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Comparative Effectiveness and Safety of Insulin Delivery and Glucose Monitoring Methods for Diabetes Mellitus

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

Acknowledgments

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Structured Abstract

Objectives: To systematically review whether the mode of intensive insulin therapy using rapid-acting insulin analogs (multiple daily injections [MDI] versus continuous subcutaneous insulin infusion [CSII]) and/or the mode of blood glucose monitoring (self-monitoring of blood glucose [SMBG] versus real time-continuous glucose monitoring [rt-CGM]) results in better glycemic control, less hypoglycemia, improved quality of life, and improved clinical outcomes in individuals with type 1 diabetes, type 2 diabetes, and pre-existing diabetes in pregnancy.

Data Sources: MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials from inception to October 2010. Additional studies were identified from reference lists and technical experts.

Review Methods: We included randomized-controlled trials (RCTs) for all outcomes and observational studies for select clinical outcomes that compared the effects of CSII with MDI or rt-CGM with SMBG among children, adolescents, or adults with either type 1 or type 2 diabetes, or pregnant women with pre-existing diabetes. Two reviewers evaluated studies for eligibility; serially abstracted data using standardized forms; and independently evaluated study quality. We conducted meta-analyses when there were sufficient data and studies were sufficiently homogenous.

Results: We included 44 articles. RCTs showed no difference in the effect of CSII and MDI on HbA_{1c} or severe hypoglycemia for children, adolescents, or adults with type 1 diabetes, or for adults with type 2 diabetes. In individuals with type 1 diabetes, CSII use was associated with improved quality of life compared with MDI. There was insufficient evidence about quality of life for adults with type 2 diabetes. The evidence regarding pregnant women with pre-existing diabetes was either low or insufficient on all outcomes. We found studies of the comparative effectiveness of rt-CGM versus SMBG in individuals with type 1 diabetes only. Compared with SMBG, rt-CGM achieved a lower HbA_{1c}, with greater reductions occurring where sensor compliance was 60% or greater. There was no difference in the rate of severe hypoglycemia or quality of life. Sensor-augmented pump use was associated with a significantly greater reduction in HbA_{1c} compared with MDI/SMBG use in non-pregnant individuals with type 1 diabetes. The evidence for other outcomes was low or insufficient.

Conclusions: The approach to intensive insulin therapy can be individualized to patient preference that will maximize their quality of life as both CSII and MDI using rapid-acting insulin analogs have similar effectiveness for glycemic control and severe hypoglycemia. These data also indicate that rt-CGM is superior to SMBG in lowering HbA_{1c}, without affecting the risk of severe hypoglycemia, in non-pregnant individuals with type 1 diabetes, particularly when compliance is high. Sensor-augmented pumps are superior to MDI/SMBG in lowering HbA_{1c}.

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Comparative Effectiveness and Safety of Insulin Delivery and Glucose Monitoring Methods for Diabetes Mellitus

Executive Summary

Background

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia resulting from: defects in insulin secretion from the pancreatic beta cells; resistance to insulin action at the level of skeletal muscle, liver, and fat; or both. The resultant hyperglycemia, if untreated, can lead to long-term complications, including microvascular complications (i.e., retinopathy, nephropathy, and peripheral and autonomic neuropathy) and macrovascular complications (i.e., coronary heart disease, cerebrovascular disease, and peripheral arterial disease).[1] The prevalence of diagnosed diabetes in the US is currently 7.7 percent and is expected to increase to nearly 10 percent by 2050, at which time an estimated 39 million people will have diabetes in the US.[2-4] Thus, a large segment of the population requires glucose-lowering therapies to maintain normal glucose levels (normoglycemia) and prevent diabetes complications.

Type 1 diabetes, which accounts for 5 to 10 percent of all diabetes cases, is characterized by insulin deficiency and a need for daily insulin administration to sustain life, maintain normoglycemia, and maintain normal body weight and promote normal growth and development in children.[1] Type 2 diabetes, which accounts for 90 to 95 percent of diabetes in the United States, is the result of a combination of insulin resistance and impaired insulin secretion by the beta cells of the endocrine pancreas.[1] Although the relative contribution of each of these factors to the course of type 2 diabetes varies by patient, eventually, beta cell failure can lead to insulin deficiency, necessitating insulin therapy. In pregnant women with pre-existing type 1 or type 2 diabetes, poor glycemic control is associated with poorer pregnancy outcomes including fetal anomalies, macrosomia, delivery complications, stillbirth, and neonatal hypoglycemia.

Importance of Tight Glycemic Control and Associated Risks in Diabetes

Tight glycemic control with intensive insulin therapy has been shown to reduce the risk of the microvascular and macrovascular complications of diabetes.[5-8] Throughout the duration of pregnancy, tight glycemic control is recommended to avoid maternal, fetal, and neonatal complications.[9] While tight glycemic control lowers the risk of diabetic complications, it can be associated with an increased risk of hypoglycemia, leading to compromised quality of life.[7] Both severe or non-severe hypoglycemia can be a source of significant distress and anxiety to patients and a barrier to achieving tight glycemic control. Finally, intensive insulin therapy can also lead to weight gain, due to more efficient fuel utilization and/or overtreatment of hypoglycemic episodes.[10 11]

Measurement of Glycemic Control

Measurement of glycosylated hemoglobin, specifically hemoglobin A_{1c} (HbA_{1c}), is the preferred method of assessing long-term glycemic control over the previous 2 to 3 months in patients with type 1 and type 2 diabetes.[12] Fasting and 2-hour post-prandial blood glucose levels are also measured and their results can assist patients and their physicians in making short-term adjustments in insulin therapy; however, these measures are more variable.[13] In pregnant women with diabetes, clinical management decisions are made on a weekly basis based on fasting and post-prandial glucose levels, as opposed to measuring HbA_{1c} every 3 months, because they provide the more rapid feedback on glycemic control needed to prevent fetal complications.[14]

Methods to Achieve Tight Glycemic Control and Minimize Risk: Insulin Delivery and Glucose Monitoring

In current practice, tight glycemic control is achieved through the use of more physiological basal and meal-time (prandial) insulins that, when used together, mimic normal pancreatic function (peakless basal insulin secretion, rapid release of insulin in response to meals, and rapid resolution of the prandial insulin peak). These regimens are delivered as at least three daily insulin injections (i.e., multiple daily injections, or MDI). In addition, the development of the external continuous subcutaneous insulin infusion (CSII) via a pump provided another means to deliver insulin in a more physiological manner.

Following publication of the Diabetes Control and Complications Trial, self-monitoring of blood glucose (SMBG) by fingerstick replaced the assessment of glucose by urine dipstick to allow more specific and timely feedback on the degree of hyperglycemia.[10] The challenge of SMBG is the associated pain that affects adherence to this technique and is a barrier to tight glycemic control. Therefore, continuous glucose monitoring (CGM) systems have been developed in recent years. These devices record blood sugar levels throughout the day and night with a significantly decreased need for fingerstick measurements.

A CGM system, in conjunction with intensive insulin treatment, can be a useful tool to lower blood glucose values in adults who are at least 25 years of age and have type 1 diabetes. Success in lowering blood glucose levels depends on adherence to ongoing use of the device.[15]

Real-time continuous glucose monitoring (rt-CGM) was first approved by the US Food and Drug Administration in 2005. rt-CGM differs from retrospective CGM in that it provides blood glucose feedback data to the patient while he or she is wearing the device and does not need to be downloaded and evaluated after data collection. This advantage of rt-CGM has resulted in it being the preferred method of CGM in the clinical setting. As a result, the focus of our review will be on studies examining rt-CGM.

Knowledge Gaps: Comparative Effectiveness of Insulin Delivery and Glucose Monitoring in Specific Diabetic Populations

Comparison of CSII with MDI. The benefits and risks of intensive insulin therapy with CSII have not clearly been established in certain populations of patients with diabetes. The majority of the evidence from comparisons of MDI with CSII in patients with type 1 diabetes indicates improved glycemic control with CSII use in adults, although its impact on other clinical outcome measures are unclear.[16 17] In children with type 1 diabetes, the benefit of CSII for glycemic control and clinical outcomes has not been established. Thus, there is still uncertainty regarding the benefit of CSII in the very young with type 1 diabetes. Another population in whom the benefits of CSII are unclear is older patients with type 1 diabetes. Because prior meta-analyses and systematic reviews have included studies using regular insulin, they have not been able to determine the comparative effectiveness of MDI with CSII using currently available rapid-acting insulin analogs.

The comparative effectiveness of CSII and MDI has not been assessed systematically in patients with type 2 diabetes.[16] While some studies suggest that CSII is comparable with MDI in attaining adequate glycemic control, other studies found a lower HbA_{1c} level with CSII than with MDI.[16 18-21]

We found one systematic review of randomized controlled trials (RCTs) published in 2007 that compared CSII with MDI in pregnant women who had pre-existing type 1 or type 2 diabetes (60 women with 61 pregnancies).[22] While mean birth weight was greater with CSII than with MDI, the data were insufficient to permit conclusions about other outcomes, such as perinatal mortality, major and minor fetal anomalies, hypoglycemia, hyperglycemia, and admission to the neonatal intensive care unit for treatment of hypoglycemia. The evidence base for the comparison of MDI with CSII in pregnant women with pre-existing type 2 diabetes is small and has not been evaluated by a systematic review. This topic is increasingly important as the prevalence of type 2 diabetes has been increasing dramatically in younger populations, including women of child-bearing age.

Comparison of SMBG with rt-CGM. Studies have given conflicting reports of the effects of rt-CGM on glycemic control, hypoglycemia frequency, or other clinically relevant outcomes in individuals with type 1 diabetes. Very little attention has been given to the comparative effectiveness of rt-CGM and SMBG on outcomes in patients with type 2 diabetes or pre-existing type 1 or type 2 diabetes in pregnancy. To gain a better understanding of the potential added utility of this new technology and determine its cost-effectiveness, clinicians need a synthesis of studies comparing the effects of rt-CGM with SMBG, ideally taking into consideration relevant factors such as the age of the patient, the effect of adherence to rt-CGM on potential benefits, and the potential interaction with the mode of insulin delivery (CSII versus MDI).

rt-CGM can be combined with CSII in the form of a sensor-augmented pump. To our knowledge, there has not been a systematic review comparing sensor-augmented pump therapy (CSII + rt-CGM) with intensive insulin therapy (CSII or MDI) and SMBG.

Objectives

The objective of our comprehensive systematic review was to address the clinically relevant question of whether the mode of intensive insulin therapy (MDI versus CSII) results in better glycemic control, less hypoglycemia, improved quality of life, and improved clinical outcomes in individuals with type 1 diabetes, type 2 diabetes, and pre-existing diabetes in pregnancy. We also sought to determine whether these outcomes differed by the type of strategy used for blood glucose monitoring (SMBG versus rt-CGM) in those same populations. Our specific Key Questions are listed below and are graphically displayed in Figure A.

KQ1: In patients receiving intensive insulin therapy, does mode of delivery (MDI versus CSII) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus? (Process measures, intermediate outcomes, and clinical outcomes of interest are summarized below in Table A.) Do these effects differ by:

a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?

KQ2: In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM versus SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes (see Table A) in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients already using intensive insulin therapy)? Do these effects differ by:

a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?
d. Intensive insulin delivery: MDI or CSII?

Table A. Summary of process measures, intermediate outcomes, and clinical outcomes relevant to studies of intensive insulin therapy and continuous glucose monitoring

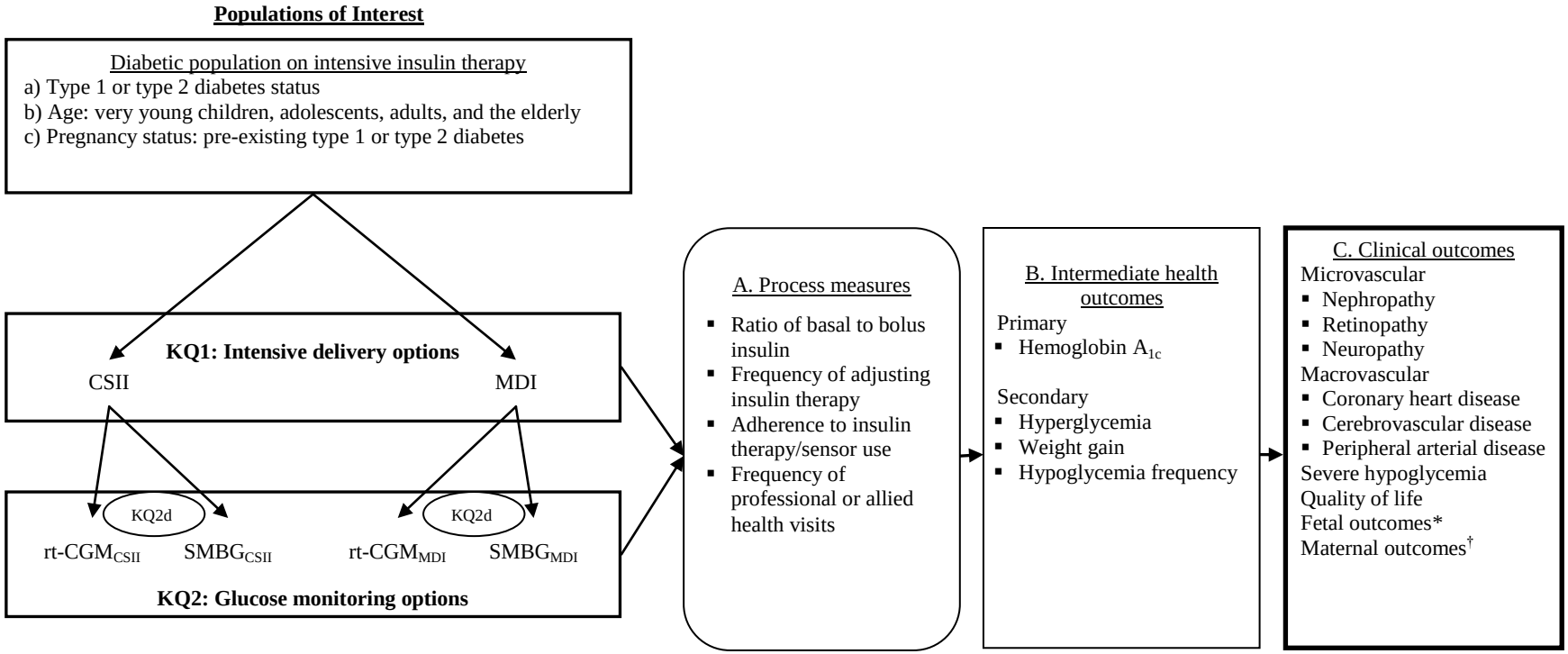
Process Measures	Intermediate Outcomes	Clinical Outcomes
Ratio of basal to bolus insulin‡	Primary	Microvascular*
Frequency of adjusting insulin therapy	Hemoglobin A_{1c}	Nephropathy
		Retinopathy
Adherence to insulin therapy/sensor use	Secondary	Neuropathy
	Hyperglycemia	
Frequency of professional or allied health visits	Weight gain	Macrovascular*
	Hypoglycemia frequency	Coronary heart disease
		Cerebrovascular disease
		Peripheral arterial disease
		Severe hypoglycemia
		Quality of life
		Fetal outcomes†
		Maternal pregnancy outcomes
		C-section rates

*We only included objective assessments of microvascular and macrovascular outcomes (i.e., we excluded patient self-reported microvascular and macrovascular outcomes).

†Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit.

‡The optimal distribution of the total daily insulin dose is 40-50% administered as basal insulin and the remaining 50-60% as bolus insulin divided over each meal. This prevents patients from being over-insulinized with basal insulin, increasing risk for hypoglycemia.

Figure A. Analytic framework for multiple daily injections or insulin pump therapy with or without continuous glucose monitoring for diabetes



Abbreviations: CSII = continuous subcutaneous insulin infusion; KQ = key question; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose.
Stratifications of interest for KQ2: diabetes status (2a), age (2b), pregnancy status (2c), and glucose monitoring strategy (2d)
*Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit.
†Maternal outcomes include cesarean section rates.

Methods

Data Sources and Selection

Search strategy. We searched the following databases for primary studies for the periods in parentheses: MEDLINE® (1966 to October 2010), EMBASE® (1974 to October 2010), and the Cochrane Central Register of Controlled Trials (1966 to October 2010). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori (Appendix A).

Study selection. Two independent reviewers scanned title and abstracts in parallel. Titles and abstracts were reviewed independently by two investigators, and were excluded if both investigators agreed that the article met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table B). We included studies comparing the effects of CSII with MDI or rt-CGM with SMBG among children, adolescents, and adults with either type 1 or type 2 diabetes, and pregnant women with pre-existing diabetes. We excluded studies that evaluated methods of insulin delivery or glucose monitoring that are no longer used in clinical practice (e.g., implantable insulin pumps, retrospective CGM, GlucoWatch CGM, and insulin pumps using regular insulin). We defined MDI as at least three injections per day and SMBG as at least three fingersticks per day. We included both RCTs and observational studies that evaluated microvascular, macrovascular, maternal, or fetal outcomes. For all other outcomes (see Table A), we included only RCTs. There were no restrictions on sample size or language. Differences between investigators regarding abstract eligibility were resolved through consensus adjudication.

Articles promoted on the basis of abstract review underwent another independent parallel review to determine if they should be included for data abstraction. Differences regarding article inclusion were resolved through consensus adjudication.

Data Extraction and Quality Assessment

Data abstraction. Each article underwent double review by the study investigators for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise.

For all articles, the reviewers extracted information on general study characteristics, study participants, eligibility criteria, interventions, adherence to wearing a treatment device, outcome measures, definitions, and the results of each outcome, including measures of variability. For the outcome of hypoglycemia, we differentiated between biochemical and symptomatic hypoglycemia. For the outcome of cesarean delivery, we abstracted information regarding the indication for cesarean delivery. For studies evaluating maternal and fetal outcomes, we abstracted information about when CSII or MDI was initiated in relation to the pregnancy (i.e., prenatal, 1st trimester, or 2nd trimester).

For this report, we classified quality of life measures into the following categories: general health-related quality of life (global, non-specific measures), disease-specific

quality of life (quality of life and health status associated with diabetes), and treatment-specific quality of life (associated with carrying out treatment for diabetes). In each category we included only studies which used validated measures.

Quality assessment. We used different quality assessment tools for RCTs and observational studies. For RCTs, the dual, independent review of article quality was based on the Cochrane Collaboration's Risk of Bias Tool[23] and supplemented with items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[24] For observational studies, we selected items from the Downs and Black quality checklist[25] and supplemented with items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[24]

Applicability. We assessed the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings were typical for the treatment of individuals with diabetes who are receiving treatment in a usual care setting. We limited the interventions in the review to those that are most applicable to the current population of patients with diabetes (i.e., those interventions that are currently used in the US population).

Data Analysis and Synthesis

We conducted meta-analyses when there were sufficient data (at least three trials) and studies were sufficiently homogenous with respect to key variables.

For continuous outcomes, we calculated a weighted mean difference by using a random-effects model with the DerSimonian and Laird formula.[26] We recorded the mean difference in outcome between groups, along with its measure of dispersion. If this information was not reported, we calculated the point estimate of the mean difference in outcome using the mean difference from baseline for each group or the baseline and final values for each group.

If studies reported the incidence of severe hypoglycemia, then we calculated a pooled relative risk (RR) using the DerSimonian and Laird random effects model.[26] If studies reported event rates (i.e., the number of events experienced per patient during the study period), we calculated a rate ratio in terms of the number of events per person-year using the DerSimonian and Laird random effects model.[26]

Heterogeneity among the trials in all the meta-analyses was tested by using a standard chi-squared test with a significance level of alpha less than or equal to 0.10. Heterogeneity was also examined among trials by using an I-squared statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[27] A value greater than 50 percent was considered to have substantial variability. If we found substantial heterogeneity, we attempted to determine reasons for this by conducting meta-regression analyses using baseline HbA_{1c} and compliance. For all meta-analyses, we conducted formal tests for publication bias using Begg's[28] and Eggers tests[29] including evaluation of the asymmetry of funnel plots for each comparison of interest. All meta-analyses were conducted using STATA (Intercooled, version 9.2, StataCorp, College Station, TX).

Rating the Body of Evidence

At the completion of our review, we graded the strength of the evidence based on the quantity, quality, and consistency of the best available evidence, addressing Key Questions 1 and 2 by adapting an evidence grading scheme recommended in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[30] We applied evidence grades to the bodies of evidence about each intervention comparison for each outcome. We assessed the risk of bias of individual studies according to study design characteristics, such as confounding and selection and information biases. We assessed the strength of the best available evidence by assessing the limitations to individual study quality (using individual quality scores), consistency directness, precision, publication bias, and the magnitude of the effect. We classified evidence bodies into four basic categories: high, moderate, low, and insufficient (see footnote to Table C for definitions).

Results

Search Results

Figure B summarizes the search results. From our search, we retrieved 6378 unique records. After title and abstract review, 701 articles were deemed potentially relevant to review, and the full articles were retrieved. A total of 44 articles were included in this review.

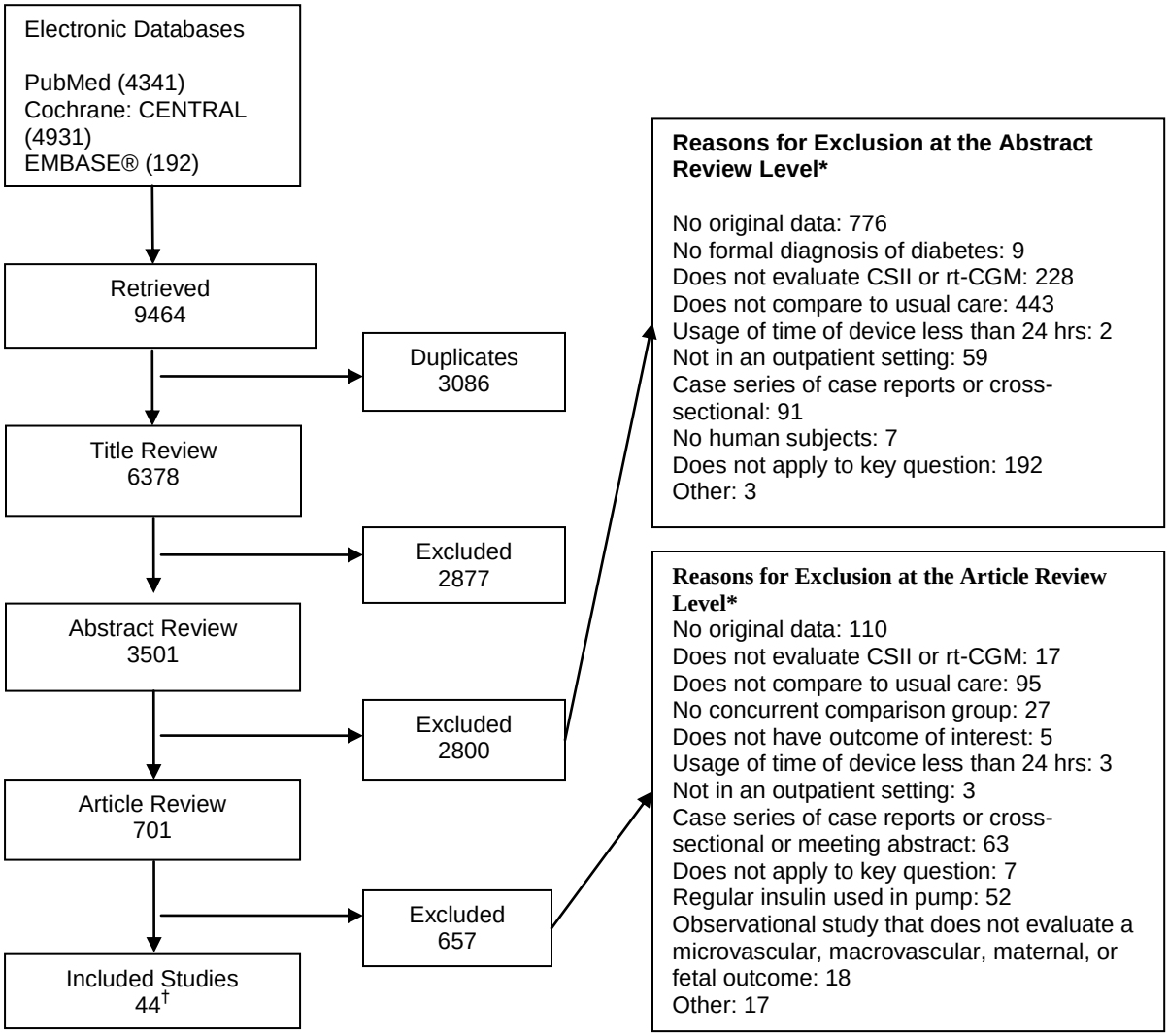
Of the included studies, 29 studies compared the effects of MDI with CSII. Twelve of these studies were conducted in children or adolescents with type 1 diabetes, nine were conducted among adults with type 1 diabetes, four were conducted among patients with type 2 diabetes, and four were conducted among pregnant women with pre-existing type 1 or type 2 diabetes.

Eight studies compared the effects of rt-CGM with SMGB in children and adults with type 1 diabetes. We did not identify any studies comparing rt-CGM with SMBG among patients with type 2 diabetes or among pregnant women with pre-existing type 1 or type 2 diabetes.

An additional three studies evaluated the effects of a sensor-augmented pump compared with MDI and SMBG.

Seventeen studies evaluated quality of life using 15 different validated quality of life assessment tools. Table B lists how the quality of life assessment tools were categorized into general quality of life, disease-specific quality of life, and treatment-specific quality of life.

Figure B. Summary of the literature search



* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
† 29 compared MDI to CSII (12 in children and adolescents with type 1 diabetes; 9 in adults with type 1 diabetes; 4 in adults with type 2 diabetes; 4 in pregnant women with pre-existing type 1diabetes); 8 compared rt-CGM with SMBG; 3 compared a sensor-augmented pump with MDI/SMBG
CENTRAL = Central Register of Controlled Trials; CSII = continuous subcutaneous insulin infusion; hrs = hours; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitor; SMBG = self-monitoring of blood glucose

Table B. Quality of life assessment tools used in each category

General health-related quality of life	Diabetes-specific quality of life	Treatment-specific quality of life
• Pediatric Quality of Life Inventory • Short Form-36 (SF-36) • Short Form-12 (SF-12) • World Health Organization-5 Well Being Index (WHO-5)	• Diabetes Quality of Life (DQOL) • Diabetes Treatment Satisfaction Questionnaire (DTSQ) • Diabetes Quality of Life Clinical Trial Questionnaire (DQOLCTQ) • Diabetes Quality of Life – Youth (DQOL-Y) • Problem Areas in Diabetes (PAID)	• Altered Hypoglycemia Awareness Questionnaire • Blood Glucose Monitoring System Rating Questionnaire (BGMSRQ) • Hypoglycemia Fear Survey • Insulin Delivery System Rating Questionnaire (IDSRQ) • Phase V Outcomes system diabetes treatment satisfaction questionnaire • User Acceptance Questionnaire (UAQ)

Key Question 1. Comparative Effectiveness of CSII versus MDI

Children and Adolescents with Type 1 Diabetes

Study design. Twelve studies evaluated CSII versus MDI therapy in children and adolescents with type 1 diabetes.[31-42] They were conducted in diverse countries, including the US,[33 40] Italy,[34 39] Sweden,[31] Spain,[35] Saudi Arabia,[36] Germany,[37] the Netherlands,[34 43] and Israel.[41 42] Of the 12 studies, five were parallel arm RCTs,[31 33 34 40] three were randomized cross-over trials,[32 41 42] two were non-randomized trials,[35 36] one was a cohort study,[39] and two were case-control studies.[37 38] The median followup time for all studies was 52 weeks, with a range of 16 to 104 weeks for clinical trials and the a range 52 to 72 weeks for observational studies. These studies enrolled a median of 32 patients (range, 16 to 72) into randomized clinical trials and a median of 56.8 (range, 22 to 104) into observational studies.

Population characteristics. The mean age of participants in the RCTs was 16.5 years (range, 4.4 to 18.9 years) and 11.4 years (range, 4.4 to 17.9 years) in the MDI and CSII groups, respectively. The mean age of participants in the observational studies was 9.2 years (range, 6.7 to 12.8 years) and 10.7 years (range, 6.7 to 13.9 years) in the MDI and CSII groups, respectively. The majority of studies did not report the racial composition of their study populations but based on location, were presumed to be predominantly Caucasian.[31 34-37 39 41 42] Glycemic control was sub-optimal in participants at the time of study enrollment. The mean HbA_{1c} in the RCTs was 8.5% and 8.6% in the MDI and CSII groups, respectively, and in the observational studies was 8.4% and 8.2% in the MDI and CSII groups, respectively.

Interventions. The MDI arms varied across studies in the type of insulin used: neutral protamine Hagedorn (NPH) and aspart,[31] NPH and lispro,[33] NPH and regular insulin,[41] glargine and regular insulin,[34 42] glargine and lispro,[35 36] and glargine and aspart.[40] The MDI schedule was three or four or more injections daily in most studies. In the CSII arm,

insulin aspart was used in three studies,[31 32 40] insulin lispro was used in nine studies,[33-36 38 39 41-43] and in one study, the type of short-acting insulin analog was not reported.[37] The duration of therapy in each intervention arm ranged from 3.5 to 24 months with nine studies having 12 or more months of followup.[31 32 34-39 41]

Outcomes. The main results in children and adolescents are presented in the first part of Table C and summarized in the following paragraphs.

HbA_{1c}. Twelve studies examined the comparative effectiveness of CSII and MDI on HbA_{1c} — five observational studies and seven RCTs. A meta-analysis of seven RCTs showed a non-significant difference between the MDI and CSII intervention groups in how the HbA_{1c} changed from baseline after 16 or more weeks of followup, decreasing slightly more with CSII than with MDI (combined mean between-group difference, -0.14%; 95% CI, -0.48 to 0.20%, *P*=0.63). Results were similar when a meta-analysis of four RCTs focusing on adolescents over 12 years of age was performed (combined mean between-group difference in the change from baseline in the HbA_{1c}, -0.10%; 95% CI, -0.47 to 0.27%). There were too few studies in children 12 years of age or younger to perform a meta-analysis.

Daytime and nocturnal hypoglycemia. Three studies examined the comparative effectiveness of CSII and MDI on daytime hypoglycemia and found no significant difference in daytime hypoglycemia frequency between the two groups.[31 33 41] Two studies examined the comparative effectiveness of CSII and MDI on nocturnal hypoglycemia and found no significant differences between the two groups.[40 41] Various measures for daytime and nocturnal hypoglycemia were reported; please see full evidence report for details.

Mild hypoglycemia. One study found significantly fewer episodes of mild hypoglycemia (defined as blood sugar below 70 mg/dL) in the CSII group compared with the MDI group.[42]

Severe hypoglycemia. Nine studies (two observational and seven RCTs) examined the frequency of severe hypoglycemia in the MDI and CSII intervention groups. The definitions of hypoglycemia used in studies varied. A meta-analysis of five RCTs did not find a significant difference in severe hypoglycemia event rates between the two intervention arms (combined mean incidence rate ratio for CSII versus MDI, 0.99; 95% CI, 0.57 to 1.71, *P*=0.37). Results were similar when a meta-analysis of three RCTs focusing on adolescents over 12 years of age was performed (combined mean incidence rate ratio for CSII versus MDI, 0.95; 95% CI, 0.42 to 2.13). There were too few RCTs in children under 12 years of age or younger to perform a meta-analysis.

Hyperglycemia. One study examined the frequency of hyperglycemia (defined as polyuria, polydipsia, or nocturia and/or a capillary blood glucose level of more than 400 mg/dL with or without urinary ketones) in the MDI and CSII intervention groups over 14 weeks and found no difference between the two groups.[42]

Ratio of basal to bolus insulin. One study examined the ratio of basal to bolus insulin in the MDI and CSII intervention groups and found no difference in the ratios between the two groups.[35]

Weight gain. Three studies compared MDI with CSII for changes in weight as measured by body mass index (BMI) standard deviation score (SDS) in children with type 1 diabetes.[40-42] Two studies were randomized open crossover trials conducted at the same institution.[41 42] One found no significant change in BMI-SDS over the course of the study in either treatment arm.[41] The other reported a slight, but statistically significant, increase in BMI-SDS during MDI therapy and no significant change during CSII.[42] The third study was an RCT that showed no BMI change from baseline in the two groups (less than 1 kg/m^2).[40]

Quality of life. Six studies examined the comparative effectiveness of CSII versus MDI on general, diabetes-specific, and diabetes treatment-related quality of life in children and adolescents with type 1 diabetes. Two studies examined general quality of life in children and adolescents with type 1 diabetes using the Pediatric Quality of Life Inventory and showed an improvement in general quality of life favoring CSII.[32 33] Four studies examined the comparative effectiveness of CSII versus MDI on diabetes-specific quality of life.[31 40-42] The three studies that used the Diabetes Treatment Satisfaction Questionnaire (DTSQ) showed an improvement in diabetes-specific quality of life favoring CSII.[41 42 44] Two studies used the Diabetes Quality of Life-Youth instrument (DQOL-Y) and while one showed improvement in quality of life favoring CSII,[41] the other study did not find a difference in quality of life between the two intervention arms.[40]

Quality and evidence grading. Among the RCTs on children and adolescents, one study was good quality,[40] three studies were fair quality,[31 32 42] and three were poor quality.[33 34 41] Among the observational studies on children and adolescents, three were fair quality[35 37 38] and one was fair or poor quality.[36] The risk of bias was medium for the outcomes of HbA_{1c}, hypoglycemia (non-severe and severe), and weight gain. The risk of bias was high for hyperglycemia and the ratio of basal to bolus insulin. Our assessment of the risk of bias was limited by a lack of reporting on most quality items.

The strength of evidence examining the comparative effectiveness of CSII versus MDI was moderate for HbA_{1c} and severe hypoglycemia outcomes. The strength of evidence was low for non-severe hypoglycemia, weight gain, and quality of life measures due to the small number of studies addressing these outcomes and heterogeneity in their assessments, which did not allow for meta-analyses. Because only one study addressed the outcomes of hyperglycemia and ratio of basal to bolus insulin, there was insufficient data to draw conclusions for these outcomes.

Applicability. The majority of studies in children and adolescents with type 1 diabetes were small, with the largest clinical trial including 72 participants[31] and the largest observational study including 104 participants.[37] The majority of studies were performed in adolescents, with fewer studies in children 12 years of age or less. Studies generally did not report race but based on the countries in which they were conducted, the majority

of which were outside of the US, most studies included Caucasian participants. Participants generally had poor glycemic control at study entry (mean HbA_{1c} 8 to 9%), were treated in the intervention groups for an average of 52 weeks, and had diabetes for 5 to 6 years prior to study entry.

Adults with Type 1 Diabetes

Study design. Nine studies evaluated the effectiveness and safety of CSII versus MDI among adults with type 1 diabetes.[45-53] No study focused solely on an elderly population with type 1 diabetes.

Five were parallel arm studies,[45 47 50-52] and four used a cross-over design.[46 48 49 53] All studies randomized participants to the intervention with the exception of a single study.[50] Studies occurred in European countries,[46 50 51 53] Canada,[52] and the US.[49] Two studies were multi-national.[45 48] The duration of interventions ranged from 5 weeks to 1 year.[45-53] Treatment lasted for 5 weeks in one study;[49] 4 months in two studies;[46 51] 4 months in one study;[53] 6 months in three studies;[45 47 48] and 9 months[54] and 1 year[50] in the other two studies. Studies included 21 to 272 participants.

Population. Studies did not report on race. The mean baseline HbA_{1c} was similar by intervention allocation with the exception of one study in which HbA_{1c} was 0.4% higher in the MDI versus CSII arm.[52] Intervention arm-specific HbA_{1c} ranged from 7.4% to 9.3% at baseline.[45 46 48 51 52] The mean duration of type 1 diabetes ranged from 14.4 to 25 years in studies reporting this.[45-48 50-53]

Intervention. Four studies used NPH insulin as the long-acting insulin for the MDI arm,[48 51-53] and the other studies used insulin glargine.[45-47 49 50] All studies used insulin aspart or insulin lispro as the short-acting insulin during MDI treatment.[45-53] Two studies incorporated seven days of CGM.[47 49]

Outcomes. The main results in adults with type 1 diabetes are presented in the second part of Table C and summarized in the following paragraphs.

HbA_{1c}. Four RCTs reported a mean decrease in HbA_{1c} in both CSII and MDI treatment groups. A meta-analysis of these trials showed that CSII and MDI had a similar reduction from baseline in HbA_{1c} (combined mean between-group difference, -0.05%; 95% CI, -0.41 to 0.31%, P=0.78).[45 47 51 52] Study duration ranged from 4 months to 1 year.[45 47 51 52]

Symptomatic hypoglycemia. Four trials evaluated documented symptomatic hypoglycemia.[45 47 49 52] Incidence rates were similar for MDI and CSII treatment in two studies (P>0.05).[45 52] The other trial reported more symptomatic hypoglycemia with CSII treatment (40 events/person-year compared with MDI treatment (21 events/person-year) over 6 months but did not report on statistical significance of this difference.[47] Of participants experiencing probable (not documented) symptomatic hypoglycemia in a cross-over trial, symptomatic hypoglycemia occurred slightly more frequently during CSII treatment compared with MDI treatment (6.9 events/person versus 6.1 events/person; P=0.05) although the percentages of participants experiencing

symptomatic hypoglycemia were similar at 5 weeks (75% for CSII versus 72% for MDI).[49]

Daytime hypoglycemia. A single randomized trial using a cross-over design reported more hypoglycemic events (symptomatic or asymptomatic with glucose less than 50 mg/dL without third party assistance) between 0800 and midnight during MDI treatment than during CSII treatment ($P<0.05$).[49]

Nocturnal hypoglycemia. Three studies reported on nocturnal hypoglycemia.[45 47 49] One cross-over trial reported a similar percentage of participants experiencing any nocturnal hypoglycemia (symptomatic, minor, or major) (72% versus 73%) or symptomatic nocturnal hypoglycemia (42% versus 48%) in the CSII and MDI treatment arms, respectively (statistical significance not reported).[49] However, of participants with any nocturnal hypoglycemia, there were slightly but significantly fewer episodes per person in the CSII compared with MDI arm over 5 weeks of treatment (3.0 events per participant versus 4.0 events per participant; $P=0.0024$).[49] A study of 58 participants also reported slightly fewer episodes of nocturnal hypoglycemia with CSII compared with MDI over 6 months, but this difference did not reach statistical significance (three events per person versus five events per person; $P=0.34$).[45] A small trial of 14 participants with a history of severe hypoglycemia reported no episodes of nocturnal hypoglycemia (definition not provided) in the CSII arm after 6 months and did not report on this outcome in the MDI treatment arm.[47]

Other non-severe hypoglycemia. Six studies evaluated the incidence of other types of mild hypoglycemia with CSII compared with MDI therapy.[45 46 48 49 51 53] Three studies found no difference in non-severe hypoglycemia during CSII compared with MDI.[45 46 53] In two studies, the incidence of mild hypoglycemia was higher during CSII compared with MDI treatment[49 51] with the relative difference statistically significant in one of these studies.[51] However, in another trial, the risk of self-managed mild hypoglycemia was higher during MDI treatment (RR, 1.12; 95% CI, 1.08 to 1.17).[48]

Severe hypoglycemia. A meta-analysis of three randomized trials indicated no difference in the incidence of severe hypoglycemia, requiring third party assistance, with CSII compared with MDI treatment (combined RR, 0.74; 95% CI, 0.30 to 1.83, $P=0.52$).[45 47 51] Another RCT reported a non-significant and small difference in the number of severe hypoglycemic events over 9 months in the CSII versus MDI treatment arm (six events versus four events) but did not report if any individuals had more than one hypoglycemic event.[52] Four cross-over trials did not provide quantitative results on severe hypoglycemia by period and were not included in the meta-analysis.[46 48 49 53] Severe hypoglycemia events were more frequent during MDI therapy compared with CSII therapy in two studies[48 49] with one study reporting a RR of 2.6 (95% CI, 2.08 to 3.25).[48] Compared with CSII therapy, severe hypoglycemia occurred less frequently during MDI therapy in one study (three events versus one event over 4 months).[53] A fourth trial reported similar rates of severe hypoglycemia during CSII and MDI therapy (1.1 events/patient and 1.3 events/patient, respectively over 4 months; $P=0.327$).[46]

Hyperglycemia. Fasting glucose did not vary significantly by treatment with CSII or MDI across three RCTs. In one RCT, fasting glucose decreased more with CSII than with MDI at 6 months (mean between-group difference, -12.3 mg/dL; 95% CI, -32.9 to 8.2 mg/dL).[45] In a non-randomized trial, CSII and MDI lowered fasting glucose similarly at 12 months (quantitative results not reported).[50] A third RCT reported a lower fasting glucose at 4 months in the CSII arm compared with the MDI arm, but this difference in fasting glucose was not statistically significant.[51] The authors did not provide estimates of these glucose levels.[51]

Three RCTs reported on the effect of CSII and MDI on pre-prandial glucose (other than pre-breakfast) and showed no significant difference between the two groups.[45 49 51] In a single study, glucose at bedtime was not significantly lower in the CSII arm compared with the MDI arm at 4 months.[51] Three RCTs reported lower post-prandial glucoses with CSII compared with MDI.[45 49 51] Two trials did not find a significant between-group difference in nocturnal glucose levels.[45 51]

Weight. Four studies examined the effects of MDI versus CSII on weight gain in adults with type 1 diabetes and showed no significant weight changes in either group.[46 47 50 51]

Quality of life. Six studies examined the comparative effectiveness of CSII versus MDI on general quality of life, diabetes-specific quality of life, and diabetes treatment-related quality of life in adults with type 1 diabetes. Two studies showed an improvement in general quality of life favoring CSII.[48 51]

Three studies showed an improvement in diabetes-specific quality of life favoring CSII,[45 48 52] one study showed improvement favoring MDI,[47] and one study found no difference between the two groups.[55] One study examined the comparative effectiveness of CSII versus MDI on diabetes treatment-related quality of life using the Altered Hypoglycemia Awareness Questionnaire and the Hypoglycemia Fear Survey and found no difference between the two intervention arms.[47]

Quality and evidence grading. We rated two studies as being of good quality[52 53] with the others rated as being of fair or poor quality.[45-51] All included studies were RCTs, and the risk of bias was medium. Our assessment of the risk of bias was limited by a lack of reporting on most quality items.

The strength of evidence examining the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes was low for all outcomes. The small number of studies affected our assessment of the overall strength of the evidence for the outcomes for the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes. The studies were small and did not use the same definitions of most outcomes, limiting our ability to combine effect estimates across studies. Notably, the evidence on the risk of severe hypoglycemia was limited by low event rates and resultant imprecise results.

Applicability. Few studies compared the effect of CSII to MDI in adults with type 1 diabetes. Studies did not report on many items of interest to determine the applicability of the studies to all adults with type 1 diabetes. Studies did not report on race, and no study focused on elderly adults with type 1 diabetes. The mean baseline HbA_{1c} was 7.4 to 9.3% across the studies. The duration of diabetes at enrollment was greater than 14 years in the

studies reporting this. Eligibility criteria for MDI and insulin pump use varied significantly across the studies.

Adults with Type 2 Diabetes

Study design. Of the four studies evaluating CSII versus MDI therapy in patients with type 2 diabetes, three were parallel-arm randomized trials,[55-57] and one was a randomized cross-over trial.[58] Treatment periods were 18 weeks in duration in the cross-over study,[58] and the parallel-arm studies were 6 or 12 months in duration.[55-57] Two studies excluded participants with HbA_{1c} greater than 12 or 15%,[57 58] and three studies excluded persons with HbA_{1c} less than 6, 7, or 8.5%.[55 57 58] All studies required that participants be treated with insulin prior to the study.[55-58]

Population characteristics. The number of participants per arm ranged from 20 to 66 in the included studies.[55-58] All studies were conducted in adults and only one study included participants 60 years of age or older.[55] Two studies did not report on the racial composition of their study populations, and the other two studies were multi-ethnic but predominantly white (> 80%).[55 57] Mean BMI ranged from 29.5 to 32.5 kg/m^2 and was similar by treatment group across the three parallel-arm studies.[55-57] The mean duration of type 2 diabetes was greater than 10 years in the two studies reporting this.[55 57]

Intervention. The MDI arms varied across studies: NPH and Regular insulin;[58] insulin glargine and insulin lispro;[55 56] and NPH insulin and insulin aspart.[57] Insulin aspart was used in the CSII arm for one study,[57] and insulin lispro was used in the CSII arm in the other studies.[55 56 58]

Outcomes. The main results in adults with type 2 diabetes are presented in the third part of Table C and summarized in the following paragraphs.

HbA1c. A meta-analysis of four RCTs of at least 18 weeks in duration showed a mean decrease from baseline in HbA_{1c} in both CSII and MDI treatment groups with the reduction greater during CSII treatment compared with MDI, although the difference was not statistically significant (combined mean between-group difference, -0.16%; 95% CI, -0.42 to 0.09%, P=0.21).[55-58]

Non-severe hypoglycemia. Three trials reported on mild hypoglycemia in patients with type 2 diabetes randomized to MDI and CSII therapy.[55 57 58] In two studies, mild hypoglycemia was more frequent in the MDI group although the difference was not statistically significant[55 57] and in one study, the rate of mild hypoglycemia did not differ between the two groups.[58]

Nocturnal hypoglycemia. In a single study, nocturnal hypoglycemia (occurring between midnight and 0600) was more common between 8 and 24 weeks in the MDI arm compared with the CSII arm (percentage of patients with nocturnal hypoglycemia, 22% versus 16%; statistical significance not reported).[57] The authors described the rates of

nocturnal hypoglycemia as similar between arms but did not report on statistical significance.[57]

Severe hypoglycemia. Three randomized trials reported on rates of severe hypoglycemia among patients with type 2 diabetes treated with MDI or CSII.[55 57 58] In one study, no participants in either treatment group experienced severe hypoglycemia (defined by glucose less than 50 mg/dL and severe central nervous system dysfunction necessitating outside assistance or parenteral treatment).[57] In the two other studies, there was no difference in severe hypoglycemia between the two treatment arms.[55 58]

Hyperglycemia. A single study reported hyperglycemia outcomes based on eight-point SMBG in patients with type 2 diabetes randomized to CSII or MDI.[57] Mean postprandial glucose (90 minutes after breakfast) was 167 mg/dL in the CSII arm and 192 mg/dL in the MDI arm at 24 weeks (mean between-group difference, -25 mg/dL; P=0.019).[57] The authors reported that glucose measurements from the other time points were similar between treatment groups at the end of the study.[57] The incidence of blood glucose above 350 mg/dL was higher in the MDI compared with the CSII arm (26 versus six events) with 18% and 5% of participants affected in the MDI and CSII arms, respectively.[57]

Weight. Two studies evaluated weight gain experienced by participants in MDI and CSII groups.[55 57] One study showed that patients gained more weight in the CSII group than in the MDI group, whereas the other showed less weight gain in the CSII group.[55 57] The difference in weight gain between the two treatment arms was not statistically significant for either study.[55 57]

Quality of life. Two studies examined the comparative effectiveness of CSII versus MDI on quality of life in adults with type 2 diabetes. One study found no difference in general or diabetes-specific quality of life between the CSII and MDI intervention groups.[55] The other study used the Phase V Outcomes System Diabetes Treatment Satisfaction Questionnaire and at the end of 24 weeks, found improvement in diabetes treatment satisfaction favoring CSII.[57]

Quality and evidence grading. All studies were of poor or fair quality.[55-58] Our assessment of the risk of bias was limited by a lack of reporting on most quality items. All included studies were RCTs, and the risk of bias was medium for all outcomes.

The strength of evidence examining the comparative effectiveness of CSII versus MDI in patients with type 2 diabetes was moderate for HbA_{1c} and low for hypoglycemia and weight outcomes. The evidence was insufficient for hyperglycemia and quality of life as only one study addressed these outcomes. The small number of studies affected our assessment of the overall strength of the evidence for the outcomes for the comparative effectiveness of CSII versus MDI in adults with type 2 diabetes.

Applicability. Studies did not generally report on items of interest in determining the applicability of the literature to the general population with type 2 diabetes. Most study participants were white when this characteristic was reported, and a single study focused on participants aged 60 years and older. Studies lasted between 18 weeks and 12 months.

The mean baseline HbA_{1c} was approximately 8 to 9% across the studies. The duration of diabetes at enrollment was greater than 10 years in the two studies reporting this. All studies required a history of insulin treatment prior to enrollment.

Pregnant Women with Pre-Existing Type 1 Diabetes

Study design. All four studies evaluating CSII versus MDI therapy in pregnant women with pre-existing type 1 diabetes were observational.[59-62] Two were retrospective followup studies.[59 60] None of the studies were conducted in the US. Women were given the choice to select either MDI or CSII in one study.[61] In all four studies, women were followed throughout the pregnancy. Some relevant details of study designs were not uniformly reported in these studies.

Population characteristics. The number of participants per arm ranged from 18 to 86 pregnant women.[59-62] Two studies reported having 100% Caucasian women.[59 60] All these patients were pregnant women with pre-existing type 1 diabetes and they entered the study at various stages of pregnancy. The mean age of the study populations ranged from 26 to 31 years. The mean HbA_{1c} during the first trimester ranged from 6.9% to 7.8%[59-62] and the mean BMI, reported in three studies, ranged from 21.8 to 23.7 kg/m^2. The duration of diabetes was reported in three studies and ranged from 7.7 to 13.9 years, with some in the CSII arm having a significantly longer duration of diabetes.[59 60 62]

Intervention. The CSII arm varied across studies. Two studies reported that primarily insulin lispro was used in the CSII arm[60 61] while the type of insulin was not specified in one study.[62] In the MDI arms, NPH insulin was used in two studies[59 60] and long-acting insulin was used in another study.[61] Three studies reported using four or more insulin injections daily in the MDI arms.[59 61 62] The mean duration of therapy was reported in three studies and it ranged from 36 to 40 weeks.[59-61]

Maternal outcomes. The main results in pregnant women with type 1 diabetes are presented in the fourth part of Table C and summarized in the following paragraphs.

HbA_{1c}. All four studies reported an improvement in HbA_{1c} in both the CSII and MDI arms during pregnancy from the first to third trimesters but no statistically significant difference between groups in HbA_{1c} in any of the trimesters.[59-62]

Rate of cesarean sections. Three studies reported the rate of cesarean section in the CSII and MDI arms. Two studies showed no difference in the rates of cesarean sections between groups.[59 60] One study showed a significantly higher rate of cesarean section in CSII compared with the MDI group.[62]

Maternal hypoglycemia. In two studies, hypoglycemia rates did not differ between the MDI and CSII arms.[59 62]

Maternal weight gain. The difference in weight gain between the CSII and MDI treatment arms was not statistically significant in the two studies that reported this outcome.[59 62]

Neonatal outcomes.

Gestational age at delivery. Three studies reported gestational age at delivery, with no difference in gestational age at delivery between the MDI and CSII groups.[59-61]

Neonatal hypoglycemia. Two studies reported rates of neonatal hypoglycemia with no difference between the CSII and MDI groups.[59 60]

Birth weight. Three studies reported mean birth weight, which ranged from 3101 to 3767 grams, in the two intervention arms.[59 60 62] One study reported a significantly higher birth weight with CSII compared with MDI[62] while another study found no difference between the two groups.[60]

Major congenital anomalies. One study reported that there were no major congenital anomalies in either intervention arm.[59] Another study reported no difference in major congenital anomalies between treatment arms.[62]

Minor congenital anomalies. Three studies reported information about minor congenital anomalies. Two studies reported that there were no minor congenital anomalies in either intervention arm.[59 61] One study reported minor congenital anomalies plus terminated pregnancy rates of 28% (22 out of 78) in the MDI arm and 20% (four out of 25) in the CSII arm.[60] It was not reported whether these differences were significant.

Neonatal intensive care unit admissions. Two studies reported on neonatal intensive care unit admissions: 9% in the MDI arm and 5% in the CSII arm;[59] and 35% in the MDI arm and 33% in the CSII arm.[62] The treatment arms did not differ in neonatal intensive care unit admission rates.

Quality and evidence grading. All studies were of poor to fair quality.[59-62] All four studies had incomplete descriptions of study setting, population, intervention, followup, and outcomes. One study did not report eligibility criteria.[62] None of the studies described details of loss to followup. Because all studies were observational, the risk of bias was medium to high.

The strength of evidence examining the comparative effectiveness of CSII versus MDI in women with pre-existing type 1 diabetes was low for the outcome of HbA_{1c} and insufficient for the outcomes of rates of cesarean section and neonatal birth weight. For outcomes examined, data were insufficient to determine the precision of effect estimates.

Applicability. All studies were observational with limited descriptions of study methodology, study populations, intervention, and outcomes. They were all small studies done in the UK, Poland, France, and Italy and did not report on inclusion of non-Caucasian participants. The mean age of study participants was 26 to 31 years with most

participants in the CSII group being enrolled into the studies prior to becoming pregnant. Most participants had diabetes duration of 7.7 to 13.9 years, with participants in the CSII groups having the longest duration of diabetes.

Key Question 2. Comparative Effectiveness of rt-CGM versus SMBG

All studies addressing this key question were conducted in patients with type 1 diabetes. We did not identify studies of the comparative effectiveness of rt-CGM and SMBG in patients with type 2 diabetes or pregnant women with pre-existing type 1 or type 2 diabetes.

Study design. Eight studies evaluated rt-CGM versus SMBG in children and adults with type 1 diabetes.[63-70] They were conducted in diverse countries, including three in the US,[66 68 69] three in multiple countries,[63 64 70] one in France,[65] and one in Australia.[67] Of the eight studies, seven were parallel arm RCTs,[64-70] and one was a randomized cross-over trial.[63] The median followup time for all studies was 24 weeks, with a range of 12 to 52 weeks. These studies enrolled a median of 141 patients (range 13 to 322). Most studies had entry criteria based on HbA_{1c}. Patients were excluded from certain studies if they had ever used rt-CGM in the past 6 months.[68 69]

Population characteristics. The mean age of participants in the RCTs was 23.7 years (range, 8.5 to 41.2 years) and 24.7 years (range, 9.1 to 44.6 years) in the rt-CGM and SMBG groups, respectively. Age of participants was not reported for four studies.[63 65 67 70] Five studies did not report the racial composition of their study populations. In other studies, more than 90% of the participants were Caucasians. The mean baseline HbA_{1c} in the RCTs was 8.5% in both the rt-CGM and SMBG groups.

Interventions. In the rt-CGM arm, four studies used Minimed Paradigm;[64 65 67 69] two used Minimed Guardian rt-CGM,[63 70] two studies used three models[66 68] including the Abbott Freestyle Navigator, Dexcom STS, and Minimed Paradigm. In five studies, participants were asked to wear monitors continuously; two studies required rt-CGM to be used more than 70% of time;[65 67] and one study did not specify the time requirement.[69] Seven studies reported sensor compliance.[63-69] The range of compliance was wide and depended on the subpopulation studied. Three studies reported on sensor compliance by age category.[65 66 68] In each of these studies, compliance was highest in individuals greater than 25 years of age (range, 74.9% to 83%) and lowest in those 15 to 24 years of age (range, 30 to 53%).

In the SMBG arm, two studies used CSII[63 65] and others did not specify the type of intensive insulin therapy. Four studies required participants to perform glucose monitoring four or more times daily;[64 66-68] one required at least three times per day;[65] and three studies did not report the frequency of monitoring.[63 69 70] The duration of intervention ranged from 12 to 52 weeks.

Outcomes. The main results for Key Question 2 are presented in the fifth part of Table C and summarized in the following paragraphs.

HbA_{1c}. Eight trials examined the comparative effectiveness of rt-CGM versus SMBG on HbA_{1c}. Meta-analysis of six trials (eight estimates) of at least 12 weeks duration showed a significant difference in the reduction from baseline HbA_{1c} between the rt-CGM and SMBG groups favoring rt-CGM (combined mean between-group difference, -0.28%; 95% CI, -0.44 to -0.13%, $P<0.001$). The analysis suggested statistical heterogeneity (I-squared, 68.9%; $P=0.002$), but no one study influenced results substantially. The heterogeneity seemed to be explained by percent of sensor compliance. In the meta-regression, we found that sensor compliance was significantly associated with the degree of HbA_{1c} reduction. In the sensitivity analysis that only included studies with more than a 60% rate of compliance with the sensor (five estimates), rt-CGM had an even greater effect on reducing HbA_{1c} as compared with SMBG (combined mean between-group difference from baseline, -0.37%; 95% CI, -0.46 to -0.28%).

Two studies reported data separately for younger age groups. One study reported no significant effect of rt-CGM as compared with SMBG for individuals 8 to 14 years of age and 15 to 24 years of age.[68] Another study showed a non-significant reduction in HbA_{1c} favoring rt-CGM in individuals 18 years of age or younger.[69] There were too few studies to perform a meta-analysis with consistent age categories.

Non-severe hypoglycemia. Six studies evaluated the incidence of non-severe hypoglycemia with rt-CGM compared with SMBG.[63 65-69] The definitions of non-severe hypoglycemia varied between studies and several studies reported multiple endpoints. The results were mixed. Three studies showed no difference in non-severe hypoglycemia between the rt-CGM and SMBG interventions.[65 67 68] Two studies showed a lower duration of time spent with non-severe hypoglycemia in the rt-CGM arm than in the MDI arm.[66 69] In the sixth study,[63] rt-CGM use was associated with a significant reduction in the number of SMBG readings below 60 mg/dL, whereas no difference was observed in the SMBG only group; however, the between-condition comparison was not statistically significant. Similar non-significant trends were observed when the number of patients with hypoglycemia (glucose < 60 mg/dL) was used as the endpoint.

Severe hypoglycemia. Seven studies reported the incidence of severe hypoglycemia over the study interval using variable definitions.[64-70] One study reported data stratified by age and we treated these groups as distinct populations.[68] A meta-analysis of six of these studies (eight separate study populations) indicated no difference in the incidence of severe hypoglycemia with rt-CGM compared with SMBG treatment (pooled RR, 0.95; 95% CI, 0.53 to 1.69, $P=0.86$).

Two of these trials reported severe hypoglycemia data specifically in a pediatric population.[64 69] In one study,[64] severe hypoglycemia was less common in those using rt-CGM than those using SMBG alone (four out of 78 with SMBG versus zero out of 76 with rt-CGM, $P=0.046$). In contrast, the pediatric subgroup (ages 8 to 14 years) of another study[68] showed a similar incidence of severe hypoglycemia in both arms (six out of 58 with SMBG versus four out of 56 with rt-CGM, $P=0.74$).

Hyperglycemia. Five studies evaluated the comparative effectiveness of rt-CGM versus SMBG on change in hyperglycemia.[65-69] The definitions of hyperglycemia varied

between studies and several studies reported multiple different endpoints. Two studies[67 69] showed no difference between the rt-CGM and SMBG arms. One study[66] showed a non-statistically significant trend toward less time with hyperglycemia in the rt-CGM arm compared with the SMBG arm. In another study, the effect differed by the age of the population.[68] In those 25 years of age or older, subjects with rt-CGM had significantly less hyperglycemia compared with those with SMBG alone. This effect was not observed in the two other age groups investigated (ages 8 to 14 years and ages 15 to 24 years). The fifth study showed significant improvements in hyperglycemia in the rt-CGM group compared with the SMBG group.[65]

Ratio of basal to bolus insulin. Two studies reported on the ratio of basal to bolus insulin in those treated with rt-CGM versus SMBG.[64 65] One study[64] reported that after 52 weeks the basal rate was a higher percentage of the total daily insulin dose in the rt-CGM group compared with the SMBG group (34%; SD, 11.8% versus 29.7%; SD, 10.4%, P=0.021). In contrast, a second study reported a higher percentage of insulin delivered as bolus in the rt-CGM group compared with the SMBG group (53.8%; SD, 10% versus 49.8%; SD, 15.8%; P not reported).[65]

Quality of life. Three studies examined the comparative effectiveness of rt-CGM versus SMBG on general, diabetes-specific, and diabetes treatment-related quality of life.[63 64 71] One study found no difference in parental satisfaction between the two intervention arms.[64] The other study assessed general quality of life using the Short Form (SF)-12 and found an improvement on the Physical Component Score (PCS) favoring rt-CGM but no difference between the intervention arms on the Mental Component Score (MCS).[71] Two studies examined diabetes-specific quality of life and found no difference between the two intervention arms in either study.[63 71] One study examined diabetes treatment-related quality of life using the Hypoglycemia Fear Survey in children and adults and found lower fear of hypoglycemia favoring rt-CGM.[71]

Quality and evidence grading. Four studies were rated with good quality[64 66 67 69] and four studies were rated with fair quality.[63 65 68 70] Those studies rated as fair were not clear in reporting allocation concealment. However, all trials were open-labeled because of the nature of the interventions. Risk of bias was low for the outcomes of HbA_{1c} and severe hypoglycemia, medium for hyperglycemia and mild hypoglycemia, and high for ratio of basal to bolus insulin and quality of life.

The strength of evidence examining the comparative effectiveness of rt-CGM versus SMBG was high for HbA_{1c}, moderate for severe hypoglycemia, and low for hyperglycemia, mild hypoglycemia, ratio of basal to bolus insulin, and quality of life. No study reported on weight gain as an outcome.

Applicability. All studies were in those with type 1 diabetes and most studies had small sample sizes, with the largest clinical trial including 322 participants.[31] The majority of studies were performed in both children and adults without stratification by age. Studies generally did not report race but based on the countries in which they were conducted (more than half were outside of the US or involved multiple countries), most studies included Caucasian participants. Participants generally had poor glycemic control at

study entry (mean HbA_{1c}, 8.5%), were treated in the intervention groups for an average of 24 weeks, and had diabetes for 11.5 years prior to study entry.

Comparative Effectiveness of Sensor-Augmented Pump (rt-CGM + CSII) Versus MDI/SMBG

Study design. Three studies evaluated a sensor-augmented pump versus MDI/SMBG in children and adults with type 1 diabetes.[72-74] Two studies were multicenter trials in North America.[72 74] The location and number of the study sites were not specified in the third study.[73] All three studies were parallel arm RCTs.[72-74] The followup time for the studies were 15, 16, and 52 weeks. In all three studies, suboptimally controlled patients were enrolled (HbA_{1c} 7.4 to-9.5%;[72] "suboptimal control";[73] and HbA_{1c} greater than or equal to 7.5%[74]).

Population characteristics. Two studies included only adults[73 75] and one study enrolled both adults and children.[72] The mean age of participants in the RCTs was reported in the combined study sample in two studies (47.2 years[73]) and 45.9 years[74]), and stratified by treatment group in the third study (32.2 years in the sensor-augmented pump group versus 31.5 years in the MDI/SMBG group).[72] In the study that included both adults and children,[72] 32% of the sample was children and the mean ages of the children were 11.7 years in the sensor-augmented pump group versus 12.7 years in the MDI/SMBG group. The majority of participants in two studies were white (92%[72]) and (79 %[73]). One study did not report the racial composition of the population.[74] The mean baseline HbA_{1c} in the RCTs was similar in all three studies (median, 8.6%; range, 8.3 to 9.5%).

Interventions. In all three studies, the MM Paradigm REALTime system was used and training in the use of the device was provided.[72-74] The frequency and intensity of the followup visits, however, differed between studies. In the longest study,[72] patients assigned to the sensor-augmented pump arm underwent initial pump training, followed by pump initiation. Two weeks later, following on-line and in-person training sessions, the rt-CGM was introduced. Patients were then seen at 3-month intervals during which glucose data were reviewed and insulin therapy was adjusted. Patients assigned to continue MDI/SMBG were also seen at 3-month intervals and insulin adjustments were made. In the MDI/SMBG group, a blinded rt-CGM device was worn for 1-week periods at baseline, 6 months, and 12 months, such that continuous glucose profiles could be compared between the study groups at the end of the study. Both arms of the study received the same instruction in intensive diabetes management and carbohydrate counting. This was the only of the three studies that reported the frequency of rt-CGM use[72] and 67% of patients used the rt-CGM over 60% of the time and 23% reported use over 80% of the time.

In a 15-week randomized trial,[74] patients assigned to a sensor-augmented pump initiated CSII and rt-CGM in a step-wise fashion over a 3-week period. Use of the rt-CGM started 2 weeks after CSII initiation. The patients in the sensor-augmented pump arm were also seen at weeks 3, 5, and 15. Those randomized to continue MDI/SMBG were seen at baseline and weeks 2, 5, and 15. In both arms, glucose data were reviewed

and insulin adjustments were made. Participants in both arms of the study received the same instruction in intensive diabetes management and carbohydrate counting.

In a 16-week randomized trial,[73] both arms received diabetes education and those randomized to a sensor-augmented pump received additional one-time instruction regarding the use to the device. No further followup visits in either arm were specified until the end of study visit at week 16. Insulin adjustments were not made as part of the study protocol.

Outcomes. The main results for Key Question 2 are presented in the sixth part of Table C and summarized in the following paragraphs.

HbA_{1c}. All three studies assessed the effect on HbA_{1c}.[72-74] A meta-analysis of these three studies showed a significant difference in the reduction from baseline HbA_{1c} between the sensor-augmented pump and MDI/SMBG groups favoring the sensor-augmented pump (combined mean between-group difference from baseline, -0.61%; 95% CI, -0.75 to -0.46%, $P<0.001$). The study duration for these three trials ranged between 15 and 52 weeks.

Non-severe hypoglycemia. One study assessed the time spent with non-severe hypoglycemia[72] defined as the area under the curve for two different cutpoints (less than 70 mg/dL and less than 50 mg/dL). The study arms had no differences in these measures during the study interval.

Severe hypoglycemia. All three studies reported on the incidence of severe hypoglycemia. In the largest study,[72] severe hypoglycemia occurred in a similar number of patients in the sensor-augmented pump arm and the MDI/SMBG group (21 out of 247 versus 17 out of 248, $P=0.58$). In another trial,[73] three hypoglycemic events occurred in the MDI/SMBG group (N = 14), whereas no events occurred in the sensor-augmented pump group (N = 14). The number of patients who experienced events was not specified. In the third trial,[74] one unspecified hypoglycemic event occurred in the eight patients randomized to continue MDI/SMBG and none in the eight patients randomized to a sensor-augmented pump.

Hyperglycemia. One study assessed the time spent with hyperglycemia,[72] which was expressed as the area under the curve calculated by the rt-CGM in both arms. Two different outcomes were used: over 250 mg/dL and over 180 mg/dL. In the entire study population and when stratified by age (adults 19 to 70 years and children 7 to 18 years of age), those randomized to a sensor-augmented pump had significantly less hyperglycemia compared with those continuing MDI/SMBG (all $P<0.001$), using either hyperglycemic threshold.

Weight. Two studies reported the change in weight. In one study,[72] only the change in weight in adults was reported, with a non-significant difference in weight gain between the sensor-augmented pump and MDI/SMBG arms favoring MDI/SMBG (2.4 kg versus 1.8 kg, $P=0.19$). In a second study,[73] mean weight increased 0.7 kg in the sensor-

augmented pump arm and 2.0 kg in the MDI/SMBG arm; however, the between arm difference was not statistically significant (*P*=0.31).

Quality of life. One study examined diabetes treatment-related quality of life and at 16 weeks, user acceptance and overall satisfaction was greater in the sensor-augmented pump arm compared to MDI/SMBG.[73]

Quality and evidence grading. One study was rated as "good,"[72] while the other two studies were rated as "poor" to "fair."[73 74] The risk of bias was medium for the HbA_{1c} outcome and high for all other outcomes.

The strength of evidence examining the comparative effectiveness of a sensor-augmented pump versus MDI/SMBG was moderate for HbA_{1c} but insufficient to draw conclusions for the outcomes of hypoglycemia, weight gain, hyperglycemia, and quality of life.

Applicability. The largest clinical trial included 485 participants,[72] and the other two trials were small with less than 30 participants.[73 74] Only one study included individuals 20 years of age or younger.[72] Two studies reported the majority of participants were Caucasian,[72 73] while the other trial did not report race distribution.[74] Participants had poor glycemic control at study entry (mean HbA_{1c}, 8 to 9%), and were treated in the intervention groups for 15 weeks to 1 year. One study reported a long duration of diabetes with a mean of 15 years.[72]

Discussion

Summary of Key Findings

Our systematic review summarizes the current state of the evidence on the impact of medical devices for insulin delivery and glucose monitoring on diabetes-related process measures, intermediate outcomes, and clinical outcomes in individuals with type 1 and type 2 diabetes mellitus.

Comparative effectiveness of CSII versus MDI (KQ 1). RCTs showed no difference in the effect on HbA_{1c} between the CSII and MDI intervention groups for children and adolescents, adults, or pregnant women with type 1 diabetes, or for adults with type 2 diabetes. The trials also showed no difference in rates of severe hypoglycemia between the two intervention groups for children and adolescents, or adults with type 1 diabetes, or adults with type 2 diabetes. The evidence was insufficient to draw definitive conclusions about severe hypoglycemia rates in pregnant women with type 1 diabetes.

In most studies of children and adolescents and adults with type 1 diabetes, compared with MDI, CSII use was associated with improvement in general and diabetes-specific quality of life measures. The evidence was insufficient to draw definitive conclusions about quality of life for pregnant women with type 1 diabetes or adults with type 2 diabetes.

In pregnant women with pre-existing type 1 diabetes, observational studies showed no difference in gestational age at delivery between the CSII and MDI intervention

groups. Because of the small number of studies of fair to poor quality in this population, the evidence was insufficient to draw definitive conclusions about other maternal and fetal outcomes.

Our systematic review and meta-analysis of the comparative effectiveness of CSII and MDI on outcomes complements and extends two previously published meta-analysis[76 77] by including more studies of individuals with type 2 diabetes as well as pregnant women with pre-existing type 1 diabetes and by only including studies using rapidly-acting insulin analogs and not regular insulin in the CSII and MDI intervention groups. Unlike one of the prior meta-analysis[77] and similar to another,[76] we excluded before and after studies and only included RCTs in our combined estimates for HbA_{1c} and severe hypoglycemia. We also examined additional non-glycemic outcomes, including weight gain, ratio of basal to bolus insulin, and quality of life. Unfortunately, for some of the defined outcomes — process measures (i.e., ratio of basal to bolus insulin), weight gain, non-severe hypoglycemia, hyperglycemia, and micro- and macrovascular complications — the evidence was insufficient to draw definitive conclusions in any population of diabetic individuals about the comparative effectiveness of CSII versus MDI or rt-CGM versus SMGB.

We found that CSII lowered HbA1c in children non-significantly by 0.14% compared with MDI and that there was no effect in adults with type 1 diabetes. This compares to a reduction of 0.63% for CSII versus MDI in subgroup analyses of studies using only insulin analogs in a prior study of adults and children with type 1 diabetes (three RCTs and one before-after study)[77] and a reduction of 0.4% in studies published after 2000 in another meta-analysis.[76] Our estimates are based on a larger number of RCTs using rapid-acting analogs only (total 11—seven in children and adolescents and four in adults). We found severe hypoglycemia rates in type 1 diabetes to be similar between the MDI and CSII groups (incidence rate ratio, 0.99 in children and adolescents and 0.74 in adults). While a prior study found a significantly higher rate of severe hypoglycemia with MDI compared to CSII (incidence rate ratio, 2.89 for RCTs), these studies included regular insulin and studies were only included if individuals reported an elevated frequency of baseline severe hypoglycemic episodes, which may have resulted in a greater likelihood of improvement.[77] An estimate was not reported for studies using rapid-acting analogs because participants in these studies did not have a high frequency of severe hypoglycemia at baseline.[77]

Comparative effectiveness of rt-CGM versus SMBG (KQ 2). We only found studies of the comparative effectiveness of rt-CGM versus SMBG in children, adolescents, and adults with type 1 diabetes. Studies have not compared these two glucose monitoring approaches in pregnant women with type 1 diabetes or individuals with type 2 diabetes. Compared with the SMBG group, the rt-CGM group achieved a lower HbA_{1c}. A sensitivity analysis showed this effect to be greater in studies where sensor compliance was 60% or greater. The intervention groups did not differ in the rate of severe hypoglycemia. A few studies that evaluated quality of life found no difference between general and diabetes-specific quality of life between the two intervention groups.

Our systematic review and meta-analysis of the comparative effectiveness of rt-CGM and SMBG on outcomes complements and extends a recently published meta-analysis[78] by including additional non-glycemic outcomes, including weight gain, ratio of basal to

bolus insulin, and quality of life. We also found that rt-CGM lowered HbA_{1c} more than SMBG (-0.28% in our study versus -0.30% in Pickup et al.) and that there was no difference in severe hypoglycemia in the two intervention groups.[78]

Comparative effectiveness of a sensor-augmented pump versus MDI/SMBG (KQ2). The sensor-augmented pump use was associated with a significantly greater reduction in HbA_{1c} compared with MDI/SMBG use in non-pregnant individuals with type 1 diabetes. The evidence was insufficient to draw definitive conclusions about severe hypoglycemia or quality life.

Limitations

Our systematic review highlights important weaknesses in the literature. Most RCTs examining the effect of insulin delivery and glucose monitoring devices were small, with the largest trial including 322 participants.[31] The majority of studies, particularly those comparing CSII with MDI, were fair to poor quality and did not report most quality items of interest. Most studies did not report the racial and ethnic composition of the study populations; however, for those that did, the majority of participants were Caucasian. Since few studies focused on or included children 12 years of age or younger or 65 years of age or older, we were unable to draw conclusions about the effectiveness of insulin delivery and glucose monitoring devices in these populations. The studies were heterogeneous in definitions of non-severe hypoglycemia, hyperglycemia, and weight gain, preventing us from combining data to determine effect estimates for these intermediate outcomes. None of the studies included data on long-term diabetes micro- and macrovascular complications. This is likely related to the fact that these complications develop over many years and the longest follow-up of our studies was 52 weeks. In the pregnancy literature, none of the studies examined insulin delivery and glucose monitoring devices in women with pre-existing type 2 diabetes and the studies in women with pre-existing type 1 diabetes have not examined the effect of rt-CGM on maternal and fetal outcomes. Finally, the studies were heterogeneous in assessing and reporting quality of life outcomes which prevented us from quantifying the effects of insulin delivery and glucose monitoring devices on quality of life. We found no studies examining the comparative effectiveness of CSII versus MDI on quality of life in pregnant women and only one study examining the effects on quality of life in type 2 diabetes.

Our systematic review and meta-analysis had several limitations. We may have not included all studies on this topic; however, our search strategy was comprehensive and included non-English language publications. There was only one article identified that we were unable to translate.[79] We cannot exclude the possibility that publication bias affected our findings. For the meta-analyses examining the comparative effectiveness of CSII versus MDI and rt-CGM versus SMBG on HbA_{1c} and severe hypoglycemia, we did not find evidence of publication bias; however, for our other glycemic (hyperglycemia, non-severe hypoglycemia) and non-glycemic outcomes for which we could not perform meta-analyses, we were unable to assess for publication bias.

Implications

Our findings indicate that intensive insulin therapy delivered either by CSII and MDI using current rapidly-acting insulin analogs are about equally effective in lowering HbA_{1c} in several diabetic patient populations — adolescents, adults, and pregnant women with type 1 diabetes. Intensive insulin therapy delivered by both methods resulted in similar rates of severe hypoglycemia for adolescents and adults with type 1 diabetes. However, from a patient-focused perspective, adolescents and adults with type 1 diabetes treated with CSII reported better overall quality of life compared with those treated with MDI. Taken together, these data suggest that the approach to intensive insulin therapy to optimize glycemic control can be individualized to patient preference that will maximize their treatment satisfaction and quality of life as both CSII and MDI using current rapid-acting insulin analogs have similar effectiveness for glycemic control.

This is the first systematic review and meta-analysis to our knowledge to examine the comparative effectiveness of both rt-CGM versus SMBG and of sensor-augmented pump versus MDI/SMBG. Our findings indicate that rt-CGM is superior to SMBG in lowering HbA_{1c}, without increasing or decreasing the risk of severe hypoglycemia, in non-pregnant individuals with type 1 diabetes, particularly those who are compliant with wearing the monitoring device (HbA_{1c} reduction 0.28% for all studies versus 0.37% in studies with >60% sensor compliance rate). Even though CSII and MDI without rt-CGM have similar effects on HbA_{1c}, the addition of rt-CGM to CSII is superior to MDI/SMBG in lowering HbA_{1c}. Thus, the addition of this monitoring technology to intensive insulin therapy can assist in achieving glycemic targets in non-pregnant individuals with type 1 diabetes. The available literature does not allow us to determine the comparative effectiveness of rt-CGM versus SMGB in patients only using CSII or only using MDI because the modes of intensive insulin therapy were mixed in the available studies.

Future Research

Our report highlights the need for several areas of future research examining the effect of insulin delivery and glucose monitoring devices in the management of diabetes mellitus. We identified a need for well conducted RCTs of intensive insulin therapy delivered via CSII versus MDI in young children with type 1 diabetes and in pregnant women and elderly patients with both type 1 and type 2 diabetes. Studies in the elderly are important as diabetes prevalence increases with age.[2] Only a small number of studies in non-adolescent children have compared CSII with MDI on glycemic and non-glycemic outcomes and studies comparing rt-CGM with SMBG have included a mixture of children and adults without stratifications focused exclusively on the young. Current studies examining the comparative effectiveness of rt-CGM versus SMBG on outcomes have included mixed populations receiving intensive insulin therapy as CSII and/or MDI; however, they have not determined the effect of these two glucose monitoring strategies in individuals treated with only CSII or only MDI. Such a study would help to elucidate whether the observed benefit of sensor-augmented pump compared with MDI/SMBG on glycemic control is secondary to the rt-CGM technology, the mode of intensive insulin delivery, or both. Future studies should also seek to identify and use an agreed upon set of general and diabetes-specific and treatment-related quality of life measures to allow

comparisons across studies, including reporting of standard errors and confidence intervals to allow quantitative, pooled assessments. Finally, future studies should include ethnically diverse populations because diabetes is relatively common in all ethnic/racial groups, and type 2 diabetes is more common in blacks than in whites.[80]

Table C. Summary of the evidence of the comparative effectiveness of insulin delivery and glucose monitoring devices

Outcome	Strength of evidence	# of studies	Main Findings
KQ 1: In patients receiving intensive insulin therapy, does mode of insulin delivery (MDI versus CSII) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus? Do these effects differ by (a) type 1 or type 2 diabetes status, (b) age—very young children, adolescents, and adults, including older adults (age 65 years or older), and (c) pregnancy status—pre-existing type 1 or type 2 diabetes?			
			Children and adolescents with type 1 diabetes mellitus
HbA_{1c}	Moderate	12 (7 RCTs; 2 non-RCTs; 3 OBS)	Mean between-group difference in how HbA_{1c} changed from baseline was -0.14% in RCTs, decreasing slightly more with CSII than with MDI (95% CI, -0.48 to 0.20%, *P*=0.63). Results were similar among adolescents over 12 years old (mean between-group difference, -0.10%; 95% CI, -0.47 to 0.27%).
Daytime hypoglycemia	Low	3 (All RCTs)	Three studies found no significant difference in daytime hypoglycemia frequency between MDI and CSII intervention groups (perceived hypoglycemic events: 1.7±0.4 for MDI versus 1.7±0.4 for CSII over 104 weeks;[31] blood sugar excursions below 70 mg/dL: 0.59±0.32 for MDI versus 1.52±0.49 over 24 weeks;[33] mean number of hypoglycemic episodes/patient/study period: 15.1±16.1 for MDI versus 11.4± 7.1 over 52 weeks[41]).
Nocturnal hypoglycemia	Low	2 (All RCTs)	Two studies found no significant difference in nocturnal hypoglycemia between the MDI and CSII intervention groups. In one study, there were 4 events/patient/study period (SD, 6.5) for MDI versus 3 events/patient/study period (SD, 3.5) over 52 weeks.[41] In the other study, there were 2 patients with 1 or more events in the CSII arm but no events reported in the MDI arm over 16 weeks.[40]
Mild hypoglycemia	Insufficient	1 (RCT)	One study found no significant difference in mild hypoglycemia (events with blood sugar less than 70 mg/dL) between the MDI (22 events/patient) and CSII (19.8 events/patient) intervention groups over 14 weeks.[42]
Severe hypoglycemia	Moderate	9 (5 RCTs; 1 non-RCT; 2 Obs)	Mean incidence rate ratio for severe hypoglycemic event rates in RCTs for CSII versus MDI was 0.99 (95% CI, 0.57 to 1.71, *P*=0.37), indicating similar rates between the two intervention arms. Results were similar among adolescents over 12 years of age (mean incidence rate ratio for CSII versus MDI, 0.95; 95% CI, 0.42 to 2.13).
Hyperglycemia	Insufficient	1 (RCT)	In one study there was no difference in the frequency of hyperglycemia between the MDI (6.7 events) and CSII (7.9 events) intervention groups over 14 weeks.[42]
Ratio basal to bolus insulin	Insufficient	1 (non-RCT)	In one study there was no difference in the ratio of basal to bolus insulin between the MDI (45.6±5.2%) and CSII (47.3±5.3%) intervention groups.[35]
Weight	Low	3 (All RCTs)	Two studies found no difference in weight, measured as BMI-SDS, between the MDI and CSII intervention groups (BMI-SDS change +0.05 for MDI and -0.07 for CSII in one study[41] and less than 1 kg/m^2 BMI change between groups in the other[40]). Another study reported a slight but statistically significant increase in BMI-SDS during MDI therapy (BMI-SDS change +0.07) but non-significant change during CSII therapy (-0.05)(*P*=0.01 for between group difference).[42]
General quality of life	Low	2 (All RCTs)	Two studies showed improvement in general quality of life favoring CSII—difference in PedsQOL from baseline to follow-up 2.8±13.1 for CSII and 0.4±17.3 for MDI over 7 months in one study[32] and 8±17 for CSII and 6.5±33 for MDI over 6 months in another study.[33]

Table C. Summary of the evidence of the comparative effectiveness of insulin delivery and glucose monitoring devices (continued)

Outcome	Strength of evidence	# of studies	Main Findings
Diabetes-specific quality of life	Low	4 (All RCTs)	Three studies showed improvement in diabetes treatment satisfaction favoring CSII—DTSQ at 24 months 33.1±0.9 in CSII versus 27.5±2.0 in MDI (*P*<0.001);[31] DTSQ baseline score 20.5±3.6 and after 6 months, 21.8±3.7 for MDI and 32±6.5 for CSII (*P*<0.05);[41] DTSQ baseline score 21.4±3.3 and after 3.5 months, 21.9±3.8 for MDI and 30.6±3.7 for CSII.[42] One showed improvement in diabetes quality of life favoring CSII (DQOL-Y baseline score 77.4±16.1 and end of study 76.4±14.3 for MDI and 82.7±13 for CSII; *P*<0.05),[41] and one study did not find a difference in diabetes quality of life between the two interventions (numerical data not presented).[40]
			Adults with type 1 diabetes mellitus
HbA_{1c}	Low	4 (All RCTs)	CSII and MDI reduced HbA_{1c} similarly (mean between-group difference from baseline, -0.05%; 95% CI, -0.41 to 0.31%, *P*=0.78).
Daytime hypoglycemia	Insufficient	1 (RCT)	One study reported more symptomatic and asymptomatic hypoglycemia between 0800 and midnight in the MDI compared with the CSII intervention arm (*P*<0.05).[49]
Nocturnal hypoglycemia	Low	3 (All RCTs)	Three studies reported nocturnal hypoglycemia. In one cross-over trial, the proportion of patients experiencing nocturnal hypoglycemia was similar between the MDI (73% for any; 48% for symptomatic) and CSII (72% for any; 42% for symptomatic) intervention arms, although there were fewer episodes per person in the CSII compared with the MDI group (3.0 versus 4.0; *P*=0.0024).[49] In two other studies, there was not a statistically significant difference in nocturnal hypoglycemic episodes between the two intervention groups.[45 47]
Symptomatic hypoglycemia	Low	4 (All RCTs)	Incidence rates for symptomatic hypoglycemia were similar for MDI and CSII in two studies (*P*>0.05).[45 81] In another study, there were more symptomatic hypoglycemic events with CSII versus MDI over 6 months (40/person-year versus 21/person-year; *P*=not reported).[47] In a different study, there were fewer symptomatic hypoglycemic events with CSII versus MDI (6.1/person versus 6.9/person; *P*=0.05), although similar proportion of participants experienced events over 5 weeks (75% for CSII and 72% for MDI).[49]
Other non-severe hypoglycemia	Low	6 (All RCTs)	Three studies found no difference in non-severe hypoglycemia between the two intervention groups (in one study, asymptomatic hypoglycemia event rate 1.4/patient for MDI versus 1.2/patient for CSII; *P*=0.97[45]). In two studies, the incidence of mild hypoglycemia was higher in the CSII compared with the MDI group[49 51] with the relative difference statistically significant in one study (between-group difference in change in hypoglycemic rate, 0.99; 95% CI, 0.11 to 1.87).[51] One additional study found a higher frequency of hypoglycemia in the MDI compared with the CSII group (RR, 1.12; 95% CI, 1.08 to 1.17).[48]
Severe hypoglycemia	Low	8 (All RCTs)	There was no difference in severe hypoglycemia incidence between the two intervention groups (combined RR, 0.74; 95% CI, 0.30 to 1.83, *P*=0.52). Four cross-over trials did not provide quantitative results on severe hypoglycemia by period and were not included in the meta-analysis. Two showed more severe hypoglycemia with MDI compared with CSII (RR, 2.6; 95% CI, 2.08 to 3.25) in one study,[82] one study showed less severe hypoglycemia with MDI compared with CSII (3 events versus 4 events over 4 months),[53] and one study found similar rates of severe hypoglycemia between the two groups (1.1 events/patient for CSII versus 1.3 events/patient for MDI over 4 months, *P*=0.33).[46]

Table C. Summary of the evidence of the comparative effectiveness of insulin delivery and glucose monitoring devices (continued)

Outcome	Strength of evidence	# of studies	Main Findings
Hyperglycemia	Low	3 (All RCTs)	The mean between group difference in fasting glucose over 6 months was -12.3 mg/dL (95% CI, -32.9 to 8.2 mg/dL; *P*=NS) favoring CSII in one study.[45] Two other studies reported no difference in fasting glucose between the MDI and CSII groups. The mean between-group difference in pre-prandial glucose over 6 months was -17.1 mg/dL (95% CI, -42.1 to 8.0 mg/dL; *P*=NS) favoring CSII.[45] Pre-dinner glucose was lower with CSII (128 mg/dL) compared with MDI (148 mg/dL) at the end of 5 weeks (*P*=NS).[49] Pre-dinner and pre-lunch glucoses were non-significantly lower with CSII compared with MDI at 4 months (estimates not reported).[83]
Weight	Low	4 (All RCTs)	Four studies examined the effects of MDI versus CSII on weight gain in adults with type 1 diabetes and there were not significant weight changes in either group. In two studies that reported estimates, the difference in weight was 0.28 kg less with CSII compared to MDI after 4 weeks[51] and 1.5 kg more with CSII compared to MDI after 6 weeks.[47]
General quality of life	Low	2 (All RCTs)	Two studies showed an improvement in general quality of life between the two intervention groups favoring CSII. In one study the SF-36 Physical Component Score change was -1.2 for CSII and 5.9 for MDI (*P*=0.048) and the Mental Component Score change was -0.6 for CSII and 5.2 for MDI (*P*=0.05).[48] The other study did not report estimates but there no difference in the Physical Component Score but a change in the Mental Component Score favoring CSII (*P*<0.05).
Diabetes-specific quality of life	Low	5 (All RCTs)	Three studies showed an improvement in diabetes-specific quality of life favoring CSII—DQOL 75 for CSII versus 71 for MDI at 8 months, *P*<0.001; between-group difference in DQOL for CSII versus MDI 7.2 (95% CI, 3.4 to 17.9; *P*=NS)[52] and 3.1 (95% CI, 0.1 to 6.1; *P*=0.042).[45] One study showed improvement favoring MDI (DQOL difference from baseline 5; SD, 28 for CSII and 11; SD, 23 for MDI).[47] Another study showed an improvement in Diabetes Quality of Life Clinical Trials Questionnaire (DQOLCTQ) scores in the CSII (52 to 81) and MDI (50 to 78) groups over 12 months with no between group difference (*P*=0.58).[55]
Diabetes treatment-related quality of life	Insufficient	1 (RCT)	Altered Hypoglycemia Awareness Questionnaire scores were similar in the CSII (baseline=7 and follow-up=3) and MDI (baseline=7 and followup=4) groups over 24 weeks. Hypoglycemia Fear Survey scores decreased in the both CSII (-3±25) and MDI (-8±33) groups.[47]
Adults with type 2 diabetes mellitus			
HbA_{1c}	Moderate	4 (All RCTs)	There was a non-significant difference in HbA_{1c} between the MDI and CSII intervention groups favoring CSII (mean between-group difference from baseline, -0.16; 95% CI, -0.42 to 0.09, *P*=0.21).
Mild hypoglycemia	Low	3 (All RCTs)	In two studies, mild hypoglycemia was more frequent in the MDI than CSII group (90% versus 81% in one study;[58] 59% versus 54% in another study[57]) although the difference was not statistically significant. In one study, there was no difference in mild hypoglycemia between the two groups.[55]
Nocturnal hypoglycemia	Insufficient	1 (RCT)	In one study, nocturnal hypoglycemia (occurring between midnight and 0600) was more common in patients in the MDI compared with CSII arm (22% versus 16%; *P*=not reported), although the rates of nocturnal hypoglycemia were similar between the two groups.
Severe hypoglycemia	Low	3 (All RCTs)	In one study, no participants in either the MDI or CSII groups experienced severe hypoglycemia.[57] In two other studies, there was no difference in severe hypoglycemia between the two intervention groups (2 patients with events for MDI and 3 patients with events for CSII:[58] incidence rate 0.23 events/person-year for MDI versus 0.08 events/person-year for CSII; *P*=0.61).[55]

Table C. Summary of the evidence of the comparative effectiveness of insulin delivery and glucose monitoring devices (continued)

Outcome	Strength of evidence	# of studies	Main Findings
Hyperglycemia	Insufficient	1 (RCT)	Mean post-prandial glucose (90 minutes after breakfast) was 167 mg/dL in the CSII arm and 192 mg/dL in the MDI arm at 24 weeks (mean between-group difference, -25 mg/dL; *P*=0.019).[57] Glucose measurements from other time points were similar between treatment groups at the end of the study. The incidence of blood glucose over 350 mg/dL was higher in the MDI compared with the CSII arm (26 versus 6 events) with 18% and 5% of participants affected in the MDI and CSII arms, respectively.[57]
Weight	Low	2 (All RCTs)	In two studies, there was not a statistically significant difference in weight gain between the two intervention arms (difference in weight gain for CSII versus MDI, 1.0 kg; *P*=NS[57] and -0.5 kg; *P*=0.7[55]).
General quality of life	Insufficient	1 (RCT)	In one study, there was no difference in general quality of life between the CSII and MDI intervention groups. Difference in SF-36v2 Physical Component Score from baseline to follow-up was 0.6 for CSII versus 0.4 for MDI and for the Mental Component Score, was 1.0 for CSII and 2.5 for MDI.[55]
Diabetes-specific quality of life	Insufficient	1 (RCT)	In one study, there was no difference in diabetes-specific quality of life between the CSII and MDI intervention groups (DQOLCTQ scores improved from 52 to 81 for CSII and from 50 to 78 for MDI over 12 months).[55]
Diabetes treatment-related quality of life	Insufficient	1 (RCT)	In one study, there was improvement in diabetes treatment satisfaction favoring CSII (Phase V Outcomes System Diabetes Treatment Satisfaction score improved from 59.4±2.1 to 79.2±1.8 for CSII compared to 63.6±1.9 to 70.3±2.3 for MDI over 24 weeks; *P*<0.001).[57]
			Pregnant women with pre-existing type 1 diabetes
HbA_{1c}	Low	4 (All OBS)	Four studies, all observational, reported an improvement in HbA_{1c} in both the CSII and MDI groups during pregnancy without any significant difference between groups in HbA_{1c} in any of the trimesters. Third trimester HbA_{1c} values were 6.1% for MDI and 6.3% for CSII,[59] 6.8% for MDI and 6.4% for CSII,[60] 6.44% for MDI and 6.63% for CSII,[61] and 6.4% for MDI and 6.6% for CSII.[62]
Cesarean section rates	Insufficient	3 (All OBS)	Two studies showed no difference in the rates of cesarean section in the CSII compared with the MDI groups (94% for MDI versus 95% for CSII, *P*=NS[59] and 46% for MDI versus 69.2% for CSII, *P*=0.235[60]). One study showed a significantly higher rate of cesarean section for CSII (70%) versus MDI (34.6%), *P*=0.016.[62]
Maternal hypoglycemia	Insufficient	2 (All OBS)	In two studies, hypoglycemia rates did not differ between the MDI and CSII groups—5% in each group in one study[59] and 9% in each group in another study.[62]
Maternal weight gain	Insufficient	2 (All OBS)	There was no difference in weight gain between the CSII and MDI intervention groups (13.4 kg; SD, 5.4 in the CSII group and 11.5 kg; SD, 3.7 in the MDI group[59] and 14.5 kg; SD, 3.9 in the CSII group and 14.4 kg; SD, 5.2 in the MDI group[62]).
Gestational age at delivery	Insufficient	3 (All OBS)	Gestational age at delivery ranged from 36.3 to 37.5 for MDI and from 36.3 to 36.6 for CSII and there was no significant difference between the MDI and CSII groups.[59-61]
Neonatal hypoglycemia	Insufficient	2 (All OBS)	Rates of neonatal hypoglycemia were 13% to 14% for MDI and 10% to 16% for CSII with no significant differences between the two groups.[59 60]
Birth weight	Insufficient	3 (All OBS)	One study reported a significantly higher birth weight in CSII compared with the MDI group (3767 versus 3384 kg, *P*=0.036),[62] while another study found no difference between the two groups (3270 kg for MDI versus 3191 kg for CSII, *P*=0.86).[60] Birth weight was 3101 kg for MDI and 3295 kg for CSII in another study (*P*=not reported).[59]
Major congenital anomalies	Insufficient	2 (All OBS)	Two studies found no difference in major congenital anomalies between the MDI and CSII groups. Major congenital anomalies occurred in 12% (4/33 patients) in CSII group versus 13% (2/23 patients) in the MDI group.[62]

Table C. Summary of the evidence of the comparative effectiveness of insulin delivery and glucose monitoring devices (continued)

Outcome	Strength of evidence	# of studies	Main Findings
Minor congenital anomalies	Insufficient	3 (All OBS)	Three studies found no difference in minor congenital anomalies between the MDI and CSII groups. There were no minor congenital anomalies in either group in two studies[59 61] and rates of minor congenital anomalies and pregnancy termination rates were 28% (22/78 patients) in the MDI group and 20% (4/25 patients) in the CSII group (*P*=not reported).[60]
NICU admissions	Insufficient	2 (All OBS)	NICU admissions rates were not significantly different between the MDI and CSII groups—9% for MDI versus 5% for CSII in one study[59] and 35% for MDI versus 33% for CSII in another study.[62]
KQ 2: In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM versus SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus? Do these effects differ by (1) type 1 or type 2 diabetes status, age--very young children, adolescents, and adults, including older adults (age >65 years), (c) pregnancy status--pre-existing type 1 or type 2 diabetes, or (d) intensive insulin delivery: MDI or CSII?			
rt-CGM versus SMBG			
HbA_{1c}	High	8 (All RCTs)	Mean between-group difference in how HbA_{1c} changed from baseline was -0.28% favoring rt-CGM over SMBG (95% CI, -0.44 to -0.13%, *P*<0.001). In the sensitivity analysis that only included studies with more than 60% of compliance rate (5 estimates) there was a greater HbA_{1c} reduction (mean between-group difference from baseline, -0.37%; 95% CI, -0.46 to -0.28%). Two studies reported data separately for younger age groups. One study reported no significant effect of rt-CGM as compared to the SMBG group for individuals 8-14 years of age and 15-24 years of age.[68] Another study showed a non-significant reduction in HbA_{1c} favoring rt-CGM in individuals 18 years of age or younger.[69]
Non-severe hypoglycemia	Low	6 (All RCTs)	Four studies showed no difference in non-severe hypoglycemia between the rt-CGM and SMBG interventions. Two studies showed a lower duration of time spent with non-severe hypoglycemia in the rt-CGM versus MDI arms—rt-CGM spent less time with non-severe hypoglycemia compared to MDI (*P*<0.05) in one study[66] and there was no change in duration of time spent with glucose less than 70 mg/dL with rt-CGM but an increase in time with SMBG (*P*=0.0002).[63]
Severe hypoglycemia	Moderate	7 (All RCTs)	There was no difference in severe hypoglycemia rates between the rt-CGM and SMBG intervention groups (pooled RR, 0.95; 95% CI, 0.53 to 1. 69, *P*=0.86). Two of these trials reported severe hypoglycemia data specifically in pediatric populations. In one study, severe hypoglycemia was less common in those using rt-CGM than those using SMBG alone (SMBG 4/78 vs rt-CGM 0/76, *P*=0.046).[64] In contrast, the pediatric subgroup (ages 8-14 years) of another study showed a similar incidence of severe hypoglycemia in both arms (SMBG 6/58 vs rt-CGM 4/56, *P*=0.74).[68]
Hyperglycemia	Low	5 (All RCTs)	Two studies showed no difference in hyperglycemia between the rt-CGM and SMBG arms.[67 69] One study showed a non-statistically significant trend towards less time with hyperglycemia in the rt-CGM arm compared with the SMBG arm.[66] In another study, the effect differed by the age of the population. In those 25 years of age or older, subjects with rt-CGM had significantly less hyperglycemia compared to those with SMBG alone.[68] This effect was not observed in the two other age groups investigated (age 8-14 years and ages 15-24 years). The fifth study showed significant improvements in hyperglycemia in the rt-CGM group compared with the SMBG group.[65]
Ratio of basal to bolus insulin	Low	2 (All RCTs)	One study reported that the basal rate was a higher proportion of the total daily insulin dose in the rt-CGM compared with the SMBG intervention group (34± 11.8% versus 29.7± 10.4%, *P*=0.021).[64] In contrast, a second study reported a higher percentage of insulin delivered as bolus in the rt-CGM group (53.8% ± 10%) compared to the SMBG group (53.8% ± 10% versus 49.8% ± 15.8%, *P* not reported).[68]

Table C. Summary of the evidence of the comparative effectiveness of insulin delivery and glucose monitoring devices (continued)

Outcome	Strength of evidence	# of studies	Main Findings
General quality of life	Low	2 (All RCTs)	One study found no difference in parental satisfaction between the two intervention arms—WHO-5 mother's well-being score 62.7±18.9 for rt-CGM versus 60.8±19 for SMBG at 12 months.[64] The other study assessed general quality of life using the SF-12 and found an improvement on the Physical Component Score favoring rt-CGM (55.5±4.9 for rt-CGM versus 54.1±6.9 for SMBG, *P*=0.03) but no difference between the intervention groups on the Mental Component Score (48.4±10.1 for rt-CGM versus 48.7±9.6 for SMBG, *P*=0.35) at 26 weeks.[71]
Diabetes-specific quality of life	Low	2 (All RCTs)	There was no difference in diabetes-specific quality of life between the rt-CGM and SMBG intervention arms in either study—PAID score 18.1±14.1 for rt-CGM versus 18.2±14.6 for SMBG at 26 weeks (*P*=0.50)[71] and mean difference DQOL score from baseline to followup 2.3±5.3 for rt-CGM versus 0.7±4.1 for SMBG.[63]
Diabetes treatment-related quality of life	Insufficient	1 (RCT)	There was a lower fear of hypoglycemia favoring rt-CGM (33.3±11.5 for rt-CGM versus 36.0±15.6 for SMBG, *P*=0.04).[71]
rt-CGM + CSII (Sensor-Augmented Pump) Versus MDI/SMBG			
HbA_{1c}	Moderate	3 (All RCTs)	Mean between-group difference in how HbA_{1c} changed was -0.61%, favoring sensor-augmented pump over MDI/SMBG (95% CI, -0.75 to -0.46, *P*<0.001).
Non-severe hypoglycemia	Low	1 (RCT)	There was no difference in time spent with non-severe hypoglycemia between the SAP and MDI/SMBG intervention groups.
Severe hypoglycemia	Low	3 (All RCTs)	There was no difference in severe hypoglycemia incidence between the SAP and MDI/SMBG intervention groups—21/247 for sensor-augmented pump versus 17/248 for MDI /SMBG (*P*=0.58);[72] 0 events for sensor-augmented pump versus 3 events for MDI/SMBG;[73] and 0 events in eight patients in sensor-augmented pump group versus 1 event in eight patients in the MDI/SMBG group.[74]
Hyperglycemia	Low	1 (RCT)	Time spent with hyperglycemia was significantly less in the sensor-augmented pump compared with the MDI/SMBG intervention group (*P*<0.001).
Weight	Low	2 (All RCTs)	There was a non-significant difference in weight gain between the sensor-augmented pump and MDI/SMBG intervention groups favoring MDI/SMBG (2.4 kg versus 1.8 kg; *P*=0.19) in one study.[72] In another study, weight increased 0.7 kg in the sensor-augmented pump group and 2.0 kg in the MDI/SMBG group but the difference was not significant (*P*=0.31).
Diabetes treatment-related quality of life	Insufficient	1 (RCT)	User acceptance and overall diabetes treatment satisfaction were greater in the sensor-augmented pump arm compared with the MDI/SMBG arm. Blood Glucose Monitoring System Rating Questionnaire scores were 83.3±21.7 for sensor-augmented pump versus 33.3±22.6 for MDI/SMBG (*P*<0.001).[73]

BMI-SDS = body mass index standard deviation score; CI = confidence interval; CSII = continuous subcutaneous insulin infusions; DQOL=Diabetes Quality of Life; DQOLCTQ=Diabetes Quality of Life Clinical Trials Questionnaire; DQOL-Y=Diabetes Quality of Life—Youth; DTSQ=Diabetes-Treatment Satisfaction Questionnaire; HbA1c = hemoglobin A1c; MCS = Mental Component Score; MDI = multiple daily injections; mg/dL = milligrams per deciliter; NICU = neonatal intensive care unit; NS=Non-significant; OBS=observational study; PAID=Problem Areas in Diabetes; PedsQOL=Pediatric Quality of Life Inventory; PCS = Physical Component Score; RCTs = randomized controlled trials; RR = relative risk; rt-CGM = real-time continuous glucose monitors; SF-12 = Short Form-12; SMBG = self monitoring of blood glucose; WHO-5=World Health Organization-5 form

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Introduction

Burden of Diabetes and Its Classification

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia resulting from: defects in insulin secretion from the pancreatic beta cells; resistance to insulin action at the level of skeletal muscle, liver, and fat; or both. The resultant hyperglycemia, if untreated, can lead to long-term complications, including microvascular complications (i.e., retinopathy, nephropathy, and peripheral and autonomic neuropathy) and macrovascular complications (i.e., coronary heart disease, cerebrovascular disease, and peripheral arterial disease).[1] The prevalence of diagnosed diabetes in the United States is currently 7.7 percent and is expected to increase to nearly 10 percent by 2050, at which time an estimated 39 million people will have diabetes in the United States.[2-4] Thus, a large segment of the population requires glucose-lowering therapies to maintain normal glucose levels (normoglycemia) and prevent diabetes complications.

Type 1 Diabetes Mellitus

Type 1 diabetes, which accounts for 5 to 10 percent of all diabetes cases, is characterized by autoimmune destruction of pancreatic islet cells that results in an inability to produce insulin and a need for daily insulin administration to sustain life.[1] Individuals with type 1 diabetes require insulin to prevent life-threatening ketosis, to maintain normoglycemia without inducing significant hypoglycemia, and to maintain normal body weight and promote normal growth and development in children.[1]

Type 2 Diabetes Mellitus

Type 2 diabetes is the result of a combination of insulin resistance and impaired insulin secretion by the beta cells of the endocrine pancreas.[1] Typically, insulin resistance predominates early, and insulin secretion decreases over time. However, the relative contribution of each of these factors to the disease course varies by patient. Eventually, the impairment in insulin resulting from beta cell dysfunction can lead to insulin deficiency, necessitating insulin therapy. Type 2 diabetes accounts for 90 to 95 percent of diabetes cases in the United States.[1]

Diabetes Mellitus in Pregnancy

In pregnant women with pre-existing type 1 or type 2 diabetes, poor glycemic control is associated with poorer pregnancy outcomes. Hyperglycemia early in pregnancy is associated with fetal anomalies, and hyperglycemia later in pregnancy can be associated with macrosomia, delivery complications, stillbirth, and neonatal hypoglycemia.

Importance of Tight Glycemic Control and Associated Risks in Diabetes

Tight glycemic control with intensive insulin therapy has been shown to reduce the risk of the microvascular and macrovascular complications of diabetes.[5-8]Throughout the duration of pregnancy, tight glycemic control is recommended to avoid maternal, fetal, and neonatal complications.[9]

While tight glycemic control lowers the risk of diabetic complications, it is not without risks. Intensive insulin therapy is associated with an increased risk of hypoglycemia, which can lead to compromised quality of life.[7] Severe hypoglycemia, which can be life threatening, is defined as an episode that requires another person to assist in treatment to resolve symptoms. Non-severe hypoglycemia may be symptomatic, but individuals are able to correct it without assistance from others. Both types of hypoglycemic episodes can be a source of significant distress and anxiety to patients and a barrier to achieving tight glycemic control. With long-standing diabetes complicated by recurrent hypoglycemia, unawareness of hypoglycemia can result, putting patients at risk for severe hypoglycemic episodes.[84] Finally, intensive insulin therapy can also lead to weight gain, due to more efficient fuel utilization and/or overtreatment of hypoglycemic episodes.[10 11]

Measurement of Glycemic Control

Measurement of glycosylated hemoglobin, specifically hemoglobin A_{1c} (HbA_{1c}), is the preferred method of assessing long-term glycemic control over the previous 2 to 3 months in patients with type 1 and type 2 diabetes.[12] Fasting and 2-hour post-prandial blood glucose levels are also measured and their results can assist patients and their physicians in making short-term adjustments in insulin therapy; however, these measures are more variable.[13] In pregnant women with diabetes, clinical management decisions are made on a weekly basis based on fasting and post-prandial glucose levels, as opposed to measuring HbA_{1c} every 3 months, because they provide the more rapid feedback on glycemic control needed to prevent fetal complications.[14]

Methods To Achieve Tight Glycemic Control and Minimize Risk: Advances in Insulin Delivery (Conventional vs. Intensive Insulin Therapy)

Insulin therapy has evolved over the last 25 years to more closely mimic normal pancreatic physiology. In the past, conventional insulin therapy consisted of one to two injections of intermediate-acting insulin mixed with short-acting insulin before breakfast and dinner. Because of the pharmacokinetics of these older insulins, tight control was difficult to achieve and often was accompanied by significant hypoglycemia due to their prolonged duration of action. This difficulty led to the development of more physiological basal and meal-time (prandial) insulins that, when used together, mimic normal pancreatic function (peakless basal insulin secretion, rapid release of insulin in response to meals, and rapid resolution of the prandial insulin peak). In addition, the development of continuous subcutaneous insulin infusion (CSII) via a pump provided another means to deliver insulin in a more physiological manner. Thus today, intensive

insulin therapy is delivered as at least three daily insulin injections (i.e., multiple daily injections, or MDI) or by the use of the external CSII.

Methods To Achieve Tight Glycemic Control and Minimize Risk: Advances in Glucose Monitoring

Self-Monitoring of Blood Glucose

Following publication of the Diabetes Control and Complications Trial, self-monitoring of blood glucose (SMBG) by fingerstick replaced the assessment of glucose by urine dipstick to allow more specific and timely feedback on the degree of hyperglycemia.[10] SMBG is the most widely used technique, whereby patients check their blood glucose with fingersticks. This allows patients to evaluate their individual response to therapy and assess whether blood sugar targets have been achieved. SMBG is accepted as part of effective diabetes treatment and has been shown to be effective, especially for patients who are being treated with insulin injection or pump therapy.[12] This type of self-monitoring is also useful for patients who may not be on insulin therapy as a guide to adjust therapy, but there are fewer data on this population. In patients with type 2 diabetes, Welschen and colleagues found a 0.4 percent reduction of hemoglobin A_{1c} (HbA_{1c}) with SMBG usage when compared with no usage.[85] As patients also were receiving diet, exercise, and health education in addition to medications, it is not entirely clear that the effect was due to use of SMBG.[85] The challenge of this technique is associated pain that affects adherence to this technique and is a barrier to tight glycemic control. Therefore, continuous glucose monitoring (CGM) systems have been developed in recent years.

Continuous Glucose Monitoring System: Retrospective and Real-Time

A CGM system is a device that records blood sugar levels throughout the day and night with a significantly decreased need for fingerstick measurements. Real-time continuous glucose monitoring (rt-CGM) was first approved by the US Food and Drug Administration in 2005. This equipment consists of a transcutaneous glucose sensor that is connected to a transmitter and receiver. CGM systems can be used in real time, retrospectively, and prospectively.[86] Some show graphical representation of glucose levels, and some have adjustable alarms for alerts of high and low glucose values. Sensor-augmented pumps are also available that combine CGM technology with CSII.[87] A CGM system, in conjunction with intensive insulin treatment, can be a useful tool to lower blood glucose values in adults who are at least 25 years of age and have type 1 diabetes. Success in lowering blood glucose levels depends on adherence to ongoing use of the device.[15] These devices are useful in detecting fluctuating blood sugars and trends in changing blood sugars, which are important in adjusting medications. Technologies for these devices are continuously improving.

rt-CGM differs from retrospective CGM in that it provides blood glucose feedback data to the patient while he or she is wearing the device and does not need to be downloaded and evaluated after data collection. This advantage of rt-CGM has resulted in it being the preferred method of CGM in the clinical setting. As a result, the focus of our review will be on studies examining rt-CGM.

Knowledge Gaps: Comparative Effectiveness of Insulin Delivery and Glucose Monitoring in Specific Diabetic Populations

Type 1 Diabetes Mellitus

Comparison of MDI with CSII. The majority of the evidence from comparisons of MDI with CSII in patients with type 1 diabetes indicates improved glycemic control with CSII use in adults, although its impact on other clinical outcome measures are unclear.[16 17] In children with type 1 diabetes, the benefit of CSII for glycemic control and clinical outcomes has not been established. Thus, there is still uncertainty regarding the benefit of CSII in the very young with type 1 diabetes. Another population in whom the benefits of CSII are unclear is older patients with type 1 diabetes. In all of these populations, CSII may be associated with uncontrolled hyperglycemia because of device malfunction and the potential risk of local infection at the catheter site. The benefits and risks of intensive insulin therapy with CSII, therefore, have not clearly been established, though they are crucial in determining the cost-effectiveness of this expensive technology. Because prior meta-analyses and systematic reviews have included studies using regular insulin, they have not been able to determine the comparative effectiveness of MDI with CSII using currently available rapid-acting insulin analogs.

Comparison of SMBG with rt-CGM. Studies have given conflicting reports of the effects of rt-CGM on glycemic control, hypoglycemia frequency, or other clinically relevant outcomes in individuals with type 1 diabetes. To gain a better understanding of the potential added utility of this new technology and determine its cost-effectiveness, clinicians need a synthesis of studies, ideally taking into consideration relevant factors such as the age of the patient, the effect of adherence to rt-CGM on potential benefits, and the potential interaction with the mode of insulin delivery (CSII versus MDI).

rt-CGM can be combined with CSII in the form of a sensor-augmented pump. To our knowledge, there has not been a systematic review comparing sensor-augmented pump therapy (CSII + rt-CGM) with intensive insulin therapy (CSII or MDI) and SMBG.

Type 2 Diabetes Mellitus

Comparison of MDI with CSII. While the literature suggests that CSII with the insulin pump, when compared with MDI, lowers HbA_{1c} more in individuals with type 1 diabetes, the comparative effectiveness of CSII and MDI has not been assessed systematically in patients with type 2 diabetes.[16] While some studies suggest that CSII is comparable with MDI in attaining adequate glycemic control, other studies found a lower HbA_{1c} level with CSII than with MDI.[16 18-21]

Comparison of SMBG with rt-CGM. To our knowledge, a systematic review of the comparative effectiveness of rt-CGM and SMBG and sensor-augmented pumps and intensive insulin therapy with SMBG on glycemic control, hypoglycemia frequency, and other clinically relevant outcomes has not been performed in individuals with type 2 diabetes.

Diabetes in Pregnancy

Comparison of MDI with CSII. We found one systematic review of randomized controlled trials (RCTs) published in 2007 that compared CSII with MDI in pregnant women who had pre-existing type 1 or type 2 diabetes.[22] The resulting review included only 60 women with 61 pregnancies. Mean birth weight was greater with CSII than with MDI, which was not viewed by the authors as clinically significant. There were insufficient data to permit conclusions about other outcomes, such as perinatal mortality, major and minor fetal anomalies, hypoglycemia, hyperglycemia, and admission to the neonatal intensive care unit for treatment of hypoglycemia. It is, therefore, important to provide an updated synthesis of the literature in this area.

The evidence base for the comparison of MDI with CSII in pregnant women with pre-existing type 2 diabetes is small and has not been evaluated by a systematic review. This topic is increasingly important as the prevalence of type 2 diabetes has been increasing dramatically in younger populations, including women of child-bearing age.

Comparison of SMBG with rt-CGM. rt-CGM and sensor-augmented pumps are new technologies whose benefits have not been clearly established in pregnant women with pre-existing type 1 or type 2 diabetes, although the theoretical utility of this tool in improving neonatal outcomes is great. A systematic review of the literature is required to assess the quality and completeness of the current knowledge base.

Scope of the Review

Our systematic review will help to address the clinically relevant question of whether the mode of intensive insulin therapy (MDI versus CSII) has a differential effect on outcomes in individuals with type 1 diabetes, type 2 diabetes, or pre-existing diabetes in pregnancy. We will also determine whether these outcomes differ by the type of strategy used for blood glucose monitoring (SMBG versus rt-CGM) in those same populations. Finally, based on the studies available in the literature, we will attempt to determine if there is an interaction between types of intensive insulin-delivery methods and blood glucose-monitoring systems on our outcomes of interest. As these effects may differ by age, we will stratify available data by the age of the study populations. Answers to these questions will facilitate clinical decision making regarding appropriate modes of insulin delivery and glucose monitoring for various populations of individuals with diabetes so that therapeutic options can be selected that result in improved outcomes.

Key Questions

Our final Key Questions (KQ), listed below, are displayed in Figure 1.

KQ1: In patients receiving intensive insulin therapy, does mode of delivery (MDI versus CSII) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus? (Process measures, intermediate outcomes, and clinical outcomes of interest are summarized below in Table 1.) Do these effects differ by:

a. Type 1 or type 2 diabetes status?

b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?

KQ2: In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM versus SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes (see Table 1) in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients already using intensive insulin therapy)? Do these effects differ by:

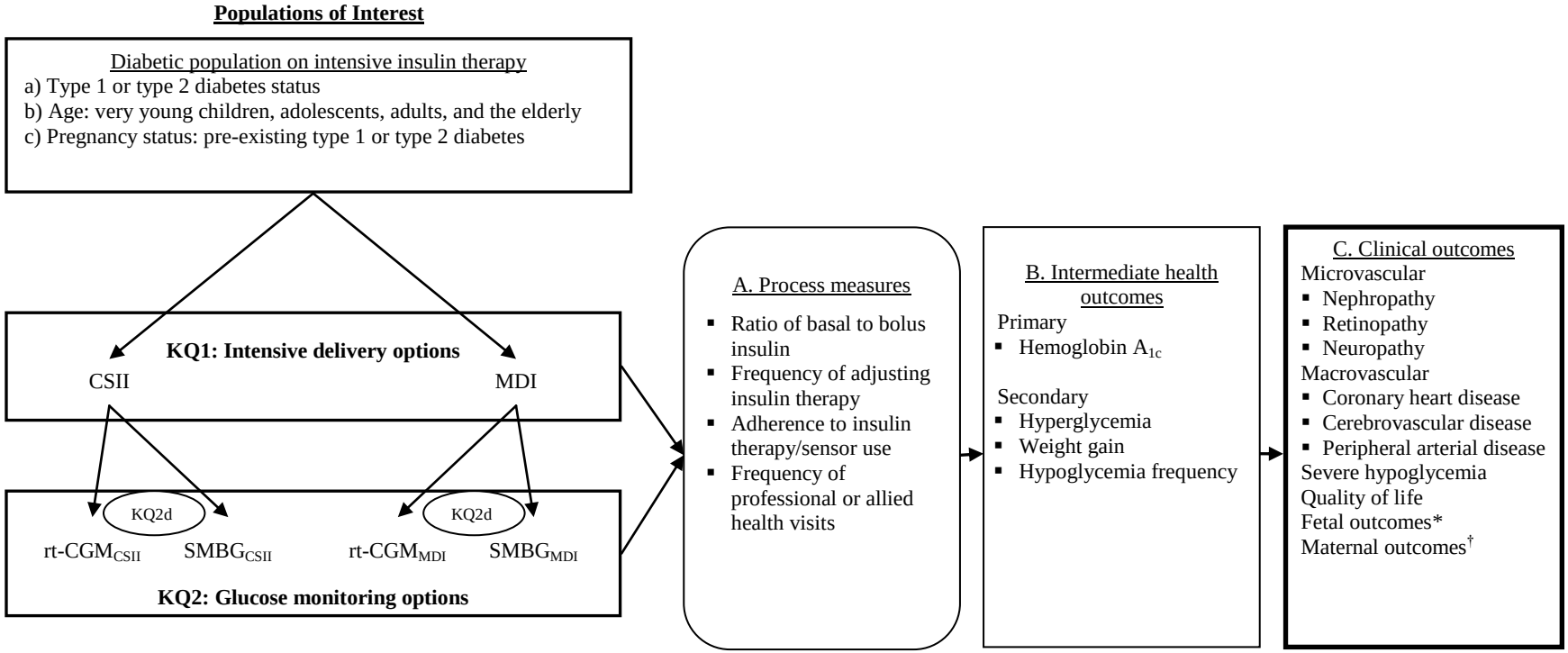
a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?
d. Intensive insulin delivery: MDI or CSII?

Table 1. Summary of process measures, intermediate outcomes, and clinical outcomes relevant to studies of intensive insulin therapy and continuous glucose monitoring

Process Measures	Intermediate Outcomes	Clinical Outcomes
Ratio of basal to bolus insulin	Primary	Microvascular*
Frequency of adjusting insulin therapy	Hemoglobin A_{1c}	Nephropathy
		Retinopathy
Adherence to insulin therapy/sensor use	Secondary	Neuropathy
	Hyperglycemia	
Frequency of professional or allied health visits	Weight gain	Macrovascular*
	Hypoglycemia frequency	Coronary heart disease
		Cerebrovascular disease
		Peripheral arterial disease
		Severe hypoglycemia
		Quality of life
		Fetal outcomes†
		Maternal pregnancy outcomes
		C-section rates

*We only included objective assessments of microvascular and macrovascular outcomes (i.e., we will be excluded patient self-reported microvascular and macrovascular outcomes).
†Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit.

Figure 1. Analytic framework for multiple daily injections or insulin pump therapy with or without continuous glucose monitoring for diabetes



Abbreviations: CSII = continuous subcutaneous insulin infusion; KQ = key question; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose.
Stratifications of interest for KQ2: diabetes status (2a), age (2b), pregnancy status (2c), and glucose monitoring strategy (2d)
*Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, and admission to a neonatal intensive care unit.
†Maternal outcomes include cesarean section rates.

Methods

This topic was nominated via the Agency for Healthcare Research and Quality's (AHRQ) website. Our Evidence-based Practice Center (EPC) established a team and a work plan to develop the evidence report. The project involved recruiting key informants, formulating and refining the questions, developing a protocol, recruiting technical experts, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review.

Topic Development

The topic for this report was nominated in a public process. At the beginning of the project, we recruited a panel of key informants to give input on key steps including the selection and refinement of the questions to be examined. The key informants included an internal expert from the Johns Hopkins University with expertise in diabetes management, and external experts, including a pediatric endocrinologist, an internist, and an obstetrician-gynecologist and perinatal epidemiologist. Our draft Key Questions were posted on AHRQ's website for public comment in October 2010.

With the key informants, representatives of AHRQ, and public comments, we developed the Key Questions that are presented in the Scope and Key Questions section of the Introduction. The final Key Questions focus on the comparative effectiveness and safety of insulin delivery (i.e., CSII versus MDI) and glucose monitoring (i.e., rt-CGM versus SMBG) methods in patients with diabetes mellitus, and how these effects may differ by type of diabetes (i.e., type 1 diabetes or type 2 diabetes), age (i.e., very young children, adolescents, adults, and elderly), and pregnancy status (i.e., pregnant women with pre-existing type 1 or type 2 diabetes).

Search Strategy

We searched the following databases for primary studies for the periods in parentheses: MEDLINE® (1966 to October 2010), EMBASE® (1974 to October 2010), and the Cochrane Central Register of Controlled Trials (1966 to October 2010). We developed a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori (Appendix A).

The results of the searches were downloaded and imported into ProCite® version 5 (ISI ResearchSoft, Carlsbad, CA). We scanned for exact article duplicates, author/title duplicates, and title duplicates using the duplication check feature in ProCite®. From ProCite, the articles were uploaded to DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a web-based software package developed for systematic review data management. This database was used to track the search results at the levels of title review, abstract review, article inclusion/exclusion, and data abstraction.

Study Selection

Two independent reviewers conducted title scans in parallel. For a title to be eliminated at this level, both reviewers had to indicate that it was ineligible. If they disagreed, the article was

promoted to the next level (Appendix B, Title Review Form). The title review was designed to capture as many studies as possible that reported on the efficacy or safety of insulin delivery or glucose monitoring methods.

Abstracts were reviewed independently by two investigators, and were excluded if both investigators agreed that the article met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 2 and the Abstract Review Form in Appendix B). Differences between investigators regarding abstract eligibility were resolved through consensus adjudication.

Articles promoted on the basis of abstract review underwent another independent parallel review to determine if they should be included for data abstraction (Appendix B, Article Review Form). Differences regarding article inclusion were resolved through consensus adjudication.

Data Abstraction

We used a systematic approach to extract all data to minimize the risk of bias in this process. We created and pilot tested standardized forms for data extraction. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

Each article underwent double review by the study investigators for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. Reviewers were not masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

For all articles, the reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, gender, race, baseline HbA_{1c}, weight, type of diabetes, duration of diabetes), eligibility criteria, interventions (including device model, type of insulin, MDI schedule, rt-CGM alarm threshold, length of use of current technology, changes in the type of insulin used, and training of patients/staff), adherence to wearing a treatment device, outcome measures, definitions, and the results of each outcome, including measures of variability. For the outcome of hypoglycemia, we differentiated between biochemical and symptomatic hypoglycemia. For the outcome of cesarean delivery, we abstracted information regarding the indication for cesarean delivery. For studies evaluating maternal and fetal outcomes, we abstracted information about when CSII or MDI was initiated in relation to the pregnancy (i.e., prenatal, 1st trimester, or 2nd trimester).

For this report, we classified quality of life measures into the following categories: general health-related quality of life (global, non-specific measures), disease-specific quality of life (quality of life and health status associated with diabetes) and treatment-specific quality of life (associated with carrying out treatment for diabetes). In each category we included only studies which used validated measures.

All information from the article review process was entered into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada) by the individual completing the review. Reviewers entered comments into the system whenever applicable. The DistillerSR database was used to maintain the data and to create detailed evidence tables and summary tables.

Table 2. Inclusion and exclusion criteria

Population and condition of interest	• All studies included human subjects exclusively.
	• We included studies of adults, adolescents, and children with a formal diagnosis of diabetes mellitus and pregnant women with pre-existing diabetes.
	  ○ Acceptable diagnoses included type 1 diabetes and type 2 diabetes. Patients with latent autoimmune or pancreatomy were considered to have type 1 diabetes. Those with steroid-induced or transplant-induced diabetes were considered to have type 2 diabetes.
	  ○ We excluded pregnant women with gestational diabetes. Patients with maturity onset diabetes of the young were excluded as the diagnosis is difficult to make without genetic testing and intensive insulin therapy is often not required.

Interventions	• We included studies that evaluated CSII and rt-CGM.
	  ○ We excluded implantable insulin pumps and retrospective CGM devices, as these are no longer used clinically.
	  ○ We excluded studies in which regular insulin was used in the insulin pump.
	  ○ We excluded studies evaluating the GlucoWatch CGM, as it is no longer used in the US.

Comparisons of interest	• We included studies that compared CSII with MDI, which was defined as at least three injections per day. • We included studies that compared rt-CGM with SMBG, which was defined as at least three fingersticks per day. • We excluded studies of premixed insulin, because patients who use a premixed insulin are rarely considered for intensive insulin therapy with CSII. • We excluded studies that do not have a concurrent comparison group.

Outcomes	• We included studies that evaluate one of the following outcomes:
	  ○ Process measures
	  ▪ Ratio of basal to bolus insulin*
	  ▪ Frequency of adjusting insulin therapy
	  ▪ Adherence to insulin therapy/sensor use
	  ▪ Frequency of professional or allied health visits
	  ○ Intermediate outcomes
	  ▪ HbA_{1c}
	  ▪ Hyperglycemia
	  ▪ Weight gain
	  ▪ Hypoglycemia frequency
	  ○ Clinical outcomes
	  ▪ Objective assessments of microvascular outcomes (nephropathy, retinopathy, and neuropathy)
	  ▪ Objective assessments of macrovascular outcomes (coronary heart disease, cerebrovascular disease, and peripheral arterial disease)
	  ▪ Severe hypoglycemia
	  ▪ Quality of life (validated measures)
	  ▪ Fetal outcomes (gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, admission to a neonatal intensive care unit)
	  ▪ Maternal pregnancy outcomes (cesarean section rates)

Type of study	• We excluded articles with no original data (reviews, editorials, and commentaries) or studies published in abstract form only. • We excluded case reports, case series, and cross-sectional studies. • We included both randomized controlled trials and observational studies that evaluated microvascular, macrovascular, maternal, or fetal outcomes. For all other outcomes, we included only randomized controlled trials. • We did not place any restrictions on sample size or language. • Because we excluded studies of outdated technologies, we excluded studies published before 1994, the 1st year that insulin analogues were used.
Timing and setting	• We excluded studies in which patients used an insulin delivery or glucose monitoring device for less than 24 hours. • We excluded studies that were not conducted in an outpatient setting.

CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitoring

*The optimal distribution of the total daily insulin dose is 40-50% administered as basal insulin and the remaining 50-60% as bolus insulin divided over each meal. This prevents patients from being over-insulinized with basal insulin, increasing risk for hypoglycemia.

Quality Assessment

We used different quality assessment tools for RCTs and observational studies. For RCTs, the dual, independent review of article quality was based on the Cochrane Collaboration's Risk of Bias Tool[23] and supplemented with items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[24] The quality assessment for RCTs included items on (1) adequate allocation sequence generation, (2) adequate allocation concealment, (3) blinding, (4) incomplete outcome data, (5) pharmaceutical support, (6) company involvement in the design, conduct, or reporting of the study, (7) loss to followup, and (8) an overall rating of the quality assessment. The overall study quality was assessed as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.[24]

For observational studies, we selected items from the Downs and Black quality checklist[25] and supplemented with items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[24] Observational studies were assessed on: (1) clear description of the setting, (2) clear description of inclusion/exclusion criteria, (3) clear description of key characteristics on the enrolled subjects, (4) recruitment of the different intervention groups from the same population, (5) adequate adjustment for confounding, (6) description of loss to followup, and (7) overall study quality.

Both the primary and secondary reviewers' responses are presented in the appendix. We used our study quality assessment to help us understand differences in results between studies.

Applicability

We assessed the applicability of studies in terms of the degree to which the study population (age, race, sex, and baseline HbA_{1c}), interventions (titration schedule), outcomes, and settings (followup interval) were typical for the treatment of individuals with diabetes who are receiving treatment in a usual care setting. We limited the interventions in the review to those that are most applicable to the current population of patients with diabetes (i.e., those interventions that are currently used in the US population).

Data Analysis and Synthesis

For each Key Question, we created a set of detailed evidence tables containing all information extracted from eligible studies. We conducted meta-analyses when there were sufficient data (at least three trials) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and insulin delivery device).

For continuous outcomes, we calculated a weighted mean difference by using a random-effects model with the DerSimonian and Laird formula.[26] We recorded the mean difference in outcome between groups, along with its measure of dispersion. If this information was not reported, we calculated the point estimate of the mean difference in outcome using the mean difference from baseline for each group or the baseline and final values for each group. Measures of dispersion were derived using standard methods.[23]

We analyzed the outcome of severe hypoglycemia using two strategies. If studies reported the incidence of severe hypoglycemia (i.e., the number of patients who experienced severe hypoglycemia), then we calculated a pooled relative risk using the DerSimonian and Laird random effects model.[26] If studies reported event rates (i.e., the number of events experienced per patient during the study period), we calculated a rate ratio in terms of the number of events per person-year using the DerSimonian and Laird random effects model.[26]

Heterogeneity among the trials in all the meta-analyses was tested by using a standard chi-squared test with a significance level of alpha less than or equal to 0.10. Heterogeneity was also examined among trials by using an I2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[27] A value greater than 50 percent was considered to have substantial variability. If we found substantial heterogeneity, we attempted to determine reasons for this by conducting meta-regression analyses using baseline HbA_{1c} and compliance. For all meta-analyses, we conducted formal tests for publication bias using Begg's[28] and Eggers tests[29] including evaluation of the asymmetry of funnel plots for each comparison of interest. All meta-analyses were conducted using STATA (Intercooled, version 9.2, StataCorp, College Station, TX).

Studies not amenable to pooling were summarized qualitatively.

Data Entry and Quality Control

After a second reviewer reviewed the data that had been entered into DistillerSR, adjudicated data were re-submitted into web-based data collection forms by the second reviewer. Second reviewers were generally more experienced members of the research team. If problems were recognized in a reviewer's data abstraction, the problems were discussed at a meeting with the reviewers. In addition, research assistants used a system of random data checks to assure data abstraction accuracy.

Rating the Body of Evidence

At the completion of our review, we graded the strength of the evidence based on the quantity, quality, and consistency of the best available evidence, addressing Key Questions 1 and 2 by adapting an evidence grading scheme recommended in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[30] We applied evidence grades to the bodies of evidence

about each intervention comparison for each outcome. We assessed the risk of bias of individual studies according to study design characteristics, such as confounding and selection and information biases. We assessed the strength of the best available evidence by assessing the limitations to individual study quality (using individual quality scores), consistency directness, precision, publication bias, and the magnitude of the effect.

We classified evidence bodies pertaining to Key Questions 1 and 2, into four basic categories: (1) “high” grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (evidence is unavailable).

Results

Search Results

Figure 2 summarizes the search results. From our search, we retrieved 6378 unique records. After title and abstract review, 701 articles were deemed potentially relevant to review, and the full articles were retrieved (see Appendix C for the list of studies excluded). A total of 44 articles were included in this review.

Of the included studies, 29 studies compared the effects of MDI with CSII. Twelve of these studies were conducted in children or adolescents with type 1 diabetes, nine were conducted among adults with type 1 diabetes, four were conducted among adults with type 2 diabetes, and four were conducted among pregnant women with pre-existing type 1 or type 2 diabetes.

Eight studies compared the effects of rt-CGM with SMGB in children and adults with type 1 diabetes. We did not identify any studies comparing rt-CGM with SMBG among patients with type 2 diabetes or among pregnant women with pre-existing type 1 or type 2 diabetes.

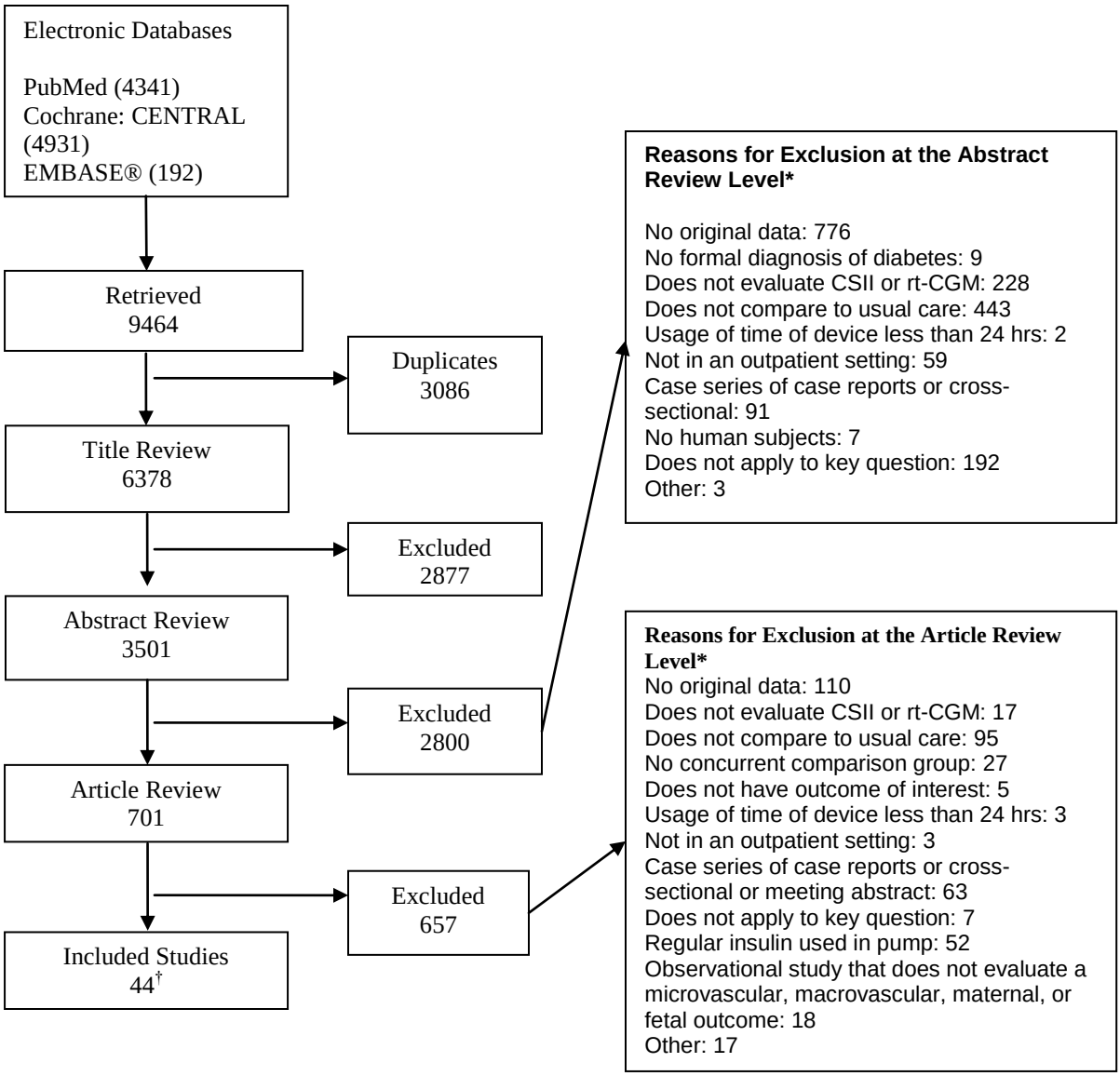
An additional three studies evaluated the effects of a sensor-augmented pump compared with MDI and SMBG.

Seventeen studies evaluated quality of life using 15 different validated quality of life assessment tools. Table 3 lists how the quality of life assessment tools were categorized into general quality of life, disease-specific quality of life, and treatment-specific quality of life.

Table 3. Quality of life assessment tools used in each category

General health-related quality of life	Diabetes-specific quality of life	Treatment-specific quality of life
• Pediatric Quality of Life Inventory • Short Form-36 (SF-36) • Short Form-12 (SF-12) • World Health Organization-5 Well Being Index (WHO-5)	• Diabetes Quality of Life (DQOL) • Diabetes Treatment Satisfaction Questionnaire (DTSQ) • Diabetes Quality of Life Clinical Trial Questionnaire (DQOLCTQ) • Diabetes Quality of Life – Youth (DQOL-Y) • Problem Areas in Diabetes (PAID)	• Altered Hypoglycemia Awareness Questionnaire • Blood Glucose Monitoring System Rating Questionnaire (BGMSRQ) • Hypoglycemia Fear Survey • Insulin Delivery System Rating Questionnaire (IDSRQ) • Phase V Outcomes system diabetes treatment satisfaction questionnaire • User Acceptance Questionnaire (UAQ)

Figure 2. Summary of the literature search



* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
†29 compared MDI to CSII (12 in children and adolescents with type 1 diabetes; 9 in adults with type 1 diabetes; 4 in adults with type 2 diabetes; 4 in pregnant women with pre-existing type 1diabetes); 8 compared rt-CGM with SMBG; 3 compared a sensor-augmented pump with MDI/SMBG
CENTRAL = Central Register of Controlled Trials; CSII = continuous subcutaneous insulin infusion; hrs = hours; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitor; SMBG = self-monitoring of blood glucose

Key Question 1: In patients receiving intensive insulin therapy, does mode of delivery (MDI versus CSII) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus?

Comparative Effectiveness of CSII versus MDI in Children and Adolescents with Type 1 Diabetes

Key Points and Evidence Grades

- The strength of the evidence was moderate comparing CSII with MDI for the outcome of HbA_{1c}. Mean between-group difference in how HbA_{1c} changed from baseline was -0.14% in RCTs, decreasing slightly more with CSII than with MDI (95% CI, -0.48 to 0.20%, *P*=0.63). Results were similar among adolescents over 12 years old (mean between-group difference, -0.10%; 95% CI, -0.47 to 0.27%).
- There was low strength of evidence to suggest no significant difference in daytime hypoglycemia frequency between MDI and CSII intervention groups (perceived hypoglycemic events: 1.7±0.4 for MDI versus 1.7±0.4 for CSII over 104 weeks;[31] blood sugar excursions below 70 mg/dL: 0.59±0.32 for MDI versus 1.52±0.49 over 24 weeks;[33] mean number of hypoglycemic episodes/patient/study period: 15.1±16.1 for MDI versus 11.4± 7.1 over 52 weeks[41]).
- There was low strength of evidence to suggest no significant difference in nocturnal hypoglycemia between the MDI and CSII intervention groups. In one study, there were 4 events/patient/study period (SD, 6.5) for MDI versus 3 events/patient/study period (SD, 3.5) over 52 weeks.[41] In the other study, there were 2 patients with 1 or more events in the CSII arm but no events reported in the MDI arm over 16 weeks.[40]
- The strength of the evidence comparing CSII with MDI was insufficient for mild hypoglycemia. One study found no significant difference in mild hypoglycemia (events with blood sugar less than 70 mg/dL) between the MDI (22 events/patient) and CSII (19.8 events/patient) intervention groups over 14 weeks.[42]
- There was moderate strength of evidence indicating similar rates of severe hypoglycemia between the two intervention arms. The mean incidence rate ratio for severe hypoglycemic event rates in RCTs for CSII versus MDI was 0.99 (95% CI, 0.57 to 1.71, *P*=0.37). Results were similar among adolescents over 12 years of age (mean incidence rate ratio for CSII versus MDI, 0.95; 95% CI, 0.42 to 2.13).
- The strength of evidence comparing CSII with MDI was insufficient for hyperglycemia. In one study there was no difference in the frequency of hyperglycemia between the MDI (6.7 events) and CSII (7.9 events) intervention groups over 14 weeks.[42]
- The strength of evidence comparing CSII with MDI was insufficient for the ratio of basal to bolus insulin. In one study there was no difference in the ratio of basal to bolus insulin between the MDI (45.6±5.2%) and CSII (47.3±5.3%) intervention groups.[35]

- There was low strength of evidence comparing CSII with MDI for weight change. Two studies found no difference in weight, measured as BMI-SDS, between the MDI and CSII intervention groups (BMI-SDS change +0.05 for MDI and -0.07 for CSII in one study[41] and less than 1 kg/m^2 BMI change between groups in the other[40]). Another study reported a slight but statistically significant increase in BMI-SDS during MDI therapy (BMI-SDS change +0.07) but non-significant change during CSII therapy (-0.05; *P*=0.01 for between group difference).[42]
- There was low strength of evidence comparing CSII with MDI for general quality of life. Two studies showed improvement in general quality of life favoring CSII—difference in Pediatric Quality of Life Inventory (PedsQOL) from baseline to follow-up 2.8±13.1 for CSII and 0.4±17.3 for MDI over 7 months in one study[32] and 8±17 for CSII and 6.5±33 for MDI over 6 months in another study.[33]
- There was low strength of evidence comparing CSII with MDI for diabetes-specific quality of life. Three studies showed improvement in diabetes treatment satisfaction favoring CSII—Diabetes Treatment Satisfaction Questionnaire (DTSQ_ at 24 months 33.1±0.9 in CSII versus 27.5±2.0 in MDI (*P*<0.001);[31] DTSQ baseline score 20.5±3.6 and after 6 months, 21.8±3.7 for MDI and 32±6.5 for CSII (*P*<0.05);[41] DTSQ baseline score 21.4±3.3 and after 3.5 months, 21.9±3.8 for MDI and 30.6±3.7 for CSII.[42] One showed improvement in diabetes quality of life favoring CSII (Diabetes Quality of Life-Youth (DQOL-Y) baseline score 77.4±16.1 and end of study 76.4±14.3 for MDI and 82.7±13 for CSII; *P*<0.05),[41] and one study did not find a difference in diabetes quality of life between the two interventions (numerical data not presented).[40]

Study Design

Twelve studies evaluated CSII versus MDI therapy in children and adolescents with type 1 diabetes (Appendix D, Table 1).[31-42] They were conducted in diverse countries, including the US,[33 40] Italy,[34 39] Sweden,[31] Spain,[35] Saudi Arabia,[36] Germany,[37] the Netherlands,[34 43] and Israel.[41 42] Studies varied in their sources of support—five received industry support,[31 37 40-42] four received government support,[31 32 35 40] and four received other sources of support.[31-33 41] Sources of support were not reported for four studies.[34 36 38 39]

Of the 12 studies, five were parallel arm RCTs,[31 33 34 40] three were randomized cross-over trials,[32 41 42] two were non-randomized trials,[35 36] one was a cohort study,[39] and two were case-control studies.[37 38] Four studies included a run-in period,[32 38 40 42] five did not,[31 34 37 39 41] and three studies did not report a run-in period.[33 35 36] Enrollment into three studies started and ended after 2000,[31 33 36] but most studies did not report the dates of enrollment period.[32 34 35 37-42] The median followup time for all studies was 52 weeks, with a range of 16 to 104 weeks for clinical trials and the a range 52 to 72 weeks for observational studies. One study did not report followup duration.[35] These studies screened 24,[42] 36,[34] 200,[35] and 665[37] patients and enrolled a median of 32 patients (range 16 to 72) into randomized clinical trials and a median of 56.8 (range 22 to 104) into observational studies. The number of patients screened was not reported for most studies.[31-33 36 38-41] Patients were being recruited from referral clinics in seven studies.[32-34 36 39-41]

The majority of studies excluded pregnant patients.[31-41] Some studies excluded patients based on HbA_{1c} greater than 11 percent,[40] or less than 6.5 percent,[40] 7.5 percent,[35] or 8 percent.[32 34 39] Patients were excluded from certain studies if they were being treated with insulin for less than 1

year[32] or less than 2 years,[42] were using regular insulin[38] or glargine insulin,[40] were not currently treated with intensive insulin therapy,[35 41] or had ever used insulin pump therapy.[40]

Population Characteristics

The mean age of participants in the randomized controlled trials was 16.5 years (range 4.4 to 18.9 years) and 11.4 years (range 4.4 to 17.9 years) in the MDI and CSII groups, respectively (see Appendix D, Table 2). The mean age of participants in the observational studies was 9.2 years (range 6.7 to 12.8 years) and 10.7 years (range 6.7 to 13.9 years) in the MDI and CSII groups, respectively. Age of participants was not reported for one study.[40] In the randomized controlled trials, males were 50 percent and 38 percent of the study populations, respectively, for the MDI and CSII groups and in observational studies, males were 41.7 percent and 38.9 percent of the study populations, respectively. The majority of studies did not report the racial composition of their study populations.[31 34-37 39 41 42] The majority of studies included Caucasian participants and one study report a very small number of African American and Hispanic participants.[40]

Glycemic control was sub-optimal in participants at the time of study enrollment. The mean HbA_{1c} in the randomized controlled trials was 8.5 percent and 8.6 percent in the MDI and CSII groups, respectively, and in the observational studies was 8.4 percent and 8.2 percent in the MDI and CSII groups, respectively. In the one study that reported baseline body mass index, the means in the MDI and CSII groups were 15.9 kg/m^{233} and 20.9 kg/m^{233} and 19.8 kg/m^{2}, respectively.[43] Weight and/or body mass index were reported as body mass index standard deviations in three studies[35 37 41] and were not reported in several studies.[36 38 39]

Interventions

The MDI arms varied across studies in the type of insulin used: neutral protamine Hagedorn (NPH) and aspart,[31] NPH and lispro,[33] NPH and regular insulin,[41] glargine and regular insulin,[34 42] glargine and lispro,[35 36] and glargine and aspart (see Appendix D, Table 3).[40] One study specified the basal insulin used in the MDI arm (glargine[39]) but did not specify the short-acting insulin used. Two studies specified the short-acting insulin used in the MDI arm but not the basal insulin.[32 38] The type of neither basal nor short-acting were specified in one study.[37] The MDI schedule was three injections daily in four studies,[32 33 35 37] four or more times daily in eight studies,[31 34 36 37 40-42 88] and not reported in one study.[38]

In the CSII arm, insulin aspart was used in three studies,[31 32 40] insulin lispro was used in nine studies,[33-36 38 39 41-43] and in one study, the type of short-acting insulin analog was not reported.[37] Five studies used the DR HTron v100,[31 32 35 38 39] two used the DR DTRON,[38 39] one used the Tayco Disetronic,[41] one used the Animas,[33] five used the MiniMed 508,[36 38-40 42] and one used the Medtronic MiniMed Paradigm 511 insulin pump.[40] In two studies, the type of insulin pump was not specified.[34 37] Four studies included training in insulin pump use prior to its initiation.[31 33 39 42]

Blood glucose was monitored using SMBG in four studies[32 38 40 42] and rt-CGM in one study.[33] The blood glucose monitoring approach was not reported in seven studies.[31 34-37 41 88] The duration of therapy in each intervention arm ranged from 3.5 to 24 months with nine studies having 12 or more months of follow up.[31 32 34-39 41] Six studies provided guidelines for insulin dose titration in the intervention arms[32 33 35 39 40 42] and in one study, insulin dose titration instructions were only provided for the CSII arm.[34] Only three studies reported their glycemic

targets—pre-prandial glucose of 70 to 140 mg/dL and 2-hour post-prandial glucose <180 mg/dL;[35] HbA_{1c} of 7 percent, pre-prandial glucose of 70 to 120 mg/dL and bedtime glucose of 90 to 150 mg/dL;[40] and pre-prandial glucose of 79.2 to 149.4 mg/dL.[42]

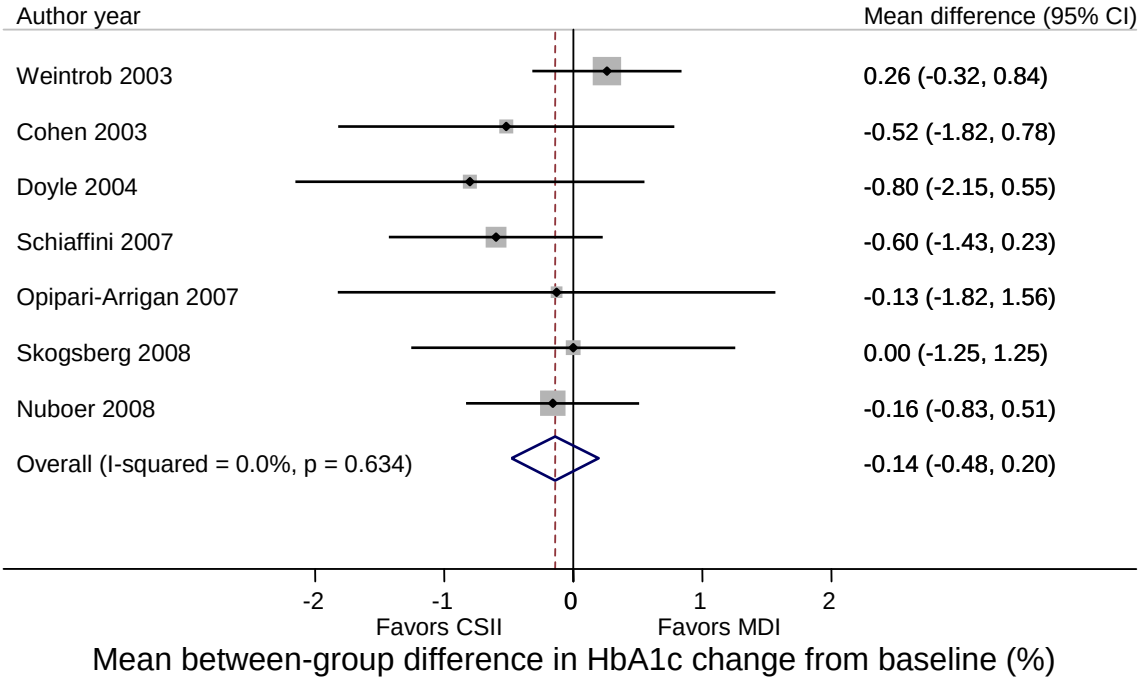
Outcomes

Details of the outcomes are reported in Appendix D, Table 4.

HbA_{1c}. Twelve studies examined the comparative effectiveness of CSII and MDI on HbA_{1c}. Four studies showed a significant reduction in HbA_{1c} favoring CSII[34 36 39 40] and one study found a significant difference in end of study HbA_{1c} between the MDI and CSII groups favoring CSII.[37] However, in this latter study, this was due to a rise in HbA_{1c} in the MDI group with the HbA_{1c} in the CSII group remaining relatively unchanged.[37] The remaining studies showed no difference in the change in HbA_{1c} between the CSII and MDI groups.[31-33 35 38 41-43]

A meta-analysis of seven RCTs showed a non-significant difference between the MDI and CSII intervention groups in how the HbA_{1c} changed from baseline after 16 or more weeks of following, decreasing slightly more with CSII than with MDI (combined mean between-group difference, -0.14; 95% CI, -0.48 to 0.20, *P*=0.63) (see Figure 3). We did not find evidence of statistical heterogeneity and no one study influenced results substantially. Egger's test (*P*=0.21) and funnel plot did not suggest publication bias.

Figure 3. Between-group difference between MDI and CSII in how HbA_{1c} changed from baseline among children and adolescents with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA1c = hemoglobin A1c; MDI = multiple daily injections

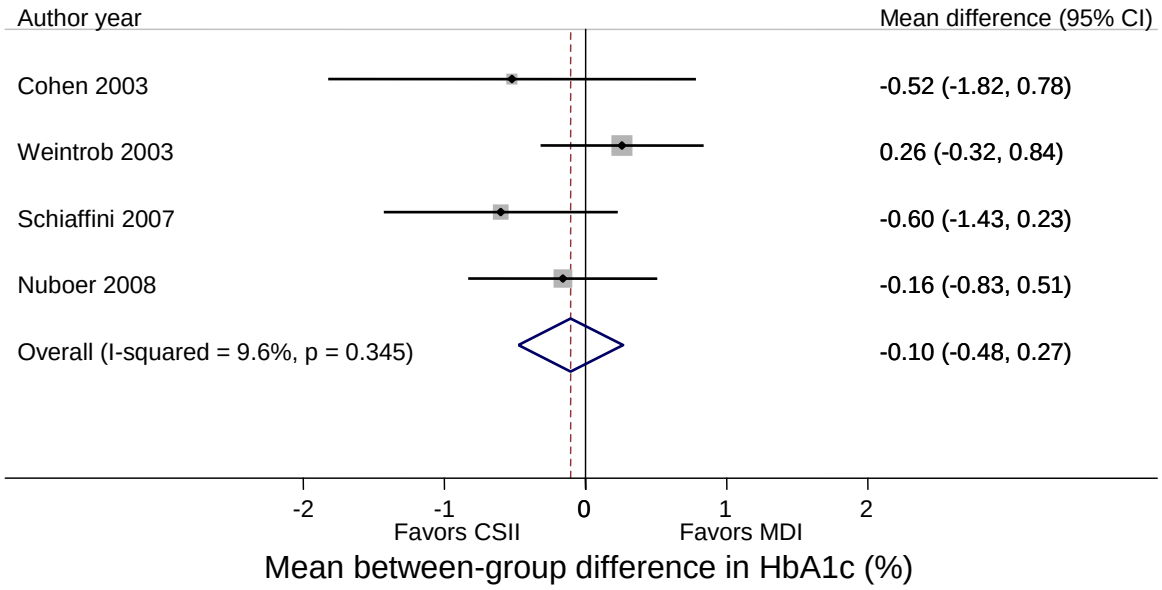
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q = 4.32 with 6 degrees of freedom (p = 0.63)

Studies in children 12 years of age or less. Two studies focused primarily on the comparative effectiveness of MDI and CSII in children whose mean age was 12 years or less based on age at diagnosis and diabetes duration.[31 33] One study showed a non-significant reduction in HbA_{1c} favoring CSII[33] while the other study found no difference in HbA_{1c} between the two groups.[31] There were too few studies to perform a meta-analysis.

Studies in adolescents (greater than 12 years of age). Four studies focused on the comparative effectiveness of MDI and CSII in adolescents whose mean age was over 12 years based on age at diagnosis and diabetes duration. In those studies, three showed a non-significant reduction in HbA_{1c} favoring CSII[32 34 41] while one study found a non-significant reduction in HbA_{1c} favoring MDI.[42] A meta-analysis of these studies showed a non-significant difference in the change from baseline HbA_{1c} between the MDI and CSII intervention groups favoring CSII (combined mean between-group difference in the change from baseline HbA_{1c}, -0.10%; 95% CI, -0.47 to 0.27%) (see Figure 4). We did not find evidence of statistical heterogeneity and no one study influenced results substantially. There were too few studies to adequately assess for publication bias, although the funnel plot suggested publication of more studies favoring CSII. One study did not report the age of participants.[40]

Figure 4. Between-group difference between MDI and CSII in how HbA_{1c} changed from baseline among adolescents with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA1c = hemoglobin A1c; MDI = multiple daily injections
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 3.32 with 3 degrees of freedom (p = 0.35)

Daytime and nocturnal hypoglycemia. Three studies examined the comparative effectiveness of CSII and MDI on daytime hypoglycemia. Hypoglycemia was defined as perceived

hypoglycemia,[31] blood sugar excursions below 70 mg/dL,[33] and mean number of hypoglycemia episodes/patient/study period.[41] There was no significant difference in daytime hypoglycemia frequency between the two groups.[31 33 41] Two studies examined the comparative effectiveness of CSII and MDI on nocturnal hypoglycemia and found no significant differences between the two groups.[40 41]

Mild hypoglycemia. One study examined the frequency of mild hypoglycemia in the MDI and CSII interventions groups[42] and found significantly fewer episodes (defined as blood sugar below 70 mg/dL) in the CSII group compared with the MDI group.[42]

Severe hypoglycemia. Nine studies examined the frequency of severe hypoglycemia in the MDI and CSII intervention groups. The definitions of hypoglycemia used in studies varied (see Table 4). While one study found a significantly lower frequency of severe hypoglycemia in the CSII group compared with the MDI group,[42] seven studies found no difference in frequency between the two groups.[33-35 37 39-41]

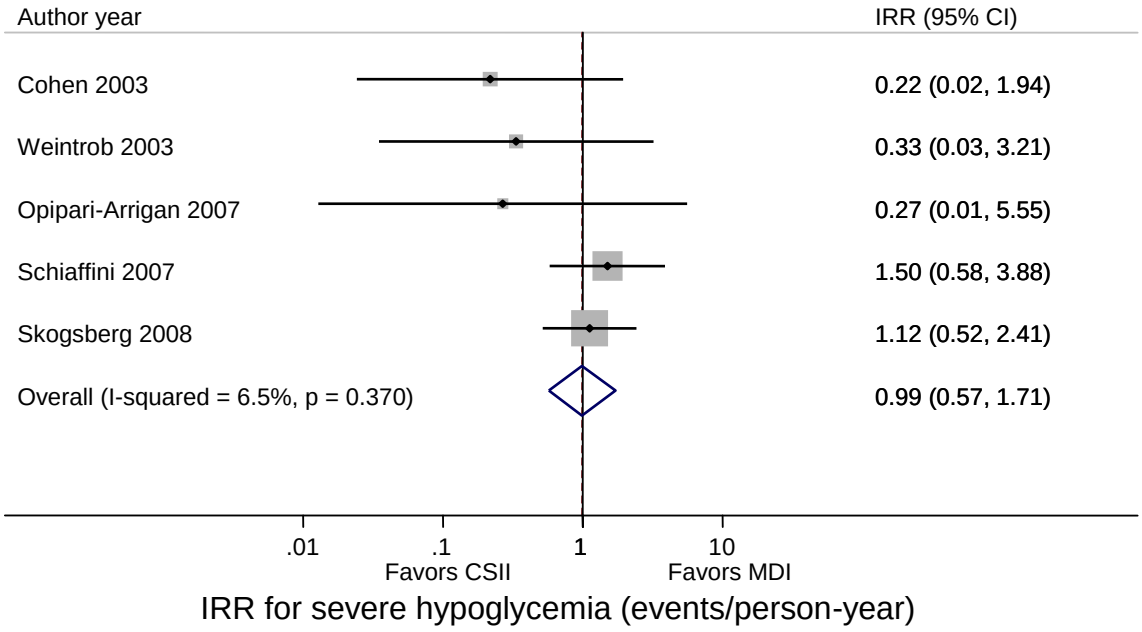
Table 4. Definitions of severe hypoglycemia in the studies of children and adolescents with type 1 diabetes

Author, year	Severe hypoglycemia definition
Opipari-Arrigan, 2007[33]	Seizure, obtundation, or combativeness preventing administration of oral glucose in association with a capillary blood glucose of less than 100 mg/dL
Schiaffini, 2007[34]	Hypoglycemic event requiring assistance from another person, infusion of glucose or resulting in severe symptoms, such as seizure or coma
Garcia-Garcia, 2007[35]	Hypoglycemia requiring parental treatment
Kordonouri, 2006[37]	As defined by the Diabetes Control and Complications Trial
Schiaffini, 2005[39]	Blood glucose values below 50 mg/dL requiring assistance from another person, infusion of glucose or resulting in severe manifestations, such as seizure or coma
Doyle, 2004[40]	Event resulting in coma or seizure
Pozzilli, 2003[43]	Not explicitly defined
Cohen, 2003[41]	Not explicitly defined
Weintrob, 2003[42]	Event requiring assistance from another person or resulting in a seizure/coma

mg/dL – milligrams per deciliter

A meta-analysis of five RCTs did not find a significant difference in severe hypoglycemia event rates between the two intervention arms (combined mean incidence rate ratio for CSII versus MDI, 0.99; 95% CI, 0.57 to 1.71, P=0.37) (see Figure 5). We did not find evidence of statistical heterogeneity and no one study influenced results substantially, Egger's test (P=0.04) and the funnel plot suggested publication bias of studies showing a benefit of CSII. One randomized clinical trial was not included in the meta-analysis because it did not report severe hypoglycemia event rates for the CSII group.[40]

Figure 5. Difference in incident rate ratios for severe hypoglycemia in MDI versus CSII interventions among children and adolescents with type 1 diabetes

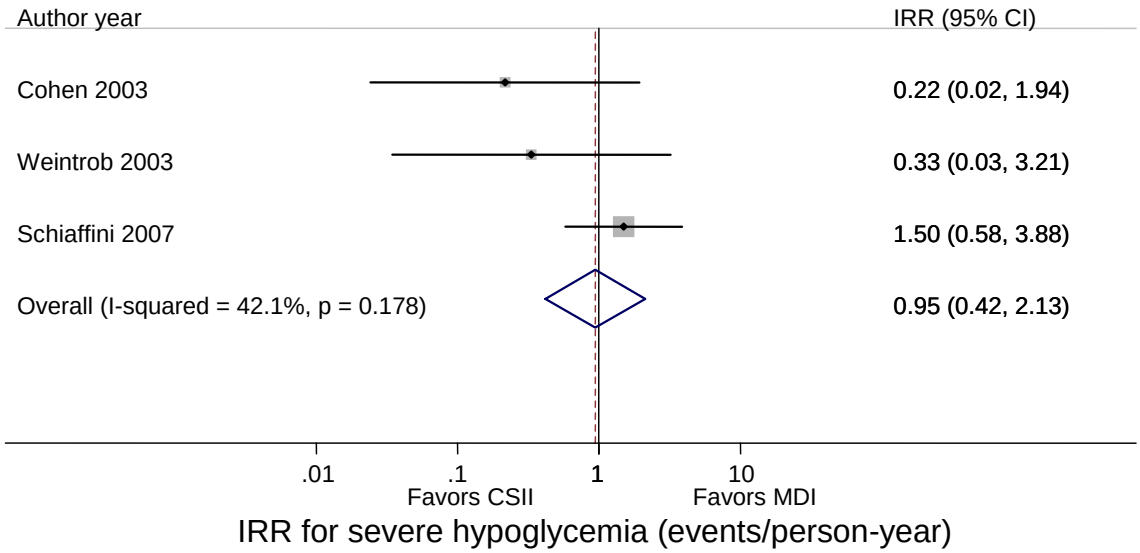


CI = confidence interval; CSII = continuous subcutaneous insulin infusion; IRR = incidence rate ratio; MDI = multiple daily injections
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 4.28 with 4 degrees of freedom (p = 0.37)

Studies in children 12 years of age or less. In the two RCTs of young children, one study showed a non-significantly lower rate of severe hypoglycemia favoring CSII[33] while the other study showed a non-significantly lower rate of severe hypoglycemia favoring MDI.[31] There were too few studies in this population to perform a meta-analysis.

Studies in adolescents greater than 12 years of age. Three of the five RCTs were performed in adolescents. Two studies showed a non-significantly lower rate of severe hypoglycemia favoring CSII[41 42] while one study showed a non-significantly lower event rate favoring MDI.[34] A meta-analysis of these three studies did not show a significant difference in the severe hypoglycemia event rates between the two intervention arms (combined mean incidence rate ratio for CSII versus MDI, 0.95; 95% CI, 0.42 to 2.13) (See Figure 6). We did not find evidence of statistical heterogeneity and no one study influenced results substantially. There were too few studies to adequately assess publication bias.

Figure 6. Difference in incident rate ratios for severe hypoglycemia in MDI versus CSII interventions among children with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; IRR = incidence rate ratio; MDI = multiple daily injections
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 3.45 with 2 degrees of freedom (p = 0.18)

Hyperglycemia. One study examined the frequency of hyperglycemia in the MDI and CSII intervention groups over 14 weeks.[42] Hyperglycemia was defined as symptoms of polyuria, polydipsia, or nocturia and/or a capillary blood glucose level of more than 400 mg/dL with or without urinary ketones. While there were more events in the CSII group (7.9) than in the MDI group (6.7), this difference was not statistically significant.

Ratio of basal to bolus insulin: proportion of basal insulin. One study examined the ratio of basal to bolus insulin in the MDI and CSII intervention groups and found no difference in the ratios between the two groups.[35]

Weight gain. Table 5 summarizes three studies that compared MDI with CSII for changes in weight as measured by body mass index (BMI) standard deviation score (SDS) in children with type 1 diabetes.[40-42] Two studies were randomized open crossover trials conducted at the same institution.[41 42] One found no significant change in BMI-SDS over the course of the study in either treatment arm.[41] The other crossover study reported a slight, but statistically significant, increase in BMI-SDS during MDI therapy and no significant change during CSII.[42] The third study was an RCT that showed a BMI change from baseline that was not statistically significant and measured less than 1 kg/m^2 in both groups.[40]

Table 5. Weight gain in MDI versus CSII interventions among children with type 1 diabetes

Author, year	MDI, N	CSII, N	Timepoints (weeks)	BMI-SDS at start – MDI	BMI-SDS at start – CSII	BMI-SDS at End - MDI	BMI-SDS at End - CSII	CSII Effect on BMI-SDS versus MDI	P value
Cohen, 2003[41]	16	16	24	0.20	0.30	0.25	0.23	No significant change	NS
Weintrob, 2003[42]	23	23	14	0.29	0.40	0.37	0.35	Decrease	0.01
Doyle 2004[40]	16	16	4	NA	NA	NA	NA	No significant change	NS

BMI = body mass index; CSII = continuous subcutaneous injections; MDI = multiple daily injections; NS = not significant; SDS = standard deviation score

Quality of life. Six studies examined the comparative effectiveness of CSII versus MDI on general, diabetes specific, and diabetes treatment-related quality of life in children and adolescents with type 1 diabetes (see Table 6). Two studies examined general quality of life in children and adolescents with type 1 diabetes using the Pediatric Quality of Life Inventory.[32 33] Both of these studies showed improvement in general quality of life favoring CSII (see Table 6). Four studies examined the comparative effectiveness of CSII versus MDI on diabetes-specific quality of life.[31 40-42] The three studies that used the Diabetes Treatment Satisfaction Questionnaire (DTSQ) showed an improvement in diabetes-specific quality of life favoring CSII.[41 42 44] Two studies used the Diabetes Quality of Life-Youth instrument (DQOL-Y) and while one showed improvement in quality of life favoring CSII,[41] the other study did not find a difference in quality of life between the two intervention arms.[40]

Table 6. Quality of life in MDI versus CSII interventions among children and adolescents with type 1 diabetes

QOL domain	Author, year	N by intervention group	Comparison	Population	Difference in QOL between comparison and baseline groups	Group favored for QOL measure
Pediatric Quality of Life Inventory*	Nuboer, 2008[32]	19 CSII, 19 MDI	CSII versus MDI with MDI run-in period	38 children and adolescents (age range 6-16 yr) with type 1 diabetes	After 7 months of followup, PedsQOL difference from baseline to end of randomization was 2.8 +/- 13.1 in CSII versus 0.4 +/- 17.3 MDI	CSII
Pediatric Quality of Life Inventory*	Opipari-Arrigan, 2007[33]	6 CSII, 8 MDI	CSII versus MDI	Sixteen children (age range 3.1–5.3 yrs) with type 1 diabetes	After 6 months of followup, PedsQOL (symptom domains) difference from baseline to end of experimental phase was 8 +/- 17 in CSII versus 6.5 +/- 33 in MDI	CSII
DTSQ†	Skogsberg, 2008[31]	34 CSII, 38 MDI	CSII versus MDI	72 children and adolescents (age range 7-17 yrs) with type 1 diabetes	At 24 months, 33.1 +/- 0.9 in CSII versus 27.5 +/- 2.0 in MDI, p<0.001.	CSII
DTSQ†	Cohen, 2003[41]	16 enrolled; 12 completed the study	CSII versus MDI (crossover study)	16 adolescents (age range 15-18 yrs) with type 1 diabetes for at least 2 years "and no other chronic disease which could interfere with diabetes treatment"	Total score was 20.5 +/- 3.6 at the beginning of the study, 21.8 +/- 3.7 at the end of the MDI arm (after 6 months), and 32 +/- 6.5 at the end of the CSII arm (after 6 months) (p<0.05)	CSII
DTSQ†	Weintrob, 2003[42]	23 children	CSII vs MDI (crossover study)	23 children (age range 9 to 13 yrs) with type 1 diabetes for at least 2 years, and "ability to cope, with the parents, with treatment"	Total score was 21.4 +/- 3.3 at the beginning of the study, 21.9 +/- 3.8 at the end of the MDI arm (after 3.5 months of treatment), and 30.6 +/- 3.7 at the end of the CSII arm (after 3.5 months of treatment (*P*< 0.001).	CSII
DQOL-Y†	Doyle, 2004[40]	16 CSII, 16 MDI	CSII vs MDI	32 children and adolescents with type 1 diabetes (age range 8 –21 yrs)	"There were no differences in DQOL-Y scores between the two groups at baseline or 16 weeks (data not shown)"	Neither
DQOL-Y†	Cohen, 2003[41]	16 enrolled; 12 completed the study; number of patients in each arm not given	CSII versus MDI (crossover study)	16 adolescents (range 15-18) with type 1 diabetes for at least 2 years "and no other chronic disease which could interfere with diabetes treatment"	Data for the individual treatment groups was not given. "The Satisfaction score was 77.4 +/- 16.1 at the beginning of the study, 76.4 +/- 14.3 at the end of the MDI arm, and 82.7 +/- 13 at the end of the CSII arm (p<0.05)"	CSII

CSII = continuous subcutaneous insulin infusion; DQOL-Y = Diabetes Quality of Life – Youth; DTSQ = Diabetes-Treatment Specific Questionnaire; MDI = multiple daily injections; PedsQoL = Pediatric Quality of Life Index; QOL = quality of life; yr = year

* General quality of life measure

† Diabetes-specific quality of life measure

Study Quality

Among the RCTs on children and adolescents, one study was good quality,[40] three studies were fair quality,[31 32 42] and three studies were poor quality (see Appendix D, Table 5).[33 34 41] Our assessment of the risk of bias was limited by a lack of reporting on most quality items. Only one study, which was rated as good quality, reported on sequence generation.[40]

Among the observational studies, three were fair quality[35 37 38] and one was fair or poor quality (see Appendix D, Table 6).[36] Most studies had incomplete[35 37 38] or no[36] description of the study setting or population and only described some key characteristics that affected outcomes. One study did not describe inclusion and exclusion criteria.[36] In one study the patients in the intervention groups were not recruited from the same population[37] and in another study it was unclear if patients in the two groups were derived from the same population.[36] All but one study[36] performed adjusted or stratified analyses. One study described losses to follow up[38] but none of the studies reported the percent of the population lost to follow up.

Strength of Evidence

The strength of evidence examining the comparative effectiveness of CSII versus MDI was moderate for HbA_{1c} and severe hypoglycemia outcomes, and low for daytime and nocturnal hypoglycemia and weight gain due to the small number of studies addressing these outcomes (see Table 7). Because only one study addressed the outcomes of mild hypoglycemia, hyperglycemia and ratio of basal to bolus insulin, there was insufficient data to determine strength of evidence for these outcomes. The magnitude of effect of the interventions on HbA_{1c} outcome was small and there was no effect on hyperglycemia, severe hypoglycemia, daytime, nocturnal, and mild hypoglycemia, ratio of basal to bolus insulin, or weight gain. Risk of bias was medium for the outcomes of HbA_{1c}, severe hypoglycemia, daytime and nocturnal hypoglycemia, and weight gain and high for mild hypoglycemia, hyperglycemia and ratio of basal to bolus insulin.

Table 7. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and overall strength of evidence for CSII versus MDI in children and adolescents with type 1 diabetes

Outcome	Number of Studies (Participants)	Domains Pertaining to Strength of Evidence					Magnitude of Effect and Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Publication bias	
HbA_{1c}	12 (536)	Medium	Consistent	Direct	Precise	No	Magnitude of effect: Small Strength of evidence: Moderate
Hyperglycemia	1 (23)	High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Insufficient
Severe hypoglycemia	9 (385)	Medium	Consistent	Direct	Precise	Yes	Magnitude of effect: No effect Strength of evidence: Moderate
Daytime hypoglycemia	3 (122)	Medium	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Nocturnal hypoglycemia	2 (64)	Medium	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Mild hypoglycemia	1 (1)	High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Insufficient
Ratio of basal to bolus insulin	1 (32)	High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Insufficient
Weight gain	3 (110)	Medium	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
General quality of life	2 (52)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Diabetes-specific quality of life	4 (143)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: Small Strength of evidence: Low

HbA1c = hemoglobin A1c

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Applicability

The majority of studies in children and adolescents with type 1 diabetes were small, with the largest clinical trial including 72 participants[31] and the largest observational study including 104 participants.[37] Most RCTs were fair or poor quality and only one RCT was good quality. The majority of studies were performed in adolescents, with fewer studies in children 12 years of age or less. Studies generally did not report race but based on the countries in which they were conducted, the majority of which were outside of the US, most studies included Caucasian participants. Participants generally had poor glycemic control at study entry (mean HbA_{1c} 8-9%), were treated in the intervention groups for an average of 52 weeks, and had diabetes for 5-6 years prior to study entry.

Comparative Effectiveness of CSII versus MDI in Adults with Type 1 Diabetes

Key Points and Evidence Grades

- There was low strength of evidence that CSII and MDI reduced HbA_{1c} similarly (mean between-group difference from baseline, -0.05%; 95% CI, -0.41 to 0.31%, P=0.78).
- There was insufficient strength of evidence comparing CSII with MDI for daytime hypoglycemia. One study reported more symptomatic and asymptomatic hypoglycemia between 0800 and midnight in the MDI compared with the CSII intervention arm (P<0.05).[49]
- There was low strength of evidence comparing CSII with MDI for nocturnal hypoglycemia. Three studies reported nocturnal hypoglycemia. In one cross-over trial, the proportion of patients experiencing nocturnal hypoglycemia was similar between the MDI (73% for any; 48% for symptomatic) and CSII (72% for any; 42% for symptomatic) intervention arms, although there were fewer episodes per person in the CSII compared with the MDI group (3.0 versus 4.0; P=0.0024).[49] In two other studies, there was not a statistically significant difference in nocturnal hypoglycemic episodes between the two intervention groups.[45 47]
- There was low strength of evidence comparing CSII with MDI for symptomatic hypoglycemia. Incidence rates for symptomatic hypoglycemia were similar for MDI and CSII in two studies (P>0.05).[45 81] In another study, there were more symptomatic hypoglycemic events with CSII versus MDI over 6 months (40/person-year versus 21/person-year; P=not reported).[47] In a different study, there were fewer symptomatic hypoglycemic events with CSII versus MDI (6.1/person versus 6.9/person; P=0.05), although similar proportion of participants experienced events over 5 weeks (75% for CSII and 72% for MDI).[49]
- The strength of the evidence comparing CSII with MDI was low for non-severe hypoglycemia.Three studies found no difference in non-severe hypoglycemia between the two intervention groups (in one study, asymptomatic hypoglycemia event rate 1.4/patient for MDI versus 1.2/patient for CSII; P=0.97[45]). In two studies, the incidence of mild hypoglycemia was higher in the CSII compared with the MDI group[49 51] with the relative difference statistically significant in one study (between-group difference in

change in hypoglycemic rate, 0.99; 95% CI, 0.11 to 1.87).[51] One additional study found a higher frequency of hypoglycemia in the MDI compared with the CSII group (RR, 1.12; 95% CI, 1.08 to 1.17).[48]

- There was low strength of the evidence to suggest no difference in severe hypoglycemia incidence between the two intervention groups (combined RR, 0.74; 95% CI, 0.30 to 1.83, *P*=0.52). Four cross-over trials did not provide quantitative results on severe hypoglycemia by period and were not included in the meta-analysis. Two showed more severe hypoglycemia with MDI compared with CSII (RR, 2.6; 95% CI, 2.08 to 3.25) in one study,[82] one study showed less severe hypoglycemia with MDI compared with CSII (3 events versus 4 events over 4 months),[53] and one study found similar rates of severe hypoglycemia between the two groups (1.1 events/patient for CSII versus 1.3 events/patient for MDI over 4 months, *P*=0.33).[46]
- There was low strength of evidence comparing CSII with MDI for hyperglycemia. The mean between group difference in fasting glucose over 6 months was -12.3 mg/dL (95% CI, -32.9 to 8.2 mg/dL; *P*=NS) favoring CSII in one study.[45] Two other studies reported no difference in fasting glucose between the MDI and CSII groups. The mean between-group difference in pre-prandial glucose over 6 months was -17.1 mg/dL (95% CI, -42.1 to 8.0 mg/dL; *P*=NS) favoring CSII.[45] Pre-dinner glucose was lower with CSII (128 mg/dL) compared with MDI (148 mg/dL) at the end of 5 weeks (*P*=NS).[49] Pre-dinner and pre-lunch glucoses were non-significantly lower with CSII compared with MDI at 4 months (estimates not reported).[83]
- There was low strength of evidence to suggest no difference in weight comparing CSII with MDI. Four studies examined the effects of MDI versus CSII on weight gain in adults with type 1 diabetes and there were not significant weight changes in either group. In two studies that reported estimates, the difference in weight was 0.28 kg less with CSII compared to MDI after 4 weeks[51] and 1.5 kg more with CSII compared to MDI after 6 weeks.[47]
- There was low strength of evidence comparing CSII with MDI for general quality of life. Two studies showed an improvement in general quality of life between the two intervention groups favoring CSII. In one study the Short Form (SF)-36 Physical Component Score change was -1.2 for CSII and 5.9 for MDI (*P*=0.048) and the Mental Component Score change was -0.6 for CSII and 5.2 for MDI (*P*=0.05).[48] The other study did not report estimates but there no difference in the Physical Component Score but a change in the Mental Component Score favoring CSII (*P*<0.05).
- There was low strength of evidence comparing CSII with MDI for diabetes-specific quality of life. Three studies showed an improvement in diabetes-specific quality of life favoring CSII—Diabetes Quality of Life (DQOL) 75 for CSII versus 71 for MDI at 8 months, *P*<0.001; between-group difference in DQOL for CSII versus MDI 7.2 (95% CI, 3.4 to 17.9; *P*=NS)[52] and 3.1 (95% CI, 0.1 to 6.1; *P*=0.042).[45] One study showed improvement favoring MDI (DQOL difference from baseline 5; SD, 28 for CSII and 11; SD, 23 for MDI).[47] Another study showed an improvement in Diabetes Quality of Life Clinical Trials Questionnaire (DQOLCTQ) scores in the CSII (52 to 81) and MDI (50 to 78) groups over 12 months with no between group difference (*P*=0.58).[55]
- The strength of evidence comparing CSII with MDI for diabetes treatment-related quality of life was insufficient. Altered Hypoglycemia Awareness Questionnaire scores were similar in the CSII (baseline=7 and follow-up=3) and MDI (baseline=7 and followup=4)

groups over 24 weeks. Hypoglycemia Fear Survey scores decreased in the both CSII (-3±25) and MDI (-8±33) groups.[47]

Study Design

Nine studies evaluated the effectiveness and safety of CSII versus MDI among adults with type 1 diabetes (see Appendix D, Table 1).[45-53] Studies occurred in European countries,[46 50 51 53] Canada,[52] and the US.[49] Two studies were multi-national.[45 48] Five were parallel arm studies,[45 47 50-52] and four used a cross-over design.[46 48 49 53] All studies randomized participants to the intervention with the exception of a single study.[50] The duration of interventions ranged from five weeks to one year.[45-53] Treatment lasted for five weeks in one study;[49] four months in two studies;[46 51] four months in one study;[53] six months in three studies;[45 47 48] and nine months[54] and one year[50] in the other two studies. Studies included 21 to 272 participants. Four studies occurred in clinical settings.[46 51-53] The other studies did not report study setting.[45 47-50] Two studies did not report on the use of a run-in period.[47 50]

No study focused solely on an elderly population with type 1 diabetes. Two studies set a lower limit for HbA_{1c} for eligibility: 6.5%[45] and 8.5%,[50] and four studies set an upper limit for HbA_{1c} for eligibility: 8.5%,[51] 9%,[45 49] and 10%.[53] Eligibility criteria for prior insulin use varied across studies with three requiring that participants be on intensified insulin therapy,[89] MDI,[45 48 52] one requiring MDI therapy be less than one year in duration,[50] three excluding based on lack of recent CSII use,[46 49] and one excluding based on prior CSII use.[45] Three studies excluded those with frequent severe hypoglycemia,[45 49 52] and another study excluded participants without severe hypoglycemia in the last six months.[47]

Population Characteristics

About one half of participants in the included studies were men with little imbalance by intervention strategy (see Appendix D, Table 2).[45 46 48 50 51 53] One study consisted mainly of men with 62% of participants male in the CSII and 71% male in the MDI arm.[52] Studies did not report on race. Mean HbA_{1c} was similar by intervention allocation with the exception of one study in which HbA_{1c} was 0.4% higher in the MDI versus CSII arm.[52] Intervention arm-specific HbA_{1c} ranged from 7.4% to 9.3% at baseline.[45 46 48 51 52] The mean duration of type 1 diabetes ranged from 14.4 to 25 years in studies reporting this.[45-48 50-53] Mean duration of diabetes was 4.9 years higher in the CSII arm compared with the MDI arm in one study[50] but otherwise similar by intervention strategy across studies.[45-49 51 52]

Five studies did not report on withdrawals by intervention allocation.[45 46 48-50] In the other studies, withdrawals varied by arm across studies: one in CSII and none in MDI,[52] seven in CSII and none in MDI,[51] and 16 in CSII and 15 in MDI during the first treatment period.[48] A cross-over trial reported five withdrawals from the CSII-MDI treatment group and four from the MDI-CSII treatment group,[49] and another cross-over trial reported a single withdrawal during MDI therapy.[53] One study reported the mistaken randomization of eight participants and an additional seven withdrawals without differentiation by treatment arm.[45]

Interventions

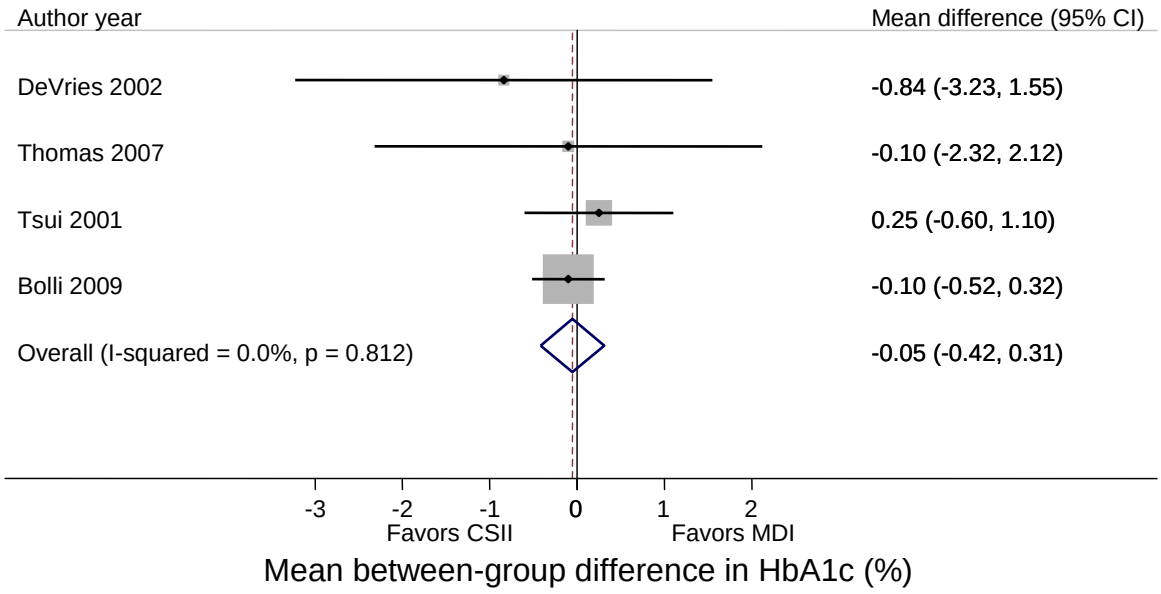
Four studies used NPH insulin as the long-acting insulin for the MDI arm,[48 51-53] and the other studies used insulin glargine (see Appendix D, Table 3).[45-47 49 50] All studies used insulin aspart or insulin lispro as the short-acting insulin during MDI treatment.[45-53] Two studies incorporated seven days of CGM.[47 49] Eight studies specified provider guidelines for insulin titration based on SMBG.[45-49 51-53] Five studies reported the use of insulin titration guidelines for participants.[47 48 51-53]

Outcomes

Details of the outcomes are reported in Appendix D, Table 4.

HbA_{1c}. Four RCTs reported a mean decrease in HbA_{1c} in both CSII and MDI treatment groups. CSII and MDI had a similar reduction from baseline in HbA_{1c} (combined mean between-group difference, -0.05%; 95% CI, -0.41 to 0.31%, *P*=0.78) (Figure 7).[45 47 51 52] Study duration ranged from 4 months to 1 year.[45 47 51 52] We did not find evidence of statistical heterogeneity, and no single study influenced results substantially. Egger's test and the funnel plot did not suggest bias due to absence of small studies.

Figure 7. Between-group difference between MDI and CSII in how HbA_{1c} changed from baseline among adults with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA1c = hemoglobin A1c; MDI = multiple daily injections
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.96 with 3 degrees of freedom (p = 0.81)

Symptomatic hypoglycemia. Four trials evaluated symptomatic hypoglycemia.[45 47 49 52] Incidence rates were similar for MDI and CSII treatment in two studies (P>0.05).[45 52] The other trial reported more symptomatic hypoglycemia with CSII treatment (40 events/person-year) compared with MDI treatment (21 events/person-year) over 6 months but did not report on statistical significance of this difference.[47] Of participants experiencing probable (not documented) symptomatic hypoglycemia in a cross-over trial, symptomatic hypoglycemia occurred slightly more frequently during CSII treatment compared with MDI treatment (6.9 events/person versus 6.1 events/person; P=0.05) although the percentage of participants experiencing symptomatic hypoglycemia were similar at 5 weeks (75% for CSII versus 72% for MDI).[49]

Daytime hypoglycemia. A single RCT using a cross-over design reported more hypoglycemic events between 0800 and midnight during MDI treatment than during CSII treatment (P<0.05).[49] Hypoglycemia could be symptomatic or asymptomatic and was defined by glucose less than 50 mg/dL not necessitating assistance from a third party.[49]

Nocturnal hypoglycemia. Three studies reported on nocturnal hypoglycemia (Table 8).[45 47 49] One cross-over trial reported a similar percentage of participants experiencing any nocturnal hypoglycemia (symptomatic, minor, or major) (72% versus 73%) or symptomatic nocturnal hypoglycemia (42% versus 48%) in the CSII and MDI treatment arms, respectively (statistical significance not reported).[49] Of participants with any nocturnal hypoglycemia, the authors reported slightly but significantly fewer episodes per person in the CSII compared with MDI arm over five weeks of treatment (3.0 events per participant versus 4.0 events per participant; P=0.0024).[49] A study of 58 participants also reported slightly fewer episodes of nocturnal hypoglycemia with CSII compared with MDI over 6 months, but this difference did not reach statistical significance (three events per person versus five events per person; P=0.34).[45] A small trial of 14 participants with a history of severe hypoglycemia reported no episodes of nocturnal hypoglycemia (definition not provided) in the CSII arm after 6 months and did not report on this outcome in the MDI treatment arm.[47] All studies employed SMBG for glucose monitoring and interval eight-point SMBG profiles.[45 47 49] One study also measured glucose with a CGM system during the last week of each treatment period.[49]

Table 8. Definition of nocturnal hypoglycemia in the studies of adults with type 1 diabetes

Author, year	Definition of nocturnal hypoglycemia
Bolli, 2009[45]	Between bedtime and rising
Hirsch, 2005[49]	Symptomatic and not documented by blood glucose measurement
Hirsch, 2005[49]	Asymptomatic glucose < 50 mg/dL, symptomatic glucose < 50 mg/dL without third party intervention required, or central nervous system symptoms requiring third party intervention
Thomas, 2007[47]	Not specified

mg/dL = milligrams per deciliter

Other mild hypoglycemia. Six studies evaluated the incidence of other types of mild hypoglycemia with CSII compared with MDI therapy (Table 9).[45 46 48 49 51 53] In one RCT, rates of asymptomatic hypoglycemia were similar in both groups over 6 months of treatment (1.4 events/patient versus 1.2 events/patient; P=0.97).[45] In two studies, the incidence of mild hypoglycemia was higher during CSII compared with MDI treatment[49 51] with the relative difference statistically significant in one of these studies.[51] However, in another trial, the risk of

self-managed mild hypoglycemia was higher during MDI treatment (RR, 1.12; 95% CI, 1.08 to 1.17).[48] Two other studies found no difference in the incidence of biochemical hypoglycemia during CSII compared with MDI treatment.[46 53]

Table 9. Definition of mild hypoglycemia in the studies of adults with type 1 diabetes

Author, year	Definition of mild hypoglycemia
Bolli, 2009[45]	Asymptomatic
Bruttomeso, 2008[46]	Measured glucose 36 to 63 mg/dL
DeVries, 2002[51]	Change in frequency of SMBG < 70 mg/dL per patient-week
Hanaire-Broutin, 2000[53]	Measured glucose < 60 mg/dL during last 14 days of treatment
Hirsch, 2005[49]	Asymptomatic glucose < 50 mg/dL or symptomatic glucose < 50 mg/dL without third party intervention required
Hoogma, 2006[48]	No third party intervention required

mg/dL = milligrams per deciliter; SMBG = self-monitoring of blood glucose

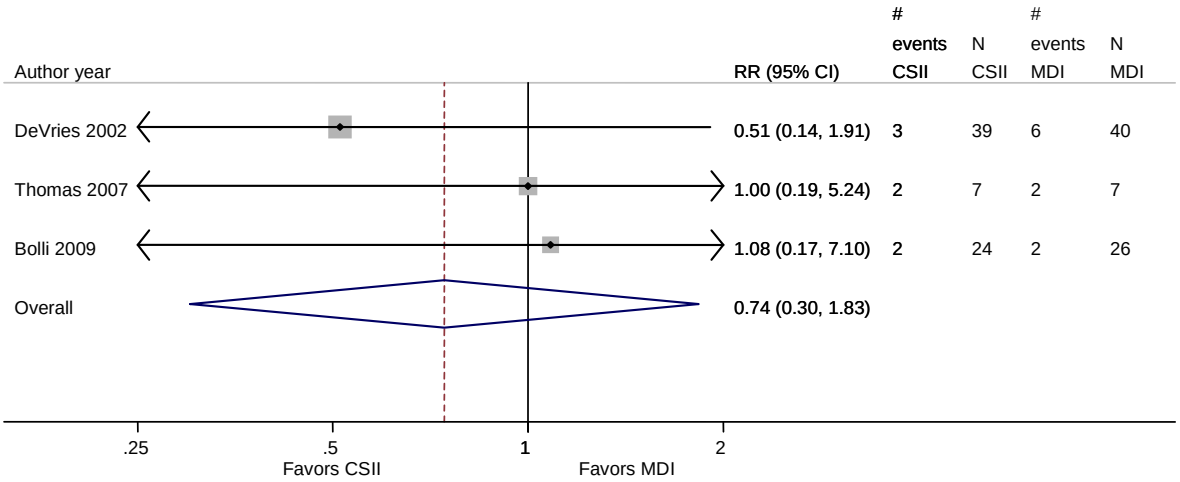
Severe hypoglycemia. A meta-analysis of three RCTs indicated no difference in the incidence of severe hypoglycemia with CSII compared with MDI treatment (combined RR, 0.74; 95% CI, 0.30 to 1.83, *P*=0.52) (Figure 8).[45 47 51] Duration of these studies ranged from 4 to 6 months, and definitions of severe hypoglycemia required assistance from a third party in all three trials (Table 10). Of note, one study included in the meta-analysis required that participants have a history of severe hypoglycemia, but event rates were similar to those in the other two studies.[47] We did not find evidence of statistical heterogeneity, and no single study influenced results substantially. Egger's test and the funnel plot did not suggest bias due to absence of small studies. Another RCT reported a non-significant and small difference in the number of severe hypoglycemic events over 9 months in the CSII versus MDI treatment arm (six events versus four events) but did not report if any individuals had more than one hypoglycemic event.[52]

Table 10. Definition of severe hypoglycemia in the RCTs of adults with type 1 diabetes

Author, year	Definition of severe hypoglycemia
Bolli, 2009[45]	Requiring management assistance and either plasma glucose <2.0 mmol/l (<36 mg/dL) or prompt recovery after oral or intravenous carbohydrate or glucagon
Thomas, 2007[47]	ADA definition: "An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration."
DeVries, 2002[51]	Requirement of third-party help
Tsui, 2001[52]	Events requiring assistance or resulting in coma

ADA = American Diabetes Association; mg/dL = milligrams per deciliter; mmol/L = millimole per liter; RCTs = randomized controlled trials

Figure 8. Pooled relative risk of severe hypoglycemia in MDI versus CSII interventions among adults with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; RR = relative risk
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.58 with 2 degrees of freedom (p = 0.75)

Four cross-over trials did not provide quantitative results on severe hypoglycemia by period and were not included in the meta-analysis.[46 48 49 53] Table 11 summarizes how severe hypoglycemia was defined in those trials. Severe hypoglycemia events were more frequent during MDI therapy compared with CSII therapy in two studies[48 49] with one study reporting a relative risk of 2.6 (95% CI, 2.08 to 3.25).[48] Compared with CSII therapy, severe hypoglycemia occurred less frequently during MDI therapy in one study (three events versus one event over 4 months.[53] A fourth trial reported similar rates of severe hypoglycemia during CSII and MDI therapy (1.1 events/patient and 1.3 events/patient, respectively over 4 months; *P*=0.327).[46]

Table 11. Definition of severe hypoglycemia in the cross-over trials of adults with type 1 diabetes

Author, year	Definition of severe hypoglycemia
Bruttomesso, 2008[46]	Plasma glucose <36 mg/dL
Hoogma, 2006[48]	Requirement of third-party help
Hirsch, 2005[49]	Episodes with severe central nervous system symptoms consistent with hypoglycemia that the patient was unable to treat himself/herself, which had either (1) blood glucose <50 mg/dL or (2) reversal of symptoms after either food intake or glucagon/intravenous glucose administration
Haiare-Broutin, 2000[53]	Events requiring external help, glucose administration, coma, or seizure

mg/dL = milligrams per deciliter

Hyperglycemia.

Fasting glucose. Fasting glucose did not vary significantly by treatment with CSII or MDI across three RCTs. In one RCT, fasting glucose decreased more with CSII than with MDI at 6 months (mean between-group difference, -12.3 mg/dL; 95% CI, -32.9 to 8.2 mg/dL).[45] In a non-randomized trial, CSII and MDI lowered fasting glucose similarly at 12 months (quantitative

results not reported).[50] A third RCT reported a lower fasting glucose at 4 months in the CSII arm compared with the MDI arm, but this difference in fasting glucose was not statistically significant.[51] The authors did not provide estimates of these glucose levels.[51]

Pre-prandial glucose (other than pre-breakfast). Three RCTs reported on the effect of CSII and MDI on pre-prandial glucose. In one RCT, CSII decreased pre-prandial glucose more than MDI at 6 months (mean between-group difference, -17.1 mg/dL; 95% CI, -42.1 to 8.0 mg/dL),[45] but this difference was not significant. In a cross-over trial, pre-dinner glucose was not significantly lower at 5 weeks at the end of the CSII period (128 mg/dL) compared with the MDI period (148 mg/dL).[49] CSII lowered pre-dinner and pre-lunch glucoses more than MDI non-significantly at 4 months in another study,[51] but the authors did not provide estimates of these glucose levels.[51]

Glucose at bedtime. In a single study, glucose at bedtime was not significantly lower in the CSII arm compared with MDI arm at 4 months.[51] The authors did not provide estimates of these glucose levels.[51]

Nocturnal glucose. Two trials did not find a significant between-group difference in nocturnal glucose levels. Nocturnal glucose increased in both arms in one study with a mean between-group difference of 54.8 mg/dL (95% CI, -7.2 to 116.7 mg/dL) at 6 months for CSII compared with MDI.[45] The other study reported equal nocturnal blood glucoses at 4 months in both arms, but the authors did not provide estimates of these glucose levels.[51]

Post-prandial glucose. Three RCTs reported lower post-prandial glucoses with CSII compared with MDI treatment. In one trial, post-prandial glucose decreased in the CSII arm and increased in the MDI arm over 6 months (mean between-group difference for CSII versus MDI, -5.5 mg/dL; 95% CI, -29.9 to 18.9 mg/dL).[45] In a cross-over trial, post-breakfast and post-dinner glucoses were lower after 5 weeks, for the CSII treatment period (mean glucose 158 mg/dL and 144 mg/dL for breakfast and dinner, respectively) compared with the MDI treatment period (mean glucose 182 mg/dL and 159 mg/dL for breakfast and dinner, respectively).[49] In a third trial, post-lunch and post-dinner glucoses were similar at 4 months in the MDI and CSII arms, but post-breakfast glucose levels were non-significantly higher in the MDI compared with CSII arm.[51] The authors did not provide estimates of these glucose levels in this study.[51]

Weight. Four studies examined the effects of MDI versus CSII on weight gain in adults with type 1 diabetes, and the results are outlined in Table 12.[46 47 50 51] Two studies provided numerical values for the observed weight changes, and the CSII group exhibited slightly less weight gain in one study and more weight gain in the other study.[47 51] Neither difference was statistically significant. The remaining two studies also reported no significant changes in weight, which one study attributed to the presence of a dietician.[46 50]

Table 12. Weight gain in MDI versus CSII interventions among adults with type 1 diabetes

Author, year	MDI, N	CSII, N	Timepoint (weeks)	Weight gain – MDI	Weight gain – CSII	CSII effect on weight gain vs. MDI (kg)	P-value
DeVries, 2002[51]	40	39	4	0.88	0.60	-0.28	0.68
Lepore, 2003[50]	16	16	12	-	-	-	-
Thomas, 2007[47]	7	7	6	-1.0	0.5	1.5	0.88; 0.94
Bruttomesso, 2008[46]	39	39	4	-	-	-	-

CSII = continuous subcutaneous insulin infusion; kg = kilogram; MDI = multiple daily injections

Quality of life. Six studies examined the comparative effectiveness of CSII versus MDI on general quality of life, diabetes-specific quality of life, and diabetes treatment-related quality of life in adults with type 1 diabetes (Table 13). General quality of life was measured using the Short Form (SF)-36[51] and SF-12.[48] Two studies showed an improvement in general quality of life favoring CSII.[48 51]

Four of five studies examining the comparative effectiveness of CSII versus MDI on diabetes-specific quality of life used the DQOL[45 47 48 52] and one used the Diabetes Quality of Life Clinical Trials Questionnaire (DQOLCTQ).[55] Three studies showed an improvement in diabetes-specific quality of life favoring CSII,[45 48 52] one study showed improvement favoring MDI,[47] and one study found no difference between the two groups.[55]

One study examined the comparative effectiveness of CSII versus MDI on diabetes treatment-related quality of life using the Altered Hypoglycemia Awareness Questionnaire and the Hypoglycemia Fear Survey.[47] There was no difference in hypoglycemia awareness or fear between the two intervention arms at the conclusion of the study.

Table 13. Quality of life in MDI versus CSII interventions among adults with type 1 diabetes

QOL Domain	Author, year	N by intervention group	Comparison	Population	Difference in QOL between comparison and baseline groups	Group favored for QOL measure
SF-36*	DeVries, 2002[51]	79 adults	CSII vs MDI (crossover study)	79 adults with type 1 diabetes, age between 18 and 70 years, and poor diabetes control with MDI	PCS: At 16 weeks, change in CSII group was -1.2 versus +5.9 in MDI (*P*=0.048) MCS: After 16 weeks, change in CSI group was -0.6 was versus +5.2 in MDI (*P*=0.050)	CSII
SF-12*	Hoogma, 2006[48]	129 MDI-CSII, 127 CSII-MDI	CSII vs MDI (crossover study)	256 adults with type 1 diabetes, aged 18 to 65 years, on MDI for at least 6 months	At 8 months: PCS: no difference MCS: CSII favored over MDI (P<0.05) (no data given)	CSII
DQOL†	Thomas, 2007[47]	7 CSII, 7 MDI, 7 education	CSII vs optimized MDI versus education and conventional insulin therapy	21 adult patients with type 1 diabetes, age 33 to 53 years, with at least 1 episode of severe hypoglycemia in the past 6 months	At 24 weeks: difference of 5±28 compared with baseline in CSII; 11±23 in MDI; -9±19 in education	MDI
DQOL†	Hoogma, 2006[48]	129 MDI-CSII, 127 CSII-MDI	CSII vs MDI (crossover study)	256 adults with type 1 diabetes, aged 18 to 65 years, on MDI for at least 6 months	At 8 months, 75 in CSII versus 71 in MDI (*P*<0.001)	CSII
DQOL†	Tsui, 2001[52]	13 CSII, 14 MDI	CSII vs MDI	27 adults aged 18 to 60 years with type 1 diabetes	At 9 months, satisfaction score in the CSII group was 75.6, in the MDI group 68.3. CSII – MDI difference was 7.2 (95% CI, 3.4 to 17.9), *P*>0.10	CSII
DQOL†	Bolli, 2009[45]	24 CSI, 26 MDI	CSII vs MDI	50 adults with type 1 diabetes	At 24 weeks: 22.8± 8.1 at baseline to 31.5 ±4.9 in the CSII group and from 24.0 ± 6.3 to 28.8 ± 5.4 in the MDI group (treatment difference: 3.1 (95% CI, 0.1 to 6.1); *P*=0.042).	CSII
DQOLCTQ†	Herman, 2005[55]	48 CSII, 50 MDI	CSII vs MDI	104 adults > 60 years of age (mean age 66 years) with insulin-treated type 2 diabetes (mean duration 16 years, BMI 32 kg/m^2, and HbA_{1C} 8.2%)	At 12 months, score improved from 52 to 81 in CSII versus 50 to 78 in MDI (*P*=0.58)	Neither

Table 13. Quality of life in MDI versus CSII interventions among adults with type 1 diabetes (continued)

QOL Domain	Author, year	N by intervention group	Comparison	Population	Difference in QOL between comparison and baseline groups	Group favored for QOL measure
Altered Hypoglycemia Awareness Questionnaire ‡	Thomas, 2007[47]	7 CSII, 7 MDI, 7 education	CSII vs optimized MDI versus education and conventional insulin therapy	21 adult patients with type 1 diabetes, age 33 to 53 years, with at least 1 episode of severe hypoglycemia in the past 6 months	At 24 weeks, AHA score in the education group was 2 compared with 7 at baseline; in the MDI group, 4 compared with 7 at baseline; in the CSII group, 3 compared with 7 at baseline	Neither
Hypoglycemia Fear Survey‡	Thomas, 2007[47]	7 CSII, 7 MDI, 7 education	CSII vs optimized MDI versus education and conventional insulin therapy	21 adult patients with type 1 diabetes, age 33-53, with at least 1 episode of severe hypoglycemia in the past 6 months	At 24 weeks, difference from baseline was -3 ± 25 in CSII; -8 ± 33 in MDI; 4 ± 20 in education	MDI

AHA = Altered Hypoglycemia Awareness; BMI = body mass index; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; DQOL = Diabetes Quality of Life; DQOLCTQ = Diabetes Quality of Life Clinical Trials Questionnaire; HbA1c = hemoglobin A1c; kg/m2 = kilograms per meters squared; MCS = Mental Component Score; MDI = multiple daily injections; PCS = Physical Component Score; QOL = quality of life; SF = Short Form

* General Quality of Life

† Diabetes-specific quality of Life

‡ Diabetes Treatment-Related Quality of Life

Study Quality

We rated two studies as being of good quality[52 53] with the others rated as being of fair or poor quality.[45-51] All included studies were RCTs. Our assessment of the risk of bias was limited by a lack of reporting on most quality items. Three studies reported an appropriate randomization sequence generation,[46 51 52] and only two studies reported appropriate allocation concealment.[51 52] Four studies did not mask outcome assessors to intervention arm.[45 48 51 53] Two studies reported one withdrawal,[52 53] and five did not handle missing data appropriately.[45 46 48 49 51] All studies reported industry support with the exception of one.[50] Studies did not otherwise report on these quality items.

Strength of Evidence

The strength of evidence examining the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes was low or insufficient for all outcomes (see Table 14). All included studies were RCTs, and the risk of bias was medium. There was no apparent difference in the effects of CSII compared to MDI on HbA_{1c}, weight change, hypoglycemia, and fasting and pre-prandial glucose. The relative magnitude of effect on post-prandial glucose was small for the interventions. The small number of studies affected our assessment of the overall strength of the evidence for the outcomes for the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes. The studies were small and did not use the same definitions of most outcomes, limiting our ability to combine effect estimates across studies. Notably, the evidence on the risk of severe hypoglycemia was limited by low event rates and resultant imprecise results.

Table 14. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and overall strength of evidence for CSII versus MDI in adults with type 1 diabetes

Outcome	Number of Studies (Participants)	Domains Pertaining to Strength of Evidence					Magnitude of Effect and Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Publication bias	
HbA_{1c}	4 (195)	Medium	Inconsistent	Direct	Imprecise	None	Magnitude of effect: No effect Strength of evidence: Low
Hyperglycemia	3 (179)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: Fasting/pre-prandial glucose – no effect Post-prandial effect – Small Strength of evidence: Low
Mild hypoglycemia	9 (682)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Severe hypoglycemia	8 (650)	Medium	Inconsistent	Direct	Imprecise	None	Magnitude of effect: No effect Strength of evidence: Low
Weight	4 (184)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Quality of life	2 (335)	High	Consistent	Direct	Imprecise	Uncertain	Magnitude: Small Strength of evidence: Low
Diabetes-specific quality of life	3 (354)	High	Inconsistent	Direct	Imprecise	Uncertain	Magnitude: Small Strength of evidence: Low
Diabetes treatment-related quality of life	1 (21)	Medium	Not applicable (single study)	Direct	Imprecise	Uncertain	Magnitude: Small Strength of evidence: Insufficient

HbA_{1c} = hemoglobin A_{1c}

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Applicability

Few studies compared the effect of CSII with MDI in adults with type 1 diabetes. Existing studies were generally of fair or poor quality and did not report on most quality items of interest.

Studies did not report on many items of interest to determining the applicability of the studies to all adults with type 1 diabetes. Studies did not report on race, and no study focused on elderly adults with type 1 diabetes. Four trials took place in outpatient clinics. Interventions lasted between 5 weeks and 12 months. The mean baseline HbA_{1c} was 7.4 to 9.3% across the studies. The duration of diabetes at enrollment was greater than 14 years in the studies reporting this. Eligibility criteria for MDI and insulin pump use varied significantly across the studies. Four studies reported training on insulin pump use.

Comparative Effectiveness of CSII versus MDI among Adults with Type 2 Diabetes

Key Points and Evidence Grades

- There was moderate strength of evidence suggesting no difference between CSII and MDI for their effects on HbA_{1c}. There was a non-significant difference in HbA_{1c} between the MDI and CSII intervention groups favoring CSII (mean between-group difference from baseline, -0.16; 95% CI, -0.42 to 0.09, P=0.21).
- The strength of the evidence comparing CSII with MDI for mild hypoglycemia was low. In two studies, mild hypoglycemia was more frequent in the MDI than CSII group (90% versus 81% in one study;[58] 59% versus 54% in another study[57]) although the difference was not statistically significant. In one study, there was no difference in mild hypoglycemia between the two groups.[55]
- The strength of the evidence comparing CSII with MDI for nocturnal hypoglycemia was insufficient. In one study, nocturnal hypoglycemia (occurring between midnight and 0600) was more common in patients in the MDI compared with CSII arm (22% versus 16%; P=not reported), although the rates of nocturnal hypoglycemia were similar between the two groups.
- The strength of the evidence comparing CSII with MDI for severe hypoglycemia was low. In one study, no participants in either the MDI or CSII groups experienced severe hypoglycemia.[57] In two other studies, there was no difference in severe hypoglycemia between the two intervention groups (2 patients with events for MDI and 3 patients with events for CSII:[58] incidence rate 0.23 events/person-year for MDI versus 0.08 events/person-year for CSII; P=0.61).[55]
- The strength of the evidence was insufficient comparing CSII with MDI for hyperglycemia. Mean post-prandial glucose (90 minutes after breakfast) was 167 mg/dL in the CSII arm and 192 mg/dL in the MDI arm at 24 weeks (mean between-group difference, -25 mg/dL; P=0.019).[57] Glucose measurements from other time points were similar between treatment groups at the end of the study. The incidence of blood glucose over 350 mg/dL was higher in the MDI compared with the CSII arm (26 versus 6 events) with 18% and 5% of participants affected in the MDI and CSII arms, respectively.[57]

- There was low strength of evidence suggesting no difference in weight gain comparing CSII with MDI. In two studies, there was not a statistically significant difference in weight gain between the two intervention arms (difference in weight gain for CSII versus MDI, 1.0 kg; *P*=NS[57] and -0.5 kg; *P*=0.7[55]).
- The strength of the evidence comparing CSII with MDI was insufficient for general quality of life. In one study, there was no difference in general quality of life between the CSII and MDI intervention groups. Difference in SF-36v2 Physical Component Score from baseline to follow-up was 0.6 for CSII versus 0.4 for MDI and for the Mental Component Score, was 1.0 for CSII and 2.5 for MDI.[55]
- The strength of the evidence comparing CSII with MDI was insufficient for diabetes-specific quality of life. In one study, there was no difference in diabetes-specific quality of life between the CSII and MDI intervention groups (DQOLCTQ scores improved from 52 to 81 for CSII and from 50 to 78 for MDI over 12 months).[55]
- The strength of the evidence comparing CSII with MDI was insufficient for diabetes treatment-related quality of life. In one study, there was improvement in diabetes treatment satisfaction favoring CSII (Phase V Outcomes System Diabetes Treatment Satisfaction score improved from 59.4±2.1 to 79.2±1.8 for CSII compared to 63.6±1.9 to 70.3±2.3 for MDI over 24 weeks; $P<0.001$).[57]

Study Design

Of the four studies evaluating CSII versus MDI therapy in patients with type 2 diabetes, three were parallel-arm randomized trials,[55-57] and one was a randomized cross-over trial (see Appendix D, Table 1).[58] Treatment periods were 18 weeks in duration in the cross-over study,[58] and the parallel-arm studies were 6 or 12 months in duration.[55-57] The cross-over study enrolled patients from diabetes centers,[58] and another study took place in a university clinic.[56] The other two studies did not report on study setting.[55 57] Three trials reported a run-in period.[55 57 58]

Two studies excluded participants with HbA_{1c} greater than 12 or 15%,[57 58] and three studies excluded persons with HbA_{1c} less than 6, 7, or 8.5%.[55 57 58] All studies required that participants be treated with insulin prior to the study.[55-58]

Population Characteristics

The number of participants per arm ranged from 20 to 66 in the included studies (see Appendix D, Table 2).[55-58] All studies were conducted in adults, only one study only included participants 60 years of age or older.[55] More men were randomized to the CSII treatment group in two studies.[55 57] Two studies did not report on the racial composition of their study populations, and the other two studies were multi-ethnic but predominantly white (> 80%).[55 57] Mean HbA_{1c} was 0.3% higher at baseline in the CSII compared with MDI arm in one study.[55] Mean BMI ranged from 29.5 to 32.5 kg/m^2 and was similar by treatment group across the three parallel-arm studies.[55-57] The mean duration of type 2 diabetes was greater than 10 years in the two studies reporting this and was 1.5 and 1.7 years higher in the CSII compared with MDI arms in these studies.[55 57] Three studies reported four to six withdrawals per intervention arm, and the number of withdrawals did not vary by arm.[55 57 58] One study had additional withdrawals after randomization (two from MDI and three from CSII) but before the treatment period began.[57]

Interventions

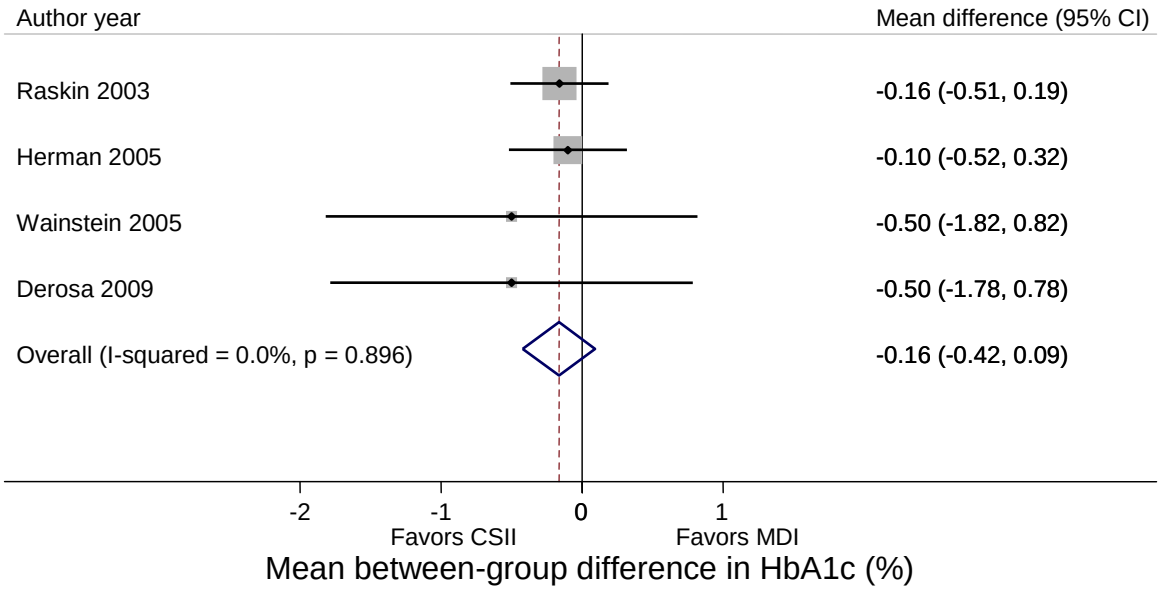
The MDI arms varied across studies: NPH and Regular insulin;[58] insulin glargine and insulin lispro;[55 56] and NPH insulin and insulin aspart (see Appendix D, Table 3).[57] Insulin aspart was used in the CSII arm for one study,[57] and insulin lispro was used in the CSII arm in the other studies.[55 56 58] Three studies reported the use of provider guidelines for medication titration,[55 57 58] but the targets varied. One study specified an HbA_{1c} target of 7%,[58] and another specified both an HbA_{1c} target (5.6%) and glucose targets of 80 to 120 mg/dL for pre-prandial glucose and 100 to 150 mg/dL at bedtime. The third study specified a fasting glucose of 80 to 120 mg/dL as its only target.[57] Two studies provided guidelines for participants to use between visits.[55 58]

Outcomes

Details of the outcomes are reported in Appendix D, Table 4.

HbA_{1c}. As shown in Figure 9, four RCTs of at least 18 weeks in duration reported a mean decrease from baseline in HbA_{1c} in both CSII and MDI treatment groups with the reduction greater during CSII treatment compared with MDI (combined mean between-group difference from baseline, -0.16%; 95% CI, -0.42 to 0.09%, *P*=0.21).[55-58] We did not find evidence of statistical heterogeneity, and no single study influenced results substantially. Egger's test (*P*=0.084) and the funnel plot suggested bias due to absence of small studies reporting a benefit of MDI over CSII, but a trim-and-fill analysis was unremarkable.

Figure 9. Between-group difference between MDI and CSII in how HbA_{1c} changed from baseline among adults with type 2 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA1c = hemoglobin A1c; MDI = multiple daily injections

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q = 0.60 with 3 degrees of freedom (p = 0.90)

Non-severe hypoglycemia. Three trials reported on mild hypoglycemia in patients with type 2 diabetes randomized to MDI and CSII therapy.[55 57 58] In one study, patients maintained a record of hypoglycemia for 1 week prior to each clinic visit, and mild hypoglycemia occurred more often with MDI compared with CSII treatment (proportion of patients with minor hypoglycemia, 90% versus 81%; *P*=0.17) over the course of the 12-month study.[55] In a shorter study lasting 6 months, patients in the MDI group were also more likely to experience mild hypoglycemia than those in the CSII group (proportion of patients with minor hypoglycemia, 59% versus 54%; statistical significance not reported).[57] The third study, a cross-over trial, did not provide quantitative results but stated that mild hypoglycemia did not vary by period of the study.[58]

The definitions of mild hypoglycemia varied slightly across the studies: blood glucose less than 54 mg/dL not requiring assistance;[58] blood glucose less than 50 mg/dL not requiring assistance;[57] and blood glucose less than 65 mg/dL not requiring assistance or symptoms of hypoglycemia that resolved with glucose intake.[55]

Nocturnal hypoglycemia. In a single study, nocturnal hypoglycemia (occurring between midnight and 0600) was more common between 8 and 24 weeks in the MDI arm compared with CSII arm (percentage of patients with nocturnal hypoglycemia, 22% versus 16%; statistical significance not reported).[57] The authors described the rates of nocturnal hypoglycemia as similar between arms but did not report on statistical significance.[57]

Severe hypoglycemia. Three RCTs reported on rates of severe hypoglycemia among patients with type 2 diabetes treated with MDI or CSII.[55 57 58] In one study, no participants in either treatment group experienced severe hypoglycemia (defined by glucose less than 50 mg/dL and severe central nervous system dysfunction necessitating outside assistance or parenteral treatment).[57] In the cross-over trial, severe hypoglycemia (that requiring outside assistance) occurred in two patients while on MDI therapy and in three patients while on CSII therapy.[58] In the third study, severe hypoglycemia occurred in six participants receiving MDI and in three patients receiving CSII (*P*=0.49).[55] Similarly, incidence rates were 0.23 events/person-year (12 events) and 0.08 events/person-year (four events) in the MDI and CSII arms, respectively (*P*=0.61).[55] One participant in the MDI arm experienced four severe hypoglycemia events.[55] One event resulted in a motor vehicle collision and hospitalization of the participant.[55]

Hyperglycemia. A single study reported hyperglycemia outcomes based on SMBG in patients with type 2 diabetes randomized to CSII or MDI.[57] Mean postprandial glucose (90 minutes after breakfast) was 167 mg/dL in the CSII arm and 192 mg/dL in the MDI arm at 24 weeks (mean between-group difference, -25 mg/dL; *P*=0.019).[57] The authors reported that glucose measurements from the other time points were similar between treatment groups at the end of the study.[57] The incidence of blood glucose greater than 350 mg/dL was higher in the MDI compared with CSII arm (26 versus 6 events) with 18% and 5% of participants affected in the MDI and CSII arms, respectively.[57]

Weight. Two studies evaluated weight gain experienced by participants in MDI and CSII groups (Table 15).[55 57] One study showed that patients gained more weight in the CSII group than in the MDI group, whereas the other showed less weight gain in the CSII group.[55 57] The difference in weight gain between the two treatment arms was not statistically significant for either study.[55 57]

Table 15. Weight gain in MDI versus CSII interventions among adults with type 2 diabetes

Author, year	MDI, N	CSII, N	Timepoint (weeks)	Weight gain – MDI	Weight gain – CSII	CSII effect on weight gain vs. MDI (kg)	*P*-value
Raskin, 2003[57]	61	66	24	0.7	1.7	1.0	NS
Herman, 2005[55]	54	53	12	2.6	2.1	-0.5	0.7

CSII = continuous subcutaneous injections; kg = kilograms; MDI = multiple daily injections; NS = not significant

Quality of life. Two studies examined the comparative effectiveness of CSII versus MDI on general, diabetes specific, and diabetes treatment-related quality of life in adults with type 2 diabetes. One study examined general quality of life using the SF-36v2 and diabetes-specific quality of life using the DQOLCTQ in 98 adults (48 in the CSII group and 50 in the MDI group) and found no difference in either quality of life measure between the two groups.[55] Another study used the Phase V Outcomes System Diabetes Treatment Satisfaction Questionnaire.[57] This study included 127 CSII-naïve men and women over 35 years of age (66 in the CSII group and 61 in the MDI group).[57] At the end of 24 weeks, there was in improvement diabetes treatment satisfaction favoring CSII.

Study Quality

All studies were of poor or fair quality (see Appendix D, Table 5).[55-58] Our assessment of the risk of bias was limited by a lack of reporting on most quality items. Only one study reported an appropriate randomization sequence generation,[57] only one study reported appropriate allocation concealment.[55] One study reported the use of an open-label design,[57] and none of the studies reported if outcome assessors were masked to the intervention assignment.[55-58] Two studies did not use appropriate methods for handling missing data,[57 58] and two studies reported commercial support.[55 57] These items were not reported in the other studies.

Strength of Evidence

The strength of evidence examining the comparative effectiveness of CSII versus MDI in patients with type 2 diabetes was moderate for HbA_{1c} and low for hypoglycemia and weight outcomes (Table 16). The evidence was insufficient for hyperglycemia, quality of life as only one study addressed these outcomes. All included studies were RCTs, and the risk of bias was medium to high for all outcomes. The magnitude of the relative effects of CSII versus MDI on outcomes, when this could be estimated, was small. The small number of studies affected our assessment of the overall strength of the evidence for the outcomes for the comparative effectiveness of CSII versus MDI in adults with type 2 diabetes.

Table 16. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and overall strength of evidence for CSII versus MDI in adults with type 2 diabetes

Outcome	Number of Studies (Participants)	Domains Pertaining to Strength of Evidence					Magnitude of Effect and Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Publication bias	
HbA_{1c}	4 (n=338)	Medium	Consistent	Direct	Precise	None	Magnitude of effect: No effect Strength of evidence: Moderate
Hyperglycemia	1 (n=127)	Medium	Unknown	Direct	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Insufficient
Mild hypoglycemia	3 (n=279)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: Small effect Strength of evidence: Low
Severe hypoglycemia	3 (n=279)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Weight	2 (n=239)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low
General quality of life	1 (n=98)	High	Unknown (single study)	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strenth of evidence: Insufficient
Diabetes-specific quality of life	1 (n=98)	High	Unknown (single study)	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Insufficient
Diabetes treatment-related quality of life	1 (n=127)	High	Unknown (single study)	Direct	Imprecise	Uncertain	Magnitude of effect: Moderate Strength of evidence: Insufficient

HbA_{1c} = hemoglobin A_{1c}

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Applicability

Few studies compared the effect of CSII with MDI in patients with type 2 diabetes. The evidence was insufficient to make definitive conclusions about the relative effects of these therapies on hyperglycemia and weight. Existing studies were small, of fair or poor quality, and did not report on most quality items of interest.

Studies did not generally report on items of interest in determining the applicability of the literature to the general population with type 2 diabetes. Most study participants were white when this characteristic was reported, and a single study focused on participants 60 years of age and older. Study setting was described in two of the trials which took place in outpatient clinics. Studies lasted between 18 weeks and 12 months. The mean baseline HbA_{1c} was approximately 8 to 9% across the studies. The duration of diabetes at enrollment was greater than 10 years in the two studies reporting this. All studies required a history of insulin treatment prior to enrollment, and a single study reported training on insulin pump use.

Comparative Effectiveness of CSII versus MDI in Pregnant Women with Pre-existing Type 1 Diabetes

Key Points and Evidence Grades

- There was low strength of evidence comparing CSII with MDI for HbA_{1c}. Four studies, all observational, reported an improvement in HbA_{1c} in both the CSII and MDI groups during pregnancy without any significant difference between groups in HbA_{1c} in any of the trimesters. Third trimester HbA_{1c} values were 6.1% for MDI and 6.3% for CSII,[59] 6.8% for MDI and 6.4% for CSII,[60] 6.44% for MDI and 6.63% for CSII,[61] and 6.4% for MDI and 6.6% for CSII.[62]
- The strength of the evidence comparing CSII with MDI among pregnant women with pre-existing diabetes was insufficient for all other maternal and neonatal outcomes.
- Two studies showed no difference in the rates of cesarean section in the CSII compared with the MDI groups (94% for MDI versus 95% for CSII, *P*=NS[59] and 46% for MDI versus 69.2% for CSII, *P*=0.235[60]). One study showed a significantly higher rate of cesarean section for CSII (70%) versus MDI (34.6%), *P*=0.016.[62]
- In two studies, hypoglycemia rates did not differ between the MDI and CSII groups—5% in each group in one study[59] and 9% in each group in another study.[62]
- There was no difference in weight gain between the CSII and MDI intervention groups (13.4 kg; SD, 5.4 in the CSII group and 11.5 kg; SD, 3.7 in the MDI group[59] and 14.5 kg; SD, 3.9 in the CSII group and 14.4 kg; SD, 5.2 in the MDI group[62]).
- Gestational age at delivery ranged from 36.3 to 37.5 for MDI and from 36.3 to 36.6 for CSII and there was no significant difference between the MDI and CSII groups.[59-61]
- Rates of neonatal hypoglycemia were 13% to 14% for MDI and 10% to 16% for CSII with no significant differences between the two groups.[59 60]
- One study reported a significantly higher birth weight in CSII compared with the MDI group (3767 versus 3384 kg, *P*=0.036),[62] while another study found no difference between the two groups (3270 kg for MDI versus 3191 kg for CSII, *P*=0.86).[60] Birth weight was 3101 kg for MDI and 3295 kg for CSII in another study (*P*=not reported).[59]

- Two studies found no difference in major congenital anomalies between the MDI and CSII groups. Major congenital anomalies occurred in 12% (4/33 patients) in CSII group versus 13% (2/23 patients) in the MDI group.[62]
- Three studies found no difference in minor congenital anomalies between the MDI and CSII groups. There were no minor congenital anomalies in either group in two studies[59 61] and rates of minor congenital anomalies and pregnancy termination rates were 28% (22/78 patients) in the MDI group and 20% (4/25 patients) in the CSII group (*P*=not reported).[60]
- NICU admissions rates were not significantly different between the MDI and CSII groups—9% for MDI versus 5% for CSII in one study[59] and 35% for MDI versus 33% for CSII in another study.[62]

Study Design

All four studies evaluating CSII versus MDI therapy in pregnant women with pre-existing type 1 diabetes were observational (see Appendix D, Table 1).[59-62] Two were retrospective followup studies.[59 60] One study enrolled patients from an outpatient clinic[59] and another study enrolled patients from a university clinic.[60] None of the studies were conducted in the US. Women were given the choice to select either MDI or CSII in one study.[61] In all four studies, women were followed throughout the pregnancy. Some relevant details of study designs were not uniformly reported in these studies.

Population Characteristics

The number of participants per arm ranged from 18 to 86 pregnant women (see Appendix D, Table 2).[59-62] Two studies reported having 100% Caucasian women.[59 60] All these patients were pregnant women with pre-existing type 1 diabetes and they entered the study at various stages of pregnancy. One study reported that CSII was started 6 months before participants became pregnant.[59] Two studies reported enrolling some of the study participants on CSII before pregnancy.[60 62] The mean age of the study populations ranged from 26 to 31 years. The mean HbA_{1c} during the first trimester ranged from 6.9 to 7.8%[59-62] and the mean BMI, reported in three studies, ranged from 21.8 to 23.72 kg/m^2. There is no statistically significant difference between groups on baseline weight.[59 60 62] The duration of diabetes was reported in three studies and ranged from 7.7 to 13.9 years, with some in the CSII arm having a significantly longer duration of diabetes.[59 60 62] None of the studies reported whether participants withdrew.

Interventions

The CSII arm varied across studies. Two studies reported that primarily insulin lispro was used primarily for CSII arm[60 61] while the type of insulin was not specified in one study.[62] In the MDI arms, NPH insulin was used in two studies[59 60] and long-acting insulin was used in another study.[61] Three studies reported using four or more insulin injections daily in the MDI arms.[59 61 62] Three studies reported providing training prior to initiating insulin pump therapy in the CSII treated group.[59 61 62] The mean duration of therapy was reported in three studies and it ranged from 36 to 40 weeks.[59-61]

Reported glycemic targets varied across studies. One study reported a HbA_{1c} target of 6.5%,[61] one study specified pre-prandial blood glucose target of 90 mg/dL and a post-prandial blood glucose target of 130 mg/dL,[59] and another specified pre-prandial blood glucose target of 59.4 to 90 mg/dL.[60] Only one study reported having guidelines regarding management of blood sugar between visits.[61] Three studies reported starting CSII prenatally in all participants[59] or a portion of their participants (66%[62] and 46%[60]).

Maternal Outcomes

Details of the outcomes are reported in Appendix D, Table 4.

HbA_{1c}. All four studies reported an improvement in HbA_{1c} in both the CSII and MDI arms during pregnancy from the first to third trimesters but no statistically significant difference between groups in HbA_{1c} in any of the trimesters (Table 17).[59-62]

Table 17. Differences in HbA_{1c} by trimester in the CSII and MDI arms in women with pre-existing type 1 diabetes

Author, year	Intervention arms, N	HbA_{1c} (%) first trimester	HbA_{1c} (%) second trimester	HbA_{1c} (%) third trimester	Statistical difference between groups
Volpe, 2010[59]	MDI, 22	7.4	-	6.1	NS
	CSII, 20	6.9	-	6.3	NS
Cypryk, 2008[60]	MDI, 86	7.8	6.7	6.8	NS
	CSII, 30	7.4	6.5	6.4	NS
Kernaghan, 2008[61]	MDI, 18	7.3	6.6	6.44	NS
	CSII, 24	6.95	6.3	6.63	NS
Hieronimus, 2005[62]	MDI, 23	7.6	6.6	6.4	NS
	CSII, 33	7.5	6.34	6.6	NS

CSII = continuous subcutaneous injections; HbA1c = hemoglobin A1c; MDI = multiple daily injections; NS = not significant

Rate of cesarean sections. Three studies reported on the rate of caesarean section in the CSII and MDI arms (Table 18). Two studies showed no difference in the rates of cesarean sections between groups.[59 60] One study showed a significantly higher rate of cesarean section in CSII compared with the MDI group.[62]

Table 18. Rates of cesarean section between MDI and CSII arms in women with pre-existing type 1 diabetes

Author, year	MDI Rate of cesarean section	CSII Rate of cesarean section	Statistical significance
Volpe, 2010[59]	94%	95%	NS
Cypryk, 2008[60]	46%	69.2%	0.235
Hieronimus, 2005[62]	34.6%	70%	0.016

CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; NS = not significant

Maternal hypoglycemia. In two studies, hypoglycemia rates did not differ between the MDI and CSII arms.[59 62] In one study, hypoglycemia was defined as requiring assistance from another person to relieve symptoms and rates were 5% in each group.[59] In the other study hypoglycemia was not defined and rates were 9% in each group.[62]

Maternal weight gain. Two studies measured weight gain in pregnant women with pre-existing diabetes treated with MDI and CSII.[59 62] The difference in weight gain between the CSII and MDI treatment arms was not statistically significant in either study.[59 62]

Neonatal Outcomes

Gestational age at delivery. Three studies reported gestational age at delivery, with no difference in gestational age at delivery between the MDI and CSII groups.[59-61] Gestational age at delivery for MDI versus CSII were 36.3 versus 36.3 weeks,[59] 36.3 versus 36.6 weeks (*P*=0.58),[60] and 37.5 versus 36.5 weeks (*P*=0.28).[61]

Frequency of neonatal hypoglycemia. Two studies reported rates of neonatal hypoglycemia with no difference between the CSII and MDI groups.[59 60] In one study neonatal hypoglycemia was defined as less than 40 mg/dL and the rate was 14% for the MDI group and 16% for the CSII group.[60] The other study reported transient hypoglycemia rates of 13% (three out of 22 patients) for the MDI group and 10% (two out of 20) for the CSII group.[59]

Birth weight. Three studies reported mean birth weight, which ranged from 3101 to 3767 grams, in the two intervention arms.[59 60 62] One study reported a significantly higher birth weight with CSII compared with MDI[62] while another study found no difference between the two groups (Table 19).[60]

Table 19. Neonatal birth weights in the CSII and MDI arms in women with pre-existing type 1 diabetes

Author, year	Weight MDI (g)	Weight CSII (g)	*P*-value
Volpe, 2010[59]	3101	3295	Not reported
Cypryk, 2008[60]	3270	3191	0.86
Hieronimus, 2005[62]	3384	3767	0.036

CSII = continuous subcutaneous insulin infusion; g = grams; MDI = multiple daily injections

Major congenital anomalies. One study reported that there were no major congenital anomalies in either intervention arm.[59] Another study reported no difference in major congenital anomalies between treatment arms (12% (four out of 33 patients) in the CSII arm versus 13% (three out of 23 patients) in the MDI arm).[62]

Minor congenital anomalies. Three studies reported information about minor congenital anomalies. Two studies reported that there were no minor congenital anomalies in either intervention arm.[59 61] One study reported minor congenital anomalies plus terminated pregnancy rates of 28% (22 out of 78 patients) in the MDI arm and 20% (four out of 25 patients) in the CSII arm.[60] It was not reported whether these differences were significant.

Neonatal intensive care unit admissions. Two studies reported on neonatal intensive care unit admissions (9% in the MDI arm and 5% in the CSII arm[59] and 35% in the MDI arm and 33% in the CSII arm).[62] The treatment arms did not differ in neonatal intensive care unit admission rates.

Study Quality

All studies were of poor to fair quality (see Appendix D, Table 6).[59-62] All four studies had incomplete descriptions of study setting, population, intervention, followup, and outcomes. One study did not report eligibility criteria.[62] Three studies reported providing training prior to starting insulin pump therapy in CSII treated group. None of the studies described details of loss to followup.

Strength of Evidence

The strength of evidence examining the comparative effectiveness of CSII versus MDI in women with pre-existing type 1 diabetes was low for the outcome of HbA_{1c} and insufficient for the outcomes of rates of cesarean section and neonatal birth weight (Table 20). Because all studies were observational and there were no RCTs, the risk of bias was medium to high. For outcomes examined, data were insufficient to determine the precision of effect estimates.

Table 20. Number of studies and subjects, strength of evidence domains, magnitude of effect, and overall strength of evidence for CSII versus MDI in pregnant women with pre-existing type 1 diabetes

Outcome	Number of Studies (Participants)	Domains Pertaining to Strength of Evidence					Magnitude of Effect and Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Publication bias	
HbA_{1c}	4 (256)	Medium to High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Rate of cesarean section	3 (216)	Medium to High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Maternal hypoglycemia	2 (110)	Medium to High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Maternal weight gain	2 (110)	Medium to High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Gestational age at delivery	3 (192)	Medium to High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Birth weight	3 (216)	Medium to High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Frequency of neonatal hypoglycemia	2 (160)	Medium to high	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Minor congential anomalies	3 (192)	Medium to High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
NICU admissions	2 (100)	Medium to High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient

HbA_{1c} = hemoglobin A_{1c}; NICU = neonatal intensive care unit

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Applicability

All studies were observational with limited descriptions of study methodology, study populations, intervention and outcomes. They were all small studies done in the UK, Poland, France, and Italy and did not report on inclusion of non-Caucasian participants. The mean age of study participants was 26 to 31 years with most participants in the CSII group being enrolled into the studies prior to becoming pregnant. Most participants had diabetes duration of 7.7 to 13.9 years, with participants in the CSII groups having the longest duration of diabetes. There was lack of consistency in reporting of the glycemic targets among the studies.

Key Question 2: In patients receiving intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM versus SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus?

Comparative Effects of rt-CGM and SMBG among Patients with Type 1 Diabetes

Key Points and Evidence Grades

- There was high strength of evidence favoring rt-CGM over SMBG for their effects on HbA_{1c}. Mean between-group difference in how HbA_{1c} changed from baseline was -0.28% (95% CI, -0.44 to -0.13%, $P<0.001$). In the sensitivity analysis that only included studies with more than 60% of compliance rate (5 estimates) there was a greater HbA_{1c} reduction (mean between-group difference from baseline, -0.37%; 95% CI, -0.46 to -0.28%). Two studies reported data separately for younger age groups. One study reported no significant effect of rt-CGM as compared to the SMBG group for individuals 8-14 years of age and 15-24 years of age.[68] Another study showed a non-significant reduction in HbA_{1c} favoring rt-CGM in individuals 18 years of age or younger.[69]
- There was low strength of evidence comparing rt-CGM with SMBG for non-severe hypoglycemia. Four studies showed no difference in non-severe hypoglycemia between the rt-CGM and SMBG interventions. Two studies showed a lower duration of time spent with non-severe hypoglycemia in the rt-CGM versus MDI arms—rt-CGM spent less time with non-severe hypoglycemia compared to MDI ($P<0.05$) in one study[66] and there was no change in duration of time spent with glucose less than 70 mg/dL with rt-CGM but an increase in time with SMBG ($P=0.0002$).[63]
- There was moderate strength of evidence suggesting no difference in severe hypoglycemia rates between the rt-CGM and SMBG intervention groups (pooled RR, 0.95; 95% CI, 0.53 to 1. 69, $P=0.86$). Two of these trials reported severe hypoglycemia data specifically in pediatric populations. In one study, severe hypoglycemia was less common in those using rt-CGM than those using SMBG alone (SMBG 4/78 versus rt-CGM 0/76, $P=0.046$).[64] In contrast, the pediatric subgroup (ages 8-14 years) of another

study showed a similar incidence of severe hypoglycemia in both arms (SMBG 6/58 versus rt-CGM 4/56, *P*=0.74).[68]

- The strength of the evidence comparing rt-CGM with SMBG for hyperglycemia was low. Two studies showed no difference in hyperglycemia between the rt-CGM and SMBG arms.[67 69] One study showed a non-statistically significant trend towards less time with hyperglycemia in the rt-CGM arm compared with the SMBG arm.[66] In another study, the effect differed by the age of the population. In those 25 years of age or older, subjects with rt-CGM had significantly less hyperglycemia compared to those with SMBG alone.[68] This effect was not observed in the two other age groups investigated (age 8-14 years and ages 15-24 years). The fifth study showed significant improvements in hyperglycemia in the rt-CGM group compared with the SMBG group.[65]
- The strength of the evidence comparing rt-CGM with SMBG was low for the ratio of basal to bolus insulin. One study reported that the basal rate was a higher proportion of the total daily insulin dose in the rt-CGM compared with the SMBG intervention group (34± 11.8% versus 29.7± 10.4%, *P*=0.021).[64] In contrast, a second study reported a higher percentage of insulin delivered as bolus in the rt-CGM group (53.8% ± 10%) compared to the SMBG group (53.8% ± 10% versus 49.8% ± 15.8%, *P* not reported).[68]
- There was low strength of evidence comparing rt-CGM with SMBG for general quality of life. One study found no difference in parental satisfaction between the two intervention arms—World Health Organization Well Being Index (WHO)-5 mother's well-being score 62.7±18.9 for rt-CGM versus 60.8±19 for SMBG at 12 months.[64] The other study assessed general quality of life using the SF-12 and found an improvement on the Physical Component Score favoring rt-CGM (55.5±4.9 for rt-CGM versus 54.1±6.9 for SMBG, *P*=0.03) but no difference between the intervention groups on the Mental Component Score (48.4±10.1 for rt-CGM versus 48.7±9.6 for SMBG, *P*=0.35) at 26 weeks.[71]
- There was low strength of evidence comparing rt-CGM with SMBG for diabetes-specific quality of life. There was no difference in diabetes-specific quality of life between the rt-CGM and SMBG intervention arms in either study—Problem Areas in Diabetes (PAID) score 18.1±14.1 for rt-CGM versus 18.2±14.6 for SMBG at 26 weeks (*P*=0.50)[71] and mean difference DQOL score from baseline to followup 2.3±5.3 for rt-CGM versus 0.7±4.1 for SMBG.[63]
- The strength of the evidence comparing rt-CGM with SMBG for diabetes treatment-related quality of life was insufficient. There was a lower fear of hypoglycemia favoring rt-CGM (33.3±11.5 for rt-CGM versus 36.0±15.6 for SMBG, *P*=0.04).[71]

Study Design

Eight studies evaluated rt-CGM versus SMBG in children and adults with type 1 diabetes (see Appendix D, Table 1).[63-70] They were conducted in diverse countries, including three in the US,[66 68 69] three in multiple countries,[63 64 70] one in France,[65] and one in Australia.[67] Studies varied in their sources of support—six received industry support,[64-67 69 70] and three received other sources of support.[63 67 68] None received government funding.

Of the eight studies, seven were parallel arm RCTs[64-70] and one was a randomized cross-over trial.[63] Three studies included a run-in period,[66 68 69] and five did not.[63-65 67 70] Enrollment into four studies started and ended after 2006,[64-66 68] but other studies did not report the dates of

enrollment period.[63 67 69 70] The median followup time for all studies was 24 weeks, with a range of 12 to 52 weeks. Five studies reported the number of patients screened.[64 65 67 69 70] These studies enrolled over half of the patients that they screened with a median of 141 patients (range 13 to 322). The number of patients screened was not reported for three studies.[63 66 68] Patients were recruited from referral clinics in two studies.[65 67] No studies reported excluding pregnant patients specifically. Most studies had entry criteria based on HbA_{1c}: some studies excluded patients based on HbA_{1c} greater than 7%,[66] greater than 7.5%,[69] greater than 8.1%,[70] greater than 8.5%,[67] or less than 8%.[65] One study enrolled patients with HbA_{1c} between 7 and 10%.[68] Patients were excluded from certain studies if they had ever used an insulin pump for less than 3 months[67] or less than one year,[63] or had ever used rt-CGM in the past 6 months.[68 69]

Population Characteristics

The mean age of participants in the RCTs was 23.7 years (range, 8.5 to 41.2 years) and 24.7 years (range, 9.1 to 44.6 years) in the rt-CGM and SMBG groups, respectively (see Appendix D, Table 2). Age of participants was not reported for four studies.[63 65 67 70] Males were 46 percent and 44 percent of the study populations, respectively, for the rt-CGM and SMBG groups. Two studies did not report gender distribution.[63 70] Five studies did not report the racial composition of their study populations. In other studies, more than 90% of the participants were Caucasians.

The mean baseline HbA_{1c} in the RCTs was 8.5% in both the rt-CGM and SMBG groups. In the two studies that reported baseline BMI, the means in the rt-CGM groups were 23.5 kg/m[265] and 26.9 kg/m[243] and in the SMBG groups were 22.5 kg/m[265] and 26.3 kg/m^2.[43]

Interventions

In the rt-CGM arm, four studies used Minimed Paradigm,[64 65 67 69] two used Minimed Guardian rt-CGM,[63 70] two studies used three models[66 68] including the Abbott Freestyle Navigator, Dexcom STS, and Minimed Paradigm (see Appendix D, Table 3). In five studies, participants were asked to wear monitors continuously; two studies required rt-CGM to be used more than 70% of time;[65 67] and one study did not specify the time requirement.[69] Seven studies reported sensor compliance.[63-69] The range of compliance was wide and depended on the subpopulation studied. Three studies reported on sensor compliance by age category.[65 66 68] In each of these studies, compliance was highest in individuals greater than 25 years of age (range, 74.9 to 83%) and lowest in those 15 to 24 years of age (range, 30 to 53%). Frequency of adjusting insulin therapy and frequency of professional or allied health visits were not reported in the available studies.

In the SMBG arm, two studies used CSII[63 65] and others did not specify the type of intensive insulin therapy. Four studies required participants to perform glucose monitoring four or more times daily;[64 66-68] one required at least three times per day;[65] and three studies did not report the frequency of monitoring.[63 69 70] Three studies reported glycemic targets: HbA_{1c} less than 7.5%;[69] pre-prandial glucose 90 to 144 mg/dL, 2-hour post-prandial glucose less than 180 mg/dL, bedtime glycemic target 122 to 182 mg/dL and overnight glycemic 82 to 164 mg/dL;[64] pre-prandial glucose 70 to 133 mg/dL, 2-hour post-prandial glucose less than 180 mg/dL, and bedtime or overnight target 100 to 150 mg/dL.[68] Two studies provided guideline for between-visit titration.[65 68]

Outcomes

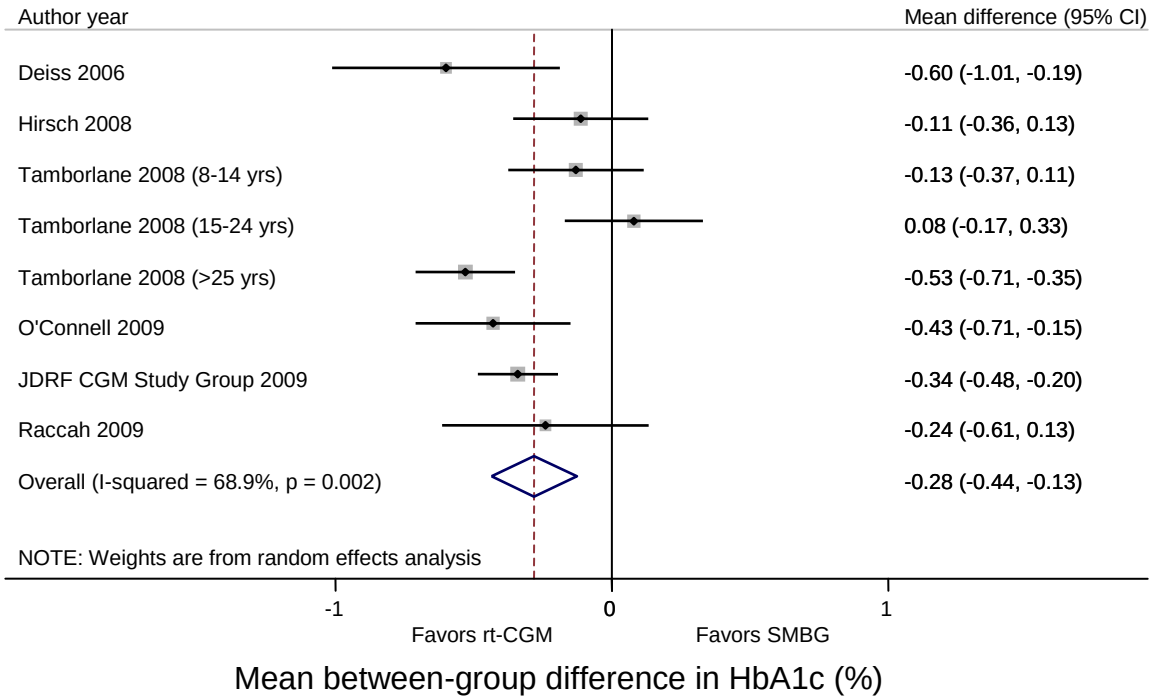
Details of the outcomes are reported in Appendix D, Table 4.

HbA_{1c}. Eight trials examined the comparative effectiveness of rt-CGM versus MDI on HbA_{1c}. Four studies showed significant differences in end of study HbA_{1c} between the rt-CGM and SMBG groups favoring rt-CGM,[66-68 70] except for the subgroup 24 years of age or younger in one study.[68] The remaining studies showed no significant difference in the change from baseline HbA_{1c} between the two groups,[63-65 68 69] including the subgroup 24 years of age or younger in the study that stratified by age.[68]

Meta-analysis of six trials (eight estimates) of at least 12 weeks duration showed a significant difference in HbA_{1c} between the rt-CGM and SMBG groups favoring rt-CGM (combined mean between-group difference from baseline, -0.28%; 95% CI, -0.44 to -0.13%, $P<0.001$; see Figure 10). The analysis suggested statistical heterogeneity (I-squared, 68.9%, $P=0.002$), but no one study influenced results substantially. Egger's test ($P=0.67$) and funnel plot did not suggest publication bias.

The heterogeneity seemed to be explained by percent of sensor compliance. In the meta-regression, we found that sensor compliance was significantly associated with the degree of HbA_{1c} reduction (see Figure 11). In the sensitivity analysis that only included studies with more than a 60% rate of compliance with the sensor (five estimates), rt-CGM had an even greater effect on reducing HbA_{1c} as compared with SMBG (combined mean between-group difference from baseline, -0.37%; 95% CI, -0.46 to -0.28%).

Figure 10. Between-group difference between SMBG and rt-CGM in how HbA_{1c} changed from baseline among adults with type 1 diabetes

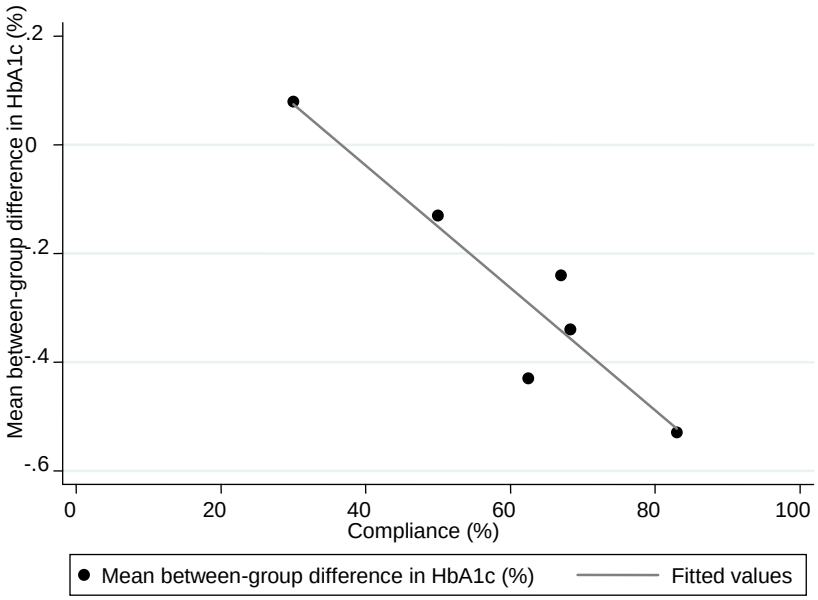


CI = confidence interval; HbA1c = hemoglobin A1c; rt-CGM = real-time continuous glucose monitor; SMBG = self-monitoring of blood glucose

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q = 22.51 with 7 degrees of freedom (p = 0.002)

Figure 11. Compliance with sensor and mean between-group difference between SMBG and rt-CGM in how HbA_{1c} (%) changed from baseline



HbA1c = hemoglobin A1c; rt-CGM = real-time continuous glucose monitoring; SMBG = self monitoring of blood glucose

Studies in younger age groups. Two studies reported data separately for younger age groups. One study reported no significant effect of rt-CGM as compared with SMBG for individuals 8 to 14 years of age and 15 to 24 years of age.[68] Another study showed a non-significant reduction in HbA_{1c} favoring rt-CGM in individuals 18 years of age or younger.[69] There were too few studies to perform a meta-analysis with consistent age categories.

Non-severe hypoglycemia. Six studies evaluated the incidence of non-severe hypoglycemia with rt-CGM compared with SMBG (see Table 21).[63 65-69] The definitions of non-severe hypoglycemia varied between studies and several studies reported multiple endpoints. The results were mixed. Three studies showed no difference in non-severe hypoglycemia between the rt-CGM and SMBG interventions.[65 67 68] Two studies showed evidence of a benefit of rt-CGM on the duration of non-severe hypoglycemia. In a RCT of patients with well controlled type 1 diabetes,[66] the rt-CGM group spent less time with non-severe hypoglycemia compared with the SMBG group (all $P<0.05$) regardless of the hypoglycemia cut-point used. In another RCT in patients with type 1 diabetes ages 12 to 72 years,[69] those in the SMBG only arm had an increase in the duration of time spent with glucose less than or equal to 70 mg/dL, whereas those in the rt-CGM arm had no change in duration of time spent with glucose less than or equal to 70 mg/dL, resulting in a statistically significant between-group difference ($P=0.0002$). In the sixth study,[63] rt-CGM use was associated with a significant reduction in the number of SMBG readings less than 60 mg/dL, whereas no difference was observed in the SMBG only group; however, the between-condition comparison was not statistically significant. Similar non-significant trends were observed when the number of patients with hypoglycemia (glucose < 60 mg/dL) was used as the endpoint.

Table 21. Non-severe hypoglycemia in the rt-CGM and SMBG interventions among patients with type 1 diabetes

Author, Year	Definition	Significant effect favoring rt-CGM
Radermecker, 2010[63]	Events <60 mg/dL in preceding 14 days	Yes (within-arm)
Raccah, 2009[65]	Change in glucose <70 /mg/dL hours per day Change in hypoglycemia AUC (mg/dL/day) Change in the number of hypoglycemia episodes	No
JDRF, 2009[66]	Minutes per day spent with glucose level ≤ 50 mg/dL Minutes per day spent with glucose level ≤ 60 mg/dL Minutes per day spent with glucose level ≤ 70 mg/dL	Yes
O'Connell, 2009[67]	Time spent with glucose ≤ 70.2 mg/dL	No
Tamborlane, 2008[68]	Minutes per day spent with glucose level ≤ 50 mg/dL Minutes per day spent with glucose level ≤ 70 mg/dL	No
Hirsch, 2008[69]	Time spent <70 mg/dL	Yes

AUC = area under the curve; JDRF = Juvenile Diabetes Research Foundation; mg/dL = milligrams per deciliter; rt-CGM = real-time continuous glucose monitor; SMBG = self monitoring of blood glucose

Severe hypoglycemia. Seven studies reported the incidence of severe hypoglycemia over the study interval using variable definitions (see Table 22).[64-70] One study reported data stratified by age and we treated these groups as distinct populations.[68] A meta-analysis of six of these studies (eight separate study populations) indicated no difference in the incidence of severe hypoglycemia with rt-CGM compared with SMBG treatment (pooled RR, 0.95; 95% CI, 0.53 to 1.69, $P=0.86$) (see Figure 12). One of study was excluded from meta-analysis because of zero events in both arms.[67] Another study was excluded from the meta-analysis because its

randomized cross-over design differed from the other studies.[63] In this study, no severe hypoglycemic events were observed.

Two of these trials reported severe hypoglycemia data specifically in a pediatric population.[64, 69] In one study,[64] severe hypoglycemia was less common in those using rt-CGM than those using SMBG alone (four out of 78 patients with SMBG versus zero out of 76 patients with rt-CGM, *P*=0.046). In contrast, the pediatric subgroup (ages 8 to 14 years) of another study[68] showed a similar incidence of severe hypoglycemia in both arms (six out of 58 patients with SMBG versus four out of 56 patients with rt-CGM, *P*=0.74).

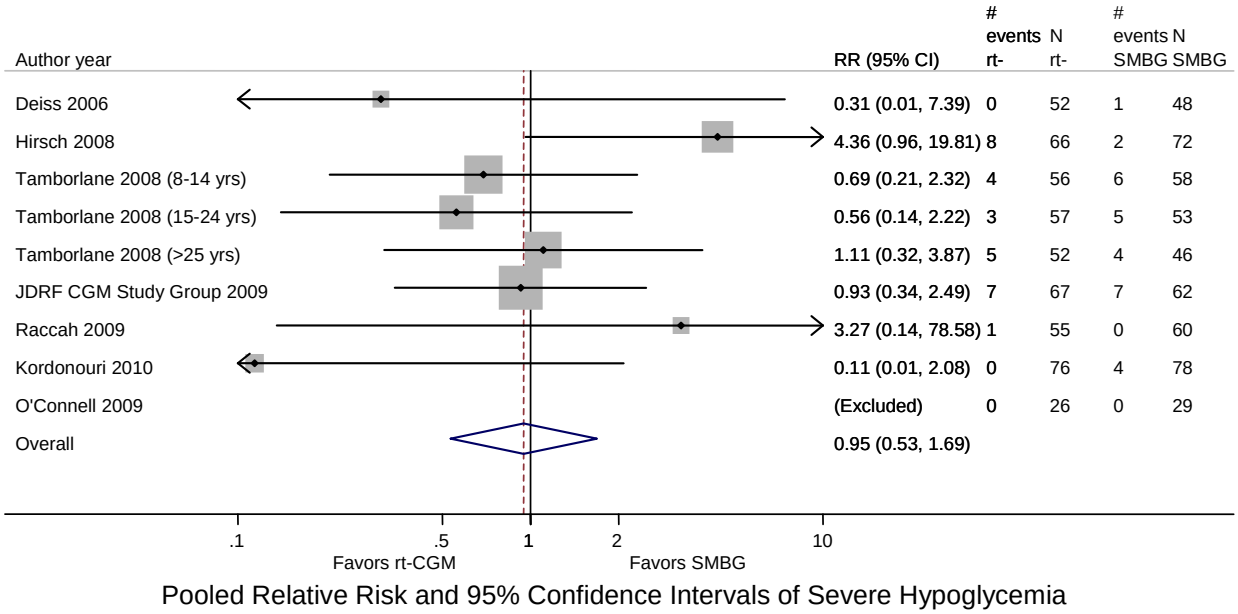
In the six studies included in the meta-analysis, the duration of intervention ranged from 12 to 52 weeks. There was no evidence of statistical heterogeneity or publication bias, using Egger's test and the funnel plot.

Table 22. Definition of severe hypoglycemia in the studies of rt-CGM and SMBG in type 1 diabetes

Author, year	Definition of hypoglycemia
Kordonouri, 2010[64]	Not further specified
Raccah, 2009[65]	Not further specified
Beck, JDRF, 2009[66]	Event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions
O'Connell[67]	Episode of hypoglycemia resulting in seizure or coma or requiring third-party assistance or the use of glucagon or intravenous glucose for recovery
Tamborlane, JDRF, 2009[68]	Event that required assistance from another person to administer oral carbohydrate, glucagon, or other resuscitative actions
Hirsch[69]	Clinical episode of hypoglycemia resulting in seizure or coma, requiring hospitalization or intravenous glucose or glucagon, or any hypoglycemia requiring assistance from another person
Deiss[90]	Not further specified

JDRF = Juvenile Diabetes Research Foundation; rt-CGM = real-time continuous glucose monitor; SMBG = self monitoring of blood glucose

Figure 12. Pooled relative risk of severe hypoglycemia in SMBG versus rt-CGM interventions among patients with type 1 diabetes



CI = confidence interval; RR = relative risk; rt-CGM = real-time continuous glucose monitor; SMBG = self monitoring of blood glucose
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 7.91 with 7 degrees of freedom (p = 0.34)
I-squared = 12%

Hyperglycemia. Five studies evaluated the comparative effectiveness of rt-CGM versus SMBG on change in hyperglycemia (Table 23).[65-69] The definitions of hyperglycemia varied between studies and several studies reported multiple different endpoints. Two studies[67 69] showed no difference between the rt-CGM and SMBG arms. One study[66] showed a non-statistically significant trend toward less time with hyperglycemia in the rt-CGM arm compared with the SMBG arm. In another study the effect differed by the age of the population.[68] In those 25 years of age and older, subjects with rt-CGM had significantly less hyperglycemia compared with those with SMBG alone; this effect was not observed in the two other age groups investigated (age 8 to 14 years and age 15 to 24 years). The fifth study showed significant improvements in hyperglycemia in the rt-CGM group compared with the SMBG group.[65]

Table 23. Hyperglycemia in the rt-CGM and SMBG interventions among patients with type 1 diabetes

Author, year	Definition	Significant effect favoring rt-CGM
Raccah, 2009[65]	Change in glucose >190 /mg/dL hours per day Change in hyperglycemia AUC (mg/dL/day)	Yes
JDRF, 2009[66]	Minutes per day spent with glucose level > 180 mg/dL Minutes per day spent with glucose level >250 mg/dL	No (trend)
O'Connell, 2009[67]	Time spent with glucose > 180 mg/dL	No
Tamborlane, 2008[68]	Minutes per day spent with glucose level > 180 mg/dL Minutes per day spent with glucose level > 250 mg/dL	Yes, in individuals 25 years of age and older. No, in other age groups
Hirsch, 2008[69]	Hyperglycemia (> 180 mg/dL) AUC	No (improvement in both arms, no between group differences)

AUC = area under the curve; JDRF = Juvenile Diabetes Research Foundation; mg/dL = milligrams per deciliter; rt-CGM = real-time continuous glucose monitor; SMBG = self monitoring of blood glucose

Ratio of basal to bolus insulin. We sought to compare rt-CGM with SMBG on four different process measures: ratio of basal to bolus insulin, frequency of adjusting insulin therapy, adherence to sensor use, and frequency of professional or allied health visits. Among these outcomes, only ratio of basal to bolus insulin (or its equivalent) was reported. One study[64] reported that after 52 weeks the basal rate was a higher proportion of the total daily insulin dose in the rt-CGM group compared with SMBG (34%; SD, 11.8% versus 29.7%; SD, 10.4%, P=0.021). In contrast, a second study reported a higher percentage of insulin delivered as bolus in the rt-CGM group compared with the SMBG group (53.8%; SD, 10% versus 49.8%; SD, 15.8%; P not reported).[65]

Quality of life. Three studies examined the comparative effectiveness of rt-CGM versus SMBG on general, diabetes specific, and diabetes treatment-related quality of life (see Table 24).[63 64 71] One study assessed the well-being of the patients' mothers using the WHO-5 and found no difference in parental satisfaction between the two intervention arms.[64] The other study assessed general quality of life using the SF-12 and found an improvement on the Physical Component Score (PCS) favoring rt-CGM but no difference between the intervention arms on the Mental Component Score (MCS).[71]

Two studies examined diabetes-specific quality of life—one using the Problem Area in Diabetes (PAID) in children and adolescents[71] and one using the DQOL in adults[63] (see Table 24). There was no difference in diabetes quality of life between the two intervention arms in either study.

One study examined diabetes treatment-related quality of life using the Hypoglycemia Fear Survey in children and adults and found lower fear of hypoglycemia favoring rt-CGM.[71]

Table 24. Quality of life in the rt-CGM and SMBG interventions among patients with type 1 diabetes

QOL Domain	Author, year	N by intervention group	Comparison	Population	Difference in QOL between comparison and baseline groups	Group favored for QOL measure
WHO-5* (mother's well-being)	Kordonouri, 2010[64]	76 rt-CGM, 78 SMBG	rt-CGM versus SMBG	154 children (aged 1-16 years, mean ± SD: 8.7 ± 4.4 years; 47.5% girls)	At 12 months, 62.7±18.9 in rt-CGM versus 60.8±19.in SMBG	Neither
SF-12*	Beck, 2010[71]	120 rt-CGM, 106 SMBG	rt-CGM vs SMBG	226 children and adults with type 1 diabetes	PCS: At 26 weeks, 55.5 ± 4.9 in rt-CGM versus 54.1 ± 6.9 in SMBG (*P*=0.03) MCS: At 26 weeks, 48.4 ±10.1 in rt-CGM versus 48.7 ± 9.6 in SMBG (*P*=0.35)	PCS: rt-CGM MCS: neither
PAID†	Beck, 2010[71]	120 rt-CGM, 106 SMBG	rt-CGM vs SMBG	226 children and adults with type 1 diabetes	At 26 weeks, 18.1 ± 14.1 in rt-CGM versus 18.2 ± 14.6 in SMBG (*P*=0.50)	Neither
DQOL†	Radermecker, 2010[63]	13 (crossover study)	rt-CGM versus SMBG	Thirteen adults with type 1 diabetes (diabetes duration: 25+/-15 years; CSII duration: 5.5+/-7.0 years)	Mean difference in the rt-CGM group from baseline was -2.3 ± 5.3 (95% CI, -6.4 to 1.7); in the SMBG group, 0.7 ± 4.1 (95% CI, 2.5 to 3.8)	Neither
Hypoglycemia Fear Survey‡	Beck, 2010[71]	120 rt-CGM, 106 SMBG	rt-CGM vs SMBG	226 children and adults with type 1 diabetes	At 26 weeks, 33.3 ± 11.5 in rt-CGM versus 36.0 ± 15.6 in SMBG (*P*=0.04)	rt-CGM

CI = confidence interval; DQOL = Diabetes Quality of Life; MCS = Mental Component Score; PAID = Problem Areas in Diabetes; PCS = Physical Component Score; QOL = quality of life; rt-CGM = real-time continuous glucose monitor; SD = standard deviation; SF-12 = Short Form-12; SMBG = self monitoring of blood glucose; WHO-5 = World Health Organization-5

* General quality of life

† Diabetes-specific quality of life

‡ Diabetes treatment-related quality of life

Study Quality

Four studies were rated with good quality[64 66 67 69] and four studies were rated with fair quality (see Appendix D, Table 5).[63 65 68 70] Those studies rated as fair were not clear in reporting allocation concealment. However, all trials were open-labeled because of the nature of the interventions.

Strength of Evidence

The strength of evidence examining the comparative effectiveness of rt-CGM versus SMBG was high for HbA_{1c}, moderate for severe hypoglycemia, and low for hyperglycemia, mild hypoglycemia, ratio of basal to bolus insulin, and quality of life (Table 25). No study reported on weight gain as an outcome. The magnitude of effect of rt-CGM versus SMBG was small but significant for the HbA_{1c} outcome, favoring rt-CGM, but there was no effect on severe hypoglycemia. Risk of bias was low for the outcomes of HbA_{1c} and severe hypoglycemia, medium for hyperglycemia and mild hypoglycemia, and high for ratio of basal to bolus insulin and quality of life.

Table 25. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and overall strength of evidence for rt-CGM versus SMBG in children and adults with type 1 diabetes

Outcome	Number of Studies (Participants)	Domains Pertaining to Strength of Evidence					Magnitude of Effect and Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Publication bias	
HbA_{1c}	8 (1126)	Low	Consistent	Direct	Precise	No	Magnitude of effect: Small Strength of evidence: High
Hyperglycemia	5 (791)	Medium	Inconsistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low
Mild hypoglycemia	6 (804)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low
Severe hypoglycemia	7 (1113)	Low	Inconsistent	Direct	Precise	No	Magnitude of effect: No effect Strength of evidence: Moderate
Ratio of basal to bolus insulin	2 (482)	High	inconsistent	Direct	Precise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low
Quality of life	2 (380)	Low	Inconsistent	Indirect	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Diabetes-specific quality of life	2 (239)	Moderate	Consistent	Direct	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Diabetes treatment-related quality of life	1 (226)	High	Not applicable (single study)	Direct	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Insufficient

HbA1c = hemoglobin A1c

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Applicability

Most studies in type 1 diabetes had small sample sizes, with the largest clinical trial including 322 participants.[31] Most RCTs were good or fair quality. The majority of studies were performed in both children and adults without stratification by age. Studies generally did not report race but based on the countries in which they were conducted (more than half were outside of the US or involved multiple countries), most studies included Caucasian participants. Participants generally had poor glycemic control at study entry (mean HbA_{1c} 8.5%), were treated in the intervention groups for an average of 24 weeks, and had diabetes for 11.5 years prior to study entry.

Effectiveness of Sensor-Augmented Pumps Compared with MDI/SMBG Among Patients With Type 1 Diabetes

Key Points and Evidence Grades

- There was moderate strength of evidence favoring sensor-augmented pumps over MDI/SMBG for their effects on HbA_{1c}. Mean between-group difference in how HbA_{1c} changed was -0.61% (95% CI, -0.75 to -0.46, $P<0.001$).
- The strength of the evidence comparing sensor-augmented pumps and MDI/SMBG for non-severe hypoglycemia was low. There was no difference in time spent with non-severe hypoglycemia between the sensor-augmented pump and MDI/SMBG intervention groups.
- There was low strength of evidence suggesting no difference in severe hypoglycemia incidence between the sensor-augmented pump and MDI/SMBG intervention groups—21/247 for sensor-augmented pump versus 17/248 for MDI /SMBG ($P=0.58$);[72] 0 events for sensor-augmented pump versus 3 events for MDI/SMBG;[73] and 0 events in eight patients in sensor-augmented pump group versus 1 event in eight patients in the MDI/SMBG group.[74]
- The strength of the evidence comparing sensor-augmented pumps with MDI/SMBG was low for hyperglycemia. Time spent with hyperglycemia was significantly less in the sensor-augmented pump compared with the MDI/SMBG intervention group ($P<0.001$).
- The strength of the evidence comparing sensor-augmented pumps with MDI/SMBG was low for weight. There was a non-significant difference in weight gain between the sensor-augmented pump and MDI/SMBG intervention groups favoring MDI/SMBG (2.4 kg versus 1.8 kg; $P=0.19$) in one study.[72] In another study, weight increased 0.7 kg in the sensor-augmented pump group and 2.0 kg in the MDI/SMBG group but the difference was not significant ($P=0.31$).
- The strength of the evidence comparing sensor-augmented pumps with MDI/SMBG was insufficient for diabetes treatment-related quality of life. User acceptance and overall diabetes treatment satisfaction were greater in the sensor-augmented pump arm compared with the MDI/SMBG arm. Blood Glucose Monitoring System Rating Questionnaire scores were 83.3±21.7 for sensor-augmented pump versus 33.3±22.6 for MDI/SMBG ($P<0.001$).[73]

Study Design

Three studies evaluated a sensor-augmented pump versus MDI/SMBG in children and adults with type 1 diabetes (see Appendix D, Table 1).[72-74] Two studies were multicenter trials in North America.[72 74] The location and number of the study sites were not specified in the third study.[73] Two studies reported receiving industry support,[72 73] and the source of support in the third study was not specified.[74] None reported receiving government funding.

All three studies were parallel arm RCTs.[72-74] Two studies described a run-in period[72 74] and one did not.[73] Of the three studies, only one described the dates of the enrollment period.[72] The followup time for the studies were 15, 16, and 52 weeks. One study reported the number of patients screened.[72] One study reported the exclusion of pregnant patients specifically.[72] In all three studies, suboptimally controlled patients were enrolled (HbA_{1c} 7.4 to 9.5%;[72] "suboptimal control";[73] and HbA_{1c} greater than or equal to 7.5%[74]).

Patients were excluded from certain studies if they had ever used an insulin pump within the past 3 years[72] or anytime in the past (i.e., CSII-naïve).[73 74]

Population Characteristics

Two studies included only adults[73 75] and one study enrolled both adults and children (see Appendix D, Table 2).[72] The mean age of participants in the RCTs was reported in the combined study sample in two studies (47.2 years[73]) and 45.9 years[74]), and stratified by treatment group in the third study (32.2 years in the sensor-augmented pump group versus 31.5 years in the MDI/SMBG group).[72] In the study that included both adults and children,[72] 32% of the sample was children and the mean ages of the children were 11.7 years in the sensor-augmented pump group versus 12.7 years in the MDI/SMBG group. The gender distribution by treatment arm was described in one study (57% males in sensor-augmented pump group versus 56% males in the MDI/SMBG group[72]) and described combining treatment arms in two studies—46% males[73] and 50% males.[74] The majority of participants in two studies were white (92%[72]) and (79%[73]). One study did not report the racial composition of the population.[74]

The mean baseline HbA_{1c} in the RCTs was similar in all three studies (median, 8.6%; range, 8.3 to 9.5%). One study reported the baseline BMI by treatment arm (sensor-augmented pump 25.3 kg/m^2 versus MDI/SMBG 25.6 kg/m^2),[72] one study reported the baseline BMI in the combined sample (mean, 27.0 kg/m^2)[73] and one study did not report baseline body mass index.[74]

Interventions

In all three studies the MiniMed Paradigm REALTime system was used and training in the use of the device was provided (see Appendix D, Table 3). The frequency and intensity of the followup visits, however, differed between studies. In the longest study,[72] patients assigned to the sensor-augmented pump arm underwent initial pump training, followed by pump initiation. Two weeks later, following on-line and in-person training sessions, the rt-CGM was introduced. Patients were then seen at 3-month intervals during which glucose data were reviewed and insulin therapy was adjusted. Patients assigned to continue MDI/SMBG were also seen at 3 month intervals and insulin adjustments were made. In the MDI/SMBG group, a blinded rt-CGM device was worn for 1-week periods at baseline, 6 months, and 12 months, such that continuous glucose profiles could be compared between the study groups at the end of the study. Both arms

of the study received the same instruction in intensive diabetes management and carbohydrate counting.

In a 15-week randomized trial,[74] patients assigned to a sensor-augmented pump initiated CSII and rt-CGM in a step-wise fashion over a 3-week period. Use of the rt-CGM started 2 weeks after CSII initiation. The patients in the sensor-augmented pump arm were also seen at weeks 3, 5, and 15. Those randomized to continue MDI/SMBG were seen at baseline and weeks 2, 5, and 15. In both arms, glucose data were reviewed and insulin adjustments were made. Participants in both arms of the study received the same instruction in intensive diabetes management and carbohydrate counting.

In a 16-week randomized trial,[73] both arms received diabetes education and those randomized to a sensor-augmented pump received additional one-time instruction regarding the use of the device. No further followup visits in either arms were specified until the end of study visit at week 16. Insulin adjustments were not made as part of the study protocol.

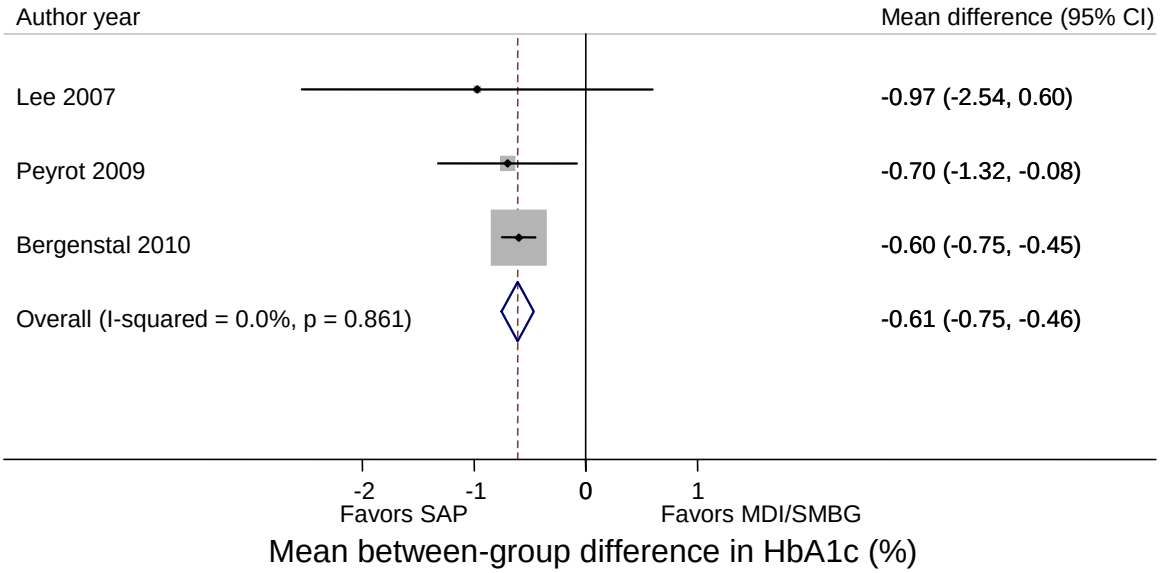
Only one study reported the frequency of rt-CGM use[72] and 67% of patients used the rt-CGM more than 60% of the time; 23% reported use more than 80% of the time.

Outcomes

Details of the outcomes are reported in Appendix D, Table 4.

HbA_{1c}. Three studies assessed the effect on HbA_{1c}.[72-74] Two studies found a significant difference in end of study HbA_{1c} between the sensor-augmented pump and MDI/SMBG groups favoring sensor-augmented pump,[72 73] and one study did not show a statistically significant difference in HbA_{1c} between the two groups.[74] A meta-analysis of all three studies showed a significant difference in the reduction from baseline HbA_{1c} between the sensor-augmented pump and MDI/SMBG groups favoring the sensor-augmented pump (combined mean between-group difference from baseline, -0.61%; 95% CI, -0.75 to -0.46%, $P<0.001$; see Figure 13). We did not find evidence of statistical heterogeneity ($P=0.86$) and no one study influenced results substantially. Egger's test ($P=0.06$) and funnel plot did not suggest publication bias.

Figure 13. Between-group difference between MDI/SMBG and sensor-augmented pumps in how HbA_{1c} changed from baseline among patients with type 1 diabetes



CI = confidence interval; HbA1c = hemoglobin A1c; MDI/SMBG = multiple daily injections and self monitoring of blood glucose
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study. The diamond at the bottom of the graph indicates the 95 percent confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.30 with 2 degrees of freedom (p = 0.86)

Non-severe hypoglycemia. One study assessed the time spent with non-severe hypoglycemia[72] defined as the area under the curve for two different cutpoints (less than 70 mg/dL and less than 50 mg/dL). The study arms had no differences in these measures during the study interval.

Severe hypoglycemia. All three studies reported on the incidence of severe hypoglycemia. In the largest study,[72] severe hypoglycemia was defined as an "episode requiring assistance and confirmed by the documentation of a blood glucose less than 50 mg/dL or recovery with restoration of plasma glucose" and occurred in a similar number of patients in the sensor-augmented pump arm and the MDI/SMBG group (21 out of 247 patients versus 17 out of 248 patients, P=0.58). In another trial,[73] three hypoglycemic events occurred in the MDI/SMBG group (N = 14), whereas no events occurred in the sensor-augmented pump group (N = 14). The number of patients who experienced events was not specified. The definition of severe hypoglycemia was not reported. In the third trial,[74] one unspecified hypoglycemic event occurred in the eight patients randomized to continue MDI/SMBG and none in the eight patients randomized to a sensor-augmented pump.

Hyperglycemia. One study assessed the time spent with hyperglycemia,[72] which was expressed as the area under the curve calculated by the rt-CGM in both arms. Two different outcomes were used: greater than 250 mg/dL and greater than 180 mg/dL. In the entire study population and when stratified by age (adults 19 to 70 years, and children 7 to 18 years of age), those randomized to a sensor-augmented pump had significantly less hyperglycemia compared with those continuing MDI/SMBG (all P<0.001), using either hyperglycemic threshold.

Weight. Two studies reported the change in weight. In one study,[72] only the change in weight in adults was reported, with a non-significant difference in weight gain between the sensor-augmented pump and MDI/SMBG arms favoring MDI/SMBG (2.4 kg versus 1.8 kg, *P*=0.19). In a second study,[73] mean weight increased 0.7 kg in the sensor-augmented pump arm and 2.0 kg in the MDI/SMBG arm; however, the between arm difference was not statistically significant (*P*=0.31).

Quality of life. One study examined diabetes treatment-related quality of life using the User Acceptance Questionnaire (UAQ) and the Blood Glucose Monitoring System Rating Questionnaire (BGMSRQ) in 28 CSII-naïve adults with type 1 diabetes.[73] At 16 weeks, user acceptance and overall satisfaction was greater in the sensor-augmented pump arm compared to MDI/SMBG.[73]

Study Quality

One study was rated as "good,"[72] while the other two studies were rated as "poor" to "fair"[73] [74] (see Appendix D, Table 5).

Strength of Evidence

The strength of evidence examining the comparative effectiveness of a sensor-augmented pump versus MDI/SMBG was moderate for HbA_{1c} but low for the outcomes of hypoglycemia, weight gain, and hyperglycemia, and insufficient for quality of life (Table 26). Risk of bias was medium for HbA_{1c} and severe hypoglycemia outcomes, and high for all other outcomes.

Table 26. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and overall strength of evidence for sensor-augmented pumps

Outcome	Number of Studies (Participants)	Domains Pertaining to Strength of Evidence					Magnitude of Effect and Strength of Evidence
		Risk of Bias: Design/ Quality	Consistency	Directness	Precision	Publication bias	
HbA_{1c}	3 (529)	Medium	Consistent	Direct	Precise	No	Magnitude of effect: Large Strength of evidence: Moderate
Hyperglycemia	1 (485)	High	Unknown (single study)	Direct	Precise	Uncertain	Magnitude of effect: High Strength of evidence: Low
Mild hypoglycemia	1 (485)	High	Unknown (single study)	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Severe hypoglycemia	3 (529)	Medium	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Weight	2 (513)	High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Diabetes treatment-related quality of life	1 (28)	High	Unknown (single study)	Direct	Precise	Uncertain	Magnitude of effect: Low Strength of evidence: Insufficient

HbA1c = hemoglobin A1c

The strength of the evidence was defined as follows: High = High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of the effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. Insufficient = Evidence is unavailable.

Applicability

The largest clinical trial had 485 participants[72] and the other two trials had less than 30 participants.[73 74] Only one study included individuals 20 years of age or younger.[72] Two studies reported the majority of participants were Caucasian,[72 73] while the other trial did not report race distribution.[74] Participants had poor glycemic control at study entry (mean HbA_{1c}, 8 to 9%), were treated in the intervention groups for 15 weeks to one year. One study reported a long duration of diabetes with a mean of 15 years.[72]

Discussion

Summary of Key Findings

Our systematic review summarizes the current state of the evidence on the impact of medical devices for insulin delivery and glucose monitoring on diabetes-related process measures, intermediate outcomes, and clinical outcomes in individuals with type 1 and type 2 diabetes mellitus.

Comparative Effectiveness of CSII versus MDI (KQ 1)

RCTs showed no difference in the effect on HbA_{1c} between the CSII and MDI intervention groups for children and adolescents, adults, or pregnant women with type 1 diabetes, or for adults with type 2 diabetes. The trials also showed no difference in rates of severe hypoglycemia between the two intervention groups for children and adolescents, or adults with type 1 diabetes, or adults with type 2 diabetes. The evidence was insufficient to draw definitive conclusions about severe hypoglycemia rates in pregnant women with type 1 diabetes.

In most studies of children and adolescents and adults with type 1 diabetes, compared with MDI, CSII use was associated with improvement in general and diabetes-specific quality of life measures. The evidence was insufficient to draw definitive conclusions about quality of life for pregnant women with type 1 diabetes or adults with type 2 diabetes.

In pregnant women with pre-existing type 1 diabetes, observational studies showed no difference in gestational age at delivery between the CSII and MDI intervention groups. Because of the small number of studies of fair to poor quality in this population, the evidence was insufficient to draw definitive conclusions about other maternal and fetal outcomes.

Our systematic review and meta-analysis of the comparative effectiveness of CSII and MDI on outcomes complements and extends two previously published meta-analysis[76 77] by including more studies of individuals with type 2 diabetes as well as pregnant women with pre-existing type 1 diabetes and by only including studies using rapidly-acting insulin analogs and not regular insulin in the CSII and MDI intervention groups. Unlike one of the prior meta-analysis[77] and similar to another,[76] we excluded before and after studies and only included RCTs in our combined estimates for HbA1c and severe hypoglycemia. We also examined additional non-glycemic outcomes, including weight gain, ratio of basal to bolus insulin, and quality of life. Unfortunately, for some of the defined outcomes — process measures (i.e., ratio of basal to bolus insulin), weight gain, non-severe hypoglycemia, hyperglycemia, and micro- and macrovascular complications — the evidence was insufficient to draw definitive conclusions in any population of diabetic individuals about the comparative effectiveness of CSII versus MDI or rt-CGM versus SMGB.

We found that CSII lowered HbA1c in children non-significantly by 0.14% compared with MDI and that there was no effect in adults with type 1 diabetes. This compares to a reduction of 0.63% for CSII versus MDI in subgroup analyses of studies using only insulin analogs in a prior study of adults and children with type 1 diabetes (three RCTs and one before-after study)[77] and a reduction of 0.4% in studies published after 2000 in another meta-analysis.[76] Our estimates are based on a larger number of RCTs using rapid-acting analogs only (total 11—seven in children and adolescents and four in adults). We found severe hypoglycemia rates in type 1 diabetes to be

similar between the MDI and CSII groups (incidence rate ratio=0.99 in children and adolescents and 0.74 in adults). While a prior study found a significantly higher rate of severe hypoglycemia with MDI compared to CSII (incidence rate ratio=2.89 for RCTs), these studies included regular insulin and studies were only included if individuals reported an elevated frequency of baseline severe hypoglycemic episodes, which may have resulted in a greater likelihood of improvement.[77] An estimate was not reported for studies using rapid-acting analogs because participants in these studies did not have a high frequency of severe hypoglycemia at baseline.[77]

Comparative Effectiveness of rt-CGM versus SMBG (KQ 2)

We only found studies of the comparative effectiveness of rt-CGM versus SMBG in children, adolescents, and adults with type 1 diabetes. Studies have not compared these two glucose monitoring approaches in pregnant women with type 1 diabetes or individuals with type 2 diabetes. Compared with the SMBG group, the rt-CGM group achieved a lower HbA_{1c}. A sensitivity analysis showed this effect to be greater in studies where sensor compliance was 60% or greater. The intervention groups did not differ in the rate of severe hypoglycemia. A few studies that evaluated quality of life found no difference between general and diabetes-specific quality of life between the two intervention groups.

Our systematic review and meta-analysis of the comparative effectiveness of rt-CGM and SMBG on outcomes complements and extends a recently published meta-analysis[78] by including additional non-glycemic outcomes, including weight gain, ratio of basal to bolus insulin, and quality of life. We also found that rt-CGM lowered HbA_{1c} more than SMBG (-0.28% in our study versus -0.30% in Pickup et al.) and that there was no difference in severe hypoglycemia in the two intervention groups.[78]

Comparative Effectiveness of Sensor-Augmented Pump versus MDI/SMBG (KQ2)

The sensor-augmented pump use was associated with a significantly greater reduction in HbA_{1c} compared with MDI/SMBG use in non-pregnant individuals with type 1 diabetes. The evidence was insufficient to draw definitive conclusions about severe hypoglycemia or quality life.

Limitations

Our systematic review highlights important weaknesses in the literature. Most RCTs examining the effect of insulin delivery and glucose monitoring devices were small, with the largest trial including 322 participants.[31] The majority of studies, particularly those comparing CSII with MDI, were fair to poor quality and did not report most quality items of interest. Most studies did not report the racial and ethnic composition of the study populations; however, for those that did, the majority of participants were Caucasian. Since few studies focused on or included children 12 years of age or younger or 65 years of age or older, we were unable to draw conclusions about the effectiveness of insulin delivery and glucose monitoring devices in these populations. The studies were heterogeneous in definitions of non-severe hypoglycemia, hyperglycemia, and weight gain, preventing us from combining data to determine effect estimates for these intermediate outcomes. None of the studies included data on long-term

diabetes micro- and macrovascular complications. This is likely related to the fact that these complications develop over many years and the longest follow-up of our studies was 52 weeks. In the pregnancy literature, none of the studies examined insulin delivery and glucose monitoring devices in women with pre-existing type 2 diabetes and the studies in women with pre-existing type 1 diabetes have not examined the effect of rt-CGM on maternal and fetal outcomes. Finally, the studies were heterogeneous in assessing and reporting quality of life outcomes which prevented us from quantifying the effects of insulin delivery and glucose monitoring devices on quality of life. We found no studies examining the comparative effectiveness of CSII versus MDI on quality of life in pregnant women and only one study examining the effects on quality of life in type 2 diabetes.

Our systematic review and meta-analysis had several limitations. We may have not included all studies on this topic; however, our search strategy was comprehensive and included non-English language publications. There was only one article identified that we were unable to translate.[79] We cannot exclude the possibility that publication bias affected our findings. For the meta-analyses examining the comparative effectiveness of CSII versus MDI and rt-CGM versus SMBG on HbA_{1c} and severe hypoglycemia, we did not find evidence of publication bias; however, for our other glycemic (hyperglycemia, non-severe hypoglycemia) and non-glycemic outcomes for which we could not perform meta-analyses, we were unable to assess for publication bias.

Implications

Our findings indicate that intensive insulin therapy delivered either by CSII and MDI using current rapidly-acting insulin analogs are about equally effective in lowering HbA_{1c} in several diabetic patient populations — adolescents, adults, and pregnant women with type 1 diabetes. Intensive insulin therapy delivered by both methods resulted in similar rates of severe hypoglycemia for adolescents and adults with type 1 diabetes. However, from a patient-focused perspective, adolescents and adults with type 1 diabetes treated with CSII reported better overall quality of life compared with those treated with MDI. Taken together, these data suggest that the approach to intensive insulin therapy to optimize glycemic control can be individualized to patient preference that will maximize their treatment satisfaction and quality of life as both CSII and MDI using current rapid-acting insulin analogs have similar effectiveness for glycemic control.

This is the first systematic review and meta-analysis to our knowledge to examine the comparative effectiveness of both rt-CGM versus SMBG and of sensor-augmented pump versus MDI/SMBG. Our findings indicate that rt-CGM is superior to SMBG in lowering HbA_{1c}, without increasing or decreasing the risk of severe hypoglycemia, in non-pregnant individuals with type 1 diabetes, particularly those who are compliant with wearing the monitoring device (HbA_{1c} reduction 0.28% for all studies versus 0.37% in studies with >60% sensor compliance rate). Even though CSII and MDI without rt-CGM have similar effects on HbA_{1c}, the addition of rt-CGM to CSII is superior to MDI/SMBG in lowering HbA_{1c}. Thus, the addition of this monitoring technology to intensive insulin therapy can assist in achieving glycemic targets in non-pregnant individuals with type 1 diabetes. The available literature does not allow us to determine the comparative effectiveness of rt-CGM versus SMGB in patients only using CSII or only using MDI because the modes of intensive insulin therapy were mixed in the available studies.

Future Research

Our report highlights the need for several areas of future research examining the effect of insulin delivery and glucose monitoring devices in the management of diabetes mellitus. We identified a need for well conducted RCTs of intensive insulin therapy delivered via CSII versus MDI in young children with type 1 diabetes and in pregnant women and elderly patients with both type 1 and type 2 diabetes. Studies in the elderly are important as diabetes prevalence increases with age.[2] Only a small number of studies in non-adolescent children have compared CSII with MDI on glycemic and non-glycemic outcomes and studies comparing rt-CGM with SMBG have included a mixture of children and adults without stratifications focused exclusively on the young. Current studies examining the comparative effectiveness of rt-CGM versus SMBG on outcomes have included mixed populations receiving intensive insulin therapy as CSII and/or MDI; however, they have not determined the effect of these two glucose monitoring strategies in individuals treated with only CSII or only MDI. Such a study would help to elucidate whether the observed benefit of sensor-augmented pump compared with MDI/SMBG on glycemic control is secondary to the rt-CGM technology, the mode of intensive insulin delivery, or both. Future studies should also seek to identify and use an agreed upon set of general and diabetes-specific and treatment-related quality of life measures to allow comparisons across studies, including reporting of standard errors and confidence intervals to allow quantitative, pooled assessments. Finally, future studies should include ethnically diverse populations because diabetes is relatively common in all ethnic/racial groups, and type 2 diabetes is more common in blacks than in whites.[80]

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Abbreviations

AHRQ = Agency for Healthcare Research and Quality
BGMSRQ = Blood Glucose Monitoring System Rating Questionnaire
BMI = body mass index
CGM = continuous glucose monitoring
CSII = continuous subcutaneous insulin infusion
DQOL = Diabetes Quality of Life
DQOLCTQ = Diabetes Quality of Life Clinical Trials Questionnaire
DQOL-Y = Diabetes Quality of Life-Youth
EPC = Evidence-based Practice Center
HbA1c = hemoglobin A1c
KQ = key questions
MCS = Mental Component Score
MDI = multiple daily injections
NPH = neutral protamine Hagedorn
PAID = Problem Area in Diabetes
PCS = Physical Component Score
RCTs = randomized controlled trials
rt-CGM = real-time continuous glucose monitoring
SAP = Sensor-Augmented Pump
SDS = standard deviation scores
SF = Short Form
SMBG = self-monitoring of blood glucose
UAQ = User Acceptance Questionnaire
WHO-5 = World Health Organization-5