	2	2.7	-	-	0	0
	C2: basal-plus regimen (glargine + SSI glulisine)	144	23	16	-	-	1	4.3
Schroeder 2012	I: SSI (short-acting human insulin)	133	17	13	-	-	1	5.9
	C: basal-bolus regimen (NPH + regular insulin)	30	0	-	-	-	0	-
Umpierrez 2011	I: SSI (regular insulin)	35	2	5.7	-	-	0	-
	C: basal-bolus regimen (glargine + glulisine)	107	6	5.6	-	-	0	-
Korytkowski 2009	I: SSI (regular insulin) + NPH	12	0	-	-	-	-	-
	C: basal-bolus regimen (glargine + SSI regular insulin)	25	5	20	-	-	-	-
Umpierrez 2007a	I: SSI (regular insulin)	25	3	12	-	-	-	-
	C: basal-bolus regimen (glargine and glulisine + SSI glulisine)	65	2	3	-	-	0	-

(Continued)

Datta 2007	I: SSI (regular insulin)	65	2	3	-	-	0	-
	C: basal regimen (glargine) + regular insulin	39	1	2.6	-	-	-	-
Gustafson 2002	I: SSI (regular insulin)	42	-	-	-	-	-	-
	C: continuous insulin infusion (regular insulin)	25	-	-	-	-	-	-

-: denotes not reported

C: comparator; **I:** intervention; **NPH:** neutral protamine Hagedorn insulin; **SSI:** sliding scale insulin

Appendix 13. Survey of authors providing information on included trials

Trial ID	Date trial author contacted	Date trial author replied	Date trial author was asked for additional information (short summary)	Date trial author provided data (short summary)
Said 2013	N/A	N/A	N/A	N/A
Umpierrez 2013	22 October 2015	22 October 2015	22 October 2015 We asked if blinding of outcome assessment was performed.	22 October 2015 Trial authors did not have an independent adjudication board.
Schroeder 2012	25 July 2015	25 July 2015	25 July 2015 We asked if the statistical data in Figure 2 of the publication were correct.	25 July 2015 Trial authors agreed with our observations.
Umpierrez 2011	22 October 2015	22 October 2015	22 October 2015 We asked if blinding of outcome assessment was performed.	22 October 2015 Trial authors did not have an independent adjudication board.
Korytkowski 2009	21 October 2015	No reply	N/A	N/A
Umpierrez 2007a	22 October 2015	22 October 2015	22 October 2015 We asked if blinding of outcome assessment was performed.	22 October 2015 Trial authors did not have an independent adjudication board.
Datta 2007	21 October 2015	No reply	N/A	N/A
Gustafson 2002	21 October 2015 16 June 2016	No reply	N/A	N/A
N/A: not applicable				

Appendix 14. Checklist to aid consistency and reproducibility of GRADE assessments

		(1) All-cause mortality	(2) Diabetes-related mortality	(3) Severe hypoglycaemic episodes	(4) Length of hospital stay	(5) Adverse events other than hypoglycaemic episodes (postoperative complications)	(6) Mean blood glucose levels	(7) Socioeconomic effects
Trial limitations (risk of bias)^a	Was random sequence generation used (i.e. no potential for selection bias)?	Unclear	N/R	Unclear	Unclear	Unclear	Unclear	N/R
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear		Unclear	Unclear	Unclear	Unclear	
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or was outcome not likely to be influenced by lack of blinding?	Yes		No (↓)	Yes	No (↓)	No (↓)	
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes		No (↓)	Yes	No (↓)	No (↓)	
	Was an objective outcome used?	Yes		Unclear	Yes	Yes	Yes	
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^e	Yes		Yes	Yes	Yes	Yes	
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes		Yes	Yes	Yes	Yes	
	No other biases reported (i.e. no potential of other bias)?	Yes		Yes	Yes	Yes	Yes	
	Did the trials end as scheduled (i.e. not stopped early)?	Yes		Yes	Yes	Yes	Yes	

Yes	Yes	No (↓)	Yes
Substantial	Substantial	Substantial	Substantial
Yes	No (↓)	No (↓)	Yes
Low	Low	High (↓)	Moderate
Not statistically significant	Not statistically significant	Statistically significant (↓)	Not Statistically significant
Applicable	Applicable	Applicable	Applicable
Applicable	Applicable	Applicable	Applicable
Unclear	Yes	Yes	Yes
Sufficient	Sufficient	Sufficient	Sufficient
Yes	Yes	Yes	Yes
No (↓)	No (↓)	Yes (↓)	Yes
Low (↓)	Low (↓)	Low (↓)	Low (↓)

(Continued)

Inconsistency^b	Point estimates did not vary widely?	Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least 1 of the included studies point estimate; some: confidence intervals overlap but not all overlap at least 1 point estimate; no: at least 1 outlier: where the confidence interval of some of the studies does not overlap with those of most included studies)?	Substantial
	Was the direction of effect consistent?	Yes
	What was the magnitude of statistical heterogeneity (as measured by I ² : low (I ² < 40%), moderate (I ² 40% to 60%), high (I ² > 60%))?	Low
Indirectness	Was the test for heterogeneity statistically significant (P < 0.1)?	Not statistically significant
	Were the populations in the included studies applicable to the decision context?	Applicable
	Were the interventions in the included studies applicable to the decision context?	Applicable
	Was the included outcome not a surrogate outcome?	Yes
	Was the outcome time frame sufficient?	Sufficient
Imprecision^c	Were the conclusions based on direct comparisons?	Yes
	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)? ^e	Low (↓)

(Continued)

	What is the magnitude of the number of included studies (large: > 10 studies, moderate: 5 to 10 studies, small: < 5 studies)? ^e	Small (↓)	Moderate	Moderate	Small (↓)	Moderate
	Was the outcome a common event (e.g. occurs more than 1/100)?	No (↓)	Yes	N/A	Yes	N/A
Publication bias^d	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	N/A	N/A	N/A	N/A	N/A
	There was no discrepancy in findings between published and unpublished trials?	N/A	N/A	N/A	N/A	N/A

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials.

^bQuestions on inconsistency are based primarily on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2 .

^cWhen judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful.

^dQuestions address the comprehensiveness of the search strategy, industry influence, funnel plot asymmetry, and discrepancies between published and unpublished trials.

^eDepends on the context of the systematic review area.

(↓): key item for potential downgrading the certainty of the evidence (GRADE) as shown in the footnotes of the 'Summary of findings' table(s)

N/A: not applicable; **N/R:** not reported

CONTRIBUTIONS OF AUTHORS

Luis E Colunga-Lozano (LECL): protocol draft, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft, and future review updates.

Francisco Javier Gonzalez Torres (FGT): data extraction, data analysis, review draft.

Netzahualpilli Delgado-Figueroa (NDF): protocol draft, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft.

Daniel A Gonzalez-Padilla (DGP): trial selection, data extraction, data analysis, data interpretation, review draft.

Adrian V Hernandez (AVH): protocol draft, trial selection, data extraction, data analysis, data interpretation, review draft.

Yuan Roman (YR): protocol draft, trial selection, data extraction, data analysis, data interpretation, review draft.

Carlos A Cuello-García (CCG): protocol draft, trial selection, data extraction, data analysis, data interpretation, review draft.

DECLARATIONS OF INTEREST

Luis E Colunga-Lozano: none known

Francisco Javier Gonzalez Torres: none known

Netzahualpilli Delgado-Figueroa: none known

Daniel A Gonzalez-Padilla: none known

Adrian V Hernandez: none known

Yuan Roman: none known

Carlos A Cuello-García: The American Society of Hematology and the American College of Rheumatology paid for the institution and I worked as a policy development consultant. I received a grant from the Cochrane Methods Innovation Fund, which was paid to my institution.

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Internal sources

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Library services to obtain the articles

- McMaster University, Canada.

Library services to obtain the articles

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

It was not possible to evaluate the outcome measure glycated haemoglobin because no trial followed participants over the prolonged period of time necessary to establish reliable glycated haemoglobin measures (three months). We instead used mean blood glucose values during the hospital stay of the participants. In addition to blood glucose measurements we also reported hyperglycaemic ranges, where provided, and the total daily insulin dose applied.

For the outcome hypoglycaemic episodes, we have reported only severe hypoglycaemic episodes in the Abstract, Plain language summary, and 'Summary of findings' table because this outcome measure is less prone to performance and detection bias compared to non-severe hypoglycaemic episodes.

NOTES

Portions of the Background and Methods sections, Appendices, Additional tables, and Figures 1 to 3 of this review are based on a standard template established by the Cochrane Metabolic and Endocrine Disorders Group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Inpatients; Cause of Death; Diabetes Mellitus, Type 2 [*drug therapy] [mortality]; Hypoglycemia [chemically induced]; Hypoglycemic Agents [*administration & dosage] [adverse effects]; Insulin [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Aged; Humans; Middle Aged