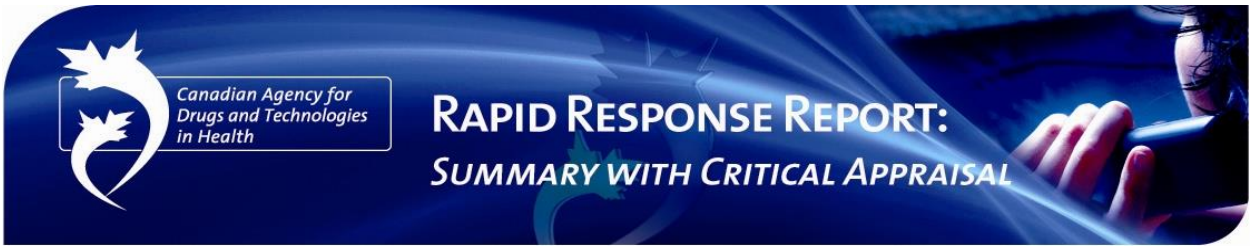

TITLE: Basal-Bolus Versus Sliding-Scale Insulin Therapy in the Acute Care Hospital Setting: A Review of Comparative Clinical Effectiveness and Cost-Effectiveness

DATE: 12 January 2017

CONTEXT AND POLICY ISSUES

When patients with diabetes are hospitalized, their glucose control may be suboptimal because oral medications are often stopped on admission.[1] In fact, high blood sugar levels, or hyperglycemia, are common among hospitalized patients[2] and linked to complications, such as increased morbidity, mortality, and hospital stay.[3] Although low blood sugar levels, or hypoglycemia are serious risks associated with insulin therapy, potentially leading to arrhythmias and other cardiac events,[2,4] better glucose control with insulin for both type 1 and type 2 diabetes may improve clinical outcomes and prevent complications in hospitals.[3]

Hyperglycemia occurring during hospital stay was traditionally controlled, using sliding-scale insulin therapy, consisting of the administration of regular or rapid-acting insulin approximately five to 30 minutes before meals, based on before-meal measurements of capillary blood glucose.[3,5] Basal-bolus insulin therapy more closely mimics physiological insulin secretion, where pancreatic beta cells release insulin continuously to maintain basal metabolic glucose regulation and extra insulin in response to meals,[2] and is recommended today.[3] In basal-bolus insulin therapy, a patient would be given a basal (long-acting) insulin once or twice daily, a nutritional (short- or rapid-acting) insulin before meals, and a correctional (short- or rapid-acting) insulin for any unanticipated before-meal hyperglycemia.[2] Long-acting insulins include detemir and glargine,[4,5] and short-acting insulins include aspart and glulisine.[5] There are also intermediate-acting insulins, such as neutral protamine Hagedorn (NPH).[4] Despite its inconsistency with physiological insulin secretion, sliding-scale insulin therapy continues to be widely used today because of its simplicity and convenience.[3,5]

The purpose of this report is to provide evidence on the clinical benefits and harms and cost-effectiveness of basal-bolus versus sliding-scale insulin therapy for adult patients with type 1 or type 2 diabetes in the acute care hospital setting.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of basal-bolus versus sliding-scale insulin therapy for adult patients with type 1 and type 2 diabetes in the acute care hospital setting?

2. What is the cost-effectiveness of basal-bolus versus sliding-scale insulin therapy for adult patients with type 1 and type 2 diabetes in the acute care hospital setting?

KEY FINDINGS

One systematic review and three primary studies on comparative clinical effectiveness in patients with type 1 or type 2 diabetes or newly-diagnosed or recurrent hyperglycemia were found. Patients receiving basal-bolus or basal-corrective insulin therapy had lower blood glucose levels and a lower risk of hyperglycemia than those receiving sliding-scale insulin therapy. No significant differences were found in the risk of adverse events between the two interventions. Results on lengths of hospitalization and the risk of hypoglycemia were mixed across the studies. No economic evaluations fulfilling the selection criteria were found.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, and Canadian and major international health technology agencies. A focused Internet search was also conducted. No filters were applied to limit the retrieval by study type. The search was limited to English language documents, published between January 1, 2011 and December 13, 2016.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially-relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with type 1 or type 2 diabetes in the acute care hospital setting (i.e., excluding critical care or ICU settings or pregnancy)
Intervention	Basal-bolus insulin therapy (i.e., administered subcutaneously or via insulin pump, to be presented separately, if possible)
Comparator	Sliding-scale insulin therapy
Outcomes	Q1: Clinical effectiveness (e.g., all-cause and diabetes-related mortality, achievement of blood glucose targets, fasting blood glucose, HbA1c, or length of hospitalization) or safety (e.g., hyperglycemia, hypoglycemia, infection rate, or pneumonia) Q2: Cost-effectiveness (e.g., cost per QALY or cost per health outcome)

Study Designs	HTAs, SRs, MAs, RCTs, non-randomized studies, and economic evaluations

HbA1c = glycated hemoglobin; HTA = health technology assessment; ICU = intensive care unit; MA = meta-analysis; QALY = quality-adjusted life years; RCT = randomized controlled trial; SR = systematic review

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, or if they were published prior to 2011.

Critical Appraisal of Individual Studies

The included systematic review (SR) was critically appraised, using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[6] The included primary studies were critically appraised, using the Downs and Black checklist.[7] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 474 citations were identified in the literature search. Following screening of titles and abstracts, 455 citations were excluded, and 19 potentially-relevant reports from the electronic search were retrieved for full-text review. No potentially-relevant publications were retrieved from the grey literature search. Of the 19 potentially-relevant articles, 15 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A summary of the characteristics of the included literature is presented in Appendix 2.

<u>Clinical Benefits and Harms of Basal-Bolus Versus Sliding-Scale Insulin Therapy in the Acute Care Hospital Setting</u>

A total of one SR[5] and three primary studies[1,3,8] provided information on the clinical effectiveness and safety of basal-bolus versus sliding-scale insulin therapy in the acute care hospital setting.

Study Design

The SR[5] included four randomized controlled trials (RCTs) and five cohort studies, with sample sizes that ranged from 20 to 353 patients. The primary studies[1,3,8] included two cross-sectional studies on 202[8] and 416[3] patients, based on a retrospective review of medical records, and one RCT on 65 patients.[1] The SR[5] was conducted in 2016, the two cross-sectional studies[3,8] were conducted in 2014, and the RCT[1] was conducted in 2012.

Country of Origin

The SR[5] and primary studies[1,3,8] were conducted in Israel,[1] Malaysia,[8] Pakistan,[3] and Spain.[5]

Patient Population

The SR[5] included adult patients with type 1 or type 2 diabetes or newly-diagnosed hyperglycemia, admitted to a non-critical medical or surgical hospital ward, with various indications. The two cross-sectional studies[3,8] included adult patients with type 2 diabetes, admitted to a non-critical medical hospital ward, with various indications[3] or severe and acute hyperglycemia.[8] The RCT[1] included patients with type 1 or type 2 diabetes or recurrent hyperglycemia, admitted to an orthopaedic hospital ward, with falls or complications of diabetic feet.

Interventions and Comparators

The SR[5] and primary studies[1,3,8] compared basal-bolus[1,3,5,8] or basal-corrective[5] insulin therapy to sliding-scale insulin therapy. The SR[5] and two primary studies[1,8] noted that the daily insulin doses used were consistently higher with basal-bolus insulin therapy, compared to sliding-scale insulin therapy, primarily because in basal-bolus-treated patients, the insulin units were calculated based on the patients' body weight and adjusted based on the blood glucose levels throughout hospitalization.[8]

Outcomes

The SR[5] and primary studies[1,3,8] included, as outcomes, blood glucose levels,[1,3,5,8] lengths of hospitalization,[1,3,5] adverse events,[1,5] and hyper[1,3]- or hypo[1,3,5,8]-glycemic events. The SR[5] rated the quality of evidence, using the Cochrane Risk of Bias tool for RCTs and Newcastle-Ottawa scale for cohort studies.

<u>Cost-Effectiveness of Basal-Bolus Versus Sliding-Scale Insulin Therapy in the Acute Care Hospital Setting</u>

No economic evaluations fulfilling the selection criteria were found.

Summary of Critical Appraisal

A summary of the critical appraisal of the included literature is presented in Appendix 3.

<u>Clinical Benefits and Harms of Basal-Bolus Versus Sliding-Scale Insulin Therapy in the Acute Care Hospital Setting</u>

The SR[5] was of mixed quality based on the assessment conducted with the AMSTAR tool.[6] The SR[5] provided a detailed literature search strategy, listed the included studies and described their characteristics, assessed the scientific quality of the included studies, used the appropriate methods to combine the study findings, and declared no conflict of interest. However, the SR[5] did not provide a priori design, did not perform duplicate study selection or data extraction, did not conduct a comprehensive literature search, did not list the excluded studies, did not use the scientific quality of the included studies in formulating conclusions, and assessed the likelihood of publication bias to be high.

The two cross-sectional studies[3,8] were also of mixed quality, based on the assessment conducted with the Downs and Black checklist,[7] excluding the non-applicable items on loss to follow-up, intervention assignment, blinding, and compliance. For reporting, both studies[3,8]

described the study objective, main outcomes, and main findings, with estimates of random variability and actual probability values. However, one study[3] reported limited characteristics of the study subjects and did not describe potential confounders. The other study[8] did not describe the interventions in detail. Both studies[3,8] did not report adverse events, other than hypoglycemic events. For external validity, in both studies,[3,8] while the study design was representative of the care setting, the study subjects were identified through a review of medical records at a single hospital and might not have been representative of the entire population of interest. For bias, the statistical tests used to assess the main outcomes were appropriate, and the main outcome measures were valid and reliable in both studies.[3,8] For confounding, in both studies,[3,8] the study subjects in different intervention groups were recruited from the same population over the same period of time. However, while there was no concern around confounding in one study,[8] because the other study[3] provided limited characteristics of the study subjects, it is unclear whether adjustment for confounding was needed. For both studies,[3,8] the study subjects were not randomized to intervention groups but rather cohorts who received different interventions in real-life settings. For power, there was no discussion on whether the study had sufficient power to detect a clinically-important effect in both studies.[3,8]

The RCT[1] was of moderate quality, based on the assessment conducted with the Downs and Black checklist,[7] excluding the non-applicable items on compliance. For reporting, the RCT[1] described the study objective, main outcomes, study subjects, interventions, and main findings, including adverse events. However, the RCT[1] did not describe potential confounders and did not provide estimates of random variability or actual probability values. For external validity, while the study design was representative of the care setting, the study subjects were identified at a single hospital and might not have been representative of the entire population of interest. For bias, the statistical tests used to assess the main outcomes were appropriate, and the main outcome measures were valid and reliable. However, whether an attempt was made to blind the study subjects to the intervention they received or the staff measuring the main outcomes was not discussed. For confounding, the study subjects in different intervention groups were recruited from the same population over the same period of time and randomized to intervention groups; there was no concern around confounding; and no study subjects were lost to follow-up. For power, there was no discussion on whether the study had sufficient power to detect a clinically-important effect.

Cost-Effectiveness of Basal-Bolus Versus Sliding-Scale Insulin Therapy in the Acute Care Hospital Setting

No economic evaluations fulfilling the selection criteria were found.

Summary of Findings

A summary of the findings of the included literature is presented in Appendix 4.

What is the comparative clinical effectiveness of basal-bolus versus sliding-scale insulin therapy for adult patients with type 1 and type 2 diabetes in the acute care hospital setting?

Blood Glucose Levels

One SR,[5] two cross-sectional studies,[3,8] and one RCT[1] reported that patients with type 1[1,5] or type 2[1,3,5,8] diabetes or newly-diagnosed[5] or recurrent[1] hyperglycemia receiving basal-bolus[1,3,5,8] or basal-corrective[5] insulin therapy had lower blood glucose levels than those receiving sliding-

scale insulin therapy. The findings were significant in the SR[5] and two primary studies.[1,8] The findings were also likely significant in the other primary study,[3] which reported *p*-values of less than 0.001 for three-group comparisons, among basal-bolus, sliding-scale, and another intervention (i.e., pre-mixed insulin therapy), which was out of scope for this report and excluded. In that study,[3] basal-bolus and sliding-scale regimens demonstrated the largest differences for the outcome.

One RCT[1] reported that in patients with type 1 or type 2 diabetes or recurrent hyperglycemia, the differences in daily blood glucose levels between basal-bolus and sliding-scale insulin therapy generally increased over time, favouring basal-bolus and reaching significance (i.e., *p*-values of less than 0.05) on the sixth day of hospitalization and onward.

Lengths of Hospitalization

One SR[5] reported that in patients with type 1 or type 2 diabetes or newly-diagnosed hyperglycemia, no significant differences were found in mean lengths of hospital stay between basal-bolus or basal-corrective insulin therapy and sliding-scale insulin therapy. However, one cross-sectional study[3] and one RCT[1] reported that patients with type 1[1] or type 2[1,3] diabetes or recurrent hyperglycemia[1] receiving basal-bolus insulin therapy had shorter hospital stay than those receiving sliding-scale insulin therapy. The findings were significant in the RCT[1] and likely also significant in the cross-sectional study,[3] which reported *p*-values of less than 0.001 for three-group comparisons, among basal-bolus, sliding-scale, and another intervention (i.e., pre-mixed insulin therapy), which was out of scope for this report and excluded. In that study,[3] basal-bolus and sliding-scale regimens demonstrated the largest differences for the outcome.

Adverse Events

One SR[5] reported that in patients with type 1 or type 2 diabetes or newly-diagnosed hyperglycemia, there were no significant differences in the risk of adverse events between those receiving basal-bolus or basal-corrective insulin therapy and those receiving sliding-scale insulin therapy. One RCT[1] also reported that in patients with type 1 or type 2 diabetes or recurrent hyperglycemia, no differences were found in the rate of complications between basal-bolus and sliding-slide insulin therapy.

Hyperglycemic Events

One cross-sectional study[3] and one RCT[1] reported that in patients with type 1[1] or type 2[1,3] diabetes or recurrent hyperglycemia,[1] the patients receiving basal-bolus insulin therapy had a lower risk of hyperglycemia, compared to those receiving sliding-scale insulin therapy. The findings were significant in the RCT[1] and likely also significant in the cross-sectional study,[3] which reported *p*-values of less than 0.001 for three-group comparisons, among basal-bolus, sliding-scale, and another intervention (i.e., pre-mixed insulin therapy), which was out of scope for this report and excluded. In that study,[3] basal-bolus and sliding-scale regimens demonstrated the largest differences for the outcome.

Hypoglycemic Events

One SR[5] reported that in patients with type 1 or type 2 diabetes or newly-diagnosed hyperglycemia, there were no significant differences in the risk of hypoglycemia or severe hypoglycemia between those receiving basal-bolus or basal-corrective insulin therapy and those

receiving sliding-scale insulin therapy. One RCT[1] also reported that in patients with type 1 or type 2 diabetes or recurrent hyperglycemia, no significant differences were found in the mean number of hypoglycemic events between basal-bolus and sliding-scale insulin therapy, although there were two episodes of severe hypoglycemia, requiring intravenous glucose administration in patients receiving basal-bolus insulin therapy.

Two cross-sectional studies[3,8] on patients with type 2 diabetes reported contradicting results. While one study[3] reported that the patients receiving basal-bolus insulin therapy had a greater risk of hypoglycemia, compared to those receiving sliding-scale insulin therapy, the other study[8] reported that the patients receiving basal-bolus insulin therapy had a lower risk of hypoglycemia, compared to those receiving sliding-scale insulin therapy. The findings were significant in one study[8] and likely also significant in the cross-sectional study,[3] which reported *p*-values of less than 0.001 for three-group comparisons, among basal-bolus, sliding-scale, and another intervention (i.e., pre-mixed insulin therapy), which was out of scope for this report and excluded. In that study,[3] basal-bolus and sliding-scale regimens demonstrated the largest differences for the outcome.

What is the cost-effectiveness of basal-bolus versus sliding-scale insulin therapy for adult patients with type 1 and type 2 diabetes in the acute care hospital setting?

No economic evaluations fulfilling the selection criteria were found.

Limitations

Of the nine studies included in the SR[5] and the three primary studies[1,3,8] included in this report, seven studies were retrospective observational in design, where patients were non-randomly assigned to interventions in real-life settings. Despite this, outcomes were obtained from cross-sectional data at a single point in time and likely have been confounded. The RCT[1] included in this report also had a sample size of 65 patients. All included studies had short follow-up durations, ranging from three days to 30 days after hospital discharge. Prospective RCTs with large samples and longer follow-up are needed[5] to confirm and clarify the findings presented in this report.

The results of the meta-analysis reported in the SR[5] were associated with large heterogeneity, reflecting significant differences in the study design, definitions of adverse events, and follow-up durations across the included studies[5] and need to be confirmed. Across the SR[5] and primary studies[1,3,8] included in this report, the insulin used in the basal-bolus and sliding-scale insulin regimens varied, and it is unclear whether the results were directly comparable.

The study subjects included in the RCT[1] were elderly people with orthopaedic indications and might have been different from the study subjects included in the SR[5] or other primary studies.[3,8] The basal-bolus intervention in the RCT[1] had additional components, such as provider and patient education, which were not provided with the sliding-scale intervention and should be taken into account when reviewing the study results.

The generalizability of the primary studies conducted in one[1,8] or two[3] health care institutions in Israel,[1] Malaysia,[8] and Pakistan[3] to Canadian settings is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One SR and three primary studies on comparative clinical effectiveness in patients with type 1 or type 2 diabetes or newly-diagnosed or recurrent hyperglycemia were found. Patients receiving basal-bolus or basal-corrective insulin therapy had lower blood glucose levels than those receiving sliding-scale insulin therapy. While the SR reported no significant differences in mean lengths of hospital stay between the two interventions, two primary studies reported that patients receiving basal-bolus insulin therapy had shorter hospital stay than those receiving sliding-scale insulin therapy. The SR and one primary study reported no significant differences in the risk of adverse events between the two interventions. Two primary studies reported that patients receiving basal-bolus insulin therapy had a lower risk of hyperglycemia, compared to those receiving sliding-scale insulin therapy. Results on the risk of hypoglycemia were mixed: the SR and one primary study reporting no significant differences between the two interventions; and two primary studies reporting contradicting results, one with a greater risk and the other with a lower risk in patients receiving basal-bolus insulin therapy, compared to those receiving sliding-scale insulin therapy. The quality of the included literature was mixed. Prospective clinical trials with large samples, longer follow-up, and high quality are needed to confirm and clarify the findings. No economic evaluations fulfilling the selection criteria were found.

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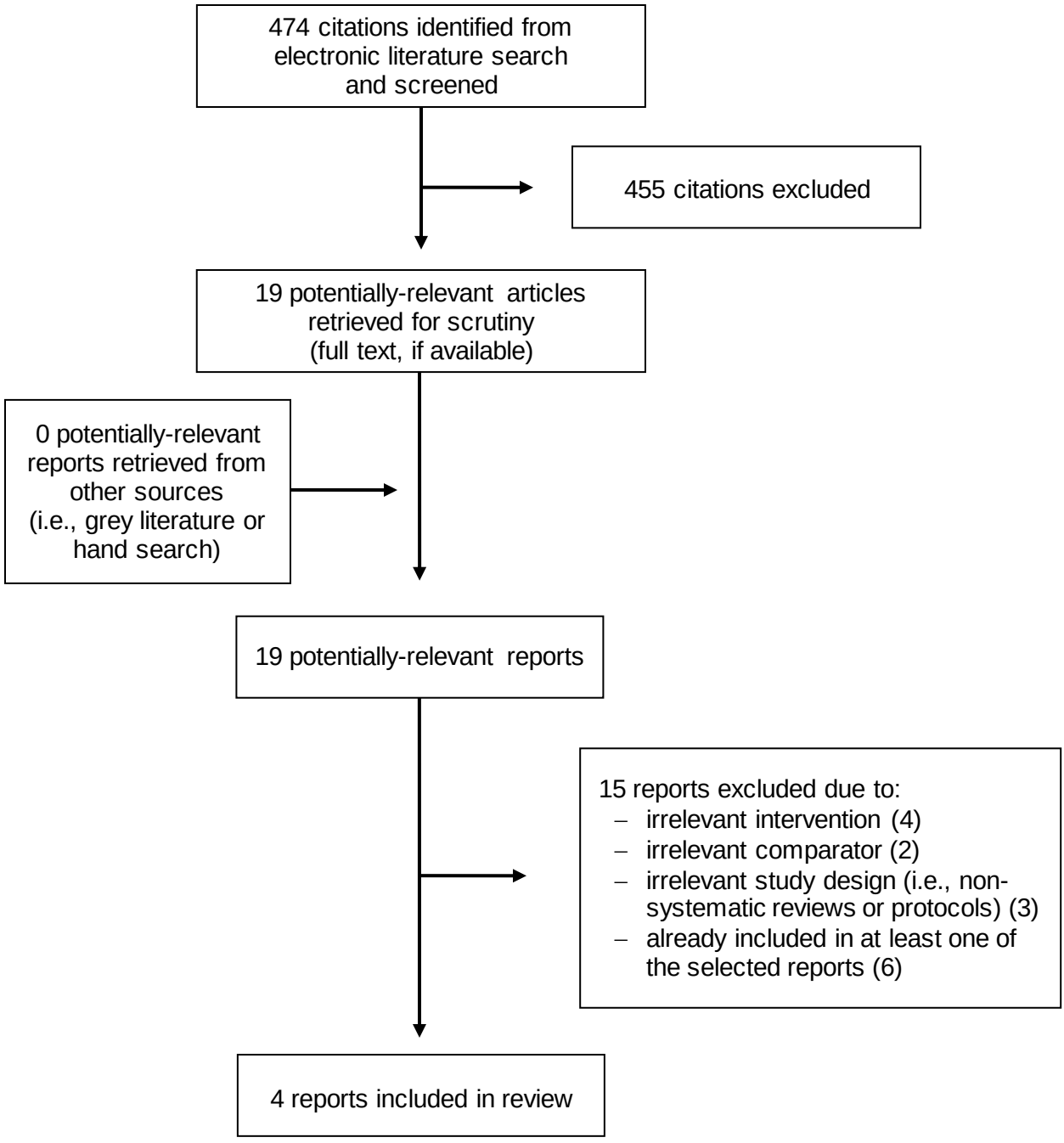
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Gómez Cuervo[5] 2016 Spain	SR of 4 RCTs and 5 cohort studies, published between 2005 and 2013 MA and quality assessment using Cochrane Risk of Bias tool for RCTs and Newcastle-Ottawa scale for cohort studies	Adult* patients with type 1 or type 2 diabetes or newly-diagnosed hyperglycemia, admitted to a non-critical medical or surgical hospital ward, with various indications *Defined as 18 years of age or older	Basal-bolus or basal-corrective insulin therapy* *Defined as the subcutaneous administration of fixed-dose lente or ultra-lente basal insulin, together with boluses of ultra-rapid-acting insulin associated with food intake (boluses may be fixed [prandial] or depend on blood glucose levels before intake [corrective])	Sliding-scale insulin therapy* *Defined as the administration of insulin boluses, based on capillary blood glucose monitoring before meals	Blood glucose levels, lengths of hospitalization, adverse events*, and hypoglycemic events Follow-up during hospital stay (in 6 studies), up to 30 days after discharge (in 2 studies), or for the first 3 days after hospital admission (in 1 study) *Defined as any complications recorded, including hospital-acquired infections and mortality, during hospital stay or follow-up periods

MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review

Table A2: Characteristics of Included Primary Studies					
First Author, Publication Year, Country	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
Akhtar[3] 2014 Pakistan	Cross-sectional study*, based on a retrospective review of medical records at two health care institutions *While this study included three cohorts receiving three different interventions for comparison, one of the interventions (i.e., pre-mixed insulin therapy) was out of scope for this report and excluded.	Adult* patients with type 2 diabetes, admitted to a non-critical medical hospital ward, with various indications *Defined as 18 years of age or older	Basal-bolus insulin therapy* *Defined as the administration of multiple short-acting insulin before each meal as boluses and intermediate insulin (i.e., NPH) as basal at bedtime	Sliding-scale insulin therapy* *Defined as the administration of regular insulin at adjusted doses in accordance with the results of preprandial blood glucose levels	Blood glucose levels, lengths of hospitalization, and hyper- and hypo-glycemic events Follow-up during hospital stay
Zaman Huri[8] 2014 Malaysia	Cross-sectional study, based on a retrospective review of medical records at a hospital	Adult* patients with type 2 diabetes, admitted to general medical hospital units, with severe and acute hyperglycemia *Defined as 18 years of age or older	Basal-bolus insulin therapy* *Using Actrapid and Insulatard	Sliding-scale insulin therapy* *Using Actrapid	Blood glucose levels and hypoglycemic events Follow-up during hospital stay
Schroeder[1] 2012 Israel	RCT at a hospital	Patients* with type 1 or type 2 diabetes or recurrent hyperglycemia, admitted to an orthopaedic hospital ward, with minor trauma (i.e., falls at home or while walking) or complications of diabetic feet	Basal-bolus insulin therapy*, accompanied by physician and nurse education on intensive glucose monitoring, diabetologist consultation with the medical staff, and patient education on proper diet and glucose	Sliding-scale insulin therapy* *Defined as the administration of short-acting insulin (i.e., Actrapid), according to the patient's blood glucose levels, 4 times	Blood glucose levels, lengths of hospitalization, adverse events*, and hyper- and hypo-glycemic events Follow-up during

Table A2: Characteristics of Included Primary Studies					
First Author, Publication Year, Country	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
		*While this study provided no inclusion criteria on age, the mean age of the included patients was 70 or 71 years old for the intervention and control groups, respectively.	control *Defined as the administration of regular insulin, 3 times a day (i.e., before each meal), and NPH, once a day (i.e., at bedtime), all according to the patient's blood glucose levels	a day (i.e., before each meal and at bedtime)	hospital stay *Including complications, such as infections and ischemic events, related or unrelated to orthopaedic operations

NPH = neutral protamine Hagedorn; RCT = randomized controlled trial

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Included Systematic Reviews Using AMSTAR[6] link to AMSTAR checklist

Strengths	Limitations
Gómez Cuervo 2016[5]	
• A detailed literature search strategy and a flow diagram for the search results were provided. • A list of the included studies and their characteristics were provided. • The scientific quality of the included studies was assessed and documented, and the included studies were rated on their quality. • The methods used to combine the findings of studies were appropriate. • No conflict of interest was declared.	• No "a priori" design was provided. • There was no duplicate study selection or data extraction. • The literature search performed was not comprehensive, including one database and no grey literature. • A list of the excluded studies was not provided. • The scientific quality of the included studies was not used in formulating conclusions. • The likelihood of publication bias was assessed to be high.

AMSTAR = Assessment of Multiple Systematic Reviews

Table A4: Strengths and Limitations of Included Primary studies Using Downs and Black[7] link to Downs and Black

Strengths	Limitations	Non-Applicable Items
Akhtar 2014[3]		
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The interventions were described. • The main findings were described. • Estimates of the random variability in the data for the main outcomes were provided. • Actual probability values were reported. External Validity • The study design was representative of the care setting. Bias • The statistical tests used to assess the main outcomes were appropriate. • The main outcome measures were accurate (i.e., valid and	Reporting • Limited characteristics of the study subjects were described. • Potential confounders in each intervention group of the study subjects were not described. • No adverse events, other than hypoglycemic events, were reported. External Validity • The study subjects were identified through a review of medical records at two health care institutions and might not have been representative of the entire population of interest. Confounding • The study subjects were not randomized to intervention groups but rather cohorts who	Reporting • The characteristics of the study subjects lost to follow-up were not described, since loss to follow-up was not applicable to this study. Bias • No attempts were made to blind the study subjects to the intervention they received or the staff measuring the main outcomes, since blinding was not applicable to this study. • Results of any post hoc analyses were not described, since no post hoc

Table A4: Strengths and Limitations of Included Primary studies Using Downs and Black[7] link to Downs and Black		
Strengths	**Limitations**	**Non-Applicable Items**
reliable). Confounding • The study subjects in different intervention groups were recruited from the same population over the same period of time.	received different interventions in real-life settings. • There was no adjustment for confounding in the analysis for the main findings. Because limited characteristics of the study subjects were described, it is unclear whether such adjustment was needed. Power • There was no discussion on whether the study had sufficient power to detect a clinically-important effect.	analyses were conducted in this study. • Reliability on compliance with the interventions was not applicable to this study and not reported. Confounding • Concealment of intervention assignment was not applicable to this study and not reported. • Loss to follow-up was not applicable to this study and not taken into account.
Zaman Huri 2014[8]		
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the study subjects were described. • The distributions of potential confounders in each intervention group of the study subjects were described. • The main findings were described. • Estimates of the random variability in the data for the main outcomes were provided. • Actual probability values were reported. External Validity • The study design was representative of the care setting. Bias • The statistical tests used to assess the main outcomes	Reporting • The interventions were not described in detail. • No adverse events, other than hypoglycemic events, were reported. External Validity • The study subjects were identified through a review of medical records at a hospital and might not have been representative of the entire population of interest. Confounding • The study subjects were not randomized to intervention groups but rather cohorts who received different interventions in real-life settings. Power • There was no discussion on whether the study had	Reporting • The characteristics of the study subjects lost to follow-up were not described, since loss to follow-up was not applicable to this study. Bias • No attempts were made to blind the study subjects to the intervention they received or the staff measuring the main outcomes, since blinding was not applicable to this study. • Results of any post hoc analyses were not described, since no post hoc analyses were

Table A4: Strengths and Limitations of Included Primary studies Using Downs and Black[7] link to Downs and Black		
Strengths	**Limitations**	**Non-Applicable Items**
were appropriate. • The main outcome measures were accurate (i.e., valid and reliable). Confounding • The study subjects in different intervention groups were recruited from the same population over the same period of time. • Based on the description of the characteristics of the study subjects separately for the intervention and control groups, there was no concern around confounding, requiring no adjustment in the analysis for the main findings.	sufficient power to detect a clinically-important effect.	conducted in this study. • Reliability on compliance with the interventions was not applicable to this study and not reported. Confounding • Concealment of intervention assignment was not applicable to this study and not reported. • Loss to follow-up was not applicable to this study and not taken into account.
Schroeder 2012[1]		
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the study subjects were described. • The interventions were described. • The main findings were described. • Important adverse events were reported. • No study subjects were lost to follow-up. External Validity • The study design was representative of the care setting. Bias • The statistical tests used to assess the main outcomes were appropriate. • The main outcome measures were accurate (i.e., valid and reliable).	Reporting • The distributions of potential confounders in each intervention group of the study subjects were not described. • Estimates of the random variability in the data for the main outcomes were not provided. • Actual probability values were not reported. External Validity • The study subjects were identified at a single hospital and might not have been representative of the entire population of interest. Bias • Whether an attempt was made to blind the study subjects to the intervention they received or the staff measuring the main outcomes was not	Bias • Results of any post hoc analyses were not described, since no post hoc analyses were conducted in this study. • Reliability on compliance with the interventions was not applicable to this study and not reported.

Table A4: Strengths and Limitations of Included Primary studies Using Downs and Black[7] link to Downs and Black		
Strengths	**Limitations**	**Non-Applicable Items**
Confounding • The study subjects in different intervention groups were recruited from the same population over the same period of time. • The study subjects were randomized to intervention groups. • Based on the description of the characteristics of the study subjects separately for the intervention and control groups, there was no concern around confounding, requiring no adjustment in the analysis for the main findings. • No study subjects were lost to follow-up.	discussed. Confounding • Whether intervention assignment was concealed from both study subjects and staff until recruitment was complete and irrevocable was not discussed. Power • There was no discussion on whether the study had sufficient power to detect a clinically-important effect.	

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusions
Gómez Cuervo 2016[5]	
Blood Glucose Levels • In eight of the nine studies that provided relevant data, patients in the BB/BC group had significantly lower blood glucose levels than those in the SS group (no summary data were provided). Lengths of Hospitalization • In all six studies that provided relevant data, no significant differences were found in mean lengths of hospital stay between the BB/BC and SS groups. Adverse Events • In the four studies that provided relevant data, there was a non-significant trend to a lower risk of adverse events in the BB/BC group, compared to the SS group (OR = 0.67; 95% CI = 0.22 to 2.04; I^2 = 71%). A similar result was obtained when the three RCTs were separately analyzed (OR = 0.89; 95% CI = 0.23 to 3.50; I^2 = 79%). Hypoglycemic Events • In the nine studies that provided relevant data, there was a non-significant trend to a greater risk of hypoglycemia in the BB/BC group, compared to the SS group (OR = 2.29; 95% CI = 0.50 to 10.49; I^2 = 70%). A similar result was obtained when the three RCTs were separately analyzed (OR = 4.72; 95% CI = 1.68 to 13.2; I^2 = 38%). • In the two studies that provided relevant data, no significant differences were found in the risk of severe hypoglycemia between the BB/BC and SS groups. Study Quality • The four included RCTs were assessed, using the Cochrane Risk of Bias tool, on five domains (i.e., sequence generation, allocation sequence concealment, blinding, incomplete outcome data, and selective outcome reporting). Two RCTs were at low risk in four domains and high risk in one domain. One RCT was at low risk in two domains, high risk in one domain, and uncertain risk in two domains. One RCT	• Blood glucose control was significantly better with BB/BC insulin therapy, compared to SS insulin therapy. • No evidence was found to show that improved blood glucose control, derived from BB insulin regimens, compared to SS insulin regimens, significantly lowers the risk of adverse events in patients hospitalized in a non-critical ward. However, because of the heterogeneity of the results, potentially stemming from different study designs, definitions of adverse events, and lengths of follow-up, new clinical trials are needed with longer follow-up.

Table A5: Summary of Findings of Included Systematic Reviews	
Main Study Findings	**Author's Conclusions**
was at low risk in one domain, high risk in three domains, and uncertain risk in one domain. • The five included cohort studies were assessed, using the Newcastle-Ottawa scale, on three domains (i.e., selection, comparability, and outcome). On a maximum of nine points, one study received seven points, two studies received six points, and two studies received five points.	

BB = basal-bolus; BC = basal-corrective; CI = confidence interval; OR = odds ratio; RCT = randomized controlled trial; SS = sliding-scale

Table A6: Summary of Findings of Included Primary Studies	
Main Study Findings	**Author's Conclusions**
Akhtar 2014[3]	
Blood Glucose Levels • Fasting blood glucose levels were lower with patients in the BB group, compared to those in the SS group (mean±SD [95% CI] = 122±9 mg/dL [121 to 124] versus 154±24 mg/dL [151 to 158]; *p* = NR*). • Random blood glucose levels were lower with patients in the BB group, compared to those in the SS group (mean±SD [95% CI] = 165±26 mg/dL [161 to 170] versus 273±40 mg/dL [267 to 279]; *p* = NR*). Lengths of Hospitalization • Lengths of hospital stay were shorter with patients in the BB group, compared to those in the SS group (mean±SD [95% CI] = 7.8±1.9 days [7.5 to 8.2] versus 15.5±3.6 days [15.0 to 16.0]; *p* = NR*). Hyperglycemic Events • Numbers of hyperglycemic events were lower with patients in the BB group, compared to those in the SS group (mean±SD [95% CI] = 1.2±0.7 events [1.1 to 1.3] versus 9.4±6.9 events [8.4 to 10.4]; *p* = NR*). Hypoglycemic Events • Numbers of hypoglycemic events were higher with patients in the BB group, compared to those in the SS group (mean±SD [95% CI] = 3.9±1 events [3.7 to 4.1] versus 2.9±0.8 events [2.8 to 3.0]; *p* = NR*). **p*-values of <0.001 were reported for three-	• Blood glucose control was better with the BB insulin regimen, compared to the SS insulin regimen. Patients on the BB insulin regimen had fewer hyperglycemic events and shorter periods of hospital stay, compared to those on the SS insulin regimen. • In non-critically ill type 2 diabetic patients, the BB insulin regimen is superior to the SS insulin regimen.

Table A6: Summary of Findings of Included Primary Studies	
Main Study Findings	**Author's Conclusions**
group comparisons, among BB, SS, and another intervention (i.e., pre-mixed insulin therapy), which was out of scope for this report and excluded, with basal-bolus and sliding-scale regimens demonstrating the largest differences for all outcomes.	
Zaman Huri 2014[8]	
Blood Glucose Levels • Fasting blood glucose levels were significantly lower with patients in the BB group, compared to those in the SS group (mean±SD = 10.8±2.3 versus 11.6±3.5 mmol/L; p = 0.028). • Blood glucose levels throughout severe or acute hyperglycemia were significantly lower with patients in the BB group, compared to those in the SS group (mean±SD = 12.3±1.9 versus 12.8±2.2; p = 0.021). Hypoglycemic Events • The rate of hypoglycemic events was significantly lower with patients in the BB group, compared to those in the SS group (2.5% versus 10.1% of patients; p = 0.005).	• Type 2 diabetes patients with severe and acute hyperglycemia achieved better glycemic control with the BB insulin regimen than with the SS insulin regimen.
Schroeder 2012[1]	
Blood Glucose Levels • Blood glucose levels were significantly lower with patients in the BB group, compared to those in the SS group (mean±SD = 161.2±3.2 mg/dL versus 175.8±2.3 mg/dL; p < 0.0005). • The blood glucose target of < 180 mg was achieved by a higher proportion of patients in the BB group, compared to the SS group (71% versus 57%). • The differences in daily blood glucose levels between the BB and SS groups generally increased over time, favouring BB and reaching significance (i.e., p < 0.05) on the sixth day of hospitalization and onward. Lengths of Hospitalization • The mean length of hospital stay was significantly shorter with patients in the BB group, compared to those in the SS group (7 days versus 9.2 days; p < 0.005). Adverse Events • No differences were found in the rate of complications between the BB and SS	• The suggested four-step BB intervention improved glycose control of hospitalized patients in an orthopaedic department, with fewer glycemic excursions and reduced hospital stay.

Table A6: Summary of Findings of Included Primary Studies	
Main Study Findings	**Author's Conclusions**
groups (no statistics were provided). Hyperglycemic Events • The mean number of hyperglycemic events was significantly lower with patients in the BB group, compared to those in the SS group (0.2 event per hospitalization versus 1.5 events per hospitalization; $p = 0.05$). Hypoglycemic Events • No significant differences were found in the mean number of hypoglycemic events between the BB and SS groups. However, there were two episodes of severe hypoglycemia, requiring intravenous glucose administration in the BB group.	

BB = basal-bolus; CI = confidence interval; NR = not reported; SD = standard deviation; SS = sliding-scale