Effective Health Care Program

Comparative Effectiveness Review
Number 57

Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness

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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 Children's Health Insurance Program (CHIP).

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

www.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 email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness

Structured Abstract

Objectives. To systematically review whether the mode of intensive insulin therapy (continuous subcutaneous insulin infusion [CSII] vs. multiple daily injections [MDI]) and/or the mode of blood glucose monitoring (real time-continuous glucose monitoring [rt-CGM] vs. self-monitoring of blood glucose [SMBG]) 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 July 2011. 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 selected 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. We excluded studies that used regular insulin in the CSII arms. 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 homogeneous.

Results. We included 41 studies (44 publications). RCTs showed no difference in the effect of CSII and MDI on HbA_{1c} (moderate strength of evidence [SOE]) or severe hypoglycemia (low SOE) for children or adolescents with type 1 diabetes, or for adults with type 2 diabetes. In adults with type 1 diabetes, HbA_{1c} decreased more with CSII than with MDI (low SOE), but results were heavily influenced by one study. There was no difference in severe hypoglycemia (low SOE). In children and adults with type 1 diabetes, CSII use was associated with improved quality of life compared with MDI (low SOE). There was insufficient evidence about quality of life for adults with type 2 diabetes. The SOE 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 percent or greater (high SOE). There was no difference in the rate of severe hypoglycemia (low SOE) or quality of life (low SOE). Sensor-augmented pump use was associated with a significantly greater reduction in HbA_{1c} compared with MDI/SMBG use in nonpregnant individuals with type 1 diabetes (moderate SOE). 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 have similar effectiveness on glycemic control and severe hypoglycemia, except in adults with type 1 diabetes where CSII had a favorable effect on HbA_{1c}. These data also indicate that rt-CGM is superior to SMBG in lowering HbA_{1c}, without affecting the risk of severe hypoglycemia, in nonpregnant

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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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 vascular complications.[1] Thirty million people in the United States are diagnosed with diabetes, and that number is expected to increase to 39 million people by 2050.[2-4] Thus, millions of people require 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] 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.

Importance of Tight Glycemic Control and Associated Risks

Tight glycemic control with intensive insulin therapy has been shown to reduce the risk of vascular complications due to 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, a barrier to tight control,[7] and can also lead to weight gain.[10,11]

Measurement of Glycemic Control

Measurement of hemoglobin A_{1c} (HbA_{1c}), reflecting blood glucose levels over a 2- to 3-month period, is the preferred method of assessing long-term glycemic control in patients with type 1 and type 2 diabetes.[12] Self-monitoring of blood glucose (SMBG) by fingerstick three or more times daily is recommended for patients using multiple insulin injections or insulin pump therapy as a way to adjust insulin therapy; however, SMBG measures are more variable than HbA_{1c}.[13] SMBG is also used by pregnant women with diabetes, since clinical management decisions are made on a weekly basis to prevent fetal complications.[14] The role of SMBG is less clear for patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy.[15]

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

Patients currently maintain tight glycemic control using physiological basal and meal-time (prandial) insulins. Patients take these medications either as multiple daily injections (MDI) or by external continuous subcutaneous insulin infusion (CSII) via a pump.

SMBG provides specific and timely feedback on the degree of hyperglycemia.[10] The problems with SMBG are pain, costs, behavioral and technical skills, required motivation, and intrusiveness.

Continuous glucose monitoring (CGM) systems address these issues by recording blood glucose levels day and night, significantly decreasing the need for fingerstick measurements. CGM, in conjunction with intensive insulin treatment, is useful in adults who are at least 25 years old and have type 1 diabetes.[16] Real-time continuous glucose monitoring (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. Rt-CGM is now the preferred method of CGM. As a result, we will focus on studies examining rt-CGM.

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

Clinical Decisionmaking and Indications

CSII is recommended for patients with type 1 diabetes who are not achieving glycemic goals despite adherence to a maximum MDI regimen and for patients with type 1 diabetes who merely prefer pump therapy.[17,18] Experts recommend rt-CGM for patients with type 1 diabetes who have no awareness of the early symptoms of hypoglycemia or who are pregnant or plan to be pregnant.[19]

Given new technologies in insulin delivery and glucose monitoring, clinicians are faced with challenges determining which populations will benefit most from CSII and rt-CGM. Both technologies are expensive and require extensive training and oversight.

Comparison of CSII With MDI

Evidence is lacking regarding the benefits and risks of CSII in certain populations of patients with diabetes. In prior systematic reviews, most of the evidence from comparisons of CSII with MDI in patients with type 1 diabetes indicated improved glycemic control with CSII use in adults, although its effect on other clinical outcome measures was unclear.[20-23] Similarly, evidence is lacking regarding the benefit of CSII in the elderly and children with type 1 diabetes.

Because prior systematic reviews have included studies using regular insulin in the CSII arms, they have not been able to determine the comparative effectiveness of MDI with currently available rapid-acting analog-based CSII.[20-23]

The benefits of CSII compared with MDI in individuals with type 2 diabetes also remain unclear. While some studies suggest that CSII is comparable with MDI in attaining adequate glycemic control,[21,24] other studies found a lower HbA_{1c} level with

CSII.[25,26] One prior meta-analysis found no significant difference in HbA_{1c} and hypoglycemic episodes between the CSII and MDI groups.[27]

The evidence comparing MDI with CSII in pregnant women with pre-existing type 2 diabetes is also limited. In one systematic review that looked at pregnant woman with pre-existing type 1 or type 2 diabetes, mean birth weight was greater with CSII than MDI, but the data were insufficient to permit conclusions about other outcomes.[28]

Comparison of rt-CGM With SMBG

A recent meta-analysis comparing rt-CGM with SMBG in type 1 diabetes showed a benefit of rt-CGM in improving glycemic control with no difference in hypoglycemia frequency; however, other nonglycemic outcomes were not reported.[29] In general, however, 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 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 question of whether the mode of intensive insulin therapy (CSII vs. MDI) 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 (rt-CGM vs. SMBG) in those same populations. Our specific Key Questions (KQs) are listed below and are displayed in Figure A. Process measures, intermediate outcomes, and clinical outcomes of interest are summarized in Table A.

KQ1. In patients receiving intensive insulin therapy, does mode of delivery (CSII vs. MDI) 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)?
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 vs. SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes 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:

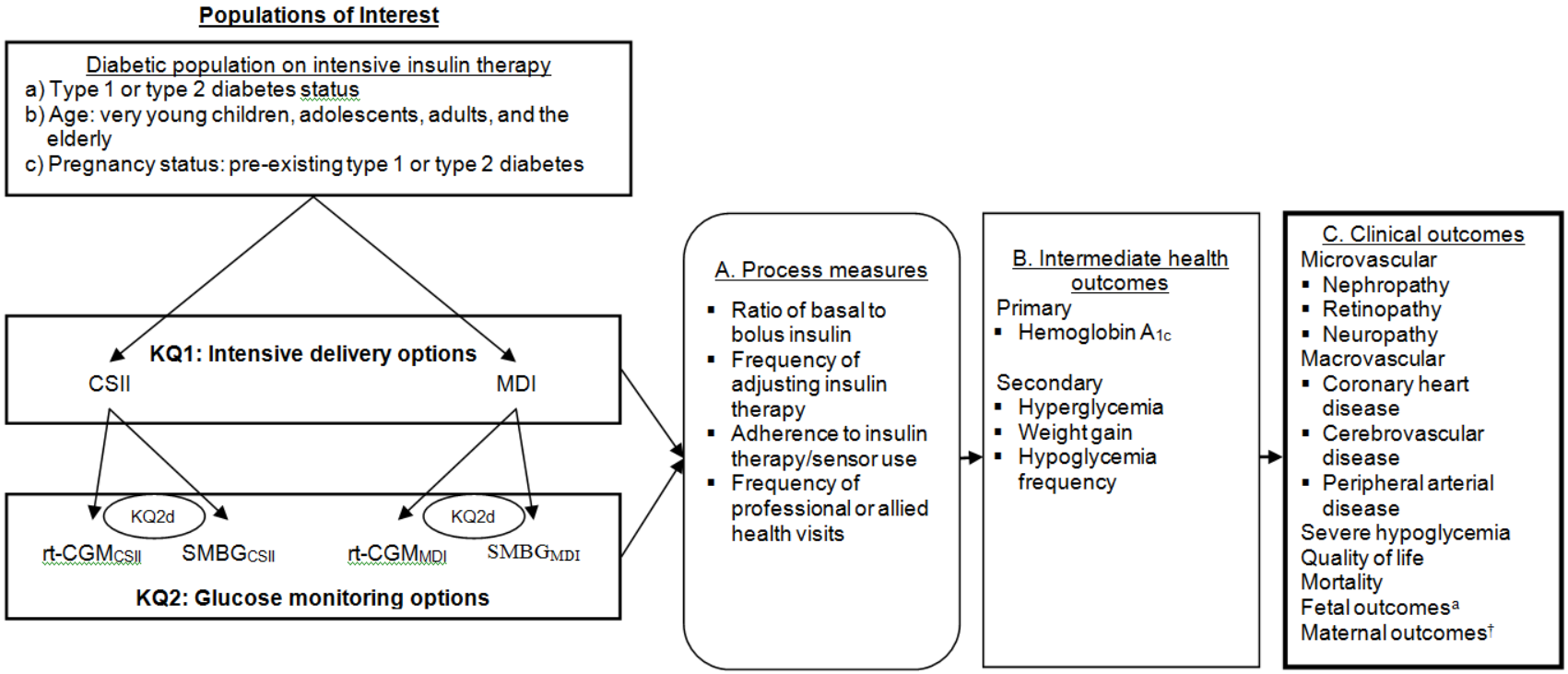
a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?
d. Intensive insulin delivery: MDI or CSII?

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[a] Frequency of adjusting insulin therapy Adherence to insulin therapy/sensor use Frequency of professional or allied health visits	**Primary** Hemoglobin A_{1c} **Secondary** Hyperglycemia Weight gain Hypoglycemia frequency	**Microvascular**[b] Nephropathy Retinopathy Neuropathy **Macrovascular**[b] Coronary heart disease Cerebrovascular disease Peripheral arterial disease Severe hypoglycemia Quality of life Mortality Fetal outcomes[c] **Maternal pregnancy outcomes** Cesarean section rates

[a]The optimal distribution of the total daily insulin dose is 40-50 percent administered as basal insulin and the remaining 50-60 percent as bolus insulin divided over each meal. This prevents patients from being overinsulinized with basal insulin, which increases the risk for hypoglycemia.
[b]We included only objective assessments of microvascular and macrovascular outcomes.
[c]Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, admission to a neonatal intensive care unit, stillbirth, and neonatal and perinatal mortality.

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



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

[*]Fetal outcomes include gestational age, birth weight, frequency of neonatal hypoglycemia, birth trauma, major and minor anomalies, admission to a neonatal intensive care unit, stillbirth, and neonatal and perinatal mortality.

[†]Maternal outcomes include cesarean section rates.

Note: Stratifications of interest for KQ2: diabetes status (2a), age (2b), pregnancy status (2c), and glucose monitoring strategy (2d).

Methods

Data Sources and Selection

Search Strategy

We searched the following databases for primary studies for the periods in parentheses: MEDLINE® (1966 to July 2011), Embase® (1974 to July 2011), and the Cochrane Central Register of Controlled Trials (1966 to July 2011). 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.

Study Selection

Titles, abstracts, and articles were independently reviewed by two reviewers. 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 evaluating methods of insulin delivery or glucose monitoring no longer used in clinical practice. We defined MDI as at least three injections per day and SMBG as at least three fingersticks per day. We included randomized controlled trials (RCTs) and observational studies of microvascular, macrovascular, maternal, or fetal outcomes. For all other outcomes (Table A), we included only RCTs.

Data Extraction and Quality Assessment

Data Abstraction

We 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., before conception, first trimester, or second trimester). We classified measures of quality of life (QOL) into the following categories: general health-related QOL, disease-specific QOL, and treatment-specific QOL.

Quality Assessment

We used different quality assessment tools for RCTs and observational studies. For RCTs, we based the dual independent review of article quality on the Cochrane Collaboration's Risk of Bias Tool,[30] supplemented with items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[31] For observational studies, we selected items from the Downs and Black quality checklist[32] and from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[31]

Applicability

We assessed the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings were typical for individuals with diabetes who are receiving treatment in a usual care setting.

Data Analysis and Synthesis

We conducted meta-analyses when there were at least two trials and when studies were sufficiently homogeneous with respect to key variables. For continuous outcomes, we calculated a weighted mean difference in the change from baseline by using a random-effects model with the DerSimonian and Laird formula.[33] If studies reported the incidence of severe hypoglycemia, then we calculated a pooled relative risk (RR) using the DerSimonian and Laird random-effects model.[33] 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.[33]

We tested heterogeneity among the trials in all the meta-analyses by using a standard chi-squared test with a significance level of alpha less than or equal to 0.10. We also examined heterogeneity among trials by using an I-squared statistic, which describes the variability in effect estimates due to heterogeneity rather than random chance.[34] If we found substantial heterogeneity, we attempted to determine reasons for this by conducting metaregressions using baseline HbA_{1c} and compliance. For all meta-analyses, we conducted formal tests for publication bias using Begg's[35] and Egger's tests.[36]

Rating the Body of Evidence

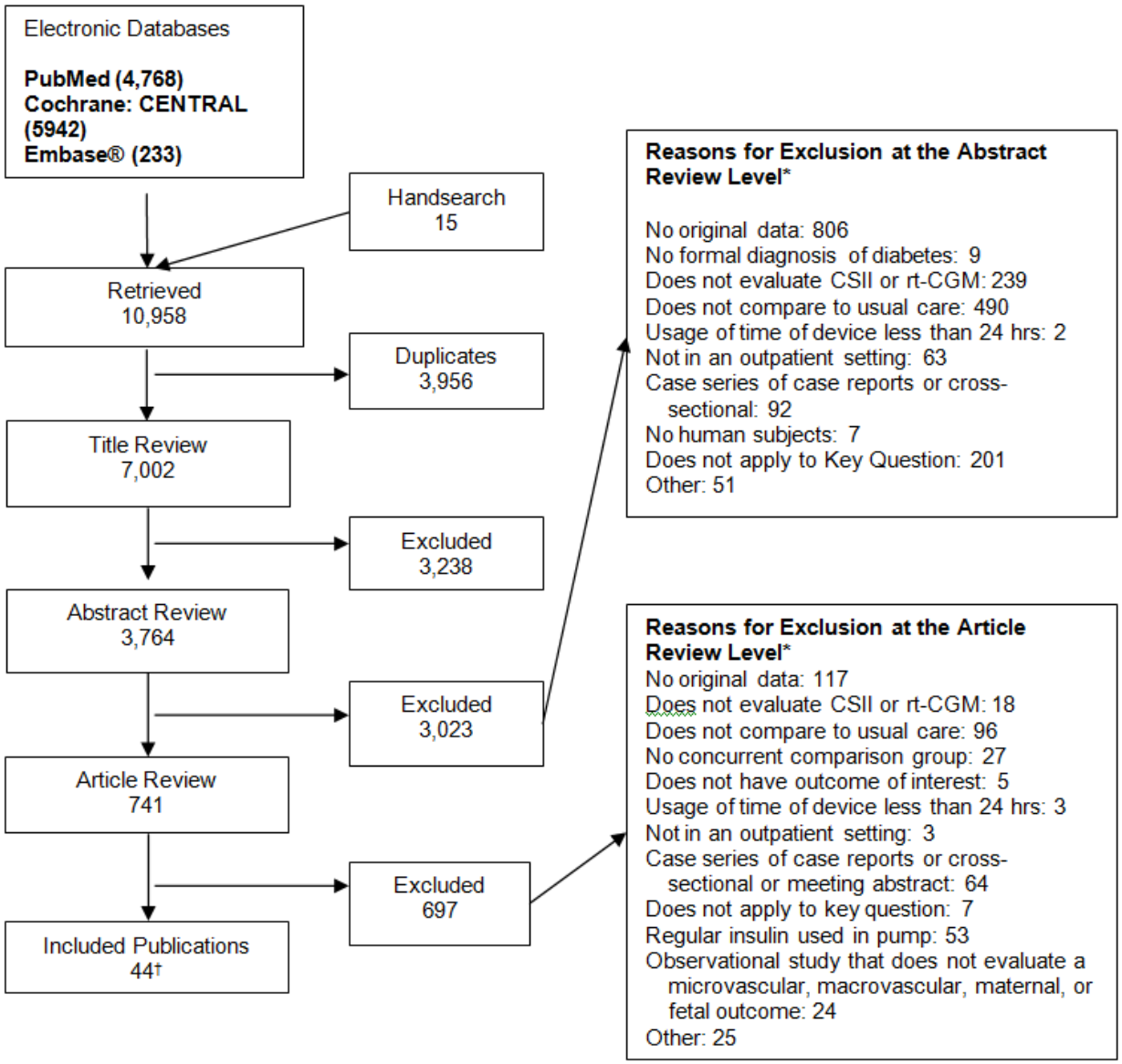
We graded the strength of the evidence addressing KQs 1 and 2 by adapting an evidence grading scheme recommended in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[37] We classified strength of evidence into four basic categories: high, moderate, low, and insufficient.

Results

Search Results

Figure B summarizes the search results. From a search of 7,002 unique records, we included a total of 41 studies (44 publications) in this review.

Figure B. Summary of the literature search



CENTRAL = Central Register of Controlled Trials; CSII = continuous subcutaneous insulin infusion; hours; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitor; SMBG = self-monitoring of blood glucose

*Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.

†41 studies in 44 publications: 28 compared CSII with MDI (9 in children and adolescents with type 1 diabetes, 9 in adults with type 1 diabetes, 4 [5 publications] in adults with type 2 diabetes, 6 in pregnant women with pre-existing type 1diabetes); 9 (10 publications) compared rt-CGM with SMBG; 4 (5 publications) compared a sensor-augmented pump with MDI/SMBG.

KQ1. Comparative Effectiveness of CSII Versus MDI

Children and Adolescents With Type 1 Diabetes

Study Design

Nine studies evaluated CSII versus MDI therapy in children and adolescents with type 1 diabetes.[38-46] Study designs are indicated in Table B.

Population Characteristics

The mean age of participants in the RCTs was 16.5 years in the MDI group and 11.4 years in the CSII group. Most studies did not report race.[38,41-43,45,46] Glycemic control was suboptimal at the time of enrollment in the RCTs, with a mean HbA_{1c} of 8.5 percent in the MDI group and 8.6 percent in the CSII group.

Interventions

The MDI arms varied across studies in the type of insulin used.[38,40-46] The MDI schedule was three, four, or more injections daily in most studies. In the CSII arm, patients used insulin aspart in three studies[38,39,44] and insulin lispro in six studies.[40-43,45,46] The duration of therapy in each intervention arm ranged from 3.5 to 24 months, with six studies having 12 or more months of followup.[38,39,41-43,45]

Applicability

Most studies in children and adolescents with type 1 diabetes were small. Few studies targeted children 12 years of age or less.

Outcomes

Table B shows the main results on the comparative effectiveness of CSII versus MDI in children and adolescents with type 1 diabetes. It includes the strength of evidence (see the definitions[47] in the footnote) for each outcome.

Table B. Summary of the evidence of the comparative effectiveness of CSII versus MDI in children and adolescents with type 1 diabetes

Outcome	Strength of Evidence	# of Studies/ # of Good-Quality Studies	Main Findings
HbA_{1c}	Moderate	9 (7 RCTs; 2 non-RCTs) / 1	Mean between-group difference in HbA_{1c} change from baseline was -0.14 percent, decreasing slightly more with CSII than with MDI (95% CI, -0.48 to 0.20%, P = 0.41). Results were similar among adolescents over 12 years old (mean between-group difference in the change from baseline HbA_{1c}, -0.10%; 95% CI, -0.47 to 0.27%) and were less different among children 12 years old or less (mean between-group difference in the change from baseline HbA_{1c}, -0.05%; 95% CI, -1.01 to 0.96%).
Daytime hypoglycemia	Low	3 (all RCTs) / 0	The frequency of daytime hypoglycemia did not differ significantly between MDI and CSII intervention groups (mean between-group difference in perceived hypoglycemic events over 104 weeks, 0; 95% CI, -1.1 to 1.1;[38] mean between-group difference in the change from baseline to 24 weeks in the number of blood glucose excursions below 70 mg/dL, -0.9; 95% CI, -2.1 to 0.3;[40] mean between-group difference in number of hypoglycemic episodes/patient at 52 weeks, -3.7; 95% CI, -13.2 to 5.8[45]).
Nocturnal hypoglycemia	Low	2 (all RCTs) / 1	The frequency of nocturnal hypoglycemia did not differ significantly between the MDI and CSII intervention groups. In 1 study, there were 4 events/patient/study period (95% CI, 0.3 to 7.7) for MDI vs. 3 events/patient/study period (95% CI, 1.0 to 5.0) for CSII over 52 weeks.[45] 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.[44]
Mild hypoglycemia	Insufficient[a]	1 (RCT) / 0	One study found no significant difference in mild hypoglycemia (events with blood glucose less than 70 mg/dL) between the MDI (22 events/patient) and CSII (19.8 events/patient) intervention groups over 14 weeks.[46]
Severe hypoglycemia	Low	6 (5 RCTs; 1 non-RCT) / 1	The rate of severe hypoglycemia was similar between the 2 intervention arms. The mean incidence rate ratio for severe hypoglycemic event rates in RCTs for CSII vs. MDI was 0.99 (95% CI, 0.57 to 1.71, P = 0.97). Results were similar among adolescents over 12 years of age (mean incidence rate ratio for CSII vs. MDI, 0.95; 95% CI, 0.42 to 2.13) and children less than 12 years of age (mean incidence rate ratio for CSII vs. MDI, 1.02; 95% CI, 0.49 to 2.16).
Hyperglycemia	Insufficient[a]	1 (RCT) / 0	One study found no difference in the frequency of hyperglycemia between the MDI (6.7 events) and CSII (7.9 events) intervention groups over 14 weeks.[46]
Ratio basal to bolus insulin	Insufficient[a]	1 (non-RCT) / 0	One study found no difference in the ratio of basal to bolus insulin between the MDI and CSII intervention groups (mean between-group difference, 1.7; 95% CI, -2.5 to 5.9).[42]
Weight	Low	3 (all RCTs) / 1	The mean between-group difference in how BMI standard deviation score changed from baseline was -0.12 units, decreasing slightly more with CSII than MDI (95% CI, -0.55 to 0.30 units).
General QOL	Low	2 (all RCTs) / 0	A meta-analysis of 2 studies showed no significant difference in general QOL between CSII and MDI in this population (mean between-group difference, 2.3; 95% CI, -6.9 to 11.5; P = 0.95).

Table B. Summary of the evidence of the comparative effectiveness of CSII versus MDI in children and adolescents with type 1 diabetes (continued)

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
Diabetes-specific QOL	Low	4 (all RCTs) / 1	One study showed improvement in diabetes QOL favoring CSII. The Diabetes Quality of Life-Youth score was 77.4 (95% CI, 69.5 to 85.3) at baseline, 76.4 (95% CI, 68.3 to 84.5) at end of study for MDI, and 82.7 (95% CI, 75.3 to 90.1) at end of study for CSII.[45] One study did not find a difference in diabetes QOL between the 2 interventions (numerical data not presented).[44]
Diabetes treatment-related QOL	Low	3 (all RCTs) / 0	A meta-analysis of 2 studies showed improvement in diabetes treatment satisfaction favoring CSII over MDI (mean between-group difference in the Diabetes Treatment Satisfaction Questionnaire, 5.7; 95% CI, 5.0 to 6.4).
Process measures, clinical outcomes	Insufficient	0	We did not find any studies addressing certain process measures (frequency of adjusting insulin therapy, adherence, health visits) and clinical outcomes (microvascular and macrovascular disease and mortality).

BMI = body mass index; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; QOL = quality of life; RCT = randomized controlled trial

[a]Strength of evidence was graded as insufficient because the body of evidence consisted of only 1 study with medium or high risk of bias, or the results were imprecise.

Note: 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, does not permit a conclusion, or consists of only 1 study with high risk of bias.[37,47]

Adults With Type 1 Diabetes

Study Design

Nine studies evaluated the effectiveness and safety of CSII versus MDI among adults with type 1 diabetes.[48-56] Study designs are indicated in Table C.

Population Characteristics

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 percent higher in the MDI versus CSII arm.[55] Intervention-arm-specific HbA_{1c} ranged from 7.4 percent to 9.3 percent at baseline.[48,49,51,54,55] The mean duration of type 1 diabetes ranged from 14.4 to 25 years.[48-51,53-56]

Interventions

Four studies used NPH (neutral protamine Hagedorn) insulin as the long-acting insulin for the MDI arm,[51,54-56] and the other studies used insulin glargine.[48-50,52,53] All studies used insulin aspart or insulin lispro as the short-acting insulin during MDI treatment.[48-56] Two studies incorporated 7 days of CGM.[50,52]

Applicability

Few studies compared the effect of CSII with 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. No study focused on elderly adults with type 1 diabetes, although this is likely a small population. The mean baseline HbA_{1c} was 7.4 to 9.3 percent across the studies. The duration of diabetes at enrollment was greater than 14 years in the studies reporting this. Eligibility criteria for MDI and CSII use varied significantly across the studies.

Outcomes

Table C shows the main results on the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes.

Table C. Summary of the evidence of the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
HbA_{1c}	Low	4 (all RCTs) / 2	HbA_{1c} decreased more with CSII than with MDI, but results were heavily influenced by one study[54] in which participants had a higher baseline HbA_{1c} than in the other studies (mean between-group difference from baseline, -0.30%; 95% CI, -0.58 to -0.02). After removing this study, the difference between CSII and MDI became null (mean between-group difference from baseline, -0.01 percent, 95% CI, -0.35 to 0.34 percent).
Daytime hypoglycemia	Low	1 (RCT) / 0	One study reported more symptomatic and asymptomatic hypoglycemia between 8 a.m. and midnight in the MDI compared with the CSII intervention arm ($P < 0.05$).[52]
Nocturnal hypoglycemia	Low	3 (all RCTs) / 0	Three studies reported nocturnal hypoglycemia. In 1 crossover trial, the proportion of patients experiencing nocturnal hypoglycemia was similar in the MDI and CSII intervention arms (RR for any, 0.98; 95% CI, 0.83 to 1.17; RR for symptomatic, 0.87; 95% CI, 0.64 to 1.19), although there were fewer episodes per person in the CSII than MDI group (IRR, 0.76; 95% CI, 0.63 to 0.91).[52] Two other studies found no statistically significant difference in nocturnal hypoglycemic episodes between the 2 intervention groups.[48,50]
Symptomatic hypoglycemia	Low	4 (all RCTs) / 1	We found an increased risk of symptomatic hypoglycemia for CSII compared with MDI (combined IRR, 1.3; 95% CI, 1.2 to 1.4), but we found evidence of substantial statistical heterogeneity for this meta-analysis. When excluding a study that required participants to have had recent severe hypoglycemia[50] (compared to the other 2, which excluded those with recent severe hypoglycemia[48,55]), we saw an IRR suggesting no relative difference in the incidence of symptomatic hypoglycemia for CSII compared with MDI (combined IRR, 1.0; 95% CI, 0.8 to 1.1). Another study, which did not provide sufficient quantitative results, reported slightly more symptomatic hypoglycemic events with CSII vs. MDI (IRR, 1.1; 95% CI, 1.0 to 1.3), although a similar proportion of participants experienced events over 5 weeks (RR, 1.0; 95% CI, 0.9 to 1.2).[52]
Other nonsevere hypoglycemia	Low	6 (all RCTs) / 1	Three studies found no difference in nonsevere hypoglycemia between the 2 intervention groups (in 1 study, mean between-group difference in asymptomatic hypoglycemia event rate, -0.2; 95% CI, -1.39 to 0.99).[48] In 2 studies, the incidence of mild hypoglycemia was higher in the CSII than MDI group,[52,54] with the relative difference statistically significant in 1 study (between-group difference in change in hypoglycemic rate, 0.99; 95% CI, 0.11 to 1.87).[54] One additional study found a higher frequency of hypoglycemia in the MDI than CSII group (RR, 1.12; 95% CI, 1.08 to 1.17).[51]
Severe hypoglycemia	Low	8 (all RCTs) / 1	The incidence of severe hypoglycemia did not differ between the 2 intervention groups (combined RR, 0.74; 95% CI, 0.30 to 1.83). Four crossover trials did not provide quantitative results on severe hypoglycemia by period and therefore were not included in the meta-analysis. Two studies showed more severe hypoglycemia with MDI than CSII,[51,52] with 1 study reporting an RR of 2.6 (95% CI, 2.08 to 3.25).[51] One study showed less severe hypoglycemia with MDI than CSII (IRR, 3.00; 95% CI, 0.24 to 157.49).[56] One study found similar rates of severe hypoglycemia between the 2 groups (1.1 events/patient for CSII vs. 1.3 events/patient for MDI over 4 months, $P = 0.33$).[49]
Hyperglycemia	Low	3 (all RCTs) / 0	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) favoring CSII in 1 study.[48] Two other studies reported no difference in fasting glucose between the MDI and CSII groups.

Table C. Summary of the evidence of the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes (continued)

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
Bedtime hyperglycemia	Insufficient[a]	1 (RCT) / 0	There was insufficient strength of evidence to determine the relative effects of CSII and MDI on glucose at bedtime. A single study reported no difference in glucose at bedtime in the CSII compared with MDI arm but did not provide glucose results.[54]
Preprandial glucose	Low	3 (all RCTs) / 0	The mean between-group difference in preprandial glucose over 6 months was -17.1 mg/dL (95% CI, -42.1 to 8.0 mg/dL) favoring CSII in 1 study. In another study, predinner glucose was lower with CSII (128 mg/dL) compared with MDI (148 mg/dL) at the end of 5 weeks (P = NS). Predinner and prelunch glucose levels were not significantly lower with CSII than MDI at 4 months in a third study.
Post-prandial glucose	Low	3 (all RCTs) / 0	The evidence suggested slightly lower post-prandial glucose levels with CSII than MDI treatment. The reported mean between-group difference in post-prandial glucose was -5.5 mg/dl (95% CI, -29.9 to 18.9 mg/dl) in 1 study[48] and -24 and -15 mg/dl post-breakfast and post-dinner, respectively, in another.[52] Post-breakfast glucose levels were not significantly higher in the MDI than CSII arm in a third study.[54]
Nocturnal hyperglycemia	Low	2 (all RCTs) / 0	Two studies found no between-group difference in nocturnal glucose,[48,54] with 1 reporting an increase in nocturnal glucose in both arms (between-group difference, 54.8; 95% CI, -7.2 to 116.7 mg/dl).[48]
Weight	Low	4 (all RCTs) / 0	Weight gain did not differ between CSII and MDI (combined mean between-group difference, -0.25 kg; 95% CI, -3.14 to 2.64 kg). Two additional studies reported no difference in weight gain but did not report sufficient quantitative results.
General QOL	Low	2 (all RCTs) / 0	Two studies showed an improvement in general QOL between the 2 intervention groups favoring CSII. In 1 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).[51] The other study did not report estimates, but there was no difference in the Physical Component Score and a change in the Mental Component Score favoring CSII (P < 0.05).
Diabetes-specific QOL	Low	5 (all RCTs) / 1	Three studies showed an improvement in diabetes-specific QOL favoring CSII. A meta-analysis favored CSII over MDI for Diabetes Quality of Life (mean between-group difference in Diabetes Quality of Life, 2.99; 95% CI, 0.006 to 5.97). One study showed improvement favoring MDI (Diabetes Quality of Life mean between-group difference in change from baseline, -18.00; 95% CI, -50.14 to 14.14).[50]

Table C. Summary of the evidence of the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes (continued)

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
Diabetes treatment-related QOL	Insufficient[a]	1 (RCT) / 0	Altered Hypoglycemia Awareness Questionnaire scores were similar in the CSII and MDI groups over 24 weeks (RR of Altered Hypoglycemia Awareness Questionnaire score greater than 4, 0.75; 95% CI, 0.26 to 2.18). Hypoglycemia Fear Survey scores decreased in both CSII (-3±25) and MDI (-8±33) groups (mean between-group difference in the change from baseline, 5; 95% CI, -32.66 to 42.66).[50]
Process measures, clinical outcomes	Insufficient	0	None of the studies evaluated the effects of MDI vs. CSII among adults with type 1 diabetes in terms of any process measures or clinical outcomes.

CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; IRR = incidence rate ratio; MDI = multiple daily injections; NS = nonsignificant; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk; SF-36 = Short Form-36

[a]Strength of evidence was graded as insufficient because the body of evidence consisted of only 1 study with high or medium risk of bias, or the results were imprecise.

Note: 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, does not permit a conclusion, or consists of only 1 study with high risk of bias.[37,47]

Adults With Type 2 Diabetes

Study Design

Four studies evaluated CSII versus MDI therapy in patients with type 2 diabetes.[24,25,57,58] Study designs are indicated in Table D.

Population Characteristics

The number of participants per arm ranged from 20 to 66 in the included studies.[24,25,57,58] All studies were conducted in adults, and only one study included participants 60 years of age or older.[58] Two studies did not report on the racial composition of their study populations, and the other two studies were multiethnic but predominantly white (> 80 percent).[24,58] Mean body mass index (BMI) ranged from 29.5 to 32.5 kg/m^2 and was similar by treatment group across the three parallel-arm studies.[24,57,58] The mean duration of type 2 diabetes was greater than 10 years in the two studies reporting this.[24,58]

Interventions

The MDI arms varied across studies: NPH and regular insulin;[25] insulin glargine and insulin lispro;[57,58] and NPH insulin and insulin aspart.[24] Insulin aspart was used in the CSII arm for one study,[24] and insulin lispro was used in the CSII arm in the other studies.[25,57,58]

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.

Outcomes

Table D shows the main results on the comparative effectiveness of CSII versus MDI in adults with type 2 diabetes.

Table D. Summary of the evidence of the comparative effectiveness of CSII versus MDI in adults with type 2 diabetes

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
Mortality	Insufficient[a]	1 (RCT) / 0	A single study reported 1 death due to cancer in the CSII treatment arm.[58]
HbA_{1c}	Moderate	4 (all RCTs) / 0	The effects on HbA_{1c} did not differ between the MDI and CSII intervention groups (mean between-group difference from baseline with negative value favoring CSII, -0.16; 95% CI, -0.42 to 0.09).
Mild hypoglycemia	Moderate	3 (all RCTs) / 0	The risk of mild hypoglycemia did not differ between MDI and CSII (combined RR, 0.90; 95% CI, 0.78 to 1.03).
Nocturnal hypoglycemia	Insufficient[a]	1 (RCT) / 0	In a single study, nocturnal hypoglycemia (occurring between midnight and 6 a.m.) was less common in patients in the CSII than MDI arm (RR, 0.73; 95% CI, 0.35 to 1.54).
Severe hypoglycemia	Low	3 (all RCTs) / 0	The risk of severe hypoglycemia did not differ between CSII and MDI (RR, 0.76; 95% CI, 0.26 to 2.19).
Hyperglycemia	Low	2 (RCTs) / 0	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; 95% CI, -45 to -5 mg/dL).[24] 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 than CSII arm (26 vs. 6 events), affecting 18% and 5% of participants in the MDI and CSII arms, respectively (RR, 0.28; 95% CI, 0.08 to 0.94).[24]
Weight	Low	2 (all RCTs) / 0	Weight gain did not differ between CSII and MDI groups (combined mean between-group difference in weight change from baseline, -0.49 kg; 95% CI, -1.25 to 0.26 kg).
General QOL	Insufficient[a]	Insufficient[a]	One study reported no difference in general QOL between the CSII and MDI intervention groups. The difference from baseline to followup was 0.6 for CSII vs. 0.4 for MDI for the SF-36v2 Physical Component Score, and 1.0 for CSII vs. 2.5 for MDI for the Mental Component Score.[58]
Diabetes-specific QOL	Insufficient[a]	Insufficient[a]	One study reported no difference in diabetes-specific QOL between the CSII and MDI intervention groups. (Diabetes Quality of Life Clinical Trials Questionnaire scores improved from 52 to 81 for CSII and from 50 to 78 for MDI over 12 months.)[58]
Diabetes treatment-related QOL	Insufficient[a]	Insufficient[a]	One study reported improvement in diabetes treatment satisfaction favoring CSII (mean between-group difference in Phase V Outcomes System Diabetes Treatment Satisfaction score change from baseline in 24 weeks, 13.1; 95% CI, 7.4 to 18.8).[24]
Process measures, microvascular disease, macrovascular disease	Insufficient	Insufficient	We did not identify any studies evaluating the effects of MDI vs. CSII among patients with type 2 diabetes in terms of any of the process measures, microvascular disease, or macrovascular disease.

CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk; SF-36 = Short Form-36

[a]Strength of evidence was graded as insufficient because the body of evidence consisted of only 1 study with high or medium risk of bias, or the results were imprecise.

Note: 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, does not permit a conclusion, or consists of only 1 study with high risk of bias.[37,47]

Pregnant Women With Pre-Existing Type 1 Diabetes

Study Design

Six studies evaluated CSII versus MDI therapy in pregnant women with pre-existing type 1 diabetes.[59-64] Study designs are indicated in Table E.

Population Characteristics

The number of participants per arm ranged from 18 to 86 pregnant women.[59-64] Two studies reported having only white 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 percent to 7.8 percent,[59-64] 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 16.5 years, with some in the CSII arm having a longer duration of diabetes than those in the MDI arm.[59,60,62]

Interventions

The CSII arm varied across studies. Four studies reported that primarily insulin lispro was used in the CSII arm[60,61,63,64] while the type of insulin was not specified in one study.[62] In the MDI groups, three studies used NPH insulin[59,60,64] and two other studies used long-acting insulin.[61,63] Three studies reported using four or more insulin injections daily in the MDI arms.[59,61,62] Three studies reported the mean duration of therapy, which ranged from 36 to 40 weeks.[59-61]

Applicability

All studies were observational, with limited descriptions of study methodology, study populations, intervention, and outcomes. They were all small studies conducted in Europe.

Outcomes

Table E shows the main results on the comparative effectiveness of CSII versus MDI in pregnant women with pre-existing type 1 diabetes.

Table E. Summary of the evidence of the comparative effectiveness of CSII versus MDI in pregnant women with pre-existing type 1 diabetes

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
HbA_{1c}	Low	6 (all OBS) / 0	Six 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. The mean between-group differences in third-trimester HbA_{1c} values in each of the studies were 0.2 (95% CI, -0.3 to 0.7),[59] -0.4 (95% CI, -0.8 to 0.04),[60] 0.6 (95% CI, -0.7 to 1.9),[61] -0.3 (95% CI, -0.6 to -0.03),[63] 0.2 (95% CI, -0.2 to 0.6),[62] and 0.4 (95% CI, -0.9 to 1.7).[64]
Cesarean section rates	Insufficient[a]	3 (all OBS) / 0	Meta-analysis of 4 retrospective studies for rate of cesarean section showed a pooled RR of 1.02 (95% CI, 0.86 to 1.20), which was inconclusive because of high risk of bias.[59,60,63,64]
Maternal hypoglycemia	Insufficient[a]	2 (all OBS) / 0	Meta-analysis of 3 retrospective studies for rate of severe hypoglycemia showed a pooled RR of 0.78, which was inconclusive because of high risk of bias (95% CI, 0.23 to 2.65).[59,63,64]
Maternal weight gain	Insufficient[a]	3 (all OBS) / 0	Weight gain did not differ between the CSII and MDI groups in 3 studies with high risk of bias. The mean between-group difference in weight gain was 1.9 kg (95% CI, -0.9 to 4.7 kg) in 1 study[59] and 0.1 kg (95% CI, -2.4 to 2.6 kg) in another study.[62] The third study reported a median weight gain of 13.5 kg in the CSII group and 13.9 kg in the MDI group.[64]
Other maternal outcomes	Insufficient	0 / 0	None of the studies evaluated maternal mortality, microvascular or macrovascular disease, quality of life, or any of the process measures.
Gestational age at delivery	Insufficient[a]	4 (all OBS) / 0	Gestational age at delivery ranged from 36.6 weeks to 37.5 weeks for MDI and from 36.3 weeks to 36.6 weeks for CSII, with no significant difference between the MDI and CSII groups, but the studies had high risk of bias.[59-61,63]
Neonatal hypoglycemia	Insufficient[a]	4 (all OBS) / 0	Meta-analysis of 4 retrospective cohort studies for frequency of neonatal hypoglycemia showed a pooled RR of 1.10 (95% CI, 0.86 to 1.20), which was inconclusive because of high risk of bias.[59,60,63,64]

Table E. Summary of the evidence of the comparative effectiveness of CSII versus MDI in pregnant women with pre-existing type 1 diabetes (continued)

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
Birth weight	Insufficient[a]	3 (all OBS) / 0	Meta-analysis of 3 retrospective cohort studies showed a pooled mean between-group difference in birth weight of 107.2 g (95% CI, -86.6 to 295.9 g), which was inconclusive because of high risk of bias.[59,60,63]
Major congenital anomalies	Insufficient[a]	2 (all OBS) / 0	Meta-analysis for only 2 retrospective cohort studies for major congenital anomalies showed a pooled RR of 2.12 favoring MDI (95% CI, 0.38 to 11.77), which was inconclusive because of high risk of bias.[63,64]
Minor congenital anomalies	Insufficient[a]	3 (all OBS) / 0	Three studies with high risk of bias found no difference in minor congenital anomalies between the MDI and CSII groups. There were no minor congenital anomalies in either group in 2 studies,[59,61] and rates of minor congenital anomalies and pregnancy termination rates were 2.3% (2/86 patients) in the MDI group and 13% (4/30 patients) in the CSII group (P = 0.05).[60]

CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; NICU = neonatal intensive care unit; OBS = observational study; RR = relative risk

[a]Strength of evidence was graded as insufficient because the body of evidence consisted of only 1 study with high or medium risk of bias, or the results were imprecise.

Note: 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, does not permit a conclusion, or consists of only 1 study with high risk of bias.[37,47]

KQ2. Comparative Effectiveness of rt-CGM Versus SMBG

We found nine studies comparing rt-CGM with SMBG in patients with type 1 diabetes, but none in pregnant women.

Study Design

Nine studies evaluated rt-CGM versus SMBG in children and adults with type 1 diabetes.[16,65-73] Study designs are indicated in Table F.

Population Characteristics

The mean age of participants in the RCTs was 24 years (range, 8.5 to 41.2 years) in the rt-CGM group and 25 years (range, 9.1 to 44.6 years) in the SMBG group. Only three studies reported race. The mean baseline HbA_{1c} in the RCTs was 8.3 percent in both the rt-CGM and SMBG groups.

Interventions

In the rt-CGM arm, four studies used Minimed Paradigm;[66,67,69,70] two used Minimed Guardian rt-CGM;[65,71] one study used Abbott FreeStyle Navigator;[72] and two studies used the Abbott Freestyle Navigator, Dexcom STS, and Minimed Paradigm.[16,68] In five studies, researchers asked participants to wear monitors continuously; in three studies, researchers required rt-CGM to be used more than 70 percent of the time;[67,69,72] and one study did not specify the time requirement.[70] Eight studies reported on sensor compliance.[16,65-70,72] Four studies reported on sensor compliance by age category.[16,67,68 72]

Five studies used CSII with or without rt-CGM,[65-67,69,70] and four studies used either MDI or CSII with or without rt-CGM.[16,68,71,72] Four studies required participants to perform glucose monitoring four or more times daily,[16,66,68,69] one required monitoring at least three times per day,[67] and four studies did not report the frequency of monitoring.[65,70-72]

Applicability

All studies targeted type 1 diabetes and most studies had small sample sizes.

Outcomes

Table F shows the main results on the comparative effectiveness of rt-CGM versus SMBG.

Table F. Summary of the evidence of the comparative effectiveness of rt-CGM versus SMBG

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
HbA_{1c}	High	8 (all RCTs) / 4	Rt-CGM was favored over SMBG for the effects on HbA_{1c}. Mean between-group difference in how HbA_{1c} changed from baseline was -0.30% (95% CI, -0.37 to -0.22%). In the sensitivity analysis that included only studies with more than 60% compliance (7 estimates), there was a greater HbA_{1c} reduction (mean between-group difference from baseline, -0.36%; 95% CI, -0.44 to -0.27%). A meta-analysis of 4 studies in children and adolescents age 18 years or younger showed a significant combined mean between-group difference in HbA_{1c} change from baseline of -0.26% favoring rt-CGM (95% CI, -0.46 to -0.06%).
Nonsevere hypoglycemia	Moderate	6 (all RCTs) / 3	A meta-analysis of 4 studies (6 estimates) showed no difference between the rt-CGM and SMBG groups in time spent in the hypoglycemic range, defined by glucose level less than 70 mg/dL. The mean between-group difference was -2.11 minutes/day (95% CI, -5.66 to 1.44 minutes/day).
Severe hypoglycemia	Low	7 (all RCTs) / 4	The rate of severe hypoglycemia did not differ between the rt-CGM and SMBG groups (pooled RR, 0.95; 95% CI, 0.53 to 1.69). Two trials reported data on severe hypoglycemia specifically in pediatric populations. In 1 study, severe hypoglycemia was less common in pediatric patients using rt-CGM than pediatric patients using SMBG alone (SMBG 4/78 vs. rt-CGM 0/76, P = 0.046).[66] 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).[16]
Hyperglycemia	Moderate	5 (all RCTs) / 3	A meta-analysis of 4 studies (6 estimates) indicated a significant reduction in time spent in the hyperglycemic range, defined by glucose level greater than 180 mg/dL, with the mean between-group difference of -68.56 minutes/day favoring rt-CGM (95% CI, -101.17 to -35.96).
Ratio of basal to bolus insulin	Low	2 (all RCTs) / 1	One study reported that the basal rate was a higher proportion of the total daily insulin dose in the rt-CGM than SMBG intervention group (mean between-group difference in final basal rate, 4.3%; 95% CI, 0.8 to 7.8%).[66] A second study reported a higher percentage of insulin delivered as bolus in the rt-CGM group than SMBG group (mean between-group difference in final percentage of insulin delivered as bolus, -4.0%; 95% CI, -9.3 to 1.3%).[67]
General QOL	Low	2 (all RCTs) / 1	One study found no difference in parental satisfaction between the intervention arms (mean between-group difference in change from baseline in World Health Organization Well Being Index-5 mother's well-being score, -2.7; 95% CI, -14.2 to 8.8) at 12 months.[66] The other study assessed general QOL using the SF-12 and found an improvement on the Physical Component Score favoring rt-CGM (mean between-group difference in change from baseline, 1.4; 95% CI, -1.5 to 4.3) but no difference between intervention groups on the Mental Component Score (mean between-group difference in change from baseline, -1.6; 95% CI, -5.9 to 2.7) at 26 weeks.[73]
Diabetes-specific QOL	Low	2 (all RCTs) / 0	The effect on diabetes-specific QOL did not differ between the rt-CGM and SMBG arms in either study (mean between-group difference in the change from baseline in Problem Areas in Diabetes score, -0.9; 95% CI, -7.9 to 6.1 at 26 weeks,[73] and mean between-group difference in the change from baseline Diabetes Quality of Life score, -3.0; 95% CI, -6.6 to 0.6[65]).

Table F. Summary of the evidence of the comparative effectiveness of rt-CGM versus SMBG (continued)

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
Diabetes treatment-related QOL	Insufficient[a]	1 (RCT) / 0	The fear of hypoglycemia was less with rt-CGM than with SMBG (mean between-group difference in change from baseline score, -2.3; 95% CI, -8.2 to 3.6).[73]
Process measures, weight, and clinical outcomes	Insufficient	0	None of the studies evaluated the effects of rt-CGM vs. SMBG in terms of mortality, microvascular or macrovascular disease, weight, or any other process measure.

CI = confidence interval; HbA_{1c} = hemoglobin A_{1c}; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk; rt-CGM = real-time continuous glucose monitoring; SF-12 = Short Form-12; SMBG = self monitoring of blood glucose

[a]Strength of evidence was graded as insufficient because the body of evidence consisted of only 1 study with high or medium risk of bias, or the results were imprecise.

Note: 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, does not permit a conclusion, or consists of only 1 study with high risk of bias.[37,47]

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

Study Design

Four studies evaluated a sensor-augmented pump versus MDI/SMBG in children and adults with type 1 diabetes.[74-77] Study designs are indicated in Table G.

Population Characteristics

Three studies included only adults,[75,77,78] and one study enrolled both adults and children.[74] The mean age of participants in the RCTs was reported in the combined study sample in two studies (47.2 years[75] and 45.9 years[76]) and stratified by treatment group in the other two studies (32.2 years in the sensor-augmented pump group versus 31.5 years in the MDI/SMBG group[74] and 39.3 in the sensor-augmented pump group vs. 37.3 in the MDI/SMBG group[77]). Most participants in two studies were white (92 percent[74] and 79 percent[75]). The mean baseline HbA_{1c} in the RCTs was similar in all three studies (median, 8.6 percent; range, 8.3 to 9.5 percent).

Interventions

All four studies provided training and used the MM Paradigm REALTime system.[74-77] The frequency and intensity of the followup visits, however, differed between studies.

Applicability

The largest clinical trial included 485 participants,[74] and the other trials were small, with less than 30 participants.[75-77] Only one study included individuals 20 years of age or younger.[74]

Outcomes

Table G shows the main results on the comparative effectiveness of rt-CGM + CSII (sensor-augmented pump) versus MDI/SMBG.

Table G. Summary of the evidence of the comparative effectiveness of rt-CGM + CSII (sensor-augmented pump) versus MDI/SMBG

Outcome	Strength of Evidence	# of Studies / # of Good-Quality Studies	Main Findings
HbA_{1c}	Moderate	4(all RCTs) / 2	Sensor-augmented pumps were favored over MDI/SMBG for their effects on HbA_{1c} (mean between-group difference in HbA_{1c} change, -0.68%; 95% CI, -0.81 to -0.54%).
Nonsevere hypoglycemia	Moderate	2(all RCTs) / 2	The time spent with nonsevere hypoglycemia did not differ between the sensor-augmented pump and MDI/SMBG intervention groups.
Severe hypoglycemia	Moderate	4(all RCTs) / 2	The incidence of severe hypoglycemia did not differ between the sensor-augmented pump and MDI/SMBG intervention groups (RR, 1.2; 95% CI, 0.7 to 2.3;[74] 0 events for sensor-augmented pump vs. 3 events for MDI/SMBG;[75] 0 events in 8 patients in sensor-augmented pump group vs. 1 event in 8 patients in the MDI/SMBG group;[76] and RR 3.5; 95% CI, 0.4 to 304[77]).
Hyperglycemia	Moderate	2(all RCTs) / 2	Two trials suggested time spent with hyperglycemia was significantly less in the sensor-augmented pump group than the MDI/SMBG intervention group (P < 0.001).
Weight	Low	2(all RCTs) / 1	One study[74] reported no significant difference in weight gain between the sensor-augmented pump and MDI/SMBG intervention groups (mean, 2.4 kg vs. 1.8 kg; P = 0.19). 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 (mean between-group difference, 1.3 kg; 95% CI, -21.2 to 23.8 kg).[75]
Diabetes treatment-related QOL	Low	2(all RCTs) / 1	User acceptance and overall diabetes treatment satisfaction were greater in the sensor-augmented pump arm than the MDI/SMBG arm. Blood Glucose Monitoring System Rating Questionnaire scores were 83.3±21.7 for sensor-augmented pump vs. 33.3±22.6 for MDI/SMBG (mean between-group difference in final scores, 50.0; 95% CI, 33.6 to 66.4).[75]
Process measures and clinical outcomes	Insufficient	0	None of the studies evaluated the effects of sensor-augmented pumps vs. MDI/SMBG in terms of mortality, microvascular or macrovascular disease, or any of the process measures.

CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose

Note: 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, does not permit a conclusion, or consists of only 1 study with high risk of bias.[37,47]

Discussion

Summary of Key Findings

Our systematic review summarizes the current state of the evidence on the effectiveness and safety of methods for intensive insulin delivery used in clinical practice and glucose monitoring in terms of diabetes-related process measures, intermediate outcomes, and clinical outcomes in individuals with type 1 and type 2 diabetes mellitus. Although studies have reported on a number of process measures and intermediate outcomes (as summarized below), we did not find any studies comparing CSII with MDI or comparing rt-CGM with SMBG for certain process measures (frequency of adjusting insulin therapy, adherence to therapy, and health visits) or for clinical outcomes (microvascular and macrovascular disease).

Comparative Effectiveness of CSII Versus MDI (KQ1)

RCTs showed no difference in the effect on HbA_{1c} between the CSII and MDI intervention groups for children and adolescents or pregnant women with type 1 diabetes, or for adults with type 2 diabetes. In adults with type 1 diabetes, CSII showed favorable effect on glycemic control, but the result was influenced by one study[54] where participants had higher HbA_{1c} values at enrollment, allowing for greater HbA_{1c} lowering compared with the other studies were participants were closer to the HbA_{1c} target at enrollment. The trials also showed no difference in rates of severe hypoglycemia between the two intervention groups for children and adolescents or adults with type 1diabetes, 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, adolescents, and adults with type 1 diabetes, CSII use resulted in improvement in both general and diabetes-specific QOL measures when compared with MDI. The evidence was insufficient to draw definitive conclusions about QOL for pregnant women with type 1diabetes 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 groups. The evidence was insufficient to draw definitive conclusions about other maternal and fetal outcomes.

Our systematic review of the comparative effectiveness of CSII and MDI complements and extends previously published meta-analyses by: (1) including more studies of individuals with type 2 diabetes as well as pregnant women with pre-existing type 1 diabetes;[20-22,27,79] (2) including only studies using rapid-acting insulin analogs and not regular insulin in the CSII intervention groups;[20-22,27] and (3) requiring the MDI groups to be receiving at least three injections per day, the current standard for intensive insulin therapy.[21,23,79,80] We believe that these latter two distinctions are extremely important, since they best reflect current clinical practice. Unlike some prior systematic reviews[21,22] and similar to others,[23,27,79,80] we excluded before-and-after studies and included only RCTs in our combined estimates for HbA_{1c} and severe hypoglycemia. We also examined additional nonglycemic outcomes, including weight gain, ratio of basal to bolus insulin, and QOL. Unfortunately, for some of these outcomes, the evidence was insufficient to draw definitive conclusions about the comparative effectiveness of CSII versus MDI or rt-CGM versus SMBG in any population of individuals with diabetes.

We found that CSII had no significant effect on lowering HbA_{1c} in children (a drop of 0.14 percent) when compared with MDI and had no effect in adults with type 1 diabetes. A prior

meta-analysis in children with type 1 diabetes found a significant (0.24 percent) reduction in HbA_{1c} favoring CSII; however, the prior meta-analysis included studies in which there were fewer than three daily injections in the MDI arm.[79] This may have biased the results to favor CSII, since the MDI arm was less intensive than CSII. Prior meta-analyses combining RCTs in children and adults with type 1 diabetes have shown HbA_{1c} reductions of 0.21 to 0.4 percent favoring CSII.[20-23] Several, however, included studies in which regular insulin was used in the pump[21,22] or the MDI arm included fewer than three daily injections.[23] In contrast to our meta-analysis, two prior reviews did not find a difference between CSII and MDI in the effect on HbA_{1c} in adults with type 1 diabetes,[80] although one systematic review did not perform a quantitative summary.[81] Our results, however, were heavily influenced by one study and when that study was excluded in a sensitivity analysis, CSII and MDI had a similar effect on HbA_{1c} in adults with type 1 diabetes. Our estimates are based on a larger number of RCTs using rapid-acting analogs only in the CSII arms and at least three daily injections in the MDI arms, making them comparable in intensity to CSII (total of 11 studies—7 in children and adolescents, and 4 in adults). Prior meta-analyses that have favored CSII have included before-and-after studies, which may be subject to selection bias (i.e., individuals doing poorly on MDI are more likely to be switched to CSII and then improve).[20,81]

Like a prior meta-analysis, 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).[80] While two prior analyses found a significantly higher rate of severe hypoglycemia with MDI than with CSII, one of these included studies only if individuals reported an elevated frequency of baseline severe hypoglycemic episodes, which may have resulted in a greater likelihood of improvement.[20] The other studies used regular insulin in the CSII arms, which would be expected to result in less hypoglycemia than regular insulin with MDI due to more steady insulin delivery.[22] Similar to two prior systematic reviews, there was no difference in HbA_{1c} or hypoglycemia frequency with CSII versus MDI in adults with type 2 diabetes.[27,80,81] Our meta-analysis is distinct from prior reviews in that it provides a quantitative effect estimate,[81] and it includes additional studies that used current rapid-acting analogs in the CSII arm.[27]

Comparative Effectiveness of rt-CGM Versus SMBG (KQ2)

We found studies of the comparative effectiveness of rt-CGM versus SMBG only in children, adolescents, and adults with type 1 diabetes. While prior studies have examined the effect of retrospective CGM in pregnant women with diabetes, no studies have compared rt-CGM with SMBG in this population.[19] These two glucose monitoring approaches have not been compared in individuals with type 2 diabetes.

Compared with the SMBG group, the rt-CGM group achieved lower HbA_{1c} (-0.3 percent). A sensitivity analysis showed this effect to be greater in studies where sensor compliance was 60 percent or greater (-0.36 percent). We also found that rt-CGM was associated with lower HbA_{1c} compared with SMBG in individuals 18 years of age or younger. These findings support recent clinical practice recommendations suggesting rt-CGM use in children and adolescents over the age of 8 years.[82] The intervention groups did not differ in the rate of severe hypoglycemia; however, there was a significant reduction in the time spent in the hyperglycemic range. A few studies that evaluated QOL found no difference in general and diabetes-specific QOL between the two intervention groups.

Our systematic review of the comparative effectiveness of rt-CGM and SMBG complements and extends a recently published meta-analysis[29] by including additional nonglycemic outcomes, including weight gain, ratio of basal to bolus insulin, and QOL. We also found that rt-CGM lowered HbA_{1c} more than SMBG (-0.28 percent in our study vs. -0.30 percent in Pickup et al.) and that there was no difference in severe hypoglycemia in the two intervention groups.[29]

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

Sensor-augmented pump use resulted in a statistically and clinically significantly greater reduction in HbA_{1c} compared with MDI/SMBG use in nonpregnant individuals with type 1 diabetes (-0.61 percent). The evidence was insufficient to draw definitive conclusions about severe hypoglycemia or QOL. No previous meta-analysis examined this comparison.

Limitations

Most RCTs examining the effect of insulin delivery and glucose monitoring devices were small. 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 on race and/or ethnic composition. Since few studies included children 12 years of age or younger, adults 65 years of age or older, or pregnant women with pre-existing type 2 diabetes, we were unable to draw conclusions about these populations. The studies were heterogeneous in definitions of nonsevere hypoglycemia, hyperglycemia, and weight gain, preventing us from combining data to determine effect estimates for these intermediate outcomes. The definition of severe hypoglycemia was not explicitly stated in all studies, making it difficult to correctly classify individuals with this condition. In studies comparing CSII and MDI, differences in the insulin regimen in the MDI arms may have been a source of heterogeneity; however, we had inadequate power to stratify by the MDI insulin regimen. Presumably, greater use of NPH and regular insulin-based MDI would have biased results to the null for glycemic and QOL outcomes. None of the studies included data on the microvascular and macrovascular complications associated with long-term diabetes. In the pregnancy literature, none of the studies in women with pre-existing type 1 diabetes examined the effect of rt-CGM on maternal and fetal outcomes. Other than the rt-CGM studies, few studies reported data on treatment adherence. The high baseline HbA_{1c} values in the CSII and MDI intervention groups in many studies may indicate poor adherence to prior treatments and intervention treatments, which may have biased results to the null. Finally, the studies were heterogeneous in assessing and reporting QOL outcomes, which prevented us from quantifying the effects of insulin delivery and glucose monitoring methods on QOL. We found no studies examining the comparative effectiveness of CSII versus MDI on QOL in pregnant women and only one study examining the effects on QOL in type 2 diabetes.

Meta-analyses in general are subject to bias based on selection criteria for articles, performing multiple comparisons, and the state of the available literature. We cannot exclude the possibility that publication bias affected our findings. However, our search strategy was comprehensive and included non-English-language publications. Our metaregression to examine potential sources of heterogeneity in the effect of rt-CGM versus SMBG on HbA_{1c} was a post hoc analysis and is hypothesis generating, not hypothesis testing.

Our data are not generalizable to nonspecialty settings or all patients with diabetes mellitus, as the initiation, instruction, monitoring, and therapeutic changes for CSII and rt-CGM use are often limited to expert settings and highly motivated patients and families. All studies of rt-CGM

are subject to ascertainment bias because rt-CGM provides more hypoglycemia and hyperglycemia data than SMBG alone. Because it is not feasible to keep patients blinded in an RCT comparing CSII with MDI or in an RCT comparing rt-CGM with SMBG, studies of QOL outcomes could have been vulnerable to reporting bias. All included studies were efficacy studies (as opposed to effectiveness studies), and 19 of the 41 studies excluded individuals with comorbidity,[24,39,40,44,45,48,49,51,52,54-58,69,77,83,84] making results less generalizable to the entire population of individuals with diabetes. (See Appendix E, Table 1, in the full report.)

Implications

Our findings indicate that intensive insulin therapy delivered by either CSII or MDI using current rapid-acting insulin analogs with CSII is equally effective in lowering HbA_{1c} in several patient populations with diabetes—adolescents and pregnant women with type 1 diabetes. Our findings suggest that CSII is superior to MDI in lowering HbA_{1c} in adults with type 1 diabetes, although the results were heavily influenced by one study. Intensive insulin therapy delivered by both methods resulted in similar rates of severe hypoglycemia for adolescents and adults with type 1 diabetes. However, adolescents and adults with type 1 diabetes treated with CSII reported better overall QOL than those treated with MDI. These data suggest that intensive insulin therapies designed to optimize glycemic control can be individualized to maximize treatment satisfaction and QOL, as CSII and MDI using current rapid-acting insulin analogs have similar effectiveness for glycemic control.

Our findings also indicate that rt-CGM is superior to SMBG in lowering HbA_{1c}, without increasing or decreasing the risk of severe hypoglycemia, in nonpregnant individuals with type 1 diabetes, particularly those who are compliant with wearing the monitoring device. The addition of rt-CGM to CSII is superior to MDI/SMBG in lowering HbA_{1c}. Thus, the addition of this monitoring method to SMBG and intensive insulin therapy can assist in achieving glycemic targets in nonpregnant individuals with type 1 diabetes. The available literature does not allow us to determine the comparative effectiveness of rt-CGM versus SMBG in patients using only CSII or using only 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] and older individuals may be at increased risk for adverse outcomes associated with intensive insulin therapy. 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 use compared with MDI/SMBG on glycemic control is secondary to the rt-CGM technology, the mode of intensive insulin delivery, or both. To allow cross-comparisons, future RCTs should use a uniform definition of hypoglycemia, preferably that recommended by the American Diabetes Association.[85]

There is also a need for well-designed prospective observational studies to determine the comparative effectiveness of CSII versus MDI and rt-CGM versus SMBG on clinically relevant long-term microvascular and macrovascular outcomes. Such studies could also advise researchers as to the feasibility of conducting RCTs to examine these outcomes. Future studies should also seek to identify and use an agreed-upon set of QOL measures to allow for better comparisons across studies. Studies should incorporate measures of adherence to treatment, as adherence is important for the effectiveness of any intensive insulin therapy or glucose monitoring system.

Future studies should focus on individuals with type 2 diabetes requiring insulin to determine the most effective manner in which to deliver intensive insulin therapy and monitor blood glucose. Finally, studies of type 2 diabetes should include ethnically diverse populations because type 2 diabetes is less common in whites than in other racial and ethnic groups.[86]

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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 (e.g., retinopathy, nephropathy, and peripheral and autonomic neuropathy) and macrovascular complications (e.g., 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] Therefore the already large number of people who require glucose-lowering therapies to maintain normal glucose levels (normoglycemia) and prevent diabetes complications, will likely only increase.

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] The prevalence and incidence of type 1 diabetes is highest among non-Hispanic whites[5] and lowest among Navajo Indians.[6] African-American and Hispanic children have a similar incidence of type 1 diabetes,[7 8] which is higher than in Asian American and Pacific Islander children.[9]

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] Among adults, 20 years of age and older, the prevalences of diagnosed diabetes are 7.1 percent in non-Hispanic whites, 8.4 percent in Asian Americans, 11.8 percent in Hispanic Americans (primarily those of Mexican and Puerto Rican descent), and 12.6 percent in non-Hispanic blacks.[10] The prevalence of diabetes increases with age and approximately 26.9 percent of adults 65 years of age and older have diagnosed and undiagnosed diabetes, the majority of which is type 2 diabetes.[10]

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. The majority of pregnant women with pre-existing diabetes have type 1 diabetes.

Importance of Tight Glycemic Control and Associated Risks in Diabetes

Evidence has shown that tight glycemic control with intensive insulin therapy reduces the risk of the microvascular and macrovascular complications of diabetes.[11-14] Throughout the duration of pregnancy, physicians recommend tight glycemic control to avoid maternal, fetal, and neonatal complications.[15] The role of tight glycemic control in older adults with diabetes is less well-established and physicians only recommend it for those who are functional, cognitively intact, and have a significant life expectancy.[16] For older adults with advanced complications, life-limiting comorbidity, or significant functional or cognitive impairments, physicians recommend less intensive glycemic goals to avoid the adverse effects of hypoglycemia.[16]

While tight glycemic control lowers the risk of diabetic complications, it can increase the risk of hypoglycemia.[13] Severe hypoglycemia, which can be life threatening, is an episode that requires another person to assist in treatment to resolve symptoms. Nonsevere 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. Unawareness of hypoglycemia can be a factor in patients with long-standing diabetes complicated by recurrent hypoglycemia, putting patients at risk for severe hypoglycemic episodes.[17] Finally, intensive insulin therapy can also lead to weight gain, due to more efficient fuel utilization and/or overtreatment of hypoglycemic episodes.[18 19]

Measurement of Glycemic Control

The recommended method for assessing long-term glycemic control over the previous 2 to 3 months in patients with type 1 and type 2 diabetes is to measure glycosylated hemoglobin, specifically hemoglobin A_{1c} (HbA_{1c}).[20] The recommended method for assessing short-term glycemic control for patients using multiple insulin injections or insulin pump therapy is self-monitoring of blood glucose (SMBG) three or more times daily. This can also assist patients and their physicians in making short-term adjustments in insulin therapy.[21] The role of SMBG is less clear for patients using less-frequent insulin injections, noninsulin therapies, or medical nutrition therapy.[16] With pregnant women with diabetes, physicians make clinical management decisions on a weekly basis based on fasting and post-prandial glucose levels. They choose this method, as opposed to measuring HbA_{1c} every 3 months, because it provides the higher level of rapid feedback on glycemic control needed to prevent fetal complications.[22]

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, patients had a more difficult time achieving tight control. Furthermore, these older insulins often resulted in significant hypoglycemia due to their prolonged duration of action. This difficulty led to the development of more physiological basal and mealtime (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, patients receive intensive insulin therapy as three or more daily insulin injections (i.e., multiple daily injections [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, SMBG by fingerstick replaced the assessment of glucose by urine dipstick and is now the most widely used technique. SMBG allows more specific and timely feedback on hyperglycemia and allows patients to evaluate their individual response to therapy and assess whether blood glucose targets have been achieved.[18] Evidence has shown that SMBG is an effective component of successful diabetes treatment, especially for patients who are being treated with insulin injection or pump therapy.[20] SMBG is also useful as a guide to adjust therapy for patients not on insulin, but there are fewer data on this population. In patients with type 2 diabetes, Welschen and colleagues found SMBG usage resulted in a 0.4 percent reduction of HbA_{1c} when compared with no usage.[23] 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.[23] The challenges to use of SMBG include the associated pain, costs, behavioral and technical skills, required motivation, and intrusiveness that affect adherence to this technique. Therefore, continuous glucose monitoring (CGM) systems have been developed in recent years to supplement SMBG.

Continuous Glucose Monitoring System: Retrospective and Real-Time

A CGM system is a device that records blood glucose levels throughout the day and night and significantly decreases but does not eliminate the need for fingerstick measurements. The U.S. Food and Drug Administration (FDA) approved CGM devices as an adjunct to, not a substitute for, SMBG. Patients wore the first CGM systems for 3 to 5 days. Patients were unaware of their glucose readings until their health care professional downloaded and evaluated the data. Clinicians used the data retrospectively to make adjustments to on-going medical therapy.[24]

"Personal" or real-time continuous glucose monitoring (rt-CGM) systems, were first approved by the FDA in 2005. This equipment consists of a transcutaneous glucose sensor that is connected to a transmitter and receiver. Patients can use CGM systems in real time, retrospectively as noted above, and prospectively.[25] 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 rt-CGM technology with CSII.[26] Success in lowering blood glucose levels depends on adherence to ongoing use of the device.[27]

These devices are useful in detecting fluctuating blood glucoses and trends in changing blood glucoses, 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 clinicians do not need to download and evaluate the data. When using rt-CGM, patients can also set alarms for hyperglycemia, hypoglycemia, or rapid glucose changes, thereby allowing patients to intervene earlier to prevent severe glycemic excursions.[24] Because of these advantages, physicians prefer rt-CGM in the clinical setting. For this reason, 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

Clinical Decisionmaking and Indications

Physicians currently recommend CSII for patients with type 1 diabetes who are not achieving glycemic goals despite an adherence to a maximal MDI regimen. This is particularly true when patients have wide and erratic glycemic excursions, frequent severe hypoglycemia and/or hypoglycemia unawareness, or marked dawn phenomenon (pre-breakfast rise in blood glucose seen when bedtime basal insulin effect diminishes).[28 29] Physicians also recommend CSII for patients who are pregnant or in preconception planning. Patients with type 1 diabetes might also consider CSII if they feel pump therapy may be more suitable to their lifestyle, regardless of the level of glycemic control.[29] Compared with MDI, CSII has the advantage of providing a constant delivery of basal insulin, permitting a peakless insulin profile that is adjustable throughout the day, and decreasing glycemic variability by allowing controlled delivery of small insulin doses.[28] While CSII eliminates the need for multiple daily needle injections compared to MDI, it is more costly than MDI therapy, increases the patient's risk for developing diabetic ketoacidosis if there is a pump malfunction due to the absence of long-acting basal insulin, and requires significant patient involvement to manage CSII procedures.[28] MDI therapy using insulin analogs can achieve more predictable and constant blood insulin levels and is cheaper, easier to use, not subject to malfunction, and requires less staff supervision than CSII.[28]

Physicians currently recommend rt-CGM for patients with type 1 diabetes who have hypoglycemia unawareness, frequent hypoglycemia where their HbA_{1c} is over the recommended target, or who have excess glycemic excursions. They also recommend rt-CGM for patients who are in preconception planning or pregnant.[24] While SMBG requires frequent fingerstick checks that cause patient discomfort, there are some disadvantages to rt-CGM compared with SMBG. First, since FDA approves rt-CGM only as an adjunctive device to SMBG, it does not eliminate the need for fingersticks. Second, rt-CGM is not as accurate in glucose determinations as glucose meters. Finally, there is a 5-10 minute physiological lag between blood (SMBG) and interstitial space glucose (measured by rt-CGM). This lag is more pronounced when glucoses are changing rapidly, potentially leading to patient-driven insulin stacking and/or overtreatment of hypoglycemia.[24]

Given new technologies in insulin delivery and glucose monitoring, clinicians are now faced with determining which patient populations benefit most from the use of CSII and rt-CGM in terms of improved glycemic, clinical, and patient-reported outcomes. Because both technologies

are expensive and require extensive training and oversight by health care professionals, it is critical to determine how to select patients for their use.

Type 1 Diabetes Mellitus

Comparison of CSII With MDI

In prior systematic reviews, the majority of the evidence from comparisons of CSII with MDI in adult patients with type 1 diabetes indicates CSII results in better glycemic control, although its impact on other clinical outcome measures are less clear.[30-33] Research is inconclusive regarding the benefit of CSII for glycemic control and clinical outcomes in children and older adults with type 1 diabetes. In all of these populations, CSII use may be linked to uncontrolled hyperglycemia, because of device malfunction, or local catheter site infections. Therefore further research is warranted in order to determine the risks and benefits and cost-effectiveness of this expensive technology. Because prior meta-analyses and systematic reviews have included studies using regular insulin in the CSII arms, they have not been able to determine the comparative effectiveness of MDI with rapid-acting analog-based CSII, which is the current practice.[30-33]

Comparison of rt-CGM With SMBG

A recent published meta-analysis comparing rt-CGM with SMBG in type 1 diabetes showed a benfit of rt-CGM in improving glycemic control with no difference in hypoglycemia frequency; however, other non-glycemic outcomes were not reported.[34] Prior studies suggest that those who benefit most are adults and individuals compliant with regular sensor use,[24 34] but this needs to be confirmed. Clinicians can combine rt-CGM with CSII therapy in the form of a sensor-augmented pump. However, to our knowledge, there has not been a systematic review comparing sensor-augmented pump therapy (CSII and rt-CGM) with intensive insulin therapy (CSII or MDI) and SMBG.

Type 2 Diabetes Mellitus

Comparison of CSII With MDI

For individuals with type 2 diabetes, it is unclear how CSII compares with MDI in improving glycemic and other outcomes.[31 35] While some studies suggest that CSII is comparable with MDI in attaining adequate glycemic control,[31 36] other studies found a lower HbA_{1c} level with CSII than with MDI.[37 38] One prior meta-analysis found no significant difference in HbA_{1c} and hypoglycemic episodes between the CSII and MDI groups; however, this review included studies where regular insulin was used in the CSII arms.[35] This remains a relevant question for individuals with type 2 diabetes being treated with intensive insulin therapy.

Comparison of rt-CGM With SMBG

To our knowledge, there is no 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 in individuals with type 2 diabetes.

Diabetes in Pregnancy

Comparison of CSII With MDI

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.[39] The resulting review included only 60 women with 61 pregnancies. Mean birth weight was greater with CSII than with MDI, however, the authors did not think that was 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 determine if there is a clinical benefit to using CSII in pregnancy since this is one group for which CSII is currently recommended.

The evidence base for the comparison of MDI with CSII in pregnant women with pre-existing type 2 diabetes is small. This topic is increasingly important as the prevalence of type 2 diabetes has been increasing dramatically in younger populations, including women of childbearing age.

Comparison of rt-CGM With SMBG

rt-CGM and sensor-augmented pumps are new technologies and the evidence is not clear as to whether pregnant women with pre-existing type 1 or type 2 diabetes would benefit from these therapies, although, the theoretical utility of this tool in improving neonatal outcomes is great.

Scope of the Review

Our systematic review will help to address the clinically relevant question of whether the mode of intensive insulin therapy (CSII versus MDI) 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 (rt-CGM versus SMBG) 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 decisionmaking 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.

Table 1 lists the outcomes included in our review. Figure 1 graphically depicts our Key Questions.

Key Questions

Key Question 1. In patients receiving intensive insulin therapy, does mode of delivery (CSII versus MDI) 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)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?

Key Question 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:

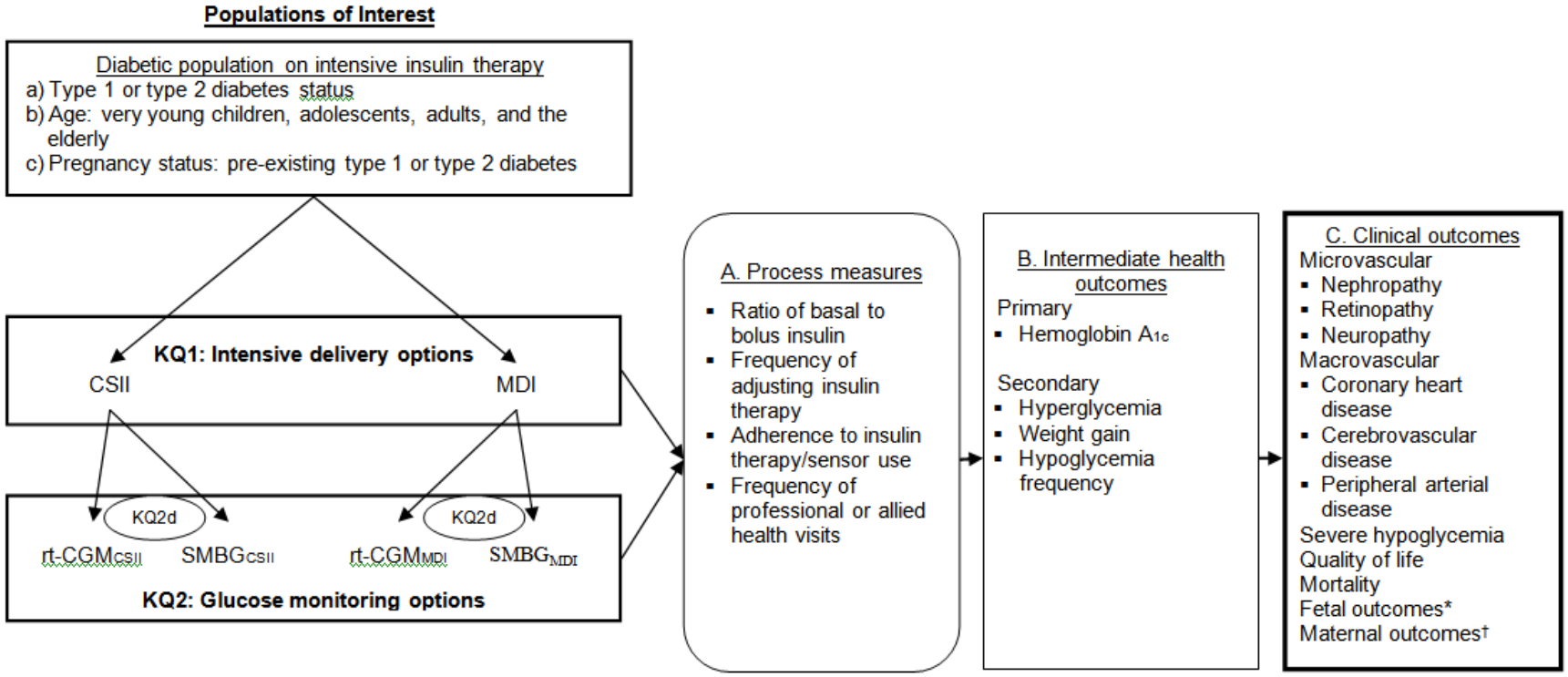
a. Type 1 or type 2 diabetes status?
b. Age: very young children, adolescents, and adults, including older adults (age >65 years)?
c. Pregnancy status: pre-existing type 1 or type 2 diabetes?
d. Intensive insulin delivery: MDI or CSII?

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 Frequency of adjusting insulin therapy Adherence to insulin therapy/sensor use Frequency of professional or allied health visits	<u>Primary</u> Hemoglobin A_{1c} <u>Secondary</u> Hyperglycemia Weight gain Hypoglycemia frequency	<u>Microvascular</u>* Nephropathy Retinopathy Neuropathy <u>Macrovascular</u>* Coronary heart disease Cerebrovascular disease Peripheral arterial disease <u>Severe hypoglycemia</u> <u>Quality of life</u> <u>Mortality</u> <u>Fetal outcomes</u>† <u>Maternal pregnancy outcomes</u> 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, admission to a neonatal intensive care unit, stillbirth, neonatal and perinatal mortality.

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



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

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

†Maternal outcomes include cesarean section rates.

Note: Stratifications of interest for KQ2: diabetes status (2a), age (2b), pregnancy status (2c), and glucose monitoring strategy (2d).

Methods

Members of the health care community nominated this topic via the Agency for Healthcare Research and Quality's (AHRQ) Web site. 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

Our panel of Key Informants gave 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. We posted our draft Key Questions on AHRQ's Web site in October of 2010 for public comment.

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 Key Questions focus on the comparative effectiveness and safety of insulin delivery (i.e., continuous subcutaneous insulin infusion [CSII] versus multiple daily injections [MDI]) and glucose monitoring methods (i.e., real-time continuous glucose monitoring [rt-CGM] versus self-monitoring of blood glucose [SMBG]) 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).

Technical Expert Panel

We drafted a protocol to address the Key Questions. Our Key Informants also served as our Technical Expert Panel. The Technical Expert Panel reviewed our protocol, and provided feedback on the Key Questions and proposed methods. With the feedback from the Technical Expert Panel and AHRQ representatives, we finalized the protocol and posted it on AHRQ's website.

Search Strategy

We searched the following databases for primary studies for the periods in parentheses: MEDLINE® (1966 to July 2011), Embase® (1974 to July 2011), and the Cochrane Central Register of Controlled Trials (1966 to July 2011). 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).

We downloaded the results of the searches 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®. We uploaded the articles from ProCite to DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based software package developed for systematic review data management. We used this database 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. Both reviewers had to indicate that the title was ineligible for it to be eliminated at this level. If they disagreed, they promoted the article to the next level (Appendix B, Title Review Form). We designed the title review to capture as many studies as possible that reported on the efficacy or safety of insulin delivery or glucose monitoring methods.

Two investigators reviewed abstracts independently, and excluded an article if both investigators agreed it 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). The team resolved differences between investigators regarding abstract eligibility through consensus adjudication.

Two reviewers performed another independent parallel full-text review of articles promoted on the basis of abstract review to determine if we should include these articles for data abstraction (Appendix B, Article Review Form). We resolved differences regarding article inclusion 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.

The study investigators performed double data abstraction on each article. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. We formed reviewer pairs that included personnel with both clinical and methodological expertise. We did not hide from the reviewers the identity of the authors of the articles, their respective institutions, or 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.

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. We considered patients with latent autoimmune or pancreatomy to have type 1 diabetes. We considered patients with steroid-induced or transplant-induced diabetes to have type 2 diabetes. We excluded pregnant women with gestational diabetes. We excluded patients with maturity onset diabetes of the young, 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 (see Appendix C for list of devices). We excluded implantable insulin pumps as they are no longer used clinically and retrospective CGM devices, as the current clinical practice is to use rt-CGM. We excluded studies in which regular insulin was used in the insulin pump as this is not consistent with current clinical practice. 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 (i.e., at least 3 injections per day). We included studies using long and rapid-acting analog and/or NPH and regular insulin in the MDI arms because both regimens are still used in clinical practice. We included studies that compared rt-CGM with SMBG (i.e., at least 3 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) and macrovascular outcomes (coronary heart disease, cerebrovascular disease, and peripheral arterial disease) Severe hypoglycemia Quality of life (validated measures) Mortality 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 RCTs and observational studies that evaluated microvascular, macrovascular, maternal, or fetal outcomes. For all other outcomes, we included only RCTs. 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; NPH = neutral protamine Hagedorn; RCT = randomized controlled trial; 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.

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

Quality Assessment

We used different quality assessment tools for randomized controlled trials (RCTs) and observational studies. For RCTs, we based the dual, independent review of article quality on the Cochrane Collaboration's Risk of Bias Tool[40] and supplemented with items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[41] 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. We assessed the overall study quality as:

- **Good (low risk of bias).** These studies had the least bias, and we considered the results 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.[41]

For observational studies, we selected items from the Downs and Black quality checklist[42] and supplemented with items from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[41] We assessed the quality of observational studies 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, and (6) description of loss to followup.

We presented both the primary and secondary reviewers' responses 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 how typical the study population (age, race, sex, and baseline HbA_{1c}), interventions (titration schedule), outcomes, and settings (followup interval) were 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 U.S. 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 two trials) and studies were sufficiently homogenous with respect to key variables (population characteristics and study duration).

For continuous outcomes, we calculated a weighted mean difference between groups in the change scores by using a random-effects model with the DerSimonian and Laird formula.[43] We recorded the mean difference in outcome between groups, along with its measure of dispersion. If the study did not report this information, 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. We derived measures of dispersion using standard methods.[40]

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.[43] 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.[43]

We tested heterogeneity among the trials in all the meta-analyses by using a standard chi-squared test with a significance level of alpha less than or equal to 0.10. We also examined heterogeneity among trials by using an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[44] We considered a value greater than 50 percent 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[45] and Egger's tests[46] 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).

We summarized studies not amenable to pooling qualitatively.

Data Entry and Quality Control

After a second reviewer checked the data that had been entered into DistillerSR, he or she resubmitted adjudicated data using Web-based data collection forms. Second reviewers were generally more experienced members of the research team. Any problems with a reviewer's data abstraction 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 addressing Key Questions 1 and 2 by adapting an evidence grading scheme recommended in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[47] We applied evidence grades to the bodies of evidence about each intervention comparison for each outcome. We assessed the strength of the body of best available evidence by assessing its limitations, consistency, directness, precision, publication bias, and the magnitude of the effect. We assessed the risk of bias of individual studies according to study design characteristics, such as confounding and selection and information biases. We rated the body of evidence as "consistent" if most of the

studies showed the same direction of effect or if the I^2 statistic from a meta-analysis was low. We rated the consistency of a single study as "unknown." We rated the body of the evidence as "direct" if most of the studies evaluated the outcome directly and there were direct comparisons. We based our rating of precision on the width of the confidence intervals. For the outcomes of HbA_{1c}, we rated the confidence interval as "precise" only when the width of the confidence interval was less than 0.5 percent. If a confidence interval could not be determined, then we rated precision as "cannot determine." We based publication bias on the results of the funnel plots. If either the Egger's or Begg's tests suggested publication bias, then we rated publication bias as "yes." If there was no meta-analysis, then we rated publication bias as "uncertain."

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, does not permit a conclusion, or consists of only one study with high risk of bias).

Peer Review and Public Commentary

Experts in adult and pediatric endocrinology and internal medicine and individuals representing stakeholder and user communities were invited to provide external peer review of this comparative effectiveness review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a "disposition of comments report" that will be made available 3 months after AHRQ posts the final comparative effectiveness review on the AHRQ Web site.

Results

Search Results

Figure 2 summarizes the search results. From our search, we retrieved 7,002 unique records. After title and abstract review, we decided 741 articles were potentially relevant to review, and retrieved the full articles (see Appendix D for the list of studies excluded). We included a total of 41 studies (in 44 publications) in this review.

Of the included studies, 28 studies compared the effects of continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI). Nine of these studies were conducted in children or adolescents with type 1 diabetes, nine were conducted among adults with type 1 diabetes, four (in five publications) were conducted among adults with type 2 diabetes, and six were conducted among pregnant women with pre-existing type 1 or type 2 diabetes.

Nine studies (in 10 publications) compared the effects of real-time continuous glucose monitoring (rt-CGM) with self-monitoring of blood glucose (SMBG) 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 four studies (in five publications) evaluated the effects of a sensor-augmented pump compared with MDI and SMBG.

We did not find any studies that reported on microvascular outcomes, macrovascular outcomes, and most process measures.

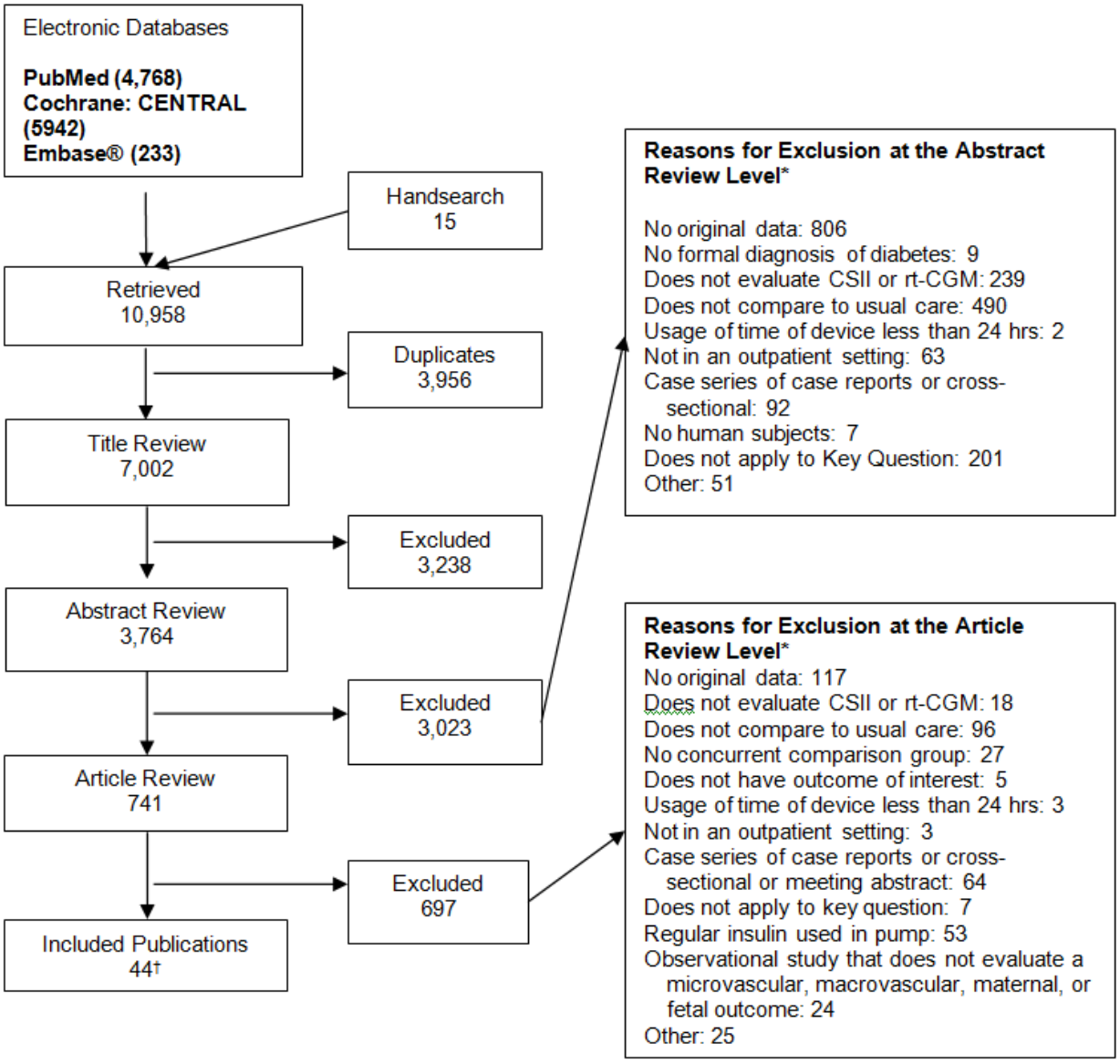
Eighteen studies evaluated health-related quality of life (QOL) using 15 different validated QOL assessment tools. Table 3 lists how the QOL assessment tools were categorized into general QOL, disease-specific QOL, and treatment-specific QOL.

Table 3. Health-related quality of life assessment tools used in each category

Domain	Instrument	Range of Total Scores (High Scores Indication)
General health-related QOL	Pediatric QOL Inventory	**0 – 100 (better QOL)**
	Short Form-36 (SF-36)	**0 – 100 (higher level of health)**
	Short Form-12 (SF-12)	**0 – 100 (higher level of health)**
	World Health Organization-5 Well Being Index (WHO-5)	**0 – 100 (better well-being)**
Diabetes-specific QOL	Diabetes QOL	**0 – 100 (better QOL)**
	Diabetes QOL Clinical Trial Questionnaire	**0 – 100 (higher satisfaction)**
	Diabetes QOL – Youth	**0 – 100 (better QOL)**
	Problem Areas in Diabetes	**0 – 100 (more serious problem)**
Treatment-related QOL	Altered Hypoglycemia Awareness Questionnaire	**0 – 7 (altered hypoglycemia)**
	Blood Glucose Monitoring System Rating Questionnaire	**0 – 100 (higher satisfaction)**
	Diabetes Treatment Satisfaction Questionnaire	**0 – 36 (higher satisfaction)**
	Hypoglycemia Fear Survey	**0 – 92 (higher level of fear)**
	Insulin Delivery System Rating Questionnaire	**0 – 100 (higher satisfaction)**
	Phase V Outcomes system diabetes treatment satisfaction questionnaire	**0 – 100 (higher satisfaction)**
	User Acceptance Questionnaire	**0 – 100 (more positive ratings (with exception of "problems" section))**

QOL = quality of life

Figure 2. Summary of the literature search



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

*Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.

†41 studies in 44 publications: 28 compared CSII with MDI (9 in children and adolescents with type 1 diabetes; 9 in adults with type 1 diabetes; 4 (5 publications) in adults with type 2 diabetes; 6 in pregnant women with pre-existing type 1diabetes); 9 (10 publications) compared rt-CGM with SMBG; 4 (5 publications) compared a sensor-augmented pump with MDI/SMBG

Key Question 1: In patients receiving intensive insulin therapy, does mode of delivery (CSII vs. MDI) 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 percent, decreasing slightly more with CSII than with MDI (95% confidence interval [CI], -0.48 to 0.20, P=0.41). Results were similar among adolescents over 12 years old (mean between-group difference in the change from baseline HbA_{1c}, -0.10 percent; 95% CI, -0.47 to 0.27) and were less different among children less than 12 years old (mean between-group difference in the change from baseline HbA_{1c}, -0.05 percent; 95% CI, -1.01 to 0.96).
- There was low strength of evidence to suggest no significant difference in daytime hypoglycemia frequency between MDI and CSII intervention groups (mean between-group difference in perceived hypoglycemic events over 104 weeks, 0; 95% CI, -1.1 to 1.1;[48] mean between-group difference in the change from baseline to 24 weeks in the number of blood glucose excursions below 70 mg/dL, -0.9; 95% CI, -2.1 to 0.3;[49] mean between-group difference in number of hypoglycemic episodes/patient at 52 weeks, -3.7; 95% CI, -13.2 to 5.8).[50]
- 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 four events/patient/study period (95% CI, 0.3 to 7.7) for MDI versus three events/patient/study period (95% CI, 1.0 to 5.0) over 52 weeks.[50] In the other study, there were two patients with one or more events in the CSII arm but no events reported in the MDI arm over 16 weeks.[51]
- 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.[52]
- The strength of evidence was low indicating similar rates of severe hypoglycemia between the two intervention arms. The mean incidence rate ratio for severe hypoglycemic event rates in randomized controlled trials (RCTs) for CSII versus MDI was 0.99 (95% CI, 0.57 to 1.71, P=0.97). 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) and children less than 12 years of age (mean incidence rate ratio for CSII versus MDI, 1.02; 95% CI, 0.49 to 2.16).
- The strength of evidence comparing CSII with MDI was insufficient for hyperglycemia. One study found no difference in the frequency of hyperglycemia between the MDI (6.7 events) and CSII (7.9 events) intervention groups over 14 weeks.[52]

- The strength of evidence comparing CSII with MDI was insufficient for the ratio of basal to bolus insulin. One study reported no difference in the ratio of basal to bolus insulin between the MDI and CSII (mean between-group difference, 1.7; 95% CI, -2.5 to 5.9) intervention groups.[53]
- The strength of evidence was low comparing CSII with MDI for weight change. The mean between-group difference in how body mass index (BMI) standard deviation score changed from baseline was -0.12 units, decreasing slightly more with CSII than MDI (95% CI, -0.55 to 0.30 units).
- The strength of evidence was low comparing CSII with MDI for general QOL. Two studies[49 54] used the Pediatric Quality of Life Inventory. A meta-analysis of these studies did not favor CSII or MDI in this population (mean between-group difference, 2.3; 95% CI, -6.9 to 11.5; P=0.95).
- The strength of evidence was low comparing CSII with MDI for diabetes-specific QOL. Three studies used the Diabetes Treatment Satisfaction Questionnaire and showed improvement in diabetes treatment satisfaction favoring CSII.[48 50 52] A meta-analysis of two of these studies favored CSII over MDI (mean between-group difference in the Diabetes Treatment Satisfaction Questionnaire, 5.7; 95% CI, 5.0 to 6.4; P<0.001). One study showed improvement in diabetes-specific QOL favoring CSII (Diabetes Quality of Life-Youth baseline score 77.4 [95% CI, 69.5 to 85.3] and end of study 76.4 [95% CI, 68.3 to 84.5] for MDI and 82.7 [95% CI, 75.3 to 90.1] for CSII).[50] One study did not find a difference in the Diabetes Quality of Life-Youth scores between the two interventions (numerical data not presented).[51]
- There was insufficient evidence comparing CSII with MDI for certain process measures (frequency of adjusting insulin therapy, adherence, health visits) and clinical outcomes (microvascular and macrovascular disease and mortality) as no studies addressed these.

Study Design

Nine studies evaluated CSII versus MDI therapy in children and adolescents with type 1 diabetes (Appendix E, Table 1).[48-56] They were conducted in diverse countries, including the U.S.,[49 51] Italy,[55] Sweden,[48] Spain,[53] Saudi Arabia,[56] the Netherlands,[55 57] and Israel.[50 52] Studies varied in their sources of support—four received industry support,[48 50-52] four received government support,[48 51 53 54] and four received other sources of support.[48-50 54] Sources of support were not reported for two studies.[55 56]

Of the nine studies, four were parallel arm RCTs,[48 49 51 55] three were randomized crossover trials,[50 52 54] and two were non-randomized trials.[53 56] Three studies included a run-in period,[51 52 54] three did not,[48 50 55] and three studies did not report a run-in period.[49 53 56] Enrollment into three studies started and ended after 2000,[48 49 56] but most studies did not report the dates of enrollment period.[50-55] The median followup time for all studies was 52 weeks, with a range of 16 to 104 weeks. One study did not report followup duration.[53] These studies screened 24,[52] 36,[55] and 200[53] patients and enrolled a median of 32 patients (range 16 to 72) into randomized clinical trials. Most studies did not report the number of patients screened.[48-51 54 56] Seven studies recruited patients from referral clinics.[49-51 54-56]

The majority of studies excluded pregnant patients.[48-51 53-56] Some studies excluded patients based on HbA_{1c} less than 6.5 percent,[51] 7.5 percent,[53] or 8 percent,[54 55] or greater than 11 percent.[51] Certain studies excluded patients if they were being treated with insulin for less than 1

year[54] or less than 2 years,[52] were using glargine insulin,[51] were not currently treated with intensive insulin therapy,[50 53] or had ever used insulin pump therapy.[51]

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 E, Table 2). One study did not report the ages of the participants.[51] Males were 50 percent and 38 percent of the study populations, respectively, for the MDI and CSII groups. The majority of studies did not report the racial composition of their study populations.[48 50 52 53 55 56] The majority of studies included Caucasian participants and one study reported a very small number of African American and Hispanic participants.[51]

Glycemic control was sub-optimal in participants at the time of study enrollment. The mean HbA_{1c} was 8.5 percent and 8.6 percent in the MDI and CSII groups, respectively. In the one study that reported baseline BMI, the means in the MDI and CSII groups were 15.9 kg/m^2[49] and 20.9 kg/m^2[49] and 19.8 kg/m^2, respectively.[57] Weight and/or BMI was reported as BMI standard deviation scores in two studies[50 53] and were not reported in one study.[56]

Interventions

The MDI arms varied across studies in the type of insulin used: neutral protamine Hagedorn (NPH) and aspart,[48] NPH and lispro,[49] NPH and regular insulin,[50] glargine and regular insulin,[52 55] glargine and lispro,[53 56] and glargine and aspart (see Appendix E, Table 3).[51] One study specified the short-acting insulin used in the MDI arm but not the basal insulin.[54] The MDI schedule was three injections daily in three studies,[49 53 54] and four or more times daily in six studies.[48 50-52 55 56]

Three studies used insulin aspart in the CSII arm[48 51 54] and six studies used insulin lispro in the CSII arm.[49 50 52 53 55 56] In terms of insulin pumps, three studies used the DR HTron v100,[48 53 54] one used the Tayco Disetronic,[50] one used the Animas,[49] three used the MiniMed 508,[51 52 56] and one used the Medtronic MiniMed Paradigm 511 insulin pump.[51] One study did not specify the type of insulin pump used.[55] Three studies included training in insulin pump use prior to its initiation.[48 49 52]

Three studies monitored blood glucose using SMBG[51 52 54] and one study monitored blood glucose using rt-CGM.[49] Five studies did not report how blood glucose was monitored.[48 50 53 55 56] The duration of therapy in each intervention arm ranged from 3.5 to 24 months with six studies having 12 or more months of followup.[48 50 53-56] Five studies provided guidelines for insulin dose titration in the intervention arms,[49 51-54] and one study provided insulin dose titration instructions only for the CSII arm.[55] Only three studies reported their glycemic targets (preprandial glucose of 70 to 140 mg/dL and 2-hour postprandial glucose <180 mg/dL;[53] HbA_{1c} of 7 percent, preprandial glucose of 70 to 120 mg/dL and bedtime glucose of 90 to 150 mg/dL;[51] and preprandial glucose of 79.2 to 149.4 mg/dL).[52]

Outcomes

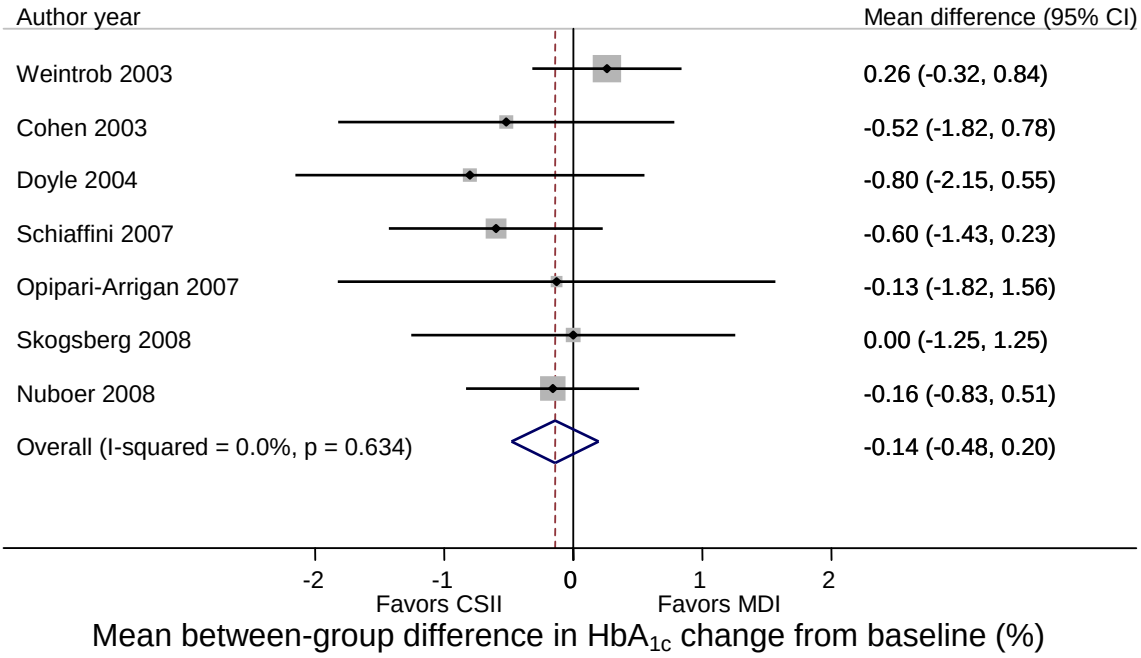
Details of the outcomes are reported in Appendix E, Table 4. We found studies evaluating HbA_{1c}, hypoglycemia (daytime, nocturnal, and mild), severe hypoglycemia, hyperglycemia, ratio of basal to bolus insulin, weight, general QOL, and diabetes-specific QOL. We did not find any studies evaluating the effects on mortality, microvascular disease, macrovascular disease, frequency of adjusting insulin therapy, adherence, or health visits.

HbA_{1c}

Nine studies examined the comparative effectiveness of CSII and MDI on HbA_{1c}. Three studies showed a significant reduction in HbA_{1c} favoring CSII.[51 55 56] The remaining studies showed no difference in the change in HbA_{1c} between the CSII and MDI groups.[48-50 52-54]

A meta-analysis of seven RCTs showed no significant difference between the MDI and CSII intervention groups in how the HbA_{1c} changed from baseline after 16 or more weeks of followup; HbA_{1c} decreasing slightly more with CSII than with MDI (combined mean between-group difference, -0.14; 95% CI, -0.48 to 0.20, P=0.41) (see Figure 3). We did not find evidence of statistical heterogeneity and none of the studies influenced results substantially. Egger's test (P=0.21) and funnel plot did not suggest publication bias.

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



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

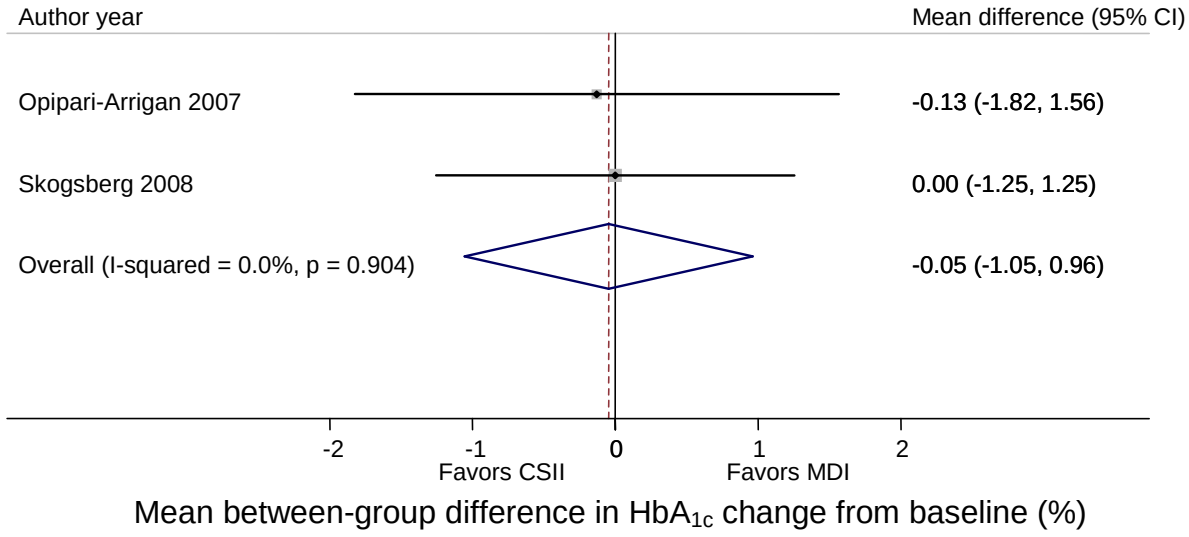
Test for heterogeneity: Q = 4.32 with 6 degrees of freedom (p = 0.63)

Studies in Children 12 Years of Age or Younger

Two studies focused primarily on the comparative effectiveness of MDI and CSII in children whose mean age was 12 years or younger based on age at diagnosis and diabetes duration.[48 49] One study showed a nonsignificant reduction in HbA_{1c} favoring CSII[49] while the other study found no difference in HbA_{1c} between the two groups.[48] A meta-analysis of these two studies showed no significant difference in the change from baseline HbA_{1c} between the MDI and CSII intervention groups (combined mean between-group difference in the change from baseline HbA_{1c}, -0.05 percent; 95% CI, -1.01 to 0.96 percent) (see Figure 4). There was no evidence of

statistical heterogeneity, and none of the studies influenced the results substantially. There were too few studies to assess for publication bias.

Figure 4. Between-group difference between CSII and MDI in how HbA_{1c} changed from baseline among children 12 years of age or less with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections

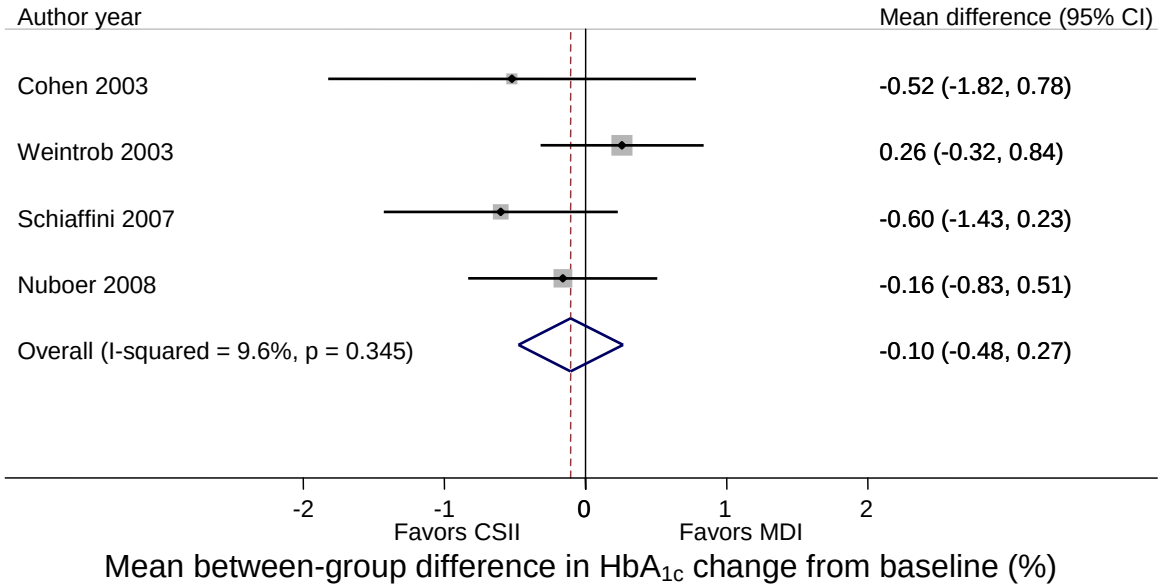
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95%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

Test for heterogeneity: Q = 0.01 with 1 degree of freedom (p = 0.90)

Studies in Adolescents (Older 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 no significant reduction in HbA_{1c} favoring CSII[50 54 55] while one study found no significant reduction in HbA_{1c} favoring MDI.[52] A meta-analysis of these studies showed no 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 percent; 95% CI, -0.48 to 0.27 percent) (see Figure 5). We did not find evidence of statistical heterogeneity and none of the studies 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.[51]

Figure 5. Between-group difference between CSII and MDI in how HbA_{1c} changed from baseline among adolescents with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% 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. The studies defined participants as being hypoglycemic if they had perceived hypoglycemia,[48] average blood sugar excursions/day below 70 mg/dL,[49] and mean number of hypoglycemia episodes/patient/study period.[50] One study did not specify the timeframe for units of measures.[48] There was no significant difference in daytime hypoglycemia frequency between the two groups.[48-50] Two studies examined the comparative effectiveness of CSII and MDI on nocturnal hypoglycemia and found no significant differences between the two groups.[50 51]

Mild Hypoglycemia

One study examined the frequency of mild hypoglycemia (defined as blood sugar below 70 mg/dL) in the MDI and CSII interventions groups[52] and found no significant difference between the CSII group (19.8 events/patient) compared with the MDI group (22 events/patient).[52]

Severe Hypoglycemia

Six 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,[52] five studies found no difference in frequency between the two groups.[49-51 53 55]

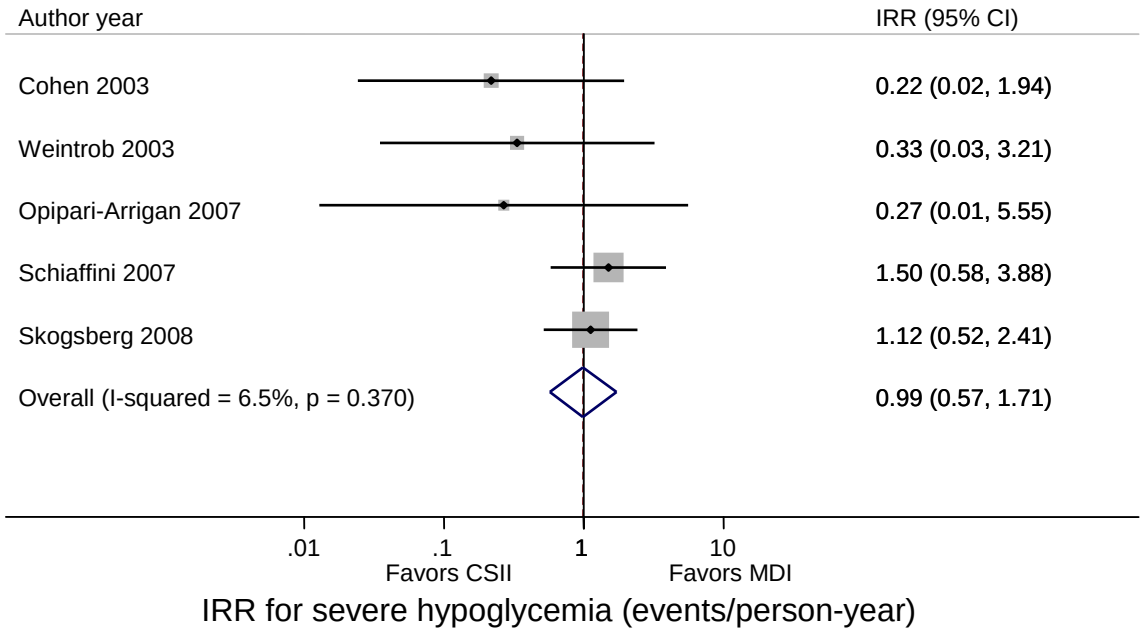
Table 4. Definitions of severe hypoglycemia in the studies of children and adolescents with type 1 diabetes

Author, Year	Severe Hypoglycemia Definition
Opipari-Arrigan, 2007[49]	Seizure, obtundation, or combativeness preventing administration of oral glucose in association with a capillary blood glucose of less than 100 mg/dL
Schiaffini, 2007[55]	Hypoglycemic event requiring assistance from another person, infusion of glucose or resulting in severe symptoms, such as seizure or coma
Garcia-Garcia, 2007[53]	Hypoglycemia requiring parental treatment
Doyle, 2004[51]	Event resulting in coma or seizure
Cohen, 2003[50]	Not explicitly defined
Weintrob, 2003[52]	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 vs. MDI, 0.99; 95% CI, 0.57 to 1.71, P=0.97) (see Figure 6). We did not find evidence of statistical heterogeneity and none of the studies 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.[51]

Figure 6. Incident rate ratios for severe hypoglycemia in CSII versus MDI 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

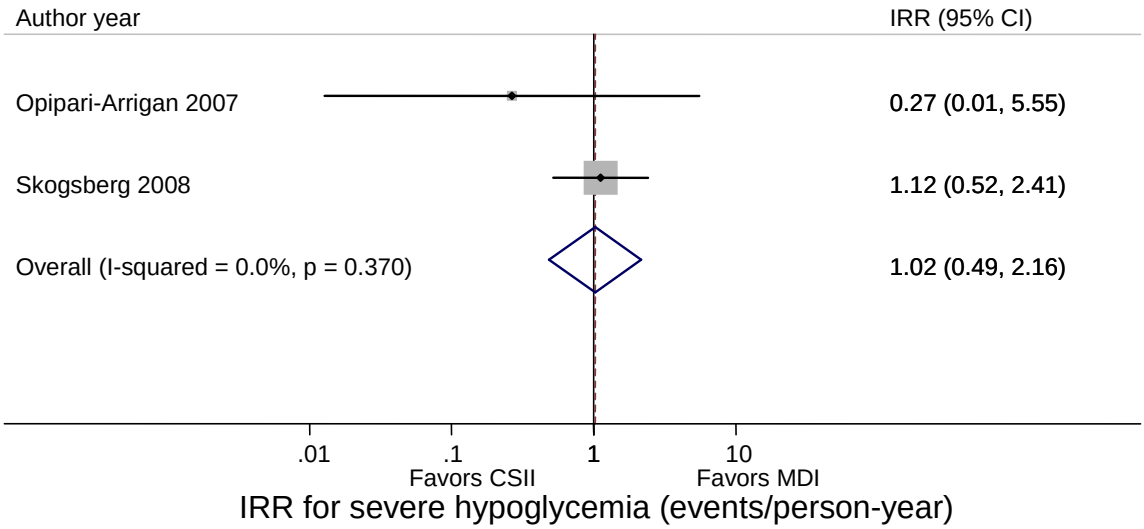
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% 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 lower rate of severe hypoglycemia favoring CSII that was not significant,[49] while the other study showed a lower rate of severe hypoglycemia favoring MDI that was also not significant.[48] A meta-analysis of these two 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, 1.02; 95% CI, 0.49 to 2.16) (See Figure 7). We did not find evidence of statistical heterogeneity and none of the studies influenced results substantially. There were too few studies to adequately assess publication bias.

Figure 7. Incident rate ratios for severe hypoglycemia in CSII versus MDI interventions among children 12 years of age or less with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; IRR = incidence rate ratio; MDI = multiple daily injections

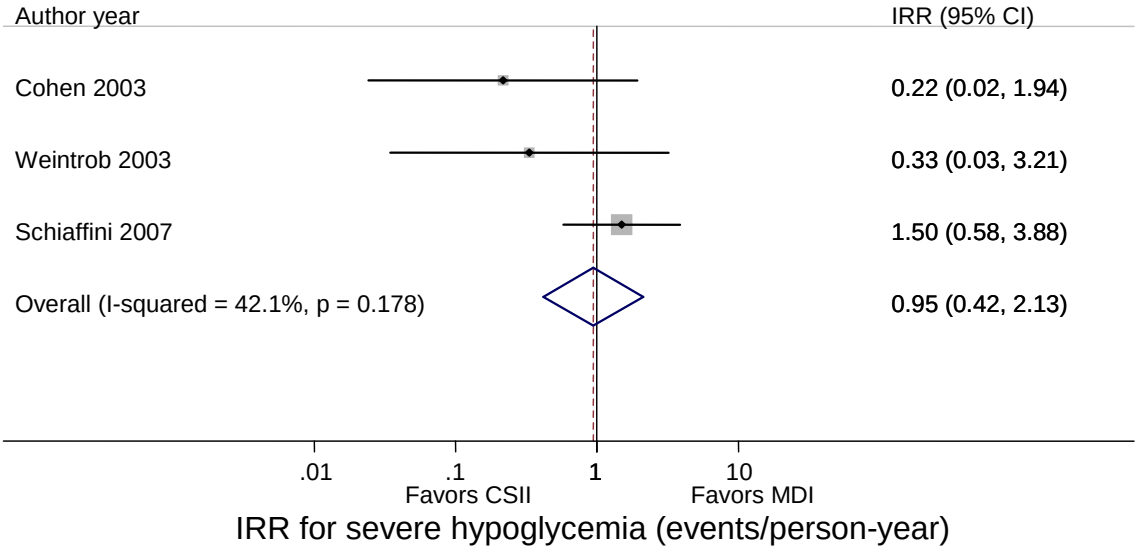
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95%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

Test for heterogeneity: Q = 0.80 with 1 degree of freedom (p = 0.37)

Studies in Adolescents Older Than 12 Years of Age

Three of the five RCTs were performed in adolescents. Two studies showed a lower rate of severe hypoglycemia favoring CSII that was not significant,[50 52] while one study showed a lower event rate favoring MDI that was also not significant.[55] 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 vs. MDI, 0.95; 95% CI, 0.42 to 2.13) (See Figure 8). We did not find evidence of statistical heterogeneity and none of the studies influenced results substantially. There were too few studies to adequately assess publication bias.

Figure 8. Incident rate ratios for severe hypoglycemia in CSII versus MDI 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% 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.[52] The study defined participants as being hyperglycemic if they had 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

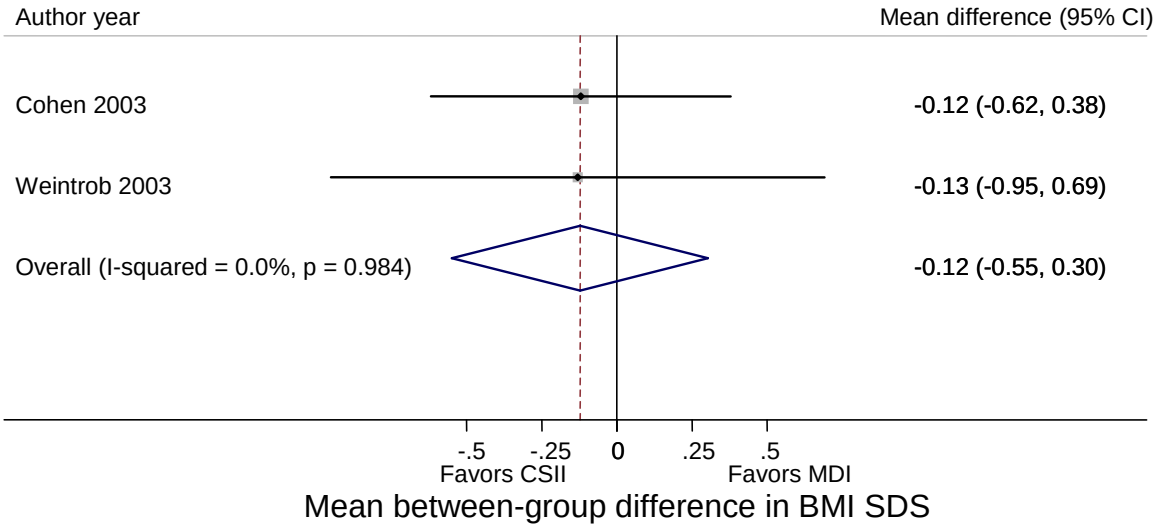
One study examined the ratio of basal to bolus insulin in the MDI and CSII intervention groups and found no difference in the ratios between the two groups.[53]

Weight Gain

Table 5 summarizes three studies that compared CSII with MDI for changes in weight as measured by BMI SDS in children with type 1 diabetes.[50-52] BMI SDS is a measure of BMI used in children that indicates how many standard deviations the measurement is above or below the median of the distribution. Two studies were randomized open crossover trials conducted at the same institution.[50 52] One found no significant change in BMI-SDS over the course of the study in either treatment arm.[50] The other crossover study reported a slight, but statistically significant, increase in BMI-SDS during MDI therapy and no significant change during CSII.[52] 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.[51] A meta-analysis of two studies showed a difference that was not significant in the change from baseline BMI SDS between the MDI and

CSII intervention groups favoring CSII (combined mean between-group difference in the change from baseline BMI SDS, -0.12; 95% CI, -0.55 to 0.30) (see Figure 9). There was no evidence of statistical heterogeneity and none of the studies influenced the results substantially. There were too few studies to assess for publication bias. We did not include one study in the meta-analysis because there was not sufficient data provided on estimates.[51]

Figure 9. Between-group difference between CSII and MDI in how BMI SDS changed from baseline among children and adolescents with type 1 diabetes



BMI SDS = body mass index standard deviation score; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.00 with 1 degree of freedom (p = 0.98)

Table 5. Weight gain in CSII versus MDI 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[50]	16	16	24	0.20	0.30	0.25	0.23	No significant change	NS
Weintrob, 2003[52]	23	23	14	0.29	0.40	0.37	0.35	Decrease	0.01
Doyle 2004[51]	16	16	4	NA	NA	NA	NA	No significant change	NS

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

Quality of Life, Including General, Diabetes-Specific, and Treatment-Related

Six studies examined the comparative effectiveness of CSII versus MDI on general, diabetes-specific, and diabetes treatment-related QOL in children and adolescents with type 1 diabetes (see Table 6). Two studies examined general QOL in children and adolescents with type 1 diabetes using the Pediatric Quality of Life Inventory (scores range from 0 to 100, with higher scores indicating better QOL).[49 54] Both of these studies showed improvement in general QOL favoring CSII (see Table 6), but not in a statistically significant fashion. It should be noted that while both of the studies used a similar measure, one of the studies used the Dutch translation of that instrument.[54] A meta-analysis of these studies did not favor CSII or MDI in this population (mean between-group difference, 2.3; 95% CI, -6.9 to 11.5) (see Figure 10).

Two studies examined the comparative effectiveness of CSII versus MDI on diabetes-specific QOL.[50 51] Two studies used the Diabetes Quality of Life-Youth instrument (scores range from 0 to 100, with higher scores indicating better QOL) and while one showed improvement in QOL favoring CSII,[50] the other study did not find a difference in QOL between the two intervention arms.[51]

Three studies examined the comparative effectiveness of CSII versus MDI on diabetes treatment-related QOL.[50 52 58] The three studies that used the Diabetes Treatment Satisfaction Questionnaire (scores range from 0 to 36, with higher scores indicating greater satisfaction) showed an improvement in diabetes-specific QOL favoring CSII.[50 52 58] A meta-analysis of two studies favored CSII over MDI (mean between-group difference, 5.7; 95% CI, 5.0 to 6.4; $P<0.001$). However, the variation in the effect due to heterogeneity was significant, with an I^2 of 64% (see Figure 11). We did not include one study in the meta-analysis because it did not present the baseline values by intervention group.[50] However, in that study the mean between-group difference in the final scores likewise favored CSII (10.2; 95% CI, 4.0 to 16.4).

Table 6. Quality of life in CSII versus MDI 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[54]	19 CSII, 19 MDI	CSII vs. 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 (95% CI, -3.1 to 8.7) in CSII vs. 0.4 (95% CI, -7.4 to 8.2) in MDI	CSII
Pediatric Quality of Life Inventory*	Opipari-Arrigan, 2007[49]	6 CSII, 8 MDI	CSII vs. 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 (95% CI, -5.6 to 21.6) in CSII vs. 6.5 (95% CI, -16.4 to 29.4) in MDI	CSII
DQOL-Y†	Doyle, 2004[51]	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[50]	16 enrolled; 12 completed the study	CSII vs. 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 (95% CI, 69.5 to 85.3) at the beginning of the study, 76.4 (95% CI, 68.3 to 84.5) at the end of the MDI arm, and 82.7 (95% CI, 75.3 to 90.1) at the end of the CSII arm (P<0.05)"	CSII
DTSQ‡	Skogsberg, 2008[48]	34 CSII, 38 MDI	CSII vs. MDI	72 children and adolescents (age range 7-17 yrs) with type 1 diabetes	At the end of 24 months, 33.1 (95% CI, 32.8 to 33.4) in CSII vs. 27.5 (95% CI, 26.8 to 28.2) in MDI, P<0.001.	CSII
DTSQ‡	Cohen, 2003[50]	16 enrolled; 12 completed the study	CSII vs. 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 (95% CI, 18.7 to 22.3) at the beginning of the study, 21.8 (95% CI, 19.7 to 23.9) at the end of the MDI arm (after 6 months), and 32 (95% CI, 28.3 to 35.7) at the end of the CSII arm (after 6 months) (P<0.05)	CSII
DTSQ‡	Weintrob, 2003[52]	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 (95% CI, 20.1 to 22.7) at the beginning of the study, 21.9 (95% CI, 19.7 to 24.1) at the end of the MDI arm (after 3.5 months of treatment), and 30.6 (95% CI, 28.4 to 32.8) at the end of the CSII arm (after 3.5 months of treatment (P<0.001).	CSII

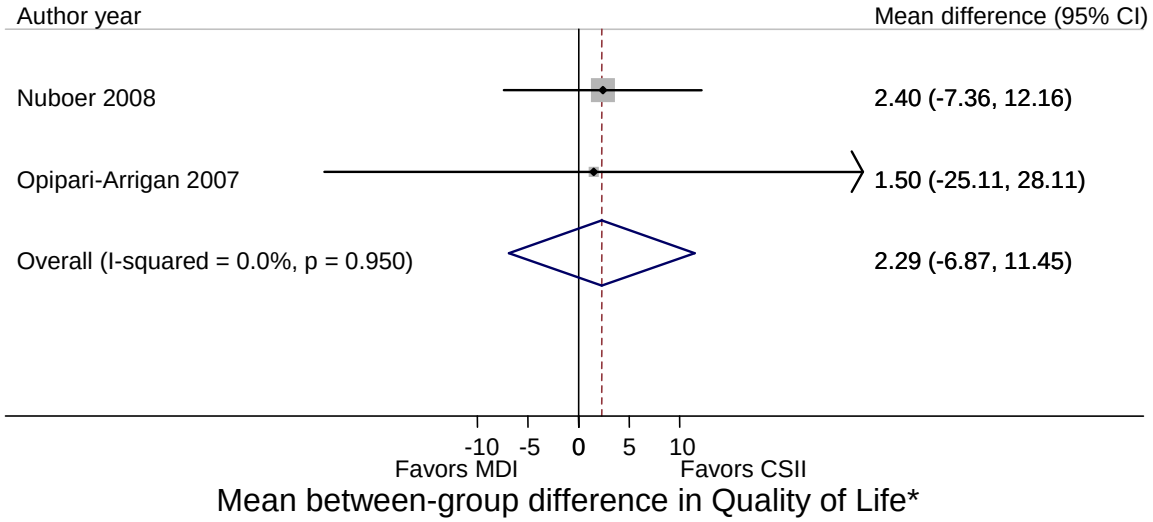
CSII = continuous subcutaneous insulin infusion; CI = confidence interval; DQOL-Y = Diabetes Quality of Life – Youth; DTSQ = Diabetes Treatment Satisfaction Questionnaire; MDI = multiple daily injections; QOL = quality of life; yr = year

*General QOL measure. Total scores from the Pediatric Qualtiy of Life Inventory range from 0 to 100, with higher scores indicating better quality of life.

†Diabetes-specific QOL measure. Total scores from the Diabetes Quality of Life-Youth range from 0 to 100, with higher scores indicating higher satisfaction.

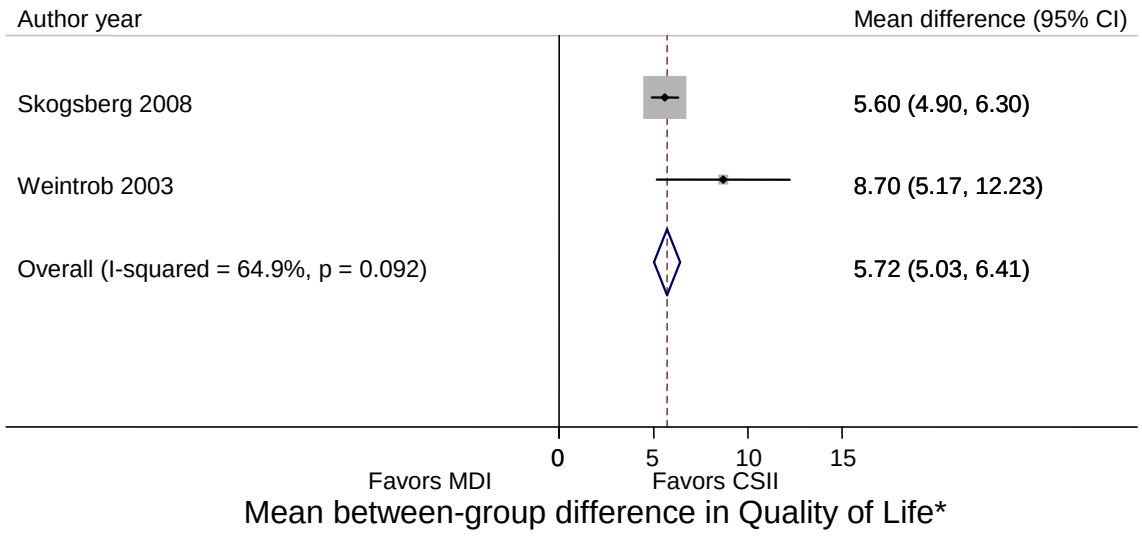
‡Diabetes treatment-related QOL measure. Total scores from the Diabetes Treatment Satisfaction Questionnaire range from 0 to 36, with higher scores indicating higher satisfaction.

Figure 10. Between-group difference between CSII and MDI in how Pediatric Quality of Life measure changed from baseline among children and adolescents with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections
*Quality of life is measured in terms of the Pediatric Quality of Life Inventory. Total scores range from 0 to 100, with higher scores indicating better quality of life.
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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.00 with 1 degree of freedom (p = 0.95)

Figure 11. Between-group difference between CSII and MDI in how Diabetes Treatment Satisfaction Questionnaire changed from baseline among children and adolescents with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections
*Quality of life is measured in terms of the Diabetes Treatment Satisfaction Questionnaire, which is an 8-item questionnaire. The total score ranges from 6 to 36. Higher scores indicate greater satisfaction.
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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 4.85 with 2 degrees of freedom (p = 0.09)

Study Quality

Among the RCTs on children and adolescents, one study was good quality,[51] three studies were fair quality,[48 52 54] and three studies were poor quality (see Appendix E, Table 5).[49 50 55] A lack of reporting on most quality items limited our assessment of the risk of bias. Only one study, which was rated as good quality, reported on sequence generation.[51]

Among the non-randomized trials, one was fair quality[53] and one was fair or poor quality (see Appendix E, Table 6).[56] Studies had incomplete[53] or no[56] 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 and it was unclear if the study derived patients in the two groups from the same population.[56] All but one study[56] performed adjusted or stratified analyses.

Strength of Evidence

The strength of evidence examining the comparative effectiveness of CSII versus MDI was moderate for HbA_{1c}, and low for daytime and nocturnal hypoglycemia, severe hypoglycemia, weight gain, and general and disease-specific quality of life 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	
Mortality	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Microvascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Macrovascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
HbA_{1c}	9 (260)	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	6 (152)	Medium	Consistent	Direct	Imprecise	Yes	Magnitude of effect: No effect Strength of evidence: Low
Daytime hypoglycemia	3 (122)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Nocturnal hypoglycemia	2 (64)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Mild hypoglycemia	1 (23)	High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Insufficient
Ratio of basal to bolus insulin	1 (32)	High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Insufficient
Frequency of adjusting insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Adherence to insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Frequency of professional or allied health visits	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient

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 (continued)

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	
Weight gain	3 (110)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
General QOL	2 (52)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Diabetes-specific QOL	2 (44)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Treatment-specific QOL	3 (107)	Medium	Inconsistent	Direct	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Low

HbA_{1c} = hemoglobin A_{1c}; NA = not applicable; QOL = quality of life

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, does not permit a conclusion, or consists of only one study with high risk of bias.

Applicability

The majority of studies in children and adolescents with type 1 diabetes were small, with the largest clinical trial including 72 participants.[48] Most RCTs were fair or poor quality and only one RCT was good quality. The majority of studies focused on 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 United States, most studies included Caucasian participants. This is consistent with the fact that the majority of children with type 1 diabetes and adolescents and are Caucasian.[5] Participants generally had poor glycemic control at study entry (mean HbA_{1c} 8–9 percent), 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

- The strength of evidence was low that CSII produced a larger reduction in HbA1c than MDI (mean between-group difference from baseline, -0.30 percent; 95% CI, -0.58 to -0.02 percent, P=0.038). However, the pooled result was influenced by one study, which had a higher HbA1c at enrollment compared with the other studies. After removing this study, the difference between CSII and MDI became null (mean between-group difference from baseline, -0.01 percent, 95% CI, -0.35 to 0.34 percent).
- There was low strength of evidence comparing CSII with MDI for daytime hypoglycemia. One study reported more symptomatic and asymptomatic hypoglycemia between 8 a.m.and midnight in the MDI compared with the CSII intervention arm (P<0.05).[59]
- The strength of evidence was low comparing CSII with MDI for nocturnal hypoglycemia. Three studies reported nocturnal hypoglycemia. In one crossover trial, the proportion of patients experiencing nocturnal hypoglycemia was similar between the MDI and CSII intervention arms (relative risk [RR] for any, 0.98; 95% CI, 0.83 to 1.17; RR for symptomatic, 0.87; 95% CI, 0.64 to 1.19), although there were fewer episodes per person in the CSII compared with the MDI group (incidence rate ratio, 0.76; 95% CI, 0.63 to 0.91; P=0.0024).[59] In two other studies, there was not a statistically significant difference in nocturnal hypoglycemic episodes between the two intervention groups.[60 61]
- We found low strength of evidence showing an increased risk of symptomatic hypoglycemia for CSII compared with MDI (combined incidence rate ratio, 1.30; 95% CI, 1.18 to 1.42; P<0.001), but we found evidence of substantial statistical heterogeneity for this meta-analysis. When excluding a study that required participants to have had recent severe hypoglycemia[61] (compared with the other two which excluded those with recent severe hypoglycemia[60 62]) we saw an incidence rate ratio suggesting no relative difference in the incidence of symptomatic hypogycemia for CSII compared with MDI (combined incidence rate ratio, 0.99; 95% CI, 0.85 to 1.14). Another study, which did not provide sufficient quantitative results, reported slightly more symptomatic hypoglycemic events with CSII versus MDI (incidence rate ratio, 1.14; 95% CI, 1.00 to 1.29; P=0.05), although a similar proportion of participants experienced events over 5 weeks (RR, 1.05; 95% CI, 0.89 to 1.24).[59]

- The strength of evidence was low 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 crossover trials did not provide quantitative results on severe hypoglycemia by period and therefore were not included in the meta-analysis. Two studies showed more severe hypoglycemia with MDI compared with CSII[59 63] with one study reporting a relative risk of 2.6 (95% CI, 2.08 to 3.25).[63] One study showed less severe hypoglycemia with MDI compared with CSII (incidence rate ratio, 3.00; 95% CI, 0.24 to 157.49).[64] One study found similar rates of severe hypoglycemia between the two groups (1.1 events/patient for CSII vs. 1.3 events/patient for MDI over 4 months, P=0.33).[65]
- The strength of the evidence comparing CSII with MDI was low for other nonsevere hypoglycemia. Three studies found no difference in nonsevere hypoglycemia between the two intervention groups (in one study, mean between-group difference in asymptomatic hypoglycemia event rate, -0.2; 95% CI, -1.39 to 0.99; P=0.97).[60] In two studies, the incidence of mild hypoglycemia was higher in the CSII compared with the MDI group[59 66] 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).[66] 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).[63]
- The strength of evidence was low comparing CSII with MDI for fasting glucose. 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.[60] Two other studies reported no difference in fasting glucose between the MDI and CSII groups.
- The strength of evidence was low comparing CSII with MDI for pre-prandial glucose. The mean between-group difference in preprandial glucose over 6 months was -17.1 mg/dL (95% CI, -42.1 to 8.0 mg/dL; P=NS) favoring CSII in one study,[60] and in another study, pre-dinner glucose was lower with CSII (128 mg/dL) compared with MDI (148 mg/dL) at the end of 5 weeks (P=NS).[59] Predinner and prelunch glucoses were not significantly lower with CSII compared with MDI at 4 months (estimates not reported) in a third study.[66]
- There was insufficient strength of evidence to determine the relative effects of CSII and MDI on glucose at bedtime. A single study reported no difference in glucose at bedtime in the CSII compared to MDI arm but did not provide glucose results.[66]
- The strength of evidence was low comparing CSII with MDI for post-prandial glucose suggesting slightly lower postprandial glucoses with CSII compared with MDI treatment. Comparing CSII and MDI, the reported mean between-group difference in post-prandial glucose was -5.5 mg/dl (95% CI, -29.9 to 18.9 mg/dl) in one study[60] and -24 and -15 mg/dl postbreakfast and postdinner, respectively, in another.[59] Postbreakfast glucoses were not significantly higher in the MDI compared with CSII arm in a third study.[66]
- The strength of evidence was low comparing CSII with MDI for nocturnal hyperglycemia. Two studies found no difference in between-group difference in nocturnal glucose[60 66] with one reporting an increase in nocturnal glucose in both arms (between-group difference for CSII compared to MDI, 54.8; 95% CI, -7.2 to 116.7 mg/dl).[60]
- The strength of evidence was low to suggest no difference in weight gain comparing CSII with MDI (combined between-group difference, -0.25 kg; 95% CI, -3.14 to 2.64 kg;

P=0.86). Two additional studies reported no difference in weight gain but did not report sufficient quantitative results.

- The strength of evidence was low comparing CSII with MDI for general QOL. Two studies showed an improvement in general QOL 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).[63] The other study did not report estimates but there was 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 QOL. Three studies showed an improvement in diabetes-specific QOL favoring CSII. A meta-analysis favored CSII over MDI for Diabetes Quality of Life (mean between-group difference in Diabetes Quality of Life, 2.99; 95% CI, 0.006 to 5.97). One study showed improvement favoring MDI (Diabetes QOL mean between-group difference in change from baseline -18.00, 95% CI, -50.14 to 14.14).[61]
- The strength of evidence comparing CSII with MDI for diabetes treatment-related QOL was insufficient. Altered Hypoglycemia Awareness Questionnaire scores were similar in the CSII and MDI groups over 24 weeks (RR of Altered Hypoglycemia Awareness Questionnaire score greater than 4, 0.75; 95% CI, 0.26 to 2.18). Hypoglycemia Fear Survey scores decreased in the both CSII (-3±25) and MDI (-8±33) groups (mean between-group difference in the change from baseline, 5; 95% CI, -32.66 to 42.66).[61]
- We found insufficient evidence of the effects of MDI versus CSII among adults with type 1 diabetes in terms of any process measures, microvascular disease, macrovascular disease, and mortality, as no studies reported on these outcomes.

Study Design

Nine studies evaluated the effectiveness and safety of CSII versus MDI among adults with type 1 diabetes (see Appendix E, Table 1).[59-67] Studies occurred in European countries,[64-67] Canada,[62] and the U.S.[59] Two studies were multi-national.[60 63] Five were parallel arm studies,[60-62 66 67] and four used a crossover design.[59 63-65] All studies randomized participants to the intervention with the exception of a single study.[67] The duration of interventions ranged from 5 weeks to 1 year.[59-67] Treatment lasted for 5 weeks in one study;[59] 4 months in three studies;[64-66] 6 months in three studies;[60 61 63] and 9 months[68] and 1 year[67] in the other two studies. Studies included 21 to 272 participants. Four studies occurred in clinical settings.[62 64-66] The other studies did not report study setting.[59-61 63 67] Two studies did not report on the use of a run-in period.[61 67]

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 percent[60] and 8.5 percent,[67] and four studies set an upper limit for HbA_{1c} for eligibility: 8.5 percent,[66] 9 percent,[59 60] and 10 percent.[64] Eligibility criteria for prior insulin use varied across studies with three studies requiring that participants be on intensified insulin therapy with MDI,[60 62 63] one study requiring MDI therapy be less than 1 year in duration,[67] two studies excluding participants based on lack of recent CSII use,[59 65] and one study excluding participants based on prior CSII use.[60] Three studies excluded participants with frequent severe hypoglycemia,[59 60 62] and another study excluded participants without severe hypoglycemia in the last 6 months.[61]

Population Characteristics

About one half of participants in the included studies were men with little imbalance by intervention strategy (see Appendix E, Table 2).[60 63-67] One study consisted mainly of men with 62 percent of participants male in the CSII and 71 percent male in the MDI arm.[62] 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 percent higher in the MDI versus CSII arm.[62] Intervention arm-specific HbA_{1c} ranged from 7.4 percent to 9.3 percent at baseline.[60 62 63 65 66] The mean duration of type 1 diabetes ranged from 14.4 to 25 years in studies reporting this.[60-67] Mean duration of diabetes was 4.9 years higher in the CSII arm compared with the MDI arm in one study[67] but otherwise similar by intervention strategy across studies.[59-63 65 66]

Five studies did not report on withdrawals by intervention allocation.[59 60 63 65 67] In the other studies, withdrawals during the first treatment period varied by arm across studies: one in CSII and none in MDI,[62] seven in CSII and none in MDI,[66] and 16 in CSII and 15 in MDI.[63] A cross-over trial reported five withdrawals from the CSII-MDI treatment group and four from the MDI-CSII treatment group.[59] And another cross-over trial reported a single withdrawal during MDI therapy.[64] One study reported the mistaken randomization of eight participants and an additional seven withdrawals without differentiation by treatment arm.[60]

Interventions

Four studies used NPH insulin as the long-acting insulin for the MDI arm,[62-64 66] and the other studies used insulin glargine (see Appendix E, Table 3).[59-61 65 67] All studies used insulin aspart or insulin lispro as the short-acting insulin during MDI treatment.[59-67] Two studies incorporated 7 days of CGM.[59 61] Eight studies specified provider guidelines for insulin titration based on SMBG.[59-66] Five studies reported the use of insulin titration guidelines for participants.[61-64 66]

Outcomes

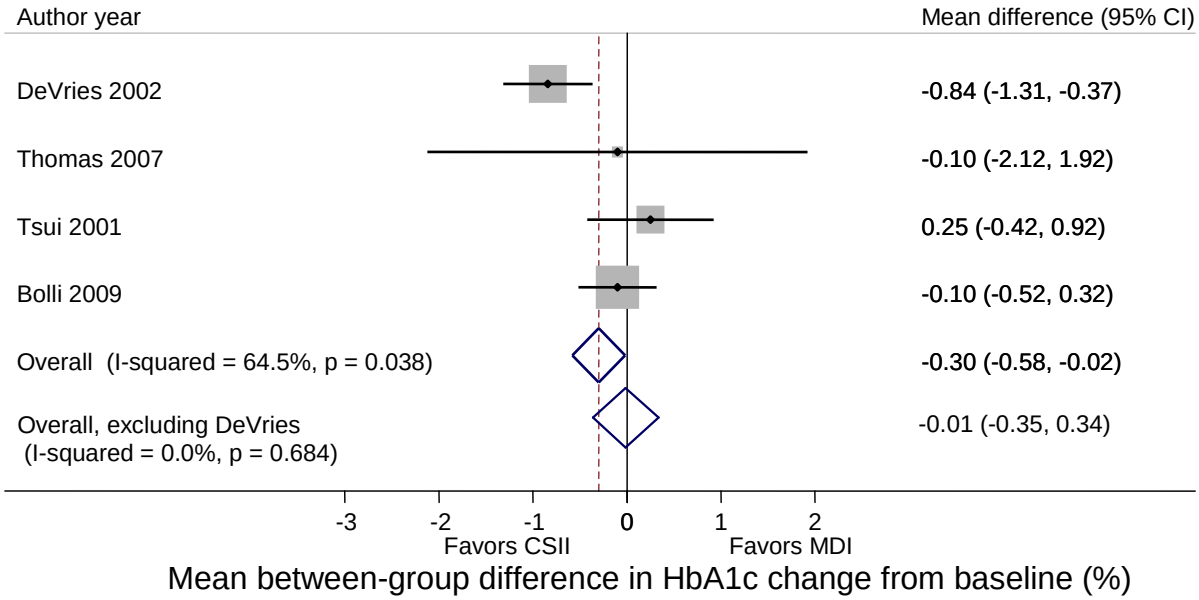
Details of the outcomes are reported in Appendix E, Table 4. These studies evaluated the effects of CSII and MDI in terms of HbA_{1c}, hyperglycemia, hypoglycemia, severe hypoglycemia, weight, and quality of life. None of the included studies reported effects on mortality, microvascular disease, macrovascular disease, or any of the process measures.

HbA_{1c}

Four RCTs reported a mean decrease in HbA_{1c} in both CSII and MDI treatment groups. CSII produced a larger reduction in HbA_{1c} than MDI (combined mean between-group difference, -0.30 percent; 95% CI, -0.58 to -0.02 percent, P=0.038) (Figure 12).[60-62 66] However, the pooled estimate was influenced by one study,[66] in which participants had a higher HbA_{1c} at enrollment (9.3 percent) compared with the other studies (7.7 to 8.2 percent), resulting in greater opportunity for a large HbA_{1c} reduction in that study (-0.84 percent) compared with the other studies (-0.1 to 0.25 percent). After removing this study, the difference between CSII and MDI became null (combined mean between-group difference, -0.01 percent, 95% CI, -0.35 to 0.34 percent; P=0.972). Study duration ranged from 4 months to 1 year.[60-62 66] Egger's test and the funnel plot did not suggest bias due to absence of small studies. A fifth study reported a nonsignificant difference in improvement in HbA_{1c} from baseline. We did not include this study in the meta-analysis because it did not provide quantitative results.[67] Because of anticipated carryover effects, we could not determine the effect of CSII and MDI on HbA_{1c} from the four crossover

studies.[59 63-65] These studies had an insufficient[63] or no[59 64 65] wash-out period between treatments and did not report results from the first treatment period. Additionally, the treatment periods in Hirsch et al. were only 5 weeks in duration.[59]

Figure 12. Between-group difference between CSII and MDI in how HbA_{1c} changed from baseline among adults with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

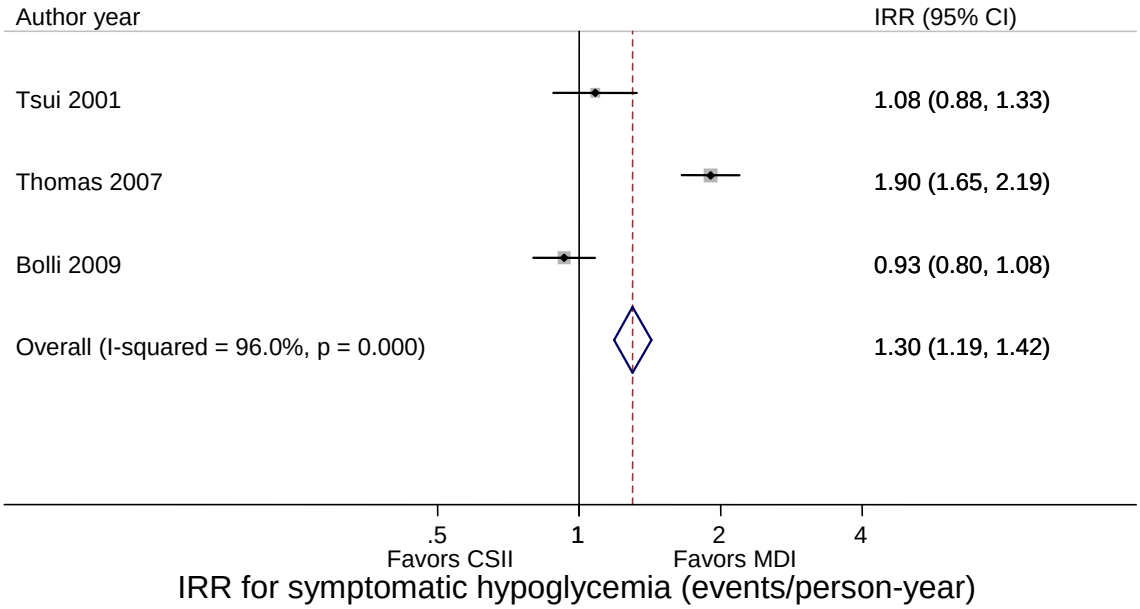
Test for heterogeneity: Q = 8.45 with 3 degrees of freedom (p = 0.038); Q = 0.76 with 2 degrees of freedom (p = 0.684)

Symptomatic Hypoglycemia

Four trials evaluated symptomatic hypoglycemia.[59-62] We combined results from three of these studies in a meta-analysis which revealed a significant increase in the incidence of symptomatic hypoglycemia events/person-year with CSII compared with MDI (combined incidence rate ratio, 1.30; 95% CI, 1.18 to 1.42; P<0.001) (see Figure 13).[60-62] We found evidence of substantial statistical heterogeneity (I^2 = 96 percent). Given the small number of studies, we were unable to perform meta-regression to formally explore causes of this heterogeneity. A likely source of the observed heterogeneity is a difference in study populations. While two of the studies excluded participants with more than two severe hypoglycemic episodes in the past 6 months,[60 62] the other only included participants with at least one episode of severe hypoglycemia in the past 6 months.[61] This study was influential and removal of this study from the meta-analysis resulted in a combined incidence rate ratio of 0.99 (95% CI, 0.85 to 1.14) for CSII versus MDI. Egger's test and the funnel plot did not reveal publication bias. 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

percent for CSII versus 72 percent for MDI).[59] We did not include this study in the meta-analysis because of its cross-over design and a lack of reporting results from a paired analysis or by period, thus precluding a valid estimate of variance for the meta-analysis.[59]

Figure 13. Incident rate ratios for symptomatic hypoglycemia in CSII versus MDI interventions among adults 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 50.32 with 2 degrees of freedom (p = 0.00)

Daytime Hypoglycemia

A single RCT using a crossover design reported more hypoglycemic events between 8 a.m. and midnight during MDI treatment than during CSII treatment (P<0.05).[59] Hypoglycemia could be symptomatic or asymptomatic and the study defined it as glucose less than 50 mg/dL not necessitating assistance from a third party.[59]

Nocturnal Hypoglycemia

Three studies reported on nocturnal hypoglycemia (Table 8).[59-61] One crossover trial reported a similar percentage of participants experiencing any nocturnal hypoglycemia (symptomatic, minor, or major) (72 percent vs. 73 percent) or symptomatic nocturnal hypoglycemia (42 percent vs. 48 percent) in the CSII and MDI treatment arms, respectively (statistical significance not reported).[59] 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 vs. 4.0 events per participant; P=0.002).[59] 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).[60] 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.[61] All studies employed SMBG for glucose monitoring and interval eight-point SMBG profiles.[59-61] One study also measured glucose with a CGM system during the last week of each treatment period.[59] We were unable to perform a meta-analysis for this outcome because of a lack of reporting of the necessary quantitative results. Hirsch, et al. was a crossover study that did not report results for a paired analysis or by period.[59] Another study did not report on nocturnal hypoglycemia in the MDI arm.[61]

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

Author, Year	Definition of Nocturnal Hypoglycemia
Bolli, 2009[60]	Between bedtime and rising
Hirsch, 2005[59]	Symptomatic and not documented by blood glucose measurement
Hirsch, 2005[59]	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[61]	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).[59 60 63-66] 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).[60] In two studies, the incidence of mild hypoglycemia was higher during CSII compared with MDI treatment[59 66] with the relative difference statistically significant in one of these studies.[66] 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).[63] Two other studies found no difference in the incidence of biochemical hypoglycemia during CSII compared with MDI treatment.[64 65] We did not combine these results in a meta-analysis because substantial heterogeneity in outcome definitions (Table 9).

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

Author, Year	Definition of Mild Hypoglycemia
Bolli, 2009[60]	Asymptomatic
Bruttomeso, 2008[65]	Measured glucose 36 to 63 mg/dL
DeVries, 2002[66]	Change in frequency of SMBG < 70 mg/dL per patient-week
Hanaire-Broutin, 2000[64]	Measured glucose < 60 mg/dL during last 14 days of treatment
Hirsch, 2005[59]	Asymptomatic glucose < 50 mg/dL or symptomatic glucose < 50 mg/dL without third party intervention required
Hoogma, 2006[63]	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 14).[60 61 66] 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.[61] 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.

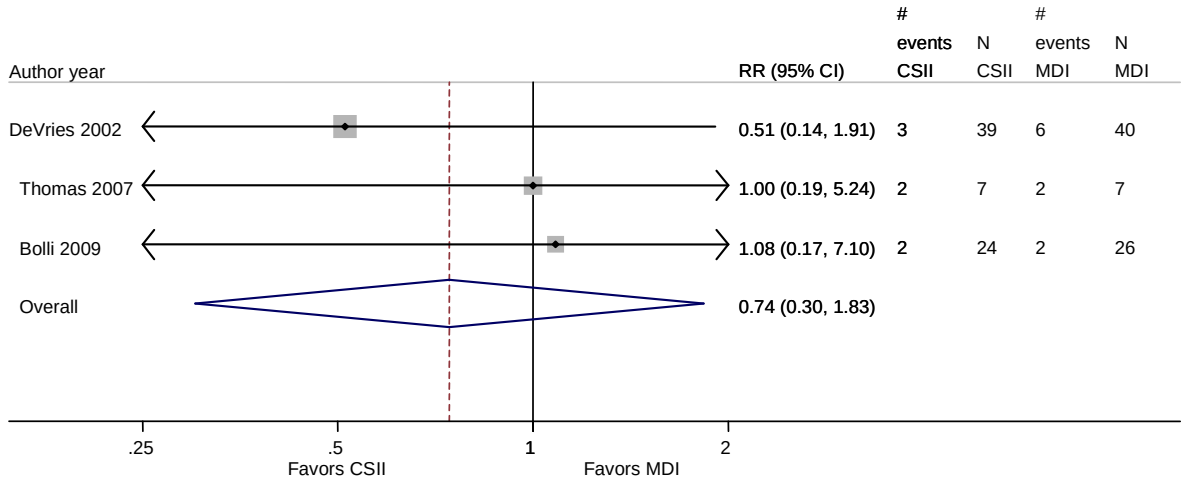
We did not include two additional studies in the meta-analysis because of a lack of quantitative results. One RCT reported a small difference that was not significant in the number of severe hypoglycemic events over 9 months in the CSII versus MDI treatment arm (six events vs. four events) but did not report if any individuals had more than one hypoglycemic event.[62] The other study was non-randomized and reported that the number of severe hypoglycemia episodes decreased in both treatment arms during the study.[67]

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

Author, Year	Definition of Severe Hypoglycemia
Bolli, 2009[60]	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[61]	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[66]	Requirement of third-party help
Tsui, 2001[62]	Events requiring assistance or resulting in coma
Lepore, 2003[67]	Event requiring assistance from another person or resulting in a seizure or coma

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

Figure 14. Pooled relative risk of severe hypoglycemia in CSII versus MDI interventions among adults with type 1 diabetes



Pooled Relative Risk and 95% Confidence Intervals of Severe Hypoglycemia

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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% 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.[59 63-65] 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,[59 63] with one study reporting a relative risk of 2.6 (95% CI, 2.08 to 3.25).[63] Compared with CSII therapy, severe hypoglycemia occurred less frequently during MDI therapy in one study (three events vs. one event over 4 months.[64] 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).[65]

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[65]	Plasma glucose <36 mg/dL
Hoogma, 2006[63]	Requirement of third-party help
Hirsch, 2005[59]	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[64]	Events requiring external help, glucose administration, coma, or seizure

mg/dL = milligrams per deciliter

Hyperglycemia

We were unable to perform meta-analyses for the hyperglycemia outcomes because of a lack of reporting of the necessary quantitative results (detailed below).

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).[60] In a non-randomized trial, CSII and MDI lowered fasting glucose similarly at 12 months (quantitative results not reported).[67] 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.[66] The authors did not provide estimates of these glucose levels.[66]

Preprandial Glucose (Other Than Prebreakfast)

Three RCTs reported on the effect of CSII and MDI on preprandial glucose. In one RCT, CSII decreased preprandial glucose more than MDI at 6 months (mean between-group difference, -17.1 mg/dL; 95% CI, -42.1 to 8.0 mg/dL),[60] but this difference was not significant. In a crossover 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).[59] CSII lowered predinner and prelunch glucoses more than MDI nonsignificantly at 4 months in another study,[66] but the authors did not provide estimates of these glucose levels.[66]

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.[66] The authors did not provide estimates of these glucose levels.[66]

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.[60] 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.[66]

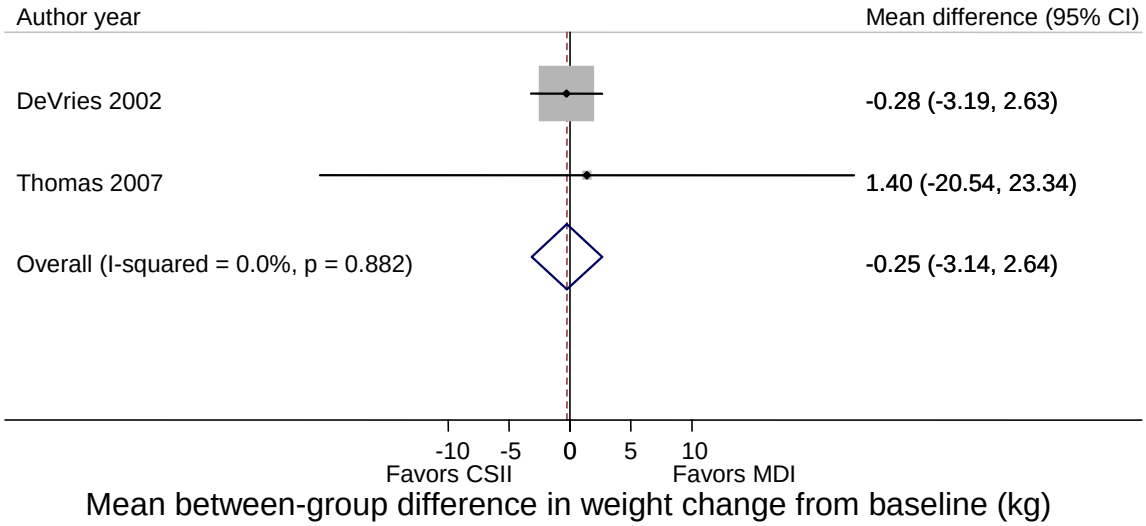
Postprandial Glucose

Three RCTs reported lower postprandial glucoses with CSII compared with MDI treatment. In one trial, postprandial 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).[60] In a crossover trial, postbreakfast and postdinner 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).[59] In a third trial, postlunch and postdinner glucoses were similar at 4 months in the MDI and CSII arms, but postbreakfast glucose levels were nonsignificantly higher in the MDI compared with CSII arm.[66] The authors did not provide estimates of these glucose levels in this study.[66]

Weight

Four studies examined the effects of MDI versus CSII on weight gain in adults with type 1 diabetes, and we outlined the results in Table 12.[61 65-67] Meta-analysis of two studies providing sufficient quantitative results showed no difference in weight gain for CSII compared with MDI (combined mean between-group difference in change from baseline, -0.25 kg; 95% CI, -3.14 to 2.64 kg; P=0.87) (Figure 15).[61 66] We did not find evidence of statistical heterogeneity. The availability of only two studies for the meta-analysis limited our ability to explore influence of publication bias. The remaining two studies reported no significant change in weight, which one study attributed to the presence of a dietician.[65 67]

Figure 15. Between-group difference between CSII and MDI in how weight changed from baseline among adults with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; kg = kilograms; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 50.32 with 2 degrees of freedom (p = 0.00)

Table 12. Weight gain in CSII versus MDI 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[66]	40	39	4	0.88	0.60	-0.28	0.68
Lepore, 2003[67]	16	16	12	-	-	-	-
Thomas, 2007[61]	7	7	6	-1.0	0.5	1.5	0.88; 0.94
Bruttomesso, 2008[65]	39	39	4	-	-	-	-

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

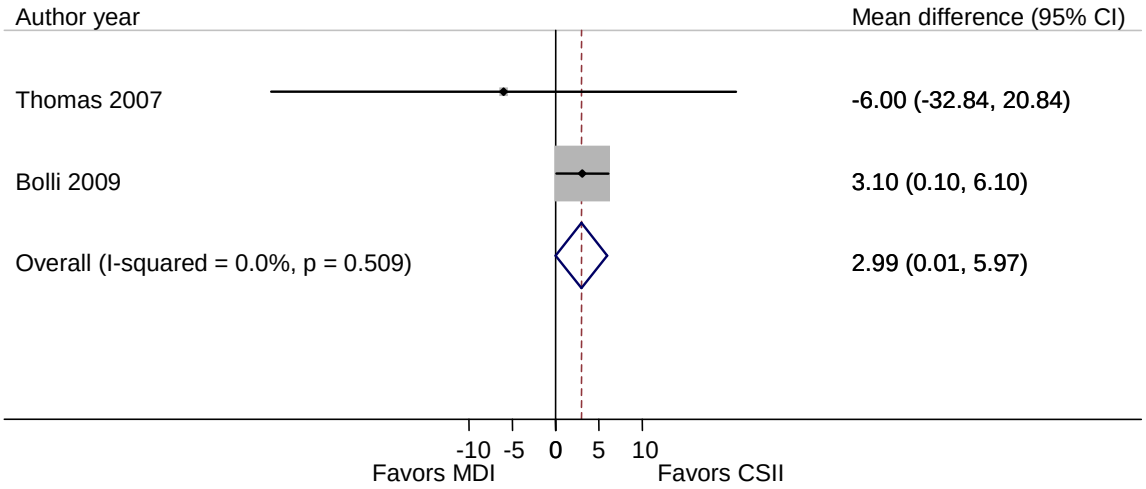
Quality of Life, Including General, Diabetes-Specific, and Treatment-Related

Five studies examined the comparative effectiveness of CSII versus MDI on general QOL, diabetes-specific QOL, and diabetes treatment-related QOL in adults with type 1 diabetes (Table 13). The studies measured general QOL using the Short Form (SF)-36[66] and SF-12.[63] Two studies showed an improvement in general QOL favoring CSII.[63 66]

Four studies examining the comparative effectiveness of CSII versus MDI on diabetes-specific QOL used the Diabetes Quality of Life questionnaire.[60-63] Three studies showed an improvement in diabetes-specific QOL favoring CSII[60 62 63] and one study showed improvement favoring MDI.[61] A meta-analysis of those studies using Diabetes Quality of Life questionnaire as a measure, including only those studies which gave confidence intervals[60 61] favored CSII (mean between-group difference, 2.99; 95% CI, 0.006 to 5.97, P=0.05) (Figure 16).

One study examined the comparative effectiveness of CSII versus MDI on diabetes treatment-related QOL using the Altered Hypoglycemia Awareness Questionnaire and the Hypoglycemia Fear Survey.[61] There was no difference in hypoglycemia awareness or fear between the two intervention arms at the conclusion of the study.

Figure 16. Between-group difference between CSII and MDI in how Diabetes Quality of Life Questionnaire score changed from baseline among adults with type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; kg = kilograms; MDI = multiple daily injections
*Quality of life is measured in terms of the Diabetes Quality of Life Questionnaire. Total scores range from 0 to 100, with higher scores indicating better quality of life.
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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.44 with 1 degree of freedom (p = 0.51)

Table 13. Quality of life in CSII versus MDI 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[66]	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[63]	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[61]	7 CSII, 7 MDI, 7 education	CSII vs. optimized MDI vs. 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[63]	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[62]	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[60]	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=0.04).	CSII
Altered Hypoglycemia Awareness Questionnaire ‡	Thomas, 2007[61]	7 CSII, 7 MDI, 7 education	CSII vs. optimized MDI vs. 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

Table 13. Quality of life in CSII versus MDI 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
Hypoglycemia Fear Survey‡	Thomas, 2007[61]	7 CSII, 7 MDI, 7 education	CSII vs. optimized MDI vs. 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; HbA_{1c} = hemoglobin A_{1c}; 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. Total scores from the Short Form-36 and Short Form-12 range from 0 to 100, with higher scores indicating higher level of health.

†Diabetes-specific Quality of Life. Total scores from the Diabetes Quality of Life questionnaire range from 0 to 100, with higher scores indicating better quality of life.

‡Diabetes Treatment-Related Quality of Life. Total scores from the Altered Hypoglycemia Awareness questionnaire range from 0 to 7, with higher scores indicating altered awareness. Total scores from the Hypoglycemia Fear Survey range from 0 to 92, with higher scores indicating a higher level of fear.

Study Quality

We rated two studies as being of good quality[62 64] with the others rated as being of fair or poor quality.[59-61 63 65-67] All included studies were RCTs. A lack of reporting on most quality items limited our assessment of the risk of bias. Three studies reported an appropriate randomization sequence generation,[62 65 66] and only two studies reported appropriate allocation concealment.[62 66] Four studies did not mask outcome assessors to intervention arm.[60 63 64 66] Two studies reported one withdrawal,[62 64] and five did not handle missing data appropriately.[59 60 63 65 66] All studies reported industry support with the exception of one.[67] 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 for HbA_{1c} and low or insufficient for all other outcomes (see Table 14). All included studies were RCTs, and the risk of bias was medium or high. CSII produced a greater reduction in HbA_{1c} compared with MDI; however, there was heterogeneity and the results were heavily influenced by one study. When this study was removed, there was no difference in the effect of CSII compared with MDI on HbA_{1c}. There was no apparent difference in the effects of CSII compared with MDI on weight change, most hypoglycemia outcomes, and fasting and pre-prandial glucose. The relative magnitude of effect on post-prandial glucose and symptomatic hypoglycemia 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, did not use the same definitions for many outcomes, and often did not report sufficient quantitative results 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	
Mortality	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Microvascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Macrovascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
HbA_{1c}	5 (227)	Medium	Inconsistent	Direct	Precise	None	Magnitude of effect: Smallt Strength of evidence: Low
Fasting glucose	3 (161)	High	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Post-prandial glucose	3 (179)	Medium	Consistent	Direct	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Pre-prandial glucose	3 (179)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Glucose at bedtime	1 (79)	Medium	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Nocturnal glucose	2 (129)	High	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Symptomatic hypoglycemia	4 (141)	Medium	Inconsistent	Direct	Precise	None	Magnitude of effect: Small Strength of evidence: Low
Daytime hypoglycemia	1 (100)	Medium	Unknown	Direct	Precise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low
Nocturnal hypoglycemia	3 (114)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low

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 (continued)

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	
Severe hypoglycemia	9 (588)	Medium	Inconsistent	Direct	Imprecise	None	Magnitude of effect: No effect Strength of evidence: Low
Other hypoglycemia	6 (515)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low
Weight	4 (184)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Ratio of basal to bolus insulin	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Frequency of adjusting insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Adherence to insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Frequency of professional or allied health visits	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
General QOL	2 (335)	High	Consistent	Direct	Imprecise	Uncertain	Magnitude: Small Strength of evidence: Low
Diabetes-specific QOL	3 (354)	High	Inconsistent	Direct	Imprecise	Uncertain	Magnitude: Small Strength of evidence: Low
Diabetes treatment-related QOL	1 (21)	Medium	Unknown	Direct	Imprecise	Uncertain	Magnitude: Small Strength of evidence: Insufficient

HbA_{1c} = hemoglobin $A_{1c;}$ NA = not applicable; QOL = quality of life

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, does not permit a conclusion, or consists of only one study with high risk of bias.

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 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, although this would be expected to be a small proportion of individuals 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 percent 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

- The strength of the evidence was insufficient comparing the relative effects of CSII and MDI on mortality. A single study reported one death due to cancer in the CSII treatment arm.[69]
- The strength of evidence was moderate suggesting no difference between CSII and MDI for their effects on HbA_{1c} (mean between-group difference from baseline, -0.16 percent; 95% CI, -0.42 to 0.09 percent, P=0.21).
- The strength of the evidence comparing CSII with MDI for mild hypoglycemia was moderate and suggested no difference in the risk of mild hypoglycemia (combined RR, 0.90; 95% CI, 0.78 to 1.03; P=0.129).
- The strength of the evidence comparing CSII with MDI for nocturnal hypoglycemia was insufficient. In a single study, nocturnal hypoglycemia (occurring between midnight and 6 a.m.) was less common in patients in the CSII compared with the MDI arm (RR, 0.73; 95% CI, 0.35 to 1.54).
- The strength of the evidence was low that the risk of severe hypoglycemia did not differ between CSII and MDI (RR, 0.76; 95% CI, 0.26 to 2.19).
- The strength of the evidence was low 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; 95% CI, -45 to -5 mg/dL).[36] 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 vs. six events), affecting 18 percent and 5 percent of participants in the MDI and CSII arms, respectively (RR, 0.28; 95% CI, 0.08 to 0.94).[36]
- The strength of evidence was low suggesting no difference in weight gain between CSII and MDI groups, based on two studies (combined between-group difference in weight change from baseline, -0.49 kg; 95% CI, -1.25 to 0.26 kg).
- The strength of the evidence comparing CSII with MDI was insufficient for general QOL. One study showed no difference in general QOL between the CSII and MDI

intervention groups. The 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, the difference from baseline to follow-up was 1.0 for CSII and 2.5 for MDI.[69]

- The strength of the evidence comparing CSII with MDI was insufficient for diabetes-specific QOL. One study showed no difference in diabetes-specific QOL between the CSII and MDI intervention groups (Diabetes Quality of Life Clinical Trials Questionnaire scores improved from 52 to 81 for CSII and from 50 to 78 for MDI over 12 months).[69]
- The strength of the evidence comparing CSII with MDI was insufficient for diabetes treatment-related QOL. One study showed improvement in diabetes treatment satisfaction favoring CSII (mean between-group difference in Phase V Outcomes System Diabetes Treatment Satisfaction score change from baseline in 24 weeks, 13.1; 95% CI, 7.4 to 18.8).[36]
- We found insufficient strength of evidence evaluating the effects of MDI vs. CSII among patients with type 2 diabetes in terms of any of the process measures, microvascular disease, or macrovascular disease, as no studies reported on these outcomes.

Study Design

Of the four studies evaluating CSII versus MDI therapy in patients with type 2 diabetes, three were parallel-arm randomized trials,[36 69 70] and one was a randomized cross-over trial (see Appendix E, Table 1).[37] Treatment periods were 18 weeks in duration in the cross-over study,[37] and the parallel-arm studies were 6 or 12 months in duration.[36 69 70] The cross-over study enrolled patients from diabetes centers,[37] and another study took place in a university clinic.[70] The other two studies did not report on study setting.[36 69] Three trials reported a run-in period.[36 37 69]

Two studies excluded participants with HbA_{1c} greater than 12 or 15 percent,[36 37] and three studies excluded persons with HbA_{1c} less than 6, 7, or 8.5 percent.[36 37 69] All studies required that participants be treated with insulin prior to the study.[36 37 69 70]

Population Characteristics

The number of participants per arm ranged from 20 to 66 in the included studies (see Appendix E, Table 2).[36 37 69 70] All studies were conducted in adults, one study only included participants 60 years of age or older.[69] More men were randomized to the CSII treatment group in two studies.[36 69] 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 percent).[36 69] Mean HbA_{1c} was 0.3 percent higher at baseline in the CSII compared with MDI arm in one study.[69] Mean BMI ranged from 29.5 to 32.5 kg/m^2 and was similar by treatment group across the three parallel-arm studies.[36 69 70] 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.[36 69] Three studies reported four to six withdrawals per intervention arm, and the number of withdrawals did not vary by arm.[36 37 69] One study had additional withdrawals after randomization (two from MDI and three from CSII) but before the treatment period began.[36]

Interventions

The type of insulin used in the MDI arms varied across studies: neutral protamine Hagedorm (NPH) and Regular insulin;[37] insulin glargine and insulin lispro;[69 70] and NPH insulin and insulin

aspart (see Appendix E, Table 3).[36] Insulin aspart was used in the CSII arm for one study,[36] and insulin lispro was used in the CSII arm in the other studies.[37 69 70] Three studies reported the use of provider guidelines for medication titration,[36 37 69] but the targets varied. One study specified an HbA_{1c} target of 7 percent,[37] and another specified both an HbA_{1c} target of 5.6 percent and glucose targets of 80 to 120 mg/dL for pre-prandial glucose, and 100 to 150 mg/dL at bedtime.[69] The third study specified a fasting glucose of 80 to 120 mg/dL as its only target.[36] Two studies provided guidelines for participants to use between visits.[37 69]

Outcomes

Details of the outcomes are reported in Appendix E, Table 4. These studies evaluated the effects of CSII and MDI in terms of mortality, HbA_{1c}, hypoglycemia, severe hypoglycemia, hyperglycemia, weight, and quality of life. We did not include any studies that evaluated microvascular disease, macrovascular disease, or any of the process measures.

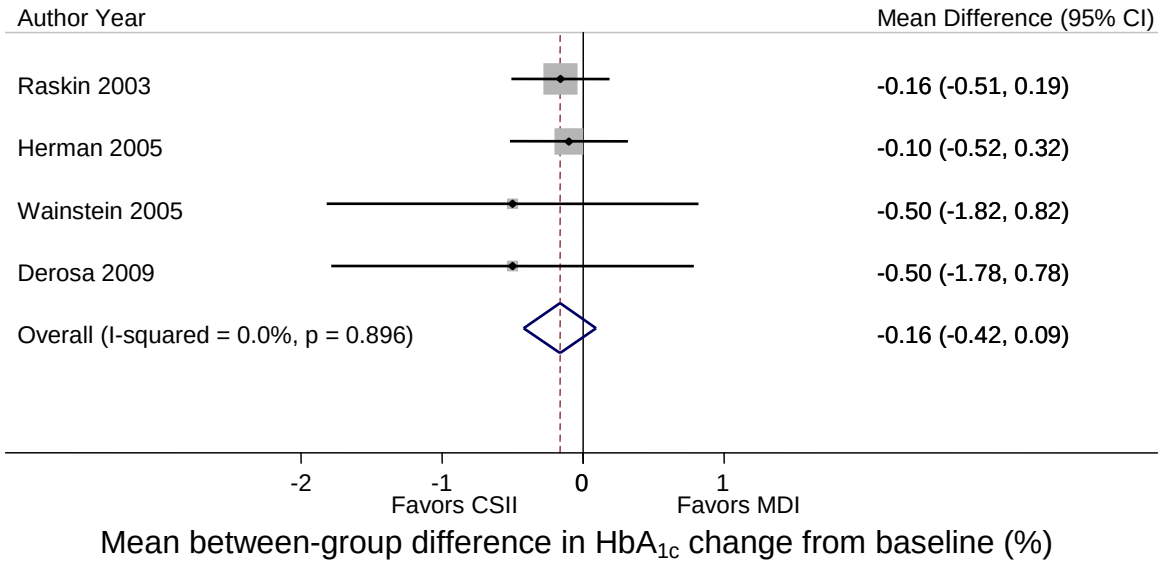
Mortality

A single study lasting 12 months reported a single death due to cancer in the CSII arm.[69] The study did not provide further information on this event or the occurrence of events in the MDI arm.[69]

HbA_{1c}

As shown in Figure 17, 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 that was not significant (combined mean between-group difference from baseline, -0.16 percent; 95% CI, -0.42 to 0.09 percent, P=0.21).[36 37 69 70] 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 17. Between-group difference between CSII and MDI in how HbA_{1c} changed from baseline among adults with type 2 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections

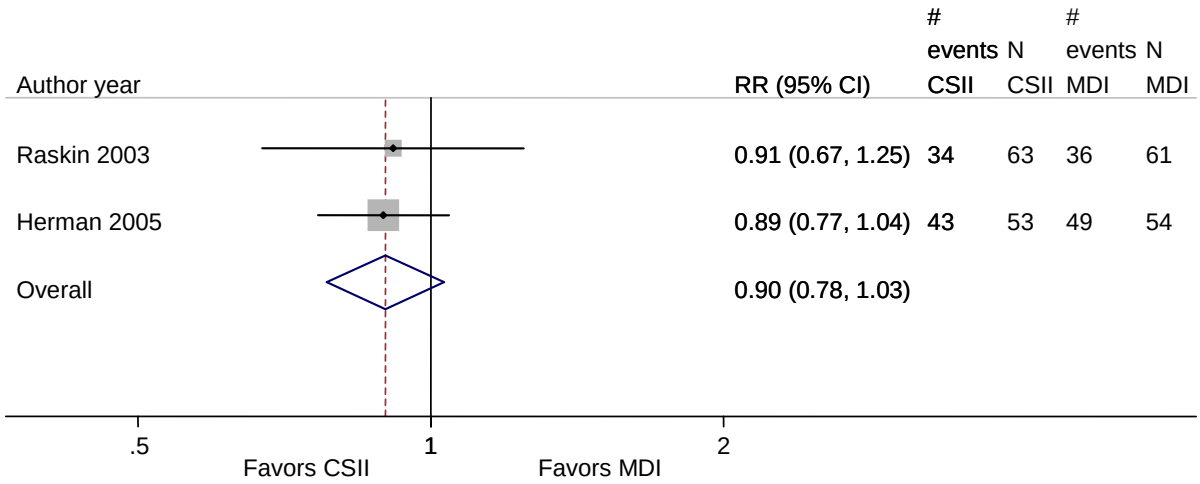
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95%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

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

Mild Hypoglycemia

Three trials reported on mild hypoglycemia in patients with type 2 diabetes randomized to MDI and CSII therapy.[36 37 69] The combined risk of mild hypoglycemia was lower with CSII compared with MDI treatment across two studies but not significant (combined relative risk 0.90; 95% CI, 0.78 to 1.03; P=0.129; Figure 18).[36 69] We did not find statistical evidence of heterogeneity in this meta-analysis.The availability of only two studies precluded the use of Egger's test to evaluate for publication bias. Both studies were small and showed similar effects that were not significant (Figure 18). The third study, a cross-over trial, did not provide quantitative results but concluded that mild hypoglycemia did not vary over the period of the study.[37]

Figure 18. Pooled relative risk of mild hypoglycemia in CSII versus MDI interventions among adults with type 2 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.02 with 1 degree of freedom (p = 0.90)

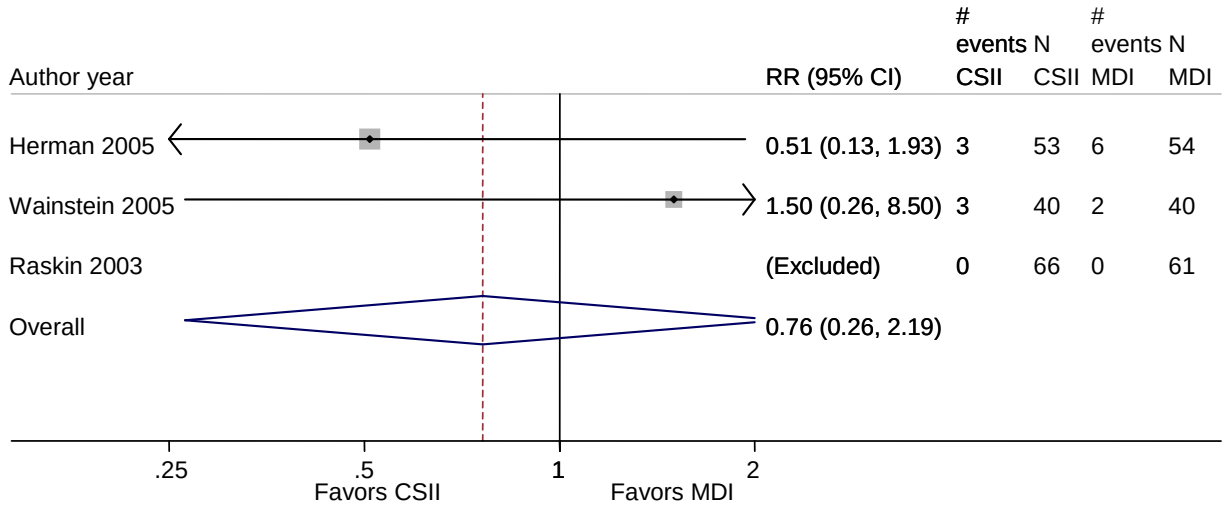
Nocturnal Hypoglycemia

In a single study, nocturnal hypoglycemia (occurring between midnight and 6 a.m.) was more common between 8 and 24 weeks in the MDI arm compared with CSII arm (percentage of patients with nocturnal hypoglycemia, 22 percent vs. 16 percent; statistical significance not reported).[36] The authors described the rates of nocturnal hypoglycemia as similar between arms but did not report on statistical significance.[36]

Severe Hypoglycemia

Three RCTs reported on rates of severe hypoglycemia among patients with type 2 diabetes treated with MDI or CSII.[36 37 69] 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).[36] In the other two studies, the combined relative risk of severe hypoglycemia was 0.76 (95% CI, 0.26 to 2.19; P=0.61; Figure 19) for CSII compared with MDI treatment.[37 69] We did not find statistical evidence of heterogeneity for this meta-analysis. The availability of only two studies precluded the use of Egger's test to evaluate for publication bias. Both studies were small and showed effects that were not significant (Figure 19).

Figure 19. Pooled relative risk of severe hypoglycemia in CSII versus MDI interventions among adults with type 2 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.94 with 1 degree of freedom (p = 0.33)

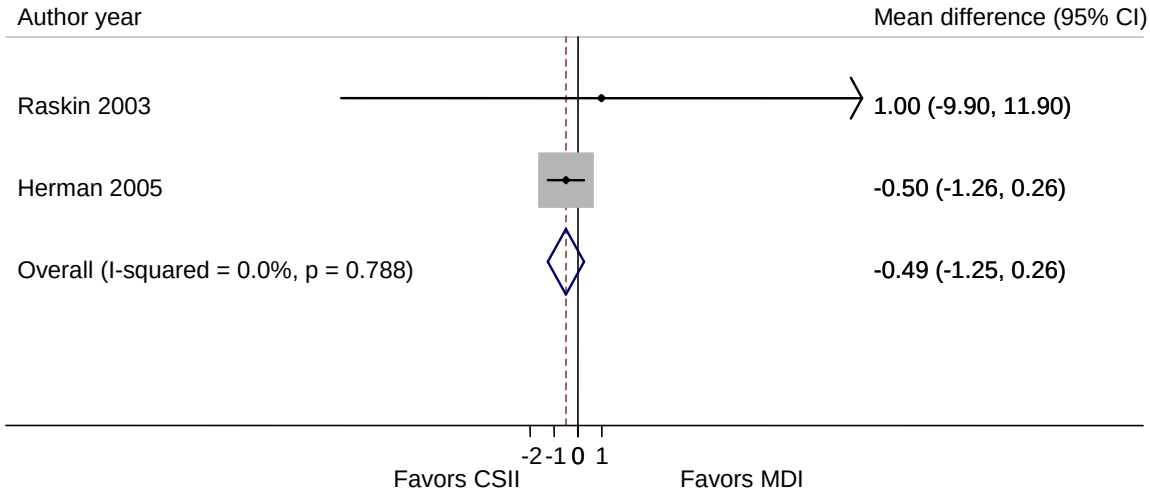
Hyperglycemia

Two studies reported hyperglycemia outcomes based on SMBG in patients with type 2 diabetes randomized to CSII or MDI.[36 71] In one study, 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).[36] The authors reported that glucose measurements from the other time points were similar between treatment groups at the end of the study.[36] The incidence of blood glucose greater than 350 mg/dL was higher in the MDI compared with CSII arm (26 versus six events) effecting 18 percent and 5 percent of participants in the MDI and CSII arms, respectively.[36] The authors reported no treatment group differences in mean pre- (P=0.88) or post-prandial glucose (P=0.59) over 12 months in the other study.[71] We did not combine the two studies reporting on hyperglycemia because one study did not provide quantitative results aside from P values.[71]

Weight

Two studies[36 69] evaluated weight gain experienced by participants in MDI and CSII groups (Table 15) and did not find a significant effect of the treatments on weight gain (combined between-group difference in weight change from baseline for CSII versus MDI, -0.49 kg; 95% CI, -1.25 to 0.26 kg; P=0.20; Figure 20). We did not find statistical evidence of heterogeneity, and the availability of only two studies precluded the use of Egger's test to evaluate for publication bias.

Figure 20. Between-group difference between CSII and MDI in how weight changed from baseline among adults with type 2 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; kg = kilograms; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.07 with 1 degree of freedom (p = 0.79)

Table 15. Weight gain in CSII versus MDI 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[36]	61	66	24	0.7	1.7	1.0	NS
Herman, 2005[69]	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, Including General, Diabetes-Specific, and Treatment-Related

Two studies examined the comparative effectiveness of CSII versus MDI on general, diabetesspecific, and diabetes treatment-related QOL in adults with type 2 diabetes. One study examined general QOL using the SF-36v2 and diabetes-specific QOL using the Diabetes QOL Clinical Trials Questionnaire in 98 adults (48 in the CSII group and 50 in the MDI group) and found no difference in either QOL measure between the two groups.[69] Another study used the Phase V Outcomes System Diabetes Treatment Satisfaction Questionnaire.[36] 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).[36] At the end of 24 weeks, there was an improvement diabetes treatment satisfaction favoring CSII.

Study Quality

All studies were of poor or fair quality (see Appendix E, Table 5).[36 37 69 70] 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,[36] and only one study reported appropriate

allocation concealment.[69] One study reported the use of an open-label design,[36] and none of the studies reported if outcome assessors were masked to the intervention assignment.[36 37 69 70] Two studies did not use appropriate methods for handling missing data,[36 37] and two studies reported commercial support.[36 69] 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 mild hypoglycemia but was low for severe hypoglycemia, hyperglycemia, and weight outcomes (Table 16). The evidence was insufficient for mortality, nocturnal hypoglycemia, and QOL. All included studies were RCTs, and the risk of bias was medium to high for all outcomes. We found a moderate benefit of CSII over MDI for diabetes treatment-specific QOL. Otherwise, we were unable to determine the magnitude of or found no relative effect of 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 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	
Mortality	1 (107)	Medium	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Microvascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Macrovascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
HbA_{1c}	4 (338)	Medium	Consistent	Direct	Precise	None	Magnitude of effect: No effect Strength of evidence: Moderate
Hyperglycemia	2 (205)	Medium	Inconsistent	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low
Mild hypoglycemia	3 (279)	Medium	Consistent	Direct	Precise	Uncertain	Magnitude of effect: No effect Strength of evidence: Moderate
Nocturnal hypoglycemia	1 (127)	Medium	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Severe hypoglycemia	3 (279)	Medium	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Weight	2 (239)	Medium	Consistent	Direct	Precise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Ratio of basal to bolus insulin	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Frequency of adjusting insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient

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 (continued)

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	
Adherence to insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Frequency of professional or allied health visits	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
General QOL	1 (98)	High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Insufficient
Diabetes-specific QOL	1 (98)	High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: No effect Strength of evidence: Insufficient
Diabetes treatment-related QOL	1 (127)	High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: Moderate Strength of evidence: Insufficient

HbA_{1c} = hemoglobin A_{1c}; NA = not applicable; QOL = quality of life

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, does not permit a conclusion, or consists of only one study with high risk of bias.

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 percent 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

Six observational studies evaluated CSII versus MDI therapy in pregnant women with type 1 diabetes. Two were prospective studies,[72 73] and four were retrospective cohort studies.[74-77]

- The strength of evidence was low comparing CSII with MDI for HbA_{1c}. Six 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. The mean between-group difference in third trimester HbA_{1c} values were 0.2 (95% CI, -0.3 to 0.7),[75] -0.4 (95% CI, -0.8 to 0.04),[74] 0.6 (95% CI, -0.7 to 1.9),[72] -0,3 (95% CI, -0.6 to -0.03),[76] 0.2 (95% CI, -0.2 to 0.6),[73] and 0.4 (95% CI, -0.9 to 1.7).[77]
- 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.
- Meta-analysis of four retrospective studies for rate of cesarean section showed a pooled RR of 1.01 (95% CI, 0.86 to 1.20) which was not significant.[74-77]
- Meta-analysis of three retrospective studies for rate of severe hypoglycemia showed a pooled RR of 0.78 which was not significant (95% CI, 0.23 to 2.65).[75-77]
- There was no difference in weight gain between the CSII and MDI intervention groups in the three studies that examined this outcome. The mean between-group difference in weight gain was 1.9 kg (95% CI, -0.9 to 4.7 kg) in one study[75] and 0.1 kg (95% CI, -2.4 to 2.6 kg) in another study.[73] The third study reported a median weight gain of 13.5 kg in the CSII group and 13.9 kg in the MDI group.[77]
- Gestational age at delivery ranged from 36.6 weeks to 37.5 weeks for MDI and from 36.3 weeks to 36.6 weeks for CSII, and there was no significant difference between the MDI and CSII groups.[72 74-76]
- Meta-analysis of four retrospective cohort studies for frequency of neonatal hypoglycemia showed a pooled RR of 1.10 (95% CI, 0.86 to 1.20).[74-77]

- Meta-analysis of three retrospective cohort studies showed a pooled mean between-group difference in birth weight of 107.2g which was not significant (95% CI, -86.6 to 295.9 g).[74-76]
- Meta-analysis for only two retrospective cohort studies for major congenital anomalies showed a pooled RR of 2.12 favoring MDI that was not significant (95% CI, 0.38 to 11.77).[76 77]
- 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,[72 75] and rates of minor congenital anomalies and pregnancy termination rates were 2.3 percent (2/86 patients) in the MDI group and 13 percent (4/30 patients) in the CSII group (P=0.05).[74]
- Meta-analysis on two retrospective cohort studies for admission to the neonatal intensive care unit showed a pooled RR of 0.84 that was not significant (95% CI, 0.43 to 1.68).[75 76]
- Meta-analysis of four retrospective cohort studies for preterm delivery showed a pooled relative risk of 0.98 that was not significant (95% CI, 0.67 to 1.43).[74-77]
- Four studies reported on stillbirth rates. Three reported that there were no stillbirths in either group,[72 75 77] and one study reported having one stillbirth in MDI group.[74]
- Three studies reported on neonatal mortality rate. Each group had one neonatal death in one study,[74] no neonatal deaths in either group in another,[72] and a 0 percent neonatal mortality rate in the MDI group and 2.7 percent rate in the CSII group in a third study.[77]
- In one study, the perinatal mortality rate was 3 percent in the CSII group and 4 percent in the MDI group.[73] Another study reported a 0 percent perinatal mortality rate in MDI group and a 2.7 percent rate in CSII group.[77]
- We did not find any studies in pregnant women with type 1 diabetes mellitus that evaluated maternal mortality, microvascular or macrovascular disease, quality of life, or any of the process measures, or birth trauma. The strength of evidence is insufficient for these outcomes.

Study Design

All six studies evaluating CSII versus MDI therapy in pregnant women with pre-existing type 1 diabetes were observational (see Appendix E, Table 1).[72-77] Four were retrospective followup studies.[74-77] One study enrolled patients from an outpatient clinic,[75] and another study enrolled patients from a university clinic.[74] No studies were conducted in the U.S. Studies were conducted in Italy,[75 76] Poland,[74] U.K.,[72] France,[73] and Spain.[77] Women were given the choice to select either MDI or CSII in one study.[72] In all six studies, women were followed throughout the pregnancy either prospectively or retrospectively. 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 E, Table 2).[72-77] Two studies reported having 100 percent Caucasian women.[74 75] 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 having one of 17 pregnant women with pre-existing type 2 diabetes in CSII arm and one of 23 with type 2 diabetes in MDI arm.[72] Two studies reported that CSII was started 6 months before participants became pregnant.[75 76] Two studies reported enrolling some of the study participants on CSII before pregnancy.[73 74] 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 percent[72-77] and the mean BMI, reported in five studies, ranged from 21.8 to 23.7 kg/m^2. There is no statistically significant difference between groups on baseline weight.[73-76] The duration of diabetes was reported in four studies and ranged from 7.7 to 16.5 years, with some in the CSII arm having a significantly longer duration of diabetes.[73-76] None of the studies reported whether participants withdrew.

Interventions

The CSII arm varied across studies. Four studies reported that insulin lispro was used primarily for CSII arm,[72 74 76 77] while the type of insulin was not specified in one study.[73] One study reported that insulin lispro was used in 90 percent of the CSII group and in 30 percent of the MDI group, human insulin was used in the rest of the subjects in the MDI arm and everyone in the MDI group used neutral protamine Hagedorn (NPH) insulin.[74] In the MDI groups, NPH insulin was used in three studies[74 75 77] and long-acting insulin was used in two other studies.[72 76] Three studies reported using four or more insulin injections daily in the MDI arms.[72 73 75] One study reported having a total of four arms, two in each group (MDI and CSII). That study included a regular insulin treated arm and lispro treated arm in each group. We have included only subjects treated with lispro in each arm for further analysis to be consistent with other included studies.[77] Four studies reported providing training prior to initiating insulin pump therapy in the CSII treated group.[72 73 75 77] The mean duration of therapy was reported in three studies and it ranged from 36 to 40 weeks.[72 74 75]

Reported glycemic targets varied across studies. One study specified a HbA_{1c} target of 6.5 percent,[72] one study specified a pre-prandial blood glucose target of 90 mg/dL and a post-prandial blood glucose target of 130 mg/dL,[75] and another study specified a pre-prandial blood glucose target of 59.4 to 90 mg/dL.[74] Only one study reported having guidelines regarding management of blood sugar between visits.[72] One study reported calculating insulin requirement based on blood glucose levels before and after meals and at bed time.[77] Four studies reported starting CSII prenatally in all participants[75 76] or a portion of their participants (66 percent[73] and 46 percent[74]).

Maternal Outcomes

Details of the outcomes are reported in Appendix E, Table 4. The included studies reported on the following maternal outcomes: HbA_{1c}, cesarean sections, hypoglycemia, and weight gain. We did not find any studies of pregnant women with type 1 diabetes mellitus that evaluated maternal mortality, microvascular or macrovascular disease, quality of life, or any of the process measures.

HbA_{1c}

All six studies reported an improvement in HbA_{1c} in both the CSII and MDI arms during pregnancy from the first to third trimesters. However, the studies reported no statistically significant difference between groups in HbA_{1c} in any of the trimesters (Table 17).[72-77] We did not perform meta-analysis because only two studies reported baseline HbA_{1c}. One was a retrospective study and the other was a prospective study.

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[75]	MDI, 22	7.4	-	6.1	NS
	CSII, 20	6.9	-	6.3	NS
Cypryk, 2008[74]	MDI, 86	7.8	6.7	6.8	NS
	CSII, 30	7.4	6.5	6.4	NS
Kernaghan, 2008[72]	MDI, 18	7.3	6.6	6.44	NS
	CSII, 24	6.95	6.3	6.63	NS
Hieronimus, 2005[73]	MDI, 23	7.6	6.6	6.4	NS
	CSII, 33	7.5	6.34	6.6	NS
Bruttomesso 2011[76]	MDI, 44	7.2	6.7	6.5	NS
	CSII, 100	6.6	6.1	6.2	NS
Chico, 2011[77]	MDI, 16	6.1	5.8	5.9	NS
	CSII, 59	6.3	6.0	6.3	NS

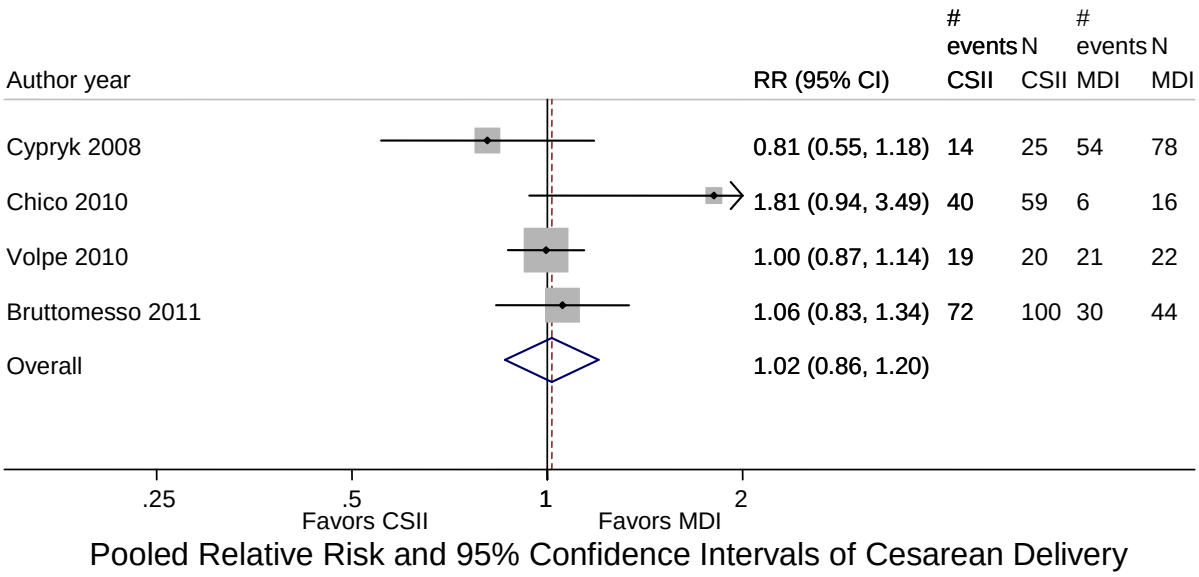
CSII = continuous subcutaneous injections; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; NS = not significant

Rate of Cesarean Sections

Five studies reported on the rate of cesarean section in the CSII and MDI arms (Table 18). Three studies showed no difference in the rates of cesarean sections between groups.[74-76] and two studies showed a significantly higher rate of cesarean section in CSII compared with the MDI group.[73 77] Another study reported a high rate of cesarean section in women in CSII arm compared with women in MDI arm, but the study did not report further calculations between groups.[77]

We performed meta-analysis for four retrospective cohort studies that reported on the rate of cesarean section and it showed a pooled RR of 1.02 that was not significant (95% CI, 0.86 to 1.20) (see Figure 21).[74-77] There was no evidence of statistical heterogeneity, and no single study significantly influenced results. We did not find any evidence of publication bias. One study was not included in this meta-analysis because it was a prospective cohort study.[73]This study showed a significantly higher rate of cesarean sections in the CSII group compared with the MDI group.

Figure 21. Pooled relative risk of cesarean delivery in CSII versus MDI interventions among pregnant women with pre-existing 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 4.53 with 3 degrees of freedom (p = 0.21)

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

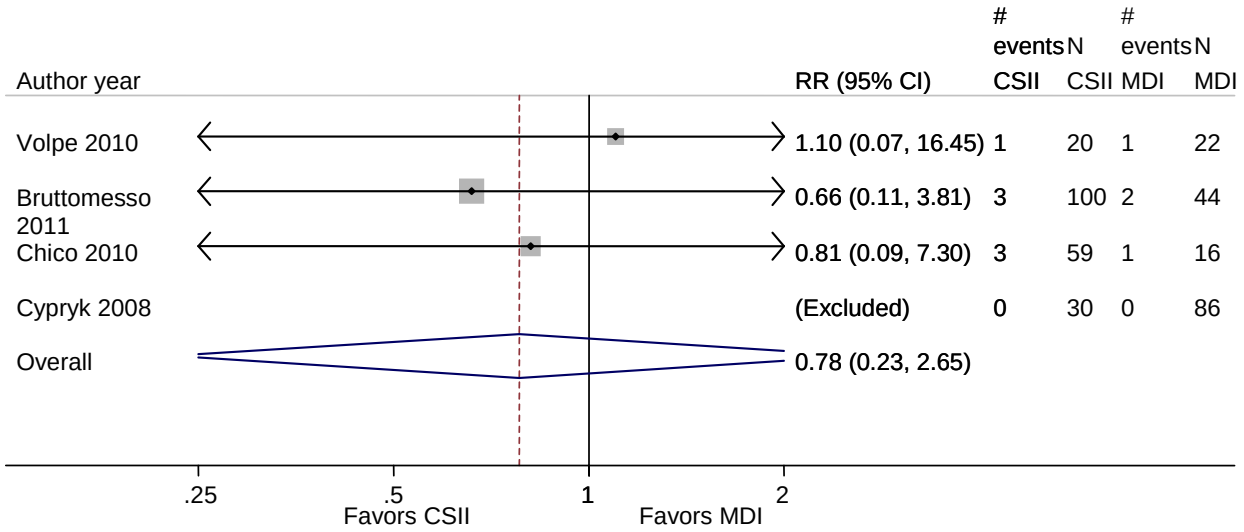
Author, Year	MDI	CSII	Statistical Significance
Volpe, 2010[75]	94%	95%	NS
Cypryk, 2008[74]	46%	69.2%	0.235
Hieronimus, 2005[73]	34.6%	70%	0.016
Bruttomesso 2011[76]	73.2%	77.4%	NS
Chico, 2011[77]	38.5%	67.6%	-

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

Maternal Hypoglycemia

Three studies reported that the severe hypoglycemia rates did not differ between the MDI and CSII arms.[73 75 76] We performed meta-analysis for four retrospective cohort studies for maternal hypoglycemia and it showed a pooled RR of 0.78 that was not significant (95% CI, 0.23 to 2.65) (Figure 22).[74-77] There was no evidence of statistical heterogeneity, and no single study influenced the results. Analysis of the funnel plot suggested that there may be some publication bias. One study was excluded from the meta-analysis because it was a prospective cohort study.[78] This study did not define hypoglycemia, but reported rates of 9 percent in each group.

Figure 22. Pooled relative risk of severe maternal hypoglycemia in CSII versus MDI interventions among pregnant women with pre-existing 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.10 with 2 degrees of freedom (p = 0.95)

Maternal Weight Gain

Three studies measured weight gain in pregnant women with pre-existing diabetes treated with MDI and CSII.[73 75 77] The difference in weight gain between the CSII and MDI treatment arms was not statistically significant in all three studies.[73 75 77] We did not perform meta-analysis because only three studies reported this outcome, two were retrospective cohort studies and one was a prospective study.

Neonatal Outcomes

Details of the outcomes are reported in Appendix E, Table 4. The included studies reported on the following neonatal outcomes: gestational age at delivery, neonatal hypoglycemia, major and minor congenital anomalies, preterm delivery, admission to a neonatal intensive care unit, stillbirth, neonatal and perinatal mortality. None of the studies reported on birth trauma.

Gestational Age at Delivery

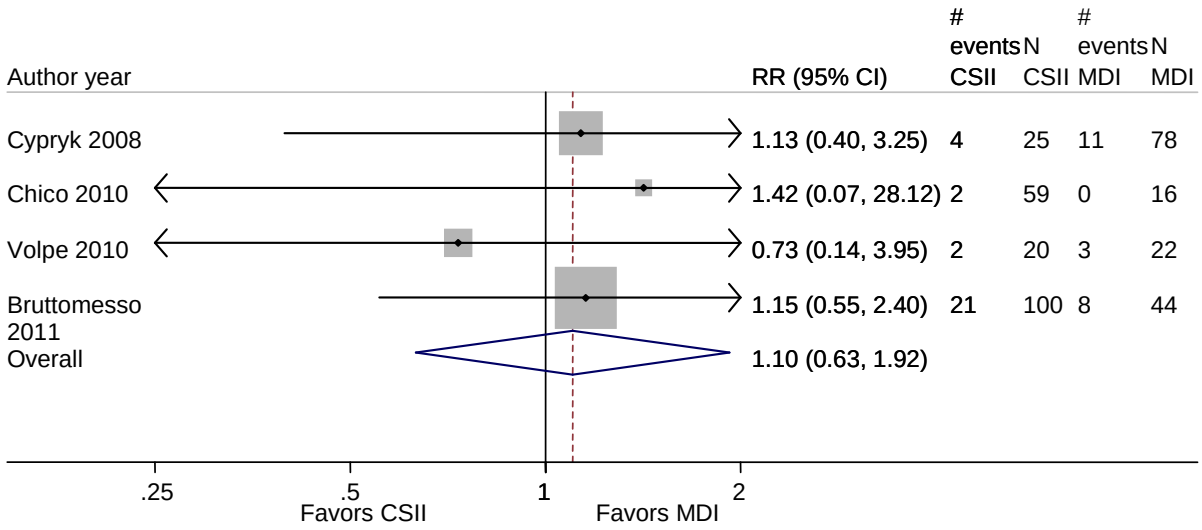
Four studies reported gestational age at delivery, with no difference in gestational age at delivery between the MDI and CSII groups.[72 74-76] Gestational ages at delivery for MDI versus CSII were 36.3 versus 36.3 weeks,[75] 36.3 versus 36.6 weeks (P=0.58),[74] 37.5 versus 36.5 weeks (P=0.28),[72] and 36.6 versus 36.7 weeks.[76]

Frequency of Neonatal Hypoglycemia

Three studies reported rates of neonatal hypoglycemia with no difference between the CSII and MDI groups.[74-76] Neonatal hypoglycemia was defined as a blood glucose less than 40 mg/dL

in three studies,[74 76 79] and was not defined in another study.[75] We performed meta-analysis for four retrospective cohort studies for frequency of hypoglycemia and it showed a pooled RR of 1.10 which was not significant (95% CI, 0.86 to 1.20) (see Figure 23).[74-77] There was no evidence of statistical heterogeneity, and no single study significantly influenced results. We did not detect publication bias.

Figure 23. Pooled relative risk of neonatal hypoglycemia in CSII versus MDI interventions among infants born to women with pre-existing 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.27 with 3 degrees of freedom (p = 0.97)

Birth Weight

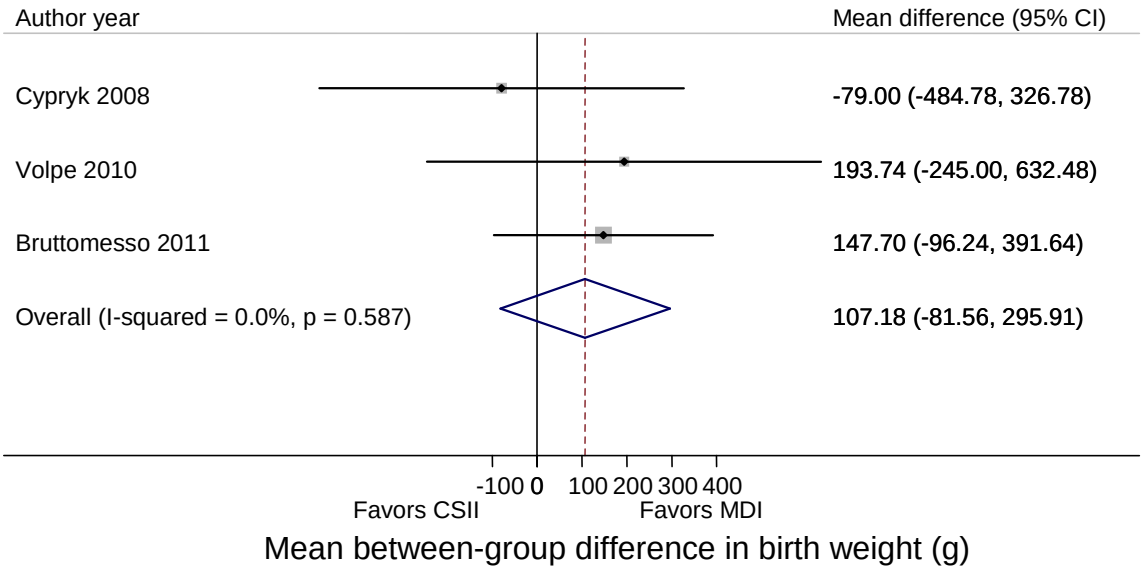
Four studies reported mean birth weight, which ranged from 3101 to 3767 grams, in the two intervention arms.[73-76] One study reported a significantly higher birth weight with CSII compared with MDI,[73] while two other studies found no difference between the two groups (Table 19).[74 76] We performed meta-analysis for three retrospective cohort studies for birth weight and it showed a pooled mean between-group difference of 107.18 g which was not significant (95% CI, -81.6 to 295.9 g) (Figure 24).[74-76] There was no evidence of statistical heterogeneity, and no single study significantly influenced results. Publication bias was not detected. We excluded one study from the meta-analysis because it was a prospective cohort study.[73] This study reported a significantly higher mean birth weight with CSII compared with MDI.

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[75]	3,101	3,295	Not reported
Cypryk, 2008[74]	3,270	3,191	0.86
Hieronimus, 2005[73]	3,384	3,767	0.036
Bruttomesso 2011[76]	3,243	3,390	NS

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

Figure 24. Between-group difference between CSII and MDI in birthweight among infants born to women with pre-existing type 1 diabetes

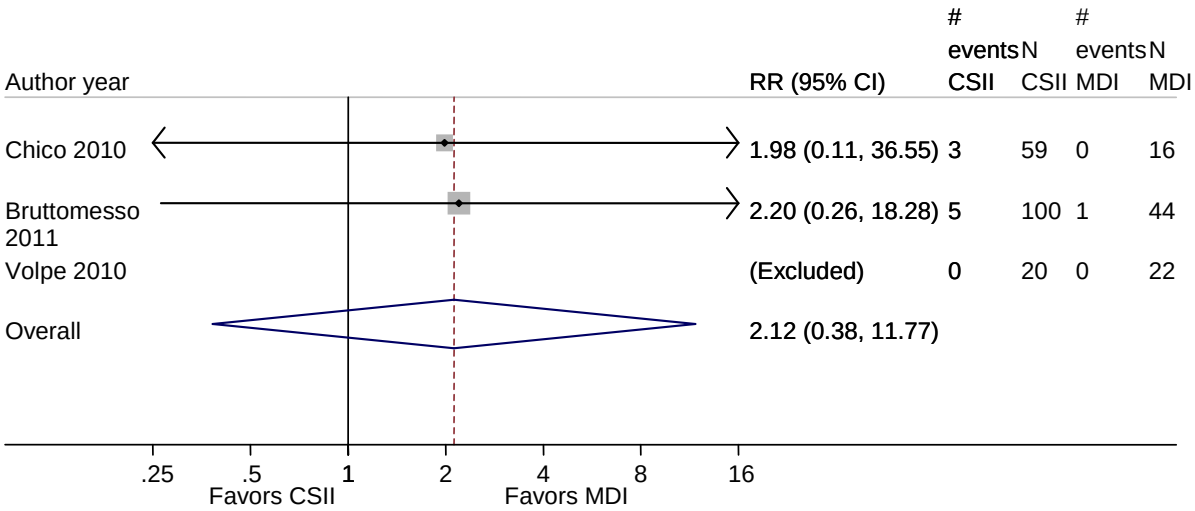


CI = confidence interval; CSII = continuous subcutaneous insulin infusion; g = gram; MDI = multiple daily injections
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.27 with 3 degrees of freedom (p = 0.97)

Major Congenital Anomalies

Four studies reported on major congenital anomalies in pregnant women treated with CSII versus MDI.[73 75-77] We performed meta-analysis for two retrospective cohort studies and it showed a pooled RR for major congenital anomalies of 2.12 favoring MDI that was not significant (95% CI, 0.38 to 11.77) (Figure 25).[76 77] We did not find evidence of statistical heterogeneity, and the availability of only two studies precluded the use of Egger's test to evaluate for publication bias. One study was not included in the meta-analysis because there were no major congenital anomalies in either intervention arm.[75] The other study was not included because it was a prospective cohort study.[73] This study reported no difference in major congenital anomalies between treatment arms (12 percent in the CSII arm vs. 13 percent in the MDI arm).[73]

Figure 25. Pooled relative risk of major congenital anomalies in CSII versus MDI interventions among infants born to women with pre-existing type 1 diabetes



Pooled Relative Risk and 95% Confidence Intervals of Major Anomalies

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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.00 with 1 degree of freedom (p = 0.96)

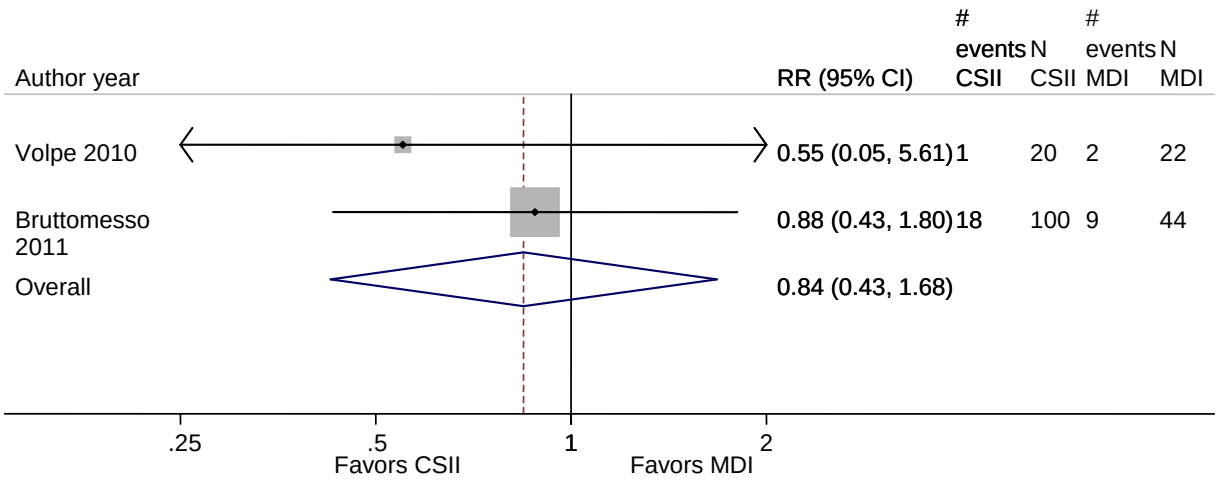
Minor Congenital Anomalies

Three studies reported information about minor congenital anomalies. Two studies reported that there were no minor congenital anomalies in either intervention arm.[72 75] One study reported minor congenital anomalies plus terminated pregnancy rates of 2.3 percent (2 out of 86 patients) in the MDI arm and 13 percent (four out of 30 patients) in the CSII arm (P=0.05).[74]

Neonatal Intensive Care Unit Admissions

Three studies reported on neonatal intensive care unit admissions.[73 75 76] We performed meta-analysis for two retrospective cohort studies for neonatal intensive care unit admissions and it showed a pooled RR of 0.84 that was not significant (95% CI, 0.43 to 1.68) (Figure 26).[75 76] There was not evidence of statistical heterogeneity, and the availability of only two studies precluded the use of Egger's test to evaluate for publication bias. One study was not included the in the meta-analysis because it was a prospective cohort study.[73] This study reported neonatal intensive care unit admission rates of 35 percent in the MDI group and 33 percent in the CSII group.[73]

Figure 26. Pooled relative risk of NICU admission in CSII versus MDI interventions among infants born to women with pre-existing type 1 diabetes



CI = confidence interval; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; NICU = neonatal intensive care unit; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.14 with 1 degree of freedom (p = 0.71)

Preterm Delivery Rate

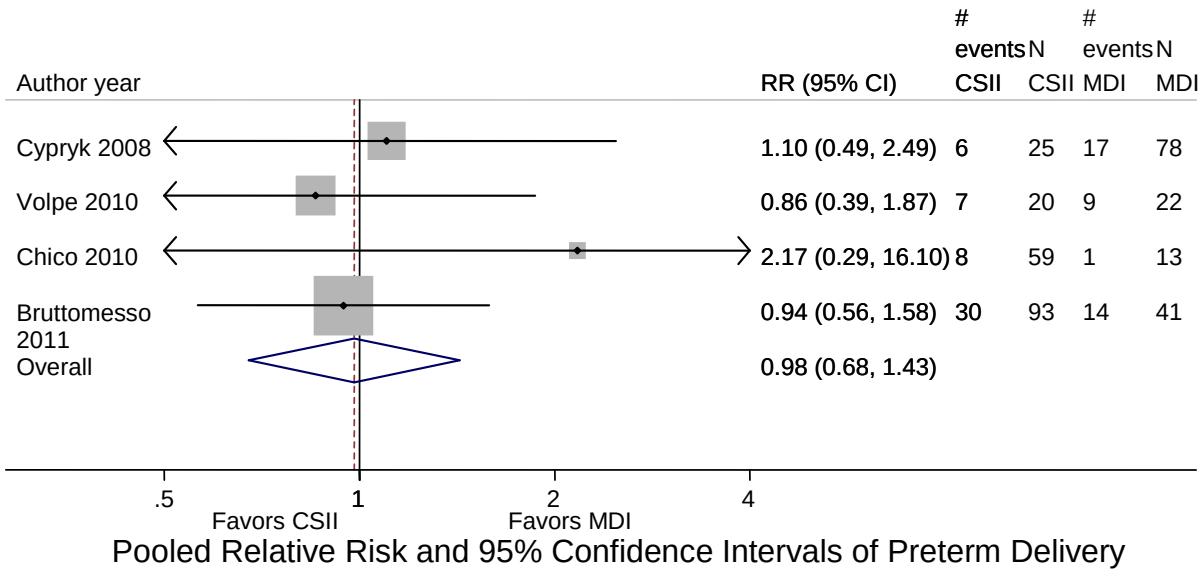
Preterm delivery rate was reported in five studies (Table 20).[73-77] The definition of preterm delivery was not reported uniformly. We performed meta-analysis for four retrospective cohort studies for preterm delivery rate and it showed a pooled RR of 0.98 that was not significant (95% CI, 0.67 to 1.43) (Figure 27).[74-77] There was no evidence of statistical heterogeneity, and no single study substantially influenced the results. We excluded one study from the meta-analysis because it was a prospective cohort study.[73] This study reported no significant difference between the treatment groups.[73]

Table 20. Rates of preterm delivery between CSII and MDI arms in women with pre-existing type 1 diabetes

Author, Year	MDI Group	CSII Group	Statistical Difference Between Groups
Volpe, 2010[75]	40	33	NS
Cypryk, 2008[74]	21.8	24	NS
Hieronimus, 2005[73]	17.4	18	NS
Bruttomesso, 2011[76]	34.2	32.3	NS
Chico, 2011[77]	7.7	13.5	-

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

Figure 27. Pooled relative risk of preterm delivery in CSII versus MDI interventions among pregnant women with pre-existing 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 0.82 with 3 degrees of freedom (p = 0.85)

Stillbirth Rate

Four studies reported on stillbirth rate. One study reported only one stillbirth in the MDI group[74] and three studies reported no stillbirths in either group.[72 75 77]

Neonatal Mortality

Three studies reported on neonatal mortality rate. Each group had one neonatal death in one study,[74] no neonatal deaths in either group in another,[72] and a 0 percent neonatal mortality rate in the MDI group and 2.7 percent rate in the CSII group in a third study.[77]

Perinatal Mortality Rate

Two studies reported on perinatal mortality rate. In one study, perinatal mortality was 3 percent in the CSII group and 4 percent in the MDI group.[73] Another study reported a 0 percent perinatal mortality rate in the MDI group and 2.7 percent in the CSII group.[77]

Study Quality

All studies were of poor to fair quality (see Appendix E, Table 6).[72-77] Most studies had incomplete descriptions of study setting, population, intervention, followup, and outcomes. One study did not report eligibility criteria.[73] 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 other outcomes (Table 21). 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 21. 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}	6 (475)	Medium to High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Rate of cesarean section	5 (435)	Medium to High	Consistent	Direct	Precise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Maternal hypoglycemia	4 (229)	Medium to High	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Maternal weight gain	3 (185)	Medium to High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Gestational age at delivery	4 (336)	Medium to High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Birth weight	4 (360)	Medium to High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Frequency of neonatal hypoglycemia	4 (379)	Medium to high	Consistent	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Minor congenital anomalies	3 (192)	Medium to High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Major congenital anomalies	4 (319)	Medium to High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient

Table 21. 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 (continued)

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	
NICU admissions	3 (244)	Medium to High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Preterm delivery	4 (465)	Medium to High	Unknown	Direct	Imprecise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Stillbirths	4 (277)	Medium to High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Neonatal mortality	3 (233)	Medium to High	Unknown	Direct	Cannot determine	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Insufficient
Perinatal mortality	2 (131)	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, does not permit a conclusion, or consists of only one study with high risk of bias.

Applicability

All studies were observational with limited descriptions of study methodology, study populations, intervention, and outcomes. They were all small studies done in the U.K., Poland, France, Spain, and Italy. Two studies in Italy 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 a 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 vs. 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

- The strength of evidence was high favoring rt-CGM over SMBG for their effects on HbA_{1c}. Mean between-group difference in how HbA_{1c} changed from baseline was -0.30 percent (95% CI, -0.37 to -0.22 percent, P<0.001). In the sensitivity analysis that only included studies with more than 60 percent of compliance rate (seven estimates) there was a greater HbA_{1c} reduction (mean between-group difference from baseline, -0.36 percent; 95% CI, -0.44 to -0.27 percent). A meta-analysis of four studies in children and adolescents age 18 years or younger showed a significant combined mean between-group difference in how HbA_{1c} changed from baseline of -0.26 percent favoring rt-CGM (95% CI, -0.46 to -0.06 percent).
- The strength of evidence was moderate comparing rt-CGM with SMBG for nonsevere hypoglycemia. A meta-analysis of 4 studies (6 estimates) showed no difference between the rt-CGM and SMBG groups in time spent in the hypoglycemic range, defined by glucose level less than 70 mg/dL. The mean between-group difference was -2.11 minutes/day (95% CI, -5.66 to 1.44 minutes/day).
- The strength of evidence was low 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). Two of these trials reported severe hypoglycemia data specifically in pediatric populations. In one study, severe hypoglycemia was less common in pediatric patients using rt-CGM than pediatric patients using SMBG alone (SMBG 4/78 vs. rt-CGM 0/76, P=0.046).[80] 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).[27]
- The strength of the evidence comparing rt-CGM with SMBG for hyperglycemia was moderate. A meta-analysis of 4 studies (6 estimates) indicated a significant reduction in time spent in hyperglycemic range, defined by glucose level greater than 180 mg/dL,

with the mean between-group difference of -68.56 minutes/day favoring rt-CGM (95% CI, -101.17 to -35.96).

- 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 (mean between-group difference in final basal rate, 4.3 percent; 95% CI, 0.8 to 7.8 percent).[80] In contrast, a second study reported a higher percentage of insulin delivered as bolus in the rt-CGM group compared with the SMBG group (mean between-group difference in final percentage of insulin delivered as bolus, -4.0 percent; 95% CI, -9.3 to 1.3 percent).[81]
- The strength of evidence was low comparing rt-CGM with SMBG for general QOL. One study found no difference in parental satisfaction between the two intervention arms (mean between-group difference in change from baseline in World Health Organization Well Being Index-5 mother's well-being score, -2.7; 95% CI, -14.2 to 8.8) at 12 months.[80] The other study assessed general QOL using the Short Form-12 and found an improvement on the Physical Component Score favoring rt-CGM (mean between-group difference in chage from baseline, 1.4; 95% CI, -1.5 to 4.3) but no difference between the intervention groups on the Mental Component Score (mean between-group difference in change from baseline, -1.6; 95% CI, -5.9 to 2.7) at 26 weeks.[82]
- The strength of evidence was low comparing rt-CGM with SMBG for diabetes-specific QOL. There was no difference in diabetes-specific QOL between the rt-CGM and SMBG intervention arms in either study (mean between-group difference in the change from baseline in Problem Areas in Diabetes score, -0.9; 95% CI, -7.9 to 6.1 at 26 weeks[82] and mean difference between-group difference in the change from baseline Diabetes Quality of Life score, -3.0; 95% CI, -6.6 to 0.6).[83]
- The strength of the evidence comparing rt-CGM with SMBG for diabetes treatment-related QOL was insufficient. There was a lower fear of hypoglycemia favoring rt-CGM (mean between-group difference in change from baseline score, -2.3; 95% CI, -8.2 to 3.6).[82]
- There was insufficient strength of evidence evaluating the effects of rt-CGM vs. SMBG in terms of mortality, microvascular or macrovascular disease, weight, or any other process measure, as we found no studies reporting on these outcomes.

Study Design

Nine studies evaluated rt-CGM versus SMBG in children and adults with type 1 diabetes (see Appendix E, Table 1).[27 80 81 83-88] They were conducted in diverse countries, including three in the U.S.,[27 84 86] four in multiple countries,[80 83 87 88] one in France,[81] and one in Australia.[85] Studies varied in their sources of support—seven received industry support,[80 81 84-88] and three received other sources of support.[27 83 85] None received government funding.

Of the nine studies, eight were parallel arm RCTs[27 80 81 84-88] and one was a randomized cross-over trial.[83] Four studies included a run-in period,[27 84 86 88] and five did not.[80 81 83 85 87] Enrollment in five studies started and ended after 2006,[27 80 81 84 88] but other studies did not report the dates of enrollment period.[83 85-87] The median followup time for all studies was 24 weeks, with a range of 12 to 52 weeks. Six studies reported the number of patients screened.[80 81 85-88] These studies enrolled over half of the patients that they screened with a median of 132 patients (range 13 to 322). The number of patients screened was not reported for three studies.[27 83 84] Patients were

recruited from referral clinics in two studies.[81 85] 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 percent,[84] greater than 7.5 percent,[86 88] greater than 8.1 percent,[87] greater than 8.5 percent,[85] or less than 8 percent.[81] One study enrolled patients with HbA_{1c} between 7 and 10 percent.[27] Patients were excluded from certain studies if they had ever used an insulin pump for less than 3 months[85] or less than 1 year,[83] or had ever used rt-CGM in the past 6 months,[27 86] or 4 weeks.[88]

Population Characteristics

The mean age of participants in the RCTs was 24.0 years (range, 8.5 to 41.2 years) and 25.0 years (range, 9.1 to 44.6 years) in the rt-CGM and SMBG groups, respectively (see Appendix E, Table 2). The age of the participants was not reported for four studies.[81 83 85 87] Males represented 47 percent and 46 percent of the study populations, respectively, for the rt-CGM and SMBG groups. Two studies did not report gender distribution.[83 87] Six studies did not report the racial composition of their study populations. In other studies, more than 90 percent of the participants were Caucasians.

The mean baseline HbA_{1c} in the RCTs was 8.3 percent in both the rt-CGM and SMBG groups. In the three studies that reported baseline BMI, the means in the rt-CGM groups were 23.5 kg/m^2,[81] 26.9 kg/m^2,[57] and 22.4 kg/m2,[88] and in the SMBG groups the means were 22.5 kg/m^2,[81] 26.3 kg/m^2,[57] and 22 kg/m^2.[88]

Interventions

In the rt-CGM arm, four studies used Minimed Paradigm,[80 81 85 86] two used Minimed Guardian rt-CGM,[83 87] one study used Abbott FreeStyle Navigator,[88] and two studies used three models[27 84] including the Abbott Freestyle Navigator, Dexcom STS, and Minimed Paradigm (see Appendix E, Table 3). In five studies, participants were asked to wear monitors continuously; three studies required rt-CGM to be used more than 70 percent of time;[81 85 88] and one study did not specify the time requirement.[86] Eight studies reported sensor compliance.[27 80 81 83-86 88] The range of compliance was wide and depended on the subpopulation studied. Four studies reported on sensor compliance by age category.[27 81 84 88] In each of these studies, compliance was highest in individuals greater than 25 years of age (range, 74.9 to 83 percent) and lowest in those 15 to 24 years of age (range, 30 to 53 percent). Frequency of adjusting insulin therapy and frequency of professional or allied health visits were not reported in the available studies.

Five studies used CSII with or without rt-CGM,[80 81 83 85 86] four studies used either MDI or CSII with or without rt-CGM.[27 84 87 88] Four studies required participants to perform glucose monitoring four or more times daily;[27 80 84 85] one required monitoring at least three times per day;[81] and four studies did not report the frequency of monitoring.[83 86-88] Four studies reported glycemic targets: HbA_{1c} less than 7.5 percent;[86] 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 target 82 to 164 mg/dL;[80] 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;[27] preprandial target 70 to 130 mg/dL with peak postprandial values below 180 mg/dL.[88] Two studies provided guideline for between-visit titration.[27 81]

Outcomes

Details of the outcomes are reported in Appendix E, Table 4. The included studies evaluated the effects of rt-CGM vs. SMBG in terms of HbA_{1c}, hyperglycemia, nonsevere and severe hypoglycemia, ratio of basal to bolus insulin, and quality of life. None of the studies evaluated mortality, microvascular or macrovascular disease, weight, or any other process measure.

HbA_{1c}

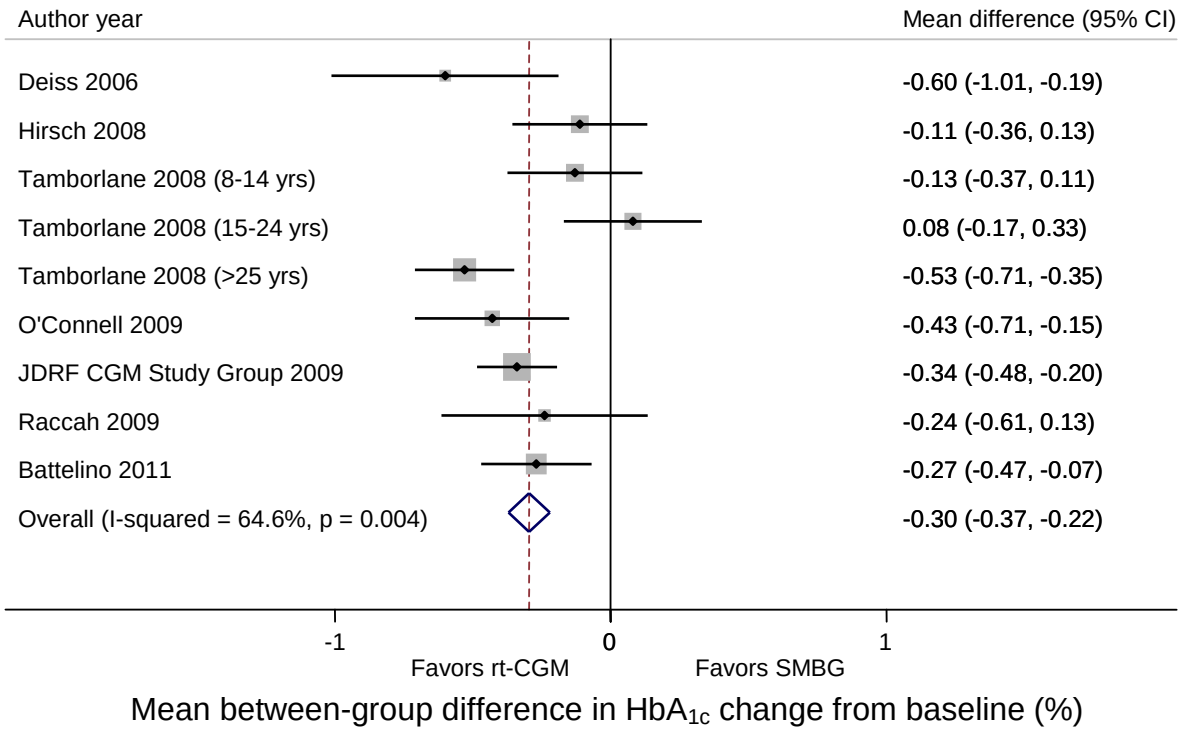
Nine trials examined the comparative effectiveness of rt-CGM versus SMBG on HbA_{1c}. Five studies showed significant differences in end of study HbA_{1c} between the rt-CGM and SMBG groups favoring rt-CGM,[27 84 85 87 88] except for the subgroup 24 years of age or younger in one study.[27] The remaining studies showed no significant difference in the change from baseline HbA_{1c} between the two groups,[27 80 81 83 86] including the subgroup 24 years of age or younger in the study that stratified by age.[27]

Meta-analysis of seven trials (nine 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, -0.30 percent; 95% CI, -0.37 to -0.22 percent; see Figure 28). The analysis suggested statistical heterogeneity (I^2, 64.6 percent, P=0.004), but no single study influenced results substantially. Egger's test (P=0.65) and funnel plot did not suggest publication bias.

Four studies used either CSII or MDI in the study. Two studies reported HbA_{1c} changes were similar in MDI and CSII users,[27 84] while the other two trials did not report results separately.[87 88]

In a post-hoc analysis, we found that the heterogeneity was explained in part by percent of sensor compliance. In the meta-regression, sensor compliance was significantly associated with the degree of HbA_{1c} reduction (see Figure 29; r=-0.8258; P=0.0221). In the sensitivity analysis that only included studies with more than a 60 percent rate of compliance with the sensor use (seven estimates), rt-CGM had an even greater effect on reducing HbA_{1c} as compared with SMBG (combined mean between-group difference from baseline, -0.36 percent; 95% CI, -0.44 to -0.27 percent; Figure 30).

Figure 28. Between-group difference between rt-CGM and SMBG in how HbA_{1c} changed from baseline among adults with type 1 diabetes

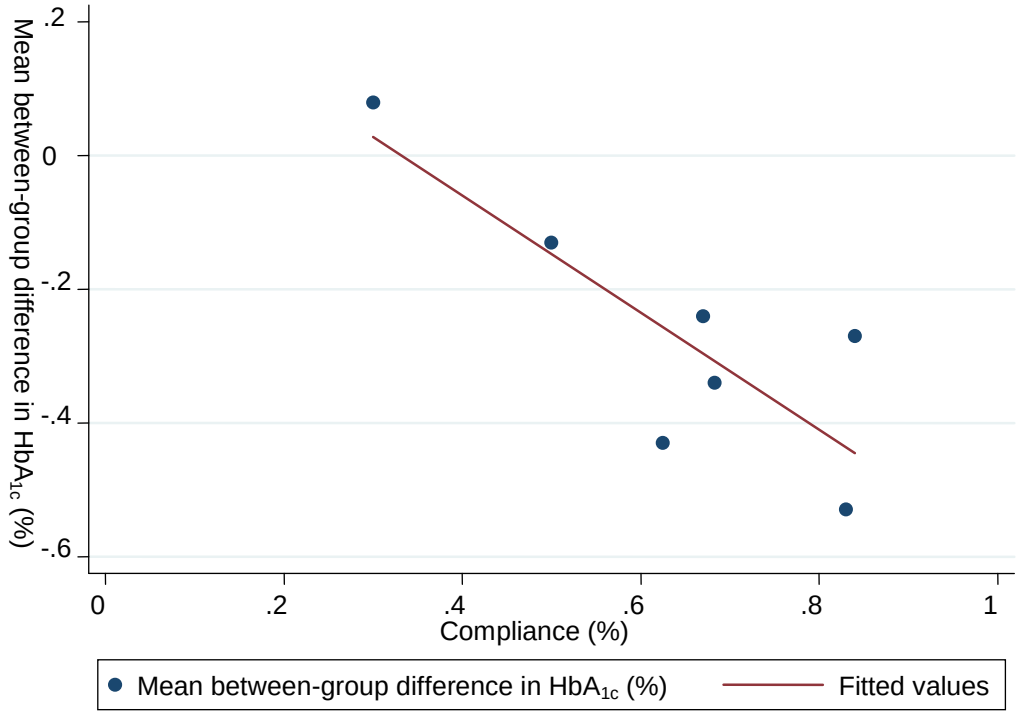


CI = confidence interval; HbA_{1c} = hemoglobin A_{1c}; rt-CGM = real-time continuous glucose monitor; SMBG = self-monitoring of blood glucose

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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

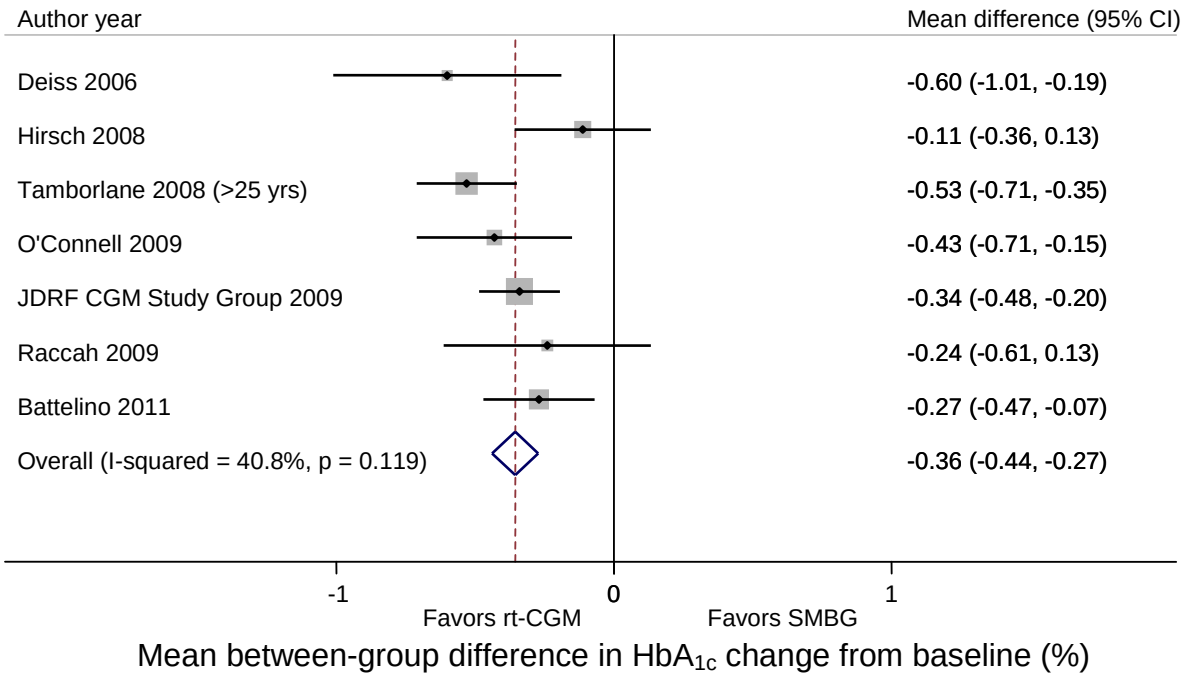
Test for heterogeneity: Q = 22.59 with 8 degrees of freedom (p = 0.004)

Figure 29. Compliance with sensor and mean between-group difference between rt-CGM and SMBG in how HbA_{1c} (%) changed from baseline



HbA_{1c} = hemoglobin A_{1c}; rt-CGM = real-time continuous glucose monitoring; SMBG = self monitoring of blood glucose

Figure 30. Between-group difference between rt-CGM and SMBG in how HbA_{1c} changed from baseline among adults with type 1 diabetes in studies where compliance was greater than 60%



CI = confidence interval; HbA_{1c} = hemoglobin A_{1c}; rt-CGM = real-time continuous glucose monitor; SMBG = self-monitoring of blood glucose

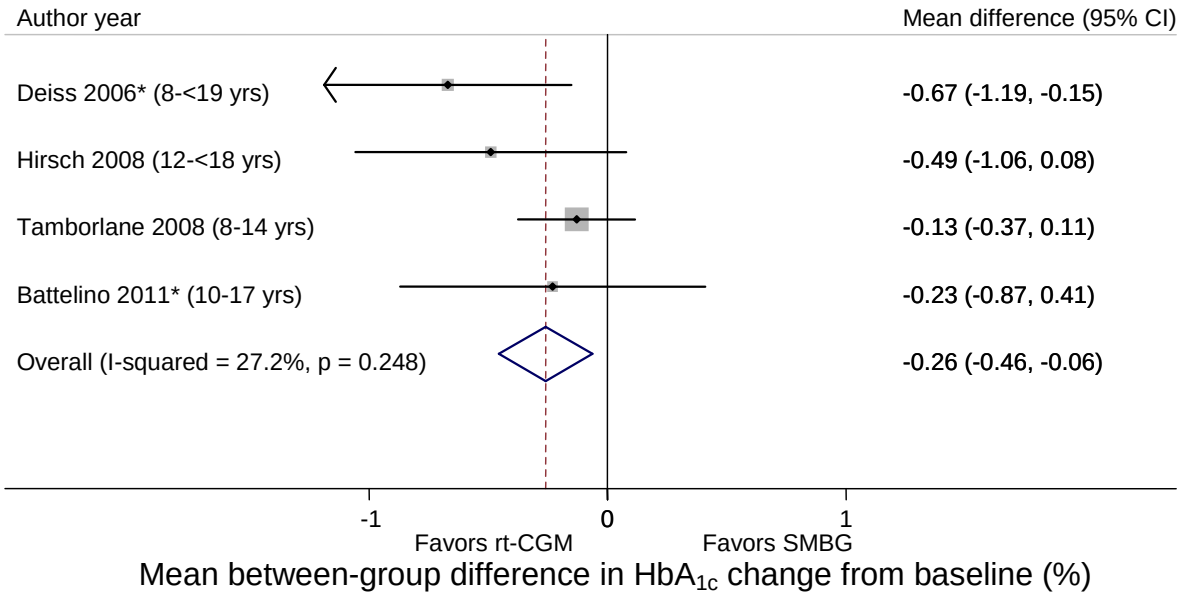
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95%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

Test for heterogeneity: Q = 10.14 with 6 degrees of freedom (p = 0.12)

Studies in Younger Age Groups

Four studies reported data separately for younger age groups. One study reported a significant effect of rt-CGM as compared with SMBG for individuals 8 to 18 years of age (personal communication). The other three trials showed no significant reduction in HbA_{1c} favoring rt-CGM (personal communication).[86 88] Meta-analysis of four studies in age 18 or younger showed a significant mean between-group difference in how HbA_{1c} changed from baseline, favoring rt-CGM (combined mean between-group difference from baseline, -0.26 percent, 95% CI, -0.46 to -0.06 percent) (Figure 31). Egger's test (P=0.75) and funnel plot did not suggest publication bias.

Figure 31. Between-group difference between rt-CGM and SMBG in how HbA_{1c} changed from baseline among children and adolescents with type 1 diabetes



CI = confidence interval; HbA_{1c} = hemoglobin A_{1c}; rt-CGM = real-time continuous glucose monitor; SMBG = self-monitoring of blood glucose

*Unpublished results.

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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q = 4.12 with 3 degrees of freedom (p = 0.25)

Nonsevere Hypoglycemia

Seven studies evaluated the incidence of nonsevere hypoglycemia with rt-CGM compared with SMBG (see Table 22).[27 81 83-86 88] The definitions of nonsevere hypoglycemia varied between studies and several studies reported multiple endpoints. The results were mixed. Three studies showed no difference in nonsevere hypoglycemia between the rt-CGM and SMBG interventions.[27 81 85] Three studies showed evidence of a benefit of rt-CGM on the duration of nonsevere hypoglycemia. In a RCT of patients with well-controlled type 1 diabetes,[84] the rt-CGM group spent less time with nonsevere 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,[86] 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 an RCT of patients with HbA_{1c} greater than or equal to7.5 percent, the time per day spent in hypoglycemia was significantly shorter in the rt-CGM group than the control group.[88] In the seventh study,[83] 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 trends that were not significant were observed when the number of patients with hypoglycemia (glucose less than 60 mg/dL) was used as the endpoint. A meta-analysis including 4 studies (6 estimates) showed no difference in time

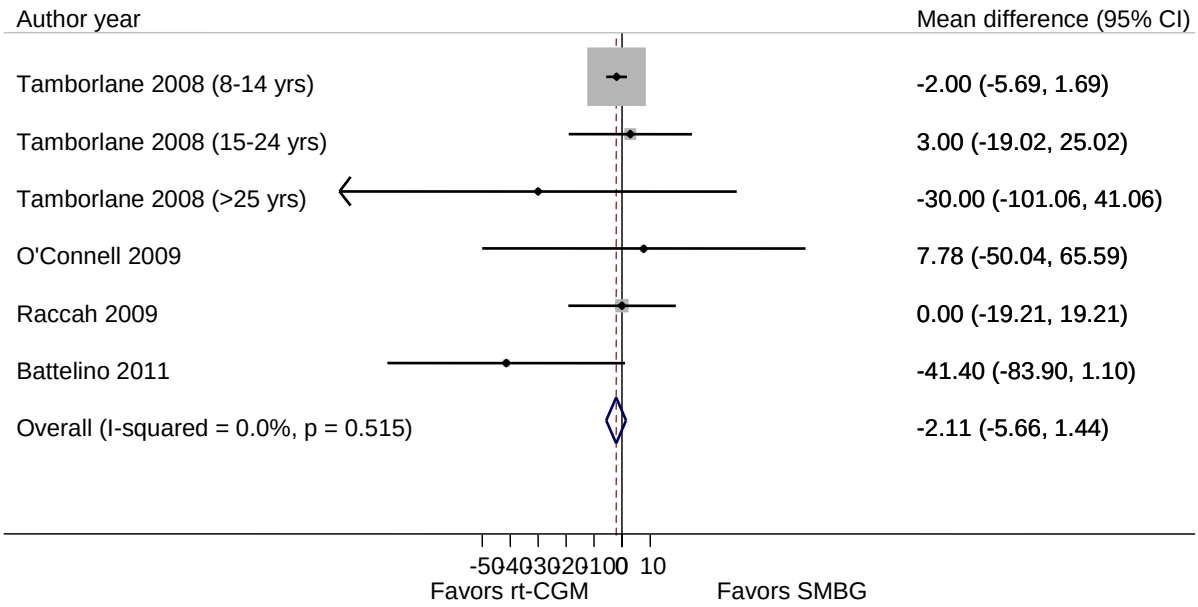
spent in hypoglycemic range, defined by glucose level less than 70 mg/dL.[27 81 85 88] The mean between group difference was -2.11 minutes/day (95% CI, -5.66 to 1.44) (see Figure 32). There was no evidence of statistical heterogeneity or publication bias, using Egger's test and the funnel plot.

Table 22. Nonsevere hypoglycemia in the rt-CGM and SMBG interventions among patients with type 1 diabetes

Author, Year	Definition	Significant Effect Favoring rt-CGM
Radermecker, 2010[83]	Events <60 mg/dL in preceding 14 days	Yes (within-arm)
Raccah, 2009[81]	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[84]	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[85]	Time spent with glucose ≤ 70.2 mg/dL	No
Tamborlane, 2008[27]	Minutes per day spent with glucose level ≤ 50 mg/dL Minutes per day spent with glucose level ≤ 70 mg/dL	No
Hirsch, 2008[86]	Time spent <70 mg/dL	Yes
Battelino, 2011[88]	Hours per day with glucose level < 63 mg/dL Hours per day with glucose level < 55 mg/dL Hours per day with glucose < 70 mg/dL	Yes Borderline, P=0.05 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

Figure 32. Between-group difference between rt-CGM and SMBG in how time spent in hypoglycemic range changed from baseline among patients with type 1 diabetes



CI = confidence interval; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 4.24 with 5 degrees of freedom (p = 0.52)

Severe Hypoglycemia

Eight studies reported the incidence of severe hypoglycemia over the study interval using variable definitions (see Table 23).[27 80 81 84-88] One study reported data stratified by age and we treated these groups as distinct populations.[27] 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 33). Two of the studies were excluded from meta-analysis because of zero events in both arms.[85 88] Another study was excluded from the meta-analysis because its randomized crossover design differed from the other studies.[83] In this study, no severe hypoglycemic events were observed.

Two of these trials reported severe hypoglycemia data specifically in a pediatric population.[80 86] In one study,[80] severe hypoglycemia was less common in those using rt-CGM than those using SMBG alone (four out of 78 patients with SMBG vs. 0 out of 76 patients with rt-CGM; P=0.046). In contrast, the pediatric subgroup (ages 8 to 14 years) of another study[27] showed a similar incidence of severe hypoglycemia in both arms (six out of 58 patients with SMBG vs. four out of 56 patients with rt-CGM; P=0.74).

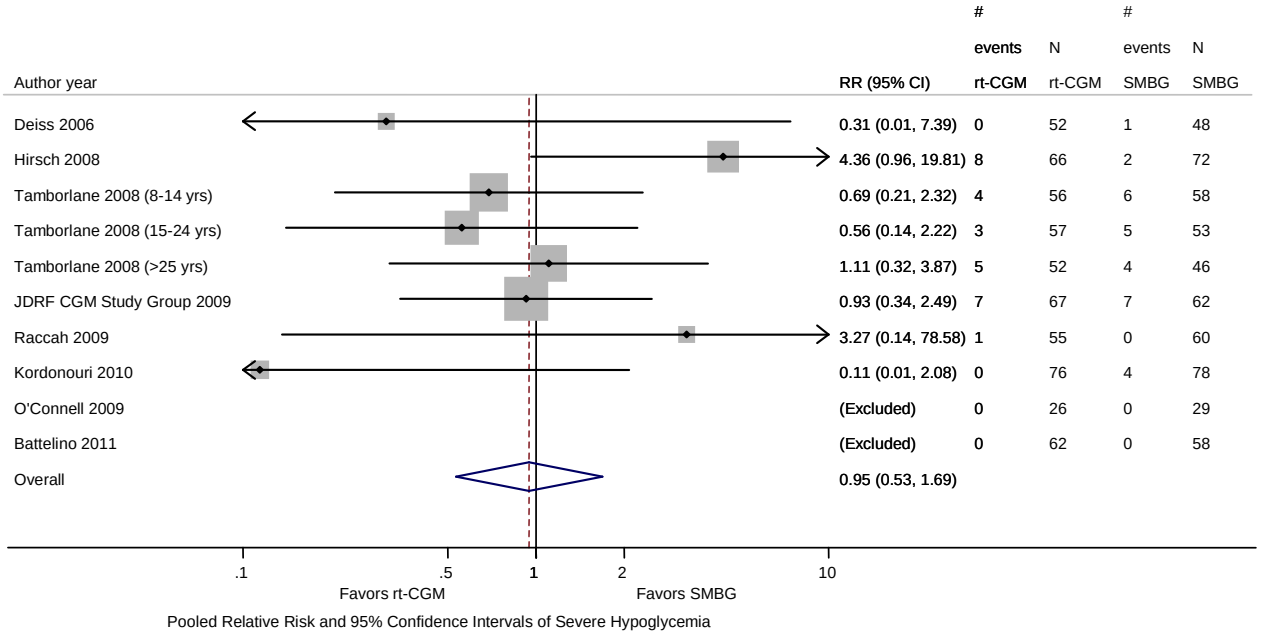
In the six studies included in the meta-analysis, the duration of intervention ranged from 12 to 52 weeks. There was no evidence of statistical heterogeneity or publication bias, using Egger's test and the funnel plot. As a sensitivity analysis, we conducted a fixed-effects meta-analysis using the treatment-arm continuity correction (0 cells were replaced by the reciprical of the other treatment arm).[89] The treatment-arm continuity correction provided a similar result (odds ratio, 0.94; 95% CI, 0.54 to 1.61).

Table 23. Definition of severe hypoglycemia in the studies of rt-CGM and SMBG in type 1 diabetes

Author, Year	Definition of Hypoglycemia
Kordonouri, 2010[80]	Not further specified
Raccah, 2009[81]	Not further specified
Beck, JDRF, 2009[84]	Event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions
O'Connell, 2009[85]	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[27]	Event that required assistance from another person to administer oral carbohydrate, glucagon, or other resuscitative actions
Hirsch, 2008[86]	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, 2006[90]	Not further specified
Battelino, 2011[88]	Not further speficied

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

Figure 33. Pooled relative risk of severe hypoglycemia in rt-CGM versus SMBG 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% 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 percent

Hyperglycemia

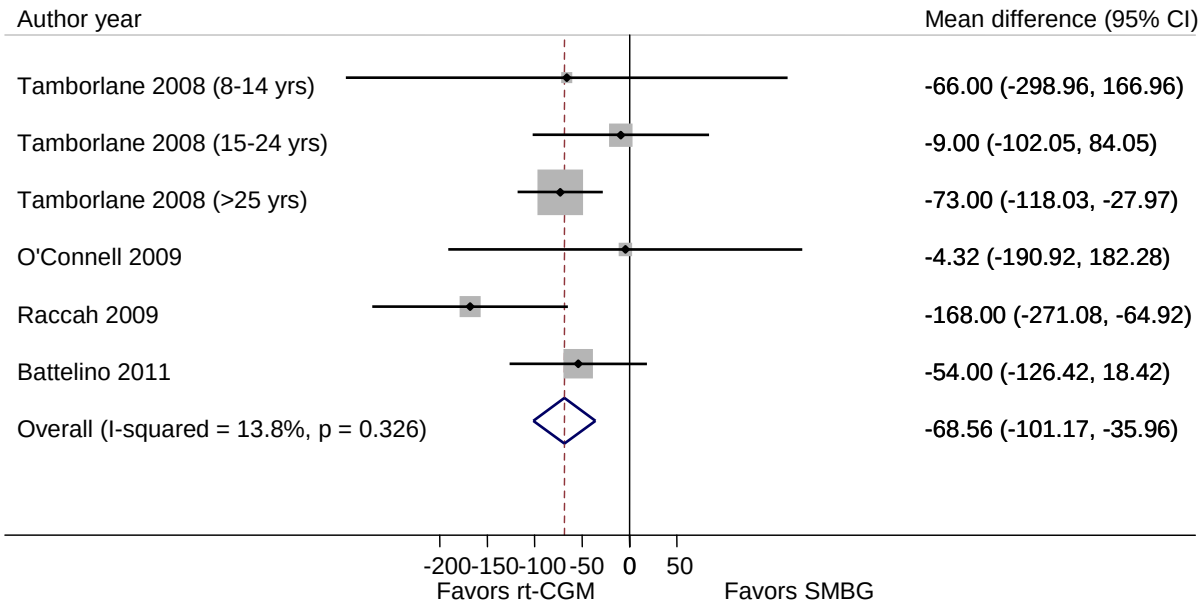
Six studies evaluated the comparative effectiveness of rt-CGM versus SMBG on change in hyperglycemia (Table 24).[27 81 84-86 88] The definitions of hyperglycemia varied between studies and several studies reported multiple different endpoints. Two studies[85 86] showed no difference between the rt-CGM and SMBG arms. Two studies[84 88]showed non-statistically significant trends 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.[27] 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.[81] A meta-analysis of four studies (six estimates) indicated a significant reduction in time spent in hyperglycemic range, defined by glucose level less than 180 mg/dL, with the mean between-group difference of -68.56 minutes/day (95% CI, -101.17 to -35.96) (Figure 34).[27 81 85 88] There was no evidence of statistical heterogeneity or publication bias, using Egger's test and the funnel plot.

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

Author, Year	Definition	Significant Effect Favoring rt-CGM
Raccah, 2009[81]	Change in glucose >190 /mg/dL hours per day Change in hyperglycemia AUC (mg/dL/day)	Yes
JDRF, 2009[84]	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[85]	Time spent with glucose > 180 mg/dL	No
Tamborlane, 2008[27]	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[86]	Hyperglycemia (> 180 mg/dL) AUC	No (improvement in both arms, no between group differences)
Battelino, 2011[88]	Hours per day with glucose level>180 mg/dL Hours per day with glucose level >250 md/dL	No, but favor rt-CGM No, but favor rt-CGM

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

Figure 34. Between-group difference between rt-CGM and SMBG in how time spent in hyperglycemic range changed from baseline among patients with type 1 diabetes



CI = confidence interval; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 5.80 with 5 degrees of freedom (p = 0.33)

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[80] 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 percent; SD, 11.8 percent vs. 29.7 percent; SD, 10.4 percent, 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 percent; SD, 10 percent vs. 49.8 percent; SD, 15.8 percent; P not reported).[81]

Quality of Life, Including General, Diabetes-Specific, and Treatment-Related

Three studies examined the comparative effectiveness of rt-CGM versus SMBG on general, diabetes specific, and diabetes treatment-related QOL (see Table 25).[80 82 83] One study assessed the well-being of the patients' mothers using the World Health Organization-5 and found no difference in parental satisfaction between the two intervention arms.[80] The other study assessed general QOL using the Short Form-12 and found an improvement on the Physical Component Score favoring rt-CGM but no difference between the intervention arms on the Mental Component Score.[82]

Two studies examined diabetes-specific QOL—one using the Problem Area in Diabetes in children and adolescents[82] and one using the Diabetes Quality of Life (DQOL) in adults[83] (see Table 25). There was no difference in DQOL between the two intervention arms in either study.

One study examined diabetes treatment-related QOL using the Hypoglycemia Fear Survey in children and adults and found lower fear of hypoglycemia favoring rt-CGM.[82]

Table 25. 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[80]	76 rt-CGM, 78 SMBG	rt-CGM vs. SMBG	154 children (aged 1-16 years, mean ± SD: 8.7 ± 4.4 years; 47.5 percent girls)	At 12 months, 62.7±18.9 in rt-CGM versus 60.8±19.in SMBG	Neither
SF-12*	Beck, 2010[82]	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[82]	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[83]	13 (crossover study)	rt-CGM vs. 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[82]	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 QOL. Total scores for the World Health Organization-5 range from 0 to 100, with higher scores indicating better well-being. Total scores for the Short Form-12 range from 0 to 100, with higher scores indicating higher levels of health.

†Diabetes-specific QOL. Total scores for the Problem Areas in Diabetes range from 0 to 100, with higher scores indicating more serious problems. Total scores for the Diabetes Quality of Life questionnaire range from 0 to 100, with higher scores indicating better quality of life.

‡Diabetes treatment-related QOL. Total scores for the Hypoglycemia Fear Survey range from 0 to 92, with higher scores indicating higher levels of fear.

Study Quality

Four studies were rated with good quality[80 84-86] and five studies were rated with fair quality (see Appendix E, Table 5).[27 81 83 87 88] 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 hyperglycemia, and mild hypoglycemia, and low for severe hypoglycemia, ratio of basal to bolus insulin and QOL (Table 26). 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 (-0.3 percent, $P<0.001$), 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 QOL.

Table 26. 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	
Mortality	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Microvascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Macrovascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
HbA_{1c}	9 (1215)	Low	Consistent	Direct	Precise	No	Magnitude of effect: Small Strength of evidence: High
Hyperglycemia	6 (886)	Medium	Inconsistent	Direct	Imprecise	No	Magnitude of effect: Moderate Strength of evidence: Moderate
Mild hypoglycemia	7 (899)	Medium	Inconsistent	Direct	Precise	No	Magnitude of effect: No effect Strength of evidence: Moderate
Severe hypoglycemia	8 (1202)	Low	Inconsistent	Direct	Imprecise	No	Magnitude of effect: No effect Strength of evidence: Low
Weight	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Ratio of basal to bolus insulin	2 (482)	High	Inconsistent	Direct	Precise	Uncertain	Magnitude of effect: Unable to determine Strength of evidence: Low
Frequency of adjusting insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Adherence to insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient

Table 26. 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 (continued)

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	
Frequency of professional or allied health visits	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Quality of life	2 (380)	Low	Inconsistent	Indirect	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Diabetes-specific QOL	2 (239)	Moderate	Consistent	Direct	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Low
Diabetes treatment-related QOL	1 (226)	High	Unknown	Direct	Precise	Uncertain	Magnitude of effect: Small Strength of evidence: Insufficient

HbA_{1c} = hemoglobin A_{1c}; NA = not applicable; QOL = quality of life

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, does not permit a conclusion, or consists of only one study with high risk of bias.

Applicability

Most studies in type 1 diabetes had small sample sizes, with the largest clinical trial including 322 participants.[48] 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 U.S. or involved multiple countries), most studies included Caucasian participants, consistent with the demographics of type 1 diabetes. Participants generally had poor glycemic control at study entry (mean HbA_{1c} 8.5 percent), were treated in the intervention groups for an average of 24 weeks, and had diabetes for 11.5 years prior to study entry.

Comparative Effects of rt-CGM and SMBG Among Patients With Type 2 Diabetes or Pregnant Women With Pre-Existing Diabetes

Key Points and Evidence Grades

- There was insufficient strength of evidence evaluating the effects of rt-CGM vs. SMBG among patients with type 2 diabetes or pregnant women with pre-existing diabetes, as we found no studies conducted in these populations.

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

Key Points and Evidence Grades

- The strength of evidence was moderate favoring sensor-augmented pumps over MDI/SMBG for their effects on HbA_{1c} (mean between-group difference in how HbA_{1c} changed was -0.68 percent; 95% CI, -0.81 to -0.54 percent).
- The strength of the evidence comparing sensor-augmented pumps and MDI/SMBG for nonsevere hypoglycemia was moderate. There was no difference in time spent with nonsevere hypoglycemia between the sensor-augmented pump and MDI/SMBG intervention groups.
- The strength of evidence was moderate suggesting no difference in severe hypoglycemia incidence between the sensor-augmented pump and MDI/SMBG intervention groups (RR, 1.2; 95% CI, 0.7 to 2.3;[91] 0 events for sensor-augmented pump vs. three events for MDI/SMBG;[92] 0 events in eight patients in sensor-augmented pump group versus one event in eight patients in the MDI/SMBG group;[93] and RR, 3.5; 95% CI, 0.4 to 304).[94]
- The strength of the evidence comparing sensor-augmented pumps with MDI/SMBG was moderate for hyperglycemia. Two trials suggested 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. In one study[91] there was no significant difference in weight gain between the sensor-augmented pump and MDI/SMBG intervention groups favoring MDI/SMBG (2.4 kg vs. 1.8 kg; $P=0.19$). 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 (mean between-group difference, 1.3 kg; 95% CI, -21.2 to 23.8 kg).[92]

- The strength of the evidence comparing sensor-augmented pumps with MDI/SMBG was low for diabetes treatment-related QOL. 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 (mean between-group difference in final scores, 50.0; 95% CI, 33.6 to 66.4).[92]
- There was insufficient strength of evidence evaluating the effects of sensor-augmented pumps vs. MDI/SMBG in terms of mortality, microvascular or macrovascular disease, or any of the process measures, as we found no studies reporting on these outcomes.

Study Design

Four studies evaluated a sensor-augmented pump versus MDI/SMBG in children and adults with type 1 diabetes (see Appendix E, Table 1).[91-94] Two studies were multicenter trials in North America.[91 93] The third study did not specify the location and number of the study sites.[92] The fourth study was a multi-center trial in Europe.[94] Two studies reported receiving industry support,[91 92] and the other two studies did not specify the sources of support.[93 94] None of the studies reported receiving government funding.

All four studies were parallel-arm RCTs.[91-94] Two studies described a run-in period[91 93] and two did not.[92 94] Of the four studies, two described the dates of the enrollment period.[91 94] The followup time for the studies were 15, 16, 26, and 52 weeks. One study reported the number of patients screened.[91] One study reported the exclusion of pregnant patients specifically.[91]

All four studies enrolled suboptimally controlled patients with HbA_{1c} between 7.4 and 9.5 percent;[91] greater than or equal to 7.5 percent;[93] or HbA_{1c} greater than or equal to 8.2 percent.[94] The other study mentioned excluding patients with "optimal" glycemic control but did not point out the HbA_{1c} criteria specifically.[92]

Certain studies excluded patients if they had ever used an insulin pump within the past 3 years[91] or anytime in the past (i.e., CSII-naïve).[92 93] One trial included current MDI users only, but did not specify exclusion criteria based on having ever used an insulin pump.[94]

Population Characteristics

Three studies included only adults[92 94 95] and one study enrolled both adults and children (see Appendix E, Table 2).[91] Two of these studies reported the mean age of participants (47.2 years[92] and 45.9 years).[93] Two reported mean age stratified by treatment group (32.2 years in the sensor-augmented pump group vs. 31.5 years in the MDI/SMBG group[91] and 39.3 in sensor-augmented pump group vs. 37.3 in the MDI/SMBG group).[94] In the study that included both adults and children,[91] 32 percent of the sample were 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. Two studies described the gender distribution by treatment arm (57 percent males in sensor-augmented pump group vs. 56 percent males in the MDI/SMBG group[91] and 50 percent males in sensor-augmented pump vs. 53.8 percent males in MDI/SMBG group).[94] And two studies described combined treatment arms (46 percent males[92] and 50 percent males).[93] The majority of participants in two studies were white (92 percent[91] and 79 percent).[92] Two studies did not report the racial composition of the population.[93 94]

The mean baseline HbA_{1c} in the RCTs was similar in all four studies (median, 8.6 percent; range, 8.3 to 9.5 percent). One study reported the baseline BMI by treatment arm (sensor-augmented pump 25.3 kg/m^2 vs. MDI/SMBG 25.6 kg/m^2),[91] one study reported the baseline BMI

in the combined sample (mean, 27.0 kg/m^2)[92] and two studies did not report baseline body mass index.[93 94]

Interventions

All four studies used the MiniMed Paradigm REALTime system and provided training in the use of the device (see Appendix E, Table 3). The frequency and intensity of the followup visits, however, differed between studies. In the longest study,[91] 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, researchers introduced the rt-CGM. Clinicians saw patients at 3-month intervals during which they reviewed glucose data and adjusted insulin therapy. Clinicians also saw patients assigned to continue MDI/SMBG at 3-month intervals and made insulin adjustments. In the MDI/SMBG group, patients wore a blinded rt-CGM device for 1-week periods at baseline, 6 months, and 12 months, so 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,[93] 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. Clinicians saw patients randomized to continue MDI/SMBG at baseline and weeks 2, 5, and 15. In both arms, clinicians reviewed glucose data and adjusted insulin. Participants in both arms of the study received the same instruction in intensive diabetes management and carbohydrate counting.

In a 16-week randomized trial,[92] both arms received diabetes education and those randomized to a sensor-augmented pump received additional one-time instructions regarding the use of the device. The trial did not specify additional followup visits in either arm until the end of study visit at week 16. Clinicians did not make insulin adjustments as part of the study protocol.

In the most recent trial,[94] clinicians trained patients to use the device within 2 weeks after randomization and to change both the insulin catheter and glucose sensor every 3 days. At 13 and 26 weeks, patients visited the investigating center and clinicians downloaded data from the sensor. Clinicians made therapy adjustments when necessary based on the downloaded data. They provided no specific instructions to the patients with regard to insulin dosing or other device specific adjustments other than during the training phase and at 13- and 26-week visits. In the second part of the trial (between 13 and 26 weeks) patients in the sensor-augmented insulin pump and MDI groups were to receive the same amount of study staff attention. Only one study reported the frequency of rt-CGM use[91] and 67 percent of patients used the rt-CGM more than 60 percent of the time; 23 percent reported using the rt-CGM more than 80 percent of the time.

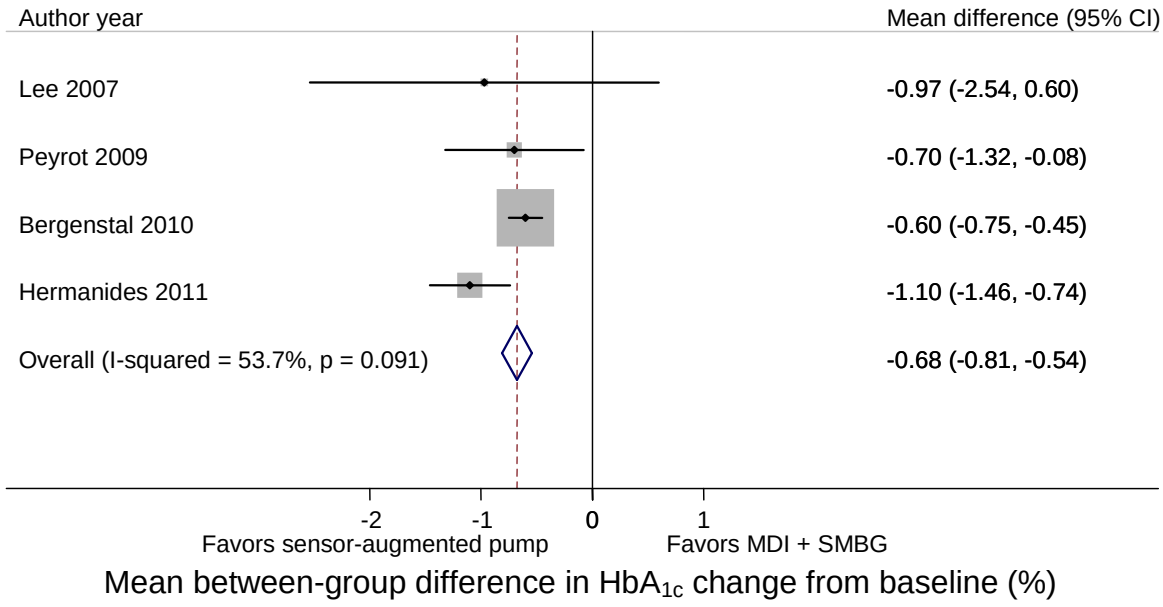
Outcomes

Details of the outcomes are reported in Appendix E, Table 4. The included studies evaluated the effects of sensor-augmented pumps vs. MDI/SMBG in terms of HbA_{1c}, nonsevere and severe hypoglycemia, hyperglycemia, weight, and quality of life. None of the studies reported on mortality, microvascular or macrovascular disease, or any of the process measures.

HbA_{1c}

All four studies assessed the effect on HbA_{1c}.[91-94] Three studies found a significant difference in end of study HbA_{1c} between the sensor-augmented pump and MDI/SMBG groups, favoring sensor-augmented pump.[91 92 94] One study did not show a statistically significant difference in HbA_{1c} between the two groups.[93] A meta-analysis of all four 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 in change from baseline, -0.68 percent; 95% CI, -0.81 to -0.54 percent, P<0.001; see Figure 35). We did not find statistical heterogeneity (P=0.09) and no one study influenced results substantially. Egger's test (P=0.08) and funnel plot did not suggest publication bias.

Figure 35. Between-group difference between sensor-augmented pumps and MDI/SMBG in how HbA_{1c} changed from baseline among patients with type 1 diabetes



CI = confidence interval; HbA_{1c} = hemoglobin A_{1c}; 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% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.
Test for heterogeneity: Q = 6.48 with 3 degrees of freedom (p = 0.09)

Nonsevere Hypoglycemia

Two studies assessed the time spent with nonsevere hypoglycemia.[91 94] The first trial calculated 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. The second trial calculated the percentage of time in hypoglycemia and number of nonsevere hypoglycemic events and showed no significance difference between the arms.

Severe Hypoglycemia

All four studies reported on the incidence of severe hypoglycemia. In the largest study,[91] 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. In the study, hypoglycemia occurred in a similar number of patients in the sensor-augmented pump arm and the MDI/SMBG group (21 out of 247 patients vs. 17 out of 248 patients, P=0.58). In another trial,[92] 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,[93] one unspecified hypoglycemic event occurred in the eight patients randomized to continue MDI/SMBG, and no events occurred in the eight patients randomized to a sensor-augmented pump. In the fourth trial,[94] there was no significant difference in the occurrence of severe hypoglycemia, with four episodes in the sensor-augmented pump group and one episode in the MDI/SMBG group (9 percent vs. 3 percent, P=0.21, i.e., 19 episodes ⁄100 person-years in the sensor-augmented pump group and six episodes ⁄100 person-years in the MDI/SMBG group).

Hyperglycemia

Two studies assessed the time spent with hyperglycemia.[91 94] The first trial calculated the area under the curve in both arms. The studies used two different outcomes, greater than 250 mg/dL and greater than 180 mg/dL. In the entire study population, 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. The second trial found the percentage of time in hyperglycemia was significantly reduced in the sensor-augmented pump group vs. the MDI/SMBG group (-17.3 percent, 95% CI, -25.1 percent to -9.5 percent). However, the number of hypoglycemic events was not different (P=0.50).[94]

Weight

Two studies reported the change in weight. One study,[91] only reported the change in weight in adults, and showed no significant difference in weight gain between the sensor-augmented pump and MDI/SMBG arms favoring MDI/SMBG (2.4 kg vs. 1.8 kg, P=0.19). In a second study,[92] 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, Including General, Diabetes-Specific, and Treatment-Related

One study examined diabetes treatment-related QOL using the User Acceptance Questionnaire and the Blood Glucose Monitoring System Rating Questionnaire in 28 CSII-naïve adults with type 1 diabetes.[92] At 16 weeks, user acceptance and overall satisfaction was greater in the sensor-augmented pump arm compared with MDI/SMBG.[92] One study examined disease treatment-related QOL using the Diabetes Treatment Satisfaction Questionnaire in 83 CSII-naïve adults with type 1 diabetes.[94] At 26 weeks, satisfaction was greater in the sensor-augmented pump arm compared with MDI/SMBG.[94] In addition, the same study examined diabetes-specific QOL using the Hypoglycemia Fear Survey and the Problem Areas in Diabetes instrument. The study found no significant difference between the study arms at 26 weeks.[94] Regarding generic QOL, there was no difference in the physical domains of the Short Form-36; one mental domain, emotional role, showed improvement at 26 weeks in the sensor-augmented pump arm.[94]

One study of children with type 1 diabetes found no significant difference at 52 weeks between the sensor-augmented pump and MDI/SMBG arms in caregiver (parent) generic QOL,

measured by the World Health Organization-5 scale, or in patient generic QOL, measured by KIDSCREEN-27.[96]

Study Quality

Two studies were rated as "good,"[91 94] while the other two studies were rated as "poor" to "fair"[92 93] (see Appendix E, 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} because study quality was poor to good but low for the outcomes of hypoglycemia, weight gain, and hyperglycemia, and insufficient for QOL (Table 27). Risk of bias was medium for HbA_{1c} and severe hypoglycemia outcomes, and high for all other outcomes.

Table 27. 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	
Mortality	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Microvascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Macrovascular outcomes	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
HbA_{1c}	4 (612)	Medium	Consistent	Direct	Precise	No	Magnitude of effect: Large Strength of evidence: Moderate
Hyperglycemia	2 (568)	High	Consistent	Direct	Precise	Uncertain	Magnitude of effect: High Strength of evidence: Moderate
Mild hypoglycemia	2 (568)	Medium	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Moderate
Severe hypoglycemia	4 (612)	Medium	Inconsistent	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Moderate
Weight	2 (513)	High	Consistent	Direct	Cannot determine	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Ratio of basal to bolus insulin	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Frequency of adjusting insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Adherence to insulin therapy	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient
Frequency of professional or allied health visits	0	NA	NA	NA	NA	NA	Strength of evidence: Insufficient

Table 27. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and overall strength of evidence for sensor-augmented pumps (continued)

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	
Diabetes treatment-related QOL	2 (111)	High	Consistent	Direct	Precise	Uncertain	Magnitude of effect: Low Strength of evidence: Low
Diabetes-specific QOL	1 (83)	Medium	Unknown	Direct	Precise	Uncertain	Magnitude of effect: No effect Strength of evidence: Low
Generic QOL	3 (237)	Medium	Consistent	Direct	Precise	Uncertain	Magnitude of effect: Low Strength of evidence: Low

HbA_{1c} = hemoglobin A_{1c}; NA = not applicable; QOL = quality of life

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, does not permit a conclusion, or consists of only one study with high risk of bias.

Applicability

The largest clinical trial had 485 participants[91] and the other three trials had less than 80 participants.[92-94] Only one study included individuals 20 years of age or younger.[91] Two studies reported the majority of participants were Caucasian,[91 92] while the other two trials did not report race distribution.[93 94] Participants had poor glycemic control at study entry (mean HbA_{1c}, 8 to 9 percent); clinicians treated the intervention groups for 15 weeks to one year. One study reported a long duration of diabetes with a mean of 15 years.[91]

Effectiveness of Sensor-Augmented Pumps Compared With MDI/SMBG Among Patients With Type 2 Diabetes or Pregnant Women With Pre-Existing Diabetes

Key Points and Evidence Grades

- There was insufficient strength of evidence evaluating the effects of sensor-augmented pumps vs. MDI/SMBG among patients with type 2 diabetes or pregnant women with pre-existing diabetes, as we found no studies conducted in these populations.

Discussion

Summary of Key Findings

Our systematic review summarizes the current state of the evidence on the effectiveness and safety of methods for intensive insulin delivery used in clinical practice and glucose monitoring in terms of diabetes-related process measures, intermediate outcomes, and clinical outcomes in individuals with type 1 and type 2 diabetes mellitus. Although studies have reported on a number of process measures and intermediate outcomes (as summarized below), we did not find any studies comparing continuous subcutaneous insulin infusion (CSII) with multiple daily injections (MDI) or comparing real-time continuous glucose monitoring (rt-CGM) with self-monitoring of blood glucose (SMBG) for certain process measures (frequency of adjusting insulin therapy, adherence to therapy, and health visits) or for clinical outcomes (microvascular and macrovascular disease).

Comparative Effectiveness of CSII Versus MDI (KQ1)

Randomized controlled trails (RCTs) showed no difference in the effect on hemoglobin A_{1c} (HbA_{1c}) between the CSII and MDI intervention groups for children and adolescents or pregnant women with type 1 diabetes, or for adults with type 2 diabetes. In adults with type 1 diabetes, CSII showed favorable effect on glycemic control, but the result was influenced by one study[66] where participants had higher HbA_{1c} values at enrollment, allowing for greater HbA_{1c} lowering compared with the other studies were participants were closer to the HbA_{1c} target at enrollment. 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, adolescents and adults with type 1 diabetes, CSII use resulted in improvement in both general and diabetes-specific quality of life (QOL) measures, when compared with MDI. The evidence was insufficient to draw definitive conclusions about QOL 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 previously published meta-analyses by: (1) including more studies of individuals with type 2 diabetes as well as pregnant women with pre-existing type 1 diabetes,[30-32 35 97] (2) only including studies using rapidly-acting insulin analogs and not regular insulin in the CSII intervention groups,[30-32 35] and (3) requiring the MDI groups to be receiving at least three injections per day, the current standard for intensive insulin therapy.[31 33 97 98] We believe that these latter two distinctions are extremely important since these characteristics of intensive insulin therapy best reflect current clinical practice. Unlike one of the prior meta-analyses and systematic reviews[31 32] and similar to others,[33 35 97 98] we excluded before and after studies and only included RCTs in our combined estimates for HbA_{1c} and severe hypoglycemia. We also examined additional nonglycemic outcomes, including weight gain, ratio of basal to

bolus insulin, and QOL. Unfortunately, for some of the defined outcomes—process measures (e.g., ratio of basal to bolus insulin), weight gain, nonsevere hypoglycemia, and hyperglycemia — 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 SMBG.

We found that CSII had no significant effect on lowering HbA_{1c} in children (a drop of 0.14 percent) when compared with MDI and that there was no effect in adults with type 1 diabetes. A prior meta-analysis in children with type 1 diabetes found a significant (0.24 percent) reduction in HbA_{1c} favoring CSII; however, the prior meta-analysis included studies in which there were less than three daily injections in the MDI arm.[97] This may have biased the results to favor CSII since the MDI arm was less intensive than CSII. Prior meta-analyses combining RCTs in children and adults with type 1 diabetes have shown HbA_{1c} reductions of 0.21 to 0.4 percent, favoring CSII.[30-33] Several, however, included studies in which regular insulin was used in the pump[31 32] or the MDI arm included less than three daily injections.[33] In contrast to our meta-analysis, two prior reviews did not find a difference between CSII and MDI in the effect on HbA_{1c} in adults with type 1 diabetes,[98] although one systematic review did not perform a quantitative summary.[99] Our results, however, were heavily influence by one study and when that study was excluded in a sensitivity analysis, CSII and MDI had a similar effect on HbA_{1c} in adults with type 1 diabetes. Our estimates are based on a larger number of RCTs using rapid-acting analogs only in the CSII arms and at least three daily injections in the MDI arms, making them comparable in intensity to CSII (total of 11—7 in children and adolescents and 4 in adults). In general, while prior meta-analyses of RCTs have shown a statistically significant reduction in HbA_{1c} favoring CSII, none reached what is considered a clinically meaningful difference of 0.5 percent.[99] Prior meta-analyses that have shown larger effect sizes favoring CSII have included before and after studies which may be subject to selection bias and confounding (i.e., individuals doing poorly on MDI are more likely to be switched to CSII and then improve).[30 99]

Similar to a prior meta-analysis 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).[98] While two prior analyses found a significantly higher rate of severe hypoglycemia with MDI compared with CSII, one of these only included studies if individuals reported an elevated frequency of baseline severe hypoglycemic episodes, which may have resulted in a greater likelihood of improvement.[30] The other included studies that used regular insulin in the CSII arms, which would be expected to result in less hypoglycemia than regular insulin with MDI due to more steady insulin delivery.[32] Similar to two prior systematic reviews, there was no difference in HbA_{1c} or hypoglycemia frequency with CSII versus MDI in adults with type 2 diabetes.[35 98 99] Our meta-analysis is distinct from prior reviews in that it includes additional studies not reported previously using current rapid-acting analogs in the CSII arms,[35] and it provides a quantitative effect estimate.[99]

Comparative Effectiveness of rt-CGM Versus SMBG (KQ2)

We only found studies of the comparative effectiveness of rt-CGM versus SMBG in children, adolescents, and adults with type 1 diabetes. While prior studies have examined the effect of retrospective continuous glucose monitoring (CGM) in pregnant women with diabetes, no studies have compared rt-CGM with SMBG in this population.[24] These two glucose monitoring approaches have not been compared in individuals with type 2 diabetes.

Compared with the SMBG group, the rt-CGM group achieved a lower HbA_{1c} (-0.3 percent). A sensitivity analysis showed this effect to be greater in studies where sensor compliance was 60 percent or greater (-0.36 percent). We also found that rt-CGM was associated with a lower HbA_{1c} compared with SMBG in individuals 18 years of age or younger. These findings support recent clinical practice recommendations suggesting rt-CGM use in children and adolescents over the age of 8 years.[100] The intervention groups did not differ in the rate of severe hypoglycemia; however, there was a significant reduction in the time spent in the hyperglycemic range. A few studies that evaluated QOL found no difference between general and diabetes-specific QOL 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[34] by including additional non-glycemic outcomes, including weight gain, ratio of basal to bolus insulin, and QOL. We also found that rt-CGM lowered HbA_{1c} more than SMBG (-0.28 percent in our study versus -0.30 percent in Pickup et al.) and that there was no difference in severe hypoglycemia in the two intervention groups.[34] Although statistically significant, these differences are below the 0.5 percent HbA_{1c} difference that experts consider clinically meaningful.[99] In addition, in one study that evaluated the fear of hypoglycemia, the fear was less with rt-CGM than with SMBG.[82] This has important clinical implications as the goal of intensive insulin therapy is to lower HbA_{1c} without inducing severe hypoglycemia, which can cause significant patient anxiety and be a barrier to safely improving glycemic control.

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

Sensor-augmented pump use resulted in a statistically and clinically significant greater reduction in HbA_{1c} compared with MDI/SMBG use in non-pregnant individuals with type 1 diabetes (-0.61 percent). The evidence was insufficient to draw definitive conclusions about severe hypoglycemia or quality life. No previous meta-analysis examined this comparison.

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.[48] 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, adults 65 years of age or older, or pregnant women with pre-existing type 2 diabetes, we were unable to draw conclusions about the effectiveness of insulin delivery and glucose monitoring methods in these populations. However, this likely reflects that fact that type 1 diabetes is much rarer in minority and elderly individuals and few pregnant women have pre-existing type 2 diabetes, making it less feasible and relevant to perform studies in these sub-populations. The studies were heterogeneous in definitions of nonsevere hypoglycemia, hyperglycemia, and weight gain, preventing us from combining data to determine effect estimates for these intermediate outcomes. While the definition of severe hypoglycemia in many studies included a requirement for third party assistance, it was not explicitly stated in all studies, so we were unable to determine if other definitions, such as a

uniform glucose cut-point or hypoglycemia treatment approach, correctly classified individuals as having severe hypoglycemia. In studies comparing CSII and MDI, differences in the insulin regimen in the MDI arms (NPH and regular insulin versus analog insulin-based) may have been a source of heterogeneity; however, we had inadequate power to stratify by the MDI insulin regimen. Presumably greater use of NPH and regular insulin-based MDI would have biased results to the null for glycemic and quality of life 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. While data on these outcomes would be ideal, it would require a very large RCT of several years duration, which may not be feasible to perform, particularly because individuals may switch therapies over time. In the pregnancy literature, none of the studies in women with pre-existing type 1 diabetes have examined the effect of rt-CGM on maternal and fetal outcomes. Other than the rt-CGM studies, the majority of studies did not report data on treatment adherence. The high baseline HbA_{1c} values in the CSII and MDI intervention groups in many studies may indicate poor adherence to prior as well as intervention treatments which may have biased results to the null (although there is also greater room for improvement). Finally, the studies were heterogeneous in assessing and reporting QOL outcomes, which prevented us from quantifying the effects of insulin delivery and glucose monitoring methods on QOL. We found no studies examining the comparative effectiveness of CSII versus MDI on QOL in pregnant women and only one study examining the effects on QOL in type 2 diabetes.

Our systematic review and meta-analysis had several limitations. Meta-analyses in general are subject to bias based on selection criteria for articles, performing multiple comparisons, and the state of the available literature. We reviewed studies of current therapies and methods for intensive insulin therapy and glucose monitoring. 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, nonsevere hypoglycemia) and non-glycemic outcomes for which we could not perform meta-analyses, we were unable to assess for publication bias. 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.[101] Our meta-regression to examine potential sources of heterogeneity in the effect of rt-CGM versus SMBG on HbA_{1c} was a post hoc analysis and is hypothesis-generating as opposed to hypothesis-testing.

Our data are not generalizable to non-specialty settings or all patients with diabetes mellitus, as the initiation, instruction, monitoring, and therapeutic changes for CSII and rt-CGM use is often limited to expert settings and highly motivated patients and families. All studies of rt-CGM are subject to ascertainment bias because rt-CGM provides more hypoglycemia and hyperglycemia data than SMBG alone. Because it is not feasible to keep patients blinded in an RCT comparing CSII with MDI or in an RCT comparing rt-SGM with SMBG, studies of QOL outcomes could have been vulnerable to reporting bias if patients believed that CSII and rt-CGM were superior. Finally, all of the studies included in our review were efficacy studies (as opposed to effectiveness studies) and 19 of the 41 excluded individuals with comorbidities such as impaired liver and renal function, microvascular complications, cardiovascular disease, mental disorders, recent severe hypoglycemia, or other chronic medical conditions,[36 49-51 54 57 59 60 62-66 69]

[70 85 94 94 102] making results less generalizable to entire population of individuals with diabetes (see Appendix E, Table 1).

Implications

Our findings indicate that intensive insulin therapy delivered either by CSII and MDI using current rapidly-acting insulin analogs with CSII are about equally effective in lowering HbA_{1c} in several diabetic patient populations—adolescents and pregnant women with type 1 diabetes. Our findings suggest that CSII is superior to MDI in lowering HbA_{1c} in adults with type 1 diabetes, although the results were heavily influenced by one study. 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 QOL 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 QOL, as both CSII and MDI using current rapid-acting insulin analogs have similar effectiveness for glycemic control.

To our knowledge this is the first systematic review and meta-analysis 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 percent for all studies versus 0.37 percent in studies with greater than 60 percent sensor compliance rate). The addition of rt-CGM to CSII is superior to MDI/SMBG in lowering HbA_{1c}. Thus, the addition of this monitoring method to SMBG and 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 SMBG 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] and because older individuals may be at increased risk for adverse outcomes associated with intensive insulin therapy, it is important to know which insulin delivery and glucose monitoring methods are most effective. Only a small number of studies in nonadolescent 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. To allow cross-comparisons, future RCTs should use a uniform definition of hypoglycemia, preferably that recommended by the American Diabetes Association.[103] There is also a need for well-designed prospective, observational studies to determine the comparative effectiveness of CSII versus MDI and rtCGM versus SMBG on clinically relevant long-term micro- and macrovascular outcomes. Such studies would also provide guidance on effect sizes for future power calculations to determine whether it is feasible to undertake RCTs examining these outcomes. Future studies should also seek to identify and use an agreed-upon set of general and diabetes-specific and treatment-related QOL measures to allow comparisons across studies, including reporting of standard errors and confidence intervals to allow quantitative, pooled assessments. Studies should incorporate measures of adherence to treatment as adherence is important for the effectiveness of any intensive insulin therapy or glucose monitoring system. Our data and others show that rt-CGM is most effective in those compliant with wearing the sensor at least 60 percent of the time.[34 84] Thus, sensor compliance may be a marker for overall treatment adherence and explain the HbA_{1c} reduction, independent of the sensor. Future studies should focus on individuals with type 2 diabetes requiring insulin to determine the most effective manner in which to delivery intensive insulin therapy and monitor blood glucose. Given the rise in prevalence of type 2 diabetes in the general population, the number of those individuals requiring insulin therapy will likely rise. Finally, studies of type 2 diabetes should include ethnically diverse populations because type 2 diabetes is more common in nonwhites[104] and minority individuals are at higher risk for adverse outcome, which might be positively or negatively impacted by the approach to intensive insulin delivery and/or glucose monitoring method.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AUC	area under the curve
BMI	body mass index
CENTRAL	Central Register of Controlled Trials
CGM	continuous glucose monitoring
CI	confidence interval
C-section	Cesarean section
CSII	continuous subcutaneous insulin infusion
dL	deciliter
DQOL	Diabetes Quality of Life
DQOLCTQ	Diabetes Quality of Life Clinical Trials Questionnaire
DQOL-Y	Diabetes Quality of Life-Youth
DTSQ	Diabetes-Treatment Specific Questionnaire
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
g	grams
HbA_{1c}	hemoglobin A1c
hrs	hours
JDRF	Juvenile Diabetes Research Foundation
KQ	Key Question
MDI	multiple daily injections
mg	milligram
NA	not applicable
NICU	neonatal intensive care unit
NPH	neutral protamine Hagedorn
NS	not significant
PAID	Problem Areas in Diabetes
PedsQoL	Pediatric Quality of Life Index
QOL	quality of life
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
U.S.	United States
WHO-5	World Health Organization-5 Well Being Index

Appendix A. Detailed Electronic Database Search Strategies

PubMed Strategy

Terms	Returns
((“Diabetes Mellitus”[mh] OR Diabet*[tiab] OR hyperglycem*[tiab] OR hyperglycaem*[tiab]) AND (“Insulin Infusion Systems”[mh] OR “continuous subcutaneous insulin”[tiab] OR CSII[tiab] OR “insulin pump”[tiab] OR “insulin pumps”[tiab] OR “pump therapy”[tiab] OR “pump treatment”[tiab] OR “artificial pancreas”[tiab] OR (“Monitoring, Ambulatory”[mh] AND (glucose[tiab] OR insulin[tiab] OR glycem*[tiab] OR glycaem*[tiab])) OR “CGM”[tiab] OR (“continuous glucose”[tiab] AND (monitor*[tiab] OR sensing[tiab] OR sensor*[tiab])))) NOT (animal[mh] NOT human [mh])	4768

Embase Strategy

(('diabetes mellitus'/exp OR diabet*:ti,ab OR hyperglycem*:ti,ab OR hyperglycaem*:ti,ab) AND ('insulin pump'/de OR “continuous subcutaneous insulin”:ti,ab OR CSII:ti,ab OR “insulin pump”:ti,ab OR “insulin pumps”:ti,ab OR “pump therapy”:ti,ab OR “pump treatment”:ti,ab OR “artificial pancreas”:ti,ab OR ('blood glucose monitoring'/exp AND (continu*:ti,ab OR real-time:ti,ab)) OR CGM:ti,ab OR (“continuous glucose”:ti,ab AND (monitor*:ti,ab OR sensing:ti,ab OR sensor*:ti,ab)))) NOT ([animals]/lim NOT [humans]/lim)	5942

The Cochrane Central Register of Controlled Trials (CENTRAL)

((Diabet*:ti,ab,kw OR hyperglycem*:ti,ab,kw OR hyperglycaem*:ti,ab,kw) AND (“continuous subcutaneous insulin”:ti,ab,kw OR CSII:ti,ab,kw OR “insulin pump”:ti,ab,kw OR “insulin pumps”:ti,ab,kw OR “pump therapy”:ti,ab,kw OR “pump treatment”:ti,ab,kw OR “artificial pancreas”:ti,ab,kw OR “CGM”:ti,ab,kw OR (“continuous glucose”:ti,ab,kw AND (monitor*:ti,ab,kw OR sensing:ti,ab,kw OR sensor*:ti,ab,kw))))	233 from Clinical Trials

Appendix B. Forms

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

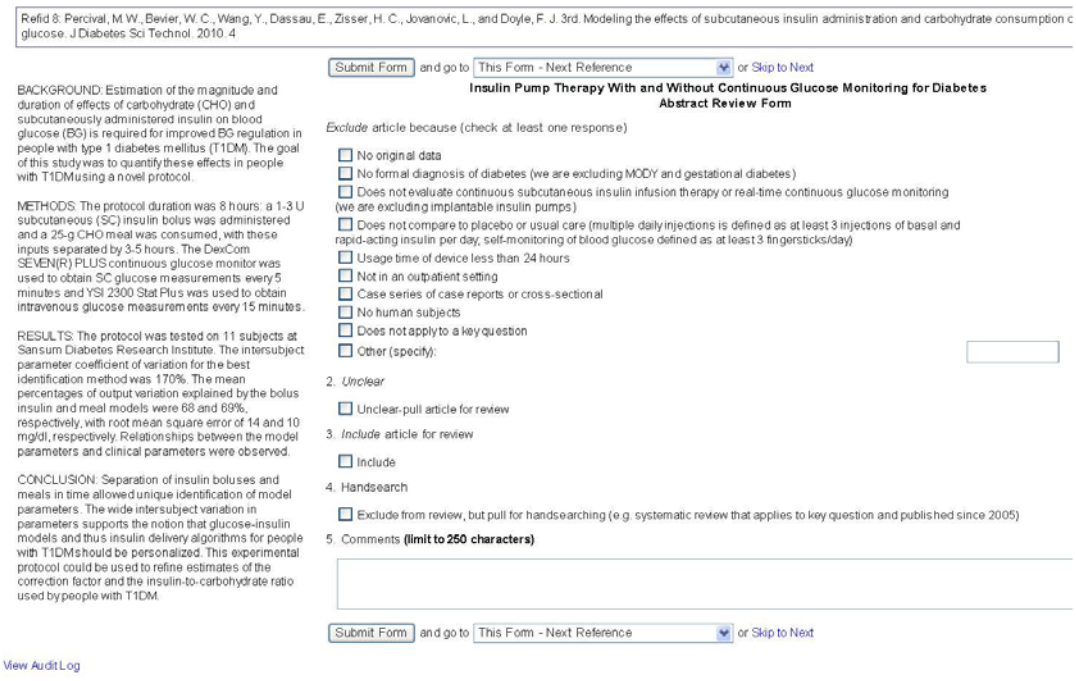
Submit Form and go to or Skip to Next

1. Does this citation **POTENTIALLY** apply to our key questions?

Yes No Clear Response

Submit Form and go to or Skip to Next

[redacted]



Refid 8: Percival, M. W., Bevier, W. C., Wang, Y., Dassau, E., Zisser, H. C., Jovanovic, L., and Doyle, F. J. 3rd. Modeling the effects of subcutaneous insulin administration and carbohydrate consumption c glucose. J Diabetes Sci Technol. 2010. 4

BACKGROUND: Estimation of the magnitude and duration of effects of carbohydrate (CHO) and subcutaneously administered insulin on blood glucose (BG) is required for improved BG regulation in people with type 1 diabetes mellitus (T1DM). The goal of this study was to quantify these effects in people with T1DM using a novel protocol.

METHODS: The protocol duration was 8 hours: a 1-3 U subcutaneous (SC) insulin bolus was administered and a 25-g CHO meal was consumed, with these inputs separated by 3-5 hours. The DexCom SEVEN(R) PLUS continuous glucose monitor was used to obtain SC glucose measurements every 5 minutes and YSI 2300 Stat Plus was used to obtain intravenous glucose measurements every 15 minutes.

RESULTS: The protocol was tested on 11 subjects at Sansum Diabetes Research Institute. The intersubject parameter coefficient of variation for the best identification method was 170%. The mean percentages of output variation explained by the bolus insulin and meal models were 68 and 69%, respectively, with root mean square error of 14 and 10 mg/dl, respectively. Relationships between the model parameters and clinical parameters were observed.

CONCLUSION: Separation of insulin boluses and meals in time allowed unique identification of model parameters. The wide intersubject variation in parameters supports the notion that glucose-insulin models and thus insulin delivery algorithms for people with T1DM should be personalized. This experimental protocol could be used to refine estimates of the correction factor and the insulin-to-carbohydrate ratio used by people with T1DM.

Submit Form and go to This Form - Next Reference or Skip to Next

Insulin Pump Therapy With and Without Continuous Glucose Monitoring for Diabetes
Abstract Review Form

Exclude article because (check at least one response)

- No original data
- No formal diagnosis of diabetes (we are excluding MODY and gestational diabetes)
- Does not evaluate continuous subcutaneous insulin infusion therapy or real-time continuous glucose monitoring (we are excluding implantable insulin pumps)
- Does not compare to placebo or usual care (multiple daily injections is defined as at least 3 injections of basal and rapid-acting insulin per day; self-monitoring of blood glucose defined as at least 3 fingersticks/day)
- Usage time of device less than 24 hours
- Not in an outpatient setting
- Case series of case reports or cross-sectional
- No human subjects
- Does not apply to a key question
- Other (specify):

2. *Unclear*

- Unclear-pull article for review

3. *Include* article for review

- Include

4. Handsearch

- Exclude from review, but pull for handsearching (e.g. systematic review that applies to key question and published since 2005)

5. Comments **(limit to 250 characters)**

Submit Form and go to This Form - Next Reference or Skip to Next

View Audit Log

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Insulin Pump Therapy With and Without Continuous Glucose Monitoring for Diabetes
Article Review Form

1. *Exclude* article because (check at least one response)

- ☐ No original data
- ☐ No formal diagnosis of diabetes (we are excluding MODY and gestational diabetes)
- ☐ Does not evaluate continuous subcutaneous insulin infusion therapy or real-time continuous glucose monitoring (we are excluding implantable insulin pumps, artificial pancreas, and closed-loop systems)
- ☐ Does not compare to placebo or usual care (multiple daily injections is defind as at least 3 fingersticks/day)
- ☐ No concurrent comparison group
- ☐ Does not have an outcome of interest (see list below)
- ☐ Usage time of device less than 24 hours
- ☐ Not in an outpatient setting
- ☐ Case series or case reports or cross-sectional or meeting abstract
- ☐ No human subjects
- ☐ Does not apply to a key question
- ☐ Other (specify):
- ☐ Regular insulin used in pump
- ☐ Observational study that does not evaluate a microvascular, macrovascular, maternal, or fetal outcome

2. *Include* article for review (indicate the following):

- ☐ RCT
- ☐ Observational
- ☐ Continuous subcutaneous insulin infusion or insulin pump
- ☐ Real-time continuous glucose monitor

3. *Handsearch*

- ☐ Exclude from review, but pull for handsearching (e.g., systematic review that applies to the key question and published since 2005)

Outcomes of interest

Process Measures	Intermediate Outcomes	Clinical Outcomes	Maternal and Fetal Outcomes
Ratio of basal to bolus insulin Frequency of adjusting insulin therapy Adherence to insulin therapy/sensor use	Primary HbA1C Secondary Quality of life Hyperglycemia Weight Gain Hypoglycemia frequency	Microvascular Retinopathy Nephropathy Neuropathy Macrovascular Coronoary heart disease Cerebrovascular disease Peripheral arterial disease Severe hypoglycemia	Maternal pregnancy outcomes Antenatal hospital stay (% requiring admission, length of stay) C-section rates Fetal outcomes Gestational age Birth weight Frequency of neonatal hypoglycemia Birth trauma Major and minor anomalies Neonatal intensive care unit admission

4. Comments **(Limit 250 characters)**


Submit Form
and go to
or Skip to Next

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
RethnamU, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Comparative Effectiveness of Insulin Pump Therapy
With or Without Continuous Glucose Monitoring in Diabetes
Study Design Form

Additional Screening Questions

1. Is this study an observational study that reports on microvascular, macrovascular, maternal, or fetal outcomes?

- ☐ No, not an observational one **(CONTINUE)**
- ☐ Yes, this is an observational study that reports on microvascular, macrovascular, maternal, or fetal outcomes **(CONTINUE)**
- ☐ No, this is an observational study DOES NOT REPORT on microvascular, macrovascular, maternal, or fetal outcomes **(STOP! E-MAIL LISA TO EXCLUDE THIS STUDY)**

2. Is regular insulin being used in the insulin pumps?

- ☐ Yes, regular insulin is being used in the insulin pumps **(STOP! EMAIL LISA TO EXCLUDE THIS STUDY)**
- ☐ No, regular insulin is NOT being used in the insulin pumps **(CONTINUE)**

Study Design Form

1. Where did the study occur? **(Check all that apply)**

- ☐ United States
- ☐ Canada
- ☐ Worldwide
- ☐ Other (specify):
- ☐ Not reported

2. When was the study enrollment period? **(enter the 4-digit year for start and/or end, or indicate not reported)**

- ☐ Start year:
- ☐ End year:
- ☐ Not reported

3. What was the total intended follow up duration or maximum possible follow up?

Select an Answer

4. What was the total number of patients screened?

Select an Answer

5. What was the total number at enrollment or cohort inception?

Select an Answer

6. What was the source of the population from which subjects were enrolled in the study? **(Check all that apply)**

- ☐ Diabetes referral clinic
- ☐ General medicine clinic
- ☐ Ob/Gyn Clinic
- ☐ Other (specify):
- ☐ Not reported

7. What study design was used? **(Check all that apply)**

Select an Answer

8. Was there a run-in period? **(Choose only one response)**

Select an Answer

9. Select trial type **(Check only one response)**

- Parallel arms
- Factorial design
- Crossover design
- Other (specify):
- Not applicable

10. Please select the included patient population

Diabetes status **(choose only one response)**	Age **(Choose all that apply)**	Pregnancy status **(choose only one response)**
Type 1 diabetes Type 2 diabetes Both Other (specify): Clear Response	Very young children Adolescents Adults Elderly Age Range	Pregnant women exclusively Pregnant women included Pregnant women excluded Not reported Clear Response

11. Please specify the exclusion criteria. Any inclusion critera should be entered as exclusion criteria **(e.g., if the study only included females, then the exclusion criteria would be males).**

- HbA1c >
- HbA1c <
- Male
- Female
- Treated with insulin:
- Not currently receiving intensive insulin therapy (either insulin pump or multiple daily injections)
- Use of insulin pump therapy within:
- Use of continuous glucose monitoring within:
- Use of oral hypoglycemic within:
- Not using adequate contraception
- Other (specify):
- Other (specify):
- Other (specify):
- Other (specify):
- Other (specify):
- Other (specify):

12. Was there industry support (funding or drug given) or government support for the study? **(Check all that apply)**

- Yes, industry support
- Yes, government support
- Yes, other support
- No
- Not reported

13. Does this study report on quality of life?

- Yes
- No

Clear Response

Comments:

Comments:

Comments:

Submit Form and go to or Skip to Next

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A

Submit Form and go to [ ] or Skip to Next

Comparative Effectiveness of Insulin Pump Therapy With or Without Continuous Glucose Monitoring in Diabetes Population Characteristics Form

	Group 1	Group 2	Group 3	Group 4
Number enrolled				
Age Age NR Clear Response	Mean: Median: Age range:	Mean: Median: Age range:	Mean: Median: Age range:	Mean: Median: Age range:
Gender Gender NR Clear Response	Male, n: Male, %:	Male, n: Male, %:	Male, n: Male, %:	Male, n: Male, %:
Race Race NR Clear Response	African American, n: African American, %: Asian or Asian American, n: Asian or Asian American, %: Caucasian, n: Caucasian, %: Hispanic, n: Hispanic, %: Other race, n: Other race, %:	African American, n: African American, %: Asian or Asian American, n: Asian or Asian American, %: Caucasian, n: Caucasian, %: Hispanic, n: Hispanic, %: Other race, n: Other race, %:	African American, n: African American, %: Asian or Asian American, n: Asian or Asian American, %: Caucasian, n: Caucasian, %: Hispanic, n: Hispanic, %: Other race, n: Other race, %:	African American, n: African American, %: Asian or Asian American, Asian or Asian American, Caucasian, n: Caucasian, %: Hispanic, n: Hispanic, %: Other race, n: Other race, %:
HbA1c HbA1c NR Clear Response	Mean HbA1c: Median HbA1c: HbA1c range:	Mean HbA1c: Median HbA1c: HbA1c range:	Mean HbA1c: Median HbA1c: HbA1c range:	Mean HbA1c: Median HbA1c: HbA1c range:
BMI/Weight BMI/Weight NR Clear Response	Mean BMI (kg/m²): Median BMI (kg/m²): Mean weight (kg): Median weight (kg):	Mean BMI (kg/m²): Median BMI (kg/m²): Mean weight (kg): Median weight (kg):	Mean BMI (kg/m²): Median BMI (kg/m²): Mean weight (kg): Median weight (kg):	Mean BMI (kg/m²): Median BMI (kg/m²): Mean weight (kg): Median weight (kg):
Duration of Diabetes Duration of diabetes NR Clear Response	Mean (years): Median (years):	Mean (years): Median (years):	Mean (years): Median (years):	Mean (years): Median (years):
Insulin delivery method (Answer question for studies evaluating blood glucose monitoring) Insulin delivery method NR Clear Response	CSII, n: CSII, %: Multiple daily injections, n: Multiple daily injections, %:	CSII, n: CSII, %: Multiple daily injections, n: Multiple daily injections, %:	CSII, n: CSII, %: Multiple daily injections, n: Multiple daily injections, %:	CSII, n: CSII, %: Multiple daily injections, r Multiple daily injections, '
Number of withdrawals Number of withdrawals NR Clear Response	N:	N:	N:	N:

Comments:

Comments:

Comments:

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A

Submit Form and go to or Skip to Next

Comparative Effectiveness of Insulin Pump Therapy With or Without Continuous Glucose Monitoring in Diabetes Intervention Characteristics Form

1. Identify study group: **(For studies evaluating insulin delivery methods, please identify group 1 as multiple daily injection. For studies evaluating blood glucose monitoring, please identify group 1 as self-monitoring of blood glucose.)**

Select an Answer

(Answer Q2-5 for insulin delivery methods)

2. What type of insulin delivery method was used? **(Select all that apply)**	3. What type of insulin was used? **(Select all that apply)**	4. Was there any training before initiating the insulin pump? **(Select one response)**	5. What was the schedule for multiple daily injections?
Multiple daily injections Insulin pump, model unspecified Abbott Aviator Abbott Freestyle Aviator Animas Model IR 1000 Animas Model IR 1200 Animas Model IR 1250 Cane Microjet Quark model U-100 Cardiac Pacemakers Betatron IV insulin infusion system Deltec/Smiths Medical Cozmo Insulin Infusion Pump Disetronic/Roche H-TRON V 100 Disetronic/Roche DAHEDI Disetronic/Roche D-TRON Disetronic/Roche ACCU-Check Spirit Insulet iXL Diabetes management system Insulet iXL-11 DMS Mendigo Solo insulin patch pump Mendigo Solo Micropump insulin delivery system Medtronic Minimed Model 506 Medtronic Minimed Model MMT-507 Medtronic Minimed Model 505 Medtronic Minimed Model 507c Medtronic Minimed Model 508 Medtronic Minimed Paradigm model 512 Medtronic Minimed REAL-time system Medtronic Minimed Paradigm 722 NiliMedix ADI Nipro Glucopro infusion pump Nipro Amigo Pharma-Plast Sooil DANA Diabecare Sooil DANA Diabecare II Sooil DANA Diabecare IIS Other type of insulin pump (Specify):	Insulin aspart Insulin detemir Insulin glargine Insulin glulisine Insulin lispro NPH insulin Regular insulin Other type of insulin (Specify): Not reported	Yes No Not reported	3 times/day 4 + times/day Other (specify): Not reported

(Answer Q6-10 for blood glucose monitoring techniques.)

6. What type of blood glucose monitoring technique was used?	7. How often was the monitor used?	8. What were the alarms for hypoglcycemia?	9. What were the alarms for hyperglycemia?	10. What was the frequency and schedule of blood glucose monitoring?
Self-monitoring blood glucose Real-time continuous glucose monitor, model unspecified Abbott Freestyle Navigator Dexcom ST.S		Select an Answer	Select an Answer	Select an Answer

- [ ] Medtronic Minimed Guardian Telemetered CGM
- [ ] Minimed Guardian Real-Time CGM
- [ ] Minimed Medtronic Paradigm RT
- [ ] Other real-time continuous glucose monitor (specify):

(Answer for all interventions.)

11. What was the total duration of therapy?

Select an Answer

12. Where there guidelines for provider insulin dose titration?

- ○ Yes
- ○ No
- ○ Not reported

Clear Response

13. Please indicate the target glycemic

- [ ] HbA1c (%):
- [ ] Fasting glucose (mg/dL):
- [ ] Fasting glucose (mmol/L):
- [ ] Preprandial glucose (mg/dL):
- [ ] Preprandial glucose (mmol/L):
- [ ] 2-hr postprandial glucose (mg/dL):
- [ ] 2-hr postprandial glucose (mmol/L):
- [ ] Other glycemic target (mg/dL):
- [ ] Other glycemic target (mmol/L):
- [ ] Not reported

14. Were there guidelines for between visit titration?

- ○ Yes
- ○ No
- ○ Not reported

Clear Response

Submit Form and go to or Skip to Next

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
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Submit Form and go to or Skip to Next

Comparative Effectiveness of Insulin Pump Therapy With or Without Continuous Monitoring in Diabetes Outcomes Form

Please complete this form for RCTs and cohort studies. Submit one form per relevant outcome.

Please select one outcome	Please define outcome	If study reports results stratified only, please indicated which population is being reported here.
Process measures ○ Ratio of basal to bolus insulin ○ Frequency of adjusting insulin therapy ○ Adherance to insulin therapy/sensor use ○ Frequency of physician or allied health visit Clear Response	○ Proportion of basal insulin ○ Number of daily boluses ○ Average use/week ○ Other definition: Clear Response	○ Type 1 diabetes ○ Type 2 diabetes ○ Age range: Clear Response
Intermediate outcomes ○ HbA1c ○ Hyperglycemia ○ Weight gain ○ Hypoglycemia frequency Clear Response	○ % ○ Fasting glucose (mg/dL): ○ Fasting glucose (mmol/L): ○ Postprandial glucose (mg/dL): ○ Postprandial glucose (mmol/L): ○ kg ○ lb ○ Mild hypoglycemia: ○ Moderate hypoglycemia: ○ Nocturnal hypoglycemia: ○ Daytime hypoglycemia: Clear Response	○ Type 1 Diabetes ○ Type 2 Diabetes ○ Age range: Clear Response
Clinical Outcomes Retinopathy Nephropathy Neuropathy Coronary heart disease Cerebrovascular disease Peripheral arterial disease Severe hypoglycemia Clear Response	Specify: Not further specified Clear Response	Type 1 diabetes Type 2 diabetes Age Range Clear Response
Fetal outcomes Gestational age Birth weight Frequency of neonatal hypoglycemia Birth trauma Major anomalies Minor anomalies Minor anomalies NICU admission NICU admission Clear Response	Weeks kg Specify: Clear Response	Type 1 diabetes Type 2 diabetes Age range: Clear Response
Maternal outcomes Cesarean delivery Clear Response	Elective Repeat Specify:	Type 1 diabetes Type 2 diabetes Age range: Clear Response

	○ Not Author specified Clear Response	

When was this outcome assessed? **(Only report the last timepoint. For pregnancy studies, record events for each trimester, however do not report results for the post natal period.)**

- ○ Weeks
- ○ Months
- ○ Years
- ○ First trimester
- ○ Second trimester
- ○ Third trimester
- ○ Not reported

Clear Response

Table 1. Incidence of outcome

Intervention Group1	N for analysis	Outcome measure	Denominator	P-value	Reference group
		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group2	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group3	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group4	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group5	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group6	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group7	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer
Intervention Group8	**N for analysis**	**Outcome measure**	**Denominator**	**P-value**	**Reference group**
		☐ # of patients with one or more events ☐ % of patients with one or more events ☐ # of events	Select an Answer		Select an Answer

Table 2. Measure of Association

Intervention	N for analysis	Point estimate (Select one response)	Measure of variability (Select one response)	95%CI	P-value	Reference group

		Select an Answer	Select an Answer			
Intervention Group1				☐ LL ☐ UL		Select an Answer
Intervention Group2				☐ LL ☐ UL		Select an Answer
Intervention Group3				☐ LL ☐ UL		Select an Answer
Intervention Group4				☐ LL ☐ UL		Select an Answer
Intervention Group5				☐ LL ☐ UL		Select an Answer
Intervention Group6				☐ LL ☐ UL		Select an Answer
Intervention Group7				☐ LL ☐ UL		Select an Answer
Intervention Group8				☐ LL ☐ UL		Select an Answer

If a multivariable analysis, what other variables were adjusted for in the model? **(Select all that apply)**

- ☐ Matching factors
- ☐ Age
- ☐ Sex
- ☐ Race/ethnicity
- ☐ Duration of disease
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Other (specify):
- ☐ Results not adjusted

Table 3. Mean difference from other group

Intervention	N for analysis	Point estimate (Select one response)	Measure of variability (Select one response)	CI or IQR (Select one response)	P-value	Reference group
		Select an Answer	Select an Answer	Select an Answer		
Intervention Group1				☐ LL ☐ UL		Select an Answer
Intervention Group2				☐ LL ☐ UL		Select an Answer
Intervention Group3				☐ LL ☐ UL		Select an Answer
Intervention Group4				☐ LL ☐ UL		Select an Answer

Intervention Group5				☐ LL ☐ UL		Select an Answer
Intervention Group6				☐ LL ☐ UL		Select an Answer
Intervention Group7				☐ LL ☐ UL		Select an Answer
Intervention Group8				☐ LL ☐ UL		Select an Answer

Table 4. Mean difference from baseline.

Intervention	N for analysis	Point estimate (Select one response) Select an Answer	Measure of variability (Select one response) Select an Answer	CI or IQR (Select one response) Select an Answer	P-value
Intervention Group1				☐ LL ☐ UL	
Intervention Group2				☐ LL ☐ UL	
Intervention Group3				☐ LL ☐ UL	
Intervention Group4				☐ LL ☐ UL	
Intervention Group5				☐ LL ☐ UL	
Intervention Group6				☐ LL ☐ UL	
Intervention Group7				☐ LL ☐ UL	
Intervention Group8				☐ LL ☐ UL	

Table 5. Baseline measures.

Intervention	N for analysis	Point estimate (Select one response) Select an Answer	Measure of variability (Select one response) Select an Answer	CI or IQR (Select one response) Select an Answer
Intervention Group1				☐ LL ☐ UL
Intervention Group2				☐ LL ☐ UL

Intervention Group3				☐ LL ☐ UL
Intervention Group4				☐ LL ☐ UL
Intervention Group5				☐ LL ☐ UL
Intervention Group6				☐ LL ☐ UL
Intervention Group7				☐ LL ☐ UL
Intervention Group8				☐ LL ☐ UL

Table 6. Final measures

Intervention	N for analysis	Point estimate (Select one response) Select an Answer	Measure of variability (Select one response) Select an Answer	CI or IQR (Select one response) Select an Answer	P-value	Reference group
Intervention Group1				☐ LL ☐ UL		Select an Answer
Intervention Group2				☐ LL ☐ UL		Select an Answer
Intervention Group3				☐ LL UL		Select an Answer
Intervention Group4				LL UL		Select an Answer
Intervention Group5				LL UL		Select an Answer
Intervention Group6				LL UL		Select an Answer
Intervention Group7				LL UL		Select an Answer
Intervention Group8				LL UL		Select an Answer

Comments **(Limit 250 characters)**

Comments **(Limit 250 characters)**

Comments **(Limit 250 characters)**

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Insulin Pump Therapy With and Without Continuous Glucose Monitoring for Diabetes
Quality form for RCTs

Sequence Generation

1. Was the allocation sequence adequately generated?
Select an Answer

Criteria for a judgment of "YES" (i.e., low risk of bias)

- *The investigators describe a random component in the sequence generation process such as:*
  - *Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization. Minimization may be implemented without a random element, and this is considered to be equivalent to being random.*

Criteria for a judgment of "NO" (i.e., high risk of bias)

- *The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:*
  - *Sequence generated by odd or even date of birth;*
  - *Sequence generated by some rule based on date (or day) of admission;*
  - *Sequence generated by some rule based on hospital or clinic record number.*
- *Other non-random approached happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorization of participants, for example:*
  - *Allocation by judgment of the clinician;*
  - *Allocation by preference of the participant;*
  - *Allocation based on the results of a laboratory test or a series of tests.*

Criteria for a judgment of "UNCLEAR" (i.e., uncertain risk of bias)

- *Insufficient information about the sequence generation process to permit judgement of "YES" or "NO."*

Allocation Concealment

2. Was allocation adequately concealed?
Select an Answer

Criteria for a judgment of "YES" (i.e. low risk of bias)

- *Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:*
  - *Central allocation (including telephone, web-based, and pharmacy-controlled, randomization);*
  - *Sequentially numbered drug containers of identical appearance;*
  - *Sequentially numbered, opaque, sealed envelopes.*

Criteria for a judgment of "NO" (i.e. high risk of bias)

- *Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:*
  - *Using an open random allocation schedule (e.g. a list of random numbers);*
  - *Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);*
  - *Alternation or rotation;*

- *Date of birth;*
- *Case record number;*
- *Any other explicitly unconcealed procedure*

Criteria for the judgment of "UNCLEAR" (i.e. uncertain risk of bias)

- *Insufficient information about the sequence generation process to permit judgment of "YES" or "NO".*
  - *This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.*

Blinding of Participants, Personnel, and Outcome Assessors

3. Was knowledge of the allocated interventions adequately prevented during the study?
Select an Answer

Criteria for a judgment of "YES" (i.e. low risk of bias)

- *Any one of the following:*
  - *No blinding, but the review authors judge that the outcome and the outcome*
  - *Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;*
  - *Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the nonblinding of others unlikely to introduce bias.*

Criteria for a judgment of "NO" (i.e. high risk of bias)

- *Any one of the following:*
  - *No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;*
  - *Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;*
  - *Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.*

Criteria for the judgment of "UNCLEAR" (i.e. uncertain risk of bias)

- *Any one of the following:*
  - *Insufficient information to permit judgment of 'Yes' or 'No';*
  - *The study did not address this outcome.*

Incomplete Outcome Data

4. Were incomplete outcome data adequately addressed?
Select an Answer

Criteria for a judgment of "YES" (i.e. low risk of bias)

- *Any one of the following:*
  - *No missing outcome data;*
  - *Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);*
  - *Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;*
  - *For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;*
  - *For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;*
  - *Missing data have been imputed using appropriate methods.*

Criteria for a judgment of "NO" (i.e. high risk of bias)

- *Any one of the following:*
  - *Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;*
  - *For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;*
  - *For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among*

missing outcomes enough to induce clinically relevant bias in observed effect size;
- *'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;*
- *Potentially inappropriate application of simple imputation*

Criteria for the judgment of "UNCLEAR" (i.e. uncertain risk of bias)

- *Any one of the following:*
  - *Insufficient reporting of attrition/exclusions to permit judgment of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided);*
  - *The study did not address this outcome.*

Pharmaceutical Support

5. Did this study receive support (research funds, medications provided, writing services, author or staff was employee) from a company having a financial interest in any of the medications studied?

Select an Answer

6. If "Yes," did the company have any involvement in the design, conduct, or reporting of the study?
For "NO," the authors are not employees of the company and the authors had complete access to the data, and the company was not involved in the design, conduct, analysis, or reporting of the study.

Select an Answer

Overall Quality of Study

7. Please rate the overall quality of the study:

Select an Answer

Criteria for a judgment of "GOOD" (i.e. low risk of bias)

- *These studies have the least bias and results are considered valid*
- *A study that adheres mostly to the commonly held concepts of high quality including the following:*
  - *A formal randomized controlled study;*
  - *Clear description of the population, setting, interventions, and comparison groups;*
  - *Appropriate measurements of outcomes;*
  - *Appropriate statistical and analytic methods and reporting;*
  - *No reporting errors;*
  - *Low dropout rate; and*
  - *Clear reporting of dropouts*

Criteria for a judgment of "FAIR"

- *These studies are susceptible to some bias, but it is not sufficient to invalidate the results.*
- *Do not meet all the criteria required for a rating of good qualities because they have some deficiencies, but no flaw is likely to cause major bias.*
- *The study may be missing information, making it difficult to assess limitations and potential problems*

Criteria for a judgment of "POOR" (i.e. high risk of bias)

- *These studies have significant flaws that imply biases of various types that may invalidate the results.*
- *Have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.*

8. Were >20% of the study participants lost to followup at any of the following time points?

Select an Answer

9. Please add comments below.

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Rethnam U, Yesupalan RS, Sinha A.

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Insulin Pump Therapy With and Without Continuous Glucose Monitoring for Diabetes
Quality Form for Observational Trials

1. Did the study describe the setting or population from which the study sample was drawn?

   - Yes, complete description including an appropriate sampling scheme (consecutive, random)
   - Yes, but without description of sampling scheme or used a scheme that could bias results (convenience)
   - No or insufficient to replicate

2. Were the inclusion and exclusion criteria for subjects described?

   - Yes
   - No

3. Is there description of key characteristics of the enrolled subjects that could affect outcomes?

   - Yes- with detailed descriptions of covarietes expected to affect outcomes (e.g. age, duration of diabetes, other therapies)
   - Some description of covariates (e.g. age, sex)
   - No

4. Were the patients in each of the intervention groups or the cases and controls recruited from the same population?

   - Yes
   - No
   - Unclear

5. Are the results presented adjusted or stratified for differences in groups or stated that the groups were comparable at baseline?

   - Yes
   - No
   - Not applicable

6. Does the study describe the number of participants who were lost to follow-up after the start of the period of observation?

   - Yes
   - No
   - Not applicable (e.g. cross-sectional study)
   - Unclear

7. What percentage of patients was lost to follow-up?

   - <10% in any group
   - 10-20% in any group
   - >20%
   - Not reported

8. Please rate the overall quality of the study.

   - Good (low risk of bias). These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.

○ Fair. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

○ Poor (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

9. **Comments (limit 250 characters)**

10. **Comments (limit 250 characters)**

11. **Comments (limit 250 characters)**

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Appendix C. List of Devices

Appendix Table A. List of insulin pump models

Manufacturer	Model	Decision Date	Features
Abbott			
	Insulin Pump	12/23/05	Insulin pumps are indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.
	Aviator	1/11/08	The Aviator insulin pump shares the same intended use and indications for use as the predicate device, the Abbott Diabetes Care infusion pump. Both the Aviator infusion pump and the predicate pump have two microprocessors to control and monitor drug delivery. The user interface on the Aviator was enhanced as a result of user needs.
	Freestyle Aviator	2/20/09	Insulin pump and BGM system-insulin infusion pump (Aviator) and wireless remote controller (Aviator companion). Aviator companion provides an alternate user interface to the Aviator pump which is useful when pump is hidden under clothing.
Animas			
	Model IR 1000	2/10/00	Subcutaneous delivery of insulin at programmable basal and bolus rates.
	Model IR 1000 LR	05/29/02	Insulin infusion pump and software for histories, basal rate program, and pump settings.
	Model IR 1200	10/16/03	The system will deliver a prescribed dosage of insulin as a single programmable bolus or at multiple programmable basal rates. The system will also provide set-up information, dosage history, alarms, error and warning messages, device status, and self test capabilities.
	Model IR 1250	12/10/04	Insulin delivery system, basal and bolus programmable options, computer software (Mac or PC available), minor differences between this and 1200 series, including food item-insulin pairings.
Cane			
	Microjet Quark model U-100	12-12-01	Pump for insulin infusion therapy.
Cardiac Pacemakers, Inc.			
	Betatron IV insulin infusion system	2-23-90	No summary information.
Deltec/Smiths Medical			
	Deltec Cozmo® TM Insulin Infusion Pump (Model1700) and Accessories	8-13-02	Compared to: MiniMed Model 508 Insulin Pump, MiniMed 3.0-ml Reservoir, Deltec CADD-Diplomat System,and MiniMed Corn-StationTM Communication System.
	Deltec Cozmo® Insulin infusion pump w/ CoZmonitor® Glucose monitor	5-27-04	Insulin infusion pump and glucose monitor.
	Deltec Cozmo® Insulin Infusion Pump model 1800 w/ CoZmonitor®	12-1-06	Insulin infusion pump and glucose monitor.

Appendix Table A. List of insulin pump models

Manufacturer	Model	Decision Date	Features
Disetronic/ Roche			
	H-TRON™ V 100 insulin infusion pump	4-12-97	No summary information.
	H-TRON™plus V 100 insulin infusion pump	9-15-97	Functionally equivalent to previous model.
	DAHEDI insulin infusion pump	6-15-99	Basic infusion insulin pump.
	D-TRON™ insulin infusion pump	12-30-99	Equivalent to H-Tron Plus V100.
	D-TRON™ insulin infusion pump	8-2-02	Slight modifications.
	D-TRON™plus insulin pump	9-11-02	Slight modifications for D-TRON.
	D-TRON™plus modification	10-29-02	Slight modifications for D-TRONplus.
	D-TRON™plus modification	12-1-04	Slight modifications for D-TRONplus.
	ACCU-CHECK® Spirit	3-18-05	Infusion insulin pump.
	ACCU-CHEK® Spirit modification	6-15-06	Minor modifications.
Insulet			
	iXL™ Diabetes management system	12-19-03	Equivalent to Medtronic MiniMed. Insulin pump.
	iXL™-11 DMS	1-3-05	Insulin pump and blood glucose measurement system.
Mendigo			
	Solo™ insulin patch pump	7-3-09	Same as prior models, insulin pump.
	Solo™ MicroPump insulin-delivery system	1-25-10	Identical to prior Solo patch pump.
Medtronic Minimed			
	Model 506 external insulin pump	7-2-90	Insulin infusion pump.
	Infusion pump Model MMT-507	4-30-96	Insulin infusion pump.
	Insulin pump model 505	4-8-97	Insulin infusion pump, simplified software.
	Model 507C	8-15-97	Slight modification to model 507.
	Model 508	6-8-99	Insulin infusion pump.
	Paradigm® model 512 Insulin pump and BD Paradigm link Glucose monitor	6-17-03	Bolus and basal insulin pump and linked glucose monitor.
	Paradigm ®Model 511	7-19-04	Insulin infusion pump.

Appendix Table A. List of insulin pump models

Manufacturer	Model	Decision Date	Features
	Model MMT-712E	1-31-06	Insulin infusion pump.
	MMT- 512, MMT-712, MMT-515, and MMT-715	4-25-08	Continuous delivery insulin pumps.
NiliMedix			
	ADI	6-6-08	Ambulatory insulin infusion pump.
Nipro			
	Glucopro infusion pump	6-24-02	Equivalent to Disetronic H-Tron plus v100.
	Amigo ®	5-9-05	Insulin infusion pump.
	Amigo ®	12-14-07	Equivalent to Animas IR 1250.
Pharma-Plast			
	Pharma-Plast insulin infusion set	6-21-89	Insulin infusion pump.
Sooil			
	DANA Diabecare®	8-14-00	Insulin infusion pump (basal and bolus).
	DANA Diabecare® II	8-2-02	Software modifications to previous DANA.
	DANA Diabecare® IIS	2-2-07	Slight modifications to previous II.

Appendix Table B. List of continuous glucose monitors

Manufacturer	Model	Decision Date	Features
Abbott			
	FreeStyle Navigator®	3-12-08	18+ CGM system, alarms
	FreeStyle Navigator® supplements	4-2-08; 5-15-08; 5-21-08; 6-2-08; 8-6-08; 8-25-08; 10-8-08; 3-6-09; 4-9-09; 4-13-09; 5-8-09; 6-24-09; 8-21-09; 9-21-09; 9-25-09; 10-29-09; 11-20-09; 1-11-10; 1-19-10; 7-9-10	Minor modifications to original
Dexcom			
	STS® Continuous Glucose Monitor	3-24-06	Detects trends and tracks patterns in adults (18+); indicated for use as an adjunctive device to complement, not replace, standard glucose monitoring devices; aids in detection of hyperglycemia and hypoglycemia, facilitates both acute and long-term therapy adjustments
	STS® supplements; Seven plus system	5-31-07; 8-12-06; 9-1-06; 9-22-06; 12-26-06; 1-23-07; 2-26-07; 3-15-07; 4-10-07; 5-25-07; 10-22-07; 11-13-07; 1-11-08; 5-15-08; 7-16-08; 12-3-08; 2-13-09; 5-5-09; 9-17-09; 9-23-09; 12-4-09; 1-28-10; 6-9-10; 7-15-10; 8-25-10; 9-9-10	Various updates/modifications to the STS Continuous Glucose Monitor system
Medtronic Minimed			
	Continuous Glucose Monitoring System	6-15-99	Continuously records interstitial glucose levels; supplements, does not replace standard at home glucose monitors. Can download the information gathered through computer software
	Guardian® Telemetered Glucose Monitoring system	2-20-02; 6-25-02; 9-5-02	Continuous Glucose Monitor
	Guardian® Real Time Continuous Glucose Monitoring System	1-7-04	Hypo- and hyperglycemia alerts; up to 21 days stored data.
	Paradigm® Real Time System	7-18-05; 8-24-05	No summary information.

Appendix Table B. List of continuous glucose monitors

Manufacturer	Model	Decision Date	Features
	Guardian® Real Time	4-7-06	Slight modifications to enable continuous glucose monitor to communicate with insulin pump directly.
	Paradigm® RT	6-14-06	Modifications to monitor and transmitter; can manually enter calibration.
	Guardian® RT	10-16-06	Approval for use in Puerto Rico.
	Paradigm® RT and Guardian® RT	3-8-07	Pediatric use approved (ages 7–17 years) and adults (ages 18+ years).
	Minimed RT transmitter, CGM system	4-18-08; 8-21-09; 11-5-09; 12-1-09; 3-20-10; 4-5-10; 6-3-10; 9-9-10	Slight modifications.
	Continuous Glucose Monitoring System	4-23-08	Slight modifications.
		7-17-08; 8-28-08; 10-2-08; 10-3-08; 11-14-08; 11-20-08; 3-16-09; 6-16-09; 6-19-09; 8-13-09; 8-21-09; 10-1-09; 10-28-09; 10-29-09; 3-26-10; 6-10-10 8-23-10	Slight modifications.

Appendix D. List of Excluded Articles

Abaci, A., Atas, A., Unuvar, T., Demir, K., Bober, E., and Buyukgebiz, A. A comparison of multiple daily insulin therapy with continuous subcutaneous insulin infusion therapy in adolescents with type 1 diabetes mellitus: a single-center experience from Turkey. J Pediatr Endocrinol Metab 2009; 22(6):539-45.

No concurrent comparison group

Adamson, U. and Lins, P. E. [Insulin pump--25 years old and with a future. It counteracts development of late diabetic complications]. Lakartidningen 2002; 99(51-52):5168-70.

Other reason

Ahmann, A., Buse, J. B., Berganstal, R. M., and Tanenberg, R. HbA1c and sensor use in adults during a 1-year randomised controlled trial comparing sensor-augmented pump therapy and multiple daily injection therapy. Diabetologia 2010; 53:S401.

Case series or cross-sectional

Akhmedova, N. D., Akbarov, Z. S., and Turakulov IaKh [Effect of long-term subcutaneous infusion of insulin using an attached drug dosing device on indices of hemocoagulation in type I diabetes mellitus]. Probl Endokrinol (Mosk) 88; 34(5):11-Jul.

No outcome of interest

Albin, F., Dazet, D., and Haardt, M. J. [Placing of an insulin pump. Subcutaneous route]. Soins 85; (459-460):III-IV.

No original data

Albisser, A. M. and Zinman, B. Insulin dependent diabetes and the artificial pancreas. Med Prog Technol 82; 9(03-Feb):113-8.

No original data

Alemzadeh, R., Ellis, J. N., Holzum, M. K., Parton, E. A., and Wyatt, D. T. Beneficial effects of continuous subcutaneous insulin infusion and flexible multiple daily insulin regimen using insulin glargine in type 1 diabetes. Pediatrics 2004; 114(1):e91-5.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Alemzadeh, R., Loppnow, C., Parton, E., and Kirby, M. Glucose sensor evaluation of glycemic instability in pediatric type 1 diabetes mellitus. Diabetes Technol Ther 2003; 5(2):167-73.

Does not evaluate CSII or rt-CGM

Alemzadeh, R., Palma-Sisto, P., Parton, E. A., and Holzum, M. K. Continuous subcutaneous insulin infusion and multiple dose of insulin regimen display similar patterns of blood glucose excursions in pediatric type 1 diabetes. Diabetes Technol Ther 2005; 7(4):587-96.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Allen, N. A. Continuous glucose monitoring improved glucose control in adults but not in young adults or children with type 1 diabetes. Evid Based Nurs 2009; 12(2):44.

No comparison with placebo or usual care

Allen, N. A., Fain, J. A., Braun, B., and Chipkin, S. R. Continuous glucose monitoring counseling improves physical activity behaviors of individuals with type 2 diabetes: A randomized clinical trial. Diabetes Res Clin Pract 2008; 80(3):371-9.

Does not evaluate CSII or rt-CGM

Allouche, C., Barjot, P., Six, T., Muller, G., and Levy, G. [Insulin dependent diabetes and pregnancy: evaluation of the insulin pump]. J Gynecol Obstet Biol Reprod (Paris) 94; 23(6):706-11.

No outcome of interest

Altaf, K., Adu, J., Morrison, G., M. Nunes, Q., Halloran, C., Neoptolemos, J. P., Weston, C. P., and Sutton, R. Continuous subcutaneous insulin infusion (CSII) therapy for management of apancreatic diabetes mellitus. Pancreas 2010; 39(8):1307.

Other reason

Alvarez, M. G. and Donlo, I. C. Cost-utility of insulin pumps in the treatment of type 1 diabetes in Spain. When most expensive is best (or not): Coste-utilidad de las bombas de insulina en el tratamiento de la diabetes tipo 1 en Espana. Cuando lo mas caro puede ser lo mejor (o no). Endocrinol. Nutr. 2007; 54(2):73-75.

No original data

Amemiya, S., Kato, K., and Asayama, K. The improved response in endogenous insulin due to continuous subcutaneous infusion of insulin therapy in juvenile diabetes. Tohoku J Exp Med 83; 141 Suppl:713-7.
No comparison with placebo or usual care
Anderson, D. G. Multiple daily injections in young patients using the ezy-BICC bolus insulin calculation card, compared to mixed insulin and CSII. Pediatr Diabetes 2009; 10(5):304-9.
Does not apply to a key question
Anon. [Continuous blood glucose values. Monitoring around the clock]. MMW Fortschr Med 2002; 144(50):68-9.
No original data
Anon. [Report from experience: diabetics in the hospital]. Pflege Z 99; 52(10):693.
No original data
Anon. Acute mishaps during insulin pump treatment. Lancet 85; 1(8434):911-2.
No original data
Anon. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial. The Kroc Collaborative Study Group. N Engl J Med 84; 311(6):365-72.
No comparison with placebo or usual care
Anon. Collaborative studies of the effects of continuous subcutaneous insulin infusion in insulin-dependent diabetes mellitus. Conclusions. The Kroc Collaborative Study Group. Diabetes 85; 34 Suppl 3:87-9.
No original data
Anon. Diabetic retinopathy after two years of intensified insulin treatment. Follow-up of the Kroc Collaborative Study. The Kroc Collaborative Study Group. JAMA 88; 260(1):37-41.
No comparison with placebo or usual care
Anon. EASD Study Group Artificial Insulin Delivery Systems Pancreas and Islet Transplantation (AIDSPIT). Report of the 13th Workshop of the EASD Study Group AIDSPIT. Diabetologia 94; 37(8):suppl 33-7.
No original data
Anon. Effect of 6 months of strict metabolic control on eye and kidney function in insulin-dependent diabetics with background retinopathy. Steno study group. Lancet 82; 1(8264):121-4.
No comparison with placebo or usual care
Anon. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes (The New England Journal of Medicine (2010) 363, (311-20)). New Engl. J. Med. 2010; 363(11):1092.
Does not evaluate CSII or rt-CGM
Anon. Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care 95; 18(3):361-76.
Regular insulin was used in the pump
Anon. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. Diabetes Care 2001; 24(10):1711-21.
Does not apply to a key question
Anon. Insulin pump therapy and serum amyloid A. Lancet 84; 1(8381):853-4.
No original data
Anon. Long-term therapy with insulin pumps assessed. PHARM. PRACT. NEWS 85; 12(11):12.
No concurrent comparison group
Anon. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. Ophthalmology 95; 102(4):647-61.
Not in an outpatient setting
Anon. Psychological aspects of continuous glucose monitoring in pediatric type 1 diabetes. Pediatr Diabetes 2006; 7(1):32-8.
Other reason
Anon. Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial(Diabetes Care (2010) 33, (2175-2177)). Diabetes Care 2010; 33(12):2725.
Other reason
Anon. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007; 50(6):1140-7.
Does not evaluate CSII or rt-CGM
Anon. Strict metabolic control and eye and kidney function in diabetes. Lancet 82; 1(8272):630-1.
No original data
Anon. The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group. Ann Intern Med 95; 122(8):561-8.
Does not evaluate CSII or rt-CGM

Anon. Update: deaths among patients using continuous subcutaneous insulin infusion pumps--United States. MMWR Morb Mortal Wkly Rep 82; 31(46):625-6.

No original data

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No comparison with placebo or usual care

Arias, P., Kerner, W., Zier, H., Navascues, I., and Pfeiffer, E. F. Incidence of hypoglycemic episodes in diabetic patients under continuous subcutaneous insulin infusion and intensified conventional insulin treatment: assessment by means of semiambulatory 24-hour continuous blood glucose monitoring. Diabetes Care 85; 8(2):134-40.

Less than 24 hours of usage

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No original data

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No formal diagnosis

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No concurrent comparison group

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Case series or cross-sectional

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No original data

Barnard, K. D. and Skinner, T. C. Cross-sectional study into quality of life issues surrounding insulin pump use in type 1 diabetes. Pract. Diabetes Int. 2008; 25(5):194-200.

Case series or cross-sectional

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No original data

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Case series or cross-sectional

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No comparison with placebo or usual care

Beck, R. W., Hirsch, I. B., Laffel, L., Tamborlane, W. V., Bode, B. W., Buckingham, B., Chase, H. P., Clemons, R., Fiallo-Scharer, R., Fox, L. A., Gilliam, L. K., Huang, E. S., Kollman, C., Kowalski, A. J., Lawrence, J. M., Lee, J., Mauras, N., O'Grady, M Juvenile diabetes research foundation continuous glucose monitoring study group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes (Diabetes Care (2009) 32, (1378-1383)). Diabetes Care 2009; 32(10):1944.

Other reason

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No comparison with placebo or usual care

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Case series or cross-sectional

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

Belicar, P. and Lassmann-Vague, V. Local adverse events associated with long-term treatment by implantable insulin pumps. The French EVADIAC Study Group experience. Evaluation dans le Diabete du Traitement par Implants Actifs. Diabetes Care 98; 21(2):325-6.

Case series or cross-sectional

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No concurrent comparison group

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Case series or cross-sectional

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No original data

Bending, J. J., Pickup, J. C., and Keen, H. Treatment with insulin pumps versus intensive conventional treatment. BR. MED. J. 84; 289(644 O):320-321.

No original data

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No comparison with placebo or usual care

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Other reason

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No original data

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Case series or cross-sectional

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No comparison with placebo or usual care

Bergis, K. H. [Patients' experiences with insulin lispro in daily use. Yesterday's innovation--today's standard therapy]. Krankenpfl J 99; 37(9):347-9.

No original data

Bergis, K., Otto, K., and Mann, M. [Painful polyneuropathy in type I diabetes: intermediate insulin-pump therapy]. Dtsch Med Wochenschr 86; 111(12):477-8.

Case series or cross-sectional

Bergman, M. and Felig, P. Newer approaches to the control of the insulin-dependent diabetic patient. Dis Mon 83; 29(7):Jan-65.

No original data

Bergua, M., Levy, I., Casamitjana, R., and Figuerola, D. [Therapeutic hyperinsulinism induced by the use of continuous insulin infusion pumps and the artificial pancreas in diabetic patients]. Med Clin (Barc) 83; 81(6):243-5.

Other reason

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No comparison with placebo or usual care

Bernsmeier, H. and Sonnenberg, G. E. [Diabetic retinopathy with continuous subcutaneous insulin infusion therapy (insulin pump)]. Fortschr Ophthalmol 84; 81(3):267-70.

Case series or cross-sectional

Bernsmeier, H., Cicmir, I., Koschinski, T., and Gries, F. A. [Comparison of the development of retinopathy in treatment with the insulin pump and intensified conventional therapy]. Fortschr Ophthalmol 86; 83(4):467-70.

No comparison with placebo or usual care

Berthe, E., Lireux, B., Coffin, C., Goulet-Salmon, B., Houlbert, D., Boutreux, S., Fradin, S., and Reznik, Y. Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. Horm Metab Res 2007; 39(3):224-9.

Other reason

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No concurrent comparison group

Biesenbach, G., Grafinger, P., Kaiser, W., Stuby, U., and Zazgornik, J. [Metabolic control in labile type I diabetes with conventional insulin therapy, basal bolus insulin therapy using pens and continuous subcutaneous insulin infusion with the pump]. Med Klin (Munich) 88; 83(12):398-401.

No concurrent comparison group

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No comparison with placebo or usual care

Bin-Abbas, B. S., Al-Fares, A., Sakati, N. A., and Al-Ashwal, A. A. Comparison of insulin pump and multiple daily injection regimens in type 1 diabetic patients. Curr. Paediatr. Res. 2006; 10(02-Jan):37-39.

Other reason

Bin-Abbas, B. S., Sakati, N. A., and Al-Ashwal, A. A. Glycemic control and treatment satisfaction in Saudi diabetic children on insulin pump therapy [5]. Ann. Saudi Med. 2006; 26(3):247-248.

No concurrent comparison group

Bin-Abbas, B. S., Sakati, N. A., and Al-Ashwal, A. A. Glycemic control and treatment satisfaction in Saudi diabetic children on insulin pump therapy. Ann Saudi Med 2006; 26(5):405.

No concurrent comparison group

Birman, P. [Conventional insulin therapy, infusion pumps, injector syringes. Different methods of administration]. Soins 89; (524):30-5.

No original data

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Case series or cross-sectional
Bloomgarden, Z. T. Aspects of insulin treatment. Diabetes Care 2010; 33(1):e1-6.
No original data
Bode, B. W. Clinical utility of the continuous glucose monitoring system. Diabetes Technol Ther 2000; 2 Suppl 1:S35-41.
Case series or cross-sectional
Boizel, R., Benhamou, P. Y., and Renard, E. Glucose monitoring and pump data management software operated on a personal digital assistant can contribute to improve diabetes control in CSII-treated patients. Diabetes Metab 2007; 33(4):314-5.
Does not evaluate CSII or rt-CGM
Boland, E. A flexible option for adolescents with diabetes. Insulin pump therapy. Adv Nurse Pract 98; 6(2):38-44.
No original data
Boland, E. A. and Tamborlane, W. V. Continuous glucose monitoring in youth with type 2 diabetes: overcoming barriers to successful treatment. Diabetes Technol Ther 2000; 2 Suppl 1:S53-9.
No original data
Boland, E. A., Grey, M., Oesterle, A., Fredrickson, L., and Tamborlane, W. V. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. Diabetes Care 99; 22(11):1779-84.
Regular insulin was used in the pump
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Case series or cross-sectional
Borisova, A. M., Koev, D., and Kirilov, G. [An improvement in insulin efficacy in patients with type-1 diabetes mellitus following treatment using an insulin infusion pump]. Vutr Boles 89; 28(1):74-7.
Regular insulin was used in the pump
Botta, R. M., Sinagra, D., Angelico, M. C., and Bompiani, G. D. [Comparison of intensified traditional insulin therapy and micropump therapy in pregnant women with type 1 diabetes mellitus]. Minerva Med 86; 77(17):657-61.
Regular insulin was used in the pump
Bougneres, P. F. [Are there indications for treatment with the insulin pump in pediatrics?]. Diabete Metab 85; 11(5):320-1.
No original data
Bougneres, P. F. [Intensive insulin therapy in the diabetic child]. Union Med Can 85; 114(10):821-8.
No original data
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Case series or cross-sectional
Boulton, A. J. M., Drury, J., and Ward, J. D. Treatment of painful and ulcerative diabetic neuropathy by continuous subcutaneous insulin infusion (CSII). DIABETOLOGIA 81; 21(3):67.
Other reason
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Other reason
Bozzetti, V., Viscardi, M., Bonfanti, R., Azzinari, A., Meschi, F., Bognetti, E., and Chiumello, G. Results of continuous glucose monitoring by GlucoWatch Biographer in a cohort of diabetic children and adolescents under real-life conditions. Pediatr Diabetes 2003; 4(1):57-8.
No original data
Bradley, C. On calculating treatment satisfaction. Diabetes Care 99; 22(10):1760.
Case series or cross-sectional
Bradley, C., Gamsu, D. S., Knight, G., Boulton, A. J., and Ward, J. D. Predicting risk of diabetic ketoacidosis in patients using continuous subcutaneous insulin infusion. Br Med J (Clin Res Ed) 86; 293(6541):242-3.
Does not evaluate CSII or rt-CGM

Bragd, J., Adamson, U., Lins, P.-E., Dobeln, A. V., and Oskarsson, P. Basal insulin substitution with glargine or CSII in adult type 1 diabetes patients - A randomized controlled trial. Diabetes 2009; 58:.

Case series or cross-sectional

Bragd, J., von Dobeln, A., Lins, P. E., Adamson, U., Bergstrom, J., and Oskarsson, P. Basal insulin substitution with glargine or continuous subcutaneous insulin infusion in adult type 1 diabetes patients-a randomized controlled trial. Diabetes Technol Ther 2010; 12(9):689-93.

No comparison with placebo or usual care

Brange, J. and Langkjaer, L. Insulin formulation and delivery. Pharm Biotechnol 97; 10:343-409.

No original data

Brinchmann-Hansen, O., Dahl-Jorgensen, K., Hanssen, K. F., and Sandvik, L. Effects of intensified insulin treatment on retinal vessels in diabetic patients. Br J Ophthalmol 88; 72(9):666-73.

Regular insulin was used in the pump

Brinchmann-Hansen, O., Dahl-Jorgensen, K., Hanssen, K. F., and Sandvik, L. Effects of intensified insulin treatment on various lesions of diabetic retinopathy. Am J Ophthalmol 85; 100(5):644-53.

Regular insulin was used in the pump

Brinchmann-Hansen, O., Dahl-Jorgensen, K., Hanssen, K. F., and Sandvik, L. Oscillatory potentials, macular recovery time, and diabetic retinopathy through 3 years of intensified insulin treatment. Ophthalmology 88; 95(10):1358-66.

Regular insulin was used in the pump

Brinchmann-Hansen, O., Dahl-Jorgensen, K., Hanssen, K. F., and Sandvik, L. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. Arch Ophthalmol 88; 106(9):1242-6.

Regular insulin was used in the pump

Brink, S. J. Diabetic ketoacidosis: prevention, treatment and complications in children and adolescents. Diabetes Nutr Metab 99; 12(2):122-35.

No original data

Brink, S. K. and Stewart, C. Insulin pumps no advantage in young diabetics. CURR. THER. 87; 28(7):200.

No original data

Brunetti, P., Bueti, A., Antonella, M. A., Calabrese, G., Fabietti, P. G., Santeusanio, F., and Massi Benedetti, M. Metabolic effects of intensified insulin therapy. Exp Clin Endocrinol 84; 83(2):130-5.

Regular insulin was used in the pump

Brynes, A. E., Lee, J. L., Brighton, R. E., Leeds, A. R., Dornhorst, A., and Frost, G. S. A low glycemic diet significantly improves the 24-h blood glucose profile in people with type 2 diabetes, as assessed using the continuous glucose MiniMed monitor. Diabetes Care 2003; 26(2):548-9.

No original data

Burkart, W., Hanker, J. P., and Schneider, H. P. Complications and fetal outcome in diabetic pregnancy. Intensified conventional versus insulin pump therapy. Gynecol Obstet Invest 88; 26(2):104-12.

Not in an outpatient setting

Buysschaert, M., Lejeune, M., and Lambert, A. E. [Treatment of insulin-dependent diabetes by continuous subcutaneous infusion of insulin (author's transl)]. Ann Endocrinol (Paris) 81; 42(3):293-4.

Other reason

Buysschaert, M., Lejeune, M., and Lambert, A. E. Treatment of juvenile diabetes with continuous subcutaneous insulin infusion (CSII). DIABETOLOGIA 80; 19(3):262.

Not in an outpatient setting

Buysschaert, M., Marchand, E., and Ketelslegers, J. M. Comparison of continuous subcutaneous insulin infusion (CSII) and intensified conventional insulin therapy (ICII) in type 1 diabetes. DIABETOLOGIA 81; 21(3):84.

Not in an outpatient setting

C⌠tΘ B, St-Hilaire C Comparison of the insulin pump and multiple daily injections in intensive therapy for Type 1 diabetes. Montreal, PQ, CAnada: Agence d'evaluation des technologies et des modes d'intervention en sante (AETMIS) 2005; :.

No original data

Calabrese, G., Bueti, A., Santeusanio, F., Giombolini, A., Zega, G., Bellomo, G., Antonella, M. A., Angeletti, G., Massi-Benedetti, M., and Brunetti, P. Hormonal and metabolic profiles in insulin-dependent diabetics under subcutaneous conventional and artificial endocrine pancreas (glucose continuous insulin infusion system Biostator) treatment. J Endocrinol Invest 83; 6(1):08-Jan.

No outcome of interest

Calle Pascual, A. L. and Charro Salgado, A. L. [Clinical course of advanced microvascular complications in diabetic patients undergoing long-term treatment with the subcutaneous insulin infusion pump]. Med Clin (Barc) 83; 81(20):904-7.

Other reason

Cander, S., Kiyici, S., Deligonul, A., Gul, O. O., Unal, O. K., Sakalli, M., Tuncel, E., and Imamoglu, S. Treatment efficacy of subcutaneous insulin infusion therapy in type 1 diabetic patients: Cilt alti insulin infuzyon tedavisinin tip 1 diyabetik hastalarda tedavi etkinligi. Turk. J. Endocrinol. Metab. 2010; 14(4):80-84.

Other reason

Canny, C. L., Kohner, E. M., Trautman, J., Puklin, J., and Morse, P. Comparison of stereofundus photographs in patients with insulin-dependent diabetes during conventional insulin treatment or continuous subcutaneous insulin infusion. Diabetes 85; 34 Suppl 3:50-5.

No comparison with placebo or usual care

Capani, F., Consoli, A., Vitacolonna, E., and Sensi, S. [Semisynthetic human insulin therapy of type 1 diabetics treated with a microinfusor. Preliminary notes on insulin requirements and antibody titer]. Minerva Endocrinol 84; 9(2):167-71.

Other reason

Carino, C., Tiboni, G. M., Fontana, M., and De Martiis, M. [Modern technologic accomplishments in the therapeutic treatment of diabetes mellitus: the artificial pancreas and micropumps]. Clin Ter 84; 109(2):173-7.

No original data

Carta, Q., Meriggi, E., and Trossarelli, G. F. Maternal and fetal metabolic control in diabetic pregnant women treated by continuous subcutaneous insulin infusion (CSII). DIABETOLOGIA 82; 23(3):294.

Case series or cross-sectional

Carta, Q., Meriggi, E., Trossarelli, G. F., Catella, G., Dal Molin, V., Menato, G., Gagliardi, L., Massobrio, M., and Vitelli, A. Continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in type I and type II diabetic pregnancy. Diabete Metab 86; 12(3):121-9.

Regular insulin was used in the pump

Casas-Onate, M. L. and Montoya-Martinez, D. [Influence of the treatment with continuous subcutaneous insulin infusion (CSII) in the improvement of the quality of life of patients with type 1 diabetes mellitus]. Enferm Clin 2010; 20(4):216-21.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Casson, I. F., Clarke, C. A., Howard, C. V., McKendrick, O., Pennycook, S., Pharoah, P. O., Platt, M. J., Stanisstreet, M., van Velszen, D., and Walkinshaw, S. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. BMJ 97; 315(7103):275-8.

Does not evaluate CSII or rt-CGM

Castillo, M. J., Scheen, A. J., and Lefebvre, P. J. Treatment with insulin infusion pumps and ketoacidotic episodes: from physiology to troubleshooting. Diabetes Metab Rev 95; 11(2):161-77.

Does not apply to a key question

Cavallo, M. G., Romeo, S., Coppolino, G., and Pozzilli, P. Continuous glucose monitoring during the European Soccer cup semifinal, Italy against Holland. Diabetologia 2001; 44(2):268.

Does not evaluate CSII or rt-CGM

Cavallo-Perin, P., Pagano, G., Tagliaferro, V., Jarre, P., Ozzello, A., and Lenti, G. The treatment of unstable type I diabetes: conventional versus portable pump insulin administration. Acta Diabetol Lat 83; 20(4):363-70.

No concurrent comparison group

Champion, M. C., Bending, J. J., Rodger, N. W., and Bilous, R. W. Conference on insulin pump therapy in diabetes. Multicenter study of effect on microvascular disease. Recruitment, Randomization, and baseline characteristics of the treatment groups. Diabetes 85; 34 Suppl 3:13-6.

No outcome of interest

Champion, M. C., Keen, H., Pickup, J. C., Tamborlane, W. V., and Dupre, J. Conference on insulin pump therapy in diabetes. Multicenter study of effect on microvascular disease. Origin and design of the Kroc Collaborative Study. Diabetes 85; 34 Suppl 3:12-May.

Other reason

Chandler, P. T. and Chandler, S. A. Outpatient self-management of severe diabetes. South Med J 81; 74(9):1061-4.

Does not apply to a key question

Chantelau, E. and Wichmann, P. Pathological proteinuria in patients with insulin-dependent diabetes mellitus: relation to intensive insulin therapy. Exp Clin Endocrinol 92; 99(3):164-8.

Regular insulin was used in the pump

Chantelau, E., Schiffers, T., Schutze, J., and Hansen, B. Effect of patient-selected intensive insulin therapy on quality of life. Patient Educ Couns 97; 30(2):167-73.

No comparison with placebo or usual care

Chase, H. P., Beck, R. W., Xing, D., Tamborlane, W. V., Coffey, J., Fox, L. A., Ives, B., Keady, J., Kollman, C., Laffel, L., and Ruedy, K. J. Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Technol Ther 2010; 12(7):507-15.

No comparison with placebo or usual care

Chase, H. P., Roberts, M. D., Wightman, C., Klingensmith, G., Garg, S. K., Van Wyhe, M., Desai, S., Harper, W., Lopatin, M., Bartkowiak, M., Tamada, J., and Eastman, R. C. Use of the GlucoWatch biographer in children with type 1 diabetes. Pediatrics 2003; 111(4 Pt 1):790-4.

Does not evaluate CSII or rt-CGM

Chen, R., Ben-Haroush, A., Weismann-Brenner, A., Melamed, N., Hod, M., and Yogev, Y. Level of glycemic control and pregnancy outcome in type 1 diabetes: a comparison between multiple daily insulin injections and continuous subcutaneous insulin infusions. Am J Obstet Gynecol 2007; 197(4):404.e1-5.

Regular insulin was used in the pump

Chiasson, J. L., Ducros, F., Poliquin-Hamet, M., Lopez, D., Lecavalier, L., and Hamet, P. Continuous subcutaneous insulin infusion (Mill-Hill Infuser) versus multiple injections (Medi-Jector) in the treatment of insulin-dependent diabetes mellitus and the effect of metabolic control on microangiopathy. Diabetes Care 84; 7(4):331-7.

Regular insulin was used in the pump

Chiasson, J. L., Lecavalier, L., Ducros, F., and Hamet, P. [The insulin pump as treatment of the insulin-dependent diabetic]. Union Med Can 85; 114(10):837-9.

Regular insulin was used in the pump

Childs, B. P. Insulin infusion pumps: new solution to an old problem. Nursing 83; 13(11):54-7.

No original data

Chimenti, E. M., de la Morena, L. H., Vaquero, P. M., Saez-de-Ibarra, L., Dominguez, M. G., and Sanchez, L. F. Assessing glycaemic variability with continuous glucose monitoring system before and after continuous subcutaneous insulin infusion in people with Type 1 diabetes. Diabetes Res Clin Pract 2010; :.

No concurrent comparison group

Chobot, A. P., Deja, G., Marcinkowski, A., Myrda, A., Minkina-Pedras, M., Jarosz-Chobot, P., and Otto-Buczkowska, E. [Treatment of type 1 diabetes mellitus revealed below 7 years of age in the Diabetes Center of Silesia, Poland]. Pediatr Endocrinol Diabetes Metab 2007; 13(2):75-8.

No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No original data

Close, C. F., Collins, A., Gregory, W., Goodwin, A., Hill, C., Jarrett, R. J., Jones, S. L., Keen, H., Scott, G. S., Viberti, G., Vora, H., Yip, J., Grenfell, A., Sampson, M. J., Watkins, P. J., Fishwick, C., Gatling, W., Hill, R. D., Marshall, S. M., Coa Predictors of the development of microalbuminuria in patients with type I diabetes mellitus: A seven-year prospective study. Diabetic Med. 99; 16(11):918-925.

Does not evaluate CSII or rt-CGM

Cohen, C. D. Nocturnal hypoglycemia in patients treated with continuous subcutaneous insulin infusion. Am J Obstet Gynecol 88; 159(2):536-7.

Case series or cross-sectional

Cohen, O., Korner, A., Chlup, R., Zoupas, C. S., Ragozin, A. K., Wudi, K., Bartaskova, D., Pappas, A., Niederland, T., Taybani, Z., Barak, L., and Vazeou, A. Improved glycemic control through continuous glucose sensor-augmented insulin pump therapy: prospective results from a community and academic practice patient registry. J Diabetes Sci Technol 2009; 3(4):804-11.

No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No original data

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Case series or cross-sectional

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Does not evaluate CSII or rt-CGM

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No comparison with placebo or usual care

Coustan, D. R., Reece, E. A., Sherwin, R. S., Rudolf, M. C., Bates, S. E., Sockin, S. M., Holford, T., and Tamborlane, W. V. A randomized clinical trial of the insulin pump vs intensive conventional therapy in diabetic pregnancies. JAMA 86; 255(5):631-6.

No comparison with placebo or usual care

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No comparison with placebo or usual care

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Case series or cross-sectional

Cyganek, K., Hebda-Szydlo, A., Katra, B., Skupien, J., Klupa, T., Janas, I., Kaim, I., Sieradzki, J., Reron, A., and Malecki, M. T. Glycemic control and selected pregnancy outcomes in type 1 diabetes women on continuous subcutaneous insulin infusion and multiple daily injections: the significance of pregnancy planning. Diabetes Technol Ther 2010; 12(1):41-7.

Regular insulin was used in the pump

Cyganek, K., Hebda-Szydlo, A., Katra, B., Skupien, J., Klupa, T., Janas, I., Kaim, I., Sieradzki, J., Reron, A., and Malecki, M. T. Pregnancy planning improves glycemic control and pregnancy outcomes in type 1 diabetes women on CSII and MDI. Eur. J. Clin. Invest. 2010; 40:8.

Case series or cross-sectional

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Regular insulin was used in the pump

Dahl-Jorgensen, K., Brinchmann-Hansen, O., Hanssen, K. F., Ganes, T., Kierulf, P., Smeland, E., Sandvik, L., and Aagenaes, O. Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. Br Med J (Clin Res Ed) 86; 293(6556):1195-9.

Regular insulin was used in the pump

Dahl-Jorgensen, K., Brinchmann-Hansen, O., Hanssen, K. F., Sandvik, L., and Aagenaes, O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J (Clin Res Ed) 85; 290(6471):811-5.

Regular insulin was used in the pump

Dahl-Jorgensen, K., Hanssen, K. F., Aagenaes, O., and Larsen, S. [New methods for subcutaneous insulin administration. A year's experience with the insulin pump and multiple insulin injection therapy]. Tidsskr Nor Laegeforen 84; 104(13):856-61.

Regular insulin was used in the pump

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Regular insulin was used in the pump

Dandona, P., Besterman, H. S., and Freedman, D. B. Continuous subcutaneous infusion of insulin (CSII) during pregnancy and fetal size. PRACT. DIABETES 86; 3(1):33-35.

No comparison with placebo or usual care

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No original data

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No comparison with placebo or usual care

de Beaufort, C. E., Bruining, G. J., Aarsen, R. S., den Boer, N. C., and Grose, W. F. Does continuous subcutaneous insulin infusion (CSII) prolong the remission phase of insulin-dependent diabetic children? Preliminary findings of a randomized prospective study. Neth J Med 85; 28 Suppl 1:53-4.

No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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Other reason

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No original data

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No concurrent comparison group

Dedov, I. I. [Biotechnological methods in the treatment of diabetes mellitus]. Sov Med 89; (9):82-4.

Other reason

DeHaven, J. W. Effecting better insulin control with the portable infusion pump. J Med Assoc Ga 82; 71(3):183-5.

No original data

Deiss, D., Kordonouri, O., Meyer, K., and Danne, T. Long hypoglycaemic periods detected by subcutaneous continuous glucose monitoring in toddlers and pre-school children with diabetes mellitus. Diabet Med 2001; 18(4):337-8.

Does not apply to a key question

Delcroix, C. [Care of type 1 diabetes in children and adolescents]. Soins Pediatr Pueric 2009; (248):19-21.

Other reason

Delvecchio, M., Zecchino, C., Salzano, G., Faienza, M. F., Cavallo, L., De Luca, F., and Lombardo, F. Effects of moderate-severe exercise on blood glucose in Type 1 diabetic adolescents treated with insulin pump or glargine insulin. J Endocrinol Invest 2009; 32(6):519-24.

Does not apply to a key question

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Regular insulin was used in the pump

DiMeglio, L. A., Pottorff, T. M., Boyd, S. R., France, L., Fineberg, N., and Eugster, E. A. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. J Pediatr 2004; 145(3):380-4.

No comparison with placebo or usual care

Dokus, K., Dokusova, S., Martinka, E., Matusek, J., Zubor, P., and Danko, J. Insulin pump therapy and metabolic goals in pregnancies complicated by type 1 diabetes mellitus. Int. J. Gynecol. Obstet. 2009; 107:S440.

Case series or cross-sectional

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No comparison with placebo or usual care

Ehrhardt, N. M., Chellappa, M., Walker, M. S., Fonda, S. J., and Vigersky, R. A. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. J Diabetes Sci Technol 2011; 5(3):668-75.

Other reason

Eichner, H. L., Selam, J. L., Holleman, C. B., Worcester, B. R., Turner, D. S., and Charles, M. A. Reduction of severe hypoglycemic events in type I (insulin dependent) diabetic patients using continuous subcutaneous insulin infusion. Diabetes Res 88; 8(4):189-93.

No concurrent comparison group

Emelyanov, A., Kuraeva, T., and Peterkova, V. CSII with real time continuous glucose monitoring versus raditional CSII: The comparative results. Pediatr. Diabetes 2009; 10:101.

Case series or cross-sectional

Emelyanov, A., Kuraeva, T., and Peterkova, V. CSII with real time continuous glucose monitoring vs. traditional CSII: Two year comparative results. Horm. Res. Paediatr. 2010; 74:57.

Other reason

Exelbert, L. L. Safety of insulin pumps, even in adolescent use, depends on thorough patient selection, evaluation, and education. Pediatrics 2008; 122(3):682; author reply 682-3.

Case series or cross-sectional

Fahlen, M., Eliasson, B., and Oden, A. Optimization of basal insulin delivery in Type 1 diabetes: a retrospective study on the use of continuous subcutaneous insulin infusion and insulin glargine. Diabet Med 2005; 22(4):382-6.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Faro, B. Maintaining good control in children with diabetes. Pediatr Nurs 83; 9(5):368-73.

No original data

Feldberg, D., Dicker, D., Samuel, N., Peleg, D., Karp, M., and Goldman, J. A. Intrapartum management of insulin-dependent diabetes mellitus (IDDM) gestants. A comparative study of constant intravenous insulin infusion and continuous subcutaneous insulin infusion pump (CSIIP). Acta Obstet Gynecol Scand 88; 67(4):333-8.

Regular insulin was used in the pump

Feldt-Rasmussen, B., Mathiesen, E. R., and Deckert, T. Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. Lancet 86; 2(8519):1300-4.

Regular insulin was used in the pump

Feldt-Rasmussen, B., Mathiesen, E. R., Hegedus, L., and Deckert, T. Kidney function during 12 months of strict metabolic control in insulin-dependent diabetic patients with incipient nephropathy. N Engl J Med 86; 314(11):665-70.

No comparison with placebo or usual care

Felig, P., Tamborlane, W., Sherwin, R. S., and Genel, M. Infusion-pump treatment of diabetes mellitus. N Engl J Med 79; 301(5):268-9.

No original data

Felsing, W., Bibergeil, H., Menzel, R., Albrecht, G., Felsing, U., Dabels, J., Reichel, G., and Luder, C. Results of treatment with continuous subcutaneous insulin infusion (CSII) in insulin-dependent (type I) diabetics. Exp Clin Endocrinol 84; 83(2):136-42.

No comparison with placebo or usual care

Fenichel, P., Verdino, P., Melandri, E., Boutte, P., Gillet, J. Y., and Harter, M. [Pregnancy in diabetics. Efficacy and tolerability of the portable insulin pump]. Presse Med 83; 12(16):1020-1.

Other reason

Festin, M. R. Continuous glucose monitoring in gestational diabetes. BMJ 2008; 337(7675):886-887.

No original data

Fiallo-Scharer, R., Cheng, J., Beck, R. W., Buckingham, B. A., Chase, H. P., Kollman, C., Laffel, L., Lawrence, J. M., Mauras, N., Tamborlane, W. V., Wilson, D. M., and Wolpert, H. Factors predictive of severe hypoglycemia in type 1 diabetes: analysis from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized control trial dataset. Diabetes Care 2011; 34(3):586-90.

Does not apply to a key question

Fischer, U. Fundamentals of glucose sensors. Diabet Med 91; 8(4):309-21.

No original data

Fischl, A. R., Conway, B. N., and Orchard, T. J. Time trends in intensive insulin therapy and self monitoring in type 1 diabetes. Diabetes 2009; 58:.

Case series or cross-sectional

Fish, L. H., Wetzler, H. P., Davidson, J. L., Ofstead, C. L., and Johnson, M. L. Advanced Insulin Management program reduces A1C levels and regimen-related distress without weight gain in patients with type 1 diabetes mellitus. Insulin 2008; 3(2):59-66.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Fisher, B. M. Insulin infusion in diabetic patients with acute myocardial infarction. Effective components of care and patients who might benefit must be determined. BMJ 97; 314(7074):145; author reply 146.

No original data

Flores d'Arcais, A., Morandi, F., Beccaria, L., Meschi, F., and Chiumello, G. Metabolic control in newly diagnosed type 1 diabetic children. Effect of continuous subcutaneous infusion. Horm Res 84; 19(2):65-9.

Regular insulin was used in the pump

Fox, L. A., Buckloh, L. M., Smith, S. D., Wysocki, T., and Mauras, N. A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. Diabetes Care 2005; 28(6):1277-81.

No comparison with placebo or usual care

Fox, L., Englert, K., and Mauras, N. Effects of continuous subcutaneous insulin infusion (CSII) in adolescents with newly-diagnosed type 1 diabetes (T1D) on insulin resistance and ss-cell function: A pilot study. Diabetes 2009; 58:.

Case series or cross-sectional

Franciosi, M., Maione, A., Pomili, B., Amoretti, R., Busetto, E., Capani, F., Bruttomesso, D., Di Bartolo, P., Girelli, A., Leonetti, F., Morviducci, L., Ponzi, P., Vitacolonna, E., and Nicolucci, A. Correlates of quality of life in adults with type 1 diabetes treated with continuous subcutaneous insulin injection. Nutr Metab Cardiovasc Dis 2010; 20(1):14-Jul.

No comparison with placebo or usual care

Fredholm, N., Vignati, L., and Brown, S. Insulin pumps. The patients' verdict. Am J Nurs 84; 84(1):36-8.

No original data

Frier, B. Hypoglycemia and continuous blood glucose monitoring in older adults. Diabetic Hypoglycemia 2010; 3(2):11.

Other reason

Gabbe, S. G., Holing, E., Temple, P., and Brown, Z. A. Benefits, risks, costs, and patient satisfaction associated with insulin pump therapy for the pregnancy complicated by type 1 diabetes mellitus. Am J Obstet Gynecol 2000; 182(6):1283-91.

Regular insulin was used in the pump

Galletti, P. M. and Altman, J. J. Extracorporeal treatment of diabetes in man. Trans Am Soc Artif Intern Organs 84; 30:675-7.

No original data

Gambardella, S., Napoli, A., Verrastro, A. M., Spallone, V., Felici, M. G., Geraldini, C., and Menzinger, G. [Improvement in peripheral and autonomic neuropathy during 18 months of treatment with subcutaneous continuous insulin infusion in type 1 diabetics]. Minerva Endocrinol 84; 9(2):91-4.

Other reason

Garcia, C., Mayaudon, H., Bordier, L., Le Berre, J. P., Dupuy, O., and Bauduceau, B. [Modifications of 24-h blood pressure profile associated with reduction of the heart rate variability in type 1 diabetic patients]. Arch Mal Coeur Vaiss 2007; 100(8):699-703.

Does not evaluate CSII or rt-CGM

Garg, S. and Jovanovic, L. Relationship of fasting and hourly blood glucose levels to HbA1c values: safety, accuracy, and improvements in glucose profiles obtained using a 7-day continuous glucose sensor. Diabetes Care 2006; 29(12):2644-9.

No comparison with placebo or usual care

Garg, S. K. Impact of insulin delivery devices in diabetes care. Diabetes Technol Ther 2010; 12 Suppl 1:S1-3.

No original data

Garg, S. K. Role of emerging new technologies. Diabetes Technol Ther 2008; 10(5):413-4.

No comparison with placebo or usual care

Garg, S. K., Kelly, W. C., Voelmle, M. K., Ritchie, P. J., Gottlieb, P. A., McFann, K. K., and Ellis, S. L. Continuous home monitoring of glucose: improved glycemic control with real-life use of continuous glucose sensors in adult subjects with type 1 diabetes. Diabetes Care 2007; 30(12):3023-5.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Garg, S. K., Voelmle, M. K., Beatson, C. R., Miller, H. A., Crew, L. B., Freson, B. J., and Hazenfield, R. M. Use of Continuous Glucose Monitoring in Subjects With Type 1 Diabetes on Multiple Daily Injections Versus Continuous Subcutaneous Insulin Infusion Therapy: A prospective 6-month study. Diabetes Care 2011; 34(3):574-9.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Garg, S. K., Voelmle, M. K., Beatson, C. R., Miller, H. A., Crew, L. B., Freson, B. J., and Hazenfield, R. M. Use of continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy: a prospective 6-month study. Diabetes Care 2011; 34(3):574-9.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Garg, S. K., Walker, A. J., Hoff, H. K., D'Souza, A. O., Gottlieb, P. A., and Chase, H. P. Glycemic parameters with multiple daily injections using insulin glargine versus insulin pump. Diabetes Technol Ther 2004; 6(1):15-Sep.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Garg, S., Zisser, H., Schwartz, S., Bailey, T., Kaplan, R., Ellis, S., and Jovanovic, L. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care 2006; 29(1):44-50.

Less than 24 hours of usage

Geldof, B. A., Oranje, A. P., and van Joost, T. Hand eczema associated with continuous subcutaneous insulin infusion. Contact Dermatitis 89; 20(5):384-5.

Case series or cross-sectional

Georgopoulos, A. CSII and ICT in treating Type I diabetic individuals. Diabetes Care 83; 6(2):201-1.

No original data

Gerich, J. E. Selection of patients for intensive insulin therapy. Arch Intern Med 85; 145(8):1383-4.

No original data

Giardina, S., Lynch, P., and Papo, N. L. A cost-effectiveness analysis of continuous subcutaneous insulin injection vs. multiple daily injections in type-1 diabetes patients in Italy. Value Health 2009; 12(7):A407.

Case series or cross-sectional

Gibson, O. J., Farmer, A. J., McSharry, P. E., and Tarassenko, L. On real-time estimates of blood glucose levels: response to Trevino. Diabetes Care 2007; 30(12):e133; author reply e134.

No original data

Gimenez, M., Conget, I., Nicolau, J., Pericot, A., and Levy, I. Outcome of pregnancy in women with type 1 diabetes intensively treated with continuous subcutaneous insulin infusion or conventional therapy. A case-control study. Acta Diabetol 2007; 44(1):34-7.

Regular insulin was used in the pump

Gimenez, M., Lara, M., and Conget, I. Sustained efficacy of continuous subcutaneous insulin infusion in type 1 diabetes subjects with recurrent non-severe and severe hypoglycemia and hypoglycemia unawareness: a pilot study. Diabetes Technol Ther 2010; 12(7):517-21.

No comparison with placebo or usual care

Giocolea, I., Hernandez, I., Fombellida, J., and Vazquez, J. A. Renal function of insulin-dependent diabetic patients, treated with continuous subcutaneous insulin infusion pump. A comparison with conventional insulin therapy during a follow-up period of one year. AN. MED. INTERNA 88; 5(4):169-172.

No comparison with placebo or usual care

Go, Y. and Hanafusa, T. [Principles of treatment and insulin therapy in type 1 diabetes]. Nippon Rinsho 2002; 60 Suppl 9:177-82.

Other reason

Goicolea Opacua, I., Hernandez Colau, I., and Vazquez Garcia, J. A. [Comparative study between the subcutaneous continuous insulin infusion pump and optimized conventional treatment. Effects at 6 months]. Rev Clin Esp 86; 179(1):07-Mar.

Other reason

Goicolea Opacua, I., Hernandez Colau, I., Cortazar Galarza, A., and Vazquez Garcia, J. A. [Comparison of metabolic control between the continuous subcutaneous insulin infusion pump and augmented conventional treatment. Effects after 12 months]. Med Clin (Barc) 87; 88(16):617-20.

No comparison with placebo or usual care

Goicolea Opacua, I., Martinez Castillo, A., Santamaria Pelarda, E., Sola Sarabia, C., and Vazquez Garcia, J. A. [Metabolic control using a subcutaneous insulin infusion pump: effects 2 years after treatment]. Rev Clin Esp 88; 182(4):200-2.

No comparison with placebo or usual care

Goicolea Opacua, I., Vazquez Garcia, J. A., Fombellida Cortazar, J., and Hernandez Collau, I. [Course of the glomerular filtration rate and other renal parameters in medium-term insulin-dependent diabetes mellitus. Effect of strict treatment with a subcutaneous continuous infusion pump]. Med Clin (Barc) 86; 87(16):657-60.

Other reason

Goicolea, I., Garcia, Y., Mancha, A. I., Ugarte, E., and Vazquez, J. A. Insulin infusion pump and acute and chronic complications in insulin dependent diabetes mellitus: Effects after 10 years: BOMBA DE INFUSION Y COMPLICACIONES AGUDAS Y CRONICAS EN LA DIABETES MELLITUS DEPENDIENTE DE LA INSULINA: EFECTOS A LOS 10 ANOS. ENDOCRINOLOGIA 96; 43(2):48-52.

No comparison with placebo or usual care

Goicolea, I., Pardo, C., and Vazquez, J. A. The effect of continuous subcutaneous insulin infusion versus intermitent subcutaneous insulin injection on the tolerance to exercise in insulin-dependent diabetics. ENDOCRINOLOGIA 89; 36(1):10-Jul.

No outcome of interest

Goicolea, I., Rueda, M., Hernandez, I., Quiroga, A., and Vazquez, J. A. [Effect of postprandial exercise in type I diabetes: comparison between the continuous-infusion insulin pump and intensified conventional therapy]. Rev Clin Esp 86; 179(7):355-8.

Other reason

Goicolea, I., Santamaria, E., Pardo, C., Vazquez, J. A., Martin, A., and Castresana, I. [Course of diabetic retinopathy and metabolic control with subcutaneous insulin infusion pump: 18-month study]. An Med Interna 89; 6(2):71-3.

Regular insulin was used in the pump

Golenko, A. and Noczynska, A. An evaluation of physical development and metabolic control in children with type 1 diabetes mellitus receiving treatment with various insulin regimens. Part 1. Diabetol. Dosw. Klin. 2008; 8(3):115-123.

Case series or cross-sectional

Gonzalez Rodiles Heredia, R. E. Effectiveness of continuous glucose sensor-augmented insulin pump therapy in type 1 diabetes mellitus: Efectividad del tratamiento con bomba de infusion continua de insulina con sensor de glucemia en diabetes mellitus tipo 1. Rev. Clin. Esp. 2011; 211(1):54.

No original data

Gonzalez-Romero, S., Gonzalez-Molero, I., Fernandez-Abellan, M., Dominguez-Lopez, M. E., Ruiz-de-Adana, S., Olveira, G., and Soriguer, F. Continuous subcutaneous insulin infusion versus multiple daily injections in pregnant women with type 1 diabetes. Diabetes Technol Ther 2010; 12(4):263-9.

Regular insulin was used in the pump

Goss, P. W. Glycaemic control in patients with type 1 diabetes after provision of public hospital-funded insulin pumps. Med J Aust 2010; 192(2):107-8.

No concurrent comparison group

Gottlieb, P. A., Crew, L. B., Moser, E. G., Voelmle, M. K., Beatson, C. R., Gutin, R. S., and Garg, S. K. Effects of continuous glucose monitoring on glycaemic control in subjects with type 1 diabetes delivering insulin via pump or multiple daily injections: A prospective study. Diabetologia 2010; 53:S25.

Case series or cross-sectional

Green, J. B., Ahmann, A., Bergenstal, R. M., Dailey, G., Tanenberg, R., and Buse, J. B. Glucose control in adults during a 1-year randomised controlled trial comparing sensor-augmented pump therapy and multiple daily injection therapy: STAR 3 study. Diabetologia 2010; 53:S24.

Case series or cross-sectional

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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes
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No concurrent comparison group

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No comparison with placebo or usual care

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Other reason
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No original data
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No comparison with placebo or usual care
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Case series or cross-sectional
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No original data
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No original data
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Regular insulin was used in the pump
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No original data
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Case series or cross-sectional

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Does not evaluate CSII or rt-CGM

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Regular insulin was used in the pump

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No original data

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No concurrent comparison group

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Regular insulin was used in the pump

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No comparison with placebo or usual care

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No original data

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Other reason

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Other reason

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Case series or cross-sectional

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Other reason
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Regular insulin was used in the pump
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Regular insulin was used in the pump
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No original data
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No original data
Kabrt, J., Masek, Z., and Pav, J. [Use of the Biostator in optimizing insulin treatment (preliminary communication)]. Vnitr Lek 85; 31(9):870-6.
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No concurrent comparison group
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Regular insulin was used in the pump
Kamaratos, A., Lentzas, J., Papathanasiou, M., Gerakari, S., Mariolis, A., Alevizos, A., Salvanos, L., Kokkoris, S., and Melidonis, A. The role of general practitioners in the follow up of type 1 diabetic patients with insulin pump therapy. Rural Remote Health 2007; 7(1):657.
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Other reason
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Case series or cross-sectional
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No original data

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Case series or cross-sectional
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No original data
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Other reason
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No original data
Keller, U., Pernet, A., and Fankhauser, S. [Intensified insulin therapy with multiple insulin injections or insulin pumps]. Schweiz Rundsch Med Prax 86; 75(21):611-3.
No original data
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No concurrent comparison group
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No original data
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No original data
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Other reason
Kishikawa, H., Soejima, H., Tamama, Y., Araki, E., and Shichiri, M. [Application and practice of intensive insulin therapy]. Nippon Rinsho 2002; 60 Suppl 9:297-303.
No original data
Kitabchi, A. E., Fisher, J. N., Matteri, R., and Murphy, M. B. The use of continuous insulin delivery systems in treatment of diabetes mellitus. Adv Intern Med 83; 28:449-90.
No comparison with placebo or usual care
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No concurrent comparison group
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No comparison with placebo or usual care
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Case series or cross-sectional
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No comparison with placebo or usual care
Koivisto, V. A. and Tronier, B. Postprandial blood glucose response to exercise in type I diabetes: comparison between pump and injection therapy. Diabetes Care 83; 6(5):436-40.
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Does not apply to a key question
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Other reason
Kordonouri, O., Hartmann, R., Lauterborn, R., Barnekow, C., Hoeffe, J., and Deiss, D. Age-specific advantages of continuous subcutaneous insulin infusion as compared with multiple daily injections in pediatric patients: one-year follow-up comparison by matched-pair analysis. Diabetes Care 2006; 29(1):133-4.
Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes
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No original data
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Case series or cross-sectional
Kritz, H., Hagmuller, G., Lovett, R., and Irsigler, K. Implanted constant basal rate insulin infusion devices for Type 1 (insulin-dependent) diabetic patients. Diabetologia 83; 25(2):78-81.
No concurrent comparison group
Kruger, D. and Marcus, A. O. Psychological motivation and patient education: a role for continuous glucose monitoring. Diabetes Technol Ther 2000; 2 Suppl 1:S93-7.
No original data
Kuhl, C., Moller-Jensen, B., Saurbrey, N., Molsted-Pedersen, L., and Pedersen, J. F. Intensified insulin treatment in diabetic pregnancy. Diabetes Educ 84; 10 SPEC NO:60-3.
No comparison with placebo or usual care
Kuntschen, F. and Zumsteg, U. [Current technologies and strategies in the treatment of insulin-dependent diabetes mellitus]. Schweiz Med Wochenschr Suppl 94; 60:76-80.
Other reason
Kurtz, F. [Our experience with portable insulin pumps in young children]. Arch Pediatr 2000; 7(6):691-2.
Other reason
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No comparison with placebo or usual care

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Case series or cross-sectional

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No comparison with placebo or usual care

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No original data

Landgraf, R., Huber, R. M., Bachmann, A., and Lohr, R. [Intensive insulin therapy]. Dtsch Med Wochenschr 2008; 133(17):901-12.

Other reason

Lane, J. T., Ferguson, A., Hall, J., McElligott, M., Miller, M., Lane, P. H., and Pfeffer, E. Glycemic control over 3 years in a young adult clinic for patients with type 1 diabetes. Diabetes Res Clin Pract 2007; 78(3):385-91.

No comparison with placebo or usual care

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Case series or cross-sectional

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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Larson, P. and Kohner, E. M. Caution advised when managing diabetic retinopathy by continuous subcutaneous insulin infusion. Am J Ophthalmol 83; 95(3):404-5.

Case series or cross-sectional

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Other reason

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No original data

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Case series or cross-sectional

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No concurrent comparison group

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No comparison with placebo or usual care

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No comparison with placebo or usual care
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Regular insulin was used in the pump
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Not in an outpatient setting
Leguerrier, A. M., Allannic, H., and Lorcy, Y. [Ketoacidosis during ambulatory treatment by continuous subcutaneous infusion of insulin. Possible role of catheter infection]. Presse Med 84; 13(16):1008.
Other reason
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No comparison with placebo or usual care
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Other reason
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No original data
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Does not apply to a key question
Lepore, G., Corsi, A., Dodesini, A. R., Nosari, I., and Trevisan, R. Continuous subcutaneous insulin infusion is better than multiple daily insulin injections in reducing glucose variability only in type 1 diabetes with good metabolic control. Diabetes Care 2010; 33(6):e81.
Does not apply to a key question
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No comparison with placebo or usual care
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No concurrent comparison group
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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes
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No comparison with placebo or usual care
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Does not evaluate CSII or rt-CGM

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No concurrent comparison group

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No original data

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No original data

Liouri, E., Koutsovasilis, A., Kounenou, K., Kamaratos, A., Koukouli, M.-P., Nikolaou, A., Iraklianou, S., Damianaki, D., and Melidonis, A. Intensified insulin therapy vs CSII: the influence on family cohesion and adaptability of type l diabetics. Diabetologia 2009; 52(S1):S371.

Case series or cross-sectional

Lombardo, A., Scavino, S., and Scornavacca, G. Insulin-dependent diabetes mellitus treated with subcutaneous insulin infusion pump: TERAPIA DEL DIABETE INSULINO-DIPENDENTE CON MICROINFUSORI SOTTOCUTANEI DI INSULINA. PROG. MED. 86; 42(11):649-658.

Other reason

Lombardo, A., Scornavacca, G., Scavino, S., Oliva, G., Cacciola, R., Amantia, L., and Motta, L. [Long-term insulin treatment using continuous subcutaneous insulin infusions: metabolic control and hemorheological aspects]. Minerva Endocrinol 87; 12(4):289-300.

Other reason

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Does not apply to a key question

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No original data

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No original data

Ludvigsson, J. and Hanas, R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. Pediatrics 2003; 111(5 Pt 1):933-8.

No concurrent comparison group

Ly, T. T., Hewitt, J., Davey, R. J., Lim, E. M., Davis, E. A., and Jones, T. W. Improving epinephrine responses in hypoglycemia unawareness with real-time continuous glucose monitoring in adolescents with type 1 diabetes. Diabetes Care 2010; :.

No outcome of interest

Lynch, P., Riedel, A. A., Samant, N., Fan, Y., Peoples, T., Levinson, J., and Lee, S. W. Improved A1C by switching to continuous subcutaneous insulin infusion from injection insulin therapy in type 2 diabetes: A retrospective claims analysis. Prim Care Diabetes 2010; :.

No concurrent comparison group

Mackowiak, L. Continuous glucose monitoring--getting started. Diabetes Self Manag 2007; 24(2):15-6, 19-20.

No original data

Marchin, J. P., O'Dorisio, T. M., and Cataland, S. Can long-term continuous subcutaneous insulin (CSII) therapy improve nerve function in type I diabetes mellitus?. CLIN. RES. 82; 30(4):744A.

Case series or cross-sectional

Marshall, S. M., Home, P. D., Taylor, R., and Alberti, K. G. Continuous subcutaneous insulin infusion versus injection therapy: a randomized cross-over trial under usual diabetic clinic conditions. Diabet Med 87; 4(6):521-5.

No comparison with placebo or usual care

Marshall, S. M., Taylor, R., Home, P. D., and Alberti, K. G. Intermediary metabolism, insulin sensitivity and insulin receptor status under comparable long-term therapy with insulin injections and continuous subcutaneous insulin infusion. Acta Endocrinol (Copenh) 88; 117(4):417-27.

No comparison with placebo or usual care

Mastrototaro, J. J. and Gross, T. M. Reproducibility of the continuous glucose monitoring system matches previous reports and the intended use of the product. Diabetes Care 2003; 26(1):256; author reply 256-7.

Case series or cross-sectional

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No comparison with placebo or usual care

Mattera, C. J. The modern diabetic: how to handle insulin pumps during emergencies. JEMS 2008; 33(5):82-91; quiz 92.

No original data

Matyka, K. Optimising glycaemic control in adolescents using CGMS. Pract. Diabetes Int. 2009; 26(3):90.

No original data

Maudelonde, T., Menez, J. F., Meskar, A., Tater, D., Lucas, D., Barbou, L. G., and Bercovici, J. P. [Glycosylated proteins and control of the diabetic: use of continuous flow insulin pumps by the subcutaneous route]. Diabete Metab 83; 9(3):193-8.

No concurrent comparison group

McDonald, J. W., Dupre, J., Rodger, N. W., Champion, M. C., Webb, C. D., and Ali, M. Comparison of platelet thromboxane synthesis in diabetic patients on conventional insulin therapy and continuous insulin infusions. Thromb Res 82; 28(6):705-12.

No comparison with placebo or usual care

McGarraugh, G. and Bergenstal, R. Detection of hypoglycemia with continuous interstitial and traditional blood glucose monitoring using the FreeStyle Navigator Continuous Glucose Monitoring System. Diabetes Technol Ther 2009; 11(3):145-50.

Does not apply to a key question

McLachlan, K., Jenkins, A., and O'Neal, D. The role of continuous glucose monitoring in clinical decision-making in diabetes in pregnancy. Aust N Z J Obstet Gynaecol 2007; 47(3):186-90.

No comparison with placebo or usual care

McVean, J. J., Eickhoff, J. C., and MacDonald, M. J. Factors correlating with improved A1C in children using continuous subcutaneous insulin infusion. Diabetes Care 2007; 30(10):2499-500.

No comparison with placebo or usual care

Mehdi, S. K., Hatfield, E., Dornhorst, A., and Oliver, N. S. Assessment of glycemic variability in continuous subcutaneous insulin infusion therapy in type 1 diabetes related to anthropometry and complication status. J Diabetes Sci Technol 2009; 3(5):1227-8.

Regular insulin was used in the pump

Mesa, J., Simo, R., Obiols, G., Faigon, L., Garcia-Pascual, L., and Tresanchez, J. M. [Continuous subcutaneous infusion of insulin and intensified conventional treatment in the control of blood glucose in pregnant diabetics]. Med Clin (Barc) 87; 88(19):760-3.

Regular insulin was used in the pump

Meschi, F., Beccaria, L., Vanini, R., Szulc, M., and Chiumello, G. Short-term subcutaneous insulin infusion in diabetic children. Comparison with three daily insulin injections. Acta Diabetol Lat 82; 19(4):371-5.

Regular insulin was used in the pump

Meschi, F., Bonfanti, R., Rigamonti, A., Giulio, F., Battaglino, R., Viscardi, M., Poscia, A., and Chiumello, G. Patients' evaluation of nocturnal hypoglycaemia with GlucoDay continuous glucose monitoring in paediatric patients. Acta Diabetol 2010; 47(4):295-300.

Not in an outpatient setting

Messer, L., Ruedy, K., Xing, D., Coffey, J., Englert, K., Caswell, K., and Ives, B. Educating families on real time continuous glucose monitoring: the DirecNet navigator pilot study experience. Diabetes Educ 2009; 35(1):124-35.

No comparison with placebo or usual care

Michon, N., Hamet, P., and Mailhot, J. [Insulin pump and intensive insulin therapy]. Union Med Can 85; 114(10):845-6.

No original data

Millet, P., Selam, J. L., and Boudet, C. [Insulin pumps for insulin-dependent diabetics]. Annee Ther Clin Ophtalmol 83; 34:99-109.

Other reason

Millet, P., Selam, J. L., and Mercadier, B. [Diabetic retinopathy under treatment by insulin pump. 1st results]. Bull Soc Ophtalmol Fr 83; 83(1):135-8.

Case series or cross-sectional

Minkina-Pedras, M., Jarosz-Chobot, P., Malecka-Tendera, E., and Deja, G. [Assessment of metabolic control and safety of continuous subcutaneous insulin infusion in prepubertal children with type 1 diabetes mellitus]. Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw 2005; 11(3):171-6.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Minkina-Pedras, M., Jarosz-Chobot, P., Polanska, J., Kalina, M. A., Marcinkowski, A., and Malecka-Tendera, E. Prospective assessment of continuous subcutaneous insulin infusion therapy in young children with type 1 diabetes. Diabetes Res Clin Pract 2009; 85(2):153-8.

No comparison with placebo or usual care

Mirouze, J., Collard, F., Selam, J. L., and Pham, J. Continuous blood glucose monitoring in insulin-treated diabetes.. Horm. Metab. Res. 77; Suppl 7:77-88.

Does not evaluate CSII or rt-CGM

Mirouze, J., Rouault, R., Misse, P., Millet, P., Bordat, B., Selam, J. L., and Boudet, C. [Diabetes and the insulin pump: functional results after 5 consecutive years of permanent use]. Bull Soc Ophtalmol Fr 89; 89(3):437-40.

Other reason

Mirouze, J., Selam, J. L., Rodier, M., Lapinski, H., Saeidi, C., and Richard, J. L. [Treatment of diabetes mellitus with insulin infusions]. Bull Acad Natl Med 84; 168(02-Jan):80-90.

Other reason

Mitka, M. Poor patient adherence may undermine aim of continuous glucose monitoring. JAMA 2007; 298(6):614-5.

No original data

Mohan, V., Shyamsunder, R., Ramchandran, A., Snehalatha, C., and Viswanathan, M. Experience with insulin pump treatment in Indian diabetics. A preliminary report. J Assoc Physicians India 83; 31(11):715-7.

Case series or cross-sectional

Moller, A., Rasmussen, L., Ledet, T., Christiansen, J. S., Christensen, C. K., Mogensen, C. E., and Hermansen, K. Lipoprotein changes during continuous subcutaneous insulin infusion in insulin-dependent diabetic patients. Scand J Clin Lab Invest 86; 46(5):471-5.

No comparison with placebo or usual care

Moller, N., Schmitz, O. E., Mortensen, H. B., Mandrup-Poulsen, T., Hommel, E. E., Parving, H. H., and Mogensen, C. E. [Insulin pumps and treatment of diabetes]. Ugeskr Laeger 2003; 165(33):3167-8; author reply 3168-9.

No original data

Montana, E., Ricart, W., Virgili, N., and Fernandez Castaner, M. [Unstable diabetes and continuous insulin infusion pump]. Med Clin (Barc) 86; 87(6):262.

Case series or cross-sectional

Muchmore, D. B., Sharp, M., and Vaughn, D. Successful implementation of blinded continuous glucose monitoring during a randomized clincal trial. Diabetes Technol. Ther. 2011; 13(2):255.

Case series or cross-sectional

Muhlhauser, I., Berger, M., Sonnenberg, G., Koch, J., Jorgens, V., Schernthaner, G., Scholz, V., and Padagogin, D. Incidence and management of severe hypoglycemia in 434 adults with insulin-dependent diabetes mellitus. Diabetes Care 85; 8(3):268-73.

No comparison with placebo or usual care

Murata, K., Toyoda, N., Ito, M., Rii, T., Sugiyama, Y., and Miyamura, Y. [Assessment of self monitoring of blood glucose (SMBG) and continuous subcutaneous insulin infusion (CSII) in diabetic pregnant women]. Nippon Sanka Fujinka Gakkai Zasshi 85; 37(12):2749-57.

Other reason

Murphy, H. R., Rayman, G., Lewis, K., Kelly, S., Johal, B., Duffield, K., Fowler, D., Campbell, P. J., and Temple, R. C. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ 2008; 337:a1680.

Not in an outpatient setting

Murphy, H. R., Raynian, G., Lewis, K., Kelly, S., Johal, B., Duffield, K., Fowler, D., Campbell, P. J., and Temple, R. C. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: Randomized clinical trial. Obstet. Gynecol. Surv. 2009; 64(4):216-218.
Does not evaluate CSII or rt-CGM
Musen, G., Jacobson, A. M., Ryan, C. M., Cleary, P. A., Waberski, B. H., Weinger, K., Dahms, W., Bayless, M., Silvers, N., Harth, J., and White, N. Impact of diabetes and its treatment on cognitive function among adolescents who participated in the Diabetes Control and Complications Trial. Diabetes Care 2008; 31(10):1933-8.
No comparison with placebo or usual care
Myneni, A., Aldasouqi, S., Page, C., Weller, L., Carella, M., and Gossain, V. V. Comparison of continuous subcutaneous insulin infusion versus basal/bolus insulin injections for treatment of type 1 diabetes in clinical practice. J Diabetes Sci Technol 2009; 3(2):403-4.
Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes
Nabhan, Z. M., Kreher, N. C., Greene, D. M., Eugster, E. A., Kronenberger, W., and DiMeglio, L. A. A randomized prospective study of insulin pump vs. insulin injection therapy in very young children with type 1 diabetes: 12-month glycemic, BMI, and neurocognitive outcomes. Pediatr Diabetes 2009; 10(3):202-8.
No comparison with placebo or usual care
Nathan, D. M., Lou, P., and Avruch, J. Intensive conventional and insulin pump therapies in adult type I diabetes. A crossover study. Ann Intern Med 82; 97(1):31-6.
Other reason
Neeser, K., Kocher, S., Weber, C., and Heister, F. CSII compared to MDI: A health economic analysis in the german health care setting. Value Health 2009; 12(7):A407.
Case series or cross-sectional
Neff, K., McCarthy, A., Forde, R., Foley, M., Coulter-Smith, S., Daly, S., Firth, R., Byrne, M. M., and Kinsley, B. T. Intensive glycaemic control in type 1 diabetic pregnancy: A comparison of continuous subcutaneous insulin infusion and multiple daily injection therapy. Diabetologia 2010; 53:S433.
Case series or cross-sectional
Newman, S. P., Cooke, D., Casbard, A., Walker, S., Meredith, S., Nunn, A., Steed, L., Manca, A., Sculpher, M., Barnard, M., Kerr, D., Weaver, J., Ahlquist, J., and Hurel, S. J. A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technol Assess 2009; 13(28):iii-iv, ix-xi, 1-194.
Does not evaluate CSII or rt-CGM
Ng Tang Fui, S., Pickup, J. C., Bending, J. J., Collins, A. C., Keen, H., and Dalton, N. Hypoglycemia and counterregulation in insulin-dependent diabetic patients: a comparison of continuous subcutaneous insulin infusion and conventional insulin injection therapy. Diabetes Care 86; 9(3):221-7.
No comparison with placebo or usual care
Nicolino, M., Sulmont, V., Bendelac, N., Reznik, Y., Guerci, B., Renard, E., Hanaire, H., Jeandidier, N., and Raccah, D. The RealTrend Study: Effect of continuous glucose monitoring on metabolic control in addition to pump therapy in poorly controlled type 1 diabetic patients. Pediatr. Diabetes 2009; 10:105.
Case series or cross-sectional
Nicolucci, A., Maione, A., Franciosi, M., Amoretti, R., Busetto, E., Capani, F., Bruttomesso, D., Di Bartolo, P., Girelli, A., Leonetti, F., Morviducci, L., Ponzi, P., and Vitacolonna, E. Quality of life and treatment satisfaction in adults with Type 1 diabetes: a comparison between continuous subcutaneous insulin infusion and multiple daily injections. Diabet Med 2008; 25(2):213-20.
Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes
Norgaard, K. [Use of insulin pumps in Denmark]. Ugeskr Laeger 2003; 165(23):2380-2.
Other reason

Nosadini, R., Velussi, M., Fioretto, P., Doria, A., Avogaro, A., Trevisan, R., Valerio, A., Vizzaccaro, A., Bruscagnin, A., Cernigoi, A., Pascoletti, R., Bernardi, G., Duner, E., Da Campo, G. L., and Costella, G. B. Frequency of hypoglycaemic and hyperglycaemic-ketotic episodes during conventional and subcutaneous continuous insulin infusion therapy in IDDM. DIABETES NUTR. METAB. CLIN. EXP. 88; 1(4):289-296.

Regular insulin was used in the pump

Nosari, I., Maglio, M. L., Lepore, G., Cortinovis, F., and Pagani, G. Is continuous subcutaneous insulin infusion more effective than intensive conventional insulin therapy in the treatment of pregnant diabetic women?. DIABETES NUTR. METAB. CLIN. EXP. 93; 6(1):33-37.

Regular insulin was used in the pump

Noto, R. A., Ginsberg, L., Lifshitz, F., Pelcovitz, D., and Kaplan, S. Improved management of brittle-psychosocial diabetes by use of a portable insulin infusion pump. J Pediatr 85; 107(1):100-2.

Case series or cross-sectional

O'Brien, B. Continuous glucose monitoring improved glycaemic control in pregnant women with diabetes and reduced infant macrosomia. Evid Based Nurs 2009; 12(2):43.

Does not apply to a key question

Olivier, P., Lawson, M., Huot, C., Richardson, C., Nakhla, M., and Romain, J. Use of the real-time continuous glucose monitor at initiation of insulin pump therapy in children and adolescents. Diabetes Technol. Ther. 2011; 13(2):258.

Case series or cross-sectional

Olohan, K. and Zappitelli, D. The insulin pump. Am J Nurs 2003; 103(4):48-56; quiz 57.

No original data

Olsen, B. S. and Johannesen, J. [Insulin pump to children with type 1 diabetes. The Danish Society for Childhood and Adolescent Diabetes]. Ugeskr Laeger 2007; 169(12):1101.

Does not apply to a key question

Olsen, T., Ehlers, N., Nielsen, C. B., and Beck-Nielsen, H. Diabetic retinopathy after one year of improved metabolic control obtained by continuous subcutaneous insulin infusion (CSII). Acta Ophthalmol (Copenh) 85; 63(3):315-9.

No comparison with placebo or usual care

Olsen, T., Richelsen, B., Ehlers, N., and Beck-Nielsen, H. Diabetic retinopathy after 3 years' treatment with continuous subcutaneous insulin infusion (CSII). Acta Ophthalmol (Copenh) 87; 65(2):185-9.

No concurrent comparison group

Olsovsky, J. and Beranek, M. [The influence of long-term therapy with the insulin pump (CSII) in patients with type 1 diabetes mellitus on metabolic compensation and on the incidence of hypoglycaemia. Comparison with intensified conventional insulin therapy (MDI)]. Vnitr Lek 2007; 53(6):637-45.

Other reason

Orsoni-Dupont, C. [Insulin pump in the treatment of diabetic retinopathy]. Bull Soc Ophtalmol Fr 82; 82(12):1547-52.

Other reason

Orsoni-Dupont, C. [Results of diabetic retinopathy following 2 years of treatment with a permanent insulin pump]. Bull Mem Soc Fr Ophtalmol 83; 95:494-9.

Other reason

Overby, N. C., Margeirsdottir, H. D., Brunborg, C., Andersen, L. F., and Dahl-Jorgensen, K. The influence of dietary intake and meal pattern on blood glucose control in children and adolescents using intensive insulin treatment. Diabetologia 2007; 50(10):2044-51.

No comparison with placebo or usual care

Ozmen, B. and Boyvada, S. Can self-monitoring blood glucose control decrease glycated hemoglobin levels in diabetes mellitus. Endocrinologist 2002; 12(4):349-356.

Does not evaluate CSII or rt-CGM

Page, C. Insulin pump therapy. Tenn Med 2000; 93(11):410-4.

Case series or cross-sectional

Palmer, A. J., Roze, S., Valentine, W. J., Spinas, G., Scuffham, P. A., and Carr, L. The cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections for the management of diabetes: Response to Schuffman and Carr [1] (multiple letters). Diabetic Med. 2004; 21(12):1372-1373.

No original data

Pankowska, E., Lipka, M., and Szypowska, A. Insulin therapy and pump therapy in pediatric patients: Insulinoterapia i osobiste pompy insulinowe w praktyce pediatrycznej. Prz. Pediatr. 2003; 33(2):158-164.
No comparison with placebo or usual care
Paris, C. A., Imperatore, G., Klingensmith, G., Petitti, D., Rodriguez, B., Anderson, A. M., Schwartz, I. D., Standiford, D. A., and Pihoker, C. Predictors of insulin regimens and impact on outcomes in youth with type 1 diabetes: the SEARCH for Diabetes in Youth study. J Pediatr 2009; 155(2):183-9.e1.
Other reason
Perelygina, A. A., Antsiferov, M. V., and Starostina, E. G. [Experience with using automated insulin infusion systems in diabetes mellitus type 1]. Sov Med 88; (5):72-5.
Other reason
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No original data
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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes
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No outcome of interest
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No original data
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Does not evaluate CSII or rt-CGM
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Case series or cross-sectional
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No concurrent comparison group

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No comparison with placebo or usual care

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Other reason

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No concurrent comparison group

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Other reason

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No original data

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Case series or cross-sectional

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Case series or cross-sectional

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Case series or cross-sectional

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Case series or cross-sectional

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No original data

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No concurrent comparison group

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Case series or cross-sectional

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No concurrent comparison group

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No concurrent comparison group

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No original data

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No comparison with placebo or usual care

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No original data

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Case series or cross-sectional

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Case series or cross-sectional

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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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Case series or cross-sectional

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No original data

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Does not evaluate CSII or rt-CGM

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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Other reason

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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

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No comparison with placebo or usual care

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No original data

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No concurrent comparison group

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Other reason

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Other reason

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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No concurrent comparison group

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No original data

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No comparison with placebo or usual care

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Does not evaluate CSII or rt-CGM
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Case series or cross-sectional
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Case series or cross-sectional
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Other reason
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No comparison with placebo or usual care
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Case series or cross-sectional
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Other reason
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Other reason
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No original data
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Regular insulin was used in the pump
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No original data
Scaramuzza, A. E., Iafusco, D., Rabbone, I., Bonfanti, R., Lombardo, F., Schiaffini, R., Buono, P., Toni, S., Cherubini, V., and Zuccotti, G. V. Use of integrated real-time continuous glucose monitoring/insulin pump system in children and adolescents with type 1 diabetes: a 3-year follow-up study. Diabetes Technol Ther 2011; 13(2):99-103.
Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes
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No original data
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No concurrent comparison group
Scheidegger, U., Allemann, S., Scheidegger, K., and Diem, P. Continuous subcutaneous insulin infusion therapy: effects on quality of life. Swiss Med Wkly 2007; 137(33-34):476-82.
No concurrent comparison group
Scheiner, G. Continuous glucose monitoring. Making sense of your numbers. Diabetes Self Manag 2008; 25(3):42, 44, 48-50.
No concurrent comparison group

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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes
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Regular insulin was used in the pump
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Regular insulin was used in the pump
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No original data
Schiffrin, A., Desrosiers, M., Moffatt, M., and Belmonte, M. M. Feasibility of strict diabetes control in insulin-dependent diabetic adolescents. J Pediatr 83; 103(4):522-7.
Regular insulin was used in the pump
Schiffrin, A., Parikh, S., Marliss, E. B., and Desrosiers, M. M. Metabolic response to fasting exercise in adolescent insulin-dependent diabetic subjects treated with continuous subcutaneous insulin infusion and intensive conventional therapy. Diabetes Care 84; 7(3):255-60.
Less than 24 hours of usage
Schmitz, A., Christiansen, J. S., Christensen, C. K., Hermansen, K., and Mogensen, C. E. Effect of pump versus pen treatment on glycaemic control and kidney function in long-term uncomplicated insulin-dependent diabetes mellitus (IDDM). Dan Med Bull 89; 36(2):176-8.
Regular insulin was used in the pump
Schmitz, O., Sorensen, S. S., Alberti, K. G., Orskov, H., and Hansen, H. E. Metabolic control in newly kidney transplanted insulin-dependent diabetics: improvement by insulin pump treatment (CSII). J Diabet Complications 87; 1(3):81-6.
No comparison with placebo or usual care
Schutt, M., Kern, W., Krause, U., Busch, P., Dapp, A., Grziwotz, R., Mayer, I., Rosenbauer, J., Wagner, C., Zimmermann, A., Kerner, W., and Holl, R. W. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. Exp Clin Endocrinol Diabetes 2006; 114(7):384-8.
No comparison with placebo or usual care
Schwedes, U. [Insulin therapy with pens and pumps]. Med Klin (Munich) 96; 91 Suppl 1:16.
No original data
Scott, R. S. Insulin pumps and other recent advances with insulin delivery in the treatment of diabetes mellitus. N Z Med J 85; 98(781):485-7.
No original data
Segato, T., Midena, E., Piermarocchi, S., Crepaldi, G., and Tiengo, A. The effect of continuous subcutaneous insulin infusion treatment on proliferative diabetic retinopathy. Am J Ophthalmol 82; 94(5):685-6.
No comparison with placebo or usual care
Seigler, D. E., LaGreca, A., Citrin, W. S., Reeves, M. L., and Skyler, J. S. Psychological effects of intensification of diabetic control. Diabetes Care 82; 5 Suppl 1:19-23.
No comparison with placebo or usual care
Selam, J. L., Haardt, M. J., Berne, C., and Slama, G. [Current role of external pumps in the treatment of insulin-dependent diabetes mellitus]. Diabete Metab 95; 21(5):378-82.
Other reason
Selam, J. L., Millet, P., Zaluski, S., and Mirouze, J. [Beneficial effect of insulin therapy by pump on the development of diabetic retinopathy]. Journ Annu Diabetol Hotel Dieu 85; :87-100.
No comparison with placebo or usual care
Senniappan, S., Hine, P., Tang, W., Campbell, J., Bone, M., Sankar, V., Robinson, M., Smith, C., Cooper, C., and Amin, R. The effect of socioeconomic deprivation on efficacy of continuous subcutaneous insulin infusion: a retrospective paediatric case-controlled survey. Eur J Pediatr 2011; :.
Does not apply to a key question

Sensi, S. and Capani, F. Treatment of type 1 diabetes with continuous subcutaneous insulin infusion system. Preliminary report on neuropathy: TRATTAMENTO DEL DIABETE DI TIPO 1 CON IL MICROINFUSORE INSULINICO. PRELIMINARI ESPERIENZE SULLA NEUROPATIA. G. ITAL. DIABETOL. 82; 2(3):283-289.

No comparison with placebo or usual care

Service, F. J., Rizza, R. A., and Gerich, J. E. Infusion-pump treatment of diabetes mellitus. N Engl J Med 79; 301(5):267-8.

No original data

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Other reason

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No comparison with placebo or usual care

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Does not evaluate CSII or rt-CGM

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Case series or cross-sectional

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No comparison with placebo or usual care

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Does not evaluate CSII or rt-CGM

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Not in an outpatient setting

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No concurrent comparison group

Sieradzki, J. [Comparative pharmacodynamic studies of insulin Maxirapid Polfa and Actrapid MC Novo using Biostator GCIIS]. Pol Tyg Lek 84; 39(18):615-7.

Does not evaluate CSII or rt-CGM

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No comparison with placebo or usual care

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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

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No original data

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No original data

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No comparison with placebo or usual care

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Does not evaluate CSII or rt-CGM

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Not in an outpatient setting

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Other reason

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Regular insulin was used in the pump

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Case series or cross-sectional

Sonnenberg, G. E., Schroer, G., Chantelau, E., and Berger, M. Long term treatment of type I diabetics with continuous s.c. insulin infusion: LANGZEITBEHANDLUNG DES TYP-I DIABETIKERS MIT DER KONTINUIERLICHEN SUBKUTANEN INSULININFUSION (CSII). AKTUEL. ENDOKRINOL. STOFFWECHSEL 82; 3(2):72.

No concurrent comparison group

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No original data

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Does not apply to a key question

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Other reason

Sternberg, F., Hoss, U., Salgado, M., and Pfeiffer, E. F. Self-monitoring of blood glucose compared with continuous tissue glucose measurement.. Diabetes Care 97; 20(7):1208-1209.

No original data

Strickland, A. L. and Strickland, J. An outpatient technique for continuous subcutaneous insulin infusion in adolescents and young adults with IDDM. J S C Med Assoc 2000; 96(9):386-9.

No concurrent comparison group

Sulmont, V., Souchon, P. F., Gouillard-Darnaud, C., Fartura, A., Salmon-Musial, A. S., Lambrecht, E., Mauran, P., and Abely, M. Metabolic control in children with diabetes mellitus who are younger than 6 years at diagnosis: continuous subcutaneous insulin infusion as a first line treatment?. J Pediatr 2010; 157(1):103-7.

Regular insulin was used in the pump

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Case series or cross-sectional

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Other reason

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No comparison with placebo or usual care

Swift, P. G. Diabetes education in children and adolescents. Pediatr Diabetes 2009; 10 Suppl 12:51-7.

No original data

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Other reason

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Case series or cross-sectional

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No concurrent comparison group

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No original data

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No original data

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No comparison with placebo or usual care

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Case series or cross-sectional

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Does not apply to a key question

Tanae, A., Kagawa, J., Nozaki, K., Hashimoto, N., and Hibi, I. Improvement of initial remission rate by introduction of CSII. Acta Paediatr Jpn 87; 29(3):401-7.

Case series or cross-sectional

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Does not evaluate CSII or rt-CGM

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Case series or cross-sectional

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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

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No original data

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Case series or cross-sectional

Testa, M. A., Puklin, J. E., Sherwin, R. S., and Simonson, D. C. Clinical predictors of retinopathy and its progression in patients with type I diabetes during CSII or conventional insulin treatment. Diabetes 85; 34 Suppl 3:61-8.

No comparison with placebo or usual care

The Dusseldorf Study Group Comparison of continuous subcutaneous insulin infusion and intensified conventional therapy in the treatment of Type 1 diabetes: a two year randomized study. Diab. Nutr. Metab. 2006; 3:203-212.

Regular insulin was used in the pump

Thielen, V., Place, J., Gerbaud, S., Scheen, A., Bringer, J., and Renard, E. Education on sensor-augmented pump use improves glucose control in type 1 diabetic patients. Diabetes Metab 2010; 36(2):170-1.

No comparison with placebo or usual care

Thielen, V., Radermecker, R. P., Renard, E., Bringer, J., and Scheen, A. J. [Therapeutic education and continuous glucose monitoring in insulin-treated diabetic patients]. Rev Med Suisse 2010; 6(260):1596-600.

Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Thomas, J. Cardiovascular disease risk in type 1 diabetes reduced by intensive treatment. Aust. J. Pharm. 2007; 88(1044):78.

No original data

Thong, K. Y., Fegan, P. G., and Yeap, B. B. Glycaemic control in patients with type 1 diabetes after provision of public hospital-funded insulin pumps. Med J Aust 2009; 191(5):291.

No comparison with placebo or usual care

Thuesen, L., Christiansen, J. S., Sorensen, K. E., Falstie-Jensen, N. F., Christensen, C. K., Hermansen, K., Mogensen, C. E., Schmitz, A., and Henningsen, P. [Increased working capacity in insulin-dependent diabetics treated with insulin pumps. A controlled study]. Ugeskr Laeger 88; 150(1):24-7.

Regular insulin was used in the pump

Thuesen, L., Christiansen, J. S., Sorensen, K. E., Falstie-Jensen, N., Christensen, C. K., Hermansen, K., Mogensen, C. E., and Henningsen, P. Exercise capacity and cardiac function in type 1 diabetic patients treated with continuous subcutaneous insulin infusion. A controlled study. Scand J Clin Lab Invest 86; 46(8):779-84.

No comparison with placebo or usual care

Tilvis, R. S., Helve, E., and Miettinen, T. A. Improvement of diabetic control by continuous subcutaneous insulin infusion therapy changes fatty acid composition of serum lipids and erythrocytes in type 1 (insulin-dependent) diabetes. Diabetologia 86; 29(10):690-4.

No concurrent comparison group

Tiselko, A., Potin, V., Borovik, N., and Patrakeeva, E. Continuous subcutaneous insulin infusion (CSII), glucose monitoring (CGM) and glucose variability (GV) in diabetes type 1 (DM1) patients during pregnancy. Diabetes Technol. Ther. 2011; 13(2):278.

Case series or cross-sectional

Tolwinska, J., Glowinska-Olszewska, B., Urban, M., Florys, B., and Peczynska, J. [Ultrasonographic evaluation of selected parameters of the endothelial function in brachial arteries and IMT measurements in carotid arteries in children with diabetes type 1 using personal insulin pumps--preliminary report]. Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw 2006; 12(3):200-4.

No outcome of interest

Toni, S., Reali, M. F., Fasulo, A., Festini, P., Medici, A., and Martinucci, M. E. The use of insulin pumps improves the metabolic control in children and adolescents with type 1 diabetes. Arch Dis Child 2004; 89(8):796-7.

Other reason

Topper, E., Gertner, J., Amiel, S., Press, M., Genel, M., and Tamborlane, W. V. Deranged alpha-adrenergic regulation of growth hormone secretion in poorly controlled diabetes: reversal of the exaggerated response to clonidine after continuous subcutaneous insulin infusion. Pediatr Res 85; 19(6):534-6.

Does not apply to a key question

Torpy, J. M., Lynm, C., and Glass, R. M. Pregnancy and diabetes. J. Am. Med. Assoc. 2008; 299(21):2590.

No original data

Torrance, T., Franklin, V., and Greene, S. Insulin pumps. Arch Dis Child 2003; 88(11):949-53.

No original data

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No concurrent comparison group

Toth, E. L., Boychuk, L. R., and Kirkland, P. A. Recurrent infection of continuous subcutaneous insulin infusion sites with Mycobacterium fortuitum. Diabetes Care 95; 18(9):1284-5.

Case series or cross-sectional

Tresanchez Trias, J. M., Mesa Manteca, J., Sanmarti Sala, A. M., Obiols Alfonso, G., and Pujol Borrell, R. [Insulin-dependent diabetes mellitus: subcutaneous insulin therapy with a portable infusion pump]. Med Clin (Barc) 83; 80(9):394-7.

Other reason

Tsuchiya, Y., Cho, H., Kotoh, S., Yokoyama, T., and Matsuo, N. Clinical use of a portable infusion pump and pen-type injector in type 1 diabetes mellitus. Acta Paediatr Jpn 87; 29(3):361-7.

No concurrent comparison group

Tubiana-Rufi, N., de Lonlay, P., Bloch, J., and Czernichow, P. [Remission of severe hypoglycemic incidents in young diabetic children treated with subcutaneous infusion]. Arch Pediatr 96; 3(10):969-76.

No comparison with placebo or usual care

Turner, R. C., Ward, E. A., Phillips, M. A., Dornan, T. L., Ward, G. M., and Hockaday, T. D. Continuous subcutaneous insulin infusion or subcutaneous insulin injections. Lancet 79; 2(8140):481.

Case series or cross-sectional

Ulahannan, T. and Mortimer, P. Successful treatment of type 1 diabetes complicated by congenital lymphoedema with continuous subcutaneous insulin infusion (CSII) and insulin analogue. Br. J. Diabetes Vasc. Dis. 2006; 6(2):95-96.

Case series or cross-sectional

Ulahannan, T. Comparison of glucose control by insulin pump, MDI and pre mix insulin in routine clinical practice. Diabetes Technol. Ther. 2011; 13(2):279.

Other reason

Valenzuela, J. M., Patino, A. M., McCullough, J., Ring, C., Sanchez, J., Eidson, M., Nemery, R., and Delamater, A. M. Insulin pump therapy and health-related quality of life in children and adolescents with type 1 diabetes. J Pediatr Psychol 2006; 31(6):650-60.

No comparison with placebo or usual care

van Ballegooie, E. [The treatment of diabetes mellitus with insulin infusion pumps]. Tijdschr Ziekenverpl 82; 35(6):178-82.

Other reason

van Ballegooie, E. and van Weerden, T. W. Skin temperature changes during CSII in patients with diabetic neuropathy. Diabetes Care 84; 7(6):612-3.

Case series or cross-sectional

Van Ballegooie, E., Reitsma, W. D., Sluiter, W. J., and Doorenbos, H. Feasibility and efficacy of long-term treatment by continuous subcutaneous insulin infusion (CSII) in insulin-dependent diabetes. Neth J Med 84; 27(5):185-92.

No comparison with placebo or usual care

Van Ballegooie, E., Visser, G. H. A., and Huisjes, H. J. Diabetes regulation in pregnancy by continuous subcutaneous insulin infusion. NED. TIJDSCHR. GENEESKD. 83; 127(5):218-219.

No concurrent comparison group

Van Ballegooie, E., Visser, G. H., and Laurini, R. N. Continuous subcutaneous insulin infusion (CSII) in pregnancy. Neth J Med 85; 28 Suppl 1:06-Mar.

No comparison with placebo or usual care

van den Brande, J. L. [Continuous subcutaneous insulin infusion in children (CSII)]. Tijdschr Kindergeneeskd 83; 51(6):227-9.

Other reason

van Faassen, I., Razenberg, P. P., Simoons-Smit, A. M., and van der Veen, E. A. Carriage of Staphylococcus aureus and inflamed infusion sites with insulin-pump therapy. Diabetes Care 89; 12(2):153-5.

No outcome of interest

Vanamo, R. [Treatment of non-insulin dependent diabetes with an insulin infusion system]. Duodecim 95; 111(7):639-43.

Other reason

Vanelli, M., Bernasconi, S., Rossi, S., Rocca, M., Turni, A., and Giovannelli, G. [Treatment of diabetic ketoacidosis in children]. Arch Fr Pediatr 82; 39(4):203-7.

Other reason

Varghese, M., Walshe, K., Bell, P. M., Hadden, D. R., Kennedy, A. L., and Weaver, J. A. Continuous subcutaneous insulin infusion (CSII) in insulin-dependent diabetes. Ir J Med Sci 83; 152(2):94-8.

Case series or cross-sectional

Vavrinec, J., Lebl, J., and Zizkovsky, V. Changes of insulin resistance in diabetic children after treatment with an insulin pump. CESKO-SLOV. PEDIATR. 87; 42(7):411-415.

No concurrent comparison group

Vavrinec, J., Lebl, J., Zizkovsky, V., Dvorak, P., and Snajderova, M. [Changes in insulin resistance in diabetic children after treatment with an insulin pump]. Cesk Pediatr 87; 42(7):411-5.

Other reason

Viberti, G. C., Bilous, R. W., Mackintosh, D., Bending, J. J., and Keen, H. Long term correction of hyperglycaemia and progression of renal failure in insulin dependent diabetes. Br Med J (Clin Res Ed) 83; 286(6365):598-602.

No comparison with placebo or usual care

Vozar, J., Kusinova, F., Komornik, J., Mikulecky, M., and Ondrejka, P. [Comparison of the effects of conventional insulin therapy and the insulin infusion pump on blood glucose values in pregnant diabetics]. Bratisl Lek Listy 86; 85(5):570-7.

Case series or cross-sectional

Wainstein, J., Metzger, M., Wexler, I. D., Cohen, J., and Raz, I. The use of continuous insulin delivery systems in severely insulin-resistant patients. Diabetes Care 2001; 24(7):1299.

Case series or cross-sectional

Waldhausl, W., Freyler, H., and Kiss, A. Hypoglycemia and other complications with continuous s.c. insulin infusion: HYPOGLYKAMIE UND ANDERE KOMPLIKATIONEN BEI KONTINUIERLICHER SUBKUTANER INSULININFUSION (CSII). AKTUEL. ENDOKRINOL. STOFFWECHSEL 82; 3(2):74.

No concurrent comparison group

Walsh, J., Roberts, R., and Bailey, T. Guidelines for insulin dosing in continuous subcutaneous insulin infusion using new formulas from a retrospective study of individuals with optimal glucose levels. J Diabetes Sci Technol 2010; 4(5):1174-81.

No comparison with placebo or usual care

Walter, C. J. Diabetic retinopathy. Aust J Ophthalmol 81; 9(2):168-9.

Does not evaluate CSII or rt-CGM

Ward, J. D. Continuous subcutaneous insulin infusion (CSII): therapeutic options. Diabet Med 84; 1(1):47-50.

No original data

Warmolts, J. R., Mendell, J. R., O'Dorisio, T. M., and Cataland, S. Comparison of the effects of continuous subcutaneous infusion and split-mixed injection of insulin on nerve function in type I diabetes mellitus. J Neurol Sci 87; 82(03-Jan):161-9.

No comparison with placebo or usual care

Weinzimer, S., Xing, D., Tansey, M., Fiallo-Scharer, R., Mauras, N., Wysocki, T., Beck, R., Tamborlane, W., and Ruedy, K. FreeStyle navigator continuous glucose monitoring system use in children with type 1 diabetes using glargine-based multiple daily dose regimens: results of a pilot trial Diabetes Research in Children Network (DirecNet) Study Group. Diabetes Care 2008; 31(3):525-7.

No concurrent comparison group

Weinzimer, S., Xing, D., Tansey, M., Fiallo-Scharer, R., Mauras, N., Wysocki, T., Beck, R., Tamborlane, W., and Ruedy, K. Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy. Pediatr Diabetes 2009; 10(2):91-6.

No concurrent comparison group

Welsh, J. B., Kannard, B., Nogueira, K., Kaufman, F. R., and Shah, R. Insights from a Large Observational Database of Continuous Glucose Monitoring Adoption, Insulin Pump Usage and Glycemic Control: The CareLink Database. Pediatr Endocrinol Rev 2010; 7 Suppl 3:413-6.

No comparison with placebo or usual care

Weng, J., Li, Y., Xu, W., Shi, L., Zhang, Q., Zhu, D., Hu, Y., Zhou, Z., Yan, X., Tian, H., Ran, X., Luo, Z., Xian, J., Yan, L., Li, F., Zeng, L., Chen, Y., Yang, L., Yan, S., Liu, J., Li, M., Fu, Z., and Cheng, H. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008; 371(9626):1753-60.

Regular insulin was used in the pump

Wentholt, I. M., Maran, A., Masurel, N., Heine, R. J., Hoekstra, J. B., and DeVries, J. H. Nocturnal hypoglycaemia in Type 1 diabetic patients, assessed with continuous glucose monitoring: frequency, duration and associations. Diabet Med 2007; 24(5):527-32.

Does not apply to a key question

Whittemore, R., Jeon, S., Jaser, S., Liberti, L., Cahill, J., and Grey, M. Quality of life and metabolic control in school-aged children with type 1 diabetes. Diabetes 2009; 58:.

Case series or cross-sectional

Wilke, W. and Huttl, I. [Portable infusion pumps for insulin administration in type I diabetic patients]. Z Arztl Fortbild (Jena) 89; 83(9):449-53.

No original data

Wilkinson, J., McFann, K., and Chase, H. P. Factors affecting improved glycaemic control in youth using insulin pumps. Diabet Med 2010; 27(10):1174-7.

No comparison with placebo or usual care

Williams, S., Honeywell, M., Hill, A., Singh, A., and Ghazvini, P. The Guardian REAL-TIME continuous glucose monitoring system. 2007; 32(12):62-65.

No original data

Wilson, D. M., Buckingham, B. A., Kunselman, E. L., Sullivan, M. M., Paguntalan, H. U., and Gitelman, S. E. A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes. Diabetes Care 2005; 28(1):15-9.

No outcome of interest

Wilson, D. P. and Endres, R. K. Continuous subcutaneous insulin infusion (CSII). J Okla State Med Assoc 85; 78(7):211-4.

Does not apply to a key question

Wilson, M. A. and Smith, C. B. Nutrient intake, glycemic control, and body mass index in adolescents using continuous subcutaneous insulin infusion and those using traditional insulin therapy. Diabetes Educ 2003; 29(2):230-2, 235-6, 238.

Other reason

Wolff-McDonagh, P., Kaufmann, J., Foreman, S., Wisotsky, S., Wisotsky, J. A., and Wexler, C. Using insulin pump therapy in poorly controlled type 2 diabetes. Diabetes Educ 2010; 36(4):657-65.

No comparison with placebo or usual care

Worm, D., Nielsen, L. R., Mathiesen, E. R., and Norgaard, K. Continuous glucose monitoring system with an alarm: a tool to reduce hypoglycemic episodes in pregnancy with diabetes. Diabetes Care 2006; 29(12):2759-60.

Case series or cross-sectional

Wredling, R. A., Adamson, U. K., and Lins, P. E. Alteration of the risk factor paradigm for discontinuance of insulin pump therapy. Diabetes Care 94; 17(8):942-3.

Case series or cross-sectional

Wu, Y. P., Graves, M. M., Roberts, M. C., and Mitchell, A. C. Is insulin pump therapy better than injection for adolescents with diabetes?. Diabetes Res Clin Pract 2010; 89(2):121-5.

Case series or cross-sectional

Wudi, K., Madarasz, E., Nadasdi, A., Turi, Z., Magenheim, R., Zsirai, L., Csakany, G. M., and Kerenyi, Z. Comparison of continuous subcutaneous insulin infusion and multiple daily insulin injections during pregnancy complicated by type 1 diabetes mellitus. Diabetes Technol. Ther. 2011; 13(2):236-237.

Case series or cross-sectional

Wyatt, S. Technology useful in managing diabetes during pregnancy. Aust Nurs J 2008; 16(2):34.

No comparison with placebo or usual care

Yagasaki, H., Kobayashi, K., Saitou, T., Nagamine, K., Mitsui, Y., Mochizuki, M., Kobayashi, K., Cho, H., Ohyama, K., Amemiya, S., and Nakazawa, S. Nocturnal blood glucose and IGFBP-1 changes in type 1 diabetes: Differences in the dawn phenomenon between insulin regimens. Exp Clin Endocrinol Diabetes 2010; 118(3):195-9.

Not in an outpatient setting

Yamaguchi, T., Kanatsuka, A., Hashimoto, N., Makino, H., and Yoshida, S. Influence of age on insulin requirement in insulin dependent diabetes mellitus patients treated with CSII. Horm Metab Res 86; 18(11):786-7.

No comparison with placebo or usual care

Yoo, H. J., An, H. G., Park, S. Y., Ryu, O. H., Kim, H. Y., Seo, J. A., Hong, E. G., Shin, D. H., Kim, Y. H., Kim, S. G., Choi, K. M., Park, I. B., Yu, J. M., and Baik, S. H. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract 2008; 82(1):73-9.

Other reason

Yudkin, J. S. Insulin infusion in diabetic patients with acute myocardial infarction. Insulin should be continued for 12 months after acute event. BMJ 97; 314(7074):145-6.

No original data

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Other reason

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No comparison with placebo or usual care

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No comparison with placebo or usual care

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Observational study that does not report on macrovascular, microvascular, maternal, or fetal outcomes

Appendix E. Evidence Tables

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Battelino, 2011[88]	RCT, parallel arms Yes run in Industry, government	Start: 2008 End: 2009 6 mo	NR	120 (122) Source population: local diabetes registries	T1DM, adults, adolescents	HbA1c >7.5%, not current pump or MDI user, CGM use within 4 wks, age <10 yrs or >65 yrs, T1DM diagnosis <1 yr, lack of reasonable metabolic control
Beck, 2010[82]	RCT, parallel arms	Enrollment NR 26 wks	NR	451 (NR)	T1DM, very young, adults, elderly	NR
Bergenstal, 2010[91]	RCT, parallel arms NR run in Industry	Start: 2007 End: 2008 1 yrs	US, Canada	485 (667) Source population: not specified but had be under the care of a PI or referring physician to get into study	T1DM, adults, elderly, 7-70 yrs, pregnant women excluded	HbA1c > 9.5%, HbA1c < 7.4%, use of insulin pump within 3 yrs, use of oral hypoglycemic within past 3 mo, not under care of PI or referring physician for at least 6 mo, no access to computer, no history of testing blood glucose on average of 4+ x/day for previous 30 days, intent to become pregnant, history of 2+ severe hypoglycemic events in yr before enrollment
Bin-Abbas, 2006[56]	Non-randomized NR run in Support NR	Start: 2002 End: 2004 12 mo	Saudi Arabia	22 (NR) Source population: Referral clinic	T1DM, pregnant women excluded	Not on conventional insulin therapy (2 injections/day)
Bolli, 2009[60]	RCT, parallel arms Yes run in Industry	Enrollment NR 24 wks	Europe	58 (67) Source population: NR	T1DM, adults, 18-70 yrs	HbA1c ≥ 6.5%, HbA1c ≤ 9.0%, not current pump or MDI user, use of insulin pump ever, fasting plasma glucose <7.0 mmol/L (<126 mg/dl), ever used insulin glargine, BMI > 27, C-peptide > 0.1 nmol/l, >2 severe hypoglycemic episodes in last 6 mo, recent DKA or impaired renal/liver function

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Bruttomesso, 2008[65]	RCT, crossover Yes run in Industry	Start: 2003 End: 2005 4 mo	Italy	42 (NR) Source population: 4 Italian centers	T1DM, adults, pregnant women excluded	Use of insulin pump within < 6 mo, unwillingness to measure blood glucose frequently, inability to adjust insulin administration, insulin allergy, untreated retinopathy, cardiovascular disease, hepatic or renal insufficiency, drug abuse, life threatening disease, lactating women, those who intend to become pregnant
Bruttomesso, 2011[76]	Cohort NR run in Support NR	Start: 2001 End: 2009 Followup NR	Europe	144 (469) Source population: NR	T1DM, adults, pregnant women only	Treated with insulin not MDI with NPH insulin, pump not started at the time of conception, pump or MDI started within 6 mo of conception
Chico, 2010[77]	Cohort NR run in Industry	Start: 1984 End: 2006 Followup NA	Europe	271 Source population: diabetes referral clinic, Ob/Gyn clinic	T1DM, adults, pregnant women only	Male, multiple gestation, same modality of basal-bolus insulin as before pregnancy
Cohen, 2003[50]	RCT, crossover No run in Industry	Enrollment NR 12 mo	Israel	16 (NR) Source population: Referral clinic, Children's medical center	T1DM, pregnant women excluded	Not current pump or MDI user, T1DM diagnosis <2 yrs, C-peptide >0.6ng/ml, chronic disease that could interfere with DM treatment, patients unable to detect hypoglycemia, evidence of microvascular complications or other clinically significant disorders
Cypryk, 2008[74]	Cohort No run in Other	Start: 2003 End: 2006 36 wks	Poland	116 (NR) Source population: Referral clinic	T1DM, adults, pregnant women only	Male

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Deiss, 2006[87]	RCT, parallel arms No run in Industry	Enrollment NR 3 mo	Europe	162 (162) Source population: NR	T1DM, very young, adults	HbA1c > 8.1%
Derosa, 2009[70]	RCT, parallel arms No run in Support NR	Enrollment NR 12 mo	Italy	64 (NR) Source population: University clinic	T1DM & T2DM, adults	Genetic condition affecting lipid metabolism, history of alcohol or drug abuse, neoplastic, infectious or autoimmune disease, poor mental condition, taking other drug able to influence lipid and glycemic metabolism
DeVries, 2002[66]	RCT, parallel arms, Yes run in Industry	Start: 1999 End: 2000 16 wks	the Netherlands	89 (NR) Source population: Referral clinic	T1DM, adults, pregnant women excluded	HbA1c > 8.5%, no contraception used, severe active retinopathy, no impaired hepatic function, no nephropathy, no insulin resistance, no substance abuse, no cardiac disease, no insulin allergy, no past or current psychiatric treatment, not pregnant or breastfeeding
Doyle, 2004[51]	RCT, parallel arms Yes run in Industry, government	Enrollment NR 16 wks	US	32 (NR) Source population: Referral clinic	T1DM, very young, 8-21 yrs, pregnant women excluded	HbA1c > 11%, HbA1c < 6.5%, use of insulin pump ever, medical problem other than treated thyroid or celiac disease, not willing to check blood glucose 4x/day
Garcia-Garcia, 2007[53]	Non-randomized NR run in Government	Enrollment NR	Spain	32 (200) Source population: Pediatric diabetes clinic	T1DM, very young, pregnant women excluded	HbA1c < 7.5%, not current pump or MDI user, T1DM diagnosis after 14 yrs of age, <2 yrs duration and followup in service, daily insulin requirement <0.75 U/kg, previous intensive treatment with <4 glycemic analyses/day, poor parental supervision, poor relationship with care team

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Hanaire-Broutin, 2000[64]	RCT, crossover, Yes run in Industry	Enrollment NR 8 mo	France	41 (NR) Source population: private diabetology practices	T1DM, adults, 21-65 yrs	HbA1c > 10%, not current pump or MDI user, C-peptide positive, untreated retinopathy, impaired renal function, gastric neuropathy, BMI > 30, insulin dose >2U/kg, history of hypoglycemia unawareness, any severe disease that could interfere with the study
Herman, 2005[69]	RCT, parallel arms Yes run in Industry, Government	Enrollment NR 12 mo	NR	107 (144) Source population: NR	T2DM, elderly	HbA1c < 7.0%, BMI > 45 kg/m2, severe impairment of cardiac hepatic or renal function, physical, psychological or cognitive impairments, > 2 episodes of severe hypoglycemia in past yr, hypoglycemia unawareness, age < 60 yrs, absence of T2DM diagnosis for at least one yr
Hermanides, 2011[94]	RCT, parallel arms No run in Industry	Start: 2007 End: 2009 26 wks	Europe	83 (93)	T1DM, adults	HbA1c < 8.2%, hearing problems that can impair hearing alarms, substance abuse other than nicotine, abdominal skin abnormalities that might hinder subcutaneous insertion, current treatment for psychiatric disorder other than depression, heart failure, cancer, kidney disease, pregnancy, CSII within 6 mo, participation in other therapeutic trial
Hieronimus, 2005[73]	Cohort No run in Support NR	Start: 1999 End: 2003	France	56 (NR) Source population: Ob/Gyn clinic	T1DM, adults, pregnant women only	Not current pump or MDI user
Hirsch, 2005[59]	RCT, crossover Yes run in Industry	Enrollment NR 5 wks	US	100 (NR) Source population: NR	T1DM, adults, pregnant women excluded	HbA1c > or = 9.0%, use of insulin pump within at least 3 mo before the screening visit, no contraception used, BMI ≥ 40, impaired hepatic, renal, or cardiac function, hypoglycemia unawareness or recurrent major hypoglycemia, breastfeeding

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Hirsch, 2008[86]	RCT, parallel arms Yes run in Industry	Enrollment NR 6 mo	US	146 (138) Source population: NR	T1DM, adults, elderly	HbA1c > 7.5%, use of CGM within 6 mo, < 12 yrs old, > 72 yrs old, diagnosed with diabetes > 1 yr
Hoogma, 2006[63]	RCT, crossover Yes run in Industry	Enrollment NR 6 mo	Europe	272 (NR) Source population: NR	T1DM, adults, 18-65 yrs, pregnant women excluded	No contraception used, hypoglycemia unawareness, progressive retinopathy, renal insufficiency (creatinine ≥ 250 micromol/L), ACS or CVA in last 6 mo, uncontrolled HTN; able to manage intensive insulin therapy, C-peptide secretion, autonomic neuropathy
JDRF CGM Study Group, 2009[84]	RCT, parallel arms, Yes run in Industry, other	Start: 2007 End: 2008 26 wks	US	129 (NR) Source population: academic, community, and managed case-based practices	T1DM, adults, elderly, 8+ years old	HbA1c > 7.0%, not using a pump or taking < 3 injections/day, had diabetes for < 1 yr
Kernaghan, 2008[72]	Cohort No run in Support NR	Start: 1998 End: 2005 40 weeks	UK	42 (NR) Source population: diabetic pregnancy clinic	T1DM & T2DM, adults, pregnant women only	Male
Kordonouri, 2010[80]	RCT, parallel arms No run in period Industry	Start: 2007 End: 2008 52 weeks	Europe	160 (295) Source population: Pediatric Health Center	T1DM, very young, 1-16 yrs	Diagnosis of type 1 diabetes > 4 wks before study entry
Lee, 2007[93]	RCT, parallel arms, No run in Support NR	Enrollment NR 15 wks	US	16 (NR) Source population: Referral clinic	T1DM, adults	HbA1c < 7.5%, not on MDI therapy, exclusion of patients that have used insulin pump

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Lepore, 2003[67]	Non-randomized NR run in Support NR	Enrollment NR 1 yrs	Italy	32 (NR) Source population: NR	T1DM, adults	HbA1c < 8.0%, treated with MDI (regular or lispro insulin before each meal plus NPH as basal insulin) for 1+ yr
Nuboer, 2008[54]	RCT, crossover Yes run in period Government, other	Enrollment NR 14 mo	Netherlands	39 (NR) Source population: Referral clinic, Children's hospital	T1DM, very young, pregnant women excluded	HbA1c < 8.0%, random C-peptide >200 pmol, age <4 yrs or >16 yrs, no T1DM diagnosis confirmed, no history of repeated symptomatic hypoglycemia, no attendance of regular school, mental retardation, insufficient Dutch proficiency, chronic complications, pregnancy, co-morbidity, psych problems in child or parent, no home phone
O'Connell, 2009[85]	RCT, parallel arms, No run in Industry	Enrollment NR 3 mo	Australia	62 (77) Source population: Referral clinic	T1DM, adults, 13-40 yrs	HbA1c > 8.5%, use of insulin pump within < 3 mo, diabetes for < 1 yr, patients without internet access, excluded patients that cannot reliably perform SMBG at least 4x/day, unwilling to use subcutaneous sensor component of system for < 70% of study period, Patients with coexistent medical issues that would interfere with their ability to use the system, history of severe hypoglycemia or coexisting illness predisposing to hypoglycemia
Opipari-Arrigan, 2007[49]	RCT, parallel arms NR run in Other	Start: 2002 End: 2003 6 mo	US	18 (NR) Source population: Referral clinic	T1DM, very young, pregnant women excluded	T1DM diagnosis history <1 yr, serious medical conditions, significant developmental delay, known psychiatric illness
Peyrot, 2009[92]	RCT, parallel arms NR run in Industry	Enrollment NR 16 wks	NR	28 (NR) Source population: NR	T1DM, adults	Use of insulin pump ever, optimal glucose control (not specified)

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Pozzilli, 2003[57]	RCT, parallel arms No run in Industry, other	Enrollment NR 2 yrs	Italy	23 (NR) Source population: unspecified clinic	T1DM, adults, pregnant women excluded	Diagnosis with age at presentation between 12 and 35 yrs, newly diagnosed, no major contraindications or other major chronic conditions, willing and able to participate in regular followup
Raccah, 2009[81]	RCT, parallel arms No run in Industry	Start: 2006 End: 2007 6 mo	France	132 (148) Source population: Referral clinic, NR	T1DM, very young, adults, 2-65 yrs	HbA1c < 8.0%, diagnosis of diabetes < 12 mo prior to randomization, follow-up by the respective investigator for < 3 mo, not being treated with basal/bolus MDI with rapid insulin analogs at mealtimes
Radermecker, 2010[83]	RCT, crossover No run in Other	Enrollment NR 12 wks	Europe	13 (NR) Source population: NR	T1DM, adults	Use of insulin pump within < 1 yr, < 6 recorded capillary blood glucose values < 60 mg/dl within the last 14 days, < 4 quarterly visits/ yr to optimize insulin therapy
Raskin, 2003[36]	RCT, parallel arms Yes run in period Industry	Start: 1999 End: 2000 24 wks	US	132 (205) Source population: NR	T2DM, adults, 35+ yrs, pregnant women excluded	HbA1c > 12%, HbA1c < 6.0%, use of insulin pump ever, no contraception used, T2DM for < 2 yrs, treatment for < 5 mo with at least 1 insulin dose per day; with or without OAD, those with impaired hepatic, renal or cardiac function, recurrent major hypoglycemia, BMI> 43, breastfeeding, C-peptide ≤0.2
Rigla, 2008[105]	RCT, crossover No run in Industry, government, other	Enrollment NR 4 mo	Spain	10 (NR) Source population: NR	T1DM, adults	NR
Schiaffini, 2007[55]	RCT, parallel arms, No run in Support NR	Enrollment NR 24 mo	Italy	36 (36) Source population: Referral clinic, Children's Hospital	T1DM, very young, pregnant women excluded	HbA1c < 8.0%, age < 9 or > 18 yrs, T1DM diagnosis <3 yrs, T1DM diagnosis not meeting ADA criteria

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Skogsberg, 2008[48]	RCT, parallel arms, No run in Industry, government, other	Start: 2001 End: 2004 24 mo	Sweden	72 (NR) Source population: 9 pediatric departments in Sweden	T1DM, very young, pregnant women excluded	NR
Tamborlane, 2008[27]	RCT, parallel arms Yes run in Other	Start: 2007 26 wks	US	322 (NR) Source population: 10 centers including academic, community, and MCOs	T1DM, adults, elderly, 8+ yrs	HbA1c > 10%, HbA1c < 7.0%, use of CGM within < 6 mo, diabetes diagnosis < 1 yr before randomization, patients not using either an insulin pump or at least three daily insulin injections
Thomas, 2007[61]	RCT, parallel arms NR run in Industry	Enrollment NR 24 wks	NR	21 (NR) Source population: NR	T1DM, adults	No episodes of severe hypoglycemia within preceding 6 mo, C-peptide positive, had used MDI insulin analogue therapy before
Tsui, 2001[62]	RCT, parallel arms Yes run in Industry	Enrollment NR 9 mo	Canada	27 (NR) Source population: Referral clinic	T1DM, adults, 18-60 yrs, pregnant women excluded	Alcohol or drug abuse, in other clinical trial in past 4 wks, diabetic for < 2 yrs, onset of diabetes after 40 yrs old, unable to comply with treatment regimen, >2 severe hypoglycemia episodes in past yr, BMI > 35, severe late complications, CVD, liver disease, cancer
Volpe, 2010[75]	Cohort No run in	Start: 2005 End: 2008 36.4 wks	Italy	42 (NR) Source population: Outpatient clinic	T1DM, adults, pregnant women only	Male

Table 1. Study design characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Study design Run in period Support	Enrollment dates Followup duration	Location	N enrolled (N Screened) Source population	Included population	Exclusion criteria
Wainstein, 2005[37]	RCT, crossover Yes run in Support NR	Enrollment NR 18 wks	NR	40 (58) Source population: diabetic centers	T2DM, adults, elderly	HbA1c < 8.5%, BMI < 30kg/m2 or > 45 kg/m2, age < 30 and > 70 yrs, diet treatment < 3 mo, metformin dose < 850 mg 2 to 3 x/day, new-onset diabetes (< 6 mo), T1DM, diabetes secondary to pancreatitis, history of CAD or CVA in last 12 mo, pre-proliferative and proliferative diabetic retinopathy, advanced nephropathy (Creatinine > 1.5 mg/dl, liver enzymes> 2 times upper limit, HbA1C >15 %
Weintrob, 2003[52]	RCT, crossover Yes run in Industry	Enrollment NR 3.5 mo	Israel	23 (24) Source population: National Institute for Childhood Diabetes of Schneider Children's Medical Center	T1DM, 8-14 yrs	Patients with sufficient C-peptide secretion (>=200 pmol/L), patients unable to cope with treatment procedures
Yoo, 2008[102]	RCT, parallel arms No run in Industry, government, other	Start: 2007 End: 2007 3 mo	Korea	65 (65) Source population: NR	T2DM, adults, elderly, 20-80 yrs	HbA1c > 10%, HbA1c < 8.0%, use of oral hypoglycemic within < 1 yr, stable insulin or OHA regimen for < 2 mo, stable dose of antihypertensive or lipid-lowering drugs for < 4 wks, severe diabetic complications (e.g. retinopathy), steroid use in previous 3 mo, liver/kidney disease, other medical problems that affected study results or trial participation

Abbreviations: ACS = acute coronary syndrome; ADA = American Diabetes Association; BMI = body mass index; CVA = cerebrovascular accident, stroke; CVD = cardiovascular disease; DKA = diabetic ketoacidosis; DM = diabetes mellitus; hr = hour; kg = kilogram; L = liter; m = meter; MCO = managed care organization; MDI = multiple daily injections; ml = milliliter; mmol = micromoles; mo = month(s); ng = nanograms; NR= not reported; OAD = oral anti diabetic; OHA = oral hypoglycemic agents; pmol = picomole; psych = psychological; RCT = randomized controlled trial; SMBG = self monitoring of blood glucose; T1DM = Type 1 Diabetes Mellitus; T2DM = Type 2 Diabetes Mellitus; U = units; wks = weeks; x/day = times per day; yrs = years

Table 2. Study population characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Inter-vention, n	Age (years) Male (%)	Race (%)	Baseline HbA1c (%)	Baseline weight (kg)/BMI (kg/m2)	Duration of diabetes (years)	Insulin delivery device (%)	With-drawals (N)
Battelino, 2011[88]	SMBG, 39	Age NR 67	NR	Mean: 6.91	Mean BMI: 22.0	Mean: 11.4	MDI: 41 CSII: 59	10
Battelino, 2011[88]	rtCGM, 44	Age NR 58	NR	Mean: 6.92	Mean BMI: 22.4	Mean: 11.6	MDI: 24 CSII: 76	9
Beck, 2010[82]	SMBG	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	NR
Beck, 2010[82]	rtCGM	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	NR
Bergenstal, 2010[91]	MDI + SMBG, 241	Age NR 56	C: 92 His: 3 Other: 5	Mean: 8.3	Mean BMI: 25.6, Mean weight: 73	Mean: 15.4	MDI:100	22
Bergenstal, 2010[91]	CSII + rtCGM, 244	Age NR 57	C: 91 His: 3 Other: 7	Mean: 8.3	Mean BMI: 25.3, Mean weight: 71.9	Mean: 15.2	CSII:100	20
Bin-Abbas, 2006[56]	MDI, 8	Mean: 9, Range: 7-12 62.5	NR	Mean: 10.1	BMI/Weight NR	Mean: 6	NA	NR
Bin-Abbas, 2006[56]	CSII, 14	Mean: 12.8, Range: 4-16 50	NR	Mean: 10.2	BMI/Weight NR	Mean: 6	NA	NR
Bin-Abbas, 2006[56]	MDI, 8	Mean: 9, Range: 7-12 62.5	NR	Mean: 10.1	BMI/Weight NR	Mean: 6	NA	NR
Bolli, 2009[60]	MDI, 26	Mean: 21.5 54	NR	Mean: 7.8	Mean BMI: 24.3, Mean weight: 70.8	Mean: 20.9	NA	NR
Bolli, 2009[60]	CSII, 24	Mean: 19.1 54	NR	Mean: 7.7	Mean BMI: 23.8, Mean weight: 70.1	Mean: 18.5	NA	NR
Bruttomesso, 2008[65]	MDI, 15	Age NR 47	NR	Mean: 7.4	Mean BMI: 22.9, Mean weight: 66.8	Mean: 15.7	NA	NR
Bruttomesso, 2008[65]	CSII, 24	Age NR 50	NR	Mean: 7.6	Mean BMI: 24.1, Mean weight: 71	Mean: 17.2	NA	NR
Bruttomesso, 2011[76]	MDI, 44	Age NR 0	NR	Mean: 7.66	BMI/Weight NR	Mean: 13.5	NA	NR
Bruttomesso, 2011[76]	CSII, 100	Age NR 0	NR	Mean: 7.20	BMI/Weight NR	Mean: 16.5	NA	NR

Table 2. Study population characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Inter-vention, n	Age (years) Male (%)	Race (%)	Baseline HbA1c (%)	Baseline weight (kg)/BMI (kg/m2)	Duration of diabetes (years)	Insulin delivery device (%)	With-drawals (N)
Chico, 2010[77]	MDI, 196	Age range: 18-43 0	NR	Mean: 6.03 Range: 4.3-9.5	Mean weight: 23	Mean: 12	NA	NR
Chico, 2010[77]	MDI, 16	Age range: 26-39 0	NR	Mean: 6.3 Range: 6-8.1	Mean weight: 22.8	Mean: 8.5	NA	NR
Chico, 2010[77]	CSII, 59	Age range: 25-42 0	NR	Mean: 6.5 Range: 5.4-9.4	Mean weight: 23.8	Mean: 16	NA	NR
Cohen, 2003[50]	MDI, 16	Median: 14.2 37.5	NR	Mean: 8.48	BMI/Weight NR	Duration NR	NA	3
Cohen, 2003[50]	CSII, 16	Median: 14.2 37.5	NR	Mean: 8.58	BMI/Weight NR	Duration NR	NA	1
Cypryk, 2008[74]	MDI, 86	Age NR 0	C: 100	HbA1c NR	Mean BMI: 23.7	Mean: 7.7	NA	NR
Cypryk, 2008[74]	CSII, 30	Age NR 0	C: 100	HbA1c NR	Mean BMI: 23.5	Mean: 12.7	NA	NR
Deiss, 2006[87]	SMBG	Age NR	NR	Mean: 9.7	BMI/Weight NR	Duration NR	NA	0
Deiss, 2006[87]	rtCGM	Age NR	NR	Mean: 9.5	BMI/Weight NR	Duration NR	NA	4
Deiss, 2006[87]	rtCGM	Age NR	NR	Mean: 9.6	BMI/Weight NR	Duration NR	NA	1
Derosa, 2009[70]	MDI, 32	Age NR 50	NR	Mean: 9.3	Mean BMI: 29.8	Duration NR	NA	NR
Derosa, 2009[70]	CSII, 32	Age NR 47	NR	Mean: 9.2	Mean BMI: 29.5	Duration NR	NA	NR
DeVries, 2002[66]	MDI, 40	Age NR 53	NR	Mean: 9.3	Mean weight: 79.8	Mean: 18	NA	0
DeVries, 2002[66]	CSII, 39	Age NR 54	NR	Mean: 9.3	Mean weight: 77.3	Mean: 17.6	NA	7
Doyle, 2004[51]	MDI, 16	Age NR 50	C: 81 AA: 6 His: 12	Mean: 8.2	BMI/Weight NR	Mean: 5.6	NA	1

Table 2. Study population characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Inter-vention, n	Age (years) Male (%)	Race (%)	Baseline HbA1c (%)	Baseline weight (kg)/BMI (kg/m2)	Duration of diabetes (years)	Insulin delivery device (%)	With-drawals (N)
Doyle, 2004[51]	CSII, 16	Age NR 38	C: 69 AA: 12 His: 19	Mean: 8.1	BMI/Weight NR	Mean: 6.8	NA	0
Garcia-Garcia, 2007[53]	MDI, 24	Mean: 12.8 41.7	NR	Mean: 7.8	BMI/Weight NR	Mean: 5.7	NA	NR
Garcia-Garcia, 2007[53]	CSII, 8	Mean: 11.6 37.5	NR	Mean: 7.6	BMI/Weight NR	Mean: 5.7	NA	NR
Hanaire-Broutin, 2000[64]	MDI + rtCGM, 41	Age NR 51	NR	Mean: 8.39	Mean BMI: 24, Mean weight: 68.2	Mean: 20	NA	1
Hanaire-Broutin, 2000[64]	CSII + SMBG	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	NR
Herman, 2005[69]	MDI, 54	Age NR 44	C: 91 AA: 4 His: 4 Other: 2	Mean: 8.1	Mean BMI: 31.8	Mean: 15.4	NA	4
Herman, 2005[69]	CSII, 53	Age NR 72	C: 81 AA: 8 His: 8 Other: 4	Mean: 8.4	Mean BMI: 32.5	Mean: 16.9	NA	5
Hermanides, 2011[94]	MDI + SMBG, 39	Age NR 54	NR	Mean: 8.64	BMI/Weight NR	Mean: 21	MDI	4
Hermanides, 2011[94]	CSII + rtCGM, 44	Age NR 50	NR	Mean: 8.47	BMI/Weight NR	Mean: 16.9	CSII	1
Hieronimus, 2005[73]	MDI, 23	Mean: 26 0	NR	Mean: 7.6	Mean BMI: 21.8	Mean: 9.8	NA	NR
Hieronimus, 2005[73]	CSII, 33	Mean: 30 0	NR	Mean: 7.5	Mean BMI: 23.8	Mean: 13.9	NA	NR
Hirsch, 2005[59]	MDI	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	NR
Hirsch, 2005[59]	CSII	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	NR

Table 2. Study population characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Inter-vention, n	Age (years) Male (%)	Race (%)	Baseline HbA1c (%)	Baseline weight (kg)/BMI (kg/m2)	Duration of diabetes (years)	Insulin delivery device (%)	With-drawals (N)
Hirsch, 2008[86]	SMBG, 72	Mean: 33.2, Median: 34, Range: 12-72 39	C: 90 AA: 1 Asian: 3 His: 6	Mean: 8.39, Median: 34, Range: 7.5-10.6	Mean BMI: 26.3, Median BMI: 25.9, Mean weight: 75.4, Median weight: 72.4	Mean: 16.7 Median: 13	CSII:100	2
Hirsch, 2008[86]	rtCGM, 66	Mean: 33, Median: 34.5, Range: 12-64 48	C: 89 AA: 2 Asian: 0 His: 9	Mean: 8.49, Median: 34.5, Range: 7.5-10.7	Mean BMI: 26.9, Median BMI: 25.9, Mean weight: 76.8, Median weight: 74	Mean: 20.8, Median: 20.5	CSII:100	6
Hoogma, 2006[63]	MDI, 129	Age NR 47	NR	Mean: 8.3	Mean BMI: 24.8	Mean: 15.4	NA	NR
Hoogma, 2006[63]	CSII, 127	Age NR 48	NR	Mean: 8.2	Mean BMI: 24.9	Mean: 14.4	NA	NR
JDRF CGM Study Group, 2009[84]	SMBG, 62	Mean: 32 48	C: 94	Mean: 6.5	BMI/Weight NR	Duration NR	CSII:79 MDI:21	2
JDRF CGM Study Group, 2009[84]	rtCGM, 67	Mean: 29.3 46	C: 94	Mean: 6.4	BMI/Weight NR	Duration NR	CSII:93 MDI:7	0
Kernaghan, 2008[72]	MDI, 18	Age NR 0	NR	Mean: 8.01	BMI/Weight NR	Duration NR	NA	NR
Kernaghan, 2008[72]	CSII, 24	Age NR 0	NR	Mean: 7.62	BMI/Weight NR	Duration NR	NA	NR
Kordonouri, 2010[80]	CSII + SMBG, 80	Mean: 9.1 50	NR	Mean: 11.5	BMI/Weight NR	Duration NR	CSII:100	2
Kordonouri, 2010[80]	CSII + rtCGM, 80	Mean: 8.5 50	NR	Mean: 11.2	BMI/Weight NR	Duration NR	CSII:100	4
Lee, 2007[93]	SMBG, 8	Age NR	NR	Mean: 8.58	BMI/Weight NR	Duration NR	MDI:100	NR
Lee, 2007[93]	rtCGM, 8	Age NR	NR	Mean: 9.45	BMI/Weight NR	Duration NR	CSII:100	NR
Lepore, 2003[67]	MDI, 16	Age NR 44	NR	HbA1c NR	BMI/Weight NR	Mean: 14.7	NA	NR
Lepore, 2003[67]	CSII, 16	Age NR 50	NR	HbA1c NR	BMI/Weight NR	Mean: 19.6	NA	NR

Table 2. Study population characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Inter-vention, n	Age (years) Male (%)	Race (%)	Baseline HbA1c (%)	Baseline weight (kg)/BMI (kg/m2)	Duration of diabetes (years)	Insulin delivery device (%)	With-drawals (N)
Nuboer, 2008[54]	MDI + SMBG, 19	Mean: 10 52.6	C: 90	Mean: 7.98	BMI/Weight NR	Mean: 4.7	NA	NR
Nuboer, 2008[54]	CSII + SMBG, 20	Mean: 10 35	C: 90	Mean: 7.66	BMI/Weight NR	Mean: 5.6	NA	1
O'Connell, 2009[85]	SMBG, 31	Age NR 29	NR	Mean: 7.5	BMI/Weight NR	Mean: 9.2	CSII:100	2
O'Connell, 2009[85]	rtCGM, 31	Age NR 29	NR	Mean: 7.3	BMI/Weight NR	Mean: 11.1	CSII:100	5
Opipari-Arrigan, 2007[49]	MDI + rtCGM, 9	Mean: 4.4 50	C: 100	Mean: 7.98	Mean BMI: 15.9	Duration NR	NA	1
Opipari-Arrigan, 2007[49]	CSII + rtCGM, 9	Mean: 4.4 62.5	C: 100	Mean: 8.26	Mean BMI: 17	Duration NR	NA	3
Peyrot, 2009[92]	MDI + SMBG, 14	Age NR	NR	Mean: 8.32	Mean weight: 82.6	Duration NR	CSII:0	1
Peyrot, 2009[92]	CSII + rtCGM, 14	Age NR	NR	Mean: 8.87	Mean weight: 77.7	Duration NR	CSII:0	0
Pozzilli, 2003[57]	MDI, 12	Mean: 18.9	NR	Mean: 10.3	Mean BMI: 20.9	Mean: 0	NA	4
Pozzilli, 2003[57]	CSII, 7	Mean: 17.9	NR	Mean: 11.7	Mean BMI: 19.8	Mean: 0	NA	0
Raccah, 2009[81]	CSII + SMBG, 60	Age NR 57	NR	Mean: 9.28	Mean BMI: 22.5, Mean weight: 62.6	Mean: 12.3	CSII:100	6
Raccah, 2009[81]	rtCGM, 55	Age NR 55	NR	Mean: 9.11	Mean BMI: 23.5, Mean weight: 65.7	Mean: 11.2	CSII:100	14
Radermecker, 2010[83]	CSII + SMBG, 13	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	1
Radermecker, 2010[83]	rtCGM, 13	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	3
Raskin, 2003[36]	MDI, 61	Age NR 57	C: 82 AA: 13 Other: 5	Mean: 8	Mean BMI: 32.2	Mean: 11.9	NA	6
Raskin, 2003[36]	CSII, 66	Age NR 64	C: 80 AA: 12 Other: 8	Mean: 8.2	Mean BMI: 32.2	Mean: 13.8	NA	6
Rigla, 2008[105]	SMBG, 10	Mean: 41.2	NR	HbA1c NR	BMI/Weight NR	Mean: 14.9	CSII:100	0

Table 2. Study population characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Inter-vention, n	Age (years) Male (%)	Race (%)	Baseline HbA1c (%)	Baseline weight (kg)/BMI (kg/m2)	Duration of diabetes (years)	Insulin delivery device (%)	With-drawals (N)
Rigla, 2008[105]	rtCGM, 10	Mean: 41.2	NR	HbA1c NR	BMI/Weight NR	Mean: 14.9	CSII:100	0
Schiaffini, 2007[55]	MDI, 17	Mean: 12.9 47.1	NR	Mean: 8.5	BMI/Weight NR	Mean: 5.7	NA	NR
Schiaffini, 2007[55]	CSII, 19	Mean: 12.5 52.6	NR	Mean: 8.3	BMI/Weight NR	Mean: 5.8	NA	NR
Skogsberg, 2008[48]	MDI, 38	Mean: 12.3 58.3	NR	Mean: 8.4	BMI/Weight NR	Duration NR	NA	5
Skogsberg, 2008[48]	CSII, 34	Mean: 11.8 58.3	NR	Mean: 8.2	BMI/Weight NR	Duration NR	NA	NR
Tamborlane, 2008[27] Age strata:8-14	SMBG, 58	Mean: 11.6 50	C: 93	Mean: 8	BMI/Weight NR	Mean: 5.3	CSII:84 MDI:16	0
Tamborlane, 2008[27] Age strata:>25	SMBG, 46	Mean: 44.6 43	C: 89	Mean: 7.6	BMI/Weight NR	Mean: 21.8	CSII:85 MDI:15	0
Tamborlane, 2008[27] Age strata:15-24	SMBG, 53	Mean: 18.2 34	C: 96	Mean: 7.9	BMI/Weight NR	Mean: 8.8	CSII:75 MDI:25	2
Tamborlane, 2008[27] Age strata:>25	rtCGM, 52	Mean: 41.2 40	C: 100	Mean: 7.6	BMI/Weight NR	Mean: 23.6	CSII:83 MDI:17	2
Tamborlane, 2008[27] Age strata:8-14	rtCGM, 56	Mean: 11.4 52	C: 91	Mean: 7.9	BMI/Weight NR	Mean: 6.2	CSII:84 MDI:16	0
Tamborlane, 2008[27] Age strata:15-24	rtCGM, 57	Mean: 18.8 49	C: 82	Mean: 8	BMI/Weight NR	Mean: 9.5	CSII:67 MDI:33	1
Thomas, 2007[61]	MDI, 7	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	NR
Thomas, 2007[61]	CSII, 7	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	NR
Tsui, 2001[62]	MDI, 14	Age NR 71	NR	Mean: 8.16	Mean BMI: 26, Median BMI: 27	Mean: 15, Median: 13	NA	0
Tsui, 2001[62]	CSII, 13	Age NR 62	NR	Mean: 7.73	Mean BMI: 27, Median BMI: 27	Mean: 17, Median: 13	NA	1
Volpe, 2010[75]	MDI, 22	Age NR 0	C: 100	HbA1c NR	Mean BMI: 23.7	Mean: 12.1	NA	NR
Volpe, 2010[75]	CSII + SMBG, 20	Age NR 0	C: 100	HbA1c NR	Mean BMI: 23	Mean: 16	NA	NR
Wainstein, 2005[37]	MDI, 20	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	6

Table 2. Study population characteristics of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Inter-vention, n	Age (years) Male (%)	Race (%)	Baseline HbA1c (%)	Baseline weight (kg)/BMI (kg/m2)	Duration of diabetes (years)	Insulin delivery device (%)	With-drawals (N)
Wainstein, 2005[37]	CSII, 20	Age NR	NR	HbA1c NR	BMI/Weight NR	Duration NR	NA	5
Weintrob, 2003[52]	MDI, 12	Mean: 11.6 50	NR	Mean: 8.6	BMI/Weight NR	Mean: 6.3	NA	0
Weintrob, 2003[52]	CSII, 11	Mean: 11.9 36	NR	Mean: 7.9	BMI/Weight NR	Mean: 5.3	NA	0
Yoo, 2008[102]	SMBG, 28	Mean: 57.5 50	NR	Mean: 8.7	Mean BMI: 25.7, Mean weight: 65.7	Mean: 13.3	NA	5
Yoo, 2008[102]	rtCGM, 29	Mean: 54.6 34	NR	Mean: 9.1	Mean BMI: 25, Mean weight: 63.3	Mean: 11.7	NA	3

Abbreviations: AA = African American; BMI = body mass index; C = Caucasian; CSII = continuous subcutaneous insulin infusion; His = Hispanic; kg = kilogram; NA = not applicable; NR = not reported; rtCGM = real time continuous glucose monitoring; SMBG = self monitoring of blood glucose

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Battelino, 2011[88]	Both	NA	SMBG	NR	6 mo	NR Preprandial: 70-130 mg/dL 2-hr postprandial: 180 mg/dL	NR
Battelino, 2011[88]	Both	NA	Abbott FreeStyle Navigator	NR	6 mo	NR Preprandial: 70-130 mg/dL 2-hr postprandial: 180 mg/dL	NR
Beck, 2010[82]	MDI	NA	SMBG Monitor use: 4+	NA	26 wks	Titration guidelines NR Targets NR	NA
Beck, 2010[82]	CSII	NA	rtCGM model unspec.	NA	26 wks	Titration guidelines NR Targets NR	NA
Bergenstal, 2010[91]	MDI	MDI Injections NR Prandial: aspart Basal: glargine	SMBG Monitor use: NA Fingerstick: NR	NA	1 yr	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Bergenstal, 2010[91]	CSII	MM REAL Prandial: aspart	MM paradigm Monitor use: unclear if just used for 1 wk at baseline, 6 mo, and 12 mo Fingerstick: NR	Yes	1 yr	Titration guidelines NR Between visit guidelines NR Targets NR	NR

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Bin-Abbas, 2006[56]	MDI	MDI 4+ times/day Prandial: lispro Basal: glargine	NA	NA	6 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Bin-Abbas, 2006[56]	MDI	MDI 4+ times/day Prandial: lispro Basal: glargine	NA	NA	6 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Bin-Abbas, 2006[56]	CSII	Minimed unspec. Prandial: lispro	NA	NR	12 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Bolli, 2009[60]	MDI	MDI 4+ times/day Prandial: lispro Basal: glargine	NA	NA	24 wks	Titration guidelines: Yes Between visit guidelines NR Preprandial: 90-140 mg 5.0-7.7 mmol, FG: 80-120 mg, 4.4-6.6 mmol, 2 hr postprandial: <7.7 mmol, other target: bedtime blood glucose 110-150 mg, 1-8.3 mmol	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Bolli, 2009[60]	CSII	MM 508, Prandial: lispro	NA	NR	24 wks	Titration guidelines: Yes Between visit guidelines NR Preprandial: 90-140 mg 5.0-7.7 mmol, FG: 80-120 mg, 4.4-6.6 mmol, 2 hr postprandial: <7.7 mmol, other target: bedtime blood glucose 110-150 mg, 6.1-8.3 mmol,	NA
Bruttomesso, 2008[65]	MDI	MDI 4+ times/day Prandial: lispro Basal: glargine	NA	NA	4 mo	Titration guidelines NR Between visit guidelines NR Preprandial: 5.0-6.7 mmol, FG: 5.0-6.7 mmol, 2 hr postprandial: 6.0-8.5 mmol (90 min after meals), other target: 6.1-7.5 mmol/l at bedtime	NA
Bruttomesso, 2008[65]	CSII	DR DTRON, Animas, DR HTron v100, MM 508 Prandial: lispro	NA	NR	4 mo	Titration guidelines NR Between visit guidelines NR Preprandial: 5.0-6.7 mmol, FG: 5.0-6.7 mmol, 2 hr postprandial: 6.0-8.5 mmol (90 min after meals), other target: 6.1-7.5 mmol at bedtime	NA
Bruttomesso, 2011[76]	MDI	Injections NR Prandial: aspart, lispro Basal: glargine	NA	NA	NR	Titration guidelines NR Between visit guidelines NR Targets NR	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Bruttomesso, 2011[76]	CSII	Insulin pump, unspecified Prandial: lispro, aspart	NA	NR	NR	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Chico, 2010[77]	MDI	MDI Injections based on SMBG result Prandial: Reg insulin Basal: NPH	SMBG	NR	NR	NR	NA
Chico, 2010[77]	MDI	MDI Injections based on SMBG result Prandial: lispro Basal: NPH	SMBG	NR	NR	NR	NA
Chico, 2010[77]	CSII	Insulin pump, unspecified Prandial: lispro	SMBG	NR	NR	NR	NA
Cohen, 2003[50]	MDI	MDI 4+ times/day Prandial: Reg insulin Basal: NPH	NA	NA	12 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Cohen, 2003[50]	CSII	Tayco Disetronic Prandial: lispro	NA	NR	12 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Cypryk, 2008[74]	MDI	MDI Injections NR Prandial: 30% used insulin lispro and 70% used regular insulin Basal: NPH	NA	NA	36 wks	Titration guidelines NR Between visit guidelines NR Preprandial: 3.3-5.0 mmol, FG: 3.3-5.0 mmol, 2 hr postprandial: <6.7 mmol	NA
Cypryk, 2008[74]	CSII	MM 507c, MM 508, Prandial: 90% used insulin lispro; 10% not reported	NA	Yes	36 wks	Titration guidelines NR Between visit guidelines NR Preprandial: 3.3-5.0 mmol, FG: 3.3-5.0 mmol, 2 hr postprandial: <6.7 mmol,	NA
Deiss, 2006[87]	NA	NA	SMBG Monitor use: NA Fingerstick: NR	NA	3 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Deiss, 2006[87]	NA	NA	MM guardian rtCGM Monitor use: continuously Fingerstick: NR	NA	3 mo	Titration guidelines NR Between visit guidelines NR Targets NR	Hyperglycemia: 170-250 mg/dL Hypoglycemia: 50-80 mg/dL
Deiss, 2006[87]	NA	NA	MM guardian rtCGM Monitor use: biweekly for 3 day periods every 2 wks Fingerstick: NR	NA	3 mo	Titration guidelines NR Between visit guidelines NR Targets NR	Hyperglycemia: 170-250 mg/dL Hypoglycemia: 50-80 mg/dL

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Derosa, 2009[70]	MDI	MDI 4+ times/day Prandial: lispro Basal: glargine	NA	NA	1 yr	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Derosa, 2009[70]	CSII	pump unspec., Prandial: lispro	NA	NR	1 yr	Titration guidelines NR Between visit guidelines NR Targets NR	NA
DeVries, 2002[66]	MDI	MDI 4+ times/day Prandial: aspart Basal: NPH	NA	NA	16 wks	Titration guidelines: Yes Between visit guidelines: Yes Preprandial: 5.0-7.0 mmol, other target: 90-min PPG: 5-9; bedtime glucose: 7-10 mmol/L	NA
DeVries, 2002[66]	CSII	Disetronic H-TRONplus Prandial: aspart Basal: no long acting	NA	Yes	16 wks	Titration guidelines: Yes Between visit guidelines: Yes Preprandial: 5.0-7.0 mmol, other target: 90-min PPG: 5-9; bedtime glucose: 7-10 mmol/L	NA
Doyle, 2004[51]	MDI	MDI 4+ times/day Prandial: aspart Basal: glargine	NA	NA	16 wks	Titration guidelines: Yes Between visit guidelines: Yes Target HbA1c: 7, preprandial: 70-120 mg, other target: 90-150mg pre bedtime	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Doyle, 2004[51]	CSII	MM 508, MM Paradigm 511 Prandial: aspart	NA	Yes	16 wks	Titration guidelines: Yes Between visit guidelines: Yes Target HbA1c: 7, preprandial: 70-120 mg, other target: 90-150mg pre bedtime	NA
Garcia-Garcia, 2007[53]	MDI	MDI 3 times/day Prandial: lispro Basal: glargine	NA	NA	24 mo	Titration guidelines: Yes Between visit guidelines NR Preprandial: 70-140 mg	NA
Garcia-Garcia, 2007[53]	CSII	DR HTron v100 Prandial: lispro	NA	NR	24 mo	Titration guidelines: Yes Between visit guidelines NR Preprandial: 70-140 mg	NA
Hanaire-Broutin, 2000[64]	MDI	MDI 4+ times/day Prandial: lispro Basal: NPH	Ayer Glucomatic Esprit memory meter Monitor use: before and 2 hr after each meal	NA	4 mo	Titration guidelines: Yes Between visit guidelines: Yes Preprandial: 70-120 mg, FG: 70-120 mg	NA
Hanaire-Broutin, 2000[64]	CSII	MM 506, MM 507c, Disetronic HTron D or V Prandial: lispro	SMBG Monitor use: before and 2 hr after each meal	NR	4 mo	Titration guidelines: Yes Between visit guidelines: Yes Preprandial: 70-120 mg, FG: 70-120 mg	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Herman, 2005[69]	MDI	MDI 4+ times/day Prandial: lispro Basal: glargine	NA	NA	12 mo	Titration guidelines: Yes Between visit guidelines: Yes Target HbA1c: 5.6, preprandial: 80 - 120 mg, other target: 100 - 150 at bed time	NA
Herman, 2005[69]	CSII	MM 508 Prandial: lispro	NA	NR	12 mo	Titration guidelines: Yes Between visit guidelines: Yes Target HbA1c: 5.6, preprandial: 80 - 120 mg, other target: 100 - 150 at bed time,	NA
Hermanides, 2011[94]	MDI	MDI 3 times/day Prandial: rapid-acting insulin analogue Basal: long-acting insulin analogue	SMBG Monitor use: NR	Yes	26 wks	Titration guidelines: NR	NR
Hermanides, 2011[94]	CSII	MM REAL	MM Paradigm Monitor use: 24 hrs/day	Yes	26 wks	Between visit guidelines: Yes	Yes
Hieronimus, 2005[73]	MDI	MDI 4+ times/day	NA	NA	NR	Titration guidelines NR Between visit guidelines NR Targets NR	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Hieronimus, 2005[73]	CSII	pump unspec.	NA	Yes	NR	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Hirsch, 2005[59]	MDI	MDI 4+ times/day Prandial: aspart Basal: glargine	NA	NA	5 wks	Titration guidelines: No Between visit guidelines NR FG: 90-126 mg, target: predinner glucose 90-126 mg	NA
Hirsch, 2005[59]	CSII	pump unspec. Prandial: aspart	NA	No	5 wks	Titration guidelines: No Between visit guidelines NR FG: 90-126 mg, target: predinner glucose 90-126 mg,	NA
Hirsch, 2008[86]	NA	NA	SMBG Monitor use: NA Fingerstick: NR	NA	6 mo	Titration guidelines NR Between visit guidelines NR Target HbA1c: 7.5	NA
Hirsch, 2008[86]	NA	NA	MM paradigm Monitor use: Not reported Fingerstick: NR	NA	6 mo	Titration guidelines NR Between visit guidelines NR Targets NR	Hyperglycemia: 180 mg/dL Hypoglycemia: 70 mg/dL

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Hoogma, 2006[63]	MDI	MDI 4+ times/day at least 3 preprandial and 1 NPH Prandial: lispro Basal: NPH	NA	NA	6 mo	Titration guidelines NR Between visit guidelines: Yes Preprandial: 4.0-7.0 mmol, FG: 4.0-7.0 mmol, other target: bedtime 6-10 mmol/L, 1hr postprandial 8-10 mmol/L	NA
Hoogma, 2006[63]	CSII	DR HTron v100, Disetronic H-TRONplus V100 Prandial: lispro	NA	Yes	6 mo	Titration guidelines NR Between visit guidelines: Yes Preprandial: 4.0-7.0 mmol, FG: 4.0-7.0 mmol, other target: bedtime 6-10 mmol/L, 1hr postprandial 8-10 mmol/L	NA
JDRF CGM Study Group, 2009[84]	NA	NA	SMBG Monitor use: NA Fingerstick: 4+ times/day	NA	26 wks	Titration guidelines NR Between visit guidelines NR Targets NR	NA
JDRF CGM Study Group, 2009[84]	NA	NA	Abbott freestyle navigator, MM paradigm, Dexcom sts, Monitor use: daily	NA	26 wks	Titration guidelines NR Between visit guidelines NR Targets NR	NR
Kernaghan, 2008[72]	MDI	MDI 4+ times/day Prandial: short-acting or rapid-acting insulin Basal: unspecified	NA	NA	40 wks	Titration guidelines NR Between visit guidelines: Yes Target HbA1c: 6.5, FG: 4-5.5 mmol, other target: 1-hr PPG between 4-7 mmol/L	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Kernaghan, 2008[72]	CSII	DR DTRON, Disetronic/Roche H-Tron, Medtronic Paradigm 508 Prandial: lispro Basal: no long acting	NA	NR	37 wks	Titration guidelines NR Between visit guidelines: Yes Target HbA1c: 6.5, FG: 4-5.5 mmol, other target: 1-hr PPG between 4-7 mmol/L	NA
Kordonouri, 2010[80]	NA	Minimed paradigm 515/715 Prandial: NR	SMBG Monitor use: NA Fingerstick: 4+ times/day	NR	52 wks	Titration guidelines NR Between visit guidelines NR Preprandial: 5.0-8.0 mmol, 2 hr postprandial: <10.0 mmol, Other target: 6.7-10.0 mmol,	NA
Kordonouri, 2010[80]	NA	MM REAL Prandial: NR	MM Paradigm Monitor use: daily Fingerstick: NR	NR	52 wks	Titration guidelines NR Between visit guidelines NR Preprandial: 5.0-8.0 mmol, 2 hr postprandial: <10.0 mmol	NR
Lee, 2007[93]	NA	NA	SMBG Monitor use: NA Fingerstick: NR	NA	15 wks	Titration guidelines NR Between visit guidelines NR Other target: 90-120 mg/dL (7am-10pm), 100-120 mg/dL (10pm-7am)	NA
Lee, 2007[93]	NA	NA	MM paradigm Monitor use: At least 5 days every wk (for a max of 72 hrs at a time) Fingerstick: 4+ times/day	NA	15 wks	Titration guidelines: Yes Between visit guidelines NR Other target: 90-120 mg/dL (7am-10pm), 100-120 mg/dL (10pm-7am)	Hyperglycemia: 200 mg/dL Hypoglycemia: 80 mg/dL

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Lepore, 2003[67]	MDI	MDI 4+ times/day Prandial: lispro Basal: glargine	NA	NR	1 yr	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Lepore, 2003[67]	CSII	pump unspec. Prandial: lispro	NA	NR	1 yr	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Nuboer, 2008[54]	MDI	MDI 3 times/day Prandial: aspart	SMBG Monitor use: NA Fingerstick: 4+ times/day	NA	14 mo	Titration guidelines: Yes Between visit guidelines: Yes Other target: 4.0-10.0 mmol/L,	NA
Nuboer, 2008[54]	CSII	DR HTron v100, Prandial: aspart	SMBG Monitor use: NA Fingerstick: 4+ times/day	NR	14 mo	Titration guidelines: Yes Between visit guidelines: Yes Other target: 4.0-10.0 mmol/L,	NA
O'Connell, 2009[85]	NA	NA	SMBG Monitor use: NA Fingerstick: 4+ times/day	NA	3 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA
O'Connell, 2009[85]	NA	NA	MM paradigm Monitor use: >70% of 3-month study period Fingerstick: 4+ times/day	NA	3 mo	Titration guidelines NR Between visit guidelines NR Targets NR	Hyperglycemia: 12 mmol/dL Hypoglycemia: 4.5 mmol/L

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Opipari-Arrigan, 2007[49]	MDI	MDI 3 times/day Prandial: lispro Basal: NPH	Medtronic MiniMed CGMS Monitor use: Median time for sensor wear was 48 hours with glucose recordings every 5 min Fingerstick: NR	NA	6 mo	Titration guidelines: Yes Between visit guidelines NR Targets NR	Hyperglycemia: >180 mg/dL Hypoglycemia: <70 mg/dL
Opipari-Arrigan, 2007[49]	CSII	Animas infusion pump Prandial: lispro Basal: NPH	Medtronic MiniMed CGMS Monitor use: Median time for sensor wear was 48 hours with glucose recordings every 5 min Fingerstick: NR	Yes	6 mo	Titration guidelines: Yes Between visit guidelines NR Targets NR	Hyperglycemia: >180 mg/dL Hypoglycemia: <70 mg/dL
Peyrot, 2009[92]	MDI	MDI, Injections NR Prandial: rapid acting analogs (unspecified) Basal: glargine	SMBG Monitor use: NA Fingerstick: NR	NA	16 wks	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Peyrot, 2009[92]	CSII	MM paradigm 722	SMBG, RT-CGM using integrated pump/monitor Monitor use: not specified Fingerstick: NR	Yes	16 wks	Titration guidelines: No Between visit guidelines: No Targets NR	NR

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Pozzilli, 2003[57]	MDI	MDI 4+ times/day Prandial: unspecified Basal: NPH	NA	NA	2 yrs	Titration guidelines: Yes Between visit guidelines: Yes Targets NR	NA
Pozzilli, 2003[57]	CSII	MM 507c Prandial: lispro Basal: no long acting	NA	Yes	2 yrs	Titration guidelines NR Between visit guidelines NR Preprandial: 3.9-8.3 mmol for those with no history of hypoglycemia; 4.4-8.9 mmol for those with reduced hypoglycemia awareness; and higher targets for those with recurrent severe hypoglycemia	NA
Raccah, 2009[81]	NA	MM paradigm 512 Prandial: NR	SMBG Monitor use: NA Fingerstick: ≥ 3 times/day	NA	6 mo	Titration guidelines: Yes Between visit guidelines: Yes Targets NR	NA
Raccah, 2009[81]	NA	NA	MM paradigm, Monitor use: 70% of the time Fingerstick: ≥ 3 times/day	NA	6 mo	Titration guidelines: Yes Between visit guidelines: Yes Targets NR	NR
Radermecker, 2010[83]	NA	pump unspec. Prandial: NR	SMBG Monitor use: NA Fingerstick: NR	NA	12 wks	Titration guidelines NR Between visit guidelines NR Targets NR	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Radermecker, 2010[83]	NA	NA	MM Guardian rtCGM Monitor use: patients were offered to use it permanently Fingerstick: Other	NA	12 wks	Titration guidelines NR Between visit guidelines NR Targets NR	Hyperglycemia: 240 mg/dL Hypoglycemia: 80 mg/dL
Raskin, 2003[36]	MDI	MDI 4+ times/day Prandial: aspart Basal: NPH	NA	NA	24 wks	Titration guidelines: Yes Between visit guidelines: No FG: 80-120 mg, 4.4-6.7 mmol	NA
Raskin, 2003[36]	CSII	MM 507c Prandial: aspart	NA	Yes	24 wks	Titration guidelines: Yes Between visit guidelines: No FG: 80-120 mg, 4.4-6.7 mmol	NA
Rigla, 2008[105]	MDI	NA	SMBG Monitor use: NA Fingerstick: Other	NA	4 wks	Titration guidelines: No Between visit guidelines NR Targets NR	NA
Rigla, 2008[105]	CSII	NA	MM guardian rtCGM Monitor use: 3 days/wk Fingerstick: Other	NA	4 wks	Titration guidelines NR Between visit guidelines NR Targets NR	NR
Schiaffini, 2007[55]	MDI	MDI 4+ times/day Prandial: Reg insulin Basal: glargine	NA	NA	24 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Schiaffini, 2007[55]	CSII	pump unspec., Prandial: lispro	NA	NR	24 mo	Titration guidelines: Yes Between visit guidelines: Yes Targets NR	NA
Skogsberg, 2008[48]	MDI	MDI 4+ times/day Prandial: aspart Basal: NPH	NA	NA	24 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Skogsberg, 2008[48]	CSII	DR HTron v100 Prandial: aspart	NA	Yes	24 mo	Titration guidelines NR Between visit guidelines NR Targets NR	NA
Tamborlane, 2008[27]	NA	NA	SMBG Monitor use: NA Fingerstick: 4+ times/day	NA	26 wks	Titration guidelines NR Between visit guidelines: Yes Preprandial: 70-130 mg, other target: 100-150 mg	NA
Tamborlane, 2008[27]	NA	NA	Dexcom sts, MM paradigm, Abbott freestyle navigator Monitor use: daily Fingerstick: NR	NA	26 wks	Titration guidelines NR Between visit guidelines: Yes Preprandial: 70-130 mg, other target: 100-150 mg	NR
Thomas, 2007[61]	MDI	MDI 4+ times/day Prandial: lispro Basal: glargine	NA	NA	24 wks	Titration guidelines: Yes Between visit guidelines: Yes Other target: avoid glucose < 4 mmol/L	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Thomas, 2007[61]	CSII	MM 508, Prandial: lispro	NA	Yes	24 wks	Titration guidelines: Yes Between visit guidelines: Yes Other target: avoidance of glucose < 4 mmol/l	NA
Tsui, 2001[62]	MDI	MDI 4+ times/day Prandial: lispro Basal: NPH	NA	NA	9 mo	Titration guidelines NR Between visit guidelines: Yes Preprandial: 4.0-6.0 mmol, 2 hr postprandial: <9 mmol	NA
Tsui, 2001[62]	CSII	Minmed 507 Prandial: lispro	NA	Yes	9 mo	Titration guidelines NR Between visit guidelines: Yes Preprandial: 4.0-6.0 mmol, 2 hr postprandial: <9 mmol	NA
Volpe, 2010[75]	MDI	MDI 4+ times/day Prandial: short insulin analogue Basal: NPH	NA	NA	36.4 wks	Titration guidelines NR Between visit guidelines: No Preprandial: 90 mg, other target: 1-hr PPG < 130 mg	NA
Volpe, 2010[75]	CSII	pump unspec., Monitor use: NA	SMBG Fingerstick: 4+ times/day	Yes	36.4 wks	Titration guidelines NR Between visit guidelines: No Preprandial: 90 mg, other target: 1-hr PPG < 130 mg	NR

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Wainstein, 2005[37]	MDI	MDI 4+ times/day Prandial: Reg insulin Basal: NPH	Monitor use: NA	NR	18 wks	Titration guidelines: Yes Between visit guidelines NR Target HbA1c: 7	NA
Wainstein, 2005[37]	CSII	pump unspec. Prandial: lispro	NA	NR	48 wks	Titration guidelines: Yes Between visit guidelines: Yes Target HbA1c: 7	NA
Weintrob, 2003[52]	MDI	MDI 4+ times/day Prandial: Reg insulin Basal: NPH	NA	NA	3.5 mo	Titration guidelines: Yes Between visit guidelines: Yes Preprandial: 4.4-8.3 mmol, 2 hr postprandial: 6.6-10 mmol, other target: 4.4-8.3 mmol/L	NA
Weintrob, 2003[52]	CSII	MM 508 Prandial: lispro	NA	Yes	3.5 mo	Titration guidelines: Yes Between visit guidelines: Yes Preprandial: 4.4-8.3 mmol, 2 hr postprandial: 6.6-10 mmol, other target: 4.4-8.3 mmol/L	NA
Yoo, 2008[102]	MDI	NA	SMBG Monitor use: NA Fingerstick: Other	NA	3 mo	Titration guidelines: No Between visit guidelines: No Targets NR	NA

Table 3. Interventions evaluated in studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	CSII or MDI	Pump type Number of injections Insulin used*	BGM type Monitor use Fingerstick frequency	Training?	Duration of therapy	Provider titration guidelines? Glycemic targets?	Alarms
Yoo, 2008[102]	CSII	NA	MM guardian rtCGM Monitor use: Once/month for 3 days Fingerstick: 3+ times/day	NA	3 mo	Titration guidelines: No Between visit guidelines: No Targets NR	Hyperglycemia: 300 mg/dL Hypoglycemia: 60 mg/dL

*Prandial is rapid-acting, or short-acting insulins, including lispro, regular insulin, aspart, and glulisine. Basal is long-acting or intermediate-acting insulins, such as glargine, detemir and NPH

Abbreviations: CSII = continuous subcutaneous insulin infusion; dL = deciliter; FG = fasting glucose; hr = hour; MDI = multiple daily injections; mg = milligram; MM = Medtronic Minimed; mmol = micromoles; mo = month; NA = not applicable; NR = not reported; PPG = post prandial glucose; reg.= regular; rtCGM = real time continuous glucose monitor; SMBG = self monitoring of blood glucose; unspec. = unspecified; wk = week; yr = year

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Battelino, 2011[88]	MDI + SMBG, 54	MDI + rtCGM, 62	Mild hypoglycemia (number of hypoglycemia excursions per day <63 mg/dL)	6 months	G2-G1: Mean, 0.76 (SD, 0.94)	G2-G1: Mean, 0.53 (SD, 0.6); P: 0.08
Battelino, 2011[88]	MDI + SMBG, 54	MDI + rtCGM, 62	Moderate hypoglycemia (number of hypoglycemic excursions per day <55 mg/dL)	6 months	G2-G1: Mean, 0.37 (SD, 0.4)	G2-G1: Mean, 0.28 (SD, 0.54); P: 0.07
Battelino, 2011[88]	CSII + SMBG, 54	CSII + rtCGM, 62	HbA1c (%)	6 months	G2-G1: Mean, 6.95	G2-G1: Mean, 6.69 (95% CI, -0.47--0.07); P: 0.008 vs. Grp1
Bergenstal, 2010[91]	MDI + SMBG, 241	CSII + rtCGM, 244	HbA1c (%)	1 years		G2-G1: Mean, -0.6 (95% CI, -0.7--0.4); P: <0.001
Bergenstal, 2010[91]	MDI + SMBG, 248	CSII + rtCGM, 247	Severe hypoglycemia (require assistance + (BG<50 mg/dl or recovery with glucose treatment))	1 years	Incidence 17 (7) Events 27 events 13.48 events / 100 person-years; P: 0.84	Incidence 21 (9) Events 32 events 13.31 events / 100 person-years
Bergenstal, 2010[91] ≥19 years (adults)	MDI + SMBG, 163	CSII + rtCGM, 166	Weight gain (kg)	1 years	F-B: Mean, 1.8	F-B: Mean, 2.4 G2-G1: 0.6; P: 0.19
Bin-Abbas, 2006[56]	MDI, 8	CSII, 14	HbA1c (%)	6 months	B: Mean, 10.1 F: Mean, 8.5; P: 0.016 F-B: Mean, 8.5; P: 0.0005 vs. baseline	B: Mean, 10.2 F: Mean, 7.5 F-B: Mean, 7.5; P: 0.0001 vs. baseline G2-G1: -1
Bin-Abbas, 2006[56]	MDI, 8	CSII, 14	HbA1c (%)	6 months	B: Mean, 10.1 F: Mean, 8.5; P: 0.016 F-B: Mean, 8.5; P: 0.0005 vs. baseline	B: Mean, 10.2 F: Mean, 7.5 F-B: Mean, 7.5; P: 0.0001 vs. baseline G2-G1: -1

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Bolli, 2009[60]	MDI, 26	CSII, 24	HbA1c (%)	24 weeks	F-B: Mean, -0.6 (SD, 0.8)	F-B: Mean, -0.7 (SD, 0.7) G2-G1: Mean, -0.1 (-0.5-0.3); P: NR
Bolli, 2009[60]	MDI, 26	CSII, 24	Hyperglycemia (Fasting glucose: before breakfast)	24 weeks		G2-G1: -0.7 (95% CI, -1.8-0.5)
Bolli, 2009[60]	MDI, 26	CSII, 24	Hyperglycemia (Fasting glucose: preprandial' - before other meal (besides breakfast))	24 weeks		G2-G1: Mean, -0.9 (95% CI, -2.3-0.4)
Bolli, 2009[60]	MDI, 26	CSII, 24	Hyperglycemia (Postprandial glucose: 2 hour after meal)	24 weeks		G2-G1: Mean, 0.3 (95% CI, -1.1-1.7); P: NR
Bolli, 2009[60]	MDI, 26	CSII, 24	Hyperglycemia (Postprandial glucose: glucose at 3 am)	24 weeks		G2-G1: Mean, 3 (95% CI, -0.4-6.5); P: NR
Bolli, 2009[60]	MDI	CSII	Hypoglycemia (Mild hypoglycemia: symptomatic + no assistance needed + PG<4 mmol/l)	24 weeks	Events 31 events / person; P: 0.97	Events 35 events / person
Bolli, 2009[60]	MDI	CSII	Hypoglycemia frequency (Mild hypoglycemia: ANY hypoglycemia)	24 weeks	Events 35 events / patient; P: 0.93	Events 41 events / patient
Bolli, 2009[60]	MDI	CSII	Hypoglycemia frequency (Mild hypoglycemia: asymptomatic' not mild)	24 weeks	Events 1.4 events / patient; P: 0.95	Events 1.2 events / patient

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Bolli, 2009[60]	MDI	CSII	Hypoglycemia frequency (Mild hypoglycemia: symptomatic, not necessary mild)	24 weeks	Events 13 events / patient; P: 0.84	Events 14 events / patient
Bolli, 2009[60]	MDI	CSII	Hypoglycemia frequency (Nocturnal hypoglycemia: between bedtime and rising)	24 weeks	Events 5 events / patient; P: 0.34	Events 3 events / patient
Bolli, 2009[60]	MDI, 26	CSII, 24	Severe hypoglycemia (symptoms+ assistance needed+(PG<2 mmol/l OR prompt recovery with glucose/glucagon))	24 weeks	Incidence 2 (8) Events 2	Incidence 2 (8) Events 2
Bruttomesso, 2008[65]	MDI, 39	CSII, 39	Hyperglycemia (severe: >20 mmol/l at any time)	4 months	Events 1.3 events / patient; P: 0.327	Events 1.1 events / patient
Bruttomesso, 2008[65]	MDI, 39	CSII, 39	Hypoglycemia frequency (Mild hypoglycemia: 2.0-3.5 mmol/l)	4 months	Events 7.8 events / patient; P: 0.775	Events 8 events / patient
Bruttomesso, 2008[65]	MDI, 39	CSII, 39	Hypoglycemia frequency (Moderate hypoglycemia: not defined)	4 months	Events 12.3 events / patient; P: 0.011	Events 9.5 events / patient
Bruttomesso, 2008[65]	MDI, 39	CSII, 39	Severe hypoglycemia (< 2mmol/l)	4 months	Events 0.1; P: 0.71	Events 0.1
Bruttomesso, 2008[65]	MDI	CSII	Weight gain	4 months	"Remained unchanged"	

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	Major anomalies (Malformations,not specified.)		Incidence 1 (2.7)	Incidence 5 (5.5) P: NS vs. Grp1
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	HbA1c (%)	(2^{nd} trimester)	G2-G1: Mean, 6.7 (SD, 1.1)	G2-G1: Mean, 6.1 (SD, 0.6); P: 0.0005 vs. Grp1
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	HbA1c (%)	(1^{st} trimester)	G2-G1: Mean, 7.2 (SD, 1.3)	G2-G1: Mean, 6.6 (SD, 0.7); P: 0.0005 vs. Grp1
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	Birth trauma (shoulder dystocia)		Incidence 2 (4.9) P: NS vs. Grp1	Incidence 1 (1.1)
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	NICU admission		Incidence 9 (21.4) P: NS vs. Grp1	Incidence 18 (19.6)
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	Gestational age (weeks)		G2-G1: Mean, 36.6 (SD, 2.3)	G2-G1: Mean, 36.7 (SD, 2); P: NS vs. Grp1
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	Cesarean delivery (Not further specified)		Incidence 30 (73.2) P: ns vs. Grp1	Incidence 72 (77.4)
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	Frequency of neonatal hypoglycemia		Incidence 8 (19.5) P: NS vs. Grp1	Incidence 21 (22.8)
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	Birth weight (grams)		G2-G1: Mean, 3243.2 (SD, 698.9)	G2-G1: Mean, 3390.9 (SD, 662.5); P: NS vs. Grp1
Bruttomesso, 2011[76]	MDI, 44	CSII, 100	HbA1c (%)	(3^{rd} trimester)	G2-G1: Mean, 6.5 (SD, 0.8)	G2-G1: Mean, 6.2 (SD, 0.7); P: 0.002 vs. Grp1
Chico, 2010[77]	MDI, 196	CSII, 59	Weight gain (kg)		G2-G1: Median, 14.2 (range, 0.5 -9.6)	G2-G1: Median, 13.5 (range, 1.4 - 28.5)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Chico, 2010[77]	MDI, 196	MDI, 16	Frequency of neonatal hypoglycemia (Capillary blood glucose lower than cutoff criterion on two or more occasions in the first 48 h of life, cutoff criterion 1.1 mmol/L preterm or SGA infants and 1.66 mmol/L otherwise)	NR	Incidence 23 (11.6) P: NS vs. Grp1	Incidence 0 (0)
Chico, 2010[77]	MDI, 196	MDI, 16	Weight gain (kg)		G2-G1: Median, 14.2 (range, 0.5 -9.6)	G2-G1: Median, 13.9 (range, 0.6 - 21.9)
Chico, 2010[77]	MDI, 196	MDI, 16	Major anomalies (defined as those that were life-limiting, caused significant functional or cosmetic impairment, or required surgery)	NR	Incidence 12 (6) P: NS vs. Grp1	Incidence 0 (0)
Chico, 2010[77]	MDI, 196	CSII, 69	Major anomalies (defined as those that were life-limiting, caused significant functional or cosmetic impairment, or required surgery)	NR	Incidence 12 (6)	Incidence 3 (5.4) P: NS vs. Grp1
Chico, 2010[77]	MDI, 196	CSII, 59	HbA1c (%)	(1^{st} trimester)	G2-G1: Mean, 6 (Range, 4.5 - 8.7)	G2-G1: Mean, 6.3 (Range, 5.4 - 9.2)
Chico, 2010[77]	MDI, 196	MDI, 16	HbA1c (%)	(1^{st} trimester)	2-G1: Mean, 6 (Range, 4.5 - 8.7)	G2-G1: Mean, 6.1 (Range, 5.9 - 7.1)
Chico, 2010[77]	MDI, 196	CSII, 59	Cesarean delivery (not further specified)	NR	Incidence 124 (63.1) P: NS vs. Grp1	Incidence 40 (67.6)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Chico, 2010[77]	MDI, 196	MDI, 16	Cesarean delivery (not further specified)	NR	Incidence 124 (63.1) P: NS vs. Grp1	Incidence 6 (38.5)
Chico, 2010[77]	MDI, 196	MDI, 16	HbA1c (%)		G2-G1: Mean, 5.7 (4.6 - 7.3)	G2-G1: Mean, 5.9 (5.6 - 6.4)
Chico, 2010[77]	MDI, 196	CSII, 59	HbA1c (%)		G2-G1: Mean, 5.7 (4.6 - 7.3)	G2-G1: Mean, 6.3 (5.3 - 7.8)
Chico, 2010[77]	MDI, 196	CSII, 59	HbA1c (%)	(2nd trimester)	G2-G1: Mean, 5.6 (4.5 - 8.1)	G2-G1: Mean, 6 (5.4 - 8)
Chico, 2010[77]	MDI, 196	MDI, 16	HbA1c (%)	(2nd trimester)	G2-G1: Mean, 5.6 (4.5 - 8.1)	G2-G1: Mean, 5.8 (5.3 - 6.2)
Chico, 2010[77]	MDI, 196	CSII, 59	Frequency of neonatal hypoglycemia (Capillary blood glucose lower than cutoff criterion 2+ occasions in first 48 h of life, cutoff criterion 1.1 mmol/L in preterm or SGA infants and 1.66 mmol/L otherwise)	NR	Incidence 23 (11.6)	Incidence 2 (2.8) P: NS vs. Grp1
Chico, 2010[77]	MDI, 16	CSII, 59	HbA1c (%)		G2-G1: Mean, 5.9 (5.6 - 6.4)	G2-G1: Mean, 6.3 (5.3 - 7.8)
Chico, 2010[77]	MDI, 16	CSII, 59	Frequency of neonatal hypoglycemia (Capillary blood glucose lower than cutoff criterion 2+ occasions in the first 48 h of life, cutoff criterion 1.1 mmol/L in preterm or SGA infants and 1.66 mmol/L otherwise)	NR	Incidence 0 (0)	Incidence 2 (2.8) P: NS vs. Grp1
Chico, 2010[77]	MDI, 16	CSII, 59	HbA1c (%)	(2nd trimester)	G2-G1: Mean, 5.8 (Range, 5.3 - 6.2)	G2-G1: Mean, 6 (Range, 5.4 - 8)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Chico, 2010[77]	MDI, 16	CSII, 59	Major anomalies (defined as those that were life-limiting, caused significant functional or cosmetic impairment, or required surgery)	NR	Incidence 0 (0) P: NS vs. Grp2	Incidence 3 (5.4)
Chico, 2010[77]	MDI, 16	CSII, 59	HbA1c (%)	(2st trimester)	G2-G1: Mean, 6.1 (Range, 5.9 - 7.1)	G2-G1: Mean, 6.3 (Range, 5.4 - 9.2)
Chico, 2010[77]	MDI, 16	CSII, 59	Cesarean deliver (not further specified)	NR	Incidence 6 (38.5) P: NS vs. Grp2	Incidence 40 (67.6)
Chico, 2010[77]	MDI, 16	CSII, 59	Weight gain (kg)		G2-G1: Median, 13.9 (range, 0.6 - 21.9)	G2-G1: Median, 13.5 (range, 1.4 - 28.5)
Cohen, 2003[50]	MDI, 13	CSII, 15	HbA1c (%)	12 months	B: Mean, 8.48 (SD, 1.4) F: Mean, 8.57 (SD, 0.44); P: NS F-B: 0.09	B: Mean, 8.58 (SD, 0.82) F: Mean, 8.15 (SD, 1.3) F-B: -0.43 G2-G1: -0.52
Cohen, 2003[50]	MDI, 13	CSII, 15	Hypoglycemia frequency (Daytime hypoglycemia: Mean/patient/study period)	12 months	F: Mean, 15.1 (SD, 16.1)	F: Mean, 11.4 (SD, 7.1)
Cohen, 2003[50]	MDI, 13	CSII, 15	Hypoglycemia frequency (Nocturnal hypoglycemia: Mean/patient/study period)	12 months	F: Mean, 4 (SD, 6.5)	F: Mean, 3 (SD, 3.5)
Cohen, 2003[50]	MDI, 13	CSII, 15	Severe hypoglycemia (Events)	12 months	Events 4; P: NS	Events 1
Cohen, 2003[50]	MDI	CSII	Weight gain (BMI-SDS)	12 months	F: 0.25 (SD, 0.44)	F: 0.23 (SD, 0.45)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Cypryk, 2008[74]	MDI, 78	CSII, 25	Birth weight (g)	36 weeks (3rd trimester)	F: Mean, 3270 (SD, 894)	F: Mean, 3191 (SD, 903)
Cypryk, 2008[74]	MDI, 78	CSII, 25	Birth weight (LGA)	36 weeks (3rd trimester)	Incidence 22 (28.6); P: 0.1159	Incidence 3 (12)
Cypryk, 2008[74]	MDI, 78	CSII, 25	Birth weight (SGA)	36 weeks (3rd trimester)	Incidence 7 (9.1); P: 0.7818	Incidence 3 (12)
Cypryk, 2008[74]	MDI, 78	CSII, 25	Cesarean delivery (Not further specified)	36 weeks (3rd trimester)	Incidence 54 (69.2); P: 0.2354	Incidence 14 (46)
Cypryk, 2008[74]	MDI, 78	CSII, 25	Frequency of neonatal hypoglycemia (<40 mg/dL)	36 weeks (3rd trimester)	Incidence 11 (14.1); P: 0.8902	Incidence 4 (16)
Cypryk, 2008[74]	MDI, 78	CSII, 25	Gestational age (weeks)	(3rd trimester)	F: Mean, 36.3 (SD, 3.2); P: 0.5805	F: Mean, 36.6 (SD, 2.4)
Cypryk, 2008[74]	MDI, 86	CSII, 30	HbA1c (%)	(3rd trimester)	F: Mean, 6.8 (SD, 1.2)	F: Mean, 6.4 (SD, 1)
Cypryk, 2008[74]	MDI, 86	CSII, 30	HbA1c (%)	(1st trimester)	F: Mean, 7.7 (SD, 2.4)	F: Mean, 7.4 (SD, 1.7)
Cypryk, 2008[74]	MDI, 86	CSII, 30	HbA1c (%)	(2nd trimester)	F: Mean, 6.6 (SD, 0.9)	F: Mean, 6.5 (SD, 1.1)
Cypryk, 2008[74]	MDI, 86	CSII, 30	Minor anomalies (congenital abnormalities, unspecified)	36 weeks (3rd trimester)	Incidence 2 (2); P: 0.05	Incidence 4 (13)
Cypryk, 2008[74]	MDI, 86	CSII, 30	Severe hypoglycemia (required treatment with parenteral glucagon administered by a third party)	36 weeks (3rd trimester)	Incidence 0 (0)	Incidence 0 (0)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Deiss, 2006[87]	SMBG	rtCGM	HbA1c (%)	3 months	B: Mean, 9.7 (SD, 1.3) F-B: Mean, 0.4 (SD, 1)	B: Mean, 9.6 (SD, 1.2) F-B: Mean, 0.7 (SD, 1.3) G2-G1: 0.3
Deiss, 2006[87]	SMBG	rtCGM	HbA1c (%)	3 months	B: Mean, 9.7 (SD, 1.3) F-B: Mean, 0.4 (SD, 1)	B: Mean, 9.5 (SD, 1.1) F-B: Mean, 1 (SD, 1.1) G2-G1: 0.6
Deiss, 2006[87]	SMBG	rtCGM	Hypoglycemia frequencySevere hypoglycemia (not further spec)	3 months		Events 1
Deiss, 2006[87]	SMBG	rtCGM	Hypoglycemia frequencySevere hypoglycemia (not further spec)	3 months		Events 1
Derosa, 2009[70]	MDI, 32	CSII, 32	HbA1c (%)	12 months	B: Mean, 9.3 (SD, 2.1) F: Mean, 8.2 (SD, 1); P: <0.05 F-B: -1.1	B: Mean, 9.2 (SD, 2) F: Mean, 7.6 (SD, 0.8) F-B: -1.6 G2-G1: -0.5
DeVries, 2002[66]	MDI, 40	CSII, 39	HbA1c (%)	16 weeks	B: Mean, 9.25 (SD, 1.4) F-B: Mean, -0.07 (SD, 0.7) G2-G1: Mean, 0.84 (95% CI, 0.36-1.31)	B: Mean, 9.27 (SD, 1.4) F-B: Mean, -0.91 (SD, 1.28) G2-G1: P: 0.002
DeVries, 2002[66]	MDI, 40	CSII, 39	Hyperglycemia (Fasting glucose: 5-hr after bedtime)	16 weeks	F: Mean, 9.8; P: NS	F: Mean, 9.8
DeVries, 2002[66]	MDI, 40	CSII, 39	Hyperglycemia (Fasting glucose: before bedtime glucose)	16 weeks	F: Mean, 11.8; P: NS	F: Mean, 10.8
DeVries, 2002[66]	MDI, 40	CSII, 39	Hyperglycemia (Fasting glucose: before breakfast glucose)	16 weeks	F: Mean, 10; P: NS	F: Mean, 8.5

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
DeVries, 2002[66]	MDI, 40	CSII, 39	Hyperglycemia (Fasting glucose: before dinner glucose)	16 weeks	F: Mean, 10.2; P: NS	F: Mean, 8.3
DeVries, 2002[66]	MDI, 40	CSII, 39	Hyperglycemia (Fasting glucose: before lunch glucose)	16 weeks	F: Mean, 9	F: Mean, 7.8
DeVries, 2002[66]	MDI, 40	CSII, 39	Hyperglycemia (Postprandial glucose: 90-min after breakfast)	16 weeks	F: Mean, 10.5; P: NS	F: Mean, 8.3
DeVries, 2002[66]	MDI, 40	CSII, 39	Hyperglycemia (Postprandial glucose: 90-min after dinner)	16 weeks	F: Mean, 8.7; P: NS	F: Mean, 9
DeVries, 2002[66]	MDI, 40	CSII, 39	Hyperglycemia (Postprandial glucose: 90-min after lunch)	16 weeks	F: Mean, 9.7; P: NS	F: Mean, 8.2
DeVries, 2002[66]	MDI, 40	CSII, 39	Hypoglycemia frequency (Mild hypoglycemia: (SMBG < 3.9 mmol/L))	16 weeks	Episodes per patient-week B: Mean, 1.97 (SD, 1.53) F-B: Mean, -0.02 (SD, 1.18) G2-G1: Mean, -0.99 (-1.87--0.11)	Episodes per patient-week B: Mean, 2.13 (SD, 2.05) F-B: Mean, 0.98 (SD, 2.02)
DeVries, 2002[66]	MDI, 40	CSII, 39	Severe hypoglycemia (requires 3rd party assistance)	16 weeks	Incidence 6 (15); P: 0.48	Incidence 3 (8)
DeVries, 2002[66]	MDI, 40	CSII, 39	Weight gain (kg)	16 weeks	B: Mean, 79.8 (SD, 13.5) F-B: Mean, 0.88 (SD, 2.74) G2-G1: Mean, 0.28 (95% CI, -1.07-1.63)	B: Mean, 77.3 (SD, 13.6) F-B: Mean, 0.6 (SD, 2.94)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Doyle, 2004[51]	MDI, 16	CSII, 16	HbA1c (%)	16 weeks	B: Mean, 8.2 (SD, 1.1) F: 8.1 (1.2) F-B: -0.1	B: Mean, 8.1 (SD, 1.2) F: 7.2 (1) F-B: -0.9 G2-G1: -0.8
Doyle, 2004[51]	MDI	CSII, 16	Hypoglycemia frequency (Nocturnal hypoglycemia: not specified)	16 weeks		Incidence 2 (12) Events 2
Doyle, 2004[51]	MDI, 16	CSII	Severe hypoglycemia (not further spec)	16 weeks	Incidence 4 (25) Events 5	
Doyle, 2004[51]	MDI, 16	CSII, 16	Weight gain		F-B: Mean, <1 kg/m2; P: NS vs. baseline	
Garcia-Garcia, 2007[53]	MDI, 24	CSII, 8	HbA1c (%)	24 months	B: Mean, 7.82 (SD, 0.7) F: Mean, 7.54 (SD, 0.74); P: 0.8 0.8 F-B: -0.28	B: Mean, 7.62 (SD, 0.62) F: Mean, 7.7 (SD, 0.64) F-B: 0.08 G2-G1: 0.36
Garcia-Garcia, 2007[53]	MDI, 24	CSII, 8	Ratio of basal to bolus insulin (Proportion of basal insulin)	24 months	F: Mean, 45.6 (SD, 5.2); P: 0.5	F: Mean, 47.3 (SD, 5.3)
Garcia-Garcia, 2007[53]	MDI, 24	CSII, 8	Severe hypoglycemia (Severe hypoglycemia/patient/year)	24 months	F: Mean, 0.04 (SD, 0.14); P: 0.8	F: Mean, 0 (SD, 0)
Hanaire-Broutin, 2000[64]	MDI + rtCGM, 41	CSII + SMBG, 41	Hyperglycemia (Postprandial glucose: mean daily blood glucose (pre- and postprandial) recorded during last 14 days of each period)	4 months	F: Mean, 175 (SD, 33); P: <0.05	F: Mean, 165 (SD, 27)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Hanaire-Broutin, 2000[64]	MDI + rtCGM, 41	CSII + SMBG, 41	Hypoglycemia frequency (Mild hypoglycemia: defind as BG levels <60 mg/dl)	4 months	Events 4.3 events / 14 day; P: NS	Events 3.9 events / 14 day
Hanaire-Broutin, 2000[64]	MDI + rtCGM, 41	CSII + SMBG, 41	Severe hypoglycemia (as defined by DCCT)	4 months	Incidence 1 (2) Events 1 events / 4 months	Incidence 2 (5) Events 3 events / 4 months
Herman, 2005[69]	MDI, 54	CSII, 53	HbA1c (%)	12 months	B: Mean, 8.1 (SD, 1.2) F: Mean, 6.4 (SD, 0.8); P: 0.19 F-B: Mean, -1.6 (SD, 1.2); P: <0.0001 vs. baseline	B: Mean, 8.4 (SD, 1.1) F: Mean, 6.6 (SD, 0.8) F-B: Mean, -1.7 (SD, 1); P: <0.0001 vs. baseline G2-G1: -0.1; P: 0.19
Herman, 2005[69]	MDI, 54	CSII, 53	Hypoglycemia frequency (Mild hypoglycemia: Capillary BG < 65 mg/dl treated by patient or symptoms that resolved with oral glucose)	12 months	Incidence 49 (90); P: 0.17	Incidence 43 (81)
Herman, 2005[69]	MDI, 54	CSII, 53	Severe hypoglycemia (confusion, LOC, seizures + (BG<50 OR resolution of symptoms with glucose/glucagon from another person))	12 months	Incidence 6 (11); P: 0.49 Events 12 events / 51.43 person-years; P: 0.61	Incidence 3 (6) Events 4 events / 49.87 person-years

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Herman, 2005[69]	MDI, 54	CSII	Severe hypoglycemia (resulting in life-threatening injury to patient/ other person, hospitalization, or death)	12 months	Incidence 1 (2) Events 1	
Herman, 2005[69]	MDI, 54	CSII, 53	Weight gain (kg)	12 months	F-B: Mean, 2.6; P: <0.001 vs. baseline	F-B: Mean, 2.1; P: <0.001 vs. baseline G2-G1: -0.5; P: 0.7
Hermanides, 2011[94]	MDI + SMBG, 33	CSII + rtCGM, 44	Severe hypoglycemia	26 weeks	Events 1 P: 0.21 vs. Grp2	Events 4
Hermanides, 2011[94]	MDI + SMBG, 31	CSII + rtCGM, 40	Hyperglycemia (Mild hypoglycemia: events defined as >11.1 mmol/l)	26 weeks	Events 2.2 P: 0.3	Events 2.1
Hermanides, 2011[94]	MDI + SMBG, 31	CSII + rtCGM, 40	Hyperglycemia (%)	26 weeks	B: Mean, 40.1 (SD, 18.4) F: Mean, 38.2 (SD, 21.5) P<0.001 vs. Grp2 G2-G1: -17.3 (95% CI, -25.1 to -9.5)	B: Mean, 38 (SD, 17.4) F: Mean, 21.6 (SD, 12.2) G2-G1: -17.3 (95% CI, -25.1 to -9.5)
Hermanides, 2011[94]	MDI + SMBG, 36	CSII + rtCGM, 41	HbA1c (%)	26 weeks	B: Mean, 8.59 (SD, 0.82) F: Mean, 8.46 (SD, 1.04) F-B: -0.13 G2-G1: Mean, -1.21, 95% CI, -1.52 to -0.90	B: Mean, 9.46 (SD, 0.95) F: Mean, 7.23 (SD, 0.65) F-B: -1.23 G2-G1: Mean, -1.21, 95% CI, -1.52 to -0.90
Hermanides, 2011[94]	MDI + SMBG, 31	CSII + rtCGM, 40	Hypoglycemia frequency (%)	26 weeks	B: Mean, 2.5 (SD, 2.8) F: Mean, 2.5 (3.6) G2-G1: 0.0 (95% CI: -1.6 to 1.7) P: 0.79 vs. Grp2	B: Mean, 3.9 (SD, 4.7) F: Mean, 2.7 (SD, 3.4) G2-G1: 0.0 (95% CI: -1.6 to 1.7)
Hermanides, 2011[94]	MDI + SMBG, 31	CSII + rtCGM, 40	Moderate hypoglycemia frequency (defined as <4.0 mmol/l)	26 weeks	Events 0.6 P: 0.4 vs. Grp2	Events 0.7

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Hieronimus, 2005[73]	MDI, 23	CSII, 33	Birth weight (kg)	(3rd trimester)	F: Mean, 3.384 (SD, 0.693); P: 0.036	F: Mean, 3.767 (SD, 0.751)
Hieronimus, 2005[73]	MDI, 23	CSII, 33	Cesarean delivery (Not further specified)	(3rd trimester)	Incidence 8 (34.6); P: 0.016	Incidence 23 (70)
Hieronimus, 2005[73]	MDI, 23	CSII, 33	Gestational age (weeks)		F: Mean, 37.2 (SD, 1.2); P: >0.05	F: Mean, 37 (SD, 1.6)
Hieronimus, 2005[73]	MDI, 23	CSII, 33	Major anomalies (Number of infants)	(3rd trimester)	Incidence 3 (13); P: >0.05	Incidence 4 (12)
Hieronimus, 2005[73]	MDI, 23	CSII, 33	NICU admission (Number of infants)	(3rd trimester)	Incidence 8 (35); P: >0.05	Incidence 11 (33)
Hieronimus, 2005[73]	MDI, 23	CSII, 33	Severe hypoglycemia (not further spec)	(3rd trimester)	Incidence 2 (9); P: >0.05	Incidence 3 (9)
Hieronimus, 2005[73]	MDI, 23	CSII, 33	Weight gain (kg)	(3rd trimester)	F: Mean, 14.4 (SD, 5.2); P: >0.05	F: Mean, 14.5 (SD, 3.9)
Hirsch, 2005[59]	MDI, 50	CSII, 50	Hyperglycemia (Postprandial glucose: SMBG 2h after breakfast)	5 weeks	F: Mean, 182 (SD, 82); P: NS	F: Mean, 158 (SD, 63)
Hirsch, 2005[59]	MDI, 50	CSII, 50	Hyperglycemia (Postprandial glucose: SMBG after dinner)	5 weeks	F: Mean, 159 (SD, 77); P: NS	F: Mean, 144 (SD, 64)
Hirsch, 2005[59]	MDI, 50	CSII, 50	Hyperglycemia (Preprandial glucose: SMBG before dinner)	5 weeks	F: Mean, 148 (SD, 71); P: NS	F: Mean, 128 (SD, 58)
Hirsch, 2005[59]	MDI, 100	CSII, 100	Hypoglycemia frequency (Daytime hypoglycemia: minor (asymptomatic and <50 or managed by patient and <50), 0800 - 0000)	5 weeks	Incidence 59 (60) Events 232; P: <0.001	Incidence 59 (60) Events 333

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Hirsch, 2005[59]	MDI, 100	CSII, 100	Hypoglycemia frequency (Daytime hypoglycemia: symptomatic, not confirmed by measurement, 0800 - 0000)	5 weeks	Incidence 64 (65) Events 305; P: 0.0124	Incidence 70 (71) Events 403
Hirsch, 2005[59]	MDI, 100	CSII, 100	Hypoglycemia frequency (Mild hypoglycemia: Daily hypoglycemia which was either asymptomatic but glucose <50 or symptomatic, glucose<50, and patient managed)	5 weeks	Incidence 68 (69) Events 387; P: 0.2099	Incidence 72 (74) Events 387
Hirsch, 2005[59]	MDI, 100	CSII, 100	Hypoglycemia frequency (Moderate hypoglycemia: daily' and symptomatic but not confirmed with measurement)	5 weeks	Incidence 71 (72) Events 434 events; P: 0.0506	Incidence 73 (75) Events 507 events
Hirsch, 2005[59]	MDI, 100	CSII, 100	Hypoglycemia frequency (Nocturnal hypoglycemia: minor (asymptomatic and glucose <50 OR symptomatic, glucose <50, and patient managed), 0000 - 0800)	5 weeks	Incidence 49 (50) Events 155; P: 0.002	Incidence 51 (52) Events 110

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Hirsch, 2005[59]	MDI, 100	CSII, 100	Hypoglycemia frequency (Nocturnal hypoglycemia: symptomatic, not confirmed by measurement, between 0000 and 0800)	5 weeks	Incidence 47 (48) Events 125; P: 0.7211	Incidence 41 (42) Events 104
Hirsch, 2005[59]	MDI, 100	CSII, 100	Severe hypoglycemia (severe CNS symptoms and pt unable to manage with either glucose <50 or improvement with food/ glucagon/ IV glucose)	5 weeks	Incidence 3 (3) Events 5	Incidence 2 (2) Events 2
Hirsch, 2008[86]	SMBG, 72	rtCGM, 66	HbA1c (%)	6 months	Incidence 12 (17); P: 0.0031 Least square mean change from baseline, 0.5879; SE, 0.0891; B: Mean, 8.39 (SD, 0.64) F: Mean, 7.84 (SD, 0.81) F-B: Mean, -0.56 (SD, 0.72)	Incidence 16 (24) Least square mean change from baseline, -0.7002; SE, 0.0887 B: Mean, 8.49 (SD, 0.76) F: Mean, 7.77 (SD, 0.92) F-B: Mean, -0.71 (SD, 0.71) G2-G1: -0.15
Hirsch, 2008[86]	SMBG, 72	rtCGM, 66	Hyperglycemia	6 months	B: Mean, 2.667 (SD, 0.649) F-B: Mean, 2.657 (SD, 0.805); P: 0.7671 vs. baseline	B: Mean, 2.635 (SD, 0.635) F-B: Mean, 2.869 (SD, 0.913); P: 0.0301 vs. baseline G2-G1: 0.21
Hirsch, 2008[86]	SMBG, 72	rtCGM, 66	Hypoglycemia frequency (Moderate hypoglycemia: <70 mg/dL)	6 months	B: Mean, 0.8348 (SD, 0.728) F: Mean, 1.1663 (SD, 0.744); 0.6154 F-B: 0.33	B: Mean, 0.8378 (SD, 0.725) F: Mean, 0.8828 (SD, 0.756) F-B: 0.05 G2-G1: -0.29

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Hirsch, 2008[86]	SMBG, 72	rtCGM, 66	Severe hypoglycemia (clinical episode of hypoglycemia resulting in seizure or coma, requiring hospitalization or intravenous glucose or glucagon, or any hypoglycemia requiring assistance)	6 months	Events 3; P: 0.04	Events 11
Hoogma, 2006[63]	MDI, 256	CSII, 256	Hypoglycemia frequency (Mild hypoglycemia: self treated)	8 months	Events 55.4 events / 1 person-years; P: 0.001 RR, 1.12; CI, 1.08 - 11.17	Events 49.3 events / 1 person-years
Hoogma, 2006[63]	MDI, 256	CSII, 256	Severe hypoglycemia (requiring outside assistance)	8 months	Events 0.5 events / 1 person-years; P: <0.001 RR, 2.6; CI, 2.08 - 3.25	Events 0.2 events / 1 person-years
JDRF CGM Study Group, 2009[84]	SMBG, 62	rtCGM, 67	(Moderate hypoglycemia: minutes per day spent at glucose level </=60 mg/dl)	26 weeks	B: Median, 40 F: Median, 35; P: 0.05 F-B: -5	B: Median, 40 F: Median, 18 F-B: -22 G2-G1: -17
JDRF CGM Study Group, 2009[84]	SMBG, 62	rtCGM, 67	(Moderate hypoglycemia: minutes per day spent with glucose level ≤ 50 mg/dl)	26 weeks	B: Median, 9 F: Median, 8; P: 0.12 F-B: -1	B: Median, 7 F: Median, 4 F-B: -3 G2-G1: -2

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
JDRF CGM Study Group, 2009[84]	SMBG, 62	rtCGM, 67	HbA1c (%)	26 weeks	Incidence 38 (61); P: <0.001 B: Mean, 6.5 (SD, 0.3) F: Mean, 6.8 (SD, 0.5) F-B: Mean, 0.33 (SD, 0.43) G2-G1: Mean, -0.34 (95% CI, -0.2--0.49)	Incidence 59 (88) B: Mean, 6.4 (SD, 0.5) F: Mean, 6.4 (SD, 0.5) F-B: Mean, 0.02 (SD, 0.45) G2-G1: P: <0.001
JDRF CGM Study Group, 2009[84]	SMBG, 62	rtCGM, 67	Hyperglycemia	26 weeks	B: Median, 972 F: 949; P: 0.003 F-B: -23	B: Median, 1063 F: 1063 F-B: 0 G2-G1: 23
JDRF CGM Study Group, 2009[84]	SMBG, 62	rtCGM, 67	Hyperglycemia	26 weeks	B: Median, 63 F: 82; P: 0.09 F-B: 19	B: Median, 40 F: 48 F-B: 8 G2-G1: -11
JDRF CGM Study Group, 2009[84]	SMBG, 62	rtCGM, 67	Hyperglycemia	26 weeks	B: Median, 331 F: Median, 341; P: 0.1 F-B: 10	B: Median, 255 F: Median, 283 F-B: 28 G2-G1: 18
JDRF CGM Study Group, 2009[84]	SMBG, 62	rtCGM, 67	Hypoglycemia frequency (Mild hypoglycemia: median minutes per day spent at a glucose level </= 70 mg/dl)	26 weeks	B: 96 F: Median, 91; P: 0.43 vs. baseline0.002 vs. baseline F-B: -5	B: 91 F: Median, 54 F-B: -37 G2-G1: -32
JDRF CGM Study Group, 2009[84]	SMBG	rtCGM	Hypoglycemia frequency (Moderate hypoglycemia: >20 min with glucose level <54 mg/dl)	26 weeks	Events 0.47 events / 24 hours; P: 0.07	Events 0.25 events / 24 hours

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
JDRF CGM Study Group, 2009[84]	SMBG, 62	rtCGM, 67	Severe hypoglycemia (event that required assistance to administer carbohydrate, glucagon, or other resuscitative actions)	26 weeks	Incidence 7 (11)	Incidence 7 (10)
Kernaghan, 2008[72]	MDI, 18	CSII, 24	Birth weight (Z score)	37 weeks (3rd trimester)	F: Mean, 2; P: 0.86	F: Mean, 2.09
Kernaghan, 2008[72]	MDI, 18	CSII, 24	Gestational age (weeks)	37 weeks (3rd trimester)	F: Median, 37.5; P: 0.28	F: Median, 36.5
Kernaghan, 2008[72]	MDI, 18	CSII, 24	HbA1c (%)	(2nd trimester)	B: Mean, 8.01 F: Mean, 6.6; P: 0.27 F-B: -1.41	B: Mean, 7.62 F: Mean, 6.3 F-B: -1.32 G2-G1: 0.09
Kernaghan, 2008[72]	MDI, 18	CSII, 24	HbA1c (%)	(1st trimester)	B: Mean, 8.01 F: Mean, 7.3; P: 0.41 F-B: -0.71	B: Mean, 7.62 F: Mean, 6.95 F-B: -0.67 G2-G1: 0.04
Kernaghan, 2008[72]	MDI, 18	CSII, 24	HbA1c (%)	37 weeks (3rd trimester)	B: Mean, 8.01 F: Mean, 6.44; P: 0.51 F-B: -1.57	B: Mean, 7.62 F: Mean, 6.63 F-B: -0.99 G2-G1: 0.58
Kernaghan, 2008[72]	MDI, 18	CSII, 24	Minor anomalies (congenital abnormalities, unspecified)	37 weeks (3rd trimester)	Incidence 0 (0)	Incidence 0 (0)

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Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Kordonouri, 2010[80]	CSII + SMBG, 77	CSII + rtCGM, 76	HbA1c (%)	52 weeks	Incidence 26 (34); P: 0.464 B: Mean, 11.5 (SD, 2.2) F: Mean, 7.6 (SD, 1.4); P: 0.451 F-B: -3.9	Incidence 30 (39) B: Mean, 11.2 (SD, 2.1) F: Mean, 7.4 (SD, 1.2) F-B: -3.8 G2-G1: 0.1
Kordonouri, 2010[80]	CSII + SMBG, 78	CSII + rtCGM, 76	Ratio of basal to bolus insulin (Number of daily boluses)	52 weeks	F: Mean, 7 (SD, 2.7); P: 0.097	F: Mean, 7.9 (SD, 3.6)
Kordonouri, 2010[80]	CSII + SMBG, 78	CSII + rtCGM, 76	Ratio of basal to bolus insulin (Proportion of basal insulin)	52 weeks	F: Mean, 29.7 (SD, 10.4)	F: Mean, 34 (SD, 11.8)
Kordonouri, 2010[80]	CSII + SMBG, 78	CSII + rtCGM, 76	Severe hypoglycemia (not further spec)	52 weeks	Incidence 4 (5); P: 0.046	Incidence 0 (0)
Lee, 2007[93]	SMBG, 8	rtCGM, 9	HbA1c (%)	15 weeks	B: Mean, 8.58 (SD, 1.3) F: Mean, 7.5 (SD, 1.01) F-B: Mean, -1.08; P: 0.04 vs. baseline	B: Mean, 9.45 (SD, 0.55) F: Mean, 7.4 (SD, 0.66) F-B: Mean, -2.05; P: 0.0004 vs. baseline G2-G1: -0.97; P: 0.02
Lee, 2007[93]	SMBG, 8	rtCGM, 8	Severe hypoglycemia (not further spec)	15 weeks	Incidence 0 (0)	Incidence 0 (0)
Lepore, 2003[67]	MDI, 16	CSII, 16	HbA1c (%)	1 years	F-B: NR	F-B: NR
Lepore, 2003[67]	MDI, 16	CSII, 16	Hyperglycemia (Fasting glucose (mg/dL))	1 years	F-B: NR; P: NS vs. baseline	F-B: NR
Lepore, 2003[67]	MDI, 16	CSII, 16	Severe hypoglycemia	1 years	"number of severe hypoglycemic episodes decreased"	"number of severe hypoglycemic episodes decreased"
Lepore, 2003[67]	MDI	CSII	Weight gain	1 years	NR	"not associated with weight gain"
Nuboer, 2008[54]	MDI + SMBG, 19	CSII + SMBG, 19	HbA1c (%)	7 months	B: Mean, 7.98 (SD, 0.57) F: Mean, 7.97 (SD, 0.78) F-B: -0.01	B: Mean, 7.66 (SD, 0.56) F: Mean, 7.49 (SD, 0.5) F-B: -0.17 G2-G1: -0.16

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
O'Connell, 2009[85]	SMBG	rtCGM, 25		3 months		Incidence 11 (44)
O'Connell, 2009[85]	SMBG, 29	rtCGM, 26	HbA1c (%)	3 months	Incidence 5 (17); P: 0.004 B: Mean, 7.5 (SD, 0.7) F: Mean, 7.8 (SD, 0.9) F-B: 0.3 G2-G1: Mean, -0.43 (95% CI, -0.75--0.19); P: 0.009	Incidence 14 (54) B: Mean, 7.3 (SD, 0.6) F: Mean, 7.1 (SD, 0.8) F-B: -0.2
O'Connell, 2009[85]	SMBG, 29	rtCGM, 26	Severe hypoglycemia (episode of hypoglycemia resulting in seizure or coma or requiring assistance or the use of glucagon or IV glucose for recovery)	3 months	Incidence 0 (0)	Incidence 0 (0)
Opipari-Arrigan, 2007[49]	MDI + rtCGM, 8	CSII + rtCGM, 6	HbA1c (%)	6 months	B: Mean, 7.98 (SD, 0.76) F: Mean, 8.24 (SD, 0.4); P: NS F-B: 0.26	B: Mean, 8.26 (SD, 1.37) F: Mean, 8.39 (SD, 0.83) F-B: 0.13 G2-G1: -0.13
Opipari-Arrigan, 2007[49]	MDI + rtCGM, 8	CSII + rtCGM, 6	Hypoglycemia frequency (Daytime hypoglycemia: Frequency of low excursions <70 mg/dL)	6 months	B: Mean, 0.59 (SD, 0.32) F: Mean, 0.85 (SD, 0.58); P: NS F-B: 0.26	B: Mean, 1.53 (SD, 0.49) F: Mean, 0.89 (SD, 1.02) F-B: -0.64 G2-G1: -0.9
Opipari-Arrigan, 2007[49]	MDI + rtCGM, 8	CSII + rtCGM, 6	Severe hypoglycemia (Episodes)	6 months	Events 2; P: NS	Events 0
Peyrot, 2009[92]	MDI + SMBG, 14	CSII + rtCGM, 14	HbA1c (%)	16 weeks	B: 8.32 (1.05) F: Mean, 7.3 (SD, 0.92) F-B: Mean, -1	B: 8.87 (0.89) F: Mean, 7.16 (SD, 0.75) F-B: Mean, -1.7 G2-G1: Mean, -0.7; P: 0.071

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Peyrot, 2009[92]	MDI + SMBG, 14	CSII + rtCGM, 14	Severe hypoglycemia (not further spec)	16 weeks	Events 3	Events 0
Peyrot, 2009[92]	MDI + SMBG, 14	CSII + rtCGM, 14	Weight gain (kg)	16 weeks	B: Mean, 82.61 (SD, 15.98) F: Mean, 84.56 (15.99) F-B: Mean, 2; P: NS vs. baseline G2-G1: Mean, 1.3	B: Mean, 77.69 (SD, 18.71) F: Mean, 78.37 (19.1) F-B: Mean, 0.7; P: NS vs. baseline G2-G1: P: 0.309
Pozzilli, 2003[57]	MDI, 12	CSII, 7	HbA1c (%)	2 years	B: Mean, 10.3 (SD, 3.4) F: Mean, 6.2 (SD, 0.3); P: NS F-B: -4.1	B: Mean, 11.7 (SD, 3.1) F: Mean, 6.3 (SD, 0.5) F-B: -5.4 G2-G1: -1.3
Pozzilli, 2003[57]	MDI, 12	CSII, 7	Severe hypoglycemia (not further spec)	2 years	Incidence 0 (0)	Incidence 0 (0)
Pozzilli, 2003[57]	MDI, 12	CSII, 7	Weight gain (kg: BMI (kg/m2))	2 years	B: Mean, 20.9 (SD, 3.8) F: Mean, 22; P: NS F-B: 1.1	B: Mean, 19.8 (SD, 3.5) F: Mean, 22.5 F-B: 2.7 G2-G1: 1.6
Raccah, 2009[81]	CSII + SMBG, 60	rtCGM, 55	HbA1c (%)	6 months	B: Mean, 9.28 (SD, 1.19) F-B: Mean, -0.57 (SD, 0.94); P: <0.001 vs. baseline	B: Mean, 9.11 (SD, 1.28) F-B: Mean, -0.81 (SD, 1.09); P: <0.001 vs. baseline G2-G1: -0.24; P: 0.087
Raccah, 2009[81]	CSII + SMBG, 54	rtCGM, 46	Hyperglycemia	6 months	F-B: Mean, -0.2 (SD, 0.7)	F-B: Mean, -0.2 (SD, 0.7) G2-G1: 0; P: >0.05
Raccah, 2009[81]	CSII + SMBG, 54	rtCGM, 46	Hypoglycemia frequency (Moderate hypoglycemia: <70 mg/dl)	6 months	F-B: Mean, 0.1 (SD, 0.7)	F-B: Mean, 0.1 (SD, 0.9) G2-G1: 0; P: >0.05
Raccah, 2009[81]	CSII + SMBG, 54	rtCGM, 46	Ratio of basal to bolus insulin (Number of daily boluses)	6 months	F: Mean, 3.9 (SD, 1.4); P: 0.005	F: Mean, 4.7 (SD, 1.4)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Raccah, 2009[81]	CSII + SMBG, 54	rtCGM, 46	Ratio of basal to bolus insulin (Proportion of basal insulin)	6 months	F: Mean, 50.2 (SD, 15.8); P: >0.05	F: Mean, 46.2 (SD, 10)
Raccah, 2009[81]	CSII + SMBG, 60	rtCGM, 55	Severe hypoglycemia (not further spec)	6 months	Incidence 0 (0)	Incidence 1 (2)
Radermecker, 2010[83]	CSII + SMBG, 9	rtCGM, 9	HbA1c (%)	12 weeks	B: Mean, 7.9 (SD, 0.5) F: Mean, 8 (SD, 0.8) F-B: Mean, -0.09 (SD, 0.5; 95% CI, -0.48-0.3); P: 0.48 vs. baseline	B: Mean, 8.3 (SD, 0.7) F: Mean, 7.7 (SD, 0.6) F-B: Mean, 0.53 (SD, 0.66; 95% CI, 0.02-1); P: 0.049 vs. baseline G2-G1: 0.62
Radermecker, 2010[83]	CSII + SMBG, 9	rtCGM, 9	Hypoglycemia frequency (Mild hypoglycemia: <60 mg/dl)	12 weeks	B: Mean, 11.8 (SD, 7.1) F: Mean, 11.1 (SD, 4.5) F-B: Mean, 0.67 (SD, 6.9; 95% CI, -4.7-6); P: 0.55 vs. baseline	B: Mean, 13.9 (SD, 9.2) F: Mean, 7.6 (SD, 6.8) F-B: Mean, 6.2 (SD, 5.2; 95% CI, 2.2-10.2); P: 0.011 vs. baseline G2-G1: 5.53
Radermecker, 2010[83]	CSII + SMBG, 9	rtCGM, 9	Severe hypoglycemia (not further spec)	12 weeks	Incidence 0 (0)	Incidence 0 (0)
Raskin, 2003[36]	MDI, 61	CSII, 66	HbA1c (%)	24 weeks	B: Mean, 8 (SD, 1.1) F: Mean, 7.5 (SD, 1.17) F-B: Mean, -0.46 (SD, 0.89); P: <0.05 vs. baseline	B: Mean, 8.2 (SD, 1.4) F: Mean, 7.6 (SD, 1.22) F-B: Mean, -0.62 (SD, 1.11); P: <0.05 vs. baseline G2-G1: -0.16; P: NS
Raskin, 2003[36]	MDI, 61	CSII, 66	Hyperglycemia (Postprandial glucose: 90 min after breakfast from 8-pt SMBG)	24 weeks	F: Mean, 192 (SD, 65); P: 0.019	F: Mean, 167 (SD, 47.5)
Raskin, 2003[36]	MDI, 61	CSII, 66	Hyperglycemia (Postprandial glucose: any BG>350 mg/dL (any time of day))	24 weeks	Incidence 11 (18) Events 26	Incidence 3 (5) Events 6

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Raskin, 2003[36]	MDI, 61	CSII, 63	Hypoglycemia frequency (Mild hypoglycemia: symptoms, no assistance required, and BG <50 mg/dl)	24 weeks	Incidence 36 (59) Events 1.2 events / person-month; P: NR	Incidence 34 (54) Events 0.8 events / person-month
Raskin, 2003[36]	MDI, 59	CSII, 62	Hypoglycemia frequency (Nocturnal hypoglycemia: 12am-6am)	8-24 weeks	Incidence 13 (22); P: similarly low	Incidence 10 (16)
Raskin, 2003[36]	MDI, 61	CSII, 66	Severe hypoglycemia (BG<50,severe CNS dysfunction (necessitating outside assistance or parenteral glucose/glucagon))	24 weeks	Incidence 0 (0)	Incidence 0 (0)
Raskin, 2003[36]	MDI, 61	CSII, 66	Weight gain (kg)	24 weeks	B: Mean, 96.9 (SD, 17.9) F: Mean, 97.6 (SD, 19.2) F-B: 0.7	B: Mean, 96.4 (SD, 17) F: Mean, 98.1 (SD, 18.1) F-B: 1.7 G2-G1: 1; P: NS
Rigla, 2008[105]	SMBG, 10	rtCGM, 10	HbA1c (%)	4 weeks	B: Mean, 8.1 F: Mean, 7.8 F-B: Mean, 0.3	B: Mean, 8.1 (SD, 1.1) F: Mean, 7.3 (SD, 0.8) F-B: Mean, 0.8; P: 0.007 vs. baseline G2-G1: 0.5; P: 0.017
Schiaffini, 2007[55]	MDI, 17	CSII, 19	HbA1c (%)	24 months	B: Mean, 8.5 (SD, 0.9) F-B: Mean, 8.2 (SD, 1.4); P: NS vs. baseline	B: Mean, 8.3 (SD, 1.1) F-B: Mean, 7.6 (SD, 1.1); P: <0.05 vs. baseline G2-G1: -0.6
Schiaffini, 2007[55]	MDI, 17	CSII, 19	Severe hypoglycemia (Episodes/patient/ year)	24 months	B: Mean, 0.25 (SD, 0.3) F-B: Mean, 0.2 (SD, 0.2); P: NS vs. baseline	B: Mean, 0.3 (SD, 0.2) F-B: Mean, 0.3 (SD, 0.3); P: NS vs. baseline G2-G1: 0.1

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Skogsberg, 2008[48]	MDI, 33	CSII, 34	HbA1c (%)	24 months	B: Mean, 8.4 (SE, 0.5) F: Mean, 6.7 (SE, 0.5); P: 0.66 F-B: -1.7	B: Mean, 8.2 (SE, 0.4) F: Mean, 6.5 (SE, 0.4) F-B: -1.7 G2-G1: 0
Skogsberg, 2008[48]	MDI, 33	CSII, 34	Hypoglycemia frequency (Daytime hypoglycemia: Episodes of perceived hypoglycemia)	24 months	G2-G1: Mean, 1.7 (SE, 0.4); P: 0.89	
Tamborlane, 2008[27] Ages 15-24	SMBG, 53	rtCGM, 57	HbA1c (%)	26 weeks	Incidence 9 (17); P: 0.8 B: Mean, 7.9 (SD, 0.8) F-B: Mean, -0.21 (SD, 0.61)	Incidence 8 (14) B: Mean, 8 (SD, 0.7) F-B: Mean, -0.18 (SD, 0.65) G2-G1: 0.03; P: 0.52
Tamborlane, 2008[27] Ages ≥25	SMBG, 46	rtCGM, 52	HbA1c (%)	26 weeks	Incidence 4 (9); P: 0.005 B: Mean, 7.6 (SD, 0.5) F-B: Mean, 0.02 (SD, 0.45)	Incidence 17 (33) B: Mean, 7.6 (SD, 0.5) F-B: Mean, -0.5 (SD, 0.56) G2-G1: -0.52; P: <0.001
Tamborlane, 2008[27] Ages 8-14	SMBG, 58	rtCGM, 56	HbA1c (%)	26 weeks	Incidence 7 (12); P: 0.01 B: Mean, 7.9 (SD, 0.6) F-B: Mean, -0.22 (SD, 0.54)	Incidence 15 (27) B: Mean, 8 (SD, 0.7) F-B: Mean, -0.37 (SD, 0.9) G2-G1: -0.15; P: 0.29
Tamborlane, 2008[27] Ages ≥25 years	SMBG, 46	rtCGM, 52	Hyperglycemia	26 weeks	B: 181 F: Mean, 161; P: <0.001 F-B: -20	B: 149 F: Mean, 101 F-B: -48 G2-G1: -28
Tamborlane, 2008[27] Ages 8-14	SMBG, 58	rtCGM, 56	Hyperglycemia	26 weeks	B: Mean, 671 F: Mean, 635 F-B: -36	B: Mean, 745 F: Mean, 643 F-B: -102 G2-G1: -66

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Tamborlane, 2008[27] Ages 8-14	SMBG, 58	rtCGM, 56	Hyperglycemia	26 weeks	B: Mean, 282 F: Mean, 268; P: 0.18 F-B: -14	B: Mean, 343 F: Mean, 242 F-B: -101 G2-G1: -87
Tamborlane, 2008[27] Ages 15-24	SMBG, 53	rtCGM, 57	Hyperglycemia	26 weeks	B: 265 F: 242; P: 0.44 F-B: -23	B: 271 F: 215 F-B: -56 G2-G1: -33
Tamborlane, 2008[27] Ages 15-24	SMBG, 53	rtCGM, 57	Hyperglycemia	26 weeks	B: Mean, 697 F: Mean, 761; P: 0.79 F-B: 64	B: Mean, 691 F: Mean, 761 F-B: 70 G2-G1: 6
Tamborlane, 2008[27] Ages 15-24	SMBG, 53	rtCGM, 57	Hyperglycemia	26 weeks	B: Mean, 641 F: Mean, 591; P: 0.85 F-B: -50	B: Mean, 650 F: Mean, 591 F-B: -59 G2-G1: -9
Tamborlane, 2008[27] Ages ≥25 years	SMBG, 46	rtCGM, 52	Hyperglycemia	26 weeks	B: Mean, 549 F: Mean, 519; P: 0.002 F-B: -30	B: Mean, 497 F: Mean, 394 F-B: -103 G2-G1: -73
Tamborlane, 2008[27] Ages 8-14	SMBG, 58	rtCGM, 56	Severe hypoglycemia (event that required assistance to administer oral carbohydrate, glucagon, or other resuscitative actions)	26 weeks	Incidence 6 (10); P: 0.74	Incidence 4 (7)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Tamborlane, 2008[27] Ages 15-24	SMBG, 53	rtCGM, 57	Severe hypoglycemia (event that required assistance to administer oral carbohydrate, glucagon, or other resuscitative actions)	26 weeks	Incidence 5 (9); P: 0.48	Incidence 3 (5)
Tamborlane, 2008[27] Ages ≥25	SMBG, 46	rtCGM, 52	Severe hypoglycemia (event that required assistance to administer oral carbohydrate, glucagon, or other resuscitative actions)	26 weeks	Incidence 4 (9); P: 1	Incidence 5 (10)
Thomas, 2007[61]	MDI, 7	CSII, 7	HbA1c (%)	24 weeks	B: Mean, 8.6 (SD, 1.1) F: Mean, 7.6 (SD, 0.7) F-B: -1	B: Mean, 8.5 (SD, 1.9) F: Mean, 7.4 (SD, 1) F-B: -1.1 G2-G1: -0.1
Thomas, 2007[61]	MDI, 7	CSII, 7	Hyperglycemia (%)	24 weeks	B: Mean, 45 (SD, 15) F: 20 (17) F-B: -25	B: Mean, 32 (SD, 19) F: 31 (15) F-B: -1 G2-G1: 24
Thomas, 2007[61]	MDI, 7	CSII, 7	Hypoglycemia frequency (Mild hypoglycemia: symptomatic and confirmed by SMBG (<4 mmol/l))		Events 21 events / person-years	Events 40 events / person-years

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Thomas, 2007[61]	MDI, 7	CSII, 7	Hypoglycemia frequency (Moderate hypoglycemia: Biochemical, <4.0 mmol/l)	24 weeks	B: Mean, 18 (SD, 13.7) F: Mean, 23 (SD, 16) F-B: 5	B: Mean, 23 (SD, 21) F: Mean, 12 (SD, 3.2) F-B: -11 G2-G1: -16
Thomas, 2007[61]	MDI, 7	CSII, 7	Hypoglycemia frequency (Nocturnal hypoglycemia: NR)			Events 0
Thomas, 2007[61]	MDI, 7	CSII, 7	Severe hypoglycemia (biochemical, <2.5 mmol/l)	24 weeks	B: Mean, 6.7 (SD, 6) F: Mean, 8 (SD, 10); F-B: 1.3	B: Mean, 6.7 (SD, 7) F: Mean, 3 (SD, 3.6) F-B: -3.7 G2-G1: -5
Thomas, 2007[61]	MDI, 7	CSII, 7	Severe hypoglycemia (defined by ADA)	24 weeks	Incidence 2 (29) Events 0.6 events / person-years	Incidence 2 (29) Events 0.9 events / person-years
Thomas, 2007[61]	MDI, 7	CSII, 7	Weight gain (kg)	24 weeks	B: Mean, 78 (SD, 15.2) F: 77 (14.8); P: 0.88 vs. baseline0.94 vs. baseline F-B: -1	B: Mean, 72.5 (SD, 8.6) F: 72.9 (7.8) F-B: 0.4 G2-G1: 1.4
Tsui, 2001[62]	MDI, 14	CSII, 13	HbA1c (%)	9 months	B: Mean, 8.16 (SD, 0.7) F: Mean, 7.56; P: >0.10 F-B: -0.6	B: Mean, 7.73 (SD, 0.6) F: Mean, 7.38 F-B: -0.35 G2-G1: Mean, 0.25 (-0.19-0.68); P: >0.10
Tsui, 2001[62]	MDI, 14	CSII, 13	Hypoglycemia frequency (Mild hypoglycemia: symptoms relieved with glucose and/or BG <3 mmol/l)	9 months	Events 7.4 events / person-month over course of study; P: >0.10	Events 8 events / person-month over course of study Relative treatment effect (CSII-MDI)/MDI, 9; CI, -37 - 87

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Tsui, 2001[62]	MDI, 14	CSII, 13	Severe hypoglycemia (events requiring assistance or resulting in a coma)	9 months	Events 4; P: >0.10	Events 6
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Birth weight (% LGA (>90th percentile))	36.4 weeks (3rd trimester)	Incidence 5 (22.7)	Incidence 9 (45)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Birth weight (% SGA)	36.4 weeks (3rd trimester)	Incidence 1 (4.5)	Incidence 1 (5)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Birth weight (g)	36.4 weeks (3rd trimester)	F: Mean, 3101.84 (SD, 699)	F: Mean, 3295.58 (SD, 747)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Cesarean delivery (Not further specified)	36.4 weeks (3rd trimester)	Incidence 21 (94)	Incidence 19 (95)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Frequency of neonatal hypoglycemia (transient hypoglycemia)	36.4 weeks (3rd trimester)	Incidence 3 (14)	Incidence 2 (10)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Gestational age (weeks)	36.4 weeks (3rd trimester)	F: Mean, 36.35 (SD, 2.3)	F: Mean, 36.38 (SD, 2.2)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	HbA1c (%)	36.4 weeks (3rd trimester)	F: Mean, 6.1 (SD, 1.1)	F: Mean, 6.3 (SD, 0.6)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	HbA1c (%)	6 weeks (1st trimester)	F: Mean, 7.4 (SD, 1.3)	F: Mean, 6.9 (SD, 0.7)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Major anomalies (congenital malformations, not further specified)	36.4 weeks (3rd trimester)	Incidence 0 (0)	Incidence 0 (0)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Minor anomalies (congenital malformations, not further specified)	36.4 weeks (3rd trimester)	Incidence 0 (0)	Incidence 0 (0)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Nephropathy (deterioration of condition)	36.4 weeks (3rd trimester)	Incidence 0 (0)	Incidence 0 (0)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	NICU admission (not further specified)	36.4 weeks (3rd trimester)	Incidence 2 (9)	Incidence 1 (5)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Retinopathy (deterioration of condition)	36.4 weeks (3rd trimester)	Incidence 0 (0)	Incidence 0 (0)
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Severe hypoglycemia (hypoglycemic emergency requiring assistance)	36.4 weeks (3rd trimester)	Incidence 1 (5) Events 1	Incidence 1 (5) Events 1
Volpe, 2010[75]	MDI, 22	CSII + SMBG, 20	Weight gain (kg)	36.4 weeks (3rd trimester)	F-B: Mean, 11.5 (SD, 3.7)	F-B: Mean, 13.4 (SD, 5.4) G2-G1: 1.9
Wainstein, 2005[37]	MDI, 20	CSII, 20	HbA1c (%)	18 weeks	B: Mean, 0.4 (SD, 1.3)	B: Mean, -0.8 (SD, 1.5) G2-G1: P: 0.007
Wainstein, 2005[37] T2DM	MDI, 20	CSII, 20	HbA1c (%)	48 weeks	B: Mean, -0.4 (SD, 1.3)	B: Mean, -0.8 (SD, 1.5) G2-G1: P: 0.4
Wainstein, 2005[37] T2DM	MDI, 20	CSII, 20	HbA1c (%)	18 weeks	F-B: Mean, 1.5 (SD, 0.8)	F-B: Mean, 0.8 (SD, 1.5); P: 0.1 vs. baseline G2-G1: -0.7
Wainstein, 2005[37]	MDI, 20	CSII, 20	HbA1c (%)	48 weeks	F: Mean, 8.8 (SD, 1.5)	F: Mean, 8.8 (SD, 1.4)
Wainstein, 2005[37]	MDI, 20	CSII, 20	HbA1c (%)	18 weeks	F: Mean, 8.4 (SD, 1.3)	F: Mean, 7.9 (SD, 1)

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Wainstein, 2005[37]	MDI	CSII	Hypoglycemia frequency (Mild hypoglycemia: BG<3 mmol/l and not requiring assistance)		"Did not vary by treatment period"	Daily insulin requirement
Wainstein, 2005[37]	MDI, 40	CSII, 40	Severe hypoglycemia (major'-intervention from others)		Events 2	Events 3
Weintrob, 2003[52]	MDI, 23	CSII, 23	HbA1c (%)	3.5 months	B: Mean, 8.3 (SD, 0.7) F: Mean, 8.2 (SD, 0.8) F-B: Mean, -0.23 (SD, 1)	B: Mean, 8 (SD, 1.1) F: Mean, 7.9 (SD, 0.7) F-B: Mean, 0.03 (SD, 1) G2-G1: 0.26
Weintrob, 2003[52]	MDI, 23	CSII, 23	Hyperglycemia	3.5 months	Events 6.7 events / patient; P: <0.05	Events 7.9 events / patient
Weintrob, 2003[52]	MDI, 23	CSII, 23	Hypoglycemia frequency (Mild hypoglycemia: <3.8 mmol)	3.5 months	Events 22 events / patient; P: <0.05	Events 19.8 events / patient
Weintrob, 2003[52]	MDI, 23	CSII, 23	Severe hypoglycemia (Any hypoglycemic event requiring assistance from another person or resulting in a seizure/coma)	3.5 months	Events 3; P: <0.05	Events 1
Weintrob, 2003[52]	MDI, 23	CSII, 23	Weight gain (BMI-SDS)	3.5 months	B: Mean, 0.29 (SD, 0.81) F: Mean, 0.37 (SD, 0.85) F-B: 0.08	B: Mean, 0.4 (SD, 0.79) F: Mean, 0.35 (SD, 0.83) F-B: -0.05 G2-G1: -0.13; P: 0.012
Yoo, 2008[102]	SMBG, 28	rtCGM, 29	HbA1c (%)	3 months	B: Mean, 8.7 (SD, 0.7) F: Mean, 8.3 (SD, 1.1) F-B: -0.4; P: 0.01 vs. baseline	B: Mean, 9.1 (SD, 1) F: Mean, 8 (SD, 1.2) F-B: -1.1; P: <0.001 vs. baseline G2-G1: -0.7; P: 0.004

Table 4. Outcomes of studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Group 1, N	Group 2, N	Outcome (definition)	Timepoint	Results, Group1	Results, Group2
Yoo, 2008[102]	SMBG, 28	rtCGM, 29	Hyperglycemia (Fasting glucose (mmol/L))	3 months	B: Mean, 6.5 (SD, 1.3) F: Mean, 7.2 (SD, 2.2) F-B: 0.7; P: >0.05 vs. baseline	B: Mean, 6.3 (SD, 1.3) F: Mean, 6.5 (SD, 1.2) F-B: 0.2; P: >0.05 vs. baseline G2-G1: -0.5; P: 0.48
Yoo, 2008[102]	SMBG, 28	rtCGM, 29	Hyperglycemia (Postprandial glucose (mg/dL))	3 months	B: Mean, 11.5 (SD, 3.6) F: Mean, 10.9 (SD, 4.1) F-B: -0.6; P: >0.05 vs. baseline	B: Mean, 11.3 (SD, 2.8) F: Mean, 10 (SD, 2.5) F-B: -1.3; P: <0.05 vs. baseline G2-G1: -0.7; P: 0.48
Yoo, 2008[102]	SMBG, 28	rtCGM, 29	Severe hypoglycemia (not further spec)	3 months	Incidence 0 (0)	Incidence 0 (0)
Yoo, 2008[102]	SMBG, 28	rtCGM, 29	Weight gain (kg)	3 months	B: Mean, 65.7 (SD, 12.3) F: Mean, 64.3 (SD, 12.5) F-B: -1.4; P: >0.05 vs. baseline	B: Mean, 63.3 (SD, 12.4) F: Mean, 61.1 (SD, 12.2) F-B: -2.2; P: <0.05 vs. baseline G2-G1: -0.8; P: 0.43

ADA = American Diabetes Association; B = baseline results; BG = blood glucose; BMI-SDS = body mass index-standard deviation score; CI = confidence interval; CNS = central nervous system; CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; F = final results; F-B = change score results; G2-G1 = between-group difference results; HbA1c = hemoglobin A1c; IV = intravenous; JDRF = Juvenile Diabetes Research Foundation; kg = kilograms; kg/m2 = kilograms per meter squared; LGA = large for gestational age; LOC = loss of consciousness; MDI = multiple daily injections; mg/dL = milligrams per deciliter; mmol/L = millimole per liter; NICU = neonatal intensive care unit; NR = not reported; NS = not significant; PG = plasma glucose; rtCGM = real-time continuous glucose monitor; SD = standard deviation; SGA = small for gestational age; SMBG = self monitoring of blood glucose

Table 5. Study quality of randomized controlled trials comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Sequence Generation	Allocation concealment	Blinding, Personnel, Outcome	Incomplete Outcome Data	Pharmaceutical support	Company involvement	Overall quality*
Battelino 2011[88]	Yes	Yes	No	Unclear	Yes	Unable to determine	Fair
Battelino 2011[88]	Yes	Yes	No	Yes	Yes	No	Fair
Bergenstal, 2010[91]	No	No	No	Yes	Yes	Unable to determine	Poor
Bolli, 2009[60]	Yes	Yes	No	Yes	Yes	Unable to determine	Fair
Bolli, 2009[60]	Unclear	Unclear	No	No	Yes	Yes	Poor
Bruttomesso, 2008[65]	Yes	Unclear	Unclear	No	Yes	Yes	Fair
Bruttomesso, 2008[65]	Unclear	Yes	No	Yes	Yes	Yes	Poor
Cohen, 2003[50]	Unclear	Unclear	No	Unclear	Yes	Unable to determine	Poor
Cohen, 2003[50]	Unclear	Unclear	No	Unclear	Yes	Unable to determine	Poor
Deiss, 2006[87]	Unclear	Unclear	Unclear	Unclear	Yes	Unable to determine	Poor
Deiss, 2006[87]	Unclear	Unclear	Yes	Yes	Yes	Unable to determine	Good
Derosa, 2009[70]	Unclear	Unclear	Unclear	No	Unable to determine		Fair
DeVries, 2002[66]	Yes	Yes	No	No	Yes	Unable to determine	Fair
DeVries, 2002[66]	Yes	Yes	No	Yes	Yes	Unable to determine	Fair
Doyle, 2004[51]	Yes	Yes	No	Yes	Yes	No	Good
Doyle, 2004[51]	Yes	Unclear	Unclear	Yes	Yes	Unable to determine	Good
Garcia-Garcia, 2007[53]	Unclear	Unclear	Unclear	Unclear	Unable to determine		Poor
Garcia-Garcia, 2007[53]	Unclear	Unclear	Unclear	Unclear	No		Poor

Author, year	Sequence Generation	Allocation concealment	Blinding, Personnel, Outcome	Incomplete Outcome Data	Pharmaceutical support	Company involvement	Overall quality*
Hanaire-Broutin, 2000[64]	Yes	No	No		Yes	Unable to determine	Fair
Hanaire-Broutin, 2000[64]	Unclear	Unclear	No	Yes	Yes	Unable to determine	Good

Table 5. Study quality of randomized controlled trials comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Sequence Generation	Allocation concealment	Blinding, Personnel, Outcome	Incomplete Outcome Data	Pharmaceutical support	Company involvement	Overall quality*
Herman, 2005[69]	Unclear	Yes	Unclear	Unclear	Yes	Unable to determine	Fair
Herman, 2005[69]	Yes	No	No	No	Yes	Unable to determine	Fair
Hermanides, 2011[94]	Yes	Yes	No	Yes	Unable to determine	Unable to determine	Good
Hirsch, 2005[59]	Yes	No	No	Yes	Yes		Fair
Hirsch, 2005[59]	Unclear	Unclear	Unclear	No	Yes	Yes	Fair
Hirsch, 2008[86]	Unclear	Unclear	No	Yes	Yes	Yes	Good
Hirsch, 2008[86]	Unclear	Unclear	Yes	Yes	Yes	Unable to determine	Good
Hoogma, 2006[63]	Unclear	Unclear	No	No	Yes	Unable to determine	Poor
Hoogma, 2006[63]	Yes	No	No	Yes	Yes		Fair
JDRF CGM Study Group, 2009[84]	Yes	Unclear	No	Yes	Yes	Unable to determine	Good
Kordonouri, 2010[80]	Yes	Yes	No	Yes	Yes	Unable to determine	Good
Kordonouri, 2010[80]	Unclear	Yes	Yes	Yes	Yes	Unable to determine	Good
Lee, 2007[93]	Unclear	Unclear	No	No	Unable to determine		Fair
Lee, 2007[93]	Unclear	Unclear	Unclear	Unclear	Unable to determine	Unable to determine	Fair
Lepore, 2003[67]	Unclear	Unclear	No	Unclear	Unable to determine	Unable to determine	Poor
Lepore, 2003[67]	Unclear	Unclear	Unclear	Unclear	Unable to determine		Fair
Nuboer, 2008[54]	Unclear	Unclear	No	Unclear	No	Unable to determine	Poor
Nuboer, 2008[54]	Unclear	Unclear	Unclear	Yes	No		Fair
O'Connell, 2009[85]	Yes	Yes	No	Yes	Yes	No	Good

Table 5. Study quality of randomized controlled trials comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Sequence Generation	Allocation concealment	Blinding, Personnel, Outcome	Incomplete Outcome Data	Pharmaceutical support	Company involvement	Overall quality*
O'Connell, 2009[85]	Yes	Yes	No	No	Yes	Unable to determine	Good
Opipari-Arrigan, 2007[49]	Unclear	Unclear	No	Unclear	No	Unable to determine	Poor
Opipari-Arrigan, 2007[49]	Unclear	Unclear	Unclear	Unclear	Unable to determine		Poor
Peyrot, 2009[92]	Unclear	Unclear	Unclear	Yes	Yes	No	Poor
Peyrot, 2009[92]	Unclear	No		Yes	Yes	No	Poor
Pozzilli, 2003[57]	Unclear	No	No	Unclear	Yes	Unable to determine	Fair
Pozzilli, 2003[57]	Unclear	No	No	No	Yes	Unable to determine	Fair
Raccah, 2009[81]	Unclear	Unclear	No	No	Yes	Unable to determine	Fair
Radermecker, 2010[83]	Unclear	Unclear	No	Yes	No	No	Fair
Radermecker, 2010[83]	Unclear	Unclear	No	No	No	Unable to determine	Fair
Raskin, 2003[36]	Yes	Unclear	Unclear	No	Yes	Unable to determine	Poor
Raskin, 2003[36]	Yes	Yes	No	Yes	Yes	Unable to determine	
Rigla, 2008[105]	Unclear	Unclear	No	Yes	Yes	No	Poor
Rigla, 2008[105]	Unclear	Unclear	Yes	Yes	Yes	Unable to determine	Good
Schiaffini, 2007[55]	Unclear	Unclear	Unclear	Unclear	No		Poor
Schiaffini, 2007[55]	Unclear	Unclear	No	Unclear	No		Poor
Skogsberg, 2008[48]	Unclear	Unclear	Unclear	Unclear	Unable to determine		Fair
Skogsberg, 2008[48]	Unclear	Unclear	No	Unclear	Yes	Unable to determine	Fair
Tamborlane, 2008[27]	Yes	Unclear	No	Unclear	Yes	Unable to determine	Fair

Table 5. Study quality of randomized controlled trials comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Sequence Generation	Allocation concealment	Blinding, Personnel, Outcome	Incomplete Outcome Data	Pharmaceutical support	Company involvement	Overall quality*
Tamborlane, 2008[27]	Unclear	Unclear	No	Yes	No	Unable to determine	Fair
Thomas, 2007[61]	Unclear	Unclear	Unclear	Unclear	Yes	No	Fair
Thomas, 2007[61]	Unclear	Unclear	No	Yes	Yes	No	Fair
Tsui, 2001[62]	Yes		Unclear	Yes	Yes	Unable to determine	Good
Tsui, 2001[62]	Yes	Yes	No	Unclear	Yes	Unable to determine	Fair
Wainstein, 2005[37]	Unclear	Unclear	Unclear	No	Unable to determine		Fair
Wainstein, 2005[37]	Unclear	No	No	Yes	Unable to determine		Fair
Weintrob, 2003[52]	Unclear	Unclear	No	Yes	Yes	Unable to determine	Fair
Yoo, 2008[102]	Yes	Yes	Yes	Yes	Yes	Unable to determine	Good
Yoo, 2008[102]	Yes	Yes	No	No	Yes	Unable to determine	Fair

CGM = continuous glucose monitor; JDRF = Juvenile Diabetes Research Foundation

* Overall quality was rated 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.[41]

Table 6. Study quality of observational studies comparing insulin delivery or glucose monitoring methods for diabetes mellitus

Author, year	Setting or population described	Eligibility criteria described	Key characteristics described	Patients recruited from same population	Adjusted or stratified results	Followup loss described	Percent lost followup	Overall quality*
Bin-Abbas, 2006[56]	No	No	Some	Unclear	No	Unclear	NR	Poor
Bin-Abbas, 2006[56]	No	No	Some	Yes	No	Unclear	NR	Poor
Bruttomesso, 2011[76]	Yes (incomplete)	Yes	Yes with description	Yes	Yes	No	NR	Fair
Bruttomesso, 2011[76]	Yes (incomplete)	Yes	Yes with description	Yes	No	No	NR	Fair
Chico, 2010[77]	Yes (incomplete)	Yes	Yes with description	Yes	No	No	NR	Fair
Chico, 2010[77]	Yes (incomplete)	Yes	Yes with description	Yes	No	No	NR	Fair
Cypryk, 2008[74]	Yes (incomplete)	Yes	Some	Yes	Yes	No	NR	Fair
Cypryk, 2008[74]	Yes (incomplete)	Yes	Some	Yes	No	No	NR	Fair
Garcia-Garcia, 2007[53]	Yes (incomplete)	Yes	Yes with description	Yes	Yes	No	NR	Fair
Hieronimus, 2005[73]	Yes (incomplete)	No	Yes with description	Unclear	No	Unclear	NR	Fair
Hieronimus, 2005[73]	Yes (incomplete)	No	Yes with description	Yes	No	NA	<10%	Fair
Kernaghan, 2008[72]	Yes (incomplete)	Yes	Some	Yes	No	No	NR	Fair
Kernaghan, 2008[72]	No	Yes	Some	Yes	No	No	NR	Fair
Volpe, 2010[75]	Yes (incomplete)	Yes	Some	Yes	No	No	NR	Fair
Volpe, 2010[75]	Yes (incomplete)	Yes	Some	Yes	No	No	NR	Fair

* Overall quality was rated 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.[41]