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COMPUS

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Long-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes – Update of CADTH Technology Report No. 92

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.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this Report.

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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 long-acting insulin analogues are greater than those for intermediate- and long-acting human insulins. 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 and safety of long-acting insulin analogues, specifically insulin glargine (IGlar) and insulin detemir (IDet), in the management of DM (type 1, type 2, and gestational).

Methods

An existing systematic review of published studies examining the clinical efficacy and safety of long-acting insulin analogues in the treatment of DM was updated. Additional research questions of interest not addressed in the systematic review were also examined. Randomized controlled trials (RCTs) comparing long-acting insulin analogues with intermediate- or long-acting unmodified human insulins, or oral anti-diabetic agents, were identified through electronic databases, grey literature, reference lists, and through stakeholder consultation. Meta-analysis was conducted to pool trial results when appropriate.

Results

Fifty-eight articles representing 52 unique RCTs were included: seven studies were conducted in pediatric type 1 DM patients, 25 in adult type 1 DM patients, and 20 in adult type 2 DM patients. The number of patients in each study ranged from 14 to 756. Trial duration ranged from four to 52 weeks. The overall quality of most RCTs was low. All studies were of open-label design.

For children with type 1 DM, comparison of IGlar with neutral protamine Hagedorn (NPH) (or lente) revealed no statistically significant differences between treatments for mean glycosylated hemoglobin (A1c) at endpoint, relative risk of severe, nocturnal or overall hypoglycemia. For IGlar (plus lispro) compared with NPH (plus human insulin (HI)), there were no statistically significant differences in A1c at endpoint, or relative risk of nocturnal hypoglycemia between treatments. Compared with NPH (plus aspart), a statistically significant reduction in the relative risk [0.85 (95% CI): (0.77, 0.94)] and frequency [rate ratio (95% CI): 0.77 (0.70, 0.84)] of nocturnal hypoglycemia was shown in favour of IDet (plus aspart).

In adult patients with type 1 DM, the pooled estimate of 11 RCTs showed a statistically significant difference in mean A1c levels at endpoint in favour of IGlar treatment compared with NPH treatment [weighted mean difference (WMD) (95%CI) = -0.11% (-0.21, -0.02)]. No significant A1c difference was observed between IDet and NPH. Pooled estimates did not show statistically significant differences for severe, nocturnal, and overall hypoglycemia between IGlar and NPH. A lower frequency of nocturnal hypoglycemia was found with the combination of IGlar and lispro than with NPH and HI [rate ratio (95% CI) =0.56, (0.48, 0.65)]. In the comparison of IDet with NPH, a statistically significant risk reduction was observed for severe and nocturnal hypoglycemia in favour of IDet. As well, the frequencies of nocturnal and overall hypoglycemia were lower [rate ratios (95% CI) were 0.66 (0.60, 0.73) and 0.84 (0.74, 0.97)], respectively. When the combination of IDet and aspart was compared with NPH and HI, there was no difference observed for severe hypoglycemia,

although nocturnal hypoglycemia frequency and risk were lowered [relative risk (RR) (95% CI) 0.65 (0.55, 0.77) and rate ratio (95% CI) 0.44 (0.39, 0.51)], respectively. Furthermore, the rate ratio for overall hypoglycemia significantly favoured IDet and aspart [rate ratio (95% CI)=0.78 (0.74, 0.82)]. Compared with IGlar, a statistically significant risk reduction was achieved in favour of IDet for severe [WMD (95%CI) = 0.25 (0.07, 0.86)], but not nocturnal or overall, hypoglycemia. Statistically significant reductions in severe [rate ratio (95% CI) 0.41 (0.2, 0.86)] and nocturnal hypoglycemia [rate ratio (95% CI) 0.66 (0.58, 0.76)], but not overall hypoglycemia, were also observed with IDet compared to IGlar. Compared to those in the NPH group, mean body weight at endpoint was statistically significantly lower in patients in the IGlar group [WMD (95%CI) = -0.36kg (-0.67, -0.04)] as well as the IDet group [WMD (95% CI)=-0.73kg (-1.42, -0.03)]. Patients in the IDet plus IAsp group had statistically significantly lower mean body weight at endpoint than did those in the NPH plus HI group [WMD (95%CI) = -1.10kg (-1.49, -0.71)]. Patients in the IDet had statistically significantly lower mean body weight at endpoint than did those in the IGlar group [WMD (95%CI) = -0.5kg (-1.21, 0.21)].

For adult patients with type 2 DM receiving oral antidiabetic agents (OADs), the pooled estimate of difference in mean A1c between treatment groups was not statistically significant for IGlar compared with NPH, and significantly favoured NPH in the comparison with IDet [WMD (95% CI) = 0.13 (0.03, 0.22)]. For patients not receiving OADs, the reduction in mean A1c for those using IGlar plus HI, compared with those using NPH plus HI, was statistically significant WMD (95% CI) = 0.28% (0.07, 0.49). Also, A1c was statistically significantly reduced in the pooled analysis of IGlar versus thiazolidinediones (TZDs) [WMD (95%CI) = -0.20% (-0.38. -0.01)]. Results from a single RCT showed a statistically significant A1c reduction for IDet plus IAsp compared to IGlar plus IAsp [WMD (95%CI) = 0.20% (0.10, 0.30)].

For fasting plasma glucose (FPG), there were no statistically significant differences in pooled estimates for treatment with IGlar versus NPH, IDet versus NPH, or IDet versus IGlar. A statistically significant decrease in FPG was shown for IGlar when compared with rosiglitazone [WMD (95%CI) = -1.04 mmol/L (-1.64, -0.45)].

The risk of nocturnal hypoglycemia was statistically significantly reduced for patients receiving IGlar plus OADs, compared to patients using NPH plus OADs [RR (95% CI) = 0.56 (0.47, 0.68)]; patients receiving IGlar but not OADs compared to those using NPH without OADs [RR (95% CI) = 0.78 (0.62, 0.98)]; patients using IDet plus OADs, compared to patients using NPH plus OADs [RR (95% CI) =0.53 (0.31, 0.91)]; patients using IDet plus IAsp, compared to patients using NPH plus IAsp [RR (95% CI) = 0.66 (0.45, 0.96)]; and patients using IDet plus IAsp, compared to patients using NPH plus HI [RR (95% CI) = 0.54 (0.30, 0.97). The frequency of nocturnal hypoglycemia, for patients receiving OADs, was significantly reduced for IGlar versus NPH [rate ratio (95%CI) = 0.41 (0.29, 0.59)], and for IDet versus NPH [rate ratio (95%CI) = 0.48 (0.42, 0.55)].

The risk of severe hypoglycemia, for patients taking OADs, was not statistically significantly different for IGlar versus NPH or IDet versus NPH. However, the frequency of severe hypoglycemia was statistically significantly decreased for IGlar versus NPH [rate ratio (95%CI) = 0.56 (0.35, 0.91)] and IDet versus NPH [rate ratio (95%CI) = 0.13 (0.02, 0.91). For patients not taking OADs, the risk of severe hypoglycemia for those using IGlar compared to those using NPH was not estimable.

The risk, but not frequency, of overall hypoglycemia for patients taking OADs was statistically significantly reduced for those using IGlar compared to those using NPH [RR (95% CI) = 0.87 (0.81, 0.93)]. For patients not taking OADs, the risk of overall hypoglycemia was not statistically significantly different for those using IGlar compared to those using NPH. Differences in frequency of overall hypoglycemia were not estimable for this treatment comparison. Conversely, the frequency, but not the risk of overall hypoglycemia, for patients taking OADs, was statistically significantly decreased for the IDet group when compared to the

NPH group [rate ratio (95%CI) = 0.549 (0.48, 0.72)]. Comparisons of frequency for nocturnal, severe, and overall hypoglycemia for IGlar versus NPH were not estimable for patients not receiving OADs.

There was no significant difference in body weight in patients with Type 2 DM treated with IGlar as compared to NPH insulin, although there was a significant difference in favour of IGlar in comparison to rosiglitazone [WMD (95% CI) = -1.45kg (-2.48, -0.42)]. Significant differences in body weight in favour of IDet as compared to NPH insulin were found in patients treated concomitantly with OADs [WMD (95% CI) = -0.96kg (-1.69, -0.23)], as well as in patients treated with pre-meal IAsp [WMD (95% CI) = -0.80kg (-1.46, -0.14)]. Furthermore, change in weight from baseline significantly favoured IDet as compated to IGlar [WMD (95% CI) = -1.50kg (-2.47, -0.53)] in combination with pre-meal IAsp, and [WMD 995% CI) = -0.80kg (-1.52, -0.08)] in combination with OADs.

In both type 1 (including pediatric and adult populations) and 2 DM patients, adverse events appeared to be similar with long-acting insulin analogues and conventional insulin. Data on diabetes-related complications, mortality, and quality-of-life were sparse.

Conclusions

Most studies of the long-acting insulin analogues were of poor quality and were not designed to measure differences in clinically important outcomes. There is no evidence that IGlar offers benefit over NPH insulin in children with type 1 DM, although IDet may have benefits in terms of reduced nocturnal hypoglycemia. Compared with NPH, IGlar but not IDet produced small reductions in A1c levels in adult patients with type 1 DM, although the clinical significance of these findings is questionable. A statistically significant risk reduction in severe and nocturnal hypoglycemia was observed with IDet compared with NPH, while no significant benefit was observed for IGlar in terms of hypoglycemia. In patients with type 2 DM treated with IGlar or IDet, mean A1c levels were similar to those achieved with NPH. Both IGlar and IDet significantly reduced the risk of nocturnal hypoglycemia in type 2 DM patients. There was limited comparative data for IGlar versus IDet. Long-term comparative studies of higher quality are needed to definitively determine the clinically relevant benefits and harms of long-acting insulin analogues compared with conventional insulins.

ABBREVIATIONS

A1c	glycosylated hemoglobin
BG	blood glucose
BMI	body mass index
CAC	COMPUS advisory committee
CI	confidence interval
DKA	diabetic ketoacidosis
DNA	deoxyribonucleic acid
DM	diabetes mellitus
DTSQ	diabetes treatment satisfaction questionnaire
FPG	fasting plasma glucose
F/P/T	federal/provincial/territorial
HI	human insulin (conventional)
HRQoL	health-related quality of life
IAsp	insulin aspart
IDet	insulin detemir
IGlar	insulin glargine
IGlu	insulin glulisine
ILis	insulin lispro
ITT	intention-to-treat
LDL	low-density lipoprotein
Metf	metformin
MI	myocardial infarction
NPH	neutral protamine Hagedorn
OAD	oral antidiabetic agent
QoL	quality of life
RCT	randomized controlled trial
Ros	rosiglitazone
RR	relative risk
SD	standard deviations
TZD	thiazolidinedione
WMD	weighted mean difference

GLOSSARY

Absolute risk reduction: 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: 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: Carryover effect occurs when the treatment given in the first period has residual effect that confounds the interpretation of result in the second period.

Confidence interval: 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: The DCCT is 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: 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: Plasma glucose level measured at the time when no caloric intake for at least 8 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: Defined as glucose intolerance with first onset during pregnancy. It is usually a temporary condition

Glycated haemoglobin A1c: A glycated form of haemoglobin, 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: 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 (χ^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, hyperglycaemic, non-ketotic coma: A syndrome consisting of extreme hyperglycaemia, serum hyperosmolarity and dehydration in the absence of ketoacidosis. The American Diabetes Association suggests that this disorder be renamed hyperglycaemic 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 appendices 10a to 11b).

Ischemic heart disease: 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: (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: It is 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 hypoglycaemia: Hypoglycaemic 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 appendices 10a to 11b).

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 appendices 10a to 11b).

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, e.g. 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: 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: An 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: 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: It is a measure of the variability between individual in the level of the factor being investigated.

Severe hypoglycemia: Severe hypoglycemia is defined as 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 appendices 10a to 11b).

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: TIAs are episodes of stroke symptoms that last only briefly; the current definition of duration is < 24 h, but the average duration of TIA is about 12 min.

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: It may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.

Weighted mean difference: 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 lifecycle.

The goal of COMPUS is to optimize drug-related health outcomes and promote cost-effective use of drugs that have been in the marketplace 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 following:

- 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 therapy in the prescribing and use of drugs across Canada.
- Stakeholder input and expert advice.

1.2 Project Overview

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 (HI), and oral antidiabetic agents (OADs)
- Comparison of rapid-acting insulin analogues, HI, and OADs
- Comparison of "glitazones" to other OADs
- Metformin 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 long-acting insulin analogues.

1.3 Goal

The goal of this systematic review was to examine the efficacy of long-acting insulin analogues relative to unmodified human insulins 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 produced by the body (previously classified as insulin-dependent DM or juvenile-onset diabetes)
- Type 2 DM – the body produces insulin but is unable to use it properly (previously classified as non-insulin dependent DM)
- GDM – is defined as glucose intolerance with 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 β-cell function; genetic defects in insulin action; disease of the pancreas; endocrinopathies, infections; uncommon forms of immune-mediated diabetes, either drug- or chemical-induced; and other genetic syndromes sometimes associated with diabetes).

Without adequate control of BG, 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 DM.[2] Assuming 10% of all diabetes cases are type 1 and 90% are type 2, 105,410 (0.48%) and 948,690 (4.32%) Canadians were diagnosed with type 1 and type 2 DM, respectively in 1998/1999.

There are no known modifiable risk factors for type 1 DM and consequently race, ethnic background, age, and genetics will determine the relative risk 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 than race or ethnic background. Aboriginal peoples and immigrants have greater susceptibility to the development of type 2 DM.[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] Adoption of a healthy lifestyle reduces the probability of acquiring hypertension, dyslipidemia, abdominal obesity, and reaching overweight or obese status[13,14] However, the industrial and social influences of the 21st century are not always 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. It has been shown that 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 National Population Health Survey, 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 who are 20 years and 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 shortened 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] 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 was estimated to range between US $4.76 and $5.23 billion dollars in 1998. Direct medical costs in patients diagnosed with diabetes accounted for approximately 7.8% of total medical expenditures in 1998, of which 50% was spent on hospital care, 19% on physician fees, and 31% on medications.[11] Over three-quarters of people with diabetes use either insulin or OAD agents to control the progression of the disease.[10]

Among Ontario residents covered by provincial drug benefit programs, approximately 29% of patients with DM took only a single oral anti-hyperglycemic drug, while 17% took more than one type of medication.[15] Insulin was used by 11% of people; 3% of beneficiaries combined insulin with

OAD medications.[15] The number of elderly people using insulins in this population increased from 30,104 in 1995 to 38,258 in 2001, representing a 27% increase. The total cost of all hyperglycemic agents among beneficiaries increased from $23 million in 1995 to $33 million in 2001.[15] Insulins accounted for over 14 million dollars in 2001, representing the highest costs in the Ontario Drug Benefit program among anti-hyperglycemic 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

One goal of DM management is to maintain control of BG levels in order to reduce the patient's risk of developing long-term diabetes-related complications. In combination with lifestyle measures (e.g., weight control, proper nutrition, and adequate exercise), medications play an important role in managing glucose control in DM.[15] There are seven classes of antidiabetic drugs currently available in Canada:

- Sulfonylureas (including glyburide and gliclazide)
- Biguanides (metformin)
- Alpha-glucosidase inhibitors (acarbose)
- Meglinitides (repaglinide and nateglinide)
- Thiazolidinediones (rosiglitazone and pioglitazone)
- Dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin)
- Insulin and insulin analogues.

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 into human insulin, insulin analogues, and animal-sourced insulin.

3.1 Human Insulin

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

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

Short-acting insulin has an onset of action 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] Ultralente insulin, 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 profiles of the human insulins are such that it is not always possible to replicate the pattern of basal and meal-time secretion of endogenous insulin, even with multiple daily injections. Glycemic control may, therefore, be sub-optimal. Apart from the potential for increased risk of diabetic complications, poor control may also increase the risk of hypoglycemia (abnormally low BG levels).[16]

3.2 Insulin Analogues

In response to the limitations of the human insulins, insulin analogues were developed to more closely mimic the basal and meal-time components of endogenous insulin secretion. The analogues were produced by introducing alterations in the amino acid sequence of HI.[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 meal-induced endogenous insulin in non-diabetic patients than does regular HI. Long-acting insulin analogues mimic the action of basal endogenous insulin secretion by providing a prolonged, non-fluctuating 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®.

Insulin lispro (ILis) and insulin aspart (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] Insulin glargine (IGlar) forms microprecipitates upon subcutaneous injection, from which the drug is released slowly into the circulation. IGlar has an effective duration of 20 to 24 hours, without evidence of a peak.[16] Insulin detemir, a long-acting insulin analog, has similar pharmacokinetic/pharmacodynamic characteristics as IGlar,[17] although there is evidence that its duration of effect may be somewhat shorter.[18]

4 STATEMENT OF THE ISSUE

The human insulins 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 human insulins. 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 human insulins. Furthermore, an increasing number of people are being diagnosed with diabetes each year.[19] 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 long-acting insulin analogues compared with intermediate- and long-acting unmodified human insulins and OAD agents, 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:

1. What are the patient-relevant and clinical benefits and harms associated with the use of long-acting insulin analogues (i.e., IGlar or IDet) compared with intermediate- or long-acting human insulins (i.e., NPH, ultralente) or OADs in the treatment of DM (type 1, type 2, or gestational)?

2. Are there sub-populations of diabetic patients (e.g., elderly people, children, aboriginal peoples and other ethnic minorities, pregnant patients) who may particularly benefit from treatment with long-acting insulin analogues, in comparison with intermediate- or long-acting human insulins or OAD agents?

3. Are there clinically important differences between the use of a combination of a long-acting insulin analogue (i.e., IGlar or IDet) and a rapid-acting insulin analogue [i.e., insulin aspart (IAsp) or insulin lispro (ILisp)], versus the combination of an intermediate- or long-acting human insulin (e.g., NPH) and short-acting human insulin, in the treatment of DM (type 1, type 2, or gestational)?

4. What are the patient-relevant and clinical benefits and harms of long-acting insulin analogues in combination with OAD agents compared with intermediate- or long-acting human insulins in combination with OAD agents in the treatment of type 2 DM?

5. Compared with intermediate- or long-acting human insulins, are there differences in the clinical effects of long-acting insulin analogues when used at the onset versus later in the course of the disease for patients with type 2 DM?

6. Are there clinically important differences between the two available long-acting insulin analogues (i.e., IDet versus IGlar) 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 (relative risk and rate ratio); mean weight, body mass index (BMI), and waist-to-hip ratio (in type 1 DM only); diabetic ketoacidosis; both generic and diabetes-specific health-related quality of life (HRQoL); patient satisfaction with diabetes care and treatment; patient self-management efficacy; resource utilization (i.e., cost of treatment; number of visits to ER, primary care, specialists; hospitalizations); long-term diabetes complications (i.e., ischemic heart disease, congestive heart failure, stroke / transient-ischemic attack (TIA),

nephropathy, retinopathy, lower-limb disease, neuropathy, peripheral vascular disease, mortality); and adverse events.

Outcomes of interest in type 2 DM were the same as in type 1, except that fasting plasma glucose (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 no. 92, Long-Acting Insulin Analogues for Diabetes Mellitus: Meta-analysis of Clinical Outcomes and Assessment of Cost-Effectiveness,[20] served as the starting point for this research. We found that while the technology report addressed research questions 1, 2, 4, and 5 (see Section 6, above), it did not address questions 3 and 6. Consequently, while we were able to use the technology report literature search results for questions 1, 2, 4, and 5, we were required to construct additional searches for questions 3 and 6.

6.1 Literature Search

The literature search strategy and methodology for CADTH Technology Report no. 92[20] are provided in Appendix 1a. COMPUS researchers reviewed results of the technology report 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 agencies, 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 questions 3 and 6 (Section 6). This search was peer-reviewed by another information specialist external to the project. This search strategy was devised to locate clinical evidence focussing specifically on the combined use of long-acting with short-acting insulin analogues.

The following bibliographic databases were searched through the Ovid interface: MedLine (1966-present; MedLine In-Process & Other Non-Indexed Citations, MedLine Daily Update), EMBASE (1980-present), and BIOSIS Previews (1989-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 long-acting insulin analogues (glargine and detemir) and short-acting insulin analogues (glulisine, lispro, and aspart). 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 also conducted for observational studies including, but not limited to, cohort, retrospective, follow-up, and prospective designs. The search strategy (shown in Appendix 1c) 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

The same study selection criteria described in the technology report[20] were used for questions 1, 2, 4, and 5 (Appendix 2a). For questions 4 and 6, additional inclusion and exclusion criteria were developed (Appendix 2b).

Considerable caution was exercised to ensure that duplicate publications of the same trial, or single-centre results from multi-centre trials, were not included. In cases where study data was reported in several publications, the most recent article was selected for each outcome of interest.

To reduce bias, oversight, and inconsistency, two reviewers independently determined whether studies met inclusion criteria. Each reviewer independently performed an initial screening of identified articles by examining titles, abstracts, and keywords for relevance to the review topic. Abstracts of articles were assessed and categorized as "included," "uncertain," or "excluded" by each reviewer. If the relevance of a citation was 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. Discrepancies were resolved by consensus or by 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[21] 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 4), 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 study-level data reported in the original CADTH report.

To ensure the accuracy of data extraction, consensus results were checked against original articles by a third reviewer. Any discrepancy identified by the third reviewer was discussed with the original reviewers until agreement was reached.

6.4.2 Data extracted from randomized controlled trials with three treatment arms

If study designs contained two analogue treatment arms to allow for assessment of two different dosing regimens or of different formulations, data were only extracted for the treatment arm in which the analogue was administered at the same time as NPH. In cases where NPH was dosed more than once daily, the arm in which the analogue was administered in the evening or at bedtime was chosen. For randomized controlled trials (RCTs) in which more than one formulation of an analogue was studied, data were only extracted for the formulation corresponding to the one marketed in Canada.

6.4.3 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].[22] 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 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. A brief description of the meta-analytic method used is provided in Appendix 5. Separate analyses were conducted for each of the following populations: gestational DM, pediatric type 1 DM, adult type 1 DM, pediatric type 2 DM, and adult type 2 DM.

6.5.1 Meta-analysis of continuous data

The effect of two or more treatments on a continuous outcome such as A1c, fasting plasma glucose (FPG), or body weight was reported in trials as one or both of mean values at endpoint and mean change from baseline to endpoint. According to the *Cochrane Handbook for Systematic Reviews of Interventions*,[23] the two measures are theoretically equivalent since, on average, baseline values across treatment arms in RCTs should be equal. In the event that some RCTs report mean values at endpoint and others changes from baseline, the *Handbook* indicates that both types of data can be included in the same meta-analysis, since they are both estimates of the same parameter.

For the meta-analysis of continuous outcomes, mean values at endpoint were pooled where reported or calculable; otherwise, mean change from baseline was used. Each meta-analysis, therefore, could contain both mean values at endpoint and mean changes from baseline.

6.5.2 Analysis of hypoglycemia outcomes

The definitions of severe, nocturnal, and overall hypoglycemia varied somewhat 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 blood

glucose 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.

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. Hypoglycemia data were analyzed in two ways: relative risk and rate ratio. The relative risk (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.[23] The rate ratio was tabulated in Review Manager as a generic inverse outcome measure.[23]

6.5.3 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.[24] When a carryover effect was reported in a RCT for a particular outcome, these data were excluded from meta-analysis.

6.5.4 Subgroup analysis

Subgroup analyses were performed to examine whether effect sizes differed by 1) the bolus insulin used in studies; 2) the intermediate or long-acting insulin used as a control (e.g., NPH or lente); or 3) for studies in which long-acting analogues were compared with OADs, the individual OAD used.

6.5.5 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,[25] trials of three months or less were excluded in 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.

6.6 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.[26,27] Hence, an assessment of methodological quality is important. Methodological quality of included trials was assessed using a modified Jadad scale (Appendix 3).[28] 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.[27] Since the same instrument was used for Technology Report 92,[20] quality assessment was not repeated for trials included in that review.

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.

6.7 Heterogeneity

Heterogeneity was examined using the χ^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.[29] Therefore, for analyses with I^2 values of more than 50%, the following potential moderator variables were explored as possible causes for systematic bias: 1) bolus insulin or OAD; 2) baseline demographic characteristics (i.e., ethnicity, age, A1c, FPG, weight, BMI, severity or duration of DM, previous treatments); 3) target FPG; 4) dosing frequency (of both NPH and analogue); 5) study design (parallel versus crossover); 6) trial duration; and 7) publication type (abstract or full article).

6.8 Publication Bias

Trials with positive results tend to be published more frequently than those with negative or null results. In addition, outcomes with null or negative results may not be reported in published RCTs. These factors may result in the introduction of publication or reporting bias.[8] The potential for such bias was explored through the use of 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.

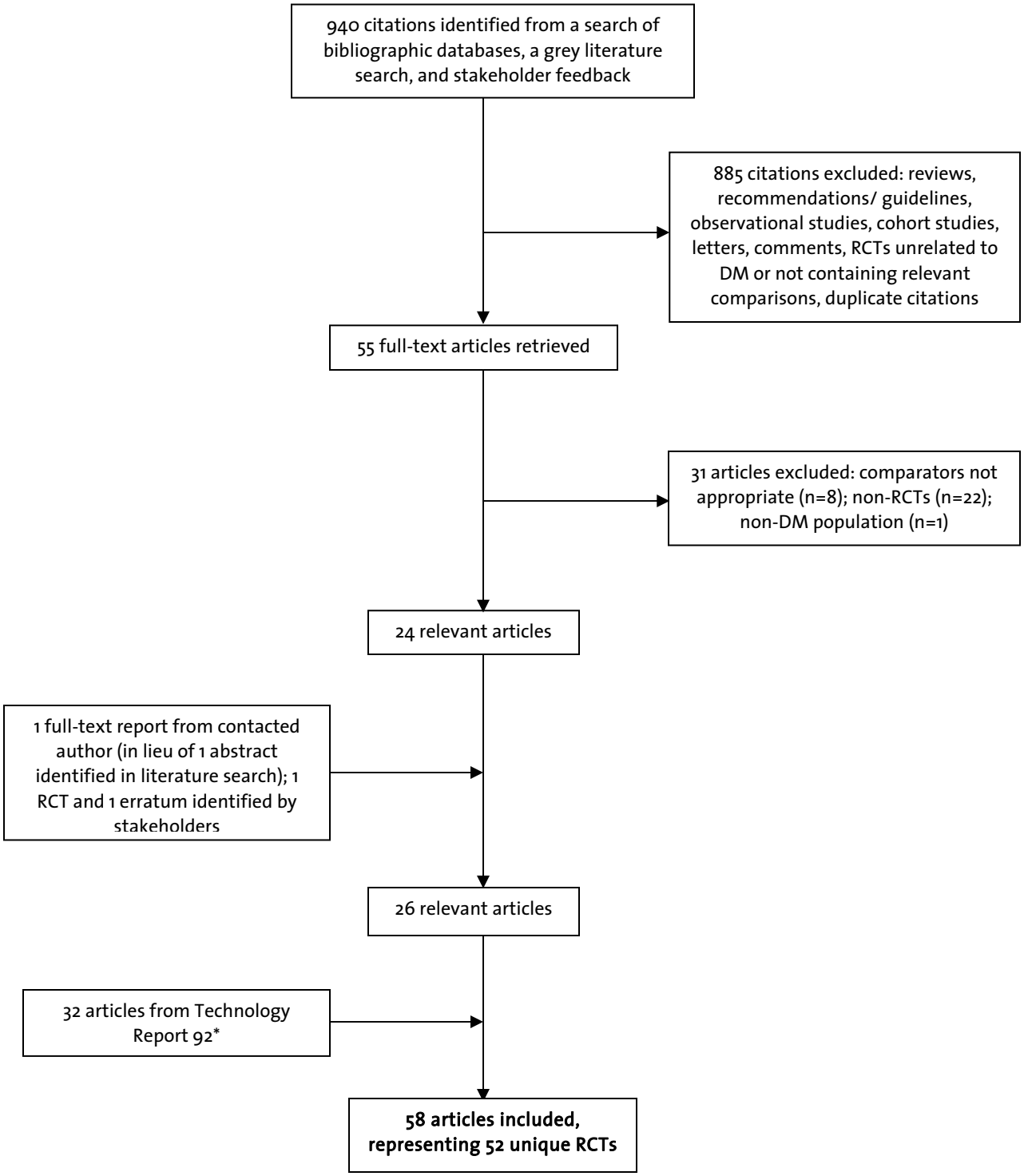
7 RESULTS

7.1 Study Selection

Figure 1 shows the study selection process. A total of 940 citations were identified from the supplemental literature search for research questions 1, 2, 4, and 5 and the additional search for questions 3 and 6. Of these, 885 citations were excluded based on titles and/or abstracts. These consisted mainly of non-RCT articles such as reviews, pre-clinical studies, pharmacokinetic/ pharmacodynamic studies, and studies with comparisons not relevant for our review. Of the 55 potentially relevant citations selected for assessment of full-text reports, 24 were included. Reasons for exclusion are reported in Appendix 6. One full-text article was received from an author contacted for missing information in an abstract. This article replaced the abstract. As well, one additional RCT and an erratum pertaining to one of the selected articles were identified by stakeholders. Therefore, a total of 26 articles were identified during the updating process. Four of these articles were found to be full-text publications of abstracts included in the previous CADTH report.[20] Data from each of three RCTs were reported in two separate publications, while data from one RCT were reported in three abstracts; because the various reports contained information on different outcomes, they were all included in the review. The combined total number of selections from the updating process and studies selected in the technology report[20] was 58. These 58 articles represented 52 unique RCTs. Forty-three reports were full-text articles and the remaining were conference abstracts.

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

Figure 1: Study selection process



* 36 studies were included in Technology Report 92,[20] but 4 abstracts were replaced by full-text publications identified during update.
DM=diabetes mellitus; RCTs=randomized controlled trials.

7.2 Study Characteristics

Of the 52 unique RCTs selected for inclusion, 32 were on type 1 DM (including both pediatric and adult populations) and 20 were on adult type 2 DM patients. No RCTs pertaining to long-acting insulin analogues in gestational DM or pediatric type 2 DM were identified. Trial and patient characteristics for all included studies are shown in Appendix 7a and 7b (for type 1 and type 2 DM, respectively), and patient inclusion/exclusion criteria from each study are presented in Appendix 8.

7.2.1 Trials in type 1 DM

a) Pediatric population

Seven articles,[30-36] each reporting the results of an unique RCT, were on type 1 pediatric patients. Of the seven RCTs, one study enrolled pre-adolescents (mean age 10.4 years),[35] three enrolled adolescents (mean age 13.2 to 14.8 years),[33,34,36] and three enrolled both children and adolescents (mean age 11.7 to 11.9 years).[30-32] Three of the seven studies were full-text articles,[30,32,36] and four were conference abstracts.[31,33-35] Three studies mentioned industry sponsorship.[32,37,38] One RCT[30] compared IDet with NPH, three compared IGlar with NPH,[31,32,35] two were on IGlar versus NPH or lente,[33,34] and one was on the combination of IGlar with lispro versus NPH with HI.[36] There were four parallel trials[30,32-34] and three crossover trials.[31,35,36] Sample sizes ranged between 14 and 361. Two trials were conducted in USA, one in UK, one in Poland, one in Japan, and two were multi-national. Five RCTs[30,32,33,35,36] reported the duration of the diabetes; mean duration ranged between 1.8 and 15 years.

b) Adult population

Twenty-seven articles on adult type 1 DM were identified.[39-65] Of these, 22[39-46,48,49,52,54-62,64,65]were full-text articles, and five[47,50,51,53,63] were conference abstracts. Twenty-one [39-46,48,49,52,54-60,63-65] mentioned industry sponsorship. Twenty two articles reported the results of parallel trials[40-42,44-49,51-63] and five those of crossover trials.[39,43,50,64,65] Twenty of the trials were multi-centre and 11 of were also multi-national. Two articles [47,54] were subgroup analyses of other studies [45,66] therefore the 27 articles included for adult type 1 diabetics represented 25 unique RCTs. Sample sizes ranged from 14 and 749. Fourteen RCT reports[50-63] compared IGlar with NPH, nine[39-47] compared IDet with NPH, one compared IDet with IGlar, one[67] compared the combination of IDet and aspart with NPH and HI, one[64] compared the combination of IGlar and ILis with NPH and HI, and one compared IGlar versus ultralente.[65]

The mean age of patients in the included studies ranged from 23.8 to 43 years. The proportion of patients who were female ranged from 18% to 61%. Five articles did not report this information. The mean duration of diabetes ranged from 9.8 to 18.6 years. Two studies did not report this information.

c) Sub-populations

Other than children, the RCTs identified did not assess the efficacy of the long-acting analogues in sub-populations relevant to diabetes treatment in Canada, such as elderly or aboriginal populations. In terms of ethnic minorities, the study by Kawamura *et al.*[31] was conducted in Japanese children. There were insufficient data to determine whether treatment response in this population differed from overall treatment effects observed across all studies.

7.2.2 Trials in type 2 DM

Twenty four articles[68-91] and one erratum [92] describing 20 RCTs in adult type 2 diabetics were selected. Of the 24 articles, 18[68-71,74-84,88-90] were full-text articles, and six[72,73,85-87,91] were conference abstracts. Three abstracts[85-87] contained data from the same RCT, two full-text articles[88,90] described a single trial, and one article[75] reported a subgroup analysis of another RCT.[74] Therefore, the 24 articles included represented 20 unique RCTs. Eighteen articles[68-71,75-78,80-84,86-90] mentioned industry sponsorship. One RCT[68] compared IDet with NPH in patients also using bolus insulins. Three RCTs[69,70,91] compared IDet with NPH in patients also using OADs. One RCT[71] was on IDet in combination with aspart versus NPH and HI. One RCT compared IDet with IGlar in patients also using bolus insulins. One RCT[56,74] compared IGlar with NPH in patients also using bolus insulins. Nine articles[77-84,93] were on IGlar versus NPH with OAD as co-therapy. Six articles[85-90] describing three RCTs reported the comparison of IGlar with thiazolidinediones (TZDs) as add-on therapy in patients inadequately controlled on sulfonylureas and metformin. All studies were of parallel design. Sample sizes ranged from 20 to 756. Among trials reporting information on centre, only one was of single-centre design. Two[83,94]of the 23 trials had a duration of less than three months.

Mean age ranged between 53 and 61.3 years. The percentage of females ranged between 33.3% and 57.1%. Three studies did not report this information. The mean duration of diabetes ranged between 8.1 and 14.5 years. Seven articles did not report this information.

Sub-populations

The RCTs identified did not assess the efficacy of the long-acting analogues in sub-populations relevant to diabetes treatment in Canada, such as elderly or aboriginal populations. In terms of ethnic minorities, three studies were conducted in Asian countries (one in China,[79] a second in Japan[91], and a third in various Asian countries[76]). One study was conducted in a Latin American population.[77] There were insufficient data to determine whether treatment response in these populations differed from overall treatment effects observed across all studies.

7.3 Study Quality

We assessed the quality of all 43 full-text publications. For the 25 RCTs conducted in type 1 DM patients,[30,32,36,39-46,48,49,52,54-62,64,65] the mean Jadad score (±SD) was 2.24±0.56. Allocation concealment was adequate in one trial[64] and unclear in the remainder. Sixty-four per cent of trials reported an intention-to-treat (ITT) analysis, 24% did not report an ITT analysis, and 12% did not report enough information to determine whether an ITT analysis was conducted. For the 18 trials conducted in type 2 DM patients,[68-71,74-84,88-90] the mean Jadad score (±SD) was 2.06±0.7. Allocation concealment was adequate in two studies[69,70] and unclear in the remainder. Eighty-three per cent of trials reported an ITT analysis, 11% did not report an ITT analysis, and 6% did not report enough information to determine whether an ITT analysis was conducted. Although it was originally intended that study quality would be used as a parameter for sensitivity analyses, this was not done, since nearly all trials were of low quality. The results of quality assessment for all studies are summarized in Appendix 9.

Hypoglycemia was categorized in various ways in different trials. Most trials reported severe (or major), nocturnal, and overall hypoglycemia. The definitions of hypoglycemia used in each trial are presented in Appendix 10a and 10b (for type 1 and type 2 DM, respectively).

7.4 Results of Meta-analysis

7.4.1 Pediatric type 1 DM

a) Glycosylated hemoglobin (A1c)

Study-level A1c data for type 1 DM are shown in Appendix 11a. 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 long-acting insulin analogues versus NPH or lente insulin in pediatric type 1 DM – Overall results and subgroup analyses for mean A1c (%)

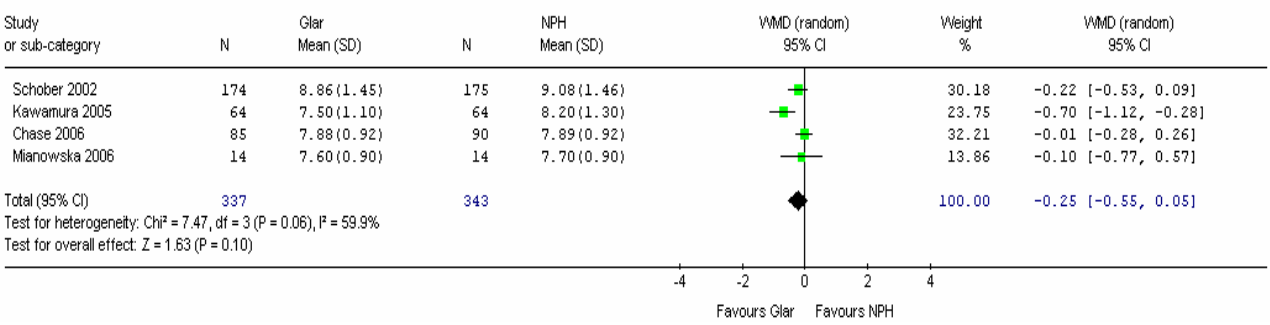
Comparison	Analysis	Number of RCTs	Sample Size	WMD (95% CI)* in A1c (%)	I^2 (%)
Glargine vs. NPH (with bolus insulin)	All RCTs	4	680	-0.25 (-0.55, 0.05)	61.8
	Subgroup analysis				
	Bolus=IAsp	1	128	-0.70 (-1.12, -0.28)	NA
	Bolus=ILis or HI	1	28	-0.10 (-0.77, 0.57)	NA
	Bolus=HI	1	349	-0.22 (-0.53, 0.09)	NA
	NPH or lente used in	1	175	-0.01 (-0.26, 0.24)	NA
Glargine+lispro vs. NPH+HI	All RCTs	1	50	-0.40 (-0.91, 0.11)	NA
Detemir vs. NPH (with aspart as co-therapy)	All RCTs	1	347	0.1 (-0.1, 0.3)	NA

* Negative values indicate benefit with long-acting insulin analogue. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; vs=versus; WMD=weighted mean difference.

Glargine versus NPH

Five RCTs[31-35] comparing IGlar with NPH were identified in this review, four of which[31-33,35] reported A1c results. Overall, there was no statistically significant difference between IGlar and NPH (Figure 2) [WMD (95% CI)=-0.25% (-0.55, 0.05)]. I^2 was 59.9% in this meta-analysis. The I^2 value was reduced to 49.2% once the Chase *et al.*, 2006 study, the only one to allow both NPH and lente in the control arm,[33] was removed from the analysis. The study by Kawamura *et al.* reported the largest treatment effect and was the only study to demonstrate a statistically significant difference.[31] This study was dissimilar to the other three in that it used aspart as bolus insulin, was conducted in a Japanese population, and included subjects as old as 21 years of age.

Figure 2: Forest plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in pediatric patients – A1c, weighted mean difference



A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; IGlar/Glar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

IGlar+lispro versus NPH+human insulin

One study[36] reported the mean difference in A1c at endpoint [mean difference (95% CI)=-0.4% (-0.91, 0.11)].

IDet versus NPH

Only one RCT[30] comparing IDet with NPH (and IAsp as bolus insulin in both arms) was identified [mean difference (95% CI)=0.10% (-0.1, 0.3)].

In summary, there was no statistically significant difference between long-acting insulin analogues and NPH insulin in terms of A1c in children or adolescents with type 1 DM.

b) Two-hour post-prandial plasma glucose

No studies reported data on this outcome.

c) Hypoglycemia

Study-level hypoglycemia data are shown in Appendix 10a. Overall pooled results and results from subgroup analyses are summarized in Tables 2 to 4.

IGlar versus NPH

Four[32-35] RCTs reported data on severe hypoglycemia, one[32] reported nocturnal hypoglycemia, and three reported overall hypoglycemia.[32-34] Results of meta-analysis are reported in Table 2. No significant differences were observed in terms of RR for severe (Figure 3), nocturnal, and overall hypoglycemia (Figure 4). The data necessary to calculate rate ratios were not reported in studies.

IGlar+lispro versus NPH+human insulin

Hypoglycemia results for this outcome are presented in Table 3. One study[36] included severe hypoglycemia as an outcome; however, no such events occurred, therefore RR was not calculable. In the same RCT, the RR of nocturnal hypoglycemia was statistically non-significant [RR (95% CI)=0.57 (0.29, 1.12)], as was the rate ratio. Data on overall hypoglycemia were not reported.

Table 2: Summary of results of meta-analyses for comparison of IGlar versus NPH for the treatment of pediatric type 1 DM – Hypoglycemia relative risks

Type of Hypoglycemia	Analysis	No. of RCTs	Sample Size	RR* (95% CI)	I^2 (%)
Severe	All RCTs	4	727	1.18 (0.59, 2.35)	48
	Subgroup analysis				
	Bolus=ILis or HI	1	28	Not estimable	NA
	Bolus=HI	1	349	0.80 (0.56, 1.18)	NA
	NPH or lente used in control arm (Bolus=ILis)	2	350	1.91 (0.83, 4.42)	0
Nocturnal	All RCTs (Bolus=HI)	1	349	0.71 (0.43, 1.18)	NA
Overall	All RCTs	3	699	1.03 (0.86, 1.25)	18
	Subgroup analysis				
	Subgroup C (HI=bolus)	1	349	1.01 (0.90, 1.12)	NA
	NPH or lente used in control arm (Bolus=ILis)	2	350	1.23 (2.68, 2.23)	46.8

* RRs less than 1 indicate benefit with analogue. CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IGlar=insulin glargine; ILis=insulin lispro; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Table 3: Summary of results for comparison of IGlar+lispro versus NPH+human insulin for the treatment of pediatric type 1 DM – Hypoglycemia relative risks and rate ratios

Type of Hypoglycemia	No. of RCTs	Sample Size	RR (95% CI)	Rate Ratio (95% CI)
Severe	1	50	Not estimable	NA
Nocturnal	1	50	0.57 (0.29, 1.12)	0.71 (0.44, 1.14)
Overall	0	NA	NA	NA

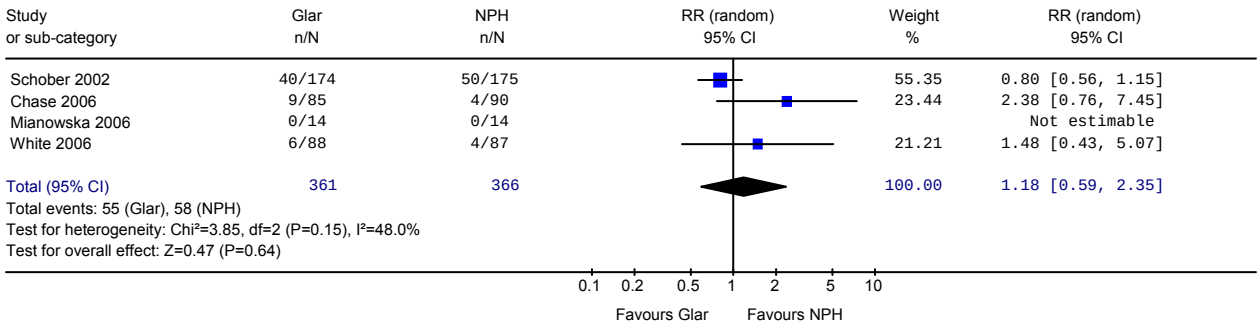
CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Table 4: Summary of results for comparison of IDet versus NPH (with aspart as bolus therapy) for the treatment of pediatric type 1 DM – Hypoglycemia relative risks and rate ratios

Type of Hypoglycemia	No. of RCTs	Sample Size	RR (95% CI)	Rate Ratio (95% CI)
Severe	1	347	0.80 (0.5, 1.28)	0.94 (0.68, 1.3)
Nocturnal	1	347	0.85 (0.77, 0.94)	0.77 (0.7, 0.84)
Overall	1	347	0.98 (0.94, 1.01)	0.89 (0.86, 0.93)

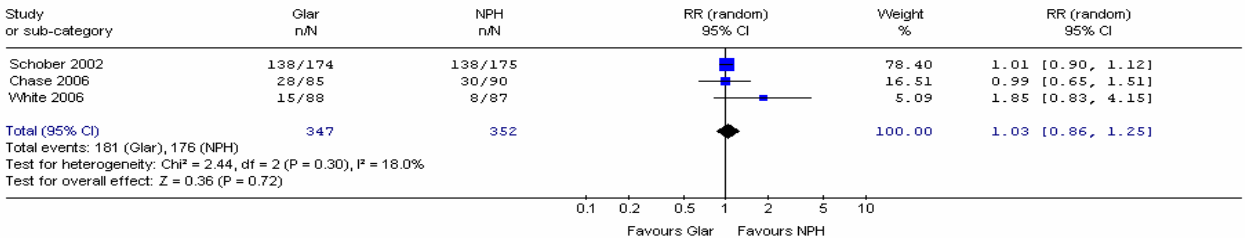
CI=confidence interval; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Figure 3: Forest plot of all RCTs that examined the use of IGlar versus NPH for the treatment of pediatric type 1 DM patients – Relative risk of severe hypoglycemia



CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Figure 4: Forest plot of all RCTs that examined the use of IGlar versus NPH for the treatment of pediatric type 1 DM patients – Relative risk of overall hypoglycemia



CI=confidence interval; DM=diabetes mellitus; Glar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

IDet versus NPH

Only one RCT[30] comparing IDet with NPH (and IAsp as bolus insulin in both arms) was identified. The relative risks and rate ratios for severe hypoglycemia, nocturnal hypoglycemia, and overall hypoglycemia are shown in Table 4. No significant differences were found in the risk or rate of severe hypoglycemia; IDet produced statistically favourable effects in both measures of nocturnal hypoglycemia. The rate ratio for overall hypoglycemia was also significantly reduced, but there was no statistically significant difference in terms of relative risk.

d) Body mass index

The available BMI data are summarized in Appendix 12a. One RCT[35] reported that there was no significant difference in mean BMI between IGlar and NPH (Table 5). Another RCT[30] comparing IDet and NPH reported body mass index Z-score. The difference in BMI Z-score was statistically significant in favour of IDet in this trial. In the RCT[36] comparing IGlar+lispro with NPH+HI, no BMI information was provided, but it was reported that there was no difference in body weight at the endpoint between treatments.

Table 5: Summary of results for comparison of long-acting insulin analogues with NPH in pediatric type 1 DM – Mean BMI

Comparison	Bolus Insulin	No. of Trials	Sample Size	Mean Difference (95% CI)
IGlar vs. NPH	ILis or HI	1	28	0.2 (-0.03, 0.43) kg/m^2
IDet vs. NPH	IAsp	1	347	-0.18 (-0.25, -0.11) (Z-score)

BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; IDet= insulin detemir; ILis=insulin lispro; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; vs.=versus.

e) Diabetic ketoacidosis

Study-level data on diabetic ketoacidosis (DKA) are presented with adverse event data in Appendix 13a. Two RCTs reported DKA for the comparison of IGlar versus NPH; very low or zero event rates occurred in one or more arms, therefore RR could not be precisely estimated. Another RCT[30] reported DKA for the comparison of IDet versus NPH. Once again, event rates were very low, and no significant differences were observed. DKA data were not reported for the comparison of IGlar+lispro with NPH+HI. A summary of RRs for DKA is shown in Table 6.

Table 6: Summary of results for comparison of long-acting insulin analogues with NPH in pediatric type 1 DM – RR of diabetic ketoacidosis

Comparison	Bolus Insulin	Number of RCTs	Number of Patients	RR (95% CI)	I^2 (%)
IGlar vs. NPH	ILis or HI	2	376	3 (0.12, 73.13)	NA*
IDet vs. NPH	IAsp	1	347	0.99 (0.18, 5.33)	NA

* One of the two studies had zero event rates in both treatment arms, therefore only one study contributed to the estimate of RR.
DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; IGlar=insulin glargine; IDet=insulin detemir; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk; vs.=versus.

f) Generic or diabetes-related quality-of-life

No trials reported quality-of-life data.

g) Satisfaction with diabetes treatment

No trials reported data on patient satisfaction.

h) Patient self-management

No trials reported data on patient self-management.

i) Resource utilization

No trials reported data on resource utilization.

j) Long-term diabetic complications

No data were reported for long-term diabetes complications such as retinopathy, cardiovascular disease, or mortality.

k) Adverse events (excluding hypoglycemia)

Adverse events (AEs) observed in each study are detailed in Appendix 13a. Five (71%) RCTs reported AEs. The most frequent AEs in both groups were injection site reactions, upper respiratory tract infection, headache, pharygitis, gastroenteritis, and influenza-like symptoms. Injection site reactions were the only AEs considered related to treatment. All injection site reactions were mild or moderate in severity and reversible.

7.4.2 Adult type 1 DM

a) Glycosylated hemoglobin

Study-level A1c data for adult type 1 DM patients are summarized in Appendix 11a. All A1c data are expressed as percentages. Meta-analytic results for each comparison are shown in Table 7.

Table 7: Summary of results of meta-analyses for comparison of long-acting insulin analogues versus NPH insulin in adult type 1 DM – Overall results, subgroup analyses, and sensitivity analyses for mean A1c (%)

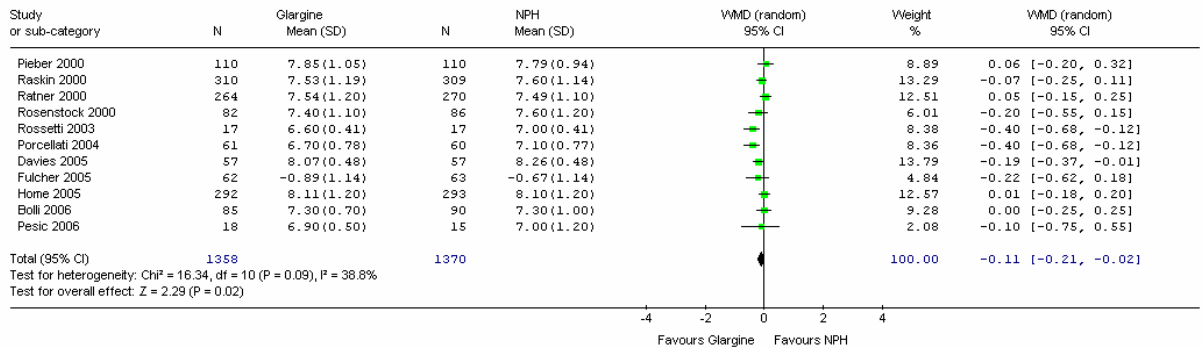
Comparison	Analysis	Number of RCTs	Sample Size	WMD (95% CI) in A1c (%)	I^2 (%)
IGlar vs. NPH	All RCTs	11	2,728	-0.11 (-0.21, -0.02)	38.8
	Subgroup analysis by bolus insulin				
	Bolus=IAsp	2	147	-0.18 (-0.35, -0.01)	0
	Bolus=HI	4	1,507	0.01 (-0.10, 0.13)	0
	Bolus=ILis	5	1,074	-0.20 (-0.37, -0.03)	51.4
	Sensitivity analysis				
	Removal of RCTs ≤3 months duration	7	2,273	-0.10 (-0.20, 0.01)	40.0
	Removal of crossover RCTs	10	2,614	-0.10 (-0.21, 0.01)	41.0
IGlar vs. ultralente	All RCTs	1	48	-0.20 (-0.56, 0.16)	NA
IDet vs. NPH	All RCTs	7	2,558	-0.06 (-0.13, 0.02)	0
	Subgroup analysis by bolus insulin				
	Bolus=IAsp	5	1,523	-0.07 (-0.16, 0.03)	0
	Bolus=HI	2	1,035	-0.02, (-0.22, 0.19)	46.3
	Sensitivity Analysis				
	Removal of crossover studies	6	2,301	-0.07 (-0.16, 0.02)	0
IDet +aspart vs. NPH+HI	All RCTs	1	595	-0.23 (-0.37, -0.09)	NA
IDet vs. glargine	All RCTs (Bolus=IAsp)	1	320	-0.03 (-0.26, 0.2)	NA

A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; vs.=versus; WMD=weighted mean difference.

IGlar versus NPH

Fourteen RCTs[50-62,74] were identified for this comparison. Of these, 11 RCTs[50-52,55-57,59-63]reported mean A1c at study end. Overall, the difference in mean A1c between IGlar and NPH was -0.11% (95% CI: -0.21, -0.02) (Figure 5). Of these 11 RCTs, four showed a statistically significant benefit in favour of IGlar,[50,60-62] and none reported a significant benefit in favour of NPH. In sensitivity analysis, removal of studies of less than three months duration or of crossover studies did not have a significant impact on the overall estimate of effect. In subgroup analysis, statistically significant benefit in favour of IGlar was observed in each of the rapid-acting analogue subgroups, but not in the HI subgroup.

Figure 5: Forest plot of all RCTs that examined the use IGlar versus NPH for the treatment of type 1 DM in adult patients – A1c, weighted mean difference



Heterogeneity I^2 describes the heterogeneity among the included studies. A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

Heterogeneity (I^2) of the overall pooled estimate wasless than 50%. In subgroup analyses, I^2 was 0% in both the HI and IAsp subgroups, and 51.4% in the ILis subgroup. Heterogeneity in the ILis subgroup was not readily explained by any of the study variables tested. The funnel plot for the overall meta-analysis did not indicate a high probability of publication bias (Appendix 14, Figure 1).

IGlar+lispro versus NPH+human insulin

A single RCT of crossover design[74] reported the mean difference in A1c for this comparison. Since the authors noted that a "marked sequence effect" was detected for the A1c outcome,[74] this result is not reported.

IGlar versus ultralente

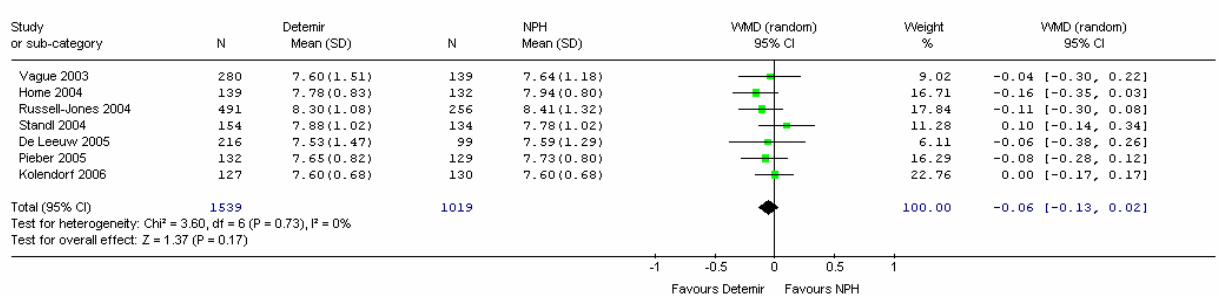
The single study[65] that reported A1c data for this comparison found no significant difference between treatments. This study also reported a non-significant RR of achieving A1c≤7% [RR (95% CI)=1.15 (0.71, 1.87)].

IDet versus NPH

Seven trials[39-42,44-46] reported mean A1c differences between IDet and NPH. Five of these[39-42,44] used IAsp as bolus and two[45,46] used HI. The pooled estimate for all eight trials showed no statistically significant difference between treatments [WMD (95% CI)=-0.06% (-0.13, 0.02)] (Figure 6). Sensitivity analysis did not demonstrate an important effect of removing crossover studies from the analysis; no studies were less than three months in duration. Pooled A1c estimates within each of

the two bolus insulin subgroups were similar to the overall estimate and neither was statistically significant.

Figure 6: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – A1c, weighted mean difference



A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

There was no heterogeneity across studies in either the overall analysis or within the IAsp subgroup (I^2=0%), while the human insulin subgroup demonstrated a moderate level of heterogeneity (I^2=46%). The likelihood of publication bias was minimal based on analysis of the funnel plot (Appendix 14, Figure 2).

IDet+aspart versus NPH+HI

Only Hermansen *et al.*[49] reported the comparison of IDet with IAsp as bolus insulin versus NPH with HI as bolus insulin. A statistically significant difference in mean A1c at endpoint was observed [mean difference (95% CI)=-0.23% (-0.37, -0.09)].

IDet versus IGlar

The single RCT comparing the two long-acting analogues used IAsp as bolus insulin in both treatment arms.[48] There was no statistically significant difference in mean A1c [mean difference (95% CI)=-0.03% (-0.26, 0.20)].

b) Two-hour post-prandial plasma glucose

No studies reported data on this outcome.

c) Hypoglycemia

Study-level hypoglycemia data for adult type 1 DM are presented in Appendix 10a. Hypoglycemia definitions are also shown in Appendix 10a. Results of meta-analysis for the various comparisons are presented in Tables 8 to 13.

IGlar versus NPH

The numbers of RCTs reporting the necessary data to calculate relative risk of experiencing at least one episode of severe, nocturnal, and overall hypoglycemia were 7,[50,52,56,59,61,62,95] 5,[52,54,55,59,60] and 6,[50,54,55,57,59,60] respectively. The numbers of RCTs that reported data allowing for calculation of rate ratio for severe, nocturnal, and overall hypoglycemia were 5,[50,56,59,60,63] 4,[59-62] and 2,[59,62] respectively.

Pooled estimates of all trials revealed no statistically significant differences between treatments in terms of the RR or rate ratio for any of severe, nocturnal, and overall hypoglycemia (Table 8). The likelihood of publication bias was minimal based on funnel plot analysis (Appendix 14, Figures 3 to 5).

Table 8: Summary of results of meta-analyses for comparison of IGlar versus NPH in adult type 1 DM – Overall results, subgroup analyses, and sensitivity analyses for RR and rate ratio of severe, nocturnal, and overall hypoglycemia

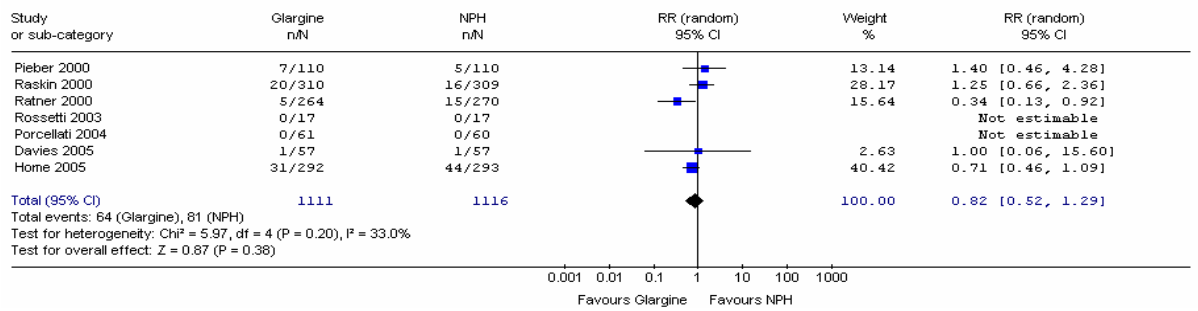
Type of Hypo-glycemia	Analysis	RR				Rate Ratio			
		No. of RCTs	Sample Size	RR (95% CI)	I^2 (%)	No. of RCTs	Sample Size	Rate Ratio (95% CI)	I^2 (%)
Severe	All RCTs	7	2,227	0.82 (0.52, 1.29)	33.0	5	1,559	0.89 (0.64, 1.23)	31.8
	Subgroup analysis by bolus insulin								
	Bolus= IAsp	1	114	1.00 (0.06, 15.60)	NA	1	114	1.00 (0.06, 15.99)	NA
	Bolus=ILis	3	774	1.25 (0.66, 2.36)	NA	3	1,538	0.98 (0.73, 1.30)	19.6
	Bolus=HI	3	1,339	0.68 (0.37, 1.26)	42.6	1	534	0.47 (0.23, 0.96)	NA
	Sensitivity analysis								
	Removal of crossover RCTs	6	2,113	0.81 (0.49, 1.36)	49.6	4	1,445	0.88 (0.61, 1.28)	48.8
Nocturnal	All RCTs	5	1,943	0.97 (0.87, 1.09)	65.6	4	916	0.67 (0.37, 1.23)	99.2
	Subgroup analysis by bolus insulin								
	Bolus=HI	3	1,199	0.91 (0.75, 1.12)	76.6	0	NA	NA	NA
	Bolus=ILis	2	744	1.02 (0.88, 1.19)	59.9	4	916	0.67 (0.37, 1.23)	99.2
Overall	All RCTs	6	2,007	1.02 (0.98, 1.07)	55.7	2	670	0.82 (0.52, 1.28)	98.4
	Subgroup analysis by bolus insulin								
	Bolus= IAsp	1	114	1.05 (0.86, 1.26)	NA	0	NA	NA	NA
	Bolus=HI	3	1,149	1.00 (0.92, 1.10)	76.5	0	NA	NA	NA
	Bolus=ILis	2	744	1.03 (0.96, 1.10)	65.3	2	670	0.82 (0.52, 1.28)	98.4
	Sensitivity analysis								
	Removal of crossover RCTs	5	1,893	1.02 (0.97, 1.07)	65.2	2	670	0.82 (0.52, 1.28)	98.4

CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; IGlar=insulin glargine; ILis=insulin lispro; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Severe hypoglycemia: For severe hypoglycemia, the overall pooled RR (95% CI) was 0.82 (0.52, 1.29) (Figure 7). Only one[56] of the seven RCTs reported a statistically significant benefit for IGlar compared with NPH. Pooled analysis for all three subgroups based on bolus insulin revealed non-significant RRs. Removal of the single crossover study in sensitivity analysis did not have a large impact on the overall result. The overall pooled rate ratio (95% CI) for severe hypoglycemia was 0.89 (0.64, 1.23) (Figure 8). The only significant difference in subgroup analysis based on bolus insulin was for HI, in which the single available study demonstrated a rate ratio of 0.47 (0.23, 0.96). Removal of the single crossover study in sensitivity analysis did not have a large impact on the overall rate ratio.

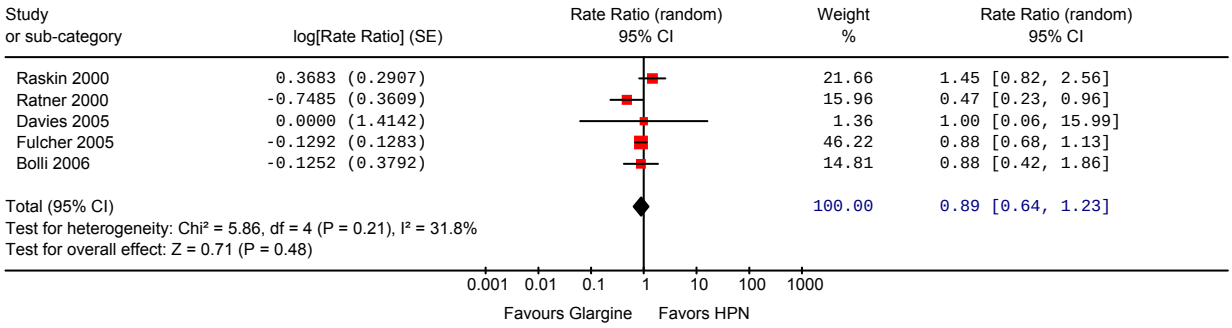
There was minimal heterogeneity for this outcome (I^2 values were 33% and 32% for the RR and rate ratio.

Figure 7: Forest plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in adult patients – RR of severe hypoglycemia



Heterogeneity I^2 describes the heterogeneity among the included studies. CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

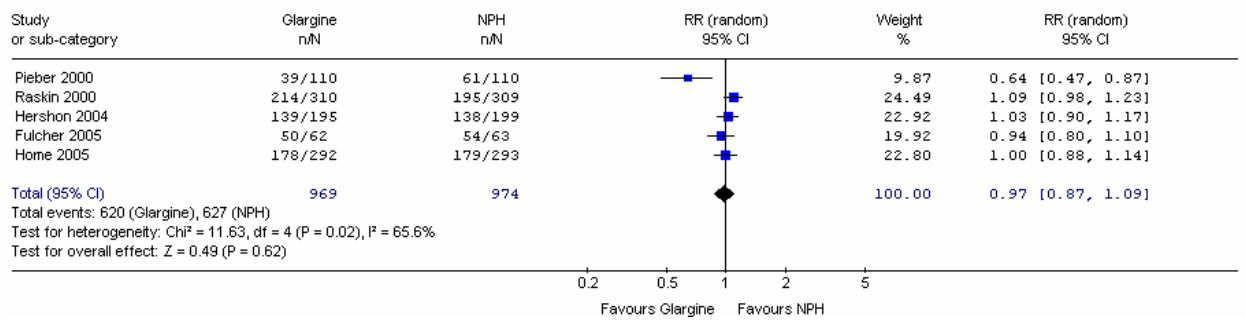
Figure 8: Forest plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in adult patients – Rate ratio of severe hypoglycemia



Heterogeneity I^2 describes the heterogeneity among the included studies. CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

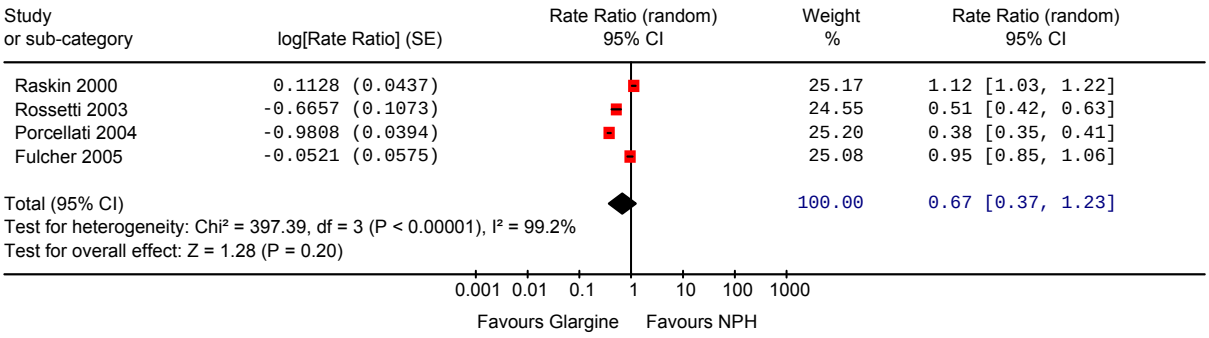
Nocturnal hypoglycemia: There was no significant difference between treatments in terms of the pooled RR of nocturnal hypoglycemia (Figure 9). Only one RCT[52] showed a statistically significant reduction in favour of IGlar. The subgroup and sensitivity analyses also demonstrated RRs of nearly 1 that were non-significant. There was also no significant difference in nocturnal hypoglycemia rate ratio (Figure 10). No sensitivity or subgroup analyses were conducted for the rate ratio, since all four studies were of parallel design and used ILis as bolus insulin.

Figure 9: Forest plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in adult patients – RR of nocturnal hypoglycemia: Events



Heterogeneity I² describes the heterogeneity among the included studies. CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Figure 10: Forest plot of all RCTs that examined the use of insulin glargine versus NPH for the treatment of type 1 DM in adult patients – Rate ratio of nocturnal hypoglycemia

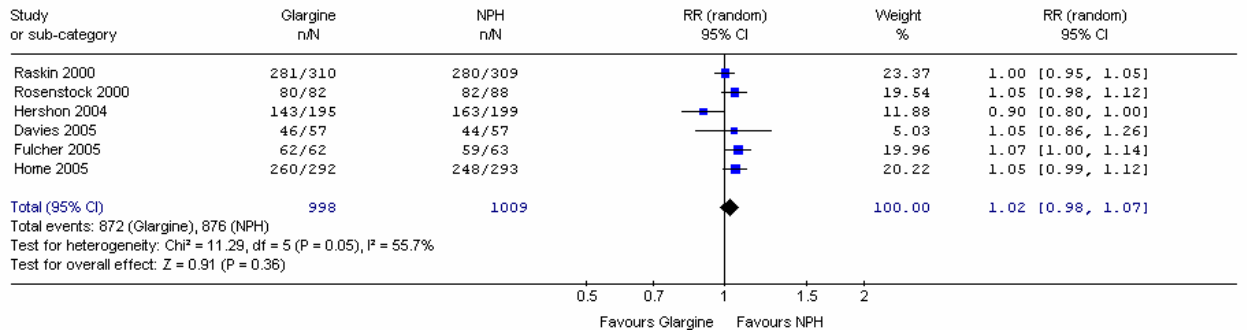


Heterogeneity I² describes the heterogeneity among the included studies. CI=confidence interval; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SE=standard error.

There was a high degree of heterogeneity in terms of both the RR and rate ratio (I^2=65.6% and 99%, respectively). In the HI subgroup, the I^2 for RR was 76.6%. At least some of this heterogeneity may have been due to inclusion of studies of varying duration, since removal of the Pieber *et al.*, 2000[52] study, a four-week trial, reduced the I^2 to 0%. In the ILis subgroup, the I^2 was 59.9%. Of the two studies included in this subgroup, the Raskin *et al.*, 2000 study[59] had a wider target FPG range than the Fulcher *et al.*, 2005[60] study. This difference may have contributed to the high degree of heterogeneity.

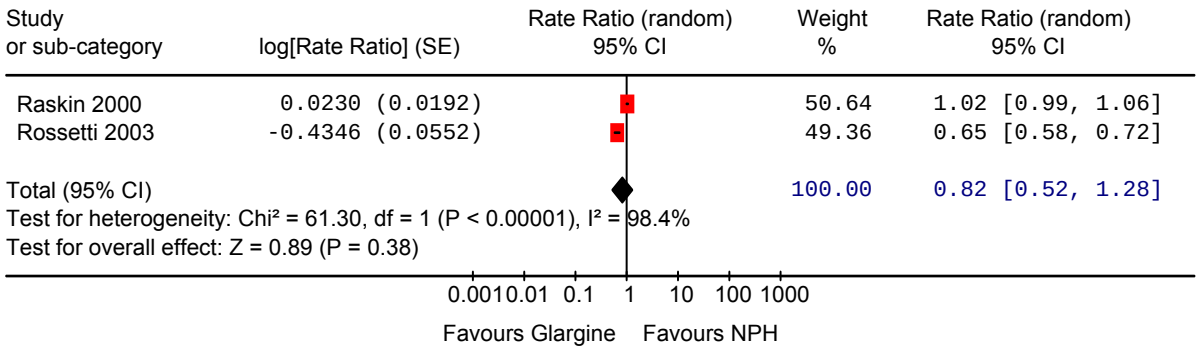
Overall hypoglycemia: For overall hypoglycemia, the overall RR was nearly 1 and not statistically significant (Figure 11). The overall rate ratio was also not significantly different from 1 (Figure 12). Similar results were obtained in subgroup and sensitivity analyses.

Figure 11: Forest plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in adult patients – RR of overall hypoglycemia: Events



Heterogeneity I^2 describes the heterogeneity among the included studies. CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Figure 12: Forest plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in adult patients – Rate ratio of overall hypoglycemia



Heterogeneity I^2 describes the heterogeneity among the included studies. CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SE=standard error.

For RR, the degree of heterogeneity (I^2) among all trials was 55.7%. Within the ILis subgroup, the Raskin *et al.*, 2000 study[59] had a wider target FPG range than that of Fulcher *et al.*, 2005;[60] this may at least partially explain the degree of heterogeneity. In the HI subgroup, differences in dosing frequency may have resulted in heterogeneity since the Hershon *et al.*, 2004[54] trial dosed NPH twice daily, while others allowed either once or twice daily dosing.[55,57] Removal of the Hershon study reduced the I^2 to 0%. The I^2 value among the two studies contributing to the pooled rate ratio was 98.4%. The rate ratio for the Rossetti study was 0.65 and statistically significant,[62] while that of Raskin was nearly 1 and non-significant.[59] It is possible that the former result was due to chance, especially in light of the small sample size of the Rossetti study.

IGlar+lispro versus NPH+human insulin

Only one RCT[64] was identified for this comparison. There was no significant difference between treatments in terms of the RR of severe and nocturnal hypoglycemia (Table 9). However, a statistically significant difference in terms of nocturnal hypoglycemia rate ratio was observed [rate ratio (95% CI)=0.56 (0.48, 0.65)]. The data required to calculate the RR and rate ratio of overall hypoglycemia, and rate ratio of severe hypoglycemia, were not reported in the study.

Table 9: Summary of results for comparison of IGlar+lispro versus NPH+human insulin in adult type 1 DM: RR and rate ratio of severe, nocturnal, and overall hypoglycemia

Type of Hypoglycemia	RR			Rate Ratio		
	No. of RCTs	Sample Size	RR (95% CI)	No. of RCTs	Sample Size	Rate Ratio (95% CI)
Severe	1	108	0.88 (0.48, 1.61)	0	NA	NA
Nocturnal	1	108	0.88 (0.71, 1.10)	1	108	0.56 (0.48, 0.65)
Overall	0	NA	NA	0	NA	NA

DM=diabetes mellitus; IGlar=insulin glargine; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

IGlar versus ultralente

The single study available for this comparison[65] reported sufficient data to calculate the rate ratios of severe, nocturnal, and overall hypoglycemia (Table 10). There was no significant difference between treatments in terms of severe hypoglycemia, ultralente was significantly favoured in terms of nocturnal hypoglycemia, and IGlar was significantly favoured in terms of overall hypoglycemia. RRs could not be calculated due to lack of data.

Table 10: Summary of results for comparison of IGlar versus ultralente in adult type 1 DM – Rate ratio of severe, nocturnal, and overall hypoglycemia

Type of Hypoglycemia	No. of RCTs	Sample Size	Rate Ratio (95% CI)
Severe	1	48	1.00 (0.17, 5.98)
Nocturnal	1	48	1.70 (1.10, 2.63)
Overall	1	48	0.78 (0.67, 0.91)

CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; RCTs=randomized controlled trials.

IDet versus NPH

The numbers of RCTs reporting sufficient data to calculate the RR of severe, nocturnal, and overall hypoglycemia were 7,[40-46] 7,[39,40,42,44-47] and 6,[39,42-46] respectively. The numbers of RCTs reporting sufficient data to calculate the rate ratio of severe, nocturnal, and overall hypoglycemia were 7,[39,41-46] 9,[39-47] and 6,[39,42-46] respectively. Results of meta-analysis are presented in Table 11.

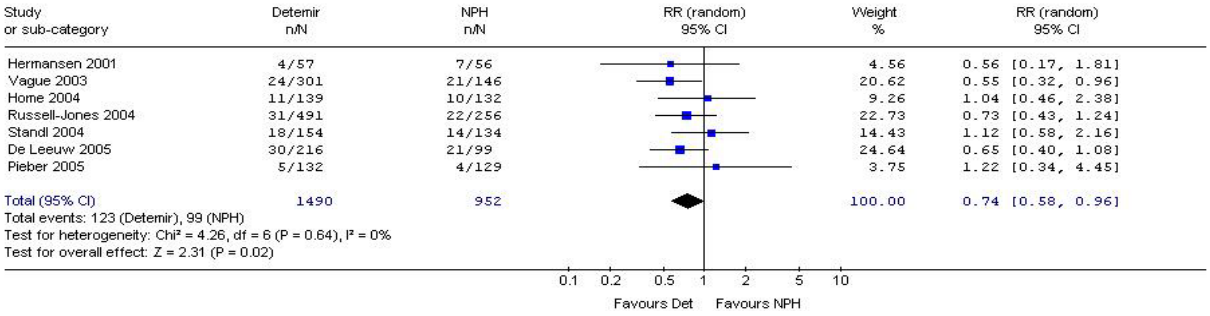
Severe hypoglycemia: For severe hypoglycemia, the pooled relative risk was statistically significant in favour of IDet [RR (95% CI)=0.74 (0.58, 0.96)] (Figure 13, Table 11). Of the seven RCTs in this analysis, only one[44] reported a statistically significant benefit compared with NPH. The RR estimate in each of the HI and IAsp bolus insulin groups was of a similar magnitude as the overall result, however, the result was statistically non-significant for HI. No studies used ILis as bolus insulin. Removal of the single crossover study did not have an appreciable effect on the overall pooled estimate. There was no significant difference in terms of the overall pooled rate ratio (Figure 14). Similar results were obtained for the HI and IAsp bolus insulin subgroups and when the single crossover study was removed from analysis.

Table 11: Summary of results of meta-analyses for comparison of IDet versus NPH in adult type 1 DM – Overall results, subgroup analyses, and sensitivity analyses for RR and rate ratio of severe, nocturnal, and overall hypoglycemia

Type of Hypo-glycemia	Analysis	RR				Rate Ratio			
		No. of RCTs	Sample Size	RR (95% CI)	I^2 (%)	No. of RCTs	Sample Size	Rate Ratio (95% CI)	I^2 (%)
Severe	All RCTs	7	2,442	0.74 (0.58, 0.96)	0	7	2,442	0.95 (0.65, 1.38)	62.3
	Subgroup analysis by bolus insulin								
	Bolus= IAsp	4	1,294	0.69 (0.50, 0.96)	0	4	1,247	0.90 (0.52, 1.53)	64
	Bolus=HI	3	1,148	0.83 (0.56, 1.22)	0	3	1,097	1.02(0.57, 1.82)	60.2
	Sensitivity analysis								
	Removal of crossover studies	6	2,329	0.75 (0.58, 0.98)	0	5	2,014	1.14 (0.77, 1.70)	58.7
Nocturnal	All RCTs	6	2,311	0.92 (0.85, 0.98)	32.2	8	2,695	0.66 (0.60, 0.73)	78.3
	Subgroup analysis by bolus insulin								
	Bolus= IAsp	4	1,276	0.87 (0.78, 0.97)	49.8	5	1,547	0.63(0.54, 0.72)	80.1
	Bolus=HI	2	1,035	0.97 (0.89, 1.06)	0	3	1,148	0.74 (0.69, 0.78)	0
	Sensitivity Analysis								
	Removal of crossover studies	5	2,058	0.94 (0.89, 0.99)	0	6	2,329	0.69 (0.64, 0.75)	70.5
Overall	All RCTs	6	2,110	1.00 (0.96, 1.04)	30.8	6	2,109	0.84 (0.74, 0.97)	97.8
	Subgroup analysis by bolus insulin								
	Bolus= IAsp	3	961	0.97 (0.92, 1.02)	29.6	3	961	0.90 (0.73, 1.10)	97.3
	Bolus=HI	3	1,149	1.03 (0.99, 1.07)	0	3	1,149	0.79 (0.62, 1.02)	98.6
	Sensitivity analysis								
	Removal of crossover studies	4	1,744	0.99 (0.94, 1.04)	52.6	4	1,996	0.88 (0.73, 1.05)	98.6

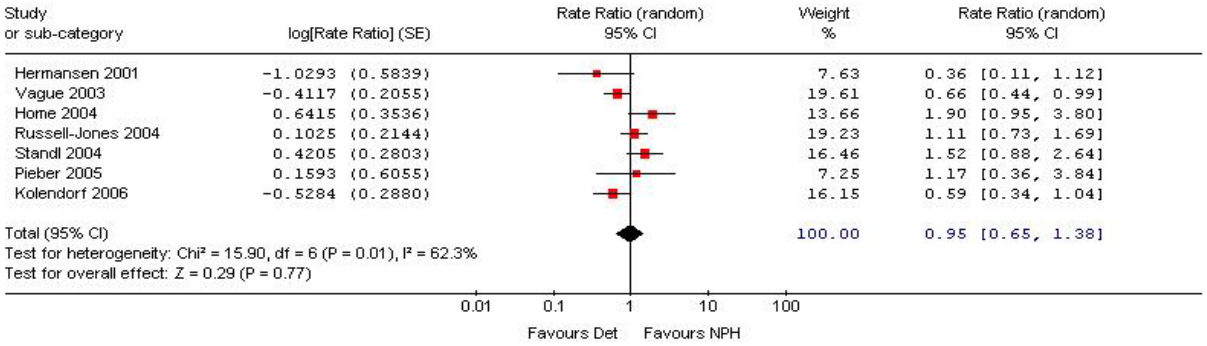
CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; IDet=insulin detemir; NPH=Neutral Protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Figure 13: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – RR of severe hypoglycemia: Number of patients with at least one episode



CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Figure 14: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Rate ratio for severe hypoglycemia



CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

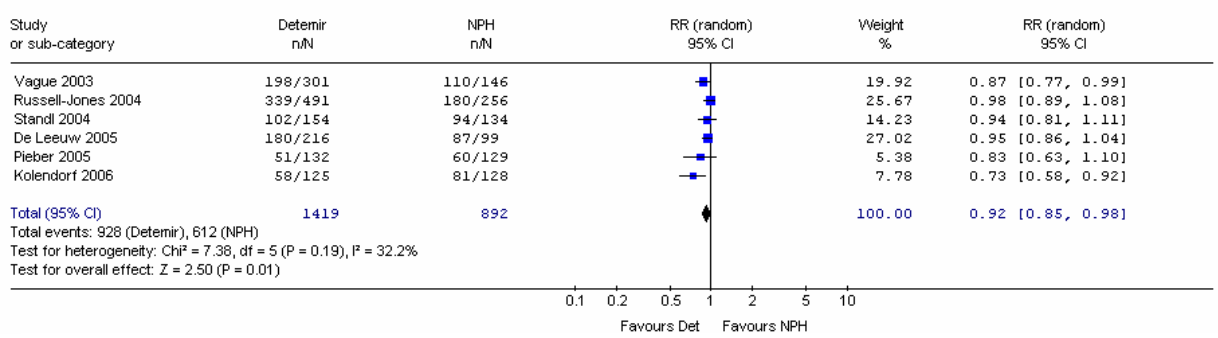
There was no heterogeneity in the meta-analysis of RR in either the overall analysis or within subgroups (I^2=0). However, there was significant heterogeneity (I^2=62.3%) for the overall rate ratio measure, as well as in both bolus insulin groups. Within the HI group, removal of the only crossover study[43] caused the I^2 to fall from 60% to 0%. The possible source of heterogeneity in the IAsp subgroup was less clear, although the wide variation in geographic region may be partly responsible.

There was a low likelihood of publication bias for this outcome based on analysis of funnel plots (Appendix 14, Figure 6-7).

Nocturnal hypoglycemia: For nocturnal hypoglycemia, there was a small but statistically significant advantage for IDet [RR (95% CI)=0.92 (0.85, 0.98)] (Figure 15, Table 11). Two studies[39,44] reported a statistically significant effect in favour of IDet. Results from subgroup analysis by bolus insulin were similar in magnitude, although the RR for HI was statistically non-significant. Removal of the single crossover study did not have a major impact on the overall result. The rate ratio for nocturnal hypoglycemia also significantly favoured IDet [rate ratio (95% CI)=0.66 (0.60, 0.73)]

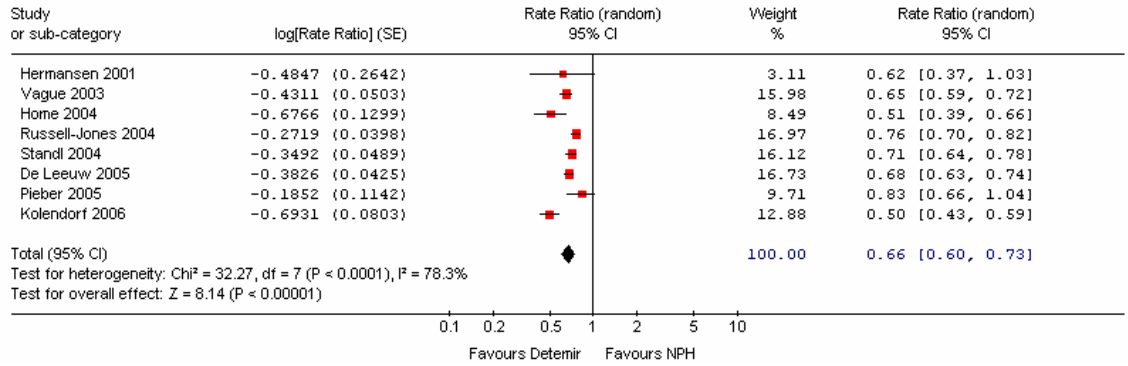
(Figure 16); similar and statistically significant effects were observed in the HI and IAsp bolus insulin subgroups. Six of the eight RCTs in this analysis had statistically significant rate ratios in favour of IDet.[39-41,44-46] Removal of the single crossover study in sensitivity analysis did not affect the overall pooled estimate. No studies used ILis as bolus insulin.

Figure 15: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – RR of nocturnal hypoglycemia: Number of patients with at least one episode



CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Figure 16: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Rate ratio for nocturnal hypoglycemia



CI=confidence interval; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SE=standard error.

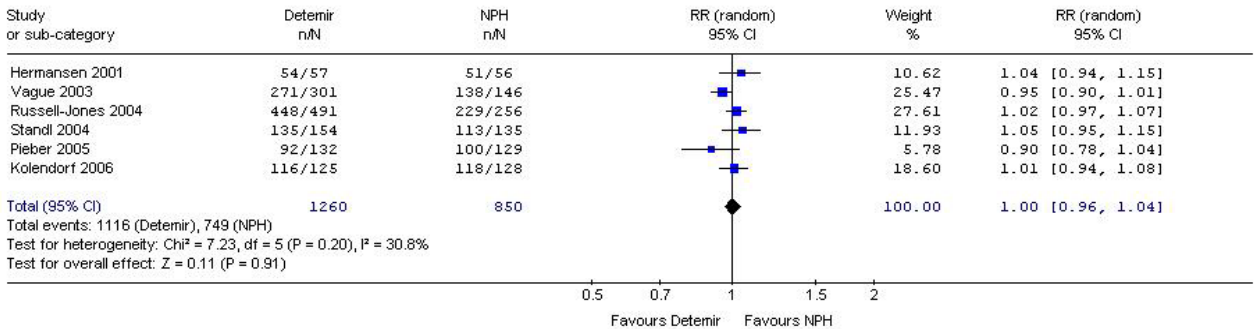
Heterogeneity in the overall meta-analysis of RR was minimal, although I^2 in the IAsp subgroup was nearly 50%. A high degree of heterogeneity was detected in the overall rate ratio analysis (I^2=79%), as well as in the IAsp subgroup (I^2=78%). In contrast, I^2 in the HI subgroup was 0%. As in the analysis of severe hypoglycemia, the diversity of geographic regions and populations studied may have contributed to the heterogeneity in the IAsp subgroup.

There was no evidence to indicate publication bias for the RR outcome (Appendix 14, Figure 8). However, a degree of asymmtery in the funnel plot for rate ratio was detected, indicating the

possibility of reporting bias in favour of IDet for this measure of nocturnal hypoglycemia (Appendix 14, Figure 9).

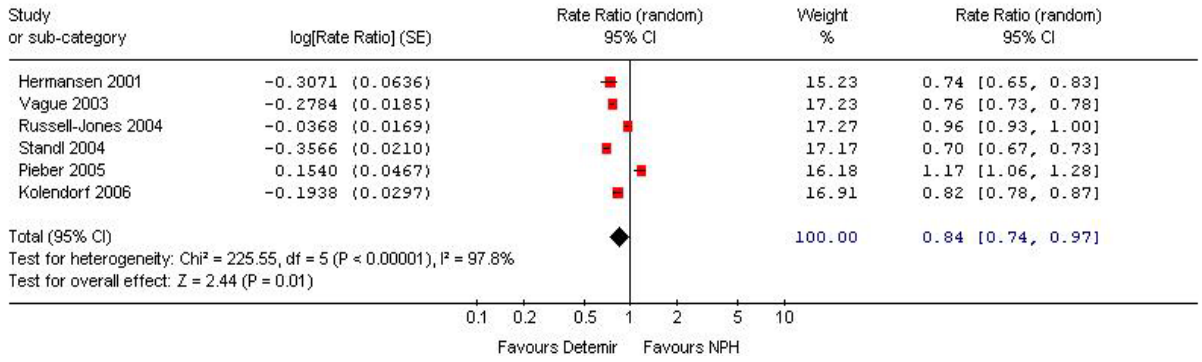
Overall hypoglycemia: For overall hypoglycemia, the pooled RR (95% CI) was 1.00 (0.96, 1.04) (Figure 17, Table 11). There was also no statistically significant difference in both bolus insulin subgroups. However, the rate ratio significantly favoured IDet in both the overall analysis [rate ratio (95% CI)=0.84 (0.74, 0.97)] (Figure 18), as well as in subgroup analysis for both HI and IAsp.

Figure 17: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – RR of overall hypoglycemia: Number of patients withat least one episode



CI=confidence interval; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Figure 18: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Rate ratio of overall hypoglycemia



CI=confidence interval; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SE=standard error.

The heterogeneity (I^2) in the overall meta-analysis of RR was 30.8%, in the IAsp subgroup, 29.6%, and in the HI subgroup, 0%. I^2 values of over 90% were observed in the rate ratio. Individual rate ratios varied widely, from a statistically significant value of 1.17 in favour of NPH in one study, to 0.70 in favour of IDet in another. Sources of heterogeneity were unclear, although geographic diversity of study sites is a possible cause. As well, the narrow confidence intervals of individual estimates contributed to overall heterogeneity.

Asymmetry in funnel plots was observed, therefore reporting bias was likely present for both the RR and rate ratio measures of overall hypoglycemia (Appendix 14, Figures 10 to 11).

IDet+aspart versus NPH+HI

In the single study that compared these strategies,[49] the RR for severe and overall hypoglycemia were nearly 1 and statistically non-significant, while the RR for nocturnal hypoglycemia significantly favoured IDet [RR (95% CI)=0.65 (0.55, 0.77)] (Table 12). The rate ratios for nocturnal and overall hypoglycemia were also statistically significant [rate ratio (95% CI)=0.44 (0.39, 0.51) and 0.78 (0.74, 0.82), respectively].

Table 12: Summary of results for comparison of IDet+aspart versus NPH+human insulin in adult type 1 DM – Relative risk and rate ratio of severe, nocturnal, and overall hypoglycemia

Type of Hypoglycemia	RR			Rate Ratio		
	No. of RCTs	Sample Size	RR (95% CI)	No. of RCTs	Sample Size	Rate Ratio (95% CI)
Severe	1	595	1.05 (0.56, 1.96)	1	595	0.89 (0.58, 1.36)
Nocturnal	1	595	0.65 (0.55, 0.77)	1	595	0.44 (0.39, 0.51)
Overall	1	595	0.92 (0.84, 1.0)	1	595	0.78 (0.74, 0.82)

CI=confidence interval; DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

IDet versus IGlar

One RCT[48] compared IDet with IGlar; IAsp was used as bolus insulin in both arms. RRs and rate ratios for severe, nocturnal, and overall hypoglycemia are shown in Table 13. Both the RR and rate ratio measures of severe hypoglycemia favoured IDet [RR (95% CI)=0.25 (0.07, 0.86) and rate ratio (95% CI)=0.41 (0.2, 0.86)]. The rate ratio for nocturnal hypoglycemia also significantly favoured IDet, although the RR was not statistically significant. There was no significant difference between treatments in either the RR or rate ratio of overall hypoglycemia.

Table 13: Summary of results for comparison of IDet versus IGlar in adult type 1 DM – RR and rate ratio of severe, nocturnal, and overall hypoglycemia

Type of Hypoglycemia	RR			Rate Ratio		
	No. of RCTs	Sample Size	RR (95% CI)	No. of RCTs	Sample Size	Rate Ratio (95% CI)
Severe	1	320	0.25 (0.07, 0.86)	1	320	0.41 (0.2, 0.86)
Nocturnal	1	320	0.94 (0.75, 1.17)	1	320	0.66 (0.58, 0.76)
Overall	1	320	1.05 (0.93, 1.19)	1	320	0.96 (0.92, 1.02)

CC=confidence interval; DM=diabetes mellitus; IDet=insulin detemir; IGlar=insulin glargine; RCTs=randomized controlled trials; RR=relative risk.

d) Body weight

Study-level weight data are presented in Appendix 12a. The results of meta-analyses for body weight for the various comparisons are summarized in Table 14.

Table 14: Summary of results of meta-analyses for comparison of long-acting insulin analogues versus NPH in adult type 1 DM: Overall results, subgroup analyses, and sensitivity analyses for body weight, WMD

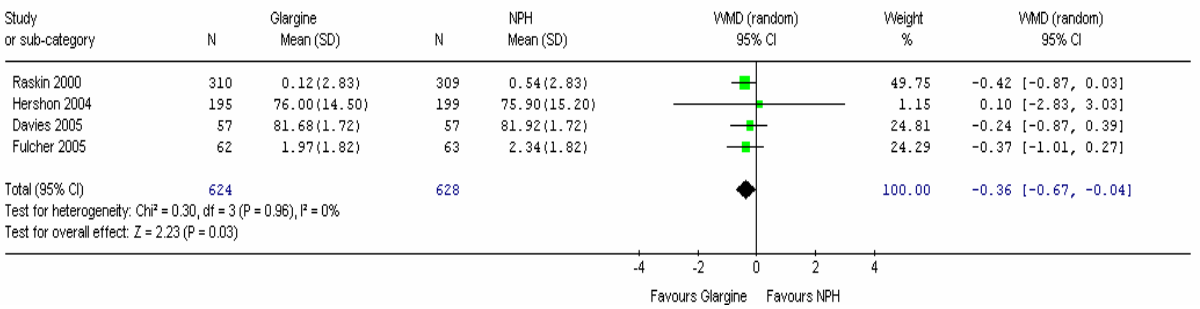
Comparison	Analysis	No. of RCTs	Sample Size	WMD (95% CI) in Body Weight (kg)	I^2 (%)
IGlar vs. NPH	All RCTs	4	1,152	-0.36 (-0.67, -0.04)	0
	Subgroup analysis by bolus insulin				
	Bolus=IAsp	1	114	-0.24 (-0.87, 0.39)	NA
	Bolus=HI	1	394	0.10 (-2.83, 3.03)	NA
	Bolus=ILis	2	744	-0.40 (-0.77, -0.04)	0
	Sensitivity analysis				
	Removal of crossover studies	3	1,138	-0.40 (-0.76, -0.03)	0
	Removal of studies reporting only mean change from baseline	2	508	-0.22 (-0.84, 0.39)	0
IDet vs. NPH	All RCTs	6	2,302	-0.73 (-1.42, -0.03)	0
	Subgroup analysis by bolus insulin				
	Bolus=IAsp	4	1,267	-0.81 (-1.58, -0.05)	0
	Bolus=HI	2	1,035	-1.26 (-1.84, 1.33)	0
IDet+aspart vs. NPH+HI	All RCTs	1	595	-1.10 (-1.49, -0.71)	NA
IDet vs. IGlar	All RCTs	1	320	-0.5 (-1.21, 0.21)	NA

CI=confidence interval; DM=diabetes mellitus; IDet=insulin detemir; IGlar=insuling glargine; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; vs.=versus; WMD=weighted mean difference.

IGlar versus NPH

Four RCTs[50,54,59,60] reported either mean body weight at endpoint or mean change in body weight from baseline. Overall, body weight was significantly lower in the IGlar arm, although the difference was small [WMD (95% CI)=-0.36 kg (-0.67, -0.04)] (Figure 19). There was no heterogeneity (I^2=0%). Removal of crossover studies, or of studies only reporting mean weight at endpoint rather than mean change from baseline, did not have a major effect on the WMD point estimate. Similarly, mean differences within subgroups defined by bolus insulin were similar to the overall estimate, with the exception of HI, for which the single available study reported a difference that was 0.10 kg higher in the IGlar arm (p>0.05).

Figure 19: Forest plot of all RCTs that examined the use IGlar versus NPH for the treatment of type 1 DM in adult patients – Body weight, WMD



Heterogeneity I^2 describes the heterogeneity among the included studies. CI=confidence interval; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

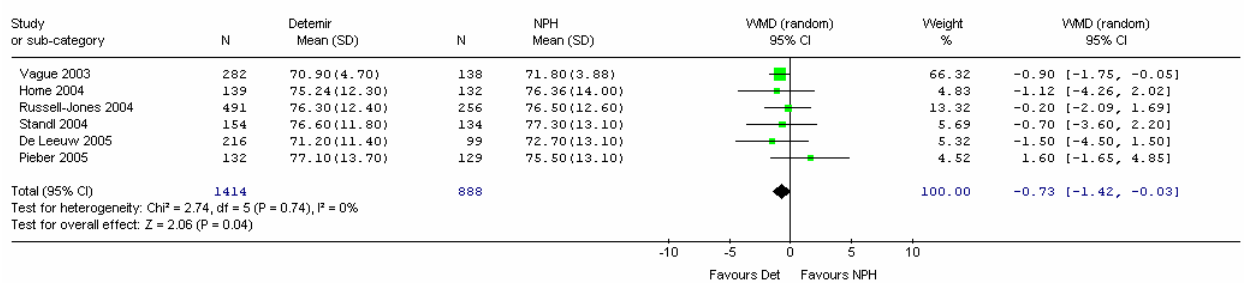
IGlar+lispro versus NPH+human insulin

Body weight data were not reported for this comparison.

IDet versus NPH

Six RCTs[40-42,44-46] reported mean body weight at endpoint for this comparison. Overall, IDet was associated with significantly lower body weight than NPH [WMD (95% CI)=-0.73 kg (-1.42, -0.03)] (Figure 20). Results within subgroups defined by bolus insulin were similar, although the pooled estimate in the HI subgroup was statistically non-significant. There were no crossover studies in this comparison.

Figure 20: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Body weight, WMD



CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

There was no significant heterogeneity among trials (I^2=0%). The potential for publication bias was minimal based on analysis of the funnel plot (Appendix 14, Figure 12).

IDet+IAsp versus NPH+ HI

One RCT[49] reported that there was a statistically significant decrease in body weight at the end of treatment in the IDet+IAsp group compared with NPH+HI [mean difference (95% CI)=-1.10 kg (-1.49, -0.71)].

IDet versus IGlar

In the single RCT reporting the results of this comparison,[48] no statistically significant difference was found in body weight [mean difference (95% CI)=-0.5 kg (-1.21, 0.21)].

e) Diabetic ketoacidosis

No studies reported data on diabetic ketoacidosis.

f) Generic or diabetes-related quality-of-life

Study-level quality-of-life data are presented in Appendix 15a. One RCT[58] reported a non-significant difference between IGlar and NPH in terms of HRQoL as measured by change from baseline in the Well-being Questionnaire (W-BQ) General Well-being score [mean difference (95% CI)=-0.35 (-1.5, 0.8). HRQoL data were not reported for other comparisons.

g) Patient satisfaction with diabetes treatment

In the same study that reported HRQoL,[58] the difference in terms of satisfaction with treatment as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) was statistically significant in favour of IGlar [WMD (95% CI)=1.83 (0.82, 2.84)]. Patient satisfaction data were not reported for other comparisons.

h) Patient self-management

No trials reported data on patient self-management.

i) Resource utilization

No studies reported data related to resource utilization.

j) Long-term diabetic complications

No studies listed long-term complications such as mortality, cardiovascular disease, or retinopathy as outcomes of interest. However, some studies reported the incidence of such events [see Appendix 13a, "Adverse Events Data (excluding hypoglycemia) for RCTs in Type 1 DM"]. In all cases, the number of events observed was too small for adequate comparisons to be made.

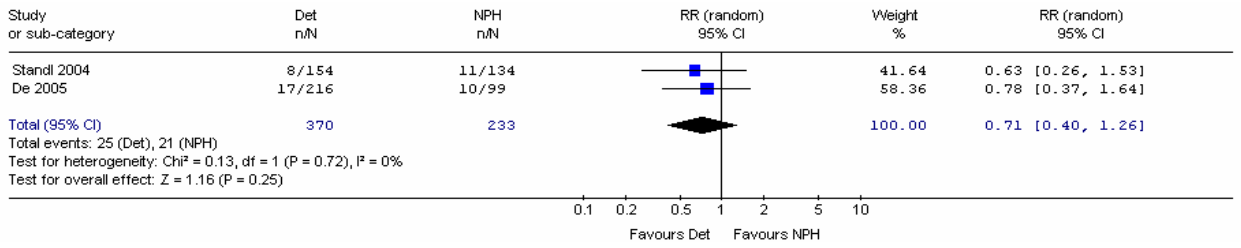
Non-fatal ischemic heart disease

Two RCTs[39,96] comparing IDet with NPH reported the incidence of ischemic heart disease. Standl *et al.*[46] reported one case in the IDet arm and none in the NPH group, while Kolendorf *et al.*[39] reported no cases in either treatment arm. Data on this outcome were not reported for other comparisons.

Retinopathy

One RCT[59] reported outcomes related to retinopathy for the comparison of IGlar versus NPH; there was no statistically significant difference between treatments [RR (95% CI)=1.28 (0.48, 3.40)]. Two RCTs[40,46] reported this outcome for the comparison of IDet versus NPH. Again, no statistically significant difference was observed [RR (95% CI)=0.71 (0.40, 1.26)] (Figure 21). In the only study comparing IDet with IGlar,[48] there was one case with retinopathy in the IDet arm and none in the IGlar arm. No data related to retinopathy were reported for the remaining comparisons.

Figure 21: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – RR of retinopathy: Number of patients



CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

Stroke / Transient-ischemic attack

One RCT[42] reported one case of stroke/TIA with IDet versus none in the NPH arm. There was no data on this outcome for other comparisons.

Mortality

Study-level mortality data are presented in Appendix 16a. Of the 14 studies comparing IGlar with NPH, only Ratner *et al.*, 2000[56] reported one death (secondary to cardiopulmonary arrest) in the NPH arm. Two RCTs[39,42] comparing IDet with NPH reported all-cause mortality. Pieber *et al.*[42] reported one death in the IDet arm and none in the NPH arm, while Kolendorf *et al.*[39] reported one death in the NPH arm and none in the IDet arm. In the single RCT[49] that compared IDet+IAsp with NPH+human insulin, a single death (due to lung tumour) occurred in the latter arm. Mortality data were not reported for the remaining comparisons.

k) Adverse events (excluding hypoglycemia)

Seventy-four per cent of trials reported the type and incidence of adverse events (Appendix 13a). The most commonly reported adverse events with the long-acting insulin analogues were local injection-site reactions, respiratory tract infection, gastrointestinal disorders, edema, rhinitis, and headache. Similar adverse events were also reported with NPH. No systemic allergic reactions with insulin treatment were reported in these trials. Overall, there were no apparent differences in the adverse event profile of the long-acting insulin analogues as compared with NPH, except that injection site reactions appeared to be more common with IGlar.

7.4.3 Pediatric type 2 DM

No RCTs of long-acting insulin analogues were identified for this population.

7.4.4 Adult type 2 DM

a) Glycosylated hemoglobin

Study-level A1c data are shown in Appendix 11b. In addition to mean A1c, some RCTs also reported the proportion of patients achieving a target A1c level of ≤7%. Results of meta-analyses for each comparison according to both A1c measures are shown in Table 15. Forest plots for analyses with more than one RCT are shown in Figures 22 to 25.

Table 15: Summary of results of meta-analyses for comparison of long-acting insulin analogues versus NPH insulin or OADs in adult type 2 DM – Overall results, subgroup analyses, and sensitivity analyses for mean A1c (%) and RRof achieving A1c≤7%.

Comparison	Analysis	Mean A1c (%)				RR of Achieving A1c≤7%			
		No. of RCTs	Sample Size	WMD (95% CI)	I^2 (%)	No. of RCTs	Sample Size	RR (95% CI)	I^2 (%)
IGlar vs. NPH (with OADs)	All RCTs	9	3,397	-0.05 (-0.13, 0.04)	13.4	2	1,237	1.19 (0.80, 1.77)	77.6
	Subgroup analysis by OAD								
	OAD=Sfu	4	1,407	-0.18 (-0.30, -0.05)	0	1	481	1.50 (1.05, 2.16)	NA
	OAD=MF	1	110	-0.02 (-0.38, 0.34)	NA	0	NA	NA	NA
	OAD=var	4	1,880	0.03 (-0.07, 0.12)	0	1	456	1.01 (0.90, 1.14)	NA
	Sensitivity analysis								
	Removal of RCTs≤3 months	7	3,241	-0.06 (-0.14, 0.03)	12.8	0	NA	NA	NA
IGlar vs. NPH (w/o OADs)*	All RCTs	1	518	0.28 (0.07, 0.49)	NA	1	100	0.81 (0.32, 2.06)	NA
IDet vs. NPH (with various OADs)	All RCTs	3	1,159	0.13 (0.03, 0.22)	2.2	1	463	0.95 (0.85, 1.06)	NA
IDet vs. NPH (with pre-meal IAsp)	All RCTs	1	505	0.10 (-0.18, 0.38)	NA	0	NA	NA	NA
IDet+IAsp vs. NPH+ HI	All RCTs	1	394	0.06 (-0.31, 0.19)	NA	0	NA	NA	NA
IDet vs. IGlar (with various OADS)	All RCTs	1	582	0.10 (-0.06, 0.26)	NA	1	582	1.00 (0.86, 1.17)	NA
IDet vs. IGlar (with pre-meal IAsp)	All RCTs	1	385	0.20 (0.10, 0.30)	NA	0	NA	NA	NA
IGlar vs. TZDs as add-on to Sfu+MF	All RCTs	3	624	-0.20 (-0.38, -0.01)	14.5	1	226	0.98 (0.74, 1.29)	NA
	Subgroup analysis by TZD								
	TZD=Pio	1	388	-0.30 (-0.05, -0.10)	NA	0	NA	NA	NA
	TZD=Ros	2	236	-0.05 (-0.30, 0.21)	0	1	226	0.98 (0.74, 1.29)	NA

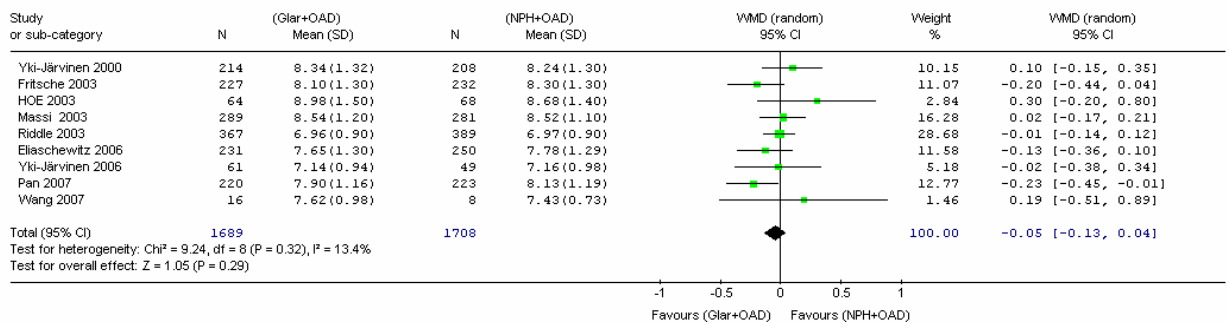
* Most subjects (>60%) also used regular human insulin for postprandial control in the single study that reported this comparison.[74]
A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; MF=metformin; NA=not applicable; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; Pio=pioglitazone; RCT=randomized controlled trial; Ros=rosiglitazone; RR=relative risk; Sfu=sulfonylurea; TZD=thiazolidinedione; var=various; vs.=versus; WMD=weighted mean difference.

IGlar versus NPH

Nine RCTs[76-84] reported A1c differences for IGlar versus NPH in patients also treated with OADs. The pooled difference in mean A1c was not significant [WMD (95% CI) = -0.05% (-0.13, 0.04)] (Figure 22). Removal of the two studies that had durations of less than three months did not have a major effect on the results. Pooled estimates within each of three subgroups defined by the type of OAD used (i.e., sulfonylurea, metformin, or various) were also similar to the overall pooled estimate, although the WMD for the sulfonylurea subgroup was statistically significant. There was no significant difference in the RR of achieving A1c ≤7% (Figure 23), although only two studies contributed data for this measure.[77,82] Heterogeneity was minimal for the mean A1c measure (I^2=13.4%), but substantial for the RR measure (I^2=77.6%). In terms of the latter, the study in which sulfonylureas were used demonstrated a statistically significant RR of 1.5,[82] while the study that used various OADs found a non-significant RR of 1.01.[77] The type of OAD may therefore have contributed to the high degree of heterogeneity in the pooled RR analysis.

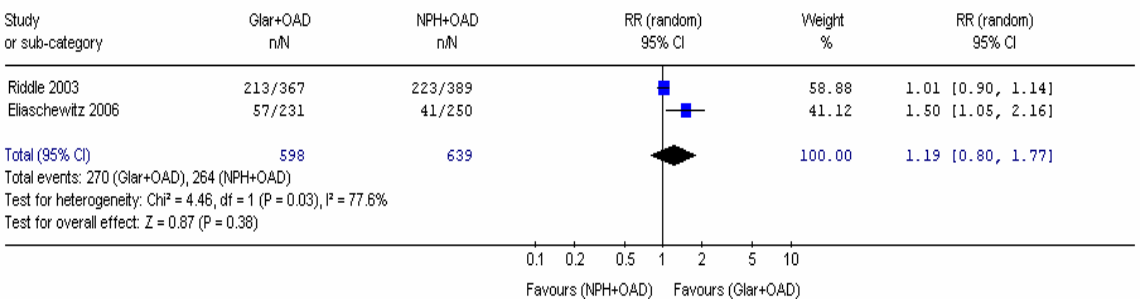
Based on visual analysis of the funnel plot, publication bias was likely in the mean A1c measure (Appendix 14, Figure 13).

Figure 22: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – A1c, WMD



A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

Figure 23: Forest plot of all RCTs that examined the use IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of achieving A1c≤7%



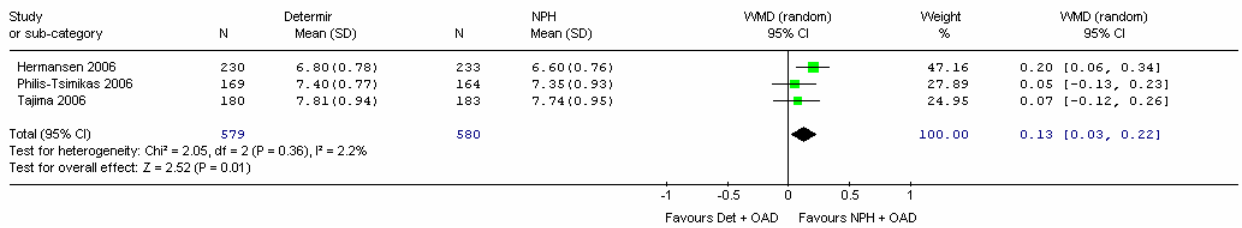
A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; RR=relative risk.

One RCT[74]compared the effects of IGlar and NPH in patients not treated with OADs. Most subjects in this study received pre-meal bolus insulins. The mean A1c difference in this study significantly favoured NPH [mean difference (95% CI)=0.28% (0.07, 0.49)]. A subgroup analysis of this study that included only those patients treated with once-daily NPH insulin[75] reported the number of patients who reached a target A1c of ≤7%. No statistically significant difference was detected.

IDet versus NPH

Three RCTs[69,70,91] reported A1c differences for IDet versus NPH in patients also treated with OADs (Figure 24). The pooled result significantly favoured NPH insulin [WMD (95% CI) = 0.13% (0.03, 0.22)]. All three studies used various OADs, therefore subgroup analysis was not possible. One study[69] also reported the number of patients who reached A1c≤7%; no significant difference was found between groups.

Figure 24: Forest plot of all RCTs that examined the use of IDet+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – A1c, WMD



A1c=glycosylated hemoglobin; CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

Only one study[68] compared IDet versus NPH in patients also treated with pre-meal insulin aspart. No statistically significant difference was found between the two treatment arms in terms of mean A1c. This study did not report the proportion achieving A1c≤7%.

IDet+IAsp versus NPH+HI

One study[71] reported the comparison of IDet with aspart versus NPH with HI. This study reported both mean A1c and the proportion achieving A1c≤7%. No significant differences were reported according to either measure.

IDet versus IGlar

One study[73] compared IDet versus IGlar in patients also treated with various OADs. This study reported both mean A1c and proportion achieving A1c≤7%. No significant differences were reported according to either measure.

One study also compared IDet and IGlar in patients treated with pre-meal insulin aspart.[72] Mean A1c was significantly higher by 0.2% in the IDet group as compared to IGlar in this study.

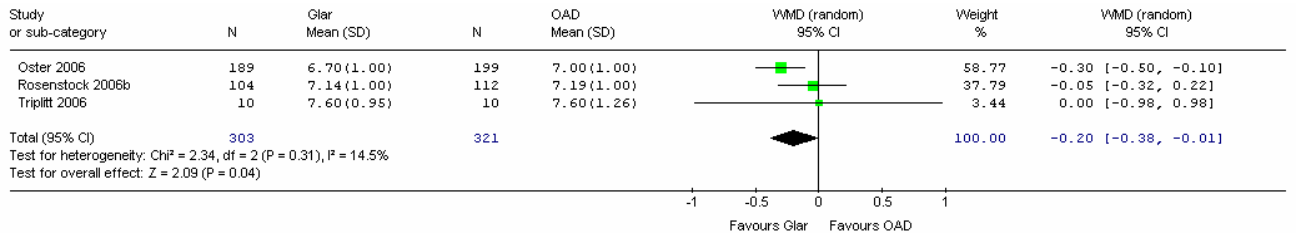
Long-acting insulin analogues versus OADs

Three RCTs[86,88,89]compared IGlar versus TZDs as add-on therapy in patients inadequately controlled on sulfonylureas and metformin. A statistically significant difference was seen in favour of IGlar in terms of mean A1c (Figure 25) [WMD (95% CI)=-0.20% (-0.38, -0.01)]. In subgroup analysis, the single

RCT that studied pioglitazone reported a statistically significant WMD of -0.30%, while the pooled WMD for the two studies that studied rosiglitazone was -0.05% and non-significant. One RCT[88] also reported the number of patients who reached A1c≤7%. There was no statistically significant difference between the two arms.

No studies comparing IGlar with OADs other than TZDs were identified. There were also no studies comparing IDet with any of the OADs.

Figure 25: Forest plot of all RCTs that examined the use of IGlar versus OAD for the treatment of type 2 DM in adult patients – A1c, WMD



A1c=glycosylated hemoglobin; CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; OAD=oral antidiabetic (thiazolidinediones); RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

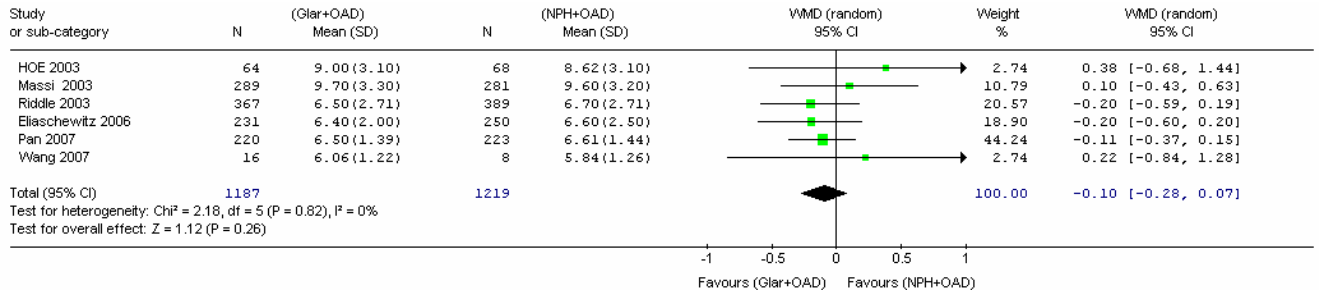
b) Fasting plasma glucose

Study-level FPG data are presented in Appendix 11b. Pooled estimates of FPG for the various comparisons are presented in Table 16.

IGlar versus NPH

Six RCTs[77,79,81-83,93] compared the effects of IGlar versus NPH on FPG in patients also treated with OADs. The pooled estimate did not indicate a statistically significant difference between treatments (Figure 26). Similar effects were observed in the subgroup of studies that used sulfonylureas and various OADs.

Figure 26: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – FPG, WMD



CI=confidence interval; DM=diabetes mellitus; FPG=fasting plasma glucose; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

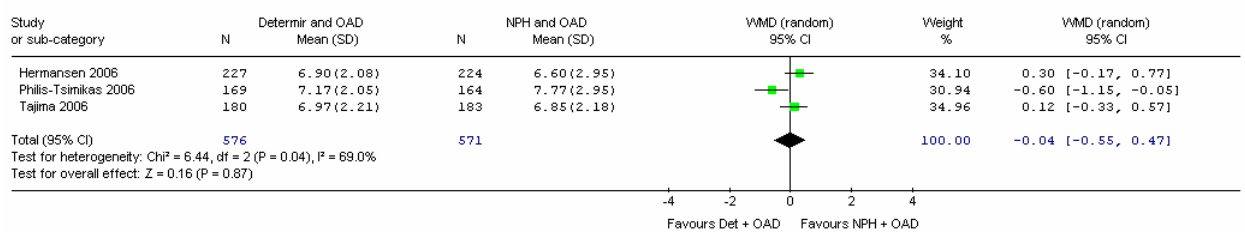
There was no heterogeneity across trials (I^2=0%). Based on funnel plot analysis, publication bias for this outcome was likely (Appendix 14, Figure 14).

The study that compared IGlar with NPH in patients not treated with OADs did not report FPG data.[74]

IDet versus NPH

Three studies[69,70,91] reported FPG data for this comparison in patients also treated with OADs. There was no significant difference between treatments (Figure 27). However, there was a high degree of heterogeneity (I^2=69.0%). One of the three studies found a statistically significant benefit in favour of IDet,[70] while the other two found a non-significant benefit in favour of NPH.[69,91] One possible cause for the observed heterogeneity may be that both insulins were administered once daily in the former study, and twice daily in the latter studies.

Figure 27: Forest plot of all RCTs that examined the use of IDet+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – FPG, WMD



CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; FPG=fasting plasma glucose; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

No significant difference in mean FPG was found in the single study that compared IDet with NPH in patients also treated with pre-meal IAsp.[68]

IDet versus IGlar

No significant difference in mean FPG was found in the only study that compared IDet with IGlar in patients also treated with OADs.[73] Similarly, there was no significant difference in the study that compared these agents in patients treated with IAsp as bolus insulin.[72]

Long-acting insulin analogues versus OADs

Two RCTs[88,89] compared the effects of IGlar with rosiglitazone on FPG. The pooled estimate revealed a significant reduction in FPG in the IGlar group compared with the TZD group [WMD (95% CI)=-1.04 mmol/L (-1.64, -0.45)] (Table 16). Each study reported a similar point estimate of the difference in FPG, although the result was statistically significant in only one study.[88]

c) Two-hour post-prandial plasma glucose

No studies reported data on this outcome.

Table 16: Summary of results of meta-analyses for comparison of long-acting insulin analogues versus NPH insulin or OADs in adult type 2 DM – Overall results, subgroup analyses, and sensitivity analyses for mean FPG (mmol/L)

Comparison	Analysis	No. of RCTs	Sample size	WMD (95% CI) in FPG (mmol/L)	I^2
IGlar vs. NPH (with OADs)	All RCTs	6	2,406	-0.10 (-0.28, 0.07)	0
	Subgroup analysis by OAD				
	OAD=Sfu	3	948	-0.12 (-0.34, 0.09)	0
	OAD=var	3	1,458	-0.06 (-0.36, 0.24)	0
IDet vs. NPH (with various OADs)	All RCTs	2	784	-0.14 (-1.02, 0.74)	83.2 %
IDet vs. NPH (with pre-meal IAsp)	All RCT	1	461	0.1 (-0.61, 0.81)	NA
IDet vs. IGlar (with various OADs)	All RCT	1	582	0.1 (-0.31, 0.51)	NA
IDet vs. IGlar (with pre-meal IAsp)	All RCT	1	385	0.1 (-0.67, 0.87)	NA
IGlar vs. Ros	All RCTs	2	236	-1.04 (-1.64, -0.45)	0
	Sensitivity analysis				
	Removal of studies only reporting mean change from baseline	1	20	-1.18 (-3.32, 0.87)	NA

CI=confidence interval; DM=diabetes mellitus; FPG=fasting plasma glucose; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; NA=not applicable; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCT=randomized controlled trial; Ros=rosiglitazone; Sfu=sulfonylurea; var=various; vs.=versus; WMD=weighted mean difference.

d) Hypoglycemia

Study-level data for hypoglycemia are presented in Appendix 10b. The definitions of hypoglycemia used in trials are also provided in Appendix 10b. Results of meta-analysis for the various comparisons are presented in Tables 17 to 22.

IGlar versus NPH (in patients also treated with OADs)

The numbers of RCTs reporting sufficient data to calculate the RR of severe, nocturnal, and overall hypoglycemia for this comparison were 7,[76-79,81-83] 7,[76,78,79,81,83,84] and 8,[76-81,83,84] respectively. The numbers of RCTs reporting sufficient data to calculate the rate ratio of severe, nocturnal, and overall hypoglycemia were 3,[76,77,82] 4,[76,77,79,82] and 4,[76,77,79,82] respectively.

Results of meta-analysis for this outcome are presented in Table 17. Overall, there was no statistically significant difference between IGlar and NPH in terms of severe hypoglycemia, although significant differences were identified for nocturnal and overall hypoglycemia.

Severe hypoglycemia: The pooled relative risk for severe hypoglycemia was not statistically significant (Figure 28). Only one RCT[76] reported a statistically significant effect in favour of IGlar. RR was not estimable in two RCTs[79,83] because of zero event rates in both treatment arms. There was a

high degree of heterogeneity in the overall result (I^2=64.3%). Publication bias was likely based on asymmetry observed in the funnel plot (Appendix 14, Figure 15).

Table 17: Summary of results of meta-analyses for comparison of insulin glargine versus NPH in adult type 2 DM, in patients also receiving oral antidiabetic agents – Overall results, subgroup analyses, and sensitivity analyses for RR and rate ratio of severe, nocturnal, and overall hypoglycemia

Type of Hypo-glycemia	Analysis	RR				Rate Ratio			
		No. of RCTs	Sample Size	RR (95% CI)	I^2 (%)	No. of RCTs	Sample Size	Rate Ratio (95% CI)	I^2 (%)
Severe	All RCTs	7	2,866	0.66 (0.29, 1.48)	64.3	3	1,681	0.56 (0.35, 0.91)	84.5
	Subgroup analysis by OAD								
	OAD=Sfu	4	1,408	0.40 (0.17, 0.94)	51.9	2	925	0.33 (0.19, 0.60)	71.4
	OAD=var	3	1,458	1.44 (0.64, 3.22)	0	1	367	1.65 (0.71, 3.81	NA
Nocturnal	All RCTs	7	2,532	0.56 (0.47, 0.68)	32.3	4	1,705	0.41 (0.29, 0.59)	92.2
	Subgroup analysis by OAD								
	OAD=Sfu	4	1,408	0.63 (0.52, 0.75)	19.1	3	949	0.36 (0.32, 0.40)	0
	OAD=var	3	1,124	0.46 (0.34, 0.60)	0	1	756	0.58 (0.53, 0.64)	NA
Overall	All RCTs	8	2,642	0.87 (0.81, 0.93)	0	4	1,705	0.82 (0.64, 1.06)	94.1
	Subgroup analysis by OAD								
	OAD=Sfu	4	1,408	0.88 (0.80, 0.96)	18.3	3	949	0.78 (0.48, 1.28)	95.5
	OAD=MF	1	110	0.95 (0.68, 1.32)	NA	NA	NA	NA	NA
	OAD=var	3	1,124	0.80 (0.69, 0.94)	0	1	756	0.79, (0.74, 0.83)	NA

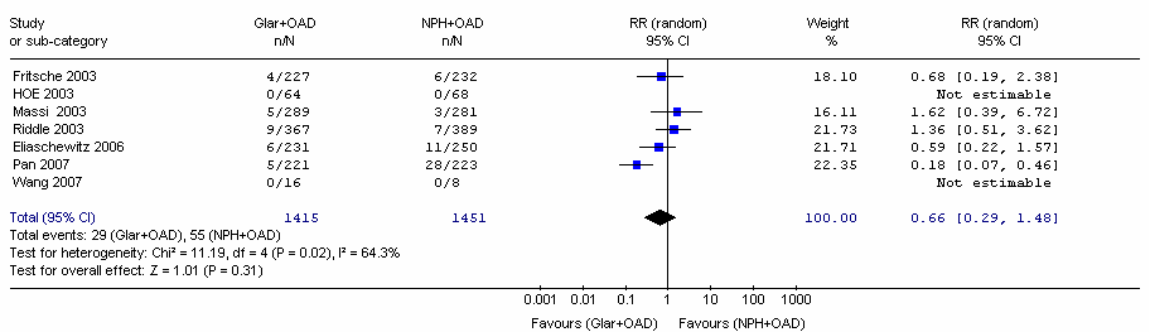
CI=confidence interval; DM=diabetes mellitus; MF=metformin; NA=not applicable; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCT=randomized controlled trial; RR=relative risk; Sfu=sulfonylurea; var=various.

Within the subgroup of RCTs that used sulfonylureas, a statistically significant risk reduction was observed in favour of IGlar [RR (95% CI)=0.40 (0.17, 0.94)]. In contrast, the subgroup of studies that used various OADs demonstrated a non-significant RR of 1.44. The residual heterogeneity observed in the sulfonylurea subgroup (I^2=51.9%) may have been due to differences in ethnicity across trials – for example, one study was conducted in China[76] and another in Latin America[77] – or to the fact that studies titrated insulin doses to achieve different FPG levels – for example, 6.3 mmol/L in the Latin American study[77] and 7.7 mmol/L in the Chinese study.[76]

In terms of the rate ratio for severe hypoglycemia, there was no significant difference between treatments (Figure 29). Significant heterogeneity was observed in this analysis (I^2=84.5%). Similar to the RR analysis, the rate ratio was significantly lower in favour of IGlar in the two studies that used sulfonylureas [pooled rate ratio (95% CI)=0.33 (0.19, 0.60)], and non-significant in the single study

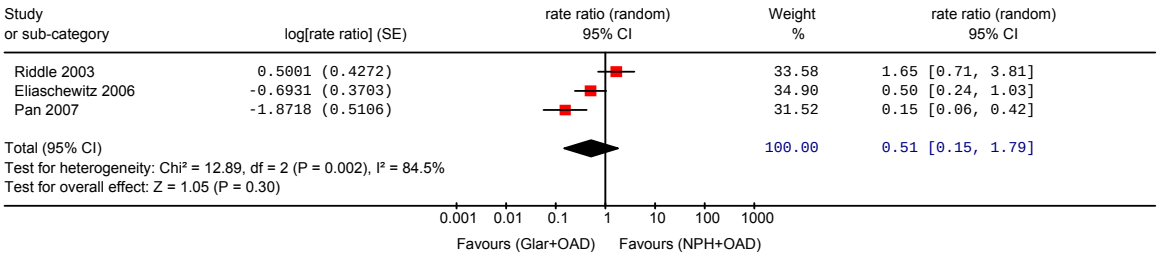
that used various OADs. A high degree of heterogeneity remained in the sulfonylurea subgroup, possibly due to the same influences described for the RR.

Figure 28: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of severe hypoglycemia



CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; RR=relative risk.

Figure 29: Forest plot of all RCTs that examined the use IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Rate ratio of severe hypoglycemia

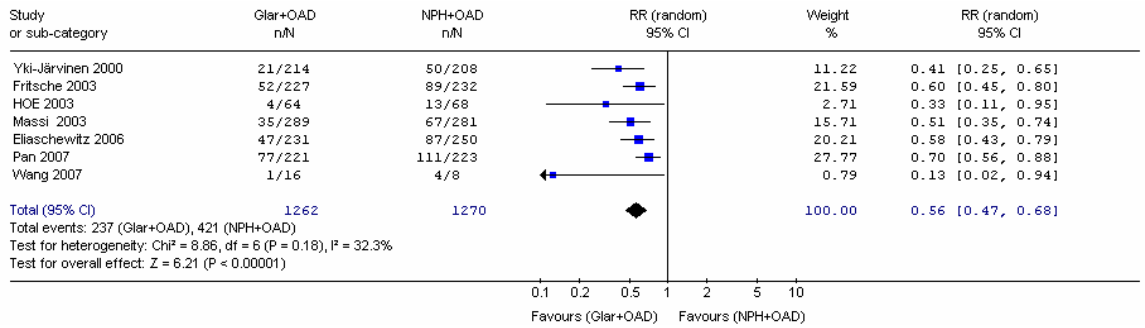


CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SE=standard error.

Nocturnal hypoglycemia: The overall RR for nocturnal hypoglycemia significantly favoured IGlar [RR (95% CI)=0.56 (0.47, 0.68)] (Figure 30). The subgroup analysis also indicated a statistically significant benefit for both the sulfonylurea and various OAD subgroups. There was no significant heterogeneity in either the overall analysis (I^2=32.3%) or within each subgroup. Publication bias was likely based on visual analysis of the funnel plot (Appendix 14, Figure 16).

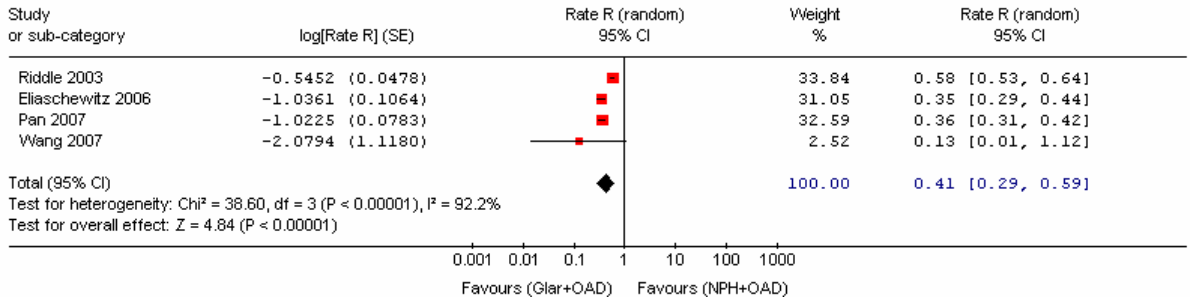
The overall pooled rate ratio, as well as pooled rate ratios from subgroup analysis by OAD, also significantly favoured IGlar (Figure 31). The heterogeneity of the overall analysis was high (I^2=92.2%), although there was no heterogeneity within each subgroup.

Figure 30: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of nocturnal hypoglycemia



CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; RR=relative risk.

Figure 31: Forest plot of all RCTs that examined the use IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Rate ratio of nocturnal hypoglycemia

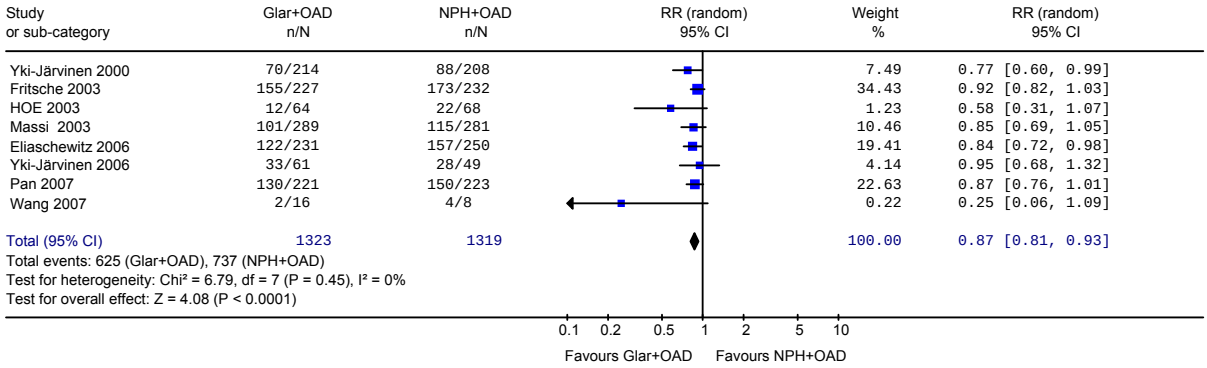


CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SE=standard error.

Overall hypoglycemia: The pooled RR for overall hypoglycemia significantly favoured IGlar [RR (95% CI)=0.87 (0.81, 0.93)] (Figure 32). The subgroup analysis showed a statistically significant benefit for studies that used sulfonylureas, as well as those that used various OADs. There was no significant heterogeneity observed in the overall analysis (I^2=0), or within each subgroup. Publication bias was unlikely based on analysis of the funnel plot (Appendix 14, Figure 17).

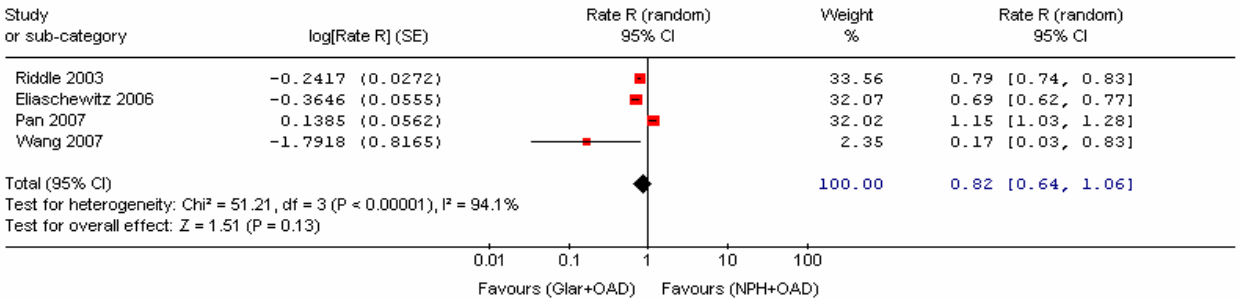
The pooled estimate of the rate ratio was not statistically significant (Figure 33). Similar results were obtained in the subgroup analysis, except that the estimate from the single study that used various OADs was statistically significant. There was a high degree of heterogeneity in both the overall analysis (I^2=94.1%) as well as in the sulfonylrea subgroup. Study differences in terms of ethnicity of subjects and target FPG levels may have contributed to heterogeneity, as described in the "Severe hypoglycemia" section. Another possible factor is study duration: only the Wang study[79] was of less than three months duration, while the remaining two studies were longer than three months.

Figure 32: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of overall hypoglycemia



CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; RR=relative risk.

Figure 33: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Rate ratio of overall hypoglycemia



CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SE=standard error.

IGlar versus NPH (without OADs)

Nocturnal and overall hypoglycemia were reported in one study[74] for this comparison, while severe hypoglycemia was reported in a subgroup analysis of this study.[75] Most subjects in this study (>60%) used pre-meal regular human insulin.[74] Compared with NPH, treatment with IGlar produced statistically significant risk reduction for nocturnal hypoglycemia, but not for overall hypoglycemia (Table 18). RR for severe hypoglycemia was not calculated because there were no events in the IGlar arm. Data required for calculation of rate ratios were not reported in either the main or subgroup analyses.

Table 18: Summary of results for comparison of IGlar versus NPH in adult type 2 DM, in patients not receiving OADs* – RR of severe, nocturnal, and overall hypoglycemia

Type of Hypoglycemia	Analysis	No. of RCTs	Sample Size	RR (95% CI)
Severe	All RCTs	1	100	NE
Nocturnal	All RCTs	1	518	0.78 (0.62, 0.98)
Overall	All RCTs	1	518	0.92, (0.81, 1.05)

* Most subjects (>60%) also used regular human insulin for postprandial control in the single study that reported this comparison.[74]
CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NE=not estimable; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk.

IDet versus NPH (in patients also treated with OADs)

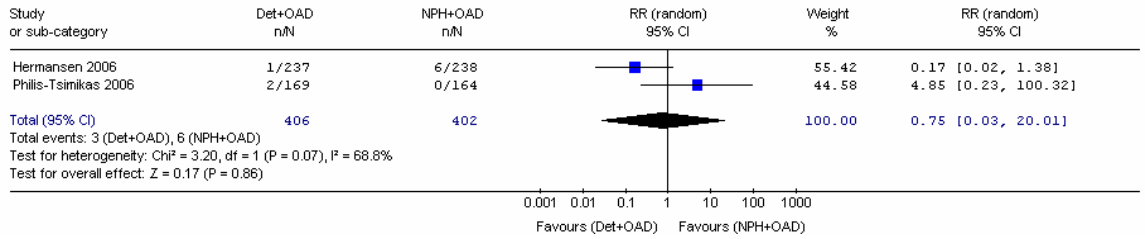
Results of meta-analysis are presented in Table 19. Statistically significant risk reduction was observed in favour of IDet in terms of nocturnal and overall hypoglycemia (Figures 35 to 36). No significant difference was seen in severe hypoglycemia (Figure 34), although the event rate was very low in both studies. Rate ratios for each of the three categories of hypoglycemia significantly favoured IDet (Figures 37 to 38). Subgroup analysis by OAD was not possible, since all three studies used various OADs.

Table 19: Summary of results of meta-analyses for comparison of IDet versus NPH in adult type 2 DM, in patients also receiving OADs – Relative risk and rate ratio of severe, nocturnal, and overall hypoglycemia

Type of Hypo-glycemia	Analysis	RR				Rate Ratio			
		No. of RCTs	Sample Size	RR (95% CI)	I^2 (%)	No. of RCTs	Sample Size	Rate Ratio (95% CI)	I^2 (%)
Severe	All RCTs	2	808	0.75 (0.03, 20.01)	68.8	1	463	0.13 (0.02, 0.91)	NA
Nocturnal	All RCTs	2	808	0.53 (0.31, 0.91)	51.6	3	1,161	0.48 (0.42, 0.55)	0
Overall	All RCTs	2	808	0.65 (0.39, 1.07)	82.1	3	1,161	0.59 (0.48, 0.72	86.9

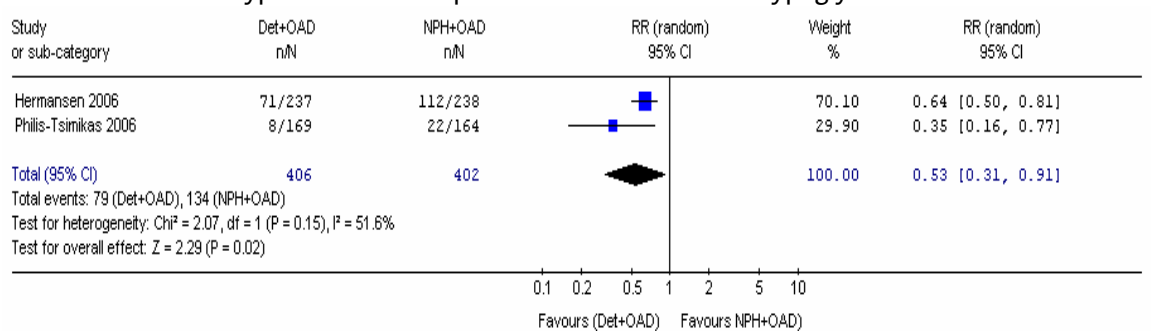
CI=confidence interval; DM=diabetes mellitus; NA=not applicable; NPH=neutral protamine Hagedorn; OADs=oral antidiabetic agents; RCTs=randomized controlled trials; RR=relative risk.

Figure 34: Forest plot of all RCTs that examined the use of IDet+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of severe hypoglycemia



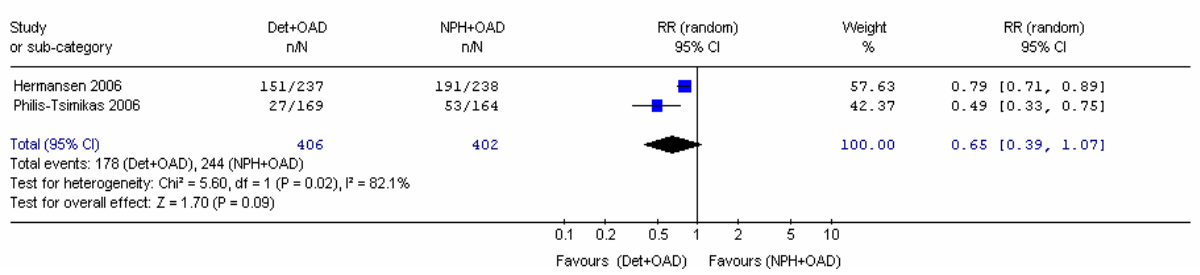
CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk.

Figure 35: Forest plot of all RCTs that examined the use of IDet+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of nocturnal hypoglycemia



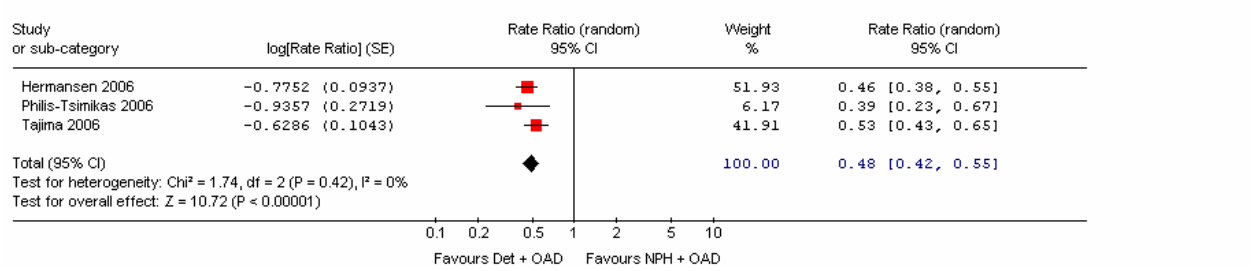
CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk.

Figure 36: Forest plot of all RCTs that examined the use of IDet+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of overall hypoglycemia



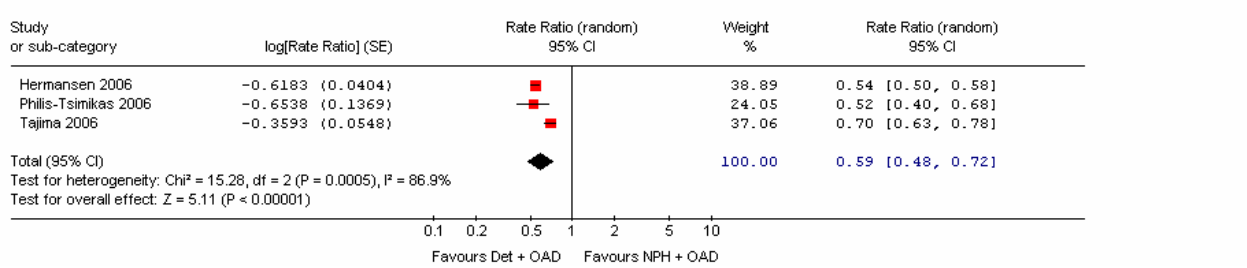
CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk.

Figure 37: Forest plot of all RCTs that examined the use of IDet+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Rate ratio of nocturnal hypoglycemia



CI=confidence interval; DM=diabetes mellitus; Det/IDet=insulin detemir; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SE=standard error.

Figure 38: Forest plot of all RCTs that examined the use of IDet+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Rate ratio of overall hypoglycemia



CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SE=standard error.

There was a high degree of heterogeneity in all three meta-analyses of RR (I^2=68.8%, 51.6% and 82.1% for severe, nocturnal, and overall hypoglycemia, respectively), as well as in the meta-analysis of overall hypoglycemia rate ratio (I2 = 86.9%). A possible cause for heterogeneity in RRs may lie in the fact that one study administered both IDet and NPH once daily,[70] while the other administered them twice daily.[69] The RRs observed in the former study for both nocturnal and overall hypoglycemia were smaller than those reported in the latter. (RR for severe hypoglycemia was not calculable for the once-daily study, since no such events were observed in the NPH arm.[70])

IDet versus NPH (with bolus insulin)

No significant differences in nocturnal and overall hypoglycemia risks were observed between IDet and NPH in the single trial identified for this comparison[68] (Table 20). This study treated patients with IAsp as pre-meal bolus insulin. There were insufficient data to calculate rate ratios.

Table 20: Summary of results for comparison of IDet versus NPH in adult type 2 DM, in patients receiving IAsp as pre-meal insulin – RR of severe, nocturnal, and overall hypoglycemia

Type of Hypoglycemia	Analysis	No. of RCTs	Sample Size	RR (95% CI)
Severe	All RCTs	0	NA	NA
Nocturnal	All RCTs	1	505	0.66 (0.45, 0.96)
Overall	All RCTs	1	505	0.91 (0.75, 1.11)

CI=confidence interval; DM=diabetes mellitus; IAsp=insulin aspart; IDet=insulin detemir; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

IDet+IAsp versus NPH+HI

Results are presented in Table 21. There was no statistically significant difference between treatments in terms of RR of severe or overall hypoglycemia in the single RCT that compared these interventions, although there was a significant difference in favour of detemir in terms of nocturnal hypoglycemia [RR (95% CI)=0.54 (0.30, 0.97)].[71,92] In terms of rate ratios, a statistically significant benefit was observed for both nocturnal hypoglycemia [rate ratio (95% CI)=0.61 (0.43, 0.87)] and overall hypoglycemia [rate ratio (95% CI)=0.85 (0.73, 0.98)].

Table 21: Summary of results for comparison of IDet+IAsp versus NPH+HI in adult type 2 DM: RR and rate ratio of severe, nocturnal, and overall hypoglycemia

Type of Hypoglycemia	Analysis	RR			Rate Ratio		
		No. of RCTs	Sample Size	RR (95% CI)	No. of RCTs	Sample Size	Rate Ratio (95% CI)
Severe	All RCTs	1	394	1.02 (0.26, 4.02)	1	394	0.51 (0.09, 2.79)
Nocturnal	All RCTs	1	394	0.54 (0.30, 0.97)	1	394	0.53 (0.39, 0.73)
Overall	All RCTs	1	394	0.87 (0.55, 1.37)	1	394	0.85 (0.73, 0.98)

CI=confidence interval; DM=diabetes mellitus; HI=human insulin; IAsp=insulin aspart; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk.

IDet versus IGlar

Rosenstock *et al.*, 2006a[73] reported the RR of nocturnal and overall hypoglycemia in patients treated with either IDet or IGlar, in combination with OADs. The RR of nocturnal hypoglycemia was 1.05 (p>0.05, NS), and RR of overall hypoglycemia was 0.94 (p>0.05, NS). There were insufficient data to calculate rate ratios.

The study comparing IDet with IGlar in patients treated with pre-meal IAsp did not report hypoglycemia data, although the authors noted that there was no significant difference in the risk of hypoglycemia.[72]

Long-acting insulin analogues versus OADs

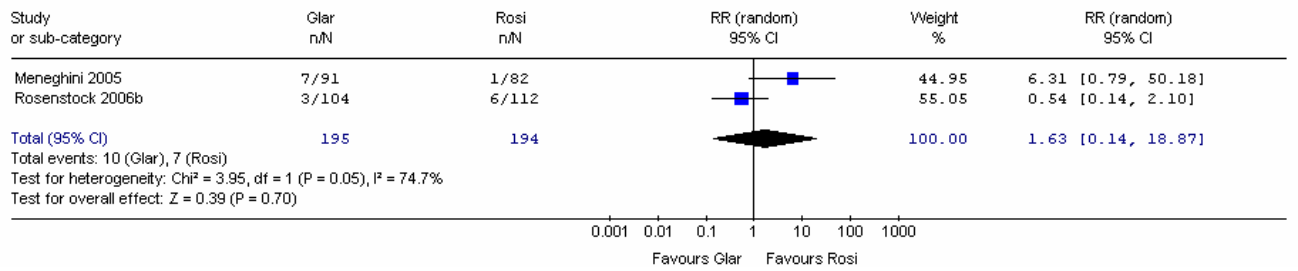
No statistically significant difference was found in the risk of severe or overall hypoglycemia in studies comparing IGlar with TZDs, however, the risk of nocturnal hypoglycemia was significantly higher in the IGlar arm [RR (95% CI)=2.6 (1.40, 4.83)] (Table 22, Figures 39 to 40). In subgroup analysis, the risk of hypoglycemia in the rosiglitazone and pioglitazone studies varied widely (RR=0.54 and 6.31), although both were non-significant. The large difference between the two studies caused a high degree of heterogeneity (I^2=74%). The pioglitazone study also demonstrated a higher RR than rosiglitazone in terms of overall hypoglycemia, hence the large I^2 value for this outcome. There were insufficient data to calculate rate ratios.

Table 22: Summary of results of meta-analyses for comparison of IGlar with TZDs in adult type 2 DM – RR of severe, nocturnal, and overall hypoglycemia

Type of Hypoglycemia	Analysis	No. of RCTs	Sample Size	RR (95% CI)
Severe	All RCTs	2	389	1.63 (0.14, 18.87)
	Subgroup analysis by TZD			
	TZD=Pio	1	173	6.31 (0.79, 50.18)
	TZD=Ros	1	216	0.54 (0.14, 2.10)
Nocturnal	All RCTs (TZD=Ros)	1	206	2.6 (1.40, 4.83)
Overall	All RCTs	3	624	1.73 (0.83, 3.58)
	Subgroup analysis by TZD			
	TZD=Pio	1	388	2.76 (1.96, 3.88)
	TZD=Ros	2	236	1.29 (0.98, 1.71)

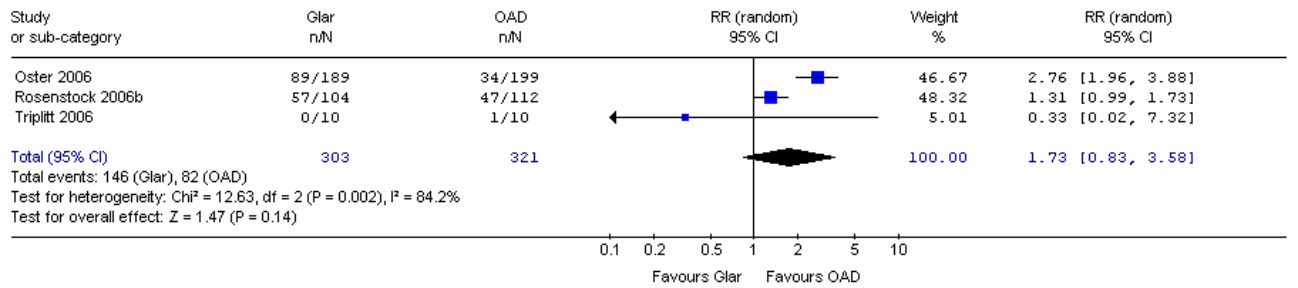
CI=confidence interval; DM=diabetes mellitus; Pio=pioglitazone; RCTs=randomized controlled trials; Ros=rosiglitazone; RR=relative risk; TZD=thiazolidinedione.

Figure 39: Forest plot of all RCTs that examined the use IGlar versus OAD for the treatment of type 2 DM in adult patients – RR of severe hypoglycemia



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; OAD=oral antidiabetic (thiazolidinediones); RCTs=randomized controlled trials; Rosi=rosiglitazone; RR=relative risk.

Figure 40: Forest plot of all RCTs that examined the use IGlar versus OAD for the treatment of type 2 DM in adult patients – RR of overall hypoglycemia



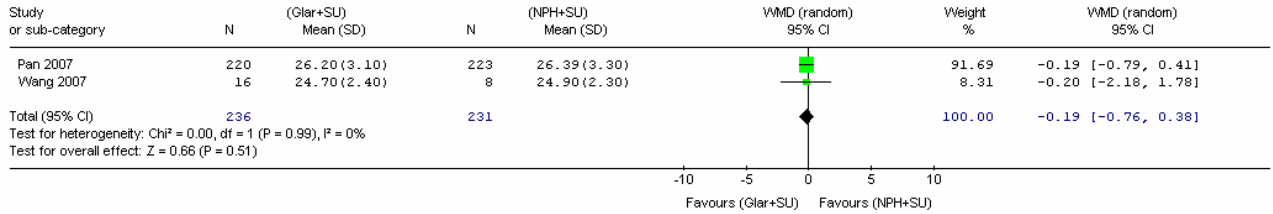
Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; OAD=oral antidiabetic (thiazolidinediones); RCT=randomized controlled trial; RR=relative risk.

e) Body mass index

IGlar versus NPH

Two studies[76,79] reported mean BMI at endpoint in patients treated with IGlar versus NPH, as well as sulfonylureas (Appendix 12b). The pooled estimate did not reveal a statistically significant difference between treatments (Figure 41, Table 23). One RCT[89] reported mean BMI at endpoint for the comparison of IGlar versus rosiglitazone; no significant difference was observed (Table 23). BMI data were not reported for the remaining comparisons.

Figure 41: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – BMI, WMD



BMI=body mass index;CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; SD=standard deviation; Sfu=sulfonylurea; RCTs=randomized controlled trials; WMD=weighted mean difference.

Table 23: Summary of results of meta-analysis for comparison of long-acting insulin analogues with NPH or TZDs in adult type 2 DM – BMI

Comparison	Analysis	No. of Trials	Sample Size	WMD (95% CI) in BMI (kg/m²)	I² (%)
Glargine vs. NPH (with Sfu)	All RCTs	2	467	-0.19 (-0.76, 0.38)	0
Glargine vs. rosiglitazone	All RCTs	1	20	-0.50 (-4.11, 3.11)	NA

BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; Sfu=sulfonylurea; TZDs=thiazolidinediones; WMD=weighted mean difference.

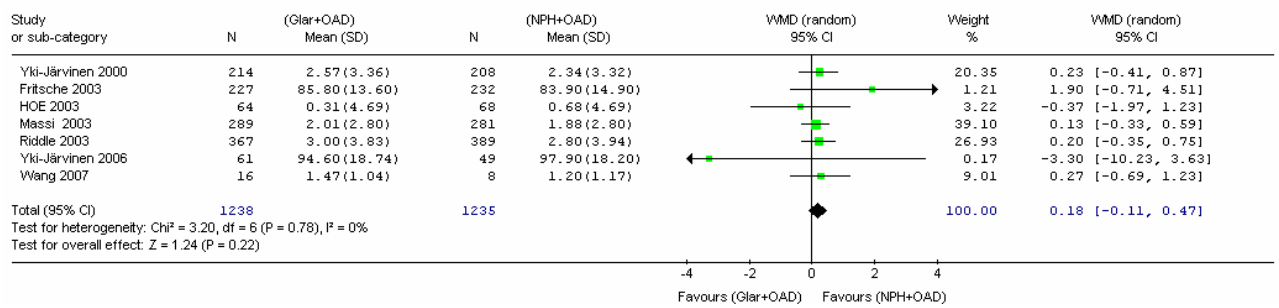
f) Body weight

The results of meta-analysis for body weight are summarized in Table 24. Study-level data are shown in Appendix 12b.

IGlar versus NPH (in patients also treated with OADs)

Seven RCTs[78-84] reported body weight data for this comparison. Overall, there was no significant difference between treatments (Figure 42, Table 24). Similar results were obtained in sensitivity analysis when the two studies that only reported mean body weight change from baseline,[78,80] instead of mean weight at endpoint, were excluded. Results were also similar and statistically non-significant in subgroups defined by OAD. However, the point estimate, although non-significant, was -3.3 kg/m² in favour of IGlar in the single study that used metformin. There was no heterogeneity (I²=0%) in the overall analysis. Publication bias was unlikely based on analysis of the funnel plot (Appendix 14, see Figure 18)

Figure 42: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Body weight (change from baseline or mean at endpoint), WMD



CI=confidence interval; DM=diabetes mellitus; Glar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

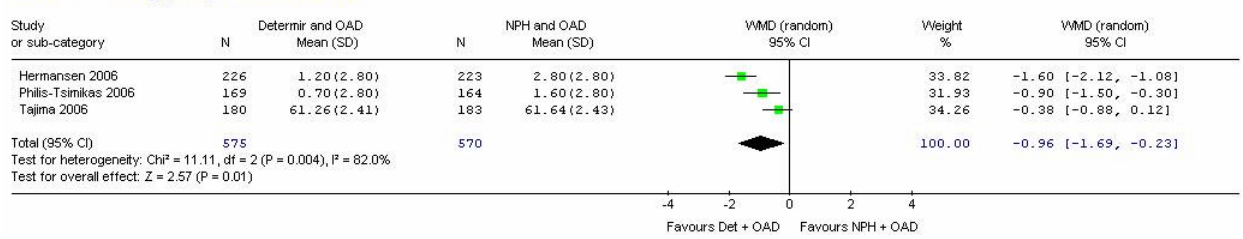
IGlar versus NPH (in patients not treated with OADs)

The only study reporting this comparison[74] found a non-significant difference in body weight between treatments (Table 24). Most subjects in this study (>60%) also used pre-meal regular human insulin.

IDet versus NPH (in patients also treated with OADs)

Three RCTs[69,70,91] reported weight change from baseline for the comparison of IDet with NPH in patients also using OADs. The pooled estimate revealed that there was significantly less weight gain in the IDet arm [WMD (95% CI) = -0.96 kg (-1.69, -0.23)] (Figure 43, Table 24). There was a high degree of heterogeneity in this analysis (I^2=82.0%). The main difference between the RCTs was that insulins were administered twice daily in one study[69] and once daily in the other two studies.[70,91] Subgroup analysis by OAD was not possible since various agents were allowed in all three studies.

Figure 43: Forest plot of all RCTs that examined the use of IDet+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Change in body weight from baseline, WMD



CI=confidence interval; Det/IDet=insulin detemir; DM=diabetes mellitus; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

Statistically significant differences in weight favouring IDet were also found in comparisons of IDet versus NPH (with pre-meal IAsp),[68] IDet+IAsp versus NPH+human insulin,[71] IDet versus IGlar (with OADs),[73] and IDet versus IGlar (with pre-meal IAsp)[72] (Table 24).

IGlar versus TZDs

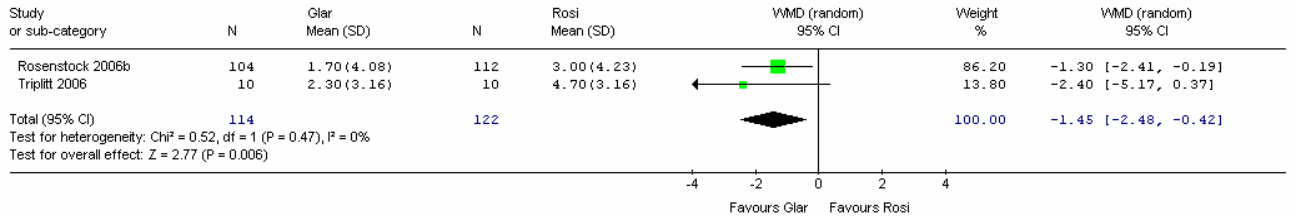
Two RCTs,[88,89] both of which studied rosiglitazone, reported weight change from baseline for this comparison. A significantly greater reduction in weight from baseline was observed with IGlar [WMD (95% CI)=-1.45 kg (-2.48, -0.42)] (Figure 44, Table 24). There was no heterogeneity in this result.

Table 24: Summary of results of meta-analysis for comparison of long-acting insulin analogues with NPH or TZDs in adult type 2 DM – Body weight

Comparison	Analysis	No. of RCTs	Sample Size	Random Effect Model	
				WMD (95% CI) in Body Weight (kg)	I^2 (%)
IGlar vs. NPH (with OADs)	All RCTs	7	2,473	0.18 (-0.11, 0.47)	0
	Sensitivity analysis				
	Removal of RCTs only reporting mean change from baseline	2	569	0.33 (-4.34, 5.01)	47.2
	Subgroup analysis				
	OAD=Sfu	2	483	0.61 (-0.69, 1.92)	24.3
	OAD=MF	1	110	-3.30 (-10.23, 3.63)	NA
	OAD=var	4	1,880	0.16 (-0.15, 0.46)	0
IGlar vs. NPH (without OADs)*	All RCTs (mean weight at endpoint)	1	518	-2.10 (-5.21, 1.01)	NA
IDet vs. NPH (with various OADs)	All RCTs (change in weight from baseline)	3	1,145	-0.96 (-1.69, -0.23)	82.0
IDet vs. NPH (with pre-meal IAsp)	All RCTs (change in weight from baseline)	1	505	-0.80 (-1.46, -0.14)	NA
IDet+IAsp vs. NPH+HI	All RCTs (change in weight from baseline)	1	394	-0.62 (-1.22, -0.02)	NA
IDet vs. IGlar (with various OADs)	All RCTs (change in weight from baseline)	1	582	-0.80 (-1.52, -0.08)	NA
IDet vs. IGlar (with pre-meal IAsp)	All RCTs (change in weight from baseline)	1	385	-1.50 (-2.47, -0.53)	NA
IGlar vs. rosiglitazone	All RCTs (change in weight from baseline)	2	236	-1.45 (-2.48, -0.42)	0

* Most subjects (>60%) also used regular human insulin for postprandial control in the single study that reported this comparison.[74]
CI=confidence interval; DM=diabetes mellitus; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; MF=metformin; NA=not applicable; NPH=neutral protamine Hagedorn; OADs=oral antidiabetic drugs; RCTs=randomized controlled trials; Sfu=sulfonylurea; TZDs=thiazolidinediones; var=various; vs.=versus; WMD=weighted mean difference.

Figure 44: Forest plot of all RCTs that examined the use of IGlar versus OAD for the treatment of type 2 DM in adult patients – Body weight gain, WMD



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; OAD=oral antidiabetic agent (thiazolidinediones); RCT=randomized controlled trial; Rosi=rosiglitazone; SD=standard deviation; WMD=weighted mean difference.

g) Diabetic ketoacidosis

No studies reported data on this outcome.

h) Hyperosmolar, hyperglycemic, non-ketotic coma

No studies reported data on this outcome.

i) Blood pressure

Study-level data on blood pressure are presented in Appendix 17. One study[84] reported no significant difference between IGlar and NPH (in patients also treated with OADs) in terms of systolic and diastolic blood pressure. Triplitt *et al.*[89] reported that there was no significant difference between IGlar and rosiglitazone in terms of systolic blood pressure, although diastolic blood pressure was significantly higher in the IGlar arm. Data from these two studies are presented in Table 25. There was no blood pressure data reported for the remaining comparisons.

j) LDL-cholesterol

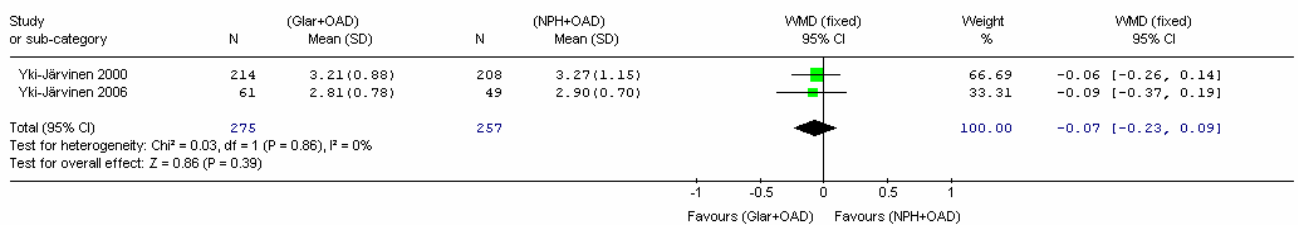
Study-level data on cholesterol are presented in Appendix 18. Two studies[80,84] reported data on LDL-cholesterol for the comparison of IGlar versus NPH (in patients also treated with OADs). There was no significant difference between the two treatments (Figure 45, Table 26). The individual estimates from the two studies, one of which used metformin,[80] and the other various OADs[84] were similar to the overall estimate and also non-significant. There was no heterogeneity in the overall result.

Table 25: Summary of results for comparison of long-acting insulin analogues with NPH or TZDs in adult type 2 DM – Blood pressure

Comparison	Analysis	No. of RCTs	Sample Size	WMD (95% CI) in Blood Pressure (mmHg)
IGlar vs. NPH (with OADs)	Systolic blood pressure	1	422	0.00 (-2.77, 2.77)
	Diastolic blood pressure	1	422	1.00 (-1.77, 3.7)
IGlar vs. rosiglitazone	Systolic blood pressure	1	20	0.00 (-12.55, 12.55)
	Diastolic blood pressure	1	20	10 (0.20, 19.8)

CI=confidence interval; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OADs=oral antidiabetic drugs; RCTs=randomized controlled trials; TZDs=thiazolidinediones; vs.=versus; WMD=weighted mean difference.

Figure 45: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – LDL cholesterol, WMD



CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; LDL=low-density lipoprotein; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SD=standard deviation; WMD=weighted mean difference.

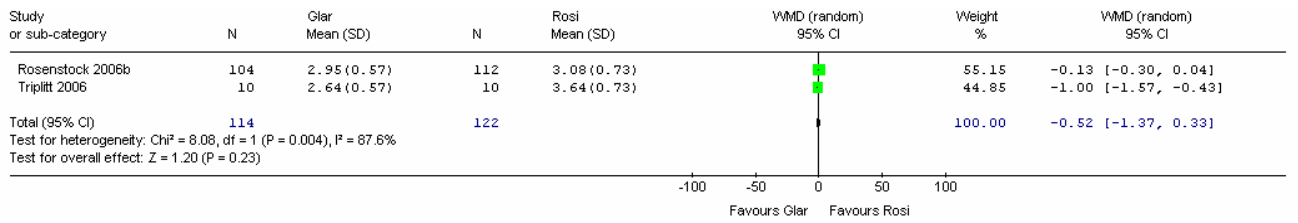
Table 26: Summary of results of meta-analysis for comparison of long-acting insulin analogues with NPH or TZDs in adult type 2 DM – LDL-cholesterol

Comparison	Analysis	No. of RCTs	Sample Size	WMD (95% CI) in LDL-cholesterol (mmol/L)	I^2 (%)
IGlar vs. NPH (with OADs)	All RCTs	2	532	-0.07 (-0.23, 0.09)	0
	Subgroup analysis by OAD				
	OAD=var	1	422	-0.06 (-0.26, 0.14)	NA
	OAD=MF	1	110	-0.09 (-0.37, 0.19)	NA
IGlar vs. rosiglitazone	All RCTs	2	236	-0.52 (-1.37, 0.33)	87.6

CI=confidence interval; DM=diabetes mellitus; LDL=low-density lipoprotein; MF=metformin; NA=not applicable; NPH=neutral protamine Hagedorn; OADs=oral antidiabetic drugs; RCTs=randomized controlled trials; TZDs=thiazolidinediones; var=various; vs.=versus; WMD=weighted mean difference.

Two RCTs[88,89] reported LDL-cholesterol data for the comparison of IGlar with rosiglitazone. The pooled estimate did not reveal a significant difference between treatments (Figure 46, Table 26). There was a high degree of heterogeneity in this analysis (I^2=88%). One of the studies, a trial enrolling only 20 patients, reported a statistically significant difference in favour of IGlar of 1 mmol/L, while the other, larger trial reported a non-significant difference of 0.13 mmol/L in favour of IGlar. Since there were no obvious methodological or population differences between these studies, the observed variation in effect size may have been due to chance effect.

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



Heterogeneity I^2 describes the heterogeneity between the included studies. CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; LDL=low-density lipoprotein; OAD=oral antidiabetic (thiazolidinediones); RCTs=randomized controlled trials; Rosi=rosiglitazone; SD=standard deviation; WMD=weighted mean difference.

LDL-cholesterol data were not reported for the remaining comparisons.

k) Generic or diabetes-related quality-of-life

Study level quality-of-life data are presented in Appendix 15b. In the comparison of IGlar versus TZDs, two RCTs[86,90] reported this outcome. To measure diabetes-related HRQoL, Oster *et al.*, 2006[86] used the Diabetes Symptom Checklist-Revised (DSC-R) and the Emotional Well-being and General Health Perceptions scales from the 36-item Short Form Health Survey (SF-36). The DSC-R contains 34 items grouped into eight symptom subscales: hyperglycemia, hypoglycemia, psychological cognitive functioning, psychological fatigue, cardiovascular functioning, neuropathic pain, neuropathic sensory, and ophthalmologic functioning. The degree to which each symptom is bothersome to the patient is scored on a scale of 1 to 5. HRQoL changes from baseline to 48 weeks generally favoured IGlar, which demonstrated statistically significant improvement over pioglitazone in the following domains: hyperglycemia distress, fatigue distress, and total distress. Vinik and Zhang, 2007[90] also used the 34-item DSC-R as well as the five mental health items and the single general health perception rating from the SF-36. In this study, HRQoL improved in both treatment arms, but IGlar-treated subjects experienced significantly greater improvement in terms of the total symptom score (-5.67 in IGlar arm versus -1.15 in rosiglitazone arm at 24 weeks, p=0.005) and the total symptom distress score (-2.81 in IGlar arm versus -1.06 in rosiglitazone arm at 24 weeks, p=0.03). Significantly greater improvements were also observed in terms of mood symptoms, ophthalmologic symptoms, ophthalmologic distress, and fatigue distress. There was also a statistically significant difference in favour of IGlar in terms of the single-item general health perception rating (difference in change from baseline=5.38, p<0.05).

HRQoL data were not reported for the other comparisons.

l) Satisfaction with diabetes treatment

Eliaschewitz *et al.*, 2006[77] reported a significantly greater improvement from baseline in the Diabetes Treatment Satisfaction Questionnaire Change (DTSQc) score with IGlar versus NPH (in patients also treated with OADs) (Appendix 15b). No other studies reported data on treatment satisfaction.

m) Patient self-management

No studies reported data related to this outcome.

o) Resource utilization

No studies reported resource utilization data.

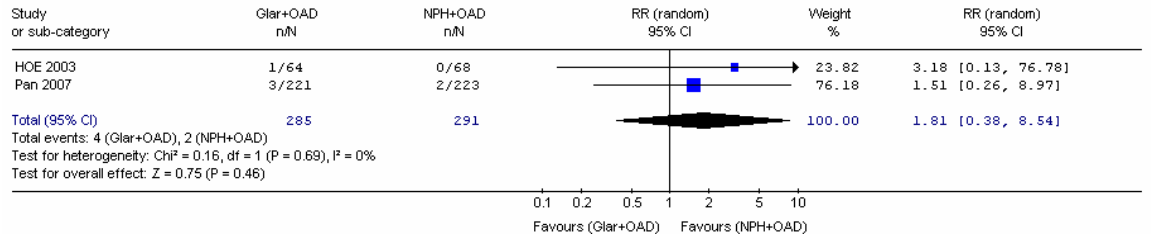
p) Long-term diabetic complications

No RCTs listed long-term complications such as mortality, cardiovascular disease, or retinopathy as outcomes of interest. However, some studies reported the incidence of such events. In all cases, the number of events observed was too small for adequate comparisons to be made. Study-level data on these events are presented in Appendix 13b ["Adverse Events Data (excluding hypoglycemia) for RCTs in Type 2 DM"].

Non-fatal ischemic heart disease: Two RCTs[77,83] reported the outcome of non-fatal ischemic heart disease for IGlar versus NPH (in patients also treated with OADs). The pooled estimate did not reveal a statistically significant difference between treatments (Figure 47, Table 27). Individual estimates in the two studies, one of which used sulfonylureas,[76] and the other, various OADs,[83] were also non-significant. There was no heterogeneity.

There were no data for this outcome for the remaining comparisons.

Figure 47: Forest plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Non-fatal MI



CI=confidence interval; DM=diabetes mellitus; Glar/IGlar=insulin glargine; MI=myocardial infarction; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk.

Table 27: Summary of results of meta-analysis for comparison of IGlar versus NPH in adult type 2 DM – Risk of non-fatal ischemic heart disease

Comparison	Analysis	No. of RCTs	Sample size	RR (95% CI)	I^2 (%)
IGlar vs. NPH (with OADs)	All RCTs	2	576	1.81 (0.38, 8.54)	0
	Subgroup analysis by OAD				
	OAD=Sfu	1	444	1.51 (0.26, 8.97)	NA

CI=confidence intervals; DM=diabetes mellitus; IGlar=insulin glargine; NA=not applicable; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk; Sfu=sulfonylurea.

Neuropathy: Only one study[76] reported the outcome of neuropathy in the comparison of IGlar versus NPH (in patients also treated with OADs). One patient with neuropathy was reported in the IGlar arm and none in the NPH arm. No data on neuropathy were reported for other comparisons.

Retinopathy: Only one study[76] reported the outcome of retinopathy in the comparison of IGlar versus NPH (in patients also treated with OADs). One patient with retinopathy was reported in the IGlar arm and none in the NPH arm. No data on retinopathy were reported for the remaining comparisons.

Mortality: Study-level mortality data are presented in Appendix 16b. Three RCTs[77,78,83] reported that there were no deaths in either IGlar or NPH arms (in patients also treated with OADs). Philis-Tsimikas *et al.*[70] reported one death in each arm in the comparison of IDet versus NPH (in patients also treated with OADs). Both deaths were due to cerebrovascular accident. Raslova *et al.*[71] reported one death in each arm in the comparison of detemir+aspart versus NPH+HI. It was indicated that the cause of death was unknown and considered unrelated to study treatments. There was no data on mortality for the remaining comparisons.

q) Adverse events (excluding hypoglycemia)

Eighty-three percent of trials selected for adult type 2 DM reported data on adverse events. Study-level details regarding the adverse reactions observed are presented in Appendix 13b. The most commonly reported adverse events with the treatment of long-acting insulin analogues were local allergic reactions, respiratory tract infections, gastrointestinal disorders, edema, rhinitis, and headache. Similar events were also reported with NPH. No systemic allergic reactions associated with insulin treatment were reported. Overall, there was no apparent difference in the adverse event profiles of the long-acting insulin analogues compared with NPH, except that injection-site reactions were more common with IGlar.

7.4.5 Early versus late initiation of long-acting analogues

No studies compared initiation of long-acting insulin analogues early versus late in the course of disease.

8 DISCUSSION

8.1 Type 1 DM

8.1.1 Pediatric population

In the comparison of IGlar with NPH for the treatment of type 1 DM in children and adolescents, there were no significant differences between treatments in terms of A1c and severe, nocturnal, and overall hypoglycemia. Within subgroups defined by the type of bolus insulin used in each treatment arm, the single study that used insulin aspart reported the largest mean difference in A1c between treatments and was the only study to demonstrate a statistically significant A1c effect in favour of IGlar.[31] However, this study also differed from the others in that it was conducted in a Japanese population and enrolled subjects as old as 21 years of age.[31] It is therefore difficult to ascertain whether glargine is truly more effective than NPH in terms of A1c reduction when aspart is used as bolus insulin. RRs for each type of hypoglycemia were statistically non-significant in all bolus insulin subgroups, as were rate ratios. No data were available on health-related quality-of-life, patient satisfaction, long-term diabetes-related complications, or mortality.

A single study also evaluated the combination of IGlar and ILis versus NPH insulin and regular human insulin.[36] Similar to the glargine studies in which the same bolus insulin was used in both treatment arms, no significant differences were observed in terms of A1c or hypoglycemia.

In the single RCT that compared insulin detemir with NPH insulin, there were no significant differences between treatments in terms of A1c and severe hypoglycemia.[30] However, in terms of nocturnal hypoglycemia, there was a 15% reduction in risk and a 23% reduction in the rate of this outcome. There was also a small (11%) reduction in the rate of overall hypoglycemia but no significant reduction in the risk of this outcome. The study did not evaluate health-related quality-of-life, patient satisfaction, diabetes-related complications, or mortality. It should be noted that the bolus insulin used in this study was aspart; whether similar results would be obtained with ILis or regular HI remains unknown.

The methodological quality of the available evidence was generally poor; studies were not blinded, and allocation concealment was unclear in most reports. The former aspect is perhaps most problematic in terms of the assessment of hypoglycemia, since this outcome was usually self-assessed by subjects based on symptoms. The possibility of a spurious result in favour of IDet due to ascertainment bias cannot, therefore, be entirely discounted.

In summary, there is little evidence that IGlar offers benefit over NPH insulin in children or adolescents with type 1 DM. On the other hand, there is evidence from one study that insulin IDet may be associated with a modest reduction in the risk and frequency of nocturnal hypoglycemia, although further studies are required to confirm these observations. This potential benefit of IDet may be an important consideration in the choice of a basal insulin, especially in patients who experience frequent nocturnal hypoglycemia, since this adverse event often goes undetected and can be more likely to cause seizures than hypoglycemia that occurs during the day.[2]

An important limitation of the available data is that all studies enrolled patients five years of age or older, therefore data on pre-school-aged children is lacking. Also, the available studies on both IGlar and IDet reported only clinical endpoints; data on quality-of-life, treatment preference, satisfaction with treatment, and health care resource utilization are lacking. Further study is therefore needed to quantify any possible benefits of the long-acting analogues in terms of these outcomes. Studies are also required to evaluate long-term safety and efficacy in terms of avoidance of diabetes-related complications.

8.1.2 Adult population

In the comparison of insulin glargine with NPH insulin for adults with type 1 DM, no significant differences were observed between treatments in terms of severe, nocturnal, or overall hypoglycemia. A statistically significant benefit of 0.11% was observed in favour of glargine in terms of A1c, however, there was evidence of publication bias, since three smaller studies demonstrated unexpectedly large effect sizes. In subgroup analysis by bolus insulin, a significant A1c benefit was observed for both IAsp and ILis but not for regular human insulin. Significant heterogeneity that could not be readily explained by population or methodological differences across studies remained in the ILis subgroup. It is noteworthy that the largest study in this subgroup reported no significant difference between treatments.[59]

In terms of severe hypoglycemia, none of the bolus subgroups had a significant reduction in risk. Similar results were obtained for severe hypoglycemia rate ratios with the exception of the human insulin subgroup, in which the single study available demonstrated a statistically significant rate ratio of 0.47. Nocturnal hypoglycemia RRs were also not significant in the ILis and HI subgroups; no studies reported this outcome for insulin aspart. In terms of nocturnal hypoglycemia rate ratio, data were available only for ILis; no significant difference between treatments was observed in the pooled rate ratio. However, a significant degree of heterogeneity remained such that two studies demonstrated statistically significant rate ratios of 0.4 to 0.5 in favour of IGlar,[61,62] one a non-significant rate ratio near unity,[60] and the largest study in this subgroup demonstrated a statistically significant rate ratio of 1.12 that favoured NPH.[59] These differences may have been due to variations in the definition of nocturnal hypoglycemia. In terms of overall hypoglycemia, no significant differences were observed within the three bolus subgroups. Although significant heterogeneity was observed in the HI and ILis subgroups, each of the studies within these subgroups demonstrated a non-significant RR. Rate ratios were only calculable for two studies, both in the lispro subgroup; however, significant heterogeneity was observed. This may have been due to the use of a more stringent definition of overall hypoglycemia (i.e., one based on blood glucose measurement rather than symptoms alone) in the study that reported a statistically significant result in favour of IGlar.

Other notable results from the studies comparing IGlar with NPH in adult type 1 diabetics were a slight but statistically significant reduction in weight and a statistically significant difference in favour of IGlar in terms of satisfaction with treatment as measured by the DTSQ. There was also a significant difference in terms of HRQoL as measured by change in the W-BQ General Well-being score from baseline, although there was no significant difference in mean values at endpoint. The treatment satisfaction and HRQoL results were reported in a single study in which human insulin was used as bolus insulin.[58] Although both the DTSQ and Well-being Questionnaire are validated scales,[58,97] the clinical significance of the observed differences is unclear.

A single study comparing the combination of insulin glargine with insulin lispro versus NPH insulin and human insulin was also identified.[64] This was a crossover study that did not demonstrate significant differences between treatments according to any measure except rate ratio for nocturnal hypoglycemia. A1c data from this crossover study were not interpretable since there was evidence of a sequence effect for this outcome.

In the comparison of IDet versus NPH insulin, all trials used either human insulin or insulin aspart as bolus. No significant difference between treatments was observed in terms of A1c; this was also true for the bolus insulin subgroups. The risks for severe and nocturnal hypoglycemia were significantly reduced in the detemir arm, although the risk of overall hypoglycemia was not. The significant reductions in risk of severe and nocturnal hypoglycemia were driven by the IAsp subgroup, since no significant differences were detected within the HI subgroup for either outcome. In terms of rate ratios, there was no significant difference in terms of severe hypoglycemia, while the rates of nocturnal and overall hypoglycemia were significantly reduced in favour of IDet. When analyzed by bolus insulin, both IAsp and HI subgroups demonstrated significant nocturnal hypoglycemia rate ratios in favour of IDet, while neither subgroup had significant rate ratios in terms of overall hypoglycemia. Most overall and subgroup analyses of hypoglycemia rate ratios demonstrated a large degree of heterogeneity that was not readily explained; although in nearly all cases, the direction of effect within individual studies was consistent with the pooled estimate. The rate ratio results for overall hypoglycemia, however, were an exception to this pattern. Within the IAsp subgroup, two studies demonstrated a significant reduction in rate with IDet,[39,44] while one demonstrated a significant effect in favour of NPH.[42] Similarly, in the HI subgroup, two studies demonstrated significant rate ratios in favour of IDet,[43,46] while one did not.[45] Attempts to explore the reason for this heterogeneity did not reveal plausible explanatory factors. In general, individual rate ratio estimates were highly precise (i.e., confidence intervals were small) due to the large number of hypoglycemic events. This contributed to statistical heterogeneity.

Another finding of note was a small but statistically significant reduction in mean weight among subjects treated with IDet. No studies assessed HRQoL, satisfaction with treatment, long-term complications, or resource utilization.

Two additional studies provided data on insulin detemir for type 1 DM in adults.[48,49] In a comparison of IDet with IAsp versus NPH with HI, a statistically significant difference of 0.23% in favour of detemir was observed in mean A1c.[49] RRs and rate ratios for nocturnal and overall hypoglycemia also demonstrated significant benefit for IDet, although there was no difference in terms of severe hypoglycemia.[49] The second trial compared IDet with IGlar, with IAsp used as bolus in both arms.[48] There was no significant difference between treatments according to most outcomes. However, there was a significantly lower risk of severe hypoglycemia with detemir as well as a lower rate ratio. The rate ratio, but not RR, for nocturnal hypoglycemia also favoured IDet.[48]

Like the pediatric studies, the methodological quality of the available evidence in adults was generally poor; studies were not blinded, and allocation concealment was unclear in most reports. The lack of blinding is of special concern in terms of the assessment of subjective outcomes such as hypoglycemia, HRQoL, and treatment satisfaction. It is possible that any observed advantages in terms of these outcomes are at least partially due to ascertainment bias.
The results of a previous systematic review (without meta-analysis) on the effect of the long-acting insulin analogues reported similar results to those reported here.[98]

To summarize, there is little evidence that shows IGlar is superior to NPH insulin in terms of hypoglycemia, although the results were somewhat heterogeneous with some studies showing marked benefit with IGlar. The observed benefit of 0.17% in A1c, although statistically significant, may be of limited clinical significance, since minimal clinically important A1c differences that have been identified in the literature range from 0.4 to 1.0%.[99,100] In contrast, IDet appears to be associated with reduced risks for severe and nocturnal hypoglycemia, although there was no difference in A1c. Furthermore, in a head-to-head comparison with IGlar, IDet demonstrated a reduced risk for severe hypoglycemia as well as a reduced rate ratio for nocturnal hypoglycemia. Therefore, IDet may be useful in adult type 1 diabetics who experience frequent nocturnal hypoglycemia or are prone to severe hypoglycemic episodes. Further studies are required to better understand the impact of the long-acting insulin analogues on quality-of-life and patient satisfaction, as well as to assess the long-term safety and efficacy of these agents in adults with type 1 DM.

8.2 Type 2 DM

Most trials that compared IGlar with NPH insulin in adult type 2 diabetics also treated with one or more OADs. The combination of IGlar or NPH with a bolus insulin (i.e., without OAD co-therapy) was only compared in one study that used HI.[74] Glycemic control as measured by A1c was no better in glargine-treated subjects regardless of the type of co-therapy. Indeed, mean A1c at endpoint was significantly higher in the glargine arm as compared with NPH in the bolus insulin study, although the difference (0.28%) is likely not clinically significant. Data on FPG were only available for the OAD studies; no significant difference between treatments was observed for this outcome. There was also no significant difference in the risk or rate of severe hypoglycemia, although subgroup analysis by OAD type revealed a statistically significant RR of 0.4 in the sulfonylurea subgroup and a non-significant RR greater than 1 in the subgroup of studies in which various OADs were allowed. A similar pattern was observed for severe hypoglycemia rate ratios. In terms of nocturnal hypoglycemia, RR significantly favoured glargine for both bolus insulin and OAD-treated subjects. Similar results were observed for nocturnal hypoglycemia rate ratio in the latter group, while the data required to calculate this statistic for the bolus insulin study were unavailable. The pooled analysis of overall hypoglycemia risk in the OAD studies also demonstrated a slight but statistically significant reduction; however, this was not the case for the rate ratio. Although a large degree of heterogeneity was observed in the nocturnal and overall hypoglycemia rate ratios, the results of individual studies were all consistent with the pooled effect. The RR for overall hypoglycemia in the bolus insulin study was not significant.

Other findings from the IGlar versus NPH studies in type 2 DM included a non-significant effect on body weight and BMI and a significant benefit in favour of IGlar in terms of patient satisfaction with treatment. The latter outcome was reported in only one study,[77] in which patient satisfaction was measured using the Diabetes Treatment Satisfaction Questionnaire Change (DTSQc) scale. The clinical significance of the observed difference (0.60) is unclear. There were no studies on HRQoL, long-term diabetes-related complications, or mortality.

Three studies compared the introduction of IGlar versus TZDs in type 2 adult diabetics poorly controlled on non-TZD OADs. Glycemic control, as measured by A1c and FPG was significantly better in glargine-treated subjects. However, this was at the expense of a significantly higher risk of nocturnal hypoglycemia. Pooled relative risks for severe and overall hypoglycemia were not significantly different, although both point estimates were greater than 1 and one study reported a significant risk of overall hypoglycemia with IGlar.[86] Significant heterogeneity was observed in the

pooled relative risk estimates for severe and overall hypoglycemia; in each of these, the single study in which the TZD was pioglitazone reported higher estimates of risk than the two studies that used rosiglitazone. It is unclear whether this is due to differences between these two agents in the propensity to cause hypoglycemia, methodological differences across studies, or chance. Other findings from the IGlar versus TZD studies were a significant reduction in weight with IGlar and statistically significant improvements in certain measures of HRQoL, such as distress due to hypoglycemia and fatigue and total distress,[86] as well as general health perception and total symptom scores.[90] No studies assessed patient satisfaction with treatment or long-term outcomes. There were also no studies that compared IGlar with other OADs.

As compared to IGlar, there were few studies that compared IDet with NPH for the treatment of type 2 DM. Only three studies with OAD co-therapy[69,70,91] and one study with bolus insulin (IAsp) therapy[68] were identified. In the latter, there was no significant difference between treatments in terms of A1c, FPG, severe hypoglycemia, or overall hypoglycemia.[68] The risk of nocturnal hypoglycemia, however, was significantly reduced with IDet. In the OAD studies, glycemic control as measured by A1c significantly favoured NPH, although the observed difference was unlikely to be clinically significant. FPG did not differ significantly between groups. Heterogeneity was evident in that one of the three studies reported significantly higher mean A1c at endpoint in the IDet arm with no significant difference in FPG,[69] another reported no difference in A1c with a significant improvement in FPG,[70] and the third reported no significant difference between groups for either measure.[91] These differences may have been due to the fact that two studies administered both IDet and NPH once daily[70,91], while the third study administered them twice daily. [69] The overall relative risks for severe and overall hypoglycemia were not statistically significant, while the rate ratios for each outcome significantly favoured IDet. Of note is the high degree of imprecision caused by the low number of severe hypoglycemia events. As well, each of the two studies that comprised the overall RR estimate reported statistically significant reductions in favour of IDet; the lack of statistical significance of the pooled estimate resulted from heterogeneity in the two individual estimates. Both the RR and rate ratio for nocturnal hypoglycemia significantly favoured IDet. Mean body weight was also significantly lower in detemir-treated subjects as compared with NPH. No studies assessed HRQoL, patient satisfaction, or long-term complications.

One additional study compared detemir with NPH, with IAsp used as bolus insulin with IDet, and HI with NPH.[71] No significant differences were reported for A1c or severe hypoglycemia, although the relative risk and rate ratio for nocturnal hypoglycemia significantly favoured IDet. As well, change in body weight from baseline significantly favoured the analogue arm.

Two studies compared IDet with IGlar in adults with type 2 DM, one in combination with IAsp[72] and the other in combination with various OADs.[73] Both studies were reported in abstract form. In the former study, the IGlar arm was found to have a small but statistically significant advantage over IDet in terms of A1c, although there was no difference in terms of FPG. This study did not report data on hypoglycemia, although the authors noted that there was no significant differences in the risk of hypoglycemia.[72] The OAD study did not demonstrate significant differences in terms of A1c, FPG, nocturnal hypoglycemia, or overall hypoglycemia.[73] Severe hypoglycemia was not reported in this study. Both studies reported statistically significant differences in body weight in favour of IDet.

Our results are similar to those reported in recent systematic reviews and meta-analysis of the long-acting insulin analogues in adult type 2 diabetics.[98,100] Horvath *et al.* also found minimal or no significant differences for both IGlar and IDet in terms of A1c as compared with NPH and no

significant difference in the odds ratio for severe hypoglycemia. The risks of symptomatic hypoglycemia and symptomatic nocturnal hypoglycemia were significantly reduced for both IGlar and IDet in this study.[100] In terms of nocturnal hypoglycemia, Brunton also reported similar results to those reported here.[98]

The quality of the available studies in type 2 DM was generally poor. No studies were blinded, and it was not clear in most reports whether allocation was adequately concealed. The lack of blinding is most problematic in terms of the assessment of hypoglycemia, since this outcome was usually self-assessed by subjects based on symptoms. The measurement of HRQoL may also be affected by the lack of blinding. The possibility of spurious results in favour of the long-acting analogues due to ascertainment bias cannot, therefore, be entirely discounted.

In summary, neither IGlar nor IDet offer advantages over NPH insulin in terms of glycemic control in adults with type 2 DM, although both agents appear to reduce the risk of nocturnal hypoglycemia. In general, risks and rates of severe hypoglycemia were not significantly reduced for either agent. The only exception was the severe hypoglycemia rate ratio for the comparison of IDet versus NPH with OAD co-therapy. In contrast to IGlar, IDet demonstrated small but statisitically significant benefits in terms of body weight comparison to NPH insulin. In head-to-head studies, there was no evidence that one long-acting analogue is superior to the other, although IDet produced significantly lower increases in body weight as compared to IGlar. IGlar and IDet may be most beneficial in insulin-treated type 2 patients who experience frequent nocturnal hypoglycemia on NPH insulin. Further research is needed to determine other potential benefits of the long-acting analogues in terms of quality-of-life and patient satisfaction with treatment and HRQoL. Comparative studies with NPH designed to assess long-term safety and prevention of diabetes-related complications are also needed. Improvements in methodological quality are also necessary to produce valid assessments of these agents.

8.3 Hypoglycemia Benefits of the Long-Acting Analogues

Although results were variable, the main benefit of the long-acting insulin analogues appears to be reduction in the risk and rate of hypoglycemia, especially nocturnal hypoglycemia. As compared with hypoglycemia that occurs during the day, nocturnal hypoglycemia is less likely to receive prompt treatment due to lack of awareness during sleep. As a result, the development of severe hypoglycemia is more likely, with its attendant complications of serious injury, seizures, coma, or even death.[98] Nocturnal hypoglycemia may also impair cognitive function, especially in children, and reduce quality-of-life due to sleep disturbance.[98] Frequent episodes may result in progressive hypoglycemic unawareness, thereby further increasing the risk of severe hypoglycemic events.[98] Furthermore, some, but not all, of the literature on the impact of hypoglycemia on glycemic control has demonstrated that a history of hypoglycemia is associated with development of fear of hypoglycemia, which in turn can cause deterioration in metabolic control as patients engage in "over-compensatory behaviours" to prevent future hypoglycemic episodes.[101] However, the lack of clinically significant benefit in terms of A1c indicates that a reduction in hypoglycemia risk with the long-acting analogues did not result in improved glycemic control. There was also little evidence to indicate that reduced hypoglycemia risk translated into a higher quality-of-life or better patient satisfaction, since these outcomes were seldom reported in studies.

8.4 Limitations

Use of the Jadad scale, a quality assessment instrument that places a large weight on double-blinding (2 of 5 points are for this characteristic), may be considered suboptimal given the practical difficulties associated with blinding trials comparing long-acting analogues (which are clear solutions) with NPH insulin (which is cloudy). Since none of the RCTs included in this meta-analysis was double-blined, the maximum score achievable was 3/5, and nearly all studies were considered to have significant methodological limitations. Despite the practical difficulties involved, however, the lack of blinding does introduce a potential source of ascertainment bias, especially for subjective outcomes such as patient-reported hypoglycemia and quality-of-life. Use of the Jadad scale was therefore considered appropriate to evaluate methodological quality, especially in light of the additional items considered. These included allocation concealment, blinding of assessors, intention-to-treat analysis, and loss to follow-up. Given that the Jadad scale and additional items together measure all aspects of trial quality that are currently considered relevant to internal validity, it is unlikely that use of a different scale would have significantly affected the results. In fact, the finding that most trials of the long-acting analogues have significant methodological limitations was also reported in a recent systematic review.[100]

Not all studies identified for a particular comparison reported all outcomes of interest. While A1c was reported in nearly all studies, other outcomes such as the various forms of hypoglycemia, fasting plasma glucose, weight, and quality-of-life were not. The latter three endpoints in particular were usually reported in only a small proportion of the available studies. These results are therefore most likely to be affected by reporting bias.

Another possible limitation lies in the methodological decision to use mean values at endpoint for continuous outcomes rather than mean change from baseline, except where such data were not reported or there was a statistically significant difference in mean baseline values. Such an approach is valid because randomization should, on average, result in groups that are evenly matched. However, chance differences at baseline, even if not statistically significant, may either reduce or amplify treatment differences, especially in analyses consisting of one or a small number of RCTs. FPG and body weight are most likely to be affected due to the small number of studies available for these outcomes.

It has been suggested that separate analysis of glycemic control and hypoglycemia is inappropriate due to the correlation between the two endpoints; that is, as A1c decreases, the risk of hypoglycemia increases. Furthermore, many of the trials of the long-acting analogues were of a non-inferiority design and were conducted by investigators who were not yet fully experienced in their optimal use. As such, many trials were unable to detect a benefit of the LAIs in terms of A1c, although hypoglycemia risk was reduced, while others were able to achieve better glycemic control with the LAIs but with little or no difference in hypoglycemia. Pooling of results from both types of studies to calculate estimates of A1c and hypoglycemia, without accounting for the correlation between the two endpoints, may therefore underestimate the beneficial effects of the long-acting analoguess on hypoglycemia. A recent study has addressed this concern by conducting a meta-regression analysis of hypoglycemia and A1c using patient-level data from RCTs of IGlar.[102] Although differences between IGlar and NPH in unadjusted hypoglycemia rates were somewhat lower as compared with adjusted rates, the absolute differences between the two were small. For example, the unadjusted percentage reduction in the event rate of severe hypoglycemia in type 1 DM was 16.8%, and 21.5% after adjustment for endpoint A1c (neither value was statistically significant).[102]

Adjustment for A1c, therefore, does not appear to have a major effect on estimates of treatment differences in hypoglycemia.

9 CONCLUSION

The bulk of the available evidence on long-acting analogues for both type 1 and type 2 diabetics consists of short- to medium-term comparisons with NPH in terms of A1c and hypoglycemia. Most studies were of poor methodological quality. Based on the available evidence, the benefits of the long-acting insulin analogues over NPH insulin appear to be marginal at best, although these agents may be useful in patients with a history of frequent or severe hypoglycemia. Further research of higher methodological quality is required to measure the impact of these agents on quality-of-life, health care resource utilization, and long-term outcomes, especially with respect to the development of diabetes complications. As well, since a number of strategies exist to reduce the risk of hypoglycemia (e.g., the use of continuous subcutaneous insulin infusion, bedtime snacks),[98] comparative studies of the long-acting analogues with these approaches are required to determine which is most effective.

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APPENDIX 1A: SEARCH STRATEGY FROM THE TECHNOLOGY REPORT – LONG-ACTING INSULIN ANALOGUES

Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness on long-acting insulin analogues (in press as of Sept 2007).[20]

We obtained published literature by searching MedLine, BIOSIS Previews, PASCAL, PubMed, and the Cochrane Database of Systematic Reviews from 1990 onwards. The strategy included both long-acting and short-acting insulin analogues, because initially a systematic review was to be conducted for both insulin types. However, a decision was made following the literature search to divide the project into two parts and perform separate systematic reviews on the short- and long-acting insulin analogues. The search was constructed using controlled vocabulary (e.g., the National Library of Medicine's Medical Subject (MeSH)) and keyword terminology. Publication filters were used to identify specific publication types, namely controlled trials, meta-analyses, and systematic reviews. Please see below for details of the search strategy.

The original search was performed in August 2005. Alert searches were run from August onward. Alert search results from August 2005 to February 2006 are incorporated into the systematic review. Relevant results found between February 2006 and June 2007 have been included in our conclusion, but they are not included in the systematic review. We obtained grey literature by searching the web sites of regulatory agencies and health assessment and near-technology assessment agencies. Specialized databases such as the University of York NHS Centre for Reviews and Dissemination and the Latin American Caribbean Center on Health Sciences Information were also searched. We searched the Internet using the Google and Dogpile search engines and found additional information on the web sites of professional associations such as the American Association of Clinical Endocrinologists, the Canadian Diabetes Association, the American Diabetes Association, and the European Association for the Study of Diabetes along with their associated conference sites.

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* (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

DATABASES	DATES/ LIMITS	SUBJECT HEADINGS/KEYWORDS
		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 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

DATABASES	DATES/ LIMITS	SUBJECT HEADINGS/KEYWORDS
		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 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*

DATABASES	DATES/ LIMITS	SUBJECT HEADINGS/KEYWORDS
		(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 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 – SUPPLEMENTAL SEARCH, LONG-ACTING INSULIN

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

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

Search Syntax:
1. Long-acting insulin AND Short-acting insulin AND RCT Filter
2. Glargine AND Detemir AND RCT Filter

Supplemental Search 1: LA and RA:

Long-Acting Insulin
1. Insulin Long-Acting/aa
2. (long acting insulin$ or long acting analog$ or slow$ acting insulin$ or slow$ acting analog$).ti,ab,hw.
3. (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn,tn,hw.
4. (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn,tn,hw.
5. or/1-4

Rapid-Acting Insulin
6. (short acting insulin$ or quick acting insulin$ or rapid acting insulin$ or rapidly 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,hw.
7. (Lispro or Lyspro or Humalog or Liprolog or "Lys(B28),pro(B29)or 133107-64-9").ti,ab,rn,tn,hw.
8. (Insulin Aspart or "Asp(B28)" or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn,tn,hw.
9. (Glulisine or 207748-29-6 or Apidra).ti,ab,rn,tn,hw.
10. or/6-9

Supplemental Search 2: Glargine versus Detemir
(glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn,tn,hw
(detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn,tn,hw

RCT Filters:
MedLine
16. Randomized Controlled Trial.pt.
17. Randomized Controlled Trials/
18. (random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab.
19. ((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab.
20. (randomi?ed control$ trial? or rct?).ti,ab.
21. or/16-20

EMBASE
22. Randomized Controlled Trial/
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/22-25

BIOSIS Previews
27. randomi?ed control$ trial?.ti,ab,hw.
28. (random$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab,hw.
29. ((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab,hw.
30. or/27-29

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 LITERATURE AND HANDSEARCHING	
Dates for Search:	August 2005 to June 2007
Keywords:	Long 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'evaluation 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.blu ecares.com/tec/index.html

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

Health Economic

Bases CODECS (Connaissances et décisions en économie de la santé) Collège des économistes 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
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APPENDIX 2A: CADTH TECHNOLOGY REPORT STUDY SELECTION CRITERIA

- Study design: Randomized controlled trials (RCT) or observational studies
- Population group(s): Patients with diabetes mellitus (type 1, type 2, or GDM)
- Intervention: Long-acting insulin analogues (IGlar or IDet)
- Comparator: Conventional HI or oral antidiabetic agents
- Outcome: Glycemic control [glycosylated hemoglobin (HbA1c) level, BG level], quality of life (QoL), hypoglycemic episodes, adverse events, complications of diabetes, or mortality

APPENDIX 2B: COMPUS STUDY SELECTION CRITERIA

Inclusion criteria

- Study design – Randomized controlled trial (RCT)
- Population – Patients with type 1 or type 2 DM or GDM
- Intervention – combination of (insulin glargine or insulin detemir) and (insulin aspart or insulin lispro or insulin glulisine)
- Comparator – combination of an intermediate- or long-acting HI (e.g., insulin isophane) and short-acting HI
- If additional insulins or antidiabetic agents are administered, they are administered equally in both the intervention and comparator arms
- Outcomes – Glycemic control (HbA1c level and BG level), quality of life (QoL), hypoglycemic episodes, adverse events, complications of diabetes, and mortality

Exclusion criteria:

- Treatment duration less than four weeks

For clinical research question 6, the same inclusion and exclusion criteria described above will be used except that the intervention and comparator of interest will differ as follows:

- Intervention – insulin glargine (or insulin detemir)
- Comparator – insulin detemir (or insulin glargine)

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: CLINICAL DATA EXTRACTION FORM

Reviewer initials: Reference (Author, Year, Source, Publication, status)	Ref ID:
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 and cost data				
Category	Units	Treatment	Control	Comment
HbA1c				
BG				
Hypoglycemia				
Diabetic complications				
Adverse events				
Mortality				
QoL				
Cost				
Other				

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

APPENDIX 5: META-ANALYTIC METHODS

The meta-analytic methods most commonly used to investigate the effectiveness of health care interventions are those presented by Cochrane *et al.*[103,104] and DerSimonian and Laird[105] 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.[106,107]

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 methods 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.[105,108] 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.[108-110] 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.[107] 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.[104]

Forest plots will be generated wherever appropriate to determine if heterogeneity exists between the results of an individual study included in the review. If significant heterogeneity does exist, the reasons for heterogeneity (e.g., study design, population characteristics, 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 (grouped by publication status, quality, publication year, etc.).

APPENDIX 6: REASONS FOR STUDY EXCLUSION

Study	Reason for Exclusion
Al, 2006[111]	Non-RCT
Al-Shaikh, 2006[112]	Non-RCT
Bailey *et al.*, 2005[113]	Non-RCT
Bhardwaj *et al.*, 2006 [114]	Non-RCT
Bin-Abbas *et al.*, 2006[115]	Non-RCT
Bin-Abbas *et al.*, 2006[116]	Non-RCT
Cesur *et al.*, 2007[117]	Non-RCT
Ciardullo *et al.*, 2006[118]	Non-RCT
Danne, 2006[119]	Non-RCT
Erickson *et al.*, 2006[120]	Non-RCT
Friedberg *et al.*, 2006[121]	Non-RCT
Gerstein *et al.*, 2006[122]	Not an appropriate comparison
Hassan *et al.*, 2006[123]	Not an appropriate comparison
Jacober *et al.*, 2006[124]	Not an appropriate comparison
Kann *et al.*, 2006[125]	Not an appropriate comparison
Liedholm *et al.*, 2006[126]	Non-RCT
Lofthouse, 2006[127]	Non-RCT
Madero *et al.*, 2006[128]	Non-RCT
Pickup *et al.*, 2006[129]	Non-RCT
Rami, 2006[130]	Non-RCT
Rafilová *et al.*,2007[131]	Non-RCT
Roach and Malone, 2006[132]	Not an appropriate comparison
Rubio Terres *et al.*, 2004[133]	Non-RCT
Secnik *et al.*, 2006 [134]	Not an appropriate comparison
Sneed and Gonzalez, 2003[135]	Non-RCT
Sulli and Shashaj, 2006[136]	Non-RCT
Terres *et al.*, 2004[137]	Non-RCT
Ulahannan and Mortimer, 2006[138]	Non-RCT
Yeldandi *et al.*, 2006[139]	Non-diabetic population
Yokoyama *et al.*, 2006[140]	Not an appropriate comparison
Zhou, 2006[67]	Not an appropriate comparison

RCT=randomized controlled trial.

APPENDIX 7A: STUDY CHARACTERISTICS OF RCTS IN TYPE 1 DM

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, Years	% Male	Race/ Ethnicity	Duration of DM, Years
Ashwell *et al.*, 2006[64]	16-week, open-label, crossover	Aventis	UK and USA	IGlar+ILis	54	2	41.1±12.2*	37	NR	21.6±13.1*
				NPH+unmodified HI	54	1				
Bolli *et al.*, 2006[63]	6-month, open-label, parallel	Sanofi-Aventis	Italy	IGlar+ILis	85	NR	35.5 [18 to 57]‡	59	NR	13.1 [1.2 to 37.6]‡
				NPH+ILis	90	NR	36.3 [19 to 58]‡	54	NR	14.3 [2.4 to 48.1]‡
Chase *et al.*, 2006[33]	16-week, open-label, crossover	NR	USA	IGlar+ILis	85	NR	13*	NR	71% white	5.5
				NPH or lente+ILis	90					
Davies *et al.*, 2005[50]	16-week, open-label, crossover	NR	UK	IGlar+IAsp	57	NR	42.7±12.5*	55	almost all white European patients	17.9±12*
				NPH (Insulatard)+ IAsp	57					
De Leeuw *et al.*, 2005[40]	12-month, open-label, parallel	Novo Nordisk	Multiple European countries	IDet+IAsp	216	5	40.1±12.8*	57	100% Caucasian	17.8±9.7*
				NPH+IAsp	99	3	40.8±13.2*	52	100% Caucasian	16.6±10.2*
Fulcher *et al.*, 2005[60]	30-week, single blind, parallel	Aventis	Australia	IGlar+ILis	62	14	41.6±12.9*	39	NR	17.9±10.5*
				NPH+ILis	63	4	39.3±13.9*	40	NR	17.1±9.7*
Garg *et al.*, 1998[53]	4-week, open-label, parallel	NR	USA	IGlar+HI	9	NR	24.6±2.9†	NR	NR	9.8±6.0
				NPH+HI	5	NR	23.8±3.8	NR	NR	12.3±6.7
Hermansen *et al.*, 200[43]	12-month, open-label, parallel	Novo Nordisk	Denmark	IDet+HI	59	3	34.5 [19 to 52]‡	82	100% Caucasian	14.8 [2.6 to 47.8]‡
				NPH+HI						
Hermansen *et al.*, 2004[49]	18-week, open-label, parallel	Novo Nordisk	Multiple European countries	IDet+IAsp	298	9	38.8±13.5*	61	NR	15.4±10.1*
				NPH+regular insulin	297	14	39.3±12.9*	65	NR	15.1±10.4
Hershon *et al.*, 2004[54]	28-week, open-label, parallel	Aventis	USA	IGlar+HI	195	24	37.9±12.6*	50	94.9% Caucasian	18.2±11.5*

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, Years	% Male	Race/ Ethnicity	Duration of DM, Years
				NPH+HI	199	16	37.8±11.4*	49	96.5% Caucasian	16.7±9.5*
Home *et al.*, 2005[55]	28-week, open-label, parallel	Aventis	UK	IGlar+HI	292	16	39±12*	55	NR	16a±12*
				NPH+HI	293	21	39±12*	57	NR	15±9
Home *et al.*, 2004[41]	16-week, open-label, parallel	Novo Nordisk	Australia and Europe	$IDet_{12h}$	137	5	40.9±13.0*	52	NR	17.1±10.6*
				$IDet_{m+b}$	139	4	41.3±11.4*	57	NR	17.6±10.7*
				NPH_{m+b}	132	8	38.3±12.4*	53	NR	15.1±10.6*
Kawamura *et al.*, 2005[31]	16-week, crossover	NR	Japan	IGlar	64	NR	8 to 21	NR	NR	NR
				NPH	NR	NR	NR	NR	NR	NR
Kolendorf *et al.*, 2006[39]	16-week, open-label, parallel	Novo Nordisk	Australia, Europe, and South Africa	IDet+IAsp	130	7	39.2±12.3*	54	93.8% Caucasian	16.6±10.2*
				NPH+IAsp						
Kudva *et al.*, 2005[65]	16-week, open-label, parallel	Aventis, Medtronic	USA	IGlar+IAsp	24 randomized; 22 evaluated	2	43 [24 to 72]‡	46	NR	16 [3 to 54]‡
				UL+IAsp						
Mianowska *et al.*, 2006[35]	16-week, open-label, parallel	NR	Poland	IGlar	14	NR	10.4* (range: 6 to 12)	50	NR	6.9* (range: 2 to 1)
				NPH						
Murphy *et al.*, 2003[36]	16-week, open-label, crossover	Aventis	UK	IGlar+ILis	26	1	14.8	44	NR	7.3* (range:1.8 to 15)
				NPH+HI	26	NR	NR	NR	NR	NR
Pesic *et al.*, 2006[51]	16-week, open-label, parallel	NR	Serbia and Montenegro	IGlar	18	NR	27	NR	NR	NR
				NPH (q.d.)	15					
				NPH (b.i.d.)	15					
Pieber *et al.*, 2000[52]	4-week, partial blinding, parallel	Novo Nordisk	European countries	HOE901 [30]+ HI	110	0	35.6 [18 to 68]‡	56	NR	Median: 11 [1 to 36]‡

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, Years	% Male	Race/ Ethnicity	Duration of DM, Years
				HOE901 [80]+HI	113	0	37.5 [19 to 70]‡	66	NR	Median: 8 [1 to 48]‡
				NPH+HI	110	0	35.7 [20 to 61]‡	62	NR	Median: 11 [2 to 48]‡
Pieber *et al.*, 2005[42]	16-week, open-label, parallel	Novo Nordisk	7 European countries	$IDet_{m+d}$+IAsp	139	7	39.0±12.4*	56	NR	14.4±10.8*
				$IDet_{m+b}$+IAsp	132	10	40.4±11.4*	68	NR	15.9±10.3*
				NPH_{m+b}+IAsp	129	4	41.1±11.9*	57	NR	14.4±9.2*
Pieber *et al.*, 2007[48]	26-week, open-label, parallel	Novo Nordisk	3 European countries, South Africa	IDet+IAsp	161	14 (8.7)	40 [18 to 79]‡	55	NR	17 [1 to 57]‡
				IGlar+IAsp	159	15 (9.4)	41 [18 to 70]‡	48	NR	16 [1 to 48]‡
Porcellati *et al.*, 2004[61]	1-year, open-label, parallel	National Ministry of Scientific Research	Italy	IGlar (dinner time)+ILis	61	0	36±1.0†	56	NR	13±0.3†
				NPH (4 times/day)+ILis	60	0	34±1.0†	55	NR	15±0.3†
Raskin *et al.*, 2000[59]	16-week, open-label, parallel	Hoechst Marion Roussel	Canada, USA	IGlar+ILis	310	15	38.9±12.2*	49	96.5% Caucasian	18.7±11.5*
				NPH+ILis	309	16	39.5±12.2*	52	97.4% Caucasian	18.4±11.8*
Ratner *et al.*, 2000[56]	28-week, open-label, parallel	Hoechst Marion Roussel	USA	All	534	53	38.5±12.0*	51	NR	17.4±10.85*
				IGlar+HI	264	31	38.2±12.2*	53	NR	17.9±11.66*
				NPH+HI	270	22	38.9±11.9*	48	NR	16.9±10.0*
Robertson *et al.*, 2007[30]	26-week, open-label, parallel	Novo Nordisk	16 European countries and Israel	IDet+IAsp	232	6	11.9±2.8*	51	NR	5.1±3.1*
				NPH+IAsp	115	6	11.7±2.7*	48	NR	4.8±2.8*
Rosenstock *et al.*, 2000[57]	4-week, double-blind, parallel	Aventis	USA	HOE901 [30]+HI	82	0	37.5±11.7*	51	92.7% Caucasian	16.7±11.3*
				HOE901 [80]+HI	86	0	37.0±11.5*	51	94.2% Caucasian	15.8±10.0*

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, Years	% Male	Race/ Ethnicity	Duration of DM, Years
				NPH+HI	88	1	37.9±12.5*	53	94.3% Caucasian	16.3±10.8*
Rossetti *et al.*, 2003[62]	3-month, open-label, parallel	National Ministry of Scientific Research	Italy	IGlar (dinner time)+ILis	17	NR	31.3±3.4†	47	NR	12.9±2.3†
				IGlar (bedtime)+ILis	17	NR	34.0±3.1†	59	NR	14.8±2.3†
				NPH (4 times/day)+ILis	17	NR	32.0±3.0†	53	NR	13.1±1.9†
Russell-Jones *et al.*, 2004[45]	6-month, open-label, parallel	Novo Nordisk	Europe and Australia	IDet+HI	491	27	40.9±12.4*	66	NR	17.1±11.3*
				NPH+HI	256	22	39.8±12.3*	61	NR	16.4±9.5*
Schober *et al.*, 2002[32]	28-week, open-label, parallel	Aventis	9 European countries and South Africa	IGlar+HI	174	0	11.8±2.46*	56	NR	5.0±3.02*
				NPH+HI	175	0	11.5±2.36*	48	NR	4.7±3.08*
Standl *et al.*, 2004[46]	6-month treatment+6-month extension, open-label, parallel	Novo Nordisk	Europe, Australia, and New Zealand	IDet+HI	154	20	40.7±13.4*	62	NR	16.1±9.1*
				NPH+HI	134	17	42.5±12.3*	66	NR	16.0±10.6*
Vague *et al.*, 2003[44]	6-month, open-label, parallel	Novo Nordisk	5 European countries	IDet+IAsp	301	17	38.9±13.3*	54	NR	17.1±9.9*
				NPH+IAsp	146	5	41.8±14.2*	51	NR	17.4±11.0*
White *et al.*, 2006[34]	24-week, open-label, parallel	NR	USA	IGlar	175	NR	13.2	49	91% Caucasian	5.4
				NPH or lente		NR	13.4	58	89% Caucasian	4.9
Witthaus *et al.*, 2001[58]	28-week, open-label, parallel	Aventis	10 European countries	IGlar+HI	261	NR	40.1±12.31*	54	NR	NR
				NPH+HI	256	NR	39.4±11.9*	57	NR	NR

*mean±SD; †mean±SE; ‡mean[range]. 12h=12 hour interval; b.i.d.=twice a day; DM=diabetes mellitus; HI=human insulin; HSI=human soluble insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and dinner time; NPH=neutral protamine Hagedorn; q.d.=every day; RCTs=randomized controlled trials; NR=not reported; UL=ultralente.

APPENDIX 7B: STUDY CHARACTERISTICS OF RCTS IN ADULT TYPE 2 DM

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, Year	% Male	Race/Ethnicity	Duration of Diabetes, Year
Eliaschewitz *et al.*, 2006[77]	24-week, open-label, parallel	Sanofi-Aventis	10 Latin American countries	IGlar+glimepiride	231	13	56.1±9.9*	43	43.7% Caucasian	10.3±6.4*
				NPH+glimepiride	250	6	57.1±9.6*	38	48.4% Caucasian	10.8±6.4*
Fonseca *et al.*, 2004[75] [Subgroup analysis of Rosenstock *et al.*[74]]	28-week, open-label, parallel	Aventis	USA	IGlar+HI	52	5	57.3±8.68*	48	82.7% Caucasian	12.4±10.02*
				NPH+HI	48	2	58.5±9.8*	67	85.4% Caucasian	12.7±9.25*
Fritsche *et al.*, 2003[78]	24-week, open-label, parallel	Aventis	13 European countries	IGlar (morning)+Glim	236	11	61±9*	52	NR	9.0** [0 to 38]‡
				IGlar (bedtime)+Glim	227	17	60±9*	58	NR	8.2** [1 to 51]‡
				NPH (bedtime)+Glim	232	27	62±9*	51	NR	9.3** [1 to 39]‡
Haak, 2005[68]	26-week, open-label, parallel	Novo Nordisk	5 European countries	IDet+IAsp	341	26	60.6±8.7*	48	99% Caucasian	12.9±7.4*
				NPH+IAsp	164	8	60.0±8.4*	57	98.8% Caucasian	13.7±8.0*
Hermansen *et al.*, 2006[69]	24-week, open-label, parallel	Novo Nordisk	10 European countries	IDet+OGLD	237	10	61.3±9.1*	49	97.9% Caucasian	9.6±6.6*
				NPH+OGLD	238	14	60.4±9.3*	57	99.6% Caucasian	9.8±6.2*
Massi Benedetti *et al.*, 2003[81]	52-week, open-label, parallel	Aventis	14 European countries and South Africa	IGlar+OAD	289	12	59.6±9.3*	53	NR	10.2±6.2*
				NPH+OAD	281	29	59.4±9.1*	54	NR	10.5±6.0*
Meneghini *et*	48-week,	NR	USA	IGlar	253	80	53	NR	NR	5.9

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, Year	% Male	Race/Ethnicity	Duration of Diabetes, Year
				Pioglitazone						
Meneghini *et al.*, 2006;[87] Oster *et al.*, 2006[86]	48-week, open-label, parallel	Sanofi-Aventis	USA	IGlar	189	71	NR	NR	NR	NR
				Pioglitazone	199	87	NR	NR	NR	NR
Pan *et al.*, 2007[76]	24-week, open-label, parallel	Sanofi-Aventis	10 Asian countries	IGlar+glimepiride	220	NR	55.6±8.4*	40	NR	10.3±6.3*
				NPH+glimepiride	223	NR	56.6±8.7*	44	NR	10.0±5.4*
Philis-Tsimikas *et al.*, 2006[70]	20-week, open-label, parallel	Novo Nordisk	6 European countries and USA	IDet+OAD (morning IDet)	165	18	58.3±10.4*	59	NR	10.5±7.6*
				IDet+OAD (evening IDet)	169	16	58.7±10.2*	54	NR	105.±7.0*
				NPH+OAD	164	17	58.4±11.0*	57	NR	10.0±6.9*
Raskin *et al.*, 2006[72]	26-week, open-label, parallel	NR	NR	All	385	NR	55.8±10.3*	54	NR	NR
				IDet+IAsp	257	NR	NR	NR	NR	NR
				Glar+IAsp	128	NR	NR	NR	NR	NR
Raslova *et al.*, 2004[71]	22-week, open-label, parallel	Novo Nordisk	8	IDet+IAsp	195	NR	58.3±9.4*	40	99.5% Caucasian	13.7±7.5*
				NPH+HSI	199	NR	58.2±9.2*	44	100% Caucasian	14.5±8.1*
Riddle *et al.*, 2003[82]	24-week, open-label, parallel	Aventis	USA and Canada	IGlar+OAD	367	33	55±9.5*	55	84% Caucasian	8.4±5.55*
				NPH+OAD	389	32	56±8.9*	56	83% Caucasian	9.0±5.57*
Rosenstock *et al.*, 2001[74]	28-week, open-label, parallel	NR	USA	IGlar+HI	259	28	59.5±9.7*	58	80.6% Caucasian	13.4±8.3*
				NPH+HI	259	21	59.2±9.9*	62	80.7% Caucasian	14.1±9.0*
Rosenstock *et al.*, 2006[88]	24-week, open-	Aventis	USA	IGlar (bedtime)+ Sfu (max)+Metf	104	6	55.9±10.5*	45	NR	8.5±5.8*

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, Year	% Male	Race/Ethnicity	Duration of Diabetes, Year
				Rosi+Sfu (max)+Metf	112	11	55.3±11.4*	58	NR	8.5±5.1*
Rosenstock *et al.*, 2006[73]	52-week, open-label, parallel	NR	USA, UK, Denmark, and Austria	IDet	582	NR	≥18	NR	NR	NR
				IGlar						
Tajima *et al., 2006*	36-week, open-label, parallel	Novo Nordisk Pharma Ltd.	Japan	IDet + NPH	363	NR	NR	NR	Japanese	NR
Triplitt *et al.*, 2006[89]	16-week, open-label, parallel	Aventis Pharma	USA	IGlar	10	0	54±6*	40	7/3/0 (Mexican American/Caucasian/African American)	NR
				rosiglitazone	10	0	41±11*	40	8/1/1	NR
Vinik and Zhang, 2007[90]	24-week, open-label, parallel	Sanofi-Aventis	USA	IGlar+Sfu+Metf	104	8 (7.6)	55.9±10.5*	45	70% Caucasian, 14% African American, 12% Hispanic	8.5±5.8*
				rosiglitazone+Sfu+Metf	112	21 (18.8)	55.3±11.4*	58	77% Caucasian, 12% African American, 9% Hispanic	8.1±5.1*
Wang *et al.*, 2007[79]	12-week, open-label, parallel	NR	China	IGlar+glipizide	16	NR	57±6*	56	NR	10.4±4.3*
				NPH+glipizide	8	NR	56±8*	50	NR	9.5±4.9*
Yki-Järvinen *et al.*, 2000[84]	52-week, open-label, parallel	Hoechst Marion Roussel	European countries	IGlar+OAD	214	NR	59±1†	55	NR	10±1†
				NPH+OAD	208	NR	59±1†	53	NR	10±1†
Yki-Järvinen *et al.*, 2006[80]	36-week, open-label,	Aventis	Finland and the UK	IGlar+Metf	61	2 (due to pancreatic cancer)	56±1†	62	NR	9±1†

Study	Study Period and Type	Sponsor	Countries	Comparators	No. of Patients	Withdrawals	Age, Year	% Male	Race/Ethnicity	Duration of Diabetes, Year
				NPH+Metf	49	1 (due to pulmonary tumour, but benign)	57±1†	65	NR	9±1†
HOE 901/2004 Study Group, 2003[83]	4-week, open-label, parallel	Aventis	Europe and South Africa	IGlar [30]+OAD	64	2	58.9 [29 to 75]‡	58	NR	9.5
				IGlar [80]+OAD	72	0	60.0 [38 to 78]‡	64	NR	9.9
				NPH+OAD	68	0	59.2 [30 to 78]‡	57	NR	9.1

*mean±SD; †mean±SE; ‡mean[range]; **median [interquartile range]. DM=diabetes mellitus; HI=human insulin; HSI= human soluble insulin; Glim=glimepiride; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; Metf=metformin; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; OGLD=oral glucose-lowering drugs; RCTs=randomized controlled trials; NR=not reported; Sfu=sulfonylurea.

APPENDIX 8: PATIENT INCLUSION AND EXCLUSION CRITERIA OF SELECTED RCTS

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Ashwell *et al.*, 2006[64]	Patients with type 1 DM; age 18 to 65 years; no previous experience of using IGlar; history of using multiple daily injection (MDI) regimen ≥1 year; a random C-peptide ≤0.1 nmol/L and HbA1c 7.0 to 9.5%; women of child-bearing potential were required to be using adequate contraception	Patients with proliferative retinopathy, recurrent severe hypoglycemia, impaired hepatic or renal function, or who worked at night shifts were excluded	1
Bolli *et al.*, 2006[63]	Patients with type 1 DM	Not reported	1
Chase *et al.*, 2006[33]	Patients with type 1 DM if screening A1c was >7.0% and <9.5%) on any insulin regimen (i.e., ≥2 injections/day or continuous subcutaneous insulin infusion); with type 1 DM	Not reported	1
Davies *et al.*, 2005[50]	Patients with type 1; age 18 to 75 years; baseline HbA1c 6 to 11%; on insulin for at least 6 months	Not reported	1
De Leeuw *et al.*, 2005[40]	Age≥18 years; type 1 DM <1 year; basal-bolus therapy ≥2 months prior to study; BMI <35 kg/m^2; A1c≤12.0%; total daily basal insulin requirement <100 IU/day; Caucasian	Proliferative retinopathy; impaired hepatic or renal function; severe cardiac problems; uncontrolled hypertension; recurrent major hypoglycemia; allergy to insulin; pregnancy or lactation	1
Eliaschewitz *et al.*, 2006[77]	Patients with type 2 DM who failed to achieve good metabolic control on OADs (HbA1c level ≥7.5% and ≤10.5%; FBG levels ≥100mg/dl (≤5.5 mmol/L); age≤75 years; BMI≤35 km/m2; history of taking OADs (any sulfonylureas or a combination of sulfonylureas with other OAD such as metformin or acarbose) for at least for 6 months; and the previous doses of sulfonylureas had been at least equivalent to glimepiride 3 mg Patients had to be able and willing to receive a tight antidiabetic therapy and to perform blood-self-monitoring at home	Patients received any insulin treatment in the 3 months before the study; pregnant or breastfeeding; patients enrolled in a previous study of IGlar; receiving a investigative drug within 3 months of the study; history of alcohol abuse; likely to require treatment with drugs not permitted by the study protocol (including non-cardioselective β-blockers and systemic corticosteroids)	2
Fonseca *et al.*, 2004[75] [Subgroup analysis of Rosenstock[74]]	Age 40 to 80 years; insulin use ≥3 months prior to study	Hepatic or renal impairment; oral antidiabetic drugs ≤3 months prior to study; night shift work	2
Fritsche *et al.*, 2003[78]	Age<75 years; BMI<35 kg/m^2; previous oral therapy; fasting blood glucose ≥6.7 mmol/L; A1c 7.5 to 10.5%	Pregnancy or lactation; treatment with insulin or investigation drugs ≤3 months prior to study; clinically relevant somatic or mental diseases	2
Fulcher *et al.*, 2005[60]	Age 18 to 80 years; insulin use ≥1 year prior to study; A1c ≥12.0%	Nightshift workers; known sensitivity to study drug or related drugs; impaired hepatic function or other clinically relevant physiological or psychological medical conditions;	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
		use of systemic corticosteroids and BG lowering drugs	
Garg *et al.*, 1998[53]	Abstract – criteria not specified	Not reported	1
Haak *et al.*, 2005[68]	Age≥35 years; type 2 DM ≥12 months; A1c≤12.0%; insulin use ≥2 months prior to study	OAD use ≤2 months prior to trial; pregnancy or lactation; proliferative retinopathy; uncontrolled hypertension; recurrent major hypoglycemia; impaired renal or hepatic function; cardiac problems; total daily basal insulin dose >100 IU/day	2
Hermansen *et al.*, 2004[49]	Patients with type 1 DM; history ≥12 months; age≥18 years; BMI ≤35 kg/m²; HbA1c ≤12%; total daily insulin dose <1.4 u/kg; current treatment with any basal-bolus insulin regimen or biphasic insulin for ≥ months	Proliferative retinopathy requiring acute treatment, impaired renal or hepatic function, severe cardiac problems, uncontrolled hypertension; recurrent major hypoglycemia; allergy to insulin; history of drug or alcohol dependence; pregnancy and breast-feeding	1
Hermansen *et al.*, 2006[69]	Patients with type 2 diabetes ≥12 months; age≥18 years; BMI ≤35 kg/m²; HbA1c of 7.5% to 10.0%; the definition of inadequate control required at least 4 months' treatment with one or two oral glucose-lowering drugs OGLDs at doses at least half the recommended maximum or highest tolerated; insulin-naïve patients	Patients using thiazolidinediones were excluded due to licensing restrictions; other exclusion criteria included secondary diabetes, maturity-onset diabetes of the young, proliferative retinopathy/maculopathy requiring treatment, hypoglycemia unawareness or recurrent major hypoglycemia, use of drugs likely to affect glycemia, impaired hepatic (alanine aminotransferase more than twice the upper local reference limit) or renal function (serum creatinine ≥150 µmol/L [1.7 mg/dl]), significant cardiovascular disease, pregnancy, and breastfeeding	2
Hermansen *et al.*, 2001[43]	Age 15 to 55 years; Caucasian; type 1 DM >2 years; use of basal-bolus treatment with NPH and HI ≥6 months prior to study; BMI ≤27.5 kg/m²; A1c ≤8.7%; glucagon-stimulated C-peptide ≤0.1 nmol/L or fasting C-peptide ≤0.04 nmol/L; NPH dosage <40 IU/day	Proliferative retinopathy; impaired hepatic or renal function; decompensated heart failure; unstable angina pectoris; myocardial infarction within last year; hypertension (≥180/100 mmHg); hypoglycemic unawareness; recurrent major hypoglycemia; allergy to insulin or any compositional component; abuse of alcohol or narcotics; use of systemic corticosteroids, β-blockers, or hormones within last month; pregnancy or lactation or using inadequate contraceptive measures; treatment with other investigational products ≤3 months prior to study; previous use of insulin detemir	1
Hershon *et al.*, 2004[54]	Age 18 to 80 years; A1c≤12.0%; postprandial C-peptide ≤0.5 mmol/L	Hepatic or renal impairment; oral antidiabetic drugs ≤3 months prior to study; pregnancy; night shift work	1
Home *et al.*, 2005[55]	Adult; C-peptide<0.50 nmol/L or <1.50 µg/L when capillary BG≥5.5 mmol/L (100 mg/dL); insulin use ≥1 year prior to study	Not reported	1
Home *et al.*, 2004[41]	Age>18 years; type 1 DM >1 year prior to study; use of basal-	Proliferative retinopathy; recurrent major hypoglycemia;	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
	bolus regimen >2 months prior to study with basal insulin dose <100 units/day; A1c≤12.0%; BMI ≤35 kg/m²	impaired hepatic or renal function; uncontrolled cardiovascular problems; use of medication known to interfere with glucose metabolism; pregnancy or lactation; other significant medical problems	
Kawamura *et al.*, 2005[31]	Age 8 to 21 years; basal-bolus insulin treatment with NPH	Not reported	1
Kolendorf *et al.*, 2004[39]	Basal-bolus treatment ≥4 months prior to study	Not reported	1
Kudva *et al.*, 2005[65]	Age ≥18 years; A1c≤7.8%; fasting C-peptide<200 pmol/L; MDI with glargine or ultralente as basal insulin + rapid-acting insulin	Not reported	1
Massi Benedetti *et al.*, 2003[81]	Diagnosis ≥3 years prior to study; oral antidiabetic drugs alone or combined with 1x daily insulin ≥3 months prior to study	Not reported	2
Meneghini *et al.*, 2005[85]	A1c 8% to 12%; sulfonylurea dosage ≥1/2 maximal dose or metformin 1 to 2.5 g/day for ≥3 months prior to study	Not reported	2
Meneghini *et al.*, 2006[87] Oster *et al.*, 2006[86]	Patients with type 2 DM; inadequately controlled on sulfonylurea or metformin; HbA1c 8% to 12%	Not reported	2
Mianowska *et al.*, 2006[35]	Not reported	Not reported	1
Murphy *et al.*, 2003[36]	Patients with type 1 DM; age between 12 and 20 years; currently in puberty (Tanner stage B2/G2 or higher); duration of diabetes longer than 1 year or C-peptide negative, and already using a basal-bolus insulin regimen	Renal or hepatic impairment; evidence of diabetic complications; unstable metabolic control (defined as HbA1c>12%)	1
Pan *et al.*, 2007[76]	Insulin-naïve Asian patients aged ≥40 and ≤80 years with type 2 DM (classified by WHO criteria); random venous plasma glucose concentration ≥11.1 mmol/L or FPG ≥7.0 mmol/L or 2h plasma glucose concentration ≥11.1 mmol/L 2-h after 75g anhydrous glucose in an oral glucose tolerance test; (part of WHO criteria) poorly controlled on OAD for ≥3 months prior to study entry; BMI 20 to 35 kg/m², HbA1c≥7.5 and ≤10.5%, FBG >120mg/dl (>6.7 mmol/L)	Pregnancy; history of ketoacidosis and likely to require drugs prohibited by the study protocol (non-selective β-blockers, systemic corticosteroids)	2
Pesic *et al.*, 2006[51]	Patients with type 1 DM on long term intensive insulin therapy	Not reported	1
Philis-Tsimikas *et al.*, 2006[70]	Insulin-naive patients with type 2 DM at least for 12 months; age≥18 years; BMI≤40 kg/m²; HbA1c 7.5% to 11%; following at least 3 months treatment with ≥1 OAD	Proliferative retinopathy/maculopathy requiring treatment; hypoglycemia unawareness or recurrent major hypoglycemia; use or anticipated use of ≥1 drug likely to affect BG regulation (e.g., systemic steroids, non-selective β-blockers); OAD treatment that did not adhere to the approved labelling in the respective country; any disease or	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
		conditions that, based on the opinion of the investigator, would make the patient unsuitable for participation (e.g., renal, cardiac or hepatic disease; uncontrolled hypertension; and/or any psychological incapacity or language barrier precluding adequate understanding or co-operation)	
Pieber *et al.*, 2000[52]	Insulin therapy >1 year prior to study	Not reported	1
Pieber *et al.*, 2005[42]	Age≥18 years; BMI≤35 kg/m²; A1c≤12.0%; type 1 DM≥1 year; basal-bolus insulin treatment ≥2 months prior to study; total daily basal insulin requirement ≤100 IU/day	Significant medical disorders; pregnancy or lactation; history of recurrent major hypoglycemia; known hypoglycemic unawareness; use of concomitant medications likely to interfere with glucose metabolism	1
Pieber *et al.*, 2007[48]	Patients with type 1 DM for≥ 1 year; age≥18 years; BMI≥35 kg/m²; HbA1c 7.5 to 12.0%; prior to the trial, patients were treated with either intermediate-/long-acting insulin injections, b.i.d., and 3 to 4 pre-meal human soluble insulin injections for 6 months; or biphasic insulin morning and evening and pre-lunch human soluble insulin injection for ≥6 months	Patients with significant medical problems, including proliferative retinopathy or maculopathy requiring acute treatment, recurrent severe hypoglycemia, hypoglycemia unawareness, impaired hepatic or renal function or uncontrolled cardiovascular problems; pregnant or breastfeeding women	1
Porcellati *et al.*, 2004[61]	Fasting C-peptide ≤0.15 nmol/L; MDI with lispro+NPH≥2 years	Microangiopathic complications; autonomic neuropathy	1
Raskin *et al.*, 2006[72]	Patients with type 2 DM	Not reported	2
Raskin *et al.*, 2000[59]	Age 18 to 80 years; use of NPH+insulin lispro ≥3 months prior to study; C-peptide≤0.5 mmol/L; FBG≥5.5 mmol/L; A1c≤12.0%	Hepatic or renal impairment; pregnancy or lactation; use of any glucose-lowering drug other than insulin ≤4 weeks prior to study	1
Raslova *et al.*, 2004[71]	Age≥18 years old; BMI≤40 kg/m2 and HbA1c<12.0%; patients with a history of type 2 DM ≥1 year; been treated on a regimen with basal insulin [biphasic insulin, insulin+oral hypoglycemic drugs (OHD), or basal+mealtime insulin] once or twice daily for at least 3 months, with a total daily insulin requirement of <1.4 IU/kg	Individuals with significant disorders, hypoglycemic unawareness or recurrent major hypoglycemia; pregnant or breastfeeding women; with allergy to insulin	
Ratner *et al.*, 2000[56]	Age 18 to 80 years; postprandial C-peptide ≤0.5 nmol/L for ≥1 year prior to study; A1c≤12.0%	Use of antidiabetic drugs other than insulin ≤1 month prior to study; pregnancy; impaired hepatic or renal function; nightshift work	1
Riddle *et al.*, 2003[82]	Age 30 to 70 years; diabetes ≥2 years prior to study; use of oral antidiabetic drugs ≥3 months prior to study; BMI 26 to 40 kg/m²; A1c 7.5% to 10.0%; FBG≥7.8 mmol/L	Prior use of insulin except for gestational diabetes or <1 week; current use of alpha-glucosidase inhibitor or rapid-acting insulin secretagogue; use of other agents affecting glycemic control; history of ketoacidosis or inability to recognize hypoglycemia; increased liver enzymes or serum creatinine; history of drug or alcohol abuse; positive anti-	2

Study	Inclusion Criteria	Exclusion Criteria	DM Type
		GAD antibody; fasting C-peptide ≤0.25 pmol/mL	
Robertson *et al.*, 2007[30]	Children and adolescents with type 1 DM; between 6 and 17 years, treated with insulin for at least 12 months (total daily dose ≤2.0 U/kg), and with HbA1c≤12.0%	Not reported	1
Rosenstock *et al.*, 2000[57]	Age 18 to 70 years; BMI 18 to 28 kg/m²; A1c≤10.0%; postprandial C-peptide <0.2 pmol/mL; basal-bolus daily insulin ≥2 months prior to study	Not reported	1
Rosenstock *et al.*, 2001[74]	Age 40 to 80 years; insulin treatment ≥3 months prior to study; A1c 7.0 to 12.0%; BMI<40 kg/m²	Hepatic or renal impairment; oral antidiabetic drugs ≤3 months prior to study	2
Rosenstock *et al.*, 2006[88]	Age>18 years; A1c≥7.5%; BMI>25 kg/m²; continuous oral use of ≥50% of the maximally labelled dose of a sulfonylurea and ≥1,000 mg metformin ≥3 months prior to study	Stroke; myocardial infarction; angina pectoris; coronary artery bypass graft; percutaneous transluminal coronary angioplasty within previous 12 months; history of congestive heart failure; use of nonselective β-blockers; hypoglycemia unawareness; impaired renal or hepatic function; substance or alcohol abuse; malignancy and planned radiological examinations requiring administration of contrasting agents	2
Rosenstock *et al.*, 2006[73]	Patients with type 2 DM; insulin-naïve men and women; age ≥18 years; HbA1c 7.5% to 10.0%; BMI ≤40.0 kg/m²; inadequately controlled on one or two OADs	Not reported	2
Rossetti *et al.*, 2003[62]	Fasting C-peptide ≤0.15 nmol/L; MDI	Not reported	1
Russell-Jones *et al.*, 2004[45]	Age≥18 years; type 1 DM ≥1 year; use of basal-bolus insulin ≥2 months prior to study	A1c>12.0%; total basal insulin dose >100 IU/d; pregnancy or lactation; proliferative retinopathy; impaired hepatic or renal function; recurrent major hypoglycemia; uncontrolled hypertension; severe cardiac problem; other significant medical problems; concomitant use of medications known to interfere with glucose metabolism	1
Schober *et al.*, 2002[32]	Age 5 to 16 years; insulin use ≥1 year prior to study with ≥3 daily injections of insulin; A1c≤12.0%	Treatment with blood glucose-lowering drugs other than insulin ≤1 month prior to study; post-menarcheal, sexually active girls not using adequate contraception; treatment with hyperglycemic drugs; treatment with investigational drugs ≤2 months prior to study; impaired hepatic or renal function	1
Standl *et al.*, 2004[46]	Age 18 to 74 years; type 1 DM ≥12 months; twice daily basal insulin and meal-related bolus insulin ≥2 months prior to study; BMI<35.0 kg/m²; A1c≤12.0%; total basal insulin dosage ≤100 IU/day	Proliferative retinopathy; impaired hepatic or renal function; severe cardiac disease; uncontrolled hypertension; recurrent major hypoglycemia; insulin allergy; pregnancy, or lactation	1
Tajima *et al.*, 2006	Insulin naïve adults with type 2 DM ≥ 1 year, BMI < 30 kg/m²,	Not reported	2

Study	Inclusion Criteria	Exclusion Criteria	DM Type
	A1C ≥ 7.5% and < 10%, taking at least one OAD		
Triplitt *et al.*, 2006[89]	Patients with type 2 DM; poorly controlled on metformin plus sulfonylurea; age 30 to 70 years; stable body weight (±3 lbs) for at least 3 months before the study; HbA1c≥9.0%. Type 2 DM patients who were taking stable, maximally effective doses of a sulfonylurea (≥20 mg/day of glyburide or glipizide) and metformin (≥2,000 mg/day); in good general health, without evidence of cardiac, hepatic, renal, or other chronic diseases; no subjects participated in any heavy exercise; no subject was taking any medication known to affect glucose metabolism	History of using insulin or a thiazolidinedione	2
Vague *et al.*, 2003[44]	Type 1 DM ≥1 year; use of basal-bolus insulin ≥2 months prior to study; A1c≤12.0%; BMI≤35.0 kg/m^2; total basal insulin dosage ≤100 IU/day	Proliferative retinopathy; impaired hepatic or renal function; severe cardiac problems; uncontrolled hypertension; recurrent major hypoglycemia; allergy to insulin; pregnancy or lactation	1
Vinik and Zhang, 2007[90]	Patients with type 2 DM; uncontrolled with sulfonylurea plus metformin; HbA1c≥7.5 and ≥11%; BMI>25 kg/m^2; 18 to 80 years old; insulin-naïve patients; continuous oral hypoglycemic treatment using stable daily dose of ≥50% of the maximally labelled dose of a sulfonylurea and at least 1,000 mg metformin for ≥3 months before the screening	The data was extracted from its companion publication (RM3497). The subject was excluded in any of the following criteria were present: patient had stroke, myocardial infarction, angina pectoris, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within previous 12 months; history of congestive heart failure; treatment with non-selective β-blockers; hypoglycemia unawareness; impaired renal function; active liver disease; substance or alcohol abuse; malignancy and planned radiological examinations requiring administration of contrasting agents.	2
Wang *et al.*, 2007 [79]	Patients with history of type 2 DM for 6 months; age 30 to 70 years; BG was not well controlled (FBG≥7.0 mmol/L and <13.0 mmol/L) with enough dose of sulphanylureas equal to 7.5 mg/day glibenclamide or combination treatment with other OAD for >3 months; no obvious renal, liver, or heart diseases All patients were treated with extended-release glipizide (Glucotrol XL) 5 mg/day before breakfast for 2 weeks in washout period and CGMS were examined for 3 days during the 2nd week	Obvious renal, liver, heart diseases	2
White *et al.*, 2006[34]	Adolescents with type 1 DM	Not reported	1
Witthaus *et al.*, 2001[58]	Insulin use ≥1 year prior to study	Not reported	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Yki-Järvinen *et al.*, 2000[84]	Age 40 to 80 years; BMI<40 kg/m²; A1c 7.5% to 12.0%; diabetes diagnosed ≥3 years prior to study; oral antidiabetic therapy with sulfonylurea alone or + acarbose or metformin or with metformin alone ≥1 year prior to study; negative history of ketoacidosis	Women not using contraceptives; pregnancy; use of regular insulin ≤4 weeks prior to study; diabetic retinopathy with surgery ≤3 months prior to study or requiring treatment for this within 3 months of entering study; night shift work; cardiovascular, hepatic (ALT or AST >2x upper limit), neurologic, endocrine, or other major systemic diseases; history of drug or alcohol abuse; impaired renal function (serum creatinine >133 µmol/L)	2
Yki-Järvinen *et al.*, 2006[80]	Age 35 to 75 years; use of a stable dose of sulfonylurea and metformin or metformin alone ≥3 months prior to study; BMI 20 to 40 kg/m²; A1c≥8.0%; mean FPG≥7 mmol/L; fasting C-peptide ≥0.33 nmol/L	Use of other oral antihyperglycemic agents; prior use of insulin; positive GAD antibodies; history of ketoacidosis; non-compliance with regard to daily measurement of FPG; abnormal safety laboratory tests including liver enzymes, serum aspartate aminotransferase, serum alkaline phosphatase, >3 times the upper limit of normal; serum creatinine ≥120 µmol/L; history of alcohol or drug abuse; night shift work; pregnancy; use of investigational drug ≤2 months prior to study; use of drugs likely to interfere with glucose control; clinically relevant major systemic disease other than diabetes that would make implementation of study protocol or interpretation of result difficult; mental health condition rendering the subject unable to understand the nature, scope, and possible consequences of the study; diabetic retinopathy requiring surgical treatment during study or <3 months prior to study	2
HOE 901/2004 Study Investigators, 2003[83]	Age 40 to 80 years; oral treatment ≥3 months; A1c≥7.0%	Prior insulin treatment	2

A1c=glycosylated hemoglobin; ALT=alanine aminotransferase; anti-GAD=anti-glutamic acid decarboxylase antibodies; AST=aspartate aminotransferase; BG=blood glucose; b.i.d.=twice a day; BMI=body mass index; CGMS=continuous glucose monitoring system; DM=diabetes mellitus; FBG=fasting blood glucose; HbA1c=glycosylated hemoglobin; HI=human insulin; IGlar=insulin glargine; MDI=multiple daily regimen; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; OHD=oral hypoglycemic drugs; RCTs=randomized controlled trials; WHO=World Health Organization.

APPENDIX 9: RESULTS OF QUALITY ASSESSMENT OF INCLUDED RCTS

Study	Score on Jadad Scale for			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat	Number of Patients	Dropouts N (%)
	Randomization	Double Blinding	Withdrawals and Dropouts						
Type 1 DM									
Ashwell *et al.*, 2006[64]	2	0	1	3	Adequate	No	No	54	3 (5.6)
De Leeuw *et al.*, 2005[40]	1	0	1	2	Unclear	NR	Yes	315	8 (2.53)
Fulcher *et al.*, 2005[60]	1	0	1	2	Unclear	Partially	Yes	125	18 (14.4)
Hermansen *et al.*, 2001[43]	1	0	1	2	Unclear	Partially	No	59	3 (5.1)
Hermansen *et al.*, 2004[49]	1	0	1	2	Unclear	No	Yes	595	23 (3.87)
Hershon *et al.*, 2004[54]	1	0	1	2	Unclear	NR	Yes	394	40 (10.2)
Home *et al.*, 2005[55]	2	0	1	3	Unclear	NR	Yes	585	37 (6.32)
Home *et al.*, 2004[41]	2	0	1	3	Unclear	NR	Yes	408	17(4.2)
Kolendorf *et al.*, 2006[39]	1	0	1	2	Unclear	No	No	131	7 (5.34)
Kudva *et al.*, 2005[65]	2	0	1	3	Adequate	Partially	No	24	2 (8.33)
Murphy *et al.*, 2003[36]	1	0	1	2	Unclear	No	No	26	1 (3.85)
Pieber *et al.*, 2000[52]	1	0	1	2	Unclear	NR	NR	333	0 (0)
Pieber *et al.*, 2005[42]	2	0	1	3	Unclear	NR	Yes	400	21 (5.25)
Pieber *et al.*, 2007[48]	1	0	1	2	Adequate	No	No	320	29(9.0)
Porcellati *et al.*, 2004[61]	2	0	0	2	Adequate	NR	Yes	121	0 (0)
Raskin *et al.*, 2000[59]	2	0	1	3	Unclear	NR	NR	619	31 (5)
Ratner *et al.*, 2000[56]	1	0	1	2	Unclear	NR	Yes	534	53 (9.93)
Robertson *et al.*, 2007[30]	1	0	1	2	Adequate	No	Yes	347	12 (3.46)
Rosenstock *et al.*, 2000[57]	1	0	1	2	Unclear	NR	Yes	256	2 (0.78)
Rossetti *et al.*, 2003[62]	1	0	0	1	Unclear	NR	NR	51	NR
Russell-Jones *et al.*, 2004[45]	2	0	1	3	Unclear	NR	Yes	749	49 (6.54)
Schober *et al.*, 2002[32]	1	0	0	1	Unclear	NR	Yes	361	12 (3.32)
Standl *et al.*, 2004[46]	1	0	1	2	Unclear	NR	Yes	289	37 (12.8)
Vague *et al.*, 2003[44]	2	0	1	3	Unclear	NR	Yes	447	22 (4.92)
Witthaus *et al.*, 2001[58]	2	0	0	2	Unclear	NR	Yes	517	NR

Study	Score on Jadad Scale for			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat	Number of Patients	Dropouts N (%)
	Randomization	Double Blinding	Withdrawals and Dropouts						
Type 2 DM									
Eliaschewitz *et al.*, 2006[77]	1	0	1	2	Unclear	No	Yes	481	19 (3.95)
Fonseca *et al.*, 2004[75]	1	0	1	2	Unclear	NR	NR	100	7 (7)
Fritsche *et al.*, 2003[78]	2	0	1	3	Unclear	NR	Yes	695	55 (7.91)
Haak *et al.*, 2005[68]	1	0	1	2	Unclear	NR	Yes	505	34 (6.73)
Hermansen *et al.*, 2006[69]	1	0	1	2	Adequate	No	Yes	475	24 (5.05)
Massi Benedetti *et al.*, 2003[81]	2	0	1	3	Unclear	NR	Yes	570	46 (8.07)
Pan *et al.*, 2007[76]	1	0	1	2	Unclear	No	No	444	49 (11.06)
Philis-Tsimikas *et al.*, 2006[70]	1	0	1	2	Adequate	No	Yes	498	51 (10.24)
Raslova *et al.*, 2004[71]	1	0	1	2	Unclear	No	Yes	394	16 (4.06%)
Riddle *et al.*, 2003[82]	2	0	1	3	Unclear	NR	Yes	756	65 (8.6%)
Rosenstock *et al.*, 2001[74]	1	0	1	2	Unclear	NR	Yes	518	49 (9.46%)
Rosenstock *et al.*, 2006[88]	1	0	1	2	Unclear	NR	Yes	216	17 (7.87%)
Triplitt *et al.*, 2006 [89]	1	0	0	1	Unclear	No	Yes	20	NR
Vinik and Zhang, 2007[90]	1	0	0	1	Unclear	No	No	216	29 (13.43)
Wang *et al.*, 2007[79]	1	0	0	1	Unclear	No	Yes	24	NR
Yki-Järvinen *et al.*, 2000[84]	1	0	0	1	Unclear	NR	Yes	426	NR
Yki-Järvinen *et al.*, 2006[80]	2	0	1	3	Unclear	NR	Yes	110	3 (2.73)
Yokoyama *et al.*, 2006[140]	1	0	0	1	Unclear	No	NR	62	NR
HOE 901/2004 Study Investigators Group, 2003[83]	2	0	1	3	Unclear	NR	Yes	204	2 (0.98)

NR=not reported; RCTs=randomized controlled trials.

APPENDIX 10A: STUDY-LEVEL HYPOGLYCEMIA DATA FOR RCTS OF TYPE 1 DM

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
Ashwell *et al.*, 2006[64]	IGlar+ILis	Severe	NR	14	Pts	NR	NR	Nocturnal: p=0.058 for # of pts and p<0.001 for episodes/ month, NS for others	Overall: anytime symptomatic (appropriate symptoms confirmed by self-monitored blood glucose concentration <2.8 mmol/L and self-treated) Severe: requiring third-party assistance Nocturnal: from bedtime until pre-breakfast BG measurement
		Nocturnal		38 (72%)	Pts (%)				
				140	Episodes				
				0.66±0.02†	Episodes/ month				
		Symptomatic		1,277	Episodes				
		Non-nocturnal		1,137					
	NPH+HI	Severe	NR	16	Pts	NR	NR		
		Nocturnal		43 (83%);	Pts (%)				
				268	Episodes				
				1.18±0.02†	Episodes/ month				
		Symptomatic		1,327	Episodes				
		Non-nocturnal		1,059					
Bolli *et al.*, 2006[63] [Abstract]	IGlar+ILis	Severe	NR	0.15	Events/pt-week (over the last month of treatment)	NR	NR	NS	Severe: confirmed serious hypoglycemia events: blood glucose <2.3 mmol/L
	NPH+ILis	Severe	NR	0.17	Events/pt-week	NR	NR		
Chase *et al.*, 2006[33] [Abstract]	IGlar+ILis	Severe	NR	9	pts	NR	NR	NR	Other: confirmed clinical relevant hypoglycemia <36 mg/dl (2 mmol/L)
		Confirmed clinically relevant		28					
	NPH (or lente)+ILis	Severe	NR	4	pts	NR	NR		
		Confirmed cinically relevant		30					
Davies *et al.*,	IGlar+IAsp	Overall	NR	80.7	%	NR	NR	risk ratio 1.21	NR

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Major		1	Events				
		Minor		NR					
	NPH+IAsp	Overall	NR	77.2	%	NR	NR		
		Major		1	Events				
		Minor		NR					
De Leeuw *et al.*, 2005[40]	IDet+IAsp	Overall	NR	207 (96)	Pts (%)	NR	NR	p=0.016 for nocturnal	Overall (Minor): BG <2.8 mmol/L; symptoms only, if not confirmed with BG measurement Severe (Major): episode with severe central nervous system symptoms, requiring assistance and either BG<2.8 mmol/L or symptom reversal achieved with food, glucose, or glucagon
		Minor		NSD					
		Major		30 (14)					
		Nocturnal		180 (1378)					
					Pts (episodes)				
	NPH+IAsp	Overall	NR	95 (96)	Pts (%)	NR			
		Minor		NSD					
		Major		21 (21)					
		Nocturnal		87 (926)	Pts (episodes)				
Fulcher *et al.*, 2005[60]	IGlar+ILis	Overall	NR	62 (100)	Pts (%)	NR	NR	NS for overall, p=0.02 for mild nocturnal (IGlar>NPH), p=0.004 for moderate nocturnal, p=0.02 for severe nocturnal	Symptomatic: symptoms consistent with hypoglycemia that was mild (2.8-3.6 mmol/L), moderate (<2.8 mmol/L), or severe Severe: requiring assistance, with BG<2.8 mmol/L or prompt recovery following oral carbohydrate, i.v. glucose, or s.c. glucagon Nocturnal: between evening insulin injection and morning insulin dose
		Nocturnal		50 (81)					
		Mild		10.78	Episodes/100 pt-days				
		Moderate		6.82					
		Severe		0.87					
		Nocturnal		4.49					
		Nocturnal: Mild		2.36					
		Nocturnal: Moderate		1.71					
		Nocturnal: Severe		0.22					
	NPH+ILis	Overall	NR	59 (93.7)	Pts (%)	NR	NR		
		Nocturnal		54 (86)					
		Mild		10.34	Episodes/100				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Moderate		7.31					
		Severe		0.99					
		Nocturnal		4.73					
		Nocturnal: Mild		1.96					
		Nocturnal: Moderate		2.21					
		Nocturnal: Severe		0.37					
Garg *et al.*, 1998[53] [Abstract]	IGlar+HI	NR	NR	NR	NR	NR	NR	NR	NR
	NPH+HI	NR	NR	NR	NR	NR	NR		
Hermansen *et al.*, 2004[49]	IDet+IAsp	Overall	NR	219 (75)	Pts (%)	NR	NR	Overall: RR (95%CI) 0.79 (0.63, 0.98) and p=0.036 All Nocturnal: 0.45 (0.35, 0.58) and p<0.001 Major Nocturnal: RR 0.17 (0.04, 0.63) and p=0.008 Minor Nocturnal: RR 0.46 (0.35,0.61) and p<0.001 Symptom only Nocturnal: RR 0.46 (0.30,0.71) and p<0.001 Major: RR 0.89 (0.35 to 2.22) and p=0.796	Nocturnal: occurs between 23:00 and 06:00 Major: requiring assistance to treat Minor: plasma glucose<3.1 mmol/L Symptoms only: no plasma glucose measurement or plasma glucose≥3.1 mmol/L
				2,497	Episodes				
				37.1	Episodes/ pt-yr				
		Nocturnal: All		113 (38.7)	Pts (%)				
				271	Episodes				
				4	Episodes/ pt-yr				
		Nocturnal: Major		3 (1.0)	Pts (%)				
				4	Episodes				
		Minor		98 (33.6)	Pts (%)				
				196	Episodes				
		Symptoms only		41 (14.0)	Pts (%)				
				71	Episodes				
		Major		19(6.5)	Pts (%)				
				40	Episodes				
		Minor		202 (69.2)	Pts (%)				
				1,780	Episodes				
		Symptom only		121 (41.4)	Pts (%)				
				677	Episodes				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
	NPH+HI	Overall	NR	238 (82.9)	Pts (%)	NR	NR		
				3192	Episodes				
				48.2	Episodes/pt-yr				
		Nocturnal: All		173 (60.3)	Pts (%)				
				608	Episodes				
				9.2	episodes/pt-yr				
		Major		12 (4.2)	Pts (%)				
				24	Episodes				
		Minor		142 (49.5)	Pts (%)				
				427	Episodes				
		Symptoms only		72 (25.1)	Pts (%)				
				157	Episodes				
		Major		18(6.3)	Pts (%)				
				45	Episodes				
		Minor		222 (77.4)	Pts (%)				
				2282	Episodes				
		Symptom only		148 (51.6)	Pts (%)				
				865	Episodes				
Hermansen *et al.*, 2001[43]	IDet+HI	Overall	NR	54 (94.7)	Pts (%)	NR	NR	NS for all	Overall (Minor): BG<3.0 mmol/L, dealt with by patient Severe (Major): requiring third-party help or i.v. glucose, or glucagon. Nocturnal: NR
		Minor		53 (93)					
		Major		4 (7)					
	NPH+HI	Overall	NR	51 (91.1)	Pts (%)	NR	NR		
		Minor		51 (91.1)					
		Major		7 (12.5)					
Hershon *et al.*, 2004[54]	IGlar+HI	BG<2.8 mmol/L	NR	143 (73.3)	Pts (%)	NR	NR	p=0.021 for BG<2.8, p=0.033	Overall: symptoms of hypoglycemia
		BG<2.0 mmol/L		71 (36.6)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Severe		5 (2.6)					
		Nocturnal		139 (71.2)					
	NPH+HI	BG<2.8 mmol/L	NR	163 (81.7)	Pts (%)	NR	NR		
		BG<2.0 mmol/L		92 (46.2)					
		Severe		10 (5.1)					
		Nocturnal		138 (69.5)					
Home *et al.*, 2005[55]	IGlar+HI	Symptom	NR	260 (89.0)	Pts (%)	NR	NR	NS for all	Symptomatic: symptoms of hypoglycemia confirmed by BG<2.8 mmol/L (50 mg/dL) Asymptomatic: BG<2.8 mmol/L (50 mg/dL) without symptoms Severe: requiring assistance, with either BG<2.8 mmol/L (50 mg/dL) or prompt recovery after administration of oral carbohydrate, i.v. glucose, or glucagon Nocturnal: during sleep, between bedtime and rising in the morning or before the morning pre-breakfast self-BG measurement and morning insulin injection
		Severe		31 (10.6)					
		Nocturnal		178 (61.0)					
	NPH+HI	Symptom	NR	248 (84.6)	Pts (%)	NR	NR		
		Severe		44 (15.0)					
		Nocturnal		179 (61.1)					
Home *et al.*,	$IDet_{12h}$+IAsp	Minor	NR	114 (84)	Pts (%)	NR	NR	$IDet_{12h}$+IAsp vs.	Minor: BG<2.8 mmol/L

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Major		6 (4)					
		Nocturnal		59 (44)					
	$IDet_{m+b}$+IAsp	Minor	NR	114 (83)	Pts (%)	NR	NR		
		Major		11 (8)					
		Nocturnal		47 (34)					
	NPH_{m+b}+IAsp	Minor	NR	107 (84)	Pts (%)	NR	NR		
		Major		10 (8)					
		Nocturnal		64 (50)					
Kawamura *et al.*, 2005[31] [Abstract]	IGlar+IAsp	Severe	NR	NR	Frequency	NR	NR	No difference	NR
	NPH+IAsp	Severe	NR	NR	Frequency	NR	NR		
Kolendorf *et al.*, 2006[39]	IDet+IAsp	Overall	NR	116 (92.8)	Pts (%)	NR	NR	Overall: RR 0.82 (95% CIL: 0.73, 0.92) and p=0.001 Severe: NS Nocturnal: RR 0.5 (0.38, 0.65) and p<0.0001 All confirmed: RR 0.84 (0.72, 0.97) and p=0.0190 All symptomatic: RR 0.81(0.68, 0.95) and p=0.012	Overall: All SMPG values <3.1 mmol/L or recorded signs and symptoms of hypoglycemia during the last 10 weeks of each treatment period and recorded in the subject diaries (They were included in the analysis of hypoglycemia.) Severe: if help from others is required Nocturnal: episodes happened between 23:00 and 6:00
				1281	Episodes				
				53.3	Episodes/pt/ year				
		Severe		19	Episodes				
		Severe at night		4					
		Hypoglycemic coma		0					
		Nocturnal		58 (46.4)	Pts (%)				
				145	Episodes				
				6	Episodes/pt/ year				
		Diurnal		108 (86.4)	Pts (%)				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
				1,120	Episodes				
				46.6	Episodes/pt/ year				
		All confirmed		103(82.4)	Pts (%)				
				699	Episodes				
				29.1	Episodes/pt/ year				
		All symptomatic		78 (62.4)	Pts (%)				
				560	Episodes				
				23.3	Episodes/pt/ year				
	NPH+IAsp	Overall	NR	118 (92.2)	Pts (%)	NR	NR		
				1,592	Episodes				
				64.7	Episodes/pt/ year				
		Severe		33	Episodes				
		Severe at night		11					
		Hypoglycemic coma		2					
		Nocturnal		81 (63.3)	Pts (%)				
				295	Episodes				
				12	Episodes/pt/ year				
		Diurnal		112 (87.5)	Pts (%)				
				1,265	Episodes				
				51.5	Episodes/pt/ year				
		All confirmed		108 (84.4)	Pts (%)				
				865	Episodes				
				35.2	Episodes/pt/ year				
		All symptomatic		84 (65.6)	Pts (%)				
				693	Episodes				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
				28.2	Episodes/pt/ year				
Kudva *et al.*, 2005[65]	IGlar+IAsp	Overall	NR	24.5±2.99†	Episodes/pt/ 32 weeks	NR	NR	p=0.05 for overall, p=0.001 for day, p=0.07 for nocturnal	Overall: symptoms of hypoglycemia with BG<60 mg/dL Serious: requiring assistance with BG<50 mg/dL
		Day		19.9±2.48†					
		Nocturnal		4.6±1.18†					
		Severe		0.1±0.07†					
	UL+IAsp	Overall	NR	31.3±4.04†	Episodes/pt/ 32 weeks	NR	NR		
		Day		28.6±3.89†					
		Nocturnal		2.7±0.59†					
		Severe		0.1±0.07†					
Mianowska *et al.*, 2006[35] [Abstract]	IGlar+(ILis or HI)	Severe	NR	0	Episodes	NR	NR	NS	NR
	NPH+(ILis or HI)	Severe	NR	0	Episodes	NR	NR		
Murphy *et al.*, 2003[36]	IGlar+ILis	Severe	NR	0	Episodes	NR	NR	NR for severe, p=0.17 for # of episodes, p=0.1 for # of pts (paired analysis) but p<0.05	Severe: requiring assistance of another person and associated with a blood glucose level <2.8 mmol/L or with prompt recovery after oral
				8 (32)	Pts (%)				
		Nocturnal		29	Episodes				
		Symptomatic		294					
	NPH+HI	Severe	NR	0	Episodes	NR	NR		
				14 (56)	Pts (%)				
		Nocturnal		41	Episodes				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Symptomatic		250					
Pesic *et al.*, 2006[51] [Abstract]	IGlar+IAsp	Mild	NR	6.7±1.0*	Episodes/pts-month	NR	NR	IGlar+IAsp vs. NPH (q.d.)+IAsp, p<0.05, IGlar+IAsp vs. NPH (b.i.d.)+IAsp, p<0.05	NR
	NPH (q.d.)+IAsp	Mild	NR	8.2±2.4*	Episodes/pts-month	NR	NR		
	NPH (b.i.d.)+IAsp	Mild	NR	9.5±1.7*	Episodes/pts-month	NR	NR		
Pieber *et al.*, 2007[48]	IDet+IAsp	Overall	NR	126 (79.7)	Pts (%)	NR	NR	RR 0.96 (95%CI: 0.68, 1.35) and p=0.811 for	Severe: if help from a third party was required Nocturnal: episodes
				1,952	Episodes				
		Nocturnal		77 (48.7)	Pts (%)				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
				254	Episodes				
		Severe		3 (1.9)	Pts (%)				
				4	Episodes				
		Confirmed		120 (75.9)	Pts (%)				
				1253	Episodes				
		Symptomatic		69 (47.3)	Pts (%)				
				695	Episodes				
	IGlar+IAsp	Overall	NR	118 (76.6)	Pts (%)	NR	NR		
				1923	Episodes				
		Nocturnal		81 (52.6)	Pts (%)				
				381	Episodes				
		Severe		12 (7.8)	Pts (%)				
				15	Episodes				
		Confirmed		108 (70.1)	Pts (%)				
				1330	Episodes				
		Symptomatic		74 (48.1)	Pts (%)				
				578	Episodes				
Pieber *et al.*, 2005[42]	$IDet_{m+d}$+IAsp	Overall	NR	100 (72)	Pts (%)	NR	NR	$IDet_{m+d}$+IAsp vs. $IDet_{m+b}$+IAsp vs. NPH_{m+b}+IAsp, NS	Nocturnal: between 23:00 and 06:00
		Nocturnal		60 (43)					
		Major		5 (4)					
		Minor		88 (63)					
		Symptom		69 (50)					
	$IDet_{m+b}$+IAsp	Overall	NR	92 (70)	Pts (%)	NR	NR		
		Nocturnal		51 (39)					
		Major		5 (4)					
		Minor		78 (59)					
		Symptom		64 (48)					
	NPH_{m+b}+IAsp	Overall	NR	100 (78)	Pts (%)	NR	NR		
		Nocturnal		60 (47)					
		Major		4 (3)					
		Minor		89 (69)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Symptom		68 (53)					
Peiber *et al.*, 2000[52]	IGlar [30]+HI	Symptom	NR	87 (79)	Pts (%)	NR	NR	IGlar [30]+HI, IGlar [80]+HI vs. NPH+HI, p=0.0037 for nocturnal, NS for symptom and severe	Overall: BG<2.8 mmol/L Severe: requiring assistance
		Nocturnal		39 (36)					
		Severe		7 (6)					
	IGlar [80]+HI	Symptom	NR	82 (73)	Pts (%)	NR	NR		
		Nocturnal		41 (36)					
		Severe		5 (4)					
	NPH+HI	Symptom	NR	87 (79)	Pts (%)	NR	NR		
		Nocturnal		61 (56)					
		Severe		5 (5)					
Porcellati *et al.*, 2004[61]	IGlar (dinner time)+ILis	Mild	NR	7.2±0.5	Episodes/pt/ 30 days	NR	NR	p<0.05 for mild, day and nocturnal	Overall: BG<4.0 mmol/L (72 mg/dL) Severe: requiring assistance Nocturnal: between 01:00 and 07:30
		Day		6.0±0.6†					
		Nocturnal		1.2±0.2†					
	NPH (4 times/day)+ ILis	Mild	NR	13.2±0.6	Episodes/pt/ 30 days	NR	NR		
		Day		10±0.8†					
		Nocturnal		3.2±0.3†					
Raskin *et al.*, 2000[59]	IGlar+ILis	Overall	NR	281 (90.6)	Pts (%)	NR	NR	NS	Overall (Symptomatic): symptoms of hypoglycemia Severe: requiring assistance, with BG<2.0
		Nocturnal		214 (69.0)					
		Severe		20 (6.5)					
	NPH+ILis	Overall	NR	280 (90.6)	Pts (%)	NR	NR		
		Nocturnal		195 (63.1)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Severe		16 (5.2)					
Ratner *et al.*, 2000[56]	IGlar+HI	Overall	NR	105 (39.9)	Pts (%)	NR	NR	I vs. II, p<0.05 for overall and nocturnal	Overall: symptoms or BG<2.0 mmol/L (36 mg/dL) Severe: requiring assistance Nocturnal: occurring while asleep after the bedtime insulin dose and before the morning BG measurement
		Nocturnal		48 (18.2)					
		Severe		5 (1.9)					
	NPH+HI	Overall	NR	133 (49.2)	Pts (%)	NR	NR		
		Nocturnal		73 (27.1)					
		Severe		15 (5.6)					
Robertson *et al.*, 2007[30]	IDet+IAsp	Overall	NR	223 (96.1)	Pts (%)	NR	NR	RR 0.89 (95%CI: 0.69, 1.14) and p=0.351 for overall, RR 0.91 (0.42, 1.95) and p=0.799 for severe, RR 0.74 (0.55, 0.99) and p=0.041 for nocturnal, RR 0.86 (0.67, 1.12) and p=0.275 for confirmed, RR	Severe: episodes requiring assistance from another person due to severe central nervous system dysfunction; based on the definition used by the DCCT (Diabetes Control and Complications Trials) Nocturnal: 22:00 (included) to 07:00 (excluded)
				9059	Episodes				
		Severe		37 (15.9)	Pts (%)				
				104	Episodes				
		Nocturnal		174 (75.0)	Pts (%)				
				1192	Episodes				
		Confirmed		216 (93.1)	Pts (%)				
				3670	Episodes				
		Symptomatic		218 (94.0)	Pts (%)				
				5,283	Episodes				
	NPH+IAsp	Overall	NR	113 (98.3)	Pts (%)	NR	NR		
				5,021	Episodes				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Severe		23 (20.0)	Pts (%)				
				55	Episodes				
		Nocturnal		101 (87.8)	Pts (%)				
				769	Episodes				
		Confirmed		110 (95.7)	Pts (%)				
				2,128	Episodes				
		Symptomatic		107 (93.0)	Pts (%)				
				2,835	Episodes				
Rosenstock *et al.*, 2000[57]	IGlar [30]+HI	Overall	NR	80 (97.6)	Pts (%)	NR	NR	NPH+HI vs. IGlar [30]+HI, or NPH+HI vs. IGlar [80]+HI, p=0.03	Overall: symptoms and/or BG<2.8 mmol/L Severe: symptoms and/or BG<2.8 mmol/L in which routine activities were curtailed or assistance was required, or the prompt recovery of patient after administration of oral carbohydrate, i.v. glucose, or glucagon administration Nocturnal: between bedtime basal insulin and BG measurement in the morning
	IGlar [80]+HI	Overall	NR	86 (100)	Pts (%)	NR			
	NPH+HI	Overall	NR	82 (93.2)	Pts (%)	NR	NR		
Rossetti *et al.*, 2003[62]	IGlar (dinnertime)+ ILis	Overall	12.8±0.2†	8.1±0.8†	Episodes/pt/ 30 days	NR	p<0.04 (for mild hyper-glycemia)	IGlar (dinnertime)+ ILis vs. IGlar (bedtime)+ILis, NS IGlar (dinnertime) +ILis and IGlar (bedtime)+ILis	Overall: BG<4.0 mmol/L Severe: requiring assistance Nocturnal: NR
		Nocturnal	NR	1.7±0.2†		NR			
	IGlar (bedtime)+ ILis	Overall	13.6±0.2†	7.7±0.9†	Episodes/pt/ 30 days	NR	p<0.04 (for mild hyper-glycemia)		
		Nocturnal	NR	2.0±0.19†		NR			
	NPH (4	Overall	13.9±0.1†	12.2±1.3†	Episodes/pt/	NR	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Nocturnal	NR	3.6±0.4[†]					
Russell-Jones *et al.*, 2004[45]	IDet+HI	Overall	NR	448 (93.3)	Pts (%)	NR	NR	p=0.003 for nocturnal	Overall (Minor): BG<2.8 mmol/L (50 mg/dL); Symptoms only if not confirmed by BG measurement Severe: requiring assistance Nocturnal: between 23:00 and 06:00
		Major		31 (6.5)					
		Minor		414 (86.3)					
		Nocturnal		339 (70.6)					
	NPH+HI	Overall	NR	229 (92.7)	Pts (%)	NR	NR		
		Major		22 (8.9)					
		Minor		207 (83.8)					
		Nocturnal		180 (72.9)					
Schober *et al.*, 2002[32]	IGlar+HI	Overall	NR	138 (79.3)	Pts (%)	NR	NR	NS	Overall: BG<2.8 mmol/L Severe: BG<2.8 mmol/L, requiring assistance or experiencing prompt recovery after oral carbohydrate or i.v. glucose, or glucagon administration Nocturnal: NR
		Severe		40 (23.0)					
		Nocturnal		22 (12.6)					
	NPH+HI	Overall	NR	138 (78.9)	Pts (%)	NR	NR		
		Severe		50 (28.6)					
		Nocturnal		31 (17.7)					
Standl *et al.*, 2004[46]	IDet+HI	Overall	NR	135 (2.45)	Pts (Episodes/pt/ 30 days)	NR	NR	p=0.067 for nocturnal	Overall (Minor): BG<2.8 mmol/L; Symptoms only if not confirmed by BG measurement Severe (Major): requiring assistance Nocturnal: NR
		Major		18 (0.02)					
		Minor		121 (1.24)					
		Nocturnal		102 (0.45)					
		Symptom		106 (1.18)					
	NPH+HI	Overall	NR	113 (3.48)	Pts (Episodes/pt/ 30 days)	NR	NR		
		Major		14 (0.01)					
		Minor		106 (1.79)					
		Nocturnal		94 (0.63)					
		Symptom		94 (1.68)					
Vague *et al.*, 2003[44]	IDet+IAsp	Overall	NR	271 (5.18)	Pts (Episodes/pt/	NR	NR	p=0.029 for overall, p=0.011	Overall (Minor): BG<2.8 mmol/L; Symptoms
		Major		24 (0.04)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (Endpoint vs. Baseline)	p-value Between Treatments	Definition of Hypoglycemia
		Minor		259 (2.19)					
		Nocturnal		198 (0.64)					
		Symptom		236 (2.94)					
	NPH+IAsp	Overall	NR	138 (6.70)	Pts (Episodes/pt/ 30 days)	NR	NR		
		Major		21 (0.06)					
		Minor		129 (3.03)					
		Nocturnal		110 (0.96)					
		Symptom		121 (3.61)					
White *et al.*, 2006[34] [Abstract]	IGlar+ILis	Confirmed	NR	15	Pts	NR	NR	NS	Overall: confirmed clinical relevant hypoglycemia: BG<36 mg/dL (2 mmol/L)
		Severe		6					
	NPH (or lente)+ILis	Confirmed	NR	8	Pts	NR	NR		
		Severe		4					
Witthaus *et al.*, 2001[58]	IGlar+HI	Perceived frequency	NR	NR	NR	NR	NR	p=0.0024 at week 20 in favour of IGlar	NR
	NPH+HI	Perceived frequency	NR	NR	NR	NR	NR		

*mean±SD; †mean±SE. 12h=12 hour interval; BG=blood glucose; b.i.d.=twice a day; DM=diabetes mellitus; HI=conventional human insulin, IAsp=insulin aspart, IDet=insulin detemir, IGlar=insulin glargine, ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and dinner time; RCT=randomized controlled trial; NPH=neutral protamine Hagedorn; NR=not reported, NS=not significant, pt=patient; q.d.=every day; RR=relative risk.

APPENDIX 10B: HYPOGLYCEMIA DATA ON TYPE 2 DM PATIENTS

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
Eliaschewitz *et al.*, 2006[77]	IGlar+Glim	Symptomatic	NR	122 (52.8)	Pts (%)	NR	NR	Symptomatic: p=0.042 and for # of patients, p=0.048 for the episodes/pt-yr Severe: p=0.303 for # of patients, p=0.369 for episodes/pt-yr Nocturnal: p<0.001 for # of patients, p=0.001 for episodes/pt-yr Confirmed nocturnal: p<0.010 for # of patients, p=0.001 for episodes/pt-yr	Severe: symptoms consistent with hypoglycemia requiring assistance from another person and associated with BG level <50 mg/dL (<2.8mmol/L) or with prompt recovery after oral carbohydrate, i.v. glucose or glucagons. Nocturnal: symptomatic hypoglycemia that occurred while the patient was asleep between bedtime and getting up in the morning. Major: not reported Moderate: BG<50mg/dl (<2.8mmol/L) Mild: BG 50 to 75mg/dL (2.8 to 4.2 mmol/L) Other: symptomatic confirmed hypoglycemia were those associated with a FBG ≤75 mg/dL (≤4.2 mmol/L)
				5	Episodes/ pt-yr				
		Severe		6 (2.6)	Pts (%)				
				0.1	Episodes/ pt-yr				
		Nocturnal		47 (20.4)	Pts (%)				
				1.1	Episodes/ pt-yr				
		Confirmed-nocturnal		39 (16.9)	Pts (%)				
				0.8	Episodes/pt-yr				
	NPH+Glim	Symptomatic	NR	157 (62.8)	Pts (%)	NR	NR		
				7.2	Episodes/pt-yr				
		Severe		11 (4.4)	Pts (%)				
				0.2	Episodes/pt-yr				
		Nocturnal		87 (34.8)	Pts (%)				
				3.1	Episodes/pt-yr				
		Confirmed-nocturnal		75 (30.0)	Pts (%)				
				2.3	Episodes/pt-yr				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
Fonseca *et al.*, 2004[75] [Subgroup analysis of Rosenstock *et al.*[74]	IGlar+HI	Symptom	NR	24 (46)	Pts (%)	NR	NR	p<0.05 for symptomatic, p<0.10 for nocturnal)	Overall: symptoms, confirmed by BG<2.8 mmol/L (50 mg/dL) Severe: requiring assistance, and BG <2.0 mmol/L (36 mg/dL) or associated with prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration Nocturnal: between bedtime basal insulin injection and before morning determination of FBG
		Severe		0 (0)					
		Nocturnal		8 (15)					
	NPH+HI	Symptom	NR	29 (60)	Pts (%)	NR	NR		
		Severe		1 (2)					
		Nocturnal		13 (27)					
Fritsche *et al.*, 2003[78]	IGlar (morning) +Glim	Overall	NR	175 (74)	Pts (%)	NR	NR	IGlar(morning)+ Glim vs. NPH (bedtime)+ Glim, p<0.001 for nocturnal IGlar (bedtime)+Glim vs. NPH (bedtime)+ Glim, p<0.001 for nocturnal IGlar (bedtime)+Glim	Overall: BG <4.2 mmol/L (75 mg/dL) Severe: requiring assistance, and BG <2.8 mmol/L (50 mg/dL) or associated with prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration Nocturnal: between bedtime after the evening injection and
		Symptom		133 (56)					
		Nocturnal		39 (17)					
		Severe		5 (2.1)					
	IGlar (bedtime) +Glim	Overall	NR	155 (68)	Pts (%)	NR	NR		
		Symptom		98 (43)					
		Nocturnal		52 (23)					
		Severe		4 (1.8)					
	NPH(bedtime) +Glim	Overall	NR	173 (75)	Pts (%)	NR	NR		
		Symptom		135 (58)					
		Nocturnal		89 (38)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
		Severe		6 (2.6)					
Haak *et al.*, 2005[68]	IDet+IAsp	Overall	NR	152 (45)	Pts (%)	NR	NR	NS	Overall (Minor): BG<2.8 mmol/L; symptoms only, not confirmed by BG measurement Severe: requiring assistance Nocturnal: between 23:00 and 06:00
		Nocturnal		52 (15)					
	NPH+IAsp	Overall	NR	80 (49)	Pts (%)	NR	NR		
		Nocturnal		38 (23)					
Hermansen *et al.*, 2006[69]	IDet+OAD	Overall	NR	151 (64)	Pts (%)	NR	NR	p<0.001 for overall; p<0.001 for nocturnal; p<0.001 for minor; p<0.001 for symptoms only	Symptomatic: confirmed by a plasma glucose value <4.0 mmol/L [<72 mg/dl] or any single plasma glucose value < 3.1 mmol/L [<56 mg/dl] in the last 12 weeks of treatment Nocturnal: occurred between 23:00 and 06:00 Major: third-party assistance required Minor: self-managed,
				908	Episodes				
				8.6	Episodes/pt-yr				
		Nocturnal		71 (30)	Pts (%)				
				160	Episodes				
				1.52	Episodes/pt-yr				
		Major		1 (0)	Pts (%)				
				1	Episodes				
				0.01	Episodes/pt-yr				
		Minor		96 (41)	Pts (%)				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
				387	Episodes				
				3.67	Episodes/pt-yr				
		Symptoms only		124 (52)	Pts (%)				
				519	Episodes				
				4.92	Episodes/pt-yr				
	NPH+OAD	Overall	NR	191 (80)	Pts (%)	NR	NR		
				1,688	Episodes				
				15.96	Episodes/pt-yr				
		Nocturnal		112 (47)	Pts (%)				
				349	Episodes				
				3.3	Episodes/pt-yr				
		Major		6 (3)	Pts (%)				
				8	Episodes				
				0.08	Episodes/pt-yr				
		Minor		153 (64)	Pts (%)				
				755	Episodes				
				7.14	Episodes/pt-yr				
		Symptoms only		160 (67)	Pts (%)				
				923	Episodes				
				8.73	Episodes/pt-yr				
HOE 901/2004 Study Group,	IGlar [30] +OAD	Overall	1.6	12 (18.8)	Pts (%)	NR	NR	IGlar [30] +OAD or IGlar [80] +OAD vs. NPH+OAD, NS	Overall: BG<2.8 mmol/L, classified as symptomatic or asymptomatic
		Nocturnal		4 (6.3)					
	IGlar [80]+OAD	Overall	1.4	18 (25)	Pts (%)	NR	NR		
		Nocturnal		6 (8.3)					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
	NPH+OAD	Overall	5.9	22 (32.4)	Pts (%)	NR	NR		
		Nocturnal		13 (19.1)					
Massi Benedetti *et al.*, 2003[81]	IGlar+OAD	Overall	NR	101 (35)	Pts (%)	NR	NR	p=0.002 for nocturnal	Overall: BG<2.8 mmol/L (50 mg/dL), classified as symptomatic or asymptomatic Severe: requiring assistance, and BG <2.8 mmol/L (50 mg/dL), or prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration Nocturnal: occurring during sleep, between the evening injection, and before morning FBG measurement or morning injection
		Nocturnal		35 (12)					
		Severe		5 (1.7)					
	NPH+OAD	Overall	NR	115 (41)	Pts (%)	NR	NR		
		Nocturnal		67 (24)					
		Severe		3 (1.1)					
Meneghini *et al.*, 2006[87] [Abstract]	IGlar (with Metf or Sfu)	NR	NR	NR	NR	NR	NR	In multivariate repeated measures analysis, IGlar was associated with significantly better outcomes for hypoglycemic (p=0.014)	NR
	Pio (with Metf or Sfu)	NR	NR	NR	NR	NR	NR		
Meneghini *et al.*, 2005[85]	IGlar (with Metf or Sfu)	Overall	NR	49 (53.8)	Pts (%)	NR	NR	NR	NR
		Severe		7 (7.7)					
	Pioglitazone	Overall	NR	19 (23.2)	Pts (%)	NR	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
		Severe		1 (1.2)					
Oster *et al.*, 2006[86] [Abstract]	IGlar (with Metf or Sfu)	Overall	NR	47	% of patients	NR	NR	p=0.0001	NR
	Pio (with Metf or Sfu)	Overall	NR	17	% of patients	NR	NR		
Pan *et al.*, 2007[76]	IGlar+Glim	Overall	NR	130 (58.8)	Pts (%)	NR	NR	p=0.056 for # of patients and p=0.004 for # of episodes for overall; p=0.016 for # of patients and p=0.026 for # of episodes for severe; p=0.001 for # of patients and p<0.001 for # of episodes for nocturnal; p=0.031 for # of patients and p=0.0002 for # of episodes for symptomatic	Severe: An event with symptoms consistent with hypoglycemia associated with a BG level <50mg/dl (<2.8 mmol/L) or with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration and the requirement of third party assistance Nocturnal: Occurring during sleep after the evening insulin injection and before getting up in the morning
				682	Episodes				
				3.06±4.99*	Mean episodes/pt				
		Severe		5 (2.3)	Pts (%)				
				5	Episodes				
				0.02±0.15*	Mean episodes/pt				
		Nocturnal		77 (34.8)	Pts (%)				
				221	Episodes				
				1.00±2.33*	Mean episodes/pt				
		Symptomatic		121 (54.8)	Pts (%)				
				515	Episodes				
				2.33±4.15*	Mean episodes/pt				
	NPH+Glim	Overall	NR	150 (67.3)	Pts (%)	NR	NR		
				1019	Episodes				
				4.57±6.21*	Mean episodes/pt				
		Severe		16 (7.2)	Pts (%)				
				28	Episodes				
				0.13±0.67*	Mean episodes/pt				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
		Nocturnal		111 (49.8)	Pts (%)				
				620	Episodes				
				2.78±5.14*	Mean episodes/pt				
		Symptomatic		144 (64.6)	Pts (%)				
				908	Episodes				
				4.07±5.98*	Mean episodes/pt				
Philis-Tsimikas *et al.*, 2006[70]	IDet (morning) +OAD	Confirmed overall	NR	32 (19.4)	Pts (%)	NR	NR	IDet (morning) +OAD vs. IDet (evening) +OAD, IDet (morning) +OAD vs. NPH+OAD, and IDet (evening) +OAD vs. NPH+OAD: NS, NS, p=0.019 for overall, respectively; NS, p<0.001, and p=0.031 for nocturnal, respectively	Nocturnal: episodes occurring between 11 p.m. and 6 a.m. Major: Requiring third-party assistance (in which case a blood glucose reading was not required) Confirmed episodes: a plasma glucose <3.1 mmol/L and patients were able to self-manage the event
				91	Episodes				
		Major		0	Pts (%)				
				0	Episodes				
		Confirmed nocturnal		4 (2.4)	Pts (%)				
				6	Episodes				
	IDet (evening) +OAD	Confirmed overall	NR	27 (16.0) 82	Pts (%)	NR	NR		
					Episodes				
		Major		2 (1.2)	Pts (%)				
				2	Episodes				
		Confirmed nocturnal		8 (4.7)	Pts (%)				
				19	Episodes				
	NPH+OAD	Confirmed overall	NR	53 (32.3)	Pts (%)	NR	NR		
				153	Episodes				
		Major		0					
				0					
		Confirmed nocturnal		22 (13.4)					
				47					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
Raskin *et al.*, 2006[72] [Abstract]	IDet+IAsp	NR	NR	NR	NR	NR	NR	No treatment differences in risk of hypoglycemic episodes were detected	NR
	IGlar+IAsp	NR	NR	NR	NR	NR	NR		
Raslova *et al.*, 2004[71]	IDet+IAsp	Overall	NR	65 (34.6)	Pts (%)	NR	NR	p=0.65 for overall; p=0.14 for nocturnal; p=0.76 for minor; p=0.65 for symptoms	Nocturnal: occurred between 23:00 and 6:00 Major: Individual unable to treat himself/herself Minor: Plasma glucose <3.1 mmol/L and individual dealt with the episode himself or herself Symptom only: if plasma glucose >3.1 mmol/L or if no plasma glucose measurement existed
				269	Episodes				
		Nocturnal		28 (14.9)	Pts (%)				
				49	Episodes				
		Major		2 (1.1)	Pts (%)				
				2	Episodes				
		Minor		45 (23.9)	Pts (%)				
				108	Episodes				
		Symptom		45 (23.9)	Pts (%)				
				159	Episodes				
	NPH+HI	Overall	NR	70 (36.1) 317	Pts (%)	NR	NR		
					Episodes				
		Nocturnal		34 (17.5)	Pts (%)				
				82	Episodes				
		Major		1 (0.5)	Pts (%)				
				1	Episodes				
		Minor		45 (23.2)	Pts (%)				
				125	Episodes				
		Symptom		49 (25.3) 191	Pts (%)				
					Episodes				
Riddle *et al.*, 2003[82]	IGlar+OAD	Overall	NR	13.9	Episodes/pt-yr	NR	NR	p<0.02 for overall, p<0.005 for symptom,	Overall: BG≤4.0 mmol/L (72 mg/dL) Severe: requiring
		Symptom		9.2					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
		Nocturnal		4					
		Severe		14 episodes/9 patients					
	NPH+OAD	Overall	NR	17.7	Episodes/pt-yr	NR	NR		
		Symptom		12.9					
		Nocturnal		6.9					
		Severe		9 episodes/7 patients					
Rosenstock *et al.*, 2006[73] [Abstract]	IDet+OAD	Overall	NR	NR	NR	NR	NR	RR 0.94 and NS for overall; RR 1.05 and NS for nocturnal	NR
		Nocturnal							
	IGlar+OAD	Overall	NR	NR	NR	NR	NR		
		Nocturnal							
Rosenstock *et al.*, 2006[88]	IGlar (bedtime)+Sfu (max)+Metf	Overall	NR	57	Pts	NR	NR	p=0.0528 for overall, p<0.0165 for symptomatic, p=0.02 for nocturnal	Overall: BG<3.9 mmol/L (70 mg/dL), <2.8 mmol/L (50 mg/dL), or <2.0 mmol/L (36 mg/dL) Severe: requiring assistance, with BG<2.0 mmol/L (36 mg/dL) or prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration Nocturnal: occurring after evening insulin injection and before getting up in the morning
		Symptom		26					
		Nocturnal		29					
		Severe		3					
	Rosi+Sfu (max)+Metf	Overall	NR	47	Pts	NR	NR		
		Symptom		14					
		Nocturnal		12					
		Severe		6					

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
Rosenstock *et al.*, 2001[74]	IGlar+HI	Overall	25.5	159 (61.4)	Pts (%)	NR	NR	NS for overall, p=0.016 for nocturnal	Overall: symptoms and BG <2.8 mmol/L Severe: requiring assistance and BG<2.0 mmol/L or prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration Nocturnal: occurring during sleep, after the evening injection and before rising in the morning (before morning BG measurement and insulin injection)
		Nocturnal		81 (31.3)					
	NPH+HI	Overall	29.7	173 (66.8)	Pts (%)	NR	NR		
		Nocturnal		104 (40.2)					
Tajima *et al.*, 2004[91]	IDet+OAD	Overall	NR	4.51	Events/Pts/ Year	NR	NR	P=0.06 for overall, p=0.08 for nocturnal	NR
	NPH+OAD	Overall	NR	6.46	Events/Pts/ Year	NR	NR		
Triplitt *et al.*, 2006[89]	IGlar+Sfu (max)+Metf (max)	Overall	NR	0	Pts	NR	NR	NR	NR
	Rosi+Sfu (max)+Metf (max)	Overall	NR	1	Pts	NR	NR		
Vinik and Zhang, 2007[90]	IGlar+Sfu+ Metf (max)	NR	NR	NR	NR	NR	NR	NR	Confirmed hypoglycemia: plasma glucose<3.9 mmol/l (from RM3497)
	Rosi+Sfu+ Metf (max)	NR	NR	NR	NR	NR	NR		
Wang *et al.*, 2007[79]	IGlar+Glip	Overall	NR	2	Pts	NR	NR	p=0.129 for overall;	Hypoglycemia event: defined as a sensor
				2	Episodes				

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
		Severe		0	Episodes				
		Nocturnal		1	Pts				
				1	Episodes				
	NPH+Glip	Overall	NR	4	Pts	NR	NR		
				6	Episodes				
		Severe		0	Episodes				
		Nocturnal		4	Pts				
				4	Episodes				
Yki-Järvinen *et al.*, 2006[80]	IGlar+Metf	Overall	3 (5)	33 (54) at weeks 25 to 36	Pts (%)	NR	NR	NS	Overall: BG≤4.0 mmol/L Severe: requiring assistance of another person and BG <3.1 mmol/L or prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration
	NPH+Metf	Overall	2 (4)	28 (57) at weeks 25 to 36		NR	NR		
Yki-Järvinen *et al.*, 2000[84]	IGlar+OAD	Overall	NR	70 (32.5)	Pts (%)	NR	NR	p=0.04 for overall, p=0.0001 for	Overall: BG<2.8 mmol/L (50 mg/dL), classified as
		Nocturnal		21 (10)					
	NPH+OAD	Overall	NR	88 (42.5)	Pts (%)	NR	NR		

Study	Comparators	Type of Hypoglycemia	Hypoglycemia at Baseline	Hypoglycemia at Endpoint	Outcome Unit	Change from Baseline	p-value (endpoint vs. baseline)	p-value between Treatments	Definition of Hypoglycemia
		Nocturnal		50 (23.8)					

*mean±SD. BG=blood glucose; DM=diabetes mellitus; FBG=fasting blood glucose; Glim=glimepiride; Glip=glipizide; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; i.v.=intravenous; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; OAD=oral antidiabetic agent; Pio=pioglitazone; pt-yr=patient-year; Pts=patients; Rosi=rosiglitazone; RR=relative risk; Sfu=sulfonylurea.

APPENDIX 11A: MEAN HBA1C AND FPG LEVELS AT ENDPOINT IN RCTS OF TYPE 1 DM

Study	Comparators	HbA1c at Baseline (%)	HbA1c at End Point (%)	A1c (Change from Baseline) (%)	p-value Endpoint vs. Baseline	p-value Between Treatments	Fasting Plasma Glucose at Endpoint (mmol/L)
Ashwell *et al.*, 2006[64]	IGlar+ILis	8.0±0.8*	7.5±0.1†	NR	NR	p<0.001	NR
	NPH+HI	8.0±0.8*	8.0±0.1†	NR	NR		
Bolli *et al.*, 2006[63] [Abstract]	IGlar+ILis	7.9±0.7*	7.3±0.7*	NR	NR	NS	NR
	NPH+ILis	7.9±0.6*	7.3±1.0*	NR	NR		
Chase *et al.*, 2006[33] [Abstract]	IGlar+ILis	8	NR	-0.12	NR	NR	NR
	NPH (or lente) +ILis	8	NR	-0.11	NR		
Davies *et al.*, 2005[50] [Abstract]	IGlar+IAsp	8.53	8.07	NR	NR	p=0.04	NR
	NPH+IAsp	8.53	8.26	NR	NR		
De Leeuw *et al.*, 2005[40]	IDet+IAsp	8.18±1.14*	7.53±0.10†	-0.64	NR	NS	NR
	NPH+IAsp	8.03±1.11*	7.59±0.13†	-0.56	NR		
Eliaschewitz *et al.*, 2006[77]	IGlar+glimepiride	NR	NR	NR	NR	NR	5.33±2.34*
	NPH+glimepiride	NR	NR	NR	NR		5.44±2.21*
Fonseca *et al.*, 2004[75] [Subgroup analysis of Rosenstock[74]]	IGlar+HI	NR	NR	NR	NR	NR	8.23±2.57*
	NPH+HI	NR	NR	NR	NR		7.85±2.11*
Fritsche *et al.*, 2003[78]	IGlar (morning)+Glim	NR	NR	NR	NR	NR	7.0±1.9*
	IGlar (bedtime)+Glim	NR	NR	NR	NR		6.8±1.9*
	NPH (bedtime)+Glim	NR	NR	NR	NR		6.9±1.9*
Fulcher *et al.*, 2005[60]	IGlar+ILis	9.2±1.1*	8.3±0.14†	-0.89	p<0.05	p=0.01	NR
	NPH+ILis	9.7±1.3*	9.1±0.14†	-0.67	p<0.05		
Garg *et al.*, 1998[53] [Abstract]	IGlar+HI	NR	NR	-0.40%	NR	P>0.05	NR
	NPH+HI	NR	NR	-0.20%	NR		
Haak *et al.*, 2005[68]	IDet+IAsp	NR	NR	NR	NR	NR	9.7±0.2†
	NPH+IAsp	NR	NR	NR	NR	NR	9.6±0.3†

Study	Comparators	HbA1c at Baseline (%)	HbA1c at End Point (%)	A1c (Change from Baseline) (%)	p-value Endpoint vs. Baseline	p-value Between Treatments	Fasting Plasma Glucose at Endpoint (mmol/L)
Hermansen *et al.*, 2004[49]	IDet+IAsp	8.48±1.12*	7.88±0.05*	-0.5	NR	p<0.001	NR
	NPH+HI	8.29±1.19*	8.11±0.05*	-0.28	NR		
Hermansen *et al.*, 2006[69]	IDet+OAD	NR	NR	NR	NR	NR	6.9
	NPH+OAD	NR	NR	NR	NR		6.6
Hermansen *et al.*, 2001[43]	IDet+HI	NR	NR	NR	NR	NR	NR
	NPH+HI	NR	NR	NR	NR		
Hershon *et al.*, 2004[54]	IGlar+HI	7.7±1.2*	NR	-0.09±0.07†	NR	NS	NR
	NPH+HI	7.7±1.1*	NR	-0.19±0.07†	NR		
Home *et al.*, 2005[55]	IGlar+HI	7.9±1.2*	NR	0.21±0.05†	NR	NS	NR
	NPH+HI	8.0±1.2*	NR	0.10±0.05†	NR		
Home *et al.*, 2004[41]	$IDet_{12h}$+IAsp	8.55±1.20*	7.75±0.07†	-0.07 (-0.85%)	NR	$IDet_{12h}$+IAsp and $IDet_{m+b}$+IAsp vs. NPH_{m+b}+IAsp, p=0.027	NR
	$IDet_{m+b}$+IAsp	8.74±1.20*	7.78±0.07†	-0.07 (-0.82%)	NR		
	NPH_{m+b}+IAsp	8.52±1.19*	7.94±0.07†	-0.07 (-0.65%)	NR		
	NPH+HI	8.2±1.3*	NR	0.12±0.19*	NR		
Kawamura *et al.*, 2005[31] [Abstract]	IGlar+IAsp	NR	7.5±1.1	NR	NR	p<0.01	NR
	NPH+IAsp	NR	8.2±1.3	NR	NR		
Kolendorf *et al.*, 2006 [39]	IDet+IAsp	7.9±0.7*	7.6±0.06†	0.3	NR	Mean HbA1c was identical after 16 weeks No p-value was reported	NR
	NPH+IAsp	7.9±0.7*	7.6±0.06†	0.3	NR		
Kudva *et al.*, 2005[65]	IGlar+IAsp	6.94±0.14†	6.82±0.13†	NR	NR	p=0.03	NR
	UL+IAsp	6.94±0.14†	7.02±0.13†	NR	NR		
Massi Benedetti *et al.*, 2003[81]	IGlar+OAD	NR	NR	NR	NR	NR	7.1±0.3†
	NPH+OAD	NR	NR	NR	NR		7.4±0.2†
Meneghini *et al.*, 2005 [Abstract][85]	IGlar (with Metf or Sfu)	NR	NR	NR	NR	NR	NR
	Pioglitazone (with Metf or Sfu)	NR	NR	NR	NR		

Study	Comparators	HbA1c at Baseline (%)	HbA1c at End Point (%)	A1c (Change from Baseline) (%)	p-value Endpoint vs. Baseline	p-value Between Treatments	Fasting Plasma Glucose at Endpoint (mmol/L)
Meneghini *et al.*, 2006[87] [abstract] Oster, 2006[86] [abstract]	IGlar	NR	NR	NR	NR	NR	NR
	Pioglitazone	NR	NR	NR	NR		NR
Mianowska *et al.*, 2006[35] [Abstract]	IGlar+(ILis or HI)	NR	7.6±0.9*	NR	NR	p=0.76	NR
	NPH+(ILis or HI)	NR	7.7±0.9*	NR	NR		
Murphy *et al.*, 2003[36]	IGlar+ILis	9.3 (7.1 to 12)‡	8.7	No mean value of the two periods	NR	p=0.13	NR
	NPH+HI	9.3 (7.1 to 2)‡	9.1	NR	NR		
Pan *et al.*, 2007[76]	IGlar+glimepiride	NR	NR	NR	NR	NR	6.5±1.39*
	NPH+glimepiride	NR	NR	NR	NR		6.6±1.44*
Pesic *et al.*, 2006[51] [Abstract]	IGlar+IAsp	7.7±1.2*	6.9±0.5*	NR	NR	NR	
	NPH (q.d.) +IAsp	NR	NR	No change	NR		
	NPH (b.i.d.) +IAsp	7.8±1.0*	7.0±1.2*	NR	NR		
Philis-Tsimikas *et al.*, 2006[70]	IDet+OAD (morning IDet)	NR	NR	NR	NR	NR	8.61±2.1* (FPG)
	IDet+OAD (evening IDet)	NR	NR	NR	NR		7.17±2.05*(FPG)
	NPH+OAD	NR	NR	NR	NR		7.77±2.95*(FPG)
Pieber *et al.*, 2007[48]	IDet+IAsp	8.9 (7.6 to 11.9)‡	8.16±0.084†	NR	NR	NR	NR
	IGlar+IAsp	8.8 (7.6 to 11.9)‡	8.19±0.082†	NR	NR		
Pieber *et al.*, 2000[52]	IGlar [30] +HI	8.09±0.11†	7.85±0.10†	-0.25±0.05†	p=0.0001	P=0.03	NR
	IGlar [80] +HI	7.96±0.11†	7.80±0.10†	-0.15±0.05†	p=0.0061		
	NPH+HI	7.85±0.11†	7.79±0.09†	-0.03±0.05†	NS		
Pieber *et al.*, 2005[42]	$IDet_{m+d}$+IAsp	8.01±1.24*	7.67±0.07†	-0.43	p<0.05	NS	NR
	$IDet_{m+b}$+IAsp	8.13±1.37*	7.65±0.07†	-0.49	p<0.05		
	NPH_{m+b}+IAsp	8.08±1.15*	7.73±0.07†	-0.39	p<0.05		
Porcellati *et al.*, 2004[61]	IGlar (dinner time) +ILis	7.1±0.1†	6.7±0.1†	NR	p<0.05	p<0.05	NR

Study	Comparators	HbA1c at Baseline (%)	HbA1c at End Point (%)	A1c (Change from Baseline) (%)	p-value Endpoint vs. Baseline	p-value Between Treatments	Fasting Plasma Glucose at Endpoint (mmol/L)
	NPH (4 times/day) +ILis	7.1±0.2†	7.1±0.1†	NR	NS		
Raskin *et al.*, 2000[59]	IGlar+ILis	7.59±1.19*	7.53±1.19*	NR	NR	NS	NR
	NPH+ILis	7.71±1.2*	7.60±1.14*	NR	NR		
Raskin *et al.*, 2006 [abstract][72]	IDet+IAsp	NR	NR	NR	NR	NR	7.2
	Glar+IAsp	NR	NR	NR	NR		7.4
Raslova *et al.*, 2004[71]	IDet+IAsp	NR	NR	NR	NR	NR	7.28±0.13†
	NPH+HSI	NR	NR	NR	NR		7.32±0.12†
Ratner *et al.*, 2000[56]	IGlar+HI	7.7±1.2*	7.54±1.2*	-0.16±0.05†	NR	NS	NR
	NPH+HI	7.7±1.1*	7.49±1.1*	-0.21±0.05†	NR		
Riddle *et al.*, 2003[82]	IGlar+OAD	NR	NR	NR	NR	NR	6.5
	NPH+OAD	NR	NR	NR	NR		6.7
Robertson *et al.*, 2007[30]	IDet+IAsp	8.8±1.2*	8.0±0.1†	-0.8	NR	NR	NR
	NPH+IAsp	8.7±1.1*	7.9±0.1+	-0.8	NR		
Rosenstock *et al.*, 2000[57]	IGlar [30] +HI	7.8±1.1*	7.4±1.1*	-0.4±0.48*	NR	NR	NR
	IGlar [80] +HI	7.9±1.2*	7.5±1.2*	-0.4±0.49*	NR		
	NPH+HI	8.0±1.2*	7.6±1.2*	-0.4±0.48*	NR		
Rosenstock *et al.*, 2001[74]	IGlar+HI	NR	NR	NR	NR	NR	NR
	NPH+HI	NR	NR	NR	NR		
Rosenstock *et al.*, 2006[88]	IGlar (bedtime)+Sfu (max) +Metf	NR	NR	NR	NR	NR	Change from baseline: -3.60±0.23* p=0.001
	Rosi+ Sfu (max) +Metf	NR	NR	NR	NR		Change from baseline: -2.57±0.22*
Rosenstock *et al.*, 2006[73] [abstract]	IDet	NR	NR	NR	NR	NR	7.1
	IGlar	NR	NR	NR	NR		7
Rossetti *et al.*, 2003[62]	IGlar (dinnertime) +ILis	6.8±0.2†	6.4±0.1†	NR	p<0.04	NR	NR
	IGlar (bedtime) +ILis	7.0±0.2†	6.6±0.1†	NR	p<0.04		
	NPH (4 times/day) +ILis	6.9±0.1†	7.0±0.1†	NR	NS		
Russell-Jones *et al.*, 2004[45]	IDet+HI	8.35±1.20*	8.30±1.08*	-0.06±0.92*	NR	NS	NR
	NPH+HI	8.35±1.21*	8.41±1.32*	0.06±1.05*	NR		

Study	Comparators	HbA1c at Baseline (%)	HbA1c at End Point (%)	A1c (Change from Baseline) (%)	p-value Endpoint vs. Baseline	p-value Between Treatments	Fasting Plasma Glucose at Endpoint (mmol/L)
Schober *et al.*, 2002[32]	IGlar+HI	8.48±0.11†, p=0.04	8.76±0.11†	0.28±0.09†	NR	NS	NR
	NPH+HI	8.81±0.11†	9.08±0.11†	0.27±0.09†	NR		
Standl *et al.*, 2004[46]	IDet+HI	7.72±1.26*	7.88±0.082†	NR	NR	NS	NR
	NPH+HI	7.66±1.19*	7.78±0.088†	NR	NR		
Tajima *et al.*, 2006[91]	IDet+OAD	7.5 to 10	7.81±0.07†	-0.59	NR	NR	6.97±0.16†
	NPH+OAD	7.5 to 10	7.74±0.07†	-0.67	NR		6.85±0.16†
Triplitt *et al.*, 2006[89]	IGlar	NR	NR	NR	NR	NR	7.72±0.28†
	rosiglitazone	NR	NR	NR	NR		8.9±1.01†
Vague *et al.*, 2003[44]	IDet+IAsp	8.18±1.14*	7.60±0.09†	-0.55	NR	NS	NR
	NPH+IAsp	8.11±1.12*	7.64±0.10†	-0.55	NR		
Vinik and Zhang, 2007[90]	IGlar+Sfu+Metf)	NR	NR	NR	NR	NR	6.78±2.12*
	rosiglitazone+Sfu+Metf	NR	NR	NR	NR		7.81±2.55*
Wang *et al.*, 2007[79]	IGlar+glipizide	NR	NR	NR	NR	NR	6.06±1.22*
	NPH+glipizide	NR	NR	NR	NR		5.84±1.26*
White *et al.*, 2006[34] [Abstract]	IGlar+ILis	9.3	NR	NR	NR	NR	NR
	NPH (or lente)+ILis	9.3	NR	NR	NR		
Witthaus *et al.*, 2001[58]	IGlar+HI	NR	NR	NR	NR	NR	NR
	NPH+HI	NR	NR	NR	NR		
Yki-Järvinen *et al.*, 2000[84]	IGlar+OAD	NR	NR	NR	NR	NR	NR
	NPH+OAD	NR	NR	NR	NR		NR
Yki-Järvinen *et al.*, 2006[80]	IGlar+Metf	NR	NR	NR	NR	NR	5.7±0.02†
	NPH+Metf	NR	NR	NR	NR		6.0±0.03†
HOE 901/2004 Study Group, 2003[83]	IGlar [30] +OAD	NR	NR	NR	NR	NR	7
	IGlar [80] +OAD	NR	NR	NR	NR		6.95
	NPH+OAD	NR	NR	NR	NR		6.53

*mean±SD; †mean (95% CI); ‡mean(range). 12h=12 hour interval; A1c=glycosylated hemoglobin; b.i.d.=twice a day; DM=diabetes mellitus; FPG=fasting blood glucose; Glim=glimepiride; HbA1c=glycosylated hemoglobin; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and dinner time; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; OAD=oral antidiabetic agent; pt=patient; q.d.=every day; Rosi=rosiglitazone; Sfu=sulfonylurea; UL=ultralente; vs.=versus.

APPENDIX 11B: MEAN HBA1C AND FPG LEVELS AT ENDPOINT IN RCTS OF TYPE 2 DM

Study	Comparators	HbA1c at Baseline (%)	HbA1c at End Point (%)	A1c (Change from Baseline) (%)	p-value Endpoint vs. Baseline	p-value Between Treatments	Fasting Plasma Glucose at Endpoint (mmol/L)
Eliaschewitz *et al.*, 2006[77]	IGlar+glimepiride	9.1±1.0*	7.65±1.30*	-1.38±1.32*	NR	NR	5.33±2.34*
	NPH+glimepiride	9.2±0.9*	7.78±1.29*	-1.44±1.33*	NR		5.44±2.21*
Fonseca *et al.*, 2004[75] [Subgroup analysis of Rosenstock[74]]	IGlar+HI	8.42±1.22*	8.01±1.22*	-0.41	NR	NR	NS
	NPH+HI	8.36±0.96*	7.90±0.96*	-0.46	NR		7.85±2.11*
Fritsche *et al.*, 2003[78]	IGlar (morning)+Glim	9.1±1.0*	7.8±1.2*	-1.24 (90%CI, -1.10 to -1.38)	NR	IGlar (morning) + Glim vs. IGlar (bedtime) + Glim, p=0.008; IGlar (morning) + Glim vs. NPH (bedtime) + Glim, p<0.001	7.0±1.9*
	IGlar (bedtime)+Glim	9.1±1.0*	8.1±1.3*	-0.96 (90%CI, -0.81 to -1.10)	NR		6.8±1.9*
	NPH (bedtime)+Glim	9.1±1.1*	8.3±1.3*	-0.84 (90%CI, -0.69 to -0.98)	NR		6.9±1.9*
Haak *et al.*, 2005[68]	IDet+IAsp	7.9±1.3*	7.6±0.1†	-0.2	p=0.004	NS	9.7±0.2†
	NPH+IAsp	7.8±1.3*	7.5±0.1†	-0.4	p=0.0001		9.6±0.3†
Hermansen *et al.*, 2006[69]	IDet+OAD	8.61±0.78*	6.8	-1.8	NS	NS	6.9
	NPH+OAD	8.51±0.76*	6.6	-1.9	NS		6.6
Massi Benedetti *et al.*, 2003[81]	IGlar+OAD	9.0±1.2*	8.54±1.2*	-0.46	NR	NS	7.1±0.3†
	NPH+OAD	8.9±1.1*	8.52±1.1*	-0.38	NR		7.4±0.2†
Meneghini *et al.*, 2005 [Abstract][85]	IGlar (with Metf or Sfu)	8–12	6.7	-2.6	NR	p≤0.05	NR
	Pioglitazone (with Metf or Sfu)	8–12	7	-2.3	NR		
Meneghini *et al.*, 2006 [abstract] [87]	IGlar	NR	NR	-2.6	NR	NR	NR
	Pioglitazone	NR	NR	-2.3	NR		

Study	Comparators	HbA1c at Baseline (%)	HbA1c at End Point (%)	A1c (Change from Baseline) (%)	p-value Endpoint vs. Baseline	p-value Between Treatments	Fasting Plasma Glucose at Endpoint (mmol/L)
Oster *et al.*, 2006[86] [Abstract]	IGlar (with Metf or Sfu)	8–12	6.7	-2.6	NR	p≤0.05	
	Pio (with Metf or Sfu)	8–12	7	-2.3	NR		
Pan *et al.*, 2007 [76]	IGlar+glimepiride	9.02±0.88*	7.90±1.16*	-1.1	NR	NR	6.5±1.39*
	NPH+glimepiride	9.05±0.84*	8.13±1.19*	-0.92	NR		6.6±1.44*
Philis-Tsimikas *et al.*, 2006 [70]	IDet+OAD (morning IDet)	9.08±0.97*	7.5±0.96*	-1.58±1.07*	NR	NS	8.61±2.1*
	IDet+OAD (evening IDet)	8.88±0.95*	7.4±0.77*	-1.48±1.01*	NR		7.17±2.05*
	NPH+OAD	9.15±1.0*	7.35±0.93*	-1.74±1.08*	NR		7.77±2.95*
Raskin *et al.*, 2006, [abstract] [72]	IDet+IAsp	NR	NR	-1.1	<0.0001	NR	7.2
	Glar+IAsp	NR	NR	-1.3	<0.0001		7.4
Raslova *et al.*, 2004 [71]	IDet+IAsp	8.16±1.28*	7.46	-0.65	<0.001	p=0.515 (NS)	7.28±0.13†
	NPH+HI	8.08±1.23*	7.52	-0.58	<0.001		7.32±0.12†
Riddle *et al.*, 2003[82]	IGlar+OAD	8.61±0.9*	6.96±0.9*	NR	NR	NS	6.5
	NPH+OAD	8.56±0.9*	6.97±0.9*	NR	NR		6.7
Rosenstock *et al.*, 2001[74]	IGlar+HI	8.6±1.2*	8.19±1.2*	-0.41±0.1*	p=0.0001	NS	NR
	NPH+HI	8.5±1.2*	7.91±1.2*	-0.59±0.1*	p=0.0001		NR
Rosenstock *et al.*, 2006[88]	IGlar (bedtime)+Sfu (max)+Metf	8.8±1.0*	7.14±1.0*	-1.66	NS	NS	Change from baseline: -3.60±0.23* p=0.001
	Rosi+Sfu (max)+Metf	8.7±1.0*	7.19±1.0*	-1.51	NS		Change from baseline: -2.57±0.22*
Rosenstock *et al.*, 2006[73] [abstract]	IDet	7.5-10	7.2	NR	NR	NR	7.1
	IGlar	7.5-10	7.1	NR	NR		7
Triplitt *et al.*, 2006 [89]	IGlar	9.1±0.4†	7.6±0.3†	-1.5±0.2†	P<0.0001	NS	7.72±0.28†
	rosiglitazone	9.4±0.3†	7.6±0.4†	-1.8±0.4†	P=0.0025		8.9±1.01†
Vinik and Zhang, 2007 [90]	IGlar+Sfu+Metf	NR	NR	NR	NR	NR	6.78±2.12*
	rosiglitazone +Sfu+ Metf	NR	NR	NR	NR	NR	7.81±2.55*
Wang *et al.*, 2007 [79]	IGlar+glipizide	IGlar+Glip	8.77±1.18*	7.62±0.98*	NR	p<0.05	6.06±1.22*
	NPH+glipizide	8.75±1.24*	7.43±0.73*	NR	p<0.05		5.84±1.26*
Yki-Järvinen *et al.*, 2000[84]	IGlar+OAD	9.1±0.1†	8.34±0.09†	NR	p<0.001	NS	NR

Study	Comparators	HbA1c at Baseline (%)	HbA1c at End Point (%)	A1c (Change from Baseline) (%)	p-value Endpoint vs. Baseline	p-value Between Treatments	Fasting Plasma Glucose at Endpoint (mmol/L)
	NPH+OAD	8.9±0.1†	8.24±0.09†	NR	p<0.001		NR
Yki-Järvinen *et al.*, 2006[80]	IGlar+Metf	9.5±0.1†	7.14±0.12†	NR	NR	p=0.55 (NS)	5.7±0.02†
	NPH+Metf	9.6±0.1†	7.16±0.14†	NR	NR		6.0±0.03†
HOE 901/2004 Study Group, 2003[83]	IGlar [30]+OAD	9.79±1.5*	8.98±1.5*	-0.82	p=0.0001	NS	7
	IGlar [80]+OAD	9.71±1.2*	8.84±1.2*	-0.86	p=0.0001		6.95
	NPH+OAD	9.47±1.4*	8.68±1.4*	-0.79	p=0.0001		6.53

*mean±SD; †mean±SE. A1c=glycosylated hemoglobin; DM=diabetes mellitus; FPG=fasting plasma glucose; Gly=glyburide; HbA1c=glycosylated hemoglobin; HI=human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; Metf=metformin; NPH= neutral protamine Hagedorn; RCTs= randomized controlled trials; NR=not reported; OAD=oral antidiabetic; Sfu=sulfonylurea; vs.=versus.

APPENDIX 12A: STUDY-LEVEL BODY WEIGHT AND BMI DATA FROM RCTS IN TYPE 1 DM

Study	Comparators	Weight at Baseline (kg)	Weight at Endpoint (kg)	Weight Change from Baseline (kg)	Weight p-value Endpoint vs. Baseline	Weight p-value between Treatments	BMI at Baseline	BMI at Endpoint	BMI Change from Baseline	BMI p-value Endpoint vs. Baseline	BMI p-value Between Treatments
Davies *et al.*, 2005[50] [Abstract]	IGlar+ILis	NR	81.68	NR	NR	p=0.45	NR	NR	NR	NR	NR
	NPH (Insulatard®) +ILis	NR	81.92	NR	NR		NR	NR	NR	NR	
De Leeuw *et al.*, 2005[40]	IDet+IAsp	71.3±10.7*	71.2±11.4*	-0.1	NR	p<0.001	NR	NR	NR	NR	NR
	NPH+IAsp	71.7±12.4*	72.7±13.1*	1.2	NR	Difference between groups (CI) 1.34 (-2.12, -0.56)	NR	NR	NR	NR	
Fulcher *et al.*, 2005[60]	IGlar+ILis	NR	NR	1.97	NR	p<0.05	NR	NR	NR	NR	NR
	NPH+ILis	NR	NR	2.34	NR		NR	NR	NR	NR	
Hermansen *et al.*, 2004[49]	IDet+IAsp	73.5±11.4*	73.0±0.14†	-0.95 (0.14)†	NR	p<0.001 for end weight and change from baseline	NR	NR	NR	NR	NR
	NPH+regular insulin	74.2±12.2*	74.1±0.14†	0.07 (0.14)†	NR		NR	NR	NR	NR	
Hershon *et al.*, 2004[54] (subgroup analysis of Ratiner[66])	IGlar+HI	75.5±14.2*	76.0±14.5*	0.7±3.3*	NR	p=0.33	NR	NR	NR	NR	NR
	NPH+HI	75.0±14.6*	75.9±15.2*	1.0±2.9*	NR		NR	NR	NR	NR	
Home *et al.*, 2004[41]	$IDet_{12h}$+IAsp	74.2±12.6*	NR	0.02±0.22†	NR	p=0.018 with IDet (both regimen)	NR	NR	NR	NR	NR
	$IDet_{m+b}$+IAsp	75.0±12.3*	NR	0.24±.022†	NR		NR	NR	NR	NR	

Study	Comparators	Weight at Baseline (kg)	Weight at Endpoint (kg)	Weight Change from Baseline (kg)	Weight p-value Endpoint vs. Baseline	Weight p-value between Treatments	BMI at Baseline	BMI at Endpoint	BMI Change from Baseline	BMI p-value Endpoint vs. Baseline	BMI p-value Between Treatments
	NPH_{m+b}+IAsp	75.5±14.0*	NR	0.86±0.23†	NR		NR	NR	NR	NR	
Mianowska *et al.*, 2006[35]	IGlar	NR	NR	NR	NR	NR	NR	18.7 kg/m²	NR	NR	NS
	NPH	NR	NR	NR	NR		NR	18.5 kg/m²	NR	NR	
Pieber *et al.*, 2005[42]	$IDet_{m+d}$+IAsp	75.6±15.0*	NR	-0.6	NR	p<0.001 vs. NPH	NR	NR	NR	NR	NR
	$IDet_{m+b}$+IAsp	77.0±13.7*	NR	0.1	NR	p<0.001 vs. NPH	NR	NR	NR	NR	
	NPH_{m+b}+IAsp	74.8±13.1*	NR	0.7	NR		NR	NR	NR	NR	
Pieber *et al.*, 2007[48]	IDet+IAsp	NR	NR	0.52	NR	p=0.193	NR	NR	NR	NR	NR
	IGlar+IAsp	NR	NR	0.96	NR		NR	NR	NR	NR	
Raskin *et al.*, 2000[59]	IGlar+ILis	NR	NR	0.12	NR	p=0.034	NR	NR	NR	NR	NR
	NPH+ILis	NR	NR	0.54	NR		NR	NR	NR	NR	
Robertson *et al.*, 2007[30]	IDet+IAsp	NR	NR	NR	NR	NR	BMI Z score: 0.15 (-2.0 to 1.7)†	BMI Z score: 0.08±0.02†	NR	NR	p<0.001
	NPH+IAsp	NR	NR	NR	NR		BMI Z score: 0.16 (-2.6 to 1.7)†	BMI Z score: 0.26±0.03†	NR	NR	

Study	Comparators	Weight at Baseline (kg)	Weight at Endpoint (kg)	Weight Change from Baseline (kg)	Weight p-value Endpoint vs. Baseline	Weight p-value between Treatments	BMI at Baseline	BMI at Endpoint	BMI Change from Baseline	BMI p-value Endpoint vs. Baseline	BMI p-value Between Treatments
Russell-Jones *et al.*, 2004[45]	IDet+HI	76.5±12.3*	76.1±12.5*	NR	NR	p=0.024	NR	NR	NR	NR	NR
	NPH+HI	76.3±12.4*	76.5±12.6*	NR	NR		NR	NR	NR	NR	
Standl *et al.*, 2004[46]	IDet+HI	76.9±11.8*	NR	-0.3	NR	p<0.001 at 6 months; p=0.002	NR	NR	NR	NR	NR
	NPH+HI	75.9±13.1*	NR	1.4	NR		NR	NR	NR	NR	
Vague *et al.*, 2003[44]	IDet+IAsp	71.5±11.9*	70.9±0.28*	NR	NR	p=0.001	NR	NR	NR	NR	NR
	NPH+IAsp	71.2±11.5*	71.8±0.33*	NR	NR		NR	NR	NR	NR	

*mean±SD; †mean±SE. 12h=12 hour interval; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and dinner time; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; RCTs=randomized controlled trials; vs.=versus.

APPENDIX 12B: STUDY-LEVEL BODY WEIGHT AND BMI DATA FROM RCTS IN TYPE 2 DM

Study	Comparators	Weight at Baseline (kg)	Weight at Endpoint (kg)	Weight Change from Baseline (kg)	Weight p-value Endpoint vs. Baseline	Weight p-value Between Treatments	BMI at Baseline (kg/m²)	BMI at Endpoint (kg/m²)	BMI Change from Baseline (kg/m²)	BMI p-value Endpoint vs. Baseline	BMI p-value Between Treatments
Fritsche *et al.*, 2003[78]	IGlar (morning) +Glim	80.7±15.8*	NR	3.9±4.5*	NR	p>0.2 among groups	NR	NR	NR	NR	NR
	IGlar (bedtime) +Glim	82.1±13.6*	NR	2.9±4.3*	NR		NR	NR	NR	NR	
	NPH (bedtime) +Glim	81.0±14.9*	NR	3.7±3.6*	NR		NR	NR	NR	NR	
Haak *et al.*, 2005[68]	IDet+IAsp	85.7±14.9*	NR	1	NR	p=0.017	NR	NR	NR	NR	NR
	NPH+IAsp	89.3±17.5*	NR	1.8	NR		NR	NR	NR	NR	
Hermansen *et al.*, 2006[69]	IDet+OGLD	NR	83.6	1.2	NR	p<0.001	NR	NR	NR	NR	NR
	NPH+OGLD	NR	85.1	2.8	NR		NR	NR	NR	NR	
HOE 901/2004 Study Group, 2003[83]	IGlar [30] +OAD	NR	NR	0.31	NR	NR	NR	NR	NR	NR	NR
	IGlar [80] +OAD	NR	NR	0.64	NR		NR	NR	NR	NR	
	NPH+OAD	NR	NR	0.68	NR		NR	NR	NR	NR	
Massi Benedetti *et al.*, 2003[81]	IGlar+OAD	NR	NR	2.01	NR	p=0.58	NR	NR	NR	NR	NR
	NPH+OAD	NR	NR	1.88	NR		NR	NR	NR	NR	
Pan *et al.*, 2007[76]	IGlar+Glim	NR	NR	NR	NR	NR	24.8±3.1*	NR	1.4	NR	Similar
	NPH+Glim	NR	NR	NR	NR		25.1±3.3*	NR	1.29	NR	

Study	Comparators	Weight at Baseline (kg)	Weight at Endpoint (kg)	Weight Change from Baseline (kg)	Weight p-value Endpoint vs. Baseline	Weight p-value Between Treatments	BMI at Baseline (kg/m²)	BMI at Endpoint (kg/m²)	BMI Change from Baseline (kg/m²)	BMI p-value Endpoint vs. Baseline	BMI p-value Between Treatments
Philis-Tsimikas *et al.*, 2006[70]	[IDet (morning)+ OAD]	NR	NR	1.2	NR	NS; IDet (morning) vs. IDet (evening) or NPH p=0.005 IDet vs. NPH	NR	NR	NR	NR	NR
	[IDet(evening) +OAD]	NR	NR	0.7	NR		NR	NR	NR	NR	
	(NPH+OAD)	NR	NR	1.6	NR		NR	NR	NR	NR	
Raskin *et al.*, 2006[72]	(IDet+IAsp)	NR	NR	1.4	NR	p=0.0026	NR	NR	NR	NR	NR
	(IGlar+IAsp)	NR	NR	2.9	NR		NR	NR	NR	NR	
Riddle *et al.*, 2003[82]	IGlar+OAD	NR	NR	3.0±0.2*	NR	p=NS	28.9±1.7†	32.3±1.4†	NR	p<0.01	p=NS
	NPH+OAD	NR	NR	2.8±0.2*	NR		31.4±1.2†	32.8±1.2†	NR	p=0.05	
Rosenstock *et al.*, 2001[74]	IGlar+HI	89.7±17.4*	90.0±17.8*	0.4	NR	p=0.0007	NR	NR	NR	NR	NR
	NPH+HI	90.7±17.8*	92.1±18.3*	1.4	NR		NR	NR	NR	NR	
Rosenstock *et al.*, 2006[88]	IGlar+ Sfu (max) +Metf	NR	NR	1.7±0.4	NR	p=0.02	NR	NR	NR	NR	NR
	Rosi+ Sfu (max) +Metf	NR	NR	3.0±0.4	NR		NR	NR	NR	NR	
Rosenstock *et al.*, 2006[73]	IDet	NR	NR	3	NR	p=0.012	NR	NR	NR	NR	NR
	IGlar	NR	NR	3.9	NR		NR	NR	NR	NR	
Tajima *et al.*, 2006[91]	IDet+OAD	NR	61.26±0.18 †	NR	NR	p=0.04	NR	NR	NR	NR	NR
	NPH+OAD	NR	61.64±0.18 †	NR	NR		NR	NR	NR	NR	
Triplitt *et*	IGlar	74.9±5.4†	77.9±5.2†	NR	p=0.03	p=0.04	NR	NR	NR	NR	NR

Study	Comparators	Weight at Baseline (kg)	Weight at Endpoint (kg)	Weight Change from Baseline (kg)	Weight p-value Endpoint vs. Baseline	Weight p-value Between Treatments	BMI at Baseline (kg/m²)	BMI at Endpoint (kg/m²)	BMI Change from Baseline (kg/m²)	BMI p-value Endpoint vs. Baseline	BMI p-value Between Treatments
	rosiglitazone	88.3±4.1†	91.9±5.5†	NR	p=0.01		NR	NR	NR	NR	
Wang *et al.*, 2007[79]	(IGlar+ glipizide)	NR	NR	1.47±1.04*	NR	p>0.05; NS	24.2±2.8†	24.7±2.4†	NR	NR	p=0.78
	(NPH+ glipizide)	NR	NR	1.20±1.17*	NR		24.6±2.5†	24.9±2.3†	NR	NR	
Yki-Järvinen *et al.*, 2006[80]	IGlar+Metf	92.0±2.4†	NR	2.6±0.6†	NR	NS	NR	NR	NR	NR	NR
	NPH+Metf	94.4±2.6†	NR	3.5±0.7†	NR		NR	NR	NR	NR	
Yki-Järvinen *et al.*, 2000[84]	IGlar+OAD	NR	NR	2.57± 0.23†	NR	Similar among groups	NR	NR	NR	NR	NR
	NPH+OAD	NR	NR	2.34± 0.23†	NR		NR	NR	NR	NR	

*mean±SD; †mean±SE. BMI=body mass index; Glim=glimprride; HI=human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; Metf=metformin; NR=not reported; NS=not significant; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic drug; OGLD=oral glucose-lowering drugs; RCTs=randomized controlled trials; Rosi=rosiglitazone; Sfu=sulfonylurea; vs.=versus.

APPENDIX 13A: ADVERSE EVENTS DATA (EXCLUDING HYPOGLYCEMIA) FOR RCTS IN TYPE 1 DM

Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Ashwell *et al.*, 2006[64]	IGlar+ILis: 2 patients (3.8%) with severe AEs NPH+HI: 4 patients (7.7%) with severe AEs	The AE profile was similar in the two groups. Of thses AEs, two events were considered by invetgator to be treatment-related. IGlar+ILis: one treatment-related AE was accidental insulin overdose NPH+HI: one treatment-related AE was urinary tract infection
Bolli *et al.*, 2006[63] [Abstract]	IGlar+ILis: NR NPH+ILis: NR	NR
Chase *et al.*, 2006[33] [Abstract]	IGlar+ILis: NR NPH (or lente) +ILis: NR	Possibly related AEs were comparable in both groups (NS)
Davies *et al.*, 2005[50] [Abstract]	IGlar+IAsp: NR NPH+IAsp: NR	NR
De Leeuw *et al.*, 2005[40]	IDet: 72.7% of patients in the first 6 months and 60.2% of patients in the 2nd 6 months experienced AEs; 12 severe AEs NPH: 76.8% in first 6 months and 69.7% in the 2nd 6 months; 6 severe AEs	IDet: CNS complaints (including migraine) were most frequent. Other AEs included retinal edema and macular degeneration, 3 moderate episodes of hyperglycemia, 2 patients with ketosis, and 1.9% of patients reported injection site reactions. NPH: vision disturbances were most frequent. Other AEs included retinal disorder, 2 patients with ketosis, and 1.0 % of patients reported injection site reactions.
Fulcher *et al.*, 2005[60]	IGlar: 277 events in 57 patients NPH: 241 events in 56 patients	Most common AEs were upper respiratory tract infections (IGlar: 7.2%; NPH: 11.2%), infections (IGlar: 7.2%; NPH: 6.2%), rhinitis (IGlar: 7.2%; NPH: 5.4%), headache (IGlar: 9.8%; NPH: 4.2%), and diarrhea (IGlar: 4.3%; NPH: 0.8%). Injection site reactions were similar (IGlar: 9 events in 5 patients; NPH: 7 events in 7 patients). Fewer than 5% of AEs were considered severe and fewer than 10% were considered related to study medication.
Garg *et al.*, 1998[53] [Abstract]	NR	NR

Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Hermansen *et al.*, 2004[49]	IDet+IAsp: 141 patients (47.3%) experienced at least one AE, 12 patients with serious AEs NPH+HI: 139 patients (46.8%) experienced at least one AE, 7 patients with severe AEs	AEs were equally distributed between treatments. IDet+IAsp: 5 patients withdrew due to AEs; 3 events (hypoglycemia*, allergic reaction, and injection site reaction) were considered to be related to the trial products. NPH+HI: 1 pt withdrew due to AEs
Hermansen *et al.*, 2001[43]	Approximately 30% of patients had AEs during either treatment period.	NR
Hershon *et al.*, 2004[54] (subgroup analysis of Ratiner[66])	IDet: 84.6% of patients experienced at least one treatment-related AE: 84.6%; 13.8% of patients experienced at least one serious AE NPH: 85.9% of patients experienced at least one treatment-related AE; 13.1% of patients experienced at least one serious AE	Increased body weight and injection site pain were the only AEs specified.
Home *et al.*, 2005[55]	IGlar: 37/292 patients (13%) experienced AEs possibly related to study medication; 9% classified as serious NPH: 39/293 patients (13%) experienced AEs possibly related to study medication; 10% classified as serious	IGlar: 8 patients (3%) had injection site mass; 3 patients (1%) had injection site reaction NPH: 9 patients (3%) had injection site mass; 6 patients (2%) had injection site reaction Similar numbers of patients for each group developed a retinopathy severity level >61(ETDRS), clinically significant macular edema and/or a 3-step progression on the ETDRS retinopathy scale.
Home *et al.*, 2004[41]	IDet: serious AEs reported for 14 patients (5%) NPH: serious AEs reported for 4 patients (3%)	AEs not considered to be related to study medication
Kawamura *et al.*, 2005[31] [Abstract]	NR	NR
Kolendorf *et al.*, 2006[39]	IDet+IAsp: NR NPH+IAsp: 1 patient died from a myocardial infarction	Overall AE profile was similar between two groups and most events were mild and considered unrelated to trial products. 3 persons withdrew due to AEs.
Kudva *et al.*, 2005[65]	NR	NR

Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Mianowska *et al.*, 2006[35] [Abstract]	IGlar+(ILis or HI): NR NPH+ (ILis or HI): NR	No ketoacidosis occurred.
Murphy *et al.*, 2003[36]	IGlar+ILis: 21 treatment-emergent AEs in 13 patients; 1 pt with potential causally related AE NPH+HI: 29 treatment-emergent AEs in 15 patients; 1 pt with serious AE	Most of these events were mild and unrelated to insulin therapy. IGlar+ILis: The only potential causally related adverse event was transient pain in the injection site which was mild and did not necessitate discontinuation of the study insulin. NPH+HI: One SAE was that one pt required a 15-hour hospital admission during an episode of gastroenteritis.
Pesic *et al.*, 2006[51] [Abstract]	IGlar+IAsp: NR NPH (q.d.) +IAsp: NR NPH (b.i.d.) +IAsp: NR	NR
Pieber *et al.*, 2007[48]	IDet+IAsp: 8.7% of patients reported SAEs IGlar+IAsp: 6.9% of patients reported SAEs	The overall frequency and severity of treatment-emergent adverse events was similar with twice-daily insulin detemir and once-daily insulin glargine.With the exception of 1 patient suffering from accidental injury and bone fracture, and one patient suffering from vomiting and cholelithiasis, all SAEs were single episodes occurring in a single patient, and most of the SEAs appeared unrelated to diabetes without any distinct pattern. 4 patients in each group had clinically significant changes in funduscopy/ fundus photography during the trial. IDet+IAsp: 1 of SAEs (hypoglycemic coma*) was probably or possibly related to treatment. 3 patients withdrew due to AEs (allergic reaction in the eyes, protruding intervertebral disc, and lumbar disc lesion). IGlar+IAsp: 4 of SAEs (proliferative retinopathy, hypoglycemic coma*, two incidences of hypoglycemia*) were probably or possibly related to treatment. 1 patient withdrew after development of proliferative retinopathy.
Pieber *et al.*, 2005[42]	Approximately 63% of all patients reported AEs IDet: 9 patients (3.3%) with serious AEs NPH: 2 patients (1.6%) with serious AEs	IDet: Only 1 serious AE considered to be related to study medication (1 transient ischemic attack); 4 patients experienced injection site reactions

Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Pieber *et al.*, 2000[52]	IGlar (HOE 901-30): 3 (3%) of patients with injection site reactions IGlar (HOE 901-80): 10 (9%) of patients with injection site reactions NPH: 3 (3%) of patients with injection site reactions	Only injection site reactions reported
Porcellati *et al.*, 2004[61]	NR	NR
Raskin *et al.*, 2000[59]	IGlar: Treatment-emergent AEs regardless of relationship to study medication occurred in 250/310 patients (80.6%) NPH: Treatment-emergent AEs regardless of relationship to study medication occurred in 236/309 patients (71.4%) in NPH group	Most common AEs were injection site events (occurring in 6.1% of IGlar patients and 0.3% NPH patients). Other AEs included headache and retinal events and increase in body weight. One NPH patient withdrew due to cancer of the pancreas.
Ratner *et al.*, 2000[56]	IGlar: 84.5% NPH: 86.7%	Only reported AEs were injection site reactions (15.2% in IGlar vs. 10.4% in NPH) and one fall in each group (due to hypoglycemia) resulting in serious events. Frequency and types of AEs similar in both groups.
Robertson *et al.*, 2007[30]	IDet+IAsp: 837 AEs in 202 children (87%) NPH+IAsp: 436 AEs in 104 children (90%)	AEs were equally distributed between two treatments. The most frequest AEs in both groups were upper respiratory tract infection, headache, pharygitis, gastroenteritis, and influenza-like symptoms. AE type was similar in the two groups apart from injection site reactions (erythema, local pain, and swelling), which were more frequent with IDet. All injection site reactions were mild or moderate and reversible. IDet+IAsp: 11 events of injection site reactions in 8 (3.4%) children; 4 events of ketoacidosis for 4 children (1.7%) NPH+IAsp: 3 events of injection site reactions in 2 children (1.7%); 2 events of ketoacidosis for 2 children (1.7%)
Rosenstock *et al.*, 2000[57]	NR	Most frequent AEs considered related to study medication were injection site reactions.
Rossetti *et al.*, 2003[62]	NR	NR
Russell-Jones *et al.*, 2004[45]	Less than 2% of patients reported serious AEs with probable/possible relation to treatment.	NR except for one episode of severe hyperglycemia in NPH group.

Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Schober *et al.*, 2002[32]	IGlar: 16 (9.2%) injection site reactions; 10 (5.7%) serious AEs; 4 (2.3%) systemic allergic reactions. NPH: 15 (8.6%) injection site reactions; 24 (13.7%) serious AEs; 2 (1.1%) systemic allergic reactions.	None of the allergic reactions was considered related to the study treatments. Other AEs reported were infection, upper respiratory tract infection, pharyngitis, rhinitis, and gastroenteritis. Injection site reactions were the only AEs considered related to treatment. Serious AEs included hyperglycemia and ketoacidosis.
Standl *et al.*, 2004[46]	IDet: 3 episodes of hyperglycemia due to missed doses; 4.5% of IDet patients had injection site reactions; 11.0% of patients experienced vision disorders; 5.2% retinal disorders. NPH: 0.7% of NPH patients had injection site reactions; 2 patients had abnormal fundoscopies after 12 months; 11.2% of patients experienced vision disorders; 8.2% retinal disorders.	AEs included hyperglycemia (due to missed doses), injection site disorders, abnormal fundoscopies, vision disorders, and retinal disorders.
Vague *et al.*, 2003[44]	Approximately 70% of patients in both groups had one or more AE IDet: 3 injection site reactions; one potentially allergic reaction to IDet NPH: One injection site reaction	Most common AEs were headache, upper respiratory tract infection, and rhinitis. Others included an allergic reaction to IDet and injection site reactions in both treatment groups. One patient in the IDet group withdrew due to headache, vomiting, and malaise (not considered to be treatment-related). One patient withdrew due to uterine carcinoma (not considered to be treatment-related).
White *et al.*, 2006[34] [Abstract]	IGlar+ILis: NR NPH (or lente) +ILis: NR	NR
Witthaus *et al.*, 2001[58]	NR	NR

* Hypoglycemia can not have been separated from other AEs. b.i.d.=twice a day; BMI=body mass index; CNS=central nervous system; DM=diabetes mellitus; Glim=glimepiride; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; OAD=oral antidiabetic agent; OGLD=oral glucose-lowering drugs; q.d.=every day; RCTs=randomized controlled trials; SAE=serious adverse event; Sfu=sulfonylurea.

APPENDIX 13B: ADVERSE EVENTS DATA (EXCLUDING HYPOGLYCEMIA) FOR RCTS IN TYPE 2 DM

Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Eliaschewitz *et al.*, 2006[77]	IGlar+Glim: 137 patients (59.3%) reported AEs 10 patients (4.3%) reported SAEs, 39 patients (16.9%) with treatment-related events NPH+Glim: 150 patients (60%) reported AEs; 10 patients (4.0%) reported SAEs; 31 patients (12.4%) with treatment-related events	Treatment-related adverse events were categorized as possibly related by the investigator. The most common possibly related AEs were injection site reactions, which were seen in: IGlar+Glim: 19 patients (8.2%) NPH+Glim: 17 patients (6.8%)
Fonseca *et al.*, 2004[75] [Subgroup analysis of Rosenstock *et al.*[74]]	IGlar: 43/52 patients (83%) experienced at least one AE, 7 (13.5%) of these possibly treatment-related; 5/52 patients (10%) experienced a serious AE NPH: 41/48 patients (85%) experienced at least one AE, 3 (6.3%) of these possibly treatment-related; 8/48 patients (17%) experienced a serious AE	Most common AEs included retinal vascular disorders, upper respiratory tract infections, neuropathy, peripheral edema, and injection site hemorrhage. Most common serious AEs were cerebrovascular accidents, coronary artery disorders, myocardial infarct, hypertension, retinal vascular disorder, retinal hemorrhage, and skin carcinoma, of which only injection site hemorrhage was considered treatment-related. Body weight increased in both groups.
Fritsche *et al.*, 2003[78]	Bedtime IGlar: 414 (36 considered possibly treatment-related) Morning IGlar: 403 (45 considered possibly treatment-related) NPH: 423 (55 considered possibly treatment-related)	Only AEs specified were weight gain.
Haak *et al.*, 2005[68]	NR	Most common AEs were gastro-intestinal disorders in IDet patients; skin and appendage disorders in NPH patients. Weight gain was experienced by both groups.
Hermansen *et al.*, 2006[69]	IDet+OAD: 3 patients withdrew due to AEs; 1 case was considered related to trial product (mild allergy) NPH+OAD: 4 patients withdrew due to AEs; 1 case was considered related to trial product (mild injection site reaction)	Both insulins were well tolerated with no major safety issues arising. The adverse event profiles of the two insulins were similar, with most adverse events mild or moderate and considered unlikely related to trial products. The only between-treatment difference with a probable relation to trial medication concerned injection site reports, which were seen in: IDet+OAD: 14 events in 13 patients (9 patients suffered injection-site reactions, 2 reports of pain, and 2 reports of hematoma) NPH+OAD: 6 events in 6 patients (6 patients suffered injection-site reactions)
HOE 901/2004 Study Group, 2003[83]	IGlar 30: 3/64 patients (4.7%) experienced AEs possibly related to treatment IGlar 80: 3/72 patients (4.2%) experienced AEs possibly related to treatment NPH: 2/68 patients (2.9%) experienced AEs possibly related to treatment	IGlar 30: tachycardia, tongue edema, and injection site reaction. One serious adverse event (myocardial infarction) was not considered to be treatment-related. IGlar 80: paraesthesia, dyspepsia, and increased appetite NPH: headache and nausea with asthenia One patient in each group experienced an injection site reaction. Mean body weight increased in all groups.

Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Massi Benedetti *et al.*, 2003[81]	IGlar: 185 patients (65%) reported at least one AE; 5.5% possibly treatment-related NPH: 193 (69%) reported at least one AE; 7.5% possibly treatment-related	Most common AEs were infection, upper respiratory tract infection, bronchitis, back pain, and injection site reactions. Other AEs included increased insulin antibodies and development of E. coli antibodies.
Meneghini *et al.*, 2006[87] [Abstract]	IGlar (with Metf or Sfu): NR Pio (with Metf or Sfu): NR	NR
Meneghini *et al.*, 2005[85] [Abstract]	NR	IGlar: Most common AEs 1 edema; 6 weight increase Pio: Most common AEs 13 edema; 9 weight increase; 5 headache
Oster *et al.*, 2006[86] [Abstract]	IGlar (with Metf or Sfu): NR Pio (with Metf or Sfu): NR	IGlar was associated with a lower overall incidence of AEs and fewer discontinuations due to AEs
Pan *et al.*, 2007[76]	IGlar+Glim: 120 patients (54.3%) experienced AEs; 22 patients (10%) experienced possibly treatment-related AEs; 10 patients reported 13 SAEs NPH+Glim: 130 patients (58.3%) experienced AEs; 23 patients (10.3%) experienced possibly treatment-related AEs; 12 patients reported 12 SAEs	The majority of the possibly treatment-related AEs were injection site reaction (45 events in 31 patients) IGlar+Glim: 10 patients reported 13 SAEs (3 myocardial infarction, 1 myasthenia, 1 neuropathy, 1 pneumonia, 1 cellulitis, 1 retinal disorder, 1 eye disorder, 1 angina pectoris, 1 arthritis, 1 bone fracture, and 1 cystitis) NPH+Glim: 12 patients reported 12 events (2 hypoglycemia*, 2 myocardial infarction, 2 accidental injury, 1 back pain, 1 breast neoplasm, 1 bone disorder, 1 bone fracture, 1 urinary tract disorder, and 1 enteritis)
Philis-Tsimikas *et al.*, 2006[70]	IDet (morning)+OAD: 123 AEs in 70 patients; 8 SAEs in 8 patients; 1 death in IDet group (could be in evening group) IDet (evening)+OAD: 150 AEs in 67 patients; 5 SAEs in 5 patients NPH+OAD: 144 AEs in 82 patients; 9 SAEs in 9 patients; 1 death	All 3 insulin regimens were well tolerated and no abnormalities were detected in routine biochemical or hematologic investigations or in vital signs. The overall profiles of AEs were statistically similar among 3 groups. Most AEs, including all of the serious events and 2 deaths were considered unrelated to the study insulins. No statistically significant between-group differences were detected in incidences of AEs, serious AEs, and potential allergic reactions possibly related to study medication. Injection site reactions were considered possibly or probably related to the study insulins. IDet (morning)+OAD: 2 injection site reactions in 2 patients; 2 potential allergic reactions in 2 patients IDet (evening)+ OAD: 7 injection site reactions in 6 patients; 5 potential allergic reactions in 5 patients NPH+OAD: 2 injection site reactions in 2 patients; 1 potential allergic reactions in 1 pt
Raskin *et al.*, 2006 [72] [Abstract]	IDet+IAsp: NR IGlar+IAsp: NR	IDet+IAsp: Patients gained 1.4 kg IGlar+IAsp: Patients gained 2.9 kg

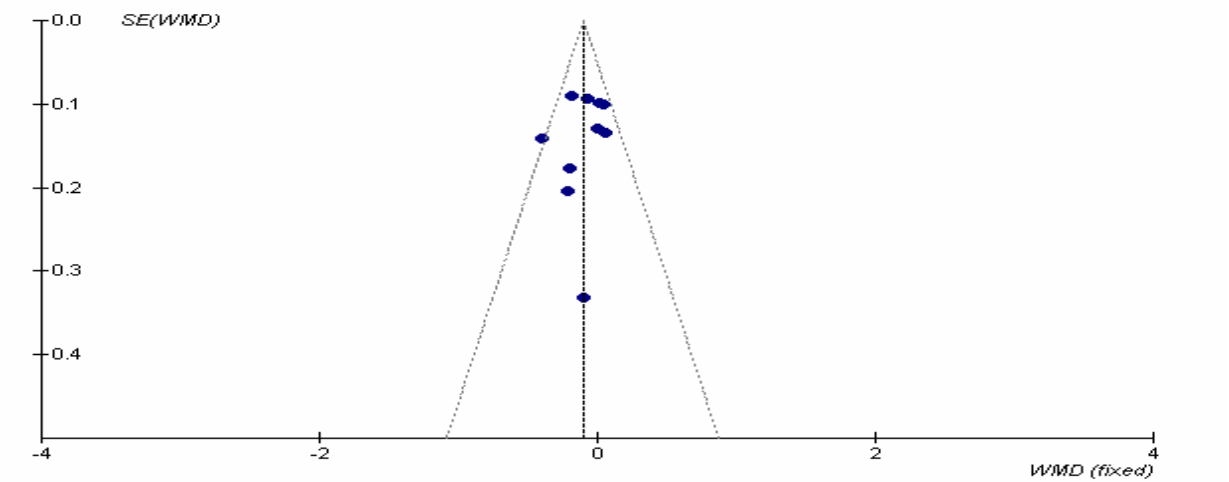
Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Raslova *et al.*, 2004[71]	IDet+IAsp: 2 patients reported; 5 patients withdrew due to AEs NPH+HI: 3 patients reported; 2 patients withdrew due to AEs	The incidence and pattern of AEs was similar between treatments, with the majority of events being mild and considered unrelated to trial products. SAEs were judged as being possibly/probably related to trial products The incidence of sudden death was considered to be unrelated to the trial products. All people recovered completely. Biochemical standard safety variables were comparable between treatments and no clinically relevant changes were observed. IDet+IAsp: 2 patients with SAE, including one who was hospitalized because of an accidental overdose of insulin and the other due to deterioration in physical ability secondary to shortness of breath at minimal exertion; 5 patients withdrew due to AEs: 1 cutaneous allergic reaction at the insulin injection site, 1 weight gain and peripheral edema, 1 pruritus, 1 shortness of breath on exertion, and 1 sudden death with unknown cause. NPH+HI: 3 patients with SAEs including 1 episode of hypolycemic coma*, one episode of severe hypoglycemia*, and one case of palpitation; 2 withdrawals were due to 1 hyperglycemia* and 1 macropapular rash with breast abscess.
Riddle *et al.*, 2003[82]	NR	Weight gain reported for both groups
Rosenstock *et al.*, 2006[73] [Abstract]	IDet+OAD: NR IGlar+OAD: NR	IDet+OAD: Body weight increased 2.7 kg IGlar+OAD: Body weight increased 3.5 kg
Rosenstock *et al.*, 2006[88]	IGlar: 2 (2%) patients discontinued due to AEs; serious AEs in 5 (4.8%) patients, none considered to be related to treatment Rosi: 9 (8%) patients discontinued due to AEs; serious AEs in 11 (9.8%) patients, 3 considered to be possibly related to treatment	IGlar: gastrointestinal infection (unrelated to treatment), average weight gain of 1.7±0.4 kg; serious AEs NR Rosi: edema (12.5% of patients), average weight gain of 3.0±0.4 kg, nausea, elevated liver function tests (considered to be related to treatment). Serious AEs included overdose, fibroid tumours, and iron deficiency (considered to be possibly related to treatment).
Rosenstock *et al.*, 2001[74]	IGlar: 27 patients (10.4%) experienced treatment-related AEs; 9 withdrew due to AEs NPH: 20 patients (7.7%) experienced treatment-related AEs; 7 withdrew due to AEs	Mild pain or cellulitis at the injection site was the only AEs specified.
Tajima *et al.*, 2006[91]	NR	No apparent differences in safety parameters.
Triplitt *et al.*, 2006[89]	IGlar+ Sfu (max) +Metf: No AEs Rosi+ Sfu (max) +Metf: No AEs	Neither therapy was associated with any AEs. No rosiglitazone-treated patient developed edema.
Vinik and Zhang, 2007[90]	IGlar+ Sfu (max) +Metf: NR Rosi+ Sfu (max) +Metf: NR	IGlar+Sfu (max) +Metf: 6.7% AEs possibly related to study medication Rosi+Sfu (max) +Metf: 28.6% AEs possibly related to study medication p<0.0001 between the two group comparison.
Wang *et al.*, 2007[79]	IGlar+Glip: NR NPH+Glip: NR	IGlar+Glip: the body weight gain was 1.47±1.04 kg NPH+Glip: the body weight gain was 1.20±1.17 kg

Study	Number of Adverse Events in Each Arm	Description of Adverse Events
Yki-Järvinen *et al.*, 2006[80]	IGlar: 33 patients (54%); one serious AE, not considered to be related to treatment NPH: 24 patients (49%); 4 serious AEs, not considered to be related to treatment	Most common AEs were infections and musculoskeletal and gastrointestinal disorders, with no differences between the groups IGlar: mean weight gain of 2.6±0.6 kg; serious AE was endometriosis; one withdrawal due to pancreatic cancer NPH: mean weight gain of 3.5±0.7 kg; serious AEs were anaphylactic reaction, atrial fibrillation and cardiac failure, gastroenteritis, and pulmonary emphysema
Yki-Järvinen *et al.*, 2000[84]	No difference in treatment-emergent AEs possibly related to study medication	IGlar: mean weight gain of 2.57±0.23 kg NPH: mean weight gain of 2.34±0.23 kg

*Hypoglycemia can not be separated from other AEs. AE=adverse events; DM=diabetes mellitus; Glim=glimepiride; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; Glim=glimepiride; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; OAD=oral antidiabetic agent; Pio=pioglitazone; RCTs=randomized controlled trials; Rosi=rosiglitazone; SAEs=serious adverse events; Sfu=sulfonylurea.

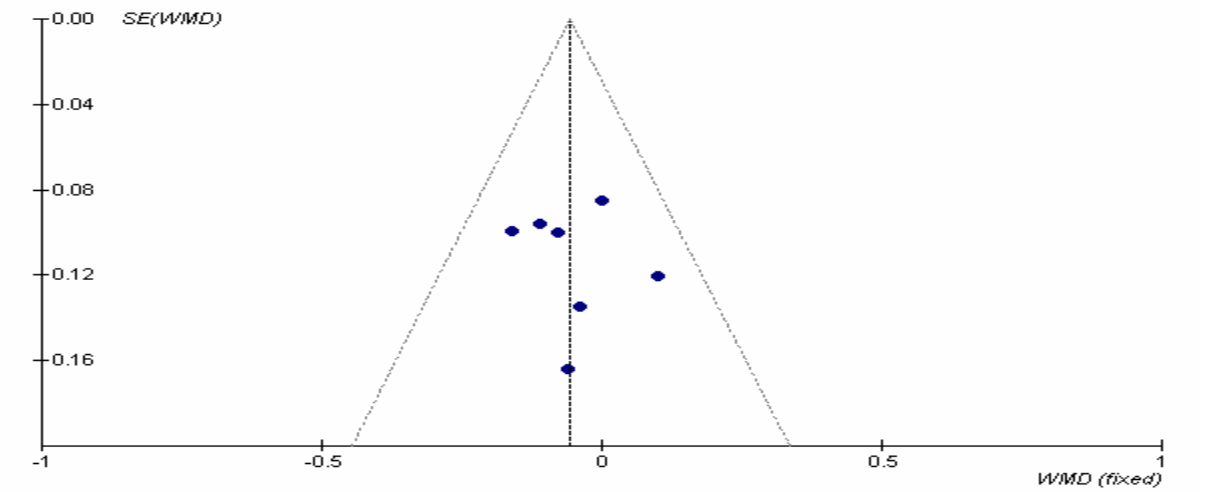
APPENDIX 14: FUNNEL PLOTS

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



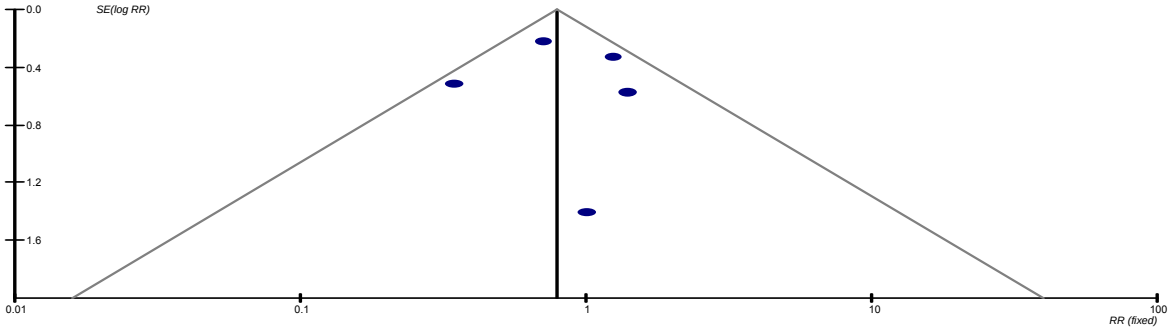
A1c=glycosylated hemoglobin; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SE=standard error; WMD=weighted mean difference.

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



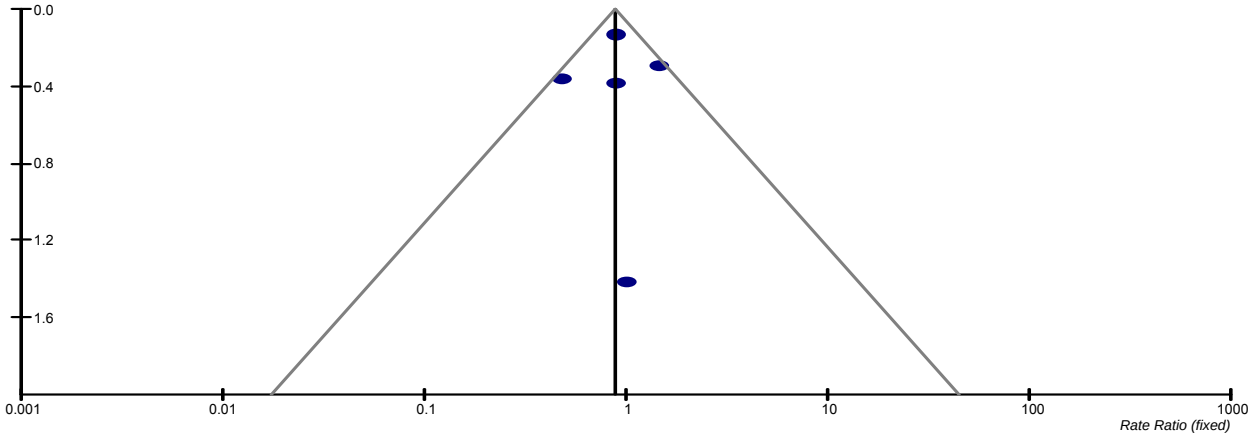
A1c=glycosylated hemoglobin; DM=diabetes mellitus; Idet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs, randomized controlled trials; SE=standard error; WMD=weighted mean difference.

Figure 3: Funnel plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in adult patients – Severe hypoglycemia: Events



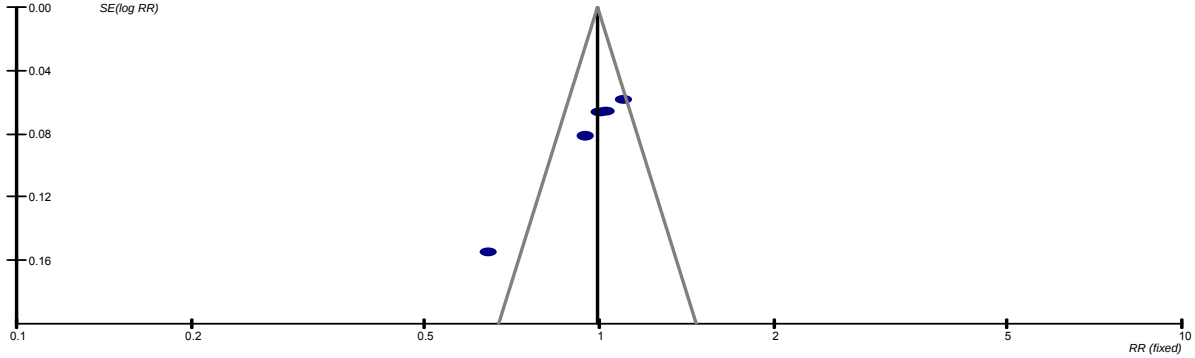
DM=diabetes mellitus; IGar=insulin glargine; log RR=log of the relative risk for hypoglycemia; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

Figure 4: Funnel plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in adult patients – Severe hypoglycemia: Rate ratio



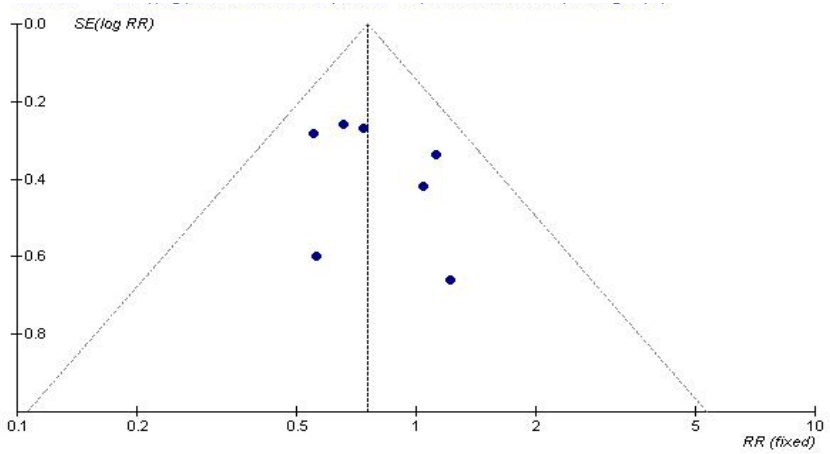
DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials.

Figure 5: Funnel plot of all RCTs that examined the use of IGlar versus NPH for the treatment of type 1 DM in adult patients – Relative risk of nocturnal hypoglycemia: Events



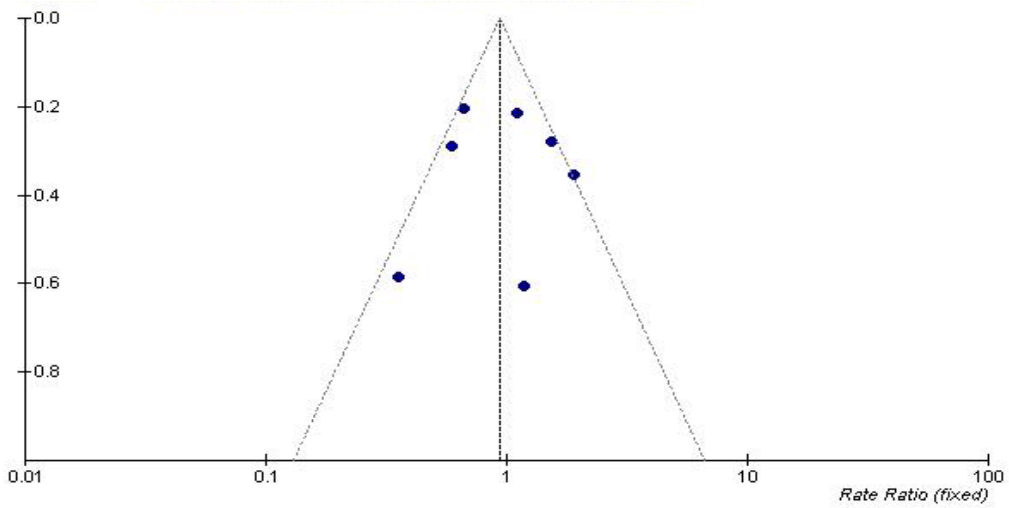
DM=diabetes mellitus; IGlar=insulin glargine; log RR=log of the relative risk for hypoglycemia; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

Figure 6: Funnel plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Severe hypoglycemia, RR



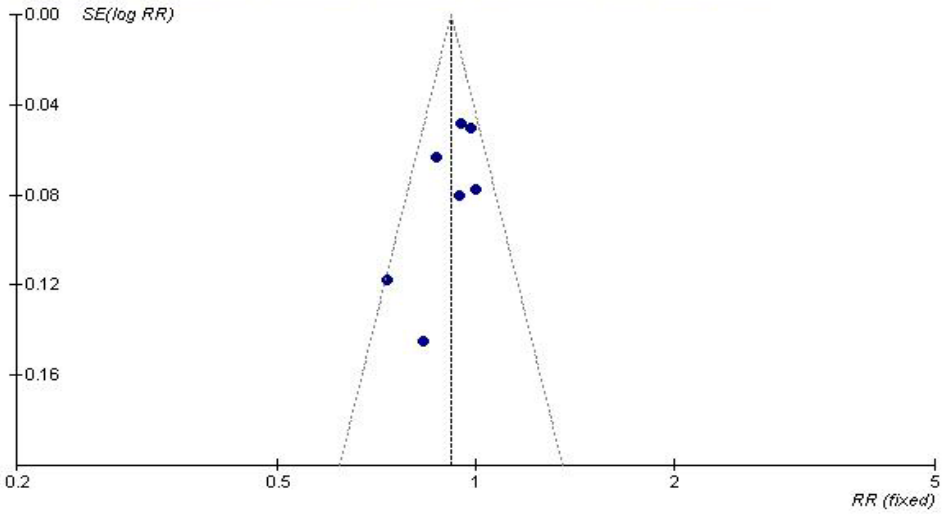
DM=diabetes mellitus; IDet=insulin detemir; log RR=log of the relative risk for hypoglycemia; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

Figure 7: Funnel plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Rate ratio of severe hypoglycemia



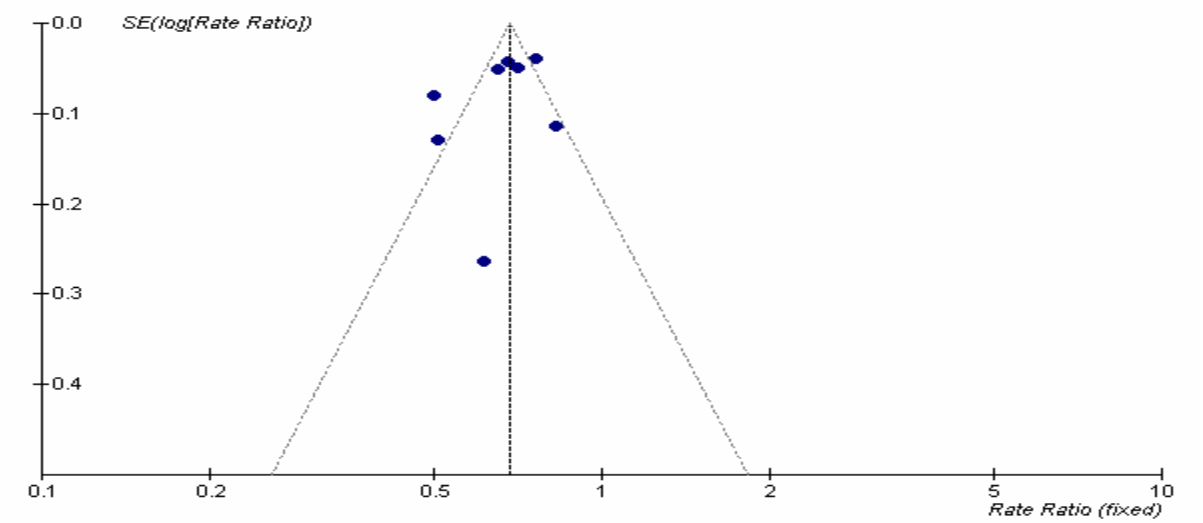
DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials.

Figure 8: Funnel plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – RR of nocturnal hypoglycemia



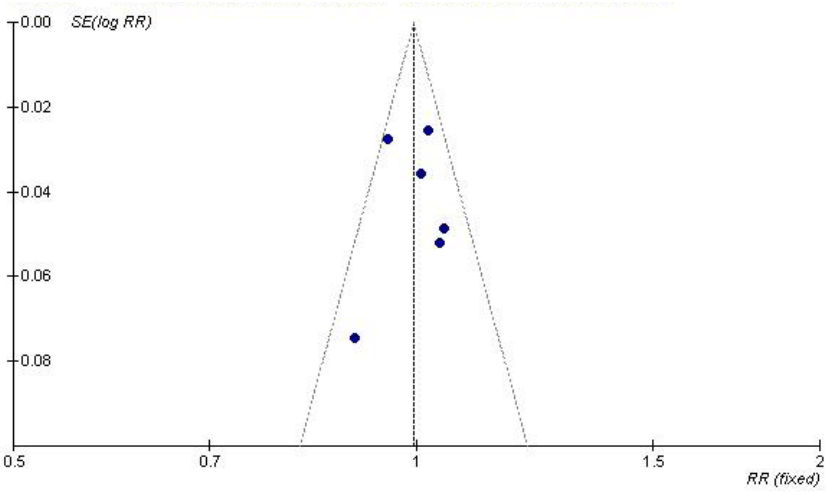
DM=diabetes mellitus; IDet=insulin detemir; log RR=log of the relative risk for hypoglycemia; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

Figure 9: Funnel plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Rate ratio of nocturnal hypoglycemia



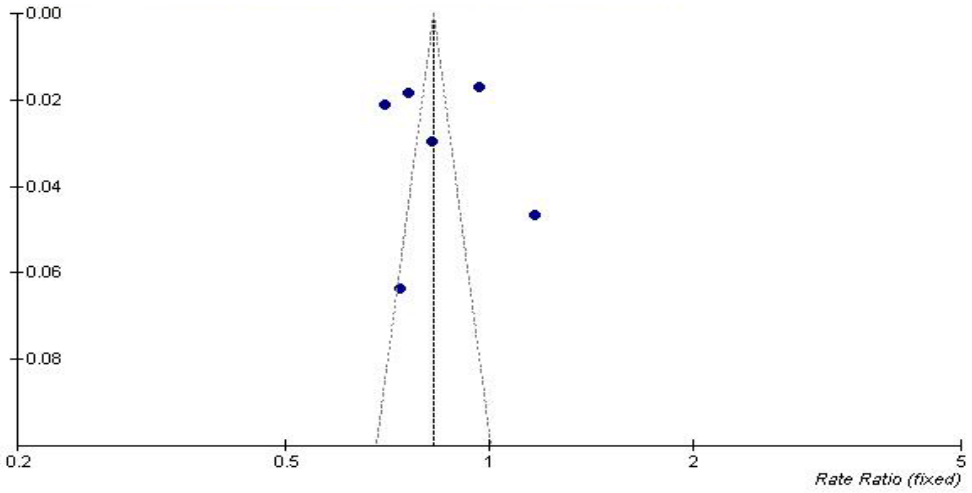
DM=diabetes mellitus; IDet=insulin detemir;NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SE=standard error.

Figure 10: Funnel plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – RR of overall hypoglycemia



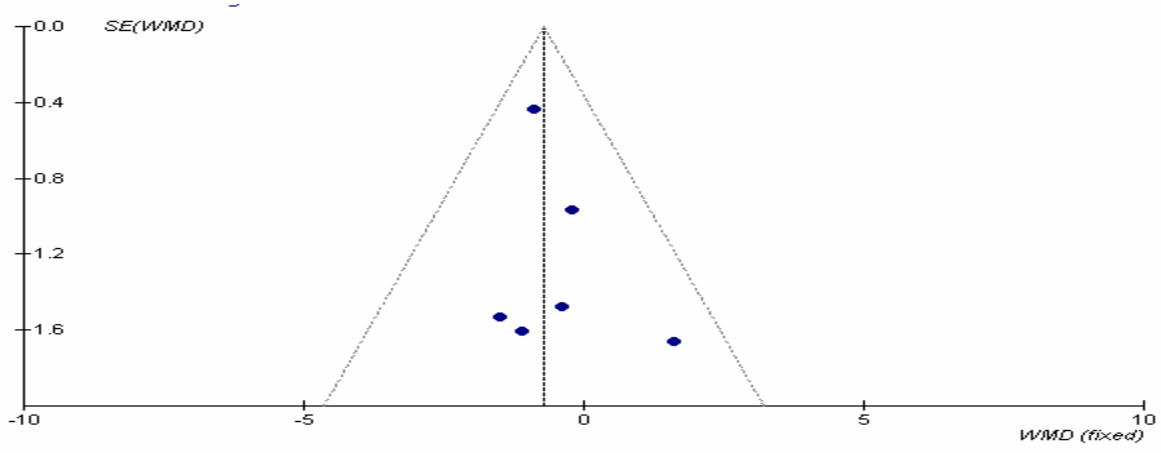
DM=diabetes mellitus; IDet=insulin detemir; log RR=log of the relative risk for hypoglycemia; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

Figure 11: Funnel plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Rate ratio of overall hypoglycemia



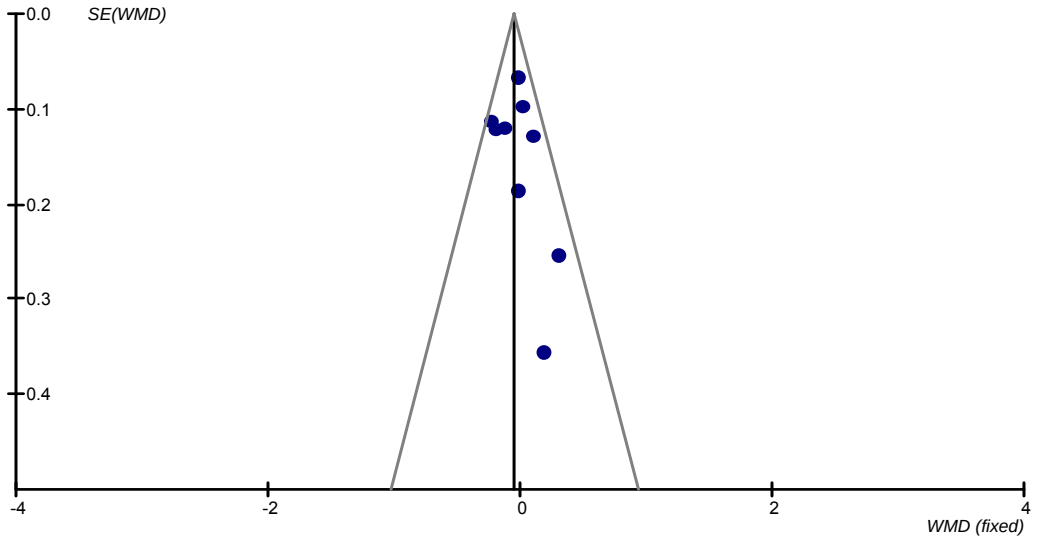
DM=diabetes mellitus; IDet=insulin detemir;NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials.

Figure 12: Funnel plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – Body weight, WMD



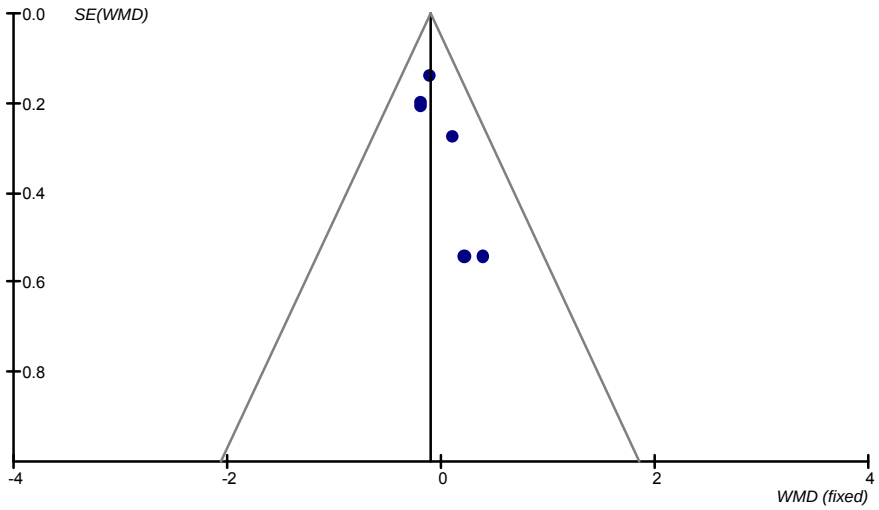
DM=diabetes mellitus; IDet=insulin detemir; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials; SE=standard error; WMD=weighted mean difference.

Figure 13: Funnel plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – A1c WMD



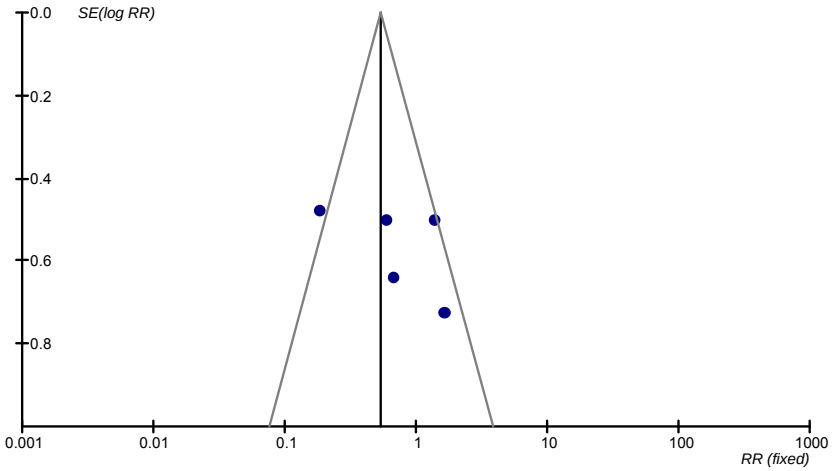
A1c=glycosylated hemoglobin; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SE=standard error; WMD=weighted mean difference.

Figure 14: Funnel plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – FPG



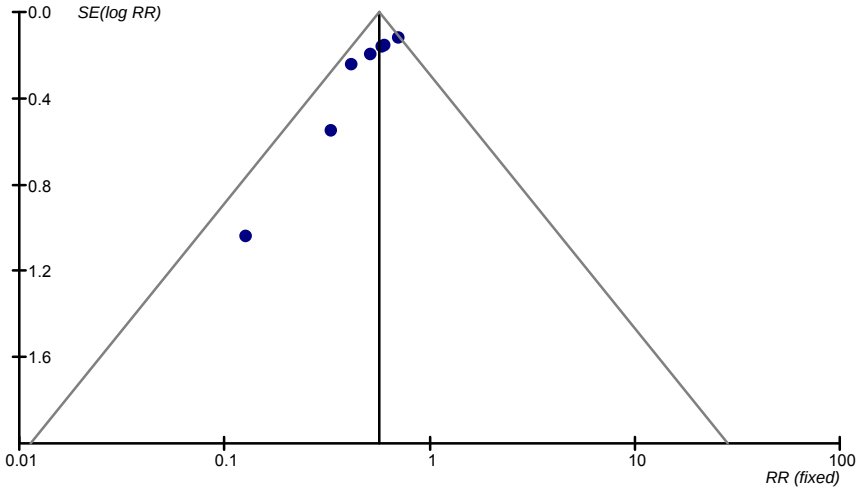
DM=diabetes mellitus; FPG=fasting plasma glucose; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SE=standard error; WMD=weighted mean difference.

Figure 15: Funnel plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of severe hypoglycemia



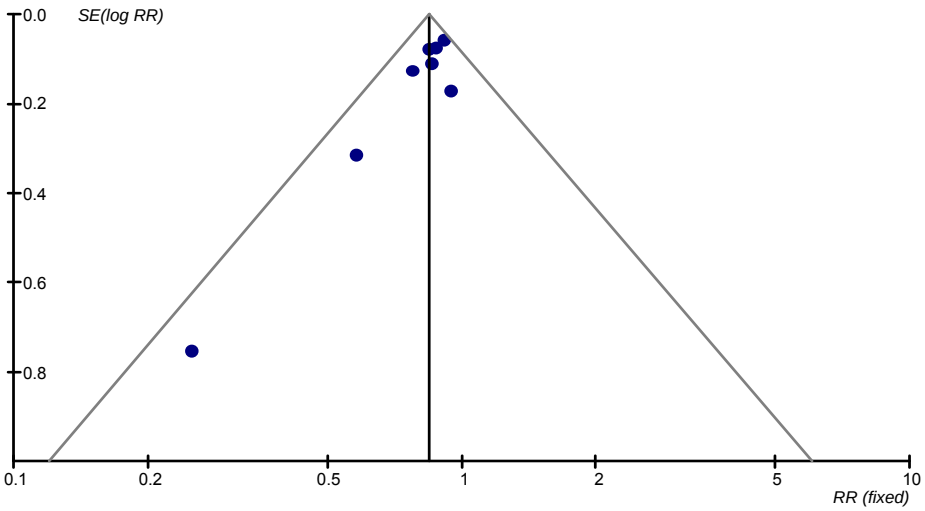
DM=diabetes mellitus; IGlar=insulin glargine;log RR=log of the relative risk for hypoglycemia; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

Figure 16: Funnel plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of nocturnal hypoglycemia



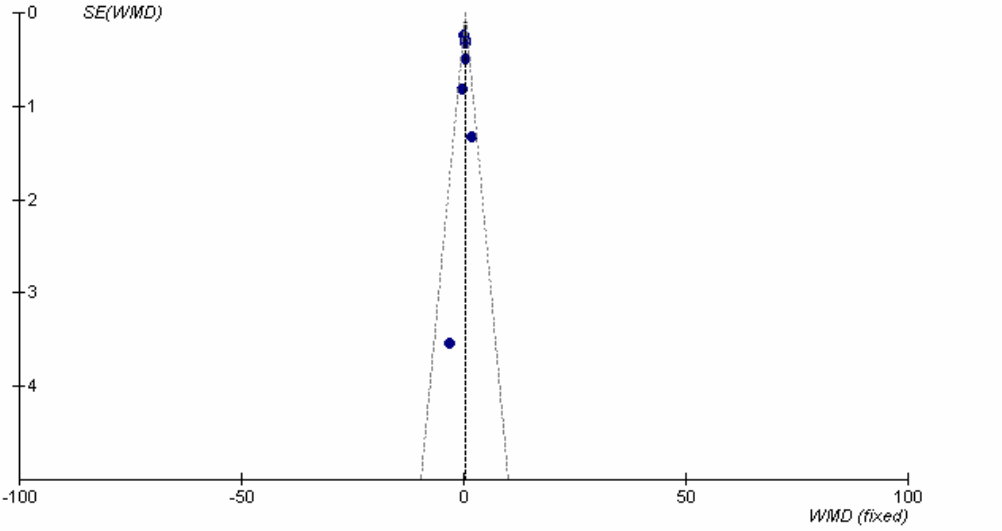
DM=diabetes mellitus; IGlar=insulin glargine; log RR=log of the relative risk for hypoglycemia; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

Figure 17: Funnel plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – RR of overall hypoglycemia



DM=diabetes mellitus; IGlar=insulin glargine; log RR=log of the relative risk for hypoglycemia; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; RR=relative risk; SE=standard error.

Figure 18: Funnel plot of all RCTs that examined the use of IGlar+OAD versus NPH+OAD for the treatment of type 2 DM in adult patients – Body weight



DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SE=standard error; WMD=weighted mean difference.

APPENDIX 15A: STUDY-LEVEL QUALITY OF LIFE AND PATIENT SATISFACTION DATA FOR RCTS IN 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 (Perceived Frequency of Hyperglycemia)
Witthaus *et al.*, 2001[58]	IGlar+HI	+1.27 (from baseline), p<0.001	0.37, p=0.002	0.32, p<0.001	0.25, p<0.001	0.39, p<0.001	1.22 (from baseline), NS	-0.19, NS	-0.31, NS	0.33, NS	0.39, NS	-0.55, p=0.038
	NPH+HI	-0.56	0.08	0.09	0.00	-0.24	1.57	-0.24	-0.53	0.40	0.35	-0.30

* Only RCTs reported the quality-of-life data are listed here. DM=diabetes mellitus; DTSQ=Diabetes Treatment Satisfaction Questionnaire; IGlar=insulin glargine; HI=human insulin; NPH=neutral protamine Hagedorn; NS=not significant; RCTs=randomized controlled trials; WBQ=well-being questionnaire.

APPENDIX 15B: STUDY-LEVEL QUALITY OF LIFE AND PATIENT SATISFACTION DATA FOR RCTS IN TYPE 1 DM*

Study	Treatment	Results		
Eliaschewitz *et al.*, 2006[77]	IGlar+ glimepiride	DTSQc Baseline: 12.6±5.9 Endpoint: 16.6±2.6		Treatment satisfaction: DTSQ scores p=<0.02 (changes from baseline: IGlar vs. NPH)
	NPH+ glimepiride	Baseline: 12.5±6.3 Endpoint: 16±3.3		
Oster *et al.*, 2006 [abstract][86] Meneghini *et al.*, 2006 [abstract][87]	IGlar Pioglitazone	HRQoL assessments were conducted at baseline and at each 10 follow-up visits and included the 34-item Diabetes Symptom Checklist–Revised (DSC-R), the Emotional Well-being scales, and General Health Perceptions scales from the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). A total of 230 patients completed the baseline and week-48 HRQoL assessments (n=118, IGlar; n=112, Pio). HRQoL change scores from baseline to week 48 generally favoured IGlar; findings were statistically significant (p<0.05) for the domains of hyperglycemia distress, fatigue distress, and total distress. In multivariate repeated-measure analyses, IGlar was associated with significantly better outcomes for hyperglycemia symptoms (p≤0.001), ophthalmologic symptoms (p=0.004), hyperglycemia distress (p<0.001), hypoglycemia distress (p=0.014), fatigue distress (p=0.005), ophthalmologic distress (p<0.001), and cardiovascular distress (p=0.025). Poorer HRQoL was associated with early study termination and higher A1C values. In oral monotherapy failures, IGlar yielded better glycemic control and better HRQoL than Pio.		
Vinik and Zhang, 2007[90] [IGlar+SU+Metf vs. rosiglitazone+SU+Metf]	**Item**	**HRQOL score:**		**comments**
		IGlar	**rosiglitazone**	
	Hyperglycemia symptoms	42.8±36.1	35.7±34.4	Fatigue distress* (p=0.017) between groups. P-values for all other HRQoL were NS. Pts with glargine had higher scores in all the diabetes symptom checklist-revised symptoms and distress domains, including total scores for symptoms and distress.
	Hyperglycemia distress	33.8±16.3	32.2±16.1	
	Mood symptoms	34.3±38.2	27.4±35.9	
	Mood distress	30.6±14.2	28.8±14.2	
	Cardiovascular symptoms	23.1±29.8	19.5±24.8	
	Cardiovascular distress	27.5±10.9	26.0±8.9	
	Neuropathic sensory symptoms	30.9±31.2	29.5±32.1	
	Neuropathic sensory distress	29.7±12.1	29.2±12.3	
	Neuropathic pain symptoms	19.3±31.1	15.6±24.1	
	Neuropathic pain distress	27.1±14.0	25.2±8.8	
	Fatigue symptoms	55.5±39.9	47.8±37.0	
	Fatigue distress*	42.5±21.2	36.2±17.1	
	Cognitive symptoms	35.8±35.9	30.8±32.9	
	Cognitive distress	32.5±15.7	29.4±12.5	
	Ophthalmologic symptoms	26.9±31.0	21.9±27.8	
	Ophthalmologic distress	27.9±11.6	25.6±7.9	

Study	Treatment	Results			
		Total symptoms	33.3±23.8	28.4±21.4	
		Total distress	31.3±10.5	29.0±8.7	
		Perception of general health	46.3±21.6	50.5±21.0	
		Emotional well-being	74.1±18.4	76.7±18.4	

* Only RCTs reporting QOL data are listed here. DM=diabetes mellitus; DTSQ=Diabetes Treatment Satisfaction Questionnaire; DTSQc=Diabetes Treatment Satisfaction Questionnaire Change; HRQOL=health-related quality of life; IGlar=insulin glargine; Metf=metformin; NPH=neutral protamine Hagedorn; NS=not significant; Pio=pioglitazone; QOL=quality of life; RCTs=randomized controlled trials; SU=sulfonylurea; vs.=versus.

APPENDIX 16A: STUDY-LEVEL MORTALITY DATA FROM RCTS IN TYPE 1 DM*

Study	Comparators	No. of Patients at Baseline	Treatment Duration	Number of Deaths (%)	Cause of Death
Hermansen *et al.*, 2004[49]	IDet+IAsp	298	18 weeks	none	NA
	NPH+HI	297	18 weeks	1	Due to a lung tumour, unlikely to be related to the trial products
Kolendorf *et al.*, 2006[39]	IDet+IAsp	131	16 weeks	none	NA
	NPH+IAsp	131	16 weeks	1	Died from a myocardial infarction during the first treatment period while receiving NPH
Pieber *et al.*, 2005[42]	$IDet_{m+d}$+IAsp	139	16 weeks	none	NA
	$IDet_{m+b}$+IAsp	132	16 weeks	1	Unknown
	NPH_{m+b}+IAsp	129	16 weeks	none	NA
Raskin *et al.*, 2000[59]	IGlar+ILis	310	16 weeks	none	NA
	NPH+ILis	309	16 weeks	none	NA
Ratner *et al.*, 2000[56]	IGlar+HI	264	28 weeks	none	NA
	NPH+HI	270	28 weeks	1	Death secondary to cardiopulmonary arrest, not considered to be related to study medication

*Only RCTs reporting mortality data are listed. DM=diabetes mellitus; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; HI=human insulin; m+b=morning and bedtime; m+d=morning and dinner time; NA=not applicable; NPH=neutral protamine Hagedorn; RCTs=randomized controlled trials.

APPENDIX 16B: STUDY-LEVEL MORTALITY DATA FOR RCTS IN TYPE 2 DM*

Study	Treatment (tx) Arm	No. of Patients at Baseline	Treatment Duration	Number of Deaths (%)	Cause of Death
Eliaschewitz *et al.*, 2006[77]	IGlar+Glim	231	24 weeks	none	NA
	NPH+Glim	250	24 weeks	none	NA
Fritsche *et al.*, 2003[78]	IGlar (morning)+Glim	236	24 weeks	none	NA
	IGlar (bedtime)+Glim	227	24 weeks	2	Not related to study medication
	NPH (bedtime)+Glim	232	24 weeks	1	Not related to study medication
Haak *et al.*, 2005[68]	IDet+IAsp	341	26 weeks	1	Patient had history of coronary heart disease; death not considered to be related to study medication
	NPH+IAsp	164	26 weeks	none	NA
Massi Benedetti *et al.*, 2003[81]	IGlar	289	52 weeks	1	Not considered to be related to study medication
	NPH	281	52 weeks	6	Not considered to be related to study medication
Meneghini *et al.*, 2005[85]	IGlar+OAD vs. Pioglitazone+OAD	253	48 weeks	1	Patient in IGlar+OAD treatment arm died from multiple blunt trauma
HOE 901/2004 Study group, 2003[83]	IGlar [30]+OAD	64	4 weeks	none	NA
	IGlar [80]+OAD	72	4 weeks	none	NA
	NPH+OAD	68	4 weeks	none	NA
Philis-Tsimikas *et al.*, 2006[70]	IDet	169	20 weeks	1	Due to cerebrovascular accident, unrelated to the study insulin
	NPH	164	20 weeks	1	Due to cerebrovascular accident, unrelated to the study insulin
Raslova *et al.*, 2004[71]	IDet+IAsp	195	22 weeks	1	Unknown cause for death and considered to be unrelated to the trial product
	NPH+HI	199	22 weeks	none	NA

*Only RCTs reporting mortality data are listed. DM=diabetes mellitus; Glim=glimepiride; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; m+b=morning and bedtime; m+d=morning and dinner time; NA=not applicable; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; tx=treatment; vs.=versus.

APPENDIX 17: STUDY-LEVEL BLOOD PRESSURE DATA FROM RCTS IN TYPE 2 DM

Study	Comparators	BP at Baseline (mmHg)	BP at Endpoint (mmHg)	BP Change From Baseline (mmHg)	p-value Endpoint vs. Baseline	p-value Between Treatments
Triplitt *et al.*, 2006[89]	IGlar	SBP 131±4* DBP 69±2*	SBP 129±5* DBP 70±3*	NR	NS NS	p<0.01
	rosiglitazone	SBP 127±4* DBP 67±2*	SBP 129±4* DBP 60±4*	NR	NS p<0.05	
Yki-Järvinen *et al.*, 2000[84]	IGlar+OAD	SBP 145±1* DBP 84±1*	SBP 145±1* DBP 83±1*	NR	NR	Remain unchanged
	NPH+OAD	SBP 145±1* DBP 85±1*	SBP 145±1* DBP 82±1*	NR	NR	

*mean±SE. BP=blood pressure; DBP=diastolic blood pressure; DM=diabetes mellitus; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; OAD=oral antidiabetic agent; RCTs=randomized controlled trials; SBP=systolic blood pressure; vs.=versus.

APPENDIX 18: STUDY-LEVEL CHOLESTEROL – LDL DATA FROM RCTS IN TYPE 2 DM

Study	Comparators	LDL at Baseline	LDL at Endpoint	LDL Change From Baseline	p-value Endpoint vs. Baseline	p-value Between Treatments
Rosenstock *et al.*, 2006[88]	IGlar+Sfu (max)+Metf	117 mg/dL	115 mg/dL	-1.4 %	NR	p=0.002
	Rosi+Sfu (max)+Metf	106 mg/dL	120 mg/dL	13.1%	NR	
Triplitt *et al.*, 2006[89]	IGlar	119±10* mg/dL	103±7* mg/dL	NR	p=0.03	p=0.003
	rosiglitazone	103±11* mg/dL	142±9* mg/dL	NR	p=0.03	
Yki-Järvinen *et al.*, 2006[80]	IGlar+Metf	2.8±0.1* mmol/L	2.8±0.1* mmol/L	NR	NR	Remained unchanged
	NPH+Metf	2.9±0.1* mmol/L	2.9±0.1* mmol/L	NR	NR	
Yki-Järvinen *et al.*, 2000[84]	IGlar+OAD	NR	3.21±0.06* mmol/L	NR	NR	No difference between the treatments
	NPH+OAD	NR	3.27±0.08* mmol/L	NR	NR	

*mean±SE. DM=diabetes mellitus; IGlar=insulin glargine; LDL=low-density lipoprotein; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; OAD=oral antidiabetic; RCTs=randomized controlled trials; Rosi=rosiglitazone; Sfu=sulfonylurea; vs.=versus.