Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

COMPUS

March 2009

Academic Detailing Upskilling Document – Insulin Analogues

Supporting Informed Decisions

À l'appui des décisions éclairées

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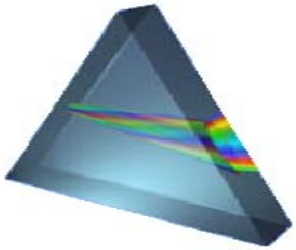
Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Canadian Optimal Medication Prescribing and Utilization Service

Academic Detailing Upskilling Document — Insulin Analogues



PrISM

Prescription Information Services of Manitoba

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ABBREVIATIONS

ACE inhibitor	angiotensin-converting enzyme (ACE) inhibitor
ADA	American Diabetes Association
ARB	angiotensin II receptor blocker
A1C	glycosylated hemoglobin
CDA	Canadian Diabetes Association
CERC	COMPUS Expert Review Committee
CIMT	carotid intima-media thickness
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CSII	continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DECODE	The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe
DTSQ	Diabetes Treatment Satisfaction Questionnaire
ICER	incremental cost-effectiveness ratio
MDI	multiple daily injections
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NNT	number needed to harm
NPH	neutral protamine Hagedorn insulin
QALY	quality-adjusted life-years
QoL	quality of life
RCT	randomized controlled trial
RR	risk ratio
UKPDS	United Kingdom Prospective Diabetes Study
WMD	weighted mean difference

INTRODUCTION

The academic detailing upskilling document on insulin analogues is intended as a companion document to the Canadian Agency for Drugs and Technologies in Health (CADTH) meta-analyses on rapid-acting insulin analogues and long-acting insulin analogues for the treatment of diabetes mellitus, and the optimal therapy recommendations report on insulin analogues.[1-3] These three documents were produced through CADTH's program, the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS).

This particular upskilling document focuses on the evidence for insulin analogue use in the management of type 1, type 2, and gestational diabetes. Organizations considering academic detailing (or related) interventions based on the COMPUS review of this topic will require additional clinical background information. The act of preparing academic detailers for intervention interactions has been called "upskilling", as it reflects the elevation of background knowledge and skill that is required. The upskilling document will provide some of this background information and enhance the ability of academic detailers to present information and respond to questions in the field. It is intended as a companion document to the two meta-analyses and optimal therapy recommendations report by providing greater clinical context. A thorough understanding of all documents will be valuable for the academic detailer.

The upskilling document on insulin analogues is divided into six sections:

Section 1: provides detailers with a better understanding of insulin analogues from a pharmacological and kinetic perspective, with emphasis on how they differ from conventional human insulins.

Section 2: looks at the concepts that are specific to the evaluation of literature on insulin efficacy and safety.

Sections 3 to 5: review type 1, type 2, and gestational diabetes, and diabetes and pregnancy, respectively. These sections provide a broader overview of the disease (epidemiology, diagnosis), as well as disease management. In addition, these sections describe insulin dosing and the management of hypoglycemia. A recommended reading list is included for each of these three sections, with key references intended to supplement the information contained in the upskilling document.

Section 6: summarizes the economic information surrounding insulin analogues and includes information from "An Economic Evaluation of Insulin Analogues for the Treatment of Patients with Type 1 and Type 2 Diabetes Mellitus in Canada," another document produced by COMPUS.[4]

At the end of the document are appendices containing additional information that may be useful for academic detailers. Appendix 1 provides a high-level comparison of the Canadian, US and National Institute for Health and Clinical Excellence (NICE) diabetes guidelines. Appendix 2 includes reference charts developed by, and being used with the permission of, RxFiles that

provide key research trial summaries, information on insulin dosing, titration, and overall diabetes management.

The combination of the CADTH meta-analyses and the academic detailing upskilling document should provide an informational cornerstone for interventions on this topic.

1 SECTION 1: PHARMACOLOGY OF INSULIN ANALOGUES

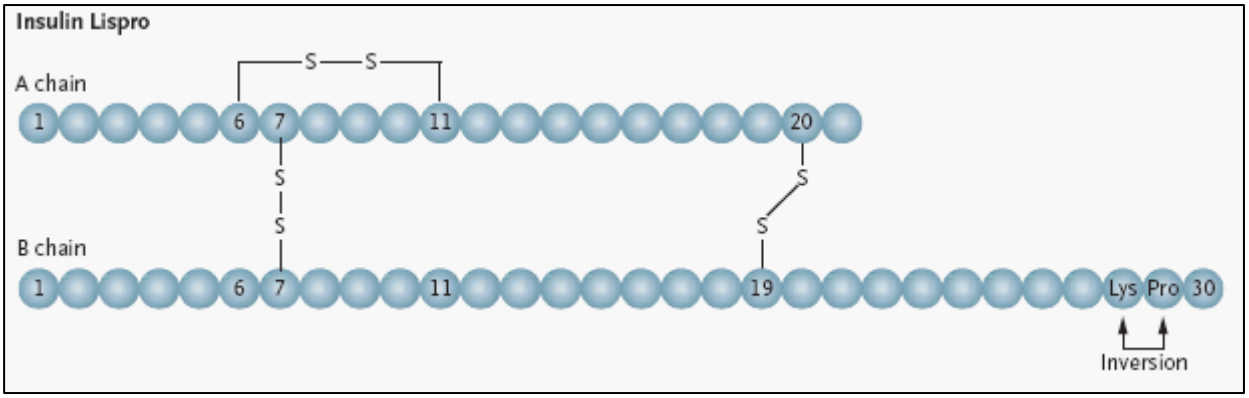
1.1 Structural Difference

1.1.1 Rapid-acting insulin analogues

a) Insulin Lispro (Humalog®)

Insulin lispro is identical to human insulin except for a transposition of two amino acids at the C terminus of the B-chain. Position 28 and 29 are changed from proline-lysine to lysine-proline (Figure 1). This minor inversion results in a conformational change that reduces the tendency for self-association relative to regular human insulin. Regular human insulin forms self-associations (hexamers and dimers), which do not diffuse into the circulation until they are broken down into monomers. Insulin lispro acts more rapidly because it has a reduced tendency to self-associate. Any complexes that do form tend to dissociate more rapidly into monomers in subcutaneous tissue. The physiological action of insulin lispro, however, is similar to human insulin and is considered equipotent on a molar basis.

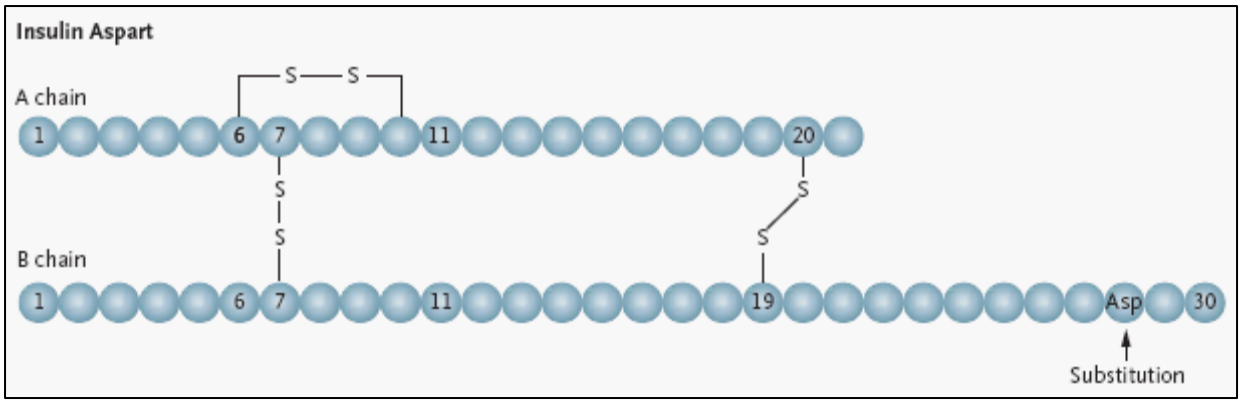
Figure 1: Molecular Structure of Insulin Lispro[5]



b) Insulin Aspart (NovoRapid®)

In another effort to improve prandial or bolus insulin, insulin aspart was developed to better mimic the endogenous insulin response to food intake. Insulin aspart is also identical to human insulin expect for the substitution of aspartic acid for proline at position 28 of the B-chain of human insulin (Figure 2). The negative charge of aspartic acid contributes to a decreased tendency of insulin aspart to self-associate. The result is more rapid absorption after subcutaneous injection. The amino acid substitution does not seem to impact the efficacy of the analogue at the insulin receptor, since the affinity of insulin aspart is similar to that of human insulin.[5,6]

Figure 2: Molecular Structure of Insulin Aspart[5]

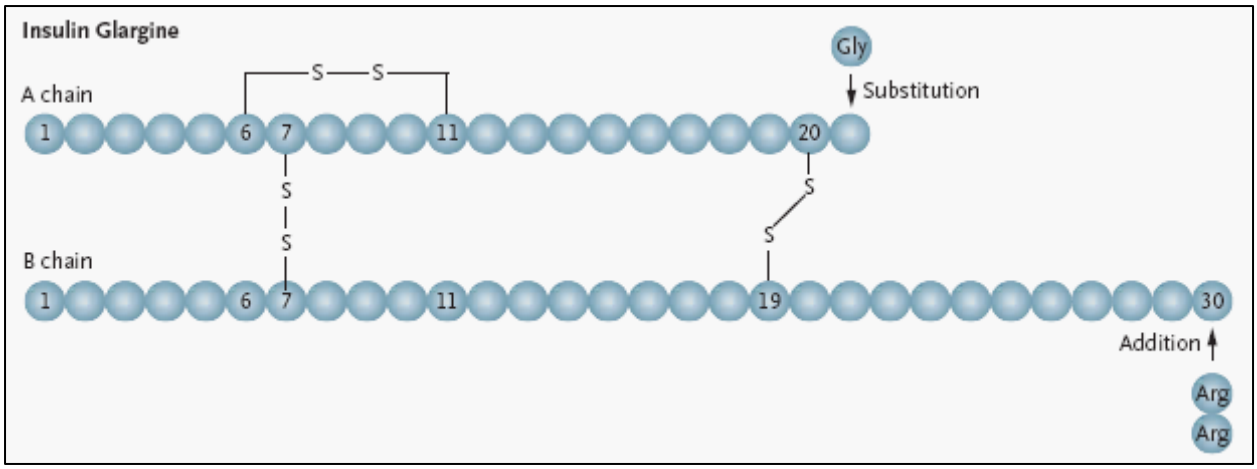


1.1.2 Long-acting insulin analogues

c) Insulin Glargine (Lantus®)

Insulin glargine is an insulin analogue that has been designed to provide more consistent steady-state insulin replacement to satisfy basal requirements. Glargine was created by substituting a glycine residue for asparagine at position 21 of the A-chain of human insulin. In addition, two arginine residues have been added to the B-chain at position 30 (Figure 3). These changes result in a shift in the isoelectric point of the molecule, making it soluble at pH 4. As a result, commercially available insulin glargine consists of a clear solution, in contrast to neutral protamine Hagedorn (NPH) insulin, which is a suspension. However, the solubility of glargine at physiological pH is lower than that of human insulin. Once injected subcutaneously, insulin glargine precipitates and exists as stabilized insulin hexamers that slowly dissociate into the systemic circulation. The result is a relatively constant concentration profile without a pronounced peak and a duration of action of approximately 24 hours.[5,7] Insulin glargine has an insulin receptor affinity that is similar to human insulin.[8]

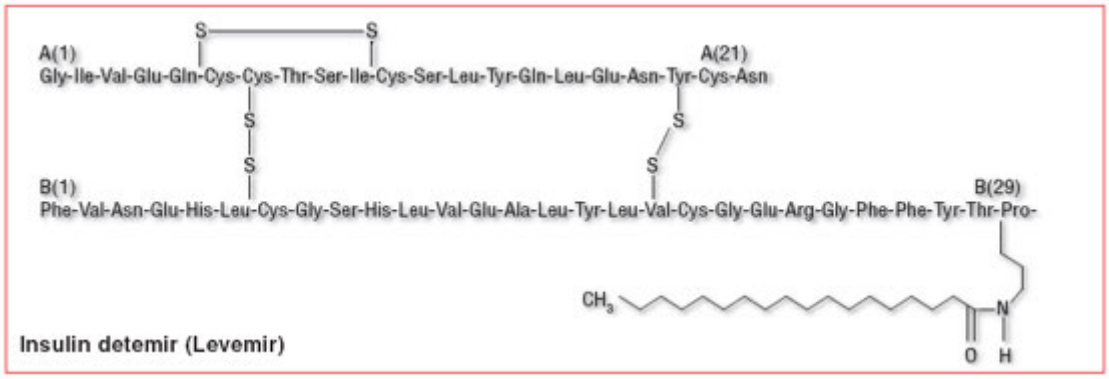
Figure 3: Molecular Structure of Insulin Glargine[5]



d) Insulin Detemir (Levemir®)

Insulin detemir is an altered human insulin designed to provide for basal insulin requirements. The threonine amino acid that normally occupies position 30 of the B-chain has been removed. This allows for the addition of a C14 fatty acid chain (myristoyl fatty acid) to be attached to the B29 amino acid (Figure 4). The resulting insulin is approximately 98% reversibly bound to endogenous albumin, resulting in delayed systemic absorption from the injection site, and slow distribution to peripheral tissues. Albumin binding not only prolongs insulin detemir's duration of action, it also plays a role in buffering against any sudden changes in absorption, thereby providing relatively consistent blood levels of free insulin. Insulin detemir has both a lower affinity for the insulin receptor and a lower metabolic potency than human insulin. However, this reduced potency has been addressed in the concentration of insulin detemir in the commercial product. The result is that 1 Unit of insulin detemir has an equivalent glucose-lowering activity to 1 Unit of NPH insulin.[9]

Figure 4: Molecular Structure of Insulin Detemir[10]



1.2 Kinetic Profile

The kinetics of the insulin analogues are designed to more closely mimic endogenous insulin secretion. The faster onset and shorter duration of the rapid-acting insulin analogues more closely resemble the body's natural postprandial insulin response. The long-acting insulin analogues provide a basal level of insulin that avoids the peak that occurs with NPH at four to 10 hours after administration that is often implicated in hypoglycemic events.[7] Whether these kinetic differences translate into improved clinical outcomes, substantively lower hypoglycemic events, or improved quality of life will be considered in depth within this document.

Table 1: Duration of Action of Human Insulins and Insulin Analogues[5,11]			
Insulin	**Onset**	**Peak**	**Duration**
Bolus Insulin			
Regular (Novolin® ge Toronto, Humulin® R)	30 min to 1 h	2 to 3 h	8 to 10 h
Lispro (Humalog®)	5 to 15 min	30 to 90 min	4 to 6 h
Aspart (NovoRapid®)	5 to 15 min	30 to 90 min	4 to 6 h
Basal Insulin			
NPH (Novolin® ge NPH, Humulin® N)	2 to 4 h	4 to 10 h	12 to 18 h
Glargine (Lantus®)	2 to 4 h	2 to 20 h	20 to 24 h
Detemir (Levemir®)	1 to 2 h	6 to 8 h	6 to 24 h

h=hour; min=minutes

2 SECTION 2: END POINTS IN CLINICAL TRIALS

A prerequisite to understanding the literature on insulin and insulin analogues is to understand both the efficacy and adverse effects end points that were measured in the various clinical trials. Consideration of how end points are defined, and whether they represent surrogate markers or clinically relevant outcomes, can have a substantial impact on the interpretation of study results.

2.1 Glycemic End Points

2.1.1 Glycosylated hemoglobin

Glycosylated hemoglobin (A1C) is the most commonly used marker for blood glucose control in clinical practice and research. The A1C value is the percentage of hemoglobin A1 that has been glycosylated through interaction with glucose in the blood.[12] Direct measures of blood glucose are impacted by time of day and intake of carbohydrates, while A1C is a marker of average, long-term blood glucose levels. It represents average glycemia over the preceding 120 days (the average lifespan of an erythrocyte), although it is more heavily influenced by recent glucose levels.[13] A positive correlation between A1C and blood glucose has been demonstrated in an analysis of data from the Diabetes Control and Complications Trial (DCCT).[13] This analysis showed that a 1% change in A1C was correlated with a 1.98 mmol/L change in mean plasma glucose.[13] In clinical practice, a formula that can be used to convert A1C values to mean plasma glucose is:[13]

Mean Plasma Glucose (mmol/L) = A1C (%) X 2 – 4.3

Inadequate glycemic control is associated with an increased risk of macrovascular and microvascular complications in people with diabetes.[14] Since A1C reflects average glycemia, it is commonly used as surrogate for the glycemic control of diabetes. To understand the validity of A1C as a surrogate outcome for the assessment of therapeutic interventions in diabetes, a review of the evidence that links A1C reduction to benefits regarding clinically relevant end points is required.

In type 1 diabetes, the link between A1C and microvascular end points comes from analysis of the DCCT.[15] In this study, patients were randomized to conventional insulin therapy with a target A1C of 9% or intensive therapy with a target of 7%.[15] The microvascular end point that was evaluated was progression of retinopathy.[15] The study showed that a 10% relative reduction in A1C (regardless of the initial A1C) resulted in a 43% relative risk reduction in progression of retinopathy and a 25% reduction in risk of microalbuminuria over an average of 6.5 years.[15]

In the type 2 diabetes population, the United Kingdom Prospective Diabetes Study (UKPDS) studied intensive glycemic control with oral antidiabetes drugs or insulin versus conventional therapy. Although there were no pre-specified A1C targets, the average A1C levels in the intensive arm was 7% compared to 7.9% in the conventional arm.[16] The study found, over 10 years, a significant 25% relative risk reduction in the composite end point of microvascular complications,

which included both retinal and kidney complications.[16] None of the macrovascular end points reached statistical significance, although they generally favoured the intensive therapy.[16] Determining a link between A1C reduction and macrovascular end points is difficult due to the requirements of large sample size and long trial duration. As such, consideration of findings from observational research and meta-analysis is required. A prospective observational study of the UKPDS participants found that each 1% reduction in A1C was associated with significant risk reductions of 21% in death related to diabetes, 14% in myocardial infarction, and 43% in amputation or death from peripheral vascular disease.[17] In a meta-analysis by Selvin et al., data were pooled from 10 prospective cohort studies in patients with type 2 diabetes and three in patients with type 1 diabetes. In patients with type 1 diabetes, they found a non-significant increase in the relative risk of coronary heart disease (1.15 [95% CI: 0.92, 1.43]) with each 1% increase in A1C, and a significant increase in peripheral arterial disease (1.32 [95% CI: 1.19, 1.45]).[18] For type 2 diabetes, the results were similar, with a relative risk of 1.13 (95% CI: 1.06, 1.20) for coronary heart disease and 1.28 (95% CI: 1.18, 1.39), with a 1% increase in A1C.[18] The authors suggest that these data indicate a moderate elevation in risk of cardiovascular events with increasing A1C.[18]

Comparative trials of insulin analogues versus conventional insulins were not adequately powered or of sufficient duration to detect differences in micro- or macrovascular end points.[1,2] The DCCT achieved a 1.9% difference in median A1C measures between the intensive and conventional treatments, while the UKPDS had a 0.9% difference in A1C.[15,16] A majority of the comparisons between the insulin analogues and conventional insulins that were considered in the COMPUS meta-analysis found no significant difference in A1C.[1,2] Those estimates that were statistically significant in favour of the analogues were marginal in magnitude and will be discussed fully in Sections 3 and 4. Based on their minimal impact in improving A1C, insulin analogues would not be expected to have an impact on micro- and macrovascular end points.

2.1.2 Postprandial glucose

Another glycemic end point that is considered in much of the type 1 and type 2 diabetes literature is postprandial glucose. Postprandial glucose is a measurement of glucose two hours after a meal. Recently published review articles suggest that postprandial glucose may be a better treatment target than fasting plasma glucose. Postprandial glucose has even been touted as the "missing link that explains the connection between type 2 diabetes and CVD [cardiovascular disease]".[19] Similar to A1C, we will consider the information that links postprandial glucose to clinically important end points and then review the literature that links postprandial glucose reduction to improvements in these end points.

The Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) study initially suggested that postprandial glucose may be a better glycemic predictor of mortality risk than fasting blood glucose. This study analyzed the combined results of 13 prospective European cohort studies assessing mortality risk according to the different diagnostic glucose measures (fasting blood glucose or two-hour post-challenge glucose) in patients with impaired oral glucose tolerance.[20] The analysis found that elevated blood glucose concentrations two hours post-challenge were associated with an increased risk of death, independent of fasting blood glucose.[20]

The authors concluded that fasting blood glucose is not as satisfactory as two-hour post-challenge blood glucose for the prediction of mortality.[20] The Fungata diabetes cohort study, published in the same year as DECODE, compared the value of fasting blood glucose and impaired glucose tolerance after an oral glucose challenge in predicting death from cardiovascular disease. The authors found greater correlation for impaired glucose tolerance compared with fasting blood glucose.[21] The notion that elevation of blood glucose after an oral challenge is superior to fasting blood glucose as a predictor of adverse outcomes is supported by other authors, although it is noted that much of the evidence base is derived from either re-analysis of the DECODE data or analysis of studies included in DECODE.[22]

Beyond the fact that most of the research in postprandial glucose is in patients with type 2 diabetes, and the implications of this surrogate in the type 1 population are unknown, there are two other key considerations. The evidence discussed thus far suggests that blood glucose measurement two hours after a standardized oral glucose challenge is a good predictor of mortality and cardiovascular events. However, this parameter is not the same as postprandial glucose, which is simply the blood glucose value after a non-standardized meal. The research that links postprandial glucose with cardiovascular end points is much more limited. A small observational study conducted by Cavalot et al. prospectively followed 529 patients with type 2 diabetes for five years to evaluate the relationship between various glycemic measures and cardiovascular events. Blood glucose levels after lunch were significantly associated with risk of cardiovascular events, while blood glucose levels after breakfast and before dinner, and fasting glucose, were not.[23] The results of the Cavalot study differed somewhat from a much earlier study, the Diabetes Intervention Study, which was an 11-year follow-up of 1,139 newly-diagnosed patients with type 2 diabetes.[24] The Diabetes Intervention Study found that postprandial hyperglycemia (after breakfast) was not an independent risk factor for myocardial infarction, but was an independent risk factor for death from any cause.[24] The rationale provided by Cavalot et al. for why their study, in contrast to the Diabetes Intervention Study, did not find a significant correlation with post-breakfast blood sugars and cardiovascular disease was the presence of dietary differences between study populations.[23] This highlights the potential pitfalls of using postprandial glucose as a diagnostic or monitoring tool. Its value is highly dependent on caloric intake, which varies from person to person or population to population.

The second consideration is that the evidence described thus far only pertains to the potential prognostic value of postprandial glucose and not the value of postprandial glucose as a treatment target (over other targets such as fasting blood glucose or A1C). Evidence from biochemical literature suggests that therapies targeting postprandial glucose reduce oxidative stress and other atherosclerotic and inflammatory mediators.[19] However, clinical evidence supporting postprandial glucose as a treatment target is limited. The most commonly cited study is the Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) — a randomized, double-blind, placebo controlled trial in which acarbose was found to significantly reduce the absolute risk of cardiovascular events by 2.5% in patients with impaired fasting glucose.[25] Acarbose, an alpha-glucosidase inhibitor, slows down the digestion of carbohydrates to glucose, thereby specifically lowering postprandial glucose. However, data from STOP-NIDDM do not provide direct evidence of the value of postprandial glucose-targeted therapy as compared to therapies that target other measures. The only active comparator trial that has supported targeting postprandial

glucose assessed the impact of repaglanide versus glyburide on carotid intima-media thickness (CIMT).[26] This small (N=175), single-blinded, one-year trial showed similar reductions in A1C with the two comparators, but greater reductions in postprandial glucose with repaglanide. Regression in CIMT was seen in significantly more patients taking repaglanide than glyburide (52% versus 19%, P<0.01).[26] While the results of these studies are certainly of interest, the fact remains that none of the agents that target postprandial glucose (repaglanide, acarbose, or rapid-acting insulin analogues) have comparative outcome data against first-line agents like metformin or regular insulin (which have a greater impact on A1C or fasting plasma glucose). The targeting of postprandial glucose as a means of reducing cardiovascular events above other glycemic measures has not been well studied.

It is important to have a thorough understanding of the evidence surrounding postprandial glucose. Its importance is being heavily promoted by pharmaceutical manufacturers, since many new therapies (e.g., rapid-acting insulin analogues and new oral antidiabetes drugs) lower postprandial glucose. In a February 2008 *Diabetes Care* review article authored by an employee of Eli Lilly, the following quote is found, "It is important to emphasize that post-challenge blood glucose correlates with glycemia in the postprandial period and may be considered a surrogate for postprandial blood glucose (20)."[22] The evidence-based implications of using random post prandial glycemia as a surrogate marker of post-challenge blood glucose, which itself has a modest level of data supporting it as a marker of risk, is unknown. To highlight the degree to which postprandial glucose is considered, the International Diabetes Federation has published "Guideline for Management of Postmeal Glucose", which detail newly marketed therapies and how they more effectively manage this surrogate.[27]

2.2 Microvascular and Macrovascular End Points

The mechanism by which chronically elevated blood glucose causes damage to the vascular bed is an issue of ongoing research.[28,29] There are four prominent biochemical theories with the end result of each being damage to the vascular endothelium.[29] Regardless of the mechanism, higher rates of microvascular and macrovascular events make them clinical end points of greatest importance to patients, as they represent the ultimate result of long-term glycemic derangement and are responsible for the morbidity and mortality associated with diabetes.

Microvascular complications, as the name implies, involve the smallest blood vessels, the capillary and the precapillary arterioles, in various organ systems.[28] Generally, microvascular complications appear before larger vessels are affected. The most common microvascular end points considered in trials are nephropathy and retinopathy. Assessments of microvascular complications are important as they are surrogate markers for severe outcomes, such as renal failure and blindness. Small vessels in the heart may also experience atherosclerosis, leading to cardiomegaly and heart failure, before the macro-vasculature of the heart (i.e., the coronary arteries) are affected.[28]

Macrovascular end points are also seen in a variety of vascular beds. Myocardial infarction and angina occur when the coronary arteries are affected; transient ischemic attack and stroke, when the neurovascular bed is affected; and end points ranging from painful extremities to amputation

when it occurs in the peripheral vascular beds are affected.[29] Events in any of these macrovascular beds can result in substantial morbidity and mortality.

2.3 Hypoglycemia

According to the 2008 Canadian Diabetes Association (CDA) guidelines, hypoglycemia is defined, as follows:[14]

- the development of autonomic or neuroglycopenic symptoms;
- a low plasma glucose level; the CDA proposes 4.0mmol/L as an operational clinical cut-off for patients treated with insulin or an insulin secretagogue; and
- symptoms responding to the administration of carbohydrate.

The guidelines further define hypoglycemia by severity as either mild (autonomic symptoms that can be self-managed), moderate (autonomic and neuroglycopenic symptoms that can be self-managed), or severe (patient requires assistance, unconsciousness may occur, glucose usually < 2.8 mmol/L).[14] Trials of oral antidiabetes drugs or insulins have tended to utilize three categories of hypoglycemia: overall, severe, and nocturnal. These subtypes of hypoglycemia are described in the meta-analyses of rapid-acting insulin analogues and long-acting insulin analogues conducted by CADTH's COMPUS program.

It is important to remember that there is more to hypoglycemia than just a low blood sugar reading. Events are characterized by unpleasant physical and psychological symptoms that can include shaking, sweating, drowsiness, nausea, poor motor coordination, confusion, negative mood, and unconsciousness.[30] Some patients develop anxiety or fear of hypoglycemia that can have numerous negative implications on lifestyle and disease management.[30]

2.3.1 Overall hypoglycemia

Although many trials of insulin analogues did not report definitions for hypoglycemia, overall hypoglycemia was often defined as any symptoms or signs of hypoglycemia and/or blood glucose < 4 mmol/L.[1,2] Some studies used more stringent blood glucose thresholds (< 2.8 mmol/L).

2.3.2 Severe hypoglycemia

Similar to the CDA guidelines, studies of insulin analogues usually defined severe hypoglycemia as an event with characteristic hypoglycemic symptoms requiring assistance of another person.[1,2] Some studies also required the presence of blood glucose values below a certain threshold, such as 2-2.3 mmol/L.

2.3.3 Nocturnal Hhpoglycemia

Nocturnal hypoglycemia refers to hypoglycemic events that occur at night, regardless of severity.[1,2] While many trials used specific time restrictions, such as events occurring between 24:00 hours to 6:00 hours, others defined it based on insulin dosing, i.e., any hypoglycemic event occurring

between the evening and morning dose of insulin. This measure of hypoglycemia was poorly defined in most of the studies assessed in the CADTH meta-analyses, making interpretation of study results difficult to assess.[31]

2.3.4 Risk ratio versus rate ratio

Evidence on hypoglycemia events are often reported as either risk ratios (also known as relative risks) or rate ratios. It is important to have an understanding of the difference between these two measures, as it will impact interpretation of the risk for hypoglycemia.

The meta-analysis provided by CADTH defines relative risk or risk ratio (RR) as the ratio of the absolute risk of the event of interest among the exposed group, to the absolute risk among the unexposed group, in an epidemiological study.[2] Regarding the hypoglycemia results, this represents the proportion of subjects experiencing one or more hypoglycemic events in the insulin analogue arm, divided by the proportion experiencing one or more events in the control arm. The rate ratio was defined as the ratio of the person-time incidence rate in the exposed group to the person-time incidence rate in the unexposed group, in an epidemiological study.[2]

To explain the difference between the measures, consider the analysis of hypoglycemia in the following trial. Gale et al. studied the difference between insulin lispro and human insulin in the management of adults with type 1 diabetes. They randomized 92 patients to the insulin lispro group and 89 patients to the human insulin group.[32] Over the course of the trial, two patients in the insulin lispro arm had a total of three episodes of severe hypoglycemia, while six patients had a total of 10 episodes in the human insulin arm. The risk ratio was calculated by dividing the proportion of subjects experiencing at least one episode of severe hypoglycemia in the insulin lispro arm by the corresponding proportion in the human insulin arm:

Rate Ratio = (2/92) ÷ (6/89) = 0.32

A risk ratio that is significant can be used to estimate a number needed to harm (NNH). The NNH values are the number of people you would treat with regular or NPH insulin (rather than an insulin analogue) to have one additional person experience the hypoglycemic event(s).

The rate is different from risk in that it is a measure of the number of episodes of an event per standardized period of time. The standardized period of time varies, depending on the event being measured. For common events, it may be events per 30 days or one year; for rare events, it may be events per 100 patient years. The study by Gale et al. reported a rate of overall hypoglycemia of 2.6 ± 3.0 episodes per 30 days in the insulin lispro arm versus 3.1 ± 4.4 in the human insulin arm:[32]

Rate Ratio = (2.6 episode/30 days) ÷ (3.1 episode/30 days) = 0.84

In this document, preference will be given to reporting hypoglycemia results based on the risk ratio. This value indicates whether or not the use of the insulin analogues will impact the number of patients experiencing hypoglycemia, and can be used to estimate NNH values. When risk ratios are not available (i.e., in situations where only the number of events were reported in trials), the rate ratio results will be discussed.

3 SECTION 3: TYPE 1 DIABETES

3.1 Epidemiology/Pathophysiology

Data from the Health Canada National Diabetes Surveillance System indicate that approximately 1.8 million (5.5%) Canadians aged 20 years and older were diagnosed with diabetes in 2004/05.[33] Using projection models, Ohinmaa et al. suggest that the number of people diagnosed with diabetes mellitus will increase to 2 million by 2010 and 2.4 million by 2016.[34] According to the CDA, the cost of providing health care to patients with diabetes is expected to reach $15.6 billion by 2010.[35]

Diabetes mellitus is a group of metabolic disorders characterized by the presence of hyperglycemia that results from a defect in insulin secretion, insulin action, or both.[14,36] Type 1 diabetes (previously known as insulin-dependant diabetes mellitus) most commonly develops before the age of 30. The condition usually manifests in those aged 10- to 14-years-old, but may occur in adults, especially when hyperglycemia first appears in the non-obese or elderly.[37] After the age of 30 years, about 5% to 10% of those who develop diabetes are classified as type 1.[29] Type 1 diabetes occurs due to pancreatic islet B-cell destruction that is most commonly (> 90% of cases) immune-mediated.[37] The etiology of the remainder of cases is idiopathic. Regardless of the cause, beta cell destruction leads to insulin deficiency that requires replacement with exogenously administered insulin.[36]

3.2 Diagnosis

The World Health Organization has established criteria for the diagnosis of diabetes that are supported by the CDA Clinical Practice Guidelines, and the American Diabetes Association (ADA) Clinical Practice Recommendations.[14,29,36] The criteria are as follows:[14]

- symptoms of diabetes (e.g., polyuria, polydipsia, unexplained weight loss) plus random blood glucose concentration ≥ 11.1 mmol/L; *or*
- fasting (no caloric intake for at least eight hours) plasma glucose ≥ 7.0 mmol/L; *or*
- two-hour plasma glucose ≥ 11.1 mmol/L during an oral glucose tolerance test (75 gram glucose solution).

These values should be confirmed with another blood glucose test on another day in the absence of unequivocal hyperglycemia that occurs with acute metabolic decompensation.[14] Of note, if type 1 diabetes is suspected and there is a risk of rapid clinical deterioration, treatment should not be delayed to accommodate confirmatory testing.[14] Type of diabetes (i.e., type 1 or type 2) is determined based on the characteristics of the patients being tested such as their age, their health status, and symptoms of the disease.

3.3 Therapeutic Management

The goals of therapy for patients with diabetes are to maintain blood sugar levels within specific parameters, while minimizing the occurrence of hypoglycemic episodes. The specific glycemic targets recommended by the CDA are, as follows:[14]

- A1C ≤ 7%
- fasting plasma glucose 4 – 7 mmol/L
- two-hour postprandial plasma glucose 5 – 10 mmol/L (5 – 8 mmol/L if A1C targets not being met).

The rationale for these target levels in patients with type 1 diabetes is largely derived from the DCCT. This trial was discussed in section 2.1.1 regarding the relationship between A1C values and microvascular outcomes. The DCCT was designed to investigate the impact of intensive insulin therapy on the development of microvascular complications (primary prevention), as well as progression of existing complications (secondary prevention).[38] Patients were randomly assigned to either conventional insulin therapy consisting of once or twice daily injections of pre-mixed intermediate-acting and regular human insulin, or to intensive therapy consisting of three or more insulin injections per day or continuous subcutaneous insulin infusion (CSII). The targets of therapy for those assigned to conventional treatment were largely symptom-related, including absence of hyper- and hypoglycemic symptoms, absence of ketonuria, and maintenance of normal growth and development. Targets for intensive treatment were pre-prandial blood glucose of 3.9-6.7 mmol/L, postprandial glucose of < 10 mmol/L, and minimal nocturnal hypoglycemia. To achieve these values, self-monitoring of blood glucose occurred four times per day and insulin doses were actively adjusted, based on diet and exercise.

Prolonged intensive therapy resulted in significant reductions in risk of developing retinopathy in the primary prevention group, and in progression of retinopathy in the secondary prevention group.[38] There was transient worsening of retinopathy in the intensive arm of the secondary prevention group, but this was reversed within 36 months, with subsequent improvement observed until the end of the trial. Beyond the benefits in terms of retinopathy, reductions were also found in the development and progression of nephropathy and neuropathy. However, the benefits of intensive glucose control were not without drawbacks, especially regarding hypoglycemic events. The intensive treatment group had three times the rate of severe hypoglycemic events (62 events per 100 patient years compared to 19 events in the control group). Hypoglycemia led to 54 hospitalizations in the intensive group versus 36 in the conventional group. Considering the number of patients (N=1,441) and length of the trial (mean follow-up of 6.5 years), the lower rates of microvascular complications were considered to outweigh the relatively low incidence of serious adverse events.[38]

Stemming from the results of the DCCT trial, the CDA recommends the following:[14]

- To achieve glycemic targets in people with type 1 diabetes, multiple daily insulin injections (prandial [bolus] and basal insulin) or the use of CSII as part of an intensive diabetes management regimen should be considered. *Grade A, Level 1A.*

Human insulins have been the cornerstone of diabetes management. However, since the release of the first insulin analogue (insulin lispro) in 1996, the use of insulin analogues has become more common, especially in the management of type 1 diabetes.[39,40] The insulin analogues feature prominently in the CDA guidelines in the following recommendations for type 1 diabetes:[14]

- Rapid-acting insulin analoges (aspart or lispro), in combination with adequate basal insulin, should be considered over regular insulin to improve A1C while minimizing the occurrence of hypoglycemia (*Grade B, Level 2*) and to achieve postprandial glucose targets. *Grade B, Level 2.*
- Insulin lispro or insulin aspart should be used when CSII is used in adults with type 1 diabetes. *Grade B, Level 2*.
- A long-acting insulin analogue (detemir or glargine) may be considered as an alternative to NPH as the basal insulin (*Grade B, Level 2*) to reduce the risk of hypoglycemia (*Grade B, Level 2 for detemir; Grade C, Level 3 for glargine*), including nocturnal hypoglycemia (*Grade 2, Level 2 for detemir; Grade D, Consensus for glargine*).

The relative value of the insulin analogues is the major focus of two meta-analyses conducted by CADTH. In these analyses, insulin analogues were compared with conventional insulins on measures of glycemic control, adverse effects, and impact on quality of life measures.

3.3.1 Bolus insulin

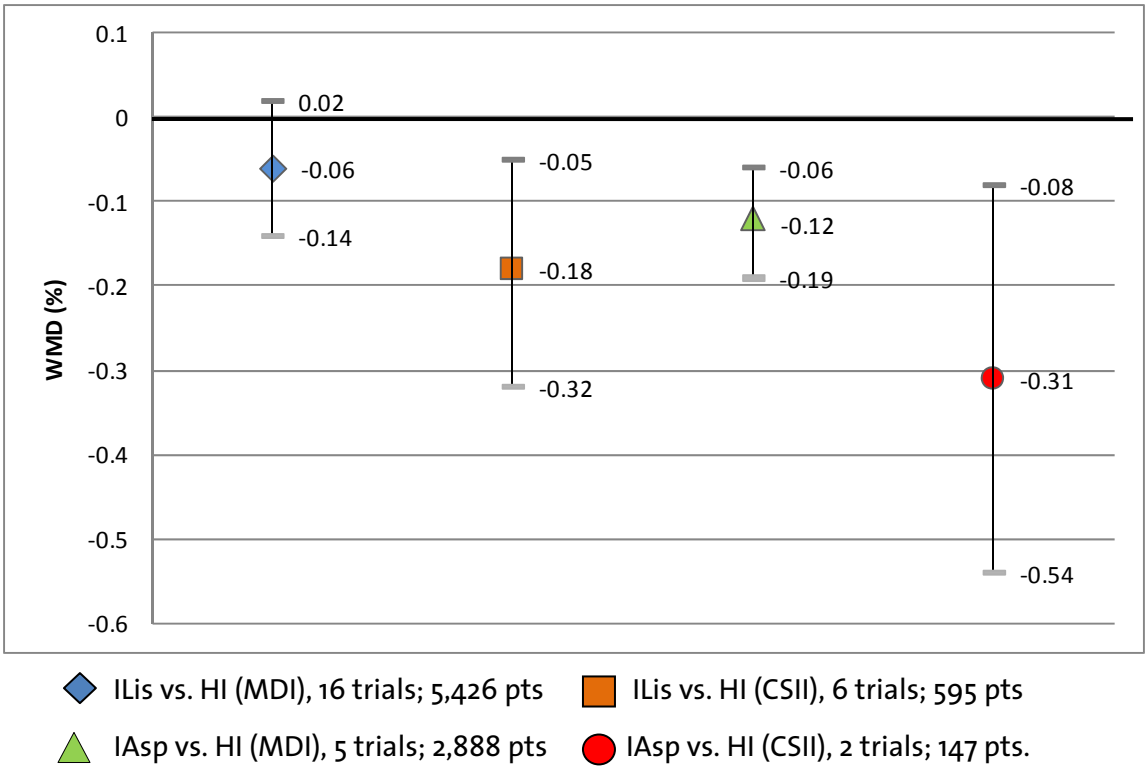
a) Glycosylated hemoglobin

Substantial research has been conducted comparing insulin lispro and insulin aspart against human insulin in adult patients with type 1 diabetes. As shown in Figure 5, the greatest amount of data exists for insulin lispro, with a total of 22 trials (multiple daily injections [MDI] and CSII) enrolling over 6,000 patients. The weighted mean difference in A1C, although favouring the rapid-acting insulin analogues in each analysis, was marginal and did not reach statistical significance in the largest group of trials (i.e., for the comparison of insulin lispro versus human insulin using MDI). For both insulin lispro and insulin aspart, administration via CSII appeared to result in larger differences in A1C than administration by MDI.

To put the observed A1C differences in perspective, intensive therapy in the DCCT reduced A1C values between 1.5% to 2%, compared to conventional therapy, over the course of 6.5 years.[38] This reduction in A1C was around 10 times greater than that observed in the comparisons of rapid-acting insulin analogues with human insulin evaluated in the CADTH meta-analyisis.[2] Some work has been done in Canada to come to a consensus on what a minimally clinically important difference in A1C should be in type 2 diabetes. The panel of family physicians, pharmacists, and specialists in internal medicine and endocrinology were convened to agree on target values or

change values for a number of diabetes management indicators.[41] The panel suggested that a 10% relative reduction in A1C would be indicative of clinically important health improvement.[41] Data on minimally clinically important difference in type 1 diabetes is lacking.

Figure 5: Pooled Differences in A1C in Comparisons of Rapid-Acting Insulin Analogues Versus Human Insulin in Adults With Type 1 Diabetes[2,3]



CSII=continuous subcutaneous insulin infusion; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; MDI=multiple daily injections; vs.=versus; WMD=weighted mean difference

A Cochrane review published by Siebenhofer et al. found similar results to the CADTH meta-analysis.[1,2,42] The Siebenhofer group reported an overall weighted mean difference (WMD) in A1C of -0.1% (95% CI: -0.2 to -0.1) for rapid-acting insulin analogues versus human insulin in patients with type 1 diabetes.[42] When subgroup analyses were conducted by administration method, studies of MDI showed a non-significant WMD in A1C of -0.1% (95% CI: -0.1 to 0.0), while studies of CSII demonstrated a statistically significant WMD of -0.2% (95% CI: -0.3 to -0.1). The marginal benefits of the rapid-acting insulin analogues were brought into question by the authors as they compared the difference to those seen in the DCCT trial: "Assuming that a reduction in HbA1C with insulin analogues would result in a similar relative benefit, approximately 650 patients would have to be treated with analogues for one year to prevent the development of retinopathy in one patient."[42]

The CADTH meta-analysis[2] and Optimal Therapy Recommendations Report[3] also considered trials conducted in preadolescents and adolescents with type 1 diabetes. The evidence reported for rapid-acting insulin analogues in preadolescents consisted of four RCTs comparing insulin lispro

with human insulin (N=286) using MDI, one RCT comparing insulin aspart with human insulin (N=24) using MDI, and one RCT comparing insulin lispro with human insulin (N=27) using CSII. The WMD in A1C was statistically non-significant in favour of human insulin for all the comparisons (0.14% [95% CI: -0.18 to 0.46] in the insulin lispro MDI trials, 0.1% [95% CI: -0.52 to 0.72] in the insulin aspart MDI trial, and 0.06% [95% CI: -0.47 to 0.59] in the insulin lispro CSII trial]).[2,3] In the adolescent population, there was one single trial by Holcombe et al. that studied insulin lispro against human insulin. This eight-month crossover trial enrolled 463 children aged nine to 18 years;[43] it did not show a significant difference in A1C values between the two treatment groups.[43]

b) Postprandial glucose

As discussed in Section 2.1.2, postprandial glucose is being heavily promoted as a treatment end point in diabetes. The quick onset of action of the rapid-acting insulin analogues makes them well-suited to reduce postprandial glucose levels.[27] However, only three of the trials comparing rapid-acting insulin analogues to human insulin in adults with type 1 diabetes reported impact on two-hour postprandial plasma glucose, although other trials have looked at two-hour postprandial blood glucose assessed by self-monitoring. The WMD in postprandial glucose was a reduction of -1.31 mmol/L (95% CI: -2.35 to -0.27) in favour of insulin lispro.[2] The difference was more marked in the single study that used CSII administration (-2.89 mmol/L [95% CI: -4.48 to -1.3]) compared to MDI administration (-0.99 mmol/L [95% CI: -1.54 to -0.45]).[2,3] The trial in adolescents by Holcombe et al. found lower mean postprandial glucose values after breakfast and supper, but not after the noon meal.[43] The absolute differences in mean postprandial glucose for both breakfast and supper were less than 1 mmol/L. The clinical relevance of a 1 mmol/L reduction in postprandial glucose is unknown, especially in patients with type 1 diabetes. The absolute postprandial glucose reduction in the CIMT trial, in which postprandial glucose reduction was shown to benefit carotid intima medial thickness, was 1.8 mmol/L (see Section 2.1.2); however, this study was conducted in patients with type 2 diabetes.[26]

c) Microvascular and macrovascular complications

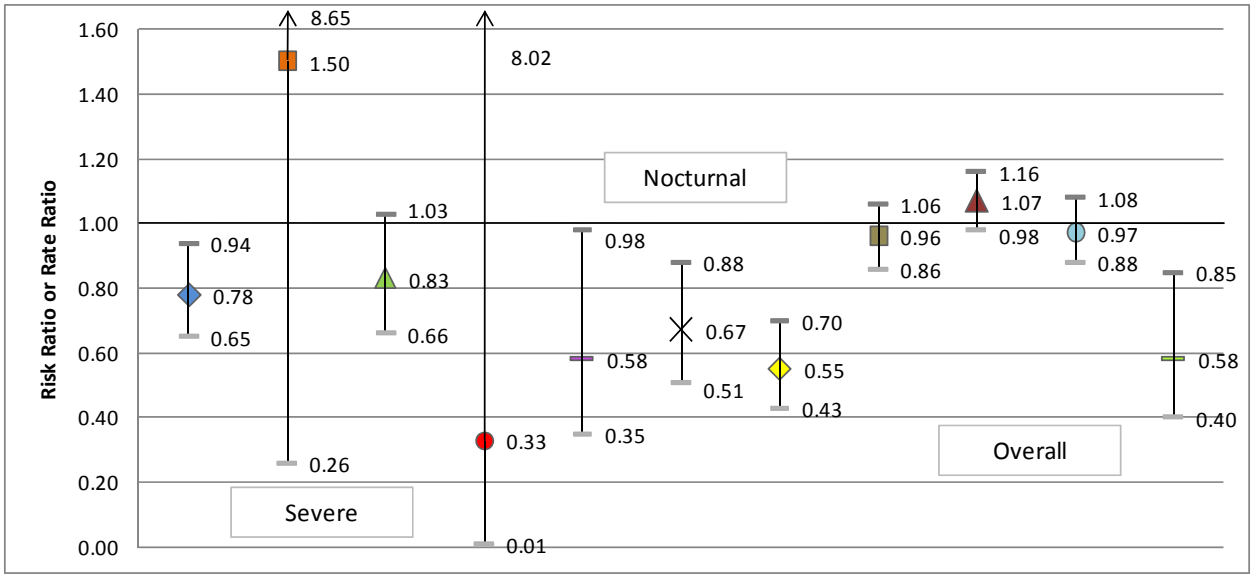
Neither the CADTH meta-analysis on rapid-acting insulin analogues nor the Cochrane review identified adequate data regarding the impact of rapid-acting insulin analogues on micro- or macrovascular events.[2,42] None of the trials that compared rapid-acting insulin analogues to human insulin were designed or sufficiently powered to detect differences in these outcomes. Four of the trials considered in the CADTH meta-analysis reported data on all-cause mortality. As expected, based on the small number of events, there were no detectable differences between treatments.[2] Therefore, there are, as yet, no data to indicate whether use of rapid-acting insulin analogues instead of human insulin results in improvements in clinically relevant outcomes.

d) Hypoglycemia

Hypoglycemia is an important concern for patients on insulin therapy. Analysis of various hypoglycemia measures were a major consideration of the CADTH meta-analysis. As with efficacy measures, much of the data on hypoglycemia was captured in studies of insulin analogues in the management of adults with type 1 diabetes. Figure 6 provides an overview of the results from the CADTH meta-analysis and Optimal Therapy Report recommendations on severe, nocturnal, and overall hypoglycemia events.[2,3] It is evident from the figure that the only comparison that showed significantly less severe hypoglycemia was the comparison of insulin lispro to human insulin

when administered by MDI.[2,3] For insulin aspart versus human insulin, the risk ratio of severe hypoglycemia non-significantly favoured insulin aspart for both CSII and MDI trials. The rate ratios for nocturnal hypoglycemia significantly favoured both insulin analogues. The results were consistent for insulin lispro administered by MDI or CSII, but the results for insulin aspart were based on results from a single CSII trial. For overall hypoglycemia, there was no significant difference between insulin lispro and human insulin when administered by MDI or CSII.[3] The overall hypoglycemia rates for all comparisons of insulin aspart versus human insulin showed no significant advantage when administered by MDI, but a substantial reduction in the rate when given by CSII.[2,3]

Figure 6: Pooled Risk and Rate Ratios for Various Forms of Hypoglycemia in Comparisons of Rapid-Acting Insulin Analogues Versus Human Insulin in Adults With Type 1 Diabetes[2,3]



ILis vs. HI (MDI), risk ratio, 6 trials; 4,221 patients
ILis vs. HI (CSII), risk ratio, 2 trials; 140 patients
IAsp vs. HI (MDI), risk ratio, 3 trials; 1,696 patients
IAsp vs. HI (CSII), risk ratio, 1 trial; 118 patients
ILis vs. HI (MDI), rate ratio, 3 trials; 658 patients
ILis vs. HI (CSII), rate ratio, 1 trial; 67 patients
IAsp vs. HI (CSII), rate ratio, 1 trial; 118 patients
ILis vs. HI (MDI), rate ratio, 12 trials; 5,193 patients
ILis vs. HI (CSII), rate ratio, 4 trials; 451 patients
IAsp vs. HI, (MDI), rate ratio, 6 trials; 3,096 patients
IAsp vs. HI (CSII), rate ratio, 2 trials; 175 patients

CSII=continuous subcutaneous insulin infusion; HI=human insulin; IAsp=insulin aspart; ILis=insulin lispro; MDI=multiple daily injections; vs.=versus

There are limitations to presenting risk and rate ratios to clinicians since these measures do not provide an indication of how many patients are likely to experience these adverse events or how frequently they tend to occur. Fortunately, risk ratios that are statistically significant can be used to estimate numbers needed to harm (NNH), a measure of absolute effect that may be more relevant to clinicians. For the rapid-acting insulin analogues, only the risk ratio for severe hypoglycemia in the comparison of insulin lispro versus human insulin was statistically significant.[2] The baseline risk of experiencing a severe hypoglycemic event from the trials of human insulin was 9.6%, and the duration of the 10 studies included in the calculation of NNH varied from six to 24 weeks. To have one less person who experiences one or more severe hypoglycemic episodes, the estimated number of people needed to treat with insulin lispro instead of human insulin is 54 (95% CI: 32 to 260).

Differences between rapid-acting insulin analogues and human insulin regarding hypoglycemia event rates are also worthy of discussion. From the DCCT trial, the estimated event rate of severe hypoglycemia with intensive insulin therapy was 0.62 episodes/patient-year.[38,44] However, the incidence rate of any type of hypoglycemia is highly dependent on the characteristics of the patient population (e.g., age, duration of diabetes, history of hypoglycemic events, baseline A1C), as well as study-related factors (e.g., intensity of insulin therapy, target A1C levels). In the Cochrane review by Siebenhofer et al., the incidence of severe hypoglycemia varied from 0 to 2.47 episodes per patient-year for insulin analogues (median 0.22) and from 0 to 5.44 for people treated with human insulin (median 0.46).[42]

Quantifying rates of nocturnal hypoglycemia is equally difficult, with few trials reporting incidence and variability in hypoglycemia definitions. In the four studies comparing insulin lispro to human insulin that were identified in the CADTH meta-analysis, there was substantial variation in the reported rates. One trial by Bode et al. assessed nocturnal hypoglycemia rates in both rapid-acting insulin analogues and human insulin. They found the mean number of hypoglycemic episodes reported per subject, per 30 days (± one standard deviation), during the maintenance phase to be lower in insulin aspart (0.5 ± 0.83) and insulin lispro (0.6 ± 0.61) compared to human insulin (0.9 ± 0.97).[45] The same trend was observed by Gale et al. They reported 0.7 ± 1.6 mean nocturnal hypoglycemia episodes per month with insulin lispro compared to 1.8 ± 3.1 with human insulin.[32] Holleman et al. did not report the rates of nocturnal hypoglycemia, only the total number of events over the course of the trial, which was significantly lower in the insulin lispro arm.[46]

Hypoglycemia in the pre-adolescent populations showed smaller differences between rapid-acting insulin analogues and human insulin. The pooled estimate across three insulin lispro trials (MDI) demonstrated non-significant differences in severe hypoglycemia (risk ratio 0.69 [95% CI: 0.24, 2.01]) and nocturnal hypoglycemia (rate ratio 0.96 [95% CI: 0.74, 1.26]).[2] A total of five trials reported overall hypoglycemia; again, there was no significant difference between insulin lispro and human insulin (rate ratio 0.99 [95% CI: 0.88, 1.12]).[2] This non-significant difference was also seen in the comparison of insulin aspart versus human insulin administered by MDI where the rate of overall hypoglycemia non-significantly favoured human insulin.[47] The one trial of insulin lispro given through CSII didn't find any difference in severe hypoglycemia compared with human insulin, but did find a small but significant advantage in overall hypoglycemia (rate ratio 0.82 [95% CI: 0.75, 0.89]).[48]

The one trial conducted in adolescent patients found no difference in risk of severe hypoglycemia; only five patients in both the insulin lispro and human insulin groups experienced this adverse effect.[43] There were, however, differences in overall hypoglycemia, which were mostly driven by a lower rate of nocturnal hypoglycemia. The study found the mean number of nocturnal hypoglycemia episodes per patient, per 30 days, to be less in patients receiving insulin lispro (1.0 ± 1.9) compared with human insulin (1.7 ± 2.6). This translated into a rate ratio of 0.61 (95% CI: 0.57, 0.64), which was similar to that seen in the adult studies.[2]

e) Quality of life and patient satisfaction

There are a number of instruments used to assess the impact of different therapies on quality of life and patient satisfaction, several of which were used in the studies of rapid-acting insulin analogues versus human insulin. The two most commonly applied instruments were the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Well-Being Questionnaire. Of the 15 rapid-acting insulin analogues studies that reported quality of life (QoL) or patient satisfaction results in the CADTH meta-analysis, five did not show any significant differences.[2] The results of the remaining trials favoured rapid-acting insulin analogues, largely based on greater convenience and flexibility or greater willingness to continue.[2]

f) Summary

The results of the CADTH meta-analysis on rapid-acting insulin analogues bring some perspective to the CDA recommendations regarding preferential use of the rapid-acting insulin analogues over human insulin. Modest improvements in quality-of-life measures, driven by improved convenience, make rapid-acting insulin analogues a viable alternative to human insulin. However, in light of their limited impact on glycemic control and the lack of data on clinically relevant outcomes, it is questionable whether the modest reductions in some measures of hypoglycemia warrant that they be considered the preferred treatment. Siebenhofer et al. provided these conclusions: "Our analysis suggests only a minor clinical benefit of short-acting insulin analogues in the majority of diabetic patients treated with insulin. Until long-term efficacy and safety data are available, we suggest a cautious response to the vigorous promotion of insulin analogues."[42]

The COMPUS Expert Review Committee (CERC) provided the following recommendations, based on the results of the CADTH meta-analysis and pharmacoeconomic study of the rapid-acting insulin analogues:[3]

- CERC suggests that **either** regular human insulin or a rapid-acting insulin analogue (i.e., insulin lispro or insulin aspart) be used in most **pre-adolescents with type 1 diabetes** (CSII or MDI).
  - CERC Rating of Overall Quality of Clinical Evidence: Low
  - Strength of Recommendation: Weak

- CERC suggests that insulin lispro be used **in preference to** regular human insulin in most **adolescents with type 1 diabetes** using MDI.*****
  - CERC Rating of Overall Quality of Clinical Evidence: Low
  - Strength of Recommendation: Weak

- CERC recommends that **either** regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) be used in most **adults with type 1 diabetes** using CSII.
  - CERC Rating of Overall Quality of Clinical Evidence: Low
  - Strength of Recommendation: Strong

- CERC recommends that either regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) be used in most adults with type 1 diabetes using MDI.
  - CERC Rating of Overall Quality of Clinical Evidence: Moderate
  - Strength of Recommendation: Strong

* This CERC recommendation was based on the assessment that the benefits of insulin lispro (regarding hypoglycemia and dosing flexibility) outweighed the incremental cost (although no cost-effectiveness information was available). It was also noted that insulin lispro provided a better fit to the unpredictable patterns of dietary intake and physical activity that are characteristic of this population.[3]

The key message for academic detailing, based on the recommendations of the CADTH Optimal Therapy Report, are:

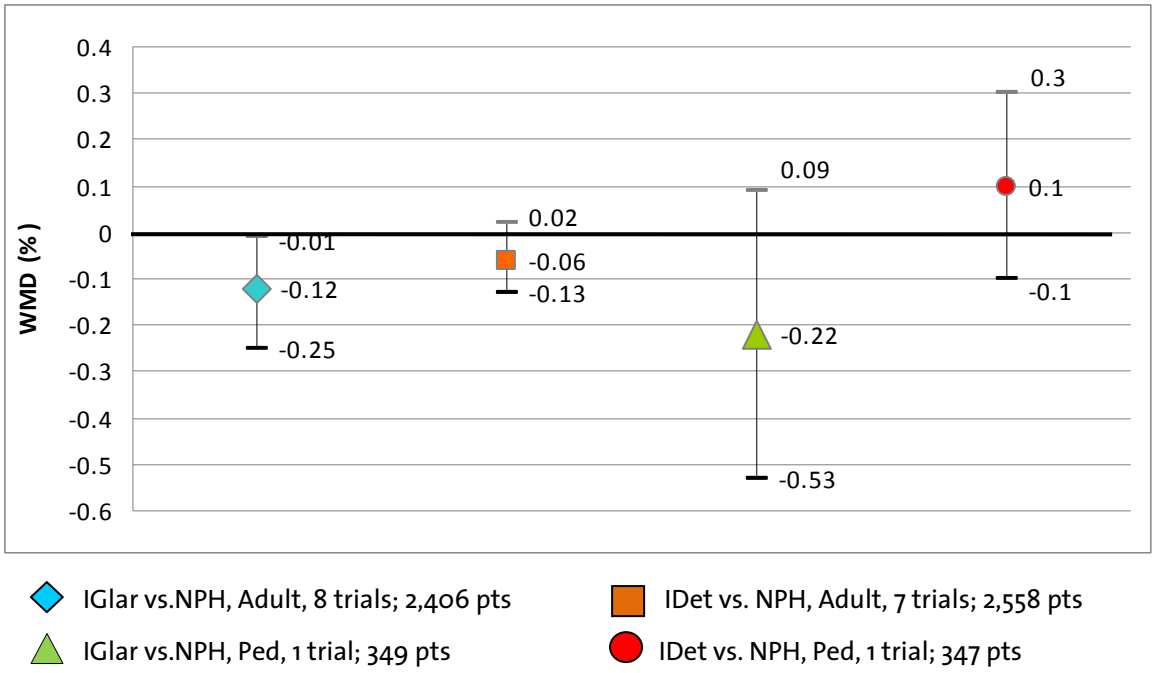
In patients with type 1 diabetes, either regular human insulin or rapid-acting insulin analogues can be considered as first-line therapy (except in adolescent patients). In adolescent patients with type 1 diabetes, rapid-acting insulin analogues may be considered as first-line therapy.

3.3.2 Basal insulin

a) Glycosylated hemoglobin

Similar to the rapid-acting insulin analogues, there is ample trial data on the use of the long-acting insulin analogues in adult patients with type 1 diabetes. Figure 7 provides a summary of the 17 trials in adult and pediatric patients that evaluated the impact of the two long-acting insulin analogues (insulin glargine and insulin detemir) on A1C compared to the conventional intermediate-acting insulin, NPH. It is evident that the effect of long-acting insulin analogues on A1C levels was somewhat inconsistent. Based on the CADTH meta-analysis and Optimal Therapy Report recommendations, the only agent to show a significant reduction in A1C levels compared to NPH was insulin glargine, with a WMD of -0.12% (95% CI: -0.25, -0.01) in adults.[1,3] In the pediatric population, there was a non-significant trend towards A1C benefit with insulin glargine versus NPH, while the single pediatric trial of insulin detemir versus NPH actually showed a non-significant advantage for NPH insulin.[1] Overall, the evidence indicates that, in comparison to NPH, the impact of long-acting insulin analogues on A1C is marginal, at best.

Figure 7: Pooled A1C Values in Comparisons of Long-Acting Insulin Analogues Versus Neutral Protamine Hagedorn in Adult and Pediatric Patients With Type 1 Diabetes[1,3]



IDet=insulin detemir; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; Ped=pediatric; pts=patients; vs.=versus

b) Microvascular and macrovascular complications

Similar to the trials done in rapid-acting insulin analogues, trials of long-acting insulin analogues were not adequately powered to measure effects on micro- or macrovascular complications, although some trials reported data on these events.[1] Retinopathy rates were reported in one trial of insulin glargine and two trials of insulin detemir, but in all cases there were insufficient events for meaningful comparisons to be made. Event rates for macrovascular complications, such as ischemic heart disease, stroke, and all-cause mortality, were reported in a few trials, but in all cases there were too few events to draw meaningful conclusions.[1]

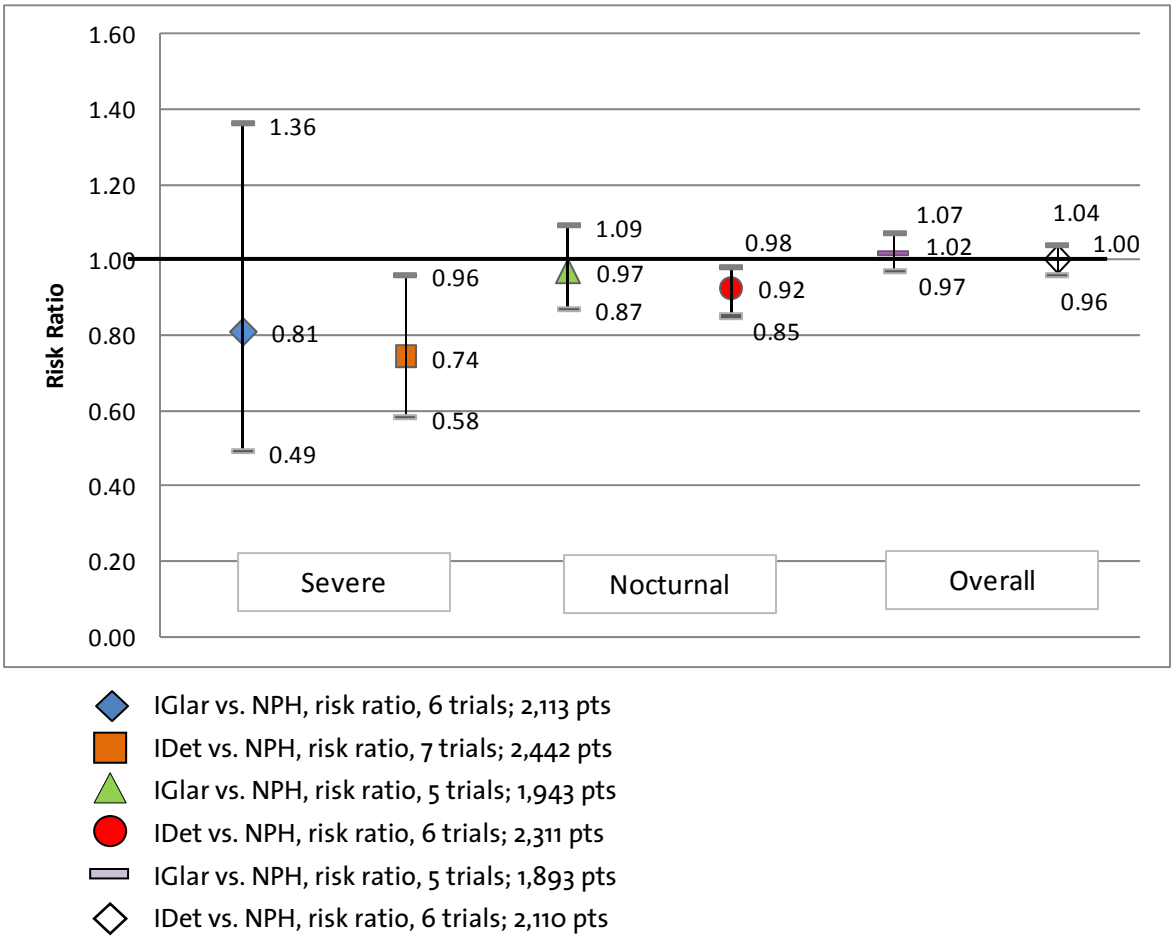
c) Body weight

In the adult population, trials found reduced weight gain in patients treated with either insulin glargine or insulin detemir compared to NPH insulin.[1] However, the magnitude of the observed differences was relatively small. For insulin glargine versus NPH, the WMD of change in body weight was statistically significant at -0.40 kg (95% CI: -0.76, -0.03), and there was a significant reduction of -0.73 kg (95% CI: -1.42, -0.03) for insulin detemir.[3] The observed differences in weight gain were, on average, <1% of the average adult body weight; weight loss of 5% or greater is generally considered clinically significant.[49]

d) Hypoglycemia

The major perceived advantage of the long-acting insulin analogues over NPH insulin is reduced rates of hypoglycemia, specifically nocturnal hypoglycemia as stated in the CDA guidelines.[14] The CADTH meta-analysis on long-acting insulin analogues evaluated both the rate ratio and risk ratio of severe, nocturnal, and overall hypoglycemia in trials comparing insulin glargine or insulin detemir to NPH. A summary of the results for adult patients is provided in Figure 8, and for pediatric patients, in Figure 9.

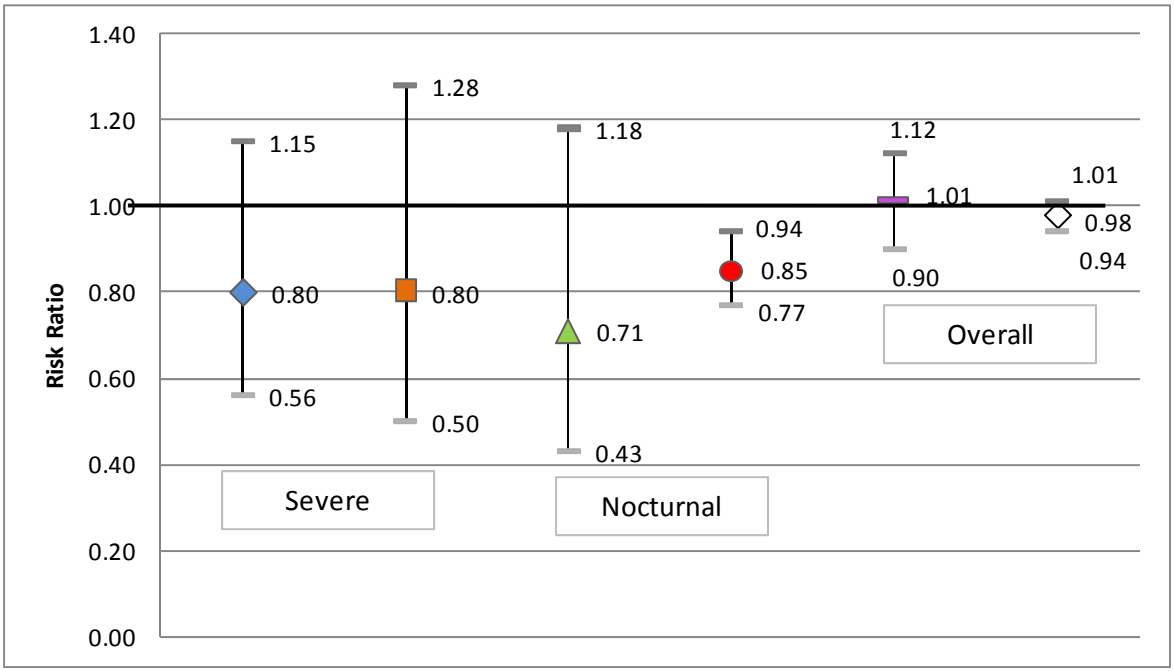
Figure 8: Pooled Risk Ratios for Various Forms of Hypoglycemia in Comparisons of Long-Acting Insulin Analogues Versus Human Insulin in Adults With Type 1 Diabetes.[1,3]



IDet=insulin detemir; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; pts=patients; vs.=versus

In both patient populations, none of the hypoglycemia measures significantly favoured insulin glargine compared to NPH insulin. In addition, none of the rate ratios significantly favoured insulin glargine over NPH. The results with insulin detemir were slightly more favourable, with significant reductions observed in nocturnal and severe hypoglycemia. Although the rate ratios in severe hypoglycemia did not show the same level of benefit (0.95 [95% CI: 0.65, 1.38]), the rate ratio in nocturnal hypoglycemia substantively favoured insulin detemir (0.66 [95% CI: 0.60, 0.73]).[1] In pediatric patients, the risk ratio for nocturnal hypoglycemia favoured insulin detemir (Figure 9), along with the rate ratios for nocturnal (0.77 [95% CI: 0.7, 0.84]) and overall hypoglycemia (0.89 [95% CI: 0.86, 0.93]).[1] It should be noted that all of the data for insulin detemir in the pediatric population were from one large randomized controlled trial.[1,50]

Figure 9: Pooled Risk Ratios for Various Forms of Hypoglycemia in Comparisons of Long-Acting Insulin Analogues Versus Human Insulin in Pediatric Patients With Type 1 Diabetes[1,3]



IGlar vs. NPH, risk ratio, 1 trial, 349 pts
IDet vs. NPH, risk ratio, 1 trial, 347 pts
IGlar vs. NPH, risk ratio, 1 trial, 349 pts
IDet vs. NPH, risk ratio, 1 trial, 347 pts
IGlar vs. NPH, risk ratio, 1 trial, 349 pts
IDet vs. NPH, risk ratio, 1 trial, 347 ps

IDet=insulin detemir; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; pts=patients; vs.=versus

For the risk ratios that showed statistically significant advantage of insulin detemir over NPH, the corresponding numbers needed to harm (NNH) are shown in Table 2. The baseline risks of hypoglycemia (risk observed in the NPH arms of each group of studies) used to calculate these NNH values were 10.4% for adult, severe; 69% for adult, nocturnal; and 75% for pediatric, nocturnal. The trial duration for studies used to calculate the NNH values in Table 2 varied between 16 weeks and 12 months for the adult population, while the one study in the pediatric population was 26 weeks.[1]

Table 2: Estimated Number Needed to Harm for Hypoglycemic Events With Insulin Detemir Versus Neutral Protamine Hagedorn				
Type of Hypoglycemia	**Risk Ratio (95% CI)**	**NNH (Point Estimate)**	**NNH (Lower Limit)**	**NNH (Upper Limit)**
Adult, Severe	0.74 (0.58, 0.96)	37	20	240
Adult, Nocturnal	0.92 (0.85, 0.98)	18	10	73
Pediatric Nocturnal	0.85 (0.77, 0.94)	9	6	25

CI=confidence interval; NNH=number needed to harm

From the data provided in Figures 8 and 9, it could be speculated that insulin detemir provides a more substantive benefit in reducing hypoglycemic events than insulin glargine. However, there are limited conclusions that we can derive from indirect comparisons of insulin detemir and insulin glargine. During CERC's discussions on the differences between hypoglycemia rates in the two long-acting insulin analogues, it was noted that subjects with a prior history of recurrent severe hypoglycemia were excluded in seven of nine trials of insulin detemir versus NPH, while none of the trials comparing insulin glargine to NPH had these restrictions.[3]

There is a head-to-head trial comparing insulin detemir with insulin glargine conducted in adults with type 1 diabetes.[51] Pieber et al. reported that the risk of severe hypoglycemia was substantially lower in the insulin detemir arm, risk ratio 0.25 (95% CI: 0.07, 0.86).[1] During the maintenance phase of the trial, the number of patients experiencing at least one episode of severe hypoglycemia were very low, with three (of 161) in the insulin detemir arm versus 12 (of 159) in the insulin glargine arm.[51] However, the risks of overall and nocturnal hypoglycemia were not significantly different between the two agents.[1,51]

e) Quality of life and patient satisfaction

Data on the impact of the long-acting insulin analogues on quality-of-life measures are very sparse. There were no trials in the pediatric type 1 diabetic population that reported quality-of-life measures.[1] There was a single trial in the adult population that reported no significant difference in well-being scores between insulin glargine and NPH.[1] The same trial also measured patient satisfaction scores using the DTSQ and found insulin glargine to be favoured significantly over NPH, with a mean difference of 1.83 (95% CI: 0.82, 2.84).[1]

f) Summary

With minimal impact on A1C and a cost more than twice that of NPH, the long-acting insulin analogues have not been shown to be cost-effective for the treatment of type 1 diabetes in adults (see Section 6.3). However, the presence of hypoglycemia may be an important consideration in determining whether a long-acting insulin analogue is preferred for the management of particular patients. Although the results are inconsistent, the long-acting insulin analogues had lower risk and rates of hypoglycemia in both adults and children, especially nocturnal events.[1] CERC provided the following recommendations, based on the results of the COMPUS meta-analyses and pharmacoeconomic study:[3]

- CERC recommends that insulin NPH be used in **preference to** either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most **adults with type 1 diabetes.**
  - CERC Rating of Overall Quality of Clinical Evidence: Low (insulin glargine)
  - Moderate (insulin detemir)
  - Strength of Recommendation: Strong
- CERC suggests that insulin NPH be used in **preference to** either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most **children with type 1 diabetes.**
  - CERC Rating of Overall Quality of Clinical Evidence: Low
  - Strength of Recommendation: Weak

The key message for academic detailing, based on the recommendations of the Optimal Therapy Report, is:

In patients with type 1 or type 2 diabetes requiring basal insulin, insulin NPH should be considered first. Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while using insulin NPH may benefit from long-acting insulin analogues.

3.3.3 Dosing strategies

At the onset of type 1 diabetes, patients may have relatively low insulin requirements (~0.2 to 0.6 units/kg/day) due to the presence of residual endogenous insulin production.[52,53] This "honeymoon period" usually lasts anywhere from eight weeks to two years.[28]

Once endogenous insulin production has failed completely, most patients require between 0.5-1.0 units/kg/day to maintain glucose control.[28,52] Guidelines from both Canada and the United States advocate an aggressive multiple daily dose (three to four doses per day) regimen. There are a wide variety of regimens that can be implemented, depending on the insulin being utilized and patient preference.

For more information on dosing and titration strategies for insulin therapy, see the RxFiles charts in Appendix 2.

3.3.4 Dosing conversion

a) Bolus insulin

The product monograph for both insulin lispro and insulin aspart suggest that, when switching a patient from human insulin, the dose can be transferred on a unit-to-unit basis; in other words, no dosage adjustment is required.[54,55] The insulin lispro product monograph notes that one year after switching type 1 diabetes patients from human insulin, the average basal insulin requirement increased by 0.04 units/kg, while requirement for bolus insulin decreased by 0.03 units/kg.[54] It is prudent to recommend increased monitoring for hypo- and hyperglycemia during periods of

transition between different types of insulin and dosing adjustment, based on individual response.

b) Basal insulin

The insulin glargine monograph provides information on switching from NPH insulin. Patients on once-daily basal NPH insulin can be switched over to the same dose of once-daily insulin glargine. However, in patients being transferred from twice-daily NPH insulin, the initial dose of insulin glargine should be reduced to approximately 80% of the NPH insulin dose, and then adjusted, based on patient response.[56] The insulin detemir monograph provides less instruction on dosing conversion. In the single crossover trial of insulin detemir versus NPH identified in the CADTH meta-analysis, patients were treated with the same initial dose (70% of the pre-trial dose) of either NPH or insulin detemir.[57] This is not to suggest that reducing a patient's insulin intake by this much is normal in clinical management, but to highlight the fact that they used the same dose for insulin detemir and NPH, lending credence to the premise that they have equivalent potency. As well, a review of insulin detemir in *The Diabetes Educator* suggests that switching from NPH insulin can be done on a unit-to-unit basis, and that insulin detemir can be dosed once or twice daily (similar to NPH).[58]

3.4 Management of Hypoglycemia

Drug-induced hypoglycemia is a serious challenge for patients with diabetes. It is estimated that on average, patients with type 1 diabetes experience two hypoglycemic episodes per week.[14] However, the incidence varies widely depending on type of therapy and presence of risk factors. Risk factors for the development of hypoglycemia (besides treatment with insulin or an insulin secreteagogue) include:[12,14]

- history of severe hypoglycemia
- tightly controlled blood sugar (current A1C <6%)
- hypoglycemia unawareness, often brought about from frequent episodes of hypoglycemia
- long duration of diabetes
- autonomic neuropathy and/or gastroparesis (delayed absorption of food)
- younger age, including adolescents and pre-school children, who are not able to detect or manage mild hypoglycemia.

The CDA provides recommendations on how different degrees of hypoglycemia should be managed:[14]

- Mild to moderate hypoglycemia should be treated by the oral ingestion of 15 g of carbohydrate, preferably as glucose or sucrose tablets or solution. These are preferable to orange juice and glucose gels. *Grade B, Level 2*. Patients should be encouraged to wait 15 minutes, retest BG and retreat with another 15 g of carbohydrate if the BG level remains <4.0 mmol/L. *Grade D, Consensus*.
- Severe hypoglycemia in a conscious adult should be treated by the oral ingestion of 20 g of carbohydrate, preferably as glucose tablets or equivalent. Patients should be encouraged to wait 15 minutes, retest BG and retreat with another 15 g of glucose if the BG level remains <4.0 mmol/L. *Grade D, Consensus*.

BG=blood glucose

Glucagon is also a therapeutic option in managing patients with severe hypoglycemia and can be administered to patients who are unable to swallow. A 1 mg dose administered subcutaneously or intramuscularly can increase serum glucose by 9 mmol/L in 60 minutes. The CDA guidelines provide vague recommendations regarding glucagon, but the ADA guidelines are more prescriptive:[14,59]

- CDA: For individuals at risk of severe hypoglycemia, support persons should be taught how to administer glucagon by injection. *Grade D, Consensus*.
- ADA: Glucagon should be prescribed for all individuals at significant risk of severe hypoglycemia, and caregivers or family members of these individuals should be instructed in its administration. Glucagon administration is not limited to health care professionals.

3.5 Recommended Reading

- Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1C) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 1995;44(8):968-83.
- Pieber TR, Treichel HC, Hompesch B, Philotheou A, Mordhorst L, Gall MA, et al. Comparison of insulin detemir and insulin glargine in subjects with type 1 diabetes using intensive insulin therapy. *Diabetic Medicine* 2007;24(6):635-42.
- Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR. Short-acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Systematic Review* 2006(2): CD003287.
- Wild D, von Maltzahm R, Brohan E, et al. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Education and Counseling* 2007;68:10-15.

4 SECTION 4: TYPE 2 DIABETES

4.1 Epidemiology and Pathophysiology

Type 2 diabetes mellitus (previously known as non-insulin-dependent diabetes) accounts for about 90% of all diabetes cases in Canada.[60] Much of the economic cost of diabetes is, therefore, due to the management of type 2 diabetes and its complications. Another notable aspect of the epidemiology of type 2 diabetes in Canada is its three- to five-fold higher prevalence among First Nations populations, as compared to the general population.[60]

Most people diagnosed with type 2 diabetes are over the age of 40 years and have some degree of obesity.[28] However, the rising rate of childhood obesity in Canada has made this disease a real concern among youth. In 2004, data from Statistics Canada showed that 8% of children aged two to 17 years were obese, and that the rate of obesity in adolescents (aged 12 to 17 years) had tripled in the past 25 years.[61] Statistics from the American Diabetes Association suggest that one in six obese adolescents are in a pre-diabetic metabolic state which, if uncorrected, substantially increases the risk of developing diabetes in adulthood.[59]

Type 2 diabetes is characterized primarily by insulin resistance, as well as variable degrees of impaired insulin secretion, excessive hepatic glucose production, and abnormal fat metabolism.[29] Unlike type 1 diabetes, which is brought on predominately by auto-immune destruction of insulin-producing islet cells, development of type 2 diabetes is a multi-factorial process that involves genetic and environmental influences.[12] Genetic risk factors for type 2 diabetes have not yet been defined, but the predominance of the condition in specific familial and ethnic lines provides a strong indication of their existence.[29] The predominant environmental factor is obesity, specifically visceral obesity, which correlates with insulin resistance.[12]

4.2 Diagnosis

The diagnostic criteria discussed in Section 3.2 apply to type 2 diabetes, as well as type 1. The factors that differentiate the two conditions are patient-related, such as the age the patient presents with diabetes, presence of obesity, and their presenting symptoms.[29] Because patients with type 2 diabetes have relative insulin deficiency, their glycemic derangement tends to present over a prolonged period that begins with a pre-diabetic state characterized by impaired glucose tolerance.[29]

4.3 Therapeutic Management

Similar to type 1 diabetes, the goal of therapeutic management of type 2 diabetes is to return patients to near-normal glycemic control while minimizing the risk of hypoglycemic events.[29] Long-term goals of treatment are to avoid or delay the development of microvascular and macrovascular complications. The glycemic targets for type 2 diabetes are the same as for type 1 diabetes and are outlined in Section 3.3.

Two large, recently published RCTs investigated whether or not more intensive glucose lowering, to near-normal levels, reduces the risk of macrovascular complications. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials, both published in June 2008, studied the impact of targeting A1C levels to ≤ 6% and ≤ 6.5%, respectively.[62,63] Intensively-treated patients in both trials achieved similar A1C levels of 6.4-6.5%.[62,63] The ACCORD study enrolled high-risk diabetic patients with significant glycemic derangement (mean A1C of 8.3%). Patients had to have established cardiovascular disease or be older (55 to 79 years) with evidence of atherosclerosis.[63] The study was stopped early because there was a significant increase in the risk of all-cause mortality in the intensive treatment group (hazard ratio 1.22 [95% CI: 1.01, 1.46]).[63] The study also found no significant difference between intensive and conventional treatment groups in the primary outcome of cardiovascular events (non-fatal myocardial infarction or stroke, or cardiovascular death).[63] The ADVANCE trial enrolled a "healthier" diabetic population, with a mean A1C of 7.5%.[62] Criteria for enrollment included history of macro- or microvascular disease, or one or more risk factors.[62] The study found a significant reduction in the risk of combined macrovascular and microvascular events in the intensive treatment arm, driven largely by reductions in nephropathy (hazard ratio 0.79 [95% CI: 0.66, 0.93]) and microalbuminuria (hazard ratio 0.70 [95% CI: 0.57, 0.85]).[62] However, there was also an increased risk of severe hypoglycemia among intensively treated subjects (hazard ratio 1.86 [95% CI, 1.42,2.40]), resulting in a NNH of 83 people over five years.[62]

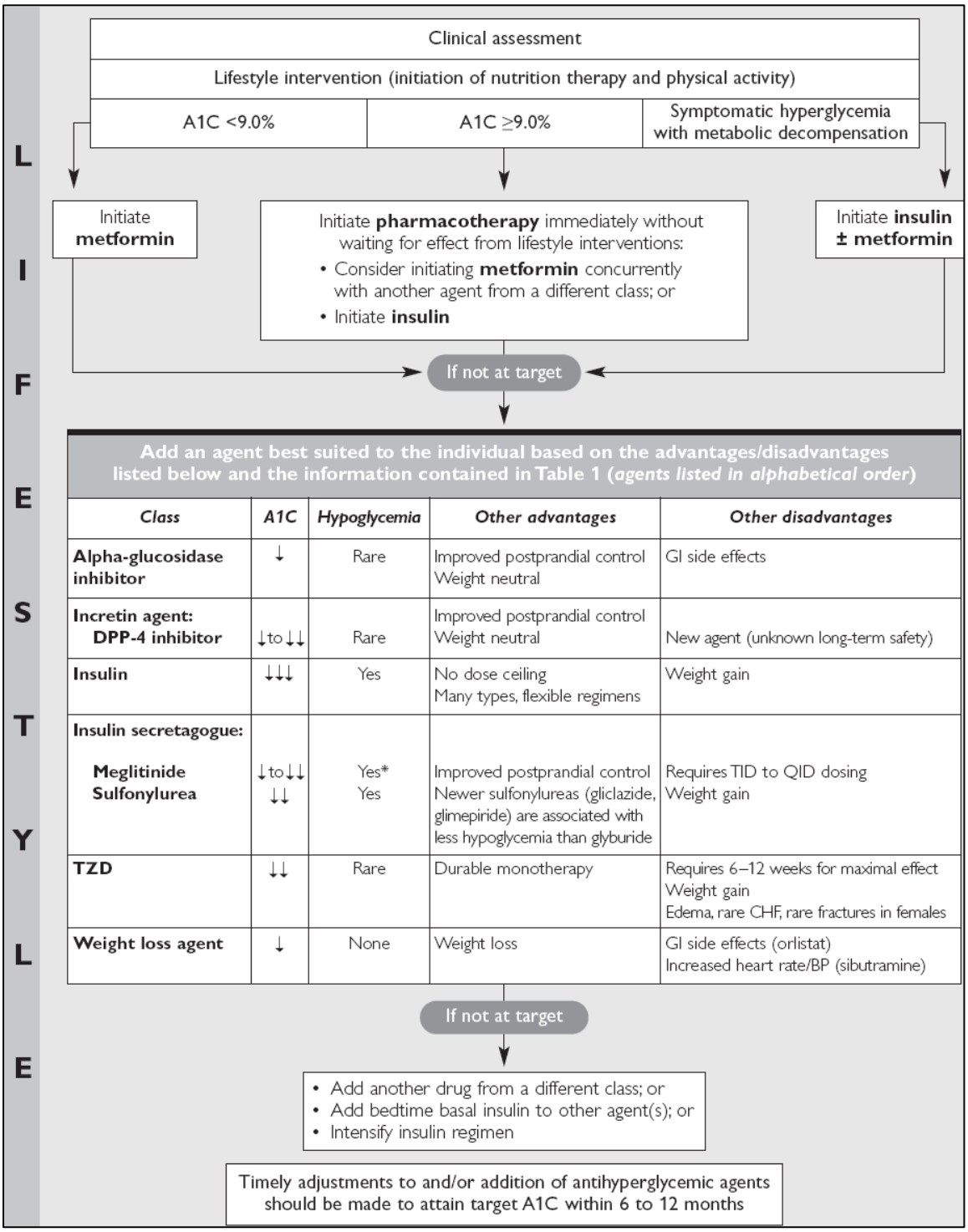
In light of the conflicting, and generally negative, results of the ACCORD and ADVANCE trials, the glycemic targets for type 2 diabetes remained unchanged from the 2003 to the 2008 CDA Guidelines.[14,64] The rationale for these targets is largely derived from the UKPDS trial, in which the fasting plasma glucose target for the intensive treatment arm was < 6 mmol/L. The intensive treatment arm achieved an average A1C of 7%.[16] Although we have considered the end points reported in this study in detail in section 2.1.1, we will now consider the therapeutic strategies used in the intensive treatment arm. Patients in the UKPDS were assigned to treatment, as follows:[16]

- 342 overweight patients were assigned to treatment with metformin.
- 2,729 patients were assigned to intensive treatment:
    - 1,156 were assigned directly to insulin therapy;
    - 1,573 were assigned directly to sulfonylurea therapy;
    - 339 of those randomized to a sulfonylurea had insulin added to their regimen after failing to achieve glycemic targets.
- 1,138 patients were assigned to conventional therapy.

Despite the aggressive use of insulin in the UKPDS, patients with type 2 diabetes are more commonly initiated on oral antidiabetes drugs in clinical practice.[29] The CDA guidelines provide an algorithm for the initiation of pharmacological therapy in patients with type 2 diabetes (Figure 10).[14] The treatment strategy is generally in line with the consensus statements of the ADA and European Association for the Study of Diabetes, although these bodies more strongly recommend the early initiation of insulin (after three months if A1C > 7%) as the most effective addition to metformin.[65]

The choice to initiate insulin therapy is often made after failure of mono- or combination therapy with oral antidiabetes drugs. The CADTH Current Practice Analysis report suggests that there are patient-related barriers to the initiation of insulin, such as fear of needles and the perception that addition of insulin represents a failure to manage the condition.[39] It was not surprising, therefore, that a study of current utilization of insulin in Canada, conducted on behalf of CADTH's COMPUS program, showed that only 3% of patients with type 2 diabetes were initiated on a regimen that included insulin. Furthermore, of patients initiated on oral hypoglycemic therapy, only 7% were switched to a regimen that included insulin, although it should be noted that the study only monitored for therapy-switching for a six-month period (*IMS Health Canada, Patient Longitudinal Database, IMS Health Consulting Analysis, Feb 2005 – Jul 2006*).

Figure 10: 2008 CDA Guidelines for Management of Type 2 Diabetes



A1C=glycated hemoglobin; BP=blood pressure; CHF=congestive heart failure; DPP-4=dipeptidyl peptidase-4; GI=gastrointestinal; TZD=thiazolidinedione; ↓ = <1.0% decrease in A1C; ↓↓= 1.0–2.0% decrease in A1C; ↓↓↓ = >2.0% decrease in A1C

Figure reprinted with permission from the Canadian Diabetes Association publication entitled Canadian Diabetes Association 2008 Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2008; 32 (suppl 1); S1-S201.

Note: Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information
*Less hypoglycemia in the context of missed meals

Beyond the general management algorithm outlined in Figure 10, the CDA guidelines make specific recommendations regarding the use of insulin therapy in patients with type 2 diabetes. These include:[14]

- When basal insulin is added to antihyperglycemic agents, long-acting analogues (insulin detemir or insulin glargine) may be considered instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia. [*Grade A, Level 1A (71)].*
- The following antihyperglycemic agents…should be considered to lower postprandial BG levels:
  - Alpha-glucosidase inhibitors. [*Grade B, Level 2 (10)]*
  - Premixed insulin analogues (i.e. biphasic insulin aspart and insulin lispro/protamine) instead of regular/NPH premixtures. [*Grade B, Level 2 (72, 73)]*
  - DPP-4 inhibitors. [*Grade A, Level 1 (13, 14, 74)]*
  - Inhaled Insulin. [Grade B, Level 2 (20)]
  - Meglitinides (repaglinide, nateglinide) instead of sulfonylureas. [*Grade B, Level 2 (75, 76)]*
  - Rapid-acting insulin analogues (aspart, glulisine, lispro) instead of short-acting insulin (i.e. regular insulin). [*Grade B, Level 2 (21, 77, 78)].*
- All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counselled about the recognition and prevention of drug-induced hypoglycemia. [*Grade D, Consensus].*

BG=blood glucose; DPP-4=Dipeptidyl peptidase-4 inhibitor; NPH=neutral protamine Hagedorn

4.3.1 Limits of oral antidiabetes drugs

It is important for clinicians to recognize the limitations of what can be achieved with oral antidiabetes drugs. Table 3 summarizes the reductions in A1C that can be expected from the various oral hypoglycemic agents. Insulin therapy lowers A1C by 1.5% to 2.5%, depending on the intensity of therapy.[65]

Table 3: Expected A1C Reductions in Response to Oral Antidiabetes Drugs in Patients With Type 2 Diabetes.[66-68]

Oral Antidiabetes Drugs	A1C Reduction
Metformin	0.9 to 1.4
Sulfonylureas	1.3 to 1.8
Rosiglitazone (Avandia®)	0.9 to 1.4
Pioglitazone (Actos®)	0.8 to 1.2
Alpha-glucosidase inhibitors	0.6 to 0.9
Repaglinide (GlucoNorm®)	0.8 to 1.9
Nateglinide (Starlix®)	0.3 to 0.8
Sitagliptin (Januvia®)	0.6 to 0.8

A1C=glycosylated hemoglobin

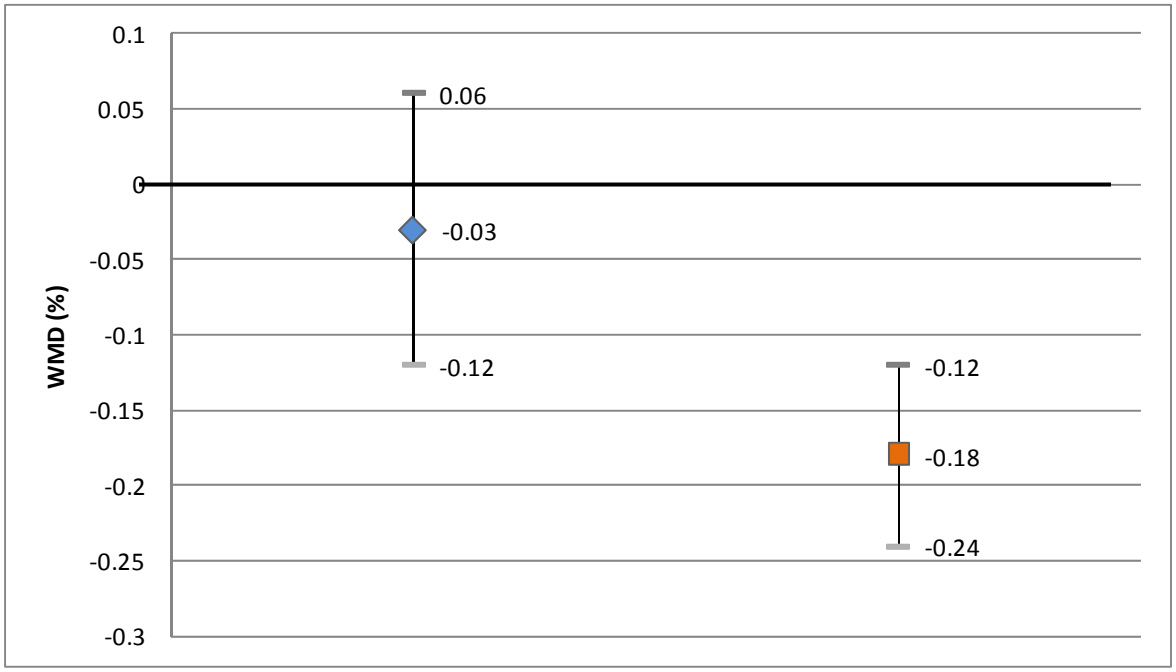
4.3.2 Bolus insulin

a) Glycosylated Hemoglobin

As in type 1 diabetes, the data on A1C differences between rapid-acting insulin analogues and human insulin is quite substantive in patients with type 2 diabetes. A notable aspect of these studies was the use of pre-mixed insulin (both rapid-acting insulin analogues and human insulin) in some trials, and separate injections for basal and bolus therapy in others. A total of 11 trials were identified that showed non-significant reductions in A1C values for insulin lispro compared with human insulin, as shown in Figure 11.[2] The four trials that evaluated insulin aspart formulations against human insulin formulations significantly favoured the analogue. Although, once again, the clinical significance of a < 0.2% reduction in A1C is unknown.[2,3]

The systematic review by Siebenhofer et al. came to a similar conclusion as the CADTH meta-analysis, finding a weighted mean difference in A1C of 0.0% (95% CI: -0.1, 0.0) based on analysis of five trials comparing rapid-acting insulin analogues to human insulin.[42]

Figure 11: Pooled A1C Differences in Comparisons of Rapid-Acting Insulin Analogues Versus Human Insulin in Adults With Type 2 Diabetes[2,3]



HI=human insulin; IAsp=insulin aspart; ILisp=insulin lispro; pts=patients; WMD=weighted mean difference

b) Postprandial glucose

The CDA guidelines suggest that rapid-acting insulin analogues used in bolus therapy will achieve improved postprandial glucose control over human insulin.[14] The CADTH meta-analysis identified a single study that compared premixed insulin lispro to premixed (30/70) human insulin that had an objective assessment of postprandial plasma glucose. Other studies did look at postprandial glucose assessed by self-monitoring, but they were not included in the analysis.[2] In the included study, premixed insulin lispro produced a non-significant -1.1 mmol/L (95%CI: -2.21, 0.01) lower mean two-hour postprandial glucose than premixed human insulin.[3,69] Although the reduction was marginally insignificant, the clinical significance of this degree of difference is still uncertain. In the CIMT trial (see Section 2.1.2), a difference of 1.8 mmol/L in favour of repaglanide over glyburide resulted in about 30% more patients having regression in their carotid intima medial thickness.[26]

c) Microvascular and macrovascular complications

None of the studies included in the CADTH meta-analysis were designed or adequately powered to measure the impact of rapid-acting insulin analogues on rates of micro- or macrovascular complications.[2] All-cause mortality was reported in a few of the comparative trials, but no significant differences were found between any of the comparators.[2]

d) Body weight

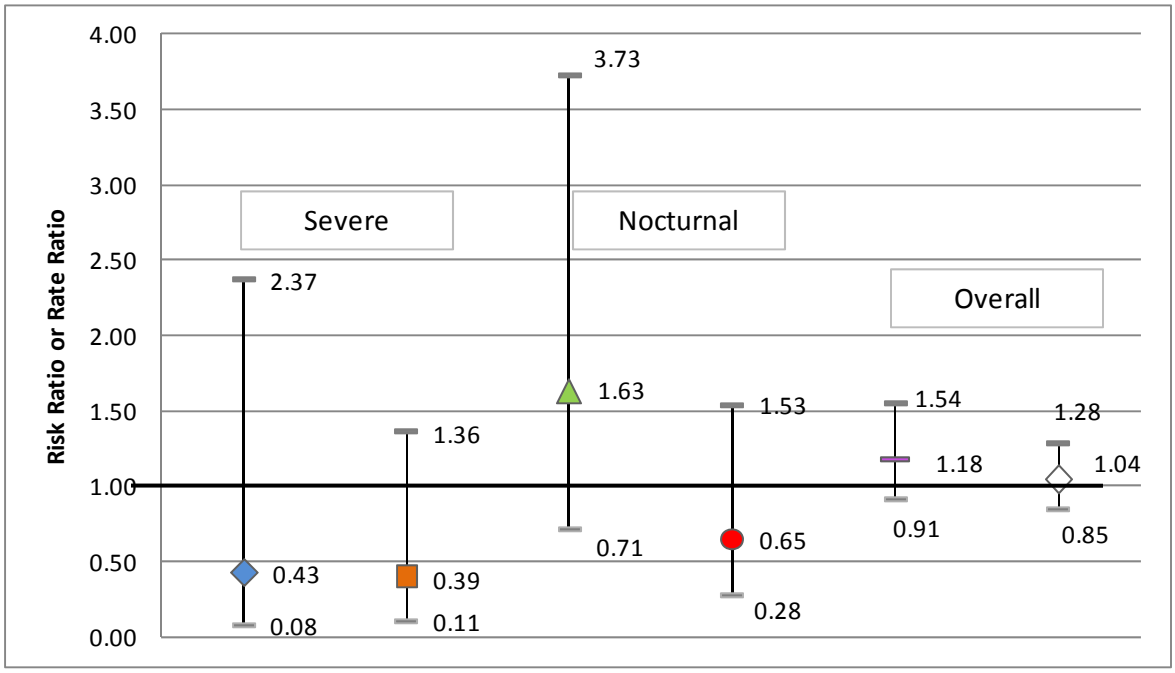
Across three trials of insulin lispro versus human insulin that reported body weight, the WMD was -0.08 kg (95% CI: -1.40, 1.24), indicating no significant difference between the comparators.[2] Similarly, the pooled WMD in body weight across two trials of insulin aspart versus human insulin was statistically non-significant (-0.87 kg [95% CI: -2.40, 0.67]).[2]

e) Hypoglycemia

Although a large number of trials provided data on the glycemic impact of the rapid-acting insulin analogues in type 2 diabetes, reporting of information on hypoglycemic events was variable. Hypoglycemia risk and rate ratios are presented in Figure 12. None of the comparisons between the rapid-acting insulin analogues and human insulin showed significant advantage in reducing the risk of any hypoglycemia measure.[2,3]

The only result that reached statistical significance was the rate ratio of nocturnal hypoglycemia for the comparison of insulin lispro with human insulin (0.58 [95% CI: 0.48, 0.70]) and the rate ratio of overall hypoglycemia for the comparison of insulin aspart versus human insulin (0.72 [95% CI: 0.64, 0.8]).[2] The low event rate and relatively few studies made meaningful comparison of the insulins difficult. Because none of the risk ratios were significant, NNH were not calculated.

Figure 12: Pooled Risk Ratios for Various Forms of Hypoglycemia in Comparisons of Rapid-Acting Insulin Analogues or Premixed Rapid-Acting Insulin Analogues Versus Human Insulin or Premixed Human Insulin in Adults With Type 2 Diabetes[2,3]



ILis or premixed ILis vs. HI, Risk Ratio, 2 trials, 1,622 patients

Premixed IAsp vs. HI, Risk Ratio, 1 trial, 121 patients

Premixed ILis vs. HI, Risk Ratio, 1 trial, 178 patients

Premixed IAsp vs. HI, Risk Ratio, 1 trial, 93 patients

ILis or premixed ILis vs. HI, Risk Ratio, 3 trials, 384 patients

IAsp or premixed IAsp vs. HI, Risk Ratio, 3 trials, 369 patients

HI=human insulin; IAsp=insulin aspart; ILis= insulin lispro; vs.=versus

f) Quality of Life and Patient Satisfaction

Data regarding the impact on quality of life and patient satisfaction of the rapid-acting insulin analogues compared to human insulin were scarce. The results of two trials using different instruments, both comparing insulin lispro with human insulin, were reported in the CADTH meta-analysis. Neither reported a difference between comparators in satisfaction scales.[2] One trial also reported no significant differences in flexibility, willingness to continue, energy/fatigue, or anxiety/health distress.[70] The second found a significant improvement in a measure of worry related to diabetes with insulin lispro compared to human insulin.[71]

g) Summary

Small differences in the A1C, coupled with marginal impacts in postprandial glucose, bring into question preferential use of rapid-acting insulin analogues in type 2 diabetes, although the small

impact on rates of hypoglycemia that are seen with these agents may be important in certain patient populations. CERC provided the following recommendations, based on the results of the CADTH meta-analyses and pharmacoeconomic study:[3]

- CERC suggests that regular human insulin be used in **preference** to the rapid-acting insulin analogues (i.e., insulin lispro and insulin aspart) in most **adults with type 2 diabetes** who require bolus insulin therapy.
  - CERC Rating of Overall Quality of Clinical Evidence: Low
  - Strength of Recommendation: Weak

- CERC recommends that either biphasic insulin lispro or biphasic insulin aspart be used in **adults with type 2 diabetes using MDI** if treatment with a biphasic rapid-acting insulin analogue preparation is chosen.
  - CERC Rating of Overall Quality of Clinical Evidence: Low
  - Strength of Recommendation: Strong

The key message for academic detailing, based on the recommendations of the Optimal Therapy Report, is:

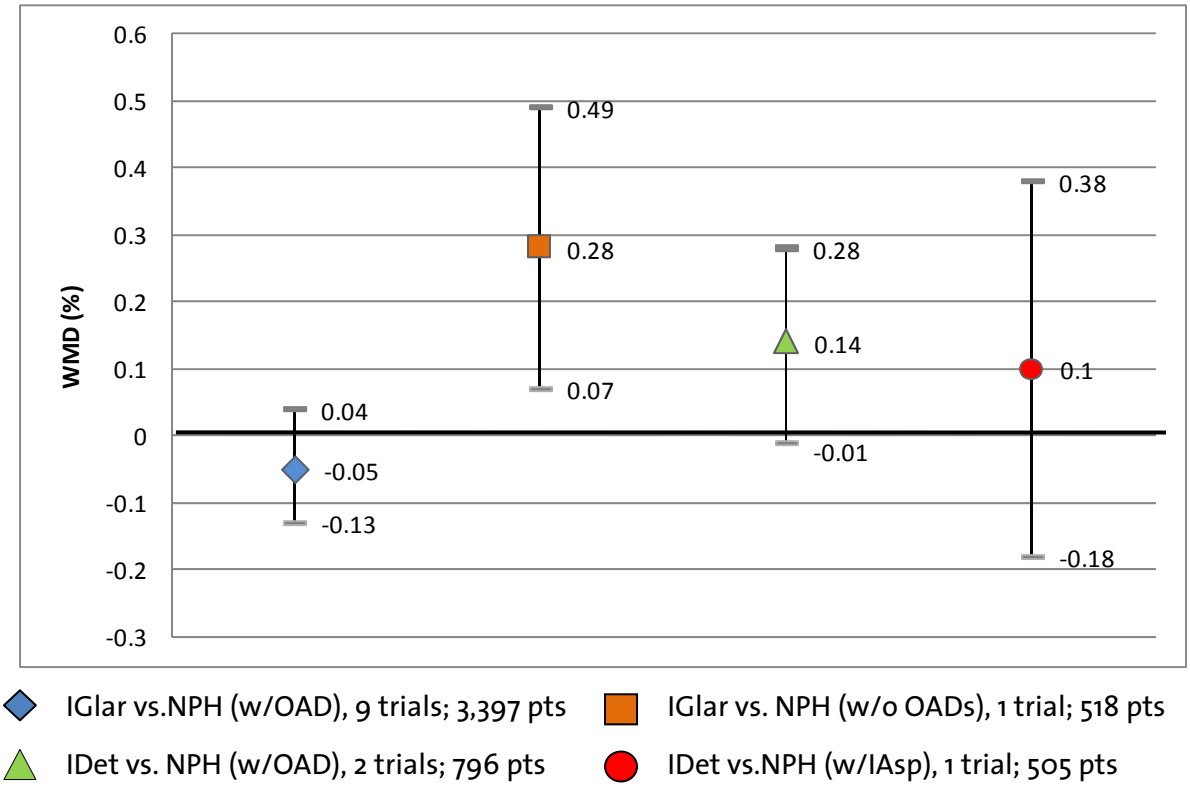
> In patients with type 2 diabetes requiring bolus insulin, regular human insulin may be considered first. Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking human insulin may benefit from the rapid-acting insulin analogues.

4.3.3 Basal insulin

a) Glycosylated hemoglobin

A variety of combinations have been investigated to assess the comparative efficacy of long-acting insulin analogues versus NPH insulin in type 2 diabetes.[1] The most common comparison was between insulin glargine and NPH added to different oral antidiabetes drugs. The overall result, shown in Figure 13, was a non-significant difference in A1C. In a subgroup analysis based on type of oral antidiabetes drug, insulin glargine added to a sulfonylurea demonstrated a statistically significant reduction in A1C of -0.18% (95% CI: -0.30, -0.05) in favour of insulin glargine.[1] There was no significant difference between insulin glargine and NPH when they were added to the other oral antidiabetes drugs. The point estimates for the rest of the comparisons of the long-acting insulin analogues versus NPH all favoured NPH, although the only one that reached statistical significance was the comparison of insulin glargine with NPH in patients managed without oral antidiabetes drug therapies from a single trial.[1,3]

Figure 13: Pooled Differences in A1C in Comparisons of Long-Acting Insulin Analogues Versus NPH in Adults With Type 2 Diabetes[1,3]



IAsp= insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; NPH=neutral protamine Hagedorn insulin; OAD=oral antidiabetes drugs; pts=patients; vs.=versus; w/=with; w/o=without; WMD=weighted mean difference

A Cochrane review published by Horvath et al. also considered the efficacy of long-acting insulin analogues versus NPH in type 2 diabetes. Their findings were similar to those of COMPUS; the pooled A1C weighted mean difference was 0.0% (95% CI: -0.1, 0.1) across the six included trials that compared NPH with insulin glargine.[72] A statistically significant weighted mean difference in A1C of 0.1% (95% CI: 0.01, 0.2) favouring NPH insulin was observed across the two included studies comparing insulin detemir with NPH, although the authors noted that this small difference was clinically unimportant.[72]

The CADTH analysis also looked at trials comparing the two long-acting insulin analogues. One trial compared insulin glargine and insulin detemir in patients treated with oral antidiabetes drugs, and the other compared these agents in patients treated with pre-meal insulin. In both trials, the A1C result favoured insulin glargine, although differences were small and statistically significant only in the latter study (WMD 0.2% [95% CI: 0.1, 0.3]).[1]

b) Microvascular and cacrovascular complications

Similar to type 1 diabetes, evidence regarding the impact of the long-acting insulin analogues on micro- or macrovascular complications is lacking for patients with type 2 diabetes. Comparative

studies have not been designed or adequately powered to measure differences in these outcomes, although a few studies reported event rates for long-term diabetes complications.[1] For all end points evaluated — including non-fatal heart disease, nephropathy, retinopathy and mortality — there were no significant differences between the long-acting insulin analogues and NPH.[1] The lack of data on clinically relevant outcomes was commented upon by Horvath et al. in their Cochrane review: "Since the differences in overall effects on metabolic control were only small for insulin glargine and NPH, even disadvantageous for insulin detemir, no important improvements in the development of microvascular late complications would be expected from treatment with long-acting insulin analogues."[72]

c) Body weight

As mentioned in the CDA guidelines, the purported benefit of long-acting insulin analogues on weight gain is considered to be one of their key advantages over NPH (see Section 4.3).[14] In seven trials that reported the impact on body weight of insulin glargine versus NPH when added to various oral antidiabetes drugs, the result was a statistically non-significant WMD of 0.18 kg (95% CI: -0.11, 0.47) in favour of NPH.[1] The mean difference in body weight in the one trial of insulin glargine versus NPH without oral antidiabetes drugs was also non-significant (-2.10 kg [95% CI: -5.21, 1.01]), although in this case the point estimate favoured insulin glargine.[1]

Studies of insulin detemir versus NPH provided slightly more support for the benefits of long-acting insulin analogues on body weight. The WMD across two trials of insulin detemir versus NPH added to oral antidiabetes drugs was statistically significant in favour of insulin detemir (-1.27 kg [95% CI: -1.95, -0.58]).[1,3] One other trial of insulin detemir versus NPH, both with pre-meal insulin, also favoured insulin detemir, with statistically significant weight differences of -0.80 kg (95% CI: -1.46, -0.14).[1,3] Direct comparisons between the two long-acting insulin analogues consisted of one trial in which insulin glargine or insulin detemir were added to an oral antidiabetes drug, and another in which pre-meal insulin was used. Both found statistically significant differences favouring insulin detemir of 0.8 kg and 1.5 kg in the oral antidiabetes drug and pre-meal insulin studies, respectively.[1] As discussed in section 3.3.2, the clinical significance of less than 5% reduction in body weight is questionable.[49]

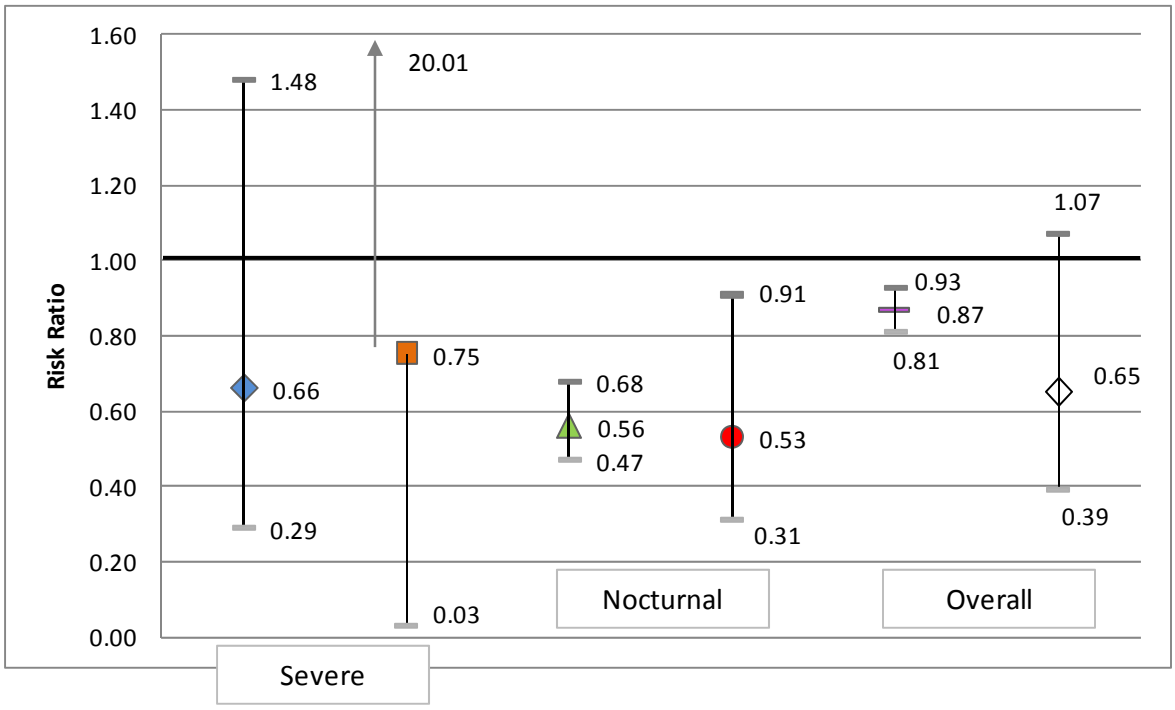
d) Hypoglycemia

The other highly touted advantage of long-acting insulin analogues is reduction in hypoglycemia. It is difficult to compare rates of hypoglycemia between patients with type 2 and type 1 diabetes, because of differences in both population characteristics and treatment strategies (e.g., use of intensive insulin therapy in type 1 diabetes). Although it has been suggested that hypoglycemia risk in type 2 diabetes is lower than in type 1 diabetes, when similar insulin regimens are employed, there appears to be little difference in rates.[73] As such, understanding the impact of the long-acting insulin analogues on incidence of hypoglycemia is as important in the type 2 diabetic population as type 1, especially since insulin is increasingly initiated earlier in the course of the disease.

Pooled hypoglycemia risk ratios from the CADTH meta-analysis across studies in adults with type 2 diabetes are shown in Figure 14. As compared to NPH, the risk ratios for severe hypoglycemia did not reach statistical significance. The baseline risk in the studies of insulin glargine and insulin

detemir versus NPH were very low at 3.8% and 1.5% respectively.[1] Both insulin glargine and insulin detemir demonstrated significantly lower risks and rates for nocturnal hypoglycemia. As was seen in the studies of insulin detemir in type 1 diabetes, patients with a history of recurrent hypoglycemia were excluded from two of the three trials.[31] Other confounding factors cited by Horvath et al. in their Cochrane review of long-acting insulin analogues use in type 2 diabetes was heterogeneity in definitions and reporting of hypoglycemia, as well as concerns regarding publication bias.[72] The authors also observed lower rates of overall and nocturnal hypoglycemia with both long-acting insulin analogues, but they were unable to draw firm conclusions due to the limitations of the data.[72]

Figure 14: Pooled Risk Ratios for Various Forms of Hypoglycemia in Comparisons of Long-Acting Insulin Analogues Versus NPH in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drug[1,3]



◆ IGlar vs. NPH, Risk Ratio, 7 trials; 2,866 patients
■ IDet vs. NPH, Risk Ratio, 2 trials; 808 patients
▲ IGlar vs. NPH, Risk Ratio, 7 trials; 2,532 patients
● IDet vs. NPH, Risk Ratio, 2 trials; 808 patients
▬ IGlar vs. NPH, Risk Ratio, 8 trials; 2,642 patients
◇ IDet vs. NPH, Risk Ratio, 2 trials; 808 patients

IDet=insulin detemir; IGlar=insulin glargine; NPH=neutral protamine Hagedorn insulin; pts=patients; vs.=versus

To provide clinicians with a measure of the absolute benefit of long-acting insulin analogues regarding hypoglycemia, NNH were estimated for risk ratios that were statistically significant (Table 4). The baseline risks of hypoglycemia (risk observed in the NPH arms of each group of studies) used to calculate these NNH values were 33% for insulin glargine, nocturnal; 33% for insulin detemir, nocturnal; and 56% for insulin glargine, overall. The trial duration for studies used to calculate the NNH values in Table 4 varied between four week and 12 months for insulin glargine versus NPH trials, and varied between 20 to 24 weeks for the insulin detemir versus NPH trials.[1]

Table 4: Estimated NNHs for Hypoglycemic Events with Long-Acting Insulin Analogues Versus NPH

Comparison	Type of Hypoglycemia	Risk Ratio (95% CI)	NNH (Point Estimate)	NNH (Lower Limit)	NNH (Upper Limit)
IGlar vs. NPH	Nocturnal	0.56 (0.47, 0.68)	7	6	9
IDet vs. NPH	Nocturnal	0.53 (0.31, 0.91)	6	4	33
IGlar vs. NPH	Overall	0.87 (0.81, 0.93)	14	9	26

CI=confidence interval; IDet=insulin detemir; IGlar=insulin glargine; NNH=number needed to harm; NPH=neutral protamine Hagedorn; vs.=versus

Rate ratios were also reported in the CADTH meta-analysis for a number of hypoglycemic measures, although fewer insulin glargine trials reported event rate data as compared to risk of events, making the results less reliable. Rate ratio estimates tended to be of either similar or smaller magnitude, as compared with corresponding risk ratios, and were statistically significant for all comparisons of insulin detemir versus NPH in combination with oral antidiabetes drug and for nocturnal hypoglycemia in the comparison of insulin glargine versus NPH.[3] This indicates that, even when the number of persons experiencing the hypoglycemic events did not significantly differ, the total number of hypoglycemic events recorded often favoured the insulin analogues.

Although the use of insulins with oral antidiabetes drugs is more common in the management of type 2 diabetes, basal bolus regimens are used in some patients. One study looking at insulin detemir with insulin aspart versus NPH with human insulin found no difference in the risk ratio of severe and overall hypoglycemia, but did find a lower risk of nocturnal hypoglycemia (0.54 [95% CI: 0.30, 0.97]).[74]

e) Quality of Life

Despite the data showing lower rates of hypoglycemia with long-acting insulin analogues versus NPH, studies showing that these agents improve quality of life (QoL) are lacking. In fact, the only QoL literature reported in the COMPUS meta-analysis pertained to the comparison of insulin glargine with thiazolidinediones. These studies found favourable effects on QoL with insulin glargine over thiazolidinediones based on better symptom and distress scores.[1]

f) Summary

The long-acting insulin analogues have no advantage over NPH insulin in terms of reducing glycosylated hemoglobin and, in some cases, appear to be marginally worse. The negligible advantage of the long-acting insulin analogues for body weight further brings into question the preferential use of long-acting insulin analogues suggested by the guidelines. The key advantage of the long-acting insulin analogues appears to be a reduction in hypoglycemia, especially nocturnal hypoglycemia, although there are concerns about the methodological quality of the research and the fact that statistically significant results were not observed across all comparisons and types of hypoglycemia.[72] CERC provided the following recommendations based on the results of the CADTH meta-analyses and pharmacoeconomic study:[3]

- CERC recommends that insulin NPH be used in **preference to** either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most **adults with type 2 diabetes** taking oral anti-diabetic agents who require a basal insulin.
  - CERC Rating of Overall Quality of Clinical Evidence: Moderate (insulin glargine); Low (insulin detemir)
  - Strength of Recommendation: Strong

- CERC recommends that insulin NPH be used in **preference to** either of the long-acting insulin analogues (i.e., insulin glargine or insulin detemir) in most **adults with type 2 diabetes** using pre-meal bolus insulin who require a basal insulin.
  - CERC Rating of Overall Quality of Clinical Evidence: Moderate (insulin glargine); Low (insulin detemir)
  - Strength of Recommendation: Strong

The key message for academic detailing, based on the recommendations of the Optimal Therapy Report, is:

In patients with type 1 or type 2 diabetes requiring basal insulin, insulin NPH should be considered first. Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking insulin NPH may benefit from long-acting insulin analogues.

4.3.4 Dosing strategies

Dosing strategies for insulin in type 2 diabetes are varied, especially in the use of the pre-mixed, fixed combination insulins that tend to be used in this population. Generally, a simple once-daily regimen can be considered in patients with type 2 diabetes who require insulin. Table 5 outlines one simplified regimen.

Table 5: Simple Insulin Initiation Regimen with Forced Weekly Titration[66,75]	
Start with 10 IU/day at Bedtime Basal Insulin and Adjust Weekly	
Mean of Self-Monitored Fasting Plasma Glucose Values From Previous 2 Days*	Increase in Insulin Dosage (IU/day)
> 10 mmol/L	8
7.8 to 10 mmol/L	6
6.7 to 7.8 mmol/L	4
5.6 to 6.7 mmol/L	2
* No increase if fasting plasma glucose < 4 mmol/L at any time in preceding week	
* No increase or decreases of 2 to 4 IU/day if severe hypoglycemia	
(i.e. requiring assistance) or fasting plasma glucose < 3.1 in preceding week	

IU – international unit

Patients that progress to require a basal-bolus insulin regimen can use the same strategy as applied in patients with type 1 diabetes (see Section 3.3.3).

For more information on dosing and titration strategies for insulin therapy, see the RxFiles charts in Appendix 2.

4.4 Management of Hypoglycemia

See section 3.4 for information on management of hypoglycemia.

4.5 Recommended Reading

- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998;352(9131):837-53.
- Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Systematic Review* 2007(2):CD005613.
- Harris S, Yale JF, Demsey E, et al. Can family physicians help patients initiate basal insulin therapy successfully? Randomized trial of patient-titrated insulin glargine compared with standard oral therapy: Lessons for family practice from the Canadian INSIGHT trial. *Canadian Family Physician* 2008;54:550-558.

5 SECTION 5: DIABETES AND PREGNANCY

5.1 Epidemiology and Pathophysiology

Diabetes has been associated with poor pregnancy outcomes. As late as the 1980s, physicians were still counselling women with diabetes to avoid pregnancy.[76] It now appears that optimal glycemic control can greatly improve pregnancy outcomes. However, since a third of the women with diabetes are undiagnosed, preconception planning and glycemic control can be difficult.[77-79] Pregnancy itself presents challenges to glycemic control, since it may decrease glucose tolerance and result in the development of gestational diabetes mellitus.[80]

5.2 Pre-existing Diabetes Mellitus

5.2.1 Preconception

The care of women with diabetes who are considering pregnancy begins before conception. An interprofessional diabetes health care team should develop an early working relationship with women attempting to conceive to ensure optimal glycemic control before and during the pregnancy. Optimal glycemic control helps to minimize the risks of spontaneous abortion, congenital malformation, pre-eclampsia, and progression of retinopathy. Compared to the general population, women with poorly controlled diabetes have two to three times the risk of congenital abnormalities.[14,81] Preconception glycemic control has also been shown to reduce the incidence of congenital abnormalities.[82,83]

The CDA suggests that during the preconception period, women with type 2 diabetes should have oral antidiabetes drug therapy discontinued and an insulin regimen established. In addition, the high risk (of nearly 1%) of neural tube defects compared to the general population makes folic acid supplementation an important risk-reduction strategy.[81] A multivitamin containing 5 mg of folic acid is recommended from three months pre-conception until at least 12 weeks post-conception. From 12 weeks post-conception until six weeks post-partum or as long as breastfeeding continues, continued supplementation with 0.4 mg to 1 mg of folic acid is recommended.[14] Assessment of the presence of diabetes-related complications begins with a baseline examination during the pre-conception period. Ophthalmologic assessment is important, as retinopathy is known to progress significantly during pregnancy and for the first year post-partum in women with poor glycemic control.[14] Baseline assessment for nephropathy is also suggested by the CDA through measurement of random albumin to creatinine ratio, or measurement of creatinine clearance with a 24-hour urine collection. Monitoring every trimester is recommended in women who display signs of early nephropathy at baseline. Microalbuminuria or overt nephropathy are associated with both maternal and fetal complications; therefore, optimal glycemic and blood pressure control are essential.

While blood pressure control is essential and angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARB) have a prominent role in the treatment of hypertensive diabetes patients, the teratogenicity of these agents makes them unsafe in pregnancy. ACE

inhibitors and ARBs should be discontinued and replaced with safer agents. Methyldopa is traditionally recommended, but existing data suggest that beta-blockers (labetolol), calcium channel blockers, and hydralazine may also be used safely in pregnancy.[14,84]

5.2.2 During pregnancy

The CDA recommends the following targets for glycemic control for women with type 1 and type 2 diabetes during pregnancy (Table 6).[14]

Table 6: Glycemic Targets for Preconception and Pregnancy

Pre-conception	Glycemic Target
A1C (%)	≤ 7%*
Pregnancy	
Fasting Plasma Glucose & Preprandial (mmol/L)	3.8 to 5.2
1-hour Postprandial (mmol/L)	5.5 to 7.7
2-hour Postprandial (mmol/L)	5 to 6.6
Pre-bedtime snack (mmol/L)	4 to 5.9
A1C (%)	≤ 6% (normal)

A1C=glycosylated hemoglobin

* A1C ≤ 6% is desirable if this can be safely achieved. Higher targets may be necessary to avoid excessive hypoglycemia.

It is thought that hyperglycemia during the first trimester may cause fetal malformations. Later in pregnancy, it may contribute to macrosomia and metabolic complications at birth. Self-monitoring with multiple daily measurements (≥ 4 times per day) of blood glucose assists women in meeting the targets in Table 6, while avoiding hypoglycemia.[14] (CADTH's COMPUS program is currently engaged in a more detailed review of the optimal frequency of self-monitoring, including during pregnancy.) Women with diabetes may be at increased risk of hypoglycemia because of blunting of normal counter-regulatory responses. Periodic monitoring of ketones is also recommended. Starvation ketosis (ketonemia and ketonuria with caloric restriction) is not uncommon in pregnancy and may also have detrimental effects on the fetus.[14,85,86]

Insulin administered through multiple daily injections or continuous subcutaneous infusion is suggested to meet glycemic targets.[14] Multiple daily injections with a basal-bolus regimen of human insulin and NPH insulin have been well-studied in pregnancy.[2] Rapid-acting insulin analogues (insulin lispro or insulin aspart) may also be used to achieve postprandial targets without causing severe hypoglycemia.[14] Insulin lispro does not appear to cross the placenta and has been shown to be safe and effective in pregnancy.[2,87] Insulin aspart has also been shown to be effective in pregnancy.[14,88] Observational studies on rapid-acting insulin analogues in pregnancy do not demonstrate increased fetal risk.[4] Data from small, randomized open-label trials comparing insulin aspart and human insulin continues to emerge and has also been reassuring with regard to its safety in pregnancy.[89,90] While it appears that rapid-acting insulin analogues may be used safely, there are no significant improvements in A1C or in fetal or maternal outcomes compared with regular human insulin [2,14,91]

There is insufficient evidence on the use of insulin detemir or insulin glargine in pregnancy.[14] In exceptional circumstances, when a woman cannot tolerate NPH because of nocturnal hypoglycemia, the CDA suggests insulin detemir be considered after an explanation of the risks and benefits. The choice of using insulin analogues in pregnancy is complicated by theoretical problems related to the amino acid changes that alter their interactions with various hormone receptors. Enhanced stimulation of insulin-like growth factor (IGF-I) is of particular concern in pregnancy. IGF-I is known to facilitate the implantation of the human embryo into the endometrium; therefore, disruption of its function could result in miscarriage, pre-eclampsia, or embryonic defects.[76] Insulin glargine has the greatest effect on IGF-1 (Table 7). As such, it is not recommended in pregnancy until its safety is fully assessed.[14]

Table 7: Insulin-like Growth Factor Receptor Binding Affinity[8,76]

Insulin	IGF-I Receptor Affinity
Human Insulin	100
Insulin Lispro	156±16
Insulin Aspart	81±9
Insulin Glargine	641±51
Insulin Detemir	16±1

IGF-I=insulin-like growth factor

While insulin is the gold standard for glycemic control in pregnancy, oral antidiabetic agents (particularly glyburide and metformin) have been studied and did not show an increase in cogenital abnormalities.[92] Some observational data has found increased perinatal mortality and eclampsia in women treated with metformin and glyburide, compared to those treated with insulin.[93,94] As a result, the 2008 CDA guidelines suggest that the evidence supporting oral agents is inadequate to recommend their use in pregnancy.[14] All oral hypoglycemic agents should be discontinued and replaced with insulin.[14]

5.3 Gestational Diabetes Mellitus

Gestational diabetes mellitus describes a state of glucose intolerance that develops or is first recognized during pregnancy.[14] Epidemiological data suggest a prevalence among pregnant women in Canada of 3.5% to 3.8%, and 8% to 18% in First Nations populations.[95,96]

5.3.1 Screening and diagnosis

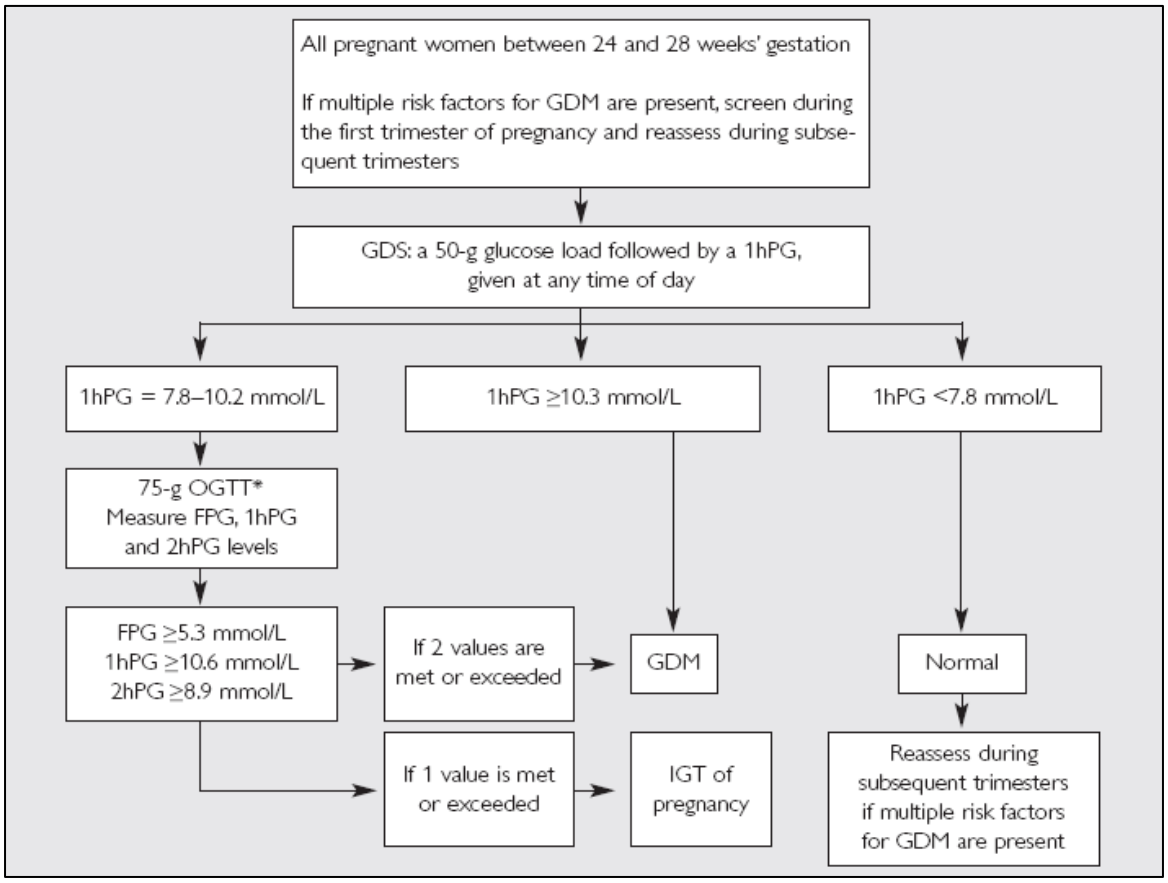
Screening for gestational diabetes mellitus allows for initiation of treatment that has been shown to reduce perinatal mortality. Hyperglycemia during pregnancy is associated with macrosomia and its associated trauma at birth; neonatal hypoglycemia, hypocalcemia, and hyperbilirubinemia; respiratory distress syndrome; and an increased risk of obesity and glucose intolerance later in the child's life.[14] A retrospective cohort study of 2,775 women showed that the rate of macrosomia in women with well-controlled (mean blood glucose of 5.3 mmol/L) glycemia (7%) was similar to that in women without diabetes (8%), and much lower than the rate in women with poor glycemic control (17%).[97]

The exact timing and method of screening for diabetes in pregnancy is the matter of some debate.[77] Different provinces may have some variation in their approach. The 2008 CDA guidelines recommend universal screening, with most women screened between 24 to 28 weeks (Figure 15). Earlier screening (i.e., in the first trimester) is suggested for those with multiple risk factors. Risk factors include:

- previous diagnosis of gestational diabetes mellitus
- previous delivery of macrosomic infant
- member of high-risk population (First Nations, Hispanic, South Asian, Asian, or African descent)
- age ≥ 35 years
- obesity – BMI ≥ 30 kg/m^2
- polycystic ovary syndrome and/or hirsutism
- acanthosis nigricans
- corticosteroid use.

A 75-g oral glucose tolerance test is indicated for women with one-hour plasma glucose screening value of 7.8 to 10.2 mmol/L after a 50 g oral glucose load (Figure 15).[14,98]

Figure 15: CDA Algorithm for Screening and Diagnosis of Gestational Diabetes Mellitus



1hPG=1-hour plasma glucose, 2hPG=2-hour postprandial plasma glucose, FPG=fasting plasma glucose, GDM= gestational diabetes mellitus, IGT=impaired glucose tolerance, OGTT=oral glucose tolerance test

Figure reprinted with permission from the Canadian Diabetes Association publication entitled Canadian Diabetes Association 2008 Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2008; 32 (suppl 1); S1-S201.

5.3.2 Therapeutic management

Lifestyle management with nutrition therapy and appropriate physical therapy is the primary treatment for gestational diabetes mellitus. The glycemic targets for gestational diabetes are the same as those outlined for pre-existing diabetes (Table 6).[14] If glycemic targets are not achieved within two weeks of lifestyle management, then insulin therapy should be initiated. A variety of protocols can be used, but multiple daily injections may be most effective.[99] Home monitoring of blood glucose levels is recommended both pre- and postprandially to guide meal planning and insulin dose adjustments.

Rapid-acting insulin analogues have been investigated in gestational diabetes. The CADTH meta-analysis found no significant difference between human insulin and insulin lispro in pooled A1C (WMD 0.06% [95% CI: -0.11, 0.23]) across two of three studies that reported this outcome.[2] Hypoglycemia was only evaluated in one of these trials; no statistically significant difference was observed in the mean percentage of readings below 3.1 mmol/L (-1.32% [95% CI: -3.07, 0.43]).[87] The meta-analysis also reported a single RCT (N=27) comparing insulin aspart and human insulin in this population. There was no significant difference observed in A1C (WMD 0.00 [95% CI: -0.30, 0.30]) and none of the hypoglycemia (severe, nocturnal, overall) measures favoured insulin aspart over human insulin.

- CERC suggests that **either** regular human insulin or a rapid-acting insulin analogue (i.e., insulin lispro or insulin aspart) be used in most **women** who develop gestational diabetes.
  - CERC Rating of Overall Quality of Clinical Evidence: Low
  - Strength of Recommendation: Weak

CERC also suggested that observational studies of rapid-acting insulin analogues do not demonstrate fetal risk and that gestational diabetes is not likely to be diagnosed until after the key period of organ development in the fetus.[3] The 2008 CDA guidelines suggest that the rapid-acting insulin analogues can help achieve blood glucose targets without severe hypoglycemia, but notes that improvements in fetal outcomes or fetal growth outcomes have not been seen compared to regular human insulin in clinical trials.[14]

Some authors have suggested that there may be a paradigm shift occurring in the role of oral antidiabetes drugs in women with diabetes.[100,101] In the past, pregnancy was considered to be a contraindication to the use of these medicines based primarily on limited evidence from case reports regarding first-generation sulfonylureas (i.e., tolbutamide, chlorpropamide).[101] First-generation agents appear to cross the placenta, a property that may have contributed to these negative outcomes. However, second generation agents such as glyburide, with their high degree of protein binding (99.7%) and relatively short elimination half-life (10 hours), do not seem to cross the placenta to a significant degree.[101,102] Glyburide can produce good glycemic control and pregnancy outcomes,[102] but some observational studies have reported more adverse perinatal outcomes (e.g., pre-eclampsia) with glyburide.[103] The CDA suggests that glyburide can be considered as a second-line agent in gestational diabetes for women who are non-adherent or refuse insulin.

Observational studies on metformin suggest that it can be considered safe during pregnancy.[100,101] Metformin does seem to cross the placenta and expose the fetus to drug levels comparable to the mother.[100] A recent unblinded RCT of 751 women with gestational diabetes compared metformin to insulin.[104] While more women preferred the metformin regimen (76.6% versus 27.2%, P < 0.001), many women receiving metformin required supplemental insulin (46.3%). The composite primary outcome (neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, five-minute APGAR < 7 or prematurity) was similar between the metformin and the insulin groups (metformin 32%, insulin 32.2%, RR 0.99; 95% CI 0.80, 1.23). Because metformin crosses the placenta,[100] further follow-up on the offspring is required to ensure safety.[14,104] The CDA suggests that glyburide may be preferred over metformin because metformin required more supplemental insulin and is known to cross the placenta.[14] All use of oral agents in pregnancy is off-label and a full discussion of risks and benefits is needed for any patient considering this therapy.[14]

Information on the safety of oral antidiabetes drugs in pregnancy and lactation is summarized in Table 8.

Table 8: Safety of Oral Antidiabetic Drugs in Pregnancy and Lactation[100,101]

Drug	Pregnancy Category*	Cross Placenta	Excreted Breast Milk
Sulfonylureas			
Glyburide	B	No	No
Meglitinides			
Repaglinide	C	Unknown	Unknown
Biguanide			
Metformin	B	Yes	No
Thiazolidinediones			
Pioglitazone	C	Unknown	In Animals
Rosiglitazone	C	Unknown	In Animals
Alpha-Glucosidase Inhibitors			
Acarbose	B	Unknown	In Animals

* Rating B: Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
Rating C:Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

5.4 Recommended Reading

- Jovanovic, L., Pettitt, D.J. Treatment with insulin and its analogs in pregnancies complicated by diabetes. *Diabetes Care*. 2007;30:S220-S224.
- Mulholland, C., Njoroge, T., Merseeau, P. and Williams J. Comparison of guidelines available in the United States for diagnosis and management of diabetes before, during, and after pregnancy. *Journal of Women's Health*. 2007:16:790-801.

6 SECTION 6: COVERAGE AND ECONOMICS

6.1 Regional Coverage of Insulin Analogues

A major consideration for physicians and patients in the use of insulin analogues is provincial program and private plan coverage. The higher cost of these agents over conventional insulins is a barrier to access for many patients, thus coverage status may determine whether or not an analogue is considered as an option. Although private drug plan coverage is highly variable and patient specific, detailers should be aware of provincial coverage. Tables 9 and 10 provide a summary of insulin analogue coverage status in all provinces, the Yukon, and the Non-insured Health Benefits (NIHB) program. The criteria for those agents that are limited coverage, limited use, special authorization, or exceptional drug status benefits are provided, following the tables in section 6.1.1.

Table 9: Regional Coverage of Insulin Analogues: Western Canada

Brand Name	Coverage	Provincial/Territorial Coverage*					
		Yukon	B.C.	Alberta	Saskatchewan	Manitoba	Ontario
LANTUS (VIAL)	INSULIN GLARGINE	Not Benefit	LC Benefit	Not Benefit	EDS Benefit	EDS Benefit	Gen. Benefit
LANTUS (CARTRIDGE)	INSULIN GLARGINE	Not Benefit	LC Benefit	Not Benefit	EDS Benefit	EDS Benefit	Gen. Benefit
LANTUS (3ML SOLOSTAR PREFILLED PEN)	INSULIN GLARGINE	Not Benefit	Not Benefit	Not Benefit	EDS Benefit	Not Benefit	Not Benefit
LEVEMIR PENFILL	INSULIN DETEMIR	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit
HUMALOG	INSULIN LISPRO	Gen. Benefit	Gen. Benefit	Gen. Benefit	EDS Benefit	Gen. Benefit	Gen. Benefit
HUMALOG CARTRIDGE	INSULIN LISPRO	Gen. Benefit	Gen. Benefit	Gen. Benefit	EDS Benefit	Gen. Benefit	Gen. Benefit
HUMALOG MIX 25 (CARTRIDGE)	INSULIN LISPRO PROTAMINE SUSPENSION	Gen. Benefit	Gen. Benefit	Gen. Benefit	Not Benefit	Gen. Benefit	Gen. Benefit
HUMALOG MIX 25 (PEN)	INSULIN LISPRO PROTAMINE SUSPENSION	Gen. Benefit	Gen. Benefit	Not Benefit	Not Benefit	Gen. Benefit	Gen. Benefit
HUMALOG MIX 50 (CARTRIDGE)	INSULIN LISPRO PROTAMINE SUSPENSION	Not Benefit	Gen. Benefit	Not Benefit	Not Benefit		Gen. Benefit
HUMALOG PEN	INSULIN LISPRO	Gen. Benefit	Gen. Benefit	Not Benefit	Not Benefit		
NOVORAPID	INSULIN ASPART	Gen. Benefit	Gen. Benefit	Gen. Benefit	EDS Benefit	Gen. Benefit	LU Benefit
NOVORAPID (10ML VIAL)	INSULIN ASPART	Gen. Benefit	Gen. Benefit	Gen. Benefit	EDS Benefit	Gen. Benefit	LU Benefit
NOVOMIX 30 (PENFILL CARTRIDGE)	INSULIN ASPART	Not Benefit	Gen. Benefit	Not Benefit	Not Benefit		Gen. Benefit

* Coverage is current as of January 16, 2009. Coverage may vary in regions over time; consult your regional formulary for exact coverage information.
LC - limited coverage; LU - limited use; SA - special authorization; EDS - exceptional drug status

Table 10: Regional Coverage of Insulin Analogues: Eastern Canada							
Brand Name	**Coverage**	**Provincial Coverage***					
		Quebec	**P.E.I.**	**Nova Scotia**	**New Brunswick**	**NL**	**NIHB**
LANTUS (VIAL)	INSULIN GLARGINE	EDS Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit
LANTUS (CARTRIDGE)	INSULIN GLARGINE	EDS Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit
LANTUS (3 ML SOLOSTAR PREFILLED PEN)	INSULIN GLARGINE	EDS Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit
LEVEMIR PENFILL	INSULIN DETEMIR	EDS Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit
HUMALOG	INSULIN LISPRO	Gen. Benefit	Gen. Benefit	EDS Benefit	SA Benefit	SA Benefit	Gen. Benefit
HUMALOG CARTRIDGE	INSULIN LISPRO	Not Benefit	Gen. Benefit	EDS Benefit	SA Benefit	SA Benefit	Gen. Benefit
HUMALOG MIX 25 (CARTRIDGE)	INSULIN LISPRO PROTAMINE SUSPENSION	EDS Benefit	Gen. Benefit	Not Benefit	Not Benefit	SA Benefit	Gen. Benefit
HUMALOG MIX 25 (PEN)	INSULIN LISPRO PROTAMINE SUSPENSION	Not Benefit	Not Benefit	Not Benefit	Not Benefit	SA Benefit	Gen. Benefit
HUMALOG MIX 50 (CARTRIDGE)	INSULIN LISPRO PROTAMINE SUSPENSION	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit
HUMALOG PEN	INSULIN LISPRO	Not Benefit	Not Benefit	Not Benefit	Not Benefit	SA Benefit	Gen. Benefit
NOVORAPID	INSULIN ASPART	Gen. Benefit	Gen. Benefit	EDS Benefit	SA Benefit	SA Benefit	Gen. Benefit
NOVORAPID (10 ML VIAL)	INSULIN ASPART	Gen. Benefit	Gen. Benefit	EDS Benefit	SA Benefit	SA Benefit	Gen. Benefit
NOVOMIX 30 (PENFILL CARTRIDGE)	INSULIN ASPART	EDS Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit	Not Benefit

*Coverage is current as of January 16, 2009. Coverage may vary in regions over time; consult your regional formulary for exact coverage information.
EDS=exceptional drug status; LC =limited coverage; LU =limited use; SA =special authorization.

6.1.1 Summary of coverage restrictions

Province: **British Columbia**
Coverage Status: Limited Coverage Benefit
Agent(s) Covered: Insulin glargine

Criteria:

Patient is over 17 years of age and has been diagnosed with type 1 or type 2 diabetes requiring insulin and is currently taking insulin NPH and/or pre-mix insulin daily at optimal dosing:
AND

1. Has experienced unexplained nocturnal hypoglycemia at least once a month, despite optimal management.

OR

2. Has documented severe or continuing systemic or local allergic reaction to existing insulin. (See Special Notes below.)

Practitioner Exemptions

- Endocrinologists

Special Notes

- For item #2 above, documentation of previous trials (i.e., specific insulin tried and patient's response) is required.

Province: **Manitoba**
Coverage Status: Exceptional Drug Status Benefit
Agent(s) Covered: Insulin glargine
Criteria:

As a first-line alternative, secondary to NPH and/or premix at daily optimal dose, for patients who have been diagnosed with type 1 or type 2 diabetes AND who have experienced unexplained nocturnal hypoglycemia at least once a month, despite optimal management OR have documented severe or continuing systemic or local allergic reaction to existing insulin.

Province: **Saskatchewan**
Coverage Status: Exceptional Drug Status Benefit
Agent(s) Covered: Insulin aspart, insulin lispro
Criteria:

For treatment of difficult-to-control diabetes in patients who have not responded to alternative agents listed in the formulary.

Agent(s) Covered: Insulin glargine
Criteria:

For the treatment of patients who have been diagnosed with type 1 or type 2 diabetes requiring insulin and are currently taking insulin NPH and/or pre-mix daily at optimal dosing AND who have experienced unexplained nocturnal hypoglycemia at least once a month, despite optimal management OR have documented severe or continuing systemic or local allergic reaction to existing insulin.

Province: **Ontario**
Coverage Status: Limited Use Benefit
Agent(s) Covered: Insulin aspart
Criteria:

- For the treatment of patients with type 1 diabetes mellitus.
  Limited Use Authorization Period: Indefinite.
- For the treatment of patients with type 2 diabetes mellitus using insulin in an intensive regimen with three or more injections per day or an insulin pump.
  Limited Use Authorization Period: Indefinite.
- For the treatment of patients with type 2 diabetes mellitus who are either experiencing recurrent hypoglycemia OR are unable to achieve adequate postprandial glucose control while on a less intensive regimen of regular insulin (one to two injections per day).
  Limited Use Authorization Period: Indefinite.

Province: **Quebec**
Coverage Status: Medication d'Exception
Agent(s) Covered: Insulin aspart and insulin aspart protamine; insulin lispro and insulin lispro protamine
Criteria:

For treatment of diabetes, where a trial of a premixture of 20/80 or 30/70 insulin did not adequately control the glycemic profile without causing episodes of hypoglycemia.

Agent(s) Covered: Insulin detemir, insulin glargine
Criteria:

For treatment of diabetes, where a prior trial of intermediate-acting insulin did not adequately control the glycemic profile without causing an episode of severe hypoglycemia or frequent episodes of hypoglycemia;

Province: **New Brunswick**
Coverage Status: Special Authorization Benefit
Agent(s) Covered: Insulin aspart, insulin lispro
Criteria:

For patients with type 1 or 2 diabetes who have experienced frequent episodes of postprandial hypoglycemia, have unpredictable mealtimes, have insulin resistance, or who are using continuous subcutaneous insulin infusion. Prescriptions written by New Brunswick endocrinologists and internists do not require special authorization. Subsequent refills ordered by other practitioners will not require special authorization.

Province: **Nova Scotia**
Coverage Status: Exceptional Drug Status Coverage
Agent(s) Covered: Insulin aspart, Insulin lispro
Criteria:

- For beneficiaries 19 years of age and older (general benefit for children 18 years of age and younger)
- For the management of type 1 and type 2 diabetes mellitus in patients undergoing intensive therapy; i.e., administering three or more injections of insulin per day, including basal insulin, and testing blood glucose levels four to six times per day. May be requested by a nurse practitioner.

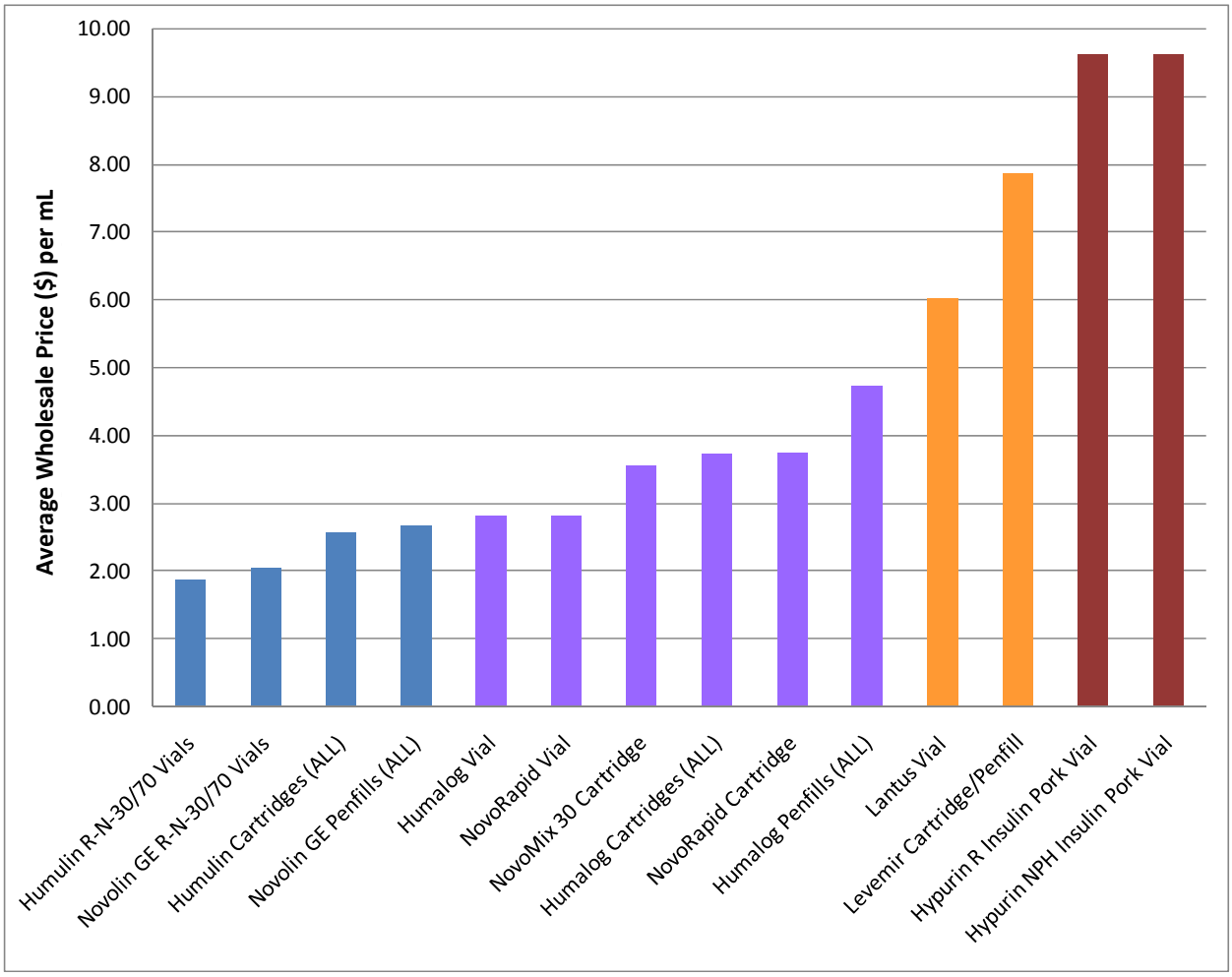
Province: **Newfoundland and Labrador**
Coverage Status: Special Authorization Benefit
Agent(s) Covered: Insulin aspart, insulin lispro
Criteria:

- For patients with insulin-dependant diabetes on multiple insulin dosing (greater or equal to three injections of regular insulin per day) and who are experiencing frequent hypoglycemia or poor glycemic control on their current regimen
- For patients with insulin-dependent diabetes who are using an insulin pump
- For patients with insulin-dependent diabetes who, for convenience purposes, wish to use this insulin and are willing to pay the difference in price from traditional regular insulin (i.e., Newfoundland and Labrador Provincial Drug Program will pay the cost normally reimbursed for regular insulin — Novolin ge Toronto — and the patient would be responsible for the difference)

6.2 Insulin Price Comparison

The price of insulin products varies between agents and also between delivery systems. The human insulins are cheapest, followed by rapid- and long-acting insulin analogues. A couple of pork insulins remain on the market and are substantially more expensive, likely due to their limited use. Regarding delivery systems, cartridges that insert into easy-to-use insulin pens are priced at a premium compared to the larger vials. Figure 16 shows the average wholesale price (average across all provinces, from McKesson Canada effective March 2008) per millilitre of insulin.

Figure 16: Price Comparison of Insulins on the Canadian Market



[redacted]

Note: Prices are for drug-cost only and do not including dispensing fee. Costs may vary between regions and over time; consult your local wholesaler for exact pricing information.

6.3 Economic Evaluation

Review of the economics of the insulin analogues in Canada can be a helpful decision aide. Many therapeutics text books now include a section on economics as drug cost and efficient use of limited health resources have become increasingly important issues. Economic evaluation allows integration of clinical and cost information to assist decision making. Economic models enable extrapolation of data from short-term trials and data from trials that use surrogate end points to forecast downstream clinical complications and their associated costs. Furthermore, economic models enable examination of the uncertainty of results. These features are relevant for insulin analogues as all trials on insulin analogues have been too small and of too short a duration to measure their effects on diabetes complications.

The CADTH economic model projects diabetes complications and the associated costs in patients prescribed insulin analogues versus conventional insulins based on differences in A1C observed in their meta-analyses. Given the latent onset of diabetes-related complications, modelling is a complex task that becomes more challenging when non-statistically significant decreases in A1C are propagated through the model. It may be argued that non-significant results should not form the basis of an economic evaluation.[105,106] The lack of sound efficacy data is poor foundation for economic analysis.[107-109] Standard quality checklists for the assessment of economic evaluations suggest that effectiveness of the intervention has to be established.[105,106] However, if the point estimate of efficacy is positive (i.e., favourable), it can be argued that statistical inference is an arbitrary threshold that may interfere with making the best economic decision.[110]

If a new medication is not clinically more effective and is more costly (e.g., insulin detemir versus NPH insulin in type 2 diabetes), it is likely to fall in the upper left quadrant of the cost-effectiveness plane (less effective, more costly (see explanation of cost-effectiveness plane, below). It could be suggested that, in this circumstance, economic analysis may be inappropriate or unnecessary.[105,106] When statistically insignificant efficacy data is used in an economic analysis there is likely to be substantial uncertainty in the results. Through sensitivity analyses, this uncertainty can be explored. However, it is likely that the sensitivity analysis will produce results that extend across multiple quadrants of the cost-effectiveness plane. The interpretation of these results may be problematic and formulation of clear recommendations is unlikely.

Through a series of economic dashboards, the key components of the CADTH "Economic Evaluation of Insulin Analogues for the Treatment of type 1 and type 2 Diabetes Mellitus in Canada" are explored. Dashboards are frequently used in management as a simple visual means to display important data for managers or board members who may not have the time or need to review the information in more detail.[111] There is a parallel for economic data and academic detailing. It is unlikely that academic detailers will deal directly with detailed economic data in a discussion with a family physician. However, since economic analysis may be used in formulary or coverage decisions, it may be helpful for detailers to have a basic understanding of the key components of the economic analysis. The dashboards are intended to give this basic, high-level overview. The dashboards contain the following components:

Efficacy Background: The meta-analytic summary information on A1C and hypoglycemia forms the basis of the economic analyses. These clinical estimates are key inputs into the economic model that attempts to extrapolate the overall cost implications of the therapy and its benefits. Differences in A1C are translated into delays in the complications of diabetes and the cost of their management. Lower hypoglycemia rates improve quality of life and reduces the cost associated with the management and correction of low blood glucose.

Benefit: The economic model allows for the projection and tabulation of benefits of insulin analogue therapy relative to human insulin. The incremental benefit, the benefit over and above the benefit seen with human insulin, is calculated. This benefit may be in terms of increased quantity of life, increased quality of life, or both. The result is a calculation of the incremental benefit in quality-adjusted life-years (QALYs). The incremental QALYs for the insulin analogues are quite small. The benefit section attempts to make this incremental value more understandable by converting the QALY (for example, 0.006 QALY in years) to days. The delay in diabetes complications is summarized (days) to provide a quick synopsis of the magnitude of benefit. The limited nature of the benefits is a potentially important message of the review of the economic data for an academic detailer.

Cost: Frequently simple reviews take only the drug acquisition cost into consideration and fail to account for the cost savings that may results from better disease control or reduced complication. The economic analysis takes into account the drug acquisition costs, but also considers any cost reductions based on lower complication rates and/or less hypoglycaemia, where appropriate. The net result is the incremental cost, the additional cost of the insulin analogue over and above the cost of human insulin, over the lifetime of the patient.

Incremental Cost-Effectiveness Ratio: Having determined the incremental benefit and the incremental cost of the insulin analogue, the incremental cost-effectiveness ratio (ICER) can be calculated by dividing the incremental cost by the incremental benefit.

$$\text{ICER} = \frac{\text{(Overall Cost of Insulin Analogue – Overall Cost of Human Insulin)}}{\text{(Overall Benefit of Insulin Analogue – Overall Benefit of Human Insulin)}}$$

$$\text{ICER} = \frac{\text{Incremental Cost}}{\text{Incremental Benefit}}$$

ICER = $/QALY

This calculation results in the point estimate for the ICER. This value is described at the start of the commentary and also appears as a diamond on the ICER scatter plot.

There is no universally accepted value for the ICER but, in rough terms, an ICER greater than $60,000 to $100,000 per QALY gained would likely be considered unfavourable. It is important also to recognize that an acceptable ICER may or may not be affordable, depending on its overall budget impact. This final assessment of affordability is driven by the size of the patient population that is likely to make use of the new medication.

ICER Scatter Plot: In a clinical study, the point estimate of efficacy would not be very meaningful without its confidence interval. Likewise, the point estimate of the ICER must be evaluated in the context of the uncertainty of this estimate. There are a large number of assumptions that make up the economic model that produces the point estimate for the ICER. A change in any of these assumptions can change the ICER. Through probabilistic sensitivity analysis, the economist is able to sample from the range of likely values for the factors that may influence the ICER. The ICER scatter plot explores the dispersion in incremental cost per QALY estimates. The result is a range of ICER estimates that, when plotted, produce the cloud of points seen in the scatter plot. The spread of this cloud gives us an idea of the level of uncertainty of our point estimate of the ICER. A tight narrow cloud confined to one quadrant of the graph indicates a greater degree of certainty. A broad cloud that extends over multiple quadrants indicates a large degree of uncertainty with the point estimate of the ICER.

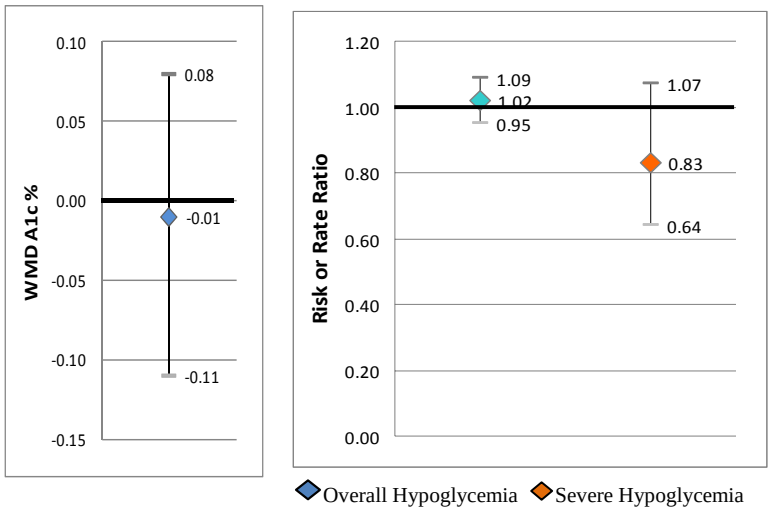
Cost-Effectiveness Plane: The ICER scatter plot is displayed on a cost-effectiveness plane. Each quadrant of the plane has a different interpretation. The north-west quadrant indicates less efficacy and higher cost and would be associated with a recommendation to reject the new medication. The south-east quadrant indicates higher efficacy and lower cost and would be associated with a recommendation to adopt the new medication.The south-west quadrant is associated with lower efficacy but lower cost. In many cases, any lower efficacy would be unacceptable, but there may be circumstances where a health system may be willing to accept a new mediation that is slightly less effective but substantially lower in cost. Most new medications fall in the upper right north-west quadrant where the new medication is associated with greater efficacy, but greater cost. The decision now becomes one of value: What are we willing to pay to achieve this greater efficacy?

Willingness to Pay/Cost-Effectiveness Acceptability: The final chart on the dashboard deals with the willingness to pay. If we knew how much our health system was willing to pay on a cost per QALY basis, we could evaluate our new medication against this benchmark. This benchmark has not been defined in Canada, but the values of $50,000 per QALY and $100,000 per QALY may be helpful guideposts. The data collected in the scatter plot can now be used to determine how many (or what percentage) of our estimates of the ICER fall under our willingness-to-pay threshold ($50,000/QALY or $100,000/QALY). Because of the uncertainty of the clinical benefit regarding some of the insulin analogues (i.e., non-significant difference in A1C), there is a plateau in the willingness-to-pay curve. On our scatter plot, some of the points fall in the upper-left north-west quadrant where there is less efficacy and higher cost. If the analogues are not more efficacious, then they will not be cost-effective regardless of a decision makers' willingness to pay for a QALY gained. This is shown by the modest increase in the probability of cost-effectiveness at the infinite willingness-to-pay threshold compared with the $100,000/QALY threshold.

Each insulin analogue economic dashboard also includes a brief commentary highlighting the major features of the economic analysis. Understanding these dashboards will help detailers and practitioners comprehend some of the rationale that has been incorporated into decisions around coverage of these agents.

Economic Dashboard 1: Insulin Lispro Versus Regular Human Insulin, Type 1 Diabetes

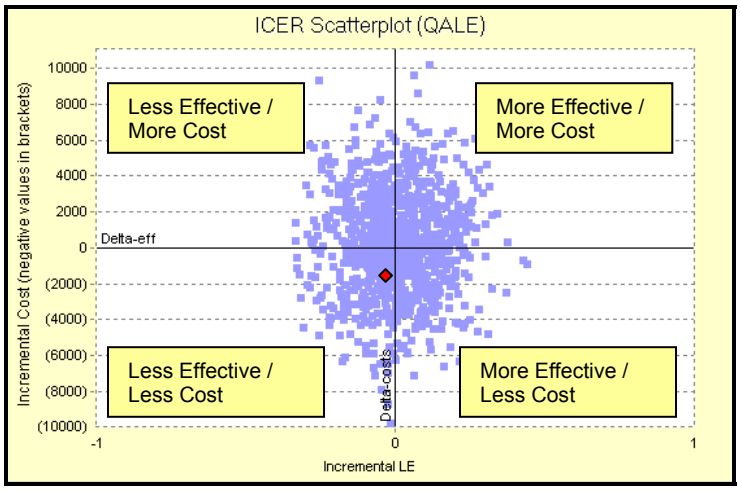
Efficacy Background



A1C=glycolsylated hemoglobin; WMD=weighted mean difference

Benefit: Based on a very small non-significant decrease in A1C, the model predicts an expected incremental benefit of 0.006 QALY or two days of perfect health. Contributing to the benefit are delays in major diabetes complications (end stage renal disease, cardiac events, blindness) of between four and 11 days.

Cost: Treatment costs are $570 higher for insulin lispro than regular human insulin. Reduced management costs do not fully offset increased treatment costs for insulin lispro; direct costs are $182 higher over the lifetime of the patient, compared with regular human insulin.



ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

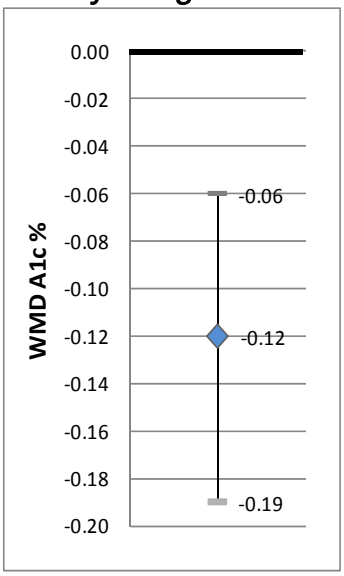
Table D1: Cost-Effectiveness Acceptability Summary

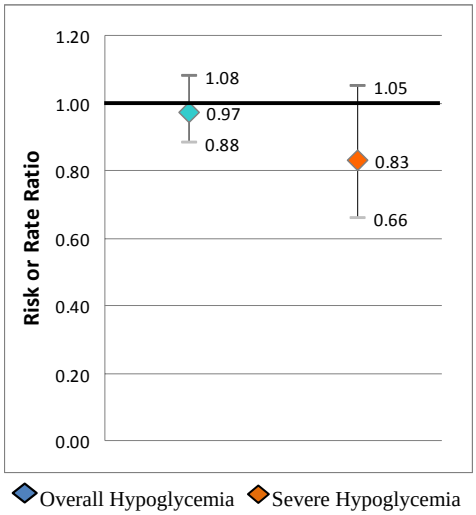
Willingness to Pay (Cost per QALY)	Probability of Cost-Effectiveness Relative to Human Insulin
$0	~ 48%
$50,000	51.20%
$100,000	~ 52%
∞	~ 52%

Commentary:
The base case (see ◆ in the ICER scatterplot) produces an incremental cost per QALY gained of $28,996. The ICER scatterplot reflects considerable uncertainty with almost equal dispersion in all four quadrants. There is a 51.2% probability that insulin lispro is cost-effective relative to regular human insulin at a willingness-to-pay threshold of $50,000/QALY gained. The cost-effectiveness acceptability curve (summarized in Table D1) is relatively flat and plateaus at approximately 52%. Therefore, there is ~48% chance insulin lispro is not cost-effective regardless what a decision maker is willing to pay for a QALY gained. In the univariate sensitivity analysis, when no difference in A1C is assumed, the incremental cost per QALY is estimated to be $673,041. Given that the A1C difference is not statistically significant, it is reasonable to consider this estimate. Consequently, marginal clinical benefit produces a level of uncertainty that limits any firm conclusions.

Economic Dashboard 2: Insulin Aspart Versus Regular Human Insulin, Type 1 Diabetes

Efficacy Background

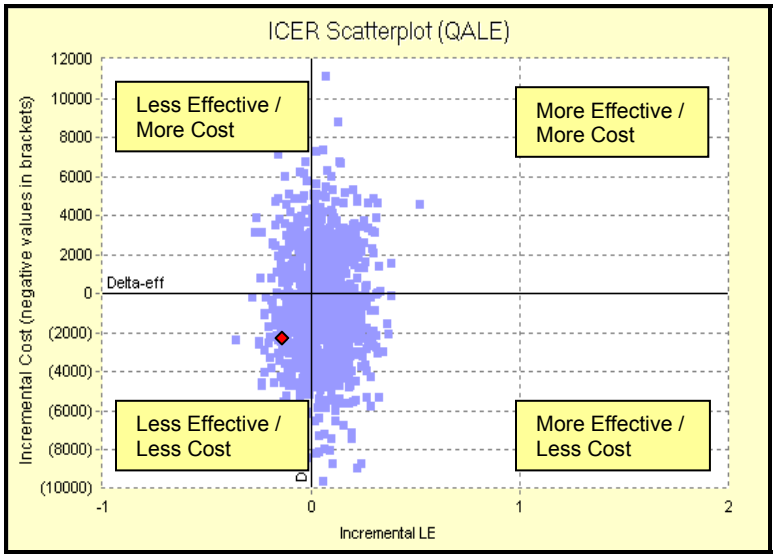




A1C=glycolsylated hemoglobin; WMD=weighted mean difference

Benefit: Based on a small decrease in A1C, the model predicts an expected incremental benefit of 0.055 QALYs or 20 days of perfect health. Contributing to the benefit are delays in major diabetes complications (end stage renal disease, cardiac events, blindness) of between 88 and 117 days.

Cost: Treatment costs are $489 dollars higher for insulin aspart than for regular human insulin. Reduced management costs offset the increased treatment costs, resulting in a net cost savings of $620 over the lifetime of the patient, compared with regular human insulin.



ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

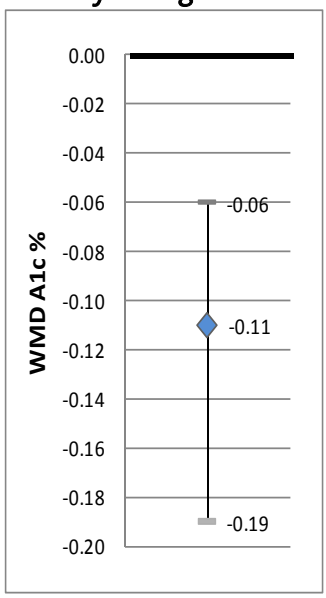
Table D2: Cost-Effectiveness Acceptability Summary

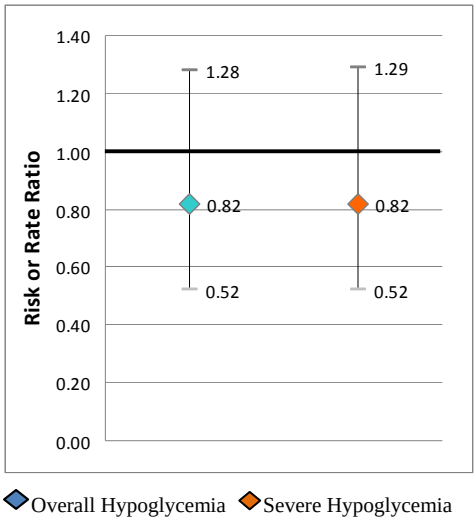
Willingness to Pay (Cost per QALY)	Probability of Cost-Effectiveness Relative to Human Insulin
$0	60%
$50,000	68.80%
$100,000	69.40%
∞	~ 70%

Commentary:
The base case (see ◆ in the ICER scatterplot) reflects a modest incremental benefit and reduced cost for insulin aspart. In fact, we have ~60% probability that insulin aspart is cost-effective, relative to human insulin, if a decision maker is willing to pay $0 for a QALY gained (i.e., only when insulin aspart saves money). However, there are a substantial number of points in all quadrants of the ICER scatterplot which clouds our decision. The relatively modest incremental benefits do not lend themselves to robust economic conclusions. The cost-effectiveness acceptability curve is relatively flat, with modest gains in the probability that insulin analogues are cost-effective as a decision maker's willingness to pay increases from $50,000 to $100,000 per QALY gained. There is about a 30% chance that insulin aspart is not cost-effective, regardless of what a decision maker is willing to pay for a QALY gained.

Economic Dashboard 3: Insulin Glargine Versus NPH Insulin, Type 1 Diabetes

Efficacy Background

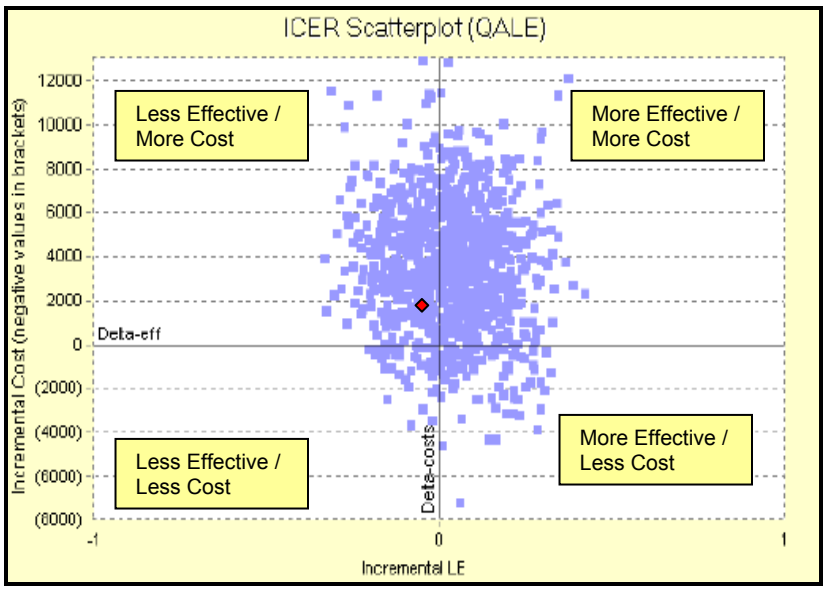




A1C=glycolsylated hemoglobin; WMD=weighted mean difference

Benefit: Based on a small statistically significant decrease in A1C, the model predicts an expected incremental benefit of 0.061 QALY or approximately 22 days of perfect health. Contributing to the benefit are delays in major diabetes complications (end stage renal disease, cardiac events, blindness) of between 62 and 113 days.

Cost: Treatment costs are $4,248 higher for insulin glargine than NPH insulin. Reduced management costs do not fully offset increased treatment costs; overall total direct costs are $3,423 higher over the lifetime of the patient for insulin glargine compared with NPH insulin.



ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

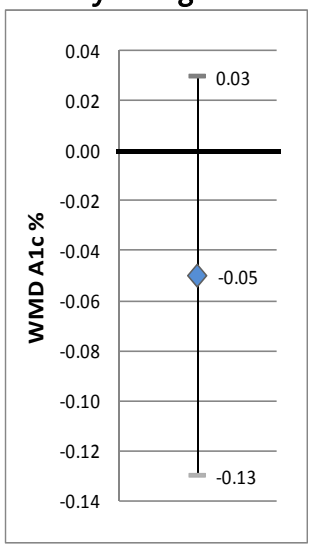
Commentary:
The base case (see ◆ in the ICER scatterplot) produces an incremental cost per QALY gained of $87,932. This is driven by a small but statistically significant difference in A1C. Elimination of this benefit in the univariate sensitivity analysis raises the incremental cost per QALY to $916,401. The majority of points lie above the x-axis, indicating a high probability that insulin glargine is more costly than NPH insulin. The cost-effectiveness acceptability curve plateaus at ~53%. Therefore, there is a 47% probability that insulin glargine will not be cost-effective relative to NPH insulin, regardless of what a decision maker is willing to pay for a QALY gained. There is a reasonable probability that insulin glargine may be less effective and more costly than NPH insulin (see points in upper-left/NW quadrant). Thus, it is likely that insulin glargine is associated with an incremental cost, and it is unclear whether this cost represents good value for the money.

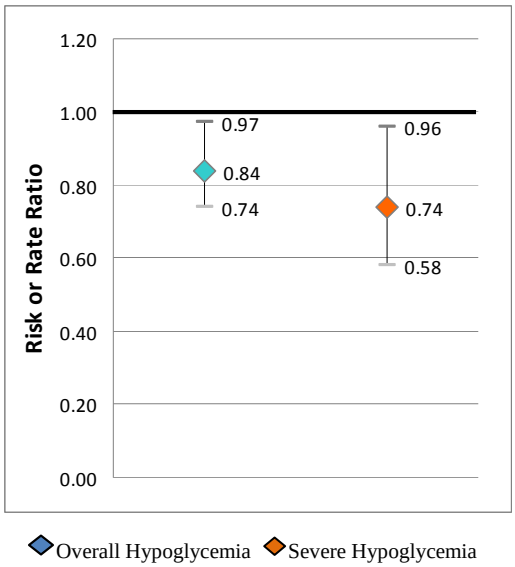
Table D3: Cost-Effectiveness Acceptability Summary

Willingness to Pay (Cost per QALY)	Probability of Cost-Effectiveness Relative to Human Insulin
$0	~ 13%
$50,000	42.5%
$100,000	51.7%
∞	~ 53%

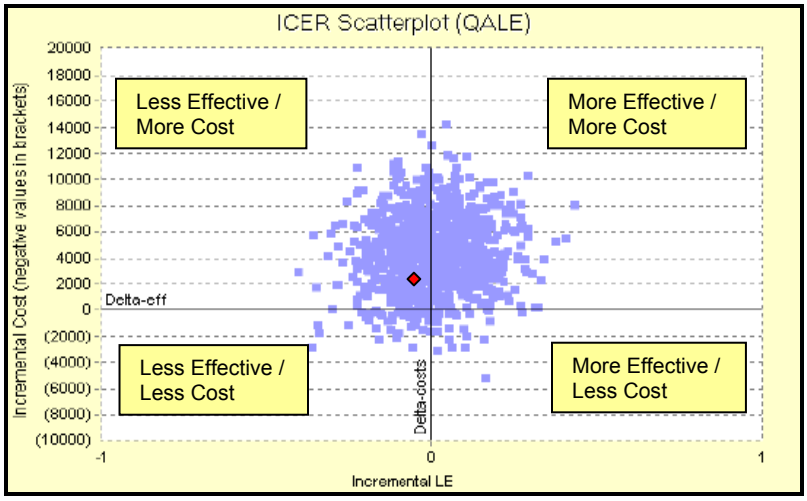
Economic Dashboard 4: Insulin Detemir Versus NPH Insulin, Type 1 Diabetes

Efficacy Background





A1C=glycolsylated hemoglobin; WMD=weighted mean difference



ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

Table D4: Cost-Effectiveness Acceptability Summary	
Willingness to Pay (Cost per QALY)	Probability of Cost-Effectiveness Relative to Human Insulin
$0	~ 4%
$50,000	29.2%
$100,000	40.5%
∞	~ 41%

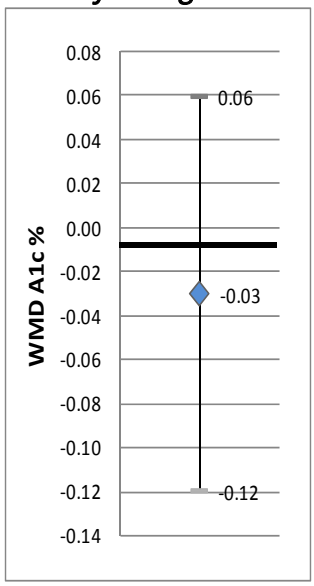
Benefit: Based on a small statistically non-significant decrease in A1C, the model predicts an expected incremental benefit of 0.011 QALY or approximately four days of perfect health. Contributing to the benefit are delays in major diabetes complications (end stage renal disease, cardiac events, blindness) of between 22 and 51 days.

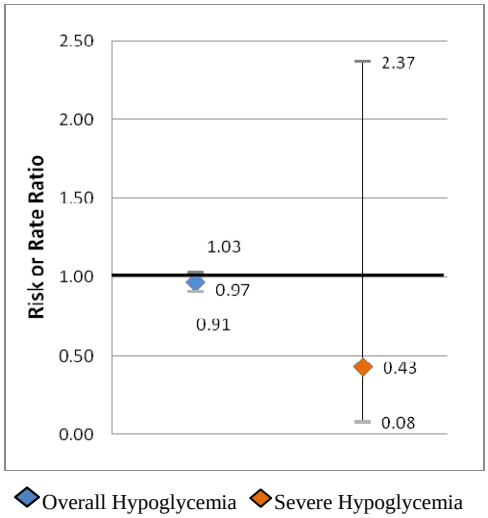
Cost: Treatment costs are $4,874 higher for insulin detemir than NPH insulin. Reduced management costs do not fully offset increased treatment costs; overall total direct costs are $4,344 for insulin detemir over the lifetime of the patient, compared with NPH insulin.

Commentary:
The base case (see ◆ in the ICER scatterplot) produces an incremental cost per QALY gained of $387,729. It is clear that insulin detemir is more costly than NPH. Some of this cost is recovered by a reduction in the cost of managing hypoglycemica. However, A1C is the main driver of efficacy outcomes in the analysis and is not significantly different. Consequently, this small benefit, in combination with high incremental costs, yields a high ICER that may not be considered economically attractive. The cost-effectiveness acceptability curve plateaus at ~40%, indicating that it is likely that insulin detemir is not cost-effective, regardless of how much a decision maker is willing to pay for a QALY gained. Overall, it seems likely that insulin detemir is not cost-effective relative to NPH insulin.

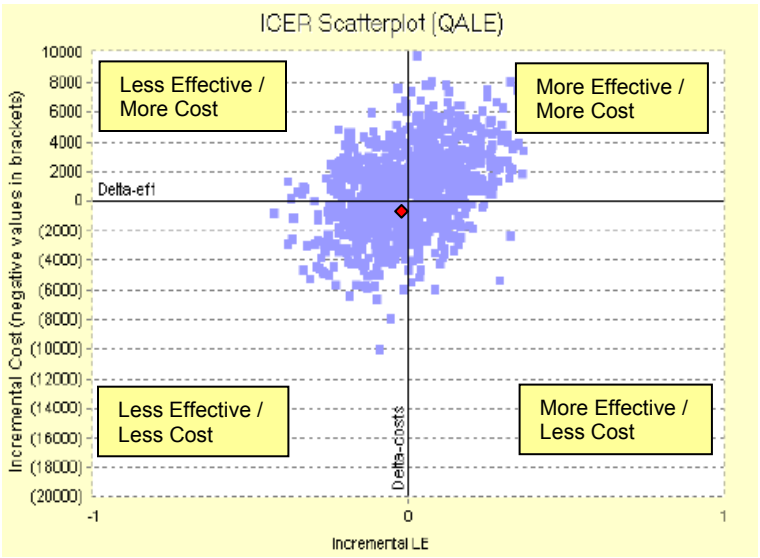
Economic Dashboard 5: Insulin Lispro Versus Regular Human Insulin, Type 2 Diabetes

Efficacy Background





A1C=glycolsylated hemoglobin; WMD=weighted mean difference



ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

Table D5: Cost-Effectiveness Acceptability Summary

Willingness to Pay (Cost per QALY)	Probability of Cost-Effectiveness Relative to Human Insulin
$0	~ 40%
$50,000	46.3%
$100,000	49.4%
∞	~ 50%

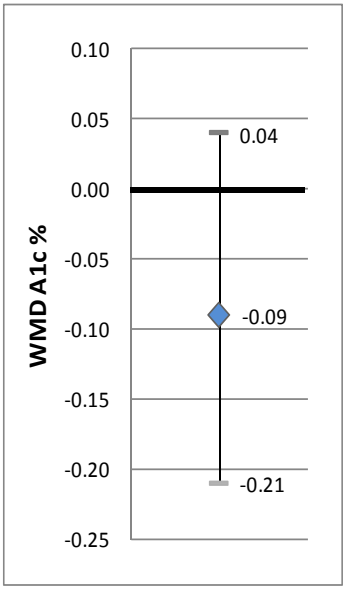
Benefit: Based on a small statistically non-significant decrease in A1C, the model predicts an expected incremental benefit of 0.006 QALY or two days of perfect health. Contributing to the benefit are delays in major diabetes complications (end stage renal disease, cardiac events, blindness) of between four and 11 days.

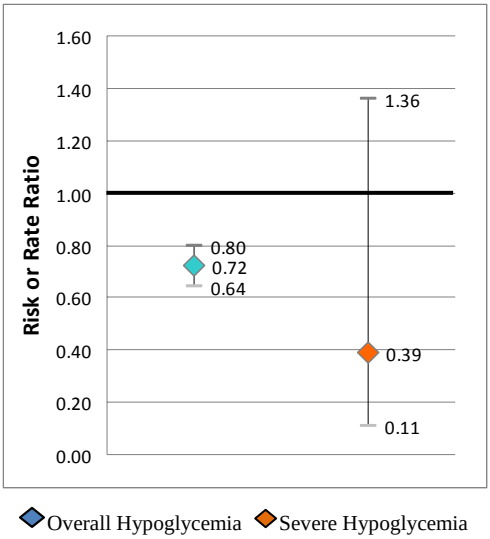
Cost: Treatment costs are $1,298 higher for insulin lispro than regular human insulin. Reduced costs in the management of complications do not fully offset the increased treatment costs; overall total direct costs are $784 higher for insulin lispro over the lifetime of the patient, relative to regular human insulin.

Commentary:
The base case (see ◆ in the ICER scatterplot) produces an incremental cost per QALY gained of $130,865. This point estimate reflects the limited clinical benefit shown in the meta-analysis with all three key outcome measures failing to show statistical significance. The cost-effectiveness acceptability curve is relatively flat and plateaus at ~50%. Therefore, there is a 50% probability that insulin lispro will not be cost effective relative to human insulin regardless of how much a decision maker is willing to pay for a QALY gained. The high degree of uncertainly in both clinical and economic outcomes makes it difficult to draw firm conclusions on the relative merit of insulin lispro over human insulin in patients with type 2 diabetes.

Economic Dashboard 6: Insulin Aspart Versus Regular Human Insulin, Type 2 Diabetes

Efficacy Background

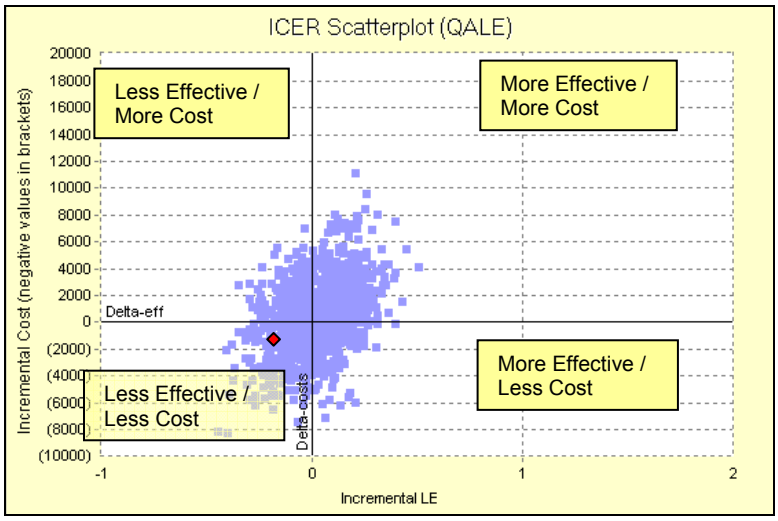




A1C=glycolsylated hemoglobin; WMD=weighted mean difference

Benefit: Based on a small statistically non-significant decrease in A1C, the model predicts an expected incremental benefit of 0.015 QALY or five days of perfect health. Contributing to the benefit are delays in major diabetes complications (end stage renal disease, cardiac events, blindness) of between 11 and 29 days.

Cost: Treatment costs are $1,181 higher for insulin aspart than regular human insulin. Reduced costs in the management of diabetes complications do not fully offset increased treatment costs; overall total direct costs are $333 higher for insulin aspart over the lifetime of the patient, relative to regular human insulin.



ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

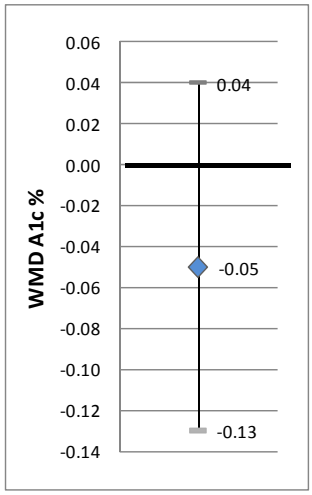
Table D6: Cost-Effectiveness Acceptability Summary

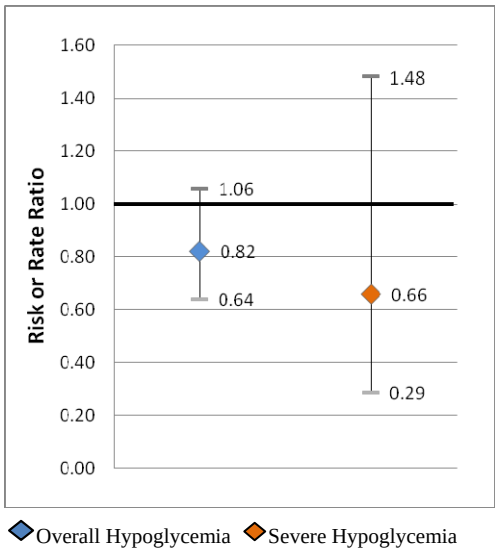
Willingness to Pay (Cost per QALY)	Probability of Cost Effectiveness Relative to Human Insulin
$0	~ 45%
$50,000	52.3%
$100,000	~ 53%
∞	~ 53%

Commentary:
The base case (see ◆ in the ICER scatterplot) produces an incremental cost per QALY gained of $22,448. There is a fair degree of uncertainty in this estimate and there is only a 52.3% probability that insulin aspart is cost-effective relative to human insulin at a willingness to pay threshold of $50,000 per QALY gained. Furthermore, the cost-effectiveness acceptability curve is relatively flat and plateaus at 53%. Therefore, there is ~47% chance that insulin aspart is not cost-effective, regardless of how much a decision maker is willing to pay for a QALY gained. Given that there is a statistically non-significant decrease in A1C, this is not a surprising conclusion. The univariate sensitivity analysis also explores the idea that there may be no difference between insulin aspart and human insulin in A1C and projects an incremental cost per QALY gained of $534,584. It is reasonable to consider this value given the lack of statistical significance in A1C.

Economic Dashboard 7: Insulin Glargine Versus NPH Insulin, Type 2 Diabetes

Efficacy Background

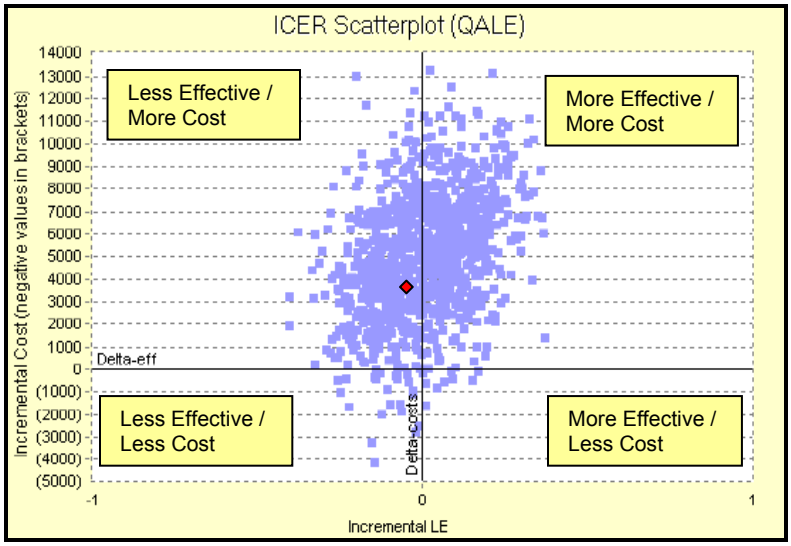




A1C=glycolsylated hemoglobin; WMD=weighted mean difference

Benefit: Based on a small statistically non-significant decrease in A1C, the model predicts an expected incremental benefit of 0.008 QALY or approximately three days of perfect health. Contributing to the benefit are delays in major diabetes complications (end stage renal disease, cardiac events, blindness) of between four and 11 days.

Cost: Treatment costs are $5,335 higher for insulin glargine than NPH insulin. Reduced costs in the management of complications do not offset increased treatment costs; overall total direct costs are $4,945 higher for insulin glargine over the lifetime of the patient, relative to insulin NPH.



ICER=incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

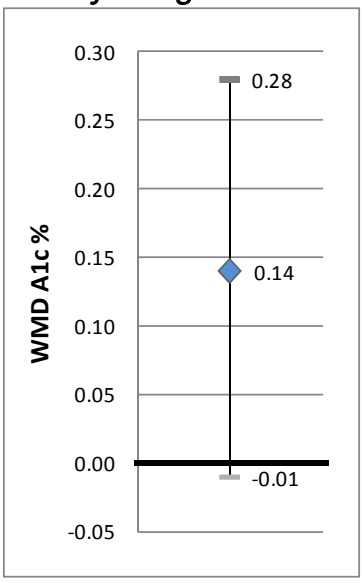
Table D7: Cost-Effectiveness Acceptability Summary

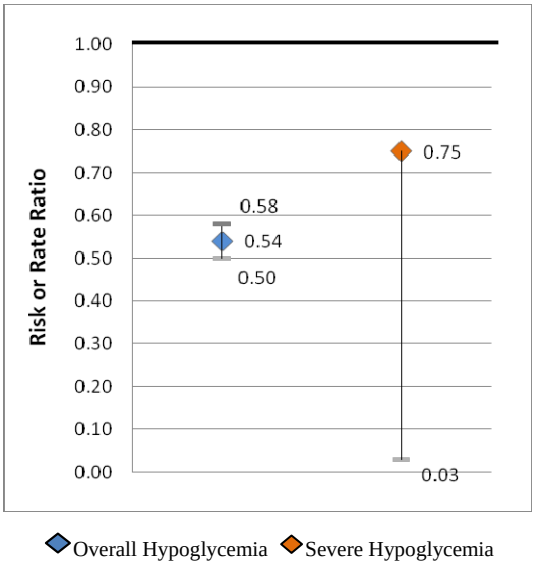
Willingness to Pay (Cost per QALY)	Probability of Cost-Effectiveness Relative to Human Insulin
$0	~ 4%
$50,000	25.1%
$100,000	~ 39.3%
∞	~ 40%

Commentary:
The base case (see ◆ in the ICER scatterplot) produces an incremental cost per QALY gained of $642,993. The very small (and statistically non-significant) difference in A1C produces a very small incremental QALY. This small benefit, in combination with the high incremental cost, resulted in a high ICER that is not considered economically attractive. Furthermore, the cost–effectiveness acceptability curve plateaus at 40%, indicating that there is a 60% chance that insulin glargine is not cost-effective relative to NPH, regardless of how much a decision maker is willing to pay for a QALY gained. Given that three statistically non-significant outcomes are propagated through the model, this conclusion seems reasonable. The univariate sensitivity analyses yielded an incremental cost of $1,577,457 per QALY gained if zero difference in A1C is assumed. Consequently, it seems very unlikely that insulin glargine is cost-effective relative to NPH insulin, in patients with type 2 diabetes.

Economic Dashboard 8: Insulin Detemir Versus NPH Insulin, Type 2 Diabetes

Efficacy Background

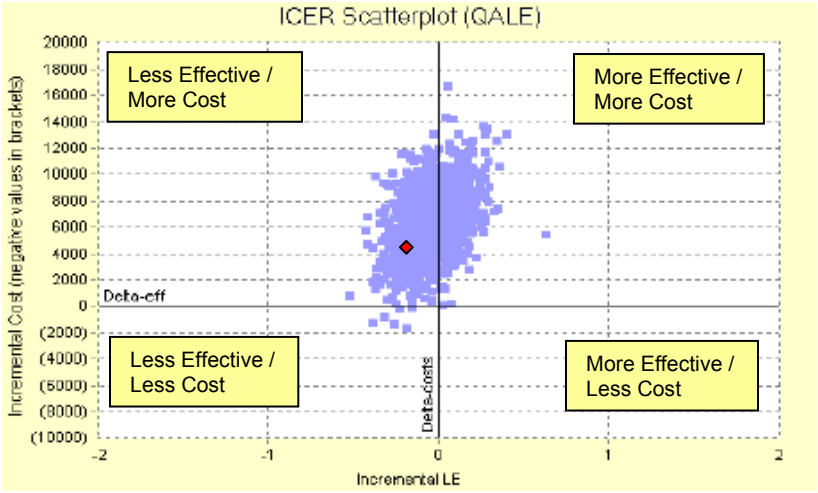




A1C=glycolsylated hemoglobin; WMD=weighted mean difference

Benefit: The point estimate for A1C actually suggests that NPH insulin may be better than insulin detemir. Consequently, this results in NPH insulin dominating insulin detemir in the base-case, cost-effectiveness analysis. This suggests that insulin detemir may be less effective and more costly than NPH insulin.

Cost: Treatment costs are $6,368 higher for insulin detemir than NPH insulin. The model projects an increase in management costs for insulin detemir and a corresponding increase in total costs of $6,521 over the lifetime of the patient, relative to NPH insulin.



ICER-incremental cost-effectiveness ratio; LE=life expectancy; QALE=quality-adjusted life expectancy

Table D8: Cost-Effectiveness Acceptability Summary

Willingness to Pay (Cost per QALY)	Probability of Cost Effectiveness Relative to Human Insulin
$0	~ 0%
$50,000	10.8%
$100,000	22.6%
∞	~ 23%

Commentary:
The base case (see ◆ in the ICER scatterplot) indicates that insulin detemir is dominated by NPH insulin (less effective and more costly). This is driven by an A1C that trends towards greater benefit with NPH insulin. There is a small probability that insulin detemir is cost-effective at widely cited cost-effectiveness thresholds. The benefits of lower hypoglycemia are not sufficient to compensate for the amount of complications that result from a higher A1C with insulin detemir. Results suggest that insulin detemir should probably not be adopted over NPH insulin.

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APPENDIX 1: COMPARISON OF DIABETES GUIDELINES FROM CANADIAN DIABETES ASSOCIATION (CDA)

American Diabetes Association (ADA) and National Institute for Health and Clinical Excellence (NICE)

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Measure	2008 CDA Guidelines	ADA Guidelines	NICE Guidelines
Diagnostic Criteria	• Symptoms of diabetes (e.g., polyuria, polydipsia, unexplained weight loss) plus random blood glucose concentration ≥11.1 mmol/L or • Fasting (no caloric intake for at least 8 hours) plasma glucose ≥7.0 mmol/L or • Two-hour plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test (75 gram glucose solution)	• Symptoms of hyperglycemia and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss. • FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h. • 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.	• Diabetes should be confirmed by a single diagnostic laboratory glucose measurement in the presence of classical symptoms, or by a further laboratory glucose measurement. The diagnosis may be supported by a raised HbA1c. • Where diabetes is diagnosed, but type 2 diabetes suspected, the diagnosis of type 1 diabetes should be considered if: - ketonuria is detected, or weight loss is marked, or the person does not have features of the metabolic syndrome or other contributing illness.
Treatment Goals	• A1c ≤ 7% • Fasting plasma glucose (FPG) 4 – 7mmol/L • 2-hour post-prandial plasma glucose 5 – 10 mmol/L (5 – 8 if A1c targets not being met)	• A1c ≤ 7% • Preprandial capillary plasma glucose 70–130 mg/dl (3.9–7.2 mmol/L) • Peak postprandial capillary plasma glucose < 180 mg/dl (10.0 mmol/l)	• Adults with type 1 diabetes should be advised that maintaining a DCCT-harmonised HbA1c below 7.5% is likely to minimise their risk of developing diabetic eye, kidney or nerve damage in the longer term. • Pre-prandial blood glucose level of 4.0–7.0 mmol/litre • Post-prandial blood glucose level of less than 9.0 mmol/litre.
Views of RAIA	• Insulin aspart or insulin lispro, in combination with adequate basal insulin, should be considered over regular insulin to improve A1C while minimizing the occurrence of hypoglycemia and to achieve postprandial glucose targets. • Insulin lispro or insulin aspart should be used when CSII is used in adults s with type 1 diabetes	• No Specific Statements	Use rapid-acting insulin analogues rather than unmodified insulin: • where nocturnal or late inter-prandial hypoglycaemia is a problem • to avoid need for snacks, while maintaining equivalent blood glucose control.

Measure	CDA Guidelines	ADA Guidelines	NICE Guidelines
Views of LAIA	• A long-acting insulin analogue (detemir or glargine) may be considered as an alternative to NPH as the basal insulin to reduce the risk of hypoglycemia.including nocturnal hypoglycemia. • When basal insulin is added to antihyperglycemic agents, long-acting analogues (insulin detemir or insulin glargine) may be considered instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia.	• No Specific Statements	Use long-acting insulin analogues (insulin glargine) when: • nocturnal hypoglycaemia is a problem on isophane (NPH) insulin • morning hyperglycaemia on isophane (NPH) insulin results in difficult day-time blood glucose control • rapid-acting insulin analogues are used for meal-time blood glucose control.
Monitoring of Glycemic Control	• A1c approximately every 3 months. Every 6 months in stabilized adults at target • Self Monitoring Blood Glucose (SMBG) at least 3x/day for type 1 • SMBG at least 1x/day for most type 2 on insulin at variable times.	• A1C test at least 2x/year in patients who are meeting treatment goals and every 3 months if not meeting goals or if therapy changing • SMBG at least 3x/day in patients on MDI or CSII; for all others SMBG may be useful in achieving glycemic goals	• A1c every 2–6 months • Frequency of SMBG depends on: characteristics of an individuas blood glucose contol; insulin treatment regimen; personal preference in using the result to achieve the desired lifestyle.
Lipid Targets	• Those considered high risk: LDL-C <2mmol/L with a statin; TC:HDL-C <4mmol/L • If serum TG >10mmol/L a fibrate should be prescribed to reduce risk of pancreatitis	•Diabetics without CVD LDL-C <100 mg/dl (2.6 mmol/l) •Diabetics with CVD LDL-C <70 mg/dl (1.8 mmol/l) using high-dose statins is an option	• No set target, for all high and moderate risk patients, start statin
Blood Pressure Targets	• Target for all diabetic patients <130/80	• Target for all diabetic patients <130/80	• Intervene if MB >130/80 mmHg if evidence of microvascular disease, or >135/85 mmHg in patients without

APPENDIX 2: RXFILES CHARTS

Insulin Management: Evidence, Tips & Pearls

Approach to Management of Type 2 Diabetes (T2DM) and Oral Hypoglycemia Agents (OHA) — Comparison Chart

Insulin Comparison Chart

Diabetes — Glucose Control: Landmark Outcome Trials — Summary

Note: These reference charts are included with the permission of RxFiles

Insulin Management: Evidence, Tips & Pearls [1,5]

M Jin, L Regier, B Jensen - © www.RxFiles.ca - Oct08

Indications for the Use of Insulin[1]

- Type 1 Diabetes Mellitus (T1DM); gestational diabetes not controlled with diet & activity; Type 2 Diabetes Mellitus (T2DM) not controlled with meal choices, activity & use of oral agents; T2DM with severe infection, major surgery, oral hypoglycemics contraindications, lactating, or requiring corticosteroid; ketoacidosis or hyperosmolar nonketotic syndrome; severe hyperglycemia where rapid glucose reduction/control is desired. {Also: Low rate of drug interactions.}

{Note: Recent Chinese trial: early intensive insulin till normal glycemia achieved x2 weeks induced remission in new T2DM.[2]; n=382; evaluated at 1year; remission in 50% CSII vs 27% oral hypoglycemics. Preliminary!}

Administering Insulin

- Abdomen (not within a 5cm radius of the umbilicus), upper arms, , anterior/lateral thigh, buttocks.
- Alcohol is no longer recommended for topical preparation of the skin; soap & H_2O adequate.
- Give insulin injections at a 90° angle subcutaneously to ensure adequate absorption.
- DO NOT pinch skin {Pinching of the skin prior to injection is only necessary when using a 12 mm pen/syringe needles, if the individual is thin and/or in children. (Most needles 6-10mm)}
- People with a BMI > 27 kg/m^2 may use the 12mm length needle (Becton Dickson recommendation)
- If leaking is occurring at the injection site, check that the client is:
  - Injecting at a 90° angle & using the appropriate needle length
  - Leaving the needle under the skin for 5 seconds after injecting

Variables That Can Affect Insulin Action

1. Mixing insulin together
   - a. Regular (short acting) insulin can be mixed with NPH with no effect on insulin action (draw up short acting first to avoid contamination with NPH e.g draw *clear before cloudy*)
   - b. Lispro *Humalog* binds rapidly with NPH & must be injected immediately after mixing
   - c. Aspart *NovoRapid* may be mixed with NPH & must be injected immediately e-CPS
   - d. Glargine *Lantus*: mixing with any other insulin not recommended {but some studies report that mixing with bolus insulin for BID administration in T1DM Pediatric suitable[3,4]}.
   - e. Detemir *Levemir*: not to be mixed with any other insulin (potential for crystallization)

Best not to mix rapid acting IAs, & not necessary with most devices.

2. Insulin dosage and absorption variance factors
   - a. Larger doses of insulin may have slightly longer duration of action. For lispro & aspart an increase in dose has no effect on the duration of action.
   - b. Daily absorption can vary up to 30% using same site at the same time
   - c. Speed/consistency of absorption: Fast to slow: abdomen → arm → thigh → buttock
   - d. Absorption ↑ by exercise, heat, massage, injection into muscle
   - e. Absorption ↓ by cold, lipohypertrophy, decreased blood flow (avoid areas of scar tissue)
   - f. Avoid injecting into SC tissue adjacent to the main muscles being used in exercise
3. Injection site: Systematically rotate injection site to prevent lipodystrophy. The abdomen is often the preferred site; most consistent & fast rate of absorption
4. Other: improper storage (too hot or too cold); proper re-suspension of suspension insulins important! (Store insulin in a cold place 2 to 8°C, preferably a fridge, but not a freezer. Avoid direct sunlight.)

Insulin Regimens - (see RxFiles Insulin Comparison Chart above)

Canadian Guidelines - Notes Regarding Insulins [5]

- CDA Guidelines 2008 & some specialist reviewers advocate for a more prominent role for the newer insulin analogues, if economic and drug plan coverage issues are not major considerations. Primary advantage valued is less hypoglycemia in some patients. (A1C & weight endpoints lack meaningful differences.) [5,6,7,8]
- Trend in current clinical thinking is to pursue tighter BG control, both basal & postprandial. Newer insulin analogues theoretically may allow for more precise tailoring of regimen if patients willing to be highly aggressive in carbohydrate counting, BG testing & titrating of insulin. Limited evidence together with varying appreciation of economic analysis result in conflicting viewpoints in this area.

References available online at www.RxFiles.ca

Insulin Analogues (IA): Systematic Reviews (Tables 1 & 2)

Insulin Analogue Systematic Reviews (SR): 1) Cochrane SAIA[6]; 2) Cochrane LAIA[7]; 3) COMPUS – IA[8]. {Many studies; however none assess long-term complications or mortality & most of low-quality.} Related LINKs[9].

Table 1: IAs: Guide to Advantages/Disadvantages of Insulins [6,7,8,10]

	Insulins	Advantages	Disadvantages
Bolus	**HI** Short Acting Human Regular Humulin R; Novolin ge Toronto	• more long-term & safety experience • low cost (10ml/mo x1yr: $430 vs 550_{ILis}$-590_{IAsp}$) • pregnancy-extensive safety experience	• injecting 20-30min pre-meal impractical (short acting but not rapid acting)
Bolus	**RAIAs** Rapid Acting **Lispro (ILis)** Humalog **Aspart (IAsp)** NovoRapid -rapid onset may ⇨ better PPG control if pre-meal (significance uncertain)	• inject & eat convenience (may give just before or within 15min of starting meals); valuable when dietary/activity patterns unpredictable, e.g. adolescents • may have less hypoglycemia • ↑ patient satisfaction in T1DM • safe in pregnancy (less extensive experience)	• moderately high cost utility in T2DM (but reasonable cost utility in T1DM)[8] • lack evidence for any clinical outcome or A1C advantage over HI {T1DM studies: A1C difference was < -0.2%} • limited long-term & safety evidence
Basal	**NPH** Intermediate Acting Human NPH Humulin N, Novolin ge NPH	• long-term safety & outcome evidence • low cost (10ml/mo x1yr: $430 vs 830_{IGar}$-1040_{IDet}$) • may avoid need for lunchtime bolus injection (↑convenience) e.g. in children	• NPH vial must be mixed before withdrawing dose affects absorption • intermediate action & peak at 4-12hrs predispose to hypoglycemia
Basal	**LAIAs** Long Acting **Detemir (IDet)** (daily or BID) Levemir **Glargine (IGlar)** (daily) Lantus	• ↓ hypoglycemia, nocturnal subjective, not blinded (T2DM: Estimated NNT= ≥6 / 6-12 mo[7,8]) • slight ↓ in weight (<1kg) vs NPH (in T2DM, only detemir had ↓ weight*) • OD dosing; IDet: some will require BID	• very high cost utility relative to NPH • no difference in severe hypoglycemia • limited long-term & safety evidence • ↑# of injections if not mixed with bolus • ↑caution in pregnancy (IDet may be an option)[5]
-	**Premixed**	• convenience;↓A1C more than HS only T2DM	• cost; limited flexibility with fixed dose

Insulins: Selection Considerations (Evidence & Economic)* Systematic Reviews 8,6,7

- **A1C differences of Insulin Analogues (IAs) compared to Regular & NPH:**
  - -Rapid Acting IA: range from -0.06% to -0.18% vs R; Long Acting IA: range from -0.11% to 0.28% vs NPH.
  - -There are no clinically significant differences in A1C control likely to impact clinical outcomes.[6,7,8]
- **T1DM – Bolus (rapid or short acting):**
  - Adults: Regular HI, Lispro or Aspart may be used. {ILis vs Reg: ↓ severe hypoglycemia (est. NNT=54/yr CI: 32-260)}
    - -Consider a Rapid Acting IA especially if meal flexibility and/or hypoglycemia concerns.
  - Adolescents: Lispro & Aspart offer convenience, flexibility & ↓hypoglycemia & preferred over regular HI.
- **T1DM – Basal (intermediate or long-acting):**
  - NPH preferred in COMPUS SR[8]; Detemir or Glargine are suitable if major hypoglycemia history or concern. {less hypoglycemia with IDet BID vs IGla OD[11]; but ↑ FG (7.7 vs 7.0) & ↑ serious adverse events (8.7% vs 6.9%) not Tx related?}
  - Preadolescent: a twice daily NPH regimen not requiring a lunch time injection may be useful in some.
- **T2DM – Bolus:** Regular HI preferred in COMPUS SR[8]; Lispro or Aspart suitable if hypoglycemia history or concern.
- **T2DM – Basal:** NPH preferred in COMPUS SR[8]; Detemir or Glargine suitable if hypoglycemia history or concern. {IDet vs IGla[12]: similar A1C; but 55% of IDet required BID where wt gain advantage lost & 2x daily dose required; ↑ site rx's with IDet}
- **Pregnancy, Pre-existing T1DM / T2DM or Gestational:**
  - Most safety experience with HI; RAIAs also safe & allow for tight PPG control, but no evidence of superiority.
  - Detemir & Glargine do not have sufficient safety data to recommend in pregnancy or preconception state.

*Evidence for insulin analogues is often limited (small, short-term trials) and benefits modest; anecdotal experience is favorable. The COMPUS systematic & economic reviews rigorously assessed benefits, risks and incremental cost.[8]

Weight change with LAIA: (T1DM: 0.36-0.71kg less than NPH); (T2DM: IDet: 0.96kg less than NPH; IGlar: no difference) [8] {There is question as to the clinical significance of the minor weight changes (<1kg here, or <5% in general).}

Hypoglycemia: Most pronounced ↓ risk for LAIA is on nocturnal hypoglycemia. {LAIA vs NPH: NNT ≥6 (CI range 4-33)}[7]

Cost Approx: Bolus: Regular $2–3/ml; Aspart $3-4/ml; Lispro $3-5/ml. Basal: NPH $2-3/ml; Glargine $6/ml; Detemir $8/ml.

{Cost estimate for converting 50% of patients to new insulin analogues ranges from $50-100million/yr Canada.[13] The COMPUS economic analysis modeled the overall impact of these costs & the potential benefits of lower A1C & hypoglycemia over the lifetime of the patient. Compared to regular insulin T2DM, the cost per Quality Adjusted Life Year (QALY) for RAIAs ranged from $22,448 - $130,865. The analysis comparing LAIAs with NPH insulin in T2DM was less favourable; for IGla the cost per QALY was $642,994 & for IDet the value was not calculated as it was less effective than NPH in terms of A1C.[14]}

MONITORING (BG, A1C, Ketones)

Blood Glucose (BG) Targets

- Preprandial: Optimal BG 4-7 mmol/L before meals
- Postprandial (PPG): BG 5-10 mmol/L 2hrs after meals (5-8 mmol/L if A1C target not being met)
  {Limited observational data suggests PPG as a potential risk factor for mortality [15]}
- Prevent extreme lows (<3.5 mmol/L) and high BG levels (>14mmol/L)
- Individualize with each person [16]: e.g. ambitious targets may be counterproductive in elderly (risk of hypoglycemia, etc.); for patient who has coronary artery disease (CAD), low BG can trigger atrial fibrillation therefore ambitious targets may not always be achievable/beneficial.[17]

Self Monitoring Blood Glucose (SMBG)[1,5]

- No gold standard of testing frequency has been firmly established.
  - Diet Only: may check occasional postprandial
  - OHA only: routine self monitoring not necessary in T2DM patients not on insulin & without hypoglycemia [18,19,20] {If done, twice a day at staggered times, e.g. pre- & post-prandial.}
  - OHA & bedtime insulin: testing once daily at variable times is recommended.[5]
  - OHA & insulin MDI: individualize
  - Insulin monotherapy: individualize eg. Tid, pre & post prandial

  ♦AC/PC meals, up to 7x/day or more in patients with intensive regimens
- Paired meal testing (AC & 2hr PC) helpful to match regimen to BG patterns; may stagger times:
  - Day 1: AC & PC breakfast; Day 2: AC &PC lunch; Day 3: AC & PC supper; Check HS somewhere.
  - This gives a good cross sectional representation of pattern of hyperglycemia, with less testing.
- Test more often: during pregnancy; illness; before driving to detect & treat hypoglycemia; when diet & activity changes; when adjusting insulin/pills; if hypoglycemic unawareness
- Rapid-acting insulin analogues, oral glitinides: e.g. repaglinide (Gluconorm®) – may be particularly important to check 2 hours postprandial to determine if the dose is accurate
- Testing at ~3:00am or overnight expected insulin peak time may be required to rule out nocturnal hypoglycemia

Variables Affecting Accuracy Of Self-Monitoring Blood Glucose (SMBG)

- Sample Size: too little blood on test strip may cause problems for some meters
- Test strips: if expired or exposed to extreme temperature or humidity.
- Clean finger needed (especially sensitive to sugar containing foods or drinks).
- Meter inaccuracy: if old, dirty, or exposed to extreme temperatures. Lab/meter comparison recommended (annually). A fasting lab/meter comparison should be done annually to check meter accuracy; acceptable reading could be within 15-20% higher or lower than the lab value.
- Hematocrit: most test strips make allowance for this (results vary from 4-30% for every 10% change in hematocrit)
  - Anemia can falsely ↑ & polycythemia can falsely ↓ the BG values obtained by meters
- Alternate site testing or misrepresentations of BG results (clients falsify the test results)

Glycated Hemoglobin (A1C): an indicator of overall glycemic control in the preceding 3 months

- A1c may be measured every 3 months in all clients taking insulin & every 6 months in people on nutrition therapy, oral antihyperglycemic agents (OHA) or during tx & lifestyle stability
- Accuracy affected by: anemia falsely ↑ if slow RBC turnover e.g iron deficiency; falsely ↓ if fast RBC turnover e.g. hemolysis; PRBC transfusion; Hemoglobinopathies; ESRD (depending on assay used)
- Target A1c for most: ≤ 7%. A1c targets should consider patient factors & intervention intensity. (Overly intensive regimens may cause harm in T2DM populations ACCORD; see Diabetes Trials chart)
- Blood Glucose & A1c relationship (derived from DCCT in T1DM) [21]
  - Mean BG (mmol/L) = [1.98 x A1C(%)] – 4.29. (E.g., A1c = 10, Mean BG= 19.8-4.29 = 15.5mmol/L)

⇨Estimated Average Glucose (eAG) is another new way to reflect A1c; reported as mmol/L [22]

- eAG (mmol/L) = 1.59 x A1C(%) – 2.59

A1c: 6% = eAG 7mmol/L
7% = eAG 8.5mmol/L
10% = eAG 13.3mmol/L

Urine Ketone Testing (Primarily in T1DM)

- Required during significant hyperglycemia periods to assess risk of potentially life-threatening ketoacidosis e.g., when pre-prandial BG >14$_{mmol/L}$, nausea, vomiting, abdominal pain, illness &/or if dehydration
- May test urine ketones during pregnancy to ensure mother & baby's nutritional needs are met (Blood ketone testing may be preferred over urine ketone testing, since assoc. with earlier detection of ketosis & response to tx.)

HYPOGLYCEMIA

- Clinically hypoglycemia is defined as a state that results in:
  - Biochemical low – e.g BG <3.5 or < 4 mmol/L (common definition in DM trials)
  - Autonomic (adrenergic) OR neuroglycopenic symptoms {better recognition if infrequent occurrence}

  {Symptoms may occur at euglycemic BG levels in chronic hyperglycemia; typically resolves with time.}
- Mild: autonomic symptoms: tremors, palpitations, sweating, excessive hunger; able to self-treat
- Moderate: autonomic & neuroglycopenic symptoms – headache, mood △, irritability, ↓ attentiveness, paresthesias, visual disturbances; may be able to self-treat
- Severe hypoglycemia = distinguished by unresponsiveness, unconsciousness, seizures or coma; unable to self-treat, requires assistance. (Some studies also use thresholds e.g. ≤2.8mmol/L)
- Nocturnal: night sweats, nightmares; patient may not be aware. (Subjectively defined in studies.)
- Causes - Iatrogenic: dose of insulin or sulfonylureas is too high; diabetes therapy too intensive; decreased renal function can result in increased frequency of hypoglycemia in those on insulin or sulfonylureas; increase in the level of activity; insufficient carbohydrates in diet; Drug Causes[23]: insulin, sulfonylureas (chlorpropamide & glyburide); alcohol delayed, beta-blockers, salicylate, chromium, marijuana {Tight glucose control in critically ill hospitalized patients offers no benefit but ↑↑ risk of hypoglycemia. JAMA 2008; 24}
- Other: develop meal & activity plan; a bedtime snack may be helpful in those at risk (if BG <7mmol/L)

Treatment For Mild To Moderate Hypoglycemia

- 15g of carbohydrate (glucose or sucrose tablets) should ↑ BG about 2.1 mmol/L in 20 min
  - {Other 15g examples: ¾ cup juice or regular soft drink, 3 teaspoonfuls table sugar or honey, 6 LifeSavers®. 3 sugar cubes, 9 jelly beans. (glucose/dextrose absorbed directly)}
- Children – 0.3g/kg (10g carbohydrate in child <5yrs or <20kg)
- Wait 15 minutes, retest BG and retreat with another 15g glucose/sucrose if BG < 4.0mmol/L
- After initial glucose treatment, another carbohydrate containing snack should be taken within 1 hour. If meal more than 1 hour away, a snack with 15g carbohydrate & protein source is also recommended.
- If on Acarbose - use glucose tablets, milk or honey; (sucrose will not be absorbed!!!)

Treatment For Severe Hypoglycemia Occurring Outside Hospital Setting*

- If conscious and able to take oral treatment:
  - Treat with 20g glucose in tablet form, then wait 15 minutes (if possible).
  - Retest BG & retreat with another 15g glucose if BG <4.0mmol/L. (Repeat till sustained >4$_{mmol/L}$)
- If unconscious / unable to swallow: (BG <2.8mmol/L associated with unconscious)
  - Administer glucagon (details below). {Kits available > $100; portable for emergencies}
  - Once the individual is conscious & able to take oral food, hospitalization is probably not necessary; however, cause should be determined so that recurrence can be avoided.
  - Glucose gel should NOT be used buccally since minimal absorption through mucosa. Glucose gel is slow to react (< 1mmol/L rise in 20 min) & must be swallowed.

Table 2: Glucagon Treatment Of Acute Hypoglycemia

- Converts stored glycogen in the liver to glucose. Glucagon is only helpful if liver glycogen is available. {Less effective if suffering from starvation, chronic hypoglycemia &/or adrenal insufficiency.}
- Adult: glucagon dose SC/IM 1mg (if IM, administer in the deltoid or anterior thigh)
  - BG may rise from 3 -12 mmol/L within 60 min
- Child: glucagon SC/IM 15-30mcg/kg [MAX 1mg/dose] {<5yrs: 0.25-0.5mg; 5-10yrs: 0.5-1mg; >10 yrs: 1mg}
  - {Also: mini-dosing for impeding hypoglycemia due to refusal to eat (20mcg/yr of age; Max 150mcg)}
- BG response is greater in T2DM than in T1DM. Glucagon side effects: may cause nausea & vomiting
- Following glucagon administration: turn patient on side to avoid aspiration; never leave alone.
- When individual becomes alert, usually 10-15 min after receiving glucagon IM/SC, he/she should be given a fast acting carbohydrate (e.g., glass of juice, or glucose/sucrose tablets) followed by a carb. snack such as crackers & cheese or a sandwich (to prevent recurrent hypoglycemia). Ongoing monitoring is essential!

* If access to hospital/medical care, IV dextrose will act rapidly (Dextrose 10 to 25 g (20 to 50 cc of D50W) should be given over 1 to 3 minutes. Repeat BG in 15-30minutes. (The pediatric dose of glucose for IV treatment is 0.5 to 1 g/kg). Follow with D5W IV.

INITIATING INSULIN

Type 2 DM (adult) on oral medications (see also RxFiles - Approach to Management of T2DM)

- Start low dose for safety, then titrate upward!!!
- 5-10 units of intermediate insulin e.g. NPH or 0.1-0.2 units/kg of total body weight (TBW) at hs; titrate by 2 units every 2-3days. {More cautious with initiation & titration in elderly & non-obese (e.g. start with 5 units)}
- Adding insulin to already established metformin may be very useful to ↓ insulin dose required; also may result in less weight gain & less hypoglycemia
- Secretagogues e.g. sulfonylureas useful with hs basal insulin; should be stopped if mealtime insulin given
- Caution/Avoid: TZD glitazone & insulin combinations; ↑ heart failure, weight gain & edema[25] (not approved).

Type 1 DM

- Adult: 0.1-0.5 units/kg of body weight. (Typical requirement 0.5 units/kg.) If newly diagnosed, but not acutely ill or ketotic – start with lower dose (e.g. 0.3 units/kg or 4 units ac meals and hs).
- Adolescent: start similar to adult; but expect eventual higher requirement e.g. ≤1 unit/kg (tight follow-up required)

SWITCHING INSULINS* {temporary ↑BG monitoring required}

Short-acting human insulin → Rapid Acting IA: may be transferred on a unit for unit basis
NPH OD → glargine OD: may use same total number of units/day
NPH BID → glargine or detemir OD: ↓ total daily dose to 80% of the NPH daily dose
NPH OD → detemir OD: may use up to the same total # of units/day (↑ in dose likely after switch; some may require BID)
Basal only hs → premixed given BID: use same or less total number of units/day (as ↑'d effect)[16]
*If hypoglycemia history or reason for switching, may be more conservative in initial dose chosen.

TIPS FOR INSULIN DOSE ADJUSTMENT

1. Fix the lows first & the highs later. Once the lows gone, rebound hyperglycemia often eliminated.
2. Adjust insulin by 5-10% per week, or 1 or 2 units at a time to prevent hypoglycemia.
3. Adjust one insulin at a time. Begin with the insulin that will correct the 1st problem BG of the day.
4. Overnight control is difficult & requires the right basal dose. {Goal: keep BG between 4-8mmol/L from bedtime to morning without causing a low & usually without requiring a bedtime snack.}
5. To assess for Somogyi (nocturnal hypoglycemia with rebound hyperglycemia in the morning) or overnight control, check BG at 0300 or 0400 not just once but a for a few nights, especially if experiencing unexplained morning highs. {Dawn phenomena also causes early AM rise but due to hormonal surge.}
6. Nightmares, restless sleep, headache on waking, wet pillow or sheets may be signs of sleeping through a low BG reaction. {One specialist uses BG from both 2AM & 5AM to assess.}
7. Postprandial targets are helpful when assessing the meal insulin. Assessing PPG control provides information to determine which insulin needs adjusting (the meal insulin or the basal insulin). The goal is to achieve PPG levels of 5-10mmol/L without lows between meals.
8. Sliding Scale Insulin: practice generally discouraged. Consider basal/bolus & supplemental regimen. {Supplemental insulin useful in addition to daily regimen (e.g. 1 unit bolus insulin for every 3mmol/L greater than 7 mmol/L; but will vary.)}

Activity/Exercise Principles:

Patient education important for success!!!

1. In general, insulin therapy does not require adjustment for periods of activity < 30 minutes.
2. If activity > 30 minutes, & the activity is spontaneous & not preplanned, supplemental CHO before and during the activity can be used to balance the effects of ambient (previously injected) insulin.
3. Self Monitoring of Blood Glucose (SMBG) is recommended post event period q1-2h to assess response to activity and food consumption and to avoid post activity hypoglycemia.
4. On days of planned activity, reduction of pre-activity dose of insulin will help prevent hypoglycemia induced by exercise. If exercise will be after breakfast, lower the dose of regular insulin that would be taken before breakfast. If rapid acting insulin is used (aspart or lispro), decrease insulin dose only if exercise takes places within 2-3 hours after injection. (See Table 3.)
5. BG readings before, after, and possibly during exercise should be used to determine the appropriate change in insulin dose or food intake the next time the activity is done.
6. Prolonged activity can have a delayed BG lowering effect; ↓ in basal insulin may be required.

{If T1DM & BG acutely high >14-16mmoL/L, exercise will speed up ketosis process & should be delayed till BG lowered.}

Table 3: Exercise Intensity & % Of Insulin Dose Reduction[26] VO2 max = max rate of O_2 consumption

Intensity (% VO2 max)	30 min of exercise		60 min of exercise
Mild exercise (25%)	25	(patient variable)	50
Moderate exercise (50%)	50		75
Strenuous activity (75%)	75		No insulin

TRAVEL THROUGH TIME ZONES

- General comment: goal is to switch to new time zone as soon as possible after arrival at new destination. {North-South travel may involve little if any time change so no insulin adjustment required.}
- In North America (3 hours max) → no adjustment
- Travel EAST (lose hours, shorter day): usually need less intermediate or long-acting insulin & less sleep

Canada →Europe *Lose 5-7 hrs; shorter day*	• Decrease bedtime dose of intermediate-acting insulin (NPH) by 1/3 or ½ on the travel day (usually on the plane crossing the Atlantic)
Europe →Canada *Gain 5-7 hrs; longer day*	• When arrive home, have an extra meal & extra dose of bolus insulin • The dose will need to last 5-6 hours, until return to usual routine

SICK DAY GUIDELINES for Patients on Insulin

- Check BG before meals &/or q4h around the clock (more often if necessary); drink extra sugar-free fluids
- Acute illness has variable effect on insulin requirement; management patient & regimen dependent
- T1DM: additional doses of bolus insulin for elevated BG or urine ketones (if BG not low); may ↓ insulin dose to avoid low BG if unable to ingest required amounts of carbohydrate & BG is not high.
- T2DM: ↓ or hold mealtime insulin if not eating; ↑ or additional doses of bolus insulin if high BG
- If on oral hypoglycemics, may need to temporarily decrease dose
- If the individual cannot eat as usual, they should replace solid food with glucose containing fluids. They should try to take 10 grams of carbohydrate every hour (see *clear fluids* below).

PRE-PROCEDURE CONSIDERATIONS e.g. outpatient with diet restrictions pre-gastroscopy [27]

- Management depends on: T1DM vs T2DM; duration of fasting; time/duration of procedure; insulin regimen
- E.g. Days Before Test: no change or ↓ basal insulin dose(s) by ~20%; ↓ bolus insulin dose(s) by ~50%. BG in range of 5-12mmol/L are OK for 1-2 days. On Day of Test: ↓ morning basal insulin by ~30% (up to 50% if very long procedure) & do not take bolus until test is done & ready to eat. Test BG before giving next insulin.
- Clear fluids containing sugar: (e.g. fruit/sports drink, pop, popsicle, regular Jell-O®); test BG more frequently (e.g. q4h); if BG <4mmol/L or symptoms, take 15-20g carbohydrate & retest in 15min

PREGNANCY & PRE-EXISTING DIABETES – Targets & Comments [5]

Pre-pregnancy: A1c (%)	≤7.0
Once pregnant:	
FBG & preprandial (mmol/L)	3.8-5.2
1-hour PPG (mmol/L)	5.5-7.7
2-hour PPG (mmol/L)	5.0-6.6
A1c (%) of somewhat limited value in pregnancy	≤6.0 if possible
In some ♀, especially T1DM or obese, higher targets may be necessary to avoid excessive hypoglycaemia!	

1. Stop OHAs, ACEI/ARB & statin prior to conception*,**
2. Use intensive insulin therapy - MDI or CSII
3. SMBG: pre & postprandial at least 4 x per day

{Hyperglycemia Effects: T1: developmental defects; T3: macrosomia, delivery & neonatal complications}

Postpartum: ◆ Insulin may not be required on the day of delivery & up to 24-48 hours postpartum
◆5-7 days post-delivery, insulin requirements have usually returned to pre-pregnancy levels. Encourage breastfeeding!

Pregnancy Category B-*Likely safe*: Human regular, NPH; Aspart, Lispro. Category C-*Caution*: Detemir, Glargine theoretical early risk
*There is evidence that glyburide & metformin e.g. in PCOS may be safe & not contraindicated in all cases. **Give 5mg/d folic acid![28]

GESTATIONAL DIABETES (GDM) [5]

- **Targets**: same as "Pre-existing" in table above. Avoid FBG < 3.3 mmol/L & 1 hr PPG < 5.0 mmol/L.
- Intervention: Diet & light exercise (small plate; walk after meals). If targets not achieved within 2 wks with nutrition alone, insulin should be initiated. {Glyburide or metformin[MtG] are 2nd line "off-label" options.} Regimen & dose depends on the pattern of hyperglycemia. Follow up: screen OGT for DM @ 6weeks-6months post-partum.
- Example of MDI regimen in GDM (dosing will depend on patient!)
  - High FBG: NPH qhs 0.1 unit/kg body weight (or start 5-8 units NPH qhs); Avoid LAIAs (Glargine, Detemir)
  - High PPG: Regular or RAIA of 1.5 units/10g CHO at breakfast due to insulin resistance, & 1 unit/10g CHO at lunch & dinner (or start 5 units bolus insulin for each meal with high PPG)

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APPROACH TO MANAGEMENT OF TYPE 2 DIABETES (T2DM) in Adults

Nonpharmacologic Therapy: {nutrition & activity ⇨ weight loss of ≥5% or ≥4kg can ↓ hyperglycemia}

◆**Lifestyle Modifications** [1] portion plate,pedometer & **Patient Education** are important at all levels! [2,3,4]

If individualized goals for glucose are not achieved in 2-3 months, ⇨reassess; advance to next level of therapy

See Health Canada's Food & Fitness Guides &/or CDA Guidelines. {Consider Mediterranean diet.}

Oral Hypoglycemic Monotherapy {Note: if A1C ≥ 9%, consider MF + 2nd agent concurrently.}

◆**For most, especially if obese or overweight**

FYI: MF target dose in UKPDS-34 (obese, age ≤65): 1700mg am + 850mg @ supper (↓ mortality NNT=14/10yr)

⇨ start **metformin (MF) 250-500mg po OD**
(Titrate dose up slowly to improve GI tolerance!; **over 3-4 weeks or longer if GI side effects**; usual dose ≤ 2,000mg/day; lower doses in elderly &/or ↓renal fx (see Table 6)

⇨ alternative agents used if metformin contraindicated/not tolerated
eg. secretagogues (e.g. sulfonylureas, repaglinide), TZDs not rosiglitazone-ADA'08, insulin, acarbose; see chart
{In rare "young, thin T2DM", sulfonylurea (SU) low-moderate dose or metformin suitable for initial tx}

⇨ If TZDs considered, these agents can take a long time before full effect seen (6+ weeks). There are theoretical advantages to early use but also concerns about ↑ weight, HF, fractures (♀) & possibly cardiovascular (CV) risk. {CV & MI risk concerns mostly with rosiglitazone.}

Repeat A1C ; Reassess lifestyle modifications in 2-4 months {Attain target A1C in 6-12 months.}

⇨*If targets for glucose control not achieved, consider advancing to combination therapy*

Oral Combination Therapy (2 agents often needed: after 3yrs 50%; after 9yrs 75%)

◆a variety of 2-drug combinations e.g. (MF + SU lower half of dose range) may be considered (see Table 7); repaglinide +sulfonylurea not usually recommended; consider risks & benefits of other combos.
{2rd line/agent options: basal insulin NPH, detemir or glargine; a TZD e.g. pioglitazone; new agents? (Consider early insulin!)

Repeat A1C ; Reassess lifestyle modifications in 2-4 months,

⇨*If targets for glucose control not achieved, consider next level of therapy* (Note lack good evidence for combos)

Add Insulin Therapy +/- Oral Agents (MF will limit wt gain & insulin dose required)

◆**Option 1: Bedtime basal insulin** (e.g. NPH or N) **+ daytime oral hypoglycemics** e.g. **metformin**

⇨**if** on SU + other oral agent, consider discontinuing or reducing the dose of the SU (or could use a metiglinide)

-**add intermediate or long-acting insulin, 5-10 units at HS** (or initial dose: ~ 0.1 - 0.2 units/kg)

-↑ insulin: Option 1) by 2 units every 3-4 days until FPG of 4 -7 (or by 1 unit/day till target is reached.)
{or Option 2) Titration is patient specific; however an example of a q-weekly titration regimen could be: if FPG in previous few days: [7.1-8 mmol/L, 2 units]; [8.1-10 mmol/L, 4 units]; [10.1-12 mmol/L, 6 units]; No ↑ or may need ↓ if ≥ 2 episodes of BG <4 mmol/L at any time in preceding week, if severe hypoglycemia (i.e. requiring assistance), FPG < 3.1 in preceding week or any nocturnal hypoglycemia.}

-if target BG not achieved at 30units/day, or ↑ in daytime BG, may switch to split-mixed or more intensive regimen (usual range: 0.25-1unit/kg/d). To add bolus insulin to basal insulin, take [current basal insulin dose ÷ 10] = bolus dose at largest meal; reduce basal insulin dose by the same amount; titrate. 2nd & 3rd mealtime injections can be added similarly in succession.

◆**Option 2: Switch to insulin therapy 1-4x/day**

⇨if starting mealtime insulin, discontinue SUs &/or glitinides (see Table 7)

-adjust insulin dose & frequency to achieve targets without hypoglycemia

Some patients may eventually require very high doses of insulin due to insulin resistance (max 400units/day used in UKPDS)

e.g. Split-mixed regimen: total starting daily dose (depends on patient, other drugs, etc.; 0.1-0.5 units/kg; safer to start lower!)
Basal/bolusTID or QID: 40% of total dose as basal; other 60% as bolus/prandial divided TID at mealtimes adjust per diet/exercise
BID: divide daily dose: 2/3 pre-breakfast; 1/3 in evening pre-supper; divide each dose: 2/3 basal & 1/3 bolus (or 30/70 mix)

(Note: insulin temporarily indicated in any pt with metabolic decompensation, severe fasting hyperglycemia, or severe illness.)

GLUCOSE TARGETS CDN '08 Adult	Target for most	Normal	Frail elderly AGS'03
A1C q3-6mon (calibrate meter q-yr)	≤ 7 (≤6.5% in some)	≤ 6	≤ 8
FPG (mmol/L)	4-7	4-6	
PPG (mmol/L) 2hr post	5-10	5-8 (consider if A1C not met)	
Note: pursue targets if can be done safely without hypoglycemia etc. ADA'07 30			

Individualize targets: More aggressive in young adult with recent diagnosis STENO-2; less aggressive in **frail elderly** 31. ACCORD A1C arm halted due to ↑death NNH= 95 / 3.5yr in aggressive target group (A1C <6 Achieved=6.4) vs standard target group (A1C: 7-7.9 Achieved=7.5); in patients with established T2DM at high CV risk ~ 10 yr hx.

Screen: if BP >135/80 USPSTF'08.; FPG: screen q3yrs if risk factors or ≥40yrs old. Estimate average glucose eAG: 8.5mmol/l = an A1C 7%

BP 2008 Diabetes→**130/80** **LIPID 2006** Diabetes most→LDL<**2-2.5** Total Chol/HDL<**4** (Lower risk: younger without risk factors)

RENAL	Normal	Microalbuminuria Start ACEI or ARB	Macroalbuminuria
Albuminuria	<30mg/day (<20ug/min)	30-300mg/day (20-200ug/min)	>300mg/day(>200ug/min)
Albumin mg/**C**reatinine mmol **R**atio	Male <2; Female <2.8	Male 2-20; Female 2.8-28	Male >20; Female >28

Self monitoring of BG in T2DM has limited effect on A1C ↓~ 0.25%, yet ↑cost $160 - $2400 / year & ↑depression. Consider if: using insulin or secretagogues, in select newly/motivated diabetics, to aid motivation or if at ↑hypoglycemic risk DiGEM,ESMON,Farmer BMJ07/08.

BMI (kg/m²)	WEIGHT (kg, lbs)																		
	45kg	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130
HEIGHT (Cm; inches) cm. / in.	99lbs	110	121	132	143	154	165	176	187	198	209	220	231	242	253	264	275	286
155cm	61	18½	21	23	25	27	29	31	33	35½	37½	39½	41½	43½	46	48	50	52	54
160	63	17½	19½	21½	23½	25½	27	29	31	33	35	37	39	41	43	45	47	49	51
165	65	16½	18½	20	22	24	26	27½	29½	31	33	35	36½	38½	40½	42	44	46	48
170	67	15½	17	19	21	22½	24	26	27½	29½	31	33	34½	36	38	40	41½	43	45
175	69	14½	16	18	19½	21	23	24½	26	28	29½	31	32½	34½	36	37½	39	41	42½
180	71	14	15½	17	18½	20	21½	23	24½	26	28	29	31	32½	34	35½	37	38½	40
185	73	13	14½	16	17½	19	20½	22	23½	25	26	28	29	30½	32	33½	35	36½	38

Underweight = <18.5kg/m²; **Normal** = 18.5-24.9kg/m²; Overweight = 25-29.9kg/m²; **Obese = ≥30kg/m²**

Waist Circumference: ♂ **<94**cm ideal, >102cm high risk; ♀ **<80**cm ideal, >88cm high risk {better risk predictor than BMI!}

Table 6: Individualization of Drug Therapy: Special Considerations

Patient Factor	Consider ⇨ possibly preferred drugs
Renal failure *	TZDs, repaglinide; insulin; (also tolbutamide or gliclazide [5])
Hepatic disease	**Insulin, repaglinide;** acarbose; (Caution:glyburide,metformin& TZDs)
Hypoglycemia {consider risk of combos below}	**Metformin**, metformin+sitagliptin, TZDs; also: repaglinide; gliclazide or glimepiride less than long-acting SUs; acarbose; {basal insulin: glargine or detemir somewhat less than intermediate e.g. NPH/ N}
Obese / Overweight	**Metformin** drug of choice if no CI's; ↓mortality (UKPDS-34); {acarbose; I-Det; new agents?}
Irregular mealtimes	**Repaglinide** (may be preferred over SU)
PPG >10mmol/L & FPG minimally ↑'d	**Repaglinide** (or **Acarbose**); Metformin + sitagliptin; Diet ↑fiber **Rapid Acting Insulin** (if PPG very high >10mmol/L) e.g. Lispro, Aspart
IGT/IFG "Prediabetes"	**Lifestyle** (↓wt, diet/exercise) DPP, FDP; MF 850mg BID DPP; orlistat Xendos, acarbose Stop-NIDDM

* **Metformin dosing**: lactic acidosis assoc. with metformin is rare (<1:10,000 treated pts) [6,7,8]

MAX Metformin Dose [9] for CrCl: 60 ml/min ≤1700mg/d; >30 ml/min ≤850mg/d; ≤30 ml/min→contraindicated

Table 7: Combination Therapy/Insulin Therapy in Type 2 Diabetes [10,11]

Drug combination	↓ in A1C	hypo-glyc.	Wt	Comments re Combinations (long-term clinical outcomes not studied!)
SU + MF	↓↓↓	↑↑	↑/↓	◆if SU initially, may add MF or TZD; SU+MF may further ↓A1C by 1.7%; 1 study ↑ mortality[12], but ADVANCE neutral* ◆if MF initial agent, may add SU or repaglinide ◆MF combos generally result in less weight gain than SU combinations; ◆MF+Pioglitazone: positive lipid effects but ↑ edema; MF+rosiglitazone: lower A1C but ↑edema ◆MF+acarbose: ↓wt & PPG but ↑GI SEs
SU + TZD [13]	↓↓	↑↑	↑↑	
MF+ repaglinide [14]	↓↓	↑	↑	
MF+ sitagliptin	↓↓	-	↓	
MF+ TZD [15,16,17]	↓↓↓	↑	↑	
MF+ acarbose [18]	↓	-	↓	
Exenatide+MF+SU [70]	↓↓↓	↑↑	↓	
Insulin monotherapy	↓↓↓	↑↑↑	↑↑↑	◆tight BG control but hypoglycemia/weight gain
Insulin + SU (UKPDS 57 ultralente @ evening)	↓↓↓	↑↑	↑↑	◆evening basal insulin; lower A1C & less hypoglycemia than insulin alone; caution in elderly (hypoglycemia)
Insulin + MF (FINFAT STUDY [19])	↓↓↓	↑	↑	◆overcomes insulin resistance; MF has positive effect on wt & lipids; preferred in obese patient; superior to insulin+SU; insulin sparing ~20-25%
Insulin+ pioglitazone or rosiglitazone	↓↓[20]	↑↑↑	↑↑↑	◆overcomes insulin resistance; but potential harms (e.g. ↑ wt, edema & risk of HF[21]); risk/benefit?.
Insulin+ repaglinide	↓↓	↑↑	↑↑	◆option to ↓ PPG
Insulin + acarbose	↓↓	↑↑↑	↑↑↑	◆↓ PPG diet high in CHOs; also ↓ wt & triglycerides
Insulin + 3 orals*	↓↓↓	↑↑↑↑	↑↑↑	◆ACCORD: >50% of pts on 3 orals+insulin; ↑ death *

*ACCORD: baseline A1C=8.3%, wt=93kg & very aggressive intervention (>50% on 3 orals + insulin); ↓A1C to 6.4% but ↑ death NNH=95 /3.5yr (& ↑wt. & hypoglycemia). In ADVANCE: baseline A1C=7.5%, wt=78kg; most on SU gliclazide + MF; ↓A1C to 6.5% & ↓ microvascular NNT=67 /5yr (esp. nephropathy) but also ↑ severe hypoglycemia NNT=83 /5yr & ↑ hospitalizations NNT=42 /5yr.

A1C = glycosylated hemoglobin **BG**= blood glucose **CHO**= carbohydrate **FPG**= fasting plasma glucose
HF= heart failure **MF**= metformin **PPG** = postprandial blood glucose **SE**= side effects www.RxFiles.ca
SU= sulfonylurea **TZD**= pioglitazone & rosiglitazone **Wt**= weight

Oral HYPOGLYCEMIC AGENTS (OHA) - Comparison Chart [22,23,24,25,26,27,28,29,30,31,32,33,34,35]

Prepared by: Loren Regier, Brent Jensen, © *www.RxFiles.ca* Oct **08**

Generic/TRADE/ (Strength) Pregnancy	KINETICS	EFFECTS ON FPG	PPG	A1C↓%	LDL	HDL	TGs	Wt	DRUG INTERACTION	COMMENTS	INITIAL & (Max.) DOSE	USUAL DOSE RANGE	$ /100 day
BIGUANIDES – reduces hepatic glucose production; increase insulin sensitivity & cellular glucose uptake & utilization; ↓ morbidity & mortality [NNT=14/10yr] in obese patients (UKPDS-34)													
Metformin [36] (MF) B GLUCOPHAGE, GLYCON generic (500ς, 850mg tab)	P = 3h D = 8-12h	↓	↓	↓ 1-1.5	↓	↑	↓	-/↓ ↓2.9kg Adopt 4yr	• **EtOH** and cimetidine ↑ effect • contrast media (long-term ↓ B_{12} & folate absorption) {**Caution/↓ dose CrCl ≤60**ml/min}	Does **not** by itself cause **hypoglycemia.** Possible **wt loss**; **⇨ DOC for OBESE ! First line agent** (Used in PCOS[37]) **SE: To avoid GI SEs, start low & titrate up q2-4wk** **Avoid**: ↓ renal fx (**<30** ml/min), acute/decompensated HF, liver dx[severe]; 48hr post [iodinated contrast]. {(Lactic acidosis <1:10,000)[7], watch Na bicarb}. Long-term ↓B12 absorption [7%]; anemia [may occur] **Elderly**: dose reduction required.[38] May **prevent** NIDDM [39 DPP]	**250-500mg od** (Max: 850mg tid; but usual max 1g bid)	500mg po bid 850mg bid [DPP] 1g po bid [Adopt] 1700mg po am, 850mg po pm: **UKPDS**	22 **43** **35** 61
Metformin GLUMETZA ✗ ⊗ 0.5&1g ER tab, Max 2g/day [$240 (OD with evening meal)]. **Metformin/Rosiglitazone AVANDAMET** ☎ ⊗ tabs: (500mg/1,2,4mg BID =$155, $270, $360 /100day tab; 1gm/2,4mg =$290, $390). {**Not in Canada: Metformin/Pioglitazone ACTOplus met** ✗ ⊗ tabs 500/15mg, 850/15mg BID}. MF/Rosi ↓A1c by ~2%; ↑edema & hypoglycemia vs MF alone.												TID dosing option for larger doses to ↓ GI intolerance (dyspepsia, nausea & diarrhea)		
SULFONYLUREAS (SU) Insulin Secretagogue – stimulates β cell insulin release; ↑peripheral glucose [utilization] (↑ #/sensitivity of insulin receptors?); ↓hepatic [gluconeogenesis]; may stop if on insulin													
Chlorpropamide ⊗ C DIABINESE,g;(100ς, 250ς mg tabs)	P = 6-8h D =24-**72h**	chlorpropamide **not recommended** due to ↑BP & ↑ retinopathy (UKPDS-33)						↑↑	**Numerous:** • ↑ Hypoglycemia with:cimetidine, **EtOH**, fluconazole MAOIs, NSAIDS, salicylates & sulfonamides. • β-Blockers may mask hypoglycemia • Disulfiram rx. with EtOH, mostly with chlorpropamide • rifampin ↓ effect	Many (~75%) require 2nd agent for adequate control (e.g. + metformin or TZD) **Hypoglycemia**: most with chlorpropamide & glyburide (see note below); **least**: tolbutamide, glimepiride[40,41] & gliclazide [42] Caution in elderly (hypoglycemia risk) & obese (wt gain). **Require consistent food intake** to avoid problems with hypoglycemia (↑risk: elderly, debilitated, malnourished) **SE: Wt gain,** headache, dizziness, **sulfa** skin reactions (rash/photosensitivity ~1%),GI side effects [1-3%];concerns with cardiac toxicity & hyperinsulinemia & hyponatremia Reduce dose if hypoglycemia or renal/hepatic dysfx **Dose titration q1-2 weeks**. Failure rates ~5-10%/year. In general, SUs achieve ~75% of effect at **1/2** their max dose.	100mg od (500mg od)	100mg po od 250mg po od	16 **13**
Gliclazide,generic ✗ ▼ **DIAMICRON** 80ς mg tab; **DIAMICRON MR**,g 30ς mg tab C	P = 4-6h D=10-**24h**	Total Wt gain with glyburide >4kg vs **>6kg insulin** (UKPDS-33)[10yr]		↓ 1-1.5	-	-	-	↑1.6kg Adopt4yr			40mg (160mg bid) 30mg MR (120mg od [Advance])	80mg po bid 60mg MR po od 120mg MR po od	**74** 41g,96 75g,180
Glyburide **DIABETA**,generic (2.5, 5mg scored tabs) B/C	O=<60min P= 2-4h D=12-**24h** ↓placenta[transfer]	**Glimepiride AMARYL**g ✗ ⊗(1,2,4mg ς tabs) 1mg od ($65); 2mg od ($65); 4mg od ($65) /100days **Glimepiride/rosiglitazone AVANDARYL** ✗ ⊗ (1,2,4/4mg tabs) od with a meal ($310) **Glimepiride/pioglitazone DUETACT** ✗ ⊗ in USA C									1.25-2.5mg od (10mg bid $31)	5mg po od-bid 7.5mg bid [Adopt] Peds: 0.05-0.45mg/kg/d	15-20 26 ←Kir6.2[mutation]
Tolbutamide,generic C **ORINASE** (500mg scored tab)	P= 3h D=6-**12h**										250mg od (1000mg tid)	500mg po bid 500mg po tid	27 **37**
THIAZOLIDINEDIONES (TZDs) or GLITAZONES –Insulin Sensitizers: ↓ hepatic output of glucose & ↑ peripheral insulin uptake; ~ 4-6+ weeks before effect (adjust dose at ~2 months)													
Pioglitazone ☎ ✆ **ACTOS**,generic (15, 30, 45 mg tab) C	**Delayed action…** Onset ~3wks	↓	↓	↓ <1 or 1-1.5	-	↑	↓	-/↑ ↑3.6kg Proactive3yr	• Cholestyramine ↓ absorption ~70% • Hepatic CYP 2C8 • rosigl. not CYP 3A4 • ↓ effect of oral contraceptives? • ↑ by gemfibrozil & ↓ by rifampin	More effective in obese or hyperinsulinemia pts. **Doesn't by itself cause hypoglycemia**; ovulation resumption in anovulatory ♀ premenopausal PCOS· **CI**: any HF; triple tx[?MF+SU+ rosigl..] **SE: Edema 4.8% (HF 2x** [43,44];HTN);**↑Wt**; anemia [~1% mild (due to hemodilution?);↑fractures [esp ♀];monitor **liver fx (ALT)** when indicated; pioglitazone may have more +ve lipid effect[45,46] **ROLE**: +MF, or SU [if MF CI]; (↑↑ HF with insulin); Rosi: ↑MI risk?[60]	15mg od (45mg/day)	15mg po od 30mg od [Periscope] 45mg od [Proactive]	200g,270 260g,**360** 380g,530
Rosiglitazone ☎ ✆ **AVANDIA** ; 1st approved 2000 (2, 4, 8mg tab) =Rosi C	**Max effect in 8-16 wks**	↓	↓	↓ or 1-1.5	47,48 -/↑	49,50 ↑	-/↓	-/↑ ↑4.8kg Adopt 4yr			4mg od {4mg max if with SU} (4mg bid) bid dose ~more effective (51)	4mg po od 4mg po bid [Adopt] 8mg po od [Dream]	250 480 **350**
?? May ↑MI, CV risk [Nissen, DREAM?, FDA·;?↑ Macular edema; advise against using rosi ADA'08]													
MEGLITINIDES (GTN) – short-acting insulin secretagogue; bind to β cell to stimulate insulin release at different site than SUs; (adjust dose at ~7days); discontinue if on insulin recommended													
Nateglinide ☎ ▼ **STARLIX** (60, 120, 180mg tab) C	O = **<20min** P=60-120min D = ~**4h**	↓	⇊	↓ **0.5**	-	-	-	-/↑	•CYP 3A4 inhib↑ effect: azole-antifungal, clarithro /erythromycin,gemfibrozil •CYP 3A4 inducers ↓ effect: barbs, carbamaz & rifampin	Restores 1st phase insulin release - (↓ PPG) Rapid, short duration ⇒ May ↓ risk of hypoglycemia vs SUs ∴option in elderly; **{Flexibility with food intake: skip dose if skip meal; take extra dose if add meal}** If stop other hypoglycemics begin next day & watch for hypoglycemia. **ROLE**: alone or + MF, TZD, or insulin Agents lack outcome data on morbidity &mortality.	60mg tid ac (180mg po tid)	60mg po tid 120mg po tid 180mg po tid	197 197 210
Repaglinide ☎ ▼ **GLUCONORM** (0.5, 1, 2mg tab) C	O=15-60min P=60-90min D = ~**4-6h**			↓ 1-1.5							0.5mg tid ac {if no prev tx or A1C <8%} (4mg qid)	0.5mg po tid 1-2mg po tid 4mg po tid	} **115** 230
α GLUCOSIDASE Inhibitors –inhibit α-glucosidases in brush border of small intestine; prevent hydrolysis & delay carbohydrate digestion {Tx hypoglycemia with glucose tablets [Dex4], honey or milk; (sucrose not absorbed)}													
Acarbose **GLUCOBAY** (prev Prandase) (50,100mg scored tabs)	Meal-time dosing; ~8 wks for max. effect	acarbose minimally absorbed; monitor 2hr PPG							• ↓ digoxin effect • Cholestyramine & cathartics ↑ effect •Enzymes[amylase/pancreatic] ↓ effect; •↓ Fe^{++}?	**SE: GI intolerance**: **flatulence** [>41%], **diarrhea** [>28%]; Little hypoglycemia. Acarbose: ↑ LFTs [3%] & hepatic failure. Accumulation in renal failure. Avoid in chronic GI disease. ↑ dose q4-8wks. ROLE minimal: if ↑PPG; + SU, MF; (+Insulin?)	**25mg od** (100mg tid) [STOP-NIDDM 52]	50mg po tid 100mg po tid	95 **130**
Miglitol ✗ ⊗ (not in Can.)		miglitol **GLYSET** (25,50,100mg tab) well absorbed									25mg od (100mg tid)	25-50mg po tid	n/a
Sitagliptin New [2007] **JANUVIA** ✗ ⊗ 100mg tab (free base) U	Onset ≤4wks; ~18 wks for max effect	**Dipeptidyl peptidase-4 inhibitor [DPP-4]**							•minimal experience •digoxin: small ↑ in dig levels (AUC 11%; Cmax 18%)	↑ insulin secretion via ↑incretin; ↓glucagon. ROLE: combo with MF SE:throat [sore] (↑ infections [URTI, UTI]Cochrane08, headache, nausea, diarrhea; arthralgias; SJS [rare (FDA caution)], less hypoglycemia [but ↑ with SU]; edema?	100mg po OD [25mg & 50mg avail. in USA] 100mg/day	100mg po OD New: no outcome data & unknown safety! (Not a tier 1 or 2 choice by ADA'08) [72]	$300
↓	⇊	↓0.7 (0.5-1)	-	-	-	-							

= ↓ dose for renal dysfx ς =scored tab **$** Cost =total cost & markup in Sask; ☎ = Exception Drug Status in SK ✗ = Non-formulary in SK ✆ =prior approval for NIHB ⊗=not covered by NIHB ▼covered by NIHB; '+' denotes combination options

A1C = glycosolated Hemoglobin (reflects glycemic control over prior 8-10 weeks) **BP**= blood pressure **DOC**= drug of choice **dysfx**= dysfunction **EtOH**= alcohol **FPG**= fasting plasma glucose **GI**= gastrointestinal **HDL**= high density lipoprotein **HF**= heart failure **Ins.**= Insulin **KINETICS**: **O**= onset **P**= peak **D**= duration; **LDL**= low density lipoprotein **PPG**= postprandial blood glucose **SE**= side effects **Wt**= weight ς = scored tablet

Drug induced ↑ glucose: antipsychotics [clozapine, olanzapine], corticosteroids, cyclosporine, diuretics [thiazides e.g. >25mg HCT], estrogens, interferon [alpha], nicotinic acid [↑ dose], phenytoin, sympathomimetics [decongestants], siro & tacro-limus, temsirolimus & thyroid meds. Beta-blockers minimal risk of altering glucose control but may alter/mask hypoglycemic response. **Pregnancy:** Encourage diet, moderate exercise; **Insulin** preferred; generally avoid oral hypoglycemics[53] (See Insulin Management Chart)

Hypoglycemia risk -UKPDS: risk of **≥1 MAJOR** hypoglycemic events/yr (ITT): chlorpropamide=1%, glyburide=1.4%, **insulin 1.8%**; risk of **ANY** hypoglycemic event/yr chlorprop.= 16%, glyburide=21%, insulin 28%.

Oral agents +/- insulin: with T2DM progression, combo tx with oral agents &/or addition of insulin will eventually be required.

PPG may reflect risk of CV disease & all-cause mortality [observational,54]; FBG & A1C are predictors of microvascular complications.

•Consider:[55] lipids/statin, orlistat [56],↓ hypertension [ACE Inhibitor/ARB/thiazide] & DC smoking! ASA ~81mg/d. Lifestyle: {↑fiber, ↓fat, low glycemic index CHO foods; exercise: aerobic150min/wk, resistance 3x/wk; but start with 5-10 minutes}

New:not in : **Exenatide BYETTA** ✗ ⊗ an incretin mimetic; 5-10ug SC bid ac ;↓PPG,↑insulin [secretion],↓A1C 1%; may ↓wt, GI ↓[gastric emptying] & ↑N&V; rare: pancreatitis [acute]. **Pramlintide SYMLIN** ✗ ⊗ an amylinomimetic,15-60-120ug SC tid ac; ↓wt & ↑N&V.

Oral HYPOGLYCEMIC AGENTS (OHA) - Comparison Chart

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Health Canada Dec/05 Association of **AVANDIA** & **AVANDAMET** with new onset and/or worsening of **macular edema** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/avandia_avandamet_hpc-cps_e.html

Health Canada Jan/06 & July/07 Association of **AVANDIA** & 6 reports of parotid gland enlargement http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n1_e.html#2

Health Canada Apr/07 is warning consumers from The Hong Kong Department of Health found **Lanmei Keili Ji to be adulterated with gliclazide**, a hypoglycaemic agent (lowers blood sugar).

Health Canada May/07 is advising consumers not to use **Xiaokeshuping Jiangtangning Jiaonang** capsules in Hong Kong to contain the undeclared pharmaceutical drugs phenformin, rosiglitazone, and glibenclamide, which may be used in diabetes to lower blood sugar.

Health Canada May& June/07 is advising consumers & health professionals about heart risks with **Avandia** http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2007/avandia_pc-cp_3_e.html

Health Canada Sept/07 is advising consumers not to use foreign health products due to concerns about possible side-effects: **Jacaranda**, **Queenmer Fat Loss**, **Li Da Dai Dai Hua Jiao Nang, J-minus** and **Jelimel Slimming Capsules**. These products are promoted for weight loss and have been found to be adulterated with the prescription drug sibutramine. Sibutramine is used for treating obesity and should only be taken under the supervision of a health professional. **Junyu Jiaonanyihao** has been found to contain the undeclared prescription drugs sibutramine and dexamethasone, as well as phenolphthalein, which is currently prohibited in Canada.. **Heng Tong Jiangtangning Jiaonang** was found to contain the prohibited drug phenformin, and the prescription drug glibenclamide (glyburide) which should only be taken under the supervision of a health professional.

Health Canada Nov/07 Rosiglitazone (**AVANDIA**®) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated. Rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated. Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV).

Health Canada April/08 warns that Singapore's Health Sciences Authority (HSA) advised the public not to use the product **Power 1 Walnut**, because it was found to contain the prescription drugs sildenafil and glibenclamide.

Health Canada April/08 is advising consumers not to use The Hong Kong Department of Health advised the public not to use the product **Tian Sheng Yi Bao** because it was found to contain two pharmaceutical products, glibenclamide and phenformin.

Health Canada June/08 **Nangen Zengzhangsu** (may also be known as Nangen or Nangeng), Sanbianwan, Jiu Bian Wang, Tian Huang Gu Shen Dan, Zui Xian Dan Gong Shi Zi, and Power Up. The Hong Kong Department of Health has warned consumers not to use these herbal/proprietary Chinese medicine products promoted for erectile dysfunction because they have been found to contain sildenafil and/or glibenclamide.

Health Canada June/08 **Zhong Hua Niu Bian**. Zhong Hua Niu Bian is an herbal/proprietary Chinese medicine product promoted for erectile dysfunction. Singapore's Health Sciences Authority has warned against the use of this product because it has been found to contain sildenafil, glibenclamide, tadalafil and sibutramine

Nov/08 Health Canada is advising consumers not to use foreign health products due to concerns about possible side-effects: The Hong Kong Department of Health warned consumers not to buy or use **Lu Quan** because it contains undeclared glibenclamide and sildenafil.

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INSULIN Comparison Chart

1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19; CDN Guidelines Sept 2008

Prepared by L Regier, B Jensen, S Downey - © **www.RxFiles.ca** Oct 08

Type of Insulin [generally 100 unit/mL] ("clear" = solution appears clear)	Form 100u/ml	Source	Onset (variable)	Peak (variable)	Duration (hrs)	~$/10ml
Bolus / Prandial						
Rapid acting (give just before or within 20min of starting meal)						
Insulin lispro Humalog ☎▼ B	{clear} v, c, p✗▼	Recombinant DNA tech analog	10-15 min	60-90 min	3.5 – 6h	36V 46c 56p
Insulin aspart NovoRapid ☎▼ B	{clear} v, c					38V 49c
{Insulin glulisine Apidra ✗ ⊗ *Not yet available*}	{clear} v,c,p		10-30 min	60min	≤5h	NA
Short-acting / Regular Insulin						
Humulin R B	{clear} v, c	Recombinant DNA tech. Human	0.5 – 1h	2 – 3h	~ 6.5hr	28V 36c
Novolin ge Toronto B	{clear} v, c				5 – 10h	29V 37c
Hypurin II R (rarely used!)	v⊗	Pork				110V
Intermediate-acting or NPH B						
Humulin N	{clear} v, c, p✗▼	Recombinnt DNA tech. Human	2 – 4h	4 – 10h	12 – 18h (range 12-24)	28V 35c
Novolin ge NPH	{clear} v, c					29V 37c
Hypurin NPH (rarely used!)	v⊗	Pork				110V
Premixed *Humulin* (*regular/intermediate*) 20/80 - Not available	c✗▼ v, c					28V 36c
30/70	c					
Novolin GE (10/90; 20/80) Plan D/C July 2007	v, c					29V 37c
30/70	c					
40/60; 50/50	c,p	Recombinant DNA tech. Human	0.5 – 1h	2-12h Dual Peak	14 – 18h (range 12-24)	37c 44c
Humalog Mix25 ✗▼ ; (Mix50 ✗⊗)	c					42c
NovoMix30 aspart 30%, aspart protamine 70% ✗⊗						
Basal						
Discontinued (DC'd) 2003: *Novolin ge Ultralente*, *Novolin ge Lente*; DC'd 2004: *Iletin II Lente* Pork; DC'd 2006: *Humulin L* , *Humulin U*						
Long-acting (LAIA)						
Insulin detemir neutral PH **Levemir** ✗⊗ C ◆ give daily or twice daily ~20% of pts; {room temp: good 42days after open}	{clear} c	Analog	1h initial ~3.5 50% effect	6 - 8 h	16 - 24h if dose ≥0.4U/kg, duration longer with ↑ dose	87p
Insulin glargine Lantus ✗ ✆ ? Type 1 C ◆ **acidic PH→ some inj site pain; a bit more absorption variability than detemir** ◆ forms microprecipitates in sc tissue⇨slow release ◆ given once daily at HS (or in the morning); split dose if >50units ◆ prefilled disposable SoloStar pen max 80u/inj/Autopen max 42u/inj	{clear} v, c, p✗⊗ vial: stable 28days	analog	>2 - 4h	No Peak	20 - 24h	69V 69c

If switching from daily NPH, use ≤ same total daily dose;
If switching from BID NPH to daily LAIA, use ~80% of total NPH daily dose;
Start ≤10units if not previously on NPH

Premix: May give 1, 2 or 3 times a day, but avoid giving at bedtime! May be useful if non-intensive regimen for T2DM patient with consistent lifestyle (bedridden/institutional/elderly).
Premixed analogues: Similar control to premixed human insulin, & tighter BG control but ↑ hypoglycaemia than LAIA. Lack clinical outcome data. Ann Int Med 2008
Administer: Humalog/NovMix just before meal; other premixes ~30min before meals.

◆↓ variability between sites, flexible, less need for snacks
◆less early night hypoglycemia than reg.
◆better control of postprandial glucose (PPG)
◆1 unit is equal to ~15g of carbohydrate VARIABLE!

Note: For **very large doses, a special 500 U/ml** Humulin R is also available

◆**Human analog insulins** generally shorter acting than Beef/Pork insulins.
◆**Beef** insulin no longer in Canada; available from the UK through Health Canada-Special Access Program at 613-941-2108.

Comments

See also *Insulin Management: Evidence, Tips & Pearls*

DOSING: (see Insulin Management chart)
Note re bolus admin: regular given 20-30min ac; rapid acting: give just before or within 20 min starting meal

Cost: Vial $; Cartridge $$ ↑30%; Humalog $$$; NovoRapid $$$; Hypurin/Detemir/Glargine $$$$
{vials good for ~28 days at room temp after opening}

MIXING:
- **Compatabilities**: Regular with all insulins; NPH with Regular; Lispro & Aspart with NPH if used immediately after mixing; {Glargine or detemir-do NOT mix per CPS}
- **always draw up short-acting/R first** to prevent contamination with longer acting
- **inject mixtures immediately** as alterations in formulation's pharmacodynamics occur dependent on concentration & elapsed time {If delayed, be consistent with mix to inj. time}

{Novolin-Pen 4: for all Novolin products & Levemir; HumaPen Luxura for Humulin & Humalog}

HYPOGLYCEMIA: (see also Insulin Management Chart)
- **Symptoms**:
  Mild/moderate = sweating, tremor, tachycardia, hunger, lethargy, weakness
  Severe = confusion, disorientation, altered behavior/speech, seizures, coma
- **Incidence**: higher with intensive vs conventional; (in UKPDS risk of ANY hypoglycemic event/year: glyburide=21%; **insulin**=28% {1.8% severe}
- **Treat Mild**: 15g glucose tabs; orange juice ¾ cup, 3 sugar cubes, honey/syrup/sugar 1 tablepoonful, 9 jelly beans, 6 LifeSavers® (glucose/dextrose absorbed directly, don't require prior digestion)
  If **Severe** (e.g. unconscious) = 1mg glucagon IM/SC > $100/dose; or D50W 20-50mL IV
- **Prevention**: regular monitoring/exercise/↓↓ alcohol, balanced meals; adjust regimen

OTHER SIDE EFFECTS:
- **Weight** ↑: more with intensive vs conventional (4.6kg/5yrs DCCT 11,12); diet & exercise encouraged; less with detemir & ?glargine
- **Lipodystrophy** - rotate sites within anatomical area

SC VARIABILITY:
- onset/peak/duration for SC insulins is **highly variable** between pts & even at different times for same pt; the longer acting the insulin, the greater the variability seen (e.g. +/- 15% with Reg; +/- 30% with NPH) not the case with detemir & glargine

SUPPLEMENT DOSING: rapid or short acting insulin used to correct hyperglycemia; conservative dose. Individual requirements will vary, somewhat according to total daily dose & response. Insulin to carbohydrate ratios used to guide bolus CSII & MDI. {Caution if <3 hrs since previous insulin, or planning exercise}.

Pregnancy: Category B. *Regular or Rapid* preferred. C (Caution): detemir, glargine & glulisine.
Tight glucose control critical in the first 42 days of pregnancy organogenesis. Minimize hypoglycemia.
Hyperglycemia: ↑ of macrosomia & pre-eclampsia. Neonatal hypoglycemia if maternal BG high before/during delivery.
If antenatal steroids used in preterm labour ↑ insulin dose. Postnatal care: insulin dose ↓ after the birth.

INSULIN REGIMEN	SCHEDULE	COMMENT –treat to effect, no maximum dose for insulin
Conventional Regimens		
RAIA = Lispro (ILis) **or Aspart** (IAsp) **R = Human Regular or Toronto** **N = NPH or N** **D = Detemir** (IDet); **G = Glargine** (IGla)	OD insulin: N, D or G at HS (or rarely before breakfast)	Useful with daytime oral hypoglycemics in T2DM. Simple but poor control; <24hr coverage
	BID insulin: N or D before breakfast & supper	Improved morning control & overnight coverage; no provision for meal coverage
	BID insulin: {also premixed options} { R or RAIA ac breakfast & supper **and** N (or D) ac breakfast & supper }	More common; better meal control (Or *breakfast & bedtime*; less hypoglycemia)
	TID insulin: { R or RAIA ac breakfast & supper **and** N ac breakfast & bedtime }	Most likely to last till next morning; (may substitute D or G for N)
Multidose Intensive Regimens (MDI) (~40% of total insulin dosed as basal insulin; bolus/prandial dosing adjusted with meal/CHO)	R or RAIA TID ac; N or D ac supper or hs (or G in am or hs)	Good control, flexible regarding meals; demands frequent & consistent testing at start!
	R or RAIA TID ac; **&** N or D BID (ac breakfast & supper or bedtime)	Better suited for people with varying schedules; flexibility with regards to meals
Intensive Continuous SC Infusion (CSII)	R or RAIA; basal & boluses prn; rapid analogues preferred most flexible	More flexible, better control; ↑$ $5000+$250/mo; ↑ risk of rapid ketoacidosis, etc. if discontinued.
Insulin + Oral Hypoglycemics esp. if A1c>9% (in Type 2 Diabetes)	Common: N, G (or D) **at bedtime**, with **1-2 oral agents during day** See Approach to ...Diabetes & Insulin Management charts for dosing information, etc.	Less insulin required ~0.1u/kg eg. 5-10u & ↓weight gain than insulin alone (esp. with Metformin!) Tip: If ↑ PM blood sugar may need bid insulin regimen. If ↑ PPG may need short acting insulin with meals, (or premix).

Eg. Lispro/Aspart/Glulisine/R 4-8u tid ac & Glargine/Detemir/NPH 8-16u hs. Breakfast 25% R & 45% N; Dinner 15% R; Bedtime 15% N. Based on total daily dose.

- Shorter acting insulins given before meals help prevent meal related hyperglycemia!
- BID regimens require regular lifestyle (e.g. institutional)
- 50-75% as long acting & 25-50% as short acting

Forms: **v**=vial **c**=cartridge **p**=pen ; **ac**=before meals **CSII**=continuous subcutaneous insulin infusion **d/c**=discontinuation **pt**=patient ☎=Exception Drug Status (EDS) in SK. ✗ =Nonformulary Sk. ▼ covered by NIHB

Tips: **Fix** the **lows first** & highs later, **correct morning blood glucose, assess Somogyi effect** if unexplained highs in the am **& only adjust one insulin** at a time. ✆=prior approval NIHB ⊗=not NIHB =↓dose for renal dysfx

EXUBERA : **Discontinued!** Inhaled (✗ ⊗adults type 1&2;dry powder given 10min ac, rapid acting, no difference in A1c from regular/NPH regimens; pts may prefer over sc; SE: cough, hypoglycemia,↓pulmonary fx tests short term, anti-insulin antibodies; CI: COPD, smoking if within prev 6 months; long term lung safety ?cancer; $$$$.

Diabetes if it was diagnosed within the first 6months of age consider genetic testing, since **Kir6.2 mutations** successfully **switched from insulin to sulfonylureas** (eg. glyburide 0.05-**0.45**-1.5mg/kg/d) Pearson NEJM Aug/06

Diabetes - Glucose Control: Landmark Outcome Trials – Summary

Loren Regier, Brent Jensen – **www.RxFiles.ca** – Oct 08

	Trials Mean follow-up	Population Risk, hx mean age, etc.	Intervention	A1C: baseline⇨final	Results	Summary of RCT Outcome Evidence
Type 1 (T1DM)	**DCCT** [1] ~6.5yrs; n=1,441 {Conducted between 1983-1993.} {note 1° & 2° endpoints, as well as 1° & 2° cohorts.}	T1DM; mean age 27 (13-39)yr; BMI=27 Excluded: if CV disease, ↑ BP,HC, complications. 1° & 2° cohorts (2° if 1-15yr hx, existing mild-mod retinopathy & microalbuminuria; 1°: 1-5yr hx)	Intensive insulin (3+ inj/day or pump) with target A1C of <6.05% (44% achieved once, but only 5% maintained), preprandial BG 3.9-6.7mmol/L, PPBG <10mmol/L, weekly 3A.M. BG >3.6mmol/L vs Standard insulin (1-2 inj/day)	Int. vs Std.: 8.8% ⇨ 7.4% vs 9.1% {Pre-prandial mean BG Int. vs Std. 8.6 vs 12.8mmol/L} {↑ Wt 4.6kg/5yr}	Endpoint 1° or 2° / △ Rate/100 pt yr NNT/H=100per pt yr / RRR 1°: Retinopathy: 1° ↓3.5 NNT=29; 2° ↓4.1 NNT=24; 63% 2°: Microalb.: 1° ↓1.2 NNT=83; 2° ↓2.1 NNT=48; 39% 2°: Macroalb.: 1° ↓0.1 NS; 2° ↓0.8 NNT=125; 54% 2°: Neuropathy @5yr: ↓6.7 NNT=15; ↓9.1 NNT=11; 60% Hypogly SEVERE: ↑43 NNH=2.3; ↑Hosp 7.6% vs 4.9%	**Type 1 Diabetes** {ENDIT nicotinamide & DPT-1 low-dose insulin not effective in T1DM prevention} • ↓ in microvascular complications in initial 6.5yrs (1° endpoint: retinal surrogates) (mostly ↓ retinal △ on fundus photo 3 steps / 25 stage scale, microalbuminuria & neuropathy) • a 10% relative reduction in A1C (regardless of what the initial A1c value was) resulted in a 43% relative risk ↓ in progression of retinopathy & a 25% relative risk ↓ in microalbuminuria. (Substantially less at lower A1C levels.) • ↑ severe hypoglycemia including coma/ seizures NNH=9 /100pt-yr & hospitalizations 54 vs 36 • possible ↓ in macrovascular complications in long-term follow up(~17yrs); however, limitations such as unmasking could bias results.
	DCCT / EDIC [2] ~17yrs; n=1,394	93% of DCCT in follow-up till Feb05. age 45; BMI=28; 24yr hx	As above, but 94% of standard group changed to intensive insulin.	7.4% ⇨ 7.9% 9.1% ⇨ 7.8%	• ↓ CV events (nonfatal MI, CV death, stroke, angina, revascularization) 5.8% vs 10.3% NNT=23/17yr CI=12-352. (RRR=42% ↓)	
Type 2 (T2DM)	**UKPDS-33** [3] ⌖ ~10yrs; n=3,867	New T2DM; age 54yrs; with FPG 6.1-15 on diet alone	Intensive SU or insulin vs diet. Target FBG <6mmol/L vs <15mmol/L	7% ⇨ 7% vs 7.9%	• ↓ microvascular endpoints NNT=42/10yr; retinal mostly • no effect on CV events⌖ • ↑ hypoglycemia esp insulin	**Type 2 Diabetes** • intensive glucose control may ↑ or ↓ risk depending on type of patient & treatment {e.g. in ACCORD type patients, overly intensive pursuit of A1C target associated with ↑death; no benefit in VADT; whereas in ADVANCE type patients, not quite as intensive tx had some benefit; UKPDS 33,34 reveal variability between extent of BG control & outcomes.} • glucose control offers predominantly microvascular benefit • metformin in newly diagnosed obese T2DM: reduces macrovascular events & all-cause death without ↑ weight or hypoglycemia UKPDS-34, 80 • pioglitazone may ↓CV events (2° outcome & statistical concerns), but ↑ HF & wt • macrovascular benefits seen with multifactorial approach to Tx -lifestyle, ↓smoking, diet, exercise, BP, ACEI, statin, ASA, A1C<6.5% STENO-2 -statin therapy { simvastatin 40mg/d HPS; atorvastatin 10mg/d CARDS } -ACEI, BP reduction {e.g. ramipril 10mg/d MICROHOPE}
	UKPDS-34 [4] ⌖ ~10.7yrs; n=1,704	Obese T2DM; age 53yrs Wt=87kg; BMI=31	Metformin 1700mg am, 850mg pm vs conventional (diet mostly)	7% ⇨ 7.4% vs 8%	• ↓ diabetes endpoint NNT=10/10yr (RRR=32%) ⌖ • ↓ all-cause death NNT=14/10yr; ↓stroke NNT=48/10yr	
	Kumamoto [5] 6yrs; n=110	Japanese with 2° & without 1° retinopathy; UAE<300mg/24hr	Multiple insulin injection tx (MIT) vs conventional insulin tx (CIT)	9.2-9.4 ⇨ 7.1 vs 8.9 ⇨ 9.4	• ↓ early microvascular complications (retinopathy [2+ steps on 19 step scale]; nephropathy & neuropathy)	
	PROACTIVE [6] ~3.5yrs; n=5,238	High CV risk; Age 61; BMI=30; A1C≥6.5	Pioglitazone 45mg po daily vs Placebo (>10% higher rate of insulin use)	7.8% ⇨ 7% vs 7.5%	• 1° composite-no effect; 2° ↓CV events NNT=50/3.5yr • ↑wt 3.6kg/yr; ↑HF NNH=30/3.5yr & edema.	
	ACCORD [7] ~3.5yrs; n=10,251	High CV risk; ~10yr hx T2DM; age 62; 93kg; North American	Intensive A1C target <6% {most on 3 oral hypoglycemics + insulin} vs standard A1C target 7-7.9%	8.1% ⇨ 6.4% vs 7.5%	• ↑ all-cause death in intensive group at 3.5yrs resulted in halting trial (NNH=95/3.5yr); also severe hypoglycemia (NNH=9/3.5yr) & ↑ weight 3.5 vs 0.4kg	
	ADVANCE [8] ~5yrs; n=11,140	Hx of CV disease; 8yr hx T2DM; age 66; 78kg; Austral-Asian/European	Intensive A1C target 6.5% {most on SU (gliclazide) + metformin} vs standard A1C target ~ 7%	7.5% ⇨ 6.5% vs 7.3%	• ↓ microvascular events over 5yrs (NNT=67/5yr), mostly nephropathy indicators; also ↑ severe hypoglycemia (NNH=83/5yr) & minimal wt change	
	STENO-2 [9]: n=160, T2DM & microalbuminuria; multifactorial intensive (A1C <6.5% <20% achieved @13yrs,8.4→7.7%; BP, lipid, ACEI, ASA) vs conventional tx for 7.8yr+ 5.5yr follow-up; ⇨ ↓ death, NNT=5 / 13.3yrs p=0.02, ↓ macro & microvascular events. (Only 1 pt achieved all 5 targets at 13yrs)					
	VADT (Dec08) [10]: n=1791, ~5.6yr, Age ~60yr, ♂ mostly, T2DM x 11.5yrs; 40% CAD Hx (Veterans Affairs). Intensive vs standard A1C Achieved: 6.9% vs 8.4%. No significant effect on CV events, deaths 102 vs 95 or microvascular complications; but ↑ serious adverse events 17.6 vs 24.1% mostly hypoglycemia.					

⌖ **UKPDS 80**: 10 year observational follow-up to UKPDS 33 & 34 (Sep08): glycemic difference lost in follow-up, however risk reduction emerged/sustained for endpoints (MI & Death), especially with MF. {SU/Insulin vs control: ↓Death 30.3⇨26.8 per 1000 patient-yrs; MF vs control: ↓ Death 33.1⇨25.9 per 1000 patient-yrs.} 11

	T2DM "Prevention" Trials *Pre-diabetes*		Intervention	Results	Summary {Note: "prevention of DM" a non-clinical outcome.}
Effective Options	**FDPS** [12] 4yr, n=522 (Finnish Diabetes Prevention Study)	Age 40-65 (ave 55yrs); BMI ≥25 (mean 31); IGT (a FBG < 7.8mmol/L; 2hBG >7.8 but <11 mmol/L)	Intensive lifestyle vs control {Lifestyle: detailed, individualized counseling with nutritionist; individualized exercise circuit. Goals: ↓ weight >5%, fat <30% of all energy, fibre >15g/1000kcal, & moderate exercise > 30 minutes/day.}	1°: incident diabetes (4yrs): 11% vs 23% RRR= 58% HR = 0.4 (0.3-0.7) NNT/4yrs = 8 Change in Body weight: -4.2 kg (-4.8 to –3.6) vs -0.8 kg (-1.3 to –0.3) control. 7 yr follow-up: effect persists 4.3 vs 7.4cases/100 person-yrs	1) **Intensive Lifestyle Interventions** ✓ a. Most effective intervention for patients with IGT b. How intensive was *intensive lifestyle*? i. Individualized counseling/education important ii. Weight loss: goal of at least 5-7% (& up to 10%) iii. Exercise: moderate activity of 30 minutes/day or 150 minutes/week iv. Diet: healthy, low calorie, low fat (<30% of total kcal & <10% saturated fat), ↑ fibre (>15g/1000kcal). 2) **Pharmacological Options** (+ some lifestyle measures) a. Effective but less so than intensive lifestyle* i. Metformin 250-850mg po BID (Meta-analysis[13]) ◆ 6 trials, n=3119, abd. obesity, IGT, family hx: ↓ time to diabetes onset ≤ 3yrs; NNT=12.5 CI: 9.1-20 {better if age <60yr} ii. Orlistat 120mg po TID ◆ Effective if able to tolerate GI side effects; high cost >$150/mo iii. Acarbose 100mg po TID (CV benefit did not persist) ◆ Effective if able to tolerate GI side effects; high cost >$120/mo b. Not Effective or Harm/Outcome Concerns* i. Ramipril: not effective ii. Glitazones (Rosiglitazone & Pioglitazone): effective but concerns {↑wt, ↑ HF, ↑ fracture, (& ?CV Rosi)}[14,15] *Prevention strategies that utilize drugs risk harming otherwise healthy people; knowledge of long term efficacy, safety & impact on healthcare resources need to be established.[16]} Of note: early intensive insulin Tx (x2 wks) may induce remission in some new T2DM.[17]
	DPP [18] 2.8yr, n=3,234 (Diabetes Prevention Project) [Troglitazone arm stopped early due to liver toxicity[19]]	Age >25 (mean 51yrs); BMI≥24 (mean=34); IGT (FBG of 5.3-6.9 mmol/L, 2hBG of 7.8-11 mmol/L.) 68% ♀; ~45% ethnic	Intensive lifestyle* n=1079 Lifestyle+ metformin 850mg po BID n=1073 Lifestyle + placebo n=1082, or *{Lifestyle: ↓ weight by 7% (healthy diet & exercise ≥ 150 minutes/week), & 16 individualized lessons, covering diet, exercise & behaviour modification. [Low-cal diet: ↓450kcal/day ave; e.g. 1500kcal/d for 80-95kg ☺]}	1°: incident diabetes (2.8yrs): 4.8 cases/100 person yrs for intensive lifestyle 7.8 cases/100 person yrs for metformin, 11 cases/100 person yrs for placebo, ◆ NNT= 7 / 2.8yrs for lifestyle (RRR: 58%; 71% age 60+) ◆ NNT= 14 / 2.8yrs for metformin (MF) (RRR: 31%) Weight ↓: 5.6kg Lifestyle, 2.1kg MF, 0.1kg (p<0.001)	
	IDDP [20] (India) 2.5yr, n=531	Mean age 46yrs; BMI 26 IGT – in Asian Indians	Lifestyle vs metformin 250mg po BID vs control	1°: incident diabetes (2.5yrs): lifestyle 39.3%, NNT=6; metformin 40.5%, NNT=7; 55% control	
	Stop-NIDDM [21] 3.3yr, n=1,429	Age 40-70 (mean 54yrs); IGT (2hBG ≥ 7.8 & <11.1mmol/L, FBG of 5.6-7.7 mmol/L).	Acarbose 100mg TID vs placebo {also encouraged exercise; met with dietitian}	1°: incident diabetes (3.3yrs): 32.4% vs 41.5%; NNT=11 / 3.3 yrs {↓CV events 2.5%; NNT=40}[22] {GI SE's 83% vs 60%; Stop Tx: 31% vs 19%}	
	XENDOS [23] 4yr, n=3,305	Age 30-60;(mean 43yrs); BMI≥30; no CV disease; 21% had IGT	Orlistat 120mg TID vs placebo (weight loss study) {also ↓calorie diet & physical activity encouraged.} {High drop-out rate.}	2°: incident diabetes: 6.2% vs 9% NNT=36/4yrs; ↓ diabetes in IGT subgroup only 18.8% vs 28.8%; NNT=10 {1°: ↓weight 5.8kg vs 3kg; ↑ GI SE's: 91% vs 65%/1yr}	
	DREAM-Rosi [24] 3yr, n=5,269	Age ≥30yrs (~55yrs); IGT +/- IFG or IFG Mean FBG=5.8mmol/l No DM or CV disease (eligibility expanded during trial)	Rosiglitazone 8mg po daily vs placebo {Trial stopped 5months early due to ↓diabetes; but ↑CV event rate approaching statistical significance.}	1°: incident diabetes or death: 11.6% vs 26%; NNT=7/3yrs (driven by diabetes; no difference in death); CV events: 2.9% vs 2.1% HR=1.37; CI 0.97-1.94	
	DREAM-Rami [25] 3yr, n=5,269		Ramipril 15mg po daily (start 5mg/d x2 months, then ↑10mg/d till 1 yr) vs placebo	1°: incident diabetes or death: 18.1% vs 19.5% NS {Also, no difference in CV event rate 2.6% vs 2.4%}	

2hBG=2hr blood glucose BMI=body mass index CV=cardiovascular FBG=fasting blood glucose HC=hypercholesterolemia HF=heart failure hx=history IGT=impaired glucose tolerance MF=metformin PPBG=post-prandial blood glucose SU=sulfonylurea Tx=treatment wt=weight yr=year

Links: CDA Professionals: http://www.diabetes.ca/for-professionals/resources/2008-cpg/ ADA Prevention/delay of type 2 diabetes.: http://care.diabetesjournals.org/cgi/content/full/30/suppl_1/S4#SEC14. AACE Prediabetes link [26] NICE T2DM: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11983 COMPUS: link [27]

EXTRAS Page

Upcoming Trials in Diabetes/CV Risk Prevention:

- **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research); **TRANSCEND** (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease); **RAPSODI** (rimonabant in diabetes prevention)

Prediabetes [ADA]:

- Includes: 1) Impaired Fasting Glucose {8hr fasting BG between 5.6-6.9mmol/L) & 2) Impaired glucose tolerance {Postprandial BG of 7.8-11.0mmol/L 2hrs post 75g oral glucose challenge}
- Risk factors: family hx, obesity – especially around waist, age >45, hypertension, gestational diabetes hx, sedentary lifestyle. Screening recommendations vary; USPSTF recommends screening particularly if BP >135/80. Oral Glucose Challenge most recommended, but A1c screen also advocated by some.

Insulin Analogues Systematic Review/Reports, 2008: http://cadth.ca/index.php/en/compus/insulin-analogs

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Q&A: Limitations & Unanswered Questions Regarding A1C Control and Clinical Outcome - Benefits or Risks

There are some important qualifiers on the commonly quoted observation that "with every one percent drop in A1C the risk of developing long-term diabetes complications decreases". (Concept originally based on observational data driven by an eye related microvascular endpoint in the UKPDS). Current evidence call this assumption into question.

- Most recently the ACCORD trial (established, higher risk T2DM) was halted after looking at whether a A1C target of <6% would result in beneficial clinical outcomes compared to 7-7.9%. According to the preliminary results still awaiting publication, it would appear from this RCT that the extra 1.1% drop in A1C seen in the intensive group was actually associated with increased all cause death compared to the standard group. Explanations for this are still pending… (See also; http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf).
- With the current RCT evidence with rosiglitazone, there is some concern that lowering A1C does not necessarily result in CV event reductions? With the limited evidence, it appears to at best be neutral, and at worst be harmful in RCTs/durations studied so far (e.g. up to 4 year RCTs.) Patients studied and hypoglycemic agents used may affect the benefit/risk potential.
- The UKPDS-33, ~ 10 year trial saw reductions predominantly in the microvascular events (predominantly photocoagulation), with stroke and heart related endpoints not significant, but trending favorably and contributing to the composite endpoint benefit. (Exception: metformin had all-cause death reduction in obese T2DM in UKPDS-34)
- In UKPDS 34,[p860] which noted a mortality benefit for metformin in obese T2DM, there is inconsistency in the association of A1C & outcomes (less A1C difference but more benefit [UKPDS34 VS 33])
- In UKPDS 34 Metformin + Sulfonylurea combination led to a lower A1C than Sulf alone (7.7 vs 8.2) but had higher incidence of DM death and all cause death (perhaps due to design issues and a several year delay in moving to combination therapy) .
- The UKPDS epidemiologic evidence for the 1% drop in A1C did not control for obesity/BMI/waist circumference. [UKPDS 35]
- In ADOPT, rosiglitazone decreased A1C more that metformin or glyburide, but glyburide had the lowest rate of CV outcomes.
- In VADT, a 1.5% reduction (6.9% [intensive] vs 8.4% [standard]) in A1C for an average follow-up of 5.6 years resulted in no benefit (microvascular or macrovascular) but increased serious adverse events (predominantly hypoglycaemia).

There is some disconcordence between randomized trial outcome evidence and the frequently reported "1% A1C..." benefit. One thing that has growing certainty is that the risks and benefits of drug regimens that lower A1C is more complex than what was previously commonly accepted. While a high A1C is not good, some methods of lowering A1C in some patient groups, may also be harmful. While we do not want to be lazy in addressing glucose control, the evidence suggests that we not assume a net benefit for all A1C lowering interventions in all Type 2 diabetes patients. {*Let the target serve the patient, and not the patient the target.*}

Multfactorial intervention - blood pressure, lipids, possibly ASA, lifestyle – in addition to glucose control, is essential in reducing macrovascular endpoints!

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