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OPTIMAL THERAPY REPORT

COMPUS

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GRADE Evidence Profiles on Long- and Rapid-Acting Insulin Analogues for the Treatment of Diabetes Mellitus

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 is a comprehensive review of the existing public literature available to CADTH at the time it was prepared and it was guided by expert input and advice throughout its preparation. The authors have also considered input from other stakeholders.

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Abbreviations

A1c	glycosylated hemoglobin
BMI	body mass index
CERC	COMPUS Expert Review Committee
CI	confidence interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
DKA	diabetic ketoacidosis
DM	diabetes mellitus
ER	emergency room
FPG	fasting plasma glucose
GD	gestational diabetes
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL-C	high-density lipoprotein cholesterol
HRQoL	health-related quality of life
ITT	intention-to-treat
LA	long-acting
LDL-C	low-density lipoprotein cholesterol
NE	no evidence
NR	not reported
PVD	peripheral vascular disease
RA	rapid-acting
RCT	randomized controlled trials
RR	relative risk
TC	total cholesterol
TIA	transient ischemic attack
WMD	weighted mean difference

Glossary

Consistency – Refers to the similarity of estimates of effect across studies included in a meta-analysis.

Directness – Refers to the extent to which the participants, interventions, and outcome measures in studies are similar to the real world in terms of patient population enrolled, treatments administered, and outcomes measured.

I^2 – This statistic denotes the percentage of heterogeneity between studies that is *not* due to random variation (i.e., chance). An I^2 of 25% is considered to represent a low level of heterogeneity; 50%, moderate heterogeneity; and 75%, a high level of heterogeneity.

Imprecision – Refers to the reliability of an estimate of effect. The width of the 95% CI is an indication of the precision of an estimate: the narrower the interval, the more precise the estimate of effect. The degree of precision is related to aspects of study design such as the sample size and the instrument used to measure the parameter, as well as the variability of the parameter in the population.

Limitations of study quality – Refers to the threats to the validity of study methods and execution.

95% confidence interval (CI) – An interval surrounding a point estimate [such as a risk ratio (RR), rate ratio, or weighted mean difference (WMD)] that has a 95% likelihood of containing the "true" value of the population parameter being measured. The 95% CI indicates the statistical significance of a result.

Rate ratio – Compares the ratio of the number of events per person-time observed in the arm of a trial exposed to the intervention, to the number of events per person-time observed in the control arm.

Relative risk – The risk of an event (or of developing an outcome) relative to exposure (i.e., treatment). Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Reporting bias – Arises from the tendency for researchers and editors to handle experimental results that are positive differently from results that are negative. A common method for assessing the possibility that negative results have been systematically under-reported is the funnel plot, a graph of the individual estimates of effect from each study included in a meta-analysis. Considerable asymmetry in the funnel plot indicates the presence of reporting bias.

Strong association – A relative risk between two and five or relative risk reduction of 50-80% as strong, and a relative risk over five or relative risk reduction of >80% as very strong.

Weighted mean difference – The average of the reported differences in an outcome between intervention and control arms in two or more studies, weighted by study precision. In most cases, precision is approximately proportional to sample size, therefore, larger studies are assigned the greater weight.

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Introduction

The Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) has applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to its work. The GRADE approach was developed to assist recommendation-making groups in making judgments about the quality of evidence and the overall strength of generated recommendations.[1] The steps in this process include identifying outcomes that are either critical or important for making a decision about the treatment of diabetes mellitus (DM), evaluating the quality of evidence across studies for each outcome, and judging the balance between benefit and harm.[1] For each treatment considered, the evidence under consideration is presented in the GRADE evidence profiles. These profiles also assess the quality of the evidence. Evidence related to the insulin analogues projects was derived from two systematic reviews[2,3] conducted by COMPUS.

For a complete discussion on the GRADE approach and its application in the recommendation-creating process, readers are referred to references[1,4,5] at the end of this report. The key components for establishing the quality of evidence and the strength of the recommendations are presented in Appendices 1 and 2, respectively.

Objective

To use the GRADE approach to present evidence to the COMPUS Expert Review Committee (CERC) on the optimal use of rapid-acting (RA) and long-acting (LA) insulin analogues for the treatment of type 1 and 2 diabetes mellitus (DM) and gestational diabetes (GD).

Methodology

1. Establishing and Ranking Outcomes

As suggested by the authors of the GRADE approach, only critical and important outcomes should be included in the GRADE evidence profiles.[1] COMPUS staff, in consultation with members of CERC, identified all potential outcomes related to DM. CERC members independently ranked each outcome for their relative importance to decision making on a nine-point scale[6] (9-7=critical, 6-4=important, 3-1=not important) for type 1 DM in adult and pediatric patients and type 2 DM in adults. The relative importance of outcomes for patients with gestational diabetes was not established due to the uniqueness of this condition. Individual votes were pooled and the results were reported back to CERC members. CERC members discussed the relative importance and decided on the final ranking of each outcome by consensus. Outcomes were identified as either critical, important, or not important based on their overall score (9-7=critical, 6-4=important, 3-1=not important).

2. Developing GRADE Evidence Profiles

COMPUS used the GRADE Profiler (GRADEpro©)[6] software to develop unique GRADE evidence profiles for each medication comparison (e.g., insulin lispro versus regular insulin) for each population of interest (e.g., adults, adolescents). Results from two meta-analyses[2,3] of RCTs were used to populate the GRADE evidence profiles. The Jadad scale[7], with three

additional criteria, was applied to determine the quality of each study (i.e. considering randomization, blinding, withdrawal, adequacy of allocation concealment, blinding of outcome assessors, and intention-to-treat (ITT) analysis). COMPUS verified the direction, magnitude, and significance of individual study effects. COMPUS also tested for heterogeneity using I^2 to judge consistency, and investigated possible causes of heterogeneity if I^2 >50%. COMPUS relied on participants, interventions, and outcome measures to determine directness. Any decisions made by COMPUS were described below the GRADE evidence profiles as footnotes.

Each GRADE evidence profile included:

- Number of studies providing evidence on the outcomes of interest
- Key components related to quality of evidence
  - Study design
  - Limitations of study quality
  - Consistency of results across studies
  - Directness of evidence to the population of interest
  - Imprecision of study results
  - Other considerations related to the quality of the evidence
- Summary of findings
  - Total number of patients per treatment arm
  - Number of patients with events
  - Relative risk (RR) or rate ratio with 95% confidence interval (CI) for dichotomous outcomes; weighted mean difference (WMD) with 95% CI for continuous outcomes
  - Overall quality of evidence
- Relative importance of outcome, as determined by the CERC.

GRADEpro[6] automatically categorizes the quality of the body of evidence as high, moderate, low, and very low for each outcome, once the profiles are filled out.

Results

CERC identified 32 outcomes as relevant to making decisions related to the use of insulin products in the management of DM. Fourteen of those outcomes were ranked as critical, and 12 as important, when considering the treatment strategies for pediatric patients. For adult patients with type 1 DM, 16 and 10 outcomes were ranked critical and important, respectively. CERC ranked 15 outcomes as critical and 17 as important for the treatment of type 2 DM in an adult population. Identified outcomes and their ranking are provided in Appendix 3.

COMPUS generated 18 GRADE evidence profiles presenting evidence on the use of RA and LA insulin analogues for the treatment of type 1 DM, 14 profiles for type 2 DM, and one profile for gestational diabetes. The 33 individual evidence profiles are presented in Appendices 4, 5, and 6 for type 1 DM, type 2 DM, and GD, respectively.

GRADE evidence profiles were not generated for the use of LA insulin analogues in pregnant adults and pre-adolescents with type 1 DM, for LA insulin analogues used in GD, and for both RA and LA insulin analogues used in pediatric and pregnant adults with type 2 DM, due to the lack of studies.

Discussion

Generating GRADE evidence profiles is a complex process that relies heavily on the researcher's ability to make informed but, nonetheless, subjective decisions about the evidence. To ensure consistency of judgment in assessing the information, steps were taken to make certain that all researchers had a comprehensive understanding of the research questions, knowledge of study methodology, and familiarity with the data included in the systematic reviews and meta-analyses.

A major advantage of using the GRADE approach is the process of identifying and ranking outcomes as critical or important to those making decisions about the prescribing and use of insulin products in the management of DM. This step, which was performed by the CERC, ensures that relevant evidence is identified, evaluated, and presented in a systematic and detailed manner to the recommendation-making group. Thus, the GRADE approach enabled COMPUS to provide an enhanced level of transparency when developing evidence-based recommendations.

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6. *GRADE Profiler 3.0.1* [software]. GRADE Working Group; 2007.
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Appendix 1 - Key components related to quality of evidence

The quality of evidence indicates the extent to which one can be confident that an estimate of effect is correct. Judgments about the quality of evidence require consideration of four key elements:[1,6]

Study design – Refers to the basic study design, which is broadly categorized as randomized trials, observational studies and any other evidence. The high, low, and very low quality is assigned to them, respectively.

Limitation of study quality – Refers to the threats to the validity of study methods and execution. For RCTs, the methodological components – such as adequacy of allocation concealment, blinding, and follow-up – should be considered. A serious limitation will lower the quality of the evidence by one level and a very serious limitation will lower it by two levels.

Consistency – Refers to the similarity of estimates of effect across studies. Differences in the direction of effect, the size of the differences in effect, and significance of the differences guide the decision about whether important inconsistency exists. If there is important, unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases.

Directness – Refers to the extent to which the participants, interventions, and outcome measures are similar to those of interest. Some uncertainty will lower the quality by one level and major uncertainty will lower it by two levels. Studies using surrogate outcomes generally provide less direct evidence than those using outcomes that are important to people. It is, therefore, prudent to use more stringent criteria when considering the directness of evidence for surrogate outcomes.

Evidence is initially categorized based on study design. Limitations of study quality, important inconsistency of results, or uncertainty about the directness of the evidence can lower the grade of evidence.

In addition, imprecise or sparse data and reporting bias can lower the quality of the evidence by one level while a strong association, presence of a dose-response gradient of the effect, and plausible confounders can raise the quality of the evidence by one to two levels.

Appendix 2 - Key components related to the strength of recommendations

The strength of a recommendation indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm.[1]

Judgments about the strength of a recommendation require consideration of the balance between benefits and harms, the quality of the evidence, translation of the evidence into specific circumstances, and the certainty of the baseline risk, as well as costs (resource utilization) prior to making recommendations.

If there is uncertainty about translating the evidence into practice in a specific setting, or uncertainty about baseline risk, this may lower the confidence in a recommendation.

Appendix 3 – All identified outcomes and their final ranking by CERC

Outcome		Type 1 Pediatric	Type 1 Adult	Type 2 Adult
SURROGATE OUTCOMES				
Blood pressure	systolic	N	N	I
	diastolic	N	N	I
Cholesterol	LDL-C levels	N	N	I
	TC:HDL-C ratio	N	N	I
HbA1c levels		C	C	C
Plasma glucose	fasting (FPG)	N	N	C
	2-hour post-prandial	I	I	I
Weight /weight gain / BMI / waist circumference / waist-hip ratio		I	I	I
SHORT-TERM COMPLICATIONS/ADVERSE EFFECTS				
DKA		C	C	I
Hyperosmolar hyperglycemic non-ketotic coma		N	N	C
Hypoglycemia	severe	C	C	C
	nocturnal	C	C	C
	overall	C	C	I
LONG-TERM COMPLICATIONS				
Congestive heart failure		C	C	C
Ischemic heart disease		I	C	C
Lower-limb		I	I	I
Mortality – all-cause		C	C	C
Nephropathy		C	C	C
Neuropathy		C	C	C
PVD		I	C	C
Retinopathy		C	C	C
Stroke/TIA		I	C	C
HUMANISTIC OUTCOMES				
HRQoL	diabetes-specific	C	C	C
	generic	C	C	I
Patient satisfaction	with diabetes care	I	I	I
	with diabetes treatment	I	I	I
Patient self-management		I	I	I
COSTS AND HEALTH CARE RESOURCE USE				
Expected cost of treatment per patient per outcome		I	C	C
ER visits		C	I	I
Hospitalizations		C	I	I
Specialist visits		I	I	I
Primary care visits		I	I	I

BMI=body mass index; C=critical; DKA=diabetic ketoacidosis; ER=emergency room; FPG=fasting plasma glucose; HDL-C=high-density lipoprotein cholesterol; HRQoL=health-related quality of life; I=important; LDL-C=low-density lipoprotein cholesterol; N=not important; PVD=peripheral vascular disease; TIA=transient ischemic attack

Appendix 4 – Individual GRADE evidence profiles for Type 1 DM

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Appendix 5 – Individual GRADE evidence profiles for Type 2 DM

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Appendix 6 – Individual GRADE evidence profiles for Gestational Diabetes

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APPENDIX 4

Individual GRADE evidence profiles for Type 1 DM

Supporting Informed Decisions

À l'appui des décisions éclairées

Appendix 4 – Individual GRADE evidence profiles for Type 1 DM

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1 Patient Population: Pregnant Adults

1.1 Rapid-acting insulin analogues

GRADE Evidence Profile – Lispro versus Human Insulin in Pregnant Adults with Type 1 DM
Research question: Should insulin lispro, rather than human insulin, be used for the treatment of type I diabetes in pregnant adult patients?
Settings: Pregnant out-patients

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
A1c												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	16	17	-	WMD 0.20 (-1.03 to 1.43)	⊕OOO Very low	**Critical**
Severe hypoglycemia												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	16	17	RR 0.21 (0.01 to 4.10)	-	⊕OOO Very low	**Critical**
Nocturnal hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with A1c ≤ 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
All-cause mortality												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Nephropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**
HRQoL (generic)												
o	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean 2-hour post prandial plasma												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or BMI												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Ischemic heart disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Peripheral vascular disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Patient satisfaction with diabetes treatment												
o[9]	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] The evidence consists of a small, open-label, parallel RCT of a total number of 33 patients (n=16 for lispro and n=17 for human insulin) and a quality score of 1 out of 5. This would reduce the quality of the evidence and would be considered as a serious limitation

GRADE Evidence Profile – Aspart versus Human Insulin in Pregnant Adults with Type 1 DM
Research Question: Should insulin aspart, rather than human insulin, be used for the treatment of type I diabetes in pregnant adult patients?
Settings: Pregnant out-patients

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
A1C												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	157	165	-	WMD -0.08 (-0.28 to 0.12)	⊕⊕OO Low	**Critical**
Severe hypoglycemia												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	157	165	RR 1.14 (0.76 to 1.71)	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	157	165	RR 1.04 (0.98 to 1.11)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with A1C ≤ 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
All-cause mortality												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean 2-hour post prandial plasma												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or BMI												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Ischemic heart disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Peripheral vascular disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] The evidence consists of a small, open-label, parallel RCT of a total number of 33 patients (n=16 for lispro and n=17 for human insulin) and a quality score of 1 out of 5. This would reduce the quality of the evidence and would be considered as a serious limitation

1.2 Long-acting insulin analogues

The systematic search of the literature did not identify any RCTs that examined the use of long-acting insulin analogues in pregnant patients.

2 Patient Population: Pre-adolescents

2.1 Rapid-acting insulin analogues

GRADE Evidence Profile – Lispro versus Human Insulin in Pediatric Pre-pubertal Patients with Type 1 DM Using Continuous Subcutaneous Insulin Infusion

Research Question: Should insulin lispro, rather than human insulin, be used to treat type I diabetes in pediatric pre-pubertal patients using continuous subcutaneous insulin infusion?

Settings: Pediatric pre-pubertal out-patients using continuous subcutaneous insulin infusion

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Glycosylated hemoglobin (A1c) (follow-up median 4 months)												
1	RT	Very serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	27	27	-	WMD 0.06 (-0.47 to 0.59)	⊕OOO Very Low	**Critical**
Diabetic ketoacidosis (follow-up mean 4 months)												
1	RT	Very serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	0/54	2/54	RR 0.2 (0.01 to 3.98)		⊕OOO Very Low	**Critical**
Severe hypoglycemia (follow-up median 4 months)												
1	RT	Very serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	2/54	2/54	RR 1 (0.15 to 6.59)		⊕OOO Very Low	**Critical**
Overall hypoglycemia (follow-up median 4 months)												
1	RT	Very serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	54	54	Rate ratio 0.82 (0.75 to 0.89)	-	⊕OOO Very Low	**Critical**

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Nocturnal hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with A1c ≤ 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
1	RT	Very serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[2]	None	19/54	7/54	RR 2.71 (1.37 to 5.37)	NNT 2 (1 to 5)	⊕OOO Very Low	Important
Mean 2-hour post prandial plasma												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or BMI												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Retinopathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; NNT=number needed to treat; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] The evidence consists of one open-labelled crossover study with unclear allocation concealment. In addition, carry-over effect was reported for A1C and results are analysed during the first period of treatment

[2] One small randomized control trial (n=29)

GRADE Evidence Profile – Lispro versus Human Insulin in Pre-adolescent Patients with Type 1 DM Using Multiple Daily Injection
Research Question: Should insulin lispro, rather than human insulin, be used to treat type 1 diabetes in pre-adolescent patients using insulin multiple daily injection?
Setting: Pre-adolescent pediatric out-patients using insulin multiple daily injection

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Glycosylated hemoglobin (A1c) (follow-up median 3.5 months[3])												
4[1]	RT	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data[2]	None	143	143	-	WMD 0.14 (-0.18 to 0.46)	⊕⊕⊕O Moderate	**Critical**
Severe hypoglycemia (follow-up median 4 months)												
2	RT	Serious limitations[4]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[4]	None	4/84	7/84	RR 0.66 (0.12 to 3.61)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia (follow-up mean 3.5 months)[6] assessment: self-reported by family + /- blood test)												
3	RT	Serious limitations[8]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[8]	None[5]	117	117	Rate ratio 0.96 (0.74 to 1.26)	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia (assessment: self reported +/- blood test)												
4	RT	Serious limitations[2]	No important inconsistency	Some uncertainty about directness[7]	Precise data[2]	None	143	143	Rate ratio 1.04 (0.93 to 1.16)	-	⊕⊕OO Low	**Critical**
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with A1C ≤ 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
All-cause mortality												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or BMI												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Ischemic heart disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Lower-limb disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Peripheral vascular disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

Number of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Patient satisfaction with diabetes care												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
0[9]	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] Results of 4 randomized control trials (RCTs) were pooled in one meta-analysis

[2] All 4 studies were open-labeled crossover RCTs with a quality score (Jadad scale) 2 out of 5. In addition, allocation concealment was not clear in 3 of the studies and intention-to-treat analysis was performed in one RCT. This reduces the quality of the evidence and is considered as a serious limitation to study design

[3] Range from 3 to 6 months

[4] The evidence consists of 2 open-labelled crossover RCTs (total n=84) with unclear allocation concealment and quality score of 2 out of 5

[5] Reporting bias cannot be assessed using 4 trials

[6] Length of follow-up was 3 months in 2 studies and 4 months in the other study

[7] There is a substantial inconsistency across studies (I^2=76.0%; p=0.006). The only moderator variable that could be identified as potentially contributing to the heterogeneity was the duration of the studies. Results of sensitivity analyses based on study duration ($\leq$ 3 months and > 3 months) found that studies (n=3) of $\leq$ 3months favoured human insulin, while the single study of > 3 months favoured lispro

[8] Two RCTs with a total number of 162 children

[9] One crossover RCT (N=24) showed that 82% of parents were willing to continue lispro because of convenience. Another crossover study found that 28/35 parents preferred lispro, with 25 children continuing on lispro after the study. The seven who chose regular insulin did so because of better glycemic control. Also, 58% of users of regular insulin followed the timing directions. In the third study, 79% of parents preferred lispro for their children

2.2 Long-acting insulin analogues

The systematic search of the literature did not identify any RCTs that exclusively examined the use of long-acting insulin analogues in pre-adolescent patients. Published studies reported results for the use of long-acting insulin analogues in mixed populations, i.e., patients were simply described as less than 18 years of age. Such studies are included in the GRADE Evidence Profiles in Type 1 DM, Table 3.2.

3 Patient Population: Adolescents

3.1 Rapid-acting insulin analogues

GRADE Evidence Profile – Lispro versus Human Insulin in Adolescent Patients Using Multiple Daily Injections with Type 1 DM
Research Question: Should insulin lispro, rather than human insulin, be used for the treatment of type 1 diabetes in adolescent patients using insulin multiple daily injection?
Setting: Adolescent pediatric out-patients using insulin multiple daily injection

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
Number of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Glycosylated hemoglobin (A1c) (follow-up median 3.5 months3)												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	463	463	-	WMD -0.01 (-0.21 to 0.19)	⊕⊕OO Low	**Critical**
Severe hypoglycemia (follow-up median 4 months)												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	5/ 463	5/ 463	RR 1.0 (0.29 to 3.43)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia (follow-up mean 3.5 months17; assessed with: self reported by family +/- blood test)												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	463	463	Rate ratio 0.61 (0.57 to 0.64)*	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia (assessed with: self reported +/- blood test)												
1[1]	RT	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	463	463	Rate ratio 0.9 (0.88 to 0.93)*	-	⊕⊕OO Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
Number of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Diabetic ketoacidosis												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with A1c ≤ 7%												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or BMI												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Lower-limb disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Retinopathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
Number of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; CSII=continuous subcutaneous insulin infusion; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

* Significant results

[1] The evidence consist of one open-label crossover randomized control trial of a total number of 463 patients. In addition, allocation concealment was not clear. This would reduce the quality of the evidence and would be considered as a serious limitation to study design

3.2 Long-acting insulin analogues

GRADE Evidence Profile – Detemir versus NPH in Children and Adolescents with Type 1 DM
Research Question: Should insulin detemir, rather than NPH insulin, be used in children and adolescents with type 1 diabetes?
Settings: Children and adolescents with type 1 diabetes using insulin

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	ID	NPH Insulin	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up 26 weeks)												
1	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	232	115	-	WMD 0.10 (-0.18 to 0.38)	⊕⊕⊕⊕ High	**Critical**
Proportion with A1c <= 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma glucose (µmol/L)												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Proportion reporting >= 1 episode of severe hypoglycemia (follow-up 26 weeks)												
1	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	37/232	23/115	RR 0.80 (0.5 to 1.28)	-	⊕⊕⊕⊕ High	**Critical**
Severe hypoglycemia - rate ratio (follow-up 26 weeks)												
1	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	232	115	Rate ratio 0.94 (0.68 to 1.3)	-	⊕⊕⊕⊕ High	**Critical**
Proportion reporting >= 1 episode of nocturnal hypoglycemia (follow-up 26 weeks)												
1	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	174/232	101/115	RR 0.85 (0.77 to 0.94)	NNT 7.6 (4.9 to 18.9)	⊕⊕⊕⊕ High	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	ID	NPH Insulin	Relative (95% CI)	Absolute		
Nocturnal hypoglycemia - rate ratio (follow-up median 26 weeks)												
1	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	232	115	Rate ratio 0.77 (0.7 to 0.84)	-	⊕⊕⊕⊕ High	**Critical**
Proportion reporting >= 1 episode of overall hypoglycemia (follow-up 26 weeks)												
1	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	223/232	113/115	RR 0.98 (0.94 to 1.01)	-	⊕⊕⊕⊕ High	**Critical**
Overall hypoglycemia - rate ratio (follow-up 26 weeks)												
1	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	232	115	Rate ratio 0.89 (0.86 to 0.93)	-	⊕⊕⊕⊕ High	**Critical**
Mean BMI (Z-score) (follow-up 26 weeks, no evidence for body weight outcome)												
1[2]	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	232	115	-	WMD -0.18 (-0.25 to 0.11)	⊕⊕⊕⊕ High	Important
Diabetic ketoacidosis (follow-up 26 weeks)												
1	RT	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	4/232	2/115	RR 0.99 (0.18 to 5.33)	-	⊕⊕⊕⊕ High	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	ID	NPH Insulin	Relative (95% CI)	Absolute		
All-cause mortality												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Retinopathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	ID	NPH Insulin	Relative (95% CI)	Absolute		
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1C=glycosylated hemoglobin; BMI=body mass index ; CI=confidence interval; det=detemir; DM=diabetes mellitus; ER emergency room; HRQoL=health-related quality-of-life; ID=insulin detemir; LDL-C=low-density lipoprotein cholesterol; NE= no evidence; NNT=number needed to treat; RR=relative risk; RT=randomized trial; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD = weighted mean difference

[1] The study scored 2 on the Jadad scale. This was an open-label study with adequate allocation concealment, intention-to-treat analysis, and reasons for withdrawal were reported

[2] The study reported BMI Z-score at baseline and endpoint

GRADE Evidence Profile – Glargine versus NPH in Children and Adolescents with Type 1 DM
Research Question: Should insulin glargine, rather than NPH insulin, be used in type 1 diabetes in children and adolescents?
Settings: Children and adolescents with type 1 diabetes using insulin

Quality Assessment						Summary of Findings						Importance
						No. of Patients		Effect			Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar	NPH Insulin	Relative (95% CI)	Absolute		
Mean A1c (follow-up median 24 weeks; [17] measured with: % A1c)												
4	RT	Serious limitations[2]	Important inconsistency [15,16]	No uncertainty about directness	Precise data	None	337	343	-	WMD -0.25 (-0.55 to 0.05)[1]	⊕⊕OO Low	**Critical**
Proportion with A1c <= 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma glucose												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Proportion reporting >= 1 episode of severe hypoglycemia (follow-up median 24 weeks[8])												
4	RT	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	55/361	58/366	RR 1.18 (0.59 to 2.35)[13]	-	⊕⊕OO Low	**Critical**
Severe hypoglycemia - rate ratio												
0[12]	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of nocturnal hypoglycemia (follow-up 28 weeks)												
1	RT	Serious limitations[11]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[10]	None	22/174	31/175	RR 0.71 (0.43 to 1.18)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia - rate ratio												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of overall hypoglycemia (follow-up median 24 weeks[8])												
3	RT	Serious limitations[9]	No important inconsistency	No uncertainty about	Precise data	None	181/347	176/352	RR 1.03 (0.86 to 1.25)[14]	-	⊕⊕⊕O Moderate	**Critical**

Quality Assessment						Summary of Findings						Importance
						No. of Patients		Effect			Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar	NPH Insulin	Relative (95% CI)	Absolute		
				directness								
Overall hypoglycemia - rate ratio												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean BMI (kg/m2) (follow-up 24 weeks)												
1[4]	RT	Serious limitations[3]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[5]	None	14	14	-	WMD 0.2 (-0.03 to 0.43)	⊕⊕OO Low	Important
Diabetic ketoacidosis (follow-up 24-28 weeks)												
2[6]	RT	Serious limitations[11]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[7]	None	1/188	0/188	RR 3 (0.12 to 73.14)	-	⊕⊕OO Low	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Retinopathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment						Summary of Findings						Importance
						No. of Patients		Effect			Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar	NPH Insulin	Relative (95% CI)	Absolute		
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; CI=confidence interval; Glar=Glargine insulin; HI= human insulin; HRQoL=health-related quality-of-life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD=weighted mean difference

[1] One of the four studies demonstrated the largest reduction in A1c and was the only study to demonstrate a significant effect. It was dissimilar to the other 3 studies in that it was conducted in a Japanese population, included subjects as old as 21 years of age (range 8 to 21), and employed insulin aspart as bolus insulin. The WMD in the remaining subgroups was not statistically significant: bolus lispro or human insulin; bolus human insulin; NPH or lente insulin as basal with lispro bolus

[2] Of the four studies, three were reported as abstracts, therefore study quality could not be assessed. The fourth received a Jadad score of 1; this study was open-label, allocation concealment was unclear, and reasons for withdrawal were not reported

[3] The single study was reported in abstract form, therefore, study quality could not be assessed
[4] Only study reported BMI among the five studies identified. No studies reported mean weight at endpoint, change in weight from baseline, or waist circumference/waist-hip ratio
[5] Small sample size
[6] Only two of the five studies reported this outcome: one patient in the insulin glargine arm had DKA in on study. No patient in either treatment arm had DKA in the other
[7] Only one event observed in insulin glargine arm in one study
[8] Range =24-28 weeks
[9] Of the three studies, two were reported as abstracts, therefore, study quality could not be assessed. The third received a Jadad score of 1; this study was open-label, allocation concealment was unclear, and reasons for withdrawal were not reported
[10] Only one study with wide 95% CI
[11] One study received a Jadad score of 1; this study was open-label, allocation concealment was unclear, and reasons for withdrawal were not reported. The other study was reported in abstract form, therefore, study quality could not be assessed.
[12] No studies reported data that allowed calculation of rate ratios for this event
[13] Two studies included patients using either NPH or lente in the comparator arm. In sensitivity analysis, removal of these studies from the meta-analysis left only one study. The RR of severe hypoglycemia in this study was 0.80 (95% CI: 0.56-1.15)
[14] Two studies included patients using either NPH or lente in the comparator arm. In sensitivity analysis, removal of these studies from the meta-analysis left only one study. The RR of overall hypoglycemia in this study was 0.99 (95% CI: 0.65-1.51)
[15] I-square value=60%. In one, NPH or lente was used as control. The I-square is 49.2% after removing that study in the MA sensitivity test
[16] In subgroup analysis by bolus, RAI. I-square within the group were <50%
[17] Range=16-28 weeks

GRADE Evidence Profile – (Glargine + Lispro) versus (NPH + Human Insulin) in Children and Adolescents with Type 1 DM

Research Question: Should insulin glargine with insulin lispro, rather than NPH insulin with human insulin, be used in children and adolescents with type 1 diabetes?

Settings: Children and adolescents with type 1 diabetes using Insulin

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar & Insulin Lispro	NPH & HI	Relative (95% CI)	Absolute		
Mean A1c (follow-up 16 weeks; measured with: % A1c; range of scores: 0-0; better indicated by less)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	25	25	-	WMD -0.40 (-0.91 to 0.11)	⊕⊕⊕O Moderate	**Critical**
Proportion with A1c <= 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma glucose												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain (follow-up 16 weeks; no actual data, text description only)												
1[3]	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[5]	None	25	25	-	WMD 0 (0 to 0)[2]	⊕⊕OO Low	Important
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of severe hypoglycemia (follow-up 16 weeks)												
1[3]	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[5]	None	0/25	0/25	RR [4]	-	⊕⊕OO Low	**Critical**
Severe hypoglycemia - rate ratio												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of nocturnal hypoglycemia (follow-up median 16 weeks)												
1[3]	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty	Sparse or imprecise	None	8/25	14/25	RR 0.57 (0.29 to	-	⊕⊕OO Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar & Insulin Lispro	NPH & HI	Relative (95% CI)	Absolute		
				about directness	data[5]				1.12)			
Nocturnal hypoglycemia - rate ratio (follow-up median 16 weeks)												
1[3]	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data[5]	None	25	25	Rate ratio 0.71 (0.44 to 1.14)	-	⊕⊕⊕O Moderate	**Critical**
Proportion reporting >= 1 episode of overall hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia - rate ratio												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Retinopathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
HRQoL (diabetes-specific)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar & Insulin Lispro	NPH & HI	Relative (95% CI)	Absolute		
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; CI=confidence interval; ER=emergency room; Glar=Glargine insulin; HI=human insulin; HRQoL=health-related quality-of-life; LDL-C=low-density lipoprotein; Lis=lispro; NE=no evidence; RR=relative risk; TC:HDL-C:=ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD=weighted mean difference

[1] The study received an overall Jadad score of 2; this was an open-label trial in which allocation concealment was unclear, and the analysis was not intention-to-treat

[2] Not calculable from information reported in this study. However, it was reported that no significant difference in mean weight at endpoint was found between treatment arms

[3] Weight data not reported in this. The only information provided is that there was no difference between treatments

[4] RR and absolute risk difference not estimable due to zero event rates in both treatment arms

[5] Only one RCT reported this outcome, the sample size is small

4 Patient Population: Adults

4.1 Rapid-acting insulin analogues

GRADE Evidence Profile – Lispro versus Aspart in Adults with Type 1 DM
Research Question: Should insulin lispro, rather than insulin aspart, be used for the treatment of type I diabetes in adult patients using continuous subcutaneous insulin infusion (CSII)?
Settings: Adult out-patients using CSII

No. of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Insulin Aspart	Relative (95% CI)	Absolute		
Glycosylated hemoglobin (A1c) (follow-up median 3.5 months)												
1[1]	Random-ized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	28	59	-	WMD 0.25 (-0.20 to 0.71)	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia (follow-up mean 3.5 months; assessed with: self reported by family +/- blood test)												
1[1]	Random-ized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	28	59	Rate ratio 1.20 (0.89 to 1.68)	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia (assessed with: self reported +/- blood test)												
1[1]	Random-ized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	28	59	Rate ratio 1.49 (1.37 to 1.63)	-	⊕⊕OO Low	**Critical**
Severe hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with A1c ≤ 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

No. of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Insulin Aspart	Relative (95% CI)	Absolute		
Mean 2-hour post prandial plasma												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or BMI												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

No. of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Insulin Aspart	Relative (95% CI)	Absolute		
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; ER=emergency room; HRQoL=health-related quality-of-life; NE=no evidence; RR=relative risk; TIA=transient ischemic attack; WMD=weighted mean difference

[1] The evidence consist of a 16-week, open-label, parallel three-arm RCT of a total number of 146 patients (n=87 for both lispro and aspart). In addition, allocation concealment was not clear. This would reduce the quality of the evidence and would be considered as a serious limitation to study design

GRADE Evidence Profile – Aspart versus Human Insulin in Adult Patients using Continuous Subcutaneous Insulin Infusion with Type 1 DM
Research Question: Should insulin aspart, rather than human insulin, be used for type I diabetes in adult patients using continuous subcutaneous insulin infusion (CSII)?
Settings: Adult out-patients using CSII

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
Glycosylated hemoglobin (A1c) (follow-up median 3 months)												
2	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	78	69	-	WMD -0.31 (-0.54 to -0.081)*	⊕⊕OO Low	**Critical**
Severe hypoglycemia												
1	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[2]	None	0/59	1/59	RR [3]	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia (follow-up mean 3 months)												
1	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[2]	None	59	59	Rate ratio 0.55 (0.43 to 0.70)*	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia (follow-up mean 3 months)												
2	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	73	65	Rate ratio 0.58 (0.4 to 0.85)*	-	⊕⊕OO Low	**Critical**
Mean weight or BMI												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Proportion with A1c≤ 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma												

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	NE	-	-	-	-	-		-	-	-	-	**Critical**
Retinopathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; CI=confidence interval; CSII=continuous subcutaneous insulin infusion; ER=emergency room; HI=human insulin; HRQoL=health-related quality-of-life; NE=no evidence; RR=relative risk; TC:HDL-C:=ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD=weighted mean difference

* Significant results

[1] The evidence consists of two open-label, parallel RCTs with unclear allocation concealment and quality score of 2 out of 5. The total number of patients in both studies was 147

[2] The evidence consists of a small open-label, parallel RCTs (n= 118) with unclear allocation concealment and quality score of 2 out of 5

[3]Very low or zero event rates in one or both arms prevent reliable estimation of relative risk

GRADE Evidence Profile- Lispro versus Human Insulin in Adult Patients with DM Type 1 using Continuous Subcutaneous Insulin Infusion
Research Question: Should insulin lispro, rather than human insulin, be used in type I adult patients using continuous subcutaneous insulin infusion (CSII)?
Setting: Adult Outpatient Using CSII

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Glycosylated hemoglobin (A1c) (follow-up median 3 months[2])												
6	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data[1]	None	282	313	-	WMD -0.18 (-0.32 to -0.05)[3]*	⊕⊕⊕O Moderate	**Critical**
Severe hypoglycemia (follow-up median 3.5 months [5])												
4	Randomized trial	Serious limitations [4]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[4]	None	7/125	4/156	RR 1.86 (0.54 to 6.46)	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia (follow-up median 3 months)												
4	Randomized trial	Serious limitations [6]	Important inconsistency [7]	No uncertainty about directness	Precise data [6]	None	210	241	Rate ratio 1.07 (0.98 to 1.16)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia (follow-up median 4 months)												
1	Randomized trial	Serious limitations [8]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[8]	None	28	59	Rate ratio 0.67 (0.51 to 0.88)*	-	⊕⊕OO Low	**Critical**
Diabetic ketoacidosis (follow-up median 3 months)												
3	Randomized trial	Serious limitations [9]	No important inconsistency	No uncertainty about directness	Precise data[9]	None	7/224	4/224	RR 1.55 (0.51 to 4.75)	-	⊕⊕⊕O Moderate	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
2-hour post prandial plasma glucose (follow-up mean 3 months)												
1	Randomized trial	Very serious Limitations[10]	No important Inconsistency	No Uncertainty about directness	Sparse or Imprecise data[10]	None	58	58	-	WMD -2.89 (-4.48 to -1.3)*	⊕OOO Very low	Important
Weight gain (follow-up median 3 months)												
3	Randomized trial	Serious limitations[11]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[11]	None	127	127	-	WMD -0.42 (-1.17 to 0.33)	⊕⊕OO Low	Important
Proportion with A1c≤ 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
HRQoL (diabetes-specific)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
1	Randomized trial	Very serious limitations[16]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[17]	None	41	41	-	WMD 0.57 (-0.05 to 1.19)	⊕OOO Very low	**Critical**
Patient satisfaction with diabetes care												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
4[12]	Randomized trial	Very serious limitations[13]	Important inconsistency[14]	No uncertainty about directness	Precise data	None	-	-	-	Data was not pooled[15]	⊕OOO Very low	Important
Patient self-management												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; CI=confidence interval; CSII=continuous subcutaneous insulin infusion; ER=emergency room; HI=human insulin; HRQoL=health-related quality-of-life; NE=no evidence; RR=relative risk; TIA=transient ischemic attack; WMD=weighted mean difference

* Significant results

[1] The evidence consists of 4 crossover and 2 parallel RCTs with unclear allocation concealment. Only one was double blinded. The median quality score (Jadad) was 2 out of 5. This would reduce the quality of the evidence and would be considered as a serious limitation to study design
[2] Range from 2 to 4 months
[3] Sensitivity analysis by study design and duration of treatment showed that insulin lispro was better than human insulin in reducing A1c in crossover trials • 3 months (WMD: -0.22; 95% CI: -0.41, -0.03) and in parallel trial > 3 months (WMD: -0.14; 95% CI: -0.34, 0.05) but the difference was not statistically significant in the later
[4] The evidence consists of three crossover open-labelled RCTs and one parallel open-labelled RCT with unclear allocation concealment and an average Jadad score of 1 out of 5. Three of the four RCTs were published articles and the fourth was a conference abstract. This would reduce the quality of the evidence and would be considered as a serious limitation to study design. The total number of patients in the four RCTs included as evidence was 281
[5] Range from 1.5 to 4 months
[6] The evidence consist of 4 RCTs (2 parallel and 2 cross over). All were not blinded with unclear allocation concealment with a median quality score (Jadad) 2 out of 5
[7] Heterogeneity among pooled RCTs was relatively high (I^2 =80.8%; p=0.05)
[8] The evidence consists of only one and open-label parallel RCT (n=87) that had a quality score of 2 out of 5. Allocation concealment was unclear in this study
[9] The evidence consists of 3 crossover and one parallel RCT. All were not blinded with unclear allocation concealment
[10] The evidence consists of only one crossover RCT (n=116) with unclear allocation concealment
[11] The evidence consists of 3 open-label crossover RCT (n=254). The median quality score was 2 out of with unclear allocation concealment
[12] Three RCTs reported the overall score of the treatment diabetes treatment satisfaction questionnaire (DTSQ) and one RCT discussed only the satisfaction scale of DTSQ
[13] All four RCTs included as evidence were not blinded and of crossover design. Unblinding of patients and investigator would be considered as a very serious limitation of the study design for investigating this outcome (patient satisfaction)
[14] There was inconsistency in reporting the overall. Two studies reported no significant difference in term of satisfaction between lispro and human insulin, while two reported statistically significant improvement in satisfaction with insulin lispro, compared to HI
[15] Variation in the scales used (0 to 36, 0 to 100 or 0 to 48) did not allow for data pooling
[16] One open-label crossover RCT with 41 patients. Unblinding of patients and investigator would be considered as a very serious limitation of the study design for investigating this outcome (HRQoL, patient well-being)
[17] Small number of patients (n=41)

GRADE Evidence Profile – Aspart versus Human Insulin in Adult Patients with Type 1 DM using Multiple Daily Injections
Research Question: Should insulin aspart, rather than human insulin, be used for the treatment of type I DM in adult patients using multiple daily injections (MDI)?
Settings: Adult out-patients using MDI

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Glycosylated hemoglobin (A1c) (follow-up median 3 months)												
5	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data[1]	None	1814	1074	-	WMD -0.12 (-0.19 to -0.06)*	⊕⊕⊕O Moderate	**Critical**
Diabetic ketoacidosis (follow-up 3 months)												
1	Randomized trial	Very serious limitations[5]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[5]	None	1/143	0/62	RR 1.31 (0.05 to 31.79)	-	⊕OOO Very low	**Critical**
Severe hypoglycemia (follow-up mean 3 months)												
3	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data[2]	None	142/ 1022	106/674	RR 0.83 (0.66 to 1.03)	-	⊕⊕⊕O Moderate	**Critical**
Nocturnal hypoglycemia (follow-up mean 3 months)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia (follow-up mean 3 months)												
6	Randomized trial	Serious limitations[3]	Important inconsistency[4]	No uncertainty about directness	Precise data[3]	Reporting bias[5]	1918	1178	Rate ratio 0.97 (0.88 to 1.08)	-	⊕OOO Very low	**Critical**
BMI												
1	Randomized trial	Very serious limitations[6]	No important inconsistency	No uncertainty about	Sparse or imprecise data[6]	None	596	286	-	Mean change from	⊕OOO Very low	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
				directness						Baseline: Asp 0.44; HI 0.48; NS		
Proportion with A1c ≤ 7%												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
o[7]	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o[7]	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o[8]	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Patient satisfaction with diabetes care												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
1	Randomized trial	Very serious limitations[9]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[9]	None	283	141	-	WMD 0.15 (-0.14 to 0.44)[10]	⊕OOO Very Low	Important
Patient self-management												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; Asp=aspart; CI=confidence interval; ER=emergency room; HI=human insulin; HRQoL=health-related quality-of-life; MDI=multiple daily injections; NE=no evidence; RR=relative risk; TIA=transient ischemic attack; WMD=weighted mean difference

* Significant results

[1] The evidence consist of 4 open-label, parallel RCTs and one crossover study, with unclear allocation concealment in 4 of them and a median quality (Jadad) score of 2 out of 5. This would reduce the quality of the evidence and would be considered as a serious limitation to study design

[2] The evidence consist of 2 open-label parallel RCTs and one crossover study, with unclear allocation concealment in 4 of them and a median quality (Jadad) score of 2 out of 5. This would reduce the quality of the evidence and would be considered as a serious limitation to study design

[3] The evidence consist of 4 open-label parallel RCTs and 2 crossover study, with unclear allocation concealment in 4 of them and a median quality (Jadad) score of 2 out of 5. This would reduce the quality of the evidence and would be considered as a serious limitation to study design

[4] There is a significant heterogeneity among studies (I^2 97.0%; p<0.00001). This could be influenced by the differences in reporting the definition of hypoglycemia in each study

[5] The evidence consists of only one poor, open-label, parallel RCT with a total number of patients of 205

[6] The evidence consists of only one poor, open-label, parallel RCT with a total number of patients of 866

[7] One RCT (n= 1065) reported one death in the aspart group from myocardial infarction, judged not related to study medication

[8] One RCT (n=205) reported one subject in the aspart group suffered from retinal disorder

[9] The evidence consists of only one poor, open-label, parallel RCT with a total number of patients of 424 and unclear allocation concealment. Failure to blind is considered as a major limitation for this outcome

[10] Based on data from the only one study

GRADE Evidence Profile – Lispro versus Human Insulin in Adult Patients with Type 1 DM using MDI

Research Question: Should insulin lispro, rather than human insulin, be used for the treatment of type I DM in adult patients using multiple daily injections (MDI)?

Settings: Adults Outpatients Using Multiple MDI

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Glycated hemoglobin (A1c) (follow-up median 3 months[2]; better indicated by less)												
16	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data[1]	None	2,702	2,724	-	WMD -0.06 (-0.14 to 0.02)	⊕⊕⊕O Moderate	**Critical**
Severe hypoglycemia (follow-up mean 3 months)[4]												
6	Randomized trial	Serious limitations[3]	No important inconsistency	No uncertainty about directness	Precise data[3]	None	162/ 2,106	214/2,115	RR 0.78 (0.65 to 0.94)	-	⊕⊕⊕O Moderate	**Critical**
Nocturnal hypoglycemia (follow-up mean 3 months)												
3	Randomized trial	Serious limitations[5]	Important inconsistency[6]	No uncertainty about directness	Precise data[5]	None	329	329	Rate ratio 0.58 (0.35 to 0.98)*	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia (follow-up mean 3 months)[9]												
12	Randomized trial	Serious limitations[7]	Important inconsistency[8]	No uncertainty about directness	Precise data[7]	None	2584	2609	Rate ratio 0.98 (0.86 to 1.06)	-	⊕⊕OO Low	**Critical**
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean weight												
7	Randomized trial	Serious limitations[10]	No important inconsistency	No uncertainty about directness	Precise data[10]	None	1,580	1,580	-	WMD -0.38 (-1.23 to 0.46)	⊕⊕⊕O Moderate	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Proportion with A1c ≤ 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma[11]												
2	Randomized trial	Serious limitations[12]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[12]	None	1,018	1,018	-	WMD -0.99 (-1.54 to -0.45)*	⊕⊕OO Low	Important
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality[13]												
0[13]	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
HRQoL (generic)												
3	Randomized trial	Serious limitations[14]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[14]	None	-	-	-	Data not pooled[15]	⊕⊕OO Low	**Critical**
Patient satisfaction with diabetes care												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
1[16]	Randomized trial	Serious limitations[14]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[16]	None	426	422	-	WMD 4.30 (1.33 to 7.27)[17]	⊕⊕OO Low	Important
Patient self-management												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; CI=confidence interval; ER=emergency room; HI=human insulin; HRQoL=health-related quality-of-life; MDI=multiple daily injections; NE=no evidence; RR=relative risk; TIA=transient ischemic attack; WMD=weighted mean difference

* Significant results

[1] The evidence consist of 16 open-labelled RCTs with unclear allocation concealment and a median Jadad score of 1 out of 5. Intention-to-treat (ITT) approach was used in only 38% of them. 11 studies were crossover RCT. This would reduce the quality of the evidence and would be considered as a serious limitation to study design
[2] Range from 1 to 12 months
[3] The evidence consists of six open-labelled RCTs with unclear allocation concealment and a median Jaded score of 2 out of 5. Four studies out of six were crossover. This would reduce the quality of the evidence and would be considered as a serious limitation to study design.
[4] Range from 2 to 6 months
[5] The evidence consists of 3 open-labelled crossover RCTs with unclear allocation concealment and a median Jadad score of 2 out of 5. This would reduce the quality of the evidence and would be considered as a serious limitation to study design
[6] There was significant heterogeneity among studies: I^2 95.6% ($p< 0.00001$)
[7] The evidence consists of 12 open-labelled RCTs with unclear allocation concealment and a median Jadad score of 2 out of 5. Intention-to-treat (ITT) approach was used in only 42% of them. Eight studies were crossover RCTs. This would reduce the quality of the evidence and would be considered as a serious limitation to study design
[8] There is significant heterogeneity among studies (I^2=97%, p<0.00001). Three studies favoured human insulin, four favoured insulin lispro, and 5 show no difference. Heterogeneity still existed when analysis was performed for RCTs > 3 months, $\leq$ 3months, parallel and crossover
[9] Range from 2 to 12 months
[10] The evidence consist of 7 open-labelled RCTs with unclear allocation concealment and median Jadad score of 2 out of 5. Five studies were crossover RCTs. In addition, intention-to-treat (ITT) approach was used in 4 out of 7. This would reduce the quality of the evidence and would be considered as a serious limitation to study design
[11] Both studies are of 3-months duration
[12] The evidence consists of 2 open-labelled crossover RCTs with unclear allocation concealment and a median Jadad score of 1 out of 5
[13] Only one crossover four-month RCT (n=135) reported one death in the human insulin group after a prolonged seizure, possibly related to hypoglycemia
[14] The evidence consists of three open-labelled small crossover RCTs. This would be considered as a major limitation to address this outcome
[15] Two RCTs showed no statistically significant difference between lispro and human insulin using the Well being Questionnaire (WBQ). One of them showed no statistically significant difference between the two treatments in anxiety and energy domains while the other one provided overall assessment. The third study showed statistically significant improvement with lispro treatment on the overall scale and in depression, anxiety and energy domains but not in positive well-being domain
[16] The evidence consists mainly of one RCT that used the Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ). One of these domains was patient satisfaction. Two other RCTs also showed a statistically significant increase in satisfaction with ILis compared to HI using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)
[17] Based on data from one study

4.2 Long-acting insulin analogues

GRADE Evidence Profile – (Glargine + Lispro) versus (NPH + Human insulin) in Adults with Type 1 DM
Research Question: Should insulin glargine with insulin lispro, rather than NPH insulin with human insulin, be used in adults with type 1 diabetes?
Settings: Adult type 1 DM patients using insulin

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar/ lispro	NPH/HI	Relative (95% CI)	Absolute		
Mean A1c												
o[1]	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with A1c <= 7%												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma glucose												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Diabetic ketoacidosis												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of severe hypoglycemia (follow-up 32 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[2]	None	14/54	16/54	RR 0.88 (0.48 to 1.61)	-	⊕⊕⊕O Moderate	**Critical**
Severe hypoglycemia - rate ratio												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of nocturnal hypoglycemia (follow-up 32 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	None	38/54	43/54	RR 0.88 (0.71 to 1.1)	-	⊕⊕⊕⊕ High	**Critical**
Nocturnal hypoglycemia – rate ratio (follow-up 32 weeks)												

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar/ lispro	NPH/HI	Relative (95% CI)	Absolute		
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	None	54	54	Rate ratio 0.56 (0.48 to 0.65)	-	⊕⊕⊕⊕ High	**Critical**
Proportion reporting >= 1 episode of overall hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia – rate ratio												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar/ lispro	NPH/HI	Relative (95% CI)	Absolute		
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; ER=emergency room; Glar=Glargine insulin; HI=human insulin; HRQoL=health-related quality-of-life; LDL-C=low-density lipoprotein; Lis=insulin lispro; NE=no evidence; RR=relative risk; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD = weighted mean difference

[1] One study was identified for this comparison. This study was a cross-over trial. Since the authors reported that a "marked sequence effect" was detected for the A1c outcome, this study was excluded from the analysis of A1c

[2] Wide 95% confidence interval

GRADE Evidence Profile – (Detemir +Aspart) versus (NPH + Human insulin) in Adults with Type 1 DM
Research Question: Should insulin detemir with insulin aspart, rather than NPH insulin with human insulin, be used in adults with type 1 diabetes?
Settings: Adult type 1 DM patients using insulin

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Det / Asp	NPH/ HI	Relative (95% CI)	Absolute		
Mean A1c (follow-up 18 weeks; measured with: % A1c)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	298	297	-	WMD -0.23 (-0.37 to -0.09)	⊕⊕⊕O Moderate	**Critical**
Proportion with A1c <= 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma glucose												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain (follow-up 18 weeks; measured with: weight in kg)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	298	297	-	WMD -1.10 (-1.49 to -0.71)	⊕⊕⊕O Moderate	Important
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of severe hypoglycemia (follow-up 18 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[2]	None	19/298	18/297	RR 1.05 (0.56 to1.96)	-	⊕⊕OO Low	**Critical**
Severe hypoglycemia - rate ratio (follow-up 18 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	298	297	Rate ratio 0.89 (0.58 to 1.36)	-	⊕⊕OO Low	**Critical**
Proportion reporting >= 1 episode of nocturnal hypoglycemia (follow-up 18 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about	Precise data	None	113/298	173/297	RR 0.65 (0.55 to 0.77)	NNT 4.9 (3.8-7.5)	⊕⊕⊕O Moderate	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Det / Asp	NPH/ HI	Relative (95% CI)	Absolute		
				directness								
Nocturnal hypoglycemia - rate ratio (follow-up 18 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	298	297	Rate ratio 0.44 (0.39 to 0.51)	-	⊕⊕⊕O Moderate	**Critical**
Proportion reporting >= 1 episode of Overall hypoglycemia (follow-up 18 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	219/298	238/297	RR 0.92 (0.84 to 1)	-	⊕⊕⊕O Moderate	**Critical**
Overall hypoglycemia - rate ratio (follow-up 18 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	298	297	Rate ratio 0.78 (0.74 to 0.82)	-	⊕⊕⊕O Moderate	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality (follow-up median 18 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[3]	None	0/298	1/297	RR[3]	-	⊕⊕OO Low	**Critical**
Nephropathy												
0	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**
Neuropathy												
0	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**
Peripheral vascular disease												
0	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Det / Asp	NPH/ HI	Relative (95% CI)	Absolute		
Retinopathy												
0	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**
Stroke/TIA												
0	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**
HRQoL (diabetes-specific)												
04	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**
HRQoL (generic)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	**NE**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Critical**
ER visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; Asp=Aspart; Det=detemir; CI=confidence interval; ER=emergency room; HI=human insulin; HRQoL=health-related quality-of-life; LDL-C=low-density lipoprotein; NE=no evidence; NNT=number needed to treat; RR=relative risk; TC:HDL-C= ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD = weighted mean difference

[1] This trial received a Jadad score of 2. It was unblinded and allocation concealment was unclear

[2] Wide 95% confidence interval

[3] Very low or zero event rates in one or both arms preclude reliable estimation of RR

GRADE Evidence Profile – Glargine versus NPH in Adults with Type 1 DM
Research Question: Should insulin glargine, rather than NPH insulin, be used in adults with type 1 diabetes?
Settings: Adult type 1 DM patients using insulin

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar	NPH	Relative (95% CI)	Absolute		
Mean A1c (follow-up median 16 weeks[2]; measured with: % A1c)												
11	Randomized trial	Serious limitations[37]	No important inconsistency[1]	No uncertainty about directness	Precise data	Reporting bias[4]	1375	1370	-	WMD -0.11 (-0.21 to -0.02)[3,9]	⊕OOO Very low	**Critical**
Proportion with A1c <= 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma glucose												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain (follow-up median 22 weeks[7]; measured with: weight in kg)												
4[5,6]	Randomized trial	Serious limitations[38]	No important inconsistency	No uncertainty about directness	Precise data	None	624	628	-	WMD -0.36 (-0.67 to -0.04)[8]	⊕⊕⊕O Moderate	Important
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of severe hypoglycemia (follow-up median 16 weeks[2])												
7	Randomized trial	Serious limitations[39]	Important inconsistency[10]	No uncertainty about directness	Precise data	None	64/1111	81/1116	RR 0.82 (0.52 to 1.29)[11]	-	⊕OOO Very low	**Critical**
Severe hypoglycemia - rate ratio (follow-up median 24 weeks[7])												
5	Randomized trial	Serious limitations[40]	No important inconsistency	No uncertainty about directness	Precise data	None	1559 (total)		Rate ratio 0.89 (0.64 to 1.23)[12]	-	⊕⊕⊕O Moderate	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar	NPH	Relative (95% CI)	Absolute		
Proportion reporting >= 1 episode of nocturnal hypoglycemia (follow-up median 28 weeks[15])												
5[6]	Randomized trial	Serious limitations[13]	Important inconsistency[14]	No uncertainty about directness	Precise data	Reporting bias[4]	620/969	627/974	RR 0.97 (0.87 to1.09)[16]	-	⊕OOO Very low	**Critical**
Nocturnal hypoglycemia - rate ratio (follow-up median 23 weeks[19])												
4	Randomized trial	Serious limitations[17]	Important inconsistency[18]	No uncertainty about directness	Precise data	None	916 (total)		Rate ratio 0.67 (0.37 to 1.23)[26]	-	⊕⊕OO Low	**Critical**
Proportion reporting >= 1 episode of overall hypoglycemia (follow-up median 22 weeks[15])												
6[6]	Randomized trial	Serious limitations[20]	Important inconsistency[21]	No uncertainty about directness	Precise data	None	872/998	876/1009	RR 1.02 (0.98 to 1.07)[22]	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia - rate ratio (follow-up median 14 weeks[25])												
2	Randomized trial	Serious limitations[23]	Important inconsistency[24]	No uncertainty about directness	Precise data	None	670 (total)		Rate ratio 0.82 (0.52 to 1.28)[26]	-	⊕⊕OO Low	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality (follow-up median 28 weeks)												
1	Randomized trial	Serious limitations[27]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[28]	None	0/264	1/270	RR -[28,31]	-	⊕⊕OO Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar	NPH	Relative (95% CI)	Absolute		
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy (follow-up median 16 weeks)												
1[29]	Randomized trial	Serious limitations[30]	No important inconsistency	No uncertainty about directness	Precise data	None	9/310	7/309	RR 1.28 (0.48 to 3.4)[26]	-	⊕⊕OO Low	**Critical**
Stroke/TIA												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic) (follow-up median 28 weeks; measured with: change in general well-being score of W-BQ22 from baseline[33])												
1	Randomized trial	Serious limitations[32]	No important inconsistency	No uncertainty about directness	Precise data	None	261	256	-	WMD -0.35 (-1.5 to 0.81)[34]	⊕⊕⊕O Moderate	**Critical**
Patient satisfaction with diabetes care												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment (follow-up median 28 weeks; measured with: change in treatment satisfaction sub-scale of DTSQ[35])												
1	Randomized trial	Serious limitations[32]	No important inconsistency	No uncertainty about directness	Precise data	None	261	256	-	WMD 1.83 (0.82 to 2.84)[36]	⊕⊕⊕O Moderate	Important
Patient self-management												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Glar	NPH	Relative (95% CI)	Absolute		
ER visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; CI=confidence interval; ER=emergency room; Glar=glargine; HI=human insulin; HRQoL=health-related quality-of-life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; TC:HDL-C= ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD = weighted mean difference

[1] I-square=38.8%. by subgroup analysis. The I -square is 0% in both HI and Aspart groups. In Lispro group, the I-square is 81.1%. If two studies were removed, the I-square is 0%. One of the two studies is an abstract

[2] Range=4-52 weeks

[3] WMD is for glargine versus NPH. In subgroup analysis, the WMD for the two studies that used aspart as bolus insulin was similar to the overall estimate and was statistically significant. The WMD across the five studies that used lispro as bolus insulin was larger than the overall estimate (-0.20) and was also statistically significant, however, a large degree of heterogeneity was observed (I-square=51%). The remaining four studies used human insulin as bolus insulin; the pooled WMD for these trials was 0.01

[4] Asymmetry observed in funnel plot

[5] Four studies reported this outcome: two reported mean weight at endpoint, and two reported mean change from baseline weight

[6] One of the four studies is a subgroup analysis of another study out of these four. Data from that study was used because this outcome was not reported by the author in another study

[7] Range=16-30 weeks

[8] WMD is for glargine versus NPH. In subgroup analysis, the single study using aspart as bolus insulin reported a similar mean difference as the overall WMD, however, the result was not statistically significant. The two studies using lispro as bolus had a pooled WMD that was slightly higher than the overall WMD (-0.40); this result was statistically significant. The single study using human insulin as bolus reported a non-significant gain of 0.10 kg with glargine versus NPH. In addition, in a sensitivity analysis to test the effect of removing the single cross-over study, the effect on the pooled WMD was minimal. The two studies using lispro as bolus reported mean change in weight from baseline rather than final mean weight. Removal of these studies from the overall analysis did not significantly impact the WMD point estimate, although the result was statistically non-significant

[9] Two other sensitivity analyses were conducted to determine the effect of methodological differences across studies on the pooled treatment effect. Removal of studies less than or equal to 3 months in duration did not significantly affect the overall effect. Similarly, removal of the single cross-over study did not affect the overall WMD

[10] Wide range of RRs across studies (range=0.34 to 1.40)

[11] In subgroup analysis, the RR from the single study that used aspart as bolus and the pooled RR from the three studies in which lispro was used as bolus were both 1 or greater and statistically non-significant. In the three studies that used human insulin as bolus, the pooled RR was 0.68 and was statistically non-significant. In sensitivity analysis to assess the effect of removing the single cross-over study, the overall RR was minimally affected.

[12] In subgroup analysis, the single study that used aspart as bolus insulin and the three studies that used lispro as bolus insulin showed no reduction in rate ratio. In contrast, the single study that used human insulin as bolus demonstrated a rate ratio of 0.47 that was statistically significant. In sensitivity analysis, removal of the single cross-over study did not greatly affect the overall rate ratio

[13] Two studies received a Jadad score of 3, three received a Jadad score of 2. All studies were unblinded and allocation concealment was not clearly described in any study

[14] I-square=66%. In human insulin bolus subgroup, the I-square is 76.6%. After removing one study, which is a 4-week trial (<3mos), the I-square is 0. In Lispro subgroup, the I-square is 59.9%.

One study had a wider target FPG range (5-7.7mmol/l) than the target FPG in other study (6.3)
[15] Range=4-30 weeks
[16] In subgroup analysis, the pooled RR for the two studies that used lispro as bolus insulin and the pooled RR for the three studies that used human insulin as bolus were both similar to the overall pooled RR and were statistically non-significant. However, a significant degree of heterogeneity (I-square >50%) remained in both subgroups
[17] One study received a Jadad score of 3, two received a Jadad score of 2, and one received a Jadad score of 1. All studies were unblinded and allocation concealment was clearly described in only one study
[18] I-square=99%. Different target FPG level may cause the heterogeneity (5-7.7mmol/l; 6.3mmol/l; 7.4-8.3 mmol/l)
[19] Range=12-52 weeks
[20] Two studies received a Jadad score of 3, three received a Jadad score of 2, and one study was reported in abstract form, therefore, study quality could not be assessed. All studies were unblinded and allocation concealment was not clearly described in any study
[21] I-square=56%. The Lis group one study has a wider target FPG range (5-7.7mmol/l) than the target FPG in another study (6.3), this may cause the heterogeneity. In HI group, one study is a subgroup analysis comparing Glar (once daily) with NPH (twice daily). In trials of two studies, the NPH dose was qd/bid. The different NPH dose frequency in different trials may cause the heterogeneity. After removing subgroup analysis study in this group, the I^2 is 0%.
[22] In subgroup analysis, the pooled RRs across studies that used aspart as bolus insulin, lispro, and human insulin were all similar to the overall pooled RR and were statistcially non-significant. However, significant heterogeneity remained in the lispro and human insulin subgroups. In sensitivity analysis, removal of the single crossover study did not affect the overall pooled RR.
[23] One study received a Jadad score of 3 and one a Jadad score of 2. Neither study was blinded, nor was allocation concealment clearly described
[24] I-square=98%
[25] Range=12-16 weeks
[26] All studies used lispro as bolus insulin
[27] One study received a Jadad score of 2; this study was unblinded and allocation concealment was unclear
[28] Very low or zero event rates in one or more arms prevent reliable estimation of RR. RR: not estimable
[29] The study defined this outcome as "retinal events"
[30] The study received a Jadad score of 3; this study was unblinded and allocation concealment was unclear
[31] The study used human insulin as bolus insulin
[32] The study received a Jadad score of 2; this study was unblinded and allocation concealment was unclear
[33] The Well-being Questionnaire (W-BQ) General Well-being Score incorporates 4 subscales that measure depression, anxiety, energy, and positive well-being
[34] WMD is for glargine versus NPH. Positive value indicates benefit with glargine. In both treatment arms, there was statistically significant improvement from baseline
[35] The Diabetes Treatment Satisfaction Questionnaire (DTSQ) measures Satisfaction with Treatment Regimen using six items. The other two subscales of the DTSQ (data not shown) are Perceived Frequency of Hyperglycemia, and Perceived Frequency of Hypoglycemia
[36] WMD is for glargine versus NPH. Positive value indicates benefit with glargine. The improvement from baseline was statistically significant in the glargine arm. There was a statistically non-significant decrease in Satisfaction in the NPH arm
[37] Two studies received a Jadad score of 3, six received a Jadad score of 2, one received a Jadad score of 1, and two studies were reported in abstract form; therefore, study quality could not be assessed. All studies were unblinded and allocation concealment was clearly described in only two studies
[38] One study received a Jadad score of 3, two studies received a Jadad score of 2, and one study was reported in abstract form; therefore. study quality could not be assessed. All trials were unblinded, and allocation concealment was unclear
[39] Two studies received a Jadad score of 3, three received a Jadad score of 2, one received a Jadad score of 1, and one study was reported in abstract form; therefore, study quality could not be assessed. All studies were unblinded and allocation concealment was clearly described in only one study
[40] One study received a Jadad score of 3, two received a Jadad score of 2, and two studies were reported in abstract form; therefore, study quality could not be assessed. All studies were unblinded and allocation concealment was not clearly described in any study

GRADE Evidence Profile: Detemir versus NPH in Adults with Type 1 DM
Research Question: Should insulin detemir, rather than NPH insulin, be used in adults with type 1 diabetes?
Settings: Adult type 1 DM patients using insulin

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	NPH Insulin	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up median 25 weeks[1])												
7	Randomized trial	Serious limitations[22]	No important inconsistency	No uncertainty about directness	Precise data	None	1,539	1,019	-	WMD -0.06 (-0.13 to 0.02)[2]	⊕⊕⊕O Moderate	**Critical**
Proportion with A1c <= 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma glucose												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain (kg) (follow-up median 26 weeks[1])												
6	Randomized trial	Serious limitations[22]	No important inconsistency	No uncertainty about directness	Precise data	Reporting bias[3]	1,414	888	-	WMD -0.71 (-1.40 to -0.02)[4]	⊕⊕OO Low	Important
Diabetic ketoacidosis												
0[5]	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of severe hypoglycemia (follow-up median 26 weeks[6])												
7[9]	Randomized trial	Serious limitations[23]	No important inconsistency	No uncertainty about directness	Precise data	None	123/1490	99/952	RR 0.74 (0.58 to 0.96)[7]	NNT 37 (250 to 23.1)	⊕⊕⊕O Moderate	**Critical**
Severe hypoglycemia – rate ratio (follow-up median 16 weeks[6])												
7[9]	Randomized trial	Serious limitations[22]	Important inconsistency[24]	No uncertainty about directness	Precise data	None	1,490	952	Rate ratio 0.95 (0.65 to 1.38)[8]	-	⊕⊕OO Low	**Critical**
Proportion reporting >= 1 episode of nocturnal hypoglycemia (follow-up median 26 weeks[1])												
6	Randomized trial	Serious limitations[25]	No important inconsistency	No uncertainty	Precise data	Reporting bias[3]	928/1,419	612/ 892	RR 0.92 (0.85 to	NNT 28 (13 to ∞)	⊕⊕OO Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	NPH Insulin	Relative (95% CI)	Absolute		
				about directness					0.98)[10,21]			
Nocturnal hypoglycemia – rate ratio (follow-up median 24 weeks[6])												
9	Randomized trial	Serious limitations[22]	Important inconsistency [26]	No uncertainty about directness	Precise data	None	2,820 (total)		Rate ratio 0.68 (0.62 to 0.75)[11]	-	⊕⊕OO Low	**Critical**
Proportion reporting >= 1 episode of overall hypoglycemia (follow-up median 21 weeks[6])												
6	Randomized trial	Serious limitations[27]	No important inconsistency	No uncertainty about directness	Precise data	None	1,116/1260	749/850	RR 1.00 (0.96 to 1.04)[12]	-	⊕⊕⊕O Moderate	**Critical**
Overall hypoglycemia – rate ratio (follow-up median 21 weeks[6])												
6	Randomized trial	Serious limitations[27]	Important inconsistency [28]	No uncertainty about directness	Precise data	None	2,109 (total)		Rate ratio 0.83 (0.73 to 0.95)[13]	-	⊕⊕OO Low	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease (follow-up median 34 weeks[1])												
2[14]	Randomized trial	Serious limitations[29]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[15]	None	1/284	0/264	RR 2.61 (0.11 to 63.6)	-	⊕⊕OO Low	**Critical**
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality (follow-up median 16 weeks[17])												
2[16]	Randomized trial	Serious limitations[30]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[15]	None	1/401	1/259	RR 0.69 (0.07 to 6.61)	-	⊕⊕OO Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	NPH Insulin	Relative (95% CI)	Absolute		
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy (follow-up median 52 weeks[19])												
2	Randomized trial	Serious limitations[31]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[18]	None	25/370	21/233	RR 0.71 (0.4 to 1.26)	-	⊕⊕OO Low	**Critical**
Stroke/TIA (follow-up 16 weeks)												
1[20]	Randomized trial	Serious limitations[32]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[15]	None	1/132	0/129	RR 2.93 (0.12 to 71.33)	-	⊕⊕OO Low	**Critical**
HRQoL (diabetes-specific)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	NPH Insulin	Relative (95% CI)	Absolute		
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; CI=confidence interval; ER=emergency room; HI=human insulin; HRQoL=health-related quality-of-life; LDL-C=low-density lipoprotein; NE=no evidence; NNT=number needed to treat; RR=relative risk; TC:HDL-C= ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD = weighted mean difference

[1] Range=16 to 52 weeks

[2] WMD is for detemir versus NPH. In subgroup analysis, the WMD for studies using human insulin as bolus insulin was similar to that of studies using insulin aspart (both WMDs were statistically non-significant). No studies using insulin lispro reported this outome. In sensitivity analysis, removal of the single cross-over study did not greatly affect the overall WMD.

[3] Funnel plot was asymmetrical; two small RCTs with large SEs reported benefit with analogue in the absence of studies of similar size reporting benefit in control arm.

[4] WMD is for detemir versus NPH. In subgroup analysis, the trials using insulin aspart as bolus insulin demonstrated a similar WMD to the overall WMD, and the result was statistically significant. The WMD across the two trials using human insulin was -1.60 kg. This result was statistically non-significant, and demonstrated a large degree of heterogeneity (I-square=70%). Although the trial populations enrolled in the two trials comprising this analysis were similar, the studies differed in their duration (26 and 52 weeks in these two studies, respectively) and basal insulin dosing frequency (once daily and twice daily in these two studies, respectively)

[5] One study reported that 2 of 216 patients in the detemir arm and 2 of 99 patients in the NPH arm experienced ketosis

[6] Range=16 to 52 weeks

[7] In subgroup analysis, the estimate of RR for studies using insulin aspart as bolus insulin was similar to the overall RR estimate, and was statistcially significant. The RR for studies using human insulin as bolus insulin was also similar to the overall RR estimate, but was not statistically signifcant. Removal of the only crossover study from the analysis had a minor effect on the overall RR and did not change the statistical significance of the result

[8] In subgroup analysis, the rate ratio for the studies using insulin aspart as bolus, and those using human insulin as bolus, were similar to the overall rate ratio. I-square values remained above 60% for both subgroups, indicating a large degree of heterogeneity. Removal of the only crossover study that used aspart as bolus, did not reduce heterogeneity for the aspart subgroup. Among the human insulin bolus studies, one study reported the largest treatment effect (RR=0.36, 95% CI: 0.11-1.12). This study was different from the others in that it was the shortest in duration (6 weeks) and was of a crossover design. When this study was removed from the analysis, the I-square value was zero, and the rate ratio was 1.25 (95% CI: 0.89-1.74)

[9] All trials reported severe hypoglycemia occurring in the maintenance phase. No data were available for severe hypoglycemia events in the titration phase

[10] In subgroup analysis, the RR for the studies using insulin aspart as bolus insulin was similar to the overall RR estimate and was statistically significant. There was no apparent difference in risk in the subgroup of studies that used human insulin as bolus (RR=0.97, 95% CI = 0.89-1.06)

[11] The rate ratios in each of the bolus subgroups (aspart and human insulin) were similar to the overall rate ratio and both were statistically significant. The human insulin subgroup was relatively homogeneous (I-square = 34%), although a large degree of heterogeneity remained in the aspart subgroup (I-square = 85%). Removal of the only crossover study, reduced the I-square value to 65%. Despite the magnitude of heterogeneity, rate ratios in the studies comprising the aspart group fell in a relatively narrow range (0.50 and 0.83), and all individual results except for one study were statistically significant.

[12] In subgroup analysis, the RRs for the insulin aspart and human insulin subgroups were similar to the overall RR estimate and were statistically non-significant. In sensitivity analysis, removal of the two cross-over studies did not significantly impact the overall RR estimate

[13] In subgroup analysis, the rate ratios for the subgroup of studies using insulin aspart or human insulin as bolus were similar to the overall rate ratio, however, both ratios were statistically non-significant. A large degree of heterogeneity remained (I-square > 90%). Removal of the two cross-over studies in sensitivity analysis did not significantly affect the overall rate ratio

[14] One study reported one non-fatal MI in the detemir arm and none in the NPH arm. The other one reported that there were no non-fatal MIs in either treatment arm

[15] Very low or zero event rates prevent valid estimation of relative risks

[16] One study reported one death in the detemir group and none in the NPH group. The other study reported one death in the NPH group and none in the detemir group

[17] Both trials were 16 weeks in duration

[18] Wide 95% confidence interval
[19] Both studies were 52 weeks in duration
[20] Only one study reported this outcome: one patient in the detemir arm and none in the control arm experienced this event
[21] In sensitivity analysis, removal of the two crossover studies did not greatly affect the overall RR, and the result remained statistically significant
[22] Four RCTs received a Jadad score of 3 and three received a Jadad score of 2. All trials were open-label and none described an adequate method of allocation concealment
[23] Three RCTs received a Jadad score of 3, and the remainder received a Jadad score of 2. All trials were open-label and none described an adequate method of allocation concealment
[24] The I-square value for the overall analysis was 62.3%. Point estimates varied widely across studies, from 0.36 to 1.52. in the HI group, the I-square is 60.2%; if we remove the crossover trial, the I-square is 0%; In the aspart group: if we remove the trials which were involved in SA and Australia, the I-square is 0%.
[25] Three RCTs received a Jadad score of 3 and three received a Jadad score of 2. All trials were open-label and none described an adequate method of allocation concealment
[26] I-square value=79%. In HI bolus group as bolus, the I-square is 33.8%. In aspart bolus group (I-square is 84.8%]. Trials included in this group were involved in Australia, Europe and South Africa. If we remove the trials which are involved in Australia and SA, the I-square is 48.7
[27] Three RCTs received a Jadad score of 3, and the remainder received a Jadad score of 2. All trials were open-label and none described an adequate method of allocation concealment
[28] I-square=97.6%. In HI bolus group, remove the trial which was conducted in Europe and Australia, the I-square is 0%. 2. In aspart group, no cause can be decided to link to the heterogeneity
[29] Both trials received a Jadad score of 2
[30] One study received a Jadad score of 3, while the other one received a Jadad score of 2. Neither study was blinded, nor was allocation concealment clearly described in either
[31] Both trials received a Jadad score of 2. Neither study was blinded, nor was allocation concealment clearly described in either
[32] The study received a Jadad score of 3. This study was unblinded and allocation concealment was unclear

GRADE Evidence profile: Detemir versus Glargine in Adults with Type 1 DM
Research question: Should insulin detemir, rather than insulin glargine, be used in adults with type 1 diabetes?
Settings: Adult type 1 DM patients using insulin.

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Det	Glar	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up 26 weeks)												
1	Randomized trial	No serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	161	159	-	WMD -0.03 (-0.26 to 0.2)	⊕⊕⊕⊕ High	**Critical**
Proportion with A1c <= 7%												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post prandial plasma glucose												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight (kg) (follow-up median 26 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	None	161	159	-	WMD -0.50 (-1.21 to 0.21)	⊕⊕⊕⊕ High	Important
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion reporting >= 1 episode of severe hypoglycemia (follow-up 26 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	None	3/161	12/159	RR 0.25 (0.07 to 0.86)	NNT 17.5 (91 to 14.3)	⊕⊕⊕O Moderate	**Critical**
Severe hypoglycemia - rate ratio (follow-up 26 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	None	161	159	Rate ratio 0.41 (0.2 to 0.86)	-	⊕⊕⊕⊕ High	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Det	Glar	Relative (95% CI)	Absolute		
Proportion reporting >= 1 episode of nocturnal hypoglycemia (follow-up 26 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	None	77/161	81/159	RR 0.94 (0.75 to 1.17)	-	⊕⊕⊕⊕ High	**Critical**
Nocturnal hypoglycemia – rate ratio (follow-up 26 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	none	161	159	Rate ratio 0.66 (0.58 to 0.76)	-	⊕⊕⊕⊕ High	**Critical**
Proportion reporting >= 1 episode of overall hypoglycemia (follow-up 26 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	None	126/161	118/159	RR 1.05 (0.93 to 1.19)	-	⊕⊕⊕⊕ High	**Critical**
Overall hypoglycemia – rate ratio (follow-up 26 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Precise data	None	161	159	Rate ratio 0.96 (0.92 to 1.02)	-	⊕⊕⊕⊕ High	**Critical**
Congestive heart failure												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Det	Glar	Relative (95% CI)	Absolute		
Neuropathy												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy (follow-up 26 weeks)												
1	Randomized trial	No serious limitations	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[3]	None	0/161	1/159	RR[2]	-	⊕⊕⊕O Moderate	**Critical**
Stroke/TIA												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Det	Glar	Relative (95% CI)	Absolute		
Primary care visits												
0	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; CI=confidence interval; Det=detemir; ER=emergency room; Glar=glargine; HI=human insulin; HRQoL=health-related quality-of-life; LDL-C=low-density lipoprotein; NE=no evidence; NNT=number needed to treat; RR=relative risk; TC:HDL-C= ratio of total cholesterol to high-density lipoprotein; TIA=transient ischemic attack; WMD = weighted mean difference

[1] Pieber 2007 received a Jadad score of 2. This was an unblinded study with adequate allocation concealment

[2] Very low or zero event rates in one or more arms preclude reliable estimation of RR

[3] Zero or 1 event was reported in the two research arms

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

APPENDIX 5

Individual GRADE Evidence Profiles for Type 2 DM

Supporting Informed Decisions

À l'appui des décisions éclairées

Appendix 5 – Individual GRADE Evidence Profiles for Type 2 DM

Table of Contents

1 Patient Population: Pregnant Adults

1.1 Rapid-acting insulin analogues

The systematic search of the literature did not identify any RCTs that examined the use of rapid-acting insulin analogues for the treatment of type 2 DM in pregnant patients.

1.2 Long-acting insulin analogues

The systematic search of the literature did not identify any RCTs that examined the use of long-acting insulin analogues for the treatment of type 2 DM in pregnant patients.

2 Patient Population: Pre-adolescents

2.1 Rapid-acting insulin analogues

The systematic search of the literature did not identify any RCTs that examined the use of rapid-acting insulin analogues for the treatment of type 2 DM in paediatric – preadolescent patients.

2.2 Long-acting insulin analogues

The systematic search of the literature did not identify any RCTs that examined the use of long-acting insulin analogues for the treatment of type 2 DM in pre-adolescent patients.

3 Patient Population: Adolescents

3.1 Rapid-acting insulin analogues

The systematic search of the literature did not identify any RCTs that examined the use of rapid-acting insulin analogues for the treatment of type 2 DM in adolescent patients.

3.2 Long-acting insulin analogues

The systematic search of the literature did not identify any RCTs that examined the use of long-acting insulin analogues for the treatment of type 2 DM in adolescent patients.

4 Patient Population: Adults

4.1 Rapid-acting insulin analogues

GRADE Evidence Profile – Biphasic lispro versus Biphasic aspart in adults with type 2 DM
Research question: Should biphasic insulin lispro, rather than insulin biphasic aspart, be used for the treatment of type 2 diabetes in adult patients using multiple daily injections (MDI)?
Settings: Adult out-patients using MDI

No. of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Insulin Aspart	Relative (95% CI)	Absolute		
Glycosylated hemoglobin (A1c) (follow-up median 3.5 months3)												
1[1]	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	127	127	-	WMD 0.14 (0.008 to 0.275)[2] p=0.082	⊕⊕OO Low	**Critical**
Overall hypoglycemia (assessed with: self reported +/- blood test)												
1[1]	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[1]	None	133	133	Rate ratio 0.90 (0.77 to 1.07)	-	⊕⊕OO Low	Important
Nocturnal hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-		**Critical**
Severe hypoglycemia												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Diabetic ketoacidosis												
0	NE	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**

No. of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Insulin Aspart	Relative (95% CI)	Absolute		
Proportion with A1c≤ 7%												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
All-cause mortality												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
ER visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Retinopathy												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Fasting plasma glucose												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

No. of Studies	Quality Assessment						Summary of Findings					Importance
							No. of Patients		Effect		Quality	
	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Insulin Aspart	Relative (95% CI)	Absolute		
Blood pressure												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol LDL-C												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol TC: HDL ratio												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or BMI												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Peripheral vascular disease												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Specialist visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	NE	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=Randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] The evidence consists of a 12-week, open-label crossover RCT of a total number of 137 patients. In addition, allocation concealment was not clear. This would reduce the quality of the evidence and would be considered as a serious limitation to study design

[2] 90% CI for non-inferiority test

GRADE Profile – Aspart versus Sulfonylurea in Adults with Type 2 DM
Research question: Should insulin aspart rather than sulfonylurea be used for the treatment of adult patients with type 2 DM?
Settings: Adult out-patients

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin aspart	Sulfo-nylurea	Relative (95% CI)	Absolute		
HbA1c (follow-up 1.5-2 months; measured with: %; range of scores: 8.4-10.1; better indicated by less)												
2	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None[2]	119	114	-	WMD -0.63 (-1.04 to -0.22)	⊕⊕⊕O Moderate	**Critical**
Diabetic ketoacidosis:												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Severe hypoglycemia												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Nocturnal hypoglycemia:												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia, relative risk (follow-up mean 4 months)												
1	Randomized trial	Serious limitations[3]	No important inconsistency[4]	No uncertainty about directness	Sparse or imprecise data[7]	None[4]	43/93	17/91	RR 2.43 (1.53 to 4.01)	NNT = 4 (2 to 7)	⊕⊕OO Low	Important
Overall hypoglycemia, rate ratio (follow-up mean 4 months)												
1	Randomized trial	Serious limitations[3]	No important inconsistency[4]	No uncertainty about directness	Sparse or imprecise data[5]	None[4]	96	91	Rate ratio 2.59 (1.85 to 3.63)	-	⊕⊕OO Low	Important
Body weight, (follow-up 1.5-4 months; measured with: kg; range of scores: 0.03-4.0; better indicated by less)												
2	Randomized trial	Serious limitations[1]	Important inconsistency[6]	No uncertainty about	Precise data	None[2]	119	114	-	WMD 1.14 (-0.40 to 2.69)	⊕⊕OO Low	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin aspart	Sulfo-nylurea	Relative (95% CI)	Absolute		
				directness								
Mean weight or BMI												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Proportion with A1C ≤ 7%												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Blood pressure												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol LDL-C												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol TC:HDL ratio												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Fasting plasma Glucose (FPG) – mean												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Fasting Plasma Glucose (FPG) - % ≤ 7µmol/L												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Hyperosmolar hyperglycemic non-ketotic coma												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Critical
Ischemic heart disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Critical
Lower-limb disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin aspart	Sulfo-nylurea	Relative (95% CI)	Absolute		
All-cause mortality												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	**-**	**Critical**
Neuropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin aspart	Sulfo-nylurea	Relative (95% CI)	Absolute		
ER visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Primary care visit												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relativerisk; RT=Randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] Both the RCTs are open label with Jadad's score of 2 and allocation concealment unclear
[2] Not performed in meta analysis of 2 RCTs
[3] This is an open label study, Jadad's score of 2 and allocation concealment unclear
[4] Single study
[5] Single study, n=187, Rate ratio 95% CI: 2.59 (1.85, 3.63)
[6] Heterogeneity: 73.1%
[7] Single study n=60

GRADE Evidence Profile – Lispro versus Sulfonylurea, in Adults with Early Type 2 DM
Research question: Should insulin lispro, rather than sulfonylurea, be used for the treatment of adult patients with early type 2 DM?
Settings: Adult out-patients

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Glyburide	Relative (95% CI)	Absolute		
HbA1c at end (folLow-up 24 weeks)												
1	Randomized trial[1]	Serious limitations[2]	No important inconsistency	Uncertainty about directness[3]	Sparse or imprecise data[4]	None	75	68	-	WMD -0.20 (-0.57 to 0.17)	⊕OOO Very low	**Critical**
Overall hypoglycemia, relative risk (folLow-up 24 weeks)												
1	Randomized trial[1]	Serious limitations[2]	No important inconsistency	Uncertainty about directness[3]	Sparse or imprecise data[4]	None	75	68	0.45 (0.14 to 1.44)	-	⊕OOO Very low	Important
Severe hypoglycemia												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Nocturnal hypoglycemia												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Diabetic ketoacidosis												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Body weight (follow-up 16 weeks)												
1	Randomized trial[1]	Serious limitations[2]	No important inconsistency	Uncertainty about directness[3]	Sparse or imprecise data[4]	None	156	159	-	WMD 2.10 (-2.10 to 6.30)	⊕OOO Very low	Important
Mean 2-hour post-prandial plasma												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Blood Pressure												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol LDL-C												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Glyburide	Relative (95% CI)	Absolute		
Cholesterol TC:HDL ratio												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Fasting plasma glucose												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Hyperosmolar hyperglycemic non-ketotic coma												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Patient satisfaction with diabetes care												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Glyburide	Relative (95% CI)	Absolute		
Patient satisfaction with diabetes treatment												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Quality of life: generic												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] Glyburide was compared with insulin lispro in this study
[2] The evidence consisted of only one small poor open-label RCT, Jadad's score of 1 out of 5 and allocation concealment unclear
[3] Patients in both studies were over 50 years old and of Caucasian origin; therefore, results may be different in other populations
[4] Sample size was small (n= 143) to draw any conclusion

GRADE Evidence Profile – Lispro mix versus Sulfonylurea in adults with Type 2 DM

Research question: Should insulin lispro Mix 25, rather than sulfonylurea, be used for the treatment of patients with adult type 2 DM who failed oral anti-diabetic agents (OAD)?

Settings: Adult out-patients

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Glyburide	Relative (95% CI)	Absolute		
HbA1c at end (follow-up 16 weeks)												
2	Randomized trial[1]	Serious limitations[2]	Important inconsistency	Uncertainty about directness[3]	Precise data	None	156	159	-	WMD -0.85 (-1.18 to -0.53)	⊕⊕OO Low	**Critical**
Overall hypoglycemia, rate ratio (folLow-up 16 weeks)												
2	Randomized trial[1]	Serious limitations[2]	Important inconsistency	Uncertainty about directness[3]	Precise data	None	156	159	12.48 (2.52 to 61.81)	-	⊕⊕OO Low	Important
Severe hypoglycemia												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Nocturnal hypoglycemia												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Diabetic ketoacidosis												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Body weight (follow-up 16 weeks)												
2	Randomized trial[1]	Serious limitations[2]	Important inconsistency	Uncertainty about directness[3]	Precise data	None	156	159	-	WMD 1.47 (-1.24 to 4.18)		Important
Mean 2-hour post-prandial plasma												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Blood pressure												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Glyburide	Relative (95% CI)	Absolute		
Cholesterol LDL-C												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol TC:HDL ratio												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Fasting plasma glucose												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Hyperosmolar hyperglycemic non-ketotic coma												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
All-Cause Mortality												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Glyburide	Relative (95% CI)	Absolute		
Patient satisfaction with diabetes care (follow-up 16 weeks)												
2	Randomized trial[1]	Serious limitations[2]	Important inconsistency[3]	No uncertainty about directness	Precise data	None	154	155	-	WMD 0.53 (0.21 to 0.86)	⊕⊕OO Low	Important
Patient satisfaction with diabetes treatment												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Quality of life: willingness to continue (follow-up 16 weeks)												
2	Randomized trial[1]	Serious limitations[2]	Important inconsistency[5]	No uncertainty about directness	Precise data	None	154	155	RR 1.27 (1.03 to 1.57)	-	⊕⊕OO Low	Important
Quality of life: overall well-being on current therapy (follow-up mean 16 weeks)												
1	Randomized trial[1]	Serious limitations[4]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[4]	None	85	87	-	WMD 0.70 (0.43 to 0.97)	⊕⊕OO Low	Important
Quality of life: overall energy (folLow-up mean 16 weeks)												
1	Randomized trial[1]	Serious limitations[4]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[4]	None	85	87	-	WMD 0.50 (0.2 to 0.8)	⊕⊕OO Low	Important
Patient self-management												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Lispro	Glyburide	Relative (95% CI)	Absolute		
Hospitalizations												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] Glyburide was used as comparison in these two studies
[2] Both the studies were open label, Jadad's score of 2 and 3 out of 5 and allocation concealment unclear
[3] Patients in both studies were over 50 years old and probably of Caucasian origin; therefore, results may be different in other populations. I^2=58.3%
[4] The evidence consists of only one small open label study (n=175) with Moderate quality (3 out of 4 using Jadad Quality Assessment scale)
[5] Patients in both studies were over 50 years old and probably of Caucasian origin; therefore, results may be different in other populations. I^2=70.1%

GRADE Evidence Profile – Aspart versus Human Insulin in Adults with Type 2 DM
Research question: Should insulin aspart, rather than human insulin, be used for the treatment of adult patients with type 2 DM?
Setting: Adult out-patients using multiple daily injections (MDI)

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
HbA1c at end (follow-up mean 6.8 months; measured with: %)												
6	Random-ized trial	Serious limitations[1]	No important inconsistency[2]	No uncertainty about directness	Precise data	Reporting bias[3]	615	416	-	WMD -0.09 (-0.21 to 0.04)	⊕⊕OO Low	**Critical**
Diabetic ketoacidosis												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Severe hypoglycemia, RR (follow-up mean 21 months)												
1	Random-ized trial	Serious limitations[4]	No important inconsistency[5]	No uncertainty about directness	Sparse or imprecise data[5]	None[5]	3/56	9/65	RR 0.39 (0.11 to 1.36)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia, RR (follow-up mean 3 months; assessed with: hypoglycemia between 2400 and 600 hours)												
1	Random-ized trial	Serious limitations[6]	No important inconsistency[5]	No uncertainty about directness	Sparse or imprecise data[5]	None[5]	7/46	11/47	RR 0.65 (0.28 to 1.53)	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia, RR (follow-up mean 8 months; assessed with: symptoms of hypoglycemia and/ or BG < 50 mg/dL)												
4	Random-ized trial	Serious limitations[7]	No important inconsistency	No uncertainty about directness	Precise data	None[16]	266/498	150/299	RR 1.01 (0.88 to 1.16)	-	⊕⊕⊕O Moderate	Important
Overall hypoglycemia, rate ratio; overall: symptoms, if possible confirmed by BG												
2	Random-ized trial	Serious limitations[8]	No important inconsistency	No uncertainty about directness	Precise data	None[9]	131	145	Rate ratio 0.72 (0.64 to 0.80)	-	⊕⊕⊕O Moderate	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
Weight gain (follow-up 3 – 21 months; measured with: kg)												
2	Random-ized trial	Serious limitations[8]	No important inconsistency[10]	No uncertainty about directness	Precise data	None[9]	104	110	-	WMD -0.87 (-2.40 to 0.67)	⊕⊕⊕O Moderate	Important
Proportion with A1c ≤ 7%												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Plasma glucose fasting (change from baseline) (follow-up mean 3 months; measurement: µmol/L)												
1	Random-ized trial	Serious limitations[6]	No important inconsistency[5]	No uncertainty about directness	Sparse or imprecise data[11]	None[5]	46	47	-	WMD -0.67 (-2.47 to 1.13)	⊕⊕OO Low	**Critical**
Mean 2-hour post-prandial plasma												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure (follow-up mean 21 months)												
1	Random-ized trial	Serious limitations[13]	No important inconsistency[5]	No uncertainty about directness	Sparse or imprecise data[14]	None[5]	1/58	0/67	RR 3.46 (0.14 to 83.27)	-	⊕⊕OO Low	**Critical**
Blood pressure												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol LDL-C												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol TC:HDL ratio (follow-up mean 1.5 months)												
1	Random-ized trial	no serious limitations	No important inconsistency[5]	No uncertainty about directness	Sparse or imprecise data[12]	None[5]	21	21	-	WMD 0.37 (-0.77 to 1.51)	⊕⊕⊕O Moderate	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
Mortality (all cause) (follow-up mean 21 months)												
1	Random-ized trial	Serious limitations[13]	No important inconsistency[5]	No uncertainty about directness	Sparse or imprecise data[15]	None[5]	3/58	1/67	RR 3.47 (0.37 to 32.41)	-	⊕⊕OO Low	**Critical**
Ischemic heart disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Aspart	Human Insulin	Relative (95% CI)	Absolute		
Patient self-management												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	No evidence	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] Quality Assessment of only 4 out of 6 RCTs was performed as 2 were in the form of abstracts. Due to limited information, no Quality Assessments were performed on trials published only as abstracts or posters. 3 out of 4 RCTs were open label and the average Jadad's Quality Assessment score (QAS) is 2.75. Allocation concealment was unclear in all the RCTs
[2] Heterogeneity 47.1%
[3] Funnel plot is asymmetrical with all the studies favouring control
[4] Open label, Jadad's QAS of 3 and allocation concealment not clear
[5] Single study
[6] Open Label, Jadad's QAS of 2 and allocation concealment unclear
[7] Out of 4 studies, 3 are as full-text articles and one as abstract. No Quality Assessments were performed on trials published only as abstracts or posters, due to limited information. The 3 studies are open label, with the Jadad QAS of 2 (2 studies) and 3 (1 study). Allocation concealment unclear in all the RCTs
[8] Two open label Trials with Jadad QAS of 2 and 3 and allocation concealment unclear in both the trials
[9] Difficult to comment in meta-analysis of 2 studies
[10] Heterogeneity of 47.9%
[11] Single study, n=93, Mean 95% CI -0.67 (-2.47, 1.13)
[12] Single study, n=42, Mean 95% CI: 0.37 (-0.77, 1.51)
[13] Open label study, Jadad QAS of 3 and allocation concealment unclear
[14] Single study, n=125, RR 95% CI: 3.46 (0.14, 83.27)
[15] Single study, n=125, RR 95% CI: 3.47 (0.37, 32.41)
[16] Not done in meta-analysis of 4 RCTs

GRADE Evidence Profile – Lispro versus Human Insulin in Adults with Type 2 DM
Research question: Should insulin lispro, rather than human insulin, be used for the treatment of adult patients with type 2 DM?
Settings: Adult out-patients using multiple daily injections (MDI)

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Others	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
A1c at end (follow-up 2-12 months; measured with: %; range of scores: 6.7-8.4; better indicated by less)												
11	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness[3]	Precise data	Reporting bias[2]	1540	1553	-	WMD -0.03 (-0.12 to 0.06)[4]	⊕⊕OO Low	**Critical**
Diabetic ketoacidosis												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Severe hypoglycemia, relative risk (follow-up 2-3 months; assessed with: patients requiring glucagon or IV glucose treatment)												
2	Randomized trial	Serious limitations[5]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[6]	None[7]	2/1139[8]	5/1139[8]	RR 0.43 (0.08 to 2.37)	-	⊕⊕OO Low	**Critical**
Severe hypoglycemia, rate ratio (follow-up mean 3 months; assessed with: patients requiring glucagon or IV glucose treatment)												
1	Randomized trial	Serious limitations[9]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[10]	None[11]	722	722	Rate ratio 0.2 (0.02 to 1.71)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia, relative risk (follow-up mean 3 months; assessed with: hypoglycemia between bedtime and breakfast)												
1	Randomized trial	Serious limitations[12]	No important inconsistency [13]	No uncertainty about directness	Sparse or imprecise data[13]	None[11]	13/89	8/89	RR 1.63 (0.71 to 3.73)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia, rate ratio (follow-up mean 4 months[16]; assessed with: hypoglycemia between 24:00 and 06:00 hours)												
3	Randomized trial	Serious limitations[14]	No important inconsistency [15]	No uncertainty about directness	Precise data	None[19]	855	863	Rate ratio 0.62 (0.52 to 0.74)	-	⊕⊕⊕O Moderate	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Others	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Overall hypoglycemia, relative risk (follow-up mean 3 months; assessed with: signs/symptoms and or blood glucose measurement)												
3	Randomized trial	Serious limitations[18]	No important inconsistency [24]	No uncertainty about directness	Precise data	None[19]	76/192	64/192	RR 1.31 (0.86 to 1.99)	-	⊕⊕⊕O Moderate	Important
Overall hypoglycemia, Rate Ratio (follow-up mean 3.8 months; assessed with: signs and or symptoms and or blood glucose measurement)												
8	Randomized trial	Serious limitations[20]	Important inconsistency [21]	No uncertainty about directness	Precise data[22]	None[23]	1368	1378	Rate ratio (Note: no change on rate ratio)	-	⊕⊕OO Low	Important
Weight (follow-up 3-5.5 months[27]; measured with: kg; range of scores: 78-84; better indicated by less)												
3	Randomized trial	Serious limitations[25]	No important inconsistency	No uncertainty about directness	Precise data[26]	None[19]	837	845	-	WMD -0.08 (-1.4 to 1.24)	⊕⊕⊕O Moderate	Important
BMI (follow-up mean 6 months; measured with: kg/M^2)												
1	Randomized trial	Serious limitations[28]	No important inconsistency[13]	No uncertainty about directness	Sparse or imprecise data	None[11]	20	20	-	WMD 0.00 (-8.51 to 8.51)	⊕⊕OO Low	Important
Proportion with A1c ≤ 7%												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2 hours post-prandial plasma glucose (follow-up mean 4 weeks; measured with: µmol/L)												
1	Randomized trial	Serious limitations[28]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[31]	None[11]	37	37	-	WMD -1.10 (-2.21 to 0.01)	⊕⊕OO Low	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Others	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Blood pressure												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Cholesterol LDL-C (follow-up 3-6 months; measured with: µmol/L; range of scores: 3.10-3.40; better indicated by less)												
2	Randomized trial	Serious limitations[14]	No important inconsis-tency[29]	No uncertainty about directness	Precise data	None[17]	742	742	-	WMD 0.00 (-0.28 to 0.27)	⊕⊕⊕O Moderate	Important
Total cholesterol: HDL ratio (follow-up 3 - 6 months; measured as ratio; range of scores: 4.08-4.64; better indicated by less)												
2	Randomized trial	Serious limitations[14]	No important inconsistency	No uncertainty about directness	Precise data	None[30]	742	742	-	WMD 0.03 (-0.86 to 0.92)	⊕⊕⊕O Moderate	Important
Fasting plasma glucose (FPG) - mean												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Fasting plasma glucose (FPG) - % ≤ 7µmol/L												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Hyperosmolar hyperglycemic non-ketotic coma												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Congestive heart failure												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality (follow-up mean 3 months)												
1	Randomized trial	Serious limitations[12]	No important inconsis-tency[11]	No uncertainty about directness	Sparse or imprecise data[32]	None[11]	0/40	1/40	RR 0.33 (0.01 to 7.95)	-	⊕⊕OO Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Others	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Nephropathy												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care (follow-up mean 3 months)												
1	Randomized trial	Serious limitations[33]	No important inconsistency	No uncertainty about directness	Precise data	None[11]	442	443	-	WMD 0.90 (-2.06 to 3.86)	⊕⊕⊕O Moderate	Important
HRQoL (diabetes-specific): energy/fatigue (follow-up mean 3 months)												
1	Randomized trial	Serious limitations[33]	No important inconsistency	No uncertainty about directness	Precise data[34]	None[11]	442	443	-	WMD -0.40 (-2.51 to 1.71)	⊕⊕⊕O Moderate	**Critical**
HRQoL (diabetes-specific): anxiety (health distress) (follow-up mean 3 months)												
1	Randomized trial	Serious limitations[33]	No important inconsistency	No uncertainty about directness	Precise data[35]	None[11]	447	445	-	WMD -0.30 (-2.29 to 1.69)	⊕⊕⊕O Moderate	**Critical**
HRQoL (diabetes-specific): flexibility (follow-up mean 3 months)												
1	Randomized	Serious	No	No	Precise	None[11]	440	439	-	WMD	⊕⊕⊕O	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Others	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
	trial	limitations[33]	important inconsistency	uncertainty about directness	data[36]					-0.70 (-1.43 to 2.83)	Moderate	
Patient satisfaction with diabetes treatment												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	No evidence	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; HRQoL=health-related quality of life; IV=intravenous; NE=no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1]Allocation concealment was unclear in all RCTs
[2] The funnel plot is not symmetrical and more studies are in favour of showing the beneficial effects of Insulin lispro
[3] Surrogate outcomes generally provide less direct evidence, however, A1c is one of the important surrogate outcomes
[4] Separate analysis of insulin lispro versus human insulin performed for studies of > 3 months - <= 3 months duration and for parallel and crossover trials did not show any marked differences in A1c
[5] Both the studies are open-label, the Jadad's Quality Assessment Score is 1 and 2. Allocation concealment unclear
[6] The confidence intervals are wide in both the studies: RR (95% CI), 0.43 (0.08, 2.37). One of these studies is having the 95% CI of 1.00 (0.6, 16.24). The Risk Difference is 0.00 (0.01, 0.00)
[7] Difficult to comment in two studies
[8] One study (n= 328) had 0 number of patients having severe hypoglycemia. It did not estimate any effect when put in meta-analysis
[9] Open label study, Jadad's score of 1, and allocation concealment unclear
[10] Wide confidence interval of (0.02, 1.71)
[11] Difficult to comment in single study
[12] This is an open-label study with the Jadad's score of 2 and allocation concealment unclear

[13] It is a single study
[14] All the studies are open label, Jadad's Quality Assessment Score is 1 (1 RCT) and 2 (2 RCTs). Allocation concealment unclear in all
[15] Heterogeneity 41.9%
[16] Only two studies are of 3 and 5.5 months of duration
[17] Difficult to comment in a meta-analysis of 2 studies
[18] All the 3 studies are open label having the average Jadad's Quality Assessment Score of less than 2. The allocation concealment is unclear in all the studies.
[19] Difficult to comment in meta-analysis of 3 studies
[20] All the studies are open label with the average Jadad's Quality Assessment Score of 2. Three studies have a score of 1, 4 studies of 2 and 1 study of 3. Allocation concealment was unclear in all of the studies
[21] Heterogeneity is 60.9%. On subgroup analysis, the heterogeneity was 76.1% with studies > 3 months' duration and parallel design and 61.4% with studies <= 3 months duration and crossover design
[22] Rate ratio 95% CI: 0.97 (0.91, 1.03)
[23] Funnel plot was quite symmetrical
[24] Heterogeneity is of 0%
[25] All the 3 studies are open label with the average Jadad's Quality Assessment Score of 2 and allocation concealment unclear
[26] The mean 95% CI: -0.08 (-1.40, 1.24)
[27] Average of about 4 months
[28] The study is open label, average Jadad's Quality Assessment Score of 2 and allocation concealment unclear
[29] Heterogeneity of 0%
[30] The mean 95% CI is: 0.03 (-0.86, 0.92)
[31] Single study, n=74, Mean 95% (CI): -1.10 (-2.21, 0.01)
[32] Single study, n=80, Wide Confidence Intervals: RR 95% CI: 0.33 (0.01, 7.95)
[33] The study is open label, Jadad's Quality Assessment Score of 2 and allocation concealment unclear
[34] Mean 95% CI -0.40 (-2.51, 1.71)
[35] Mean 95% CI -0.30 (-2.29, 1.69)
[36] Mean 95% CI -0.70 (-1.43, 2.83)

4.2 Long-acting insulin analogues

GRADE Evidence Profile – Detemir (+ bolus insulin) versus Glargine (+ bolus insulin) in Adults with Type 2 DM
Research question: Should insulin detemir, rather than insulin glargine, be used in combination with bolus insulin in adults with type 2 diabetes?
Setting: Out-patient

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	Insulin Glargine	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up 26 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	257	129	-	WMD 0.20 (0.1 to 0.3)[4]	⊕⊕⊕O Moderate	**Critical**
Proportion with A1c <=7%												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean fasting plasma glucose (µmol/L) (follow-up 26 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[3]	None	257	128	-	WMD 0.10 (-0.67 to 0.87)	⊕⊕OO Low	**Critical**
Proportion with FPG <=7 µmol/L												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Diabetic ketoacidosis												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Severe hypoglycemia - proportion reporting >= 1 episode												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Severe hypoglycemia - rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	Insulin Glargine	Relative (95% CI)	Absolute		
Nocturnal hypoglycemia - proportion reporting >=1 episode												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Nocturnal hypoglycemia - rate ratio												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia - proportion reporting >= 1 episode												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Overall hypoglycemia - rate ratio												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain (kg) (follow-up 22 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	257	128	-	WMD -1.50 (-2.47 to -0.53)[4]	⊕⊕⊕O Moderate	Important
Mean systolic blood pressure												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Mean diastolic blood pressure												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Mean LDL-C												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Mean TC:HDL-C ratio												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	Insulin Glargine	Relative (95% CI)	Absolute		
All-cause mortality												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	Insulin Glargine	Relative (95% CI)	Absolute		
Hospitalizations												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	-	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; FPG=fasting plasma glucose; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein;WMD=weighted mean difference

[1] Insulin aspart was used as bolus insulin in this study
[2] This was an open-label RCT reported in abstract form, therefore, study quality could not be assessed
[3] Wide 95% confidence interval
[4] This is the difference in mean change from baseline (detemir versus glargine)

GRADE Evidence Profile – Detemir (+bolus insulin) versus NPH (+bolus insulin) in Adults with Type 2 DM
Research question: Should insulin detemir, rather than NPH insulin, be used in combination with bolus insulin in adults with type 2 diabetes?
Setting: Out-patient

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin detemir	NPH insulin	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up 26 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	341	164	-	WMD 0.10 (-0.18 to 0.38)	⊕⊕⊕O Moderate	**Critical**
Proportion with A1C <= 7%												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean fasting plasma glucose (mmol/L) (folLow-up 26 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	309	152	-	WMD 0.10 (-0.61 to 0.81)	⊕⊕⊕O Moderate	**Critical**
Mean 2-hour post-prandial plasma glucose (mmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Proportion with FPG <= 7 mmol/l												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Diabetic ketoacidosis												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Severe hypoglycemia - Proportion reporting >= 1 episode												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Severe hypoglycemia - Rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin detemir	NPH insulin	Relative (95% CI)	Absolute		
Nocturnal hypoglycemia - Proportion reporting >= 1 episode (folLow-up 26 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	52/341	38/164	RR 0.66 (0.45 to 0.96)*	NNT = 13 (8 to 108)[3]*	⊕⊕⊕O Moderate	**Critical**
Nocturnal hypoglycemia - Rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia - Proportion reporting >= 1 episode (folLow-up 26 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	152/341	80/164	RR 0.91 (0.75 to 1.11)	-	⊕⊕⊕O Moderate	Important
Overall hypoglycemia - Rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain (kg) (folLow-up 26 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	341	164	-	WMD -0.80 (-1.46 to -0.14)*	⊕⊕⊕O Moderate	Important
Mean systolic blood pressure (mmHg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean diastolic blood pressure (mmHg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean LDL-C (mmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean TC:HDL-C ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin detemir	NPH insulin	Relative (95% CI)	Absolute		
Congestive heart failure												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	-	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin detemir	NPH insulin	Relative (95% CI)	Absolute		
Expected cost of treatment per patient per outcome												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; FPG=fasting plasma glucose; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein;WMD=weighted mean difference

* Significant results

[1] The bolus insulin in this study was aspart

[2] The study received a Jadad Quality Assessment Score of 2. This was an open-label study in which allocation concealment was not clearly described

[3] Calculated by multiplying the control event rate in this study by the RR

GRADE PROFILE – (Detemir + Aspart) versus (NPH + Human insulin) in Adults with Type 2 DM

Research question: Should insulin detemir, in combination with insulin aspart, rather than NPH insulin, in combination with regular human insulin, be used in adults with type 2 diabetes?

Settings: Out-patient

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir with Insulin Aspart	NPH Insulin with Human Insulin	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[2]	None	195	199	-	WMD 0.06 (-0.31 to 0.19)	⊕⊕OO Low	**Critical**
Proportion with A1c <= 7% (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	78/195	80/199	RR 1.0 (0.78 to 1.27)	-	⊕⊕⊕O Moderate	**Critical**
Mean fasting plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with FPG <= 7 µmol/l												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Diabetic ketoacidosis												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Severe hypoglycemia - proportion reporting >= 1 episode (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about	Sparse or imprecise data[2,3]	None	2/195	2/199	RR 1.02 (0.26 to 4.02)	-	⊕⊕OO Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir with Insulin Aspart	NPH Insulin with Human Insulin	Relative (95% CI)	Absolute		
				directness								
Severe hypoglycemia - rate ratio (folLow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[2]	None	195	199	Rate ratio 0.51 (0.09 to 2.79)	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia - proportion reporting >= 1 episode (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	31/195	44/199	RR 0.54 (0.30 to 0.97)	NNT 16 (7 to ∞)	⊕⊕⊕O Moderate	**Critical**
Nocturnal hypoglycemia - rate ratio (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	195	199	Rate ratio 0.53 (0.39 to 0.73)	-	⊕⊕⊕O Moderate	**Critical**
Overall hypoglycemia - proportion reporting >= 1 episode (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	65/195	70/199	RR 0.87 (0.55 to 1.37)	-	⊕⊕⊕O Moderate	Important
Overall hypoglycemia - rate ratio (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	195	199	Rate ratio 0.85 (0.73 to 0.98)	-	⊕⊕⊕O Moderate	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir with Insulin Aspart	NPH Insulin with Human Insulin	Relative (95% CI)	Absolute		
Mean weight or weight gain (kg) (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	195	199	-	WMD -0.62 (-1.22 to -0.02)	⊕⊕⊕O Moderate	Important
Mean systolic blood pressure (mm Hg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean diastolic blood pressure (mm Hg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean LDL-C (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean TC:HDL-C ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	-	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality (follow-up 22 weeks)												
1	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[3]	None	1/195	0/199	RR[3]	-	⊕⊕OO Low	**Critical**
Nephropathy												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir with Insulin Aspart	NPH Insulin with Human Insulin	Relative (95% CI)	Absolute		
Peripheral vascular disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; FPG=fasting plasma glucose; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein; NE=no evidence; NNT=number needed to treat; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; WMD=weighted mean difference [1] The study received a Jadad Quality Assessment score of 2. An intention-to-treat approach was not used in this study, nor was allocation concealment clearly described;[2] Wide 95% CI;[3] Very Low or zero event rates in one or more arms preclude reliable estimation of RR.

GRADE Evidence Profile – Detemir (+oral antidiabetics) versus Glargine (+ oral antidiabetics) in Adults with Type 2 DM

Research question: Should insulin detemir, rather than insulin glargine, be used in combination with oral anti-diabetic agents in adults with type 2 diabetes?

Setting: Out-patient

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	Insulin Glargine	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up 52 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	291	291	-	WMD 0.10 (-0.06 to 0.26)	⊕⊕⊕O Moderate	**Critical**
Proportion with A1C <= 7% (follow-up 52 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	151/291	151/291	RR 1 (0.86 to 1.17)	-	⊕⊕⊕O Moderate	**Critical**
Mean fasting plasma glucose (µmol/L) (follow-up 52 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	291	291	-	WMD 0.10 (-0.31 to 0.51)	⊕⊕⊕O Moderate	**Critical**
Proportion with FPG <=7 mmol/l												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Diabetic ketoacidosis												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Severe hypoglycemia - proportion reporting >=1 episode												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	Insulin Glargine	Relative (95% CI)	Absolute		
Severe hypoglycemia – rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Nocturnal hypoglycemia - proportion reporting >=1 episode												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[5]	None	291	291	RR 1.05[3,5]	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia - rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia - proportion reporting >=1 episode												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[5]	None	291	291	RR 0.94[4,5]	-	⊕⊕OO Low	Important
Overall hypoglycemia - rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain (kg) (follow-up 52 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	291	291	-	WMD -0.80 (-1.52 to -0.08)*	⊕⊕⊕O Moderate	Important
Mean systolic blood pressure (mm Hg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean diastolic blood pressure (mm Hg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean LDL-C (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean TC:HDL-C ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	Insulin Glargine	Relative (95% CI)	Absolute		
Congestive heart failure												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	-	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	Insulin Glargine	Relative (95% CI)	Absolute		
Expected cost of treatment per patient per outcome												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; FPG=fasting plasma glucose; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; WMD=weighted mean difference

* Significant results

[1] Patients enrolled in this study were poorly controlled on one or two oral anti-diabetic agents, which were continued after initiation of insulin. The oral agents used were not identified in the study

[2] The study was published as a conference abstract, therefore, study quality could not be assessed. The trial was conducted in an open-label fashion

[3] The study only reported that the RR (detemir versus glargine) of nocturnal hypoglycemia at endpoint was 1.05 (p>0.05, NS) at study endpoint. The number or proportion of subjects experiencing this outcome in each treatment arm was not specified

[4] The study only reported that the RR (detemir versus glargine) of overall hypoglycemia at endpoint was 0.94 (p>0.05, NS) at study endpoint. The number or proportion of subjects experiencing this outcome in each treatment arm was not specified

[5] The study reported RR without a 95% CI, therefore, precision cannot be determined

GRADE Evidence Profile – Detemir (+ oral antidiabetics) versus NPH (+ oral antidiabetics) in Adults with Type 1 DM
Research question: Should insulin detemir, rather than NPH insulin, be used in combination with oral anti-diabetic agents in adults with type 2 diabetes?
Setting: Out-patient

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	NPH Insulin	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up mean 22 weeks[6])												
2[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	399	397	-	WMD 0.14 (-0.01 to 0.28)	⊕⊕⊕O Moderate	**Critical**
Proportion with A1c <= 7% (follow-up 24 weeks)												
1	Randomized trial	Serious limitations[4]	No important inconsistency	No uncertainty about directness	Precise data	None	161/230	172/233	RR 0.95 (0.85 to 1.06)	-	⊕⊕⊕O Moderate	**Critical**
Mean fasting plasma glucose (µmol/L) (follow-up mean 22 weeks[6])												
2[1]	Randomized trial	Serious limitations[2]	Important inconsistency[3,10]	No uncertainty about directness	Precise data	None	396	388	-	WMD -0.14 (-1.02 to 0.74)	⊕⊕OO Low	**Critical**
Proportion with FPG <=7 µmol/L												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Diabetic ketoacidosis												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	NPH Insulin	Relative (95% CI)	Absolute		
Severe hypoglycemia - proportion reporting >= 1 episode (follow-up mean 22 weeks[6])												
2[1]	Randomized trial	Serious limitations[2]	Important inconsistency[3,10]	No uncertainty about directness	Sparse or imprecise data[5]	None	3/406	6/402	RR 0.75 (0.03 to 20.01)	-	⊕OOO Very low	**Critical**
Severe hypoglycemia - rate ratio (follow-up 24 weeks)												
1	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[5]	None	237	238	Rate ratio 0.13 (0.02 to 0.91)*	-	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia - proportion reporting >=1 episode (follow-up mean 22 weeks[6])												
2[1]	Randomized trial	Serious limitations[2]	No important inconsistency[3,10]	No uncertainty about directness	Precise data	None	79/406	134/402	RR 0.53 (0.31 to 0.91)*	NNT = 6 (4 to 33)[7]*	⊕⊕⊕O Moderate	**Critical**
Nocturnal hypoglycemia - rate ratio (follow-up mean 22 weeks)												
2[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	406	402	Rate ratio 0.45 (0.38 to 0.54)*	-	⊕⊕⊕O Moderate	**Critical**
Overall hypoglycemia - proportion reporting >= 1 episode (follow-up mean 22 weeks[6])												
2[1]	Randomized trial	Serious limitations[2]	Important inconsistency[3,10]	No uncertainty about directness	Precise data	None	178/406	244/402	RR 0.65 (0.39 to 1.07)	-	⊕⊕OO Low	Important
Overall hypoglycemia - rate ratio (follow-up mean 22 weeks)												
2[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	406	402	Rate ratio 0.54 (0.5 to	-	⊕⊕⊕O Moderate	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	NPH Insulin	Relative (95% CI)	Absolute		
									0.58)*			
Mean weight or weight gain (kg) (follow-up mean 22 weeks[6])												
2[1]	Randomized trial	Serious limitations[2]	Important inconsistency[3,10]	No uncertainty about directness	Precise data	None	395	387	-	WMD -1.27 (-1.95 to -0.58)*	⊕⊕OO Low	Important
Mean systolic blood pressure (mm Hg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean diastolic blood pressure (mm Hg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean LDL-C (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean TC:HDL-C ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	-	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality (follow-up 20 weeks)												
1	Randomized trial	Serious limitations[8]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[9]	None	1/169	1/164	RR 0.97 (0.06 to 15.4)	-	⊕⊕OO Low	**Critical**
Nephropathy												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Detemir	NPH Insulin	Relative (95% CI)	Absolute		
Peripheral vascular disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; FPG=fasting plasma glucose; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; WMD=weighted mean difference

* Significant results
[1] Two studies used various oral anti-diabetics
[2] Both studies received a Jadad Quality Assessment score of 2. Both were open-label studies without intention-to-treat (ITT) analyses.
[3] I-square > 50%
[4] One of the two included studies received a Jadad Quality Assessment Score of 2. This was an open-label study which did not report an ITT analysis.
[5] Wide 95% CI
[6] Range=20-24 weeks
[7] Calculated by multiplying the event rate in the control arm by the RR
[8] The other study of the two was an open-label trial that received a Jadad Quality Assessment score of 2
[9] Very low or zero event rates preclude reliable estimation of RR
[10] The two studies appeared similar in terms of trial design and the population enrolled. The main difference between them was that in one study, basal insulins were administered twice daily while in the other, basal insulins were administered once daily. This may explain the observed heterogeneity

GRADE Evidence Profile – Glargine versus TZDs in Adults with Type 2 DM
Research question: Should insulin glargine, rather than thiazolidinediones (TZDs), be used in adults with type 2 diabetes?
Setting: Out-patient

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	TZDs	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up median 24 weeks[18,25])												
3	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	303	321	-	WMD -0.20 (-0.38 to -0.01)[19]	⊕⊕⊕O Moderate	**Critical**
Proportion with A1c <= 7% (follow-up 24 weeks)												
1	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	50/104	58/112	RR 0.98 (0.74 to 1.29)	-	⊕⊕⊕O Moderate	**Critical**
Mean fasting plasma glucose (µmol/L) (follow-up median 20 weeks[20])												
2[4]	Randomized trial	Serious limitations[5]	No important inconsistency	No uncertainty about directness	Precise data	None	114	112	-	WMD -1.04 (-1.64 to -0.45)	⊕⊕⊕O Moderate	**Critical**
Proportion with FPG <= 7 µmol/L												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Diabetic ketoacidosis												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Severe hypoglycemia - Proportion reporting >= 1 episode (follow-up median 36 weeks[21])												
2	Randomized trial	Serious limitations[2,12]	Important inconsistency[11,13]	No uncertainty about directness	Sparse or imprecise data[6]	None	10/195	7/194	RR 1.63 (0.14 to 18.87)	-	⊕OOO Very Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	TZDs	Relative (95% CI)	Absolute		
Severe hypoglycemia - rate ratio												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Nocturnal hypoglycemia - proportion reporting >= 1 episode (follow-up 24 weeks)												
1	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	29/104	12/112	RR 2.6 (1.4 to 4.83)	NNT = 6 (3, 23)	⊕⊕⊕O Moderate	**Critical**
Nocturnal hypoglycemia - rate ratio												
0	NE	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia - proportion reporting >= 1 episode (follow-up median 24 weeks[20])												
3	Randomized trial	Serious limitations[1]	Important inconsistency [11,16]	No uncertainty about directness	Precise data	None	146/303	82/321	RR 1.73 (0.83 to 3.58)[14]	-	⊕⊕OO Low	Important
Overall hypoglycemia - rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean weight or weight gain (kg) (follow-up median 20 weeks[20])												
2[7]	Randomized trial	Serious limitations[2,9]	No important inconsistency	No uncertainty about directness	Precise data	None	114	122	-	WMD -1.45 (-2.48 to -0.42)	⊕⊕⊕O Moderate	Important
BMI (kg/m[1]) (follow-up 16 weeks)												
1[8]	Randomized trial	Serious limitations[9]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[6]	None	10	10	-	WMD -0.50 (-4.11 to 3.11)	⊕⊕OO Low	Important
Mean systolic blood pressure (mm Hg) (follow-up 16 weeks)												
1[8]	Randomized trial	Serious limitations[9]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[6]	None	10	10	-	WMD 0 (-12.55 to 12.55)	⊕⊕OO Low	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	TZDs	Relative (95% CI)	Absolute		
Mean diastolic blood pressure (mmHg) (follow-up 16 weeks)												
1[8]	Randomized trial	Serious limitations[9]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[6]	None	10	10	-	WMD 10 (0.2 to 19.8)	⊕⊕OO Low	Important
Mean LDL-C (µmol/L) (follow-up median 20 weeks[20])												
2[7]	Randomized trial	Serious limitations[2,9]	Important inconsistency [11,24]	No uncertainty about directness	Precise data	None	114	122	-	WMD -0.52 (-1.37 to 0.33)	⊕⊕OO Low	Important
Mean TC:HDL-C ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
0	-	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	TZDs	Relative (95% CI)	Absolute		
HRQoL (diabetes-specific and generic) (follow-up median 36 weeks[21])												
2[17]	Randomized trial	Serious limitations[3]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[10]	None	388	216	-	[15,22] -	⊕⊕OO Low	**Critical[23]**
Patient satisfaction with diabetes care												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	-	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; FPG=fasting plasma glucose; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; TZD=thiazolidinediones; WMD=weighted mean difference

[1] One study received a Jadad Quality Assessment Score (QAS) of 2, and another one received a Jadad QAS of 1. The third study was in abstract form, therefore, study quality could not be evaluated. None of the 3 RCTs was blinded, and allocation concealment was not clearly described in any study

[2] The study received a Jadad QAS of 2; this was an open-label trial in which allocation concealment was unclear

[3] One of the two studies received a Jadad QAS of 1. It was not blinded, nor was allocation concealment clearly described. The other one was published as an abstract, therefore, study quality could not be assessed

[4] Two RCTs reported this outcome: one only reported the mean change in FPG from baseline to endpoint for each treatment arm, while the other one reported the mean FPG at endpoint. In both studies, glargine was compared to rosiglitazone

[5] One study received a Jadad QAS of 2, and the other one received a Jadad QAS of 1. None of them were blinded trials; allocation concealment was unclear in both studies.

[6] Wide 95% CI
[7] In both studies, glargine was compared to rosiglitazone
[8] One RCT compared glargine with rosiglitazone
[9] The study received a Jadad QAS of 1; it was an open-label trial in which allocation concealment was unclear
[10] One study did not report mean values of final HRQoL scores, only p-values for differences between treatment arms. The other one only reported mean changes from baseline in HRQoL scores without standard errors or standard deviations
[11] I^2 >50%
[12] The study was published as an abstract, therefore, study quality could not be assessed
[13] The observed heterogeneity may have been due to the fact that one report studied rosiglitazone while the other studied pioglitazone. One reported a statistically non-significant RR of 6.31 while the other reported a statistically non-significant RR of 0.54
[14] In the single study comparing pioglitazone with glargine (OSTER 2006), the RR of overall hypoglycemia was higher than the overall pooled RR and was statistically significant. The pooled RR from the two remaining studies, both of which used rosiglitazone, was not statistically significant
[15] The study reported that HRQoL changes from baseline to 48 weeks generally favoured glargine, and that glargine demonstrated statistically significant improvement over pioglitazone in the following domains: hyperglycemia distress, fatigue distress, and total distress
[16] The I^2 values of the pooled estimate for the two studies that studied rosiglitazone was less than 50%, while pioglitazone was only studied in one RCT
[17] Two RCTs reported this outcome. To measure HRQoL, one study 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. The other one 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
[18] Range=16-48 weeks
[19] In subgroup analysis, the single study that used pioglitazone reported a statistically significant WMD in favour of glargine of -0.30. The remaining two studies used rosiglitazone; the pooled WMD of these studies was nearly zero and not statistically significant
[20] Range=16-48 weeks
[21] Range=24-48 weeks
[22] The study reported that HRQoL improved in both treatment arms, but that glargine-treated subjects experienced significantly greater improvement in terms of the total symptom score (-5.67 in the glargine arm versus -1.15 in the rosiglitazone arm at 24 weeks, p=0.005) and the total symptom distress score (-2.81 in the glargine arm versus -1.06 in the rosiglitazone arm at 24 weeks, p=0.03). Significantly greater improvements were also observed in mood symptoms, ophthalmologic symptoms, ophthalmologic distress, and fatigue distress. There was also a statistically significant difference in favour of glargine in the single-item general health perception rating (difference in change from baseline=5.38, p<0.05)
[23] Diabetes-specific HRQoL was rated by CERC as 'Critical' while generic HRQoL was rated as 'Important'
[24] The source of the heterogeneity in these two studies in terms of mean LDL-C at endpoint is unclear. Both studies used rosiglitazone in combination with the insulin analogues, and both samples had similar LDL-C values at baseline. Triplitt 2006, the study with the larger (and statistically significant) effect in favour of glargine, was conducted in only 20 patients, therefore, the observed difference may have been a chance effect
[25] It is unclear whether the outcome was assessed at 24 or 48 weeks. A duration of 48 weeks was assumed for all outcomes

GRADE Evidence Profile – Glargine (+ bolus insulin) versus NPH (+ bolus insulin) in Adults with Type 2 DM
Research question: Should insulin glargine, rather than NPH insulin, be used in combination with bolus insulin in adults with type 2 diabetes?
Setting: Out-patient

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH insulin	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up 28 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	259	259	-	WMD 0.28 (0.07 to 0.49)*	⊕⊕⊕O Moderate	**Critical**
Proportion with A1c <= 7% (follow-up 28 weeks)												
1[3]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[4]	None	7/52	8/48	RR 0.81 (0.32 to 2.06)	-	⊕⊕OO Low	**Critical**
Mean fasting plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Proportion with FPG <= 7 µmol/L												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Diabetic ketoacidosis												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Severe hypoglycemia - proportion reporting >= 1 episode (follow-up 28 weeks)												
1[3]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[6]	None	0/52	1/48	RR[6]	-	⊕⊕OO Low	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH insulin	Relative (95% CI)	Absolute		
Severe hypoglycemia - rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Nocturnal hypoglycemia - proportion reporting >= 1 episode (follow-up 28 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	81/259	104/259	RR 0.78 (0.62 to 0.98)*	NNT = 11 (7 to 125)[5]*	⊕⊕⊕O Moderate	**Critical**
Nocturnal hypoglycemia - rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Overall hypoglycemia – proportion reporting >= 1 episode (follow-up 28 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Precise data	None	159/259	173/259	RR 0.92 (0.81 to 1.05)	-	⊕⊕⊕O Moderate	Important
Overall hypoglycemia - rate ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean weight (kg) (follow-up 28 weeks)												
1[1]	Randomized trial	Serious limitations[2]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[4]	None	259	259	-	WMD -2.10 (-5.21 to 1.01)	⊕⊕OO Low	Important
Mean systolic blood pressure (mm Hg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean diastolic blood pressure (mm Hg)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean LDL-C (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Mean TC:HDL-C ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH insulin	Relative (95% CI)	Absolute		
Congestive heart failure												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Ischemic heart disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Lower-limb disease												
o	-	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Nephropathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Peripheral vascular disease												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Stroke/TIA												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes care												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Patient self-management												
o	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH insulin	Relative (95% CI)	Absolute		
Expected cost of treatment per patient per outcome												
o	-	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
o	-	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; FPG=fasting plasma glucose; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; WMD=weighted mean difference

* Significant results

[1] Bolus insulin in this study was human insulin

[2] The study received a Jadad Quality Assessment score of 2; this trial was not blinded and allocation concealment was unclear

[3] Another study, a subgroup analysis of the above study, reported this outcome. Data from this study was used because this outcome was not reported in the study cited in reference #1

[4] Wide 95% confidence interval

[5] Calculated by multiplying the event rate in the control arm of this study by the RR

[6] Very low or zero event rates observed in one or both treatment arms prevent reliable estimation of RR

GRADE Evidence Profile – Glargine (+ oral antidiabetics) versus NPH (+ oral antidiabetics) in Adults with Type 2 DM
Research question: Should insulin glargine, rather than NPH insulin, be used in combination with oral anti-diabetic agents in adults with Type 2 diabetes?
Setting: Out-patient

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH Insulin	Relative (95% CI)	Absolute		
Mean A1c (%) (follow-up median 24 weeks[2])												
9	Randomized trial	Serious limitations[1]	No important inconsistency	No uncertainty about directness	Precise data	None	1689	1708	-	WMD -0.05 (-0.13 to 0.04)[3]	⊕⊕⊕O Moderate	**Critical**
Proportion with A1c <= 7% (follow-up median 24 weeks[6])												
2	Randomized trial	Serious limitations[4]	Important inconsistency[5]	No uncertainty about directness	Precise data	None	270/598	264/639	RR 1.19 (0.80 to 1.77)[8]	-	⊕⊕OO Low	**Critical**
Mean fasting plasma glucose (µmol/L) (follow-up median 24 weeks[2])												
6	Randomized trial	Serious limitations[4]	Important inconsistency[5]	No uncertainty about directness	Precise data	None	1187	1219	-	WMD -0.10 (-0.28 to 0.07)[10]	⊕⊕⊕O Moderate	**Critical**
Proportion with FPG <= 7 µmol/L												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Mean 2-hour post-prandial plasma glucose (µmol/L)												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Diabetic ketoacidosis												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hyperosmolar hyperglycemic non-ketotic coma												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH Insulin	Relative (95% CI)	Absolute		
Severe hypoglycemia - proportion reporting >= 1 episode (follow-up median 24 weeks[2])												
7	Randomized trial	Serious limitations[18]	Important inconsistency[1] [9,43,47]	No uncertainty about directness	Sparse or imprecise data[20]	None	29/1415	55/1451	RR 0.66 (0.29 to 1.48)[33]	-	⊕OOO Very low	**Critical**
Severe hypoglycemia - Rate ratio (follow-up median 24 weeks[6])												
3	Randomized trial	Serious limitations[21]	important inconsistency[2] [2,23,43]	No uncertainty about directness	Sparse or imprecise data[20]	None	819	862	Rate ratio 0.51 (0.15 to 1.79)[29]	-	⊕OOO Very low	**Critical**
Nocturnal hypoglycemia - proportion reporting >= 1 episode (follow-up median 24 weeks[2])												
7	Randomized trial	Serious limitations[2] [4]	No important inconsistency	No uncertainty about directness	Precise data	Reporting bias[25]	237/1262	421/1270	RR 0.56 (0.47 to 0.68)[26]*	NNT = 7 (6 to 9)[7]*	⊕⊕OO Low	**Critical**
Nocturnal hypoglycemia - rate ratio (follow-up median 24 weeks[13])												
4	Randomized trial	Serious limitations[2] [4]	Important inconsistency	No uncertainty about directness	Precise data	None	835	870	Rate ratio 0.41 (0.29 to 0.59)[30]*	-	⊕⊕OO Low	**Critical**
Overall hypoglycemia - proportion reporting >= 1 episode (follow-up median 24 weeks[2])												
8	Randomized trial	Serious limitations[2] [4]	No important inconsistency	No uncertainty about directness	Precise data	Reporting bias[25]	625/1323	737/1319	RR 0.87 (0.81 to 0.93)[32]*	NNT = 14 (9 to 36)[7]*	⊕⊕OO Low	**Important**
Overall hypoglycemia - rate ratio (follow-up median 24 weeks[13])												
4	Randomized trial	Serious limitations[27]	Important inconsistency[3] [6]	No uncertainty about directness	Precise data	None	835	870	Rate ratio 0.82 (0.64 to 1.06)[37]	-	⊕⊕OO Low	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH Insulin	Relative (95% CI)	Absolute		
BMI (kg/m[1]) (follow-up median 18 weeks[13])												
2[11]	Randomized trial	Serious limitations[12]	No important inconsistency	No uncertainty about directness	Precise data	None	236	231	-	WMD -0.19 (-0.76 to 0.38)	⊕⊕⊕O Moderate	Important
Mean weight or weight gain (kg) (follow-up median 24 weeks[2])												
7	Randomized trial	Serious limitations[3] [4]	No important inconsistency	No uncertainty about directness	Precise data	None	1238	1235	-	WMD 0.18 (-0.11 to 0.47)[35]	⊕⊕⊕O Moderate	Important
Mean systolic blood pressure (mm Hg) (follow-up 52 weeks)												
1	Randomized trial	Serious limitations[14]	No important inconsistency	No uncertainty about directness	Precise data	None	214	208	-	WMD 0 (-2.77 to 2.77)	⊕⊕⊕O Moderate	Important
Mean diastolic blood pressure (mm Hg) (follow-up 52 weeks)												
1	Randomized trial	Serious limitations[14]	No important inconsistency	No uncertainty about directness	Precise data	None	214	208	-	WMD 1.00 (-0.23 to 0.09)	⊕⊕⊕O Moderate	Important
Mean LDL-C (µmol/L) (follow-up median 44 weeks[16])												
2	Randomized trial	Serious limitations[14]	No important inconsistency	No uncertainty about directness	Precise data	None	275	257	-	WMD 0.07 (-1.77 to 3.77)	⊕⊕⊕O Moderate	Important
Mean TC:HDL-C ratio												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Congestive heart failure												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH Insulin	Relative (95% CI)	Absolute		
Ischemic heart disease (follow-up median 14 weeks[40])												
2	Randomized trial	Serious limitations[42]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[39]	None	4/285	2/291	RR 1.81 (0.38 to 8.54)	-	⊕⊕OO Low	**Critical**
Lower-limb disease												
0	-	-	-	-	-	-	-	-	-	-	-	Important
All-cause mortality (follow-up median 14 weeks[40])												
2	Randomized trial	Serious limitations[38]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[39]	None	0/295	0/318	RR[39]	-	⊕⊕OO Low	**Critical**
Nephropathy												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Neuropathy (follow-up 24 weeks)												
1	Randomized trial	Serious limitations[41]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[41]	None	1/221	0/223	RR[39]	-	⊕⊕OO Low	**Critical**
Peripheral vascular disease												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
Retinopathy (follow-up 24 weeks)												
1	Randomized trial	Serious limitations[41]	No important inconsistency	No uncertainty about directness	Sparse or imprecise data[41]	None	1/221	0/223	RR[39]	-	⊕⊕OO Low	**Critical**
Stroke/TIA												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (diabetes-specific)												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
HRQoL (generic)												
0	-	-	-	-	-	-	-	-	-	-	-	Important

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other	Insulin Glargine	NPH Insulin	Relative (95% CI)	Absolute		
Patient satisfaction with diabetes care												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Patient satisfaction with diabetes treatment (DTSQc[45]) (follow-up 24 weeks)												
1	Randomized trial	Serious limitations[41]	No important inconsistency	No uncertainty about directness	Precise data	None	231	250	-	WMD 0.60 (0.07 to 1.13) [46]	⊕⊕⊕O Moderate	**Important**
Patient self-management												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Expected cost of treatment per patient per outcome												
0	-	-	-	-	-	-	-	-	-	-	-	**Critical**
ER visits												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Hospitalizations												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Specialist visits												
0	-	-	-	-	-	-	-	-	-	-	-	Important
Primary care visits												
0	-	-	-	-	-	-	-	-	-	-	-	Important

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room; FPG=fasting plasma glucose; HRQoL=health-related quality of life; LDL-C=low-density lipoprotein; NE=no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; TC:HDL-C=ratio of total cholesterol to high-density lipoprotein; WMD=weighted mean difference

* Significant results

[1] Five of the 9 studies received a Jadad Quality Assessment Score (QAS) of 3, two received a Jadad QAS of 2, and the remainder, a Jadad QAS of 1. No trial was double-blinded, nor was allocation concealment adequately described in any study

[2] Range=4-52 weeks

[3] In subgroup analysis, the four studies in which oral anti-diabetic (OAD) therapy consisted of sulfonylureas, the WMD was somewhat larger than the overall WMD and the result was statistically significant. The WMD was statistically non-significant for the single study in which metformin was the OAD and the remaining four studies that allowed various OADs. In sensitivity analysis, removal of the two studies that were <=3 months in duration did not have an appreciable effect on the overall WMD

[4] Two studies received a Jadad QAS of 3 and 2, respectively. Neither study was double-blinded, nor was allocation concealment clear in either study

[5] I-square=78%. The observed heterogeneity may have been due to the fact that different OADs were used in the each of the two studies

[6] All studies were of 24 weeks duration

[7] Calculated by multiplying the control event rate across studies by the RR from MA

[8] In subgroup analysis, the single study that used sulfonylureas as OAD demonstrated a statistically significant RR of 1.5 in favour of glargine. The remaining RCT used various OADs; the RR was nearly 1 and statistically non-significant in this study
[9] Three of the 6 studies received a Jadad QAS of 3, two received a Jadad QAS of 2, and the remaining study, a Jadad QAS of 1. No trial was double-blinded, nor was allocation concealment adequately described in any study
[10] In subgroup analysis, both the pooled WMD for the three studies in which OAD therapy consisted of sulfonylureas, and the pooled WMD across the remaining studies that used various OADs, were similar to the overall WMD and remained statistically non-significant
[11] Both studies used a sulfonylurea as OAD therapy
[12] One study received a Jadad QAS of 2 while the other received a score of 1. Neither study was double-blinded, nor was allocation concealment adequately described in either report
[13] Range=12-24 weeks
[14] The study received a Jadad QAS of 1. This trial was open-label and allocation concealment was not adequately described
[15] One study received a Jadad QAS of 3 while the other received a Jadad QAS of 1. Neither study was double-blinded, nor did either adequately describe allocation concealment
[16] Range=36-52 weeks
[17] The OAD was metformin in one study while various OADs were used in the other. The individual estimates of effect were similar to the overall WMD in both studies, and both were statistically non-significant
[18] Four of the 9 studies received a Jadad QAS of 3, two received a Jadad QAS of 2, and the remaining trial, a Jadad QAS of 1. No trial was double-blinded, nor was allocation concealment adequately described in any study
[19] I-square=64%.
[20] Wide 95% confidence interval
[21] One study received a Jadad QAS of 3 and the remaining two trials received a score of 2. No trial was double-blinded, nor was allocation concealment adequately described in any study
[22] I-square=84%
[23] Wide range of rate ratios in individual studies (range=0.15-1.65)
[24] Three of the 7 studies received a Jadad QAS of 3, two received a Jadad QAS of 2, and the remaining studies, a Jadad QAS of 1. No trial was double-blinded, nor was allocation concealment adequately described in any study
[25] Asymmetry observed in funnel plot
[26] In subgroup analysis, the pooled RR across studies using sulfonylureas as OAD therapy in four studies and the pooled RR across studies using various OADs in the other three studies were similar to the overall RR, and both estimates were statistically significant
[27] Of the four studies, one study received a Jadad QAS of 3, two received a score of 2, and the remaining one received a score of 1. No trial was double-blinded, nor was allocation concealment adequately described in any study
[28] I-square=92%. There was no significant heterogeneity in subgroups defined by OAD class
[29] In subgroup analysis, the pooled rate ratio from the two RCTs that used sulfonylureas as OAD was smaller than the overall rate ratio and was statistically significant. However, a significant degree of heterogeneity remained (I-square=71%). The single study using various OADs had a rate ratio greater than 1 that was statistically non-significant
[30] In subgroup analysis, the pooled rate ratio for the three studies that used sulfonylureas as OAD was similar to the overall rate ratio (0.36) and was statistically significant. There was no heterogeneiity in this subgroup (I-square=0). The single study that used various OADs also had a rate ratio similar to the overall rate ratio, but the result was statistically non-significant
[31] Four of the 8 studies received a Jadad QAS of 3, two received a Jadad QAS of 2, and the remainder, a Jadad QAS of 1. No trial was double-blinded, nor was allocation concealment adequately described in any study
[32] In subgroup analysis, the pooled RR from four studies using sulfonylureas as OADs and the pooled RR from three studies using various OADs were both similar to the overall pooled RR, and both were statistically significant. However, the single study that used metformin as OAD had a RR that was not significantly different from 1
[33] In subgroup analysis, the pooled RR across the four studies that used sulfonylureas as OAD was 0.40; this result was statistically significant. However, a significant degree of heterogeneity remained (I-square=52%). The pooled RR from the remaining three studies, all of which used various OADs, was 1.44, a result that was statistically non-significant
[34] Five of the 7 studies received a Jadad QAS of 3 and the remainder received a Jadad QAS of 1. No trial was double-blinded, nor was allocation concealment adequately described in any study
[35] All subgroups defined by OAD type (i.e., sulfonylurea, metformin, various) had statistically non-significant pooled WMDs. Five of the 7 studies reported mean change from baseline weight in each treatment arm, while the remaining two studies reported mean weight at endpoint. In sensitivity analysis, the pooled WMDs from these two sets of studies were similar, and both were statistically non-significant
[36] I-square=94%. Significant heterogeneity remained in the subgroup of studies in which sulfonylureas were used as OAD. The 3 trials in this subgroup studied different populations:

Chinese, Asian, and Latin American. In addition, one study had a higher target fasting plasma glucose than the other two trials. Furthermore, this study was of 3 months duration while the other two studies were > 3 months

[37] In subgroup analysis, the pooled rate ratio from the 3 RCTs that used sulfonylureas as OAD and the rate ratio from the single study that used various OADs were both similar to the overall pooled rate ratio, however, the latter value was statistically significant while the sulfonylurea subgroup's value was not. A significant degree of heterogeneity remained in the sulfonylurea subgroup (I-square=96%)

[38] One study received a Jadad QAS of 3 while the other received a score of 2. Neither study was double-blinded or had an adequate description of allocation concealment.

[39] Very low or zero event rates in one or both arms preclude reliable estimation of RR

[40] Range=4-24 weeks

[41] The study received a Jadad QAS of 2. This trial was not double-blinded, nor did it have an adequate description of allocation concealment

[42] One study received a Jadad QAS of 3 while the other received a score of 2. Neither study was double-blinded, nor was allocation concealment made clear in either study

[43] In subgroup analysis, significant heterogeneity remained among the studies that used a sulfonylurea as OAD. Ethnic diversity may explain this heterogeneity since one study was conducted in a Chinese population while another was conducted in a Latin American population. Furthermore, one study titrated insulin dose to a lower target fasting plasma glucose (6.3 µmol/L) than another one (target 7.7 µmol/L)

[44] The study received a Jadad QAS of 2. This study was not blinded, nor was allocation concealment adequately described

[45] The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) is an 8-item questionnaire, in which each item is measured on a 7-point scale ranging from 3 to -3. The sum of items 1, 4, 5, 6, 7, and 8 of the DTSQc indicates the level of treatment satisfaction. A higher DTSQc indicates greater treatment satisfaction

[46] WMD is for mean treatment satisfaction scores at endpoint. The trial report also notes that the improvement from baseline in the glargine arm was significantly greater than the improvement in the NPH arm ($p<0.02$)

[47] Wide range of RRs in individual studies (range=0.18-1.62)

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

APPENDIX 6

Individual GRADE evidence profiles for Gestational Diabetes

Supporting Informed Decisions

À l'appui des décisions éclairées

Appendix 6 – Individual GRADE evidence profiles for Gestational Diabetes

Table of Contents

1 Patient Population: Pregnant Women

1.1 Rapid-acting insulin analogues

GRADE Evidence Profile – Lispro versus Human Insulin in Women with Gestational Diabetes
Research Question: Should insulin lispro, rather than human insulin, be used for the treatment gestational diabetes (GD)?
Settings: Pregnant women with GD

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other Considerations	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Glycated hemoglobin (A1c), WMD (follow-up range 6 weeks from enrollment to end of pregnancy)												
2	Randomized trial	Serious limitations[1]	No important inconsistency	Uncertainty about directness[2]	Sparse or imprecise data[1]	none	44	47	-	WMD 0.06 (-0.11 to 0.23)	⊕OOO Very low	
Overall hypoglycemia, WMD (follow-up end of pregnancy)												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Severe hypoglycemia												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Nocturnal hypoglycemia												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Mean weight gain (kg) at end of pregnancy												
1	Randomized trial	Serious limitations[3]	No important inconsistency	Uncertainty about directness[4]	Sparse or imprecise data[3]	None	25	24	-	ILis: 10.9 (7-17) HI: 11.1 (8-14) Not significant	⊕OOO Very low	
Proportion with A1c ≤ 7%												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Diabetic ketoacidosis												
0	No evidence	-	-	-	-	-	-	-	-	-	-	

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other Considerations	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
Fasting plasma glucose (FPG) - mean												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Fasting plasma glucose (FPG) - % ≤ 7 µmol/L												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Mean 2-hour post-prandial plasma glucose												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Hyperosmolar hyperglycemic non-ketotic coma												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Blood pressure (mm Hg)												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Cholesterol LDL-C												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Cholesterol TC:HDL-C ratio												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Congestive heart failure												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Ischemic heart disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Lower-limb disease												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
All-cause mortality												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Nephropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Neuropathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Peripheral vascular disease												
o	No evidence	-	-	-	-	-		-	-	-	-	
Retinopathy												
o	No evidence	-	-	-	-	-	-	-	-	-	-	
Stroke/TIA												
o	No evidence	-	-	-	-	-	-	-	-	-	-	

Quality Assessment							Summary of Findings					Importance
							No. of Patients		Effect		Quality	
No. of Studies	Design	Limitations	Consistency	Directness	Imprecision	Other Considerations	Insulin Lispro	Human Insulin	Relative (95% CI)	Absolute		
HRQoL (diabetes-specific)												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
HRQoL (generic												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Patient satisfaction with diabetes care												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Patient satisfaction with diabetes treatment												
0[5]	No evidence	-	-	-	-	-	-	-	-	-	-	
Patient self-management												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Expected cost of treatment per patient per outcome												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
ER visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Hospitalizations												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Specialist visits												
0	No evidence	-	-	-	-	-	-	-	-	-	-	
Primary care visit												
0	No evidence	-	-	-	-	-	-	-	-	-	-	

A1c=glycosylated hemoglobin; BMI=body mass index; CI=confidence interval; DM=diabetes mellitus; ER=emergency room FPG=fasting plasma glucose; HRQoL=health-related quality of life; NE= no evidence; RR=relative risk; RT=randomized trial; TIA=transient ischemic attack; WMD=weighted mean difference

[1] The evidence consists of two open-label parallel randomized controlled trials (RCTs) with unclear allocation concealment and quality score of 2 out of 5. The total number of patients in both studies was 91

[2] Women in one study were mainly Hispanic and, in the other study, were mainly Caucasian

[3] The evidence consists of a small open-label parallel RCT (n= 49) with unclear allocation concealment and quality score of 2 out of 5

[4] Women in the study were mainly Caucasian

[5] An abstract showed that 95% and 50% were compliant with insulin lispro and human insulin respectively, probably due to the shortened lag time between injection and meal

1.2 Long-acting insulin analogues

The systematic search of the literature did not identify any randomized controlled trials that examined the use of long-acting insulin analogues for the treatment of pregnant patients with gestational diabetes.