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Continuous Subcutaneous Insulin Infusion (CSII) Pumps for Type 1 and Type 2 Adult Diabetic Populations

An Evidence-Based Analysis

Presented to the Ontario Health Technology Advisory Committee in June, 2009

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis, please contact the Medical Advisory Secretariat: MASinfo.moh@ontario.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

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List of Abbreviations

ADRR	Average daily risk range
BMI	Body mass index
HbA1c	Glycosylated haemoglobin
CI	Confidence interval
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes control and complications trial
DM	Diabetes mellitus
DTSQ	Diabetes treatment satisfaction questionnaire
DQOLCTQ	Diabetes quality of life clinical trial questionnaire
IDDM	Insulin-dependent diabetes mellitus
ITT	Intention to treat
MAS	Medical Advisory Secretariat
MAGE	Mean amplitude of glycemic excursions
MDI	Multiple daily injection
NPH	Neutral protamine gagedorn
ODEM	Ontario diabetes economic model
QALY	Quality adjusted life year
QOL	Quality of life
RCT	Randomized controlled trial
SAE	Serious adverse event
SD	Standard deviation
SMBG	Self monitoring of blood glucose
UKPDS	United Kingdom prospective diabetes study

Executive Summary

In June 2008, the Medical Advisory Secretariat began work on the Diabetes Strategy Evidence Project, an evidence-based review of the literature surrounding strategies for successful management and treatment of diabetes. This project came about when the Health System Strategy Division at the Ministry of Health and Long-Term Care subsequently asked the secretariat to provide an evidentiary platform for the Ministry's newly released Diabetes Strategy.

After an initial review of the strategy and consultation with experts, the secretariat identified five key areas in which evidence was needed. Evidence-based analyses have been prepared for each of these five areas: insulin pumps, behavioural interventions, bariatric surgery, home telemonitoring, and community based care. For each area, an economic analysis was completed where appropriate and is described in a separate report.

To review these titles within the Diabetes Strategy Evidence series, please visit the Medical Advisory Secretariat Web site, http://www.health.gov.on.ca/english/providers/program/mas/mas_about.html,

1. Diabetes Strategy Evidence Platform: Summary of Evidence-Based Analyses
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5. Community-Based Care for the Management of Type 2 Diabetes: An Evidence-Based Analysis
6. Home Telemonitoring for Type 2 Diabetes: An Evidence-Based Analysis
7. Application of the Ontario Diabetes Economic Model (ODEM) to Determine the Cost-effectiveness and Budget Impact of Selected Type 2 Diabetes Interventions in Ontario

Objective

The objective of this analysis is to review the efficacy of continuous subcutaneous insulin infusion (CSII) pumps as compared to multiple daily injections (MDI) for the type 1 and type 2 adult diabetics.

Clinical Need and Target Population

Insulin therapy is an integral component of the treatment of many individuals with diabetes. Type 1, or juvenile-onset diabetes, is a life-long disorder that commonly manifests in children and adolescents, but onset can occur at any age. It represents about 10% of the total diabetes population and involves immune-mediated destruction of insulin producing cells in the pancreas. The loss of these cells results in a decrease in insulin production, which in turn necessitates exogenous insulin therapy.

Type 2, or 'maturity-onset' diabetes represents about 90% of the total diabetes population and is marked by a resistance to insulin or insufficient insulin secretion. The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. The condition tends to develop gradually and may remain undiagnosed for many years. Approximately 30% of patients with type 2 diabetes eventually require insulin therapy.

CSII Pumps

In conventional therapy programs for diabetes, insulin is injected once or twice a day in some combination of short- and long-acting insulin preparations. Some patients require intensive therapy regimes known as multiple daily injection (MDI) programs, in which insulin is injected three or more times a day. It's a time consuming process and usually requires an injection of slow acting basal insulin in the morning or evening and frequent doses of short-acting insulin prior to eating. The most common form of slower acting insulin used is neutral protamine gagedorn (NPH), which reaches peak activity 3 to 5 hours after injection. There are some concerns surrounding the use of NPH at night-time as, if injected immediately before bed, nocturnal hypoglycemia may occur. To combat nocturnal hypoglycemia and other issues related to absorption, alternative insulins have been developed, such as the slow-acting insulin glargine. Glargine has no peak action time and instead acts consistently over a twenty-four hour period, helping reduce the frequency of hypoglycemic episodes.

Alternatively, intensive therapy regimes can be administered by continuous insulin infusion (CSII) pumps. These devices attempt to closely mimic the behaviour of the pancreas, continuously providing a basal level insulin to the body with additional boluses at meal times. Modern CSII pumps are comprised of a small battery-driven pump that is designed to administer insulin subcutaneously through the abdominal wall via butterfly needle. The insulin dose is adjusted in response to measured capillary glucose values in a fashion similar to MDI and is thus often seen as a preferred method to multiple injection therapy. There are, however, still risks associated with the use of CSII pumps. Despite the increased use of CSII pumps, there is uncertainty around their effectiveness as compared to MDI for improving glycemic control.

Part A: Type 1 Diabetic Adults (≥19 years)

An evidence-based analysis on the efficacy of CSII pumps compared to MDI was carried out on both type 1 and type 2 adult diabetic populations.

Research Questions

1. Are CSII pumps more effective than MDI for improving glycemic control in adults (≥19 years) with type 1 diabetes?

2. Are CSII pumps more effective than MDI for improving additional outcomes related to diabetes such as quality of life (QoL)?

Literature Search

Inclusion Criteria

- Randomized controlled trials, systematic reviews, meta-analysis and/or health technology assessments from MEDLINE, EMBASE, CINAHL
- Adults (≥ 19 years)
- Type 1 diabetes
- Study evaluates CSII vs. MDI
- Published between January 1, 2002 – March 24, 2009
- Patient currently on intensive insulin therapy

Exclusion Criteria

- Studies with <20 patients
- Studies <5 weeks in duration
- CSII applied only at night time and not 24 hours/day
- Mixed group of diabetes patients (children, adults, type 1, type 2)
- Pregnancy studies

Outcomes of Interest

- The primary outcomes of interest were glycosylated hemoglobin (HbA1c) levels, mean daily blood glucose, glucose variability, and frequency of hypoglycaemic events. Other outcomes of interest were insulin requirements, adverse events, and quality of life.

Search Strategy

The literature search strategy employed keywords and subject headings to capture the concepts of:

1) insulin pumps, and

2) type 1 diabetes.

The search was run on July 6, 2008 in the following databases: Ovid MEDLINE (1996 to June Week 4 2008), OVID MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (1980 to 2008 Week 26), OVID CINAHL (1982 to June Week 4 2008) the Cochrane Library, and the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment. A search update was run on March 24, 2009 and studies published prior to 2002 were also examined for inclusion into the review. Parallel search strategies were developed for the remaining databases. Search results were limited to human and English-language published between January 2002 and March 24, 2009. Abstracts were reviewed, and studies meeting the inclusion criteria outlined above were obtained. Reference lists were also checked for relevant studies.

Summary of Findings

The database search identified 519 relevant citations published between 1996 and March 24, 2009. Of the 519 abstracts reviewed, four RCTs and one abstract met the inclusion criteria outlined above. While efficacy outcomes were reported in each of the trials, a meta-analysis was not possible due to missing data around standard deviations of change values as well as missing data for the first period of the crossover arm of the trial. Meta-analysis was not possible on other outcomes (quality of life, insulin requirements, frequency of hypoglycemia) due to differences in reporting.

HbA1c

In studies where no baseline data was reported, the final values were used. Two studies (Hanaire-Broutin et al. 2000, Hoogma et al. 2005) reported a slight reduction in HbA1c of 0.35% and 0.22% respectively for CSII pumps in comparison to MDI. A slightly larger reduction in HbA1c of 0.84% was reported by DeVries et al.; however, this study was the only study to include patients with poor glycemic control marked by higher baseline HbA1c levels. One study (Bruttomesso et al. 2008) showed no difference between CSII pumps and MDI on Hba1c levels and was the only study using insulin glargine (consistent with results of parallel RCT in abstract by Bolli 2004). While there is statistically significant reduction in HbA1c in three of four trials, there is no evidence to suggest these results are clinically significant.

Mean Blood Glucose

Three of four studies reported a statistically significant reduction in the mean daily blood glucose for patients using CSII pump, though these results were not clinically significant. One study (DeVries et al. 2002) did not report study data on mean blood glucose but noted that the differences were not statistically significant. There is difficulty with interpreting study findings as blood glucose was measured differently across studies. Three of four studies used a glucose diary, while one study used a memory meter. In addition, frequency of self monitoring of blood glucose (SMBG) varied from four to nine times per day. Measurements used to determine differences in mean daily blood glucose between the CSII pump group and MDI group at clinic visits were collected at varying time points. Two studies use measurements from the last day prior to the final visit (Hoogma et al. 2005, DeVries et al. 2002), while one study used measurements taken during the last 30 days and another study used measurements taken during the 14 days prior to the final visit of each treatment period.

Glucose Variability

All four studies showed a statistically significant reduction in glucose variability for patients using CSII pumps compared to those using MDI, though one, Bruttomesso et al. 2008, only showed a significant reduction at the morning time point. Brutomesso et al. also used alternate measures of glucose variability and found that both the Lability index and mean amplitude of glycemic excursions (MAGE) were in concordance with the findings using the standard deviation (SD) values of mean blood glucose, but the average daily risk range (ADRR) showed no difference between the CSII pump and MDI groups.

Hypoglycemic Events

There is conflicting evidence concerning the efficacy of CSII pumps in decreasing both mild and severe hypoglycemic events. For mild hypoglycemic events, DeVries et al. observed a higher number of events per patient week in the CSII pump group than the MDI group, while Hoogma et al. observed a higher number of events per patient year in the MDI group. The remaining two studies found no differences between the two groups in the frequency of mild hypoglycemic events. For severe hypoglycemic events, Hoogma et al. found an increase in events per patient year among MDI patients, however, all of the other RCTs showed no difference between the patient groups in this aspect.

Insulin Requirements and Adverse Events

In all four studies, insulin requirements were significantly lower in patients receiving CSII pump treatment in comparison to MDI. This difference was statistically significant in all studies. Adverse events were reported in three studies. Devries et al. found no difference in ketoacidotic episodes between CSII pump and MDI users. Bruttomesso et al. reported no adverse events during the study. Hanaire-Broutin et al. found that 30 patients experienced 58 serious adverse events (SAEs) during MDI and 23 patients had 33 SAEs during treatment out of a total of 256 patients. Most events were related to severe hypoglycemia and diabetic ketoacidosis.

Quality of Life and Patient Preference

QoL was measured in three studies and patient preference was measured in one. All three studies found an improvement in QoL for CSII users compared to those using MDI, although various instruments were used among the studies and possible reporting bias was evident as non-positive outcomes were not consistently reported. Moreover, there was also conflicting results in two of the studies using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). DeVries et al. reported no difference in treatment satisfaction between CSII pump users and MDI users while Brutomesso et al. reported that treatment satisfaction improved among CSII pump users.

Patient preference for CSII pumps was demonstrated in just one study (Hanaire-Broutin et al. 2000) and there are considerable limitations with interpreting this data as it was gathered through interview and 72% of patients that preferred CSII pumps were previously on CSII pump therapy prior to the study. As all studies were industry sponsored, findings on QoL and patient preference must be interpreted with caution.

Quality of Evidence

Overall, the body of evidence was downgraded from high to low due to study quality and issues with directness as identified using the GRADE quality assessment tool (see Table 1) While blinding of patient to intervention/control was not feasible in these studies, blinding of study personnel during outcome assessment and allocation concealment were generally lacking. Trials reported consistent results for the outcomes HbA1c, mean blood glucose and glucose variability, but the directness or generalizability of studies, particularly with respect to the generalizability of the diabetic population, was questionable as most trials used highly motivated populations with fairly good glycemic control. In addition, the populations in each of the studies varied with respect to prior treatment regimens, which may not be generalizable to the population eligible for pumps in Ontario. For the outcome of hypoglycaemic events the evidence was further downgraded to very low since there was conflicting evidence between studies with respect to the frequency of mild and severe hypoglycaemic events in patients using CSII pumps as compared to CSII (see Table 2). The GRADE quality of evidence for the use of CSII in adults with type 1 diabetes is therefore low to very low and any estimate of effect is, therefore, uncertain.

Table ES 1: GRADE Quality Assessment for CSII pumps vs. MDI on HbA1c, Mean Blood Glucose, and Glucose Variability for Adults with Type 1 Diabetes

Outcome	Study	Design	Study Quality	Consistency	Directness	Other modifying factors	Overall quality of evidence
HbA1c Mean Blood Glucose Glucose Variability	Hanaire-Broutin 2000	RCT	Serious limitations*	Consistency†	Indirect‡	Not applicable	**LOW**
	Brutomesso 2008	RCT					
	DeVries 2002	RCT					
	Hoogma 2005	RCT HIGH	MODERATE	MODERATE	LOW		

*Inadequate or unknown allocation concealment (3/4 studies); Unblinded assessment (all studies) however lack of blinding due to the nature of the study; No ITT analysis (2/4 studies); possible bias SMBG (all studies)

†HbA1c: 3/4 studies show consistency however magnitude of effect varies greatly; Single study uses insulin glargine instead of NPH; Mean Blood Glucose: 3/4 studies show consistency however magnitude of effect varies between studies; Glucose Variability: All studies show consistency but 1 study only showed a significant effect in the morning

‡Generalizability in question due to varying populations: highly motivated populations, educational component of interventions/ run-in phases, insulin pen use in 2/4 studies and varying levels of baseline glycemic control and experience with intensified insulin therapy, pumps and MDI.

Table ES 2: GRADE Quality Assessment for CSII pumps vs. MDI on Frequency of Hypoglycemic Events for Adults with Type 1 Diabetes

Outcome	Study	Design	Study Quality	Consistency	Directness	Other modifying factors	Overall quality of evidence
Frequency of Hypoglycemic Events	Hanaire-Broutin 2000	RCT	Serious limitations*	Inconsistent†	Indirect‡	Not applicable	**VERY LOW**
	Brutomesso 2008	RCT					
	DeVries 2002	RCT					
	Hoogma 2005	RCT					
		HIGH	MODERATE	LOW	VERY LOW		

*Inadequate or unknown allocation concealment (3/4 studies); Unblinded assessment (all studies) however lack of blinding due to the nature of the study; No ITT analysis (2/4 studies); possible bias SMBG (all studies)

†Conflicting evidence with respect to mild and severe hypoglycemic events reported in studies

‡Generalizability in question due to varying populations: highly motivated populations, educational component of interventions/ run-in phases, insulin pen use in 2/4 studies and varying levels of baseline glycemic control and experience with intensified insulin therapy, pumps and MDI.

Economic Analysis

One article was included in the analysis from the economic literature scan. Four other economic evaluations were identified but did not meet our inclusion criteria. Two of these articles did not compare CSII with MDI and the other two articles used summary estimates from a mixed population with Type 1 and 2 diabetes in their economic microsimulation to estimate costs and effects over time. Included were English articles that conducted comparisons between CSII and MDI with the outcome of Quality Adjusted Life Years (QALY) in an adult population with type 1 diabetes.

From one study, a subset of the population with type 1 diabetes was identified that may be suitable and benefit from using insulin pumps. There is, however, limited data in the literature addressing the cost-effectiveness of insulin pumps versus MDI in type 1 diabetes. Longer term models are required to estimate the long term costs and effects of pumps compared to MDI in this population.

Conclusions

CSII pumps for the treatment of adults with type 1 diabetes

1. Based on low-quality evidence, CSII pumps confer a statistically significant but not clinically significant reduction in HbA1c and mean daily blood glucose as compared to MDI in adults with type 1 diabetes (>19 years).
2. CSII pumps also confer a statistically significant reduction in glucose variability as compared to MDI in adults with type 1 diabetes (>19 years) however the clinical significance is unknown.
3. There is indirect evidence that the use of newer long-acting insulins (e.g. insulin glargine) in MDI regimens result in less of a difference between MDI and CSII compared to differences between MDI and CSII in which older insulins are used.
4. There is conflicting evidence regarding both mild and severe hypoglycemic events in this population when using CSII pumps as compared to MDI. These findings are based on very low-quality evidence.

5. There is an improved quality of life for patients using CSII pumps as compared to MDI however, limitations exist with this evidence.
6. Significant limitations of the literature exist specifically:
   - All studies sponsored by insulin pump manufacturers
   - All studies used crossover design
   - Prior treatment regimens varied
   - Types of insulins used in study varied (NPH vs. glargine)
   - Generalizability of studies in question as populations were highly motivated and half of studies used insulin pens as the mode of delivery for MDI
7. One short-term study concluded that pumps are cost-effective, although this was based on limited data and longer term models are required to estimate the long-term costs and effects of pumps compared to MDI in adults with type 1 diabetes.

Part B: Type 2 Diabetic Adults

Research Questions

1. Are CSII pumps more effective than MDI for improving glycemic control in adults (≥19 years) with type 2 diabetes?
2. Are CSII pumps more effective than MDI for improving other outcomes related to diabetes such as quality of life?

Literature Search

Inclusion Criteria

- Randomized controlled trials, systematic reviews, meta-analysis and/or health technology assessments from MEDLINE, Excerpta Medica Database (EMBASE), Cumulative Index to Nursing & Allied Health Literature (CINAHL)
- Any person with type 2 diabetes requiring insulin treatment intensive
- Published between January 1, 2000 – August 2008

Exclusion Criteria

- Studies with <10 patients
- Studies <5 weeks in duration
- CSII applied only at night time and not 24 hours/day
- Mixed group of diabetes patients (children, adults, type 1, type 2)
- Pregnancy studies

Outcomes of Interest

The primary outcome of interest was a reduction in glycosylated hemoglobin (HbA1c) levels.
Other outcomes of interest were mean blood glucose level, glucose variability, insulin requirements, frequency of hypoglycemic events, adverse events, and quality of life.

Search Strategy

A comprehensive literature search was performed in OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, The Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published between January 1, 2000 and August 15, 2008. Studies meeting the inclusion criteria were selected from the search results. Data on the study characteristics, patient characteristics, primary and secondary treatment outcomes, and adverse events were abstracted. Reference lists of selected articles were also checked for relevant studies. The quality of the evidence was assessed as high, moderate, low, or very low according to the GRADE methodology.

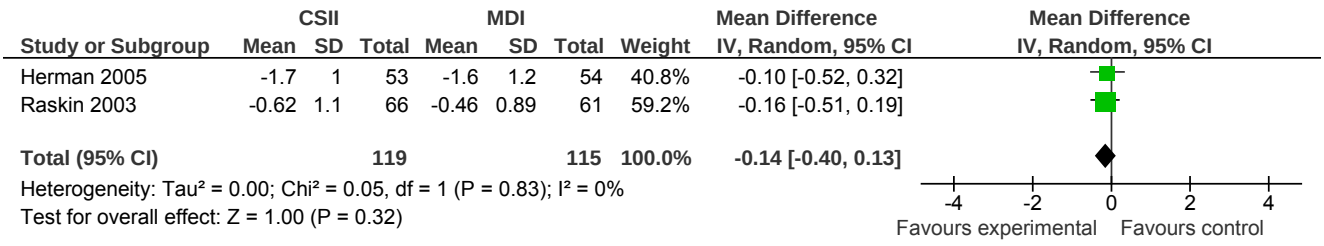
Summary of Findings

The database search identified 286 relevant citations published between 1996 and August 2008. Of the 286 abstracts reviewed, four RCTs met the inclusion criteria outlined above. Upon examination, two studies were subsequently excluded from the meta-analysis due to small sample size and missing data (Berthe et al.), as well as outlier status and high drop out rate (Wainstein et al) which is consistent with previously reported meta-analyses on this topic (Jeitler et al 2008, and Fatourechi M et al. 2009).

HbA1c

The primary outcome in this analysis was reduction in HbA1c. Both studies demonstrated that both CSII pumps and MDI reduce HbA1c, but neither treatment modality was found to be superior to the other. The results of a random effects model meta-analysis showed a mean difference in HbA1c of -0.14 (-0.40, 0.13) between the two groups, which was found not to be statistically or clinically significant. There was no statistical heterogeneity observed between the two studies (I^2=0%).

Figure 1: Forrest plot of two parallel, RCTs comparing CSII to MDI in type 2 diabetes



Secondary Outcomes

Mean Blood Glucose and Glucose Variability

Mean blood glucose was only used as an efficacy outcome in one study (Raskin et al. 2003). The authors found that the only time point in which there were consistently lower blood glucose values for the CSII group compared to the MDI group was 90 minutes after breakfast. Glucose variability was not examined in either study and the authors reported no difference in weight gain between the CSII pump group and MDI groups at the end of study. Conflicting results were reported regarding injection site reactions between the two studies. Herman et al. reported no difference in the number of subjects experiencing site problems between the two groups, while Raskin et al. reported that there were no injection site reactions in the MDI group but 15 such episodes among 8 participants in the CSII pump group.

Frequency of Hypoglycemic Events and Insulin Requirements

All studies reported that there were no differences in the number of mild hypoglycemic events in patients on CSII pumps versus MDI. Herman et al. also reported no differences in the number of severe hypoglycemic events in patients using CSII pumps compared to those on MDI. Raskin et al. reported that there were no severe hypoglycemic events in either group throughout the study duration. Insulin requirements were only examined in Herman et al., who found that daily insulin requirements were equal between the CSII pump and MDI treatment groups.

Quality of Life

QoL was measured by Herman et al. using the Diabetes Quality of Life Clinical Trial Questionnaire (DQOLCTQ). There were no differences reported between CSII users and MDI users for treatment satisfaction, diabetes impact, and worry-related scores. Patient satisfaction was measured in Raskin et al. using a patient satisfaction questionnaire, whose results indicated that patients in the CSII pump group had significantly greater improvement in overall treatment satisfaction at the end of the study compared to the MDI group. Although patient preference was also reported, it was only examined in the CSII pump group, thus results indicating a greater preference for CSII pumps in this groups (as compared to prior injectable insulin regimens) are biased and must be interpreted with caution.

Quality of Evidence

Overall, the body of evidence was downgraded from high to low according to study quality and issues with directness as identified using the GRADE quality assessment tool (see Table 3). While blinding of patient to intervention/control is not feasible in these studies, blinding of study personnel during outcome assessment and allocation concealment were generally lacking. ITT was not clearly explained in one study and heterogeneity between study populations was evident from participants' treatment regimens prior to study initiation. Although trials reported consistent results for HbA1c outcomes, the directness or generalizability of studies, particularly with respect to the generalizability of the diabetic population, was questionable as trials required patients to adhere to an intense SMBG regimen. This suggests that patients were highly motivated. In addition, since prior treatment regimens varied between participants (no requirement for patients to be on MDI), study findings may not be generalizable to the population eligible for a pump in Ontario. The GRADE quality of evidence for the use of CSII in adults with type 2 diabetes is, therefore, low and any estimate of effect is uncertain.

Table ES 3: GRADE Quality Assessment for CSII pumps vs. MDI on HbA1c Adults with Type 2 Diabetes

Study	Design	Study Quality	Consistency	Directness	Other modifying factors	Overall quality of evidence
Raskin 2003	RCT	Serious limitations*	Consistent	Indirect†	Not applicable	**LOW**
Herman 2005	RCT					
	HIGH	MODERATE	LOW	LOW		

*Inadequate or unknown allocation concealment (all studies); Unblinded assessment (all studies) however lack of blinding due to the nature of the study; ITT not well explained in 1 of 2 studies

†Indirect due to lack of generalizability of findings since participants varied with respect to prior treatment regimens and intensive SMBG suggests highly motivated populations used in trials.

Economic Analysis

An economic analysis of CSII pumps was carried out using the Ontario Diabetes Economic Model (ODEM) and has been previously described in the report entitled "Application of the Ontario Diabetes Economic Model (ODEM) to Determine the Cost-effectiveness and Budget Impact of Selected Type 2 Diabetes Interventions in Ontario", part of the diabetes strategy evidence series. Based on the analysis, CSII pumps are not cost-effective for adults with type 2 diabetes, either for the age 65+ sub-group or for all patients in general. Details of the analysis can be found in the full report.

Conclusions

CSII pumps for the treatment of adults with type 2 diabetes

1. There is low quality evidence demonstrating that the efficacy of CSII pumps is not superior to MDI for adult type 2 diabetics.
2. There were no differences in the number of mild and severe hypoglycemic events in patients on CSII pumps versus MDI.
3. There are conflicting findings with respect to an improved quality of life for patients using CSII pumps as compared to MDI.
4. Significant limitations of the literature exist specifically:
    - All studies sponsored by insulin pump manufacturers
    - Prior treatment regimens varied
    - Types of insulins used in study varied (NPH vs. glargine)
    - Generalizability of studies in question as populations may not reflect eligible patient population in Ontario (participants not necessarily on MDI prior to study initiation, pen used in one study and frequency of SMBG required during study was high suggesting highly motivated participants)

1. Based on ODEM, insulin pumps are not cost-effective for adults with type 2 diabetes either for the age 65+ sub-group or for all patients in general.

Background

In June 2008, the Medical Advisory Secretariat began work on the Diabetes Strategy Evidence Project, an evidence-based review of the literature surrounding strategies for successful management and treatment of diabetes. This project came about when the Health System Strategy Division at the Ministry of Health and Long-Term Care subsequently asked the secretariat to provide an evidentiary platform for the Ministry's newly released Diabetes Strategy.

After an initial review of the strategy and consultation with experts, the secretariat identified five key areas in which evidence was needed. Evidence-based analyses have been prepared for each of these five areas: insulin pumps, behavioural interventions, bariatric surgery, home telemonitoring, and community based care. For each area, an economic analysis was completed where appropriate and is described in a separate report.

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Objective

The objective of this analysis is to review the efficacy of continuous subcutaneous insulin infusion (CSII) pumps as compared to multiple daily injections (MDI) for the type 1 and type 2 adult diabetics.

Clinical Need: Target Population and Condition

Insulin therapy is an integral component of the treatment of many individuals with diabetes. Type 1, or juvenile-onset diabetes, constitutes approximately 10% of the total diabetic population and involves immune-mediated destruction of insulin producing cells in the pancreas. The loss of these cells results in a decrease in insulin production, which in turn necessitates exogenous insulin therapy. Type 1 diabetes is a life-long disorder that commonly manifests in children and adolescents, but onset can occur at any age. Type 2, or maturity-onset diabetes, constitutes about 90% of the total diabetic population and is marked by a resistance to insulin or insufficient insulin secretion. The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. (5) The condition tends to develop gradually and may remain undiagnosed for many years. Approximately 30% of patients with type 2 diabetes eventually require insulin therapy.

Reducing the Risk of Diabetes Complications

- Two large-scale, long-term randomized controlled trials (RCTs) have demonstrated that intensive treatment and tight glycemic control can significantly reduce the risk of the microvascular complications of diabetes. (6-8)
- Data from the Diabetes Control and Complications Trial (DCCT) showed that in type 1 diabetics, a 10% relative decrease in HbA1c (a measure of averaged blood glucose levels) led to a 43% reduction in retinopathy progression and other complications of insulin-dependent diabetes mellitus (IDDM). (9)
- Data from the United Kingdom Prospective Diabetes study (UKPDS) showed that in type 2 diabetics, every 1.0 % absolute decrease in HbA1c led to a 21% relative decrease in any end-point related to diabetes, a 14% relative decrease in all-cause mortality, a 14% relative decrease in myocardial infarction, and a 37% relative decrease in micro-vascular endpoints. (6)

Insulin Treatment

When used properly, insulin treatment is a safe and effective method of achieving glycemic control; however, some complications may arise. (10) Specifically, insulin therapy may cause blood glucose levels to drop below normal levels, a state referred to as hypoglycemia. Mild hypoglycemia is a relatively common occurrence among insulin dependent diabetics and may cause hunger, dizziness, shakiness, and sweating. It may also occur during sleep, resulting in excessive perspiration and confusion in the morning. (11) In its mild form, hypoglycemia can be corrected by immediately ingesting food and/or juice.

The risk of hypoglycemia is higher in people with diabetes who endure intensive treatment. In a meta-analysis of RCTs comparing intensive insulin treatment with conventional treatments, the incidence of severe hypoglycemia ranged from 0 to 33 per 100 person-years in traditionally treated patients. Subsequently, the incidence increased from 0 to 66 in intensively treated patients. (12)

A small subset of the diabetes population is also at risk of developing severe hypoglycemia. The danger of developing the condition is higher at night, particularly in those individuals who maintain plasma glucose levels below 5.5 mmol/L. (13)

Continuous Subcutaneous Insulin Infusion (CSII) Pumps

CSII pumps were invented in the United Kingdom (UK) and the first report of their use was published by Pickup et al. in 1978. (14) These devices attempt to closely mimic the behaviour of the pancreas, continuously providing a basal level insulin to the body with additional boluses at meal times.

Modern CSII pumps are comprised of a small battery-driven pump that is designed to administer insulin subcutaneously into the abdominal wall through a butterfly needle. The insulin dose is adjusted in response to measured capillary glucose values in a fashion similar to multiple injection therapy.

Advancements in CSII technology continue to develop and pumps have become much more reliable in recent years. Colquitt et al. cited that trials using pumps in the 1980s showed many patients discontinuing pump use after switching over from multiple daily injections (MDI). More recent studies have demonstrated, however, that many patients now prefer the use of CSII to MDI. (13;15) In 2002, it was estimated that more than 200,000 patients with diabetes worldwide use CSII pumps for everyday treatment. (16) There are, however, still risks associated with the use of CSII pumps, including hypoglycemia related death in rare cases. (17)

Regulatory Status

According to the Health Canada, medical devices program, CSII pumps and their accessories are all licensed for use in Canada. The devices are distributed in Canada by Medtronic MiniMed and Disetronic Medical Systems. In 1999, the MiniMed MMT-103 was the first pump to be issued a license from Health Canada.

In Ontario, CSII pumps are covered by the Assisted Devices Program (ADP) for use in children with type 1 diabetes (since April 2006) and type 1 adult diabetics (since September 2008). CSII pumps are not currently funded in Ontario for use in type 2 diabetics.

Alternatives: Intensive Insulin Therapy

In conventional therapy programs for diabetes, insulin is injected once or twice a day in some combination of short- and long-acting insulin preparations. Some patients require intensive therapy regimes known as multiple daily injections (MDI) programs, in which insulin is injected three or more times a day. MDI is time consuming and usually requires an injection of slow-acting basal insulin in the morning or evening and frequent doses of short-acting insulin prior to eating. The most common form of slow acting insulin used is neutral protamine Hagedorn, or NPH, which reaches peak activity approximately 3 to 5 hours after injection. (18) There are some concerns surrounding the use of NPH at nighttime as, however, if injected immediately before bed, nocturnal hypoglycemia (a drop in blood glucose occurring overnight) may occur. To combat nocturnal hypoglycemia and other issues surrounding absorption, the industry has developed slow-acting insulins such as insulin glargine. Insulin glargine has no peak action time and instead acts consistently over a twenty-four hour period, which can help reduce the frequency of hypoglycemic episodes. In recent reviews, slow-acting insulins have been shown to offer better glycemic control than MDI and to reduce hypoglycemic risk in certain diabetic populations. (19-21)

Evidence-Based Analysis of Effectiveness: Adult (≥ 19 years), Type 1 Diabetes

Objective

To determine if CSII pumps are more effective than MDI for adults (≥ 19 years) with type 1 diabetes.

Research Questions

1. Do CSII pumps improve glycemic control in adults (≥ 19 years) with type 1 diabetes?
2. Do CSII pumps improve quality of life in adults with type 1 diabetes?

Literature Search

Inclusion Criteria

- Randomized controlled trials, systematic reviews, meta-analysis and/or health technology assessments from MEDLINE, EMBASE, CINAHL
- Adults (≥ 19 years)
- Type 1 diabetes
- Study evaluates CSII vs. MDI
- Published between January 1, 2002 – March 24, 2009
- Patient currently on intensive insulin therapy

Exclusion Criteria

- Studies with <20 patients
- Studies <5 weeks in duration
- CSII applied only at night time and not 24 hours/day
- Mixed group of diabetes patients (children, adults, type 1, type 2)
- Pregnancy studies

Outcomes of Interest

The primary outcomes of interest were:

- glycosylated hemoglobin (HbA1c) levels,
- mean daily blood glucose,
- glucose variability, and
- frequency of hypoglycaemic events.

Other outcomes of interest were insulin requirements, adverse events, and quality of life.

Search Method

The literature search strategy employed keywords and subject headings to capture the concepts of 1) insulin pumps and 2) type 1 diabetes. The search was run on July 6, 2008 in the following databases: Ovid MEDLINE (1996 to June Week 4 2008), OVID MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (1980 to 2008 Week 26), OVID CINAHL (1982 to June Week 4 2008) the Cochrane Library, and the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment. A search update was run on March 24, 2009 and studies published prior to 2002 were also examined for inclusion into the review. The literature search strategies for MEDLINE, CINAHL and EMBASE are reproduced in Appendix 1. Parallel search strategies were developed for the remaining databases. Search results were limited to human and English-language studies published between January 2002 and March 24, 2009. Abstracts were reviewed and those meeting the inclusion criteria outlined above were obtained. Reference lists were also checked for relevant studies.

Statistical Challenges for Meta-Analysis

While HbA1c, mean blood glucose, and glucose variability were reported in each of the trials, a meta-analysis was not possible due to missing data around standard deviations of change values, as well as missing data for the first period of the crossover arm of the trials. Meta-analysis was not possible on other outcomes (quality of life, insulin requirements, frequency of hypoglycemia) because of differences in reporting. Insulin dose was either reported as total insulin requirement per person or per body weight, per day. Similarly, hypoglycemia and quality of life were not reported consistently between the trials, making meta-analysis of these outcomes impossible.

Clinically Meaningful Endpoints

For the measures of glycemic control, including HbA1c (%), mean daily blood glucose, and glucose variability, clinically relevant endpoints for the type 1 diabetic population were determined from the literature and from consultation with experts. For HbA1c (%), the DCCT demonstrated that a 10% relative decrease (i.e., from 10.0% to 9.0%, or from 8.0% to 7.2%) reduces the risk of micro- and macrovascular complications by clinically meaningful rates in IDDM. For mean daily blood glucose (mmol/L), we estimated clinical significance based on the knowledge that a difference in HbA1c of 1.0% is equivalent to a difference in average glucose value of 1.6 mmol/L. As the type 1 diabetic population is prone to huge swings in their glucose levels over time, an average measure such as HbA1c and mean blood glucose may not accurately reflect the glycemic control of a patient. Glucose variability has thus emerged in recent literature as an important efficacy measure. However, despite this knowledge, a clinically meaningful difference in glucose variability is still unknown.

Assessment of Quality of Evidence

The quality assigned to individual studies was determined using MAS' adaptation of the levels-of-evidence hierarchy proposed by Goodman. (22) The overall quality of the evidence was examined according to the GRADE Working Group criteria. (23)

- Quality refers to criteria such as the adequacy of allocation concealment, blinding, and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the differences in effect, and the significance of the differences guide the decision about whether important inconsistency exists.

Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions were used in grading the quality of the evidence.

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

The database search identified 519 relevant citations published between January 2000 and March 24, 2009. Of the 519 abstracts identified, 11 studies met the inclusion criteria as described above (Table 1). A detailed description of the studies can be found in Appendix 2. Of these, seven articles were systematic reviews and/or meta-analyses and the remaining four studies were RCTs. One additional abstract by Bolli et al. was found through a manual search. (24) Two of the four RCTs identified (25;26) were defined as small (total sample sizes N=42 and N=41 respectively) (Table 1).

Table 1: Quality of Evidence of Included Studies

Study Design*	Level of Evidence	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	9
Large RCT unpublished but reported to an international scientific meeting	1(g)	1
Small RCT	2	2
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

*For each included study, levels of evidence were assigned according to a ranking system based on a hierarchy proposed by Goodman. (22) An additional designation "g" was added for preliminary reports of studies that have been presented at international scientific meetings. Non-RCT, clinical trial that is not randomized, e.g., a cohort study; RCT refers to a randomized controlled trial.
Adapted from the Oxford Centre for Evidence (22)

Summary of Existing Evidence

Six reviews were identified through our literature search examining the efficacy of CSII pumps compared to MDI therapy in type 1 adult diabetic populations (Table 2). One additional review was identified (27) but is not described below as it included studies examining conventional treatment as a comparator to CSII in its analysis. Three of the six reviews identified included mixed diabetic populations (type 1 and type 2 diabetics). In addition, five of the six reviews included both child and adult populations.

The two most recent reviews are meta-analyses conducted by Fatourechi et al. in 2009 and Jeitler et al. in 2008 (3;4). In the review by Jeitler et al., the authors examined HbA1c as a primary outcome measure and used six RCTs in their analysis of CSII pumps compared to MDI for use among type 1 adult diabetics. The authors found a between-treatment difference of -0.4% in HbA1c levels in favour of CSII pumps. There was no difference between the two treatment groups with respect to hypoglycaemic events. Total insulin requirements were found to be lower with CSII pump treatment than MDI therapy; however, a large degree of heterogeneity was found among the studies.

Fatourechi et al 2009. also examined HbA1c as their primary outcome. The authors concluded that CSII pumps slightly reduced HbA1c compared to MDI, demonstrated by a between-treatment difference of -0.2% HbA1c in favour of CSII pumps, but noted an unclear impact of CSII pumps on reducing hypoglycaemic events.

Limitations of the previous reviews included:

- The quality of the studies included in the reviews was reported to be low
- The meta-analysis of differences in HbA1c showed high heterogeneity between studies
- Few meta-analyses or descriptions of alternate outcomes of glycemic control were outlined (e.g. glucose variability and mean daily blood glucose).
- There was inconsistency in the inclusion criteria used by reviews (e.g. study design, population, length of follow up, prior treatment regimes, baseline HbA1c, sample size etc…)
- The studies lacked generalizability of findings due to substantial heterogeneity among the reviews.

Table 2: Summary table of existing systematic reviews on CSII pump therapy versus MDI

Review	Type of Review (Search years)	Type of Studies included (# of trials*)	Population	Outcomes	Conclusions for Type 1 Adult Diabetics
Fatourechi et al. 2009 (3)	Meta-analysis (2002-2008)	RCTs (15)	▪ Type 1 & type 2 ▪ Adults ▪ Adolescents	▪ HbA1c ▪ Hypoglycemic events	▪ CSII pumps slightly reduced HbA1c compared to MDI ▪ WMD [-0.2% 95% CI (-0.3, -0.1)], with unclear impact on hypoglycemia.
Jeitler et al. 2008 (4)	Meta-analysis (up to March 2007)	RCTs (17†)	▪ Type 1 & type 2 ▪ Adults ▪ Children	▪ HbA1c ▪ Hypoglycemic episodes ▪ Adverse events ▪ Insulin requirements	▪ There was a between-treatment difference of −0.4% HbA1c in favour of CSII therapy as compared to MDI. ▪ No difference in hypoglycemic events was found between the two treatments. ▪ Total daily insulin requirements were lower with CSII than with MDI therapy.
Retnakaran et al. 2004 (28)	Meta-analysis (1982-2002)	RCTs (3)	▪ Type 1 ▪ Adult	▪ HbA1c ▪ Insulin dose ▪ Hypoglycemia ▪ Adverse events	▪ No significant overall difference in HbA1c reduction between CSII and MDII. ▪ An effect may be more apparent in those with higher baseline HbA1c. ▪ There is no significant difference in hypoglycemic risk between patients using CSII and MDI.
Colquitt et al. 2004, NICE (13)	Meta-analysis (NR)	RCTs, cohort and case series (20‡)	▪ Type 1 & type 2 ▪ Adults ▪ Children ▪ Adolescents ▪ Pregnant women	▪ HbA1c, ▪ Mean BG ▪ Daily insulin dose ▪ Body Weight ▪ Patient preferred ▪ QOL ▪ Adverse events	▪ A mean improvement in HbA1c of 0.5% was found with CSII compared with MDI in both short-term and longer term studies§. Insulin dose was reduced in short-term studies using CSII. ▪ Body weight, cholesterol levels, patient preference and hypoglycemic episodes did not differ between CSII and MDI groups.
Pons 2000 (29) (English summary only available)	Meta-analysis (NA)	NA	▪ Type 1 ▪ Adults ▪ Children	▪ Metabolic control - details NA	▪ CSII pumps do not conclusively offer a better metabolic control than intensive schedules with MDI in type 1 diabetics¥. ▪ No consistent data exists defining special characteristics in type I diabetes patients that would make them eligible for pumps.
AETMIS 2005 (30)	Systematic review (2002-2004)	RCTs, cohort, case series	▪ Type 1 ▪ Adults ▪ Children	▪ HbA1c level ▪ Mean blood glucose ▪ QOL ▪ Adverse effects ▪ Hypoglycemic episodes	▪ Studies comparing CSII pumps and MDI with NPH found that pumps are slightly superior in terms of metabolic control, particularly in groups with inadequate glycemic control at baseline (HbA1c ≥8.5%) ▪ Studies comparing CSII and MDI with glargine found no significant improvement in HbA1c level with CSII pumps.

BG: blood glucose; CSII: continuous subcutaneous insulin infusion ; NA: not available; NPH: neutral protamine hagedorn; NR: not reported; QOL: quality of life

*Including all DM patient populations; †Only 6 RCTs used in meta-analysis of HbA1c;

‡14 on type 1 adults; § excluding one trial using bovine ultralente in the control arm; ¥ including children

Literature Review Findings

The database search identified 519 relevant citations published between 1996 and March 24, 2009. Of the 519 abstracts reviewed, four RCTs and one abstract met the inclusion criteria outlined above. A meta-analysis was not carried out on these trials due to differences in methodological design and outcomes reporting. There was also missing data from the first crossover phase in the trials and authors could not be contacted regarding this data.

Table 3 highlights the main study characteristics between the four RCTs identified in the search. A detailed description of each study can be found in Appendix 2.

Table 3: Overview of study characteristics of included studies

RCT Characteristics	DeVries et al. 2002	Bruttomesso 2008	Hanaire-Broutin 2000	Hoogma et al. 2005
Design	Crossover*	Crossover	Crossover	Crossover
Length of Study	4 mo	8 mo	8 mo	16 mo
Run-In Period	14-wk qualification stage†	4-wk on CSII with insulin lispro	6-wk on CSII w/ regular insulin	8-wk prior to each treatment arm
Sample Size	79	42	41	272
Mean Age (yrs)	~37	~38	~43	~36
Patient Population	Highly motivated Poor glycemic control HbA1c≥8.5%‡	Highly motivated Good glycemic control Prev. on CSII ≥6 mo	32/41 pts prev. on CSII 9/41 pts prev. on MDI HbA1c<10.0%	Highly motivated Well controlled Prev. on MDI ≥6 mo
Baseline HbA1c (%)	9.3	7.6	8.4	7.9
CSII Pump	Disetronic HTRONplus – insulin aspart	Multiple pumps (Animas, D-Tron, H-Tron, V-100, MiniMed 508) using insulin lispro	Programmable external pump (MiniMed 506 or 507; MiniMed, and HTRON D or V; Disetronic with Insulin lispro	Disetronic H-TRON V100 or H-TRON plus V100 using insulin lispro
MDI	Insulin pen – Insulin aspart and NPH insulin	Insulin lispro and insulin glargine	Insulin pen – Insulin lispro and NPH	Insulin lispro and insulin NPH
SMBG for Mean Blood Glucose	SMBG nine-point profiles recorded in glucose diary on last day prior to visits	SMBG 4x/day plus after meals 2 d/wk and once 3 am in glucose diary; Last 30 days data used	SMBG 6x/day using memory meter; Last 14 days data used	SMBG eight-point profiles recorded in glucose diary on last day prior to visit
Industry Sponsored	Yes	Yes	Yes	Yes

CSII: Continuous subcutaneous insulin infusion; MDI: multiple daily injection; SMBG: wk: week; mo: month

*Analysed as a parallel study due to high drop-out

†Included strong educational component

‡HbA1c≥8.5% inclusion to qualification stage then HbA1c≥7.5% inclusion to randomization

In addition to the four RCTs outlined above, an abstract by Bolli et al. (24) published in *Diabetes* in 2004 was identified in our search (described below). While the abstract was not included in the graded body of evidence, it is included in this report due to its relevance and importance to this topic. It was the only study to use a parallel design and it examined the use of MDI using a long-acting analog insulin glargine compared to CSII. The goal of the study was to establish whether treatment using MDI with insulin glargine achieves glycemic control, as measured by HbA1c equivalent to CSII. The study involved 57 patients over a duration of 6 months. The population of interest were those with type 1 diabetes (HbA1c ≤9.0%) naïve to CSII and glargine.

The authors found no significant difference in HbA1c, mean blood glucose, or glucose variability between patients on CSII pumps versus an MDI regimen. They also confirmed that, over the 6 months study period, hypoglycemic events per patient were not statistically different between the two groups. Based on an economic analysis, the authors also estimated that the average cost per treatment was approximately four times more expensive with CSII. The authors thus concluded that both CSII and a once-daily glargine-based MDI regimen improve blood glucose to a similar extent with no differences in mean blood glucose, HbA1c, blood glucose excursions and frequency of hypoglycemia.

Patient Demographics

Across the four studies, a total of 434 patients were included with reported mean ages of 35.3 – 43.5 years. The mean duration of diabetes was similar across participants ranging from 14.5 – 20 years. Three of the four studies included participants with good glycemic control (as measured by mean HbA1c) at baseline from 7.5% to 8.3%. One study (15) included participants with poor glycemic control (10.0%) upon entering the study; at randomization (post qualification phase), however, the participants had reduced there HbA1c to 9.3%.

Prior treatment regimens also varied greatly between the trials. In one study, 78% of participants included were on CSII pumps at baseline and 22% on MDI. (26) A second study included patients that had been using CSII pumps for at least 6 months (25), while the two remaining studies included patients on MDI for at least 6 months. (15;31) Furthermore, for patients to be included in the DeVries study, they had to have had poor glycemic control (mean HbA1c ≥8.5%) in the 6 months prior to the trial while on MDI. (15) Three of the four trials included highly motivated participants demonstrated by their willingness to comply with good clinical practice throughout the trials and high frequency of blood glucose self-monitoring.

Summary of Study Design

All four RCTs were designed as crossover studies however, one study (15) was analyzed as a parallel study because of high drop-out after cross-over. All studies included a run-in phase prior to randomization, which varied in duration, type of treatment regimen used, and intensity of education received. Moreover, one study (15) used this phase as a qualification phase to exclude patients that were not able to comply with demands of good clinical practice.

Follow-up visits varied greatly between studies contributing to their overall heterogeneity. One study reported an intense follow-up schedule for patients during the trial that was carried out via in-person visits and telephone contact. (25) All studies required patients to adhere to an intense SMBG schedule, some having to monitor additional complications such as ketonuria, hypoglycemia, and technical or metabolic incidents.

CSII Pumps Regimen

A wide variety of pump systems were used across studies to deliver CSII treatment. Multiple pumps were also used in one single study. (25) Three of four studies used insulin lispro (25;26;31) while one study used insulin aspart (15) for CSII treatment. As mentioned previously, all studies included a training session explaining how to use the pump.

MDI Regimen

The comparison arm of each of the four studies was insulin treatment with MDI. Three of the studies used insulin lispro and the fourth used insulin aspart as bolus insulin. (15) The type of basal insulin used varied between studies with NPH being used in three (15;26;31) and insulin glargine was used in the most recent study. (25) Insulin pens were also used in two of the studies. (15;26)

Summary of Outcome Characteristics

All studies reported measures of glycemic control, specifically:

- HbA1c,
- mean daily blood glucose,
- glucose variability, and
- frequency of hypoglycaemic events.

Other outcomes examined were insulin requirements adverse events and quality of life. Patient preference was examined in one study.

Quality of Evidence

Overall, the body of evidence was downgraded from high to low according to study quality and issues with directness, as identified using the GRADE quality assessment tool. While blinding of patients to intervention/control was not feasible in these studies, blinding of study personnel during outcome assessment and allocation concealment were generally lacking.

Trials reported consistent results for the outcomes of HbA1c, mean blood glucose, and glucose variability, but the directness or generalizability of studies, particularly with respect to the generalizability of the diabetic population, was questionable as most trials used highly motivated populations with fairly good glycemic control (Table 4). In addition, the population in each of the studies varied with respect to prior treatment regimens, which may not be generalizable to the population eligible for CSII pumps in Ontario.

For the outcome of hypoglycaemic events, the evidence was further downgraded to very low since there was conflicting evidence between studies with respect to the frequency of mild and severe events among patients using CSII pumps as compared to MDI (Table 5).

The GRADE quality of evidence for the use of CSII in adults with type 1 diabetes is, therefore, low to very low and any estimate of effect is uncertain.

Table 4: Summary of GRADE Quality Assessment for CSII pumps versus MDI on HbA1c, Mean Blood Glucose and Glucose Variability for Adults with Type 1 Diabetes

Outcome	Study	Design	Study Quality	Consistency	Directness	Other modifying factors	Overall quality of evidence
HbA1c Mean Blood Glucose Glucose Variability	Hanaire-Broutin 2000	RCT	Serious limitations*	Consistency†	Indirect‡	Not applicable	**LOW**
	Bruttomesso 2008	RCT					
	DeVries 2002	RCT					
	Hoogma 2005	RCT					
		HIGH	**MODERATE**	**MODERATE**	**LOW**		

*Inadequate or unknown allocation concealment (3/4 studies); Unblinded assessment (all studies); however, lack of blinding due to the nature of the study; No ITT analysis (2/4 studies); possible bias self-measured blood glucose (all studies)

†HbA1c: 3/4 studies showed consistency, however, the magnitude of effect varied greatly between studies; Mean Blood Glucose: 3/4 studies showed consistency, however, the magnitude of effect varies between studies; Glucose Variability: All studies show consistency however one study only showed a significant effect in the morning

‡Generalizability in question due to varying populations: highly motivated populations, educational component of interventions/ run-in phases, insulin pen use in 2/4 studies and varying levels of baseline glycemic control and experience with intensified insulin therapy, pumps and MDI.

Table 5: Summary of GRADE Quality Assessment for CSII pumps versus MDI on Frequency of Hypoglycemic Events for Adults with Type 1 Diabetes

Outcome	Study	Design	Study Quality	Consistency	Directness	Other modifying factors	Overall quality of evidence
Frequency of Hypoglycemic Events	Hanaire-Broutin 2000	RCT	Serious limitations*	Inconsistent†	Indirect‡	Not applicable	**VERY LOW**
	Bruttomesso 2008	RCT					
	DeVries 2002	RCT					
	Hoogma 2005	RCT					
		HIGH	**MODERATE**	**LOW**	**VERY LOW**		

*Inadequate or unknown allocation concealment (3/4 studies); Unblinded assessment (all studies), however, lack of blinding due to the nature of the study; No ITT analysis (2/4 studies); possible bias SMBG (all studies)

†Conflicting evidence with respect to mild and severe hypoglycemic events reported in studies

‡Generalizability in question due to varying populations: highly motivated populations, educational component of interventions/ run-in phases, insulin pen use in 2/4 studies and varying levels of baseline glycemic control and experience with intensified insulin therapy, pumps and MDI.

Summary of Results

The primary outcome examined in this analysis was glycemic control measured by HbA1c, blood glucose, glucose variability, and the frequency of hypoglycemic events. Additional outcomes examined were insulin requirements, adverse events, quality of life and/or patient preference. Meta-analyses could not, however, be carried out due to differences in the reporting of outcomes and missing data.

HbA1c

Two studies (26;31) reported slight reductions in HbA1c of 0.35% and 0.22% for CSII pumps in comparison to MDI. A slightly larger reduction in HbA1c of 0.84% was reported in the DeVries study; however, this study was the only study to include patients with poor glycemic control marked by higher baseline HbA1c levels. One study, the only one to use insulin glargine, (25) showed no difference between CSII pumps and MDI therapy on HbA1c levels, which was consistent with the results of a parallel RCT abstract by Bolli et al. 2004. While there was a statistically significant reduction in HbA1c in three of the four trials, there is no evidence to suggest these results are clinically significant. Table 6 highlights the between-group differences in HbA1c levels from baseline to end of treatment.

Table 6: Efficacy of CSII compared to MDI measured by HbA1c levels

Study	Group	Baseline Mean HbA1c % ±SD	End of Treatment Mean HbA1c % ±SD	Between Group Difference	p*
DeVries 2002; (10)	MDI	9.25 ±1.4	9.18	0.84	0.002
	CSII	9.27 ±1.4	8.36		
Bruttomesso 2008; (19)	MDI	7.40 ±0.7	7.30 ±0.7	0.00	Not reported
	CSII	7.40 ±0.7	7.30 ±0.7		
Hanaire-Broutin 2000; (20)	MDI	NR	8.24 ±0.77	0.35	<0.001
	CSII	NR	7.89 ±0.77		
Hoogma 2005; (28)	MDI	NR	7.67 ±1.04	0.22	<0.001
	CSII	NR	7.45 ±0.96		

*Statistical significance of the difference between the CSII pump-treated group and the MDI group
NR: p-value not reported; SD: standard deviation

Mean Blood Glucose

Three of four studies reported a statistically significant reduction in mean daily blood glucose for patients using CSII pumps compared to those using MDI; however, according to the previously outlined definitions, these results are not clinically significant (see 'Clinically Meaningful Endpoints'). One study did not report mean blood glucose but noted that the differences were not statistically significant. (15) There was difficulty with interpreting study findings as blood glucose was measured differently across the studies. Three studies used a glucose diary while the fourth used a memory meter. In addition, frequency of SMBG varied from 4 to 9 times per day. Measurements used to determine differences in mean daily blood glucose between the CSII pump and MDI groups at clinic visits were collected at varying time points. Two studies use measurements from the last day prior to the final visit (15;31) while one used measurements taken during the last 30 days and the last study used measurements taken during the 14 days prior to the final visit of each treatment period. Table 7 summarizes the between-group differences in mean daily blood glucose from baseline to end of treatment for each of the four RCTs.

Table 7: Efficacy of CSII pumps compared to MDI measured by Mean Blood Glucose

Study	Group	Mean Daily BG (mmol/L) ±SD	Difference in Mean Daily BG Pump vs. MDI (95% CI) (mmol/L)	P
DeVries 2002*	MDI	NR	Authors note differences NOT statistically significant (NR)	NR
	CSII	NR		
Bruttomesso 2008	MDI	8.5 ±3.9	-0.35† (-0.62, -0.08)	0.012
	CSII	8.2 ±3.8		
Hanaire-Broutin 2000	MDI	9.7 ±1.8	-0.50†	<0.05
	CSII	9.2 ±1.5		
Hoogma 2005	MDI	9.4 ±1.9	-0.80†	<0.001
	CSII	8.6 ±1.8		

CI: confidence interval; NR: not reported

*Analyzed as a parallel study; †Statistically significant

Glucose Variability

All four studies measured glucose variability using the SD of blood glucose values, but Bruttomesso et al. also used three other measures for glucose variability: the Lability index, mean amplitude of glycemic excursions (MAGE), and average daily risk range (ADRR). (25) Since glucose variability was determined from blood glucose values, the differences in data collection of these values across the studies was also applicable to these findings. Table 8 summarizes the between-group differences in glucose variability from baseline to end of treatment for each of the four RCTs.

Table 8: Efficacy of CSII compared to MDI measured by Glucose Variability

Study	Group	Glucose Variability (Mean SD of BG ±SD) mmol/L	Mean Difference End of Treatment SD of Mean Daily BG Pump vs. MDI (95% CI) mmol/L	P
DeVries 2002‡	MDI	-0.40 ±1.77 ¥	-0.95* (-1.83, -0.05)¥	0.039
	CSII	-1.35 ±1.88 ¥		
Bruttomesso 2008	MDI	All day: 3.7±0.7 Morning: 3.7±0.8	All Day -0.18 (-0.37, 0.004)	All Day 0.054
	CSII	All day: 3.5±30.8 Morning: 3.3±0.9	Morning -0.40* (0.71, -0.10)	Morning 0.011
Hanaire-Broutin 2000	MDI	4.6 ±1.0	-0.50*	<0.01
	CSII	4.1 ± 0.8		
Hoogma 2005	MDI	4.3	-0.80*	<0.001
	CSII	3.9		

BG: blood glucose; CI: confidence interval; MDI: multiple daily injections; SD: standard deviation

*Statistically significant; †at end of first crossover phase; ‡Analyzed as parallel study; ¥Change from baseline

As seen in Table 8, all four studies showed a statistically significant reduction in glucose variability for patients using CSII pumps compared to those on MDI, however, one study (25) only showed a statistically significant reduction at the morning time point. Bruttomesso et al. also found that both the Lability index and MAGE were in concordance with the findings using the SD values of mean blood glucose, however, no difference was found in the ADRR between the CSII pump and MDI groups.

Frequency of Hypoglycemia

The frequency of hypoglycemic events was reported in all studies, but they varied in their definitions and reporting methods (Table 9). In one study, for example, mild events were defined as those that were self-treated, while in the three remaining studies these were defined using blood glucose values (range <2.0 mmol/l to <3.9 mmol). Severe events were defined more consistently with three studies defining them as events requiring external help and one study again using blood glucose measurements (<2.0 mmol/l).

Table 9: Efficacy of CSII compared to MDI measured by Frequency of Hypoglycemic Events

Study	Type of Event	Treatment Group		P
		CSII	MDI	
DeVries 2002	Mild (<3.9 mmol/l)	~1 event/pt-wk higher in CSII vs. MDI		0.028*
	Severe (External help)	3.0 pts with events/study	6.0 pts with events/study	0.48
Bruttomesso 2008	Mild (2.0-3.5 mmol/l)	8.0 events/pt	7.8 events/pt	0.775
	Severe (<2.0 mmol/l)	0.1 events/pt	0.1 events/pt	0.710
Hanaire-Broutin 2000	Mild (<3.3 mmol/L)	3.9 events/14 days	4.3 events/14 days	NS
	Severe (External help)	3.0 events/study	1.0 event/study	NR
Hoogma 2005	Mild (Self-treated)	49.3 events/pt-year	55.4 events/pt-year	0.001*
	Severe (External help)	0.2 events/pt-year	0.5 events/pt-year	<0.001*

NS: not significant; NR: not reported; pts: patients; wk: week
*Statistically significant

As demonstrated in Table 9, there is conflicting evidence regarding the efficacy of CSII pumps in decreasing the frequency mild and severe hypoglycemic events. For mild hypoglycemic events, DeVries et al. observed a higher number of events per patient week in the CSII pump group, while Hoogma et al. observed a higher number of events per patient year in the MDI group. The remaining two studies did not find a difference between the two treatment groups. For severe hypoglycemic events, Hoogma et al. found an increase in events per patient year among patients treated with MDI, however, all three other RCTs showed no difference between patients using CSII pumps and those using MDI.

Insulin Requirements and Adverse Events

In all studies, insulin requirements were significantly lower in the CSII pump treatment groups in comparison to the MDI groups (this difference was statistically significant in all studies).

Adverse events were reported in studies. The key findings this area were that:

- Devries et al. found no difference in ketoacidotic episodes between CSII pump and MDI users.
- Bruttomesso reported no adverse events during the study.
- Hanaire-Broutin et al. found that 30 patients experienced 58 serious adverse events while using MDI and 23 patients had 33 serious events during CSII treatment out of a total of 256 patients. Most of these events were related to severe hypoglycemia and diabetic ketoacidosis.

Quality of Life and Patient Preference

Quality of life (QOL) was measured in three studies and patient preference was measured in one (see Table 10). All three studies found an improvement in QOL among CSII users compared to those receiving MDI, however, various instruments were used among the studies and reporting bias was evident as non-positive outcomes were not consistently reported. Moreover, there were conflicting results in the two studies using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). DeVries et al. reported no difference in treatment satisfaction between CSII pump users and MDI users, while Bruttomesso reported that treatment satisfaction improved among CSII pump users.

Patient preference for CSII pumps was demonstrated in one study (26), however, there are considerable limitations to interpreting this data it was gathered via interview and 72% of those patients that indicated a preference for CSII pumps had already used CSII pump therapy prior to the study. Lastly, as all studies were industry sponsored, findings on QOL and patient preference must be interpreted with caution.

Table 10: Quality of life outcomes for RCTs of CSII pumps vs. MDI for type 1 adult diabetics

Study	QOL Instrument	Result	Comment
Quality of Life			
Devries 2002	SF 36-Item Survey Diabetes Treatment Satisfaction Questionnaire (DTSQ)	▪ General health: improved (p=0.048) ▪ Mental Health: improved (p=0.050) ▪ Treatment Satisfaction: No difference (p=0.199)	▪ Highly motivated patient group ▪ Industry sponsored/lack of blinding of investigators
Hoogma 2005	Diabetes Quality of Life Scale (DQoL) SF-12	▪ Overall QOL: improved (p<0.001) ▪ Treatment Satisfaction: improved (p<0.001) ▪ Treatment Impact: improved (p<0.001) ▪ Diabetes-Related Worry: improved (p<0.01) ▪ Perception of Mental Health: improved (p<0.05) ▪ Perception of Physical Health: no difference	▪ Highly motivated patient group ▪ Pts prev. on MDI ≥6 mo ▪ Industry sponsored/lack of blinding of investigators
Bruttomesso 2008	DTSQ	▪ Treatment Satisfaction: improved (p<0.0001) ▪ Perceived Freq. of Hypoglycemia: improved (p=0.001)	▪ Highly motivated patient group ▪ Pts prev. on CSII ≥6 mo ▪ Industry sponsored/lack of blinding of investigators
Patient Preference			
Hanaire-Broutin 2000	Interview	▪ Greater number of patients chose CSII over pumps (see NOTE)	▪ 72% patients that chose CSII were previously on CSII therapy ▪ No valid tool used

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Economic Literature Scan of Insulin Pumps in Adults with Type 1 Diabetes Mellitus

Figure 1 is a description of the number of abstracts identified in the literature and screened for eligibility, as well as those full text articles reviewed and included for the economic analysis.

The inclusion criteria were:

- Studies relating to CSII in adults with type 1 diabetes mellitus
- Studies comparing CSII with MDI therapy
- Full economic evaluations including Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA), and Cost-Benefit Analysis (CBA)

One article by Scuffham and Carr (2003) was included in the analysis from the economic literature scan. (32) Four other economic evaluations were identified but did not meet our inclusion criteria. Two of these articles (33;34) did not compare CSII with MDI and the other two (35;36) used summary estimates from a mixed population with Type 1 and 2 diabetes in their economic microsimulation to estimate costs and effects over time. We included English articles that conducted comparisons between CSII and MDI with the outcome of Quality Adjusted Life Years (QALY) in an adult population with type 1 diabetes.

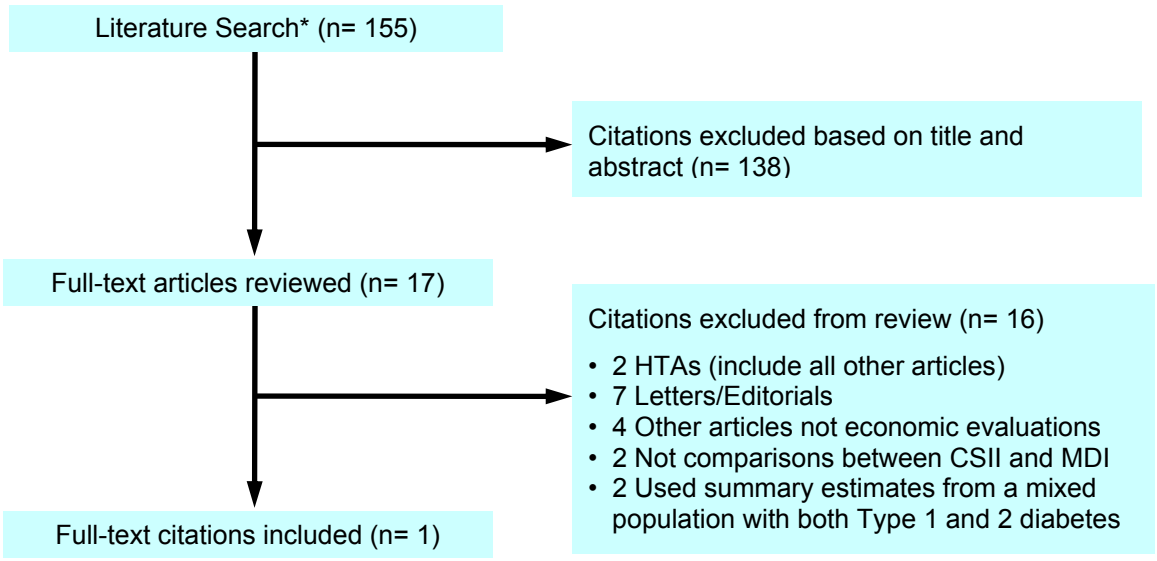


Figure 1. Flow chart model for the economic literature scan of CSII therapy for adults with type 1 diabetes

Results of Literature Review

Scuffman and Carr conducted an analysis of the cost-effectiveness of CDII compared to MDI for the management of type 1 diabetes. The objective of the study was to estimate the expected additional costs per QALY gained (as CSII is more expensive than MDI) and to identify subgroups for which CSII is likely to be most beneficial. They constructed a short-term Markov model to estimate the costs and health outcomes for two hypothetical patient cohorts with insulin-dependent diabetes: one treated with CSII and the other with MDI. The model was populated using data on procedures and costs for England and Wales. The perspective of costs to the healthcare funder i.e. the National Health Service was used for the study. The estimated life of the insulin pump, 8 years, was used as the time horizon for the analysis.

The model consisted of two health states: well and dead. For a patient in the well state, short-term transitions such as hypoglycemic events requiring assistance and ketoacidosis may occur. To reflect differences in severity of hypoglycemia, these events were divided into those requiring hospital treatment versus those not requiring treatment. Risk of death was also attributed to these events.

The effectiveness of CSII versus MDI and short-term health event rates were identified from two key papers: one systematic review (37;38) and one-meta-analysis. (16;39) Uncertainty of parameters was identified through sensitivity analyses. Distributions were assigned to parameters and Monte Carlo simulations were conducted. The main outcome modeled was QALYs, derived from one Quality of Life (QoL) study. Overall, the resulting scores for MDI were 5.3% worse than if CSII was used. Crude utility weights were calculated by indexing CSII to 1.00 and MDI to 0.947, based on this one QoL study. Costs were obtained from health-related grouping codes, the literature, and the manufacturer.
For 10,000 simulated cases over 8 years, CSII costs an average of £9,514 (£1,337) per patient and MDI costs £4,052 (£1,792). On average, patients using CSII could expect to have 7.32 (0.39) QALYs and MDI patients could expect 6.85 (0.48) QALYs. The mean incremental cost effectiveness ratio was £11,461 (£3,656). At a willingness to pay threshold of £12,500 per QALY, 70.1% of cases would be acceptable; at £15,000 per QALY, 81.4% would be acceptable. For the most cost-effective cases (i.e. those with an ICER of <£3,000), the patients most likely to benefit from insulin pumps were those who

had more than two severe hypoglycemic events per year and hospital in-patient treatments at least once every 8 months for hypoglycemia. For the least cost-effective cases (i.e. those with an ICER of >£24,000), the patients least likely to benefit from insulin pumps were those who had few hypoglycemic events and whose diabetes was well managed.

Sensitivity analyses showed that changes in the utility estimates and in the rate of hypoglycemic events produced a wide range in ICERs. At high levels of hypoglycemic events, CSII was cost-saving but with the utility gained reduced, the ICER increased. The results were stable when other parameters were changed including the life of the pump.

The authors recognized that the analysis was limited by the fact that there is a large variation among patients in the rate of hypoglycemic events as documented in the literature. Furthermore the utility weight calculation was not ideal as utilities should be derived from a preference-based utility instrument.

The authors concluded that for cases in which diabetes is well controlled with few severe hypoglycemic events, CSII may not be economically feasible. In contrast, for patients who have difficulty managing their diabetes (i.e. experiencing high rates of hypoglycemia), the study showed that they could benefit from insulin pumps. The authors' final conclusion was that suitable patients must be motivated and that the risk of therapy discontinuation must be small in order for patients to use insulin pumps.

Conclusion

From one study, a subset of the population with type 1 diabetes was identified that may be suitable for and benefit from the use of insulin pumps. Date addressing the cost-effectiveness of insulin pumps versus MDI in the literature is, however, limited. Longer-term models are required to estimate the long-term costs and effects of CSII compared to MDI in this population.

Overall Conclusions

CSII pumps for the treatment of adults with type 1 diabetes

8. Based on low-quality evidence, CSII pumps confer a statistically significant but not clinically significant reduction in HbA1c and mean daily blood glucose as compared to MDI in adults with type 1 diabetes (>19 years).
9. CSII pumps also confer a statistically significant reduction in glucose variability as compared to MDI in adults with type 1 diabetes (>19 years) however the clinical significance is unknown.
10. There is indirect evidence that the use of newer long-acting insulins (e.g. insulin glargine) in MDI regimens result in less of a difference between MDI and CSII compared to differences between MDI and CSII in which older insulins are used.
11. There is conflicting evidence regarding both mild and severe hypoglycemic events in this population when using CSII pumps as compared to MDI. These findings are based on very low-quality evidence.
12. There is an improved quality of life for patients using CSII pumps as compared to MDI however, limitations exist with this evidence.
13. Significant limitations of the literature exist specifically:
    - All studies sponsored by insulin pump manufacturers
    - All studies used crossover design
    - Prior treatment regimens varied
    - Types of insulins used in study varied (NPH vs. glargine)
    - Generalizability of studies in question as populations were highly motivated and half of studies used insulin pens as the mode of delivery for MDI
14. One short-term study concluded that pumps are cost-effective, although this was based on limited data and longer term models are required to estimate the long-term costs and effects of pumps compared to MDI in adults with type 1 diabetes.

Evidence-Based Analysis of Effectiveness: Adult (≥ 19 years), Type 2 Diabetes

Objective

To determine if CSII pumps are more effective than MDI for adults (≥ 19 years) with type 2 diabetes.

Research Questions

1. Do CSII pumps improve glycemic control in adults (≥ 19 years) with type 2 diabetes?
2. Do CSII pumps improve quality of life in people with type 2 diabetes?

Literature Search

Inclusion Criteria

- Randomized controlled trials, systematic reviews, meta-analysis and/or health technology assessments from MEDLINE, Excerpta Medica Database (EMBASE), Cumulative Index to Nursing & Allied Health Literature (CINAHL)
- Any person with type 2 diabetes requiring intensive insulin treatment
- Published between January 1, 2000 – August 2008

Exclusion Criteria

- Studies with <10 patients
- Studies <5 weeks in duration
- CSII pump applied only at night time and not 24 hours/day
- Mixed group of diabetes patients (children, adults, type 1, type 2)
- Pregnancy studies

Outcomes of Interest

The primary outcome of interest was a reduction in HbA1c level. Other outcomes of interest were:

- mean blood glucose level
- glucose variability
- insulin requirements
- frequency of hypoglycaemic events
- adverse events
- quality of life.

Search Method

A search was performed in OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, The Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published between January 1, 2000 and August 15. 2008. The search strategy is detailed in Appendix 1. Abstracts were reviewed and those studies meeting the inclusion criteria outlined above were obtained. Reference lists were also checked for relevant studies.

HbA1c outcomes from individual studies were meta-analyzed using RevMan 5.0 from the Cochrane Collaboration using a random-effects model to account for between-study differences.

Clinically Meaningful Endpoints

For the measurement of glycemic control, HbA1c (%) was examined as the primary outcome of interest. From the UKPDS, it is well-established that HbA1c decrease by at least 1% in order for the change to be considered clinically meaningful.

Assessment of Quality of Evidence

The quality assigned to individual studies was determined using MAS' adaptation of the levels-of-evidence hierarchy proposed by Goodman as described in the previous relevant section of the evidence-based analysis for Adult type 1 diabetes. (22)

Results of Evidence-Based Analysis

The database search identified 286 relevant citations, of which seven met the inclusion criteria. Three studies were systematic reviews while four were RCTs. A detailed description of the RCTs can be found in Appendix 3. Two of the four RCTs were defined as small (see Table 11).

Table 11: Quality of Evidence of Included Studies

Study Design*	Level of Evidence	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	4
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	2
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

*For each included study, levels of evidence were assigned according to a ranking system based on a hierarchy proposed by Goodman. (22) An additional designation "g" was added for preliminary reports of studies that have been presented at international scientific meetings. Non-RCT, clinical trial that is not randomized, e.g., a cohort study; RCT refers to a randomized controlled trial.
Adapted from the Oxford Centre for Evidence (22)

Summary of Existing Evidence

The literature search identified two reviews, Jeitler et al. 2008 and Fatourechi et al. 2009, which examined the efficacy of CSII pumps in comparison to MDI in type 2 diabetic populations (as well as in type 1 diabetics). The fundamentals of these studies have been previously described in Table 2 of this report (see page 25) and Table 12 below highlights the main conclusions the authors arrived at with respect to the type 2 population. Both studies were meta-analyses conducted over 2008 to 2009.

It should be noted that these reviews are limited by low study quality and a lack of meta-analysis or descriptions of alternate outcomes of glycemic control (e.g. glucose variability and/or mean daily blood glucose). Also of note, Colquitt et al. 2004 included type 2 adult diabetics in their review but found only observational studies examining the efficacy of CSII pumps compared to MDI in poorly controlled type 2 diabetics. The authors noted that the evidence was poor and that clear conclusions could not be deduced from these studies.

Table 12: Summary of existing systematic reviews on CSII pump therapy versus MDI that examine Type 2 Populations

Review	Type of Review (Search years)	Type of Studies included (# of trials*)	Population	Outcomes	Conclusions for Type 2 Adult Diabetics
Fatourechi et al. 2009 (3)	Meta-analysis (2002-2008)	RCTs (15†)	▪ Type 1 & type 2 ▪ Adults ▪ Adolescents	▪ HbA1c ▪ Hypoglycemic events	▪ There were no significant differences in glycemic control or hypoglycemia outcomes in patients with type 2 DM treatment with CSII pumps vs. MDI. ▪ Unclear impact on patients with at high risk of hypoglycemia.
Jeitler et al. 2008 (4)	Meta-analysis (up to March 2007)	RCTs (17‡)	▪ Type 1 & type 2 ▪ Adults ▪ Children	▪ HbA1c ▪ Hypoglycemic episodes ▪ Adverse events ▪ Insulin requirements	▪ CSII and MDI treatment showed no statistically significant difference for HbA1c. ▪ The incidence of mild hypoglycemic events was comparable between the treatment groups.

BG: blood glucose; CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injections; QOL: quality of life

*including all DM populations

†‡Only 2 RCTs used in meta-analysis for Type 2 adult population.

Summary of Literature Review Findings

The database search identified 286 relevant citations published between 1996 and August 2008. Of the 286 abstracts reviewed, four RCTs met the inclusion criteria outlined above Upon examination, two were subsequently excluded from the meta-analysis due to small sample size and missing data (40), as well as outlier status and high drop out rate (41), which is consistent with previously reported meta-anlayses on this topic. (3;4) Table 13 highlights the main study characteristics of the four RCTs. A detailed description of the studies can be found in Appendix 3.

Table 13: Overview of study characteristics of identified from literature search

RCT Characteristics	Herman et al. 2005	Raskin et al. 2003	Wainstein et al. 2005	Berthe et al. 2006
Design	Parallel	Parallel	Cross-over	Cross-over
Length of Follow-up	52 weeks	24 weeks	18 weeks	24 weeks
Run-In Period	NR 1-wk monitoring period between randomization & treatment	NR Dose adjustment period for first 8 wks	2-wk with insulin therapy plus metformin	6 wk with conventional insulin treatment
Sample Size	107	127	40‡	17
Mean Age	~66 years	~55 years	30-70 years (range)	~55 years
Mean Diabetes Duration	~16 years	~13 years	≥6 months†	~17 years
Patient Population	Prior treatment with ≥1insulin dose/day in past month w or w/o oral anti-diabetics BMI: ~32	CSII pump naïve Prior treatment with ≥1 insulin dose/day for previous 6 mo. w or w/o oral anti-diabetics BMI: ~32	Prior treatment of ≥3 months of ≥ insulin injections/day, diet and metformin Obese BMI (30-45 kg/m^2) Poor glycemic control Severe insulin resistance	Prior treatment >6 months of insulin therapy Poorly controlled on conventional insulin therapy BMI 33.7
Baseline HbA1c (%)	CSII: 8.4 ±1.1 MDI group: 8.1±1.2	CSII: 8.2±1.4 MDI: 8.0±1.1	MDI-CSII: 10.3±1.2 CSII-MDI: 10.2±1.4	9.0±1.6
CSII Pump	MiniMed 508-insulin lispro	MiniMed 507C-insulin aspart	Minimed- insulin lispro	Medtronic 508 - Insulin lispro
MDI	Insulin lispro + insulin glargine	NovoPen 3.0 - Insulin aspart + NPH	Actrapid HM or Humulin R + NPH or Humulin N	Insulin lispro + NPH
Industry Sponsored	Yes	Yes	No	Yes

BMI: body mass index; CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injection; NPH: Neutral Protamine Hagedorn; NR: not reported; Wk: week; Mo: month

Note: Wainstein et al. 2005 and Berthe et al. 2006 were excluded from the meta-analysis

†Inclusion criteria;

‡High drop out reported - only 29 patients completed study

Patient Demographics

A total of 234 patients were included in the two RCTs used in the meta-analysis. The reported mean age of participants across trials ranged from 55-66 years. The mean duration of diabetes was similar across participants ranging from 13-16 years. Participants in both studies also had similar baseline HbA1c ranging from 8.0% to 8.4% and a BMI of approximately 32. Inclusion criteria for participants differed between the studies. Herman et al. included participants with prior treatment regimens of at least one insulin dose per day for the previous month (with or without oral anti-diabetics), while Raskin et al. included participants with prior treatment regimens of at least one insulin dose per day for the previous 6 months and included patients that were CSII pump naïve.

Summary of Study Designs

Both RCTs were designed as parallel studies but they varied in duration with Herman et al. having conducted a 52-week study while Raskin et al. conducted a study lasting 24 weeks. Neither study reported a run-in phase prior to randomization (often reported in similar studies examining these interventions). Raskin et al. 2003 did, however, report a dose adjustment period over the first 8 weeks after randomization and Herman et al. 2005 reported a 1-week period between randomization and treatment initiation where subjects monitored their diet, physical activity, and blood glucose levels.

Participants in both studies received education on intensive insulin therapy. Those in the Raskin et al. trial received education at two separate study visits during the 2 week training period prior to receiving their CSII pumps or MDI therapy, while participants in the Herman et al. trial received training at baseline assessment. Participants in the Herman trial also received nutritional instruction as needed throughout the trial.

Of note, patient in the Herman et al. study were contacted frequently and monitored throughout the study duration, as demonstrated by daily contact during the first month of therapy and with a minimum of weekly contact throughout the remainder of the treatment period. In contrast, the frequency of contact and monitoring was not clearly described in Raskin et al. 2003 and it was, therefore, difficult to determine its contribution to heterogeneity between the studies. The authors did report that participants were followed-up at weeks 8, 20, and 24 for efficacy assessments. Participants in the Herman et al. 2005 study were followed up 2 months after randomization and at 2 month intervals for the duration of the study (12 months).

CSII Pumps Regimen

Both studies used MiniMed pumps (MiniMed 508 and MiniMed 507C). Raskin et al. used insulin aspart for CSII therapy while Herman et al. used insulin lispro for CSII therapy.

MDI Regimen

The comparison arm in both studies was insulin treatment with MDI. Herman et al. used insulin lispro and Raskin et al. used insulin aspart as bolus insulin. The type of basal insulin used varied between studies, with NPH being used in the Raskin trial and insulin glargine used in the Herman study. In addition, insulin pens were used for MDI delivery in the Raskin trial.

Summary of Outcome Characteristics

All studies reported measures of glycemic control, specifically HbA1c. Other outcomes examined in both studies included the frequency of hypoglycaemic events, body weight, and injection side reactions. Raskin et al. also reported on pump compatibility and Herman et al. reported on technical and mechanical problems related to both the CSII and MDI therapies, as well as insulin requirements. Quality of life was examined by Herman et al. and patient satisfaction was examined by Raskin.

Quality of Evidence

Overall, the body of evidence was downgraded from high to low according to study quality and issues with directness as identified using the GRADE quality assessment tool (Table 14). While blinding of patients to intervention/control is not feasible in these studies, blinding of study personnel during outcome assessment and allocation concealment was also generally lacking. ITT analysis was not clearly explained in one study and the heterogeneity between study populations was evident from participants' treatment regimens prior to study initiation. Although trials reported consistent results for the outcome HbA1c, the directness or generalizability of studies, particularly with respect to the generalizability of the

diabetic population, was questionable as the trials required patients to adhere to an intense SMBG regimen, suggesting that patients were highly motivated. In addition, since prior treatment regimens varied between participants (there was no requirement for patients to be on MDI), study findings may not be generalizable to the population eligible for a pump in Ontario. The GRADE quality of evidence for the use of CSII in adults with type 2 diabetes is, therefore, low and any estimate of effect is uncertain.

Table 14: Summary of GRADE Assessment for CSII vs. MDI on HbA1c Adults with Type 2 Diabetes

Study	Design	Study Quality	Consistency	Directness	Other modifying factors	Overall quality of evidence
Raskin 2003 (42)	RCT	Serious limitations*	Consistent	Indirect†	Not applicable	**LOW**
Herman 2005 (43)	RCT	**MODERATE**	**LOW**	**LOW**		
	HIGH					

*Inadequate or unknown allocation concealment (all studies); Unblinded assessment (all studies), however, lack of blinding due to the nature of the study; ITT not well explained in 1 of 2 studies

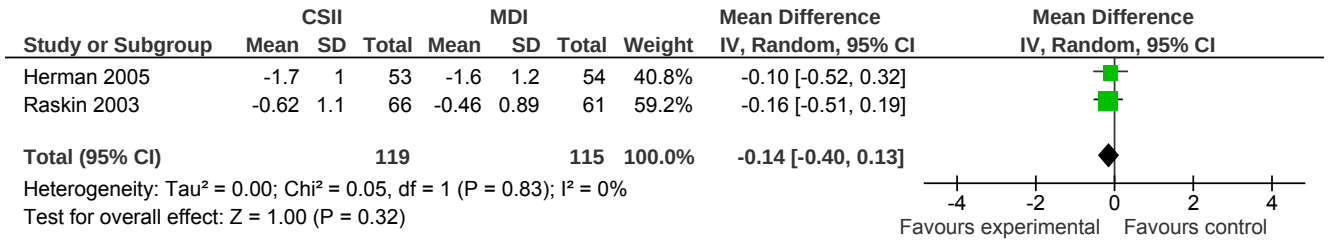
†Indirect due to lack of generalizability of findings as participants varied with respect to prior treatment regimens and intensive SMBG suggests highly motivated populations used in trials.

Summary of Results

HbA1c

The primary outcome in this analysis was a reduction in HbA1c. Both studies demonstrated that both CSII pumps and MDI reduce HbA1c, but neither treatment modality was shown to be superior to the other (see Figure 2). The results of a random effects model meta-analysis showed a mean difference in HbA1c of -0.14 (-0.40, 0.13) between the two groups, which was not found to be statistically or clinically significant. No statistical heterogeneity was observed between the two studies (I^2=0%).

Figure 2: Forrest plot of two parallel, RCTs comparing CSII to MDI in type 2 diabetes



Secondary Outcomes

Mean Blood Glucose, Glucose Variability

Mean Blood glucose was only used as an efficacy outcome in Raskin et al. 2003. The authors found that the only time point in which there blood glucose values were consistently lower in the CSII group was 90 minutes after breakfast. Glucose variability was not examined in either study.

Adverse Events

Weight Gain

Weight and injection site reactions were examined in both studies. The authors reported no difference in weight gain between the CSII pump group and MDI groups at the end of study.

Injection Site Reactions

Conflicting results were reported regarding injection site reactions between the two studies. While Herman et al. reported no difference in the number of subjects experiencing site problems between the two groups, Raskin et al reported that no injection site reactions occurred in the MDI group but 15 such episodes occurred among 8 participants in the CSII pump group.

Hypoglycemic Events and Insulin Requirements

All studies reported that there were no differences in the number of mild hypoglycemic events in patients on CSII pumps versus those treated with MDI. Herman et al. also reported no differences in the number of severe hypoglycemic events in each group. Raskin et al. reported that no severe hypoglycemic events occurred in either group throughout the duration of the study.

Insulin requirements were only examined in Herman et al., in which the authors found that daily insulin requirements were equal between treatment groups.

Quality of Life

QOL was measured by Herman et al. using the Diabetes Quality of Life Clinical Trial Questionnaire (DQOLCTQ). There were no differences reported between CSII users and MDI users for treatment satisfaction, diabetes impact, and worry-related scores.

Patient satisfaction was measured in Raskin et al. using a patient satisfaction questionnaire and results showed that patients treated with CSII pumps exhibited a significant improvement in overall treatment satisfaction at the end of the study compared to those treated with MDI. Patient preference was also reported in this study, but only for the CSII pump group. Therefore, results indicating a greater preference for CSII pumps in this study (as compared to prior injectable insulin regimens) are biased and must be interpreted with caution.

Economic Analysis

An economic analysis of CSII pumps was carried out using the Ontario Diabetes Economic Model (ODEM), which has been described previously in the report "Application of the Ontario Diabetes Economic Model (ODEM) to Determine the Cost-effectiveness and Budget Impact of Selected Type 2 Diabetes Interventions in Ontario" (part of the diabetes strategy evidence series). From the analysis, it was determined that CSII pumps are not cost-effective for adults with type 2 diabetes, either for the age 65+ subgroup or for all patients in general. Details of the analysis can be found in the full report.

Overall Conclusions

CSII pumps for the treatment of adults with type 2 diabetes

1. There is low quality evidence demonstrating that the efficacy of CSII pumps is not superior to MDI for adult type 2 diabetics.
2. There were no differences in the number of mild and severe hypoglycemic events in patients on CSII pumps versus MDI.
3. There are conflicting findings with respect to an improved quality of life for patients using CSII pumps as compared to MDI.
4. Significant limitations of the literature exist specifically:
   - All studies sponsored by insulin pump manufacturers
   - Prior treatment regimens varied
   - Types of insulins used in study varied (NPH vs. glargine)
   - Generalizability of studies in question as populations may not reflect eligible patient population in Ontario (participants not necessarily on MDI prior to study initiation, pen used in one study and frequency of SMBG required during study was high suggesting highly motivated participants)
5. Based on ODEM, insulin pumps are not cost-effective for adults with type 2 diabetes either for the age 65+ sub-group or for all patients in general.

Appendices

Appendix 1: Literature Search Strategies

Final Search Strategy – Insulin Pumps Type 1 DM
Search date: July 6, 2008
Databases searched: OVID MEDLINE, In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, Cochrane Library and the International Agency for Health Technology Assessment/Centre for Reviews and Dissemination Database

Database: Ovid MEDLINE(R) <1996 to June Week 4 2008>
Search Strategy

1 exp Diabetes Mellitus, Type 1/ (22805)
2 (t1dm or IDDM).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3411)
3 (diabet$ adj2 (juvenile$ onset or brittle or Insulin Depend$ or sudden onset or auto?immune or Ketosis Prone or typ$ 1 or typ$ I)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (30616)
4 or/1-3 (30864)
5 exp Infusion Pumps/ (4058)
6 exp Insulin/ (46813)
7 5 and 6 (683)
8 exp insulin infusion systems/ (848)
9 csii.mp. (303)
10 (insulin$ adj2 (pump$ or infusion or continuous subcutaneous)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2538)
11 ((pump$ or insulin) adj5 (animas or dana diabecare or minimed or paradigm or accu-chek or cozmore or amigo or omnipod)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (51)
12 or/7-11 (2647)
13 4 and 12 (967)
14 limit 13 to (english language and humans and yr="2002 - 2008") (529)
15 limit 14 to "all child (0 to 18 years)" (222)
16 14 (529)
17 limit 16 to "all adult (19 plus years)" (229)
18 14 and 15 and 17 (69)
19 14 not 15 (307)
20 18 or 19 (376)
21 limit 20 to (controlled clinical trial or meta analysis or randomized controlled trial) (60)
22 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (32851)
23 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (600)
24 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (62247)
25 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (357955)
26 exp Double-Blind Method/ (51664)
27 exp Control Groups/ (601)
28 exp Placebos/ (8960)
29 (RCT or placebo$ or sham$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (91906)
30 or/21-29 (460611)
31 20 and 30 (92)

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to June Week 4 2008>
Search Strategy

1 exp Diabetes Mellitus, Insulin-Dependent/ (5147)
2 (t1dm or IDDM).mp. [mp=title, subject heading word, abstract, instrumentation] (425)
3 (diabet$ adj2 (juvenile$ onset or brittle or Insulin Depend$ or sudden onset or auto?immune or Ketosis Prone or typ$ 1 or typ$ I)).mp. [mp=title, subject heading word, abstract, instrumentation] (15276)
4 or/1-3 (15299)
5 exp Infusion Pumps/ or exp Infusion Devices/ or exp Infusions, Intravenous/ (3812)
6 exp INSULIN/ (6531)
7 5 and 6 (456)
8 exp Insulin Infusion Systems/ (494)
9 csii.mp. (106)
10 (insulin$ adj2 (pump$ or infusion or continuous subcutaneous)).mp. [mp=title, subject heading word, abstract, instrumentation] (817)
11 ((pump$ or insulin) adj5 (animas or dana diabecare or minimed or paradigm or accu-chek or cozmore or amigo or omnipod)).mp. [mp=title, subject heading word, abstract, instrumentation] (15)
12 or/7-11 (914)
13 4 and 12 (410)
14 limit 13 to (english and yr="2002 - 2008") (271)
15 (random$ or sham$).mp. or exp RANDOM ASSIGNMENT/ or exp RANDOM SAMPLE/ [mp=title, subject heading word, abstract, instrumentation] (74731)
16 (health technology adj2 assess$).mp. [mp=title, subject heading word, abstract, instrumentation] (405)
17 RCT.mp. (927)
18 exp Meta Analysis/ (6655)
19 exp "Systematic Review"/ (3778)
20 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or medline or embase or data synthesis or data extraction or cochrane).mp. (24411)
21 exp double-blind studies/ or exp single-blind studies/ or exp triple-blind studies/ (14641)
22 exp PLACEBOS/ (4508)
23 exp "Control (Research)"/ (2392)
24 (control$ adj2 clinical trial$).mp. [mp=title, subject heading word, abstract, instrumentation] (3286)
25 or/15-24 (100171)
26 14 and 25 (45)

Database: EMBASE <1980 to 2008 Week 26>
Search Strategy

1 exp Insulin Dependent Diabetes Mellitus/ (36190)
2 (t1dm or IDDM).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (6563)
3 (diabet$ adj2 (juvenile$ onset or brittle or Insulin Depend$ or sudden onset or auto?immune or Ketosis Prone or typ$ 1 or typ$ I)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (91196)
4 or/1-3 (91502)
5 exp Insulin/ (113492)
6 exp Infusion Pump/ or exp Infusion/ (23737)
7 5 and 6 (3067)
8 exp insulin infusion/ (1779)
9 (insulin$ adj2 (pump$ or infusion or continuous subcutaneous)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (6547)
10 csii.mp. (707)
11 ((pump$ or insulin) adj5 (animas or dana diabecare or minimed or paradigm or accu-chek or cozmore or amigo or omnipod)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (70)
12 or/7-11 (7621)
13 4 and 12 (3163)
14 limit 13 to (human and english language and yr="2002 - 2008") (1041)

15 limit 14 to (adult <18 to 64 years> or aged <65+ years>) (449)
16 14 (1041)
17 limit 16 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (199)
18 14 and 15 and 17 (61)
19 14 not 17 (842)
20 18 or 19 (903)
21 Randomized Controlled Trial/ (159009)
22 exp Randomization/ (25724)
23 exp RANDOM SAMPLE/ (1155)
24 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (286782)
25 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (617)
26 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (59012)
27 Double Blind Procedure/ (69613)
28 exp Triple Blind Procedure/ (10)
29 exp Control Group/ (1880)
30 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (202381)
31 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (411560)
32 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (274955)
33 or/21-32 (762773)
34 20 and 33 (288)

Final Search – Insulin Pumps Type 2 DM
Search date: August 27, 2008
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, Cochrane Library, and CRD/INAHTA

Database: Ovid MEDLINE(R) <1996 to August Week 2 2008>
Search Strategy
1 exp Diabetes Mellitus, Type 2/ (37500)
2 ((ketosis resistant or adult onset or slow onset or maturity onset or non?insulin dependent or stable or type 2 or type II) adj2 (diabet$ or DM)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (46322)
3 (t2dm or NIDDM).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4199)
4 or/1-3 (46873)
5 exp Infusion Pumps/ (4115)
6 exp Insulin/ (47465)
7 5 and 6 (694)
8 exp Insulin Infusion Systems/ (866)
9 csii.mp. (308)
10 (insulin$ adj2 (pump$ or infusion or continuous subcutaneous)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2575)
11 ((pump$ or insulin) adj5 (animas or dana diabecare or minimed or paradigm or accu-chek or cozmore or amigo or omnipod)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (52)
12 or/7-11 (2685)
13 4 and 12 (488)
14 limit 13 to (english language and humans and yr="2000 - 2008") (322)
15 limit 14 to (controlled clinical trial or meta analysis or randomized controlled trial) (69)
16 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (33561)
17 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (611)

18 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (63509)
19 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (363428)
20 exp Double-Blind Method/ (52281)
21 exp Control Groups/ (668)
22 exp Placebos/ (9091)
23 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (92306)
24 or/15-23 (467221)
25 14 and 24 (101)

Database: EMBASE <1980 to 2008 Week 34>

Search Strategy

1 exp Non Insulin Dependent Diabetes Mellitus/ (54345)
2 (T2DM or NIDDM).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (7229)
3 ((ketosis resistant or adult onset or slow onset or maturity onset or non?insulin dependent or stable or type 2 or type II) adj2 (diabet$ or DM)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (38449)
4 or/1-3 (62203)
5 exp Insulin/ (114641)
6 exp Infusion Pump/ or exp Infusion/ (24222)
7 5 and 6 (3105)
8 exp Insulin Infusion/ (1788)
9 (insulin$ adj2 (pump$ or infusion or continuous subcutaneous)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (6585)
10 ((pump$ or insulin) adj5 (animas or dana diabecare or minimed or paradigm or accu-chek or cozmore or amigo or omnipod)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (70)
11 csii.mp. (715)
12 or/7-11 (7686)
13 4 and 12 (1194)
14 limit 13 to (human and english language and yr="2000 - 2008") (634)
15 Randomized Controlled Trial/ (161572)
16 exp Randomization/ (26131)
17 exp RANDOM SAMPLE/ (1211)
18 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (290781)
19 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (635)
20 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (61100)
21 Double Blind Procedure/ (70219)
22 exp Triple Blind Procedure/ (11)
23 exp Control Group/ (2071)
24 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (205631)
25 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (417622)
26 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (278263)
27 or/15-26 (772805)
28 14 and 27 (220)

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to August Week 4 2008>

Search Strategy

1 exp Diabetes Mellitus, Non-Insulin-Dependent/ (11031)
2 (T2DM or NIDDM).mp. [mp=title, subject heading word, abstract, instrumentation] (610)
3 ((ketosis resistant or adult onset or slow onset or maturity onset or non?insulin dependent or stable or type 2 or type II) adj2 (diabet$ or DM)).mp. [mp=title, subject heading word, abstract, instrumentation] (7552)
4 3 or 2 or 1 (12651)
5 exp INSULIN/ (6810)
6 exp Infusion Devices/ (1712)
7 exp Infusions, Subcutaneous/ (255)
8 6 or 7 (1893)
9 5 and 8 (351)
10 exp Insulin Infusion Systems/ (512)
11 (insulin$ adj2 (pump$ or infusion or continuous subcutaneous)).mp. [mp=title, subject heading word, abstract, instrumentation] (814)
12 ((pump$ or insulin) adj5 (animas or dana diabecare or minimed or paradigm or accu-chek or cozmore or amigo or omnipod)).mp. [mp=title, subject heading word, abstract, instrumentation] (16)
13 csii.mp. (108)
14 or/9-13 (844)
15 4 and 14 (116)
16 limit 15 to (english and yr="2000 - 2008") (91)
17 (random$ or sham$).mp. or exp RANDOM ASSIGNMENT/ or exp RANDOM SAMPLE/ [mp=title, subject heading word, abstract, instrumentation] (77085)
18 (health technology adj2 assess$).mp. [mp=title, subject heading word, abstract, instrumentation] (157)
19 RCT.mp. (978)
20 exp Meta Analysis/ (6900)
21 exp "Systematic Review"/ (3924)
22 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or medline or embase or data synthesis or data extraction or cochrane).mp. (25250)
23 exp double-blind studies/ or exp single-blind studies/ or exp triple-blind studies/ (15033)
24 exp PLACEBOS/ (4657)
25 exp "Control (Research)"/ (2421)
26 (control$ adj2 clinical trial$).mp. [mp=title, subject heading word, abstract, instrumentation] (1815)
27 or/17-26 (102499)
28 27 and 16 (17)

Appendix 2: Design characteristics for studies examining type 1 adult diabetics

Study, year Design	Patients characteristics	Experience with IIT/ pump	Description of Treatment Groups	Training/ Similar intensity of support between groups	SMBG for Mean Blood Glucose	Results	Other Comments
Bruttomesso 2008 Crossover	N=42 38 years DM duration 8 yrs Mean hbA1c 7.6% Good glycemic control Highly motivated No exclusions based on hypoglycemia experience	Experience with CSII for at least 6 months	CSII: Multiple pumps (animas, D-Tron, H-Tron V-100, MiniMed 508) using insulin lispro MDI: Insulin lispro and insulin glargine	Participants received 4 wk of basal bolus optimization while using CSII **Yes**	SMBG 4x/day plus after meals 2 d/wk and once 3 am in glucose diary; Last 30 days data used	HbA1c – no difference between arms During CSII – overall BG variability was lower than during MDI but significance of this finding varied according to the method used (only significant in the morning) Mean daily bg: Before lunch & before dinner were sign. lower during CSII Moderate hypoglycemia were less freq. during CSII; episodes of severe hyperglycemia had similar frequency # of episodes of biochemically severe hypoglycemia was similar between arms.	Primary end-point glucose variability Imbalance in number of pts. In each arm (15 starting on MDI, 24 with CSII) Industry sponsored
Hoogma, 2006 Crossover	N=272 36 years old DM for 15 years Mean HbA1c= 7.9% Excluded patients: pts. With a history of severe hypoglycemia or hypoglycemia unawareness	Experienced with MDI, new to CSII	CSII: Disetronic H-TRON V100 or H-TRONplus V100 using insulin lispro MDI: Insulin lispro and insulin NPH	Participants received 8 wk of training after randomization Yes	SMBG eight-point profiles recorded in glucose diary on last day prior to visit	HbA1c MDI: B: 8.3 (1.1), F: 7.67 (1.04) CSII: B: 8.2 (1.1), F: 7.45 (.96) Mean daily BF values were significantly lower with CSII. EOT mean daily BG was 9.4 (1.9) for MDI vs. 8.6 (1.8) for CSII. 24-profilles show sign. Higher mean BF before breakfast and evening using MDI vs. CSII Glucose variability BG fluctuation was ±3.9 on CSII compared with ±4.3 on MDI (highly significant) Hypoglycemia -CSII usage resulted in fewer episodes of mild hypoglycemia compared with MDI and of severe hypoglycemia	High drop out 223/272 completed study Hypoglycemic events - mild (self treated) - severe (requiring third-party help)

Study, year Design	Patients characteristics	Experience with IIT/pump	Description of Treatment Groups	Training/ Similar intensity of support between groups	SMBG for Mean Blood Glucose	Results	Other Comments
Devries 2002 Crossover but analyzed as parallel	N=79 Motivated / willing to comply with SMBG regimen Long-standing poor glycemic control 36 years old Mean DM duration 17.5 years Mean HbA1c 9.3% Inclusion criteria – poor diabetic control (mean HbA1c ≥8.5%)	Not mentioned	CSII: Disetronic HTRONplus insulin pump – insulin aspart MDI: NovoPen - Insulin aspart before meals and NPH insulin dose in the night time	CSII group received education on pump usage NR	SMBG nine-point profiles recorded in glucose diary on last day prior to visits	HbA1c MDI: B: 9.25 (1.4), F: 9.18 Change -0.07 (0.7) CSII: B: 9.27 (1.4), F: 8.36 Change -0.91 (1.28) Difference 0.84% (95% CI-1.31 to -0.36) 24-Mean glucose did not differ sig. btw grps Glucose variability → Declined more with CSII: -1.35 (1.88) vs. -0.40 (1.77) in MDI (P=0.039), mean difference -0.95 (95% CI -1.83 to -0.05). Mild hypoglycemic episodes increased with CSII vs. to MDI 0.98 (2.02) vs. -0.02 (1.18) episodes per pt. week, difference 0.99 (95% CI 0.11-1.87) episodes per pt. week. # of pts. Suffering severe hypoglycemic episodes was similar in either group.	High drop out after cross-over therefore analyzed data as parallel after 1st phase
Hanaire-Broutin 2000 Crossover	N=41 21-65 years DM Duration 20 years BMI 24 HbA1c% 8.39 Inclusion criteria HbA1c <10.0%, experience of intensified insulin therapy Patients enrolled did NOT have history of hypoglycemia unawareness	32 pts. At enrollment treatment by CSII with reg. insulin	CSII: programmable external pump (MiniMed 506 or 507; Minimed, and HTron D or V; Disetronic, using insulin lispro MDI: 3 injections of lispro (before meals) and 2 injections of NPH (before breakfast and at bedtime)	Yes	SMBG 6x/day using memory meter; Last 14 days data used	Within group difference – HbA1c statistically lower in CSII group than in MDI. BG stability was better with CSII than with MDI Safety: Hypoglycemic events (BG levels <60 mg/dl) – no difference between groups; severe hypoglycemic events were reported 4 times (3times with CSII and 1 time with MDI) Satisfaction: 20 patients preference CSII (21 previously on CSII) and 11 chose MDI (10 were previously on CSII)	6-wk run-in period of CSII tx w regular insulin Statistical analysis accounted for crossover design Low drop out: 40/41 pts. completed Routine conditions of follow-up (every 2 mos. by their usual physician)

Appendix 3: Design characteristics for studies examining type 2 adult diabetics

Authors, Year, Type of Study	Study Population, Details and Duration	Results	Conclusions	Limitations
Wainstein et al. 2005 (41) Randomized, Crossover trial	N=40 (HbA1c>8.5%) 30-70 years old Diabetes for ≥3 months, treated with diet, OAD and MDI insulin 48 weeks in duration Pump:MM	A1c (%) Change from baseline CSII: -0.8±1.5 MDI: +0.4±1.3 Difference between CSII and MDI = 1.2%, p=0.007 Insulin Dose Baseline similar by group; at end of period one MDI had increase dose while CSII had decreased; however difference not demonstrated after crossover Hypoglycemia Minor events similar between groups; 3 major events on CSII and 2 in MDI (p=NS)	CSII appears superior to MDI in reducing HbA1c in obese, uncontrolled type 2 diabetes	Patients in extremely poor glycemic control at baseline (A1c >10%) Obese patients at baseline Blinding not possible
Berthe et al. 2006 (40) Randomized, Crossover trial	N=17 (HbA1c≥6.5%) 55.2±6.6 years 16.8±5 years with diabetes 24 weeks in duration Pump:MM-508	A1c (%) Change from baseline CSII: -1.3 (SD not reported) MDI: -0.4 (SD not reported) (p < 0.03) Difference between CSII and MDI = -0.9%, p=not reported Blood Glucose Capillary BG was lowered at all time points with CSII, but only in mornings with MDI Minor Hypoglycemia Compared to conventional therapy pump reduced area under by 73% (p<0.01), MDI by 32% (p=0.08) Quality of Life Both groups satisfied with insulin regimens; slight preference for MDI compared to CSII (Not significant); 10 patients chose CSII while 7 chose MDI	CSII provides better control than injections. CSII is safe and convenient for patients.	6 week run-in period with conventional insulin treatment (2 NPH/day) instead of MDI Unclear whether wash-out period occurred before crossover Blinding not possible

Authors, Year, Type of Study	Study Population, Details and Duration	Results	Conclusions	Limitations
Raskin et al., 2003 (42) Randomized, parallel-group trial	N=127 patients (HbA1c > 8.0%) 55-56 years old 12-14 years with diabetes 24 weeks in duration Pump:MM-507	A1c (%) Change from baseline CSII: -0.62±1.11 MDI: -0.46±0.89 Difference between CSII and MDI = -0.16%, p=NS Mean Blood Glucose Similar 8-point BG profiles at baseline; both groups experienced improvements at the end of the study Mild Hypoglycemia CSII: 34/63 (54%) MDI: 36/61 (59%) Quality of Life (SF-36) Improvement in treatment satisfaction using CSII (59.4±2.1 at baseline to 79.2±1.8 at end of study; mean±SE) compared to MDI (63.6±1.9 at baseline to 70.3±2.3 at end of study; mean±SE) (P<0.001)	Insulin aspart in CSII provided efficacy and safety comparable to MDI for type 2 diabetes.	Patients in poor glycemic control at baseline Blinding not possible Pump used insulin aspart instead of lispro
Herman et al. 2005 (43) Randomized Parallel group trial	N=107 (HbA1c>8.0%) 66-67 years old 15-17 years with diabetes 52 weeks in duration Pump:MM-508	A1c (%) Change from baseline CSII: -1.7±1.0 MDI: -1.6±1.2 Difference between CSII and MDI = -0.1%, p=NS Insulin Requirement (units/day) CSII: 108±63 MDI: 108±62 p=NS Minor Hypoglycemia CSII: 81% (43/53) MDI: 90% (49/54) p=NS Quality of Life (DQoLCTQ) Improved over time in both groups (CSII from 52 to 81, MDI 50 to 78) which was significant but was not different between groups	Insulin treated type 2 diabetes achieved excellent glycemic control in both the CSII and the MDI group. Safety and patient satisfaction was also good and equal amongst treatment groups.	Blinding not possible

Appendix 4: Relevant Guidelines

National Institute for Health and Clinical Excellence (NICE)

Guidelines for the use of CSII for the treatment of diabetes (review), July 2008 (44)

CSII therapy is recommended as a treatment option for adults and children 12 years and older with type 1 diabetes mellitus provided that:

- Attempts to achieve target HbA1c levels with MDI result in the person experiencing disabling hypoglycaemia. For the purpose of this guidance, disabling hypoglycaemia is defined as a repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life

or

- HbA1c levels have remained high (that is, at 8.5% or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.

It is recommended that CSII therapy be initiated only by a trained specialist team, which should normally be comprised of a physician with a specialist interest in insulin pump therapy, a diabetes specialist nurse, and a dietitian. Specialist teams should provide structured education programmes and advice on diet, lifestyle and exercise appropriate for people using CSII.

Following initiation in adults and children 12 years and older, CSII therapy should only be continued if it results in a sustained improvement in glycemic control, evidenced by a fall in HbA1c levels, or a sustained decrease in the rate of hypoglycaemic episodes. Appropriate targets for such improvements should be set by the responsible physician, in discussion with the person receiving the treatment or their carer.

CSII therapy is not recommended for the treatment of people with type 2 diabetes mellitus.

Canadian Diabetes Association

2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (45)

Recommendations for insulin therapy in type 1 diabetes:

- To achieve glycemic targets in adults 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 is the treatment of choice *[Grade A, Level 1A (6)]*.

Rapid-acting insulin analogues (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 (9,11)]* and to achieve postprandial glucose targets *[Grade B, Level 2 (76)]*.

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