Comparative Effectiveness Review
Number 57

Effective Health Care Program

Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness

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.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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Effective Health Care

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 women

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?

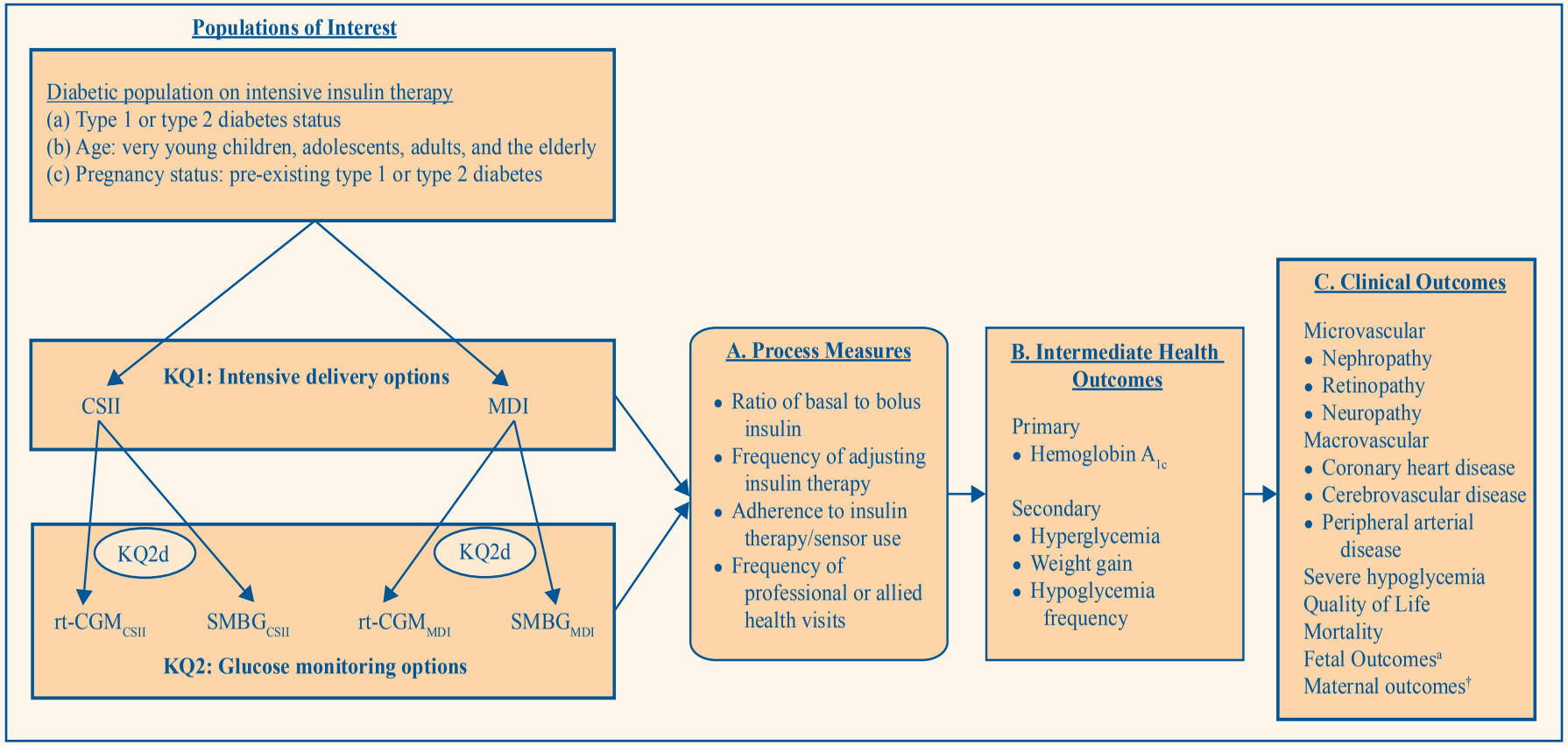
KQ2. In patients using intensive insulin therapy (MDI or CSII), does the type of glucose monitoring (rt-CGM vs. SMBG) have a differential effect on process measures, intermediate outcomes, and clinical outcomes in patients with diabetes mellitus (i.e., what is the incremental benefit of rt-CGM in patients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

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.

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

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?

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.

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.

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.

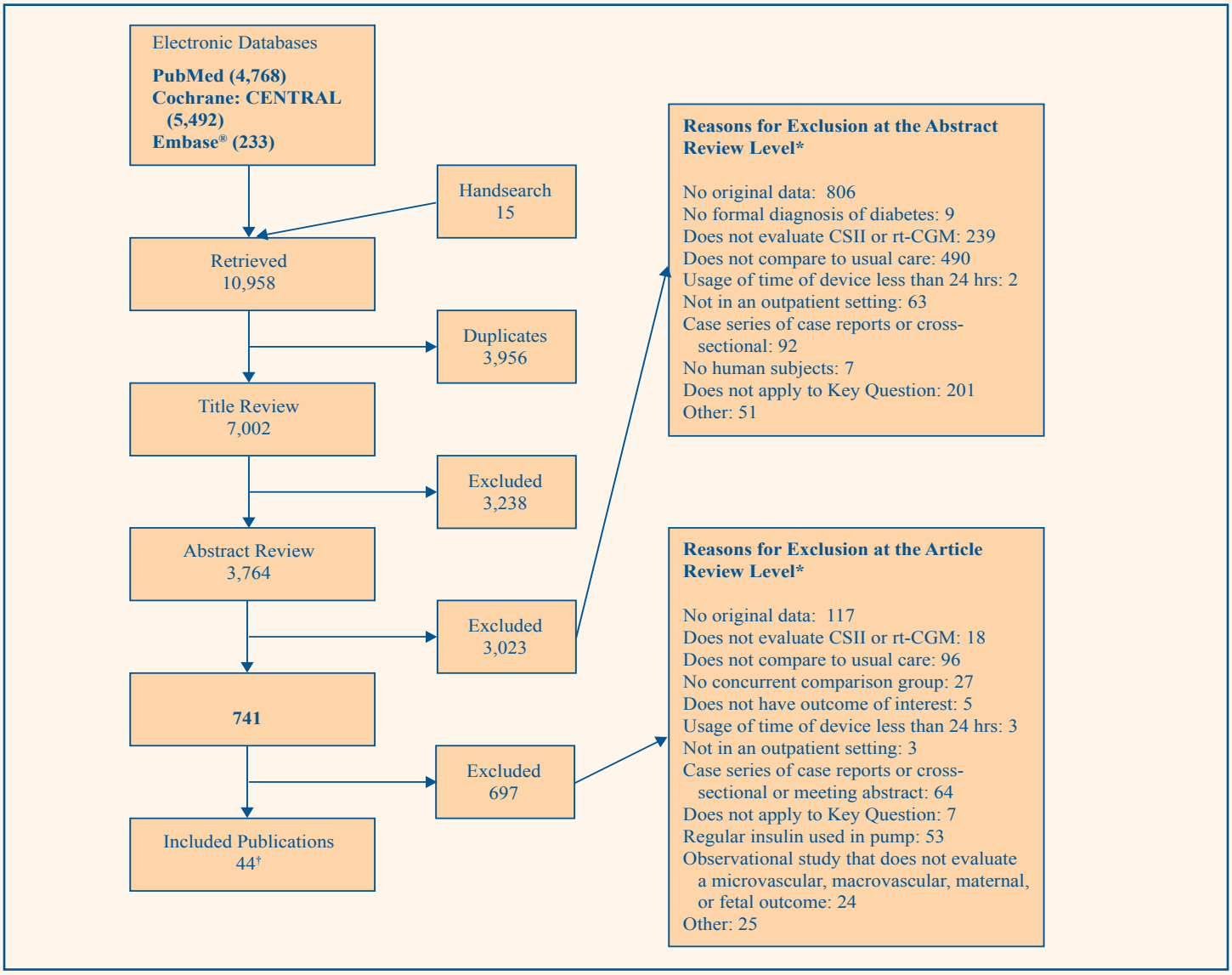
Outcomes. Table C shows the main results on the comparative effectiveness of CSII versus MDI in adults with type 1 diabetes.

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]

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 1 diabetes); 9 (10 publications) compared rt-CGM with SMBG; 4 (5 publications) compared a sensor-augmented pump with MDI/SMBG.

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.

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.

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.

KQ2. 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 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]

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**
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).
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).

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

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 nonsensitive 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]

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**
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.
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.

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**
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]
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]

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]	1 (RCT) / 0	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]

Table D. Summary of the evidence of the comparative effectiveness of CSII versus MDI in adults with type 2 diabetes (continued)			
Outcome	**Strength of Evidence**	**# of Studies/# of Good-Quality Studies**	**Main Findings**
Diabetes-specific QOL	Insufficient[a]	1 (RCT) / 0	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]	1 (RCT) / 0	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	0	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]

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]
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]

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**
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]
NICU admissions	Insufficient[a]	2 (all OBS) / 0	Meta-analysis of 2 retrospective cohort studies for admission to the NICU showed a pooled RR of 0.84 (95% CI, 0.43 to 1.68), which was inconclusive because of high risk of bias.[59,63]
Preterm delivery	Insufficient[a]	4 (all OBS) / 0	Meta-analysis of 4 retrospective cohort studies for preterm delivery showed a pooled RR of 0.98 (95% CI, 0.67 to 1.43), which was inconclusive because of high risk of bias.[59,60,63,64]
Stillbirth rates	Insufficient[a]	4 (all OBS) / 0	Four studies reported on stillbirth rates. Three reported that there were no stillbirths in either group,[59,61,64] and 1 study reported having 1 stillbirth in the MDI group.[60]
Neonatal mortality	Insufficient[a]	3 (all OBS) / 0	Three studies reported on neonatal mortality rate. Each group had 1 neonatal death in 1 study,[60] there were no neonatal deaths in either group in another,[61] and the neonatal mortality rate was 0% in the MDI group and 2.7% in the CSII group in a third study.[64]
Perinatal mortality	Insufficient[a]	2 (all OBS) / 0	In 1 study, the perinatal mortality rate was 3% in the CSII group and 4% in the MDI group.[62] Another study reported a 0% perinatal mortality rate in the MDI group and a 2.7% rate in the CSII group.[64]
Birth trauma	Insufficient	0	None of the studies reported on birth trauma.

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]

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]

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**
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]).
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]

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 HbA1c 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 where 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 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 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, 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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