

Diabetes Technology—Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline

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Objective: To formulate clinical practice guidelines for the use of continuous glucose monitoring and continuous subcutaneous insulin infusion in adults with diabetes.

Participants: The participants include an Endocrine Society-appointed Task Force of seven experts, a methodologist, and a medical writer. The American Association for Clinical Chemistry, the American Association of Diabetes Educators, and the European Society of Endocrinology co-sponsored this guideline.

Evidence: The Task Force developed this evidence-based guideline using the Grading of Recommendations, Assessment, Development, and Evaluation system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned one systematic review and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, the American Association for Clinical Chemistry, the American Association of Diabetes Educators, and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

Conclusions: Continuous subcutaneous insulin infusion and continuous glucose monitoring have an important role in the treatment of diabetes. Data from randomized controlled trials are limited on the use of medical devices, but existing studies support the use of diabetes technology for a wide variety of indications. This guideline presents a review of the literature and practice recommendations for appropriate device use. (*J Clin Endocrinol Metab* 101: 3922–3937, 2016)

Summary of Recommendations

1. Insulin pump therapy without sensor augmentation

1.1 We recommend continuous subcutaneous insulin infusion (CSII) over analog-based basal-bolus multiple daily

injections (MDI) in patients with type 1 diabetes mellitus (T1DM) who have not achieved their A1C goal, as long as the patient and caregivers are willing and able to use the device. (1⊕⊕⊕⊕)

1.2 We recommend CSII over analog-based basal-bolus MDI in patients with T1DM who have achieved their A1C

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Abbreviations: CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; RAA, rapid-acting analog; RCT, randomized controlled trial; RT-CGM, real-time CGM; SAP, sensor-augmented pump; SIP, sensor-integrated pump; SMBG, self-monitoring blood glucose; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

goal but continue to experience severe hypoglycemia or high glucose variability, as long as the patient and caregivers are willing and able to use the device. (1|⊕⊕○○)

1.3 We suggest CSII in patients with T1DM who require increased insulin delivery flexibility or improved satisfaction and are capable of using the device. (2|⊕⊕○○)

2. Insulin pump therapy in type 2 diabetes mellitus

2.1 We suggest CSII with good adherence to monitoring and dosing in patients with type 2 diabetes mellitus (T2DM) who have poor glycemic control despite intensive insulin therapy, oral agents, other injectable therapy, and lifestyle modifications. (2|⊕⊕○○)

3. Insulin pump use in the hospital

3.1 We suggest that clinicians continue CSII in patients admitted to the hospital with either type of diabetes if the institution has clear protocols for evaluating patients as suitable candidates and appropriate monitoring and safety procedures. (2|⊕⊕○○)

4. Selection of candidates for insulin pump therapy

4.1 We recommend that before prescribing CSII, clinicians perform a structured assessment of a patient's mental and psychological status, prior adherence with diabetes self-care measures, willingness and interest in trying the device, and availability for the required follow-up visits. (1|⊕⊕○○)

5. Use of bolus calculators in insulin pump therapy

5.1 We suggest encouraging patients to use appropriately adjusted embedded bolus calculators in CSII and have appropriate education regarding their use and limitations. (2|⊕⊕○○)

6. Real-time continuous glucose monitors in adult outpatients

6.1 We recommend real-time continuous glucose monitoring (RT-CGM) devices for adult patients with T1DM who have A1C levels above target and who are willing and able to use these devices on a nearly daily basis. (1|⊕⊕⊕⊕)

6.2 We recommend RT-CGM devices for adult patients with well-controlled T1DM who are willing and able to use these devices on a nearly daily basis. (1|⊕⊕⊕⊕)

Use of continuous glucose monitoring in adults with type 2 diabetes mellitus

6.3 We suggest short-term, intermittent RT-CGM use in adult patients with T2DM (not on prandial insulin) who have A1C levels $\geq 7\%$ and are willing and able to use the device. (2|⊕⊕○○)

Education and training on the use of continuous subcutaneous insulin infusion and continuous glucose monitoring

6.4 We suggest that adults with T1DM and T2DM who use CSII and continuous glucose monitoring (CGM) receive education, training, and ongoing support to help achieve and maintain individualized glycemic goals. (Ungraded Good Practice Statement)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed diabetes technology a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that the Task Force considered in making the recommendation; in some instances, there are remarks, a section in which the Task Force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the Task Force and their values and preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the Task Force made several statements to emphasize the importance of shared decision-

making, general preventive care measures, and basic principles of diabetes technology. They labeled these “Ungraded Good Practice Statement.” Direct evidence for these statements was either unavailable or not systematically appraised and was considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles; one should not consider these statements as graded recommendations (3).

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All Task Force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society’s Council approves the members to participate on the Task Force and periodically during the development of the guideline. All others participating in the guideline’s development must also disclose any conflicts of interest in the matter under study, and a majority of these participants must be without any conflicts of interest. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests (eg, stocks and stock options [excluding diversified mutual funds]); honoraria and other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided all funding for this guideline; the Task Force received no funding or remuneration from commercial or other entities.

Commissioned systematic review

The Task Force commissioned a systematic review and individual patient data meta-analysis of randomized controlled trials (RCTs) that enrolled individuals with T1DM and compared RT-CGM versus control groups. A two-step regression model was used to pool individual patient data, which came from trial lists and device manufacturers. Pooled data from 11 RCTs suggested that the use of RT-CGM was associated with a significant reduction in A1C (-0.276 ; 95% confidence interval, -0.465 to -0.087). The improvements in A1C were primarily seen in ages ≥ 15 years. There was no statistically significant difference in time spent in hypoglycemia or the number of hypoglycemic episodes, although these analyses were imprecise and warrant lower confidence. There was no difference between males and females.

Introduction

The goal of glucose management in all types of diabetes is to minimize and hopefully eliminate the acute and chronic complications associated with diabetes, such as the risks of microvascular complications and potentially (to a lesser degree) macrovascular complications and mortality (4–9). All persons with T1DM require insulin, and persons with T2DM frequently need insulin for adequate glucose control. Patients requiring intensive insulin therapy take insulin as needed, adjusting both basal and prandial doses to reach specific glucose goals (10). However, intensification increases the risk of hypoglycemia, which is associated with both morbidity and mortality. Advances in the pharmacokinetics and pharmacodynamics of insulin products and in the methods of insulin delivery and glucose monitoring are geared toward improving glucose control, minimizing hypoglycemia, and improving quality of life. Two such advances include CSII and CGM. And whereas these and other new technologies hold the potential for enhancing outcomes and improving quality of life for people with diabetes, reliable data on the efficacy of new advances is lacking. This is due in part because the U.S. Food and Drug Administration (FDA) regulates medical devices less rigorously than it regulates pharmaceuticals, which lessens the demand for large clinical trials comparing one device to another. Of the studies that do exist, many include devices that are outdated or obsolete at the time of publication and thus do not reflect current technologies. This guideline attempts to assess all available data on existing and emerging technologies and procedures for improving glucose control for patients with diabetes.

Important to note, success of these devices and technologies is directly linked to the level to which people are educated, capable, and willing to use them. Patients on CSII therapy, as well as MDI of insulin, can have inadequate glucose control. Therefore, in every stage of this guideline we stress the need for patient and practitioner education and training in conjunction with clearly defined processes for patient follow-up, analysis of device data, and access to care (should a problem arise). Finally, human factors relating to the use of these technologies are as important as other considerations in device development, although in many cases true effectiveness data are lacking (11).

Clinicians began developing CSII therapy as early as 1963, and it gained increasing general acceptance in the 1980s. This was in part due to the Diabetes Control and Complications Trial, which compared CSII with MDI in patients with T1DM. The trial lasted from 1982 to 1993 and placed roughly 40% of patients on CSII and the remaining patients on MDI (12). Results showed that pa-

tients treated with CSII had a slightly lower A1C mean relative to patients treated with MDI. These results, however, do not necessarily apply to today's diabetes patients because the last 30 years have seen many technological improvements in insulin products and pump technologies, and the use of insulin pumps has grown dramatically (primarily for treating T1DM). Despite these improvements, comprehensive reliable data are lacking on the number of people with T1DM and the number of people who use insulin pumps who have T1DM. Likewise, data are lacking that demonstrate a clear superiority of CSII over MDI. This is due to a general lack of studies and is confounded by the ongoing development of newer insulin analogs and advanced glucose monitoring and insulin delivery technologies, making comparisons between studies complex. However, diabetes specialists have confidence in pump therapy, despite its greater expense. The T1D Exchange, a registry of diabetes specialty clinics in the United States, reported in 2012 that 56% of the adult T1DM patients in these clinics were using CSII and had lower A1C levels than those using MDI (13).

Early pumps were heavy, crude syringe pumps with suboptimal quality control, inadequate battery power, and limited dosing flexibility that used infusion sets with rigid needles. The modern age of CSII use in the clinical setting began in the 1980s with new manufacturers entering the market and significant technological advances. Today, there are five FDA-approved pumps available in the United States providing numerous features to improve accuracy, safety, dosing decisions, convenience, and overall usability (14). This guideline only reviewed pumps that allow for multiple basal rates and use bolus dose calculators. We feel there is insufficient research evidence and experience to include single-basal-rate pumps or bolus-only pumps (Calibra Finesse) in this analysis. Finally, these guidelines are meant for individuals using rapid-acting analog (RAA) insulin in their pumps (although we do mention U-500 insulin).

There are few professional organization recommendations or guidelines related to CSII (15–17). The latest standards of care from the American Diabetes Association simply say that clinicians should treat most people with T1DM with MDI or CSII (10).

CGM is a more recently developed device for managing diabetes. For years, clinicians have used standard capillary blood glucose measurements (self-monitoring blood glucose [SMBG]) to guide therapy; however, these discrete values offer only a limited perspective on the constant daily changes in blood glucose levels, do not provide alarms that indicate when blood glucose levels are above or below various thresholds, and do not indicate trends in blood glucose levels. Current models of CGM measure the

glucose concentration in the interstitial fluid, and devices are evolving steadily in terms of accuracy and ease of use. We reviewed the data regarding current CGM devices, giving specific consideration to more recent device technology. We excluded devices designed for intensive care units and the Abbott Libre system, which, although unique in terms of its claim as strip replacement without the need for calibration, does not provide true CGM in terms of providing alerts for high and low blood glucose levels.

1. Insulin pump therapy without sensor augmentation

1.1 We recommend CSII over analog-based basal-bolus MDI in patients with T1DM who have not achieved their A1C goal, as long as the patient and caregivers are willing and able to use the device. (1⊕⊕⊕⊕)

Evidence

The alternative therapy for T1DM is basal-bolus therapy with a RAA insulin and a basal analog insulin (10). Unfortunately, many of the comparative effectiveness trials for pumps took place before these modern analogs (which are associated with less hypoglycemia) were available (18). Some studies compared CSII using RAA vs MDI using non-analog or a mixture of insulin types; however, this is not directly applicable to current MDI regimens, which primarily use analog insulin. Continual advancements in pump design have also complicated analysis. The user interface, size, and shape, and bolus calculators on pumps are evolving, as is data communication (eg, via CGM, meters, Internet). The added benefit of advancements in pump design would be obscured in a meta-analysis of multiple studies that also included outdated pumps. Finally, double-blind trials are not possible because individuals would be aware of their assigned treatment.

Given these limitations, however, a couple of meta-analyses have reviewed the small number of comparative effectiveness RCTs of therapies for T1DM in adults (18–23). The 2010 Cochrane Review of CSII in T1DM found a statistically significant reduction in A1C of 0.3% in those adults treated with CSII (19). However, that review included many studies completed before 2000 with pumps that used regular insulin. Due to the changes in available insulin and the technological changes in pumps, the most relevant systematic reviews are those evaluating studies reported over the last 15 years with pumps that used RAAs. The most recent meta-analysis by Yeh et al (20) only included studies that used RAA and only found four qualifying trials. They again found a significant benefit to CSII with a reduction in A1C of 0.3% compared to MDI. However, the results were significantly influenced by the

largest study that found a reduction in A1C of 0.84% with CSII; however, this was also the study with the highest randomization A1C (9.3% mean) (24). This 16-week study was intended to be a 32-week crossover trial, but the authors only reported the first phase due to a high dropout rate at the time of crossover. Despite this significant flaw, this study was unique in that it included a 14-week “qualification phase” to randomize only patients who completed at least 70% of the recommended glucose monitoring. There is no evidence that other studies took measures to identify patients for inclusion who were similarly motivated. Only one of the reported studies was of more than 16 weeks in duration. In a small 9-month study, Tsui et al (25) reported that baseline A1C was approximately 0.5% higher in the MDI group, although they said it represented a nonsignificant difference. None of the studies in the Yeh et al (20) analysis used a bolus dose calculator, although one of the studies included a pump that did have that feature available (26). This study was the only one that used a modern basal insulin (glargine).

A 5-week crossover design study using CGM reported that the area under the curve for glucose levels over 140 mg/dL was reduced by 40% in T1DM patients on CSII of insulin aspart vs MDI of insulin aspart/insulin glargine (27). Fructosamine reduction was also highly significant with CSII vs MDI.

Observational studies performed at clinics with significant insulin pump experience and carefully applied protocols of patient selection and education suggest that glucose control may be better in these clinics vs research settings where patient inclusion criteria are variable and rarely optimized for ideal candidates. For example, a recent observational study of 200 adults with T1DM transitioned to CSII from MDI demonstrated that in these poorly controlled patients, CSII reduced A1C by a mean of > 1.0% and maintained a significant improvement for the average 6 years of follow-up (28). RCTs do not consistently utilize (and meta-analyses do not typically analyze) the selection criterion, educational approach, or ongoing evaluation and support that experienced clinicians and clinics implement. We describe in detail what defines a reasonable pump candidate below (*4. Selection of candidates for insulin pump therapy*).

Despite the limitations of the available literature, there is relatively consistent evidence that current CSII is likely to improve glucose control in motivated patients with inadequate glucose control who are appropriately educated and supported. Because this area of insulin treatment technology is progressing in the direction of sensor augmentation, it is unlikely that we will see meaningful studies evaluating the isolated benefit of CSII that will advance the present body of evidence.

1.2 We recommend CSII over analog-based basal-bolus MDI in patients with T1DM who have achieved their A1C goal but continue to experience severe hypoglycemia or high glucose variability, as long as the patient and caregivers are willing and able to use the device. (1|⊕⊕○○)

Evidence

Data on the reduction of hypoglycemia are mixed and difficult to analyze with systematic reviews due to variable study definitions of hypoglycemia and variable patterns of monitoring to detect overall or nocturnal hypoglycemia (19, 20). On balance, there is no good evidence that CSII reduces overall hypoglycemia in patients with T1DM. Most comparative trials of CSII vs MDI have excluded patients experiencing severe hypoglycemia (usually defined as requiring assistance) in the months before entry into the study (19, 22). In studies where these patients are specified, meta-analysis shows that severe hypoglycemia is significantly reduced on CSII compared to MDI, although these studies used insulin regimens that are outdated (29).

There is also evidence that CSII is associated with reduced glucose variability (30–33). This is important because variability is one of the primary indications for CSII in some clinics (34). Furthermore, higher variability is often associated with more hypoglycemia, and there is an unproven concern that variability may have an independent effect on complications (35).

1.3 We suggest CSII in patients with T1DM who require increased insulin delivery flexibility or improved satisfaction and are capable of using the device. (2|⊕⊕○○)

Evidence

As noted above, there is no evidence from systematic reviews that indicates inferior glucose control with CSII relative to MDI (19, 21, 36). Therefore, expanded CSII use is limited by higher cost and marginal benefit, unless there are other advantages beyond glucose control. The flexibility provided by CSII with RAA insulin could be an advantage for those who exercise and potentially those with gastroparesis because the basal delivery dose and pattern can be modified (37–41). A case series of patients with gastroparesis who converted from MDI to CSII showed fewer hospitalizations, improved A1C, and less glucose variability (41). However, there are no RCTs supporting this potential benefit. Many studies have demonstrated improved quality of life or improved patient satisfaction with CSII therapy relative to MDI therapy, some of which may be due to improvements in glycemic control. However, a patient’s attitude toward different technologies and methods of implementation, while significant, is not easily defined.

Unfortunately, various studies used different measurement tools or reported on different specific categorical findings (42). Therefore, whereas almost all positive findings are in favor of CSII, the inconsistencies provide limited clarity in meta-analysis (20, 24–26, 32, 43, 44).

2. Insulin pump therapy in type 2 diabetes mellitus

2.1 We suggest CSII with good adherence to monitoring and dosing in patients with T2DM who have poor glycemic control despite intensive insulin therapy, oral agents, other injectable therapy, and lifestyle modifications. (2|⊕⊕○○)

Evidence

Although several uncontrolled studies have reported that T2DM patients treated with CSII have improved glucose control and patient-reported outcomes, RCTs have shown mixed results, and subsequent meta-analyses have failed to show significant reductions of A1C or reductions in hypoglycemia for T2DM patients on CSII (20, 22, 45–51). Additionally, the older studies did not compare CSII to MDI using insulin analogs. A recent RCT of 331 T2DM patients on MDI randomized to CSII or MDI using analog insulin reported a statistically superior reduction in A1C of 1.1% from the baseline mean of 9.0% in the CSII group; the MDI group experienced a 0.4% reduction from the same baseline A1C level (52). In contrast to other studies, this study only enrolled patients with an A1C level between 8.0 and 10.0% who demonstrated adherence to monitoring during a 2-month run-in period. Hypoglycemia rates were not different between the two groups. Based on cost and limited generalizable evidence, CSII does not represent standard of care for the routine patient with T2DM who requires insulin therapy. However, this study indicates that properly chosen patients on advanced insulin therapy may benefit from CSII. New pharmacological treatments, such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 agonists, can delay the progression to intensive basal-bolus therapy and further reduce the need for CSII in T2DM (53).

The above statements all pertain to the use of U-100 analog insulin in pumps. Nonrandomized retrospective studies that moved patients from U-100 insulin MDI to U-500 insulin by CSII have demonstrated a significant reduction in A1C (54–57). However, there have been no RCTs that have compared CSII with MDI using U-500 regular insulin. The only comparison in the literature is based on a loosely designed meta-analysis that compared U-500 by MDI vs CSII between studies, suggesting equal efficacy but less weight gain and less increase in insulin dose with CSII (56). Because MDI of U-500 insulin is quite effective in highly insulin-resistant patients, we will need

to clearly demonstrate that CSII of U-500 insulin is more effective to justify the added expense (58, 59).

Until we have adequate reliable data supporting the benefit of CSII vs MDI of U-500 insulin, we suggest limiting this approach to patients whose total daily insulin dose is greater than 200 U/d despite using all alternative modalities for treating T2DM. Furthermore, a provider who is knowledgeable about CSII of U-500 should supervise its use.

3. Insulin pump use in the hospital

3.1 We suggest that clinicians continue CSII in patients admitted to the hospital with either type of diabetes, if the institution has clear protocols for evaluating patients as suitable candidates and appropriate monitoring and safety procedures. (2|⊕⊕○○)

Evidence

No RCTs have evaluated the relative benefit of continuing CSII vs transitioning to iv insulin infusions or MDI therapy when patients on ambulatory pump therapy are hospitalized for acute medical illness or surgery. However, studies have reported that hospitals that have well-developed criteria and processes for diabetes care can deliver safe and effective in-patient CSII therapy (60–65).

Both the American Diabetes Association and the American Association of Clinical Endocrinologists support these findings, assuming the patient has the physical and mental capacity for continued CSII use (15, 66). There are factors (eg, medical illness, co-medications, the degree of acute insulin resistance, mental status changes) that could determine whether CSII therapy is suitable for a hospitalized patient; however, no studies have systematically investigated these factors. Therefore, institutions that are unable to guarantee appropriate evaluation and support may decide against CSII use for inpatients (for reasons such as concerns for medical liability). It is often recommended that this evaluation be completed by an endocrinologist experienced in insulin pump therapy. No specific evidence exists in this regard, and it is likely that any provider with in-depth pump knowledge and experience could appropriately guide this process. If CSII is discontinued, appropriate transition to basal-bolus therapy is imperative.

CSII can generally be continued in patients undergoing same-day or outpatient surgery, which may involve fasting and/or conscious sedation. However, clinicians need to know that the patient is on an insulin pump and provide him/her with recommendations on how to prepare for surgery with regard to pump settings. If clinicians are not comfortable with continuing CSII therapy, they should give insulin as an injection.

4. Selection of candidates for insulin pump therapy

4.1 We recommend that before prescribing CSII, clinicians perform a structured assessment of a patient's mental and psychological status, prior adherence with diabetes self-care measures, willingness and interest in trying the device, and availability for the required follow-up visits. (1|⊕○○○)

Evidence

There are few studies and no RCTs or systematic reviews that have specifically examined or identified which factors predict successful CSII use (15, 19–22, 29, 67), and some patients do well with CSII who don't exhibit characteristics that are considered favorable for success. Even less evidence is available to determine what knowledge, expertise, and resources clinicians need to teach and support CSII use. Of the studies that did examine factors for successful CSII use, there is relatively consistent evidence that higher A1C levels at baseline are associated with greater A1C reduction on CSII (28, 29, 68–70). However, Orr et al (28) reported that an A1C level over 10% was associated with poor outcomes with CSII. Interestingly, Nixon et al (71) recently reported that among those placed on CSII for elevated A1C, about 12% show no benefit at any time after transitioning from MDI, and 57% showed early A1C reduction with later deterioration. In regards to other factors, the study by Orr et al (28) found that mental illness and a history of missed appointments predicted worse outcomes with CSII. Likewise, Grant et al (72) reported that significant anxiety or depression was associated with poorer outcomes with CSII. Data are lacking on the relationship between the frequency of SMBG and success with CSII. However, one study that evaluated clinic experience did report an association between the frequency of SMBG and success with CSII (73). Among adults, age does not appear to be a major determinant (74).

In summary, there is modest evidence that certain criteria are relevant in choosing patients for CSII therapy. Clinical experience suggests that adult CSII candidates should receive a thorough evaluation before initiating therapy to assess a wide range of diabetes self-care behaviors. Factors to consider are: baseline A1C, patient history of adherence to follow-up appointments and provider-recommended glucose monitoring, a realistic recognition by the patient of the limitations of CSII, evidence of a significant psychological disease that is likely to impact adherence, and confirmed availability for follow-up in the immediate post-pump initiation period. It is also recommended that before initiating CSII, clinicians assess and address general gaps in patient diabetes knowledge or self-

care behaviors, including carbohydrate counting and sick-day rules.

5. Use of bolus calculators in insulin pump therapy

5.1 We suggest encouraging patients to use appropriately adjusted embedded bolus calculators in CSII and to have appropriate education regarding their use and limitations. (2|⊕○○○)

Evidence

Many intensively managed individuals rely on estimations to calculate prandial and correction insulin (75). As time passes, there may be a tendency to approximate the prandial bolus based on the “usual” or “typical” carbohydrate content of the meals with variable success (76). In 2002, the Deltec Cozmo pump first introduced technology that helps patients calculate bolus insulin (carbohydrate to insulin ratios as well as correction ratios in the event of hyperglycemia) as part of CSII therapy. Other companies soon introduced their own calculators for this purpose, hoping to reduce variability and patient errors (77). Studies evaluating the effect of a dose calculator have found some beneficial outcomes, such as reduced mean glucose, reduced need for glucose treatment of hypoglycemia, decreased frequency of correction boluses (reduced stacking), and decreased postprandial glucose levels (78–80). However, findings have not been consistent, and no large RCTs have specifically demonstrated the benefit of bolus calculators.

The calculator feature was unique to CSII, but this capability is now available for those on MDI, where it has reduced A1C by at least 0.5% and improved patient satisfaction but not hypoglycemia (81–83). To facilitate the transition from one therapeutic approach to another and to help achieve glycemic targets, we suggest that before initiating CSII therapy, clinicians should determine individualized prandial and correction insulin dosing algorithms (insulin-to-carbohydrate ratio and insulin sensitivity factors), blood glucose targets, and active insulin time (84). We do not recommend the general use of insulin calculators unrelated to CSII, such as smart phone apps that are not FDA approved. The FDA has only approved the meter bolus calculator mentioned above (69).

The current approach to prandial insulin dose calculation (based on carbohydrate-to-insulin ratios) assumes that carbohydrates are the only macronutrient that impacts postprandial glucose control in T1DM. However, as summarized in a recent systematic review of the literature (85), high-fat/protein meals require more insulin than lower-fat/protein meals with identical carbohydrate content to optimize postprandial glucose control (86, 87). However, Bell et al (85) reported that available studies have

significant methodological differences (88–90), and reliable definitive data are lacking on the optimum split and duration of advanced pump boluses needed to adjust glucose levels associated with high fat and protein content meals.

6. Real-time continuous glucose monitors in adult outpatients

6.1 We recommend RT-CGM devices for adult patients with T1DM who have A1C levels above target and who are willing and able to use these devices on a nearly daily basis. (1|⊕⊕⊕⊕)

Evidence

The Juvenile Diabetes Research Foundation (JDRF) study (91), the Guard Control Study (92), and O’Connell et al (93) demonstrated that adults with A1C levels $\geq 7.0\%$ had a greater reduction in A1C using RT-CGM than with intermittent SMBG (0.5, 0.6, and 0.43%, respectively). Furthermore, unlike findings with SMBG, the improvement in A1C with CGM is not accompanied by an increase in biochemical hypoglycemia (92, 94). The improvement in A1C in the CGM subjects in the 6-month JDRF trial was sustained during the 6-month observational period that followed completion of the trial (95). This ongoing benefit occurred despite a reduction in office-visit frequency during this observational period to levels similar to routine care (2.7 ± 1.2 visits over 6 months). Furthermore, the incidence rate of severe hypoglycemia declined from 20.5 events per 100 patient-years during the initial 6-month RCT to 12.1 events per 100 patient-years during the 6-month observational follow-up period.

To date, CGM trials have enrolled patients using continuous CSII pumps and MDI, and no studies have evaluated the added benefit of starting CGM in adult patients using MDI therapy. In the JDRF trial (91), the patients using CSII and MDI had a similar reduction in A1C; however, because MDI users comprised only 20% of the total study population, the improvement in this subgroup did not reach statistical significance. The ongoing Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes study (96) examining RT-CGM in T1DM and T2DM adults using MDI should provide conclusive data regarding the benefit of this technology in these individuals.

6.2 We recommend RT-CGM devices for adult patients with well-controlled T1DM who are willing and able to use these devices on a nearly daily basis. (1|⊕⊕⊕⊕)

Evidence

The JDRF study demonstrated that when compared with standard blood glucose monitoring, T1DM patients

with A1C levels $< 7.0\%$ that use RT-CGM can reduce the frequency of biochemical hypoglycemia (which they defined as a blood glucose level below 70 mg/dL) and maintain A1C levels $< 7.0\%$ over a 6-month study period. Of the 129 enrolled subjects, 62 (48%) were younger than 25 years of age, and 67 (52%) were older than 25 years. The median time per day with a glucose level of ≤ 70 mg/dL was less in the RT-CGM group than in the control group; however, the difference was not statistically significant. In this study, almost all the other analyses (including the time per day ≤ 60 mg/dL, time per day between 71 and 180 mg/dL, and combined outcomes involving A1C coupled with hypoglycemia) statistically favored the RT-CGM group compared with the control group. Treatment effects were generally similar across age groups (95). For RT-CGM users who were 25 years and older, the incidence rate of severe hypoglycemia was 21.8 events per 100 person-years during the 6-month RCT and 7.1 events per 100 person-years during the 6 months of CGM use after the trial. For those in this group whose A1C levels were below 7.0%, the incidence rate of severe hypoglycemia was 23.6 events per 100 person-years during the 6-month RCT and 0 per 100 patient-years during the 6 months of CGM use after the trial (97). This evidence of improvements in glycemic control over the long-term points to the role of the user’s skills and knowledge of new CGM technology, and this may partly account for the failure of other RCTs (that enrolled individuals with poorer glycemic control) to demonstrate a reduction in severe hypoglycemia (98, 99). In a multicenter European/Israeli RCT that included adults with T1DM whose A1C levels were $< 7.5\%$, a post hoc per protocol analysis demonstrated that time spent in hypoglycemia below 63 mg/dL was reduced by 50% ($P = .02$) in the adults (100).

Use of CGM in adults with T2DM

6.3 We suggest short-term, intermittent RT-CGM use in adult patients with T2DM (not on prandial insulin) who have A1C levels $\geq 7\%$ and are willing and able to use the device. (2|⊕⊕○○)

Evidence

This recommendation is based on data from one well-performed large-scale RCT performed by Vigersky and colleagues (101, 102) and one other smaller study (103) showing similar outcomes. The Vigersky trial involved 100 adults with T2DM on therapies including diet and exercise alone and various combinations of other antihyperglycemic medications, including basal but not prandial insulin. Results showed that intermittent RT-CGM use for 12 weeks (four cycles of 2 weeks use/1 week off) resulted in significant improvements in A1C, sustained during a

40-week follow-up period (the changes in A1C [mean \pm SEM] at 12 and 52 weeks were $1.0 \pm 1.1\%$ and $0.8 \pm 1.5\%$ in the RT-CGM group vs $0.5 \pm 0.8\%$ and $0.2 \pm 1.3\%$ in the SBGM control group; $P = .04$ for control vs RT-CGM group). This improvement in the RT-CGM group occurred without a greater intensification of medication, as compared to the control group, indicating that it probably reflected changes in self-care prompted by CGM use. Yoo et al (103) randomized patients (with T2DM and A1C levels of 8–10% on oral agents or insulin) to RT-CGM use for 3 days per month for 12 weeks vs SBGM six times per week for 12 weeks in the control group. Both the RT-CGM and SBGM control groups had significant reductions in A1C at the 12-week follow-up (RT-CGM, $9.1 \pm 1.0\%$ to $8.0 \pm 1.2\%$, $P < .001$; SBGM, $8.7 \pm 0.7\%$ to $8.3 \pm 1.1\%$, $P = .01$) with a significant difference in the improvement between the two groups ($P = .004$). The relative difference in improvements in A1C between the RT-CGM and control groups may have been exaggerated by the fact that the control group only performed SBGM 6.1 times per week in the trial, and this may limit the relevance of the trial findings, especially to patients who perform SBGM multiple times per day.

We need consistent data from additional well-performed RCTs in patients with different health literacy and sociodemographic characteristics (compared to patients enrolled in the above two trials) to confirm that these findings are generalizable to the broader T2DM population. At present, no data exist for RT-CGM use in patients with T2DM on prandial insulin. The ongoing Daily Injections and Continuous Glucose Monitoring in Diabetes study (96) should provide conclusive data regarding the potential benefits of this technology in this T2DM population.

We excluded several studies on CGM in T2DM that were incorporated in a previous meta-analysis (104) because they employed older technology (105) and involved blinded (instead of real-time) CGM use (106). Retrospective data analysis from blinded CGM devices has a role in the care of patients with both T1DM and T2DM, especially the elderly population who, because of restrictions on Medicare coverage, do not have access to RT-CGM. This older population has a relatively high incidence of hypoglycemia. Munshi et al (107) demonstrated that blinded CGM is helpful in therapeutic decision-making in this vulnerable age group, and it also helps detect hypoglycemia that is otherwise unrecognized with intermittent capillary blood glucose monitoring.

Education and training on the use of CSII and CGM

6.4 We suggest that adults with T1DM and T2DM who use CSII and CGM receive education, training, and on-

going support to help achieve and maintain individualized glycemic goals. (Ungraded Good Practice Statement)

Evidence

There are few high-quality comparative studies regarding the effectiveness of educational components and strategies for CSII use. As a result, there are limited data about how best to train individuals on using CSII to optimize glycemic control. It should also be noted that primary care providers manage a good number of patients using CSII, and in this setting, insulin pump company employees or contracted consultants provide initial training. We found no studies that compared this form of education and training to that delivered in an endocrinology practice by diabetes educators using a formal CSII education curriculum. No RCTs have evaluated the effectiveness of educational strategies and protocols for transitioning patients from MDI to CSII with stand-alone RT-CGM or sensor-integrated pump (SIP) therapy (where the CGM is integrated with the insulin pump but does not necessarily control insulin delivery, as occurs with sensor-augmented pump [SAP] therapy). It is important to be aware of insurance plan requirements with regard to participation in a comprehensive diabetes program. Some require participation in these programs within 6 months before either a new pump application or CGM application; this is also true for patients seeking an upgraded device.

Continuous subcutaneous insulin infusion

A 2011 systematic review that included five descriptive studies of individuals with T1DM over the age of 16 years recommended that adults with T1DM starting CSII or already utilizing CSII receive comprehensive advice, education, and training (84). The authors concluded, however, that it was difficult to draw strong conclusions about the effectiveness of educational components and strategies due to the lack of high-quality comparative studies. They concluded that no educational method was significantly more effective than any other method. One descriptive study of 250 participants with T1DM found a highly significant impact on A1C levels ($P < .0001$) and a reduction in hypoglycemia ($P < .001$) over a 12-month period after a 7-day teaching and training program that included instructions regarding managing daily living, using CSII, adjusting insulin doses, preventing and managing hypoglycemia and diabetic ketoacidosis, and understanding the role of SMBG (108). Consensus statements and guidelines from the American Association of Clinical Endocrinologists and the American Association of Diabetes Educators also recommend education and training on technical aspects of pump operation, day-to-day self-care management, and how to handle emergency situations (15, 67). A

pilot study (n = 30) that adapted the 5-day Dose Adjustment for Normal Eating curriculum for people with T1DM reported that patients were receptive to starting CSII use, and CSII reduced A1C by 0.5% at 6 months (109, 110). Unfortunately, even less research has been conducted on CSII education and training for individuals with T2DM (49, 50, 111). Table 1 outlines education and training for CSII therapy.

SIP therapy or CSII with stand-alone CGM

To be successful with SIP or CSII, stand-alone CGM patients need to understand how to use this technology as part of their daily diabetes self-management. Providing information about how these devices work before initiation, as well as supporting patients thorough education and training is key to safe and effective use of this technology. Unfortunately, research is lacking in this area as well. Although not designed to study the effectiveness of educational components associated with CGM use, two multicenter RCTs did provide detailed information on the education and training interventions provided in the treatment arms (91, 112). The JDRF CGM Study Group trial provided both the investigational and control groups with

one-on-one training on RT-CGM or a glucose meter, as well as written instructions on how to make real-time adjustments of insulin doses and use computer software (91). Participants with SIP or CSII plus RT-CGM received additional instructions on modifying insulin doses by using treatment algorithms based on glucose trends. Another trial randomized participants with T1DM (who were naive to both CSII and RT-CGM) to either continue MDI or transition to SIP and provided a stepwise education protocol for introducing these different devices (112). The subjects in the SIP arm were introduced to CSII first and RT-CGM approximately 2 weeks later. The SIP arm also received technology-specific training over an additional 3-week period. The study used the patients' own data as a teaching tool to enhance experience-based training. In all subjects using SIP, A1C levels fell rapidly from baseline to 3 months ($8.3 \pm 0.5\%$ to 7.5% [absolute reduction of $0.8 \pm 0.8\%$; $P < .001$]) and remained significantly lower throughout the study compared to those using MDI therapy ($8.3 \pm 0.5\%$ to 8.1% [absolute reduction of $0.2 \pm 0.9\%$; $P < .001$]). In the absence of evidence from RCTs on training methods, clinical experience guides practice.

Table 1. CSII—Considerations for Education and Training

Patient

Collaborate with HCP overseeing CSII use and/or the multidisciplinary diabetes team by returning for follow-up.
Participate in using data management resources to make adjustments to therapy and evaluate self-care behaviors.

Provider

Provide education as indicated to address deficiencies or when upgrading to new technology.
Assess CSII use and evaluate for the loss of ability to operate insulin pump due to cognitive, physical, or age-related changes; changes in insurance coverage; or changes in healthcare-provider-managing CSII use.

Time periods to assess patient self-care behaviors and knowledge

Before initiating CSII, assess:

Glucose monitoring via SMBG frequency, and/or CGM use defined by HCP to meet individualized glycemic goals.
Carbohydrate counting or another method of mealtime bolus determination.
Ability to operate CSII and make setting changes due to factors such as dexterity, vision impairment, mental health, or cognition---independently or with assistance from a designated care provider.
Infusion site health and selection.
DKA prevention and treatment.
Hypoglycemia---prevention, detection, and treatment.
Emergency supplies.
If using bolus calculator, assess these settings: insulin-to-carbohydrate ratio, insulin sensitivity factor, glucose targets, and active insulin time.

Annually and/or when upgrading to a new CSII device, re-assess:

Glucose monitoring via SMBG frequency and/or CGM use defined by HCP to meet individualized glycemic goals.
Basal settings via basal rate testing across different time periods, adjust as indicated.
Bolus calculator settings, if using feature, adjust as indicated.
Infusion sites and type of infusion set, adjust as indicated.
Ability to troubleshoot insulin pump malfunction.
DKA prevention and treatment.
Hypoglycemia prevention, detection, and treatment.
Emergency supplies.
Back-up plan for use of injected insulin should pump fail.

When discontinuing CSII or transitioning to MDI, re-assess:

Glucose monitoring via SMBG frequency and/or CGM use defined by HCP to meet individualized glycemic goals.
New insulin plan for MDI.

Table 2 outlines education and training for RT-CGM. Table 3 lists clinical and administrative resources that should be in place to support CSII and RT-CGM use.

The evolution of CSII and CGM toward the bionic pancreas

Although SIP therapy is not new, there are no large RCTs comparing it directly to basal-bolus insulin injections using similar blood glucose monitoring strategies. However, there is an RCT involving 329 adult patients with T1DM that showed that SIP resulted in a 0.6% greater A1C reduction vs MDIs of analog insulin (112). The study did not include an arm with CSII alone or MDI with RT-CGM.

A new product, SAP, has advanced SIP technology by adding a “low glucose suspend” function. A sensor reads glucose levels and adjusts the insulin pump accordingly, discontinuing insulin delivery when glucose reaches a programmed level. One study in adults with documented nocturnal hypoglycemia randomly assigned 247 patients to an SIP or an SAP that could stop insulin delivery for up to 2 hours (116). Overall nocturnal hypoglycemia (defined as 65 mg/dL or less for at least 20 minutes between 10 PM and 8 AM) was reduced by 31.8% without rebound hyperglycemia (1.5 ± 1.0 vs 2.2 ± 1.3 per patient week; $P < .001$); there were four episodes of severe hypoglycemia (defined as hypoglycemia resulting in coma or seizures or requiring medical assistance), all in the SIP-alone group.

This RCT indicates that SAP can reduce nocturnal hypoglycemia in populations at high risk for hypoglycemia.

Current technologies, combined with faster insulin, better sensor accuracy, and improved pumps that can adjust or discontinue insulin delivery to prevent hypoglycemia and excessive hyperglycemic exposure, make the promise of a “closed loop” seem reasonable. It is unclear at this time whether a dual hormone system would be superior (117, 118). It is premature to grade the early data from studies on these new technologies, but the future for a commercial version of one or more of these devices is promising. To realize large-scale and long-term use of these devices, we need a better understanding of the catheter and site problems common with CSII and RT-CGM and appropriate cost-benefit analysis when compared to current therapies. A European Association for the Study of Diabetes and American Diabetes Association Diabetes Technology Working Group statement discusses suggestions for future research on the efficacy and safety of CSII (119). Finally, prior to the arrival of these new technologies, efforts have been ongoing to standardize the reporting of data from various devices so this information can be more easily interpreted and incorporated into electronic medical records (112). It is imperative that as devices proliferate, we consider the human factor, both in terms of how easily, safely, and effectively people with diabetes and their caregivers can use these devices and how easily and

Table 2. RT-CGM Technology—Considerations for Education and Training for Personal Use

Patient

Collaborate with HCP overseeing RT-CGM use and/or the multidisciplinary diabetes team by returning for follow-up.
Participate in use of data management resources to make adjustments to therapy and evaluate self-care behaviors.

Provider

Provide education as indicated to address deficiencies or when upgrading to new CGM technology.
On an ongoing basis, assess CGM use and evaluate for the loss of ability to operate CGM system due to: cognitive, physical, or age-related changes; changes in insurance coverage; or changes in healthcare provider managing CSII use.

Time periods to assess patient self-care behaviors and knowledge

Before initiating RT-CGM, assess:

Patient understanding that CGM does not replace SMBG.
Factors and self-care behaviors that may influence success with CGM.

When initiating RT-CGM, assess:

Knowledge of CGM system components—receiver, sensor, and transmitter.
Understanding of how CGM data differ from SMBG data.
Use of trend information based on changing glucose levels to adjust insulin doses.
Use of SMBG to calibrate CGM system.
Site selection and care.

Alarms (Check that alarms are set in a fashion to optimize patient benefit and minimize alarm fatigue. The initial focus is often on low alerts and falling blood glucose alarms. High alerts can be turned off or set well above target at first if patient is consistently high and doesn't benefit from high alerts.)

Annually and/or when upgrading technology (for ongoing RT-CGM use), re-assess:

Ability to make insulin adjustment based on trend information.
Use of SMBG to calibrate.
Sensor site health and care.

Abbreviations: DKA, diabetic ketoacidosis; HCP, health care professional. [Derived from Powers et al (113), Evert et al (114), and Gilliam et al (115).]

Table 3. Suggested Health Care Provider Resources to Support the Safe and Effective Use of CSII and RT-CGM

- Clinicians should implement a formalized educational plan for the initiation and long-term support of CSII and RT-CGM that is established by the practice setting. Clinicians should communicate education plans to potential candidates and individuals new to the practice setting.
- Clinics should have a designated multidisciplinary diabetes team to evaluate potential candidates, initiate therapy and education, and to support long-term CSII and RT-CGM use that is part of the practice setting. Alternatively, a sole practitioner may also provide medical care and CSII education supported by other healthcare professionals or industry consultants as indicated. CSII and RT-CGM diabetes care team members could include the following health care providers: endocrinologist, advanced practice registered nurse, physician's assistant, primary care provider, certified diabetes educator, registered dietitian with expertise in diabetes medical nutrition therapy, and mental health/behavioral therapists.
- The clinical support staff or patient should know how to download data from glucose meters, insulin pumps, and RT-CGMs, and they should download data before an appointment in order to review data via print format, online secure patient pump portal, or the patient's electronic health record.
- Designated staff members (diabetes educators, medical assistants, or patient service representatives) should be available to help clinics obtain prior authorizations, schedule peer-to-peer reviews, submit supporting documents for determining coverage, answer insurance and distributor/third party vendor queries for additional documentation, and issue letters of support and/or appeal if therapy is declined.

effectively caregivers can access data from these devices and provide feedback to patients to optimize care.

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