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COMPUS

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Rapid-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes. Update of CADTH Technology Report No. 87

Supporting Informed Decisions

À l'appui des décisions éclairées

This report is prepared by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS), a service of the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation. The conclusions [statements] were provided by experts. The authors have also considered input from other stakeholders.

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Conflicts of Interest

Dr. Denis Daneman was co-chair of a satellite symposium at an International Diabetes Federation meeting in Cape Town, South Africa. He received partial funding from Eli Lilly Canada for a study of the role of pioglitazone in glycemic control among adolescents with poorly controlled type 1 diabetes. He is a member of the Hvidore Study Group on Childhood Diabetes, which is funded by Novo Nordisk (Denmark). He was a speaker at a workshop on long-acting analogues of insulin for children (funded by Sanofi-Aventis).

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EXECUTIVE SUMMARY

The Issue

Acquisition costs of rapid-acting insulin analogues are greater than those for conventional human insulins (HI). Given limited resources, are these insulin analogues justified for all diabetic patients? In view of the increasing number of people diagnosed with diabetes mellitus (DM) each year, health care providers, consumers, and policy makers require evidence-based information on the optimal use of these agents.

Objective

To identify and synthesize the available evidence on the clinical efficacy of the rapid-acting insulin analogues, insulin lispro (ILis), and insulin aspart (IAsp) in the management of DM (type 1, type 2, and gestational).

Methods

An existing systematic review from CADTH of published studies examining the clinical efficacy of rapid-acting insulin analogues in the treatment of DM was updated. Additional research questions, not addressed in the original systematic review, were also examined. Randomized controlled trials (RCTs) comparing rapid-acting insulin analogues with HI, or oral antidiabetic agents, were identified through searches of electronic databases, grey literature, reference lists, and through stakeholder consultation. Meta-analyses were conducted to pool trial results when appropriate.

Results

Fifty RCTs were included in the meta-analyses for patients with type 1 DM: eight for pediatrics (age range from 5 to 15 years) and 42 for adults (age range from 23 to 48 years). Sample sizes ranged from 10 to 1,008 patients. For patients with type 2 DM, 30 RCTs were included (age range from 42 to 68 years) and the number of patients ranged from seven to 876. Three RCTs were available for gestational DM (age range from 30 to 35 years), and the number of patients in each trial ranged from 41 to 49. The duration of diabetes ranged from 1 to 30 years for patients with type 1 and type 2 DM. The majority of RCTs were of low methodological quality (Jadad score $\leq$2). Due to incomplete reporting of data, not all outcomes reported in RCTs could be pooled in meta-analyses.

For adult patients with type 1 DM, glycosylated hemoglobin (A1c) was significantly lower with ILis compared with HI in the combined analysis of multiple daily injection (MDI) and continuous subcutaneous insulin infusion (CSII) users; the weighted mean difference (WMD) was estimated to be -0.09% [95% confidence interval (CI): -0.16 to -0.02]. This was also the case in the CSII subgroup [WMD (95% CI)= -0.18% (-0.32, -0.05)], but it was not the case in the MDI subgroup [WMD (95% CI)= -0.06 (-0.14, 0.02)]. IAsp also significantly decreased A1c compared with HI [WMD (95% CI)= -0.13% (-0.20, -0.07)]. A1c was not significantly different between ILis and IAsp. ILis significantly decreased the relative risk (RR) for severe hypoglycemia compared with HI [RR (95% CI)=0.80 (0.67, 0.96)]. There was no significant difference in the RR of severe hypoglycemia between IAsp and HI. The frequency of nocturnal hypoglycemia was significantly decreased with ILis or IAsp compared with HI [rate ratio (95% CI)=0.60 (0.40, 0.90) and 0.55 (0.43, 0.70), respectively]. There was no difference in the rate ratio of nocturnal hypoglycemia between ILis and IAsp. The rate ratio of overall hypoglycemia was not significantly different between IAsp and HI, except for IAsp used as CSII [rate ratio (95% CI)=0.58 (0.40, 0.85)]. ILis demonstrated a significantly higher rate ratio of overall hypoglycemia compared with IAsp [rate ratio (95% CI)=1.49 (1.37, 1.63)]. Mean two-hour post-prandial plasma glucose was significantly decreased with ILis compared with HI [WMD (95% CI)= -1.31 mmol/L (-2.35,

-0.27)]. There was no difference in body weight and diabetic ketoacidosis between the rapid-acting insulin analogues and HI. Only a few RCTs provided mortality data; no differences between treatments were apparent. In terms of quality-of-life, limited evidence indicated that ILis was better than HI. Overall, patients seemed to prefer ILis over HI due to its convenience of use.

In children with type 1 DM, there were no significant differences in A1c or RR of severe hypoglycemia between ILis and HI. The rate ratios of nocturnal and overall hypoglycemia also did not differ significantly between the two insulins in pre-adolescent patients, although the rate ratio significantly favoured ILis in adolescents. The families of pre-adolescent patients reported an increased willingness to continue with ILis versus HI. Rate ratios for nocturnal and overall hypoglycemia are 0.61 (95% CI: 0.57, 0.64) and 0.90 (95% CI: 0.99, 0.93) respectively for ILis versus HI in adolescents using MDI.

In pregnant patients with type 1 DM, there were no significant differences in A1c, severe hypoglycemia, or overall hypoglycemia between rapid-acting insulin analogues and HI. Studies in gestational DM patients showed no significant differences in A1c levels or overall hypoglycemia rates with ILis versus HI.

In adult patients with type 2 DM, there was no significant difference in A1c levels between either of the rapid-acting insulin analogues and HI. There was no difference in A1c between ILis and oral antidiabetic agents (OADs), however, patients who had failed previous OAD therapy demonstrated a greater decrease in A1c with biphasic ILis compared with OAD [WMD (95% CI)= -0.85% (-1.18, -0.53)] and versus metformin [WMD (95% CI)= -0.60% (-1.09, -0.11). IAsp significantly decreased A1c compared with sulfonylurea (Sfu) [WMD (95% CI)= -0.63% (-1.04, -0.22)]. The RR of severe hypoglycemia was similar between the rapid-acting insulin analogues and HI or Sfu. The RR of nocturnal hypoglycemia was also not significantly different between rapid-acting insulin analogues and HI, but was significantly lower with ILis compared with Sfu [RR (95% CI)=0.20 (0.06, 0.70)]. The rate of nocturnal hypoglycemia was significantly decreased with ILis compared with HI [rate ratio (95% CI)=0.58 (0.48, 0.70)] and Sfu [RR (95% CI)=0.20 (0.06, 0.70)]. For overall hypoglycemia, there was no difference in the RR between ILis or IAsp and HI. The rate ratio of overall hypoglycemia was not significantly different between ILis and HI or ILis and IAsp, but significantly favoured IAsp compared with HI [rate ratio (95% CI)=0.72 (0.64, 0.80)]. ILis and IAsp both increased the rate of overall hypoglycemia compared with Sfu and metformin. There was no difference in fasting plasma glucose between IAsp and HI or ILis and Sfu. Mean two-hour post-prandial plasma glucose showed a tendency to favour ILis compared with HI. There was no difference in body weight or body mass index, cholesterol levels, or all-cause mortality between rapid-acting insulin analogues and HI or Sfu. There was no improvement in quality-of-life with ILis compared with HI, except on the "worry related to diabetes" scale. However, ILis demonstrated a significant improvement in quality-of-life compared with Sfu.

Conclusions

The bulk of the available evidence on rapid-acting insulin analogues for both type 1 and type 2 diabetes consists of short- to medium-term comparisons with HI in terms of A1c and hypoglycemia. Most studies were of poor methodological quality. Based on the available evidence, the benefit of rapid-acting insulin analogues over HI appears to be marginal at best.

In adult patients with type 1 DM, treatment with ILis significantly reduced A1c levels compared with HI when used as CSII. IAsp also improved A1c as compared with HI. The rates of overall and severe hypoglycemia were similar between the two rapid-acting insulin analogues and HI, but nocturnal hypoglycemia occurred less frequently with ILis or IAsp compared with HI.

In children with type 1 DM, A1c levels and rates of hypoglycemia were similar between ILis and HI. However, a small benefit in terms of reduced rates of overall and nocturnal hypoglycemia in adolescent patients was shown.

In adult patients with type 2 DM, there were no differences in A1c levels, risk of hypoglycemia, or quality-of-life with rapid-acting insulin analogues compared with HI, although a slight reduction in the rates of nocturnal and overall hypoglycemia was observed. Marginal improvements in A1c and quality-of-life, but no reduction in hypoglycemia, were observed with rapid-acting insulin analogues compared with Sfu.

The limited evidence regarding pregnant women with type 1 DM or gestational diabetes showed no difference between rapid-acting insulin analogues and HI in terms of A1c level, overall hypoglycemia, or severe hypoglycemia.

High-quality, long-term studies are required to measure the impact of rapid-acting insulin analogues on quality of life, health care resource utilization, and long-term diabetes-related complications.

ABBREVIATIONS

A1c	glycosylated hemoglobin
ARR	absolute risk reduction
BG	blood glucose
BMI	body mass index
CAC	COMPUS Advisory Committee
CAD	Canadian
CI	confidence interval
CSII	continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DIGAMI	Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction
DIN	drug identification number
DKA	diabetic ketoacidosis
DNA	deoxyribonucleic acid
DM	diabetes mellitus
DTSQ	Diabetes Treatment Satisfaction Questionnaire
FPG	fasting plasma glucose
F/P/T	Federal/Provincial/Territorial
HDL	high-density lipoprotein
HI	human insulin (conventional)
HRQoL	health-related quality of life
IAsp	insulin aspart
IDet	insulin detemir
IGlar	insulin glargine
IGlu	insulin glulisine
IHD	ischemic heart disease
ILis	insulin lispro
LDL	low-density lipoprotein
MDI	multiple daily injection
Metf	metformin
MI	myocardial infarction
NNT	number needed to treat
NPH	neutral protamine Hagedorn
NPL	neutral protamine lispro
NR	not reported
OAD	oral antidiabetic agent
QoL	quality of life
RCT	randomized controlled trial
Ros	rosiglitazone
RR	relative risk

SBP	systolic blood pressure
SD	standard deviation
TC:HDL-C	total cholesterol to high-density lipoprotein (HDL) cholesterol ratio
WBQ	well-being questionnaire
WMD	weighted mean difference

GLOSSARY

Absolute risk reduction (ARR): The arithmetic difference between event rates across treatment and control groups. It is the inverse of the number needed to treat.

Adverse drug events: Events resulting from administration of a drug or other circumstance surrounding use of the drug, but not necessarily caused by the drug itself.

Body mass index (BMI): A statistical measure of the weight of a person scaled according to height, and it is defined as the individual's body weight divided by the square of their height.

Carryover effect: Occurs when the treatment given in the first period has a residual effect that confounds the interpretation of results in the second period.

Confidence interval (CI): The probable range in which a population parameter lies based on a random sample of the population. The most commonly reported conference interval is the 95% confidence interval.

Congestive heart failure: A condition in which an abnormality of cardiac structure or function is responsible for the inability of the heart to fill with or eject blood at a rate commensurate with the requirements of the metabolizing tissues.

Cross-over trial: A variation of the traditional randomized controlled trial in which the intervention is applied at different times to each subject; that is, after a specified period of time the original experiment group becomes the control group, and the original control group becomes the experimental group.

Diabetes Control and Complications Trial (DCCT): A clinical study conducted from 1983 to 1993 by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). It is the largest, most comprehensive diabetes study ever conducted.

Diabetes mellitus (DM): A group of common metabolic disorders characterized by hyperglycemia.

Diabetic ketoacidosis: An acute complication of diabetes caused by increased fatty acid metabolism and the accumulation of ketoacids. It was formerly considered a hallmark of type 1 DM, but it also occurs in individuals who lack of immunologic features of type 1 DM and who can subsequently be treated with oral glucose-lowering agents (in type 2 DM).

Effectiveness: The extent to which a specific intervention, procedure, regimen, or service produces the intended outcomes when deployed under routine circumstances.

Efficacy: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial outcome under ideal circumstances.

Fasting plasma glucose (FPG): Plasma glucose level measured at the time when there has been no caloric intake for at least eight hours.

Fixed effect model: A method for pooling data in a meta-analysis. It is assumed that the true effect of treatment is the same value in each study or fixed, the difference between study results being due solely to chance.

Funnel plots: A graphical method used to detect publication bias. Funnel plots are simple scatter plots, where treatment effects estimated from individual studies are plotted on the horizontal axis against some measure of study size on the vertical axis.

Gestational diabetes mellitus: Glucose intolerance with first onset during pregnancy. It is usually a temporary condition.

Glycated hemoglobin (HbA1c): A glycated form of hemoglobin, formed by the attachment of sugars to the molecule when glucose levels are elevated. HbA1c levels increase with the average concentration of glucose in the blood.

Health-related quality of life (HRQoL): A broad theoretical construct developed to explain and organize measures concerned with the evaluation of health status, attitudes, values, and perceived levels of satisfaction and general well being with respect to either specific health conditions or life as a whole from the individual perspective.

Heterogeneity ($\chi 2$ or I^2): This statistic describes the degree of variation, as a percentage, between the results of individual studies within a meta-analysis.

Hyperglycemia: A qualitative term used to describe blood glucose that is above the normal range.

Hyperosmolar, hyperglycemic, non-ketotic coma: A syndrome consisting of extreme hyperglycemia, serum hyperosmolarity, and dehydration in the absence of ketoacidosis. The American Diabetes Association suggests that this disorder be renamed "hyperglycemic hyperosmolar state (HHS)." The prototypical patient with HHS is an elderly individual with type 2 DM with a several-week history of polyuria, weight loss, and diminished oral intake that culminates in mental confusion, lethargy, or coma.

Hypoglycemia: A qualitative term used to describe blood glucose that is below the normal range and defined by 1) the development of autonomic or neuroglycopenic symptoms, 2) a low plasma glucose level of 4.0 mmol/L for patients with insulin or an insulin secretagogue, and 3) symptoms responding to the administration of carbohydrate (Canadian Diabetes Association 2003). This definition has not been used in all the studies used in the analysis (please see Appendix 11).

Ischemic heart disease (IHD): Heart disease due to inadequate blood perfusion of the myocardium, which causes an imbalance between oxygen supply and demand.

Long-acting insulin analogues: A class of insulin analogue, produced by introducing alterations in the amino acid sequence of human insulin, which mimic the action of basal endogenous insulin secretion by providing a prolonged, non-fluctuating level of insulin activity.

Meta-analysis: Statistical synthesis of the results of individual studies that examine the same question, for the purpose of integrating findings and producing a single estimate of effect.

Myocardial infarction (MI): (Also called "heart attack") is the death of a portion of heart muscle resulting from a sudden loss of blood supply due to occlusive coronary artery thrombus, atherosclerotic plaque, vasospasm, inadequate myocardial blood flow (e.g., hypotension), or excessive metabolic demand.

Number needed to treat (NNT): The number of patients who need to be treated with a new treatment rather than the standard (control) treatment in order for one additional patient to benefit. It is calculated as the inverse of the absolute risk difference.

Nocturnal hypoglycemia: Hypoglycemic events that occur at night, usually from 24:00 h to 6:00 h. This definition has been used in most of the included studies (please see Appendix 11).

Overall hypoglycemia: Overall hypoglycemia is usually defined by either symptoms or sign of hypoglycemia and/or blood glucose <4 mmol/L. This definition has been used in most of the included studies (please see Appendix 11).

Per-protocol analysis: An analysis of clinical trial data from which the results for subjects with major violations of the study protocol are omitted.

Publication bias: Unrepresentative publication of research reports that is not due to the scientific quality of the research but to other characteristics, for example tendencies of investigators to submit, and publishers to accept, positive research reports (i.e., ones with results showing a beneficial treatment effect of a new intervention).

Random effects model: This model assumes that 1) the studies included in the meta-analysis are a random sample from all possible studies, 2) the true effects observed in each study may be different from each other, and 3) those differences are normally distributed.

Randomized controlled trial (RCT): A prospective study designed to test the efficacy of an intervention in which patients are randomly allocated to either a treatment group or the control group.

Rapid-acting insulin analogue: A class of insulin analogue, produced by introducing alterations in the amino acid sequence of human insulin, which more closely mimic the short duration of action of meal-induced endogenous insulin in non-diabetic patients than does regular human insulin.

Relative risk (RR): The ratio of the absolute risk of a disease among the exposed group to the absolute risk of the disease among the unexposed group in an epidemiological study.

Rate ratio: The ratio of the person-time incidence rate in the exposed group to the person-time incidence rate in the unexposed group in an epidemiological study.

Standard deviation (SD): A measure of the variability between individuals in the level of the factor being investigated.

Severe hypoglycemia: An event with characteristic hypoglycemic symptoms requiring assistance of another person, although some studies also required the presence of blood glucose values below a certain threshold. This definition has been used in most of the included studies (please see Appendix 11).

Systematic review: A summary of the medical literature that uses explicit methods to identify, select, appraise, and analyze studies relevant to a particular clinical question.

Transient ischemic attack (TIA): Episodes of stroke symptoms that last only briefly; the current definition of duration is <24 hours, but the average duration of TIA is about 12 minutes.

Type 1 diabetes mellitus: Diabetes that is primarily the result of pancreatic beta cell destruction and that is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the aetiology of beta cell destruction is unknown.

Type 2 diabetes mellitus: Diabetes that may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.

Weighted mean difference (WMD): A method of meta-analysis used to combine measures on continuous scales (such as weight), where the mean standard deviation and sample size in each group are known. The weight given to each study (e.g., how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect and, in the statistical software in RevMan, is equal to the inverse of variance. This method assumes that all the trials have measured the outcome on the same scale.

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1 INTRODUCTION

1.1 COMPUS

The Canadian Optimal Medication Prescribing and Utilization Service (COMPUS), a directorate of the Canadian Agency for Drugs and Technologies in Health (CADTH), is a collaborative, national service funded by Health Canada. In partnership with federal, provincial, and territorial (F/P/T) health ministries, COMPUS identifies and promotes evidence-based optimal practices in drug prescribing and use among health care providers and consumers and contributes to the re-assessment of a drug or class of drugs during its/their lifecycle.

The goal of COMPUS is to optimize drug-related health outcomes and promote cost-effective use of drugs that have been in the market place for some time. Individual jurisdictions promote optimal drug therapy in a variety of unique and successful ways. COMPUS coordinates and builds on those existing initiatives to provide a national collaborative to ensure that messages directed at prescribers, patients, and third-party payers (including governments) reflect new information in a timely manner. By creating efficiencies and reducing duplication of effort, COMPUS contributes to the quality and effectiveness of the Canadian health care system. The COMPUS mandate directly addresses one of the original nine strategies of the National Pharmaceuticals Strategy: "Enhance action to influence the prescribing behaviour of health care professionals so that drugs are used only when needed and the right drug is used for the right problem."

Direction and advice are provided to COMPUS through various channels, including:

- **The COMPUS Advisory Committee (CAC).** The CAC is comprised of representatives from the F/P/T health ministries and related health organizations. The mandate of the CAC is to provide advice to the CADTH Board of Directors and the COMPUS Directorate on priorities and topics for optimal practice initiatives, COMPUS activities and products, and other issues, where appropriate, to enable COMPUS to meet its goals and objectives.
- **The COMPUS Expert Review Committee (CERC).** CERC is an expert advisory body of health and other professionals with expertise in drug therapy and evaluation of evidence. The mandate of CERC is advisory in nature and is to provide recommendations and advice to the COMPUS Directorate at CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada.
- **Stakeholder input and expert advice.**

1.2 Project Overview

The CAC has identified management of diabetes mellitus (DM) as being a priority area for optimal practice initiatives. Management of DM was identified as a priority area based on criteria including:

- Over- or under-use of prescription medications
- Size of patient populations
- Potential impact on health outcomes and cost-effectiveness
- Potential to effect change
- Benefit to multiple jurisdictions
- Measurable outcomes.

Within DM management, six priority areas were identified by F/P/T jurisdictions:

- Comparison of long-acting insulin analogues, human insulins (HIs), and oral antidiabetic agents (OADs)
- Comparison of rapid-acting insulin analogues, HI, and OADs
- Comparison of "glitazones" to other OADs
- Metformin (Metf) as first line agent in type 2 DM
- Identification of optimal blood glucose (BG) testing frequency in type 2 DM
- Identification of optimal BG testing frequency in type 1 DM

Research efforts for each priority area focus on the following six areas: 1) clinical evaluation, 2) economic evaluation, 3) current utilization analysis, 4) current practice analysis, 5) gap analysis, and 6) barriers to optimal use. The clinical and economic evaluations are used by a CERC to generate recommendations for the optimal prescribing and use of the technology under study.

This report describes the results of a systematic review and meta-analysis conducted as part of the clinical evaluation of the rapid-acting insulin analogues.

1.3 Goal

The goal of this systematic review was to examine the efficacy of rapid-acting insulin analogues relative to unmodified HIs in the treatment of patients with type 1, type 2, and gestational DM.

2 BACKGROUND

DM comprises a group of common metabolic disorders characterized by hyperglycemia (elevated BG levels).[1] It is a chronic condition in which the body is unable to produce sufficient insulin and/or unable to properly use insulin.[1] Insulin, a hormone secreted by pancreatic islet cells in response to increased BG levels, promotes the uptake of glucose into cells where it can be used as a source of energy.[1] Diabetes is classified as:[2]

- Type 1 DM – little or no insulin made by the body (previously classified as insulin-dependent DM or juvenile-onset DM)
- Type 2 DM – the body makes insulin but is unable to use it properly (previously classified as non-insulin dependent DM)
- Gestational DM – is defined as glucose intolerance, with its first onset during pregnancy; it is usually a temporary condition
- Other – mainly specific genetically defined forms of diabetes, or diabetes associated with other disease or drug use (e.g., genetic defects of beta cell function; genetic defects in insulin action; disease of the pancreas; endocrinopathies; infections; uncommon forms of immune-mediated diabetes, either drug or chemically induced; and other genetic syndromes sometimes associated with diabetes).

Without adequate control of blood glucose, vascular and non-vascular complications may ensue. These can be further subdivided into microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary artery disease, peripheral artery disease, and cerebrovascular disease) complications. Non-vascular complications include problems such as gastroparesis, infections, and skin changes. Successful management of DM requires an educated and motivated patient with support from a multidisciplinary health care team. In combination with diet modifications, weight control, and adequate exercise, medications can assist patients in controlling BG levels to reduce their risk of developing long-term diabetic complications.[3] Maintaining glycemic levels near normal has been shown to lower the risk of microvascular complications[3,4] and macrovascular complications.[5-8]

The prevalence of diabetes worldwide is estimated to be 177 million, and this number is projected to increase to 300 million by 2025.[9] According to the Health Canada National Diabetes Surveillance System, over 1 million (4.8%) Canadians aged 20 years and older were diagnosed with diabetes in 1998/1999.[10] However, the true prevalence of diabetes may actually approach 1.9 million, as many cases are undiagnosed.[11] It is estimated that 2.7% of the general adult population have undiagnosed type 2 diabetes.[2] Assuming 10% of all diabetes cases are type 1 and 90% are type 2, approximately 105,410 (0.48%) and 948,690 (4.32%) Canadians were diagnosed with type 1 and type 2 DM in 1998/1999 respectively.

There are no known modifiable risk factors for type 1 DM, and consequently race, ethnic background, age, and genetics will determine the relative risk (RR) of a person acquiring this disease.[10] Type 1 DM is more prevalent among Caucasian individuals compared with those of African or Hispanic decent, whereas type 2 DM is more highly correlated with socio-economic status (SES) than race or ethnic background, leaving Aboriginal peoples and immigrants at a greater susceptibility of developing the second type of this disease.[10,12] People with a family history of type 1 DM also have a slightly increased risk of developing diabetes. In patients with type 2 DM, modifiable risk factors include quality and quantity of nutritional intake as well as the amount and type of physical activity.[2] Adopting a healthy lifestyle reduces the probability of acquiring hypertension, dyslipidemia, abdominal obesity, and reaching overweight or obese status.[13,14] However, the current industrial and social influences of the 21st century are not conducive to the incorporation of optimal dietary and physical activity behaviours. Consequently, more Canadians are gaining weight – mostly by increasing fat stores – and increasing their risk for developing type 2 DM. For example, the prevalence of type 2 DM increases by 5% to 10% among adults for every 1 kg increase in population measured body weight.[10]

The quality and duration of life is often significantly diminished in individuals who have DM. According to the 1998/1999 NPHS, only 64.5% of individuals with DM reported their health to be good or better compared with 90.8% of individuals without DM ($p<0.05$). Individuals, 20 years or older with diabetes are also less active than those without diabetes (17.3% versus 11.1%, $p<0.05$).[10] Life expectancy for people with type 1 DM may be shorted by as much as 15 years, and by five to 10 years for those with type 2 DM.[10] Diabetes is one of the top 10 leading causes of death in Canada,[10] though the death rate may be a dramatic underestimation.

In 1999, Health Canada[10] reported 6,137 deaths as being directly attributable to DM. This number is projected to increase to almost 17,500 deaths per year, with a similar distribution between men and women.[10] The total economic burden of diabetes (diagnosed and undiagnosed) and its complications in Canada were estimated to range between US$4.76 billion and US$5.23 billion in 1998. Direct medical costs in patients diagnosed with diabetes accounted for approximately 7.8% of total medical expenditures in 1998. Of this, 50% of costs were spent on hospital care, whereas 19% and 31% were spent on physician care and medications, respectively.[11] Over three-quarters of people with diabetes use either insulin or OADs to control the progression of the disease.[10]

In the Ontario Drug Benefits Formulary (ODBF), approximately 29% of patients with DM took only a single oral anti-hyperglycemic drug, while 17% took more than one type.[15] Insulin was used by 11% of people and in combination with oral medications in 3% of beneficiaries.[15] The number of elderly patients taking insulin medications in the ODBF formulary increased from 30,104 in 1995 to 38,258 in 2001, representing a 27% increase. The total cost of all hyperglycemic agents among beneficiaries in the ODBP increased from 23 million in 1995 to 33 million in 2001.[15] Insulin medications accounted for over $14 million in 2001, representing the highest costs in the ODB program among antihyperglycemic agents.[15]

Given this sharp increase in the use of insulin agents and associated costs, the optimal prescribing of these drugs is paramount.

3 TECHNOLOGY DESCRIPTION

Insulin is indicated for all patients with type 1 DM as well as for patients with type 2 DM who are unable to achieve adequate glycemic control by other measures (exercise, diet, and/or other antidiabetic agents). Insulin products can be classified according to the source of insulin as human insulin, insulin analogues, or animal-sourced insulin.

3.1 Human Insulin

Human insulin (HI), a biosynthetic insulin that is prepared using recombinant deoxyribonucleic acid (DNA) technology, is available in three types:

- Short-acting HI – Humulin®, Novolin Toronto
- Intermediate-acting HI – neutral protamine Hagedorn (NPH), Lente® (recently discontinued by the manufacturer)
- Long-acting HI – UltraLente® (discontinued by the manufacturer)

Short-acting HI has an onset of action (reaches the bloodstream) of 30 to 60 minutes, reaches its peak in two to three hours, and has an effective duration of eight to 10 hours.[16] NPH or intermediate-acting insulin has an onset of action of two to four hours, reaches its peak in four to 10 hours, and has an effective duration of 12 to 18 hours.[16] Long-acting HI, recently discontinued by the manufacturer, has an onset of action of six to 10 hours, reaches its peak in 10 to 16 hours, and has an effective duration of 18 to 25 hours.[16] The pharmacokinetic/pharmacodynamic profile of HI is such that it does not replicate basal and meal-time endogenous insulin secretion and may not always provide optimal glycemic control. There have been reports of hypoglycemia (decreased BG levels) resulting from this lack of control.[16]

3.2 Insulin Analogues

In response to the limitations of HI, insulin analogues have been developed that more closely mimic the basal and meal-time components of endogenous insulin secretion. Alterations in the amino acid sequence of HI were introduced to these agents.[16] There are two types of insulin analogues: rapid-acting and long-acting. Rapid-acting insulin analogues more closely mimic the short duration of action of endogenous insulin in non-diabetic patients than do HI insulins. Long-acting insulin analogues do not mimic the action of endogenous insulin; rather, they promote a prolonged, non-fluctuating basal level of insulin activity.

Rapid-acting insulin analogues approved for use in Canada include:

- Insulin lispro (ILis), marketed as Humalog®
- 25% ILis, 75% ILis protamine, marketed as Humalog Mix 25
- 50% ILis, 50% ILis protamine, marketed as Humalog Mix 50
- Insulin aspart (IAsp), marketed as NovoRapid®
- 30% IAsp, 70% IAsp protamine, marketed as Novomix™ 30
- Insulin glulisine (IGlu) not currently marketed in Canada (Apidra®).

Long-acting insulin analogues approved for use in Canada include:

- Insulin glargine (IGlar), marketed as Lantus®

- Insulin detemir (IDet), marketed as Levemir®.

ILis and IAsp have an onset of action of five to 15 minutes, reach their peak in 30 to 90 minutes, and have an effective duration of four to six hours.[16] IGlar has an onset of action of two to four hours, does not have a peak, and has an effective duration of 20 to 24 hours.[16] IDet, a long-acting insulin analog, has similar pharmacokinetic/pharmacodynamic characteristics as IGlar.[17]

4 STATEMENT OF THE ISSUE

The HIs are listed for reimbursement on all provincial and territorial public drug plan formularies. However, this is not the case for the insulin analogues, which are more expensive than the HIs. Long-acting insulin analogues are not listed for reimbursement on any of the public drug plans (except for IGlar in B.C., under Special Authority Coverage), while coverage for rapid-acting insulin analogues differs by jurisdiction.

Drug plans, however, are receiving an increasing number of requests for insulin analogues as initiation therapy over HIs. Furthermore, an increasing number of people are being diagnosed with diabetes each year.[18] Thus, a need exists to provide evidence-based information surrounding the optimal use of insulin analogues for the management of DM in Canada. The first step in this process is synthesis of the available clinical data on the comparative efficacy and safety of these agents.

5 OBJECTIVE

The objective of this study was to conduct a systematic review and meta-analysis of the clinical efficacy and safety of the rapid-acting insulin analogues compared with intermediate-acting unmodified HI, and OADs, for the treatment of type 1, type 2, and gestational DM.

5.1 Research Questions

- To achieve the stated objective, the following research questions were developed.
- What are the patient-relevant and clinical benefits and harms associated with rapid-acting insulin analogues (i.e., IAsp, ILis) compared with short-acting HI or OADs in the treatment of DM (type 1, type 2, or gestational)?
- Are there subpopulations of diabetic patients [e.g., pregnant patients, children, elderly people, aboriginal people / ethnic minorities, patients using continuous subcutaneous insulin infusion (CSII)] who may particularly benefit from treatment with rapid-acting insulin analogues, in comparison to short-acting HI or OADs?
- What are the benefits and harms of combining rapid-acting insulin analogues with OADs compared with combining short-acting HI with OADs in the treatment of type 2 DM from a clinical and patient perspective?
- Compared with short-acting HI, do rapid-acting insulin analogues produce different clinical differences when used at the onset of the disease versus later on, for patients with type 2 DM?
- Are there any clinical significant differences between various rapid-acting insulin analogues (IAsp and ILis) in the treatment of DM (type 1, type 2, or gestational)?

5.2 Outcomes of Interest

Outcomes of interest for gestational and type 1 DM were glycosylated hemoglobin (A1c) (both mean at endpoint and proportion achieving ≤7%); mean two-hour post-prandial plasma glucose; severe, nocturnal, and overall hypoglycemia (RR and rate ratio); mean weight, body mass index (BMI), and waist-to-hip ratio (in Type 1 DM only); diabetic ketoacidosis (DKA); health-related quality of life (HRQoL), both generic and diabetes-specific; patient satisfaction with diabetes care and treatment; patient self-management efficacy; resource utilization (i.e., cost of treatment; number of emergency room visits, primary care, specialists; hospitalizations); long-term diabetes complications [i.e., ischemic heart disease (IHD), congestive heart failure, stroke/ transient ischemic attack, nephropathy, retinopathy, lower-limb disease, neuropathy, peripheral vascular disease, mortality]; and adverse effects.

Outcomes of interest in type 2 DM were the same as in type 1, except that fasting plasma glucose (FPG) (both mean at endpoint and proportion achieving ≤7 mmol/L); hyperosmolar, hyperglycemic, non-ketotic coma; systolic and diastolic blood pressure; low-density lipoprotein (LDL)-cholesterol; and the ratio of total cholesterol to high-density lipoprotein (HDL)-cholesterol (i.e., TC: HDL-C) were also assessed.

6 METHODS

CADTH *Technology Report 87*: *Short-acting insulin analogues for diabetes mellitus: Meta-analysis of clinical outcomes and assessment of cost-effectiveness*[19] formed the basis of the current research. The following methods were used to update this report for research questions 1 to 4 (Section 3.1), and to address question 5 (Section 3.1) that was not posed in the original work.

6.1 Literature Search

The literature search strategy and methodology for *Short-acting insulin analogues for diabetes mellitus: Meta-analysis of clinical outcomes and assessment of cost-effectiveness, Technology Report 87*[19] are provided in Appendix 1A. COMPUS researchers reviewed results of the Technology Report 87 search from March 2006, when the authors stopped reviewing citations, until April 2007. The grey literature search results were supplemented by updated searches of selected HTA agency, guideline organizations, and diabetes association web sites from 2005, when the technology report search was run, onward. Particular emphasis was placed on searching for conference abstracts.

An information specialist constructed a search strategy to address question 5 (Section 3).
This search was peer-reviewed by another information specialist external to the project. This search strategy was devised to locate clinical evidence focusing specifically on the combined use of rapid-acting insulin analogues.

The following bibliographic databases were searched through the OVID interface: MedLine (1966 to present, MedLine In-Process & Other Non-Indexed Citations, MedLine Daily Update), EMBASE (1980 to present), and BIOSIS Previews (1989 to present). The Cochrane Library was searched using the Wiley interface. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were diabetes and rapid-acting insulin analogues (glulisine, ILis, IAsp). A literature filter was applied to limit retrieval to randomized controlled trials. See Appendix 1B for the detailed search strategy.

The search was restricted only by date, from 1990 onward, and by human population. Monthly update searches were established following the initial search in December 2006. Alert results were reviewed from January 2006 until April 2007.

Literature searches were conducted for observational studies including, but not limited to, cohort, retrospective, follow-up, and prospective designs. The search strategy was developed by an information specialist with input from COMPUS researchers. The search was peer-reviewed by an information specialist outside of the project. The following bibliographic databases were searched through the Ovid interface: MedLine (1950-June 2007; In-Process & Other Non-Indexed Citations; Daily Update), EMBASE (1975-June 2007), BIOSIS Previews (1985-1989 and 1989-June 2007). The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. No limits were placed on the search. The main search concepts were diabetes and insulin analogues. Study design filters were applied to limit retrieval to observational studies

6.2 Study Selection

Study selection criteria described in the *Technology Report 87*[9] were modified to include additional inclusion/exclusion criteria.

Inclusion criteria:

- Study design – Randomized controlled trial (RCT)
- Population – Patients with type 1 or type 2 DM or gestational DM
- Intervention – Insulin analogues (ILis or IAsp)
- Comparator – Regular insulin, insulin analogues, or OADs
- Studies containing insulin premixed formulation or combination therapy were included only if the additional antidiabetic agents were given equally to both the intervention and comparator groups
- Outcomes – Glycemic control [glycosylated hemoglobin (HbA1c) level], hypoglycemia, quality of life (QoL), adverse events complications of diabetes, and mortality.

Exclusion criteria:

- RCTs that addressed pharmacokinetic/pharmacodynamic differences among rapid-acting insulin analogues
- Treatment duration of less than four weeks
- RCTs that compared glulisine and other rapid acting insulin analogues or HI. This drug is not marketed in Canada.
- RCTs that reported the outcomes for a mixed population of type 1 and type 2 DM together.

Articles were accepted for inclusion if they satisfied inclusion criteria established a priori; the presence of any exclusion criteria resulted in rejection of the article from the review. Considerable caution was exercised to ensure that duplicate publications of the same trial or published articles of single-centre trials, which are part of a multi-centre trial, are not included. In the case of studies published several times, the most recent and/or informative article was selected.

To reduce bias, oversight, and inconsistency, two reviewers independently determined whether studies meet inclusion criteria. Each reviewer independently performed an initial screening of identified articles by examining titles and abstracts for relevance to the review topic. Abstracts of articles were assessed and categorized as "included" or "rejected" by each reviewer. If the relevance

of a citation is considered uncertain, the citation was retained. Full-text articles were obtained for those citations identified as "included" or "uncertain" by each reviewer. All full-text articles were independently assessed by each reviewer against the inclusion and exclusion criteria. Reasons for exclusion were recorded. Discrepancies were resolved by consensus or a third reviewer in the event that consensus was not reached.

6.3 Stakeholder Feedback

A list of studies included in *Technology Report 87*: *Short-acting insulin analogues for diabetes mellitus: Meta-analysis of clinical outcomes and assessment of cost-effectiveness*[19] was posted on the COMPUS web site to give stakeholders the opportunity to provide additional evidence. Evidence from stakeholders was considered only if it met the selection criteria.

6.4 Data Handling

6.4.1 Data extraction

A data extraction form (Appendix 2), designed a priori, was used to document study design, population characteristics, interventions, and data on relevant outcomes. Two reviewers independently extracted data from each article. Differences were discussed and resolved by consensus. When necessary, authors were contacted for missing data. Data extraction was not repeated for RCTs reported in *Technology Report 87*.[19]

6.4.2 Handling of missing data

Where standard deviations (SD) were not reported in the RCT, they were calculated using standard formulae based on the available information [e.g., 95% confidence interval (CI) of treatment effect].[20] Where there was insufficient information to calculate the SD for the mean value of a particular outcome, the SD at baseline was used. Authors were contacted for missing SD values in some instances. Imputation of SD values from similar studies was reserved for cases when none of these strategies was successful.

If the number of patients analyzed in each treatment arm was not reported, the number randomized was used. If the number randomized was also not reported, it was assumed that the total sample size was equally divided across treatment arms.

6.5 Study Quality Assessment

The accuracy of the inference of a systematic review is dependent on the validity of the primary studies included. Studies of low methodological quality have the potential to overestimate treatment benefits.[21,22] Hence, an assessment of methodological quality is important. Methodological quality of included trials was assessed using a modified Jadad scale (Appendix 3).[23] The original Jadad scale was modified to record the extent of allocation concealment, blinding of assessors, and whether the study results were reported as an intention-to-treat analysis.[22] Since a Jadad scale was used for both *Technology Report 87*[19] and for this systematic review, the quality of all studies included in the technology report was not re-evaluated.

Two independent reviewers assessed the quality of trials. Discrepancies were discussed and resolved by consensus. Consensus results were checked against original articles by a third reviewer.

Any discrepancies identified by the third reviewer were discussed with the original two reviewers until agreement was reached.

6.6 Data Analysis

Where appropriate, quantitative pooling of results through random-effects meta-analysis was conducted using Review Manager 4.2 to generate estimates of treatment effect. Summary estimates (weighted mean difference or RR or rate ratio) were computed using the random effects model. See Appendix 4 for details.

Data from two different study designs (crossover and parallel) were pooled, only if the crossover RCTs reported no carry-over effect (order, period, or sequence effect). When carryover effect was reported in the RCT for some outcome, the RCT was excluded from the meta-analysis for that outcome. In the crossover trial, patients were counted twice for the meta-analysis, because they participated in both treatment arms. For continuous data, RCTs were pooled only if they reported SD values or contained sufficient data to enable the SD to be calculated. In crossover RCTs, patients were counted twice for the meta-analysis, because they participated in both the treatment arms.

6.6.1 Analysis of continuous outcomes

Weighted mean differences (WMDs) were calculated for continuous outcomes including percentage of A1c, FPG, and body weight. Data were reported as endpoint means or the differences of baseline and endpoint means (change from the baseline).

Some RCTs reported mean values at endpoint, while others reported changes from the baseline. We mainly pooled the endpoint means in meta-analysis. However, if only the change from the baseline was reported, we calculated the endpoint mean by adding the change to the baseline measurement and imputed the SD. In some instance where all the RCTs in a meta-analysis reported only the change from the baseline, in that case this change was meta-analyzed as such.

Where endpoint SD values were not reported in the RCT, the SD was calculated using algebraic or approximate algebraic recalculation, as described by Wiebe *et al.*,[20] to recover missing variances. In instances where this approach could not be utilized, the SD was calculated using imputation from the baseline or a sufficiently similar study.[20]

6.6.2 Analysis of hypoglycemia outcomes

Definitions of severe, nocturnal, and overall hypoglycemia varied across studies. Most studies defined severe hypoglycemia as an event with characteristic hypoglycemic symptoms requiring assistance of another person, although some studies also required the presence of BG values below a certain threshold. Overall hypoglycemia was usually defined by either symptoms of hypoglycemia and/or blood glucose below a certain threshold. Nocturnal hypoglycemia included all hypoglycemic events occurring at night, although the specific time frame varied somewhat across studies.

Hypoglycemia data were analyzed in two ways: RR and rate ratio. The RR is a measure of the probability of experiencing at least one hypoglycemic episode during the course of the trial. Frequency of episodes (i.e., number of episodes per patient per unit of time) was analyzed using the rate ratio, an outcome measurement often utilized to capture recurrent events.[24] The rate ratio was tabulated in Review Manager as a generic inverse outcome measure.[24] Data for each type of

hypoglycemia were pooled across studies despite differences in definition. Where significant statistical heterogeneity was observed, differences in hypoglycemia definition were considered as a possible explanatory factor.

6.6.3 Handling of crossover RCTs

In the absence of reported carryover effects, data from crossover trials were combined with those from parallel trials in a single meta-analysis. Carryover effects occur when the treatment given in the first period has residual effects that confound the interpretation of results in the second period. Carryover effects in crossover trials can be analyzed by examining the possibility of a statistical interaction between treatment and period.[25] When a carryover effect was reported in a RCT for a particular outcome, these data were excluded from meta-analysis.

6.6.4 Subgroup analysis

For type 1 DM, subgroup analyses were performed for patients using multiple daily injections (MDIs) and for those using CSII to examine whether the effect sizes influenced by insulin delivery methods.

6.6.5 Sensitivity analysis

A number of sensitivity analyses were conducted to determine whether methodological differences between RCTs affected estimates of overall effect. Because A1c is a measure of long-term glycemic control,[26] trials of three months or less were excluded in the sensitivity analysis for this outcome to determine the impact on the weighted mean difference. For all outcomes, crossover studies were removed in the sensitivity analysis to determine the impact on pooled estimates of effect. Where it was necessary to pool mean endpoint values and mean changes from baseline, a sensitivity analysis was conducted to determine the effect of removing the studies for which only mean changes from baseline were available. Although originally planned, sensitivity analyses based on quality assessment results were not conducted because almost all included RCTs were of poor quality.

6.7 Heterogeneity

Heterogeneity was examined using the $\chi 2$ and I^2 statistics. I^2 is a quantity that describes the degree of inconsistency across studies in a meta-analysis as a percentage. An I^2 of 50% is considered to represent moderate heterogeneity,[27] therefore possible explanatory factors were investigated for meta-analyses with I^2 values of more than 50%. In the event of significant heterogeneity, a search was made to look for moderator variables, for example patients (age, duration of diabetes), study (design of trial), and duration of treatment.

6.8 Publication Bias

Publication bias was explored by funnel plots (i.e., a plot of effect size versus standard error) for meta-analyses containing more than five RCTs. Plots were examined visually for asymmetry, an indication of selective reporting.

7 RESULTS

Most RCTs reported final values and not change from baseline values at the end of treatment; hence, the analyses were performed with final values.

7.1 Study Selection

7.1.1 Randomized controlled trials

Figure 1 shows the RCT selection process. A total of 765 citations were identified from the updated literature search, from March 2006 to April 2007. Of these, 739 citations were excluded based on title and/or abstract. The excluded citations were mainly reviews, editorials, observational studies, non-randomized studies, and studies with comparisons that were not relevant (e.g., different routes of administration of intervention and comparator). Of the 26 potentially relevant citations, 21 were excluded after reviewing the full text articles. Reasons for exclusion are reported in Appendix 5. Only five RCTs were selected to be included in the review. Of those, three were for type 1 DM[28-30] and 2 were for type 2 DM.[31,32]

Technology Report 87[19] included 89 reports describing 86 unique trials. After applying the new inclusion/exclusion criteria, 12 RCTs were excluded. The main reasons for exclusion were no comparable insulin regimen in the intervention and control group (eight RCTs)[33-40] and data were reported for both type 1 and type 2 DM together (four RCTs).[41-44] Details are reported in Appendix 5.

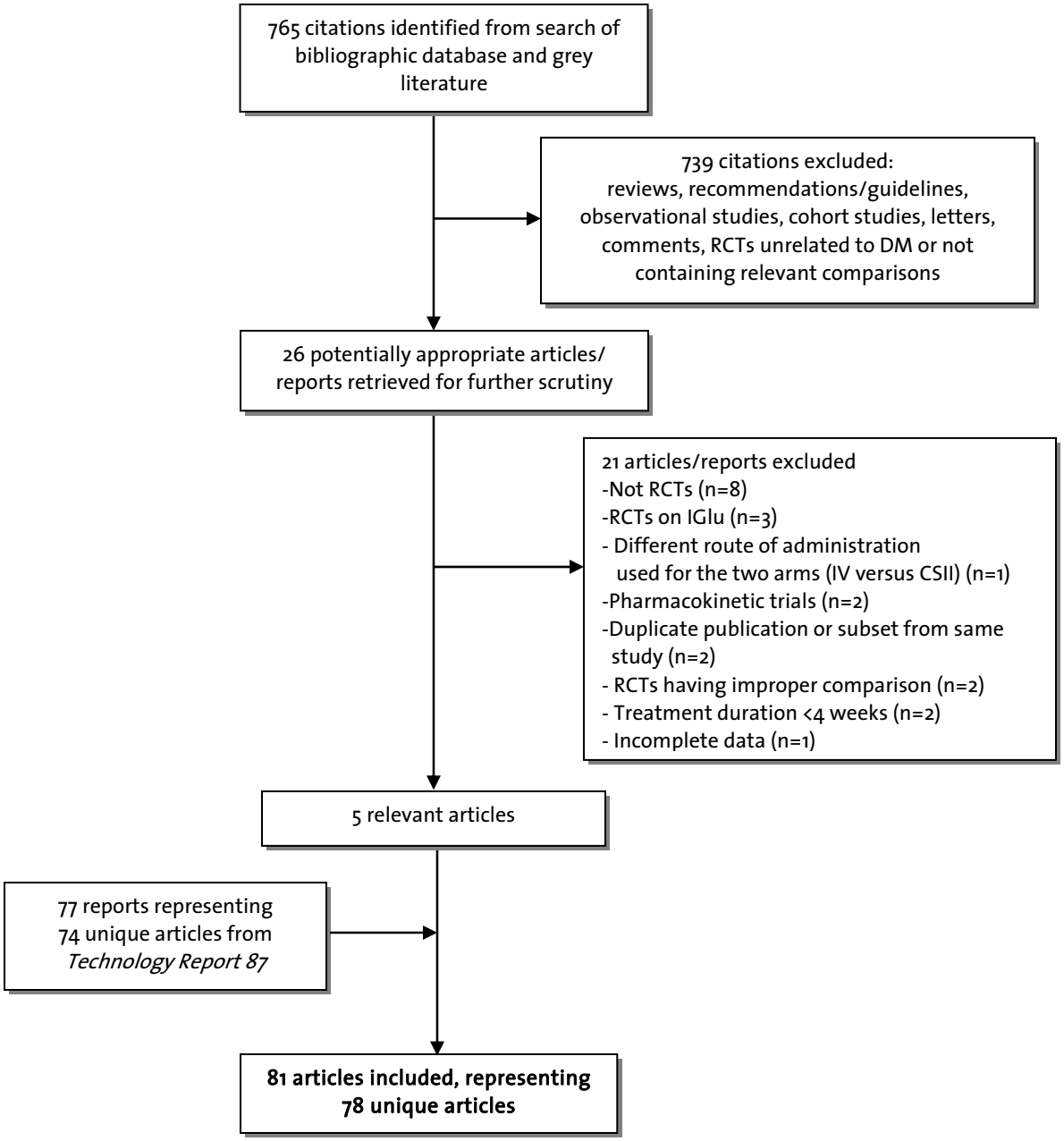
No additional studies were selected from the 13 articles that were obtained from the stakeholders' feedback.

The combined total number of RCTs included in this review from the updating process and from the previous review was 81 reports describing 78 unique trials. Forty-five RCTs addressed type 1 DM, 24 addressed type 2 DM, six RCTs[45-50] addressed both type 1 and type 2 DM, and three[51-53] RCTs were about gestational DM. Five[45-47,49,50] of the six RCTs that addressed type 1 and type 2 DM were included in the analysis of type 1 and type 2 DM, while one[48] was included in the analysis of type 2 DM.

7.1.2 Observational studies

The literature search identified 242 articles for potential inclusion in the meta-analyses. However, none of those studies satisfied inclusion and exclusion criteria.

Figure 1: Study selection process



CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; IGlu=insulin glulisine; IV=intravenous; RCTs=randomized controlled trials.

7.2 Study Characteristics

Characteristics of the RCTs comparing ILis or IAsp with HI in patients with type 1 DM, type 2 DM, and gestational DM are shown in Appendices 6A, 6B, and 6C respectively.

Of the 50 RCTs selected for patients with type 1 DM, five[30,54-57] were published as abstracts, 32 mentioned industrial sponsorship, four had investigators from industry, two mentioned sponsorships from other organizations, and 11 did not report any sponsorship or funding. Thirty-six RCTs were on ILis, 12 on IAsp, and two on both ILis and IAsp. Patient numbers in the RCTs ranged from 10 to 1,008. Many of the RCTs were on multicentre and multinational RCTs (63%). Thirty-two RCTs (65%) were crossover and 18 of parallel design. Most of the crossover RCTs did not have or mention the wash-out period.

Of the 30 RCTs selected for the analysis of patients with type 2 DM, two[58,59] were published as abstracts. Twenty-two RCTs mentioned industrial sponsorship, three had investigators from industry, and five did not report any sponsorship or funding. Twenty-one RCTs were on ILis, eight on IAsp, and one compared ILis and IAsp. The number of patients included in the RCTs ranged from seven to 876. Many of the RCTs were multicentre and multinational (66%). Thirteen RCTs (43%) were crossover and 17 of parallel design (57%). Most of the crossover RCTs did not have or mention the wash-out period.

Of the three RCTs[51-53] on patients with gestational DM (Appendix 6C), two were journal articles [52,53] and one was abstract.[51] The industrial sponsorship was mentioned in one of the RCTs. All the RCTs compared ILis with HI and were of parallel design. The number of patients ranged from 41 to 49.

7.3 Patient Characteristics

The characteristics of patients included in the RCTs for type 1 DM, type 2 DM and gestational DM are presented in Appendices 6A, 6B, and 6C respectively. The inclusion and exclusion criteria for selecting patients in each study are presented in Appendix 7A for type 1 DM, Appendix 7B for type 2 DM and Appendix 7C for gestational DM.

Of the 50 RCTs on patients with type 1 DM, eight[28,54,55,60-64] involved only pediatric populations (mean age ranged between five and 15 years). All the RCTs reported the number of males and females, and for males the range varied from 45% to 70%. Duration of diabetes was mentioned in all the RCTs: six reported mean value between two and six years, one reported mean value as >1 year, and two did not report the duration of diabetes. Two RCTs[29,65] included pregnant women with type 1 DM with a mean/median age of approximately 30 years. Duration of diabetes was 12 years (mean) in Mathiesen *et al.*[29] and approximately 13.5 years (median) in Persson *et al.* [65] The remaining 42 RCTs involved adult patients with type 1 DM. Two RCTs[56,66] did not mention the age of patients, and the mean age in the remaining RCTs ranged from 23 years to 48 years. Of the 42 RCTs, five did not report the number of males and females, and one[67] had only males. The percentage of males ranged from 20% to 70%. The duration of diabetes was not reported in two RCTs.[56,66] One RCT[68] included newly diagnosed patients of eight weeks, two RCTs reported the duration of diabetes as >1 year[69] and >2 years,[70] and one RCT[71] reported the duration in a range from two years to 25 years. Two RCTs reported a median duration of diabetes of approximately 13 years.[72,73] The remaining RCTs for adult patients with type 1 DM reported the mean duration of diabetes ranging from four years to 30 years.

Of the 30 RCTs on patients with type 2 DM, two RCTs[58,59] did not mention the age of the patients. The mean age ranged from 42 years to 68 years in the remaining RCTs. Four RCTs did not mention the percentage of male and female patients.[48,58,59,74] The percentage of males in the remaining RCTs ranged from 17% to 77%. The duration of diabetes was not mentioned in three RCTs,[58,75,76] and one RCT[59] reported the duration as >2 years. The mean duration of diabetes in the remaining RCTs ranged from six years to 16 years.

Of the three RCT in patients with gestational DM, age of the patients was not mentioned in one RCT,[51] and the mean age in the other RCTs[52,53] ranged from 30 to 35 years. The weeks of gestation at the diagnosis was not mentioned in two RCTs,[51,52] and it was 28 weeks in Mecacci *et al.* [53]

7.4 Study Quality

RCTs published as full reports for type 1 DM, type 2 DM, and gestational DM were assessed for quality (Appendix 8A, 8B, and 8C respectively).

For the 45 full articles on type 1 DM patients, the mean Jadad score out of five was 1.8±0.7. All RCTs were randomized, but method of randomization was mentioned in four RCTs, assessment was blinded in three RCTs, allocation concealment was adequate in two RCTs,[61,70] withdrawals were reported in 65% of the RCTs, and intent to treat analysis was reported in 50% of the RCTs.

For the 28 full reports on patients with type 2 DM, the mean Jadad score was 2.0±0.7. All RCTs were randomized, but the method of randomization was mentioned in six RCTs, assessment was blind in one RCT, allocation concealment was unclear in all, withdrawals or dropouts were mentioned in 79% of the RCTs, and the intent-to-treat analysis was reported in 75% of the RCTs.

For the two full articles on gestational DM, mean Jadad score was two out of a scale of five. Method of randomization was mentioned in one RCT, both the RCTs were open label, withdrawal was mentioned in one RCT, allocation concealment was unclear, and analysis was not intent-to-treat in both the RCTs.[52,53]

7.5 Results of Meta-analysis

Because of incomplete reporting of data, we could not include all RCTs in the meta-analyses to derive summary estimates. For continuous data, RCTs were pooled only if they reported SD values or contained sufficient data to enable SD to be calculated. Most RCTs reported final values and not change from baseline values at the end of treatment; hence, the analyses were performed with final values. Summary estimates (WMD or RR or rate ratio) were computed using the random effects model. In crossover RCTs, patients were counted twice for the meta-analysis because they participated in both the treatment arms.

7.5.1 Adult patients with type 1 DM

a) Glycosylated hemoglobin

Study level A1c data for adult type 1 DM patients are summarized in Appendix 9A. All A1c data are expressed as percentages. Meta-analytic results for each comparison are presented in Table 1.

Table 1: Summary of results of meta-analyses for comparison of rapid-acting insulin analogues versus human insulin in adults with type 1 DM – Overall results and subgroup and sensitivity analyses for mean A1c (%)

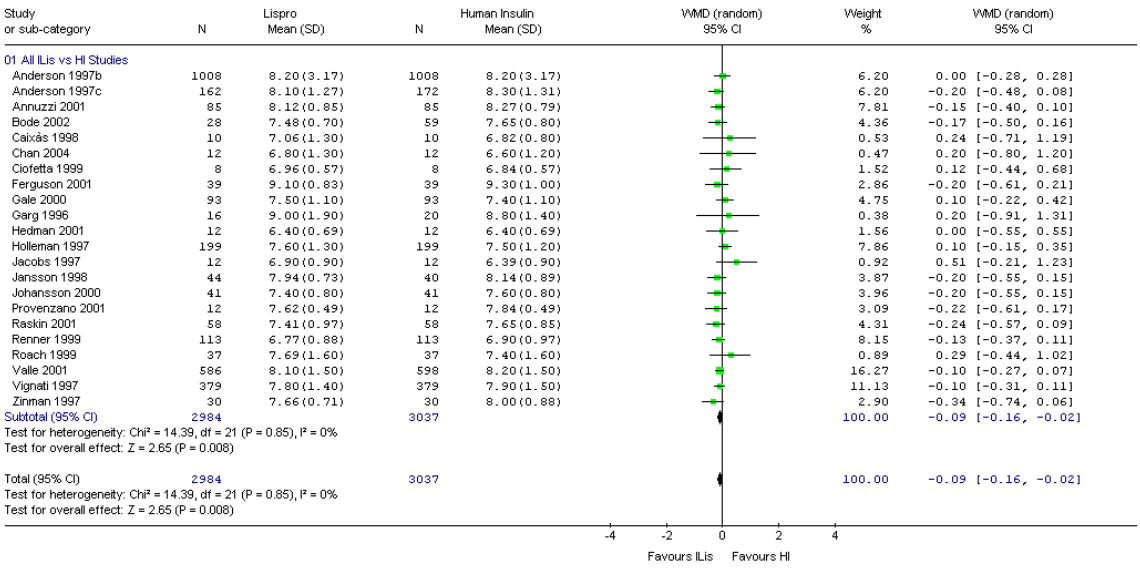
Comparison	Subgroup	Sensitivity Analysis	No. of RCTs	No. of Patients	Random Effects Model	
					WMD (95% CI)	Heterogeneity I^2 (p value)
ILis versus HI	Overall	All RCTs	22	6,021	-0.09 (-0.16, -0.02)	0% (0.85)
		Removal of RCTs≤3 months duration	6	854	-0.17 (-0.30, -0.03)	0% (0.99)
		Removal of crossover RCTs	7	1,967	-0.13 (-0.24, -0.02)	0% (0.95)
	MDI	All RCTs	16	5,426	-0.06 (-0.14, 0.02)	0% (0.76)
		Removal of RCTs≤3 months duration	4	532	0.19 (-0.38, 0.00)	0% (0.92)
		Removal of crossover RCTs	5	1,654	0.12 (-0.25, 0.01)	0% (0.81)
	CSII	All RCTs	6	595	-0.18 (-0.32, -0.05)	0% (0.93)
		Removal of RCTs≤3 months duration	2	313	-0.14 (-0.34, 0.05)	0% (0.85)
		Removal of crossover RCTs	2	313	-0.14 (-0.34, 0.05)	0% (0.85)
IAsp versus HI	Overall	All RCTs	7	3,035	-0.13 (-0.20, -0.07)	0% (0.45)
		Removal of RCTs≤3 months duration	5	2,491	-0.13 (-0.21, -0.05)	16.7% (0.31)
		Removal of crossover RCTs	6	2,734	-0.15 (-0.22, -0.09)	0% (0.72)
	MDI	All RCTs	5	2,888	-0.12 (-0.19,-0.06)	0% (0.66)
		Removal of RCTs≤3 months duration	4	2,462	-0.11 (-0.18, -0.04)	0% (0.57)
		Removal of crossover RCTs	4	2,587	-0.14 (-0.21, -0.07)	0% (0.89)
	CSII	All RCTs	2	147	-0.31 (-0.54, -0.08)	0%
		Removal of RCTs≤3 months duration	1	29	-0.20 (-0.66, 0.26)	-

A1c=glycosylated hemoglobin; CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; WMD=weighted mean difference.

ILis versus HI: Twenty-eight RCTs[30,45,46,49,50,57,68,69,73,77-95] were identified for this comparison. Of those, six RCTs were excluded from this analysis for the following reasons: one RCT[30] used IGlar as a basal insulin, which is different from the rest of the studies; two RCTs[57,68] did not report A1c data; and three further RCTs[93-95] reported carryover effects. Nineteen of the 22 RCTs that compared ILis to HI in type 1 diabetic adult patients reported mean A1c at the end of the treatment period.

Overall, the WMD of A1c between ILis and HI was estimated to be -0.09 (95% CI: -0.16, -0.02) (Figure 2). The test for heterogeneity gave an I^2 value of 0% (p=0.85). Sensitivity analysis, by removal of studies of less than or equal to three months duration or of crossover design, revealed similar results as the main analysis (Table 1). Visual examination of the funnel plot did not reveal any publication bias (Appendix 10, Figure 1).

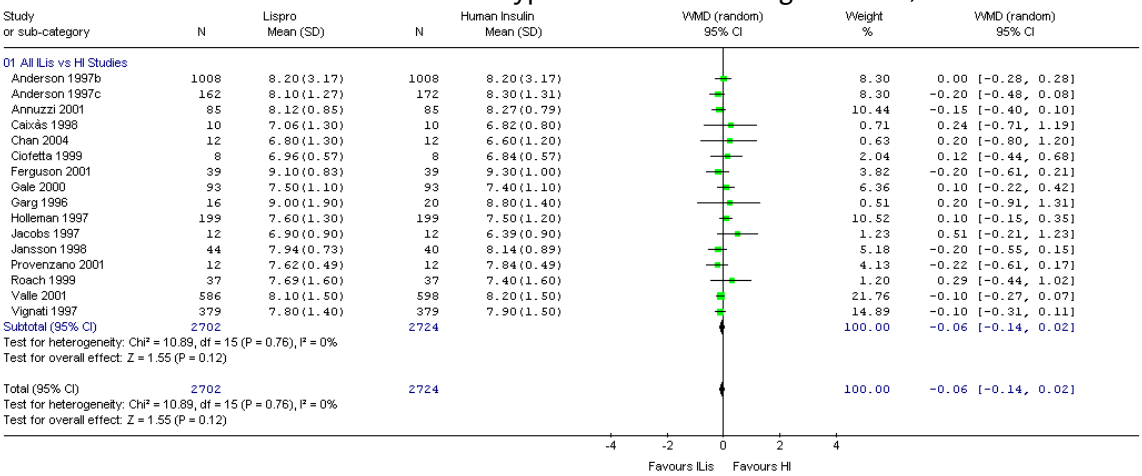
Figure 2: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adult patients – A1c, WMD



Heterogeneity I^2 describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

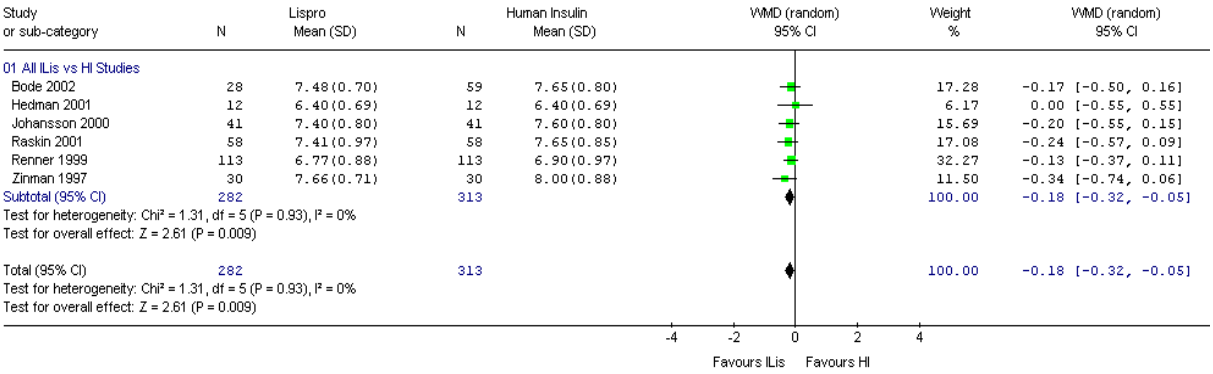
RCTs were further grouped according to delivery methods: CSII and MDI. Sixteen RCTs[45,46,49,50,66,73,77-83,85-87] with a total of 5,426 patients used MDI and six RCTs[69,88-92] with a total of 595 patients used CSII. For studies using MDI, the WMD in A1c was -0.06 (95% CI: -0.14, 0.02) comparing ILis to HI, whereas for CSII studies the WMD in A1c was -0.18 (95% CI: -0.32, -0.05) (Figures 3 and 4). There was no statistical statistically significant heterogeneity among MDI studies or CSII studies (I^2=0% for both). Sensitivity analysis was also performed for MDI and CSII studies and revealed similar results as the main analysis for MDI studies but not for CSII studies (Table 1).

Figure 3: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using MDI – A1c, WMD



Heterogeneity I² describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

Figure 4: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using CSII – A1c, WMD

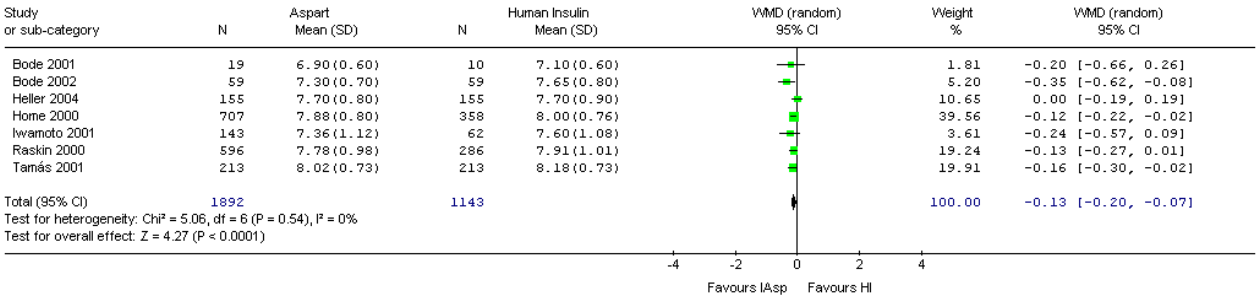


Heterogeneity I² describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

IAsp versus HI: Ten RCTs[30,67,69-71,96-100] were identified for this comparison. Three were excluded for the following reasons: one RCT[30] used IGlar as a basal insulin, which is different from the rest of studies; one RCT[67]did not report A1c data; and a third RCT[100] was an extension of another RCT.[96] Of the seven RCTs[69-71,96-99] included in the analysis that compare IAsp to HI , 5 RCTs[70,96-99] involving 2,888 patients used MDI and two RCTs[69,71] involving 147 patients used CSII.

Overall, the WMD of A1c between IAsp and HI was estimated to be -0.13 (95% CI: -0.20, -0.07) in favour of IAsp compared with HI (Figure 5). The test for heterogeneity gave I² value of 0% (p=0.45). Sensitivity analysis, by removal of studies of less than or equal to three months' duration or of crossover design, revealed similar results as the main analysis (Table 1). The visual examination of funnel did indicate publication bias (Appendix 10, Figure 2).

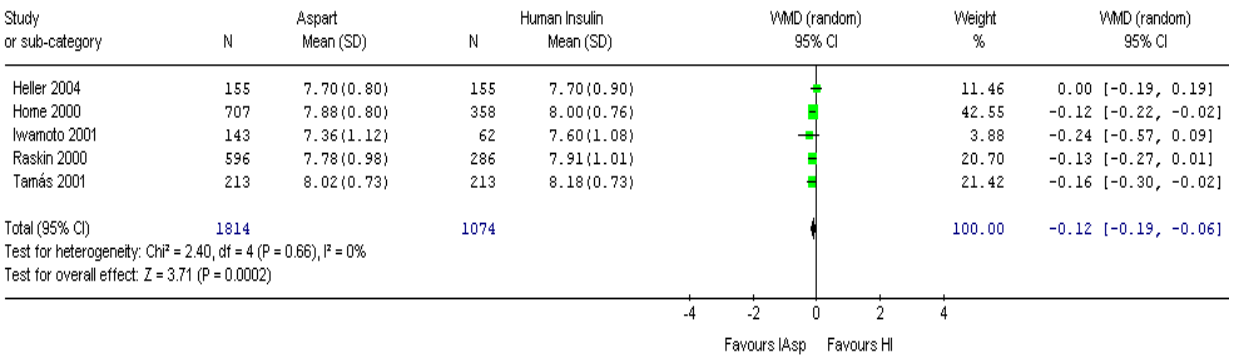
Figure 5: Forest plot of all RCTs that examined the use of IAsp versus HI for the treatment of type 1 DM in adults – A1c, WMD



Heterogeneity I² describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

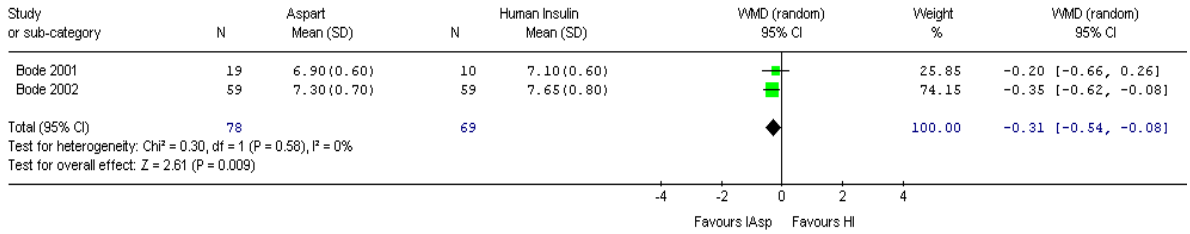
For MDI, the pooled WMD for A1c levels between IAsp and HI was -0.12 (95% CI -0.19, -0.06), indicating significant decrease of A1c with IAsp therapy compared with HI (Figure 6). There was no heterogeneity across RCTs for MDI (I^2=0%). Sensitivity analysis showed similar results as the main analysis (Table 1), whereas, for CSII the pooled WMD for A1c after treatment with IAsp and HI was -0.31 (95% CI: -0.54, -0.08), indicating significant decrease of A1c using IAsp compared with HI (Figure 7). There was no heterogeneity across RCTs for pooled analysis (I^2=0%).

Figure 6: Forest plot of RCTs that examined the use of IAsp versus HI for the treatment of type 1 DM in adults using MDI – A1c, WMD



Heterogeneity I² describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; MDI=multiple daily injection; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

Figure 7: Forest plot of RCTs that examined the use of IAsp versus HI for the treatment of type 1 DM in adults using CSII – A1c, WMD



Heterogeneity I^2 describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

In summary, adult patients with type 1 DM treated with ILis or IAsp had statistically significant lower A1c levels than those treated with HI. For MDI, the difference in A1c was small but not significant for ILis versus HI (varying from -0.14 to 0.02) and was small and significant for IAsp versus HI (varying from -0.19 to -0.06), whereas, for CSII the difference in A1c was significantly lower for both rapid-acting analogues, varying from -0.32 to -0.05 for ILis versus HI and from -0.5 to -0.08 for IAsp versus HI.

ILis versus IAsp: Bode *et al.*,[69] with a total population of 87 patients using CSII, reported no significant difference in the A1c level between treatment with ILis and IAsp in an adult population with type 1 DM. The difference in A1c level at the end of treatment between the two treatment groups was 0.25 (95% CI: -0.20, 0.71).

b) Hypoglycemia

Study-level data for hypoglycemia for adult type 1 DM are presented in Appendix 11A. RR of the patients with at least one episode of hypoglycemia and rate ratio of hypoglycemic episode frequency was sought for each treatment arm. Overall pooled results and results from subgroup analyses are summarized in Tables 2, 3, and 4 for severe, nocturnal, or overall hypoglycemia respectively.

There were variations in the reporting of hypoglycemia data. Data were expressed in different units (e.g., as patients with episodes and as rate or episode frequency) and were sometimes categorized (e.g., severe, nocturnal, overall). Also, the definition of hypoglycemia varied between RCTs (Appendix 11A). We collected and analyzed the data pertaining to the rate of overall hypoglycemia, severe or major hypoglycemia, and nocturnal hypoglycemia. When hypoglycemia was expressed as an episode rate, the rate ratio was calculated, and when hypoglycemia was expressed in terms of a number of patients having an episode(s) the RR was calculated. Due to insufficient data, not all RCTs could be used to derive summary statistics.

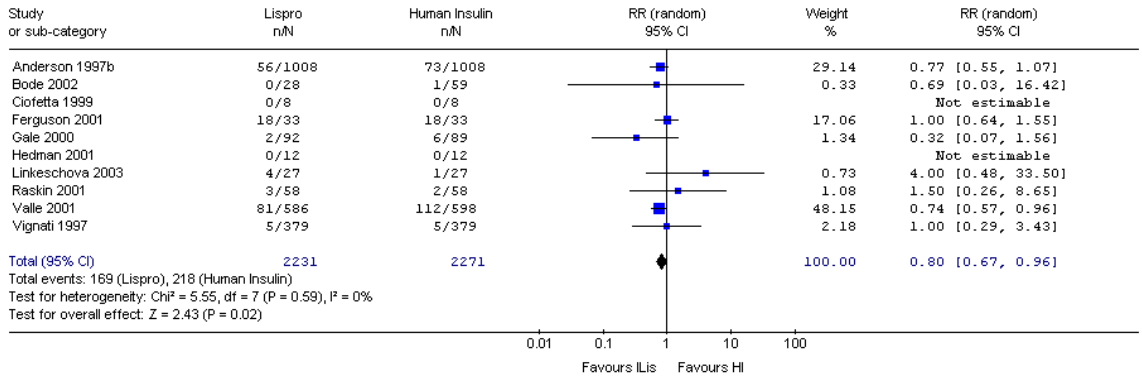
Severe hypoglycemia

ILis versus HI: In 10 RCTs[50,57,69,73,77,80,81,87,88,90] of type 1 adult diabetic patients, data on the number of patients who had at least one episode of severe hypoglycemia could be extracted. Patients in six[50,73,77,80,81,87] of these trials used MDI, while they used CSII in the other four.[57,69,88,90]

The overall pooled RR was 0.80 (0.67, 0.96), indicating a statistically significant reduction in the number of patients with at least one episode of severe hypoglycemia with the treatment with ILis

compared with HI treatments (Figure 8, Table 2). There was no evidence of heterogeneity (I^2=0%, p=0.59). Visual examination of the funnel plot did not indicate publication bias, although the number of studies included was very small (Appendix 10, Figure 3).

Figure 8: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adult patients – Severe hypoglycemia, RR



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; RR=relative risk.

Table 2: Summary of results of meta-analyses for comparison of rapid-acting insulin analogues versus HI in adults with type 1 DM – Overall results and subgroup and sensitivity analyses for severe hypoglycemia (RR)

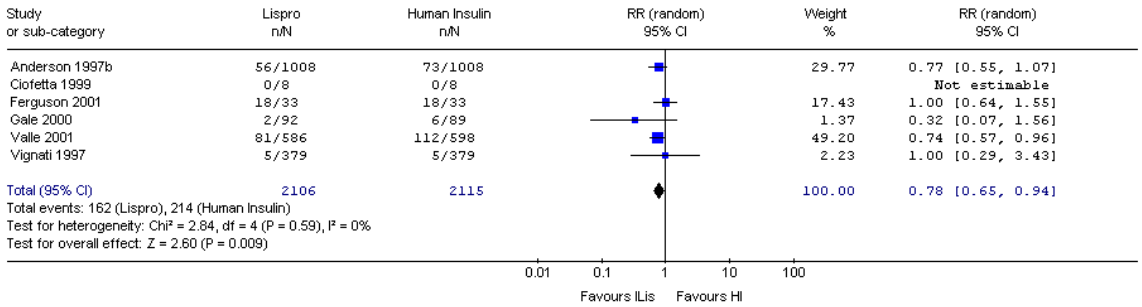
Comparison	Category	Sensitivity Analysis	No. of RCTs	No. of Patients	Random Effects Model	
					RR (95% CI)	Heterogeneity I^2 (p value)
ILis versus HI	Overall	All RCTs	10	4502	0.80 (0.67, 0.96)	0% (0.59)
	MDI	All RCTs	6	4221	0.78 (0.65, 0.94)	0% (0.59)
	CSII	All RCTs	4	281	1.86 (0.54, 6.46)	0% (0.63)
IAsp versus HI	MDI	All RCTs	3	1,696	0.83 (0.66, 1.05)	0% (0.71)
		Removal of crossover RCTs	2	1,488	0.87 (0.67, 1.12)	0% (0.95)
	CSII	All RCTs	1	118	0.33 (0.01, 8.02)	NA

CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; RR=relative risk.

The pooled RR (95% CI) between ILis and HI using MDI was 0.78 (0.65, 0.94), indicating a statistically significant reduction in the number of patients with at least one episode of severe hypoglycemia with the treatment of ILis compared with HI treatments using MDI (Figure 9). There was no statistically significant heterogeneity across the RCTs (I^2=0%) (Figure 9, Table 3). For CSII studies that compare ILis with HI in 170 adult patients with type 1, the pooled RR (95% CI) was 1.86 (0.54, 6.46), indicating no statistically significant

differences between ILis and HI treatments (Figure 10). There was no statistically significant heterogeneity across the RCTs (I^2=0%, Figure 10, Table 2).

Figure 9: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using MDI – Severe hypoglycemia, RR



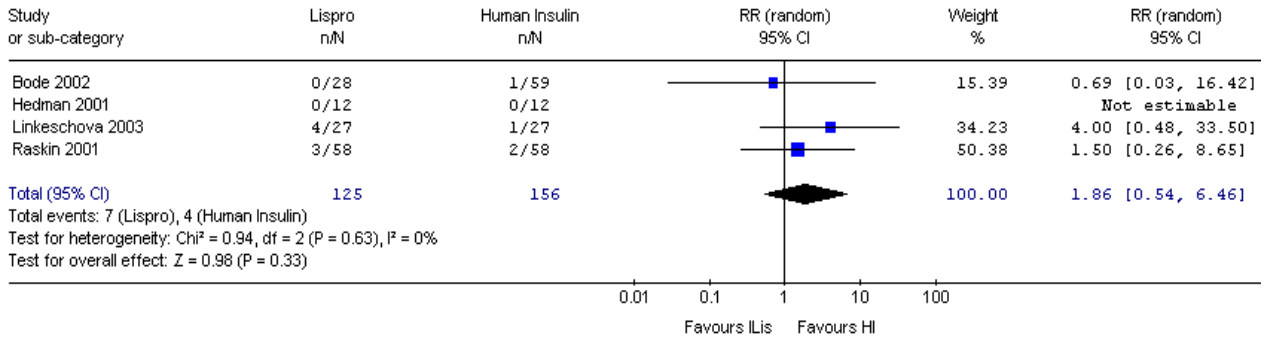
Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; RR=relative risk.

Table 3: Summary of results of meta-analyses for comparison of rapid-acting insulin analogues versus HI in adults with type 1 DM – Overall results and subgroup analyses for nocturnal hypoglycemia (rate ratio)

Comparison	Subgroup	Sensitivity Analysis	No. of RCTs	No. of Patients	Random Effects Model	
					Rate Ratio (95% CI)	Heterogeneity I^2 (p value)
ILis versus HI	Overall	All RCTs	4	725	0.60 (0.40, 0.90)	93.6% (<0.00001)
	MDI	All RCTs	3	658	0.58 (0.35, 0.98)	95.6% (<0.00001)
	CSII	All RCTs	1	67	0.67 (51, 0.88)	NA
IAsp versus HI	Overall	All RCTs	1	118	0.55 (0.43, 0.70)	NA
ILis versus IAsp	Overall	All RCTs	1	87	1.20 (0.89, 1.68)	NA

CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; MDI=multiple daily injection; NA=not applicable; RCTs=randomized controlled trials.

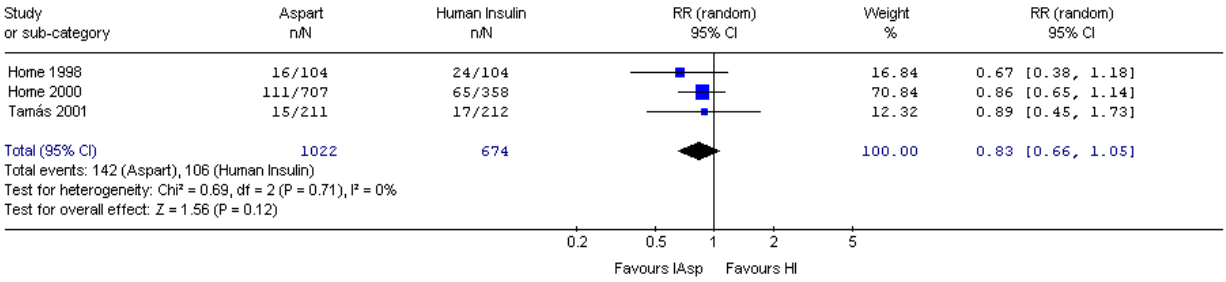
Figure 10: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using CSII – Severe hypoglycemia, RR



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; RR=relative risk.

IAsp versus HI: Three RCTs[67,96,99] with a total population of 1,696 adult type 1 DM patients reported severe hypoglycemia as a number of patients having an event. Patients in all three RCTs used MDIs. The pooled RR (95% CI) was 0.83 (0.66, 1.05), indicating no significant difference in the number of patients reporting severe hypoglycemia between IAsp and HI (Figure 11). There was no statistically significant heterogeneity across the RCTs (I^2=0%) (Figure 11, Table 3). One RCT[69]showed no significant difference in the number of patients with severe hypoglycemia in type 1 DM patients who used CSII [RR: 0.33; 95% (CI: 0.01, 8.02)].

Figure 11: Forest plot of RCTs that examined the use of IAsp versus HI for the treatment of type 1 DM in adults using MDIs – Severe hypoglycemia, RR



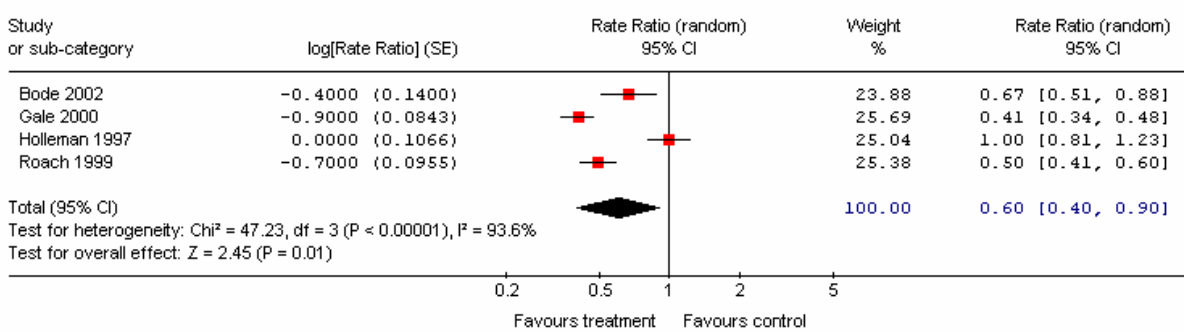
Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; MDIs=multiple daily injections; RCTs=randomized controlled trials; RR=relative risk.

Nocturnal hypoglycemia

ILis versus HI: Four RCTs[49,69,73,83] with a total of 658 adult patients with type 1 DM reported nocturnal hypoglycemia as the event rate from which the rate ratio between ILis and HI was calculated. Patients in all four RCTs except one[69] used MDI. The overall rate ratio was 0.60 (95% CI: 0.40, 0.90) in favour of ILis, but the pooled studies showed a significantly high degree of heterogeneity among them (I^2=93.6%; p<0.00001) (Figure 12, Table 3).

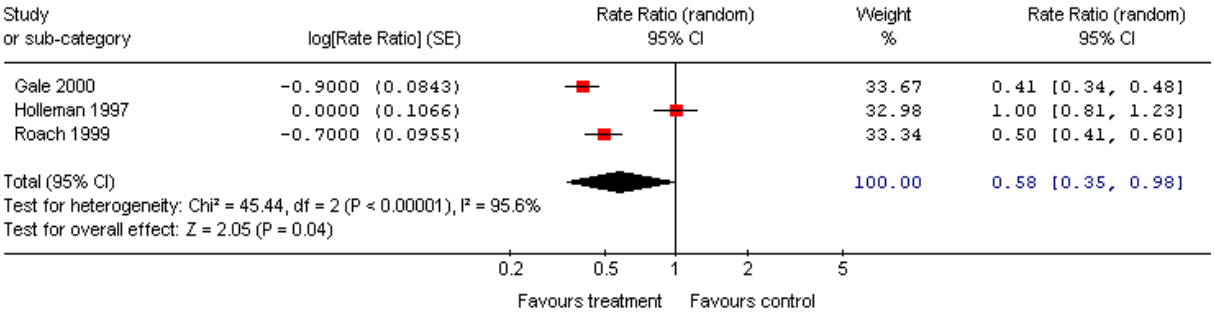
For MDI studies, the pooled rate ratio (95% CI) of three RCTs[49,73,83] was 0.58 (0.35, 0.98), indicating significant decrease of nocturnal hypoglycemia events when patients were treated with ILis compared with treatment with HI (Figure 13, Table 3). There was a statistically significant large degree of heterogeneity among studies (I^2=95.6%; p< 0.00001). All RCTs were crossover with a duration of less than or equal to three months.

Figure 12: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults – Nocturnal hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SE=standard error.

Figure 13: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using MDI – Nocturnal hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials.

A single RCT[69] with a total of 67 adult patients with type 1 DM compared for events for nocturnal hypoglycemia with ILis and HI using CSII. The rate ratio (95% CI) was 0.67 (0.51, 0.88), indicating significant decrease of events for nocturnal hypoglycemia using ILis therapy compared with HI, using CSII (Table 3).

IAsp versus HI: Bode *et al.*[69] showed significant reduction in the event rate of nocturnal hypoglycemia between IAsp and HI in 118 adult patients who used CSII. The rate ratio (95% CI) was 0.55 (0.43, 0.70) (Table 3). Two other studies[70,100] reported a significant reduction in the events rate of major nocturnal hypoglycemia in the IAsp group compared with the HI group. One of these studies[101] examines the long-term effect (three years) of IAsp and HI in 753 patients and found no statistically significant difference in major nocturnal hypoglycemia between the two groups.

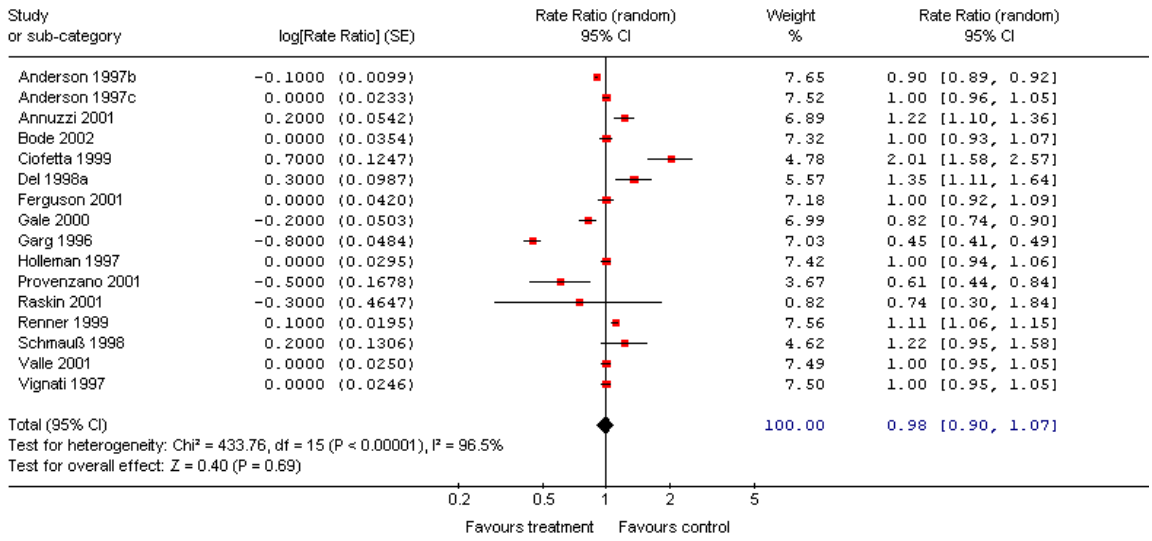
ILis versus IAsp: Bode *et al.*[69] also showed no significant difference in the event rate of nocturnal hypoglycemia between ILis and IAsp in the 87 patients who used CSII. The rate ratio (95% CI) between treatments was 1.20 (0.89, 1.68) (Table 3).

Overall hypoglycemia

ILis versus HI: Data about rates of overall hypoglycemia were extracted from 16 RCTs[45,50,69,73,77,78,80-83,86,87,90,91,95,102] involving 5,731 adult patients with type 1 DM. These data were used to calculate the rate ratio between ILis and HI. Two other RCTs[68,85] were excluded from the analysis for the following reasons: one RCT[85] reported a significant difference of the hypoglycemia rate between ILis and HI at baseline and another RCT included only new diabetic patients.[68] Twelve[45,50,73,77,78,80-83,86,87,102] of the 16 RCTs, with a total of 5,193 patients, used MDI and four RCTs[69,90,91,95] with a total of 451 patients used CSII.

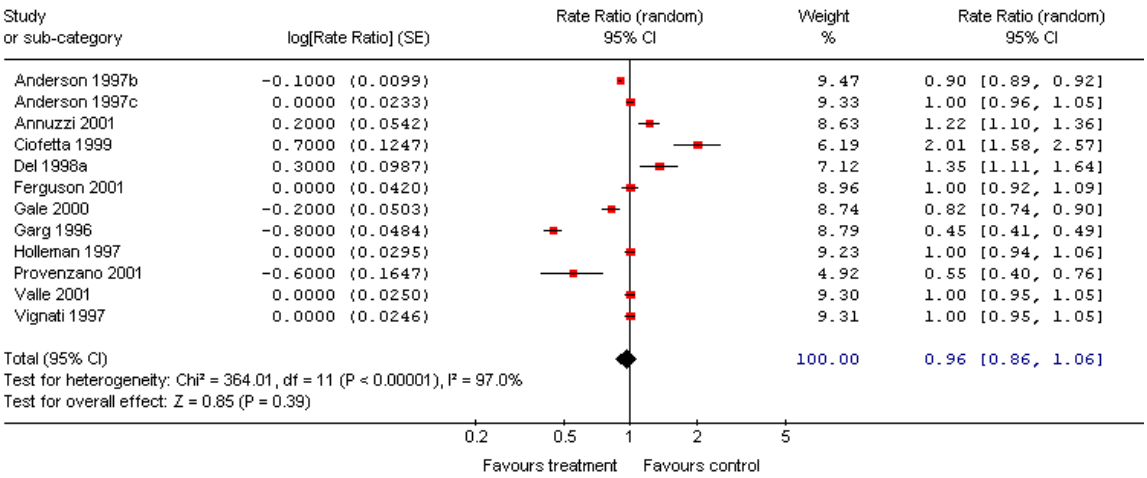
The overall, MDI, and CSII analyses showed no statistically significant difference in the rates of overall hypoglycemia measured by the rate ratio: 0.98 (95% CI: 0.90, 1.07), 0.96 (95% CI: 0.86, 1.06), and 1.07 (95% CI: 0.98, 1.16) respectively (Figure 14 to 16). Heterogeneity was high among studies in all analyses as indicated by I^2, which ranged from 60.8% ($p<0.05$) in the CSII analysis to 96.5% in the overall analysis ($p<0.00001$). Sensitivity analysis, by removing crossover studies, revealed similar results as the main analyses (Table 4). Funnel plot did not indicate publication bias (Appendix 10, Figure 4).

Figure 14: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults – Overall hypoglycemia, rate ratio



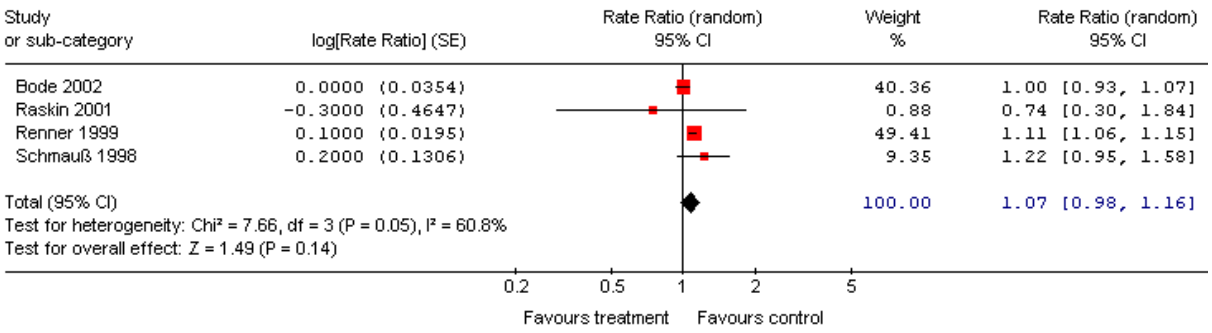
Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SE=standard error.

Figure 15: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using MDI – Overall hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; SE=standard error.

Figure 16: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using CSII – Overall hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SE=standard error.

IAsp versus HI: Eight RCTs[67,69-71,96-99] comparing the effect of IAsp versus HI reported event rates for overall hypoglycemia and were included in the analyses: six RCTs[67,70,96-99] used MDI and two RCTs[69,71] used CSII. One RCT[100] also reported overall hypoglycemia event rates but was excluded because it was an extension of another included study.[96]

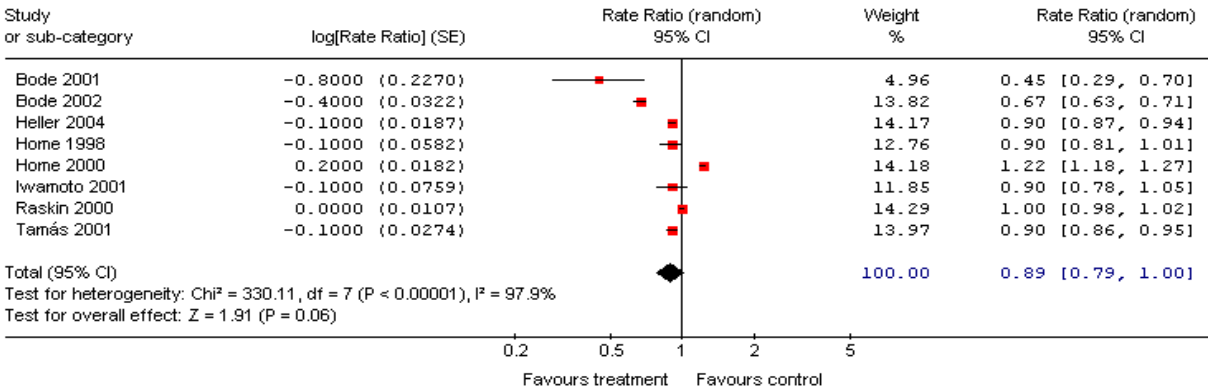
Similar to ILis, no statistically significant difference between IAsp and HI was observed regarding the rate of overall hypoglycemia when all studies and MDI studies were analyzed (Table 4, Figure 17 and 18). The rate ratios (95% CI) were 0.89 (0.79, 1.00) and 0.97 (0.88, 1.08) respectively. Whereas pooling of the two CSII studies[69,71] revealed a significant reduction in the rate of overall hypoglycemia (rate ratio: 0.58; 95% CI: 0.40, 0.85) (Table 4, Figure 19). A statistically significant heterogeneity was observed in the overall, MDI, and CSII analysis (I^2: 97.9%, 97.0%, and 67.1%, respectively).

Table 4: Summary of results of meta-analyses for comparison of rapid-acting insulin analogues versus HI in adult type 1 DM – Overall results and subgroup and sensitivity analyses for overall hypoglycemia (rate ratio)

Comparison	Category	Sensitivity Analysis	No. of RCTs	No. of Patients	Random Effects Model	
					Rate Ratio (95% CI)	Heterogeneity I^2 (p value)
ILis versus HI	Overall	All RCTs	16	5,644	0.98 (0.90, 1. 07)	92.5% (<0.00001)
		Removal of crossover RCTs	6	1,975	1.00 (0.97, 1.02)	98.5% (<0.00001)
	MDI	All RCTs	12	5,193	0.98 (0.86, 1.06)	97.0% (<0.00001)
		Removal of crossover RCTs	4	1,575	0.96 (0.68, 1.35)	98.9% (<0.00001)
	CSII	All RCTs	4	451	1.07 (0.98, 1.16)	60.8% (0.05)
		Removal of crossover RCTs	2	313	1.06 (0.96, 1.16)	83.7% (0.01)
IAsp versus HI	Overall	All RCTs	8	3,771	0.89 (0.79, 1.00)	97.9% (<0.00001)
		Removal of crossover RCTs	6	2,753	1.0 (0.99, 1.02)	98.3% (<0.00001)
	MDI	All RCTs	6	3,096	0.97 (0.88, 1.08)	97.0% (<0.00001)
		Removal of crossover RCTs	4	2,578	1.01 (0.88, 1.15)	97.5% (<0.00001)
	CSII	All RCTs	2	175	0.58 (0.40, 0.85)	67.1% (0.08)

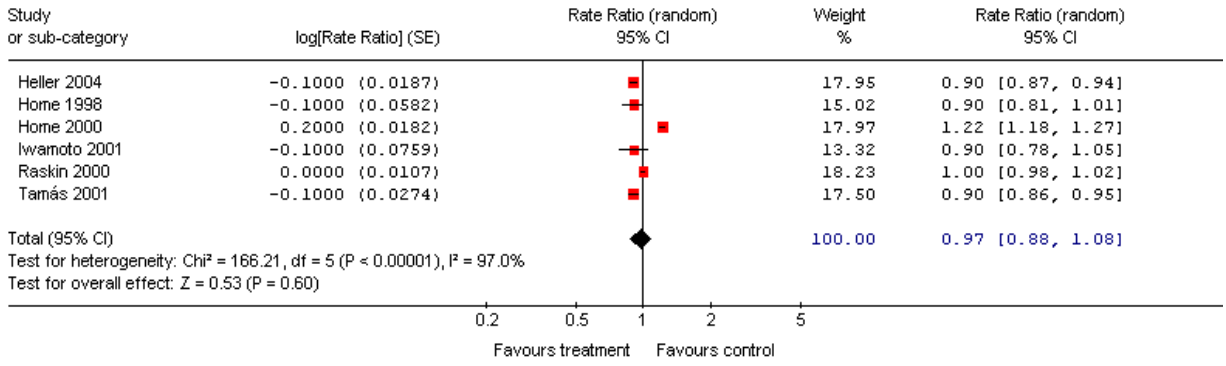
CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials.

Figure 17: Forest plot of all RCTs that examined the use of IAsp versus HI for the treatment of type 1 DM in adults – Overall hypoglycemia, rate ratio



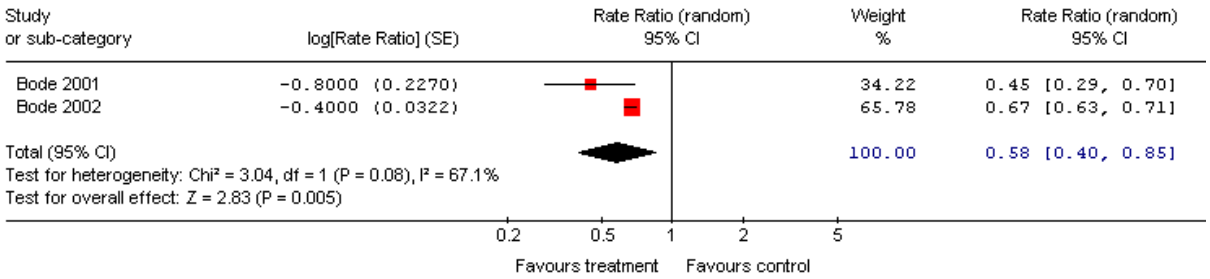
Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized controlled trials; SE=standard error.

Figure 18: Forest plot of RCTs that examined the use of IAsp versus HI for the treatment of type 1 DM in adults using MDI – Overall hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; RCTs=randomized controlled trials; MDI=multiple daily injection; SE=standard error.

Figure 19: Forest plot of RCTs that examined the use of IAsp versus HI for the treatment of type 1 DM in adults using CSII – Overall hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized controlled trials; SE=standard error.

ILis versus IAsp: Bode *et al.*[69] showed a significant increase in the event rate of overall hypoglycemia with ILis compared with IAsp in the 87 patients who used CSII. The rate ratio (95% CI) was 1.49 (1.37, 1.63).

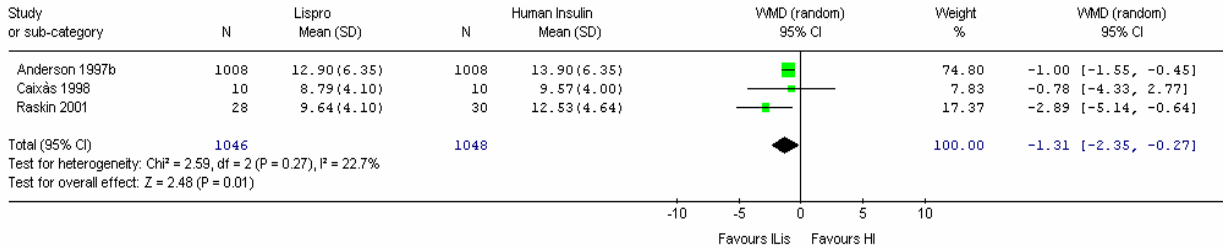
In summary, the available evidence showed a statistically significant reduction in the incidence of severe hypoglycemia in patients treated with ILis compared with HI. This significant reduction was observed for all RCTs and MDI RCTs but not for the CSII RCTs. Whereas the incidence for severe hypoglycemia was lower for IAsp compared with HI, the pooled results did not reach statistical significance perhaps due to the small number of RCTs for this comparison. It also appeared that treatment with ILis or IAsp resulted in a lower rate of nocturnal hypoglycemia than treatment with HI.

The rate of overall of hypoglycemia was similar between the treatment with ILis and HI in patients using either MDI or CSII. Whereas when IAsp was compared with HI, a significant decrease was observed only in the rate of overall hypoglycemia in patients who used CSII. There was no difference in ILis and IAsp regarding rates of nocturnal hypoglycemia, but analyzing overall hypoglycemia showed a significant increase in the rate of overall hypoglycemic events when ILis was used compared with IAsp. All hypoglycemia analyses showed that a significant degree of heterogeneity occurred among pooled studies.

c) Plasma glucose (two-hours post-prandial)

ILis versus HI: Three RCTs[77,79,90] involving 21,094 adults with type 1 DM and reporting two-hour post-prandial plasma glucose data were pooled. All three RCTs were of crossover design and of three months in duration. The overall WMD (95% CI) was -1.31 (-2.35 , -0.27) in favour of ILis (Figure 20). No statistically significant heterogeneity was observed (I^2=22.7%; p=0.27). Similar results were observed when the two MDI studies[77,79] and the single CSII study[90] were analyzed separately (Table 5). The WMD (95% CI) were -0.99 (-1.54, -0.45) and -2.89 (-4.48, -1.3) respectively.

Figure 20: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults – Two-hour post-prandial, WMD



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; RR=relative risk; SD=standard deviation; WMD=weighted mean difference.

Table 5: Summary of results of meta-analyses for comparison of rapid-acting insulin analogues versus HI in adults with type 1 DM – Overall results and subgroup analyses for two-hour post-prandial plasma glucose

Comparison	Category	Sensitivity Analysis	No. of RCTs	No. of Patients	Random Effects Model	
					WMD (95% CI)	Heterogeneity I^2
ILis versus HI	Overall	All RCTs	3	2,094	-1.31 (-2.35, -0.27)	22.7% (0.27)
	MDI	All RCTs	2	2,036	-0.99 (-1.54, -0.45)	0% (0.90)
	CSII	All RCTs	1	58	-2.89 (-5.14 to -0.64)	NA

CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; NA=not applicable; RCTs=randomized controlled trials; WMD=weighted mean difference.

c) Weight

Study-level data for weight and BMI for adults with type 1 DM are presented in Appendix 12A.

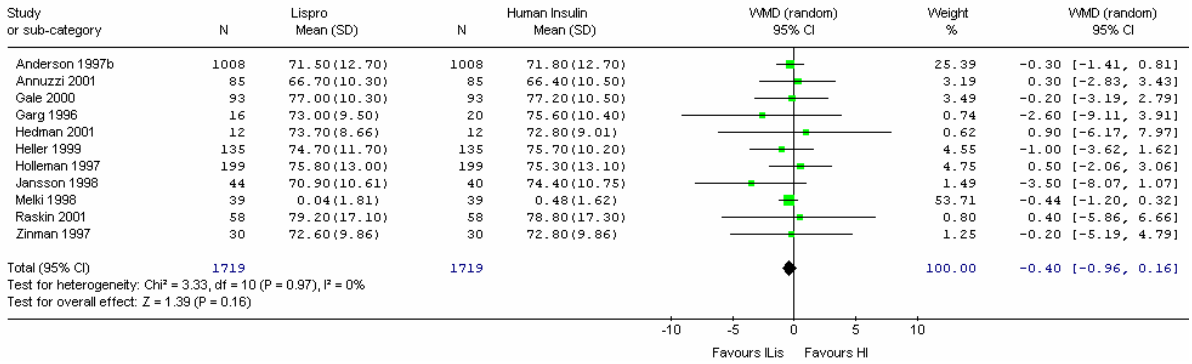
ILis versus HI: Eleven RCTs[73,77,78,82,83,85,88,90,92-94] involving 3,438 adult patients with type 1 DM reported body weight outcomes for both the ILis and HI groups. Of these, seven RCTs[73,77,78,82,83,85,93] involving 3,160 adult patients used MDI and four RCTs involving 278 patients used CSII. The pooled WMD did not show any difference in the weight gain between the ILis group and HI group for overall, MDI, and CSII analyses. The WMDs (95% CI) were -0.40 (-0.96, 0.16), -0.38 (-1.23, 0.46), and -0.41 (-1.15, 0.34) respectively. There was no evidence of heterogeneity in all analyses (I^2=0%) and no evidence of publication bias as examined by funnel plot (Appendix 10, Figure 6). Removal of crossover studies from all analyses revealed similar results as the main analyses. Summary results are presented in Table 6 and in Figures 21 to 23.

Table 6: Summary of results of meta-analyses for comparison of rapid-acting insulin analogues versus HI in adult type 1 DM – Overall results and subgroup and sensitivity analyses for weight gain

Comparison	Category	Sensitivity Analysis	No. of RCTs	No. of Patients	Random Effects Model	
					WMD (95% CI)	Heterogeneity I^2 (p value)
ILis versus HI	Overall	All RCTs	11	3,438	-0.40 (-0.96, 0.16)	0% (0.97)
		Removal of crossover RCTs	2	120	-3.20 (-6.95, 0.54)	0% (0.82)
	MDI	All RCTs	7	3,160	-0.38 (-1.23, 0.46)	0% (0.79)
		Removal of crossover RCTs	2	120	-3.20 (-6.95, 0.54)	0% (0.82)
	CSII	All RCTs	4	278	-0.41 (-1.15, 0.34)	0% (0.98)

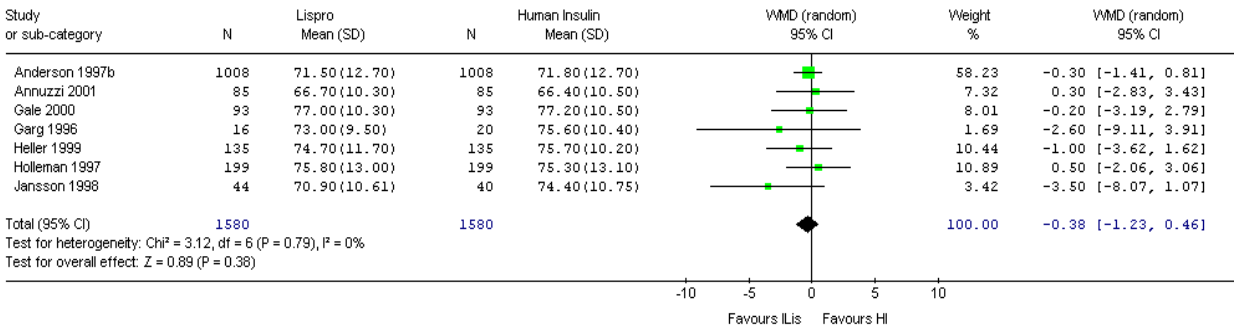
CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; WMD=weighted mean difference.

Figure 21: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults – Weight gain



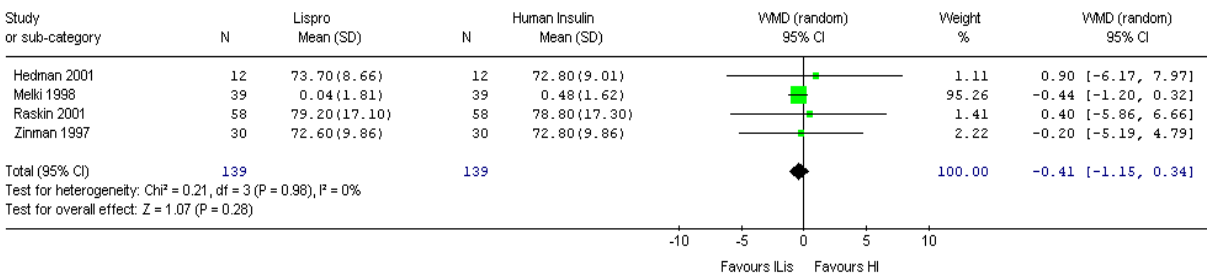
Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

Figure 22: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using MDI – Weight gain



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

Figure 23: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults using CSII – Weight gain



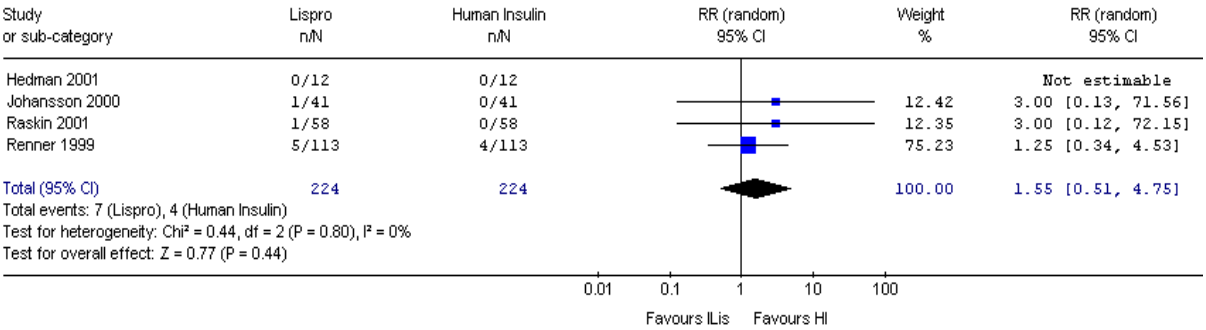
Heterogeneity I² describes the heterogeneity between the included studies. CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

d) Diabetic ketoacidosis

Study-level data for DKA for adult type 1 DM are presented in Appendix 13.

ILis versus HI: Four RCTs[88-91] with a total population of 448 adult patients with type 1 DM compared the effect of the treatment with ILis and HI on the incidence of DKA. Patients in all four studies used CSII. The pooled RR (95% CI) of the difference in the number of patients reporting DKA events between ILis and HI was 1.55 (0.51, 4.75), indicating no significant difference between the two treatments (Figure 24). There was no statistically significant heterogeneity across the studies (I^2=0%, Figure 24).

Figure 24: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adults – DKA, RR



Heterogeneity I² describes the heterogeneity between the included studies. CI=confidence interval; DKA=diabetic ketoacidosis; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; RR=relative risk; WMD=weighted mean difference.

IAsp versus HI: One RCT involving 205 adults with type 1 DM compared the effect of IAsp and HI on the number of patients reporting an event of DKA. Patients in this RCT used MDI. The RR (95% CI) between IAsp and HI was 1.31 (0.05, 31.79), indicating no difference between the two treatments.

e) Quality of life

ILis versus HI: Twelve RCTs[47,56,57,73,78,81,83,85,89,91,94,95] of ILis versus HI, reported full or partial QoL data, measured using a Diabetes Treatment Satisfaction Questionnaire (DTSQ) and/or well-being questionnaire (WBQ) scales. These studies used different scaling methods which made it difficult to pool the data into a meta-analysis. Details of the QoL data from each study are shown in Appendix 14A.

Of 12 RCTs conducting DTSQ, four[57,73,81,89] showed no significant difference between treatments on the total scale; QoL and treatment satisfaction variables were comparable. Fergurson *et al.*[81] showed that ILis treatment was not associated with improved QoL despite a lower incidence of severe hypoglycemia. Schmauss *et al.*[95] noted no significant differences in treatment satisfaction; however, all patients elected to continue with ILis because of its greater flexibility.

Five RCTs[56,78,83,91,94] reported significant dominance of ILis over HI on the total scale. Five RCTs[47,78,83,85,94] showed significant preference data for ILis on the satisfaction scale, four[56,78,83,94] on the convenience scale, five[47,78,83,94,95] on the flexibility scale, and five[56,78,83,94,95] on the willingness-to-continue scale.

Of those RCTs conducting WBQ, only one RCT of Janes *et al.*[56] showed a significant preference for ILis in dealing with depression, anxiety, and energy, but not with positive well-being. Melki *et al.*[94,94] noted that patients taking ILis felt better and had their glycemia best balanced. Three RCTs[57,73,89] found no treatment effects on total scores of WBQ.

IAsp versus HI: Three RCTs[55,72,99] compared the QoL, measured by DTSQ, between IAsp and HI in adult patients with type 1 DM. All patients used MDI. Of those, two[55,72] showed a significant superiority of IAsp over HI on the total scale. One RCT[99] showed no significant difference between treatments, although IAsp gave more flexibility than HI. WBQ scores were not reported on any of those RCTs. See Appendix 14A for full details from each study.

Overall, adult patients with type 1 DM appear to prefer ILis or IAsp over HI because of its convenience. Rapid-acting analogues usually have a faster onset of action than HI and can be used immediately before a meal, whereas patients on HI need to plan to take it one-half to one hour before eating.

f) Total mortality

ILis versus HI: Two RCTs[83,93] compared the effect of ILis and HI on mortality. Holleman *et al.*[83] reported one death, but did not specify the treatment arm, and Heller *et al.*[93] reported no death in the ILis group and one death (0.7%) HI group.

IAsp versus HI: Two RCTs[96,100] comparing IAsp and HI described mortality data. Home *et al.*[96] reported one (0.1%) death in the IAsp treatment arm and none in the HI arm. This RCT lasted for six months and involved 1,065 adult patients. When the same RCT was extended for another 30 months,[100] no death was reported in the IAsp arm while two (1%) deaths were reported in the HI arm. Details of mortality data from each study are reported in Appendix 15A.

7.5.2 Adolescent patients with type 1 DM

Two RCTs were identified from the literature search.[54,62] Details of both studies are provided in Appendix 6A and 7A. Arslanian *et al.*[54] was excluded from this analysis because it reported results for a mixture of adolescents and pre-adolescents.

a) A1c

Holcombe *et al.*[62] compared the effect of ILis and HI on A1c level in 926 adolescent patients with type 1 DM using MDI. The WMD (95% CI) was -0.01 (-0.21, 0.19), indicating no significant difference on the level of A1c between ILis and HI.

b) Hypoglycemia

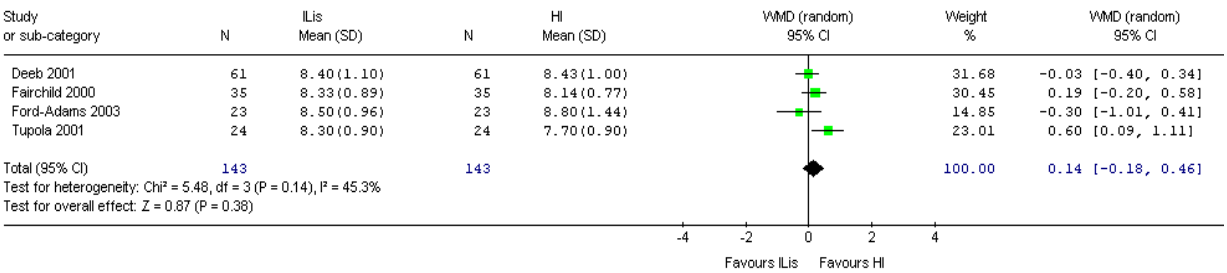
The same RCT[62] also examined the effect of ILis and HI on severe, nocturnal, and overall hypoglycemia outcomes. The RR (95% CI) for number of patients reporting severe hypoglycemia between treatment with ILis and HI using MDI was 1.0 (0.29, 3.43), indicating no statistically significant difference between the two treatments. For nocturnal and overall hypoglycemia, the rate ratios were calculated. The rate ratios (95% CI) were 0.61 (0.57, 0.64) and 0.90 (0.88, 0.93), indicating a significant decrease in the rate of nocturnal and overall hypoglycemia respectively when ILis was used compared with HI.

7.5.3 Pre-adolescent patients with type 1 DM

a) A1c

Five RCTs[28,60,61,63,64]compared the effect of ILis and HI on A1c level in pre-adolescent patients with type 1 DM. One RCT[64] was excluded because it reported carryover effect. The remaining four RCTs[28,60,61,63] included in the meta-analysis were crossover, had treatment duration of three months, and involved MDI. The pooled WMD (95% CI) was 0.14 (-0.18, 0.46), indicating no significant difference on the A1c levels between the treatment with ILis and the treatment with HI (Figure 25). There was no statistically significant heterogeneity across the studies (I^2=45.3%, Figure 25). Sensitivity analysis by including only the single study that had parallel design (n=46) also showed a non-significant difference between ILis and HI regarding A1c level (WMD -0.30; 95% CI: -1.01, 0.41).

Figure 25: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in pre-adolescents – A1c, WMD



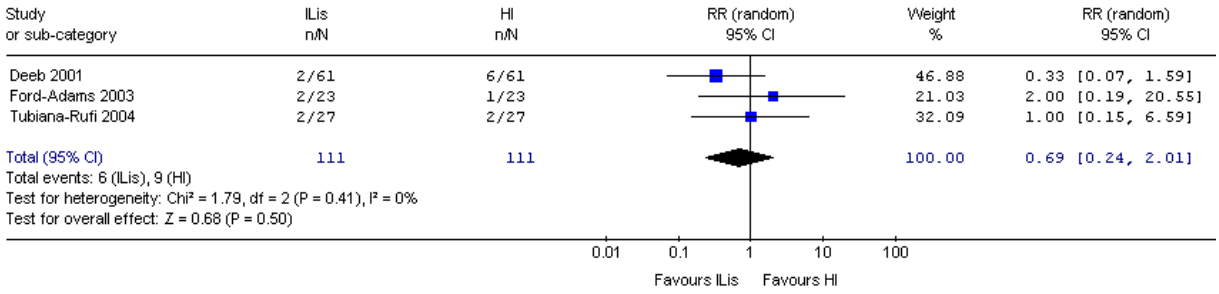
Heterogeneity I^2 describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

b) Hypoglycemia

Severe hypoglycemia

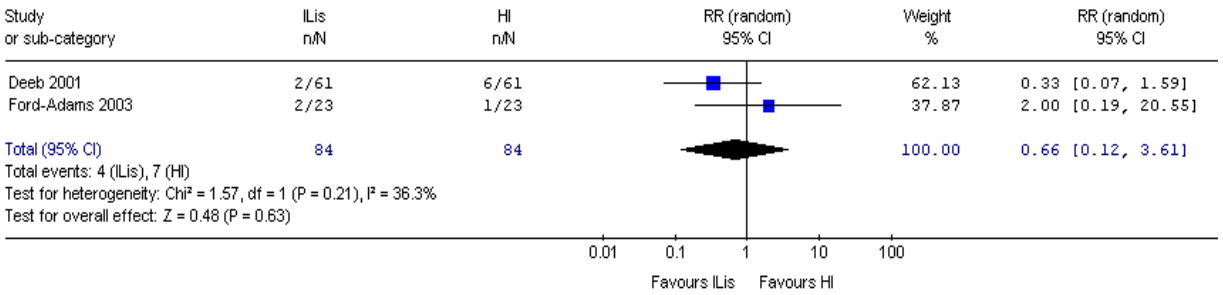
Three RCTs[60,61,64] with a total of 222 pre-adolescent patients with type 1 DM compared the effect of ILis and HI on severe hypoglycemia. The pooled RR was 0.69 (95% CI: 0.24, 2.01); indicating no significant difference between ILis and HI on the incidence rate of severe hypoglycemia (Figure 26). There was no statistically significant heterogeneity across the studies (I^2=36.3%, Figure 23, Table 9). A subgroup analysis by insulin delivery method (MDI versus CSII) also revealed a non-significant difference between the two treatments. The pooled RR (95% CI) was 0.66 (0.12, 3.61) for the two MDI[60,61] studies (Figure 27) and was 1.0 (0.15, 6.59) for the single CSII study.[64] Faichild *et al.*[28] reported a non-statistically significant lower rate of severe hypoglycemia (episodes per person per three months) with ILis (0.032) compared with HI (0.065).

Figure 26: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in pre-adolescents – Severe hypoglycemia, RR



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; RR=relative risk.

Figure 27: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in pre-adolescents using MDI – Severe hypoglycemia, RR

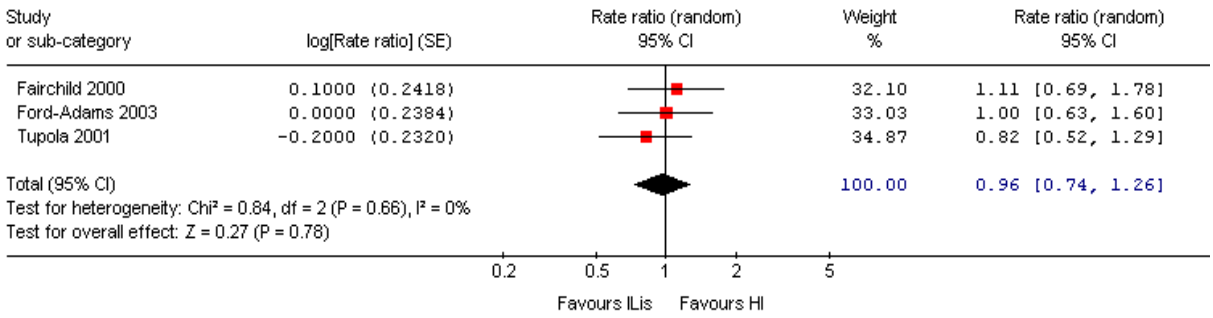


Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; RR=relative risk.

Nocturnal hypoglycemia

Three RCTs[61,63,93] with a total of 234 pre-adolescent patients with type 1 DM compared the effect of ILis and HI on events rate of nocturnal hypoglycemia. Patients in all three studies used MDI. The rate ratio (95% CI) for nocturnal hypoglycemia was estimated to be 0.96 (0.74, 1.26), indicating no difference in event rate between ILis and HI (Figure 28). There was no statistically significant heterogeneity across the studies (I^2=0%).

Figure 28: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in pre-adolescents – Nocturnal hypoglycemia, rate ratio



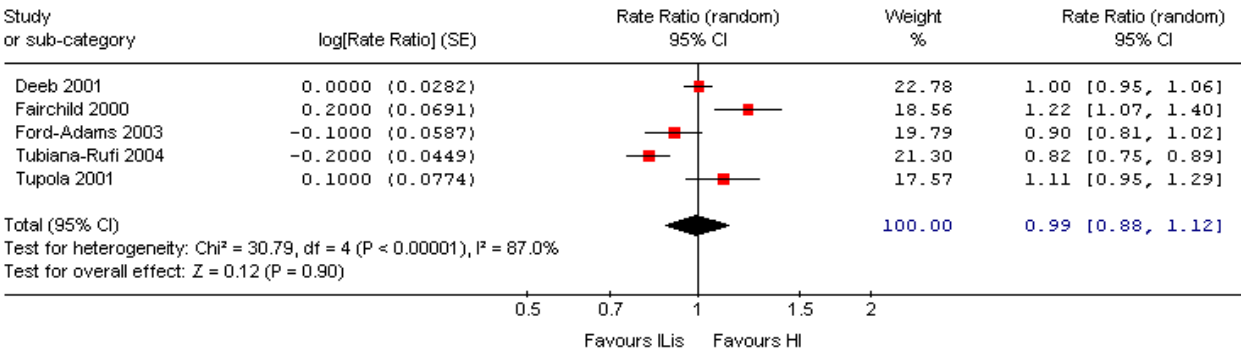
Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SE=standard error.

Overall hypoglycemia

Five RCTs[28,60,61,63,64] with a total of 338 pre-adolescent patients with type 1 DM compared the effect of ILis and HI on the event rate of overall hypoglycemia. The rate ratio (95% CI) between ILis and HI was 0.99 (0.88, 1.12), indicating no significant difference between ILis and HI (Figure 29). There was statistically significant heterogeneity across the studies (I^2=76%). Subgroup analysis by insulin delivery method (MDI versus CSII) revealed similar results as the overall analysis. The pooled rate ratio (95% CI) was 1.04 (0.93, 1.16) for the four MDI studies[28,60,61,63](Figure 30) and was 0.82 (0.75, 0.89) for the single CSII.

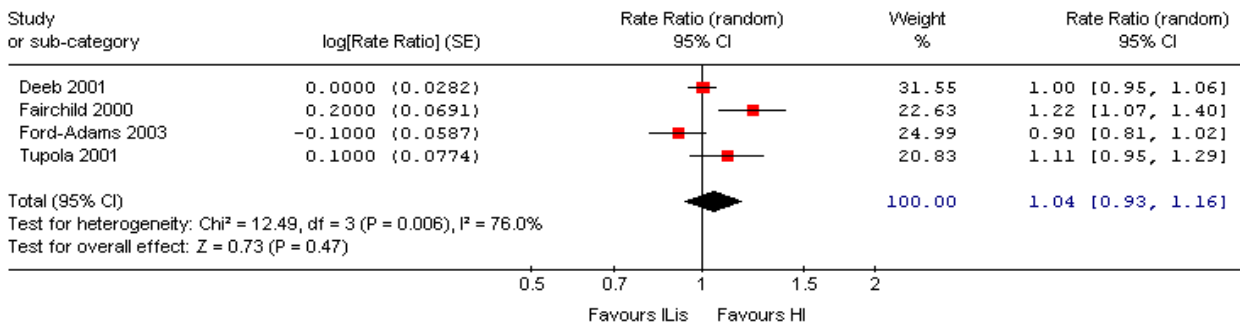
Danne *et al.*[55] reported a similar risk of overall hypoglycemia between IAsp and HI in pre-adolescent children. RR (IAsp/HI) was 1.06 (95% CI: 0.96, 1.17; p=0.225).

Figure 29: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in pre-adolescents – Overall hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SE=standard error.

Figure 30: Forest plot of RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in pre-adolescents using MDI – Overall hypoglycemia, rate ratio



CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; MDI=multiple daily injection; RCTs=randomized controlled trials; SE=standard error.

c) Diabetic ketoacidosis

One RCT[64] with a total of 54 pre-pubertal patients with type 1 DM compared the effect of ILis and HI on the incidence of DKA in patients using CSII. The RR (95% CI) was 0.2 (0.01, 3.98), indicating no difference between ILis and HI on the incidence of DKA.

d) QoL

Tupola *et al.*,[63] with a total population of 24 pre-adolescent patients with type 1 DM who were using MDI, compared the effect of ILis and HI on the satisfaction of patients and their families. At the end of the three-month study period, 18 out of 22 (82%) patients and their families wanted to continue treatment with ILis because of convenience.

Tubiana-Rufi *et al.*,[64] involving 54 pre-adolescent patients with type 1 DM who were using CSII, reported significant willingness to continue ILis therapy compared with HI (74%, ILis versus HI, p=0.01). The same RCT reported significantly more convenience in daily life using ILis therapy (70% easier in daily life on a scale of 0 to 100) compared with HI (26%, p=0.02).

7.5.4 Pregnant patients with type 1 DM

a) A1c

ILis versus HI: Persson *et al.*,[65] involving 33 pregnant patients with type 1 DM, showed that the difference in the change from baseline for A1c was not significant between the ILis group and HI group. The difference between the two groups (95% CI) was 0.20 (-1.03, 1.43).

IAsp versus HI: Mathiesen *et al.*,[29] involving 322 pregnant patients with type 1 DM, compared the effect of IAsp and HI on A1c level. The WMD (95% CI) between IAsp and HI was -0.08 (-0.28, 0.12), indicating no difference in the A1c level using IAsp compared with HI.

b) Hypoglycemia

Severe Hypoglycemia

ILis versus HI: Persson *et al.*[65] showed that the RR of severe hypoglycemia was not significant between ILis and HI. The RR (95% CI) was 0.21 (0.01, 4.10).

IAsp versus HI: Mathiesen *et al.*[29] also showed a non significant difference in the risk of severe hypoglycemia between IAsp and HI. The RR (95% CI) between IAsp and HI was 1.14 (0.76, 1.71).

Overall hypoglycemia

IAsp versus HI: Mathiesen *et al.*[29] also reported overall hypoglycemia. The RR (95% CI) between IAsp and was 1.04 (0.98, 1.11), indicating no significant difference between IAsp and HI regarding the incidence of overall hypoglycemia.

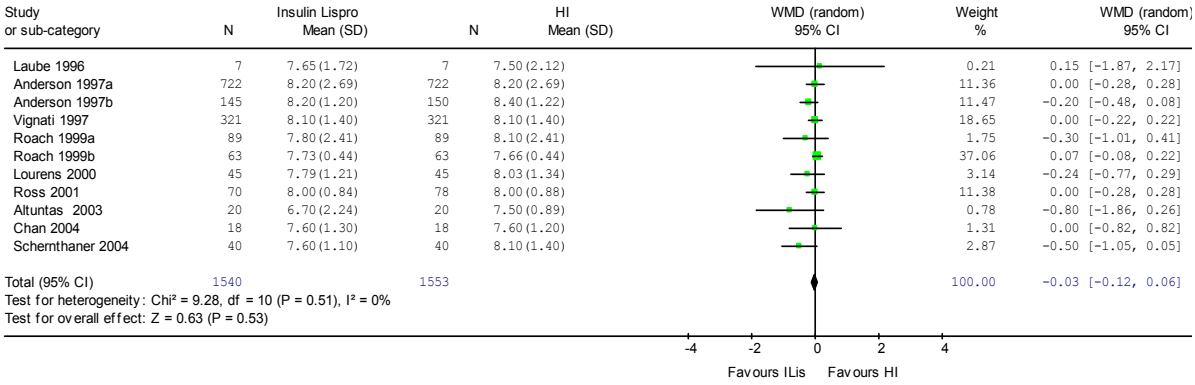
7.5.5 Adult patients with type 2 DM

a) A1c

Seventeen RCTs[45,46,48-50,58,59,74,75,103-110] were found that compared rapid-acting insulin analogues and HI on A1c levels in adults with type 2 DM. In 11 RCTs,[45,46,48-50,74,103-107] the rapid-acting insulin analogue was ILis or ILis mix, and in the other six RCTs[58,59,75,108-110] it was IAsp or IAsp mix. Eight RCTs[111-118] were also found that compared rapid-acting insulin analogues and sulfonylurea on A1c levels in type 2 DM. Of those, six RCTs[111-116]compared ILis or ILis mix versus sulfonylurea, whereas two RCTs[117,118] compared IAsp mix versus sulfonylurea. Details are provided in Appendix 9B.

ILis or ILis mix versus HI: The pooled WMD (95% CI) for A1c from the 11 RCTs[45,46,48-50,74,103-107] was -0.03 (-0.12, 0.06), indicating no significant difference between the treatment with ILis or ILis mix and with HI (Figure 31). There was no statistically significant heterogeneity across RCTs (I^2=0%, Figure 31). The funnel plot showed a potential for publication bias (Appendix 10, Figure 7). Sensitivity analysis by removal of crossover studies or studies of less than or equal to three months' duration also revealed no significant difference between ILis or ILis mix and HI in reducing A1c levels in patients with type 2 DM (Table 7).

Figure 31: Forest plot of all RCTs that examined the use of ILis or ILis mix versus HI for the treatment of type 2 DM in adults – A1c, WMD



Heterogeneity I^2 describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

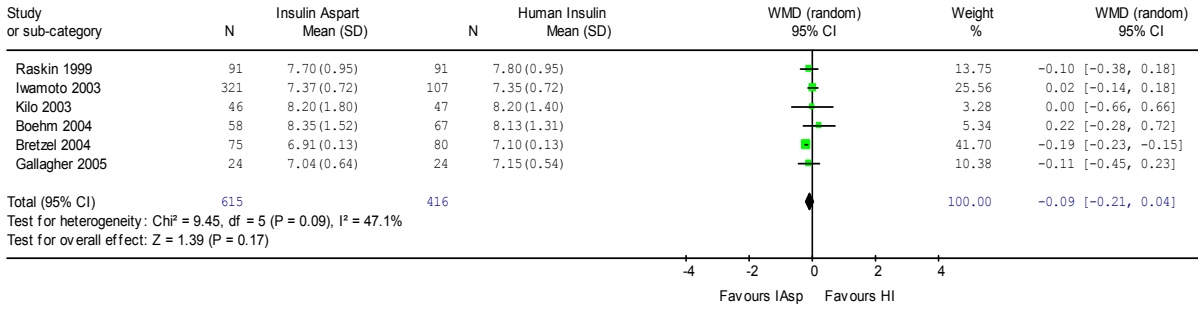
Table 7: Summary of results of meta-analyses for comparison of rapid-acting insulin analogues versus HI or Sfu in adult type 2 DM for A1c (%)

Comparison	Sensitivity Analysis	No. of RCTs	No. of Patients	Random Effects Model	
				WMD (95% CI)	Heterogeneity I^2
ILis versus HI	All RCTs	11	3,093	-0.03 (-0.12, 0.06)	0%
	Removal of ≤3 months RCTs	3	483	-0.13 (-0.37, 0.10)	24%
	Removal of crossover RCTs	3	483	-0.13 (-0.37, 0.10)	24%
IAsp versus HI	All RCTs	6	1,031	-0.09 (-0.21, 0.04)	47.1%
	Removal of ≤3 months RCTs	3	735	0.01 (-0.13, 0.14)	0%
	Removal of crossover RCTs	5	983	-0.08 (-0.22, 0.07)	57.1%
ILis mix versus Sfu	All RCTs	2	315	-0.85 (-1.18, -0.53)	0%
ILis+glyburide versus Metf+glyburide	All RCTs	1	81	-0.60 (-1.09, -0.11)	-
IAsp mix+glitazone versus Sfu+glitazone	All RCTs	2	233	-0.63 (-1.04, -0.22)	0%

A1c=glycosylated hemoglobin; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; RCTs=randomized controlled trials; Sfu=sulfonylurea; WMD=weighted mean difference.

IAsp versus HI: The pooled WMD (95% CI) from six RCTs[58,59,75,108-110] was -0.09 (-0.21, 0.04), indicating no significant difference between the treatment with IAsp or IAsp mix and treatment with HI regarding A1c levels (Figure 32). There was no statistically significant heterogeneity across the RCTs (I^2=47.1%, Figure 32). The funnel plot did not indicate any potential for publication bias (Appendix 10, Figure 8). Sensitivity analysis by removal of the single crossover study[109] or the three studies of less than or equal to three months' duration[75,109,110] showed no significant difference in the levels of A1c between IAsp or IAsp mix and HI (Table 7).

Figure 32: Forest plot of all RCTs that examined IAsp or IAsp mix versus HI in the treatment of adult type 2 DM – A1c, WMD



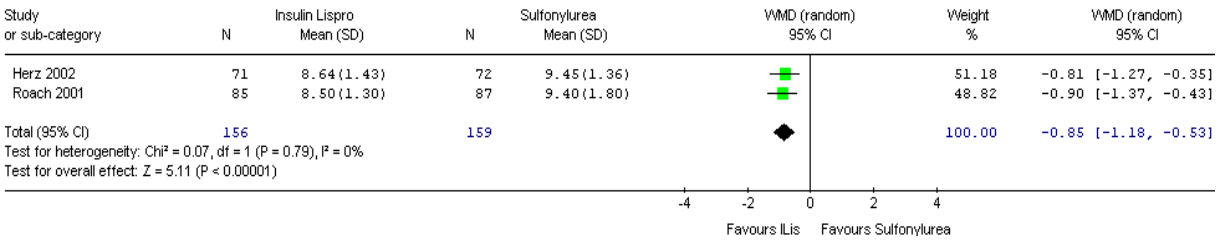
Heterogeneity I^2 describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

ILis versus IAsp: Niskanen *et al.*,[31] involving 133 adult patients with type 2 DM compared the effect between ILis mix and IAsp mix and found no statistically significant difference in the A1c level (p=0.082).

ILis versus sulfonylurea: Six RCTs[111-116] compared the treatment effects of ILis or ILis mix and sulfonylurea. Pooling of A1c data from all RCTs was not possible, because the treatment regimen was different among studies: one RCT[112]compared ILis (bolus insulin) with glyburide in early type 2 DM, a second RCT[114]compared ILis plus Metf with glimepride plus Metf in patients who failed OAD, a third RCT[111]compared ILis plus NPH with sulfonylurea plus NPH in patients with secondary OAD failure, a fourth RCT[115] compared ILis mix plus Metf with glyburide plus Metf in patients who failed OAD and, finally, two RCTs[113,116] compared ILis mix (bolus-basal regimen) with glyburide in patients with type 2 DM who failed OAD.

The difference in A1c levels at end of treatments (95% CI) between the two treatment arms was -0.20 (-0.57, 0.17) for ILis versus gluburide in early type 2 DM, -0.52 (-1.18, 0.14) for ILis plus Metf versus glimepride plus Metf in patients who failed OAD, -2.0 (-0.54, 0.14) for ILis plus NPH versus sulfonylurea plus NPH in patients with secondary OAD failure, and -0.04 (-0.21, 0.13) for ILis mix plus Metf versus glyburide plus Metf in patients who failed OAD. The pooled WMD was -0.85 (95% CI: -1.18, -0.53) for the two RCTs that compared ILis mix with glyburide in patients with type 2 DM who failed OAD (Figure 33, Table 7).

Figure 33: Forest plot of all RCTs that examined the use of ILis mix 25 versus glyburide for the treatment of type 2 DM in adults who failed OAD – A1c, WMD

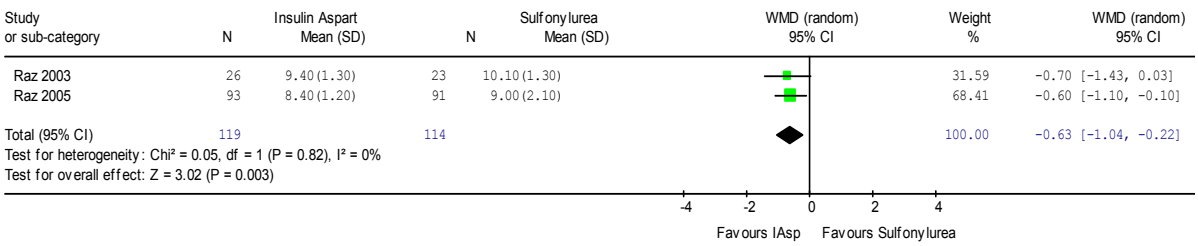


Heterogeneity I^2 describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; ILis=insulin lispro; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

ILis versus Metf: Bastyr *et al.*[119] showed a significant decrease in A1c level in patients treated with ILis plus glyburide after secondary OAD failure compared with those treated with Metf plus glyburide. The mean difference (95% CI) was -0.60 (-1.09, -0.11).

IAsp versus sulfonylurea: Two RCTs[117,118] with a total population of 233 adult patients with type 2 DM compared adding glitazone to sulfonylurea versus switching to IAsp mix and adding glitazone in patients who failed sulfonylurea monotherapy. A significant difference in A1c of -0.63% (95% CI: -1.04, -0.22) was observed in favour of IAsp mix with glitazone. There was no heterogeneity across RCTs (I^2=0%, Figure 34, Table 8).

Figure 34: Forest plot of all RCTs that examined IAsp mix plus glitazone versus sulfonylurea plus glitazone in the treatment of type 2 DM in adults who failed OAD – A1c, WMD



Heterogeneity I² describes the heterogeneity between the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; IAsp=insulin aspart; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

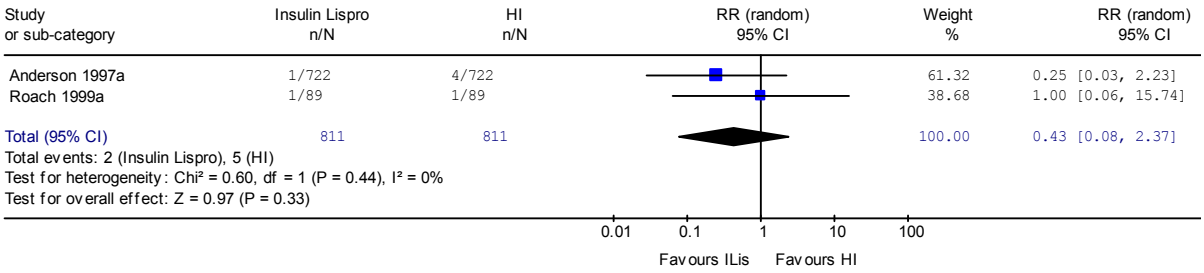
b) Hypoglycemia

Hypoglycemia details from the studies included in this review are provided in Appendix 11B.

Severe hypoglycemia

ILis versus HI: Two RCTs,[103,105] with at total population of 1,622 adult patients with type 2 DM who were previously treated with HI, compared the effect of ILis or ILis mix with HI on the incidence of severe hypoglycemia. The pooled RR from the two RCTs (95% CI) was 0.43 (0.08, 2.37), indicating no difference between ILis and HI on the incidence of severe hypoglycemia (Figure 35). There was no statistically significant heterogeneity across the RCTs (I^2=0%, Figure 35). Event rate ratio between the two treatments was estimated from only one study[103] and was 0.20 (0.02, 1.71), indicating also no difference in the severe hypoglycemic events rate between ILis and HI.

Figure 35: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 2 DM in adult patients – Severe hypoglycemia, RR



Heterogeneity I² describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RR=relative risk; SD=standard deviation.

IAsp versus HI: Boehm *et al.*,[108] with a total population of 121 adult type 2 DM patients who were previously treated with HI, compared the effect of IAsp mix with HI mix on the incidence of severe hypoglycemia. The RR (95% CI) between the two treatments was 0.39 (0.11, 1.36), indicating no difference in the number of patients presenting with severe hypoglycemia between the treatment with IAsp mix or HI mix.

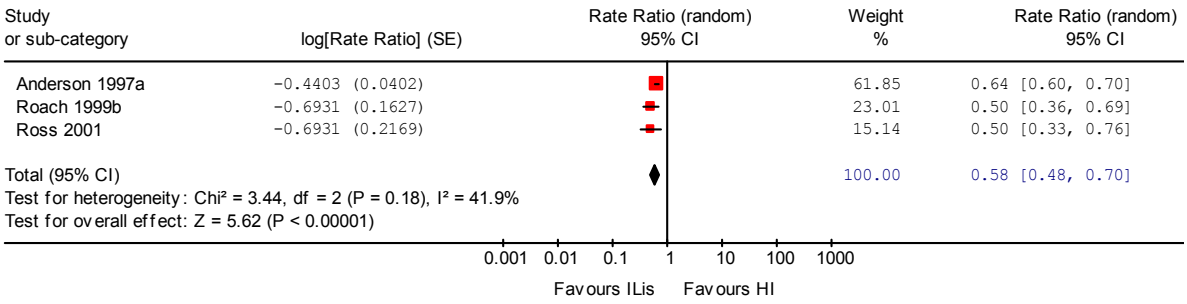
ILis versus sulfonylurea: Malone *et al.*,[115] with a total population of 597 adult patients with type 2 DM who failed sulfonylurea or Metf therapy, compared the effect of a combination therapy of ILis

mix plus Metf with a combination therapy of glyburide plus Metf on the incidence of severe hypoglycemia. The RR (95% CI) between ILis and sulfonylurea was 0.76 (0.17, 3.38), indicating no statistically significant difference between the two combination therapies regarding the incidence of severe hypoglycemia.

Nocturnal hypoglycemia

ILis versus HI: Roach *et al.*,[105] involving 178 adult patients with type 2 DM, compared the effect of ILis mix and HI mix on number of patients presenting with nocturnal hypoglycemia. The RR (95% CI) between ILis mix and HI mix was 1.63 (0.71, 3.73), indicating no difference in number of patients presenting with nocturnal hypoglycemia. Three other RCTs,[49,103,106] with a total of 1,718 adult type 2 DM patients, compared treatment with ILis or ILis mix or ILis plus NPH with treatment with HI or HI mix or HI plus NPH on the events rate for nocturnal hypoglycemia. The pooled rate ratio (95% CI) for nocturnal hypoglycemia was 0.58 (0.48, 0.70), indicating a statistically significant decrease in events of nocturnal hypoglycemia with ILis as compared with HI (Figure 36). There was no statistically significant heterogeneity across the studies (I^2=41.9%, Figure 36).

Figure 36: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 2 DM in adult patients – Nocturnal hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SE=standard error.

IAsp versus HI: Kilo *et al.*,[110] involving 93 adult patients with type 2 DM who failed OAD treatment and who had no previous insulin therapy, compared the effect of the treatment with IAsp mix with the treatment with HI mix on the number of patients reporting nocturnal hypoglycemia. The RR (95% CI) between the two treatments was 0.65 (0.28, 1.53), indicating no statistically significant difference.

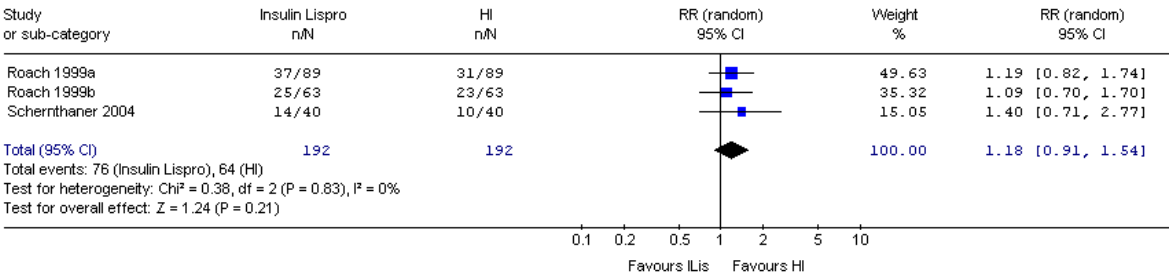
ILis versus sulfonylurea: Malone *et al.*[115] also reported nocturnal hypoglycemia. The RR (95% CI) between the ILis mix plus Metf group and glyburide plus Metf group was 0.20 (0.06, 0.70), indicating a statistically significant decrease in the number of patients presenting with nocturnal hypoglycemia using a combination of ILis mix plus Metf compared with glyburide plus Metf in type 2 DM patients who failed OAD therapy. The event rate ratio was also estimated from the same study and showed a significant decrease in the rate of nocturnal hypoglycemia with ILis plus Metf therapy.

Bastyr *et al.*[111] compared the effect of bolus-basal treatment with ILis plus NPH with treatment with glyburide plus NPH in type 2 DM patients who had a secondary OAD failure on the rate of nocturnal hypoglycemia. The rate ratio between the two treatment regimens was estimated to be 0.77 (0.47, 1.25), indicating no significant difference between the two treatment regimens.

Overall hypoglycemia

ILis versus HI: Data on the number of patients reporting at least one event of overall hypoglycemia were pooled from three RCTs[103,105,107], with a total of 1,702 adult patients with type 2 DM. Of those, two RCTs[105,107] compared the treatment with ILis mix with the treatment with HI mix and one RCT[103] compared ILis with HI in patients with type 2 DM who were previously treated with HI. The pooled RR (95% CI) between ILis or ILis mix and HI or HI mix was 1.18 (0.91, 1.54), indicating no difference in the number of patients reporting at least one event of overall hypoglycemia between ILis or ILis mix and HI or HI mix (Figure 37). There was no statistically significant heterogeneity across the RCTs (I^2=0%, Figure 37).

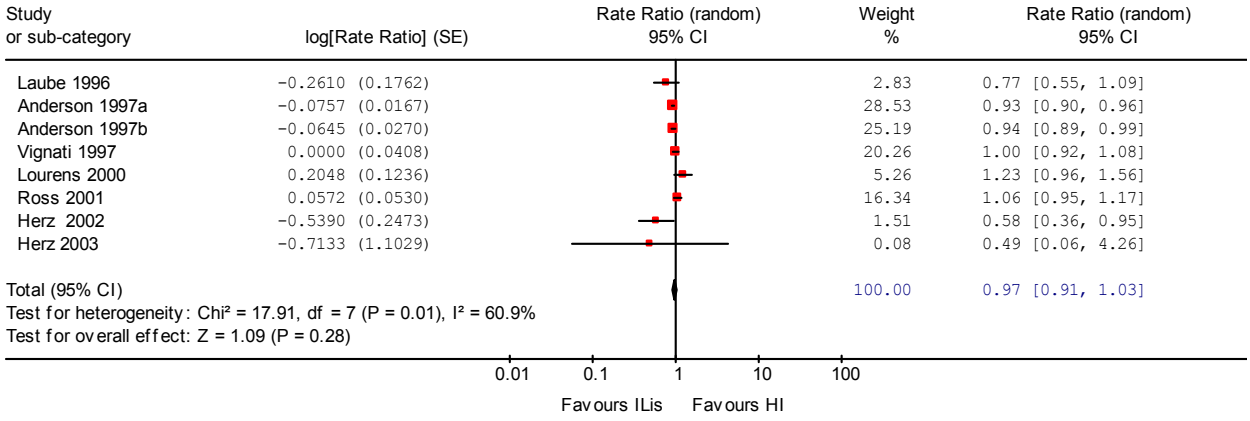
Figure 37: Forest plot of all RCTs that examined the use of ILis or ILis mix versus HI or HI mix for the treatment of type 2 DM in adult patients – Overall hypoglycemia, RR



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; RR=relative risk.

Data on the overall hypoglycemic event rate were extracted from eight RCTs[45,48,50,76,103,104,106,120] of 2,746 adults with type 2 DM. These data were used to estimate the overall hypoglycemic rate ratio for ILis versus HI. The pooled rate ratio (95% CI) was 0.97 (0.91, 1.03), indicating no statistically significant difference in events for overall hypoglycemia between ILis and HI. However there was statistically significant heterogeneity across the studies (I^2=60.9%, Figure 38). The funnel may indicate potential for publication bias (Appendix 10, Figure 8).

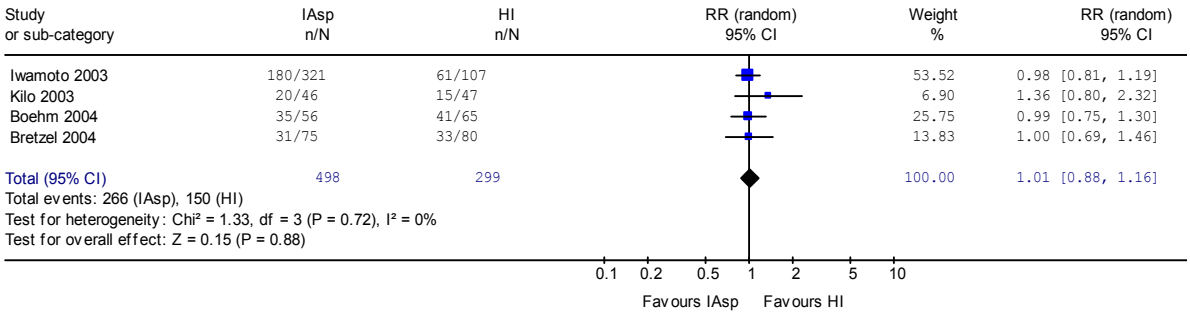
Figure 38: Forest plot of all RCTs that examined the use of ILis or ILis mix versus HI or HI mix for the treatment of type 2 DM in adult patients – Overall hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SE=standard error.

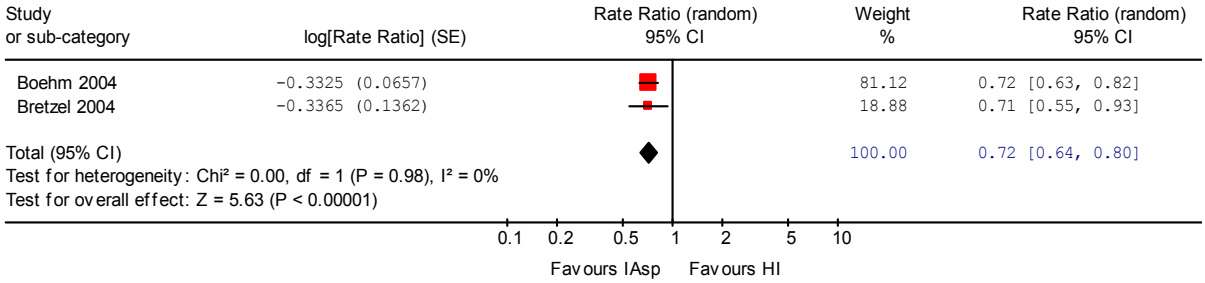
IAsp versus HI: Four RCTs[58,75,108,110] compared the effect of IAsp or IAsp mix versus HI or HI mix in 797 adults with type 2 DM on the number of patients presenting with at least one event of hypoglycemia. The pooled RR (95% CI) for overall hypoglycemia between IAsp and HI was 1.01 (0.88, 1.16), indicating no difference between the two treatments regarding the risk of developing overall hypoglycemia (Figure 39). There was no statistically significant heterogeneity across the studies (I^2=0%, Figure 39). Two[75,108] of the four RCTs reported data on the event rate of overall hypoglycemia from which overall hypoglycemic rate ratio was estimated for IAsp or IAsp mix versus HI or HI mix in patients with type 2 DM. The pooled rate ratio (95% CI) between IAsp and HI was 0.72 (0.64, 0.80), indicating a decrease in events of overall hypoglycemia using IAsp or IAsp mix compared with HI or HI mix (Figure 40).

Figure 39: Forest plot of all RCTs that examined IAsp or IAsp mix versus HI or HI mix in the treatment of adult type 2 DM patients – Overall hypoglycemia, RR



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized controlled trials; RR=relative risk.

Figure 40: Forest plot of all RCTs that examined IAsp versus HI in the treatment of adult type 2 DM patients – Overall hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized controlled trials; SE=standard error.

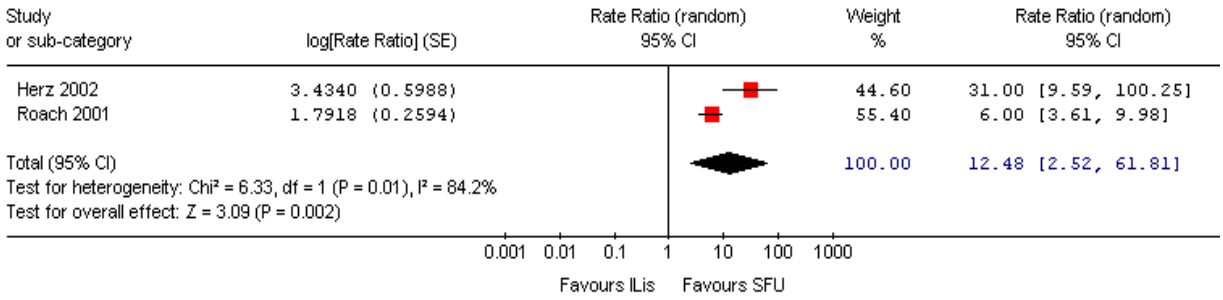
ILis versus IAsp: Niskanen *et al.*[31] compared the effect of ILis mix and IAsp mix on event rate of overall hypoglycemia. The estimated rate ratio (95% CI) for overall hypoglycemia was 0.90 (0.77, 1.07), indicating no difference between the two treatments.

ILis versus sulfonylurea: Five RCTs[111-113,115,116] were found for this comparison. One RCT compared ILis (bolus insulin) with glyburide in early type 2 DM,[112] a second RCT compared ILis plus NPH with sulfonylurea plus NPH in patients with secondary OAD failure,[111] a third RCT compared ILis mix plus Metf with glyburide plus Metf in patients who failed OAD[115] and, finally, two RCTs compared ILis mix (bolus-basal regimen) with glyburide in type 2 DM patients who failed OAD.[113,116] Data on the number of patients who had at least one overall hypoglycemic event were reported in two RCTs,[112,116]

while data on hypoglycemic event ratio were available from four RCTs.[111,113,115,116] Pooling of RCTs to estimate RR or rate ratio was not possible due to the variation of treatment regimen used in these studies. Only data from the two RCTs that compared ILis mix with glyburide were pooled.

Roach *et al.*[116] showed a significant reduction in the risk of overall hypoglycemia with glyburide treatment compared with the treatment with ILis mix (RR: 4.32; 95% CI: 2.23, 8.38) in adults with type 2 DM who failed sulfonylurea oral therapy. The pooled overall hypoglycemic rate ratio from Roach *et al.*[116] and Herz *et al.*[113] also revealed a significant decrease in the rate of overall hypoglycemic events in the glyburide group compared with the ILis mix group (rate ratio: 12.48; 95% CI: 2.52, 61.81; Figure 41). Different results were obtained from Malone *et al.*[115] when ILis mix plus Metf was compared with glyburide plus Metf in type 2 DM patients who failed sulfonylurea or Metf oral therapy. This study showed a significant reduction in the rate of overall hypoglycemic events with the treatment with ILis mix plus Metf (rate ratio: 0.65; 95% CI: 0.57, 0.74). Finally, the RR (95% CI) estimated from Forest *et al.*[112] was 0.45 (0.14 to 1.44), indicating a significant reduction in the risk of developing overall hyperglycemia with ILis treatment compared with gluburide treatment in patients who had early type 2 DM.

Figure 41: Forest plot of RCTs that examined the use of ILis mix 25 versus glyburide for the treatment of type 2 DM in adult patients who failed OAD – Overall hypoglycemia, rate ratio



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; ILis=insulin lispro; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SE=standard error; Sfu=sulfonylurea.

ILis versus Metf: Bastyr *et al.* (3,541) showed a significant increase in the rate of overall hypoglycemia in the ILis plus glyburide group compared with the Metf plus glyburide group. The rate ratio (95% CI) between the two treatments was 1.57 (1.2, 2.06).

IAsp versus sulfonylurea: Raz *et al.*,[118] involving 184 adult patients with type 2 DM, compared the effect of adding glitazone to sulfonylurea versus switching to IAsp mix and adding glitazone in patients who failed sulfonylurea monotherapy. The RR (95% CI) between the two groups was 2.48 (1.53, 4.01), indicating a significant increase in the number of patients who had at least one event with IAsp plus glitazone therapy. The hypoglycemic rate ratio estimated from the same study was 2.59 (1.85, 3.63), indicating a statistically significant increase in rate of overall hypoglycemia during IAsp plus glitazone treatment compared with sulfonylurea plus glitazone therapy.

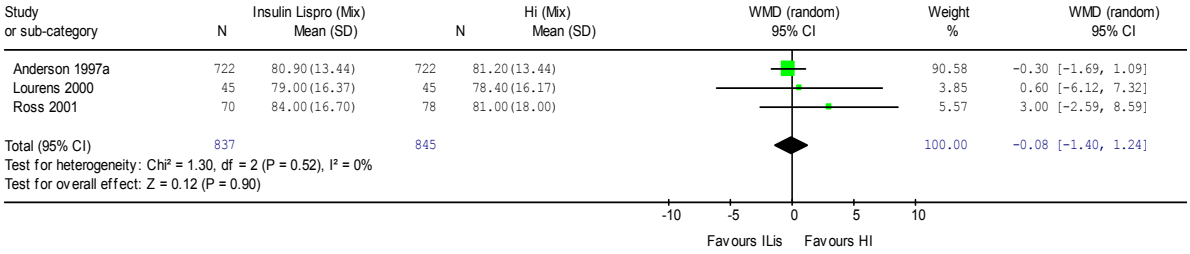
c) Weight

Study-level details for weight and BMI for patients with type 2 DM are provided in Appendix 12B.

ILis versus HI: Three RCTs[103,104,106] with a total of 1,682 adult patients with type 2 DM compared the effect of ILis or ILis mix with HI or HI mix on body weight gain. The pooled WMD (95% CI) between

ILis and HI was -0.08 (-1.40, 1.24), indicating no difference in body weight at the end of treatment using ILis compared with using HI (Figure 42). There was no statistically significant heterogeneity across the RCT (I^2=0%).

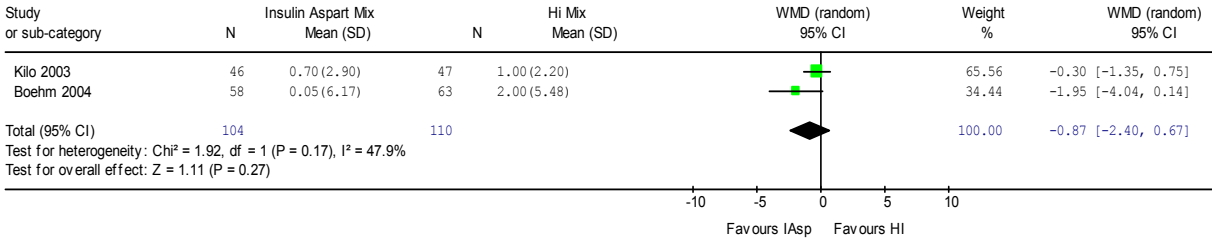
Figure 42: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 2 DM in adult patients –Weight, WMD



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

IAsp versus HI: Two RCTs,[108,110] with a total 214 adult patients with type 2 DM, compared the effect of IAsp mix with HI mix on the change of body weight (from baseline). The pooled WMD (95% CI) between IAsp and HI was -0.87 (-2.40, 0.67), indicating no difference in the change of body weight (from baseline) between IAsp and HI. There was no statistically significant heterogeneity across the RCTs (I^2=47.9%, Figure 43)

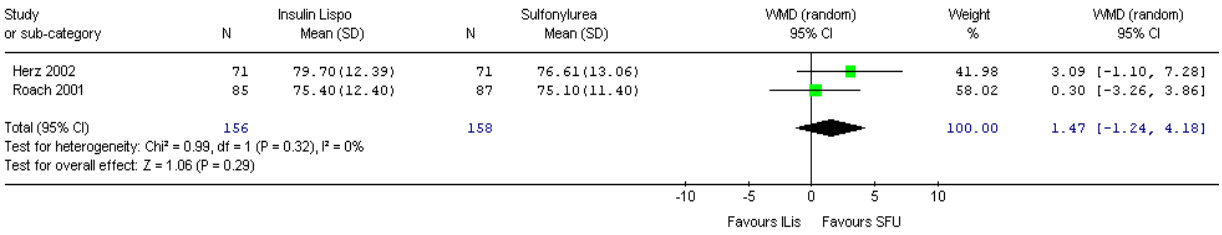
Figure 43: Forest plot of all RCTs that examined IAsp versus HI in the treatment of adult type 2 DM patients – Weight gain, WMD



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

ILis versus sulfonylurea: Pooled data from the two RCTs[113,116] that compared ILis mix with glyburide in patients who failed OAD showed no significant difference in body weight gain between the two treatment groups. The pooled WMD (95% CI) was -1.47 (-1.24, 4.18, Figure 44). Weight gain data from other RCTs could not be pooled because of the following reason: One RCT compared ILis plus NPH with sulfonylurea plus NPH in patients with secondary OAD failure,[111] a second RCT compared ILis (bolus insulin) with glyburide in early type 2 DM,[112] a third RCT compared ILis mix plus Metf with glyburide plus Metf in patients who failed OAD.[115]

Figure 44: Forest plot of RCTs that examined the use of ILis mix 25 versus glyburide for the treatment of type 2 DM in adult patients who failed OAD – Body weight, WMD

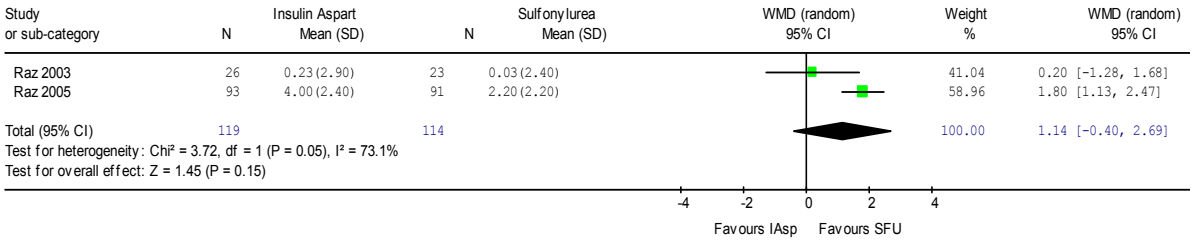


Heterogeneity I² describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; ILis=insulin lispro; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SD=standard deviation; Sfu=sulfonylurea; WMD=weighted mean difference.

ILis versus Metf: Bastyr *et al.*[119] showed a significant body weight gain with the treatment with ILis plus glyburide compared with Metf plus glyburide. The mean difference (95% CI) was 3.00 (1.88, 4.12).

IAsp versus sulfonylurea: Two RCTs[117,118] were used for this comparison. The pooled WMD was 1.14 (-0.40, 2.69), indicating no statistically significant difference between the IAsp plus glitazone group and the sulfonylurea plus glitazone group. However, a statistically significant heterogeneity did exist across studies. (I^2=73.1%, Figure 45).

Figure 45: Forest plot of all RCTs that examined IAsp mix plus glitazone versus sulfonylurea plus glitazone in the treatment of type 2 DM in adults who failed OAD – Weight gain, WMD



Heterogeneity I² describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; IAsp=insulin aspart; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SD=standard deviation; Sfu=sulfonylurea; WMD=weighted mean difference.

d) BMI

ILis versus HI: Altuntas *et al.*,[74] involving 40 patients, showed that the change in BMI was not statistically different with ILis compared with HI therapy in patients with type 2 DM who failed OAD therapy. The difference (95% CI) was 0.00 (-8.51, 8.51).

ILis versus sulfonylurea: Bastyr *et al.*,[111] involving 284 patients, showed a significant increase in BMI with ILis plus glitazone compared with sulfonylurea plus glitazone in type 2 DM patients who failed OAD. The difference in the change in BMI from baseline (95%) was 0.31 (0.09, 0.53).

e) Fasting plasma glucose

IAsp versus HI: Kilo *et al.*,[110] involving 93 patients, compared the effect of IAsp mix with HI mix on fasting plasma glucose. The difference (95% CI) between IAsp and HI was -0.67 (-2.47, 1.13), indicating no difference in the FPG levels between IAsp and HI.

ILis versus sulfonylurea: Malone *et al.*[115] compared the effect of a combination therapy of ILis mix plus Metf and glyburide plus Metf on FPG in 234 patients who had OAD failure. The difference (95% CI) was -0.76 (-1.62, 0.10), indicating no significant difference between the two treatment groups.

f) Mean two-hour post-prandial plasma glucose

ILis versus HI: Herz *et al.*,[120] involving 93 patients, compared the effect of ILis mix and HI mix on mean two-hour post-prandial plasma glucose. The mean difference (95% CI) between the two treatments was -1.10 (-2.21, 0.01), indicating a tendency toward decreasing two-hour post-prandial plasma glucose with ILis mix as compared with HI mix (p=0.05).

ILis versus SFU: Mean two-hour postprandial plasma glucose was reported only by one RCT comparing ILis mix plus Metf with glyburide plus Metf in patients who failed OAD.[115]

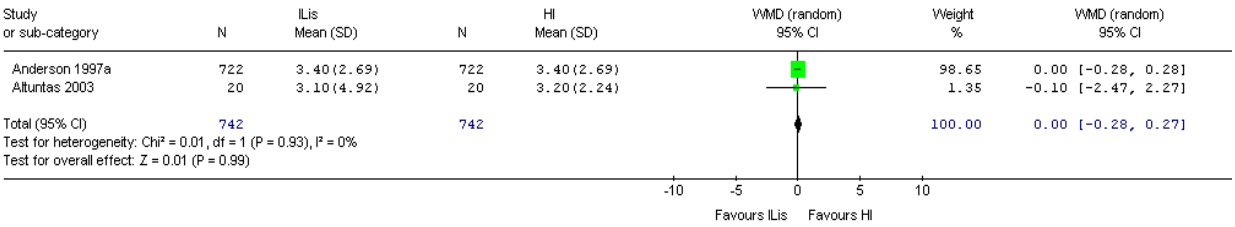
g) Cholesterol

Study-level details for cholesterol outcome for type 2 DM are provided in Appendix 16A and 16B.

LDL cholesterol

ILis versus HI: Two RCTs[74,103] showed no difference between ILis and HI on LDL cholesterol levels. The pooled WMD (95% CI) was 0.00 (-0.28, 0.27, Figure 46).

Figure 46: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 2 DM in adult patients – Cholesterol LDL, WMD

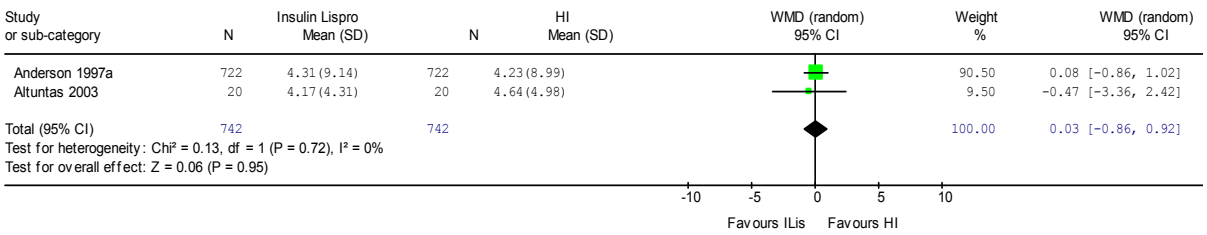


Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; LDL=low-density lipoprotein; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

HDL cholesterol ratio

ILis versus HI: Pooled data from two RCTs[74,103] revealed no statistically significant difference between ILis and HI on HDL cholesterol ratio. The pooled WMD (95% CI) was 0.03 (-0.86, 0.92; Figure 47).

Figure 47: Forest plot of all RCTs that examined the use of ILis versus HI for the treatment of type 2 DM in adult patients – HDL cholesterol ratio, WMD



Heterogeneity I² describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; HDL=high-density lipoprotein; HI=human insulin; ILis=insulin lispro; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

IAsp versus HI: Gallagher *et al.*[109] did not show any difference in HDL cholesterol ratio between IAsp and HI. The difference (95% CI) was 0.37 (-0.77, 1.51).

h) All-cause mortality

ILis versus HI: Schernthaner *et al.*,[107] of 12 weeks' duration, reported a single death (2.5%) in the ILis mix group compared with none in the HI mix group, but it was judged to be not related to trial treatments.

IAsp versus HI: Boehm *et al.,*[108] of three months' initial treatment and 21 months' extension treatment period, reported three deaths (two lung cancers and one cardiac failure) in the IAsp mix group compared with one death (malignant lymphoma) in the HI mix group, but the cause of mortality was judged to be not related to study medications. Details of mortality data from each study are reported in Appendix 15B.

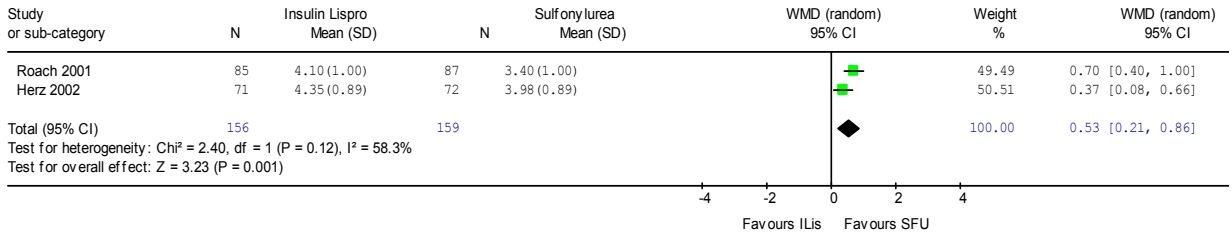
ILis versus SFU: Two RCTs [115,116] in adult patients with type 2 DM compared the effect of ILis and SFU on all cause mortality. The RR (95% CI) was 1.06 (0.07, 16.66) with the first RCT[115] and 3.05 (0.12, 74.53) with the other RCT[116], indicating no statistically significant differences on the all cause mortality between ILis and SFU.

i) Quality of life

ILis versus HI: Kostanos *et al.*[47] demonstrated no significant difference between ILis and HI on the satisfaction scale (difference: 0.90; 95% CI: -2.06, 3.86), flexibility scale (difference: 0.70; 95% CI: -1.43, 2.83), or the Willingness-to-Continue WBQ subscales (anxiety and energy). The differences (95% CI) between ILis and HI for energy/fatigue and anxiety/health distress were -0.40 (-2.51, 1.71) and -0.30 (-2.29, 1.69) respectively. Ross *et al.*[106] reported no difference on the satisfaction scale, but there was a significant improvement in worry related to diabetes using ILis therapy compared with HI (p=0.008). Details from each study are provided in Appendix 14B.

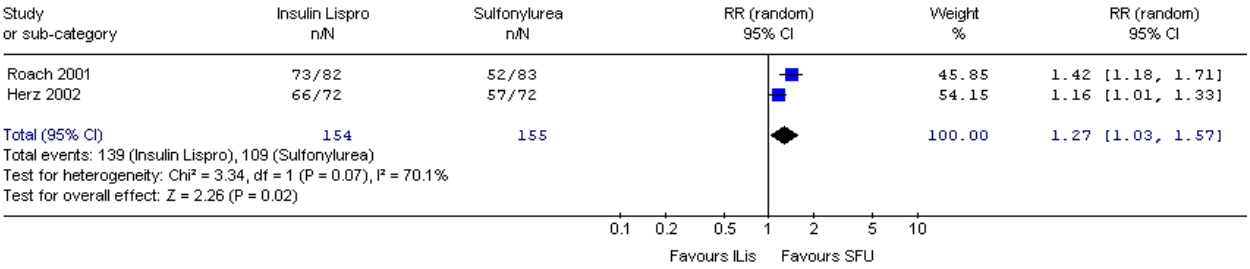
ILis versus sulfonylurea: Pooled data from the two RCTs[113,116] that reported patient satisfaction showed a significant increase in the degree of satisfaction in patients treated with ILis mix compared with treatment with glyburide. The WMD (95% CI) was 0.53 (0.21, 0.86), but a statistically significant heterogeneity did exist across studies (I^2=58.3%, Figure 48). Pooled data from the same two RCTs[113,116] also showed a significant increase in the number of patients who were willing to continue the ILis mix therapy compared with glyburide. The RR (95% CI) was 1.27 (1.03, 1.57), however there was a statistically significant heterogeneity across the RCTs (I^2: 70.1%, Figure 49).

Figure 48: Forest plot of RCTs that examined the use of ILis mix 25 versus glyburide for the treatment of type 2 DM in adult patients who failed OAD – satisfaction scales, WMD



Heterogeneity I² describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; ILis=insulin lispro; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SD=standard deviation; Sfu=sulfonylurea; WMD=weighted mean difference.

Figure 49: Forest plot of RCTs that examined the use of ILis mix 25 versus glyburide for the treatment of type 2 DM in adult patients who failed OAD – Willingness to continue, RR



Heterogeneity I² describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; ILis=insulin lispro; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk; Sfu=sulfonylurea.

Malone *et al.*[115]reported improvement of satisfaction in the majority of patients after treatment with ILis mix plus Metf or glyburide plus Metf. Details from each study are provided in Appendix 14B.

Roach *et al.*[116] showed also a significant increase in well being on current therapy and on energy scales with the ILis mix group compared with the glyburide group. The difference (95% CI) was 0.70 (0.43, 0.97) and 0.50 (0.20, 0.80), respectively. Malone *et al.*[115] reported greater well being (p=0.003) after treatment with ILis mix plus Metf compared with glyburide plus Metf.

ILis versus Metf: Bastyr *et al.*, (3,541) showed no difference in the composite satisfaction scores at the end point between treatment with ILis plus glyburide and Metf plus glyburide (30.45±5.34 versus 31.87±5.45).

7.5.6 Pregnant women with gestational DM

a) A1c

Of the three RCTs[52,53] on patients with gestational DM, two[52,53] reported HbA1c data. These two trials compared ILis with HI in 91 patients. HbA1c level was higher with ILis treatment compared with HI, but the difference was not statistically significant. The WMD (95% CI) was 0.06 (-0.11, 0.23). Details from each study are provided in Appendix 9C.

b) Hypoglycemia

In one RCT [121,122] involving 42 patients, the risk for overall hypoglycemia was higher for ILis than for HI, but it was not significant. The WMD (95% CI) was 1.32 (-0.44, 3.08). Details from each study are provided in Appendix 11C.

8 DISCUSSION

8.1 Adults with Type 1 DM

For adult patients with type 1 DM using MDI, treatment with ILis or IAsp resulted in statistically significant lower A1c levels than treatment with HI, but the difference was very small. For patients who used CSII, the difference was more pronounced and statistically significant for both ILis and IAsp when compared with HI.

Sensitivity analyses for ILis versus HI in patients using MDI, where pooled estimates were from studies of parallel design or studies with duration of intervention longer than three months, also favoured ILis rather than HI, but the pooled estimate was not statistically significant. All other sensitivity analyses, by duration of treatment or study design, showed A1c results similar to the overall analysis.

Two-hour post-prandial plasma glucose was statistically significantly lower with ILis compared with HI when used either as MDI or by CSII. Estimates, however, were derived from only three[77,79,90] studies.

In terms of severe hypoglycemia, there was a statistically significant reduction in the incidence of severe hypoglycemia with ILis treatment compared with HI when all RCTs or MDI RCTs were analyzed but not for the CSII RCTs. IAsp also showed a lower incidence rate of severe hypoglycemia, but the pooled estimate did not reach significance, perhaps due to the small number of RCTs for this comparison.

For overall hypoglycemia, a non-significant difference was observed between the analogues and HI when administered as MDI for either ILis or IAsp or by CSII for ILis. However, significant heterogeneity was observed when studies were pooled. This was more pronounced for RCTs with parallel study designs for overall hypoglycemia with rapid acting insulin analogues using MDI[45,80,87,96-99] and ILis using CSII (Table 4). Variation in definitions for overall hypoglycemia among studies may have contributed to the heterogeneity. Conversely, the rate of overall hypoglycemia was significantly lower, 42%, with IAsp as compared with HI when used by CSII. However, caution is again necessary with interpreting this result, as the meta-analysis consisted of two small RCTs with a total number of 138 patients.

The rate of nocturnal hypoglycemia was statistically lower for both ILis and IAsp compared with HI when used by CSII. However, this finding was estimated from a single three-arm RCT.[69] Results from pooling three RCTs[49,73,83] showed a significant reduction (42%) in the rate of nocturnal hypoglycemia for ILis versus HI in patients using MDI. However, significant heterogeneity existed among those studies. The reason for the large degree of heterogeneity among studies is unclear, but it may have been due to variations in the definition of nocturnal hypoglycemia used by investigators.

The summary estimate for DKA, derived from the pooling of three studies,[89-91] showed a non-significant increase in the risk of DKA with ILis compared with HI in adults using CSII. A similar finding was also derived from a single study[97] that reported DKA for IAsp versus HI in adults using MDI.

In terms of body weight gain, treatment with ILis showed a small non-significant reduction in body weight compared with treatment with HI.

Limited evidence[56,72,78,83,96] suggested that adult patients found ILis to be more convenient than HI. This may be because ILis can be administered immediately before meals versus 30 to 45 minutes before meals with HI. Caution should be taken when interpreting those results due to the open label design of most studies and the variation in the instruments. At this time, there is no available data on complications or mortality associated with long-term use of ILis or IAsp.

8.2 Pre-adolescents with Type 1 DM

Of five RCTs[60,61,63,64,93] that compared ILis with HI in pre-adolescent patients with type 1 DM, four[60,61,63,93] used MDI and one[64] used CSII. There were no significant differences in term of A1c and severe, nocturnal, and overall hypoglycemia. Similar results were derived when studies were pooled based on duration of treatment. Results from a single small RCT[64] that evaluated the use ILis versus HI in pre-adolescent patients using CSII showed a small but significant benefit (18% rate reduction) for overall hypoglycemia with ILis use.

In terms of QoL and patient satisfaction, limited evidence[63,64] suggests that parents of pre-adolescent children prefer ILis over HI because of convenience for both MDI and CSII. At this time, there is no available data on complications or mortality associated with long-term use of ILis or IAsp.

No studies were identified that compared IAsp with HI in pre-adolescents; therefore, it remains unknown if there are differences in outcomes in this population due to treatment strategy.

8.3 Adolescents with Type 1 DM

The only RCT[62] to investigate the use of ILis compared with HI in adolescents reported no significant difference between treatments in term of A1c and severe hypoglycemia. In contrast, there were statistically significant rate reductions for nocturnal hypoglycemia and overall hypoglycemia. No data were available for quality-of-life, patient satisfaction, diabetes-related complications, or mortality. Therefore, further research is needed to investigate the use of rapid-acting insulin analogues rather than HI in terms of these outcomes.

8.4 Adults with Type 2 DM

In adult patients with type 2 DM, there were no significant differences in A1c levels; FPG (IAsp versus HI); two-hour post-prandial plasma glucose; the RR of developing overall, severe, or nocturnal hypoglycemia; body weight gain; or total HDL cholesterol ratio for patients treated with rapid-acting analogues compared with those treated with HI. However, data for FPG and two-hour post-prandial plasma glucose were provided by single studies.[110,115,120]

When considering events per patient for nocturnal hypoglycemia (three RCTs: ILis versus HI)[49,103,106] and for overall hypoglycemia (two RCTs: IAsp versus HI),[75,108] episodes of nocturnal hypoglycemia were significantly reduced by ILis, but not by IAsp compared with HI. Conversely, the episodes of overall hypoglycemia were significantly reduced by IAsp, but not by ILis compared with HI. Compared with HI, treatment with ILis did not show any difference on satisfaction or flexibility scales or on the WBQ scale. Data for QoL, long-term outcomes, and mortality were not reported.

Studies that compared rapid-acting insulin analogues with Sfus were different in terms of patient population and treatment regimen. Some studies involved insulin therapy alone, while others included a combination of insulin therapy plus OADs. Most studies included type 2 DM patients who had failed OADs (mainly Sfus). The Sfu drug was glyburide in most studies. In general, there was a marginal reduction in A1c levels with ILis/ILis mix and IAsp/IAsp mix compared with Sfu. The RR and or rate ratio of nocturnal and overall hypoglycemia were significantly increased with rapid-acting insulin analogues compared with Sfu and Metf. Limited data indicate that ILis was superior to Sfu for increasing patient well being. None of the trials reported on mortality or long term complications. Further research is needed to investigate the long-term benefit of using rapid-acting insulin analogues rather than Sfu in type 2 DM patients who failed OAD therapy.

8.5 Pregnant Women

Based on the limited evidence comparing rapid-acting insulin analogues and HI for the treatment of pregnant women who had either type 1 DM or gestational DM, there was no significant difference in A1c level or rates of overall hypoglycemia. There was also limited evidence that showed no significant difference in severe hypoglycemia rates between ILis or IAsp compared with HI in pregnant women with type 1 DM.

8.6 Limitations

This systematic review and meta-analyses has limitations. Not all studies reported data on all the outcomes of interest. Also, not all RCTs could be included in the meta-analyses of all outcomes, thereby reducing power. There was heterogeneity among trials in some cases, as indicated by high I^2 values. Heterogeneity may have resulted from variations in patient population or in study methods. The larger degree of heterogeneity was observed among trials that reported hypoglycemia outcome. This may be due to the variation in the way that investigators defined hypoglycemia.

Methodological quality of the available evidence was generally poor. For example, allocation concealment was not mentioned in most trials, which may have introduced bias. Low quality trials can contribute to increased estimates of benefit; as a result, the results of this systematic review should be viewed cautiously.

Although QoL is important in the treatment of DM patients, not all trials addressed this issue. Those that did address this issue did not always use the same QoL scale, making comparisons difficult.

Most trials excluded patients with diabetes complications and none of them addressed long-term complications associated with diabetes. Also, most trials lasted $\leq$6 months. These limitations suggested the need for trials with longer duration to investigate the benefit of rapid-acting insulin analogues rather than HI on the progression of long-term complications associated with DM.

9 CONCLUSION

The bulk of available evidence on rapid-acting insulin analogues for both type 1 and type 2 DM consists of short- to medium-term comparisons with HI in terms of A1c and hypoglycemia. Most studies were of poor methodological quality. Based on the available evidence, the benefit of short-acting insulin analogues over HI appears to be marginal at best.

In adult patients with type 1 DM, treatment with ILis or IAsp significantly reduced A1c levels compared with HI when used by CSII. IAsp but not ILis also reduced A1c levels when used by MDI. The rate of overall or severe hypoglycemia was similar between the two rapid-acting insulin analogues and HI, but nocturnal hypoglycemia was less frequent with ILis or IAsp compared with HI.

In children with type 1 DM, A1c levels and the rate of hypoglycemia was similar between ILis and HI. A small benefit in reducing the rate of overall and nocturnal hypoglycemia in adolescent patients was shown by a single study.[62]

In adult patients with type 2 DM, there were no differences in A1c levels, risk of hypoglycemia, and QoL with rapid-acting insulin analogues compared with HI. A slight reduction of rate of nocturnal and overall hypoglycemia was observed with rapid-acting insulin analogues compared with HI. A marginal improvement of A1c levels and well-being, but no reduction of hypoglycemia, was observed with insulin analogues compared with Sfu.

The limited evidence regarding pregnant women with type 1 DM or gestational DM showed no difference between rapid-acting insulin analogues and HI for A1c level, overall hypoglycemia, and severe hypoglycemia.

High quality and long-term studies are required to measure the impact of rapid-acting insulin analogues on QoL, health care resource utilization, and long-term diabetes-related complications.

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APPENDIX 1A: LITERATURE SEARCH STRATEGY: SHORT-ACTING INSULIN ANALOGUES FOR DIABETES MELLITUS: META-ANALYSIS OF CLINICAL OUTCOMES AND ASSESSMENT OF COST-EFFECTIVENESS, TECHNOLOGY REPORT 87[19]

Guide to Search Syntax (DIALOG®)

!	Explode the search term. Retrieve the search concept plus all narrower terms.
?	Truncation symbol, single character. Retrieve plural and variant ending of search terms.
" "	Search phrases.
()	Proximity operator. Words must be adjacent.
(l)	Proximity operator. Links descriptors and subheadings.
(n)	Proximity operator. Words must be near each other in any order.
(w)	Proximity operator. Words must be adjacent.
ab	Search in article abstract.
de	Descriptor i.e., subject heading (a controlled, thesaurus term).
dt	Document type.
id	Identifier (includes CAS Registry Number and natural language indexing terms).
rn	CAS Registry Number.
ti	Search in titles.
tn	Brand name.
tw	Text word.

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
DIALOG OneSearch® MEDLINE® BIOSIS Previews® EMBASE® PASCAL	Human 1990 -	Insulin Long-Acting(l)aa/de *[MeSH heading for MEDLINE®]* *OR* (Insulin Glargine OR Insulin Detemir)/de *[EMTREE terms for EMBASE®]* *OR* TN=(Lantus OR Levemir) *[Brand names in EMBASE®]* *OR* (glargine OR Lantus OR HOE()901 OR 160337()95()1)/ti,ab,id OR RN=160337-95-1 OR (detemir OR Levemir OR NN()304 OR 169148()63()4)/ti,ab,id OR RN=169148-63-4 *[Textwords searched in title, abstract, identifier, registry number]* *OR*

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		(long()acting()insulin? OR slow?()acting()insulin? OR long()acting()analog? OR slow?()acting()analog?)/ti,ab *[Textwords searched in title, abstract]* *OR* Insulin(l)aa/de *[MeSH heading for MEDLINE®]* *OR* (Insulin Derivative OR Insulin Aspart OR Insulin()B28()Lysine()B29()Proline)/de *[EMTREE terms for EMBASE®]* *OR* TN=(Humalog OR NovoLog OR NovoRapid OR NovoMix OR Apidra) *[Brand names in EMBASE®]* *OR* Insulin Lispro/de *[BIOSIS Previews® thesaurus term]* *OR* (insulin?(1n)analog? OR insulin?(1n)derivat? OR new()insulin? OR novel()insulin?)/ti,ab *OR* (133107()64()9 OR insulin?(2n)(Lys?()28()B) OR (28()B()Lys?()29()B)(2n)insulin? OR Lispro? OR Humalog? OR B28 OR 28()B()lysine()29()B()prolineinsulin?)/ti,ab,id OR Lyspro?/ti,ab OR insulin()Lys()B28()Pro()B29/id OR RN=133107-64-9 *OR* (116094()23()6 OR insulin?()aspart? OR B28()asp? OR Asp()B28 OR NovoLog OR NovoRapid OR NovoMix?)/ti,ab OR insulin()Asp()B28/id OR RN=116094-23-6 *OR* (insulin()glulisine OR apidra OR 207748()29()6 OR insulin()Lys()B3()Glu()B29

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		OR insulin()lysyl()B3()glutamyl()B29 OR B3()lysyl()B29()glutamylinsulin)/ti,ab,id OR RN=207748-29-6 *OR* (quick()acting()insulin? OR rapid()acting()insulin? OR rapidly()acting()insulin? OR short()acting()insulin? OR fast()acting()insulin? OR quick()acting()analog? OR rapid()acting()analog? OR rapidly()acting()analog? OR short()acting()analog? OR fast()acting()analog?)/ti,ab ***AND*** Diabetes Mellitus!/de *[MeSH heading for MEDLINE®]* *OR* (Insulin-Dependent Diabetes OR Insulin-Dependent Diabetes Mellitus OR Diabetes OR Diabetes Insipidus OR Diabetes Mellitus OR "Maturity-Onset Diabetes of the Young" OR Non-Insulin-Dependent Diabetes Mellitus OR "Gestational Diabetes" OR "Gestational Diabetes Mellitus")/de *[BIOSIS Previews® thesaurus terms]* *OR* (Diabetes Control OR Diabetes Insipidus! OR Diabetes Mellitus! OR Experimental Diabetes Mellitus! OR Pregnancy Diabetes Mellitus!)/de *[EMTREE terms for EMBASE®*] *OR* (diabet? OR IDDM OR NIDDM OR MODY OR "type 1" OR "type I" OR "type 2" OR "type II" OR insulin()depend?()DM OR matur?()onset()DM OR late()life()DM OR gestational()DM OR juvenile()onset()DM OR juvenile()DM OR ketosis()prone()DM OR sudden()onset()DM OR non()insulin()depend?()DM OR adult()onset()DM)/ti,ab ***AND*** (Controlled Clinical Trials OR Multicenter Studies OR Randomized Controlled Trials OR Double-Blind Method OR Random Allocation OR Single-Blind Method OR Placebos)/de *[MeSH headings for MEDLINE®]* *OR* dt=(Multicenter Study OR Randomized Controlled Trial OR Controlled

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		Clinical Trial) *[Document type in MEDLINE®]* *OR* (Multicenter Study OR Randomized Controlled Trial OR Randomized Clinical Trial OR Randomized Trial OR Evidence-Based Medicine)/de *[BIOSIS Previews® thesaurus terms]* *OR* (Major Clinical Study OR Multicenter Study OR Controlled Study! OR Randomized Controlled Trial)/de *[EMTREE terms for EMBASE®]* *OR* (random? OR sham? OR placebo? OR singl?()(blind? OR dumm? OR mask?) OR doubl?()(blind? OR dumm? OR mask?) OR tripl?()(blind? OR dumm? OR mask?) OR trebl?()(blind? OR dumm? OR mask?) OR control?()(study OR studies OR trial?) OR RCT? ? OR (multicent? OR multi()cent?)()(study OR studies OR trial?))/ti,ab ***OR*** (Meta-Analysis OR Technology Assessment, Biomedical)/de *[MeSH headings for MEDLINE®]* *OR* dt=Meta-Analysis *[Document type in MEDLINE®]* *OR* Meta-Analysis/de *[BIOSIS Previews® thesaurus term]* *OR* (Meta Analysis OR Systematic Review OR Biomedical Technology Assessment)/de *[EMTREE terms for EMBASE®]* *OR* (meta()analy? OR metaanaly? OR met()analy? OR metanaly? OR health()technology()assessment? OR meta()regression? OR

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		metaregression? OR mega()regression? OR systematic?()(literature()review? OR review? OR overview?) OR methodologic?()(literature()review? OR review? OR overview?) OR quantitative()(review? OR overview? OR synthes?) OR research()(integration? OR overview?) OR integrative(2w)(review? OR overview?) OR collaborative()(review? OR overview?) OR pool?()analy? OR data()synthes? OR data()extraction? OR data()abstraction? OR handsearch? OR hand()search? OR mantel()haenszel OR peto OR der()simonian OR dersimonian OR fixed()effect? OR latin()square?)/ti,ab *Search performed on 3 August 2005; monthly alerts set up on MEDLINE®, EMBASE® and BIOSIS Previews® and were ongoing until 1 January 2006.* *Total Hits=850 Records (817 "clinical" results + 33 systematic review / meta-analysis results), 442 Unique Records after comparison with PubMed records (423 "clinical" results + 19 systematic review / meta-analysis results)*
Cochrane Library Issue 3, 2005	1990 -	Same MeSH and keywords as per MEDLINE® search, excluding study design filter. Appropriate syntax used. *Initial search performed on 2 August 2005 and updated with subsequent database updates. Last update performed on 6 February 2006.* *Total Hits=* *Cochrane Database of Systematic Reviews=2 Records, 1 Unique* *DARE=2 Records, 0 Unique* *CENTRAL =276 Records, 13 Unique* *Abstracts by INAHTA and other HTAs=6 Records, 3 Unique*
PubMed	Human 1990 -	Same MeSH and keywords as per MEDLINE® search. Appropriate syntax used. *Total Hits=407 Unique Records*
Web sites of health technology assessment (HTA) and related agencies; trial registries; other databases		AHRQ; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; LILACS; etc.

APPENDIX 1B: LITERATURE SEARCH STRATEGY – QUESTION FIVE

OVERVIEW	
Interface:	OVID
Databases:	BIOSIS Previews <1989 - >; EMBASE <1996 - >; OVID MEDLINE® In-Process & Other Non-Indexed Citations; OVID MEDLINE® <1966- > * Note: Subject headings have been customized for each database.
Date of Search:	December 18, 2006
Alerts:	Monthly search updates began January 2007 and ran to April 2007.
Study Types:	Randomized controlled trials
Limits:	Publication years 1990 onward Humans
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.af	All fields

SEARCH STRATEGIES:

MedLine, MedLine Daily Update, MedLine In-Process, EMBASE, BIOSIS Previews

Search Syntax:

Lispro AND Aspart AND RCT Filter
Lispro AND Glulisine AND RCT Filter
Aspart AND Glulisine AND RCT Filter

MedLine, MedLine Daily Update, MedLine In-process

1. Lispro$.ti,ab,rn.
2. Lyspro$.ti,ab,rn.
3. 133107-64-9.ti,ab,rn.
4. (Humalog or Liprolog).ti,ab,rn.
5. "Lys(B28),pro(B29)".ti,ab,rn.
6. or/1-5
7. Aspart.ti,ab.
8. (insulin aspart or Insulin AspB28).ti,ab,rn.
9. (asp adj b28).ti,ab,rn.
10. 116094-23-6.ti,ab,rn.
11. (NovoLog or NovoRapid or NovoMix).ti,ab,rn.
12. or/7-11
13. Glulisine.af.
14. 207748-29-6.ti,ab,rn.
15. Apidra.ti,ab,rn.
16. or/13-15

21. Randomized Controlled Trial.pt.
22. Randomized Controlled Trials/
23. (random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab.
24. ((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab.
25. (randomi?ed control$ trial? or rct?).ti,ab.
26. or/21-25
27. 20 and 26

EMBASE

28. Insulin lispro/
29. "insulin[b28 lysine b29 proline]"/
30. Lispro$.ti,ab,rn,tn,hw.
31. Lyspro$.ti,ab,rn,tn,hw.
32. 133107-64-9.ti,ab,rn.
33. (Humalog or Liprolog).ti,ab,rn,tn,hw.
34. "Lys(B28),pro(B29)".ti,ab,rn,tn,hw.
35. or/28-34
36. Insulin aspart/
37. aspart.ti,ab,rn,tn,hw.
38. (asp adj b28).ti,ab,rn,tn,hw.
39. 116094-23-6.ti,ab,rn.
40. (NovoLog or NovoRapid or NovoMix).ti,ab,rn,tn,hw.

SEARCH STRATEGIES:
MedLine, MedLine Daily Update, MedLine In-Process, EMBASE, BIOSIS Previews

41. or/36-40
42. Insulin Glulisine/
43. Glulisine/
44. Glulisine.ti,ab,rn,tn,hw.
45. Apidra.ti,ab,rn,tn,hw.
46. 207748-29-6.ti,ab,rn.
47. or/42-46
48. 35 and 41
49. 35 and 47
50. 41 and 47
51. or/48-50
52. Randomized Controlled Trial/
53. (random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab.
54. ((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab.
55. (randomi?ed control$ trial? or rct?).ti,ab.
56. or/52-55
57. 51 and 56

BIOSIS

58. Insulin lispro.ti,ab,hw.
59. "insulin[b28 lysine b29 proline]".ti,ab,hw.
60. Lispro$.ti,ab,hw.
61. Lyspro$.ti,ab,hw.
62. 133107-64-9.ti,ab,hw.
63. (Humalog or Liprolog).ti,ab,hw.
64. "Lys(B28),pro(B29)".ti,ab,rn.
65. or/58-64
66. Insulin Aspart.ti,ab,hw.
67. (asp adj b28).ti,ab,hw.
68. 116094-23-6.ti,ab,hw.
69. (NovoLog or NovoRapid or NovoMix).ti,ab,hw.
70. or/66-69
71. Glulisine.af.
72. Apidra.af.
73. 207748-29-6.ti,ab,hw.
74. or/71-73
75. 65 and 70
76. 65 and 74
77. 70 and 74
78. or/75-77
79. randomi?ed control$ trial?.ti,ab,hw.
80. (random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab,hw.
81. ((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab,hw.
82. or/79-81

SEARCH STRATEGIES: MedLine, MedLine Daily Update, MedLine In-Process, EMBASE, BIOSIS Previews		
83. 78 and 82		
OTHER DATABASES		
Cochrane Library Issues 3, 2007 ECRI www.ecri.org	Same MeSH, keywords, and date limits used as per MedLine search, excluding study types and human restrictions. Syntax adjusted for Cochrane Library databases.	

GREY LITERATIRE AND HANDSEARCHING

Dates for search: August 2005 – June 2007
Keywords: Rapid acting insulin; insulin brand names and substance names

This section lists the main agencies, organizations, and web sites searched; it is not a complete list.

Health Technology Assessment Agencies

Alberta Heritage Foundation for Medical Research (AHFMR)
http://www.ahfmr.ab.ca

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), Québec
http://www.aetmis.gouv.qc.ca

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca

Centre for Evaluation of Medicines (Father Sean O'Sullivan Research Centre,
St. Joseph's Healthcare, Hamilton; and McMaster University, Faculty of Health Sciences, Hamilton, Ontario)
http://www.thecem.net/

Centre for Health Services and Policy Research, University of British Columbia
http://www.chspr.ubc.ca/cgi-bin/pub

Health Quality Council of Alberta (HQCA)
http://www.hqca.ca

Health Quality Council, Saskatchewan.
http://www.hqc.sk.ca/

Institute for Clinical Evaluative Sciences (ICES), Ontario
http://www.ices.on.ca/

Institute of Health Economics (IHE), Alberta
http://www.ihe.ab.ca/

Manitoba Centre for Health Policy (MCHP)
http://www.umanitoba.ca/centres/mchp/

Ontario Ministry of Health and Long-Term Care, Health Technology Reviews
http://www.health.gov.on.ca/english/providers/program/mas/tech/tech_mn.html

The Technology Assessment Unit of the McGill University Health Centre
http://www.mcgill.ca/tau/

Therapeutics Initiative, Evidence-Based Drug Therapy, University of British Columbia
http://www.ti.ubc.ca

Health Technology Assessment International (HTAi)
http://www.htai.org

International Network for Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org

WHO Health Evidence Network
http://www.euro.who.int/HEN

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)
http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm

Centre for Clinical Effectiveness (Monash University)
http://www.med.monash.edu.au/healthservices/cce/

Medicare Services Advisory Committee (Department of Health and Aging)
http://www.msac.gov.au/

NPS RADAR (National Prescribing Service Ltd.)
http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html

ITA – Institute of Technology Assessment
http://www.oeaw.ac.at/ita/index.htm

Danish Centre for Evaluation and Health Technology Assessment (DCEHTA), National Board of Health
http://www.dihta.dk/

Finnish Office for Health Care Technology and Assessment (FinOHTA), National Research and Development Centre for Welfare and Health
http://finohta.stakes.fi/EN/index.htm

L'Agence nationale d'accréditation et d'évaluation en santé (ANAES), Ministère de la Santé, de la Famille, et des Personnes handicapées)
http://www.anaes.fr/anaes/anaesparametrage.nsf/HomePage?ReadForm

Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT)
http://cedit.aphp.fr/english/index_present.html

German Institute for Medical Documentation and Information (DIMDI), Federal Ministry of Health
http://www.dimdi.de/static/de/hta/db/index.htm

Health Service Executive
http://www.hebe.ie/ProgrammesProjects/HealthTechnologyAssessment

College voor Zorgverzekeringen/Health Care Insurance Board (CVZ)
http://www.cvz.nl

Health Council of the Netherlands
http://www.gr.nl

New Zealand Health Technology Assessment Clearing House for Health Outcomes and Health Technology Assessment (NZHTA)
http://nzhta.chmeds.ac.nz/

Norwegian Centre for Health Technology Assessment (SMM)
http://www.kunnskapssenteret.no/index.php?show=38&expand=14,38

Agencia de Evaluación de Tecnologías Sanitarias (AETS), Instituto de Salud "Carlos III"/Health Technology Assessment Agency
http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

Basque Office for Health Technology Assessment (OSTEBA), Departemento de Sanidad
http://www.osasun.ejgv.euskadi.net/r52-2536/es/

Catalan Agency for Health Technology Assessment and Research (CAHTA)
http://www.aatrm.net/html/en/Du8/doc7850.html

CMT – Centre for Medical Technology Assessment
http://www.cmt.liu.se/pub/jsp/polopoly.jsp?d=6199&l=en

Swedish Council on Technology Assessment in Health Care (SBU)
http://www.sbu.se/www/index.asp

Swiss Network for Health Technology Assessment
http://www.snhta.ch/about/index.php

European Information Network on New and Changing Health Technologies (EUROSCAN), University of Birmingham, National Horizon Scanning Centre
http://www.euroscan.bham.ac.uk

National Horizon Scanning Centre (NHSC)
http://www.pcpoh.bham.ac.uk/publichealth/horizon

NHS Health Technology Assessment /National Coordinating Centre for Health Technology Assessment (NCCHTA), Department of Health R&D Division
http://www.hta.nhsweb.nhs.uk

NHS National Institute for Clinical Excellence (NICE)
http://www.nice.org.uk

NHS Quality Improvement Scotland
http://www.nhshealthquality.org

University of York NHS Centre for Reviews and Dissemination (NHS CRD)
http://www.york.ac.uk/inst/crd

The Wessex Institute for Health Research and Development, Succinct and Timely Evaluated Evidence Review (STEER)
http://www.wihrd.soton.ac.uk/

West Midlands Health Technology Assessment Collaboration (WMHTAC)
http://www.publichealth.bham.ac.uk/wmhtac/

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/

Department of Veterans Affairs Research & Development, general publications
http://www1.va.gov/resdev/prt/pubs_individual.cfm?webpage=pubs_ta_reports.htm

VA Technology Assessment Program (VATAP)
http://www.va.gov/vatap/

Institute for Clinical Systems Improvement
http://www.icsi.org/index.asp

Technology Evaluation Center (Tec). BlueCross BlueShield Association
http://www.bluecares.com/tec/index.html

University HealthSystem Consortium (UHC)
http://www.uhc.edu/

Health Economic

Bases CODECS (COnnaissances et Décision en EConomie de la Santé) Collège des Economistes de la Santé/INSERM
http://www.inserm.fr/codecs/codecsanglais.nsf/(Web+English+Startup+Page)?OpenForm

Centre for Health Economics and Policy Analysis (CHEPA), Department of Clinical Epidemiology and Biostatistics, Faculty of Health Sciences. McMaster University, Canada
http://www.chepa.org

Health Economics Research Group (HERG), Brunel University, UK
http://www.brunel.ac.uk/about/acad/herg

Health Economics Research Unit (HERU), University of Aberdeen
http://www.abdn.ac.uk/heru/

The Hospital for Sick Children (Toronto), PEDE Database
http://pede.bioinfo.sickkids.on.ca/pede/index.jsp

University of Connecticut, Department of Economics, RePEc database
http://ideas.repec.org

Conferences

Endocrine abstracts
http://www.endocrine-abstracts.org/ea/default.htm

American Association of Clinical Endocrinologists Annual Meeting and Clinical Congress (AACE)
http://www.aace.com/calendar.php

American Diabetes Association (ADA) Scientific Sessions
http://scientificsessions.diabetes.org/index.cfm?fuseaction=Custom.Content&MenuID=1000

European Association for the Study of Diabetes, Annual Meeting
http://www.easd.org/

Association of British Clinical Diabetologists
www.diabetologists.org.uk

ENDO (Endocrine Society) Conference
http://www.abstracts2view.com/endo/

Societies/Organizations/Associations

Canadian Diabetes Association
http://www.diabetes.ca/

American Diabetes Association
http://www.diabetes.org

Search Engines

Google
http://www.google.ca/

APPENDIX 2: CLINICAL DATA EXTRACTION FORM

Reviewer initials:	**Ref ID:**
Reference: (Author, Year, Source, Publication status)	

Trial characteristics	
Study design	
No. of centres	
Country	
Sponsor	
No. of patients	
Type of diabetes	
Disease state	
Investigator's definition of hypoglycemia	
Procedure	
Other	

Patient characteristics					
Category	**Unit**	**Treatment**	**Control**	**All Arms Combined**	**Comment**
Age					
Male/Female					
Duration of diabetes					
Baseline HbA1c					
Baseline BMI					
Race/Ethnicity					
Withdrawals or lost to follow-up					
Other					

Outcomes				
Category	Units	Treatment	Control	Comment
HbA1c				
BG				
Hypoglycemia				
Diabetic complications				
Adverse events				
Mortality				
QoL				
Other				

BG=blood glucose; BMI=body mass index; HbA1c=glycosylated haemoglobin; QoL=quality of life.

APPENDIX 3: RCT STUDY QUALITY ASSESSMENT TOOL

Project:	Statement #:	Author:
Title:		
Reviewer:	Date:	RefMan #:

Jadad Five-Point Scale:

No.	Category	Score
1	Randomization:	
	Was the study described as randomized (i.e., including words such as randomly, random, randomization)? A trial reporting that it is randomized is to receive one point. Yes=1 or No=0 Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point. Appropriate=1 or Not Appropriate=0 If the report describes the trial as randomized and uses an inappropriate method of randomization (e.g., date of birth, hospital numbers), a point is deducted. Inappropriate= -1	
Total Randomization Score:		
2	Double-blinding:	
	Was the study described as double-blind? A trial reporting that it is double-blind is to receive one point. Yes=1 or No=0. Trials describing an appropriate method of double-blinding (identical placebo: colour, shape, taste) are to receive an additional point. Yes=1 or No=0 If the report describes a trial as double-blind and uses an inappropriate method (e.g., comparison of tablets versus injection with no dummy), a point is deducted. Inappropriate= -1	
Total Double-Blinding Score:		
3	Withdrawals and dropouts:	
	Was there a description of withdrawals and dropouts? A trial reporting the number and reasons for withdrawals or dropouts is to receive one point. If there is no description, no point is given. Yes=1 or No=0	
Total Jadad Score:		

Additional Items of Interest:

4	Adequacy of allocation concealment:	Adequacy Level
	Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes etc.=Adequate Alternation; reference to case record # or date of birth, etc.=Inadequate Allocation concealment is not reported, or, fits neither category=Unclear	
5	Blinding of outcome assessor:	
	Was the outcome assessor blinded?	
6	Analyses: Intention-to-treat:	
	Was ITT analysis used?	

APPENDIX 4: META-ANALYTIC METHODS

The meta-analytic methods most commonly used to investigate the effectiveness of health care interventions are those presented by Cochrane[123,124] and DerSimonian and Laird.[125] Those methods involve combining results of individual randomized controlled trials (RCTs) to provide a comparison of success rates between two drugs and an estimation of the effect size.[126,127]

There are two statistical models available for meta-analytic studies – the fixed effects model and the random effects model. To determine the appropriate model for the meta-analysis, it will be necessary to make assumptions about the data that are to be combined. The fixed effects model is based on the mathematical assumption that all the studies to be included in the meta-analysis use identical methods, patients, and measurements and are evaluating the same effect. That is, the effect is the same in all studies, and the results of the studies vary randomly around the true common fixed effect. The diversity around the true common fixed effect is called the *within-study* variance.[125,128] Thus, fixed effect models consider only *within-study* variability.

The random effects model does not make the same assumptions as the fixed effect model. It deals with the lack of knowledge about why real, or apparent, treatment effects differ by considering the differences as if they were random. The model assumes that 1) the studies included in the meta-analysis are a random sample from all possible studies, 2) the true effects observed in each study may be different from each other, and 3) those differences are normally distributed. The differences are called random effects and describe the *between-study* variation.[128-130] Thus, random effects models consider both *between-study* and *within-study* variability. This method of combining results weights by sample size and adjusts for between study variance, serving to reduce the impact of between study differences.[127] The underlying assumption of this model is that the true effect (outcome) of each study is different; that is, not all studies are measuring the same effect. The model assumes that there may be differences between studies due to study aspects, including different populations, and different methods of outcome assessment. Despite the differences between studies, it is assumed that the degree of difference is so great as to make the estimated common effect meaningless.[124]

Forest plots will be generated wherever appropriate to determine if heterogeneity exists between the results of individual study included in the review. If significant heterogeneity does exist, the reasons for heterogeneity (e.g., study design, population characteristics, and study quality) will be explored. Should significant variation between studies be observed, analysis of subgroups based on factors potentially responsible for heterogeneity will be attempted and the influence of these factors will be assessed. If outliers are present, then results will be pooled with and without the outliers to investigate their impact on the overall result. If necessary, sensitivity analysis will be performed to investigate the robustness of the results of statistical synthesis by estimating and comparing the effects of the intervention in different trial categories (e.g., grouped by publication status, quality, and publication year).

APPENDIX 5: REASONS FOR EXCLUSION OF STUDIES FROM THE REVIEW

Not RCTs
Bin-Abbas *et al.*[131]
Bin-Abbas *et al.*[132]
Fiallo-Scharer *et al.*[133]
Garber *et al.*[134]
Westphal *et al.*[135]
Bailey *et al.*[136]
Chlup *et al.*[137]
Di Bartolo *et al.*[138]

RCTs comparing glulisine to human insulin
Dreyer *et al.*[139]
Hoogma *et al.*[140]
Rayman *et al.*[141]

Different insulin delivery methods in both arms
Boullu-Sanchis *et al.*[142]

Studies mention pharmacokinetic data only
Homko *et al.*[143]
Plank *et al.*[144]

Duplicate publication or subset from the same study
Heller *et al.*[145]
Kaaja *et al.*[146]

RCTs with no comparable insulin regimen in both arms
Chen *et al.*[147]
Mortensen *et al.*[38]
Colombel *et al.*[33]
DeVries *et al.*[34]
Herz *et al.*[35]
Janssen *et al.*[36]
Lalli *et al.*[37]

Treatment duration less than four weeks
Alfonso *et al.*[148]
Rave *et al.*[149]

Incomplete data
Fuji *et al.*[150]

RCTs included both type 1 and type 2 DM together in the analysis
Skrha *et al.*[41]
Howorka *et al.*[42]
Roach *et al.*[43]
Boehm *et al.* [44]

APPENDIX 6A: STUDY CHARACTERISTICS OF RCTs IN TYPE 1 DM

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
Anderson *et al.*, 1997[77]	3-month, open-label, crossover, no washout period	Some investigators from Eli Lilly	17	ILis+NPH or UL	1,008	48 (4.8%), no difference between the two groups	33.2±0.4†	58	NR	12.0±0.3†
				HI+NPH or UL						
Anderson *et al.*, 1997[45]	12-month, open-label, parallel	Some investigators from Eli Lilly	11	ILis+basal	162	25 (7.4%)	32.2±0.9†	51	NR	12.7±0.7†
				HI+basal	174		32.0±09†	49	NR	12.1± 0.7†
Annuzzi *et al.*, 2001[78]	3-month, open-label, crossover, no washout period reported	Eli Lilly	Italy	ILis+NPH	85	5 (5.9%) total; 3 during HI and 2 during ILis	31.4±7.6*	44	NR	12.1±7.6*
				HI+NPH						
Arslanian *et al.*, 2005[54] [Poster]	24-week, open-label, parallel	NR	US	IAsp+NPH	187	78 (21%)	11.8±3.1*	46	76% Caucasian	4.8±3.3*
				ILis+NPH	95		11.4±2.9*	55	77% Caucasian	4.4±3.1*
				HI+NPH	96		11.5±2.7*	56	72% Caucasian	4.6±3.1*
Bode and Strange, 2001[71]	7-week, open-label, parallel	Author associated with Novo Nordisk	US	IAsp	19	1 (3.4%) in IAsp group	38±10.4*	68	Caucasian	2 to 25
				HI	10		34±12.5*	50	Caucasian	2 to 25
Bode *et al.*, 2002[69]	16-week, open-label, parallel	Novo Nordisk	US	IAsp+basal	59	14 (9.6%)	42.3±12.0*	39	98% Caucasian	≥12 months
				ILis+basal	28		39.9±11.1*	32	93% Caucasian	≥12 months
				HI+basal	59		43.1±9.4*	32	98% Caucasians	≥12 months

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
Bott *et al.*, 2003[72]	6-month, open-label, parallel	Novo Nordisk	Germany, Austria, and Switzerland	IAsp	283	NR	37.0 [18.5]††	51	NR (German-speaking patients)	13.0 [14.5]††
				HI	141		36.6 [15.3]††	62		11.3 [16.2]††
Caixàs *et al.*, 1998[79]	3-month, open-label, crossover, no washout period reported	Eli Lilly	Spain	ILis+UL	10	NR	29.0±6.5*	20	NR	5.5±5.0*
				HI+UL						
Chan *et al.*, 2004[46]	12-week, open-label, crossover, no washout period reported	NR	China	ILis+NPH	12	0	42.2 [20 to 67]‡	53	NR (probably Asian)	7.8±2.7*
				HI+NPH						
Ciofetta *et al.*, 1999[80]	3-month, open-label, parallel	B.B. & Sons	Italy	ILis+NPH	24	NR	33±4*	71	NR	13±2.1*
				HI+NPH						
Danne *et al.*, 2005[55] [Abstract]	6-week, open-label, crossover, no washout period reported	NR	Germany	IAsp+NPH	26	NR	[2.4 to 6.9]‡	65	NR	NR
				HI+NPH						
Deeb *et al.*, 2001[60]	3-month, open-label, crossover, no washout period reported	One author from Eli Lilly	Canada and US	ILis (before meal)+NPH, lente or ultralente	61	2 (3.3%) (1 before randomization and 1 during treatment)	7.6 [2.9 to 11.4]‡	48	NR	3.7 [1 to 8]‡
				ILis (after meal)+NPH, lente or ultralente						

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
				HI+NPH, lente or ultralente						
Del Sindaco *et al.*, 1998[102]	3-month, open-label, crossover, no washout period reported	NR	Italy	ILis versus HI (both with 1 or 2 NPH)	15	NR	33±6.9*	47	NR	15.2±11.6*
				ILis+3 or 4 NPH versus HI+1 or 2 NPH	18		34±7.2*	50	NR	14.1± 8.9*
				ILis versus HI (both with 3 or 4 NPH)	12		32±5.2*	50	NR	13±8.6*
				HI 5 minutes pre-meal versus HI 10 to 40 minutes pre-meal	24		30±8.8*	54	NR	14±10.2*
Fairchild *et al.*, 2000[28]	3-month, open-label, crossover, no washout period reported	NR	Australia	ILis+NPH	35	0	8.05±1.39	46	NR	3.01[1.59 to 5.18]
				HI+NPH	35					
Ferguson *et al.*, 2001[81]	24-week, open-label, crossover, no washout period reported	Eli Lilly	UK	ILis+NPH	33	5 (12.8%) withdrew and 1 was not included in the analysis	46±11*	55	NR	25.8±9.8*
				HI+NPH						
Ford-Adams *et al.*, 2003[61]	4-month, open-label, crossover, no washout period reported	Eli Lilly	UK	ILis+NPH [NPH: pre-breakfast and pre-bed]	23	none	9.4 (7 to 11)‡	70	NR	>1
				HI+NPH [NPH: pre-breakfast and pre-bed]						

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
Gale, 2000[73]	3-month, double-blind, crossover, no washout period reported	Eli Lilly	UK	lLis+NPH	93	6 (6.5%)	35 (18 to 63)‡	43	NR	13.1 [1 to 51]‡
				HI+NPH						
Garg *et al.*, 1996[82]	12-month, open-label, parallel	Eli Lilly	US	lLis+NPH or UL	18	2 (5.1%)	22.7±4.5*	49	NR	11.6±8.4*
				HI+NPH or UL	21		22.3±4.8*			10.3±7.5*
Hedman *et al.*, 2001[88]	6-week, open-label, crossover, no washout period reported, CSII	Swedish Medical Research Council, Swedish Diabetes Association & University	Sweden	lLis+basal	12	none	47.8±2.4†	33	NR	30.5±3.2†
				HI+basal						
Heller *et al.*, 1999[93]	4-month, open-label, crossover, no washout period reported	Eli Lilly	UK	lLis+NPH [NPH: bedtime]	135	1 (0.7%)	38±11†	53	NR	16.5±9.2†
				HI+NPH [NPH: bedtime]						
Heller *et al.*, 2004[70]	16-week, double-blind, crossover with 4-week washout	Novo Nordisk	UK, Denmark, Norway, Australia, and the Netherlands	lAsp+NPH [NPH: bedtime and pre-breakfast]	155	16 (10.3%)	35.7±9.4* [18 to 65]‡	NR	NR	≥2
				HI+NPH [NPH: bedtime and pre-breakfast]						
Holcombe *et al.*, 2002[62]	4-month, open-label, crossover, no washout period reported	Eli Lilly	15	lLis+NPH [NPH: 1 to 3 times daily]	463	18 (3.7%) discontinued before randomization	14.9±2.0*	45	NR	6.1±3.7*
				HI+NPH [NPH: 1 to 3 times daily]						

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
Holleman *et al.*, 1997[83]	12-week, open-label, crossover, no washout period reported	Eli Lilly	UK, Belgium, and the Netherlands	ILis+NPH	96	10 (5.0%)	34.9±9.6*	60	NR	14.2±9.9*
				HI+NPH	103		35.9±9.7*	66		12.0±8.1*
Home *et al.*, 1998[67]	4-week, double-blind, crossover, no washout period reported	Novo Nordisk	UK	IAsp+NPH [NPH: bedtime]	104	14 (13.5%)	34.3±8.6*	100	NR	14.8±8.7*
				HI+NPH [NPH: bedtime]						
Home *et al.*, 2000[96]	6-month, open-label, parallel	Novo Nordisk	8 European countries	IAsp+NPH	707	59 (5.5%)	38±11*	55	99% Europid	15±10*
				HI+NPH	358		38±12*	56	99% Europid	15±10*
Home *et al.*, 2006[100] [Extension study of Home *et al.*, 2000[96]]	30-month, open-label, parallel	Novo Nordisk	8 European countries	IAsp+NPH	567	155 (2.1%)	37.9±11.4*	58	99% Europid	14.8±10.2*
				HI+NPH	186		39.6±12.4*	59	98% Europid	15.6±11.0*
Iwamoto *et al.*, 2001[97]	24-week, open-label, parallel	NR	Japan	IAsp+basal	143	15 (7.1%)	33.9±15.5* [12 to 78]‡	41	Japanese	10.60±7.03* [2 to 40.7]‡
				HI+basal	62		32.2±13.2* [12 to 68]‡	34		10.65±6.16* [2.6 to 33.7]‡
Jacobs *et al.*, 1997[66]	4-week, open-label, crossover, no washout period reported	Eli Lilly	The Netherlands	ILis+NPH [NPH: bedtime]	12	NR	NR	NR	NR	NR
				HI+NPH [NPH: bedtime]						
Janes *et al.*,	3-month,	Eli Lilly	UK	ILis+basal: NR	97	NR	NR	NR	NR	NR

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
1997[56] [Abstract]	open-label, crossover, no washout period reported			HI+basal: NR						
Jansson *et al.*, 1998[85]	4-month, open-label, parallel	Eli Lilly	Sweden, Finland, Spain, and Italy	ILis+NPH	44	NR	35±1†	NR	NR	15.6±1.2†
				HI+NPL	40		35±1†			15.5±1.1†
Johansson *et al.*, 2000[89]	2-month, open-label, crossover, no washout period reported	Eli Lilly	Sweden	ILis+NPH	41	0	42.0±10.0*	54	NR	21.0±11*
				HI+NPH						
Kotsanos *et al.*, 1997[47]	3-month, open-label, crossover, no washout period reported	Eli Lilly	Canada, France, Germany, and US	ILis+basal: NPH or UL	468	26 (2.8%)	33.8±12.1*	44.2	96.6% Caucasian	12.6±9.0*
				HI+basal: NPH or UL						
Linkeschova *et al.*, 2003[57]	4-month, double-blind, crossover, no washout period reported	NR	Germany	ILis+basal: NR	27	NR	40±13*	52	NR	18±9*
				HI+basal: NR						
Mathiesen *et al.*, 2007[29]	Period NR, but drugs started in pregnant or likely-to-become-pregnant women up to 3rd trimester, open-label, parallel	Novo Nordisk	15 European countries, Argentina, Israel, and Canada	IAsp+NPH	157	58	29.0±4.7	0	NR	12.2±7.1
				HI+NPH	165		29.0±4.5	0	NR	11.8±7.4

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
Melki *et al.*, 1998[94]	3-month, open-label, crossover, no washout period reported	Eli Lilly	France	ILis+basal	39	1 (2.5%)	39.4±1.5†	56	NR	22.5±1.6†
				HI+basal						
Persson *et al.*, 2002[65]	6-month, open-label, parallel	NR	Sweden	ILis+NPH	16	NR	31 (25 to 33)**	0 pregnant women	NR	15 (1 to 25)**
				HI+NPH	17		30 (21 to 34)**	0 pregnant women	NR	12 (2 to 29)**
Provenzano *et al.*, 2001[86]	1-year, open-label, crossover, no washout period reported	NR	Italy	ILis+basal	12	NR	28 (14 to 44)‡	58	NR	11.5
				HI+basal						
Raskin *et al.*, 2001[90]	12-week, open-label, crossover, no washout period reported	Eli Lilly	US	ILis+basal	28	4 (6.9%)	40.5±8.7*	57	NR	18.8±7.6*
				HI+basal	30		37.8±9.7*	47	NR	17.4±8.5*
Raskin *et al.*, 2000[98]	12-month (6-month with voluntary 6-month extension), open-label, parallel	Novo Nordisk	US and Canada	IAsp+NPH	596	67 (7.6%) after 6 months; additional 39 after second 6 months	38.9±10.5*	51	94% Caucasian	15.7±9.7*
				HI+NPH	286		39.9±12.2*	53	93% Caucasian	15.8±9.3*
Recasens *et al.*, 2003[68]	1-year, open-label, parallel	NR	Spain and Italy	ILis+NPH	22	NR	24.4±5.7*	64	NR	Newly diagnosed (8.0±3.8 weeks)

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
				HI+NPH	23		22.8±5.1*	61	NR	Newly diagnosed (8.1±8.0 weeks)
Renner *et al.*, 1999[91]	4-month, open-label, crossover, no washout period reported	Eli Lilly	Germany	ILis+basal	113	NR	37.1±11.6*	53	NR	19.1±9.2*
				HI+basal						
Roach *et al.*, 1999[49]	3-month, open-label, crossover, no washout period reported	Eli Lilly	Germany, Hungary, the Netherlands, Switzerland, and UK	ILis/HI	19	3 (3.0%)	42.2	63	NR	14.3
				HI/ILis	18		36.5	72	NR	11.4
Schmauß *et al.*, 1998[95]	3-month, open-label, crossover, no washout period reported	Eli Lilly	Germany	ILis+basal	11	0	30±2.5	45	NR	14±1.0
				HI+basal						
Tamás *et al.*, 2001[99]	64 weeks/12 weeks was period analyzed in article, open-label, parallel	Novo Nordisk	11 countries	IAsp+NPH	213	16 (3.5%)	35.6±11.4*	58	NR	14.0±9.1*
				HI+NPH	213		36.1±11.7*	55	NR	14.2±9.2*
Tubiana-Rufi *et al.*, 2004[64]	16-week, open-label, crossover, no washout period reported	Eli Lilly	France	ILis+basal	29	2 (6.9%)	4.6±2.2* [1.8 to 9]‡	67	NR	2.2±1.8* [0.3 to 8]‡
				HI+basal						
Tupola *et al.*, 2001[63]	3-month, open-label,	Eli Lilly	Finland	ILis+NPH [NPH: 2 times daily]	24	2 (8.3%)	6.2 [3.9 to 9.9]‡	50	NR	3.1 [1.0 to 5.0]‡

Study	Study Period and Type	Sponsor	Country	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity	Duration of DM, years
	crossover, no washout period reported			HI+NPH [NPH: 2 times daily]						
Valle *et al.*, 2001[87]	3-month, open-label, parallel	Eli Lilly	Italy	ILis+NPH [NPH: 1 to 3 times daily]	1,184	NR	38.7±12.8*	56	NR	14±9*
				HI+NPH [NPH: 1 to 3 times daily]						
Vignati *et al.*, 1997[50]	2-month, open-label, crossover, no washout period reported	Eli Lilly	16	ILis+NPH	379	29 (4.1%)	39.1 [18 to 70]‡	56	NR	13.1 [0.2 to 48.2]‡
				HI+NPH						
Zinman *et al.*, 1997[92]	3-month, double-blind, crossover, no washout period reported	Eli Lilly	Canada	ILis+basal	30	0	35.1±1.5	43	NR	17.5±1.6
				HI+basal						

*mean±SD; †mean±SE; ‡mean (range); **mean (90% CI); ††median (interquartile). DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; NPH=neutral protamine Hagedorn; NR=not reported; RCTs=randomized controlled trials; UL=ultralente.

APPENDIX 6B: STUDY CHARACTERISTICS OF RCTs IN TYPE 2 DM

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity (%)	Duration of DM, years
Altuntas *et al.*, 2003[74]	6-month, open-label, parallel	NR	Turkey	ILis+NPH	20	0	54.8±7.5†	NR	NR	6.1
				ILis+Metf	20		53.8±3.1†			5.2
				HI+NPH	20		54.5±7.7†			10.2
Anderson *et al.*, 1997[45]	12-month, open-label, parallel	Some investigators from Eli Lilly	11	ILis+basal	145	15 (5.1%)	55.8±0.7†	51	NR	12.4±0.6†
				HI+basal	150		56.0±0.7†	53		12.0±0.7†
Anderson *et al.*, 1997[103]	3-month, open-label, crossover, no washout period	Some investigators from Eli Lilly	16	ILis+basal	722	36 (5.0%)	59±1†	54	NR	12.4±0.3†
				HI+basal						
Bastyr *et al.*, 1999[111]	2-month, open-label, parallel	Eli Lilly	11	ILis+NPH	423	27 (6.4%)	60.16	52	91% Caucasian	9
				ILis+NPH	149		59.61	58	88% Caucasian	9
				ILis+Sfu	139		60.19	44	94% Caucasian	10
				NPH+Sfu	135		60.74	54	92% Caucasian	9
Bastyr *et al.*, 2000[119]	3-month, open-label, parallel	Eli Lilly	US	ILis+Gly	41	17 (12.6%)	55.9	66	70.7% Caucasian	7.1
				Metf+Gly	40		58.1	55	60.0% Caucasian	8.9
				NPH+Gly	50		56.6	60	58.0% Caucasian	7.3
Boehm *et al.*, 2004[108]	3-month+21-month extension, open-label, parallel	Novo Nordisk	Germany, Ireland, and UK	BIAsp30	58	30 (24.0%)	62.8±8.0*	55	NR	15.5±9.7
				BHI30/70	67		62.6±8.6*	51	NR	12.9±6.6
Bretzel *et al.*,	3-month,	Novo Nordisk	Germany	IAsp+NPH	75	27 (11.7%)	61.4±9*	59	NR	NR

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity (%)	Duration of DM, years
2004[75]	open-label, parallel			HI+NPH	80		62±3.3*	50	NR	NR
				BHI30/70+NPH	76		63.1±8.9*	61	NR	NR
Chan *et al.*, 2004[46]	12-week x 2, open-label, crossover, no washout period reported	NR	China	ILis+NPH	18	0	42.2 [20 to 67]‡	53	NR, (probably Asian)	7.8±2.7*
				HI+NPH						
Forst *et al.*, 2003[112]	26-week, open-label, parallel	Eli Lilly	Germany, Sweden, and Switzerland	ILis	75	NR	58.7±7.3*	51	99% Caucasian	4.4±2.9*
				Glib	68		56.6±8.6*	57	99% Caucasian	4.3±3.4*
Gallagher and Home, 2005[109]	6-week, double-blind, crossover, no washout period reported	Novo Nordisk	UK	IAsp+NPH	24	3 (14.3%)	66±5*	76	NR	11±4*
				HI+NPH						
Herz *et al.*, 2003[76]	4-week, open-label, crossover, no washout period reported	Eli Lilly	South Africa	Mix25	13	4 (16.0%)	54.8±1.82†	77	NR	NR
				BHI30/70	12		53.6±2.15†	58		
Herz *et al.*, 2002[120]	4-week, open-label, crossover, no washout period reported	Eli Lilly	Croatia	Mix25	19	4 (10.8%)	56.3±1.79†	63	NR	8.9±1.28†
				BHI30/70	18		55.3±1.84†	33	NR	7.5±1.30†
Herz *et al.*, 2002a[113]	16-week, open-label, parallel	Eli Lilly	8	Mix25	71	16 (11.2%)	68.1±4.9*	52	NR	11.4±7.9*
				Gly	72		67.7±4.9*	44		12.4±7.3*

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity (%)	Duration of DM, years
Iwamoto, 2003[58] [Abstract]	48-week, open-label, parallel	NR	Japan	BIAsp30	321	NR	comparable	comparable	NR	comparable
				BHI30/70	107					
Kilo *et al.*, 2003[110]	12-week, open-label, parallel	Novo Nordisk	US	BIAsp30+Metf	46	9 (6.4%)	57.2±12.6*	54	72% Caucasian	10.4±8.6*
				BHI30/70+ Metf	47		55.4±11.0*	62	74% Caucasian	8.4±4.9*
				NPH+Metf	47		55.1±12.6*	40	64% Caucasian, 20% Black	10.7±7.3*
Koki *et al.*, 2003[114]	3-month, open-label, parallel	NR	Croatia	ILis+Metf	29	NR	62.3±7.2	51	NR	9.5±3.1
				BHI30/70+NPH	29		63.6±4.8	35	NR	10.5±3.2
				Metf+Glim	29		60.9±6.5	45	NR	9.3±2.5
Kotsanos *et al.*, 1997[47]	3-month x 2, open-label, crossover, no washout period reported	Eli Lilly	Canada, France, Germany, and US	ILis+NPH or UL	474	26 (2.8%)	58.2±9.9*	43	87.1% Caucasian	12.5±7.5*
				HI+NPH or UL						
Laube *et al.*, 1996[48]	3-month, open-label, crossover, no washout period reported	NR	Germany	ILis+NPH	7	0	57.9 [53 to 74]‡	NR	NR	16.6±4.6
				HI+NPH						
Lourens *et al.*, 2000[104]	3 months x 2, open-label, crossover, no washout period reported	Eli Lilly	South Africa	ILis+NPL	22	5 (11.1%)	58.34±1.91†	55	55% Caucasian, 5% Black, 41% Other	12.28±1.94†
				HI+NPH	23		56.89±2.38†	43	57% Caucasian, 4% Black, 39% Other	11.80±1.59†

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity (%)	Duration of DM, years
Malone *et al.*, 2003[115]	16-week, open-label, parallel	Eli Lilly	14	ILis Mix25+Metf	296	54 (9.0%)	58±8.8*	57	88.9% Caucasian	8.0±5.8*
				Glib+Metf	301		59±9.3*	49	89.0% Caucasian	7.4±5.4*
Niskanen *et al.*, 2004[31]	1-week open-label crossover	Novo Nordisk	Finland, Norway, Sweden, and UK	BIAsp30	264	8	62.3±9.2*	59	NR	12.1±7.1*
				ILis Mix25						
Raskin *et al.*, 1999[59] [abstract]	6-month, open-label, parallel	NR	NR	IAsp+NPH	91	NR	NR	NR	NR	≥2
				HI+NPH	91					≥2
Raz *et al.*, 2003[117]	6-week, open-label, parallel	Novo Nordisk	Israel	BIAsp30+Ros	26	5 (10.2%)	60.3±9.7* (43 to 77)	73	84.6% Caucasian, 3.8% Asian, 11.5% Other	10.9±5.2*
				Glib+Ros	23		57.8±7.9* (43 to 71)	57	82.6% Caucasian, 8.7% Asian, 8.7% Other	10.3±6.5*
Raz *et al.*, 2005[118]	18-week, open-label, parallel	Novo Nordisk	8 countries	BIAsp+Pio	93	36 (12.8%)	56.7±10.5*	53	NR	9.2±5.3*
				Glib+Pio	91		55.8±11.0*	52	NR	9.9±6.5*
Roach *et al.*, 2001[116]	4-month, open-label, parallel	Eli Lilly	Romania and Russia	ILis Mix25	85	18(10.3%)	58.7±8.9*	35	100% Caucasian	10.3±7.1*
				Glib	87		60.3±7.5*	36	100% Caucasian	10.2±6.2*
Roach *et al.*, 1999a[105]	3-month, open-label,	Eli Lilly	Spain, South Africa, and	ILis+NPL	44	9 (10.1%)	56.5	52	NR	12.8

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, years	% Male	Race/ Ethnicity (%)	Duration of DM, years
	crossover, no washout period reported		UK	HI+NPH	45		57.4	42		11.5
Roach *et al.*, 1999[49]	3-month, open-label, crossover, no washout period reported	Eli Lilly	5	ILis followed by HI	34	3 (3.0%)	58	53	NR	12.2
				HI followed by ILis	29		60.2	41		13.1
Ross *et al.*, 2001[106]	5.5-month, open-label, parallel	2 investigators from Eli Lilly	Canada	ILis+NPH	70	5 (3.4%)	59±1[†]	37	NR	10.9±0.9[†]
				HI+NPH	78		58±1[†]	38		11.2±0.8[†]
Schernthaner *et al.*, 2004[107]	Approxi-mately 12-weeks x 2, open-label, crossover, no washout period reported	Eli Lilly	Austria	ILis+NPL	18	5 (12.5%)	66.1±8.5*	17	NR	16.2±8.4*
				HI+NPH	17		67.8±8.4*	29		14.2±7.3*
Vignati *et al.*, 1997[50]	2-month x 2, open-label, crossover, no washout period reported	Eli Lilly	16	ILis+NPH	328	29 (4.1%)	57.6 [30 to 71][‡]	53	NR	12.8 [0.4 to 41.4][‡]
				HI+NPH						

*mean±SD; [†]mean±SE; [‡]mean [range]; **mean [90% CI]; [††]median [interquartile]; [‡‡]mean. BHI30/70=30% HI+70% NPH; BIAsp30=biphasic insulin aspart (30% aspart; 70% protamine insulin aspart); DM=diabetes mellitus; Glib=glibenclamide; Glim=glimepride; Gly=glyburide; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; Metf=metformin; Mix25=biphasic human lispro (25% lispro, 75 % neutral protamine lispro); NPH=neutral protamine Hagedorn; NPL=neutral protamine lispro; NR=not reported; PIA=protamine-crystallized IAsp; Pio=pioglitazone; RCTs=randomized controlled trials; Ros=rosiglitazone; Sfu=sulfonylurea (in Europe, generic glibenclamide); UL=ultralente.

APPENDIX 6C: CHARACTERISTICS OF RCTS IN GESTATIONAL DM

Study	Study Period	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, years	Race/ Ethnicity	Weeks of Gestation at Diagnosis
Ilic *et al.*, 1999[51] [Abstract]	Period NR, open-label, parallel	NR	US	ILis	19	NR	NR	NR	NR
				HI	22				
Jovanovic *et al.*, 1999[52]	As early as 14-week gestation to delivery, open label, parallel	Eli Lilly	US	ILis+NPH	19	1 (2.4%)	34.2±1.3*	89% Hispanic	NR
				HI+NPH	23		29.8±1.0*	100% Hispanic	
Mecacci *et al.*, 2003[53]	From 25-week gestation to delivery, parallel	NR	Italy	ILis	25	NR	34.5 [24 to 40]†	NR	28 [25 to 32]†
				HI	24		35 [28 to 41]†		28 [26 to 32]†

*mean±SE; †median [range]. DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; NR=not reported.

APPENDIX 7A: INCLUSION AND EXCLUSION CRITERIA FOR SELECTING PATIENTS IN THE RCTS FOR TYPE 1 DM

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Anderson *et al.*, 1997[77]	IDDM (WHO criteria); age 12 to 70 years; HI therapy ≥2 months prior to study	Other severe disease; BMI>35 kg/m^2; insulin dosage>2.0 U/kg; history of clinically significant hypoglycemia unawareness; pregnancy	1
Anderson *et al.*, 1997[45]	IDDM (WHO criteria) and age 12 to 70 years; NIDDM (WHO criteria) and age 35 to 70 years; HI therapy ≥2 months prior to study	Other severe disease; current use of OADs; insulin infusion therapy	1, 2
Annuzzi *et al.*, 2001[78]	Type 1 DM (WHO criteria); age 18 to 50 years; diagnosis of diabetes before age 35; interval between diagnosis and insulin therapy <1 year; diabetes duration >2 years; ≥3 daily insulin injections for >2 months; insulin dose >0.3 U/Kg; HbA1c 7.5% to 10.0%	History of cancer; cerebrovascular or symptomatic peripheral vascular disease; heart failure; liver or renal disease; visual impairment; pregnancy or lactation; clinically significant hypoglycemia unawareness	1
Arslanian *et al.*, 2005[54]	Type 1 DM for ≥12 months; age 6 to 18 years; HbA1c≤12.0%	NR	1
Bode *et al.*, 2002[69]	Type 1 DM for ≥12 months; fasting C-peptide <0.5 ng/ml; adult; CSII therapy continuously ≥3 months; BMI ≤35.0 kg/m^2; HbA1c 5.7% to 9.7%	Impaired hepatic function (liver enzymes 2 times upper limit of normal); impaired renal function (serum creatinine >2.0 mg/dL); impaired cardiac function; recurrent major hypoglycemia; pregnancy; lactation; women not using contraception	1
Bode and Strange, 2001[71]	Type 1 DM for 2 to 25 years prior to study; adult; C-peptide negative; CSII therapy with IAsp or buffered regular HI ≥7 weeks	Hypoglycemia unawareness; recurrent severe hypoglycemia; deficiency of hypoglycemic counter regulation; significant cardiovascular, renal, or retinal disease	1
Bott *et al.*, 2003[72]	Type 1 DM (WHO criteria) ≥2 years prior to study; adult; BMI ≤35.0 kg/m^2; HbA1c ≤11.0%; HI therapy ≥1 year previous to study	NR	1
Caixàs *et al.*, 1998[79]	Type 1 DM; previously treated with MII	Diabetic complications or other diseases known to affect lipid metabolism	1
Chan *et al.*, 2004[46]	Type 1 or 2 DM; age 18 to 70 years; twice-daily insulin regimen	Weakened liver function (liver enzymes 2 times upper limit of normal); impaired renal function (serum creatinine >300 µmol/L; cardiovascular events in previous 6 months; history of symptomatic peripheral vascular disease; pregnancy or planned pregnancy during study; lactation; inability to give self-injections; history of insulin allergies	1, 2
Ciofetta *et al.*, 1999[80]	Type 1 DM; C-peptide negative (plasma C-peptide <0.15 nmol/L, 6 minutes after 1 mg glucagon i.v.); adult; undergoing intensive insulin therapy	Microangiopathic complications	1
Danne *et al.*, 2005[55]	Preschool children with type 1 DM	NR	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Deeb *et al.*, 2001[60]	Type 1 DM for ≥12 months previous to study; prepubertal children; insulin therapy ≥2 months previous to randomization	NR	1
Del Sindaco *et al.*, 1998[102]	Type 1 DM; HbA1c 6.0% to 7.5%; undergoing intensive insulin therapy; C-peptide negative (plasma C-peptide <0.15 nmol/L)	Microangiopathic complications; autonomic neuropathy	1
Fairchild *et al.*, 2000[28]	Prepubertal (<Tanner stage 2 breast development in girls, <4 mL testicular volume in boys) **and had** diabetes for at least 12 months	Poor compliance **or glycemic control** (HbA1c>10%) **and** those with language or social difficulties	1
Ferguson *et al.*, 2001[81]	Type 1 DM for >5 years; adult; reduction in warning symptoms of hypoglycemia for ≥2 years; ≥2 episodes of severe hypoglycemia in previous 2 years; HbA1c <13.0%	Systemic renal or hepatic disease; pregnancy	1
Ford-Adams *et al.*, 2003[61]	Type 1 DM for >1 year; prepubertal children; 3 times daily insulin regimen (isophane insulin and soluble insulin)	Previous use of ILis; diabetic complications; obesity (BMI <97th centile for age); other chronic diseases; HbA1c>12%; repeated severe hypoglycemia	1
Gale, 2000[73]	Type 1 DM for >1 year, developed before age 40; adult; HbA1c<1.5 times upper limit of non-diabetic range; insulin dose 4 times daily, injected within 15 minutes of meals on >50% of occasions	Major complications due to diabetes	1
Garg *et al.*, 1996[82]	Type 1 DM (WHO criteria); currently treated with NPH or ultralente	NR	1
Hedman *et al.*, 2001[88]	Type 1 DM; adult; currently using CSII therapy	NR	1
Heller *et al.*, 2004[70]	Type 1 DM for ≥2 years; adult; BMI≤35 kg/m^2; HbA1c<9.0%	Impaired renal or hepatic function; uncontrolled hypertension; cardiac problems; progressed late-diabetic complications; drug or alcohol abuse; concurrent use of systemic corticosteroids	1
Heller *et al.*, 1999[93]	Type 1 DM for ≥2 years; adult; basal-bolus regimen for ≥3 months; HbA1c<8.0%; desire for tight glucose control	Proliferative retinopathy; symptomatic peripheral neuropathy; serum creatinine >250 µmol/L; admittance to hospital >3 times with severe hypoglycemia in previous 12 months	1
Holcombe *et al.*, 2002[62]	Type 1 DM (WHO criteria); use of regular insulin≥12 months before randomization; age 9 to 18 years and reached Tanner stage II puberty (genital or breast development)	NR	1
Holleman *et al.*, 1997[83]	Type 1 DM (WHO criteria); age 18 to 65 years; use of insulin ≥1 year including MDI ≥3 months; HbA1c ≤1.5 times top normal range	History of hypoglycemia unawareness; >2 hospitalizations for hypoglycemia in last year	1
Home *et al.*, 1998[67]	Type 1 DM; age 18 to 60 years; BMI≤29.0 kg/m^2; HbA1c<9.0%	Active proliferative retinopathy; nephropathy; recurrent severe hypoglycemia; insulin resistance; other systemic diseases; drug abuse; women	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Home *et al.*, 2000[96]	Type 1 DM (WHO criteria) for ≥2 years; adult; use of insulin ≥1 year; BMI≤35.0 kg/m²; HbA1c≤11.0%	Active proliferative retinopathy; nephropathy (serum creatinine >150 µmol/L); recurrent severe hypoglycemia; significant cardiovascular disease; use of systemic corticosteroids; insulin dosage >1.4 U/kg/day; pregnancy; drug abuse	1
Home *et al.*, 2006[100]	Type 1, >18 years old ≥2 years, HbA1c≤11.0%; use of insulin ≥1 year; BMI≤35.0 kg/m²	Evidence of significant late diabetic complications, any other significant disease or condition likely to affect trial outcomes or requiring >1.4 U/kg/day insulin	1
Iwamoto *et al.*, 2001[97]	Type 1 DM	NR	1
Jacobs *et al.*, 1997[66]	Type 1 DM; HbA1c 6.8±0.9%; MDI with short-acting insulin and NPH at bedtime; C-peptide <0.07 nmol/L (6 minutes after 1 mg i.v. glucagons stimulation); BMI<30 kg/m²	Serious underlying disease; nephropathy; proliferative retinopathy, pregnancy; history of hypoglycemia unawareness; >2 hospitalizations for hypoglycemia in the last year	1
Janes *et al.*, 1997[56]	IDDM	NR	1
Jansson *et al.*, 1998[85]	Type 1 DM (WHO criteria); age 18 to 60 years; duration of diabetes ≥5 years; HbA1c 7.5% to 9.0%	Proliferative retinopathy, overt nephropathy (serum creatinine >200 µmol/L) or other concomitant diseases	1
Johansson *et al.*, 2000[89]	Type 1 DM; adult; CSII therapy ≥6 months prior to study; HbA1c≤9.0%; post-prandial p-C-peptide <0.25 nmol/L	Pregnancy	1
Kotsanos *et al.*, 1997[47]	A: Type 1 DM (WHO criteria); age 12 to 70 years; HI use ≥2 months before study with optimum compliance B: Type 2 DM (WHO criteria); age 35 to 85 years; HI use ≥2 months prior to study with optimum compliance	Cancer; cerebrovascular or symptomatic peripheral vascular disease; cardiac class III or IV; renal transplantation or dialysis; liver disease, acute or chronic hepatitis, or aspartate transaminase >2 times upper normal limit; drug or alcohol abuse; life expectancy of <3 years; allergy to insulin; pregnancy; women not practicing birth control; lactation; serum creatinine >264 µmol/L; CSII therapy; participation in clinical trial within last 6 months; insulin dosage >2.0 U/kg; BMI<35 kg/m²; history of hypoglycemia unawareness; >2 hospitalizations for hypoglycemia in past year; adrenal insufficiency; hemoglobinopathy or chronic anemia	1, 2
Linkeschova *et al.*, 2003[57]	Type 1 DM; CSII therapy	NR	1
Mathiesen *et al.*, 2007[29]	Subjects age ≥18 years with insulin-treated type 1 DM for ≥12 months and were pregnant with a singleton pregnancy (gestational age ≤10 weeks) or planning to become pregnant. A1C was ≤8% at confirmation of pregnancy.	Subjects not pregnant at screening were withdrawn if not pregnant ≤12 months after randomization. Subjects with multiple pregnancy, fertility treatment, clinically significant gynecological conditions, diabetic nephropathy, or medical problems or previous child born with major congenital malformation, multiple miscarriage, or stillbirths (>2) were excluded.	1
Melki *et al.*, 1998[94]	Type 1 DM; treated with HI by CSII≥1 year prior to study; HbA1c<8.5%; negative C-peptide response after intravenous injection of 1 mg	Untreated retinopathy; impaired renal function; gastric neuropathy; BMI>30 kg/m²; daily insulin dose >2 IU/kg; history of hypoglycemia unawareness, or any severe disease that could interfere with the study	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
	glucagon; anti-insulin antibodies <70%		
Persson *et al.*, 2002[65]	Type 1 DM (onset before age 35, requiring insulin treatment within 1 year of diagnosis); pregnancy	NR	1
Provenzano *et al.*, 2001[86]	Type 1 DM; adult; optimum diabetic diet compliance; use of s.c. HI ≥2 months before study	NR	1
Raskin *et al.*, 2000[98]	Type 2 DM for ≥18 months; age 18 to 75 years; BMI<35.0 kg/m^2; HbA1c<11%	Impaired hepatic, renal, or cardiac function; recurrent major hypoglycemia; active proliferative retinopathy; insulin dosage ≥1.4 IU/kg; pregnancy; lactation; women not practicing birth control	1
Raskin *et al.*, 2001[90]	Type 1 DM (WHO criteria); age 13 to 60 years; acceptable compliance with CSII and nutritional regimen; CSII therapy ≥6 months before study	HbA1c>2 times upper limit of normal; clinically significant renal, hepatic, or cardiac disease; cancer; drug or alcohol abuse; insulin allergy; recurrent severe hypoglycemia; anemia; life expectancy of <3 years; pregnancy; lactation; intention of pregnancy; requiring dilution of insulin in pump	1
Recasens *et al.*, 2003[68]	Type 1 DM (NDDG criteria) newly diagnosed	NR	1
Renner *et al.*, 1999[91]	Type 1 DM (WHO criteria) for >2 years; CSII therapy ≥6 months before study	Insulin allergy; cardiovascular or cerebrovascular symptoms of atherosclerosis; cancer; renal or hepatic failure; drug abuse; life-threatening disease; pregnancy; lactation; intention of pregnancy	1
Roach *et al.*, 1999[49]	Type 1 or 2 DM (WHO criteria); age 18 to 70 years; use of HI 2 times daily ≥120 days before study	HbA1c>9.2%; significant renal, hepatic, or cardiac disease; cancer; drug or alcohol abuse; insulin allergy; recurrent severe hypoglycemia; anemia; hemoglobinopathy; treatment with OADs; use of systemic glucocorticoids; insulin dosage >2.0 U/kg daily	1, 2
Schmauβ *et al.*, 1998[95]	Type 1 DM; age 18 to 65 years; use of intensified insulin therapy ≥2 years; CSII therapy ≥6 months before study	Insulin allergy; severe complications of diabetes; HbA1c>10%; life-threatening disease; drug abuse; pregnancy; intention of pregnancy	1
Tamás *et al.*, 2001[99]	Type 1 DM (WHO criteria) for ≥2 years; age 18 to 70 years; treated with intensified meal-time+basal insulin regimen; BMI≤35 kg/m^2; HbA1c 7.0% to 10.0%	Insulin requirements of >1.4 U/kg/day; active proliferative retinopathy or nephropathy (serum creatinine >150 µmol/L); recurrent severe hypoglycemia; hypoglycemia unawareness; significant cardiovascular or hepatic disease; systemic corticosteroid treatment; pregnancy; abuse of drugs	1
Tubiana-Rufi *et al.*, 2004 [64]	Type 1 DM; prepubertal children; CSII therapy ≥3 months	NR	1
Tupola *et al.*, 2001[63]	Type 1 DM ≥1 year; age<10 years with no signs of puberty; insulin dosage >0.5 U/kg daily	Insulin allergy; other chronic diseases; previous treatment with ILis	1
Valle *et al.*, 2001[87]	Type 1 DM; insulin treatment ≥60 days prior to study; HbA1c≥7.5%	Clinically relevant concomitant disease; insulin allergy; daily insulin dose >2 IU/kg; clinically significant unawareness of hypoglycemia or >2 hospitalizations for hypoglycemia in previous year	1
Vignati *et al.*, 1997[50]	Type 1 or 2 DM (WHO criteria); use of HI+NPH 2 times daily ≥2 months	Other severe concomitant disease; use of oral hypoglycemic agents	1, 2

Study	Inclusion Criteria	Exclusion Criteria	DM Type
	prior to study; age 18 to 70 years		
Zinman *et al.*, 1997[92]	Type 1 DM; adult; CSII therapy ≥3 months	Severe retinopathy; neuropathy; >1 severe hypoglycemic episode in past year	1

BMI=body mass index; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; HbA1c=glycosylated hemoglobin; HI=human insulin; IAsp=insulin aspart; IDDM=insulin-dependent diabetes mellitus; ILis=insulin lispro; i.v.=intravenous; MDI=multiple daily injections; MII=multiple insulin injections; NDDG=National Diabetes Data Group; NIDDM=non-insulin-dependent diabetes mellitus; NPH=neutral protamine Hagedorn; NR=not reported; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; s.c.=subcutaneous; WHO=World Health Organization.

APPENDIX 7B: INCLUSION AND EXCLUSION CRITERIA FOR SELECTING PATIENTS IN THE RCTS FOR TYPE 2 DM

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Altuntas *et al.*, 2003[74]	Type 2 DM (ADA criteria); secondary OAD failure using maximal doses of a sulfonylurea	NR	2
Anderson *et al.*, 1997[103]	NIDDM (WHO criteria); age 35 to 85 years; HI therapy ≥2 months before study	Other severe disease; β-adrenergic receptor blocking therapy; glucocorticoids therapy; insulin infusion therapy; history of severe hypoglycemia unawareness; insulin dosage >2.0 U/kg; BMI>35 kg/m^2	2
Anderson *et al.*, 1997[45]	IDDM (WHO criteria) and age 12 to 70 years; NIDDM (WHO criteria) and age 35 to 70 years; HI therapy ≥2 months before study	Other severe disease; current use of OADs; insulin infusion therapy	1, 2
Bastyr *et al.*, 2000[119]	Type 2 DM (WHO criteria); secondary oral agent failure; HbA1c<8.5%; >20% of all FBG>8.9 µmol/L and/or before a meal BG>10 mmol/L after maximal doses of a sulfonylurea during 1-week period before initial visit	NR	2
Bastyr *et al.*, 1999[111]	Type 2 DM (WHO criteria); secondary oral agent failure; FBG>7.8 mmol/L (140 mg/dL) or post-prandial BG>10 mmol/L (180 mg/dL) ≥3 times in preceding 3 months or HbA1c>150% upper limit of the non-diabetic range	NR	2
Boehm *et al.*, 2004[108]	Type 2 DM for >24 months previous to study; age ≥18 years; BMI ≤35.0 kg/m^2; HbA1c≤11.0%; using either biphasic insulin or mix of short- and intermediate-acting insulin in a twice-daily regimen (total daily doses <1.4 U/kg)	Use of oral glucose-lowering drugs in the previous month	2
Bretzel *et al.*, 2004[75]	Type 2 DM (WHO criteria) >1 year prior to study; age ≥35 years; antidiabetic agents >1 year; HbA1c≤10.0%; BMI 23 to 37 kg/m^2	Unstable/untreated proliferative retinopathy; clinical significant nephropathy, neuropathy, or hepatic disease; heart failure; uncontrolled hypertension; systemic treatment with corticosteroids; insulin dosage >1.4U/kg	2
Chan *et al.*, 2004[46]	Type 1 or 2 DM; age 18 to 70 years; twice-daily insulin regimen	Weakened liver function (liver enzymes 2 times upper limit of normal); impaired renal function (serum creatinine >300µmol/L; cardiovascular events in previous 6 months; history of symptomatic peripheral vascular disease; pregnancy or planned pregnancy during study; lactation; inability to give self-injections; history of insulin allergies	1, 2

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Forst *et al.*, 2003[112]	Type 2 DM; OAD therapy; age 35 to 70 years; HbA1c<1.7 times upper limit of normal; C-peptide response ≥ 0.4 nmol/L after i.v. administration of 1.0 mg glucagon	Insulin therapy	2
Gallagher and Home, 2005 [109]	Type 2 DM, currently treated with insulin	NR	2
Herz *et al.*, 2002[120]	Type 2 DM; adult; HbA1c <10%	BMI>35 kg/m^2; use of OAD therapy; use of systemic glucocorticoids; insulin dosage >2.0 U/kg	2
Herz *et al.*, 2002[113]	Type 2 DM for >1 year; treated with oral anti-hyperglycemic agent for >6 months and treated with maximum dose of a sulfonylurea for ≥1 month before study; age 60 to 80 years; HbA1c>1.2 times upper limit of normal range; FBG>7.8 mmol/L at least 2 times during 4-week lead-in period	Treatment with insulin in last 6 months; treatment with oral anti-hyperglycemic other than a sulfonylurea or acarbose; proliferative diabetic retinopathy; history is IHD or NYHA Class III or IV cardiac disease; liver disease; renal dialysis or renal transplantation; known allergy to insulin BMI>35 kg/m^2	2
Herz *et al.*, 2003[76]	Type 2 DM (WHO criteria); age 40 to 70 years; HbA1c<10%; treatment with HI 30/70 2 times daily ≥3 months before study	Injection of HI 30 to 45 minutes before meals; BMI>35 kg/m^2; use of oral anti-hyperglycemic agents; use of systemic glucocorticoids; insulin dosage >2.0 U/kg	2
Iwamoto, 2003 [abstract][58]	Type 2 DM; Japanese population	NR	2
Kilo *et al.*, 2003[110]	Type 2 DM (ADA); body weight ≤100 kg; BMI ≤40 kg/m^2; naïve to insulin treatment; HbA1c ≥7.5% on ≥3-month therapy with Metf alone or combined with a sulfonylurea or repaglinide	Significantly impaired hepatic or renal function or significant cardiac disease, unstable angina pectoris, or an MI within 12 months	2
Kokic *et al.*, 2003[114]	Type 2 DM; HbA1c>8.5%, FBG>8.9 mmol/L in more than 20% of recorded BG values and/or BG>10 mmol/L before meal after maximal doses of a sulfonylurea during ≥ 3 months previous to study	NR	2
Kotsanos *et al.*, 1997[47]	A: Type 1 DM (WHO criteria); age 12 to 70 years; HI use ≥2 months before study with optimum compliance B: Type 2 DM (WHO criteria); age 35 to 85 years; HI use ≥2 months before study with optimum compliance	Cancer; cerebrovascular or symptomatic peripheral vascular disease; cardiac class III or IV; renal transplantation or dialysis; liver disease, acute or chronic hepatitis or aspartate transaminase >2 times upper normal limit; drug or alcohol abuse; life expectancy of <3 years; allergy to insulin; pregnancy; women not practicing birth control; lactation; serum creatinine >264 µmol/L; CSII therapy; participation in clinical trial within last 6 months; insulin dosage >2.0 U/kg; BMI <35 kg/m^2; history of hypoglycemia unawareness; >2 hospitalizations for hypoglycemia in past year; adrenal insufficiency; hemoglobinopathy or chronic anemia	1, 2

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Laube *et al.*, 1996[48]	Type 1 or 2 DM	NR	1, 2
Lourens *et al.*, 2000[104]	Type 2 DM (WHO criteria); treated with twice daily insulin for ≥30 days before study; HbA1c≤150% of upper limit of normal	Significant cardiac, renal, or liver disease; insulin allergy; use of oral agents within 14 days of study entry; chronic systemic glucocorticoid therapy; insulin dose >2.0 units/kg	2
Malone *et al.*, 2003[115]	Type 2 DM (WHO criteria); ages 30 to 75; BMI<40 kg/m^2; HbA1c>125% upper limit of normal; using a single oral-antidiabetic agent for ≥3 months prior to study at a maximally clinically effective dose within the last 30 days	NR	2
Niskanen *et al.*, 2004[31]	Type 2 DM patients on insulin therapy for the past 6 months, total daily insulin dose <1.80 IU/kg, age≥18 years, HbA1c ≤12%, BMI≤35kg/m^2. Patients had to be eligible for b.i.d. mixed insulin treatment and willing to perform self-monitoring of BG.	Previous treatment with insulin analogues or use of oral hypoglycemic agents within the last four weeks; abnormal renal, hepatic, or cardiac function; severe uncontrolled hypertension; known or suspected allergy to trial drugs; pregnancy or drug or alcohol abuse.	2
Raskin *et al.*, 1999[59]	Type 2 insulin-requiring, diabetes ≥2 years, and treated with HI for ≥12 months	NR	2
Raz *et al.*, 2003[117]	Type 2 DM based on etiology; age≥30 yrs; BMI≤35 kg/m^2; not responding to glibenclamide monotherapy; treated with glibenclamide (7.5 to 15.0 mg/day) as the only antidiabetic therapy for ≥ 4 weeks prior to screening; HbA1c 8.0% to 13.0%	Significant disease or condition (including history of drug or alcohol dependence, impaired hepatic function, or cardiac disease) or other condition deemed by the investigator as likely to affect the trial or health outcomes	2
Raz *et al.*, 2005[118]	Type 2 DM (male and female) aged ≥18 years; BMI≤40 kg/m^2, treatment with SFU (any SFU as monotherapy or combination therapy) ≥ 3 months before screening, and sufficient glycemic control (HbA1c, 7.4% to 14.7%)	Patients with any significant disease or condition (including history of drug or alcohol dependence, impaired hepatic function, or cardiac disease) likely to affect trial or health outcomes. Women who were pregnant or possibly pregnant were excluded, in addition to those judged not to be using adequate contraceptive measures.	2
Roach *et al.*, 1999[49]	Type 1 or 2 DM (WHO criteria); age 18 to 70 years; use of HI 2 times daily ≥120 days before study	HbA1c>9.2%; significant renal, hepatic or cardiac disease; cancer; drug or alcohol abuse; insulin allergy; recurrent severe hypoglycemia; anemia; hemoglobinopathy; treatment with OADs; use of systemic glucocorticoids; insulin dosage >2.0 U/kg daily	1, 2
Roach *et al.*, 1999[105]	Type 2 DM (WHO criteria); age 18 to 75 years; insulin therapy (mixtures of long- and short-acting insulin) 2 times daily ≥30 days before study	HbA1c>9.2%; significant renal, hepatic or cardiac disease; cancer; drug or alcohol abuse; insulin allergy; recurrent severe hypoglycemia; anemia; hemoglobinopathy; proliferative retinopathy; BMI<35 kg/m^2; pregnancy; lactation; intention of pregnancy; treatment with OADs; use of systemic	2

Study	Inclusion Criteria	Exclusion Criteria	DM Type
		glucocorticoids; insulin dosage >2.0 U/kg	
Roach *et al.*, 2001[116]	Type 2 DM (WHO criteria) for ≥3 months; age ≥30 years; treated with glyburide for ≥3 months; HbA1c>1.4 times upper limit of normal; fasting BG >7.8 mmol/L or post-prandial BG>10 mmol/L	BMI>32 kg/m2; serum creatinine >176 µmol/L; proliferative retinopathy; hemoglobinopathy; adrenal insufficiency; known allergy to insulin or excipients; history of IHD; liver disease or hepatitis	2
Ross *et al.*, 2001[106]	Type 2 DM; using maximum-tolerated doses of oral hypoglycemic agents (Metf and sulfonylurea) without achieving acceptable glycemic control; HbA1c>130% upper normal limit; not on long-term insulin therapy	Severe retinopathy; neuropathy; >2 severe hypoglycemic episodes in past year	2
Schernthaner *et al.*, 2004[107]	Type 2 DM (WHO criteria) diagnosed after age 35 years; long-standing DM; use of insulin	Severe diabetic complications; cardio/cerebrovascular disease; renal disease; liver disease	2
Vignati *et al.*, 1997[50]	Type 1 or 2 DM (WHO criteria); use of HI+NPH 2 times daily ≥2 months before study; age 18 to 70 years	Other severe concomitant disease; use of oral hypoglycemic agents	1, 2

ADA=American Diabetes Association; BG=blood glucose; b.i.d.=twice a day; BMI=body mass index; DM=diabetes mellitus; FBG=fasting plasma glucose; IHD=ischemic heart disease; Metf=metformin; MI= myocardial infarction; NIDDM=non-insulin-dependent diabetes mellitus; NR=not reported; NYHA=New York Heart Association; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SFU=sulfonylurea; WHO=World Health Organization.

APPENDIX 7C: INCLUSION AND EXCLUSION CRITERIA FOR SELECTING PATIENTS IN THE RCTS FOR GESTATIONAL DM

Study	Inclusion Criteria	Exclusion Criteria
Ilic *et al.*, 1999[51]	Women with gestational DM	NR
Jovanovic *et al.*, 1999[52]	Gestational DM diagnosed at 14 to 32 weeks gestation (NDDG criteria) with inadequate glucose control using diet and exercise (adequate control=pre-prandial glucose <90 mg/dL and 1 hour post-prandial glucose <120 mg/dL); ultrasound documentation of anatomically normal fetus	Prior treatment with insulin; pre-gestational diabetes; significant concurrent organic disease
Mecacci *et al.*, 2003[53]	Gestational diabetes (Carpenter and Coustan criteria) contracted at 25 to 32 weeks; Caucasian; singleton pregnancy; pre-gestational BMI 19 to 25 kg/m^2	NR

BMI=body mass index; DM=diabetes mellitus; NDDG=National Diabetes Data Group; NR=not reported; RCT=randomized controlled trials.

APPENDIX 8A: QUALITY ASSESSMENT OF TRIALS FOR RAPID-ACTING INSULIN ANALOGUES IN PATIENTS WITH TYPE 1 DM

Study	Score on Jadad Scale for			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat	Number of Patients	Dropout Number (%)
	Randomization	Double Blinding	Withdrawals and Dropouts						
Anderson *et al.*, 1997 [77]	1	0	0	1	Unclear	NR	Yes	1,008	48 (4.8%)
Anderson *et al.*, 1997 [45]	1	0	0	1	Unclear	NR	Yes	336 type 1	151(45%)
Annuzzi *et al.*, 2001[78]	1	0	0	1	Unclear	NR	NR	85	5 (5.9%)
Bode and Strange, 2001[71]	1	0	1	2	Unclear	NR	NR	29	1 (3.4%)
Bode *et al.*, 2002[69]	1	0	1	2	Unclear	NR	NR	146	14 (9.6%)
Bott *et al.*, 2003 [72]	1	0	0	1	Unclear	NR	NR	424	NR
Caixàs *et al.*, 1998 [79]	1	0	0	1	Unclear	NR	NR	10	NR
Chan *et al.*, 2004 [46]	1	0	0	1	Unclear	NR	NR	12 type 1	NR
Ciofetta *et al.*, 1999 [80]	1	0	0	1	Unclear	NR	NR	24	NR
Deeb *et al.*, 2001 [60]	1	0	1	2	Unclear	NR	NR	61	2 (3.3%)
Del Sindaco *et al.*, 1998 [102]	1	0	0	1	Unclear	NR	NR	69	NR
Fairchild *et al.*, 2000 [28]	1	0	1	2	Unclear	NR	NR	70	0
Ferguson *et al.*, 2001 [81]	1	0	1	2	Unclear	NR	NR	39	5 (12.8%)
Ford-Adams *et al.*, 2003 [61]	1	0	1	2	Adequate	Partially	Yes	23	None
Gale, 2000 [73]	1	2	1	4	Unclear	Yes	Yes	93	6 (6.5%)
Garg *et al.*, 1996 [82]	1	0	1	2	Unclear	NR	No	39	2 (5.1%)

Study	Score on Jadad Scale for			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat	Number of Patients	Dropout Number (%)
	Randomiza-tion	Double Blinding	Withdrawals and Dropouts						
Hedman *et al.*, 2001[88]	1	0	1	2	Unclear	NR	Yes	12	None
Heller *et al.*, 1999[93]	1	0	1	2	Unclear	NR	Yes	135	1 (0.7%)
Heller *et al.*, 2004[70]	2	1	1	4	Adequate	NR	NR	155	16 (10.3%)
Holcombe *et al.*, 2002[62]	1	0	1	2	Unclear	NR	Yes	481	18 (3.7%)
Holleman *et al.*, 1997[83]	1	0	1	2	Unclear	NR	Yes	199	10 (5.0%)
Home *et al.*, 1998[67]	1	1	1	3	Unclear	NR	Yes	104	14 (13.5%)
Home *et al.*, 2000[96]	1	0	1	2	Unclear	NR	Yes	1070	59 (5.5%)
Home *et al.*, 2006[100]	1	0	1	2	Unclear	NR	Yes	753	155 (21%)
Iwamoto *et al.*, 2001[97]	1	0	0	1	Unclear	NR	Yes	211	15 (7.1%)
Jacobs *et al.*, 1997[66]	1	0	0	1	Unclear	NR	NR	12	NR
Jansson *et al.*, 1998[85]	1	0	0	1	Unclear	NR	NR	84	NR
Johansson *et al.*, 2000[89]	1	0	1	2	Unclear	NR	Yes	41	0
Kotsanos *et al.*, 1997[47]	1	0	1	2	Unclear	NR	NR	468 type 1	26 (2.8%)
Mathiesen *et al.*, 2007[29]	1	0	1	2	Unclear	NR	Yes	322	58 (18%)
Melki *et al.*, 1998[94]	1	0	1	2	Unclear	NR	NR	39	1 (2.5%)
Persson *et al.*, 2002[65]	1	0	0	1	Unclear	NR	Yes	33	NR
Provenzano *et al.*, 2001[86]	2	0	0	2	Unclear	NR	NR	12	NR
Raskin *et al.*, 2001[90]	1	0	1	2	Unclear	NR	Yes	58	4 (6.9%)

Study	Score on Jadad Scale for			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat	Number of Patients	Dropout Number (%)
	Randomiza-tion	Double Blinding	Withdrawals and Dropouts						
Raskin *et al.*, 2000[98]	1	0	1	2	Unclear	NR	Yes	882	67 (7.6%) after 6 months; additional 39 after subsequent 6 months
Recasens *et al.*, 2003[68]	1	0	0	1	Unclear	NR	NR	45	NR
Renner *et al.*, 1999[91]	1	0	0	1	Unclear	NR	NR	113	NR
Roach *et al.*, 1999[49]	1	0	1	2	Unclear	No	Yes	37 type 1	3 (3.0%)
Schmau *et al.*, 1998[95]	1	0	1	2	Unclear	NR	Yes	11	0
Tamás *et al.*, 2001[99]	2	0	0	2	Unclear	NR	Yes	426	16 (3.5%)
Tubiana-Rufi *et al.*, 2004[64]	1	0	1	2	Unclear	NR	No	29	2 (6.9%)
Tupola *et al.*, 2001[63]	1	0	1	2	Unclear	NR	No	24	2 (8.3%)
Valle *et al.*, 2001[87]	1	0	0	1	Unclear	NR	Yes	1,184	NR
Vignati *et al.*, 1997[50]	2	0	1	3	Unclear	NR	NR	379 type 1	29 (4.1%)
Zinman *et al.*, 1997[92]	1	1	1	3	Unclear	NR	Yes	30	0

No quality assessments were performed on trials published only as abstracts or posters, due to limited information; DM=diabetes mellitus; NR=not reported.

APPENDIX 8B: QUALITY ASSESSMENT OF TRIALS FOR RAPID-ACTING INSULIN ANALOGUES IN PATIENTS WITH TYPE 2 DM

Study	Score on Jadad Scale for			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat	Number of Patients	Dropout Number (%)
	Randomization	Double Blinding	Withdrawals and Dropouts						
Altuntas *et al.*, 2003[74]	1	0	1	2	Unclear	NR	Yes	60	0
Anderson *et al.*, 1997[103]	1	0	0	1	Unclear	NR	Yes	722	36 (5.0%)
Anderson *et al.*, 1997[45]	1	0	0	1	Unclear	NR	Yes	295 type 2	105 (36%)
Bastyr *et al.*, 1999[111]	2	0	1	2	Unclear	NR	Yes	423	27 (6.4%)
Bastyr *et al.*, 2000[119]	1	0	1	2	Unclear	NR	Partially	135	17 (12.6%)
Boehm *et al.*, 2004[108]	2	0	1	3	Unclear	NR	Yes	125	30 (24.0%)
Bretzel *et al.*, 2004[75]	1	0	1	2	Unclear	NR	Yes	231	27 (11.7%)
Chan *et al.*, 2004[46]	1	0	0	1	Unclear	NR	NR	18 type 2	NR
Forst *et al.*, 2003[112]	1	0	0	1	Unclear	NR	Yes	143	NR
Gallagher and Home, 2005[109]	2	1	1	4	Unclear	NR	NR	21	3 (14.3%)
Herz *et al.*, 2002[120]	1	0	1	2	Unclear	NR	Yes	37	4 (10.8%)
Herz *et al.*, 2003[76]	1	0	1	2	Unclear	NR	Yes	25	4 (16.0%)
Herz *et al.*, 2002a[113]	1	0	1	2	Unclear	NR	Yes	143	16 (11.2%)
Kilo *et al.*, 2003[110]	1	0	1	2	Unclear	NR	Yes	140	9 (6.4%)
Kokic *et al.*, 2003[114]	1	0	0	1	Unclear	NR	NR	87	NR
Kotsanos *et al.*, 1997[47]	1	0	1	2	Unclear	NR	NR	474 type 2	26 (2.8%)
Laube *et al.*, 1996[48]	1	0	0	1	Unclear	NR	NR	7 type 2	0
Lourens *et al.*, 2000[104]	1	0	1	2	Unclear	NR	Yes	45	5 (11.1%)
Malone *et al.*, 2003[115]	1	0	1	2	Unclear	NR	Yes	597	54 (9.0%)
Niskanen *et al.*, 2004[31]	2	0	1	3	Adequate	NR	Yes	264	8 (3%)
Raz *et al.*, 2003[117]	1	0	1	2	Unclear	NR	Yes	49	5 (10.2%)
Raz *et al.*, 2005[118]	1	0	1	2	Unclear	NR	Yes	281	36 (12.8%)
Roach *et al.*, 1999[105]	1	0	1	2	Unclear	NR	Yes	89	9 (10.1%)
Roach *et al.*, 1999[49]	1	0	1	2	Unclear	no	Yes	63 type 2	3 (3.0%)
Roach *et al.*, 2001[116]	2	0	1	3	Unclear	Yes	Yes	175	18(10.3%)

Study	Score on Jadad Scale for			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat	Number of Patients	Dropout Number (%)
	Randomization	Double Blinding	Withdrawals and Dropouts						
Ross *et al.*, 2001[106]	1	0	1	2	Unclear	NR	Yes	148	5 (3.4%)
Schernthaner *et al.*, 2004[107]	1	0	1	2	Unclear	NR	No	40	5 (12.5%)
Vignati *et al.*, 1997[50]	2	0	1	3	Unclear	NR	NR	328 type 2	29 (4.1%)

Note: No quality assessments were performed on trials published only as abstracts or posters, due to limited information; NR=not reported.

APPENDIX 8C: QUALITY ASSESSMENT OF TRIALS FOR RAPID-ACTING INSULIN ANALOGUES IN GESTATIONAL DM

Study	Score on Jadad Scale			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat	Number of Patients	Dropout number (%)
	Randomization	Double Blinding	Withdrawals and Dropouts						
Jovanovic *et al.*, 1999[52]	2	0	0	2	Unclear	NR	NR	42	1 (2%)
Mecacci *et al.*, 2003[53]	1	0	1	2	Unclear	NR	No	49	NR

No quality assessments were performed on trials published only as abstracts or posters, due to limited information; $ blinding for the lab measurements. DM=diabetes mellitus; NR=not reported.

APPENDIX 9A: HbA1C DATA IN PATIENTS WITH TYPE 1 DM

		HbA1c					Plasma Glucose, mmol/L (mg/dL)				
Study	**Comparators**	**HbA1c at Baseline (%)**	**HbA1c at Endpoint (%)**	**HbA1c Change from Baseline**	**p-value Endpoint versus Baseline**	**p-value between Treatments**	**Fasting**	**Pre-prandial**	**1-Hour Post-Prandial**	**2- Hour Post-Prandial**	**p-value between Treatments**
Anderson *et al.*, 1997[77]	ILis+NPH or UL	8.5±0.1†	8.2±0.1†	NR	p<0.01	NS	NR	11.6±0.2†	12.9±0.2†	11.2±0.2†	1 and 2 hours post-prandial p<0.001
	HI+NPH or UL	8.5±0.1†	8.2±0.1†	NR	p<0.01		NR	11.3±0.2†	13.9±0.2†	12.9±0.2†	
Anderson *et al.*, 1997[45]	ILis+basal	8.2±0.1†	8.1±0.1†	NR	NS	p<0.05	NR	NR	NR	NR	NR
	HI+basal	8.2±0.1†	8.3±0.1†	NR	NS						
Annuzzi *et al.*, 2001[78]	ILis+NPH	8.67±0.72*	8.12±0.85*	NR	NR	p<0.05	NR	NR	NR	NR	NR
	HI+NPH	8.67±0.72*	8.27±0.79*	NR	NR						
Arslanian *et al.*, 2005 (Poster)[54]	IAsp+NPH	8.3±1.2*	8.4±1.4*	0.1±1.0*	NR	NR	NR	NR	NR	NR	NR
	ILis+NPH	8.4±1.2*	8.2±1.2*	-0.1±1.0*	NR						
	HI+NPH	8.3±1.3*	8.5±1.4*	0.1±1.1*	NR						
Bode and Strange, 2001[71]	IAsp+basal	7.2±0.8*	6.9±0.6*	NR	NS	p>0.05	NR	NR	NR	NR	NR
	HI+basal	7.2±0.9*	7.1±0.6*	NR	NS						
Bode *et al.*, 2002[69]	IAsp+basal	7.3±0.7*	NR	0.00±0.51†	NS	NS	NR	NR	NR	NR	NR

		HbA1c					Plasma Glucose, mmol/L (mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-Prandial	2- Hour Post-Prandial	p-value between Treatments
	ILis+basal	7.3±0.7*	NR	0.18±0.84†	NS						
	HI+basal	7.5±0.8*	NR	0.15±0.63†	NS						
Caixàs *et al.*, 2004[79]	ILis+UL	7.13±1.2*	7.06±1.3*	NR	NS	NS	9.11±4.1*	NR	NR	8.79±4.1*	NR
	HI+UL	7.13±1.2*	6.82±0.8*	NR	NS		10.2±4.0*	NR	NR	9.57±4.0*	
Chan *et al.*, 2004[46]	ILis+NPH	9.0±2.2*	6.8	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	9.0±2.2*	6.6	NR	NR						
Ciofetta *et al.*, 1999[80]	ILis+NPH	6.89±0.16†	6.96±0.2†	NR	NR	ILis+NPH versus HI+NPH, NS; ILis+NPH versus ILis/NPH+NPH, p<0.05 ILis/NPH+NPH versus HI+NPH, p<0.05	NR	NR	NR	NR	NR
	ILis/NPH+NPH	6.83±0.18†	6.41±0.12†	NR	NR						
	HI+NPH	6.79±0.17†	6.84±0.2†	NR	NR						
Danne *et al.*, 2005 [Abstract][55]	IAsp+basal	NR	~7.7	NR	NR	NS	NR	NR	NR	NR	NR
	HI+basal	NR	~7.7	NR	NR						
Deeb *et al.*, 2001[60]	ILis (before meal)+basal	8.4 ±1.0* [5.8 to 10.2]**	8.4±1.1*	NR	NR	NS	NR	NR	NR	NR	NR
	ILis (after meal)+basal	8.4 ±1.0* [5.8 to 10.2]**	8.54±1.0*	NR	NR						

		HbA1c					Plasma Glucose, mmol/L (mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-Prandial	2- Hour Post-Prandial	p-value between Treatments
	HI (before meal)+basal	8.4±1.0* [5.8 to 10.2]**	8.43±1.0*	NR	NR						
Fairchild *et al.*, 2002[28]	ILis+NPH	8.21±0.73*	8.33±0.89*	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	8.21±0.73*	8.14±0.77*	NR	NR						
Ferguson *et al.*, 2001[81]	ILis+NPH	9.0±1.1* [6.5 to 11.7]**	9.1±0.83*	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	9.0±1.1* [6.5 to 11.7]**	9.3±1.0*	NR	NR						
Ford-Adams *et al.*, 2003[61]	ILis+NPH	8.4±0.24*	8.5±0.2†	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	8.4±0.24*	8.8±0.3†	NR	NR						
Gale, 2000[73]	ILis+basal	<1.5 times the upper limit of non-diabetic range	7.5±1.1*	NR	NR	NS	NR	NR	NR	NR	NR
	HI+basal	same	7.4±1.1*	NR	NR						
Garg *et al.*, 1996[82]	ILis+NPH or UL	9.1±1.4*	9.0±1.9*	NR	NS	NS	NR	NR	NR	NR	NR
	HI+NPH or UL	8.4±2.1*	8.8±1.4*	NR	NS						
Hedman *et al.*, 2004[88]	ILis+basal	6.7±0.9†	6.4±0.2†	NR	NR	NS	NR	NR	NR	NR	NR

		HbA1c					Plasma Glucose, mmol/L (mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-Prandial	2- Hour Post-Prandial	p-value between Treatments
	HI+basal	6.7±0.9†	6.4±0.2†	NR	NR						
Heller *et al.*, 1999[93]	ILis+NPH	Period 1: 6.2±1.1*	Period 1: 6.0±0.9 *	NR	NR	NR	NR	NR	NR	NR	NR
		Period 2: 6.2±0.8*	Period 2: 6.4±1.1*								
	HI+NPH	Period 1: 6.4±0.9*	Period 1: 6.2±0.8*	NR	NR						
		Period 2: 6.0±0.9*	Period 2: 6.4±1.1*								
Heller *et al.*, 2004[70]	IAsp+NPH	7.9±0.7*	7.7±0.8*	NR	NR	NR	NR	NR	NR	NR	NR
	HI+NPH	7.9±0.7*	7.7±0.9*	NR	NR						
Holcombe *et al.*, 2002[62]	ILis+NPH	8.61±1.5*	8.69±1.52*	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	8.61±1.5*	8.70±1.65*	NR	NR						
Holleman *et al.*, 1997[83]	ILis+NPH	7.3±1.1*	7.6±1.3*	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	7.3±1.1*	7.5±1.2*	NR	NR						
Home *et al.*, 1998[67]	IAsp+NPH	7.1±1.0*	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HI+NPH	7.1±1.0*	NR	NR	NR						
Home *et al.*, 2000[96]	IAsp+NPH	7.96±1.16*	7.88±0.03†	NR	NR	p<0.02	NR	NR	NR	NR	NR
	HI+NPH	7.98±1.17*	8.00±0.04†	NR	NR						

		HbA1c					Plasma Glucose, mmol/L (mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-Prandial	2- Hour Post-Prandial	p-value between Treatments
Home *et al.*, 2006[100] [Extension of Home, 2000][96]	IAsp+NPH	NR	8.09±0.04†	-0.16 [-0.32, -0.01]††	p=0.035	NR	NR	NR	NR	NR	NR
	HI+NPH	NR	8.25±0.07†	NR							
Iwamoto *et al.*, 2001[97]	IAsp+basal	7.51±1.12*	7.36±1.12*	-0.15±0.77* [-0.28, -0.01]††	p<0.05	NS	NR	NR	NR	NR	NR
	HI+basal	7.57±1.09*	7.60±1.08*	0.03±0.69* [-0.14, 0.21]††	NS						
Jacobs *et al.*, 1997[66]	ILis+NPH	6.8±0.9*	NR	0.1±0.48*	NS	NR	NR	NR	NR	NR	NR
	HI+NPH	6.8±0.9*	NR	-0.41±0.34*	p=0.03						
Jansson *et al.*, 1998[85]	ILis+NPH	7.98±0.11†	NR	0.3	NR	p<0.01	NR	NR	NR	NR	NR
	HI+NPH	7.84±0.14†	NR	-0.04	NR						
Johansson *et al.*, 2000[89]	ILis+basal	7.7±0.8* [6.2 to 9.0]**	7.4	NR	NR	p=0.047	NR	NR	NR	NR	NR
	HI+basal	7.7±0.8* [6.2 to 9.0]**	7.6	NR	NR						
Linkeschova *et al.*, 2003[57]	ILis	NR	NR	NR	NR	p=0.026	NR	NR	NR	NR	NR
	HI	NR	NR	NR	NR						

		HbA1c					Plasma Glucose, mmol/L (mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-Prandial	2- Hour Post-Prandial	p-value between Treatments
Mathiesen *et al.*, 2006[29]	IAsp+NPH	7.0±0.8*	2nd trimester 6.0 3rd trimester 6.18	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	6.9±1.0*	2nd trimester 6.04 3rd trimester 6.26	NR	NR		NR	NR	NR	NR	NR
Melki *et al.*, 1998[94]	ILis+basal	7.84±0.12†	7.11±0.15†	-0.62±0.13†	NR	p=0.01	NR	NR	NR	NR	NR
	HI+basal	7.84±0.12†	7.88±0.16†	-0.09±0.15†	NR						
Persson *et al.*, 2002[65]	ILis+NPH	6.5 [4.8 to 8.6]**	5.2 [4.6 to 5.9]** last week before delivery	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	6.6 [4.5 to 8.6]**	5.0 [4.5 to 6.7]** last week before delivery	NR	NR						
Provenzano *et al.*, 2001[86]	ILis+basal	7.59±0.47*	7.62±0.49*	NR	NR	NR	NR	NR	NR	NR	NR
	HI+basal	7.59±0.47*	7.84±0.49*	NR	NR						
Raskin *et al.*, 2001[90]	ILis+basal	7.9±1.1*	7.41±0.97*	-0.34±0.59*	NR	p=0.004	NR	NR	11.16±4.29*	9.64±4.10*	1 hour post-prandial

		HbA1c					Plasma Glucose, mmol/L (mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-Prandial	2- Hour Post-Prandial	p-value between Treatments
	HI+basal	7.6±0.8*	7.65±0.85*	-0.09±0.63*	NR		NR	NR	13.20±4.68*	12.53±4.64*	p=0.012 2 hours post-prandial p=0.001
Raskin *et al.*, 2000[98]	IAsp+NPH	7.90±1.13*	7.78±0.04†	NR	NR	p=0.046	NR	NR	NR	NR	NR
	HI+NPH	7.95±1.25*	7.91±0.06†	NR	NR						
Recasens *et al.*, 2003[68]	ILis+NPH	10.5±2.4*	6.1±1.11*	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	11.4±1.9*	6.22±1.11*	NR	NR						
Renner *et al.*, 1999[91]	ILis+basal	7.24±1.0*	6.77±0.88*	NR	NR	p<0.02	NR	NR	NR	NR	NR
	HI+basal	7.24±1.0*	6.90±0.97*	NR	NR						
Roach *et al.*, 1999[49]	Mix50 (a.m.)+Mix25 (p.m.)	NR	7.69	NR	NR	NS	NR	NR	NR	NR	NR
	HI50 (a.m.)+HI30 (p.m.)	NR	7.4	NR	NR						
Schmauss *et al.*, 1998[95]	ILis+basal	6.5±0.3†	6.0±0.3†	NR	NR	NS	NR	NR	NR	NR	NR
	HI+basal	6.5±0.3†	6.4±0.3†	NR	NR						
Tamás *et al.*, 2001[99]	IAsp+NPH	8.36±0.05†	8.02±0.05†	NR	NR	p=0.013	NR	NR	NR	NR	NR
	HI+NPH	8.29±0.05†	8.18±0.05†	NR	NR						

		HbA1c					Plasma Glucose, mmol/L (mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-Prandial	2- Hour Post-Prandial	p-value between Treatments
Tubiana-Rufi *et al.*, 2004[64]	ILis+basal	8.02±0.67* [7.2 to 10.3]**	NR	0.15±0.13* (period 1)	NR	NS	NR	NR	NR	NR	NR
	HI+basal	8.02±0.67* [7.2 to 10.3]**	NR	0.11±0.63* (period 1)	NR						
Tupola *et al.*, 2001[63]	ILis+NPH	8.1±0.9*	NR	0.2±0.8*	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	8.1±0.9*	NR	-0.4±0.7*	NR						
Valle *et al.*, 2001[87]	ILis+NPH	8.7±1.8*	8.1±1.5*	NR	p<0.001	NS	NR	NR	NR	NR	NR
	HI+NPH	8.7±1.8*	8.2±1.5*	NR	p<0.001						
Vignati *et al.*, 1997[50]	ILis+NPH	8.0±1.5*	7.8±1.4*	NR	NR	p=0.660 (NS)	NR	NR	NR	NR	NR
	HI+NPH	8.0±1.5*	7.9±1.5*	NR	NR		NR	NR	NR	NR	NR
Zinman *et al.*, 1997[92]	ILis+basal	8.03±0.13†	7.66±0.13†	NR	NR	p=0.0041	NR	NR	NR	NR	NR
	HI+basal	8.03±0.13†	8.00±0.16†	NR	NR						

*mean±SD; †mean±SE; ‡mean (95% CI); **mean (range); ††mean (95%CI); ‡‡median (interquartile range); ***median (range). BHI30/70=30% HI+70% NPH; DM=diabetes mellitus; HbA1c=glycosylated hemoglobin; HI=conventional human insulin, IAsp=insulin aspart; ILis=insulin lispro; Mix25=25% ILis, 75% neutral protamine lispro; Mix50=biphasic human lispro (50% ILis, 50% neutral protamine lispro); NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; UL=ultralente.

APPENDIX 9B: HbA1c DATA IN PATIENTS WITH TYPE 2 DM

		HbA1c					Plasma Glucose, mmol/L(mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-prandial	2-Hour Post-prandial	p-value between Treatments
Altuntas *et al.*, 2003[74]	ILis+NPH	10.1±1.5†	6.7±0.5†	NR	NR	ILis+NPH versus ILis+Metf, p=0.013; ILis+Metf versus HI+NPH, p>0.05; ILis+NPH versus HI+NPH, p=0.001	NR	NR	NR	NR	NR
	ILis+Metf	9.4±1.5†	7.4±0.3†	NR	NR						
	HI+NPH	9.6±1.4†	7.5±0.2†	NR	NR						
Anderson *et al.*, 1997[45]	ILis+basal	8.7±0.1†	8.2±0.1†	NR	p<0.05	NS	NR	NR	NR	NR	NR
	HI+basal	8.9±0.1†	8.4±0.1†	NR	p<0.05						
Anderson *et al.*, 1997[103]	ILis+NPH or UL	8.9±0.1†	8.2±0.1†	NR	NS	NS	NR	NR	NR	NR	NR
	HI+NPH or UL	8.9±0.1†	8.2±0.1†	NR	NS						
Bastyr *et al.*, 1999[111]	ILis+NPH	9.99± 1.68*	8.54±1.42*	-1.4±1.46*	p<0.001	ILis+Sfu versus NPH+Sfu, p=0.003; others NS	NR	NR	NR	NR	NR
	ILis+Sfu	10.00± 1.67*	8.36±1.32*	-1.60±1.27*	p<0.001						
	NPH+Sfu	9.91± 1.66*	8.74±1.52*	-1.21±1.21*	p<0.001						
Bastyr *et al.*, 2000[119]	ILis+Gly	10.03	7.7±0.9*	-2.4±0.9*	p<0.001	ILis+Gly versus	NR	NR	NR	NR	NR
	Metf+Gly	10.19	8.3±1.3*	-1.8±1.3*	p<0.001						

		HbA1c					Plasma Glucose, mmol/L(mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-prandial	2-Hour Post-prandial	p-value between Treatments
	NPH+Gly	10.39	8.5±1.4*	-1.8±1.4*	p<0.001	Metf+Gly, p=0.025; ILis+Gly versus NPH+Gly, p=0.003; Metf+Gly versus NPH+Gly, NS					
Boehm *et al.*, 2004[108]	BIAsp30	8.11±1.22†	8.35±0.20†	NR	NR	NR	NR	NR	NR	NR	NR
	BHI30/70	8.21±1.22†	8.13±0.16†	NR	NR						
Bretzel *et al.*, 2004[75]	IAsp+NPH (bedtime)	7.82± 0.13*	NR	-0.91±1.00*	NR	HI+NPH versus BHI30/70, p=0.006; others NS	NR	NR	NR	NR	NR
	HI+NPH (bedtime)	7.83±0.13*	NR	-0.73±0.87*	NR						
	BHI30/70	7.78±0.13*	NR	-0.65±1.1*	NR						
Chan *et al.*, 2004[46]	ILis+NPH	9.0±2.2*	7.6	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	9.0±2.2*	7.6	NR	NR						
Forst *et al.*, 2003[112]	ILis	7.5±1.0*	7.4±0.9*	NR	NR	NS	NR	NR	NR	NR	NR
	Glib	7.7±1.2*	7.6±1.3*	NR	NR						
Gallagher and Home, 2005[109]	IAsp+NPH	7.8±0.6*	7.04±0.13†	NR	p<0.001	NS	NR	NR	NR	NR	NR
	HI+NPH	7.8±0.6*	7.15±0.11†	NR	p<0.001						
Herz *et al.*, 2002[120]	Mix25	9.82±1.51*	8.64±0.17†	-1.14±0.18	p=0.001	p<0.001	NR	NR	NR	10.5±0.4†	2 hours post-prandial p=0.016
	Gly	9.90± 1.30*	9.45±0.16†	-0.36±0.15	NR		NR	NR	NR	11.6±0.4†	
Iwamoto,	BIAsp30	NR	7.37±0.04†	NR	NR	NR	NR	NR	NR	NR	NR

		HbA1c					Plasma Glucose, mmol/L(mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-prandial	2-Hour Post-prandial	p-value between Treatments
2003[58]	BHI30/70	NR	7.35±0.07†	NR	NR						
Kilo *et al.*, 2003[110]	BIAsp30+ Metf	9.5±1.8*	NR	-1.3	NR	NR	241± 74.8* (mg/dL)	Change -75±72.3* (mg/dL)	NR	NR	NS
	NPH+Metf	9.5±1.6*	NR	-1.2	NR		242.7±69.7* (mg/dL)	-91±72.0* (mg/dL)	NR	NR	NS
	BHI30/70+ Metf	9.3±1.4*	NR	-1.1	NR		227± 67.2* (mg/dL)	Change -63±86.2* (mg/dL)	NR	NR	NS
Kokić *et al.*, 2003[114]	Glim+Metf	9.21±1.72*	8.52±1.7*	-0.88±1.31	p<0.05	Glim+Metf versus ILis+Metf, p=0.00235, others NS	NR	NR	NR	NR	NR
	BHI30/70+ NPH	9.21±1.54*	8.03±1.05*	-1.17±1.34*	p<0.05						
	ILis+Metf	10.0±1.73*	8.00±0.63*	-1.96±1.72*	p<0.05						
Lourens *et al.*, 2000[104]	Mix25	NR	7.79±0.18†	NR	NR	NS	NR	NR	NR	NR	NR
	BHI30/70	NR	8.03±0.20†	NR	NR						
Malone *et al.*, 2003[115]	Mix25+Metf	9.17±1.50*	7.29±1.00*	-1.87±1.35	p<0.001	NS	13.30±3.79	8.67±3.36	NR	-6.89±4.69	Pre-prandial p=0.173; 2 hours post-prandial p< 0.009
	Glib+Metf	9.27±1.55*	7.33±1.14*	-1.98±1.28	p<0.001		12.99 ±3.78	9.43±3.39	NR	-3.83±4.72	
Niskanen *et al.*, 2004[31]	BIAsp30	8.5±1.1*	8.15	NR	NR	p=0.82 (NS)	NR	NR	NR	NR	NR
	ILisMix25	8.5±1.1*	8.01	NR	NR						
Raskin *et al.*, 1999[59] [Abstract]	IAsp+NPH	8.1±0.13†	7.7±0.1†	NR	NR	NS	NR	NR	NR	NR	NR
	HI+NPH	7.9±0.12†	7.8±0.1†	NR	NR						
Raz *et al.*, 2005[118]	BIAsp30	[7.5 to 13.0]**	9.0±1.3*	-0.5	NS	BIAsp30 versus	NR	NR	NR	NR	NR

		HbA1c					Plasma Glucose, mmol/L(mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-prandial	2-Hour Post-prandial	p-value between Treatments
	BIAsp30+Pio	[7.4 to 12.7]**	8.4±1.2*	-1.2	NS	BIAsp30+Pio, p=0.008; BIAsp30+Pio versus Glib+Pio, p=0.005 other, NS					
	Glib+Pio	[7.5 to 14.7]**	9.0±2.1*	-0.4	NS						
Raz *et al.*, 2003[117]	BIAsp30+Ros	9.9±1.3*	9.4	-0.7	NR	NR	NR	NR	NR	NR	NR
	Glib+Ros	10.3±1.3*	10.1	-0.2	NR						
Roach *et al.*, 2001[116]	Mix25	9.85±1.2*	8.5±1.3*	NR	NR	p=0.001	NR	NR	NR	NR	NR
	Gly (maximum dose)	10.07± 1.4*	9.4±1.8*	NR	NR						
Roach *et al.*, 1999[105]	Mix25	<9.2	7.8	NR	NR	NS	NR	NR	NR	NR	NR
	BHI30/70	<9.2	8.1	NR	NR						
Roach *et al.*, 1999[49]	Mix50	NR	7.73	NR	NR	NS	NR	NR	NR	NR	NR
	BHI50	NR	7.66	NR	NR						
Ross *et al.*, 2001[106]	ILis+NPH	10.7±0.2†	8.0±0.1†	-2.5±0.2†	NR	NR	NR	NR	NR	NR	NR
	HI+NPH	10.6±0.2†	8.0±0.1†	-2.3±0.2†	NR						
Schernthaner *et al.*, 2004[107]	Mix50	8.4±1.0*	7.6±1.1*	-0.8±1.1*	p<0.001	p=0.021	NR	NR	NR	NR	NR
	BHI30/70	8.4±1.0*	8.1±1.4*	-0.3±1.1	p=0.034						
Vignati *et al.*, 1997[50]	ILis+NPH	8.1±1.3*	8.1±1.4*	NR	NS	p=0.648 (NS)	NR	NR	NR	NR	NR
	HI+NPH	8.2±1.3*	8.1±1.4*	NR	NS						

mean±SD; †mean±SE; ‡mean (95% CI); **mean (range); ††mean (90%CI). BHI30/70=30% HI+70% NPH; BIAsp30=30% IAsp+70% PIA; Glib=glibenclamide; Glim=glimepride; Gly=glyburide; HI=conventional human insulin; IAsp=insulin aspart; ILis=insulin lispro; ILisMix25=biphasic insulin lispro (25% lispro, 75% neutral protamine lispro); Metf=metformin; Mix25=biphasic human lispro (25% lispro, 75% neutral protamine lispro); Mix50=biphasic human lispro (50% ILis, 50% neutral protamine lispro); NPH=neutral protamine Hagedorn; NPL=neutral protamine lispro; NR=not reported; NS=not significant; OAD=oral antidiabetic agent; PIA=protamine insulin aspart; Pio=pioglitazone; Ros=Rosiglitazone; Sfu=sulfonylurea.

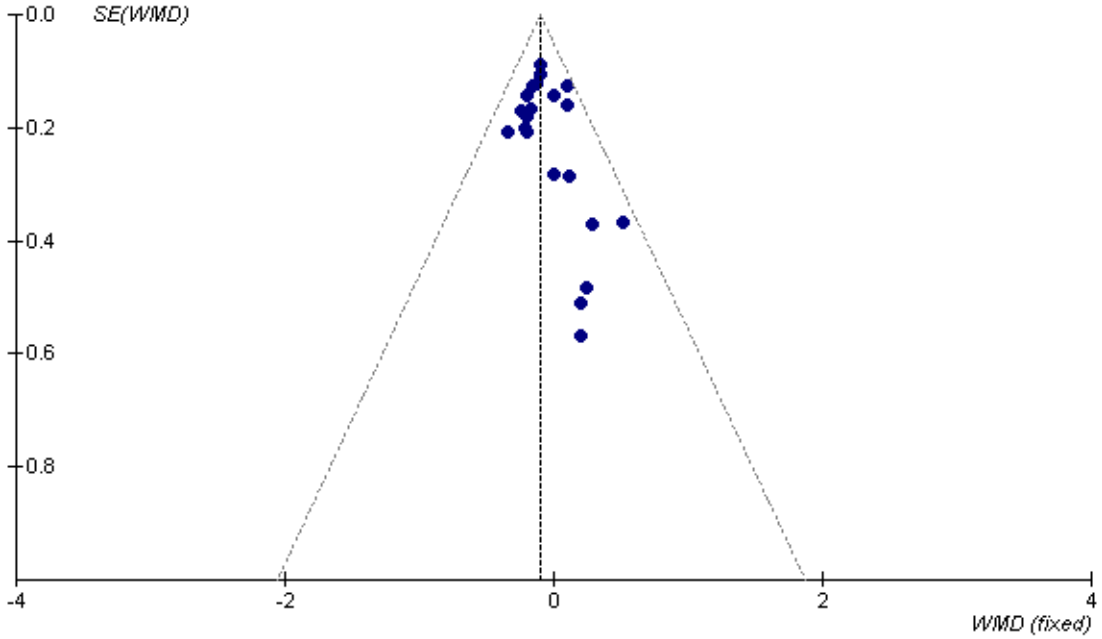
APPENDIX 9C: HbA1c DATA IN PATIENTS WITH GESTATIONAL DM

		HbA1c					Blood Glucose, mmol/L(mg/dL)				
Study	Comparators	HbA1c at Baseline (%)	HbA1c at Endpoint (%)	HbA1c Change from Baseline	p-value Endpoint versus Baseline	p-value between Treatments	Fasting	Pre-prandial	1-Hour Post-prandial	2-Hour Post-prandial	p-value between Treatments
Jovanovic *et al.*, 2000[52]	ILis	5.47±0.09†	5.12±0.11†	0.35	NR	p=0.7508 and 0.0018 for final and change values respectively	NR	NR	NR	NR	NR
	HI	5.24±0.09†	5.16±0.12†	0.07	NR						
Mecacci *et al.*, 2003[53]	ILis	5.5±0.2	5.2±0.4	-0.3±0.3	NR	NS	NR	NR	NR	NR	NR
	HI	5.4±0.2	5.1±0.3	-0.3±0.1	NR						

†mean±SE. DM=diabetes mellitus; HbA1c=glycosylated hemoglobin; HI=conventional human insulin, ILis=insulin lispro, NR=not reported; NS=not significant.

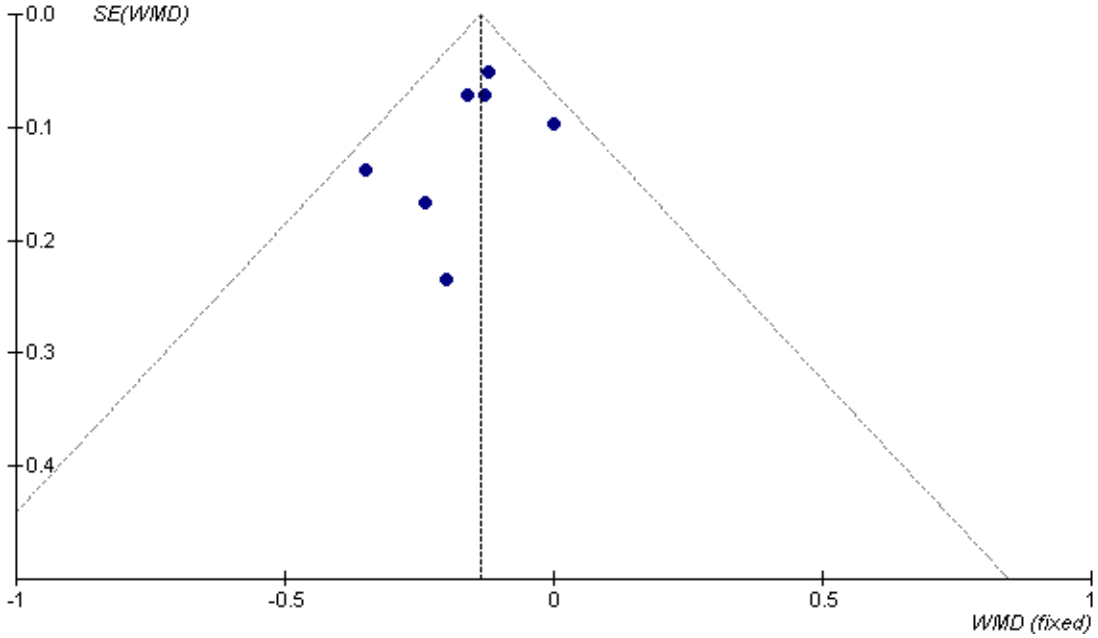
APPENDIX 10: FUNNEL PLOTS

Figure 1: Funnel plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adult patients – A1c, WMD



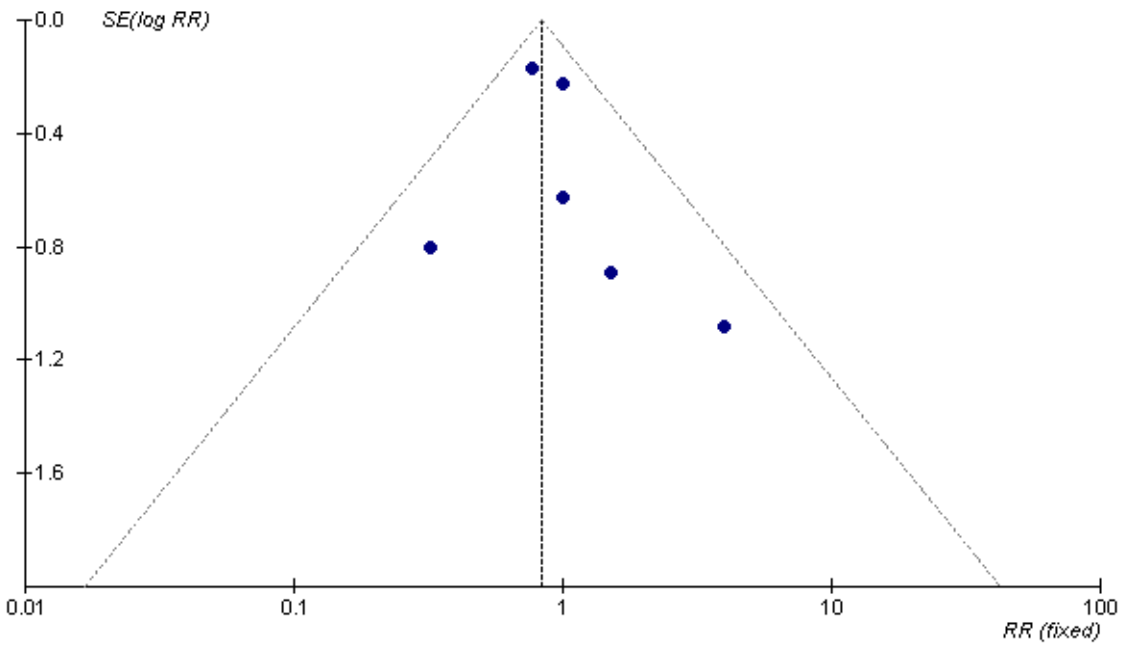
A1c=glycosylated hemoglobin; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized control trials; SE=standard error; WMD=weighted mean difference.

Figure 2: Funnel plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adult patients – A1c, WMD



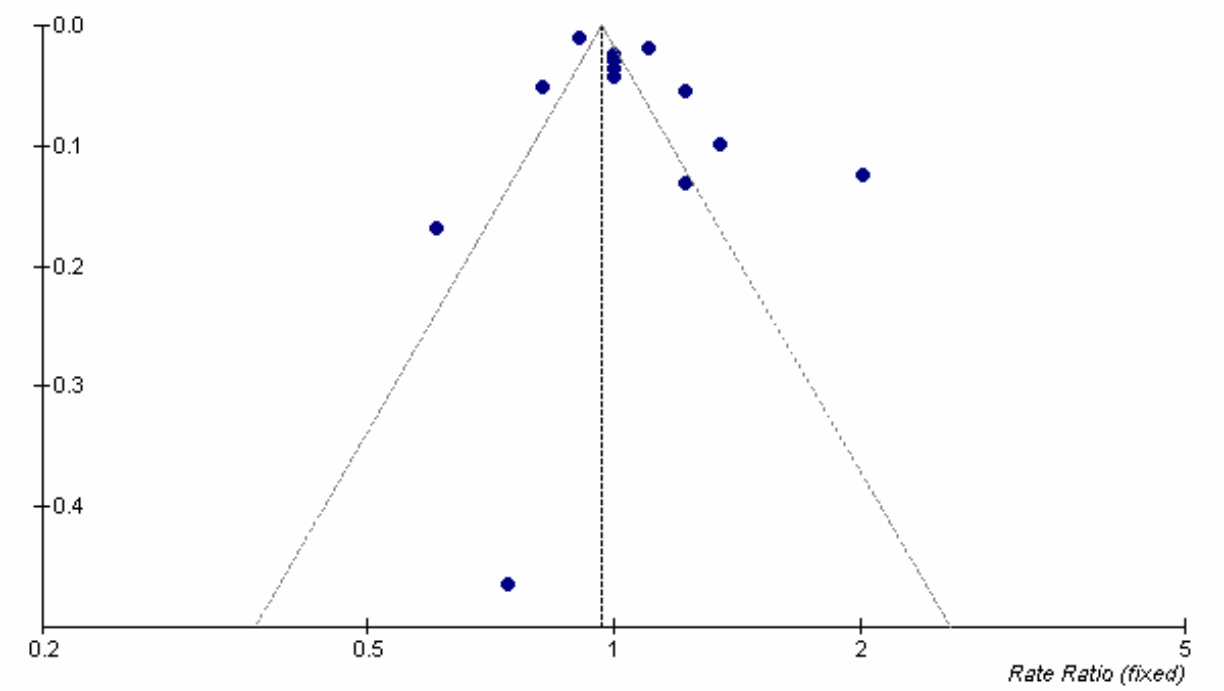
A1c=glycosylated hemoglobin; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized control trials; SE=standard error; WMD=weighted mean difference.

Figure 3: Funnel plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adult patients – Severe hypoglycemia, RR



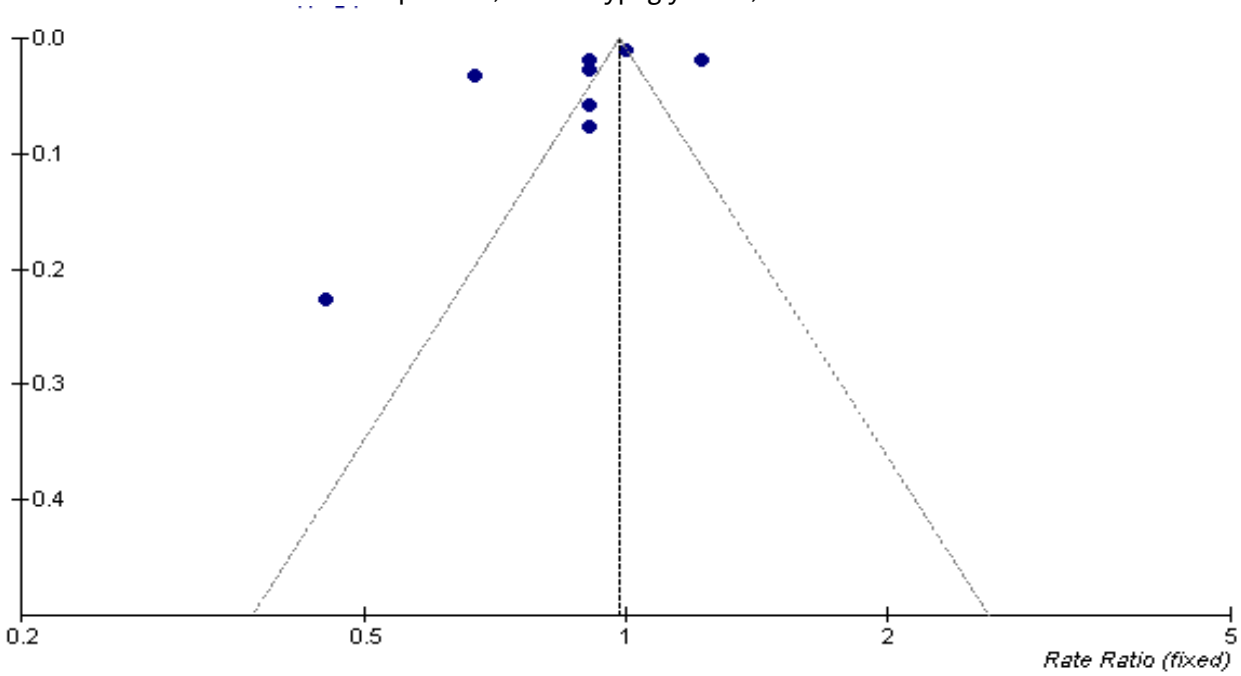
DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized control trials; RR=relative risk; SE=standard error; WMD=weighted mean difference.

Figure 4: Funnel plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adult patients – Overall hypoglycemia, rate ratio



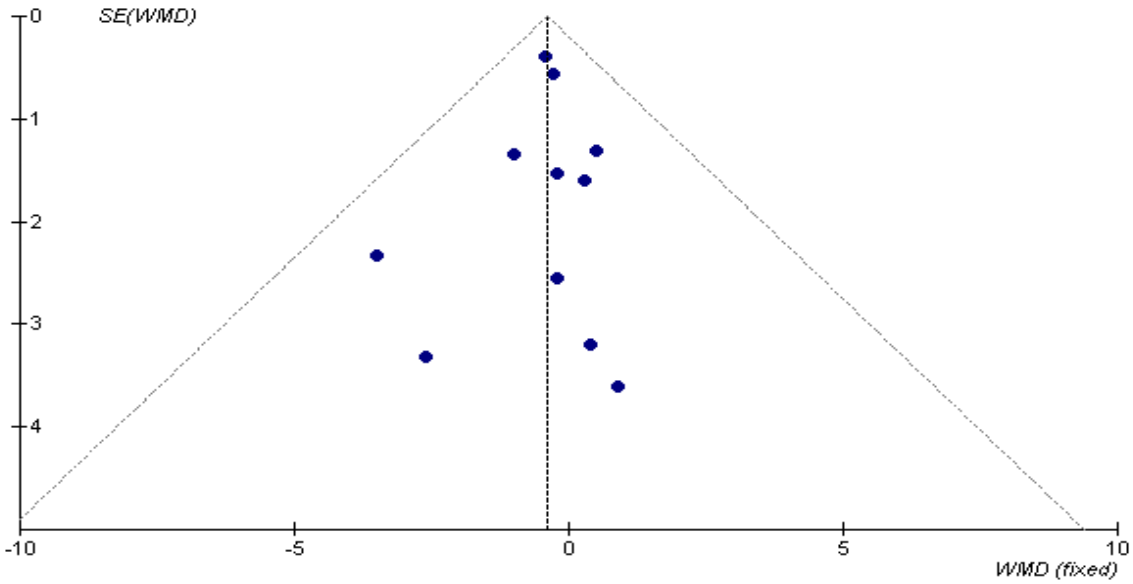
DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized control trials.

Figure 5: Funnel plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adult patients, overall hypoglycemia, rate ratio



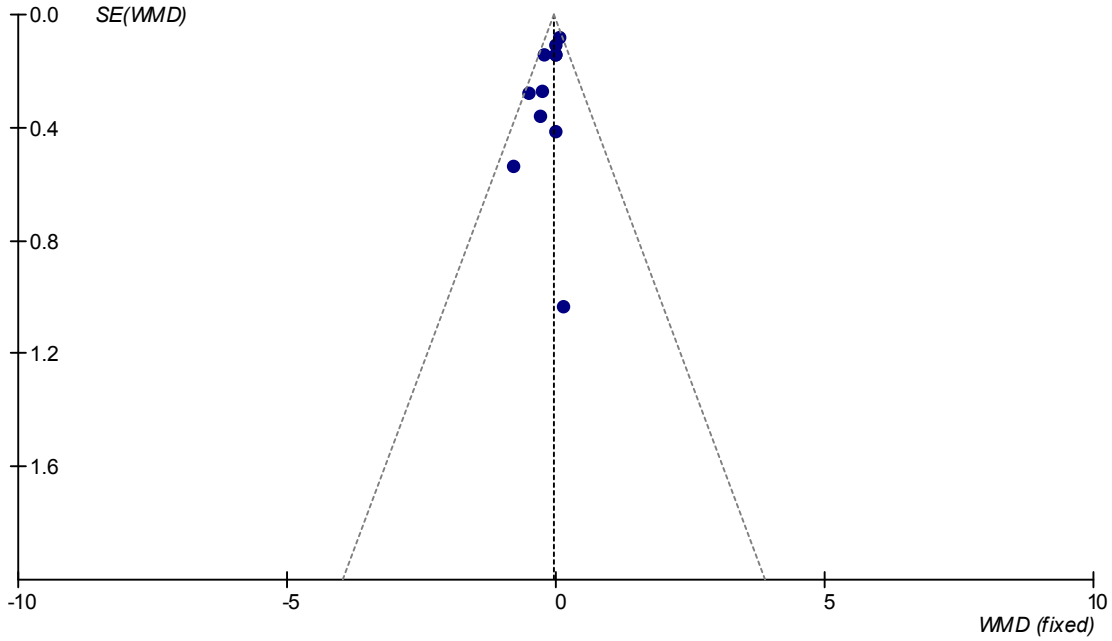
DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized control trials.

Figure 6: Funnel plot of all RCTs that examined the use of ILis versus HI for the treatment of type 1 DM in adult patients – Weight gain



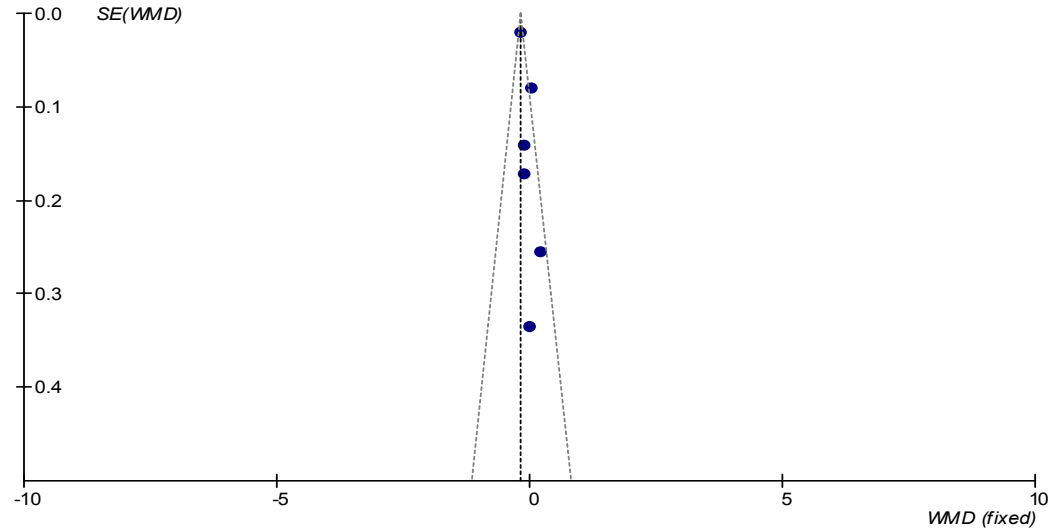
DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized control trials; SE=standard error; WMD=weighted mean difference.

Figure 7: Funnel plot of all RCTs that examined the use of ILis or ILis mix versus HI for the treatment of type 2 DM in adult patients – A1c, WMD



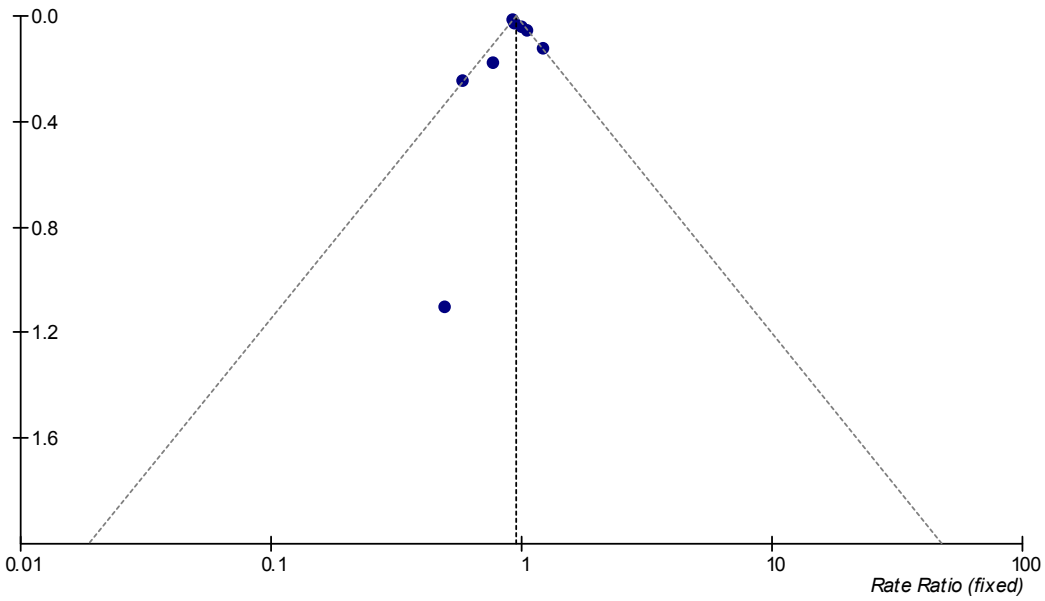
A1c=glycosylated hemoglobin; DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized control trials; SE=standard error; WMD=weighted mean difference.

Figure 8: Funnel plot of all RCTs that examined the use of IAsp versus HI for the treatment of type 2 DM – A1c, WMD



A1c=glycosylated hemoglobin; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; RCTs=randomized control trials; SE=standard error; WMD=weighted mean difference.

Figure 9: Funnel plot of all RCTs that examined the use of ILis or ILis mix versus HI or HI mix for the treatment of type 2 DM in adult patients – Overall hypoglycemia, rate ratio



DM=diabetes mellitus; HI=human insulin; ILis=insulin lispro; RCTs=randomized control trials.

APPENDIX 11A: HYPOGLYCEMIA IN PATIENTS WITH TYPE 1 DM

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
Anderson *et al.*, 1997[77]	ILis+NPH or UL	Overall	NR	6.4±0.2†	Episodes/patient /30 days	NR	NR	p<0.001 for both types	Overall: sign or symptom normally associated with that state or with BG<3.5 mmol/L Severe: external help required and episodes resulting in coma or requiring i.v. glucose or glucagon Nocturnal: NR
		BG<3.5 mmol/L		5.6±0.2†					
	HI+NPH or UL	Overall	NR	7.2±0.3†	Episodes/patient /30 days	NR	NR		
		BG<3.5 mmol/L		6.3±0.2†					
Anderson *et al.*, 1997[45]	ILis+basal	Overall	6.2±0.5†	4.4±0.5†	Episodes/patient /30 days	NR	p<0.05	NS	Overall: sign or symptom normally associated with hypoglycemia or BG<2.0 mmol/L Severe: NR Nocturnal: NR
	HI+basal	Overall	7.3±0.6†	4.5±0.4†	Episodes/patient /30 days	NR	p<0.05		
Annuzi *et al.*, 2001[78]	ILis +NPH	Overall	271	256	Episodes/patient /30 days	NR	NS	NS	Overall: presence of hypoglycemic signs/symptoms and/or BG<3.3 mmol/L
		Severe	3	0.7					
		Asymptomatic	35	27					
	HI+NPH	Overall	271	204	Episodes/patient /30 days	NR	NS		
		Severe	3	1					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Asymptomatic	35	22					Severe: requiring external help or resulting in coma Nocturnal: NR
Arslanian *et al.*, 2005[54] (Poster)	IAsp+NPH	Minor	NR	26.4	Episodes/patient /year	NR	NR	NS for all	Minor: confirmed by BG<50 mg/dL Severe: NR Nocturnal: NR
		Major		0.2					
	ILis+NPH	Minor	NR	26	Episodes/patient /year	NR	NR		
		Major		0.2					
	HI+NPH	Minor	NR	31.8	Episodes/patient /year	NR	NR		
		Major		0.3					
Bode *et al.*, 2001[71]	IAsp+basal	Overall	NR	14 (74%)	# of patients	NR	NR	NR	Overall: BG<2.5 mmol/L (45 mg/dL) without an appropriate explanation, e.g., delaying a meal after taking a bolus dose Severe: NR Nocturnal: NR
	HI+basal	Overall	NR	6 (60%)	# of patients	NR	NR		
Bode *et al.*, 2002[69]	IAsp+basal	Overall	NR	6.7±5.4*	Episodes/patient /30 days	NR	NR	IAsp versus HI, p=0.034 for overall, p=0.004 for nocturnal. IAsp versus ILis, p=0.044 for overall	Overall (Minor): having a hypoglycemic symptom (e.g., palpitations, tiredness, sweating, strong hunger, dizziness, tremor)
		BG<50 mg/dL		3.7±3.6*					
		Nocturnal		0.5±0.83*					
	ILis+basal	Overall	NR	10.5±8.1*	Episodes/patient /30 days	NR	NR		
		BG<50 mg/dL		4.4±4.7*					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Nocturnal		0.6±0.61*					confirmed by BG meter reading <50 mg/dL and could deal with the episode on their own Severe (Major): BG meter reading <50 mg/dL and an event associated with severe central nervous system dysfunction that required administration of parenteral glucose or glucagon or patient could not deal with it on their own Nocturnal: NR
	HI+basal	Overall	NR	10.5±8.9*	Episodes/patient /30 days	NR	NR		
		BG<50 mg/dL		4.8±4.2*					
		Nocturnal		0.9±0.97*					
Ciofetta *et al.*, 1999[80]	ILis+NPH	Mild	NR	8.1±0.8†	Episodes/patient /30 days	NR	NR	ILis+NPH versus NI+NPH, p<0.05 for mild. ILis+NPH versus ILis/NPH+NPH, NS for	Overall: any self-treated episode, BG≤3.9 mmol/L Severe: coma or neuroglycopenia requiring assistance from third party,
		Severe		0					
	ILis/NPH +NPH	Mild	NR	5.2±1.2†	Episodes/patient	NR	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Severe		0	/30 days			mild	with or without the need for i.v. glucose or glucagon or emergency hospitalization Nocturnal: NR
	HI+NPH	Mild	NR	4±0.5†	Episodes/patient /30 days	NR			
		Severe		0					
Danne *et al.*,2005[55] [Abstract]	IAsp+basal	Overall	NR	143	Episodes/year	NR	NR	NS	NR
	HI+basal	Overall	NR	142		NR	NR		
Deeb *et al.*, 2001[60]	ILis (before meal)+basal	Overall	NR	14.7±11.9*	Episodes/patient /30 days	NR	NR	NS for all	NR
		Severe		2 patients					
	ILis (after meal)+basal	Overall	NR	13.6±9.3*	Episodes/patient /30 days	NR	NR		
		Severe		3 patients					
	HI (before meal)+basal	Overall	NR	13.8±9.8*	Episodes/patient /30 days	NR	NR		
		Severe		6 patients					
Del Sindaco *et al.*,1998[102]	ILis+2x NPH versus HI+2x NPH	Overall	NR	5.3±4.8* versus 4.0±3.4*	Episodes/patient /30 days	NR	NR	p<0.05 versus HI	NR
		BG: 3.3 to 2.8 mmol/L		3.2±3.0* versus 2.6±2.1*					
		BG: 2.7 to 2.3 mmol/L		1.5±1.1* versus 1.0±0.7*					
		BG <2.2 mmol/L		0.6±0.7* versus 0.4±0.7*					
	ILis+4x NPH versus HI+2x NPH	Overall	NR	3.65±2.9* versus 3.39±2.9*	Episodes/patient /30 days	NR	NR		
		BG: 3.3 to 2.8 mmol/L		2.18±1.6* versus 1.93±1.6*					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		BG: 2.7 to 2.3 mmol/L		0.99±1.2* versus 0.97±0.8*					
		BG <2.2 mmol/L		0.5±0.8* versus 0.5±0.8*					
	ILis+4x NPH versus HI+4x NPH	Overall	NR	4.4±3.8* versus 11±4.8*	Episodes/patient /30 days	NR	NR		
		BG: 3.3 to 2.8 mmol/L		3.1±2.4* versus 6.5±4.1*					
		BG: 2.7 to 2.3 mmol/L		1.4±1.3* versus 3.4±2.4*					
		BG<2.2 mmol/L		0.6±0.3* versus 1.1±0.7*					
Fairchild *et al.*, 2000[28]	ILis+NPH	Overall	NR	13.47	Episodes/patient /3 months	NR	NR	NS	Overall: Include all episodes. Hypoglycemic episode was defined as any time a patient felt (or another person observed) that he or she was experiencing a sign/symptom that would be associated with hypoglycemia
		BG<3 mmol/L		6.55					
		Severe		0.032					
		Nocturnal		1.03					
		BG<3 mmol/L		0.62					
	HI+NPH	Overall	NR	10.77	Episodes/patient /3 months		NR		
		BG< 3 mmol/L		6.83					
		Severe		0.065					
		Nocturnal		0.93					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		BG<3 mmol/L		0.62					(where possible, confirmed by BG<4.0mmol/L) or any asymptomatic BG measurement <3.0 mmol/L. Severe: Episodes associated with convulsion or coma Nocturnal: Episodes happened at 24:00 to 06:00
Ferguson *et al.*,2001[81]	ILis+NPH	Overall	NR	1,156	Episodes	NR	NR	NR	Overall: symptoms associated with hypoglycemia or BG≤3.5 mmol/L (65 mg/dL) Severe: episodes that required third-party assistance to facilitate recovery Nocturnal: NR
		Mild		1,101					
		Severe		55					
		Severe Nocturnal		25					
		Severe Morning		13					
		Severe Afternoon		4					
		Severe Evening		13					
	HI+NPH	Overall	NR	1,115	Episodes	NR	NR		
		Mild		1,031					
		Severe		84					
		Severe Nocturnal		47					
		Severe Morning		11					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Severe Afternoon		9					
		Severe Evening		17					
Ford-Adams *et al.*, 2003[61]	ILis+NPH	Overall	NR	6.25±1†	Episodes/patient /30 days	NR	NR	NS	Overall: grade 1, extra carbohydrate; grade 2, carbohydrate administered by another person; grade 3, hypoglycemia requiring glucagon or hypostop; grade 4, convulsion Severe: NR Nocturnal: NR
		Nocturnal		0.25					
		Morning		1.25±0.5†					
		Afternoon		3.5±0.75†					
	HI+NPH	Overall	NR	6.75±1.25†	Episodes/patient /30 days	NR	NR		
		Nocturnal		0.25					
		Morning		1±0.25†					
		Afternoon		4±0.75†					
Gale, 2000[73]	ILis+basal	Overall	NR	2.6±3.0*	Episodes/patient /30 days	NR	NR	NS for overall, p<0.001 for nocturnal, p=0.029 for morning, NS for severe	Overall: symptoms experienced by patients, signs noted by an observer, or BG <2.5 mmol/L Severe: coma and/or requirement for IM glucagon or i.v. glucose Nocturnal: NR
		Nocturnal		0.7±1.6*					
		Morning		2.8±3.7*					
		Severe		3 episodes in 2 of 92 patients					
	HI+basal	Overall	NR	3.1±4.4*	Episodes/patient /30 days	NR	NR		
		Nocturnal		1.8±3.1*					
		Morning		2.2±3.0*					
		Severe		10 episodes in 6 of 89 patients					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
Garg *et al.*, 1996[82]	ILis+NPH or UL	Overall	3.7±0.8†	13.3±4.3†	Episodes /patient/12 months	NR	NR	NS	Overall: patient experiencing or another person observing signs or symptoms of hypoglycemia, or BG <2.0 mmol/L. For the 7 new onset subjects, BG <3.5 mmol/L was also considered as hypoglycemia Severe: any time help was needed from another person and included episodes in which i.v. dextrose or IM glucagon was necessary Nocturnal: NR
	HI+NPH or UL	Overall	5.3±1.0†	17.7±4.0†	Episodes /patient/12 months	NR	NR		
Hedman *et al.*, 2004[88]	ILis+basal	Severe	NR	0	Episodes	NR	NR	NR	NR
	HI+basal	Severe	NR	0	Episodes	NR	NR		
Heller *et al.*,1999[93]	ILis+NPH	Overall	NR	1,658	Episodes/8 months	NR	NR	p=0.001 for nocturnal at period 1 only	Overall (Minor): patients could deal with episode themselves Severe (Major):
		Severe		21 in 5 patients	Episodes/4 months				
		Nocturnal		52 (period 1, 4 months)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
	HI+NPH	Overall	NR	1,858	Episodes/8 months	NR	NR		patients required help from another person by administration of oral glucose, i.v. glucose or glucagon treatment Nocturnal: between 24:00 and 06:00
		Severe		16 in 7 patients	Episodes/4 months				
		Nocturnal		181 (period 1, 4 months)					
Heller *et al.*, 2004 [70]	IAsp+NPH	Minor	NR	35.8	Episodes/patient /year	NR	NR	p=0.048 for minor, p=0.001 for night	Overall: as symptoms or signs experienced by patient or observed by another person, or BG <3.0 mmol/L Severe: patient requiring assistance from another person Nocturnal: between 24:00 and 06:00
		Major all		0.85					
		Major night		0.8					
		Major day		0.86					
	HI+NPH	Minor	NR	38.2	Episodes/patient /year	NR	NR		
		Major all		1.12					
		Major night		2.7					
		Major day		0.58					
Holcombe *et al.*, 2002 [62]	ILis+NPH	Overall	NR	4.02±4.5*	Episodes/patient /30 days	NR	NR	p=0.023 for overall, p<0.001 for nocturnal	Overall: any experience of (or observed to have) symptoms
		Nocturnal		1.0±1.9*					
		Morning		4.4±5.8*					
		Afternoon		6.2±7.2*					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Evening		5.0±6.4*					associated with hypoglycemia, or BG<3.0 mmol/L Severe: needing assistance or requiring glucose or glucagon injection Nocturnal: NR
		Severe		6 in 5 patients	Episodes				
	HI+NPH	Overall	NR	4.37±4.5*	Episodes/patient /30 days	NR	NR		
		Nocturnal		1.7±2.6*					
		Morning		4.2±5.2*					
		Afternoon		6.7±8.1*					
		Evening		5.4±6.0*					
		Severe		5 in 5 patients	Episodes				
Holleman *et al.*,1997[83]	ILis +NPH	Overall	[5.7±5.8* episodes/patient/30 days]	2,249	Episodes	NR	NR	p=0.037 for severe, p<0.001 for nocturnal, p=0.015 for morning	Overall: BG<3 mmol/L Severe: an episode where the patient could not self-treat and/or received i.v. glucose or glucagon and/or experienced coma Nocturnal: NR
		Severe		36					
		Nocturnal		176					
		Morning		783					
		Afternoon		720					
		Evening		546					
	HI+NPH	Overall	[5.7±5.8* episodes/patient/30 days]	2,344	Episodes	NR	NR		
		Severe		58					
		Nocturnal		312					
		Morning		612					
		Afternoon		790					
		Evening		604					
Home *et al.*, 1998[67]	IAsp+NPH	Overall	NR	567	Episodes	NR	NR	NS for overall, p<0.002 for major	Overall: an event dealt with by patient Severe: requiring help
		Major		20 events in 16 patients					
	HI+NPH	Overall	NR	615	Episodes	NR	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Major		44 events in 24 patients					from a third party Nocturnal: NR
Home *et al.*, 2000[96] [Bott, 2003]	IAsp+NPH	Minor	NR	563 (80)	# patients (% patients)	NR	NR	NS for minor and major, p<0.05 for major night grade B	Overall (Minor): symptomatic events dealt with by patient Severe (Major): major grade A as requiring third-party help; major grade B as requiring parenteral glucose or glucagon Nocturnal: NR
		Major all		111 (16)					
		Major Nocturnal		54 (7.6)					
	HI+NPH	Minor	NR	270 (75)	# patients (% patients)	NR	NR		
		Major all		65 (18)					
		Major Nocturnal		39 (10.9)					
Home, 2006[100] [Extension study of Home *et al.*, 2000]	IAsp+NPH	Minor	563 (80)	488 (86)	# patients (%)	NR	NR	p<0.05 for minor, NS for major and nocturnal	Minor: managed by patient without assistance from others Major: Grade A as requiring third-party help; Grade B as requiring parenteral glucose or glucagon
		Major all	111 (16)	162 (29)					
		Major Nocturnal	54 (7.6)	86 (15)					
	HI+NPH	Minor	270 (75)	153 (82)	# patients (%)	NR	NR		
		Major all	65 (18)	58 (31)					
		Nocturnal	39 (10.9)	32 (17)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
Iwamoto *et al.*,2001[97]	IAsp+basal	NR	NR	542/66 (46.2)	# of events / # of patients (% of patients)	NR	NR	NR	Overall: hypoglycemic episodes listed in table with 15 specific symptoms (not graded)
	HI+basal	NR	NR	255/31 (50.0)	# of events / # of patients (% of patients)	NR	NR		
Jacobs *et al.*, 1997[66]	ILis+NPH	Overall	NR	6.5±4.2*	Frequency (no units given)	NR	NR	NR	Overall: I, vague feeling, no action taken; II, extra carbohydrates required; III, assistance of another person necessary
	HI +NPH	Overall	NR	6.7±4.6*	Frequency (no units given)	NR	NR		
Jansson *et al.*, 1998[85]	ILis+NPH	Overall	4.14±0.53†	3.36±0.59†	Episodes/patient /30 days	-0.78	NR	NR	Overall: BG≤3.0 mmol/L Severe: NR Nocturnal: NR
	HI+NPH	Overall	2.70±0.45†	2.70±0.43†	Episodes/patient /30 days	-0.11	NR		
Johansson *et al.*, 2000[89]	ILis+basal	NR	NR	9.7	Episodes/patient /30 days	NR	NR	NS	Overall: BG <3.0 mmol/L and/or subjective signs of hypoglycemia Severe: NR Nocturnal: NR
	HI+basal	NR	NR	8	Episodes/patient /30 days	NR	NR		
Linkeschova *et al.*, 2003[57]	ILis	Severe	NR	4 (2 treated with i.v. glucose)	# cases	NR	NR	NR	Overall: NR Severe: requiring

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
	HI	Severe	NR	1 (treated with i.v. glucose)	# cases	NR	NR		external help Nocturnal: NR
Mathiesen *et al.*, 2007[29]	IAsp+NPH	Overall	NR	149 (94.9%); 8,507 (102.1)	N (% of patients); events (rate episodes/year)	NR	NR	NS	Nocturnal: Episodes between midnight and 6:00. Major: Requiring third-party assistance with plasma glucose <3.1 mmol/L or reversal of symptoms after food, glucagon, or intravenous glucose during pregnancy Minor: Plasma glucose <3.1 mmol/L with or without symptoms Symptoms only: No plasma glucose measured or plasma glucose >3.0 mmol/L
		Major		38 (24.2%) 113 (1.4)					
		Minor		148 (94.3%); 7,197 (86.4)					
		Symptoms		85 (54.1%); 1,055 (12.7)					
		Not classified		19 (12.1%); 142 (1.7)					
	HI+NPH	Overall	NR	150 (90.9%); 9,261 (110.1)	N (% of patients); events (rate episodes/year)	NR	NR	NS	
		Major		35 (21.2%); 174 (2.1)					
		Minor		148 (89.7%); 7,944 (94.5)					
		Symptoms		85 (51.5%); 742 (8.8)					
		Not classified		20 (12.1%); 401 (4.8)					
Melki *et al.*, 1998[94]	ILis+basal	Overall	NR	7.03±0.94[†]	Episodes/patient /30 days	NR	NR	I versus II, p<0.05 for BG<2.0 mmol/L	Overall: BG <3.0 mmol/L, <2.0 mmol/L Severe: requiring
		BG<2.0 mmol/L		0.05±0.05[†]					
		Severe		3 episodes in 3 patients					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
	HI+basal	Overall	NR	7.94±0.88[†]	Episodes/patient /30 days	NR	NR		external help to take sugar, but not requiring glucagon or glucose injection Nocturnal: NR
		BG<2.0 mmol/L		0.47±0.19[†]					
		Severe		7 episodes in 4 patients					
Persson *et al.*, 2002[65]	ILis+NPH	BG<3.0 mmol/L	NR	5.50%	Rate	NR	NR	NR	Overall: BG<3.0 mmol/L Severe: coma or the need of assistance Nocturnal: NR
		Severe		0 patients					
	HI+NPH	BG<3.0 mmol/L	NR	3.90%	Rate	NR	NR		
		Severe		2 patients					
Provenzano *et al.*, 2001[86]	ILis+basal	Overall	NR	24	Episodes	NR	NR	NR	Overall: S1, spontaneous resolution of symptoms and signs; S2, resolution after glucose ingestion; S3, resolution after glucagon injection; S4, resolution after i.v. glucose; S5, coma Severe: NR Nocturnal: NR
	HI+basal	Overall	NR	36	Episodes	NR	NR		
Raskin *et al.*, 2001[90]	ILis+basal	Overall	NR	8 in 7 patients	Episodes	NR	NR	NR	Overall: patient experiencing or another person
		Severe		3 in 3 patients					
	HI+basal	Overall	NR	11 in 7 patients	Episodes	NR	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Severe		3 in 2 patients					observing a sign or symptom associated with hyperglycemia or BG<3.0 mmol/L (54 mg/dL) Severe: NR Nocturnal: NR
Raskin *et al.*, 2000[98]	IAsp+NPH	Major	NR	0.91	Episodes/patient /year	NR	NR	NR	Overall (Minor): BG<2.5 mmol/L (45 mg/dl) or symptoms of hypoglycemia and patient could deal with the episode on their own Severe (Major): episode that required third-party help or administration of parenteral glucose or glucagon Nocturnal: between 24:00 and 06:00
		Minor		43.44					
	HI+NPH	Major	NR	1.13	Episodes/patient /year	NR	NR		
		Minor		45.48					
Recasen *et*	ILis+NPH	Overall	NR	0.3	Episodes/week	NR	NR	NR	Overall (Mild):

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
al., 2003[68]	HI+NPH	Overall	NR	0.8	Episodes/week	NR	NR		symptoms or signs associated with hypoglycemia which did not require third-party assistance Severe: those associated with neuroglycopenia requiring assistance from a third party Nocturnal: NR
Renner *et al.*, 1999[91]	ILis+basal	Overall	NR	12.4±13.9*	Episodes/patient /30 days	NR	NR	NS	Overall: BG<3.3 mmol/L, <2.9 mmol/L, and <2.2 mmol/L Severe: NR Nocturnal: NR
		BG<2.2 mmol/L		0.08±0.2*					
	HI+basal	Overall	NR	11.0±11.2*	Episodes/patient /30 days	NR	NR		
		BG<2.2 mmol/L		0.2±0.6*					
Roach *et al.*, 1999[49]	Mix50 (a.m.)+Mix25 (p.m.)	Overall	NR	71	% patients	NR	NR	NS (for % patients), p=0.127	Overall: patient experiencing a symptom or another person
		Nocturnal		1.5±2.3*	Episodes/patient /3 months				
	BHI50	Overall	NR	68	% patients	NR	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
	(a.m.)+BHI30/70 (p.m.)	Nocturnal		2.9±5.1*	Episodes/patient /3 months				observing a sign associated with hypoglycemia, or BG<3.0 mmol/L Severe: occurrence of coma or requirement for i.v. glucose, glucagon, or both Nocturnal: between 22:30 and 07:45
Schmau *et al.*, 1998[95]	ILis+basal	Overall	NR	4.0±0.9†	Episodes/patient /30 days	NR	NR	NS	Overall: as BG<3.mmol/L and/or subjective signs or symptoms of hypoglycemia Severe: NR Nocturnal: NR
	HI+basal	Overall	NR	3.2±0.7†	Episodes/patient /30 days	NR	NR		
Tamás *et al.*, 2001[99]	IAsp+NPH	Minor	NR	178 (2,495)	# patients (# episodes)	NR	NR	NR	Overall (Minor): self-treated Severe: major grade A as requiring third-party help; major grade B as requiring i.v. glucose or IM glucagon Nocturnal: NR
		Major		15 (32)					
	HI+NPH	Minor	NR	173 (2,838)	# patients (# episodes)	NR	NR		
		Major		17 (31)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
Tubiana-Rufi *et al.*, 2004[64]	ILis+basal	BG≤60 mg/dL	NR	11.0±6.4*	Episodes/patient /30 days	NR	NR	NR	Overall: BG≤60 mg/dL, ≤40 mg/dL, or events with ketonuria Severe: NR Nocturnal: NR
		BG≤40 mg/dL		0.6±1.1*					
	HI+ basal	BG≤60 mg/dL	NR	13.8±8.5*	Episodes/patient /30 days	NR	NR		
		BG≤40 mg/dL		1.0±1.1*					
Tupola *et al.*, 2001[63]	ILis +NPH	Overall	NR	4.9	Episodes/patient /30 days	NR	NR	NR	Overall: signs or symptoms associated with hypoglycemia or BG<3.0 mmol/L Severe: episodes resulting in unconsciousness Nocturnal: between 23:00 and 06:00
	HI +NPH	Overall	NR	4.4	Episodes/patient /30 days	NR	NR		
Valle *et al.*, 2001[87]	ILis+NPH	Overall	4.6±3.6*	1.8±1.8*	Episodes/patient /30 days	NR	p<0.001	p<0.001 for severe	Overall: BG<3.0 mmol/L(54 mg/dL) or signs or symptoms associated with
		Severe	12.9	13.8	% of total				
	HI+NPH	Overall	4.6±3.6*	1.8±1.7*	Episodes/patient /30 days	NR	p<0.001		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Severe	12.9	18.7	% of total				hypoglycemia Severe: episodes requiring assistance from another person or administration of glucagon or i.v. glucose Nocturnal: NR
Vignati *et al.*, 1997[50]	ILis +NPH	Overall	6.1±6.0*	4.6±5.5*	Episodes/30 days	NR	NR	p=0.677 (for epidodes/30 days)	Overall: BG<3.5 mmol/L (63 mg/dL), even if not associated with signs or symptoms Severe: NR
		Severe		5	# patients				
	HI +NPH	Overall	6.1±6.0*	4.5±5.0*	Episodes/30 days	NR	NR		
		Severe		5	# patients				
Zinman *et al.*, 1997[92]	ILis+basal	Overall	12.7±1.6†	8.6±1.4†	Episodes/patient /30 days	NR	p=0.035	NS for overall	Overall: BG<3.0 mmol/L or symptoms associated with hypoglycemia Severe: NR Nocturnal: NR
		BG	8.4±1.3†	6.0±0.9†			p=0.03		
	HI+basal	Overall	12.7±1.6†	10.8±1.8†	Episodes/patient /30 days	NR	NS		
		BG	8.4±1.3†	7.6±1.3†			NS		

*mean±SD; †mean SE. BG=blood glucose; BHI30/70=30% HI+70% NPH; DM=diabetes mellitus; HI=regular human insulin; IAsp=insulin aspart; ILis=insulin lispro; IM=intramuscular; i.v.=intravenous; Mix25=biphasic human lispro (25% lispro, 75% neutral protamine lispro); Mix50=biphasic human lispro (50% ILis, 50% neutral protamine lispro); NPH=neutral protamine Hagedorn; NPL=neutral protamine lispro; NR=not reported; NS=not significant; UL=ultralente.

APPENDIX 11B: HYPOGLYCEMIA IN PATIENTS WITH TYPE 2 DM

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
Altunas *et al.*, 2003[74]	ILis+NPH	Overall	NR	0.57	Episodes/patient (%)	NR	0.012 for groups	Overall: symptoms associated with hypoglycemia or BG<3.3 mmol/L Severe: NR Nocturnal: NR
	ILis+Metf	Overall	NR	0.4	Episodes/patient (%)	NR		
	HI+NPH	Overall	NR	0.009	Episodes/patient (%)	NR		
Anderson *et al.*, 1997[103]	ILis	Overall	3.13±0.20†	3.18±0.16†	Episodes/30 days/patient	NR	p<0.02 for overall; p=0.007 for symptomatic	Overall: Asymptomatic hypoglycemia as no symptoms and BG<3.5 mmol/L (<63 mg/dL); symptomatic hypoglycemia as symptoms and BG<3.5 mmol/L (<63 mg/dL) Severe: patient requiring glucagon or i.v. glucose treatment Nocturnal: between 24:00 and 06:00
		Severe		1 (1)	Patients (episodes)			
		Symptomatic and BG<3.5 mmol/L		2,934	Episodes			
		Nocturnal		0.47±0.05	Episodes/30 days/patient			
	HI	Overall	3.13±0.20†	3.43±0.19†	Episodes/30 days/patient	NR		
		Severe		4 (5)	Patients (episodes)			
		Symptomatic and BG<3.5 mmol/L		3,215	Episodes			
		Nocturnal		0.73±0.07	Episodes/30 days/patient			
Anderson *et al.*, 1997[45]	ILis	Overall	2.1±0.3†	1.5±0.2†	Episodes/30 days/patient	<0.05	NR	Overall: sign or symptom normally associated with hypoglycemia or BG<2.0 mmol/L Severe: NR Nocturnal: NR
	HI	Overall	2.5±0.4†	1.6±0.3†	Episodes/30 days/patient	<0.05		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
Bastyr *et al.*, 1999[111]	ILis+NPH	Overall	NR	1.17	Episodes/30 days/patient	NR	ILis+NPH versus ILis+Sfu, p=0.001 for nocturnal; ILis+Sfu versus NPH+Sfu, p<0.001 for nocturnal	Overall: BG<3.0 mmol/L (54 mg/dL), with or without symptoms Severe: NR Nocturnal: NR
		Nocturnal		0.10±0.37*				
	ILis+Sfu	Overall	NR	0.98	Episodes/30 days/patient	NR		
		Nocturnal		0				
	NPH+Sfu	Overall	NR	0.75	Episodes/30 days/patient	NR		
		Nocturnal		0.13±0.47*				
Bastyr *et al.*, 2000[119]	ILis+Gly	Overall	NR	1.1±1.4*	Episodes/30 days/patient	NR	NR	Overall: patient experiencing a symptom associated with hypoglycemia or BG<3.9 mmol/L Severe: NR Nocturnal: NR
	Metf+Gly	Overall	NR	0.7±1.5*	Episodes/30 days/patient	NR		
	NPH+Gly	Overall	NR	0.6±1.3*	Episodes/30 days/patient	NR		
Boehm *et al.*, 2004[108]	BIAsp30	Major	NR	3 (3)	Patients (episodes)	NR	NR	Overall (Minor): symptoms, if possible, confirmed by BG (value not specified) Severe (Major): requiring assistance and/or treatment with an i.v. injection of glucose or glucagon Nocturnal: NR
		Minor		35 (398)				
	BHI30/70	Major	NR	11 (19)	Patients (episodes)	NR		
		Minor		41 (555)				
Bretzel *et al.*, 2004[75]	IAsp	Overall	NR	0.4 (41)	Episodes/30 days/patient (% of patients)	NR	IAsp versus HI, p=0.122; HI versus BHI30/70, p=0.090; IAsp versus BHI30/70, p=0.827	NR
	HI	Overall	NR	0.56 (41)	Episodes/30 days/patient (% of patients)	NR		
	BHI30/70	Overall	NR	0.19 (30)	Episodes/30 days/patient (% of patients)	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
Forst *et al.*, 2003[112]	ILis	Overall	NR	4 (6.5)	Patients (% of patients)	NR	NS	Overall: BG <3.0 mmol/L (54 mg/dL); Severe: requiring outside assistance; Nocturnal: NR
	Glib	Overall	NR	8 (13.8)	Patients (% of patients)	NR		
Gallagher and Home, 2005[109]	IAsp	NR	NR	NR	NR	NR	NR	NR
	HI	NR	NR	NR	NR	NR		
Herz *et al.*, 2003[76]	Mix25	outpatient (4 weeks)	NR	0.049±0.018†	Episodes/30 days/patient	NR	NS	Overall: any time a patient experienced or another person observed a patient experiencing a self-assessed sign/symptom associated with hypoglycemia, or BG<3.0 mmol/L (54 mg/dL) Severe: NR Nocturnal: NR
		inpatient (3 days)		0.241±0.053				
	BHI30/70	outpatient (4 weeks)	NR	0.100±0.018†	Episodes/30 days/patient	NR		
		inpatient (3 days)		0.222±0.053				
Herz *et al.*, 2002[120]	Mix25	outpatient (4 weeks)	NR	0.7±0.2†	Episodes/30 days/patient	NR	p=0.042 for outpatient, NS for inpatient	Overall: any time a patient felt, or another person observed, that he or she was experiencing a symptom associated with this or any BG measurement <3.0 mmol/L (54 mg/dL) Severe: NR Nocturnal: NR
		inpatient (3 days)		0.9±0.2†				
	BHI30/70	outpatient (4 weeks)	NR	1.2±0.3†	Episodes/30 days/patient	NR		
		inpatient (3 days)		0.9±0.1†				
Herz, 2002[113]	Mix25	NR	0.14±0.14†	0.31±0.21†	Episodes/30 days/patient	NR	0.028 (post-treatment); 0.077	Overall: BG<3.0 mmol/L or any time hypoglycemic symptoms were experienced by the patient or observed by another person Severe: requiring
	Gly	NR	0.01±0.01†	0.01± 0.02†	Episodes/30 days/patient	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
								assistance by another person Nocturnal: NR
Iwamoto, 2003[58] [Abstract]	BIAsp30	NR	NR	56.1	% of patients having ≥1 episode	NR	NR	Overall: NR Severe (Major): requiring third-party assistance Nocturnal: NR
	BHI30/70	NR	NR	57	% of patients having ≥1 episode	NR		
Kilo *et al.*, 2003[110]	BIAsp30+Metf	Overall	NR	20 (43%)	patients (% patients)	NR	NR	Overall: symptoms of hypoglycemia and/or BG<50 mg/dL that did not require third-party assistance Severe (Major): BG<50 mg/dL with severe CNS symptoms, requiring third-party assistance Nocturnal: between 24:00 and 06:00
		Major		0				
		Nocturnal		7 (15)				
	NPH+Metf	Overall	NR	13 (28%)	patients (% patients)	NR		
		Major		0				
		Nocturnal		11 (23)				
	BHI30/70+ Metf	Overall	NR	15 (32%)	patients (% patients)	NR		
		Major		0				
		Nocturnal		11 (23)				
Laube *et al.*, 1996[48]	ILis	Overall	NR	57	Episodes	NR	NS	Overall: BG<65 mg% (3.5 mmol/L) Severe: 4 degrees of severity: 0=hypoglycemia without symptoms; degree 1=minor symptoms; degree 2=moderately severe symptoms; degree 3=severe impairment requiring outside help Nocturnal: NR
	HI	Overall	NR	74	Episodes	NR		
Lourens *et al.*, 2000[104]	Mix 25	NR	NR	1.08±0.27[†]	Episodes/30 days/patient	NR	NS	Overall: BG<3.0 mmol/L or symptoms of

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
	BHI	NR	NR	0.88±0.22†	Episodes/30 days/patient	NR		hypoglycemia felt by the patient or observed by another person Severe: NR Nocturnal: NR
Malone *et al.*, 2003[115]	Mix25+Metf	Overall	0.08±0.59*	0.31±1.07*	Episodes/30 days/patient (% of patients)	NR	NS for overall and severe, p=0.07 for nocturnal	Overall: any time a patient felt or another person observed the patient experiencing a sign or symptom of hypoglycemia or BG<3.5 mmol/L Severe: requiring assistance with treatment or BG≤2.0 mmol/L Nocturnal: after bedtime and before awakening
		Severe	0.01±0.09* (0.3)	0.01±0.11* (1.0)				
		Nocturnal	0.03±0.23 (1.4)	0.01±0.11* (1.0)				
	Glib+Metf	Overall	0.01±0.09*	0.48±1.17*	Episodes/30 days/patient (% of patients)	NR		
		Severe	0.00±0.00* (0.0)	0.02±0.15* (1.3)				
		Nocturnal	0	0.08±0.40* (5)				
Niskanin *et al.*, 2004[31]	ILis Mix25 (using pen)	Minor episodes		101	1st 4 weeks		NS	Major: requiring third-party assistance Minor: BG<2.8 mmol/L with or without symptoms of hypoglycemia Symptomatic: not confirmed by BG reading
		Minor rate		0.69	last 8 weeks (episodes/patient/month)			
	BIAsp 30 versus (using pen)	Minor episodes		79	1st 4 weeks			
		Minor rate		0.62	last 8 weeks (episodes/patient/month)			
Raskin *et al.*, 1999[59] [Abstract]	IAsp+NPH	Minor	NR	Same (descriptive)	NR	NR	NS	NR
		Major						
	HI+NPH	Minor	NR	Same (descriptive)	NR	NR		
		Major						
Raz *et al.*, 2003[117]	BIAsp30+Ros	Overall	NR	5.3	Episodes/year	NR	p<0.01	Overall (Minor): BG<50 mg/dL, handled without assistance from others; symptomatic as not
		Major		0				
	Glib+Ros	Overall	NR	0	Episodes/year	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Major		0				confirmed with BG measurement Severe (Major): requiring assistance from others and either BG<50 mg/dL or severe central nervous system symptoms requiring i.v. glucose or IM glucagon or ingestion of food Nocturnal: NR
Raz *et al.*, 2005[118]	BIAsp30	Major	NR	0	# of patients (episodes)	NR	NR	Symptomatic: symptoms of hypoglycemia present but not confirmed by BG measurement Minor: BG<50 mg/dL and not requiring assistance from others Major: BG<50 mg/dL and patient required assistance from others or symptoms remitted after administration of i.v. glucose or IM glucagon or after food intake
		Minor		15 (47)				
		Symptom		39 (171)				
		Nocturnal		(8)				
	BIAsp30+Pio	Major	NR	0	# of patients (episodes)	NR		
		Minor		11 (15)				
		Symptom		32 (115)				
		Nocturnal		0				
	Glib+Pio	Major	NR	0	# of patients (episodes)	NR		
		Minor		3 (3)				
		Symptom		14 (42)				
		Nocturnal		0				
Roach *et al.*, 2001[116]	Mix25	Overall	NR	0.30±0.53	Episodes/30 days/patient	NR	<0.0001 for episodes/patient/30 days; p<0.001 for No. of patients having ≥1 episode	Overall: signs or any symptoms associated with hypoglycemia or BG<3.0 mmol/L(54 mg/dL) Severe: NR Nocturnal: NR
				38 (44.7)	No. (%) of patients having ≥1 episode	NR		
	Gly	Overall	NR	0.05±0.20	Episodes/30 days/patient	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
			NR	9 (10.3)	No. (%) of patients having ≥1 episode	NR		
Roach *et al.*, 1999[105]	Mix25	Severe	NR	1	# of patients (% of patients)	NR	NR	Overall: any time a patient experienced a symptom or another person observed a sign associated with hypoglycemia or BG<3.0 mmol/L Severe: NR Nocturnal: between the mean reported bedtime and the mean reported breakfast time for each country
		Nocturnal		13 (15)				
	BHI30/70	Severe	NR	1	# of patients (% of patients)	NR		
		Nocturnal		8 (9)				
	Mix25	NR	NR	19 (21)	# (%) of patients having >2 episodes/30 days	NR	NS	
	BHI30/70	NR	NR	13 (15)	No. (%) of patients having >2 episodes/30 days	NR		
Roach *et al.*, 1999[49]	Mix25	Overall	NR	(40)	Episodes/30 days/patient (% of patients)	NR	NS	Overall: patient experiencing a symptom or another person observing a sign associated with hypoglycemia, or BG<3.0 mmol/L Severe: occurrence of coma or requirement for i.v. glucose, glucagon, or both Nocturnal: between 22:30 and 07:45
		Nocturnal		0.3±1.0*				
	BHI30/70	Overall	NR	(37)		NR		
		Nocturnal		0.6±1.4*				
Ross *et al.*, 2001[106]	ILis	Overall	NR	1.8±0.3†	Episodes/30 days/patient	NR	p=0.057 for nocturnal	Overall: BG<3 mmol/L or development of typical hypoglycemic symptoms Severe: an event requiring
		Nocturnal		0.08				
	HI	Overall	NR	1.7±0.3†	Episodes/30	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
		Nocturnal		0.16	days/patient			assistance by another person or a coma or seizure Nocturnal: NR
Schernthaner *et al.*, 2004[107]	Mix25	Overall	NR	14 (41.2)	No. (%) of patients having ≥1 episode	NR	NS for frequency	Overall: BG<65 mg/dL or signs or symptoms of hypoglycemia felt by patient or observed by others Severe: BG<36 mg/dL, coma or treatment with glucagon or i.v. glucose Nocturnal: NR
	BHI30/70	Overall	NR	10 (29.4)	No. (%) of patients having ≥1 episode	NR		
Vignati *et al.*, 1997[50]	ILis+NPH	Overall	2.5±4.7*	1.9±3.9*	Episodes/30 days/patient (# of patients)	NR	NS	Overall: BG<3.5 mmol/L (63 mg/dL), even if not associated with signs or symptoms Severe: NR Nocturnal: NR
		Severe		0				
	HI+NPH	Overall	2.5±4.7*	1.9±3.7*	Episodes/30 days/patient (# of patients)	NR		
		Severe		0				

*mean±SD; †mean±SE. BG=blood glucose; BHI30/70=30% HI + 70% NPH; BIAsp30=30% IAsp +70%; PIA; Glib=glibenclamide; Gly=glyburide; HI=conventional human insulin; IAsp=insulin aspart; IGlu=insulin glulisine; ILis=insulin lispro; IM=intramuscular; i.v.=intravenous; Metf=metformin; Mix25=biphasic human lispro (25% lispro, 75% neutral protamine lispro); NPH=neutral protamine Hagedorn; NPL=neutral protamine lispro; NR=not reported; NS=not significant; Ros=rosiglitazone; Sfu=sulfonylurea.

APPENDIX 11C: HYPOGLYCEMIA IN PATIENTS WITH GESTATIONAL DM

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint versus baseline)	p-value between Treatments	Definition of Hypoglycemia
Jovanovic *et al.*, 1999[52]	ILis	BG<55mg/mL	NR	0.88±0.25†	Episodes/ patient	NR	NR	NR	Overall: BG<55 mg/dL (3.1 mmol/L) or symptoms associated with hypoglycemia Severe: NR Nocturnal: NR
	HI	BG<55mg/mL	NR	2.20±0.86†	Episodes/ patient	NR	NR		
Mecacci *et al.*, 2003[53]	ILis		NR	NR	NR	NR	NR	NR	NR
	HI		NR	NR	NR	NR	NR		

*mean±SD; †mean±SE. BG=blood glucose; DM=diabetes mellitus; HI=conventional human insulin; ILis=insulin lispro; NR=not reported.

APPENDIX 12A: BODY WEIGHT AND BMI IN PATIENTS WITH TYPE 1 DM

Study	Comparators	Weight at Baseline (Kg)	Weight at Endpoint (Kg)	Weight Change from Baseline (Kg)	p-value Endpoint versus Baseline	p-value between Treatments	BMI at Baseline (kg/m²)	BMI at Endpoint (kg/m²)	BMI Change from Baseline (kg/m²)	p-value Endpoint versus Baseline	p-value between Treatments
Anderson *et al.*, 1997[77]	ILis+NPH or UL	71.2±0.4†	71.5±0.4†	NR	NR	NR	NR	NR	NR	NR	NR
	HI+NPH or UL	71.2±0.4†	71.8±0.4†	NR	NR						
Annuzzi *et al.*, 2001[78]	ILis+NPH	65.9±9.9*	66.7±10.3*	p < 0.05	NR	NR	NR	NR	NR	NR	NR
	HI+NPH	65.9±9.9*	66.4±10.5*	p < 0.05	NR						
Gale *et al.*, 2000[73]	ILis+basal	NR	77	NR	NR	p=0.305	NR	NR	NR	NR	NR
	HI+basal	NR	77.2	NR	NR						
Garg *et al.*, 1996[82]	ILis+NPH or UL	74.8±9.7*	73.0±9.5*	NR	NR	NR	NR	NR	NR	NR	NR
	HI+NPH or UL	74.7±11.1*	75.6±10.4*	NR	NR						
Heller *et al.*, 1999[93]	ILis+NPH	74.8±11.8*	74.7±11.7*	NR	p=0.048	NR	NR	NR	NR	NR	NR
	HI+NPH	73.5±10.1*	75.7±10.2*	NR	NS						
Holleman *et al.*, 1997[83]	ILis+NPH	75.0±12.7*	75.3±13.1*	NR	NR	p=0.03	NR	NR	NR	NR	NR
	HI+NPH	75.0±12.7*	75.8±13.0*	NR	NR						
Jansson *et al.*, 1998[85]	ILis+NPH	70.7±1.6†	70.9±1.6†	NR	NR	NR	NR	NR	NR	NR	NR
	HI+NPH	74.2±1.7†	74.4±1.7†	NR	NR						
Melki *et al.*, 1998[94]	ILis+basal	NR	NR	0.04±0.29†	NR	NR	NR	NR	NR	NR	NR
	HI+basal	NR	NR	0.48±0.26†	NR						
Raskin *et al.*, 2000[98]	IAsp+NPH	NR	NR	NR	NR	NR	25.6±3.6*	NR	0.44	NR	NR
	HI+NPH	NR	NR	NR	NR	NR	25.7±3.2 *	NR	0.48	NR	NR
Raskin *et al.*, 2001[90]	ILis+basal	78.3±17.9*	79.2±17.1*	NR	NR	p=0.780	NR	NR	NR	NR	NR
	HI+basal	77.3±16.7*	78.8±17.3*	NR	NR						
Zinman *et al.*, 1997[92]	ILis+basal	72.7±1.8†	72.6±1.8†	NR	NR	NR	NR	NR	NR	NR	NR
	HI+basal	72.7±1.8†	72.8±1.8†	NR	NR						

*mean±SD; †mean±SE. BMI=body mass index; DM=diabetes mellitus; HI=conventional human insulin; IAsp=insulin aspart; ILis=insulin lispro; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; UL=ultralente.

APPENDIX 12B: BODY WEIGHT AND BMI IN PATIENTS WITH TYPE 2 DM

Study	Comparators	Weight at Baseline (Kg)	Weight at Endpoint (Kg)	Weight Change from Baseline (Kg)	p-value Endpoint versus Baseline	p-value between Treatments	BMI at Baseline (kg/m²)	BMI at Endpoint (Kg/m²)	BMI Change from Baseline (Kg/m²)	p-value Endpoint versus Baseline	p-value between Treatments
Altuntas *et al.*, 2003[74]	ILis+NPH	NR	NR	NR	NR	NR	31.2±7.8†	32.6±2.7†	NR	NR	NR
	ILis+Metf						31.8±2.7†	31.0±7.0†	NR	NR	NR
	HI+NPH						31.3±3.8†	32.6±3.4†	NR	NR	NR
Anderson *et al.*, 1997[103]	ILis+NPH	80.2±0.5†	80.9±0.5†	NR	NR	p=0.10	NR	NR	NR	NR	NR
	HI+NPH	80.2±0.5†	81.2±0.5†	NR							
Bastyr *et al.*, 1999[111]	ILis+NPH	84.15	NR	1.54±3.05*	NR	p=0.02 (ILis+NPH versus NPH+Sfu) p=0.04 (ILis+Sfu versus NPH+Sfu)	29.84	NR	0.52±1.10*	NR	ILis+Sfu versus NPH+Sfu p=0.031 ILis+NPH versus NPH+Sfu p=0.007
	ILis+Sfu	80.53	NR	0.57±2.23*	NR		29.16	NR	0.46±1.04*	NR	
	NPH+Sfu	79.4	NR	0.21±0.80*	NR		28.71	NR	0.21±0.80*	NR	
Bastyr *et al.*, 2000[119]	ILis+Gly	87.7	NR	3.4±2.9*		p<0.001 for ILis or NPH versus Metf; p=0.05 for ILis versus NPH	NR	NR	NR	NR	NR
	Metf+Gly	82.6	NR	0.4±2.2*							
	NPH+Gly	82.8	NR	2.3±2.4*							
Boehm *et al.*, 2004[108]	BIAsp30	NR	NR	0.05±0.81†	NR	p=0.07	NR	NR	NR	NR	NR
	BHI30/70	NR	NR	2.0±0.69†	NR						
Forst *et al.*, 2003[112]	ILis	87.2±12.3*	86.5±12.2*	NR	NR	P=0.306	NR	NR	NR	NR	NR
	Glib	84.1±13.7*	84.4±13.3*	NR	NR						
Herz *et al.*,	Mix25	78.65±11.5*	79.70±1.47†	1.02±0.35†	NR	p=0.151 at	NR	NR	NR	NR	NR

Study	Comparators	Weight at Baseline (Kg)	Weight at Endpoint (Kg)	Weight Change from Baseline (Kg)	p-value Endpoint versus Baseline	p-value between Treatments	BMI at Baseline (kg/m²)	BMI at Endpoint (Kg/m²)	BMI Change from Baseline (Kg/m²)	p-value Endpoint versus Baseline	p-value between Treatments
2002[113]	Gly	77.34±12.0*	76.61±1.55†	-0.85±0.18†	NR	end point; p<0.001 for change from baseline					
Kilo *et al.*, 2003[110]	BIAsp30+Metf	NR	NR	0.7	NR	p=0.251 between treatments	NR	NR	NR	NR	NR
	NPH+Metf	NR	NR	0.1	NR						
	BHI30/70+Metf	NR	NR	1	NR						
Lourens *et al.*, 2000[104]	Mix25	NR	79.0±2.44†	NR	NR	NS	NR	NR	NR	NR	NR
	BHI30/70	NR	78.4±2.41†	NR	NR						
Malone *et al.*, 2003[115]	Mix25+Metf	83.0±15.2*	84.0±15*	0.8±3.4*	NR	p=0.330	NR	NR	NR	NR	NR
	Glib+Metf	81.7±15.7*	82.2±15.4*	0.3±2.8*	NR						
Raz *et al.*, 2005[118]	BIAsp30	NR	NR	2.2	NR	NR	NR	NR	NR	NR	NR
	BIAsp30+Pio	NR	NR	4	NR						
	Glib+Pio	NR	NR	2.2	NR						
Raz *et al.*, 2003[117]	BIAsp30+Ros	NR	NR	0.23	NR	NR	NR	NR	NR	NR	NR
	Glib+Ros	NR	NR	0.03	NR						
Roach *et al.*, 2001[116]	Mix25	74.1±12.4*	NR	1.32±2.4*	p<0.001	p<0.001 for change	NR	NR	NR	NR	NR
	Gly (maximum dose)	75.8±11.4*	NR	-0.70±2.6*	p=0.014						
Ross *et al.*, 2001[106]	ILis+NPH	79±2†	84±2†	NR	NR	NR	NR	NR	NR	NR	NR
	HI+NPH	77±2†	81±2†	NR	NR						

*mean±SD; †mean±SE. BHI30/70=30% HI+70% NPH; BIAsp30=30% IAsp+70% PIA; BMI=body mass index; DM=diabetes mellitus; Glib=glibenclamide; Gly=glyburide; HI=conventional human insulin; ILis=insulin lispro; Metf=metformin; Mix25=biphasic human lispro (25% lispro, 75% neutral protamine lispro); NPH=neutral protamine Hagedorn; NPL=neutral protamine lispro; NR=not reported; PIA=protamine insulin aspart; Pio=pioglitazone; Ros=Rosiglitazone; Sfu=sulfonylurea; NS=not significant.

APPENDIX 12C: WEIGHT IN PATIENT WITH GESTATIONAL DM

Study	Trial Type	Treatment Arm Number	Treatment Arm	No. of Patients at Baseline	Weight at Baseline (Kg)	Treatment Duration	Weight at End (kg) of Treatment	Weight (change from baseline) at End of Treatment (kg)	p-value (post-treatment versus baseline)	p-value (analogue versus control)
Mecacci *et al.*, 2003[53]		I	ILis	25	61.4 (55 to 78)*	As early as 16-week gestation to 38-week gestation	NR	10.9 (7 to 17)*	NR	p=NS
		II	HI	24	60.5 (50 to 79)*	As above	NR	11.1 (8 to 14)*	NR	

*Median (range). DM=diabetes mellitus; HI=conventional human insulin; ILis=insulin lispro; NR=not reported; NS=not significant.

APPENDIX 13: DKA IN PATIENTS WITH TYPE 1 DM

Study	Comparators	DKA		
		Basal Level		Post-treatment
		Total Number of Patients	Number of Patients with DKA	Number of Patients with DKA
Hedman *et al.*, 2001[88]	ILis+basal	12	NR	0
	HI+basal	12	NR	0
Iwamoto *et al.*, 2001[97]	IAsp+basal	143	NR	1
	HI+basal	62	NR	0
Johansson *et al.*, 2000[89]	ILis+NPH	41	NR	1
	HI+NPH	41	NR	0
Raskin *et al.*, 2001[90]	ILis+basal	58	NR	1
	HI+basal	58	NR	0
Renner *et al.*, 1999[91]	ILis+basal	113	NR	5
	HI+basal	113	NR	4
Tubiana-Rufi *et al.*, 2004[64]	ILis+basal	27	NR	0
	HI+basal	27	NR	2

DKA=diabetic ketoacidosis; HI=conventional human insulin; IAsp=insulin aspart; ILis=insulin lispro; NPH=neutral protamine Hagedorn; NR=not reported.

APPENDIX 14A: QoL DATA IN PATIENTS WITH TYPE 1 DM

Study	Treatment	DTSQ					WBQ					
		Total (scale)	Satisfaction (scale)	Convenience (scale)	Flexibility (scale)	Willingness to Continue (scale)	Total	Depression	Anxiety	Energy	Positive Well-Being	Others
Annuzzi *et al.*, 2001[78]	ILis+NPH		4.80±0.23* p<0.001 (0 to 6)	4.53±0.20* p<0.001 (0 to 6)	4.33±0.20* p<0.001 (0 to 6)	5.0±0.27* p<0.001 (0 to 6)	NR	NR	NR	NR	NR	NR
	HI+NPH		4.20±0.20* (0 to 6)	3.40±0.17* (0 to 6)	3.53±0.17* (0 to 6)	4.13±0.16* (0 to 6)	NR	NR	NR	NR	NR	NR
Bott *et al.*, 2003[72] (combined with Home *et al.*[96])	IAsp+NPH	32.0±0.30† p<0.001 (0 to 36)	4.88±0.09† p<0.001 (0 to 6)	4.96±0.09† p<0.01 (0 to 6)	5.18±0.08† p<0.0001 (0 to 6)	5.43±0.08† p<0.0001 (0 to 6)	NR	NR	NR	NR	NR	NR
	HI+NPH	29.70±0.40† (0 to 36)	4.73±0.12† (0 to 6)	4.75±0.12† (0 to 6)	4.80±0.10† (0 to 6)	4.98±0.10† (0 to 6)	NR	NR	NR	NR	NR	NR
Danne *et al.*, 2005[55] (Abstract)	IAsp+basal	Positive for IAsp	NR	NR	NR	Satisfied to continue with IAsp (p=0.045)	NR	NR	NR	NR	NR	NR
	HI+basal		NR	NR	NR		NR	NR	NR	NR	NR	NR
Ferguson *et al.*, 2001[81]	ILis+NPH	No improvements despite lower incidence of severe hypoglycemia	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HI+NPH		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gale, 2000[73]	ILis+NPH	NSD between treatments	NR	NR	NR	NR	NSD between treatments	NR	NR	NR	NR	NR
	HI+NPH							NR	NR	NR	NR	NR
Holleman *et al.*, 1997[83]	ILis+NPH	NR	NR	General: 86% easier versus 2% more difficult, p<0.0001 Timing of meals: 70% versus 3%, p<0.0001 Physical planning: 51% versus 9%, p<0.0001		72% (0 to 100)	NR	NR	NR	NR	NR	NR

Study	Treatment	DTSQ					WBQ					
		Total (scale)	Satisfaction (scale)	Convenience (scale)	Flexibility (scale)	Willingness to Continue (scale)	Total	Depression	Anxiety	Energy	Positive Well-Being	Others
				Social activities: 60% versus 8%, p<0.0001 (0 to 100)								
	HI+NPH	NR	NR				NR	NR	NR	NR	NR	NR
Janes *et al.*, 1997[56]	ILis+basal	MD: 2.89, p=0.001 (0 to 36)	NR	MD: 0.71, p=0.001 (0 to 6)	NR	83% (0 to 100)	MD: 4.50, p=0.002 (0 to 66)	MD: -1.20, p=0.006 (0 to 18)	MD: -1.50, p=0.001 (0 to 18)	MD: 0.72, p=0.001 (0 to 12)	MD: 0.36, NSD (0 to 18)	NR
	HI+basal		NR	NR	NR	NR						
Jansson *et al.*, 1998[85]	ILis+NPH	NR	Change from baseline: 0.91±0.64 (0 to 6)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HI+NPH	NR	Change from baseline: -5.45±1.45, p<0.001 (0 to 6)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Johansson *et al.*, 2000[89]	ILis+basal	29.8±6.7* (0 to 36) NSD	NR	NR	NR	NR	52.5±7.1* NSD (0 to 66)	3.0±1.9* NSD (0 to 18)	2.7±2.2* NSD (0 to 18)	8.8±1.9* NSD (0 to 12)	13.4±3.2* NSD (0 to 18)	NR
	HI+basal	28.8±5.2* (0 to 36)	NR	NR	NR	NR	47.9±10.1* (0 to 66)	3.3±2.4* (0 to 18)	3.0±2.7* (0 to 18)	8.6±1.8* (0 to 12)	13.0±3.1* (0 to 18)	NR
Kotsanos *et al.*, 1997[47]	ILis+NPH or UL	NR	Change from baseline: 4.7±21.9* p<0.001	NR	Change from baseline: 3.1±16.1* p=0.001	NR	NR	NR	Change from baseline: 1.2±14.6* NSD	Change from baseline: -1.0±16.1* NSD	NR	NR

Study	Treatment	DTSQ					WBQ					
		Total (scale)	Satisfaction (scale)	Convenience (scale)	Flexibility (scale)	Willingness to Continue (scale)	Total	Depression	Anxiety	Energy	Positive Well-Being	Others
	HI+NPH or UL	NR	0.4±22.0*	NR	0.8±15.8*	NR	NR	NR	1.0±14.4*	-1.8±15*	NR	NR
Linkeschova *et al.*, 2003[57]	ILis+basal	NSD between treatments	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HI+basal (?)		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Melki *et al.*, 1998[94]	ILis+basal	95% (0 to 100)	89% to 92% (0 to 100)	84.2% (0 to 100)	84% to 87% (0 to 100)	94.7% (0 to 100)	NR	NR	NR	NR	NR	NR
	HI+basal	5% (0 to 100)	5.3% (0 to 100)	5.3% (0 to 100)	5% to 8% (0 to 100)	5.3% (0 to 100)	NR	NR	NR	NR	NR	NR
Renner *et al.*, 1999[91]	ILis+basal	35.16±4.25* p<0.001 (0 to 48)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HI+basal	32.36±5.87* (0 to 48)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schmauß *et al.*, 1998[95]	ILis+basal	NR	NSD, though all patients decided to continue therapy with ILis, probably owing to greater flexibility	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HI+basal	NR		NR	NR	NR	NR	NR	NR	NR	NR	NR
Tamás *et al.*, 2001[99]	IAsp+NPH	NSD between treatments	NR	NR	More flexible (mean difference): 0.26; 95% CI, 0.04 to 0.47, p=0.022)	NR	NR	NR	NR	NR	NR	NR
	HI+NPH		NR	NR		NR	NR	NR	NR	NR	NR	NR
Tubiana-Rufi *et al.*, 2004[64]	ILis+basal	NR	NR	70% found easier in daily life	NR	74% (0 to 100) p=0.01	NR	NR	NR	NR	NR	NR

Study	Treatment	DTSQ					WBQ					
		Total (scale)	Satisfaction (scale)	Convenience (scale)	Flexibility (scale)	Willingness to Continue (scale)	Total	Depression	Anxiety	Energy	Positive Well-Being	Others
				(0 to 100) p=0.02								
	HI+basal	NR	NR	26% (0 to 100)	NR		NR	NR	NR	NR	NR	NR
Tupola *et al.*, 2001[63]	ILis+NPH	NR	NR	NR	NR	82% (0 to 100) because of convenience	NR	NR	NR	NR	NR	NR
	HI+NPH	NR	NR	NR	NR		NR	NR	NR	NR	NR	NR

*mean±SD; †mean±SE. DTSQ=Diabetes Treatment Satisfaction Questionnaire; HI=conventional human insulin; IAsp=insulin aspart; ILis=insulin lispro; MD=mean difference; NPH=neutral protamine Hagedorn; NR=not reported; NSD=no significant difference; QoL=quality of life; UL=ultralente; WBQ=Well-Being Questionnaire.

APPENDIX 14B: QoL DATA IN PATIENTS WITH TYPE 2 DM

Study	Treatment	DTSQ					WBQ					
		Total (scale)	Satisfaction (scale)	Convenience (scale)	Flexibility (scale)	Willingness to Continue (scale)	Total	Depression	Anxiety	Energy	Positive Well-Being	Others
Bastyr *et al.*, 2000[119]	ILis+Gly	30.45±5.34* (0 to 36) NSD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Metf+Gly	31.87±5.45* (0 to 36) NSD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	NPH+Gly	31.25±6.56* (0 to 36) NSD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Herz *et al.*, 2002[113]	Mix25	NR	4.35, p=0.014 (0 to 5)	NR	NR	92%, p=0.041 (0 to 100)	NR	NR	NR	NR	NR	NR
	Gly	NR	3.98 (0 to 5)	NR	NR	79% (0 to 100)	NR	NR	NR	NR	NR	NR
Kotsanos *et al.*, 1997[47]	ILis+NPH or UL	NR	Change from baseline: 10.9±22.6* NSD	NR	Change from baseline: 1.0±16.5* NSD	NR	NR	NR	Change from baseline: 1.8±15.5* NSD	Change from baseline: -1.4±16.1* NSD	NR	NR
	HI+NPH or UL	NR	10.0±22.4*	NR	0.3±15.7*	NR	NR	NR	2.1±14.8*	-1.0±15.9*	NR	NR
Malone *et al.*, 2003[115]	Mix25+Metf	NR	majority	NR	NR	92%	Greater, p=0.003 [lower thirst, fewer trips to bathroom]	NR	NR	NR	NR	NR
	Glib+Metf	NR	majority	NR	NR	97%, p=0.016		NR	NR	NR	NR	NR

Study	Treatment	DTSQ					WBQ					
		Total (scale)	Satisfaction (scale)	Convenience (scale)	Flexibility (scale)	Willingness to Continue (scale)	Total	Depression	Anxiety	Energy	Positive Well-Being	Others
Roach *et al.*, 2001[116]	Mix25	NR	4.1±1.0*, p<0.001 (0 to 5)	NR	NR	(Yes/No): 89%/11% p=0.001	3.9±1.0*, p<0.001 (0 to 5)	NR	NR	3.7±0.9*, p<0.001 (0 to 5)	NR	Weighted combined score: 2.0±1.3*, p<0.001
	Gly	NR	3.4±1.0* (0 to 5)	NR	NR	(Yes/No): 62.7%/37.3 %	3.2±0.8* (0 to 5)	NR	NR	3.2±1.1* (0 to 5)	NR	0.7±1.3*
Ross *et al.*, 2001[106]	ILis+NPH	NR	NSD	NR	NR	NR	NR	NR	NR	NR	NR	Diabetes-related worry scale, p=0.008 NSD on other subscales
	HI+NPH	NR		NR	NR	NR	NR	NR	NR	NR	NR	

*mean±SD. DTSQ=Diabetes Treatment Satisfaction Questionnaire; Glib=glibenclamide; Gly=glyburide; HI=conventional human insulin; ILis=insulin lispro; MD=mean difference; Metf=metformin; MI=myocardial infarction; Mix 25=25%, ILis 75%; NPH=neutral protamine Hagedorn; NR=not reported; NSD=no significant difference; QoL=quality of life; UL=ultralente; WBQ=Well-Being Questionnaire.

APPENDIX 15A: MORTALITY DATA IN PATIENTS WITH TYPE 1 DM

Study	Comparators	Number of Patients at Baseline	Treatment Duration	Number of Deaths (%)	Cause of Death
Heller *et al.*, 1999[93]	ILis+NPH	135	4 months	0	NA
	HI+NPH	135		1 (0.7%)	Death after a prolonged seizure, possibly related to hypoglycemia
Holleman *et al.*, 1997[83]	ILis+NPH versus HI+NPH	199	12 weeks	1 (0.5%)	One patient died of IHD, treatment arm not specified
Home *et al.*, 2000[96]; Home *et al.*, 2006[100] (Extension study)	IAsp+NPH	707	6 months	1	One death from MI, judged to be not related to study medication
	HI+NPH	358		0	NA
	IAsp+NPH	567	30-month extension	0	NA
	HI+NPH	186		2	NR

DM=diabetes mellitus; HI=conventional human insulin; IAsp=insulin aspart; IHD=ischemic heart disease; ILis=insulin lispro; NA=not applicable; NPH=neutral protamine Hagedorn; NR=not reported.

APPENDIX 15B: MORTALITY DATA IN PATIENTS WITH TYPE 2 DM

Study	Comparators	Number of Patients at Baseline	Treatment Duration	Number of Deaths (%)	Cause of Death
Boehm *et al.*, 2004[108]	IAsp	58	3-month+21-month extension	3 (5.2%)	2 lung cancer, 1 cardiac failure (none considered to be treatment-related)
	HI	67		1 (1.5%)	Malignant lymphoma (not considered to be treatment-related)
Malone *et al.*, 2003[115]	Mix25+Metf	301	16 weeks	1 (0.3%)	NR (not considered to be treatment-related)
	Glib+Metf	296		0	NA
Roach *et al.*, 2001[116]	Mix 25	85	16 weeks	1 (1%)	NR (not considered to be treatment-related)
	Gly	90		1 (1%)	
Schernthaner *et al.*, 2004[107]	ILis versus HI	40	Approximately 12 weeks x 2	1 (2.5%)	NR (not considered to be treatment-related)

DM=diabetes mellitus; Gly=glyburide; HI=conventional human insulin; IAsp=insulin aspart; ILis=insulin lispro; NA=not applicable; NR=not reported; OAD=oral antidiabetic agent.

APPENDIX 16A: LDL CHOLESTEROL LEVELS IN PATIENTS WITH TYPE 2 DM

Study	Comparators	Number of Patients	Baseline LDL Cholesterol Level	Endpoint LDL Cholesterol Level	p-value at Endpoint
Altuntas *et al.*, 2003[74]	ILis+NPH	20	3.0±1.1†	3.1±0.9*	NR
	HI+NPH	20	3.2±0.8†	3.2±0.5*	NR
Anderson *et al.*, 1997[103]	ILis+NPH	722	3.4±0.1†	3.4±0.1*	p=78
	HI+NPH	722	3.4±0.1†	3.4±0.1*	

*mean±SD; †mean±SE. HI=conventional human insulin; ILis=insulin lispro; LDL=low-density lipoprotein; NPH=neutral protamine Hagedorn; NR=not reported.

APPENDIX 16B: CHOLESTEROL – HDL RATIO IN PATIENTS WITH TYPE 2 DM

Study	Comparators	Number of Patients	Baseline HDL Cholesterol Level	Endpoint HDL Cholesterol Level	p-value at Endpoint
Altuntas *et al.*, 2003[74]	ILis+NPH	20	4.17	4.17±4.31*	NR
	HI+NPH	20	5.5	4.64±4.98*	NR
Anderson *et al.*, 1997[103]	ILis+NPH	722	4.5±1.0†	4.31±9.14*	NR
	HI+NPH		4.5±1.0†	4.23±4.98*	NR
Gallagher and Home, 2005[109]	IAsp+NPH	21	4.36±2.0*	4.45±2.03*	NR
	HI+NPH	21	4.36±2.0*	4.08±1.74*	NR

*Mean±SD; †Mean±SE. HDL=high-density lipoprotein; HI=conventional human insulin; IAsp=insulin aspart; ILis=insulin lispro; NPH=neutral protamine Hagedorn; NR=not reported.