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

A Systematic Review and Meta-analysis

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Background: Patients with diabetes mellitus need information about the effectiveness of innovations in insulin delivery and glucose monitoring.

Purpose: To review how intensive insulin therapy (multiple daily injections [MDI] vs. rapid-acting analogue–based continuous subcutaneous insulin infusion [CSII]) or method of monitoring (self-monitoring of blood glucose [SMBG] vs. real-time continuous glucose monitoring [rt-CGM]) affects outcomes in types 1 and 2 diabetes mellitus.

Data Sources: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through February 2012 without language restrictions.

Study Selection: 33 randomized, controlled trials in children or adults that compared CSII with MDI ($n = 19$), rt-CGM with SMBG ($n = 10$), or sensor-augmented insulin pump use with MDI and SMBG ($n = 4$).

Data Extraction: 2 reviewers independently evaluated studies for eligibility and quality and serially abstracted data.

Data Synthesis: In randomized, controlled trials, MDI and CSII showed similar effects on hemoglobin A_{1c} (HbA_{1c}) levels and severe hypoglycemia in children or adults with type 1 diabetes mellitus and adults with type 2 diabetes mellitus. In adults with type 1 diabetes mellitus, HbA_{1c} levels decreased more with CSII than with MDI, but 1 study heavily influenced these results. Compared with SMBG, rt-CGM achieved a lower HbA_{1c} level (between-group difference of change, −0.26% [95% CI, −0.33% to −0.19%]) without any difference in severe hypoglycemia. Sensor-augmented insulin pump use decreased HbA_{1c} levels more than MDI and SMBG did in persons with type 1 diabetes mellitus (between-group difference of change, −0.68% [CI, −0.81% to −0.54%]). Little evidence was available on other outcomes.

Limitation: Many studies were small, of short duration, and limited to white persons with type 1 diabetes mellitus.

Conclusion: Continuous subcutaneous insulin infusion and MDI have similar effects on glycemic control and hypoglycemia, except CSII has a favorable effect on glycemic control in adults with type 1 diabetes mellitus. For glycemic control, rt-CGM is superior to SMBG and sensor-augmented insulin pumps are superior to MDI and SMBG without increasing the risk for hypoglycemia.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2012;157:336-347. www.annals.org
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This article was published at www.annals.org on 10 July 2012.

Tight glycemic control with intensive insulin therapy reduces the risk for diabetic microvascular and macrovascular complications (1–4). Innovations in insulin delivery and glucose monitoring are designed to improve glycemic control and quality of life (QOL) while limiting adverse effects, such as hypoglycemia and weight gain. These advances include continuous subcutaneous insulin infusion (CSII) and real-time continuous glucose monitoring (rt-CGM).

Although these technologies are widely used, their effectiveness has not been consistently demonstrated and the populations most likely to benefit are unclear. Health professionals and their diabetic patients need objective information when making decisions about these technologies, which may be expensive or heavily marketed. Such information is important to persons who decide on reimbursement policies and to companies developing new treatments and devices.

Intensive insulin therapy consists of CSII or multiple daily injections (MDI). Although most evidence indicates better glycemic control with CSII, its effect on other outcomes is less clear (5–8). A major limitation of previous reviews of CSII is the inclusion of studies that used regular insulin (5–7, 9), which offers less physiologic pharmacokinetics than insulin analogues (10–12). Rapid-acting insulin analogues are preferred for use with CSII, but whether rapid-acting analogue–based CSII confers additional benefit over currently used MDI strategies is unclear. Moreover, the benefits of CSII in children and older adults with type 1 diabetes mellitus have not been conclusively demonstrated.

Glucose monitoring is a critical part of insulin therapy, because patients can adjust their insulin doses and behavior on the basis of the results. Self-monitoring of blood glucose (SMBG) has been used with both MDI and CSII (13). Challenges that affect adherence to SMBG include pain, costs, behavioral and technical skills, motivation, and intrusiveness. Systems for rt-CGM have been developed to supplement SMBG.

A recent meta-analysis comparing SMBG with rt-CGM in adults and children with type 1 diabetes mellitus showed that the latter improved glycemic control, but there was no difference in the frequency of hypoglycemia; other nonglycemic outcomes were not reported (14). Cur-

rent sensor-augmented pumps for insulin delivery (SAPs) combine rt-CGM technology with CSII (15). Pickup and colleagues' meta-analysis (14) did not compare SAP use with intensive insulin therapy and SMBG. To critically evaluate current evidence and fill in the literature gaps, we performed a systematic review to assess whether intensive insulin therapy (MDI vs. CSII) has a differential effect on outcomes in persons with type 1 or 2 diabetes mellitus and whether outcomes differ by monitoring strategy (SMBG vs. rt-CGM).

Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (16) and developed and followed a protocol for the review that was posted on the Agency for Healthcare Research and Quality (AHRQ) Web site (17). Questions for the review were refined on the basis of input from diabetes mellitus experts and public feedback. A comprehensive technical report that details the methods of the review and additional findings is available (17).

Data Sources and Searches

We searched for original studies in MEDLINE between 1966 and February 2012, EMBASE between 1974 and February 2012, and the Cochrane Central Register of Controlled Trials between 1966 and February 2012. Consistent with PRISMA guidelines (16), the detailed search strategies are reported in **Appendix Table 1** (available at www.annals.org). Our search string included Medical Subject Headings and text terms related to diabetes mellitus, CSII, and continuous glucose monitoring and was not limited by language. We searched the reference lists of included articles and relevant reviews. We also searched ClinicalTrials.gov, a public registry of clinical trials, and contacted authors as needed.

Study Selection

Two investigators independently reviewed citations for eligible studies. We included studies of adults, adolescents, or children with type 1 or 2 diabetes mellitus. We included studies comparing CSII with MDI (at least 3 injections per day), rt-CGM with SMBG (at least 3 fingersticks per day), or SAP use with MDI and SMBG. We excluded studies where regular insulin was used in the CSII group because this is not the preferred clinical practice (10–12). We included studies using long- and rapid-acting analogues or neutral protamine Hagedorn and regular insulin in the MDI groups, because both regimens are used in current practice.

We included randomized, controlled trials (RCTs) that evaluated process measures, intermediate outcomes, QOL, or severe hypoglycemia, and we included both RCTs and observational studies with a concurrent comparison group that evaluated microvascular or macrovascular outcomes or mortality. We excluded studies conducted in inpatient settings or that involved patients who used the device for less than 24 hours. If reviewers disagreed about inclusion after reviewing the full-text article, they discussed the article to finalize a decision.

Data Extraction and Quality Assessment

Using standardized forms, 1 reviewer extracted information on study characteristics (design, study period, and follow-up); participants (age, sex, race, baseline hemoglobin A_{1c} [HbA_{1c}] level, weight, and type and duration of diabetes mellitus); eligibility criteria; interventions (device model, insulin type, MDI schedule, rt-CGM alarm threshold, length of technology use, and patient or staff training); adherence to wearing a device; and outcome measures, including measures of variability. A second reviewer checked the abstracted data for completeness and accuracy.

We classified QOL measures as general health-related, diabetes mellitus–specific, and treatment-specific QOL. We included only validated measures (**Appendix Table 2**, available at www.annals.org).

Two reviewers independently assessed study quality. The assessment of RCTs was based on the Cochrane Collaboration's risk of bias tool (18) and the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (19). The assessment of observational studies was based on the Downs and Black checklist (20).

Data Synthesis and Analysis

We critically appraised and qualitatively described characteristics of trials and conducted meta-analyses when there were at least 2 trials that were homogeneous with respect to population characteristics and study duration. For continuous outcomes, we calculated a weighted mean difference in change scores between groups by using a random-effects model with the DerSimonian and Laird formula (21).

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 by using the mean difference from baseline for each group or the baseline and final values for each group. We derived measures of dispersion by using standard methods (18).

If a study did not report the SD for the change from baseline, we imputed it by assuming a correlation coefficient of 0.5 (18). For crossover trials, we incorporated results only from the first period (19). If studies reported the incidence of hypoglycemia (that is, the number of patients who experienced hypoglycemia), we calculated a pooled fixed-effect Mantel–Haenszel odds ratio (22).

If studies reported event rates (that is, the number of events per patient during a period), we calculated a fixed-effect rate ratio in terms of the number of events per person-year (22). When 0 hypoglycemic events occurred in both groups, we calculated pooled fixed-effects Mantel–Haenszel odds ratios with continuity corrections of 0.001 (22). Similar results were obtained in sensitivity analyses with continuity corrections of 0.0001 or by using the double-arcsine transformation (23).

Heterogeneity among trials was tested by using a chi-square test ($\alpha \leq 0.10$) or I^2 statistic (>50%) (24). In cases of substantial heterogeneity, we investigated by conducting meta-regression using such study characteristics as baseline HbA_{1c} levels, patient age, or adherence to technology. We defined clinically meaningful between-group absolute differences as 0.5% for HbA_{1c} (25), 30% for severe hypoglycemia (26), 15 mg/dL for fasting glucose (equal to 0.5% reduction in HbA_{1c} levels) (27), 5 kg for weight (28), and an SD of 0.5 for QOL outcomes (29). Meta-analyses were conducted by using STATA, version 9.2 (StataCorp, College Station, Texas).

Grading of Evidence

We graded the strength of the evidence by adapting a scheme recommended in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (30). We applied evidence grades to the bodies of evidence about each intervention comparison for each outcome. We assessed the strength of the evidence by assessing its limitations, consistency, directness, precision, publication bias, and magnitude of effect.

Role of the Funding Source

The AHRQ reviewed the questions, protocol, and draft report but did not have a role in the literature search, analysis, or interpretation of findings. The authors prepared the manuscript, and the AHRQ granted copyright assertion.

RESULTS

Study Characteristics

We included 33 studies in 37 articles, including 24 parallel RCTs and 9 randomized crossover trials (**Appendix Figure 1**, available at www.annals.org). Nineteen studies compared the effects of MDI with those of CSII, 10 studies compared the effects of rt-CGM with those of SMBG, and 4 studies compared the effects of SAP use with those of MDI and SMBG. In searching ClinicalTrials.gov, we identified 4 additional studies for our comparisons—2 were completed, but results were not published; the other 2 are ongoing.

We found no RCTs or observational studies that reported on long-term microvascular or macrovascular outcomes. Ten studies were conducted in North America, 14 in Europe, 2 in the Middle East, and 1 in Australia; 6 did not mention location. Study duration ranged from 12 to 52 weeks. Pharmaceutical company support was reported in 24 articles (**Appendix Table 3**, available at www.annals.org). **Table 1** summarizes the main findings. Many studies had significant risk of bias because their methods of handling random assignment of participants was unclear, and very few had any blinding of outcome assessment (see **Appendix Table 4**, available at www.annals.org, for details).

Comparative Effectiveness of CSII Versus MDI

Children and Adolescents With Type 1 Diabetes Mellitus

Seven studies compared MDI with CSII in children and adolescents with type 1 diabetes mellitus (31–37).

HbA_{1c} Level. **Figure 1** shows the comparative effectiveness of CSII versus MDI, where strength of evidence was moderate. Our meta-analysis showed no difference between groups in the HbA_{1c} level change from baseline after 16 or more weeks of follow-up. Results were similar among adolescents older than 12 years (combined mean between-group difference in change from baseline in HbA_{1c}, −0.10% [95% CI, −0.48% to 0.27%]; $I^2 = 0\%$) and less precise among children aged 12 years or younger (combined mean between-group difference in change from baseline in HbA_{1c}, −0.05% [CI, −1.01% to 0.96%]; $I^2 = 0\%$) (**Appendix Table 5**, available at www.annals.org). One (32) of the 7 studies was of good quality; all 7 studies had medium risk of bias.

Severe Hypoglycemia. We excluded 1 study (32) from the meta-analysis because it reported the hypoglycemia rate only in the MDI group. Strength of evidence was low for CSII versus MDI; our meta-analysis found a similar rate of severe hypoglycemia in the 2 intervention groups, although the CI was wide (**Figure 2**). The risk reduction favoring CSII was 9 events per 1000 patients, with a wide CI ranging from 118 fewer events to 100 more events per 1000 patients. Results were similar in our meta-analysis of 3 RCTs in adolescents and of 2 RCTs in children aged 12 years or younger, although the estimate was less precise in the latter (**Appendix Table 5**). None of these 5 studies was of good quality, and all 5 had medium risk of bias.

Other Glycemic Outcomes. Continuous subcutaneous insulin infusion and MDI generally had similar effects on daytime, nocturnal, or mild hypoglycemia and weight gain. However, for most subgroups, the strength of evidence was low, primarily because of imprecise results (**Table 1**). Data were insufficient to draw conclusions on the effect of CSII and MDI on hyperglycemia. Risk of bias was medium to high in the small number of studies reporting these outcomes, and there were no good-quality studies (**Appendix Tables 4** and **5**).

QOL. Six studies (31–34, 36, 37) examined the comparative effectiveness of CSII versus MDI on QOL in children and found similar effects on general QOL (33, 34) and better satisfaction with CSII (36, 37) (**Appendix Tables 4** and **5**). Different instruments measured outcomes; strength of evidence was low, with medium risk of bias and only 1 good-quality study (32).

Adults With Type 1 Diabetes Mellitus

Eight studies compared MDI with CSII in adults with type 1 diabetes mellitus (38–45).

HbA_{1c} Level. Our meta-analysis showed that CSII decreased HbA_{1c} levels more than MDI did, with low strength of evidence (combined mean between-group difference, −0.30% [CI, −0.58% to −0.02%]; $I^2 = 64.5\%$) (**Figure 1**). However, the pooled estimate was influenced by 1 study (40) in which participants had a higher HbA_{1c} level at enrollment (9.3%) compared with that of the other studies (7.7% to 8.2%) (39, 45), resulting in greater op-

Table 1. **Summary of Findings and Strength of Evidence Comparing Insulin Delivery and Glucose-Monitoring Methods for Reported Outcomes***

Outcome	CSII vs. MDI						rt-CGM vs. SMBG		SAP vs. MDI	
	Children and Adolescents With T1DM		Adults With T1DM		Adults With T2DM		Adults and Children With T1DM		Adults and Children With T1DM	
	Findings	Strength of Evidence	Findings	Strength of Evidence	Findings	Strength of Evidence	Findings	Strength of Evidence	Findings	Strength of Evidence
HbA_{1c}	No difference	Moderate	Favors CSII†	Low	No difference	Moderate	Favors rt-CGM	High	Favors pump	Moderate
Hyperglycemia	Cannot conclude	Insufficient	No difference	Low‡§	Cannot conclude	Insufficient	Favors rt-CGM	Moderate	Favors pump	Moderate
Severe hypoglycemia	No difference	Low§	No difference	Low	No difference	Low§	No difference	Low§	No difference	Moderate
Mild hypoglycemia	Cannot conclude	Insufficient	No difference	Low§	No difference	Moderate	No difference	Moderate	No difference	Moderate
Nocturnal hypoglycemia	No difference	Low§	No difference	Low§	Cannot conclude	Insufficient	–	–	–	–
Symptomatic hypoglycemia	–	–	Favors MDI	Low‖¶	–	–	–	–	–	–
Weight gain	No difference	Low§	No difference	Low§	No difference	Low**	–	–	No difference	Low‡
General QOL	No difference	Low§	Favors CSII	Low‡§	Cannot conclude	Insufficient	No difference	Low‖**	Cannot conclude	Insufficient
Diabetes mellitus–specific QOL	Favors CSII	Low§	Favors CSII	Low‡§	Cannot conclude	Insufficient	No difference	Low¶	–	–
Diabetes mellitus treatment–related QOL	Favors CSII	Low§¶	Cannot conclude	Insufficient	Cannot conclude	Insufficient	No difference	Low‡	No difference	Low‡

CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; QOL = quality of life; rt-CGM = real-time continuous glucose monitoring; SAP = sensor-augmented pump for insulin delivery; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

* For strength of the evidence: *High* indicates high confidence that evidence reflects the true effect; further research is unlikely to change confidence in the estimate of the effect. *Moderate* indicates moderate confidence that evidence reflects the true effect; further research may change confidence in the estimate of the effect and may change the estimate. *Low* indicates low confidence that evidence reflects the true effect; further research is likely to change confidence in the estimate of the effect and is likely to change the estimate. *Insufficient* indicates that evidence is unavailable, does not permit a conclusion, or consists of only 1 study with high risk of bias.

† Results were influenced by 1 study.

‡ Low evidence due to high risk of bias.

§ Low evidence due to imprecise results.

‖ Low evidence due to inconsistent results.

¶ Low evidence due to medium risk of bias.

** Low evidence due to indirect measures.

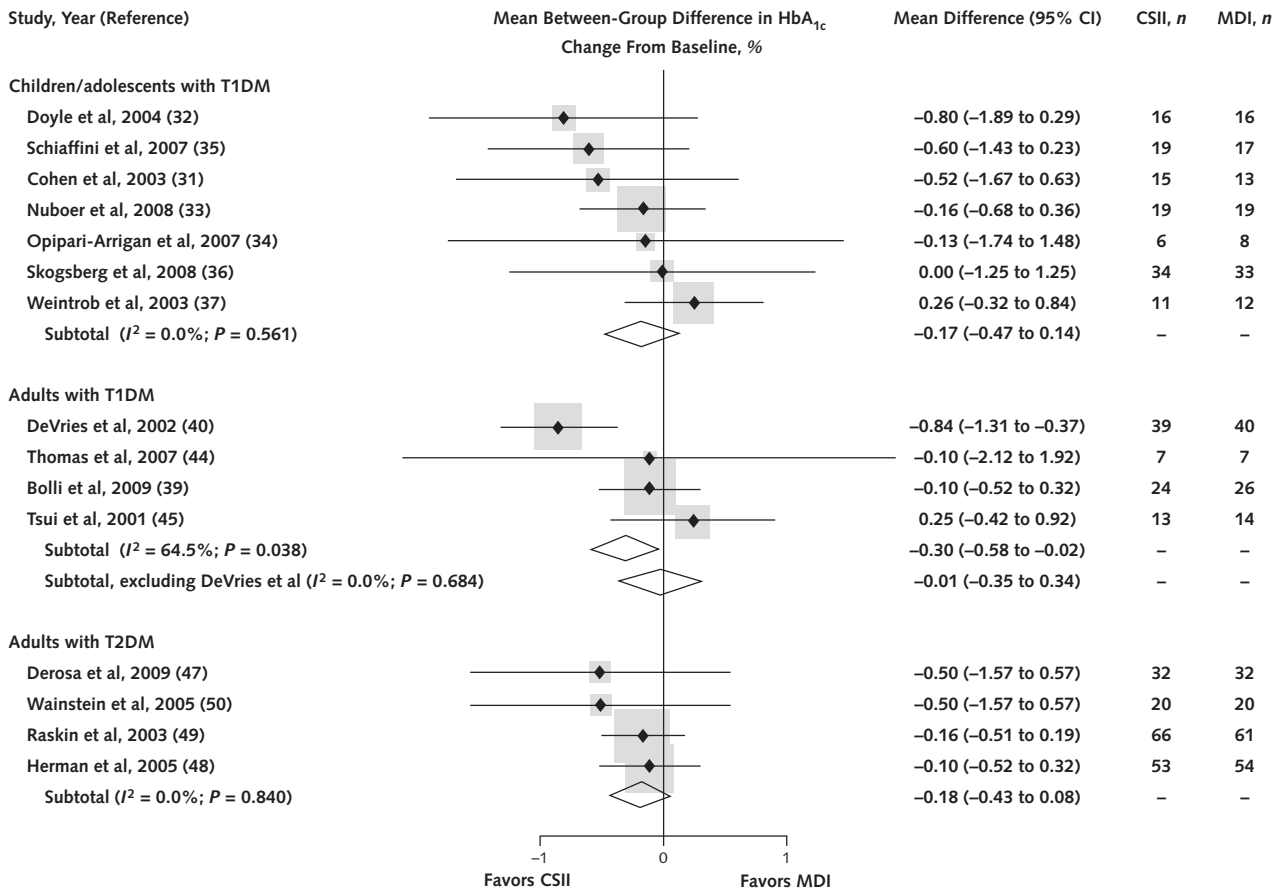
portunity for a large decrease in HbA_{1c} levels in that study (−0.84%) than in the other studies (−0.1% to 0.25%). The difference between CSII and MDI became null (combined mean between-group difference, −0.01% [CI, −0.35% to 0.34%]; $I^2 = 0\%$) after this study was removed. Two of the studies (41, 45) were good quality, with medium risk of bias in all 4 studies.

Severe Hypoglycemia. All 8 studies evaluated severe hypoglycemia. One study (45) was excluded from meta-analysis because it reported only the number of severe hypoglycemic events. In our meta-analysis of 3 RCTs that defined severe hypoglycemia as requiring third-party assistance, CSII and MDI had a similar incidence but the CI was wide (39, 40, 44) (**Figure 3**). The risk reduction favoring CSII was 38 events per 1000 patients, with a CI ranging from 142 fewer events to 66 more events per 1000 patients. Our meta-analysis excluded 4 crossover trials that did not provide quantitative results by period (38, 41–43) (**Appendix Table 5**); results were mixed: One trial favored CSII (43), 1 favored MDI (41), and 2 showed no between-group differences (38, 42). The overall strength of evidence was low, with 2 good-quality studies (41, 45) and medium risk of bias in the 8 studies.

Other Glycemic Outcomes. The incidence of symptomatic hypoglycemia was higher with CSII than with MDI, but the strength of evidence was low; there was significant statistical heterogeneity, medium risk of bias, and 1 good-quality study (45). Six studies evaluated the incidence of other types of mild hypoglycemia (38–43), but definitions varied and strength of evidence was low, with medium risk of bias and 1 good-quality study (41).

Four studies reported no difference in nonsevere hypoglycemia, 1 reported higher risk for mild hypoglycemia with CSII than with MDI (40), and another reported an increased risk for self-managed mild hypoglycemia with MDI (43). The strength of evidence generally was insufficient to draw firm conclusions about other symptomatic hypoglycemia, daytime hypoglycemia, nocturnal hypoglycemia, or fasting glucose levels.

Figure 1. **Mean between-group difference in the change from baseline HbA_{1c} comparing CSII with MDI among children and adolescents with T1DM, adults with T1DM, and adults with T2DM.**



Error bars represent 95% CIs. Shaded boxes represent individual study point estimates. Box size corresponds to weight of study. CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Weight Gain. Weight gain was similar between the CSII and MDI groups. However, the strength of evidence was low, with medium risk of bias in 4 studies and no good-quality studies (**Appendix Tables 4** and **5**) (38, 40, 44, 46).

QOL. Three studies showed improved diabetes mellitus–specific QOL favoring CSII (39, 43). However, the strength of evidence was low, with high risk of bias and 1 good-quality study (**Appendix Tables 4** and **5**) (44).

Adults With Type 2 Diabetes Mellitus

Four studies compared MDI with CSII in adults with type 2 diabetes mellitus (47–50).

HbA_{1c} Level. Our meta-analysis of 4 RCTs of at least 18 weeks in duration showed no difference between CSII and MDI in mean decrease of HbA_{1c} levels (combined mean between-group difference, −0.18% [CI, −0.43% to 0.08%]; $I^2 = 0.0\%$; $P = 0.84$) (**Figure 1**). Strength of evidence was moderate, with medium risk of bias and no good-quality studies.

Severe Hypoglycemia. The incidence of severe hypoglycemia did not differ much between CSII and MDI in our meta-analysis of 2 studies (48, 50), but the CI of the difference was wide (**Appendix Table 5**). The strength of evidence was low because of imprecision, medium risk of bias and no good-quality studies.

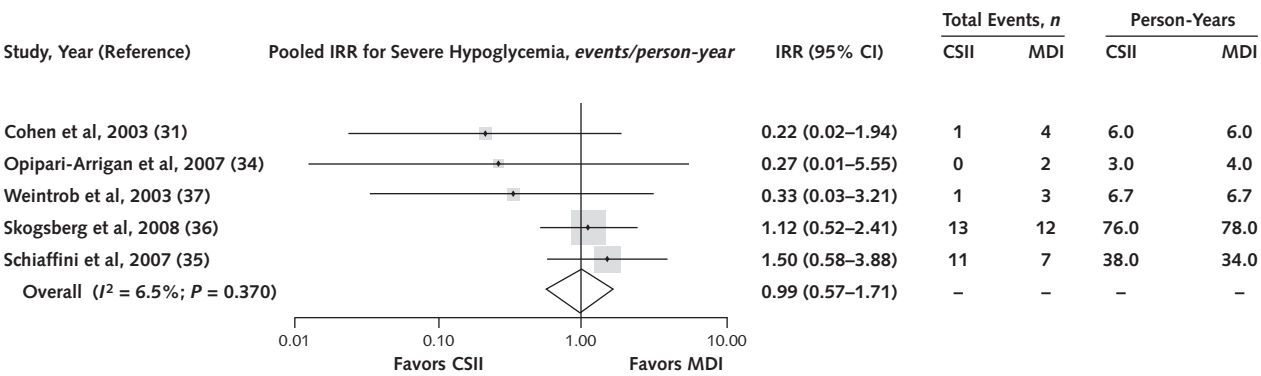
Weight Gain. Weight gain did not differ between CSII and MDI, with low strength of evidence, high risk of bias in 2 studies (48, 49), and no good-quality studies (**Appendix Tables 4** and **5**).

Evidence was insufficient to make conclusions about the effects of CSII versus MDI on nocturnal hypoglycemia, hyperglycemia, or QOL in adults with type 2 diabetes mellitus.

Comparative Effectiveness of rt-CGM Versus SMBG

All 10 trials addressing the comparative effectiveness of rt-CGM versus SMBG were conducted in patients with type 1 diabetes mellitus (51–60). None of the studies reported on mortality or any of the process measures. The insulin delivery

Figure 2. **Pooled IRR for severe hypoglycemia comparing CSII with MDI among children and adolescents with T1DM.**



Error bars represent 95% CIs. Shaded boxes represent individual study point estimates. Box size corresponds to weight of study. CSII = continuous subcutaneous insulin infusion; IRR = incidence rate ratio; MDI = multiple daily injections; T1DM = type 1 diabetes mellitus.

method was CSII in 5 studies (51–53, 55, 57) and either MDI or CSII in the other 5 studies (54, 56, 58–60).

HbA_{1c} Level

Two studies were excluded from our meta-analysis because of heterogeneity in study design. One had a crossover design (51) but did not report results by study period. The other study (52) was excluded because it compared SAPs with CSII and SMBG.

Our meta-analysis of 8 trials (10 estimates, because 2 studies had >1 subgroup) of at least 12 weeks in duration showed that rt-CGM reduced HbA_{1c} levels more than SMBG did (**Figure 4**, *top*). The analysis suggested statistical heterogeneity (I^2 = 69.9%; P = 0.000), but no study influenced results substantially. The heterogeneity was explained in part by percentage of adherence to sensor use. In metaregression, we found that sensor adherence was associated with HbA_{1c} level reduction (r = −0.858; P = 0.007) (**Appendix Figure 2**, available at www.annals.org). In a sensitivity analysis that included only studies with a rate of adherence to sensor use higher than 60%, the rt-CGM group had an even greater reduction in HbA_{1c} levels than SMBG (**Table 2**). Strength of evidence was high, risk of bias was low, and 6 studies (52, 54, 55, 57, 58, 60) were good-quality.

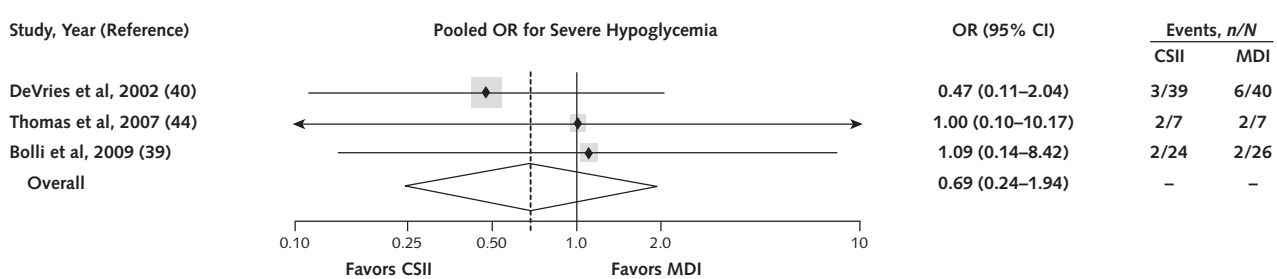
Five trials reported data separately for younger age groups. One study (58) reported a significant effect of rt-CGM compared with SMBG for persons aged 8 to 18 years. The other 4 trials showed no significant decrease in HbA_{1c} levels, but all favored rt-CGM (56, 57, 59–61).

Our meta-analysis of 5 studies in patients aged 18 years or younger showed no mean between-group difference in change from baseline HbA_{1c} level favoring rt-CGM (**Table 2**). We performed a subsidiary analysis for 3 studies (56, 57, 59) that reported data separately for adults. Our meta-analysis of these 3 studies showed a between-group mean difference in HbA_{1c} levels; however, heterogeneity was significant (**Table 2**). Three other studies did not present results separately for adults and children and were excluded from this subsidiary meta-analysis (53–55).

Severe Hypoglycemia

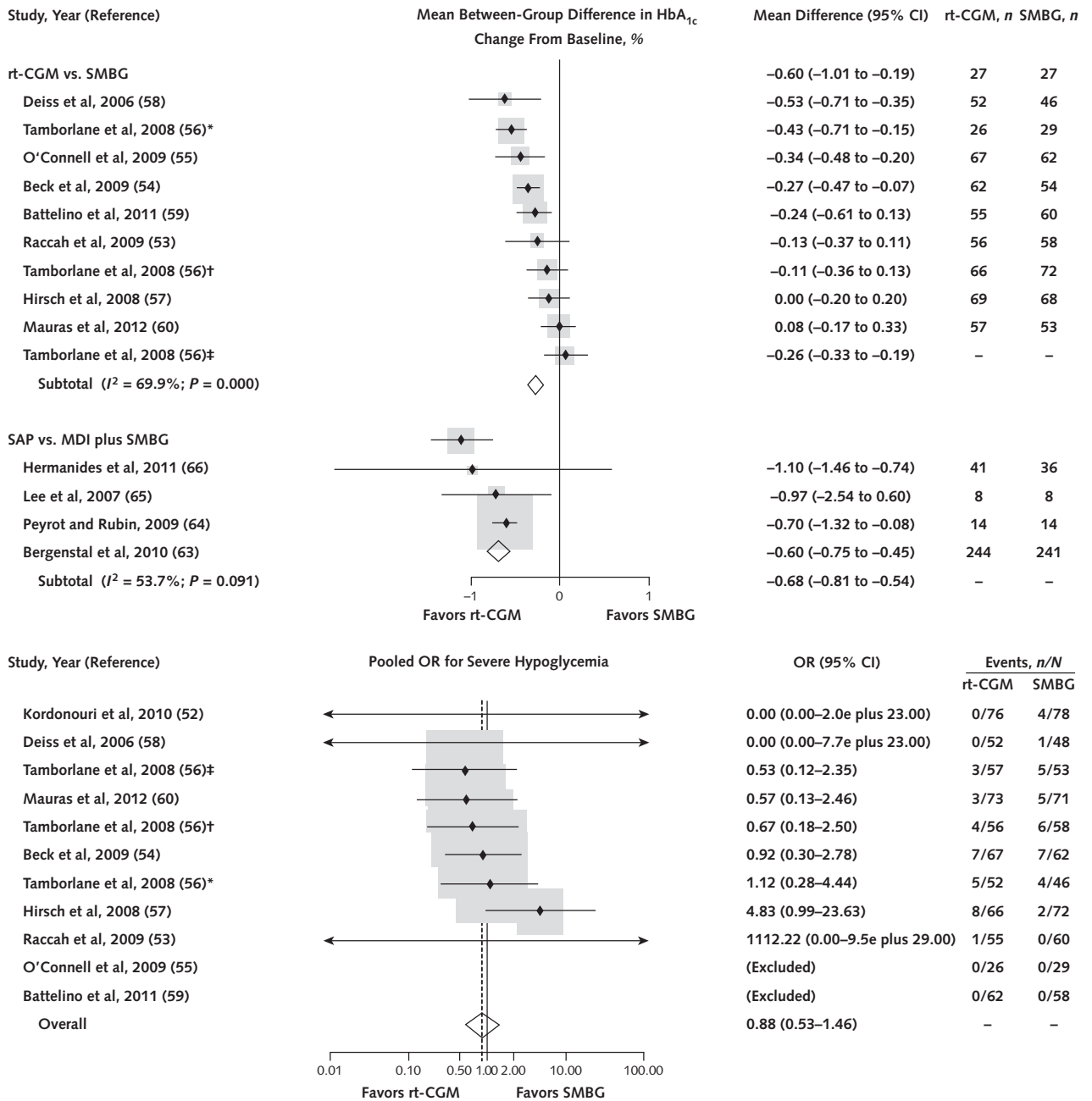
Nine studies reported the incidence of severe hypoglycemia (52–60). In our meta-analysis, the incidence of se-

Figure 3. **Pooled OR for severe hypoglycemia comparing CSII with MDI among adults with T1DM.**



Error bars represent 95% CIs. Shaded boxes represent individual study point estimates. Box size corresponds to weight of study. CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; OR = odds ratio; T1DM = type 1 diabetes mellitus.

Figure 4. **Comparison of rt-CGM with SMBG and SAP use with MDI plus SMBG among patients with T1DM.**



Mean between-group difference in the change from baseline HbA_{1c} among patients with T1DM comparing rt-CGM with SMBG and SAP with MDI plus SMBG (*top*). Pooled OR of severe hypoglycemia comparing rt-CGM with SMBG among patients with T1DM (*bottom*). Error bars represent 95% CIs. Shaded boxes represent individual study point estimates. Box size corresponds to weight of study. HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; OR = odds ratio; rt-CGM = real-time continuous glucose monitoring; SAP = sensor-augmented pump for insulin delivery; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus.

* Patients aged 15–24 y.

† Patients aged 8–14 y.

‡ Patients aged >25 y.

vere hypoglycemia did not differ between rt-CGM and SMBG (pooled relative risk, 0.88 [CI, 0.53 to 1.46]) (**Figure 4**, *bottom*). The risk difference between 2 groups favoring rt-CGM was 6 events per 1000 patients, with a CI ranging from 31 fewer events to 19 more events per 1000 patients. The strength of evidence was low, with medium risk of bias and 6 good-quality studies (52, 54, 55, 57, 58, 60). Three trials reported data on severe hypoglycemia in a

pediatric population (52, 56, 60), but 1 trial showed less hypoglycemia by using rt-CGM (52), whereas the other studies showed no difference (56, 60).

Other Hypoglycemic Outcomes

Eight studies evaluated the incidence of nonsevere hypoglycemia with rt-CGM compared with SMBG (51, 53–57, 59, 60). The definitions of hypoglycemia varied, and several studies reported multiple end points. Our meta-analysis of 4 studies (6 estimates) showed no difference in time spent in the hypoglycemic range, defined by glucose levels less than 3.9 mmol/L (<70 mg/dL) (**Appendix Figure 3**, available at www.annals.org) (53, 55, 56, 59). The strength of evidence was moderate, with medium risk of bias and 4 good-quality studies (55, 56, 59, 60).

Hyperglycemia

Seven studies evaluated hyperglycemia with rt-CGM versus SMBG (53–57, 59, 60). Four were excluded from our meta-analysis because definitions of hyperglycemia varied, and several studies reported multiple end points. Our meta-analysis indicated a significant reduction in time spent in the hyperglycemic range, defined by glucose levels greater than 10.0 mmol/L (180 mg/dL), with a mean between-group difference of −68.56 minutes/day (CI, −101.17 to −35.96 min/d) (**Appendix Figure 4**, available at www.annals.org) (53, 55, 56, 59). The strength of evidence was moderate, with medium risk of bias and 4 good-quality studies (54, 55, 57, 60).

QOL

Four studies compared QOL with rt-CGM versus SMBG (51, 52, 60, 62). Although QOL was measured by using different instruments, all studies reported no difference between groups. Strength of evidence was low, with low to medium risk of bias and 3 good-quality studies (52, 60, 62).

Comparison of SAP Versus MDI or SMBG

Four studies evaluated a SAP versus MDI and SMBG in children and adults with type 1 diabetes mellitus (63–66). All 4 studies used the MiniMed Paradigm REAL-Time Revel System (Medtronic, Northridge, California) and provided training in use of the device (63–66).

HbA_{1c} Level

Our meta-analysis of 4 RCTs showed that the SAP decreased HbA_{1c} levels more than MDI or SMBG did (combined mean between-group difference from baseline, −0.68%) (**Figure 2**, *top*). One (63) of the 4 studies included in our meta-analyses was much larger than the other 3 and dominated the results. Strength of evidence was moderate, risk of bias was medium, and 2 studies (63, 66) were good quality.

Table 2. **Summary of the Subgroup Analyses in the Between-Group Change From Baseline HbA_{1c} Among Patients With T1DM Comparing rt-CGM with SMBG**

Analysis	Studies Included (Participants Included), *n (n)*	Mean Difference in HbA_{1c} (95% CI), %	I^2, %
All studies*	8 (1066)†	−0.26 (−0.33 to −0.19)	66.6
Adults ≥18 y‡	3 (312)§	−0.38 (−0.53 to −0.23)	77.3
Children <18 y‖	5 (434)¶	−0.13 (−0.27 to 0.01)	46.0
Adherence >60%	7 (705)**	−0.36 (−0.44 to −0.27)	40.8

HbA_{1c} = hemoglobin A_{1c}; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus.
* Three studies (53–55) reported results combining all age groups.
† References 53 to 60.
‡ Only patients aged >25 y in reference 56 were included in this subgroup analysis.
§ References 56, 57, and 59.
‖ Only patients aged <15 y in reference 56 were included in this subgroup analysis.
¶ References 56 to 60.
** References 53 to 59.

Hyperglycemia

In 2 studies (63, 66), the time spent with hyperglycemia was significantly shorter with the SAP than with MDI or SMBG ($P < 0.001$). Heterogeneity in defining hyperglycemia did not permit pooling of results.

Severe Hypoglycemia

Four studies reported on the incidence of severe hypoglycemia, but use of different measures precluded a pooled analysis (**Appendix Table 5**). In the largest trial (63), severe hypoglycemia occurred at a similar rate in the SAP and MDI or SMBG groups (21 out of 247 vs. 17 out of 248; $P = 0.58$) with a risk difference of 1.6% (CI, −3.0% to 6.3%). Strength of evidence was moderate, risk of bias was medium, and 2 studies (63, 66) were good quality.

Included studies provided moderate strength of evidence for the effects of rt-CGM plus CSII versus MDI or SMBG on nonsevere hypoglycemia and hyperglycemia. However, these studies provided insufficient to low strength of evidence for weight and QOL (**Appendix Table 5**).

Applicability of Evidence and Publication Bias

Most studies did not report the racial and ethnic composition of the study populations; however, for those that did, more than 80% of participants were white. Few studies included patients younger than 12 years or older than 65 years. The small numbers of studies did not allow us to make conclusions about publication bias.

DISCUSSION

Comparative Effectiveness of CSII Versus MDI

Our review showed that CSII and MDI have similar effects on glycemic control and the incidence of severe hypoglycemia in children and adolescents with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. In adults with type 1 diabetes mellitus, CSII showed favor-

able effects on glycemic control. However, the result was influenced by 1 study in which participants had higher HbA_{1c} levels at enrollment, allowing for a greater decrease in HbA_{1c} levels than that of other studies, where participants were closer to the target HbA_{1c} level at enrollment (40). Compared with MDI, CSII yielded better satisfaction with diabetes mellitus treatment in children with type 1 diabetes mellitus and better diabetes mellitus–specific QOL in adults with type 1 diabetes mellitus, but the strength of evidence on QOL effects was low. The evidence was insufficient to draw definitive conclusions about other nonglycemic outcomes.

Our systematic review complements and extends previous meta-analyses on the comparative effectiveness of CSII versus MDI by including more studies of persons with type 2 diabetes mellitus (5–7, 9, 67); including only studies using rapidly acting insulin analogues in the CSII groups (5–7, 9); and requiring the MDI groups to receive at least 3 injections per day, the current standard for intensive insulin therapy (6, 8, 67, 68). Although some meta-analyses have shown a significant reduction in HbA_{1c} levels with CSII, none reached what is considered a clinically meaningful difference of 0.5% (25). Previous meta-analyses that have shown larger effect sizes favoring CSII have included before-and-after studies that were vulnerable to selection bias and confounding (5). Some analyses included fewer than 3 daily injections in the MDI group, which may have biased the results to favor CSII (8, 67).

Similar to a previous meta-analysis, we found that severe hypoglycemia rates in persons with type 1 diabetes mellitus were similar between MDI and CSII groups (68). Although 2 analyses found a higher rate of severe hypoglycemia with MDI than with CSII, 1 analysis included only studies in which participants reported an increased frequency of baseline severe hypoglycemia, which may have resulted in a greater likelihood of improvement (5). The other analysis included studies using regular insulin in the CSII groups, which would be expected to result in less hypoglycemia than regular insulin with MDI because of steadier insulin delivery (7). Our meta-analysis is distinct from previous reviews because it includes heretofore unreported studies that use current rapid-acting analogues in the CSII groups (9) and provides a quantitative effect estimate (25).

Comparative Effectiveness of rt-CGM Versus SMBG

Our review of the comparative effectiveness of rt-CGM and SMBG complements a recent meta-analysis (14) by including a comprehensive set of outcomes. Compared with SMBG, rt-CGM achieved a lower HbA_{1c} level (absolute difference, −0.26%) that was significant but below the 0.5% difference that we defined as clinically meaningful. A sensitivity analysis showed that this effect was slightly greater in studies where sensor adherence was 60% or more (−0.36%). We also found that rt-CGM was associated with a lower HbA_{1c} level than MDI in persons aged 18 years or younger.

The intervention groups did not differ in the rate of severe hypoglycemia, the fear of which can be a barrier to glycemic control. A few studies that evaluated weight gain or QOL found no difference between intervention groups. These findings provide modest support for recommendations to use rt-CGM in children older than 8 years (69).

Comparative Effectiveness of SAP Versus MDI or SMBG

Sensor-augmented insulin pump use resulted in a statistically and clinically significant greater reduction in HbA_{1c} levels than with MDI or SMBG in persons with type 1 diabetes mellitus. The evidence was insufficient to draw definitive conclusions about severe hypoglycemia or QOL. No previous meta-analysis examined this comparison.

Limitations

Our review highlights important weaknesses in the literature. Most RCTs of devices that deliver insulin and monitor glucose levels were small, with the largest having 322 participants (36). Most studies 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 samples. For those that did, most participants were white. Few studies included children younger than 12 years or adults older than 65 years. This is probably because type 1 diabetes mellitus is less prevalent in minority and elderly persons, making it less feasible to perform studies in these subpopulations.

The studies were heterogeneous in definitions of hypoglycemia, hyperglycemia, and weight gain, making it difficult to combine data across studies. None of the studies included data on long-term micro- or macrovascular complications. These complications develop over many years, and the longest follow-up among the studies was 52 weeks. Data on these outcomes would be ideal but would require a large RCT several years in duration that could sustain clinically meaningful HbA_{1c} level reductions; this RCT may not be feasible, particularly because persons may switch therapies over time.

Other than the rt-CGM studies, most studies did not report on treatment adherence. The high baseline HbA_{1c} levels in the CSII and MDI groups in many studies may indicate poor adherence to previous 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 QOL, which prevented us from quantifying the effects on QOL.

Our review had several limitations. Meta-analyses in general are subject to bias based on article selection criteria, multiple comparisons, and the state of the literature. We reviewed studies of current methods for intensive insulin therapy and glucose monitoring. However, there were few studies for each of the comparisons and publication bias could not be definitely excluded. We may have missed unpublished studies on this topic, but our search strategy

was comprehensive and included non–English-language publications.

Our data are not generalizable to all patients with diabetes mellitus, because management of CSII and rt-CGM is often limited to expert settings and highly motivated patients. All studies of rt-CGM are subject to ascertainment bias because rt-CGM provides more data on hypo- and hyperglycemia than on SMBG alone. Because blinding patients in an RCT comparing CSII with MDI or comparing rt-SGM with SMBG is not feasible, studies of QOL outcomes could have been vulnerable to reporting bias if patients believed that CSII and rt-CGM were superior. Because of the small number of studies in each targeted population, we could not adjust the analyses for all potential effect modifiers, such as baseline HbA_{1c} level, diabetes mellitus duration, and age.

Finally, our study did not address availability, costs, or insurance coverage of CSII, rt-CGM, and SAPs, which may be obstacles to their use. In general, insulin pumps cost between $6000 and $7000, and supplies cost approximately $2000 per year. Real-time continuous glucose monitoring costs approximately $5000 per year. The extent to which insurance covers these costs will contribute to their use in practice.

Implications

Our findings indicate that MDI and rapid-acting analogue–based CSII are similarly effective in lowering HbA_{1c} levels with similar rates of hypoglycemia in patients with type 1 diabetes mellitus. From a patient-focused perspective, CSII yielded better satisfaction with diabetes mellitus treatment in children with type 1 diabetes mellitus and better diabetes mellitus–specific QOL in adults with type 1 diabetes mellitus. These data suggest that the approach to intensive insulin therapy can be individualized to patient preference and maximize treatment satisfaction and QOL, because both MDI and rapid-acting analogue–based CSII have similar effectiveness for glycemic control.

This is the first systematic review to examine the comparative effectiveness of both rt-CGM versus SMBG and the SAP versus MDI or SMBG. Our findings indicate that rt-CGM is superior to SMBG in lowering HbA_{1c} levels without increasing the risk for severe hypoglycemia in persons with type 1 diabetes mellitus, particularly those who are adherent to the monitoring device. Even though CSII and MDI without rt-CGM have similar effects on HbA_{1c} levels, addition of rt-CGM to CSII is superior to MDI and SMBG in decreasing HbA_{1c} levels. Thus, the addition of this monitoring method to SMBG and intensive insulin therapy can assist in achieving glycemic targets in type 1 diabetes mellitus. The literature does not allow us to determine the comparative effectiveness of rt-CGM versus SMBG in patients using only CSII or MDI because the modes of insulin therapy were mixed in the studies.

Future research should include larger studies in populations in which diabetes mellitus is increasing (elderly persons, persons with insulin-requiring type 2 diabetes mellitus, and minority populations). Studies should report on important clinical outcomes, consider effects of adherence on outcomes, and assess cost-effectiveness.

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Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

Acknowledgment: The authors thank Dr. Christine Chang, Task Order Officer, for her support throughout the project and for helpful suggestions for improving the clarity and presentation of the findings; Dr. Ari Eckerman and research assistants Drs. Elie Donath and Ghanshyam Palamaner Subash Shantha for their help in reviewing articles; Dr. Felicia Hill-Briggs for her consultation on quality-of-life outcomes; and the late Dr. Christopher Saudek for his contribution and guidance in the early stage of this work.

Grant Support: By the AHRQ.

Potential Conflicts of Interest: Disclosures can be also viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-0156.

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70. **Rubin RR, Peyrot M; STAR 3 Study Group.** Health-related quality of life and treatment satisfaction in the Sensor-Augmented Pump Therapy for A1C Reduction 3 (STAR 3) trial. Diabetes Technol Ther. 2012;14:143-51. [PMID: 22133037]

Appendix Table 1. Search Strategies

Terms	Returns
PubMed	
(("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])	5031
EMBASE	
(('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)	6898
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))))	256

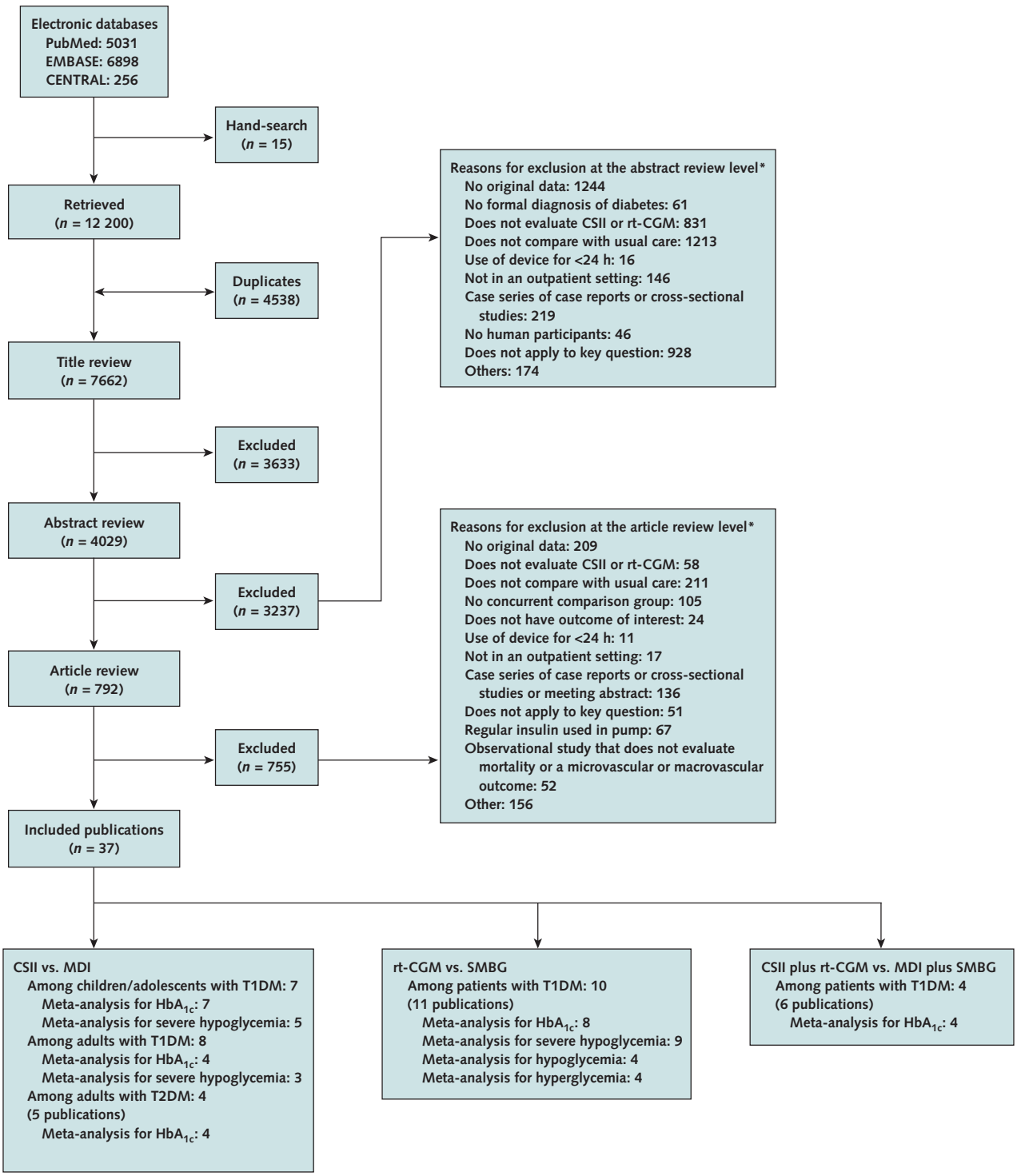
CENTRAL = Cochrane Central Register of Controlled Trials.

Appendix Table 2. Health-Related QOL Assessment Tools Used in Each Category

Domain	Instrument	Range of Total Scores (Indication of High Score)
General health-related QOL	Pediatric QOL Inventory	0–100 (better QOL)
	SF-36	0–100 (higher level of health)
	SF-12	0–100 (higher level of health)
	WHO-5	0–100 (better well-being)
Diabetes mellitus–specific QOL	Diabetes QOL	0–100 (better QOL)
	Diabetes QOL Clinical Trial Questionnaire	0–100 (higher satisfaction)
	Diabetes QOL for 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, except for the "Problems" section)

QOL = quality of life; SF-12 = Short Form-12 Health Survey; SF-36 = Short Form-36 Health Survey; WHO-5 = World Health Organization-5 Well-Being Index.

Appendix Figure 1. **Summary of evidence search and selection.**



CENTRAL= Cochrane Central Register of Controlled Trials; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

* Total number of articles may exceed the number in the corresponding box because articles could be excluded for more than 1 reason.

Appendix Table 3. **Population Characteristics of Studies Comparing Methods of Insulin Delivery or Glucose Monitoring for Diabetes Mellitus**

Study, Year (Reference)	Design	Support	Study Duration	Location	Participants, *n*	Type of Insulin Used	Mean Baseline HbA_{1c} Level, %	Diabetes Mellitus Duration, *y*	Study Outcome	Overall Quality*
CSII vs. MDI in children and adolescents with T1DM										
Cohen et al, 2003 (31)	RCT crossover	Industry	12 mo	Israel	16	MDI: NPH, regular insulin CSII: lispro	MDI: 8.48 CSII: 8.58	NR	HbA_{1c}, severe hypoglycemia, other hypoglycemia, weight, QOL	Poor
Doyle et al, 2004 (32)	RCT parallel	Industry, government	16 wk	United States	32	MDI: glargine, aspart CSII: aspart	MDI: 8.2 CSII: 8.1	MDI: 5.6 CSII: 6.8	HbA_{1c}, other hypoglycemia, severe hypoglycemia, weight, QOL	Good
Nuboer et al, 2008 (33)	RCT crossover	Government, other	14 mo	Netherlands	39	CSII: aspart	MDI: 7.98 CSII: 7.66	MDI: 4.7 CSII: 5.6	HbA_{1c}, QOL	Poor, fair
Opipari-Arrigan et al, 2007 (34)	RCT parallel	Other	6 mo	United States	28	MDI: NPH, lispro CSII: lispro	MDI: 7.98 CSII: 8.26	NR	HbA_{1c}, other hypoglycemia, severe hypoglycemia, QOL	Poor
Schiaffini et al, 2007 (35)	RCT parallel	Support NR	24 mo	Italy	36	MDI: glargine, regular insulin CSII: lispro	MDI: 8.5 CSII: 8.3	MDI: 5.7 CSII: 5.8	HbA_{1c}, severe hypoglycemia	Poor
Skogsberg et al, 2008 (36)	RCT parallel	Industry, government, other	24 mo	Sweden	72	MDI: NPH, aspart CSII: aspart	MDI: 8.4 CSII: 8.3	NR	HbA_{1c}, other hypoglycemia, QOL	Fair
Weintrob et al, 2003 (37)	RCT crossover	Industry	3.5 mo	Israel	23	MDI: glargine, regular insulin CSII: lispro	MDI: 8.6 CSII: 7.9	MDI: 6.3 CSII: 5.3	HbA_{1c}, hyperglycemia, other hypoglycemia, severe hypoglycemia, weight, QOL	Fair
CSII vs. MDI in adults with T1DM										
Bolli et al, 2009 (39)	RCT parallel	Industry	24 wk	Europe	58	MDI, long-acting: glargine MDI, short-acting: lispro, aspart	MDI: 7.8 CSII: 7.7	MDI: 20.9 CSII: 18.5	HbA_{1c}, hyperglycemia, other hypoglycemia, severe hypoglycemia, QOL	Fair, poor
Bruttomesso et al, 2008 (38)	RCT crossover	Industry	4 mo	Italy	42	MDI, long-acting: glargine MDI, short-acting: lispro, aspart	MDI: 7.4 CSII: 7.6	MDI: 15.7 CSII: 17.2	Severe hyperglycemia, other hypoglycemia, severe hypoglycemia, weight	Fair, poor
DeVries et al, 2002 (40)	RCT parallel	Industry	16 wk	Netherlands	89	MDI, long-acting: NPH MDI, short-acting: lispro, aspart	MDI: 9.3 CSII: 9.3	MDI: 18 CSII: 17.6	HbA_{1c}, other hyperglycemia, other hypoglycemia, severe hypoglycemia, weight, QOL	Fair
Hanaire-Broutin et al, 2000 (41)	RCT crossover	Industry	8 mo	France	107	MDI, long-acting: NPH MDI, short-acting: lispro, aspart	MDI: 8.1 CSII: 8.4	MDI: 15.4 CSII: 16.9	Other hyperglycemia, severe hypoglycemia	Fair, good
Hirsch et al, 2005 (42)	RCT crossover	Industry	6 mo	United States	146	MDI, long-acting: glargine MDI, short-acting: lispro, aspart	NR	NR	Other hyperglycemia, other hypoglycemia, severe hypoglycemia	Fair
Hoogma et al, 2006 (43)	RCT crossover	Industry	6 mo	Europe	272	MDI, long-acting: NPH MDI, short-acting: lispro, aspart	MDI: 8.3 CSII: 8.2	MDI: 15.4 CSII: 15.4	Mild hypoglycemia, severe hypoglycemia, QOL	Poor, fair
Thomas et al, 2007 (44)	RCT parallel	Industry	26 wk	NR	21	MDI, long-acting: glargine MDI, short-acting: lispro, aspart	NR	NR	HbA_{1c}, hyperglycemia, other hypoglycemia, severe hypoglycemia, weight, QOL	Fair
Tsui et al, 2001 (45)	RCT parallel	Industry	9 mo	Canada	27	MDI, long-acting: NPH MDI, short-acting: lispro, aspart	MDI: 8.16 CSII: 7.73	MDI: 15 CSII: 17	HbA_{1c}, other hypoglycemia, severe hypoglycemia, QOL	Good, fair

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Appendix Table 3—**Continued**

Study, Year (Reference)	Design	Support	Study Duration	Location	Participants, *n*	Type of Insulin Used	Mean Baseline HbA_{1c} Level, %	Diabetes Mellitus Duration, *y*	Study Outcome	Overall Quality*
CSII vs. MDI in adults with T2DM										
Derosa et al, 2009 (47)	RCT parallel	Support NR	12 mo	Italy	64	MDI: glargine, lispro CSII: lispro	MDI: 9.3 CSII: 9.2	NR	HbA_{1c}	Fair, poor
Herman et al, 2005 (48)	RCT parallel	Industry, government	12 mo	NR	107	MDI: glargine, lispro CSII: lispro	MDI: 8.1 CSII: 8.4	MDI: 15.4 CSII: 16.9	HbA_{1c}, other hypoglycemia, severe hypoglycemia, weight, QOL	Fair
Raskin et al, 2003 (49)	RCT parallel	Industry	24 wk	United States	132	MDI: NPH, aspart CSII: aspart	MDI: 8 CSII: 8.2	MDI: 11.9 CSII: 13.8	HbA_{1c}, hyperglycemia, other hypoglycemia, severe hypoglycemia, weight, QOL	Fair, poor
Wainstein et al, 2005 (50)	RCT crossover	Support NR	18 wk	NR	40	MDI: NPH, regular insulin CSII: lispro	NR	NR	HbA_{1c}, severe hypoglycemia	Fair
rt-CGM vs. SMBG in children and adults with T1DM										
Battelino et al, 2011 (59)	RCT parallel	Industry, government	6 mo	NR	120	NA	SMBG: 6.91 rt-CGM: 6.92	SMBG: 11.4 rt-CGM: 11.6	HbA_{1c}, other hypoglycemia	Fair
Deiss et al, 2006 (58)	RCT parallel	Industry	3 mo	Europe	162	NA	SMBG: 9.7 rt-CGM: 9.6	NR	HbA_{1c}, severe hypoglycemia	Poor, good
Hirsch et al, 2008 (57)	RCT parallel	Industry	6 mo	United States	146	NA	SMBG: 8.39 rt-CGM: 8.49	SMBG: 16.7 rt-CGM: 20.8	HbA_{1c}, hyperglycemia, other hypoglycemia, severe hypoglycemia	Good
Beck et al, 2009 (54)	RCT parallel	Industry, other	26 wk	United States	129	NA	SMBG: 6.5 rt-CGM: 6.4	NR	HbA_{1c}, hyperglycemia, other hypoglycemia, severe hypoglycemia, QOL	Good
Kordonouri et al, 2010 (52)	RCT parallel	Industry	52 wk	Europe	160	NA	SMBG: 11.5 rt-CGM: 11.2	NR	HbA_{1c}, ratio of basal to bolus insulin, severe hypoglycemia, QOL	Good
Mauras et al, 2012 (60)	RCT parallel	Industry, government	26 wk	NR	146	NA	SMBG: 7.9 rt-CGM: 7.9	SMBG: 2.9 rt-CGM: 3.9	HbA_{1c}, severe hypoglycemia, QOL	Good
O'Connell et al, 2009 (55)	RCT parallel	Industry	3 mo	Australia	62	NA	SMBG: 7.5 rt-CGM: 7.2	SMBG: 9.2 rt-CGM: 11.1	HbA_{1c}, severe hypoglycemia	Good
Raccah et al, 2009 (53)	RCT parallel	Industry	6 mo	France	132	NA	SMBG: 9.28 rt-CGM: 9.11	SMBG: 12.3 rt-CGM: 11.2	HbA_{1c}, ratio of basal to bolus insulin, severe hypoglycemia, hyperglycemia, other hypoglycemia	Fair
Radermecker et al, 2010 (51)	RCT crossover	Other	12 wk	Europe	12	NA	NR	NR	HbA_{1c}, other hypoglycemia, severe hypoglycemia, QOL	Fair
Tamborlane et al, 2008 (56)†	RCT parallel	Other	26 wk	United States	322	NA	SMBG: 8 rt-CGM: 7.9	SMBG: 5.3 rt-CGM: 6.2	HbA_{1c}, hyperglycemia, severe hypoglycemia	Fair
Tamborlane et al, 2008 (56)‡	RCT parallel	Other	26 wk	United States	322	NA	SMBG: 7.9 rt-CGM: 8	SMBG: 8.8 rt-CGM: 9.5	HbA_{1c}, hyperglycemia, severe hypoglycemia	Fair
Tamborlane et al, 2008 (56)§	RCT parallel	Other	26 wk	United States	322	NA	SMBG: 7.6 rt-CGM: 7.6	SMBG: 21.8 rt-CGM: 23.6	HbA_{1c}, hyperglycemia, severe hypoglycemia	Fair

Continued on following page

Appendix Table 3—**Continued**

Study, Year (Reference)	Design	Support	Study Duration	Location	Participants, *n*	Type of Insulin Used	Mean Baseline HbA_{1c} Level, %	Diabetes Mellitus Duration, *y*	Study Outcome	Overall Quality*
SAP vs. MDI plus SMBG										
Bergenstal et al, 2010 (63)	RCT parallel	Industry	1 y	United States, Canada	485	NA	CSII plus rt-CGM: 8.3 MDI plus SMBG: 8.3	CSII plus rt-CGM: 15.4 MDI plus SMBG: 15.2	HbA_{1c}, severe hypoglycemia, hyperglycemia, weight, QOL	Fair
Hermanides et al, 2011 (66)	RCT parallel	Industry	26 wk	Europe	83	NA	CSII plus rt-CGM: 8.64 MDI plus SMBG: 8.47	CSII plus rt-CGM: 21 MDI plus SMBG: 16.9	HbA_{1c}, severe hypoglycemia, other hyperglycemia, other hypoglycemia	Good
Lee et al, 2007 (65)	RCT parallel	Support NR	15 wk	United States	16	NA	CSII plus rt-CGM: 8.58 MDI plus SMBG: 9.45	NR	HbA_{1c}, severe hypoglycemia	Fair
Peyrot and Rubin, 2009 (64)	RCT parallel	Industry	16 wk	NR	28	NA	CSII plus rt-CGM: 8.32 MDI plus SMBG: 8.87	NR	HbA_{1c}, severe hypoglycemia, weight, QOL	Poor

CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; NA = not available; NPH = neutral protamine Hagedorn; NR = not reported; QOL = quality of life; RCT = randomized, controlled trial; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

* Studies rated as *good* (low risk of bias) 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. Studies rated as *fair* 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. Studies rated as *poor* (high risk of bias) 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 (19).

† Patients aged 8–14 y.

‡ Patients aged 15–24 y.

§ Patients aged >25 y.

Appendix Table 4. **Study Quality and Risk of Bias Assessment of Clinical Trials Comparing Methods of Insulin Delivery or Glucose Monitoring for Diabetes Mellitus***

Study, Year (Reference)	Sequence Generation	Allocation Concealment	Blinding, Personnel, Outcome	Incomplete Outcome Data	Device Company Support	Device Company Involvement	Overall Quality†
CSII vs. MDI in children and adolescents with T1DM							
Cohen et al, 2003 (31)	Unclear	Unclear	No	Unclear	Yes	Unable to determine	Poor
Cohen et al, 2003 (31)	Unclear	Unclear	No	Unclear	Yes	Unable to determine	Poor
Doyle et al, 2004 (32)	Yes	Yes	No	Yes	Yes	No	Good
Doyle et al, 2004 (32)	Yes	Unclear	Unclear	Yes	Yes	Unable to determine	Good
Nuboer et al, 2008 (33)	Unclear	Unclear	No	Unclear	No	Unable to determine	Poor
Nuboer et al, 2008 (33)	Unclear	Unclear	Unclear	Yes	No	Unable to determine	Fair
Opipari-Arrigan et al, 2007 (34)	Unclear	Unclear	No	Unclear	No	Unable to determine	Poor
Opipari-Arrigan et al, 2007 (34)	Unclear	Unclear	Unclear	Unclear	Unable to determine	Unable to determine	Poor
Schiaffini et al, 2007 (35)	Unclear	Unclear	Unclear	Unclear	No	Unable to determine	Poor
Schiaffini et al, 2007 (35)	Unclear	Unclear	No	Unclear	No	Unable to determine	Poor
Skogsberg et al, 2008 (36)	Unclear	Unclear	Unclear	Unclear	Unable to determine	Unable to determine	Fair
Skogsberg et al, 2008 (36)	Unclear	Unclear	No	Unclear	Yes	Unable to determine	Fair
Weintrob et al, 2003 (37)	Unclear	Unclear	No	Yes	Yes	Unable to determine	Fair
Weintrob et al, 2003 (37)	Unclear	Unclear	No	Yes	Yes	Unable to determine	Fair
CSII vs. MDI in adults with T1DM							
Bolli et al, 2009 (39)	Yes	Yes	No	Yes	Yes	Unable to determine	Fair
Bolli et al, 2009 (39)	Unclear	Unclear	No	No	Yes	Yes	Poor
Bruttomesso et al, 2008 (38)	Yes	Unclear	Unclear	No	Yes	Yes	Fair
Bruttomesso et al, 2008 (38)	Unclear	Yes	No	Yes	Yes	Yes	Poor
DeVries et al, 2002 (40)	Yes	Yes	No	No	Yes	Unable to determine	Fair
DeVries et al, 2002 (40)	Yes	Yes	No	Yes	Yes	Unable to determine	Fair
Hanaire-Broutin et al, 2000 (41)	Yes	No	No	Yes	Yes	Unable to determine	Fair
Hanaire-Broutin et al, 2000 (41)	Unclear	Unclear	No	Yes	Yes	Unable to determine	Good
Hirsch et al, 2005 (42)	Yes	No	No	Yes	Yes	Yes	Fair
Hirsch et al, 2005 (42)	Unclear	Unclear	Unclear	No	Yes	Yes	Fair
Hoogma et al, 2006 (43)	Unclear	Unclear	No	No	Yes	Unable to determine	Poor
Hoogma et al, 2006 (43)	Yes	No	No	Yes	Yes	Yes	Fair
Thomas et al, 2007 (44)	Unclear	Unclear	Unclear	Unclear	Yes	No	Fair
Thomas et al, 2007 (44)	Unclear	Unclear	No	Yes	Yes	No	Fair
Tsui et al, 2001 (45)	Yes	Yes	Unclear	Yes	Yes	Unable to determine	Good
Tsui et al, 2001 (45)	Yes	Yes	No	Unclear	Yes	Unable to determine	Fair
CSII vs. MDI in adults with T2DM							
Derosa et al, 2009 (47)	Unclear	Unclear	Unclear	No	Unable to determine	Unable to determine	Fair
Derosa et al, 2009 (47)	Unclear	Unclear	No	Unclear	Unable to determine	Unable to determine	Poor
Herman et al, 2005 (48)	Unclear	Yes	Unclear	Unclear	Yes	Unable to determine	Fair
Herman et al, 2005 (48)	Yes	No	No	No	Yes	Unable to determine	Fair
Raskin et al, 2003 (49)	Yes	Unclear	Unclear	No	Yes	Unable to determine	Poor
Raskin et al, 2003 (49)	Yes	Yes	No	Yes	Yes	Unable to determine	Fair
Wainstein et al, 2005 (50)	Unclear	Unclear	Unclear	No	Unable to determine	Unable to determine	Fair
Wainstein et al, 2005 (50)	Unclear	No	No	Yes	Unable to determine	Unable to determine	Fair
rt-CGM vs. SMBG in children and adults with T1DM							
Battelino et al, 2011 (59)	Yes	Yes	No	Unclear	Yes	Unable to determine	Fair
Battelino et al, 2011 (59)	Yes	Yes	No	Yes	Yes	No	Fair
Deiss et al, 2006 (58)	Unclear	Unclear	Unclear	Unclear	Yes	Unable to determine	Poor
Deiss et al, 2006 (58)	Unclear	Unclear	Yes	Yes	Yes	Unable to determine	Good
Hirsch et al, 2008 (57)	Unclear	Unclear	No	Yes	Yes	Yes	Good
Hirsch et al, 2008 (57)	Unclear	Unclear	Yes	Yes	Yes	Unable to determine	Good
Beck et al, 2009 (54)	Unclear	Yes	No	Yes	Yes	Unable to determine	Good
Beck et al, 2009 (54)	Yes	Unclear	No	Yes	Yes	Unable to determine	Good
Kordonouri et al, 2010 (52)	Yes	Yes	No	Yes	Yes	Unable to determine	Good
Kordonouri et al, 2010 (52)	Unclear	Yes	Yes	Yes	Yes	Unable to determine	Good
Mauras et al, 2012 (60)	Yes	Unclear	Unclear	Yes	Yes	Unable to determine	Fair
Mauras et al, 2012 (60)	Unclear	Unclear	No	Yes	No	No	Fair
O'Connell et al, 2009 (55)	Yes	Yes	No	Yes	Yes	No	Good
O'Connell et al, 2009 (55)	Yes	Yes	No	No	Yes	Unable to determine	Good
Raccah et al, 2009 (53)	Unclear	Unclear	No	No	Yes	Unable to determine	Fair
Raccah et al, 2009 (53)	Unclear	Unclear	No	No	Yes	Unable to determine	Fair
Radermecker et al, 2010 (51)	Unclear	Unclear	No	Yes	No	No	Fair
Radermecker et al, 2010 (51)	Unclear	Unclear	No	No	No	Unable to determine	Fair
Tamborlane et al, 2008 (56)	Yes	Unclear	No	Unclear	Yes	Unable to determine	Fair
Tamborlane et al, 2008 (56)	Unclear	Unclear	No	Yes	No	Unable to determine	Fair

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Appendix Table 4—**Continued**

Study, Year (Reference)	Sequence Generation	Allocation Concealment	Blinding, Personnel, Outcome	Incomplete Outcome Data	Device Company Support	Device Company Involvement	Overall Quality†
SAP vs. MDI plus SMBG							
Bergenstal et al, 2010 (63)	No	No	No	Yes	Yes	Unable to determine	Fair
Bergenstal et al, 2010 (63)	Unable to determine	Unable to determine	No	Yes	Yes	Yes	Fair
Hermanides et al, 2011 (66)	Yes	Yes	No	Yes	Unable to determine	Unable to determine	Good
Hermanides et al, 2011 (66)	Yes	Yes	No	Yes	Yes	Yes	Good
Lee et al, 2007 (65)	Unclear	Unclear	No	No	Unable to determine	Unable to determine	Fair
Lee et al, 2007 (65)	Unclear	Unclear	Unclear	Unclear	Unable to determine	Unable to determine	Fair
Peyrot and Rubin, 2009 (64)	Unclear	Unclear	Unclear	Yes	Yes	No	Poor
Peyrot and Rubin, 2009 (64)	Unclear	No	Unclear	Yes	Yes	No	Poor

CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

* Each study is cited twice because 2 separate reviewers independently assessed risk of bias.

† Studies rated as *good* (low risk of bias) 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. Studies rated as *fair* 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. Studies rated as *poor* (high risk of bias) 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 (19).

Appendix Table 5. **Summary of the Evidence of the Comparative Effectiveness of CSII With MDI, rt-CGM With SMBG, and SAP Therapy With MDI and SMBG in Children, Adolescents, or Adults With T1DM or T2DM**

Outcome	Risk of Bias	Strength of Evidence	Studies/Studies of Good Quality, *N/n*	Main Findings
MDI vs. CSII in children and adolescents with T1DM				
HbA_{1c}	Medium	Moderate	7/1	Mean between-group difference in HbA_{1c} levels changed from baseline was −0.14%, decreasing slightly more with CSII than with MDI (95% CI, −0.48% to 0.20%; $P = 0.41$). Results were similar among adolescents >12 y (mean between-group difference in the change from baseline HbA_{1c} level, −0.10% [CI, −0.47% to 0.27%]) and among children <12 y (mean between-group difference in the change from baseline HbA_{1c} level, −0.05% [CI, −1.01% to 0.96%]).
Daytime hypoglycemia	Medium	Low	3/0	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 wk, 0 [CI, −1.1 to 1.1 events] [36]; mean between-group difference in the change from baseline to 24 wk in the number of blood glucose measurements <3.9 mmol/L [70 mg/dL], –0.9 [CI, −2.1 to 0.3] [34]; mean between-group difference in number of hypoglycemic episodes per patient at 52 wk, −3.7 [CI, −13.2 to 5.8] [31]).
Nocturnal hypoglycemia	Medium	Low	2/1	One study reported 4 events per patient per study period (CI, 0.3 to 7.7) for MDI vs. 3 events per patient per study period (CI, 1.0 to 5.0) over 52 wk (31). The other study reported 2 patients with ≥1 event in the CSII group but no events in the MDI group over 16 wk (32).
Mild hypoglycemia	High	Insufficient	1/0	One study found no significant difference in mild hypoglycemia (events with blood glucose levels <3.9 mmol/L [70 mg/dL]) between the MDI group (22 events per patient) and CSII group (19.8 events per patient) over 14 wk (37).
Severe hypoglycemia	Medium	Low	5/1	The mean IRR for severe hypoglycemic event rates in RCTs for CSII vs. MDI was 0.99 (CI, 0.57 to 1.71; $P = 0.97$). Results were similar among adolescents >12 y (mean IRR for CSII vs. MDI, 0.95 [CI, 0.42 to 2.13]) and children <12 y (mean IRR for CSII vs. MDI, 1.02 [CI, 0.49 to 2.16]).
Hyperglycemia	High	Insufficient	1/0	One study found no difference in the frequency of hyperglycemia between the MDI group (6.7 events) and CSII group (7.9 events) over 14 wk (37).
Weight	Medium	Low	3/1	A pooled analysis of 2 studies show no between-group mean difference in BMI SD score changed from baseline of –0.12 units, decreasing slightly more with CSII than MDI (CI, –0.55 to 0.30 units).
General QOL	Medium	Low	2/0	A pooled analysis of 2 studies showed no significant difference with mean between-group difference of 2.3 (CI, –6.9 to 11.5; $P = 0.95$).
Diabetes mellitus–specific QOL	Medium	Low	4/1	One study showed improvement in diabetes mellitus–specific QOL favoring CSII (Diabetes QOL Questionnaire for Youth baseline score, 77.4 [CI, 69.5 to 85.3] and end-of-study score, 76.4 [CI, 68.3 to 84.5] for MDI and 82.7 [CI, 75.3 to 90.1] for CSII) (31). One study did not find a difference in diabetes mellitus–specific QOL between the 2 interventions (numerical data not presented) (32).
Diabetes mellitus treatment–related QOL	Medium	Low	3/0	A meta-analysis of 2 studies showed improvement in diabetes mellitus treatment satisfaction favoring CSII over MDI (mean between-group difference in the Diabetes Treatment Satisfaction Questionnaire, 5.7 [CI, 5.0 to 6.4]).
MDI vs. CSII in adults with T1DM				
HbA_{1c}	Medium	Low	4/2	Our meta-analysis showed that CSII produced a larger reduction in HbA_{1c} levels than MDI, with low strength of evidence (combined mean between-group difference, −0.30% [CI, −0.58% to −0.02%]; $I^2 = 64.5\%$). However, the pooled estimate was influenced by 1 study (40). After removing this study, the difference between CSII and MDI became null (combined mean between-group difference, −0.01% [CI, −0.35% to 0.34%]; $I^2 = 0\%$).
Daytime hypoglycemia	Medium	Low	1/0	One study reported more symptomatic and asymptomatic hypoglycemia between 8:00 a.m. and midnight in the MDI group compared with the CSII group ($P < 0.05$) (42).

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Appendix Table 5—**Continued**

Outcome	Risk of Bias	Strength of Evidence	Studies/Studies of Good Quality, *N/n*	Main Findings
Nocturnal hypoglycemia	Medium	Low	3/0	Three studies reported nocturnal hypoglycemia. In 1 crossover trial, the proportion of patients experiencing nocturnal hypoglycemia was similar between the MDI group and CSII group (RR for any, 0.98 [CI, 0.83 to 1.17]; RR for symptomatic hypoglycemic episodes, 0.87 [CI, 0.64 to 1.19]), although there were fewer episodes per person in the CSII group compared with the MDI group (IRR, 0.76 [CI, 0.63 to 0.91]) (42). Two other studies found no significant difference in nocturnal hypoglycemic episodes between the 2 intervention groups (39, 44).
Symptomatic hypoglycemia	Medium	Low	4/1	We found an increased risk for symptomatic hypoglycemia for CSII compared with MDI (combined IRR, 1.30 [CI, 1.18 to 1.42]), but we found evidence of substantial statistical heterogeneity for this meta-analysis. After excluding a study that required participants to have had recent severe hypoglycemia (44) (compared with the other 2, which excluded those with recent severe hypoglycemia [39, 45]), the IRR suggested no relative difference in the incidence of symptomatic hypoglycemia for CSII compared with MDI (combined IRR, 0.99 [CI, 0.85 to 1.14]). Another study, which did not provide sufficient quantitative results, reported slightly more symptomatic hypoglycemic events with CSII vs. MDI (IRR, 1.14 [CI, 1.00 to 1.29]), although a similar proportion of participants experienced events over 5 wk (RR, 1.05 [CI, 0.89 to 1.24]) (42).
Other nonsevere hypoglycemia	Medium	Low	6/1	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 [CI, −1.39 to 0.99]) (39). In 2 studies, the incidence of mild hypoglycemia was higher in the CSII than in the MDI group (40, 42), with the relative difference significant in 1 study (between-group difference in change in hypoglycemic rate, 0.99 [CI, 0.11 to 1.87]) (40). One additional study found a higher frequency of hypoglycemia in the MDI group than in the CSII group (RR, 1.12 [CI, 1.08 to 1.17]) (43).
Severe hypoglycemia	Medium	Low	8/2	The incidence of severe hypoglycemia did not differ between the 2 intervention groups (combined RR, 0.74 [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 compared with CSII (42, 43), with 1 study reporting a RR of 2.6 (CI, 2.08 to 3.25) (43). One study showed less severe hypoglycemia with MDI than with CSII (IRR, 3.00 [CI, 0.24 to 157.49]) (41). One study found similar rates of severe hypoglycemia between the 2 groups (1.1 events per patient for CSII vs. 1.3 for MDI over 4 mo; $P = 0.33$) (38).
Hyperglycemia		Low	3/0	The mean between-group difference in fasting glucose level over 6 mo was −0.7 mmol/L (−12 mg/dL) (CI, −1.8 to 0.5 mmol/L [−32.9 to 8.2 mg/dL]) favoring CSII in 1 study (39). Two other studies reported no difference in fasting glucose levels between the MDI and CSII groups.
Bedtime hyperglycemia	Medium	Insufficient	1/0	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 levels at bedtime in the CSII group compared with the MDI group but did not provide glucose results (40).
Preprandial glucose	Medium	Low	3/0	The mean between-group difference in preprandial glucose levels over 6 mo was −0.9 mmol/L (−17 mg/dL) (CI, −2.3 to 0.4 mmol/L [−42.1 to 8.0 mg/dL]) favoring CSII in 1 study; in another study, predinner glucose levels were lower with CSII (7.1 mmol/L [128 mg/dL]) compared with MDI (8.2 mmol/L [148 mg/dL]) at the end of 5 wk (P = NS). Predinner and prelunch glucose levels were not significantly lower with CSII than with MDI at 4 mo in a third study.

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Appendix Table 5—**Continued**

Outcome	Risk of Bias	Strength of Evidence	Studies/Studies of Good Quality, *N/n*	Main Findings
Postprandial glucose	Medium	Low	3/0	The strength of evidence was low comparing CSII with MDI for postprandial glucose levels, suggesting slightly lower postprandial glucose levels with CSII compared with MDI. Comparing CSII and MDI, the reported mean between-group difference in postprandial glucose level was −0.3 mmol/L (−5 mg/dL) (CI, −1.6 to 1.0 mmol/L [−30 to 19 mg/dL]) in 1 study (39) and −1.3 mmol/L (−24 mg/dL) postbreakfast and −0.8 mmol/L (−15 mg/dL) postdinner; in another (42), postbreakfast glucose levels were not significantly higher in the MDI group compared with the CSII group in a third study (40).
Nocturnal hyperglycemia	High	Low	2/0	Two studies found no difference in between-group difference in nocturnal glucose levels (39; 40), with 1 reporting an increase in nocturnal glucose levels in both groups (between-group difference for CSII compared with MDI, 3/0 mmol/L (55 mg/dL) (CI, −0.4 to 6.4 mmol/L [−7 to 117 mg/dL]) (39).
Weight	Medium	Low	4/0	Weight gain did not differ between CSII and MDI (combined mean between-group difference, −0.25 kg [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.
General QOL	High	Low	2/0	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) (43). 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 mellitus–specific QOL	High	Low	4/1	Three studies showed an improvement in diabetes mellitus–specific QOL favoring CSII (39, 43, 44). A meta-analysis of 2 studies favored CSII over MDI for Diabetes QOL (mean between-group difference in Diabetes QOL, 2.99 [CI, 0.006 to 5.97]) (39, 44). One study showed improvement favoring MDI (Diabetes QOL mean between-group difference in change from baseline, −18.00 [CI, −50.14 to 14.14]) (44).
Diabetes mellitus treatment–related QOL	High	Insufficient	1/0	Altered Hypoglycemia Awareness Questionnaire scores were similar in the CSII and MDI groups over 24 wk (RR of Altered Hypoglycemia Awareness Questionnaire score >4, 0.75 [CI, 0.26 to 2.18]). Hypoglycemia Fear Survey scores decreased in both the CSII group (−3 ± 25) and MDI group (−8 ± 33) (mean between-group difference in the change from baseline, 5 (CI, −32.66 to 42.66]) (44).
MDI vs. CSII in adults with T2DM				
HbA_{1c}	Medium	Moderate	4/0	The effects on HbA_{1c} level did not differ between the MDI and CSII intervention groups (mean between-group difference from baseline favoring CSII, −0.18% [CI, −0.43% to 0.08%]; P = 0.17).
Mild hypoglycemia	Medium	Moderate	3/0	The risk for mild hypoglycemia did not differ between MDI and CSII (combined RR, 0.90 [CI, 0.78 to 1.03]) (46, 48).
Nocturnal hypoglycemia	Medium	Insufficient	1/0	In a single study, nocturnal hypoglycemia (occurring between midnight and 6:00 a.m.) was less common in patients in the CSII group than in the MDI group (RR, 0.73 [CI, 0.35 to 1.54]).
Severe hypoglycemia	Medium	Low	3/0	The risk for severe hypoglycemia did not differ between CSII and MDI (RR, 0.76 [CI, 0.26 to 2.19]).
Hyperglycemia	Medium	Insufficient	2/0	Mean postprandial glucose levels (90 min after breakfast) were 9.2 mmol/L (167 mg/dL) in the CSII group and 10.6 mmol/L (192 mg/dL) in the MDI group at 24 wk (mean between-group difference, 1.4 mmol/L [−25 mg/dL] [CI, −2.5 to 0.3 mmol/L {−45 to −5 mg/dL}]) (49). Glucose measurements from other time points were similar between treatment groups at the end of the study. The incidence of blood glucose levels higher than 19.4 mmol/L (350 mg/dL) was higher in the MDI group than in the CSII group (26 vs. 6 events), affecting 18% of participants in the MDI group and 5% in the CSII group (RR, 0.28 [CI, 0.08 to 0.94]) (49).
Weight	Medium	Low	2/0	Weight gain did not differ between CSII and MDI groups (combined mean between-group difference in weight change from baseline, −0.49 kg [CI, −1.25 to 0.26 kg]).
General QOL	High	Insufficient	1/0	One study reported 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 vs. 0.4 for MDI and for the Mental Component score was 1.0 for CSII vs. 2.5 for MDI (48).

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Appendix Table 5—**Continued**

Outcome	Risk of Bias	Strength of Evidence	Studies/Studies of Good Quality, *N/n*	Main Findings
Diabetes mellitus–specific QOL	High	Insufficient	1/0	One study reported no difference in diabetes mellitus–specific QOL between the CSII and MDI intervention groups (Diabetes QOL Clinical Trials Questionnaire scores improved from 52 to 81 for CSII and from 50 to 78 for MDI over 12 mo) (48).
Diabetes mellitus treatment–related QOL	High	Insufficient	1/0	One study reported improvement in diabetes mellitus treatment satisfaction favoring CSII (mean between-group difference in Phase V Outcomes System Diabetes Treatment Satisfaction score change from baseline in 24 wk, 13.1 [CI, 7.4 to 18.8]) (49).
rt-CGM vs. SMBG				
HbA_{1c}	Low	High	10/6	rt-CGM was favored over SMBG for the effects on HbA_{1c}. Mean between-group difference in how HbA_{1c} changed from baseline was −0.26% (CI, −0.33% to −0.19%). In the sensitivity analysis that included only studies with >60% of adherence rate (7 estimates), there was a greater HbA_{1c} reduction (mean between-group difference from baseline, −0.36% [CI, −0.44% to −0.27%]). Meta-analysis of 5 studies in patients aged ≤18 y showed no significant difference with mean between-group difference in change from baseline HbA_{1c} level favoring rt-CGM. A meta-analysis of these 3 studies in adults showed a between-group HbA_{1c} level mean difference of −0.38 (CI, −0.53 to −0.23); however, there was significant heterogeneity (I^2 = 77.3%).
Nonsevere hypoglycemia	Medium	Moderate	8/3	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 blood glucose levels <3.9 mmol/L (70 mg/dL). The mean between-group difference was −2.11 min/d (CI, −5.66 to 1.44 min/d).
Severe hypoglycemia	Medium	Low	9/6	The rate of severe hypoglycemia did not differ between the rt-CGM and SMBG groups (pooled RR, 0.88 [CI, 0.53 to 1.46]). Three of these trials reported severe hypoglycemia data specifically in pediatric populations. In 1 study, severe hypoglycemia was less common in pediatric patients using rt-CGM than those using SMBG alone (SMBG, 4/78, vs. rt-CGM, 0/76; P = 0.046) (52). In contrast, the pediatric subgroup (ages 8–14 y) of another study showed a similar incidence of severe hypoglycemia in both groups (SMBG, 6/58, vs. rt-CGM, 4/56; P = 0.74) (56) and the third trial showed 3 participants (4%, 3 total events) in the rt-CGM group and 5 participants (7%, 6 total events) in the control group experienced at least 1 severe hypoglycemic event, with no significant differences comparing treatment groups (incidence rate, 8.6 per 100 person-years in the rt-CGM group and 17.6 per 100 person-years in the SMBG group; P = 0.80) (60).
Hyperglycemia	Medium	Moderate	7/3	A meta-analysis of 4 studies (6 estimates) indicated a significant reduction in time spent in hyperglycemic range, defined by a glucose level >9.9 mmol/L (180 mg/dL), with the mean between-group difference of −68.56 min/d favoring rt-CGM (CI, −101.17 to −35.96 min/d).
General QOL	Low	Low	2/2	One study found no difference in parental satisfaction between the 2 intervention groups (mean between-group difference in change from baseline in World Health Organization-5 Well-Being Index mother's well-being score, −2.7 [CI, −14.2 to 8.8]) at 12 mo (52). The other study assessed general QOL by 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 [CI, −1.5 to 4.3]) but no difference between the intervention groups in the Mental Component score (mean between-group difference in change from baseline, −1.6 [CI, −5.9 to 2.7]) at 26 wk [62].
Diabetes mellitus–specific QOL	Medium	Low	3/2	The effect on diabetes-specific QOL did not differ between the rt-CGM and SMBG groups in either study (mean between-group difference in the change from baseline in Problem Areas in Diabetes score, −0.9 [CI, −7.9 to 6.1 at 26 wk [62] and mean between-group difference in the change from baseline Diabetes QOL score, −3.0 [CI, −6.6 to 0.6]] [51]). One study reported no difference between rt-CGM and SMBG from parents who filled out the Pediatric Assessment in Diabetes Survey (44 ± 17 for rt-CGM and 49 ± 16 for SMBG; P = 0.42) (60).

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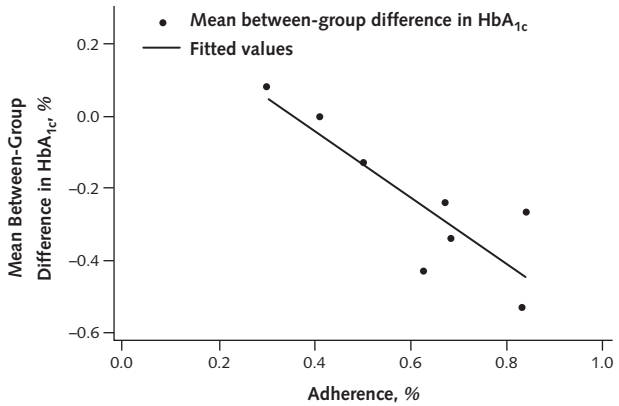
Appendix Table 5—**Continued**

Outcome	Risk of Bias	Strength of Evidence	Studies/Studies of Good Quality, *N/n*	Main Findings
Diabetes mellitus treatment–related QOL	Low	Low	2/0	The fear of hypoglycemia was less with rt-CGM than with SMBG (mean between-group difference in change from baseline score, −2.3 [CI, −8.2 to 3.6]) for 1 study (62). One study reported no difference between rt-CGM and SMBG for fear of hypoglycemia (38 ± 17 for rt-CGM, 42 ± 19 for SMBG; $P = 0.38$), but parents generally reported higher than neutral on the Continuous Glucose Monitoring Satisfaction Scale (60).
SAP (rt-CGM plus CSII) vs. MDI plus SMBG				
HbA_{1c}	Medium	Moderate	4/2	SAPs were favored over MDI/SMBG for their effects on HbA_{1c} levels (mean between-group difference in HbA_{1c} level change, −0.68% [CI, −0.81% to −0.54%]).
Nonsevere hypoglycemia	Medium	Moderate	2/2	The time spent with nonsevere hypoglycemia did not differ between the SAP and MDI/SMBG intervention groups.
Severe hypoglycemia	Medium	Moderate	4/2	The incidence of severe hypoglycemia did not differ between the SAP and MDI/SMBG intervention groups: RR, 1.2 (CI, 0.7 to 2.3) (63); 0 events for the SAP group vs. 3 events for the MDI/SMBG groups (64); 0 events in 8 patients in the SAP group vs. 1 event in 8 patients in the MDI/SMBG group (64); and RR, 3.5 (CI, 0.4 to 304) (66).
Hyperglycemia	High	Moderate	2/2	Two trials suggested that time spent with hyperglycemia was significantly less in the SAP compared with the MDI/SMBG intervention group ($P < 0.001$).
Weight	High	Low	2/1	One study (63) reported no significant difference in weight gain between the SAP and MDI/SMBG intervention groups (mean, 2.4 vs. 1.8 kg; $P = 0.19$). In another study, weight increased by 0.7 kg in the SAP group and 2.0 kg in the MDI/SMBG group, but the difference was not significant (mean between-group difference, 1.3 kg [CI, −21.2 to 23.8 kg]) (64).
General QOL	High	Insufficient	1/0	One study found no difference in adults in both between-group and baseline differences by using the SF-36 Mental Component Summary and Physical Component Summary scores. The same study found no significant change among children and caregivers in the PedsQL Health Summary scores for between-group or baseline changes and found significant improvement in the PedsQL Psychosocial Health Summary score among children in the MDI/SMBG group in change of baseline (mean change from baseline, 3.54; $P < 0.01$) (63, 70).
Diabetes mellitus treatment–related quality of life	High	Low	2/1	User acceptance and overall diabetes mellitus treatment satisfaction were greater in the SAP group than in the MDI/SMBG group. Blood Glucose Monitoring System Rating Questionnaire scores were 83.3 ± 21.7 for SAP vs. 33.3 ± 22.6 for MDI/SMBG (mean between-group difference in final scores, 50.0 [CI, 33.6 to 66.4]) (64). Hypoglycemia fear measured by hypoglycemia-avoidant behavior improved significantly in adults, children, and caregivers in the SAP group and in children in the MDI/SMBG groups (hypoglycemia-avoidant behavior mean change from baseline in adults, −2.30; in children, −4.01; in caregivers, −4.16; $P < 0.001$) and for caregivers in children in the MDI/SMBG group (mean change from baseline, −2.25; $P < 0.01$). Hypoglycemia worry improved significantly from baseline in adults, children, and caregivers treated with SAPs (−6.36, $P < 0.001$; −3.62, $P < 0.01$; −3.64, $P < 0.01$). All significant between-group difference in change of the Insulin Delivery System Rating Questionnaire was greater for the key measures of convenience, efficiency, and overall preference in adults, children, and caregivers ($P < 0.001$) (63, 70).

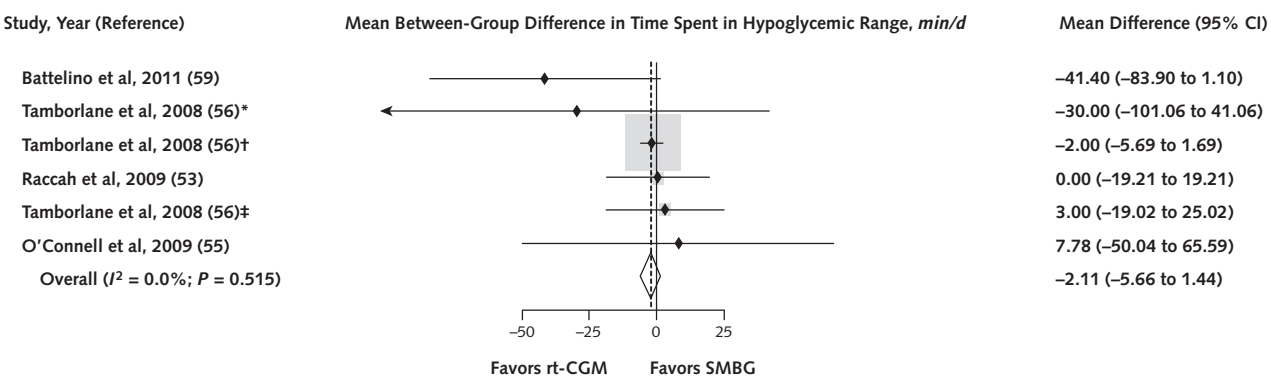
BMI = body mass index; CSII = continuous subcutaneous insulin infusion; HbA_{1c} = hemoglobin A_{1c}; IRR = incidence rate ratio; MDI = multiple daily injections; NS = not significant; PedsQL = Pediatric Quality of Life Inventory; QOL = quality of life; RCT = randomized, controlled trial; RR = relative risk; rt-CGM = real-time continuous glucose monitoring; SAP = sensor-augmented pump for insulin delivery; SF-12 = Short Form-12 Health Survey; SF-36 = Short Form-36 Health Survey; SF-36v2 = Short Form-36 Health Survey, version 2.0; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Appendix Figure 2. **Adherence with sensor use and mean between-group difference between rt-CGM and SMBG in HbA_{1c} changed from baseline.**



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

Appendix Figure 3. **Between-group difference between rt-CGM and SMBG in time spent in hypoglycemic range changed from baseline among patients with T1DM.**



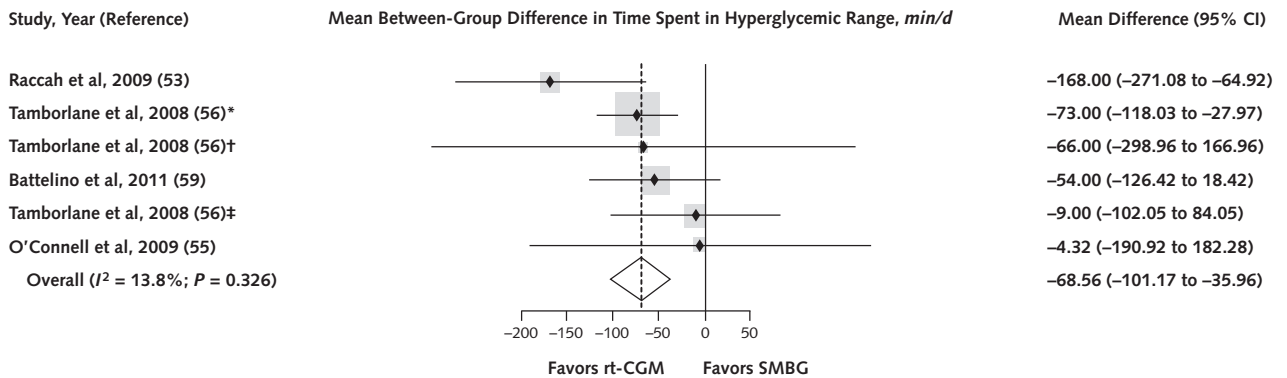
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% CI for each study. The diamond at the bottom of the figure indicates the 95% CI for the random-effects pooled estimate. Test for heterogeneity: $Q = 4.24$ ($P = 0.52$). rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus.

* Patients aged >25 y.

† Patients aged 8–14 y.

‡ Patients aged 15–24 y.

Appendix Figure 4. **Between-group difference between rt-CGM and SMBG in time spent in hyperglycemic range changed from baseline among patients with T1DM.**



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% CI for each study. The diamond at the bottom of the figure indicates the 95% CI for the random-effects pooled estimate. Test for heterogeneity: $Q = 5.80$ ($P = 0.33$). rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus.

* Patients aged >25 y.

† Patients aged 8–14 y.

‡ Patients aged 15–24 y.