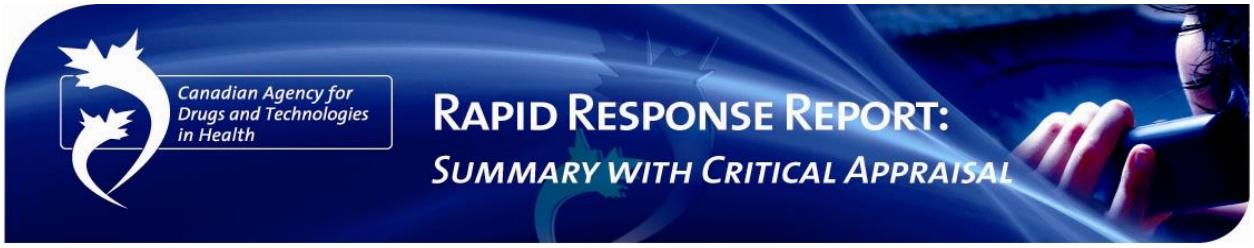

TITLE: Insulin Pumps for Adults with Type 1 Diabetes: A Review of Clinical Effectiveness, Cost-effectiveness and Guidelines

DATE: 10 December 2015

CONTEXT AND POLICY ISSUES

The global prevalence of diabetes among adults was estimated to be 6.4% in 2010 and will be 7.7% in 2030.[1] In Canada, the prevalence of diabetes was 7.6% in 2010 and will be 10.8% in 2020.[2] More than 300,000 Canadians live with type 1 diabetes.[2] The cost of diabetes to the Canadian health care system and economy was $11.7 billion in 2010, and is projected to increase to $16 billion by 2020.[2] The prevalence of Canadian adults living with type 1 diabetes, and the costs associated with this population could not be identified.

For patients who require insulin, glycemic control can be achieved via multiple daily injections (MDI) or by continuous subcutaneous insulin infusion (CSII).[3] Although it has been the standard of care for patients with type 1 diabetes, the use of MDI can lead to an increased risk of severe hypoglycemia.[4] CSII may result in additional benefits over MDI since basal insulin is continuously delivered through subcutaneous infusion.[4] Patients on CSII therapy wear a portable electromechanically pump that infuses insulin at pre-selected basal rates, which can be adjusted by patients as required.[3] However, it is difficult to avoid hypoglycemia, especially at night, when blood glucose level is not regularly checked with self-monitoring blood glucose (SMBG) measurement from finger-pricks.[4]

Recent advances in pump technology have resulted in sensor-augmented pumps, where the pump is integrated with a real-time continuous glucose monitor (CGM).[3] With the sensor-augmented insulin pump therapy (SAPT), insulin delivery could be stopped for up to two hours when sensor glucose drops below a preset threshold.[3] However, the CGM system measures glucose levels in the interstitial fluid, and not the blood glucose values.[3] A 2015 review identified several potential insulin pump-associated adverse events, such as pump malfunction, infusion set or site issues, and cutaneous problem.[5] Therefore, it remains to be determined whether CSII is more effective and safer than MDI, and whether CSII plus real-time CGM is more effective and safer than CSII alone in terms of glycemic control and patient relevant outcomes including severe hypoglycemia, quality of life and adverse events.

The aim of this report is to review the clinical and cost-effectiveness, and guidelines of insulin pumps for adults with type 1 diabetes. This report is an update to a previous Rapid Response report, “Continuous Subcutaneous Insulin Infusion for Type 1 Diabetes: Clinical Effectiveness,

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Cost-Effectiveness, and Guidelines", published in April 2015. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/apr-2015/RA0750%20Insulin%20Pumps%20for%20Type%201%20Diabetes%20Final.pdf

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of insulin pumps versus multiple daily injections for adults with type 1 diabetes?

2. What is the comparative clinical effectiveness of insulin pump models with continuous glucose monitors versus standard insulin pumps for adults with type 1 diabetes?

3. What is the cost-effectiveness of insulin pumps for adults with type 1 diabetes?

4. What are the evidence-based guidelines for insulin delivery in adults with type 1 diabetes?

KEY FINDINGS

The clinical effectiveness of CSII versus MDI in adult patients or in pregnant women with type 1 diabetes remains uncertain. Insulin pumps with integrated CGM (SAPT) appear to have better glycemic control without increasing the risk of hypoglycemia compared with MDI. We did not identify relevant evidence on the comparative clinical effectiveness of insulin pumps plus CGM compared with standard insulin pump in adults with type 1 diabetes. CSII may not be cost-effective compared with MDI. According to the guidelines, glycemic targets in adults with type 1 diabetes can be achieved with MDI or CSII. CSII therapy is recommended for patients who are unable to maintain a satisfactory glycemic control with MDI.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI Institute, Canadian and major international health technology agencies, as well as a focused Internet search. For research questions 1, 2 and 3 methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and economic studies. For research questions 2 and 3, the search was also limited to English language documents published between Jan 1, 2010 and Nov 12, 2015. For research question 4 methodological filters were applied to limit retrieval to guidelines. For research questions 1 and 4, the search was also limited to English language documents published between Jan 1, 2015 and Nov 12, 2015.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults with type 1 diabetes Subgroups of interest: pregnant women, older adults
Intervention	Q1, 2, and 4: Insulin pumps (continuous subcutaneous insulin infusion) Q2: Insulin pumps (continuous subcutaneous insulin infusion) with continuous glucose monitors (sensors) (built-in or added)
Comparator	Q1: Multiple daily injections (intermittent subcutaneous insulin injections) Q2: Standard insulin pumps (continuous subcutaneous insulin infusion) without continuous glucose monitors (sensors) Q3: Any alternate mode of insulin delivery Q4: No comparator required
Outcomes	Q1 and 2: Clinical benefits and harms (e.g., control of blood glucose levels; reduced complications related to diabetes [e.g., retinopathy, peripheral neuropathy, kidney failure], cardiovascular events, mortality, quality of life, hypoglycemic events) Q3: Cost-effectiveness outcomes Q4: Evidence-based guidelines regarding optimal methods of insulin delivery in adults with type 1 diabetes
Study Designs	Health technology assessments, systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-randomized studies, economic evaluations, and guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2010, duplicate publications of the same study, or included in a selected health technology assessment or systematic review. Also, meta-analyses without a systematic review also were excluded, and non-RCTs were included only when there were no systematic reviews found. Studies included a mixture of children, adolescents and adults in the populations were excluded.

Critical Appraisal of Individual Studies

The SIGN checklists were used to assess the quality of systematic reviews and meta-analyses (SR/MA),[6] randomized controlled trials (RCTs),[7] and economic evaluations.[8] The Appraisal of Guidelines Research & Evaluation (AGREE II) instrument was used to evaluate the quality of the included guidelines.[9]

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 507 citations. Upon screening titles and abstracts, 48 potential relevant articles were retrieved for full-text review. Three additional relevant reports were retrieved from other sources. Of the 51 potentially relevant articles, eight reports were included

in this review including two systematic reviews,[10,11] three RCTs,[12-14] one economic evaluation study[15] and two guidelines.[16,17] The study selection process is outlined in a PRISMA flowchart (Appendix 1). Studies that involved mixed populations, such as children and adults, or guidelines that did not specifically address adults with type 1 diabetes are listed as articles of potential interest in Appendix 2.

Summary of Study Characteristics

The characteristics of the clinical and economic studies are summarized in Appendix 3 and Appendix 4, respectively. Appendix 5 presents the grading of recommendations and levels of evidence of the included guidelines.

Clinical studies

Insulin pumps versus multiple daily injections

For this comparison, two SR/MAs[10,11] and three RCTs[12-14] were identified. The two SR/MAs were from USA, and the RCTs were from Denmark,[12] UK,[13] and Canada and USA.[14] Patient populations included pregnant women with type 1 diabetes,[10] adults or children with type 1 or type 2 diabetes,[11,14] and adults only with type 1 diabetes.[12,13] The study findings for adults with type 1 diabetes were presented in this report.

The literature search period of the SR/MA for pregnant women was up to May 2013, and seven cohort studies were identified.[10] The study duration of the cohort studies ranged from 36 to 40 weeks, and the duration of diabetes of the women ranged from 7.7 to 16.5 years. Another SR/MA[11] identified 33 RCTs with a literature search time frame between 1966 and February 2012. Among these studies, four trials compared CSII versus MDI, and four compared sensor-augmented insulin pump versus MDI and SMBG in adults with type 1 diabetes. The study duration across the trials ranged from 12 to 52 weeks.

The RCTs[12-14] were open-label and parallel in design, with study duration from 24 weeks[13] to one year.[12,14]

Both maternal and neonatal outcomes were analysed and reported one SR/MA,[10] but the maternal outcomes were presented in this report. Change in HbA1c and hypoglycemia were common outcomes reported across all studies.

One RCT[12] measured the change in urine albumin creatinine ratio as primary outcome among adults patients with type 1 diabetes and a history of albuminuria. One RCT[14] was the follow-up study of STAR3 trial and exclusively reported health-related quality of life. The STAR3 trial was excluded because the study findings were presented in a SR/MA[11] included in this report. Two SR/MAs[10,11] and one RCT[13] received public funding, and two RCTs[12,14] were funded by industry.

Insulin pump models with CGM versus standard insulin pumps

No relevant studies were identified for this comparison.

Economic Studies

Insulin pumps versus multiple daily injections

One economic evaluation study[15] was identified for this comparison.

The cost-effectiveness study by Kamble et al., 2012[15] used the Center for Outcomes Research (CORE) diabetes model version 7.0 for the analyses. The CORE diabetes model is a computer simulation model validated for type 1 and type 2 diabetes through 66 internal and external validations analyses.

The primary outcome measured was the incremental cost-effectiveness ratio (ICER) calculated from the US health care system perspective for a 60-year time horizon. The discount rate was 3%, and the clinical outcomes were derived from the results of the STAR3 trial using data for adults. The direct costs included costs of pumps, insulin therapy, supplies and medications, which were reduced by 16% to represent prices paid by the larger private and public payers. The study was funded by Medtronic.

Insulin pump models with CGM versus standard insulin pumps

No economic evaluation studies were identified for this comparison.

Guidelines

Two evidence-based guidelines[16,17] were identified. One was from Canada (Canadian Diabetes Association [CDA], 2013[16]), and one was from US (Veteran Affairs and Department of Defence [VA/DoD], 2010[17]). These guidelines presented recommendations for the use of insulin pump therapy in adults with type 1 diabetes.

Summary of Critical Appraisal

The results were summarized in Appendix 6, 7, and 8, respectively. The overall assessment of the study was scored as "*High*", "*Moderate*", or "*Low*". The definitions of the scores are presented as footnotes of each appendix table. AGREE II checklist[9] was used to evaluate the quality of the guidelines (Appendix 9). Each question was answered as "*Yes*", "*No*" or "*Not clear*".

Two SR/MAs[10,11] were of high quality as they "adequately addressed" or "well covered" items including an explicit focused question, description of methodology, comprehensive literature search, quality assessment of included studies, and meta-analysis of similar studies.

The RCTs[12-14] were of poor quality. The method of randomization was not described in one RCT,[13] while the method of concealment was not addressed in two RCTs.[12,14] All RCTs were open-labelled design, which may have resulted in treatment and reporting bias toward newer technologies. Although the patient characteristics in both treatment arms seemed balanced based on the data reported, none of the trials explicitly stated whether the difference between groups was limited to the treatment under investigation. All RCTs reported relevant outcomes, had dropout rates less than 15%, and used intention to treat analysis. Although they were multicentred, none of the RCTs reported whether the results were comparable for all sites.

The economic evaluation study[15] was of high quality as all of the items in the checklist were "adequately addressed".

The evidence-based guidelines[16,17] were explicit in terms of scope and purpose, stakeholder involvement, and clarity of recommendations. As well, the applicability of the recommendations, such as advice or tools on how they can be put into practice, facilitators and barriers to their application and potential resource implications, were addressed in the CDA guidelines,[16] but not in the VA/DoD guidelines.[17]

Summary of Findings

The main findings of the clinical studies and economic studies are presented in Appendix 10 and 11, respectively. The guideline recommendations for insulin delivery in adults with type 1 diabetes are outlined in Appendix 12.

Clinical studies

Insulin pumps versus multiple daily injections

Change in HbA1c

In adults with type 1 diabetes, the SR/MA[11] showed that CSII was associated with a statistically significant decrease in HbA1c compared with MDI based on the results of four RCTs. In another analysis from the same SR/MA[11] that compared SAPT (i.e., a combined system of CSII and CGM) with MDI plus SMBG, the pooled results showed that SAPT was associated with a statistically significant decrease in HbA1c. The results of two RCTs[12,14] also showed a statistically significant reduction in HbA1c favoring SAPT over MDI in adults with type 1 diabetes.

In pregnant women with type 1 diabetes, all seven studies identified in the SR/MA[10] reported an improvement in HbA1c in both the CSII and MDI groups. However, none of the studies showed a statistically significant difference between groups in all three trimesters.

Hypoglycemia

There were no differences in the rate of severe hypoglycemia between CSII and MDI[11,13] or between SAPT and MDI[11,12] in adults with type 1 diabetes. Similar findings were observed for pregnant women with type 1 diabetes.[10]

Hyperglycemia

There was no difference in time spent with hyperglycemia between CSII and MDI.[11] The time spent with hyperglycemia was shorter with SAPT than with MDI.[11]

Quality of life

The SR/MA[11] found that improvement in the general quality of life (QoL) and diabetes mellitus-specific QoL outcomes favoured CSII. One RCT[13] also found that treatment satisfaction favoured CSII over MDI as measured by the Diabetes Treatment Satisfaction Questionnaire score, despite no difference in hypoglycemia awareness and fear of hypoglycemia. The results

of SR/MA[11] for diabetes treatment-related QoL for CSII versus MDI and general QoL for SAPT versus MDI were inconclusive due to insufficient evidence.[11] One RCT[14] found that, compared with MDI, patients in the SAPT group had reduced fear of hypoglycemia and higher treatment satisfaction.[14] However, there was no significant difference between SAPT and MDI in health-related QoL measured by SF-36 (both physical and mental components).[14]

QoL was not reported in the SR/MA for pregnant women with type 1 diabetes.[10]

Weight gain

There were no differences in weight gain between CSII and MDI or between SAPT and MDI in adults with type 1 diabetes.[11] Similar observations were found for pregnant women with type 1 diabetes.[10]

Diabetic ketoacidosis

Ketoacidosis was rare, and there was no difference in the number of episodes between treatment groups.[10,12,14]

Urine albumin creatinine ratio

In patients with history of albuminuria, SAPT was found to be associated with a reduction in urine albumin creatinine ratio (UACR), with no difference in glomerular filtration rate.[12] After one year of treatment, the mean change of UACR was -13% (95% confidence interval [CI] -39 to 22) for SAPT versus 30% (95% CI -12 to 92) for MDI.

Caesarean delivery

There was no difference in the rate of caesarean delivery between CSII and MDI in pregnant women with type 1 diabetes.[10]

Economic Studies

Insulin pumps versus multiple daily injections

The economic evaluation[15] found that the combined CSII and CGM in the SAPT system used in adults with type 1 diabetes was not cost-effective compared with MDI and SMBG. The ICER was US$229,674 per quality adjusted life years (QALY) or US$168,104 per QALY with three-day sensors use or with six-day sensors use, respectively.

Guidelines

The CDA 2013 guidelines[16] recommended the use of either MDI or CSII in adults with type 1 diabetes. It also recommended the use of CSII with rapid-acting insulin analogues, such as insulin aspart or lispro.

The VA/DoD 2010 guidelines[17] recommended that insulin pump therapy be considered in patients with type 1 diabetes who have poor glycemic control despite MDI treatment being optimized to yield greater returns (Appendix 11).

Limitations

None of the studies reported results specific to older adults with type 1 diabetes, and the evidence in the SR/MA of pregnant women was based on observational studies. The findings, therefore, were susceptible to confounding and selection bias. Heterogeneity across the studies was substantial, probably due to differences in definitions of outcome measures, the types of insulin used, treatment duration diabetes duration, and age of the study populations.

The RCTs included in both the SR/MAs and in this report were mostly of poor quality due to a lack of adequate concealment method and blinding of outcome accessors. As the blinding of patients in RCTs that compared CSII with MDI or SAPT with CSII was not feasible, the results of patient-reported outcomes were prone to reporting bias, if patients believed that the interventions were superior. Moreover, the results of the clinical studies sponsored by industry should be interpreted with caution due to a potential for funding bias. Finally, the findings of the economic evaluation may not be transferrable to the Canadian setting since they were derived from the US health care perspective.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The comparative clinical effectiveness of CSII versus MDI in adult patients or in pregnant women with type 1 diabetes remains uncertain. The results suggest that SAPT has better glycemic control without increasing risk of hypoglycemia compared with MDI. However, SAPT system does not appear to be cost-effective compared with MDI from a US health care system perspective. We did not identify relevant studies on the clinical effectiveness of insulin pump models with continuous glucose monitors compared with insulin pump in adults with type 1 diabetes or any studies that reported results specific to older adults with type 1 diabetes. The CDA guidelines stated that glycemic targets in adult with type 1 diabetes can be achieved by MDI or CSII, while the VA/DoD guidelines recommended that CSII therapy should be used in patients with poor glycemic control despite optimized MDI and lifestyle modification. Recommendations on the use of SAPT were not identified in the guidelines.

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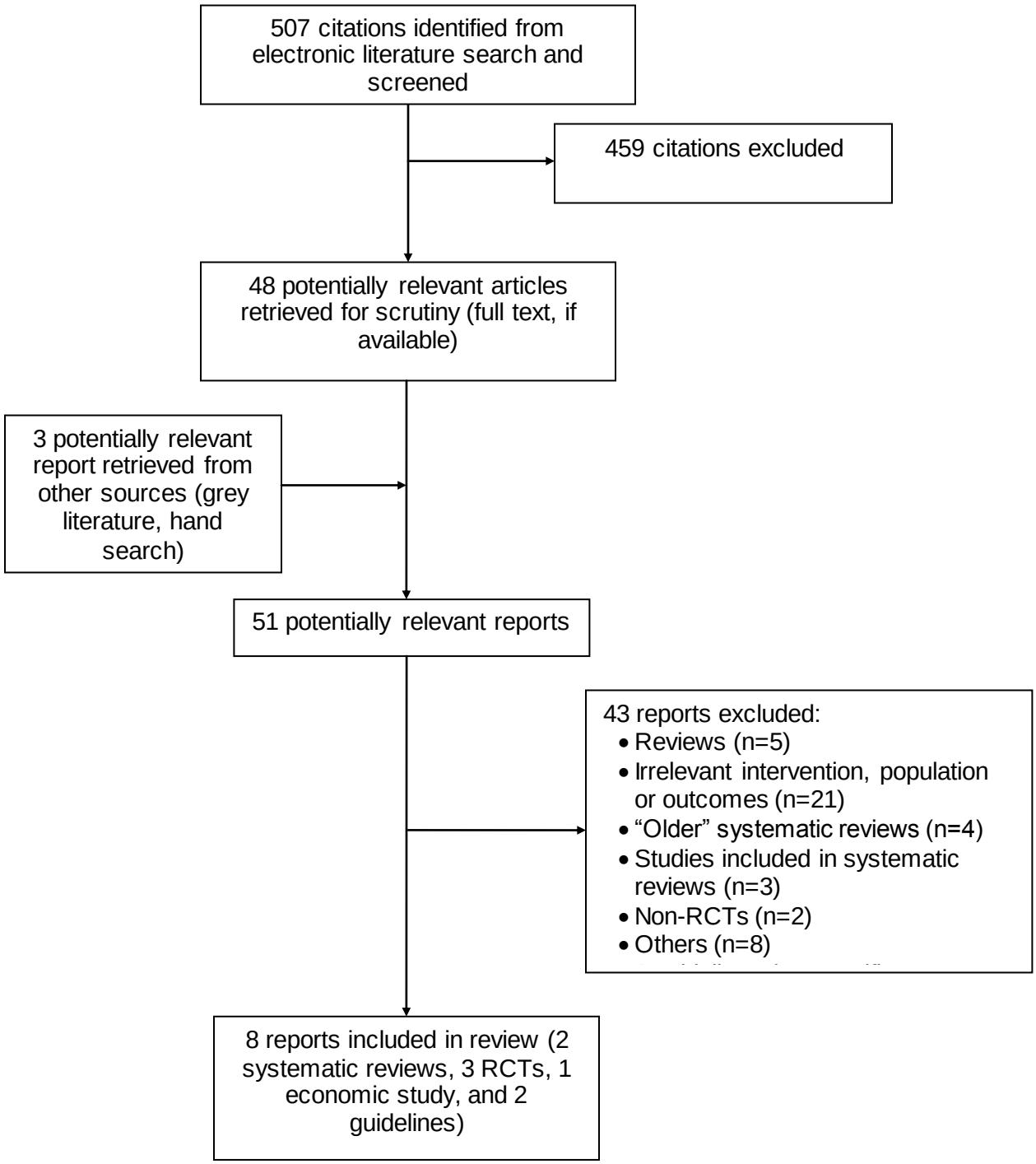
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Articles of Potential Interest

Mixed Populations (Children, Adolescents, and Adults with Type 1 Diabetes)

Clinical studies

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APPENDIX 3: Characteristics of Included Clinical Studies

Study, Year, Country, Design, Funding	Study Characteristics	Patient characteristics	Interventions of interest	Clinical Outcomes
Ranasinghe et al., 2015[10] USA SR/MA Funding: public	Lit search: up to May 2013 onward 7 cohort studies • CSII vs MDI Study duration: 36 to 40 weeks Duration of diabetes: 7.7 to 16.5 years	Pregnant women with type 1 diabetes	• CSII vs MDI	• Maternal outcomes (HbA1c, caesarean delivery, hypoglycemia, weight gain, ketoacidosis)
Yeh et al., 2012[11] USA SR/MA Funding: public	Lit search: 1966 to February 2012 33 RCTs (24 parallel, 9 crossover trials) • CSII vs MDI: 19 trials • CGM vs SMBG: 10 trials • SAPT vs MDI + SMBG: 4 trials Study duration: 12 to 52 weeks	Adults or children with type 1 or 2 diabetes Separate analyses for adults and children	• CSII vs MDI • SAPT vs MDI + SMBG	• HbA1c • Severe hypoglycemia • Other glycemic outcomes • Weight gain • QoL
Rosenlund et al., 2015[12] Denmark Open-label, parallel RCT Funding : Private (Medtronic)	60 patients (30 per group) with sample size calculation Modified ITT analysis One screening visit and 6 visits SAPT: Pradigm Veo model MMT-554 or MMT-754 (Medtronic) Study duration: 1 year	Adults (18 to 75 years; 51 ± 10 years) with type 1 diabetes and history of albuminuria Male: 63% Diabetes duration: 33 ± 12 years GFR ≥ 45 ml / min / 1.73 m^2 UACR ≥ 30 mg/g	• SAPT • MDI All patients used glucose meter and were encouraged to measure four blood glucoses daily	1° outcome: Change in UACR 2° outcomes: Changes in GFR, BP, HbA1c, glycemic variability
Little et al., 2014[13] UK Open-label, parallel RCT Funding:	96 patients with sample size calculation Modified ITT analysis Visits: every 4 weeks up to 24 weeks CSII: Paradigm Veo	Adults (18 to 74 years ; 49 ± 12 years) with type 1 diabetes Male: 36% Diabetes duration: 29 ± 12 years	• CSII + SMBG • CSII + SMBG and CGM • MDI + SMBG • MDI + SMBG and CGM	1° outcome: hypoglycemia awareness (by Gold score) 2° outcomes: hypoglycemia awareness (by

Study, Year, Country, Design, Funding	Study Characteristics	Patient characteristics	Interventions of interest	Clinical Outcomes
Public	insulin pump (Medtronic) Study duration: 24 weeks		Comparison of interest: CSII vs MDI	Clarke and HypoA-Q scores); biochemical hypoglycemia; severe hypoglycemia rate; HbA1c; QoL
Rubin et al., 2012[14] Follow-up study of STAR3 Open-label, parallel RCT Canada and USA Funding: Private (Medtronic)	STAR 3: 485 patients with sample size calculation Modified ITT analysis SAPT: Mini-Med Paradigm REAL-time system; Medtronic Visits: baseline, 3, 6, 9 and 12 months Study duration: 1 year	Children and adults (7 to 70 years; 32 ± 18 years) with type 1 diabetes; naïve to insulin pump and CGM Male: 57% Diabetes duration: 15 years This study presented subgroup results for adults	• SAPT • MDI + SMBG In the MDI group, CGM device was attached, collected data, but did not display	Health-related QoL

CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin injection; GFR = glomerular filtration rate; MA = meta-analysis; ITT = intention to treat; MDI = multiple daily injection; QoL = quality of life; RCT = randomized controlled trial; SAPT = sensor-augmented pump therapy (combine CGM with CSII); SMBG = self-monitoring of blood glucose; SR = systematic review; UACR = urine albumin creatinine ratio

APPENDIX 4: Characteristics of Economic Studies

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Intervention, comparator	Cost included
Kamble et al., 2012[15] USA Private (Medtronic)	Cost-effectiveness 1° outcome: ICER Treatment effects: HbA1c, Utility: CORE Diabetes Model default values Sensitivity analyses	Perspective: US health care system Time horizon: 60-year time horizon Currency: US$ Discount: 3%	STAR 3 population (adults only in US and Canada)	SAPT MDI and SMBG	Costs: • Pumps • Insulin therapy • Supplies • Medications Costs were reduced by 16% to represent prices paid by larger private and public payers

ICER = incremental cost-effectiveness ratio; QoL = quality of life; SAPT = sensor-augmented pump therapy; SMBG = self-monitoring blood glucose; SPT = standard pump therapy

APPENDIX 5: Grading of Recommendations and Levels of Evidence

Guideline Society or Institute	Grade of Recommendation	Level of Evidence
Canadian diabetes Association (CDA)[16] 2013 Canada	**A** The best evidence was at Level 1 **B** The best evidence was at Level 2 **C** The best evidence was at Level 3 **D** The best evidence was at Level 4 or consensus	**1A** Systematic overview of meta-analysis of high quality RCTs or appropriate designed RCT with adequate power to answer the question posed by the investigators **1B** Nonrandomized clinical trial or cohort study with indisputable results **2** RCT or systematic review that does not meet Level 1 criteria **3** Nonrandomized clinical trial or cohort study; systematic review or meta-analysis of level 3 studies **4** Other
Veterans Affairs and Department of Defence (VA/DoD)[17] 2010 USA	**A** A strong recommendation that clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important outcomes and concludes that benefits substantially outweigh harm.* **B** A recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.* **C** No recommendation for or against the routine provision of the intervention is made. *At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.* **D** Recommendation is made against routinely providing the intervention to asymptomatic patients. *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.* **I** The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. *Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*	

CI = confidence interval; RCT = randomized controlled trial

APPENDIX 6: Quality Assessment of Systematic Reviews and Meta-analyses

SIGN Checklist: Systematic Reviews and Meta-analyses		
Internal Validity	Ranasingle et al., 2015[10]	Yeh et al., 2012[11]
The study addresses an appropriate and clearly focused question	Well covered	Well covered
A description of the methodology used is included	Well covered	Well covered
The literature search is sufficient rigorous to identify all the relevant studies.	Adequately addressed	Well covered
Study quality is assessed and taken into account	Adequately addressed	Well covered
There are enough similarities between the studies selected to make combining them reasonable.	Adequately addressed	Well covered
Overall Assessment of the Study		
High, Moderate, Low	High	High

For overall assessment of the study: *High* indicated that all items in the checklist were well covered or adequately addressed; *Moderate* indicates that there is one item that was not well covered or adequately addressed; *Poor* indicates that at least two items were not well covered or adequately addressed.

APPENDIX 7: Quality Assessment of Randomized Controlled trials

SIGN Checklist: Randomized Controlled Trials			
Internal Validity	Rosenlund et al., 2015[12]	Little et al., 2014[13]	Rubin et al., 2012[14]
The study addresses an appropriate and clearly focused question.	Well covered	Adequately addressed	Well covered
The assignment of subjects to treatment groups is randomized.	Well covered	Poorly addressed	Well covered
An adequate concealment method is used.	Not addressed	Adequately addressed	Not addressed
Subjects and investigators are kept "blind" about treatment allocation.	Not applicable	Not applicable	Not applicable
The treatment and control groups are similar at the start of trial.	Adequately addressed	Adequately addressed	Adequately addressed
The only difference between groups is the treatment under investigation.	Not addressed	Not addressed	Not addressed
All relevant outcomes are measured in a standard, valid and reliable way.	Adequately addressed	Adequately addressed	Adequately addressed
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	13% in SAPT and 3% in MDI	Total dropped out: 6%	Total dropped out: 11%
All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Adequately addressed	Adequately addressed	Adequately addressed
Where the study is carried out more than one site, results are comparable for all sites.	Not reported	Not reported	Not reported
Overall Assessment of the Study			
High, Moderate, Low	Poor	Poor	Poor

For overall assessment of the study: *High* indicated that all items in the checklist were well covered or adequately addressed; *Moderate* indicates that there are at most two items that were not well covered or adequately addressed; *Poor* indicates that at least three items were not well covered or adequately addressed.

APPENDIX 8: Quality Assessment of Economic Evaluations

SIGN Checklist: Economic Evaluations	
Internal Validity	Kamble et al., 2012[15]
There is a defined and answerable study question.	Adequately addressed
The economic importance of the question is clear.	Adequately addressed
The choice of study design is justified.	Adequately addressed
All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately.	Adequately addressed
The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately.	Adequately addressed
If discounting of the future costs and outcomes is necessary, it has been performed correctly.	Adequately addressed
Assumptions are made explicit and a sensitivity analysis performed.	Adequately addressed
The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes.	Adequately addressed
The results provide information of relevance to policy.	Adequately addressed
Overall Assessment of the Study	
High, Moderate, Low	High

For overall assessment of the study: *High* indicated that all items in the checklist were well covered or adequately addressed; *Moderate* indicates that there is one item that was not well covered or adequately addressed; *Poor* indicates that at least two items were not well covered or adequately addressed.

APPENDIX 9: Quality Assessment of Guidelines

AGREE II checklist: Guidelines		
	CDA,[16] 2013, Canada	VA/DoD,[17] 2010, USA
Scope and purpose		
Objectives and target patients population were explicit	Yes	Yes
The health question covered by the guidelines is specifically described	Yes	Yes
The population to whom the guidelines is meant to apply is specifically described	Yes	Yes
Stakeholder involvement		
The guideline development group includes individuals from all relevant professional groups	Yes	Yes
The views and preferences of the target population have been sought	Yes	Yes
The target users of the guideline are clearly defined	Yes	Yes
Rigour of development		
Systematic methods were used to search for evidence	Yes	Yes
The criteria for selecting the evidence are clearly described	Yes	Yes
The strengths and limitations of the body of evidence are clearly described	Yes	Not clear
The methods of formulating the recommendations are clearly described	Yes	Yes
The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes
There is an explicit link between the recommendations and the supporting evidence	Yes	Yes
The guideline has been externally reviewed by experts prior to its publication	Yes	Yes
A procedure for updating the guideline is provided	Yes	Yes
Clarity of recommendation		
The recommendations are specific and unambiguous	Yes	Yes
The different options for management of the condition or health issue are clearly presented	Yes	Yes
Key recommendations are easily identified	Yes	Yes
Applicability		
The guidelines provides advice and/or tools on how the recommendations can be put into practice	Yes	Not clear
The guideline describes facilitators and barriers to its application	Yes	Not clear
The potential resource implications of applying the recommendations have been considered	Yes	Not clear
The guideline presents monitoring and/or auditing criteria	No	Yes
Editorial independence		
The views of the funding body have not influenced the content of the guideline	Not clear	Not clear
Competing interests of guideline development group members have been recorded and addressed	Yes	Yes

APPENDIX 10: Main Study Findings and Authors' Conclusions – Clinical

<table>
<tr><th>Study, Year, Country, Design, Funding</th><th>Main Findings</th></tr>
<tr><td>Ranasinghe et al., 2015[10]

USA

SR/MA

Funding: public</td><td>MDI vs CSII in pregnant women with type 1 diabetes (for Q1)

7 cohort studies
Strength of the evidence: low

<table>
<tr><th colspan="2">Maternal outcomes</th></tr>
<tr><td>HbA1c</td><td>All studies showed no statistically significant difference for mean differences between groups in the third trimester HbA1c. No meta-analysis was performed.</td></tr>
<tr><td>Caesarean delivery</td><td>RR (95% CI) = 1.03 (0.92, 1.15); I^2 = 5.0% (6 studies)</td></tr>
<tr><td>Severe hypoglycemia</td><td>RR (95% CI)= 0.78 (0.23, 2.65); I^2 = 0.0% (3 studies)</td></tr>
<tr><td>Maternal weight gain</td><td>Three studies measured weight gain. No statistically significant difference in weight gain between CSII and MDI</td></tr>
<tr><td>Ketoacidosis</td><td>One study reported there were two episodes (4.7%) in the MDI and one episode (1.1%) in the CSII.</td></tr>
<tr><td colspan="2">CI = confidence interval; MD = mean difference; NICU = neonatal intensive care unit; RR = relative risk</td></tr>
</table></td></tr>
<tr><td colspan="2">Authors' conclusions: "Observational studies reported similar improvements in HbA1c with CSII and MDI during pregnancy, but evidence was insufficient to rule out possible important differences between CSII and MDI for maternal and fetal outcomes."[10] p.237</td></tr>
<tr><td>Yeh et al., 2012[11]

USA

SR/MA

Funding: public</td><td>CSII vs MDI in adults with type 1 diabetes (for Q1)

8 RCTs with 762 participants
Strength of the evidence: Low

<table>
<tr><th>Outcomes</th><th>Meta-analysis</th><th>Findings</th><th>Strength of evidence</th></tr>
<tr><td>HbA1c</td><td>MD (95% CI) = -0.30% (-0.58 to -0.02); 4 RCTs (n=195); I^2=64.5%</td><td>Favors CSII</td><td>Low</td></tr>
<tr><td>Hyperglycemia</td><td>No meta-analysis</td><td>No difference</td><td>Low</td></tr>
<tr><td>Severe hypoglycemia</td><td>OR (95% CI) = 0.69 (0.24 to 1.94); 3 RCTs (n=168)</td><td>No difference</td><td>Low</td></tr>
<tr><td>Mild hypoglycemia</td><td>No meta-analysis</td><td>No difference</td><td>Low</td></tr>
<tr><td>Nosturnal hypoglycemia</td><td>No meta-analysis</td><td>No difference</td><td>Low</td></tr>
<tr><td>Symptomatic hypoglycemia</td><td>No meta-analysis</td><td>Favors MDI</td><td>Low</td></tr>
<tr><td>Weight gain</td><td>No meta-analysis</td><td>No difference</td><td>Low</td></tr>
<tr><td>General QoL</td><td>No meta-analysis</td><td>Favors CSII</td><td>Low</td></tr>
<tr><td>Diabetes mellitus-specific QoL</td><td>No meta-analysis</td><td>Favors CSII</td><td>Low</td></tr>
<tr><td>Diabetes treatment-related QoL</td><td>No meta-analysis</td><td>Cannot conclude</td><td>Insufficient</td></tr>
<tr><td colspan="4">CI = confidence interval; CSII = continuous subcutaneous insulin infusion; MD = mean difference; MDI = multiple daily injections</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study, Year, Country, Design, Funding</th><th>Main Findings</th></tr>
<tr><td></td><td>SAPT (CSII + CGM) vs MDI + SMBG in adults with type 1 diabetes (for Q1)

4 RCTs with 612 participants
Strength of the evidence: low to moderate

<table>
<tr><th>Outcomes</th><th>Meta-analysis</th><th>Findings</th><th>Strength of evidence</th></tr>
<tr><td>HbA1c</td><td>MD (95% CI) = -0.68% (-0.81 to -0.54); 4 RCTs (n=612); I^2=53.7%</td><td>Favors SAPT</td><td>Moderate</td></tr>
<tr><td>Hyperglycemia</td><td>No meta-analysis</td><td>Favors SAPT</td><td>Moderate</td></tr>
<tr><td>Severe hypoglycemia</td><td>RD (95% CI) = 1.6% (-3.0 to 6.3); 1 RCT (n=485)</td><td>No difference</td><td>Moderate</td></tr>
<tr><td>Weight gain</td><td>No meta-analysis</td><td>No difference</td><td>Low</td></tr>
<tr><td>General QoL</td><td>No meta-analysis</td><td>Cannot conclude</td><td>Insufficient</td></tr>
<tr><td colspan="4">CI = confidence interval; CSII = continuous subcutaneous insulin infusion; MD = mean difference; MDI = multiple daily injections; RD = risk difference; SAPT = sensor-augmented pump therapy</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Authors' conclusions: "CSII has a favorable effect on glycemic control in adults with type 1 diabetes. Sensor-augmented insulin pumps are superior to MDI and SMBG without increasing the risk of hypoglycemia"[11] p.336</td></tr>
<tr><td>Rosenlund et al., 2015[12]

Denmark

Open-label, parallel RCT

Funding : Private (Medtronic)</td><td>SAPT (n=26) vs MDI (n=29) in adult patients with type 1 diabetes with history of albuminuria (for Q1)

After 1 year of treatment:
• Change in UACR: favors SAPT
Mean (95% CI): -13% (-39 to 22) vs 30% (-12 to 92); p=0.051; adjusted p value 0.04
• Change in HbA1c: favors SAPT
Percent ± SD: -1.3 ± 1.0 vs 0.6 ± 1.0%; p=0.013
• Change in blood glucose variability: favors SAPT
Concentration ± SD: -0.9 ± 1.1 vs -0.3 ± 1.0 mmol/L; p=0.04
• Change in GFR: no difference
Rate ± SD: 5.6 ± 9.6 vs 3.4 ± 13 ml/min/1.73m^2; p=0.50
• Two episodes of ketoacidosis, all were in two patients with SAPT (one died)
• Three episodes with severe hypoglycemia, all were with MDI</td></tr>
<tr><td colspan="2">Authors' conclusions: "SAP treatment reduced UACR in a randomized controlled trial in type 1 diabetes patients with a history of albuminuria on stable renin-angiotensin system inhibition. Significance was reached after adjustment. SAP treatment reduced HbA1c and glucose variability."[12] p.4181</td></tr>
<tr><td>Little et al., 2014[13]

UK

Open-label, parallel RCT

Funding: Public</td><td>CSII (n=46) vs MDI (n=50) in adult patients with type 1 diabetes (for Q1)

After 24 weeks of treatment:
• Hypoglycemia awareness: no difference
Gold score (mean ± SD): 4.2 ± 1.7 vs 4.1 ± 1.6; p=0.756
• Severe hypoglycemia: no difference
Annualized rate (mean ± SD): 0.6 ± 1.7 vs 1.0 ± 2.1; p=0.34
• Treatment satisfaction: favors CSII
DTSQ score (mean ± SD): 32 ± 3 vs 29 ± 6; p=0.0003
• Fear of hypoglycemia: no difference
HFS II score (mean ± SD): 44 ± 23 vs 45 ± 25; p=0.824</td></tr>
</table>

Study, Year, Country, Design, Funding	Main Findings
Authors' conclusions: "*Restoration of hypoglycemia awareness and prevention of severe hypoglycemia, without worsening overall metabolic control, can be achieved with conventional MDI*"[13] p.2121	
Rubin et al., 2012[14] Follow-up study of STAR3 Open-label, parallel RCT Canada and USA Funding: Private (Medtronic)	**SAPT (n=166) vs MDI (n=168) in adults with type 1 diabetes** (for Q1) After 12 months of treatment: • Change in HbA1c in adults: favors SAPT MD (95% CI): -0.6% (-0.8 to -0.4); p<0.001 • Severe hypoglycemia: no difference • Ketoacidosis: only 2 events in SAPT • Health-related quality of life: ○ SF-36: no difference ○ Hypoglycemia fear survey: favors SAPT Change from baseline scores: -6.36 vs -1.87; p<0.001 ○ Insulin Delivery System Rating Questionnaire (change from baseline scores): favors SAPT ✓ Convenience: 19.49 vs 1.20; p<0.001 ✓ Problems: -6.89 vs -0.44; p<0.001 ✓ Interference: -3.48 vs -1.62; p<0.01 ✓ Blood Glucose burden: -16.16 vs -9.28; p<0.001 ✓ Efficacy: 35.57 vs 6.16; p<0.001 ✓ Worries: -12.75 vs -4.94; p<0.001 ✓ Social burden: -11.74 vs -6.20; NS ✓ Well-being: -4.94 vs -1.50; p<0.01 ✓ Overall preference: 40.63 vs 6.94; p<0.001
Authors' conclusions: "*SAPT had significant advantages for hypoglycemia fear in adults …and for treatment satisfaction in adults…*"[14], p.143	

CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin injection; DSTQ = Diabetes Treatment Satisfaction Questionnaire; GFR = glomerular filtration rate; HFS-II = Hypoglycemia Fear survey II; MA = meta-analysis; ITT = intention to treat; MD = mean difference; MDI = multiple daily injection; QoL = quality of life; RCT = randomized controlled trial; SAPT = sensor-augmented pump therapy (combine CGM with CSII); SMBG = self-monitoring of blood glucose; SR = systematic review; UACR = urine albumin creatinine ratio

APPENDIX 11: Main Study Findings and Authors' Conclusions – Economic

Study, Year, Country, Design, Funding	Main Findings
Kamble et al., 2012[15] Cost-effectiveness USA Private (Medtronic)	**SAPT (CSII + CGM) vs MDI + SMBG in adults with type 1 diabetes (US health care system perspective)** • With 3-day sensors use Discounted lifetime direct costs: $253,493 vs $167,170 QALYs: 10.794 vs 10.418 ICER (95% CI): $229,675 per QALY (139,071 to 720,865) • With 6-day sensors use Discounted lifetime direct costs: $230,352 vs $168,104 QALYs: 10.794 vs 10.418 ICER (95% CI): $168,104 per QALY (102,819 to 523,161) • Sensitivity analyses: Most sensitive with varying number of glucose meter test strips for SAPT
Authors' conclusions: "*Despite superior clinical superior benefits of SAPT compared with MDI, SAPT does not appear to be economically attractive in the United States for adults with type 1 diabetes in its current state of development*."[15] p.632	

GBP = Great British Pound; ICER = incremental cost-effectiveness ratio; LGS = low Glucose Suspend; QoL = quality of life; SAPT = sensor-augmented pump therapy; SEK = Swedish Krona; SMBG = self-monitoring blood glucose; SPT = standard pump therapy

APPENDIX 12: Guidelines and Recommendations for Insulin Delivery in Adults with Type I Diabetes

Guideline Society or Institute	Recommendations
Canadian diabetes Association (CDA)[16] 2013 Canada	• "*To achieve glycemic targets in adults with type 1 diabetes, basal-bolus insulin regimens or CSII as part of an intensive diabetes management regimen should be used* [**Grade A, Level 1A**]"[16] p. S56 • "*Rapid-acting insulin analogues (aspart or lispro) should be used with CSII in adults with type 1 diabetes*" [**Grade B, Level 2**][16] p.S56
Veterans Affairs and Department of Defence (VA/DoD)[17] 2010 USA	1. "*CSII therapy should only be initiated and managed by an endocrinologist/diabetes team with expertise in insulin pump therapy* 2. *CSII therapy should only be considered in patients who either documented type 1 diabetes [history of DKA, low c-peptide or evidence of pancreatic autoimmunity] or be insulin deficient with a need for intensive insulin therapy to maintain glycemic control and are not able to maintain it using multiple daily injections (MDI) therapy. This may include patients with*: a. *Poor glycemic control (including wide glucose excursions with hyperglycemia and serious hypoglycemia and those not meeting HbA1c goal) despite an optimized regimen using MDI in conjunction with lifestyle modification*. [**Grade A**] b. *Marked dawn phenomenon (fasting AM hyperglycemia) not controlled using NPH at bedtime, glargine or detemir*. [**Grade B**] c. *Recurrent nocturnal hypoglycemia despite optimized regimen using glargine or detemir*. [**Grade B**] d. *Circumstances of employment or physical activity, for example shift work, in which MDI regimens have been unable to maintain glycemic control*. [**Grade I**] 3. *Patients using CSII should have*: a. *Demonstrated willingness and ability to play an active role in diabetes self-management to include frequent self-monitoring of blood glucose (SMBG), and to have frequent contact with their healthcare team*. b. *Completed a comprehensive diabetes education program*."[17] p.64