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Management of Individuals With Diabetes at High Risk for Hypoglycemia: An Endocrine Society Clinical Practice Guideline

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Abstract

Context: Hypoglycemia in people with diabetes is common, especially in those taking medications such as insulin and sulfonylureas (SU) that place them at higher risk. Hypoglycemia is associated with distress in those with diabetes and their families, medication nonadherence, and disruption of life and work, and it leads to costly emergency department visits and hospitalizations, morbidity, and mortality.

Objective: To review and update the diabetes-specific parts of the 2009 *Evaluation and Management of Adult Hypoglycemic Disorders: Endocrine Society Clinical Practice Guideline* and to address developing issues surrounding hypoglycemia in both adults and children living with diabetes. The overriding objectives are to reduce and prevent hypoglycemia.

Methods: A multidisciplinary panel of clinician experts, together with a patient representative, and methodologists with expertise in evidence synthesis and guideline development, identified and prioritized 10 clinical questions related to hypoglycemia in people living with diabetes. Systematic reviews were conducted to address all the questions. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the certainty of evidence and make recommendations.

Results: The panel agreed on 10 questions specific to hypoglycemia risk and prevention in people with diabetes for which 10 recommendations were made. The guideline includes conditional recommendations for use of real-time continuous glucose monitoring (CGM) and algorithm-driven insulin pumps in people with type 1 diabetes (T1D), use of CGM for outpatients with type 2 diabetes at high risk for hypoglycemia, use of long-acting and rapid-acting insulin analogs, and initiation of and continuation of CGM for select inpatient populations at high risk for hypoglycemia. Strong recommendations were made for structured diabetes education programs for those at high risk for hypoglycemia, use of glucagon preparations that do not require reconstitution vs those that do for managing severe outpatient hypoglycemia for adults and children, use of real-time CGM for individuals with T1D receiving multiple daily injections, and the use of inpatient glycemic management programs leveraging electronic health record data to reduce the risk of hypoglycemia.

Conclusion: The recommendations are based on the consideration of critical outcomes as well as implementation factors such as feasibility and values and preferences of people with diabetes. These recommendations can be used to inform clinical practice and health care system improvement for this important complication for people living with diabetes.

Key Words: glucagon, structured counseling, insulin pumps, continuous glucose monitoring, insulin analogs, systems of care, blood glucose, blood glucose self-monitoring, diabetes mellitus, hyperglycemia, hypoglycemia, hypoglycemic agents, insulin

Abbreviations: ADIP, algorithm-driven insulin pump; BG, blood glucose; CGM, continuous glucose monitoring; CMS, Centers for Medicaid and Medicare; DKA, diabetic ketoacidosis; EHR, electronic health record; ED, emergency department; EMS, emergency medical services; EtD, evidence to decision; FDA, US Food and Drug Administration; HbA$_{1c}$, hemoglobin A$_{1c}$; HCP, health care professional; IAH, impaired awareness of hypoglycemia; IRR, incidence rate ratio; LOS, length of stay; MD, mean difference; MDIs, multiple daily injections; MI, myocardial infarction; NPH, neutral protamine Hagedorn; OR, odds ratio; POC-BG, point-of-care blood glucose; QALY, quality-adjusted life year; QOL, quality of life; RCT, randomized controlled trial; SMBG, self-monitoring of blood glucose; SU, sulfonylurea; T1D, type 1 diabetes; T2D, type 2 diabetes; TIR, time in range.

List of Recommendations

Question 1. Should continuous glucose monitoring vs self-monitoring of blood glucose be used for people with type 1 diabetes receiving multiple daily injections?

Recommendation 1

We recommend continuous glucose monitoring (CGM) rather than self-monitoring of blood glucose (SMBG) by fingerstick for patients with type 1 diabetes (T1D) receiving multiple daily injections (MDIs). (1⊕⊕OO)

Remarks

- Comprehensive patient education on how to use and troubleshoot CGM devices and interpret these data is critically important for maximum benefit and successful outcomes.
- SMBG continues to be necessary to validate or confirm CGM values; for example, when symptoms do not match sensor glucose values and during the sensor warm-up period. Therefore, patients using CGM must continue to have access to SMBG.

Question 2. Should real-time continuous glucose monitoring and algorithm-driven insulin pumps vs multiple daily injections with self-monitoring of blood glucose three or more times daily be used for people with type 1 diabetes?

Recommendation 2

We suggest using real-time continuous glucose monitoring (CGM) and algorithm-driven insulin pumps (ADIPs) rather than multiple daily injections (MDIs) with self-monitoring of blood glucose (SMBG) three or more times daily for adults and children with type 1 diabetes (T1D). (2⊕⊕OO)

Remark. Fingerstick blood glucose (BG) monitoring may still be necessary to validate or confirm CGM values; therefore, with respect to use and insurance coverage, there will be times when SMBG must be used.

Question 3. Should professional or personal real-time continuous glucose monitoring vs no continuous glucose monitoring be used for people with type 2 diabetes in the outpatient setting who take insulin and/or sulfonylureas and are at high risk for hypoglycemia?

Recommendation 3

We suggest real-time continuous glucose monitoring (CGM) be used rather than no continuous glucose monitoring (CGM) for outpatients with type 2 diabetes (T2D) who take insulin and/or sulfonylureas (SUs) and are at risk for hypoglycemia. (2⊕OOO)

Remarks

- Professional CGM is a diagnostic tool used for the short-term investigation of an individual's glycemic profile to determine glycemic patterns and to assist with therapeutic management.
- Personal CGM is a tool for patients to use in real time at home to assist the patient and their health care providers (HCPs) in making both short- and long-term adjustments in their therapeutic management.

Question 4. Should initiation of continuous glucose monitoring in the inpatient setting vs not using continuous glucose monitoring be used for select people at high risk for hypoglycemia?

Recommendation 4

We suggest initiation of continous glucose monitoring (CGM) in the inpatient setting for select inpatients at high risk for hypoglycemia. (2⊕OOO)

Remarks

- This should be performed via a hybrid approach in which CGM use is combined with periodic point-of-care blood glucose (POC-BG) testing to validate the accuracy of CGM.
- Inpatient CGM use is not currently approved by the US Food and Drug Administration (FDA) but currently has enforcement discretion. It has been used in hospitals recently with emergency use authorization during the COVID-19 pandemic.

Question 5. Should continuation of personal continuous glucose monitoring in the inpatient setting vs discontinuation of continuous glucose monitoring be used for people at high risk for hypoglycemia who are already using it?

Recommendation 5

We suggest continuation of personal continuous glucose monitoring (CGM) in the inpatient setting with or without algorithm-driven insulin pump (ADIP) therapy rather than discontinuation. (2⊕OOO)

Remarks

- This should be performed via a hybrid approach in which CGM use is combined with periodic point-of-care blood glucose (POC-BG) testing to validate the accuracy of CGM.
- Inpatient CGM use is not currently approved by the US Food and Drug Administration (FDA) but currently has enforcement discretion. It has been used in hospitals recently with emergency use authorization during the COVID-19 pandemic.

Question 6. Should inpatient glycemic surveillance and management programs leveraging electronic health record data vs standard care be used for hospitalized people at risk for hypoglycemia?

Recommendation 6

We recommend that inpatient glycemic surveillance and management programs leveraging electronic health record (EHR) data be used for inpatients at risk for hypoglycemia. (1⊕OOO)

Remarks

- The panel defined leveraging EHR data as specific hospital staff using glycemic data collected within the EHR (from all admitted patients) to identify those at risk for and those having hypoglycemic and hyperglycemic episodes to develop mechanisms for managing and mitigating these adverse outcomes. Standard care is lack of such a program.
- EHR data leveraged includes patterns of glycemia with proactive alerts for high and for low trends, so that hypoglycemia and severe hyperglycemia can be identified in a systematic fashion. Staff can then intervene on these trends (eg, adjusting insulin infusion rates) to avoid unwanted outcomes (repeat hypoglycemia, glycemic variability, etc).

Question 7. Should long-acting insulin analogs vs human insulin be used for people on basal insulin therapy who are at high risk for hypoglycemia?

Recommendation 7

We suggest long-acting insulin analogs be used rather than human neutral protamine Hagedorn (NPH) insulin for adult and pediatric outpatients on basal insulin therapy who are at high risk for hypoglycemia. (2⊕OOO)

Remarks

- Patients who are at high risk for hypoglycemia are defined as those with a history of severe hypoglycemia (requiring assistance to manage), impaired awareness of hypoglycemia (IAH), and/or medical conditions that predispose them to severe hypoglycemia including renal and hepatic dysfunction.
- The panel placed high value on reducing severe hypoglycemia and found moderate-certainty evidence for severe hypoglycemia reduction as an outcome in those using long-acting analog insulins vs NPH insulin. However, the panel acknowledges that most studies of long-acting analog insulins do not assess for significant adverse effects (including cardiovascular outcomes) and that many studies were designed to demonstrate noninferiority of analog insulin compared with human NPH insulin.

Question 8. Should rapid-acting analogs vs regular (short-acting) human insulin be used for people on basal-bolus therapy who are at high risk for hypoglycemia?

Recommendation 8

We suggest that rapid-acting insulin analogs be used rather than regular (short-acting) human insulins for adult and pediatric patients on basal-bolus insulin therapy who are at high risk for hypoglycemia. (2⊕OOO)

Remarks

- Patients who are at high risk for hypoglycemia are defined as those with a history of severe hypoglycemia (requiring assistance to manage), impaired awareness of hypoglycemia (IAH), and/or medical conditions that predispose them to severe hypoglycemia including renal and hepatic dysfunction.
- The panel placed high value on reducing severe hypoglycemia and found moderate-certainty evidence for reduction of mild-to-moderate and severe hypoglycemia as an outcome in those using rapid-acting analog insulins vs regular (short-acting) insulin. However, the panel acknowledges that many studies were designed to demonstrate noninferiority of analog insulin compared with human regular (short-acting) insulin. Also, many of the data available for review demonstrating reductions in hypoglycemia were in adults with T1D; very few data were available regarding the pediatric population.

Question 9. Should a structured program of patient education with follow-up vs unstructured advice be used for people receiving insulin therapy who are at high risk for hypoglycemia?

Recommendation 9

We recommend that a structured program of patient education over unstructured advice be used for adult and pediatric outpatients with type 1 diabetes (T1D) or type 2 diabetes (T2D) receiving insulin therapy. (1⊕⊕OO)

Remarks

- Structured education on how to avoid repeated hypoglycemia is critical, and this education should be performed by experienced diabetes clinicians. Moreover, insurance coverage for education should be available for all insulin-using patients.
- The recommendation is not intended to limit structured education only to those on insulin therapy; for example, patients using sulfonylureas (SUs) and meglitinides are also at risk for hypoglycemia, and the recommendation also applies to this patient population.

Question 10. Should glucagon preparations that do not have to be reconstituted vs preparations that do have to be reconstituted be used for people with severe hypoglycemia?

Recommendation 10

We recommend that glucagon preparations that do not have to be reconstituted over glucagon preparations that do have to be reconstituted (ie, available as a powder and diluent) be used for outpatients with severe hypoglycemia. (1⊕OOO)

Introduction

Hypoglycemia, defined as a low plasma glucose level in an individual with or without symptoms that may cause them harm, is both common and costly for people living with diabetes (1). Individuals with type 1 diabetes (T1D) may have clinically significant episodes of hypoglycemia as often as twice per week (2). Those with type 2 diabetes (T2D) are at lower risk for hypoglycemia, unless they have specific clinical characteristics that increase that risk, including the use of medications known to be associated with hypoglycemia (eg, insulin, sulfonylureas [SUs]), long duration of diabetes, and renal and/or hepatic dysfunction (3) (Table 1). Hypoglycemia adversely affects both pediatric and adult populations, as well as those in the inpatient and in the outpatient settings, and is associated with a number of unwanted outcomes including distress in those with diabetes and their caregivers; reductions in quality of life (QOL); and reductions in medication adherence, leading to increased risks for diabetes-related comorbidities (4–8). Hypoglycemia in people with diabetes is costly and is associated with expensive emergency department (ED) visits, prolonged hospital admissions, and missed work (5, 9, 10). Hypoglycemia disproportionately affects individuals with diabetes with low income and low education and those with food insecurity (11, 12). Further, racial disparities also exist, with disproportionately high rates of hypoglycemia in Black individuals living with diabetes (13).

Table 1. Individuals at high risk for developing hypoglycemia

- Individuals taking medications known to cause hypoglycemia (eg, insulin, sulfonylureas, meglitinides)
- Individuals with impaired kidney or liver function
- Older-age patients
- Preschool-age children
- Individuals with a history of severe hypoglycemia
- Individuals with cognitive impairment or intellectual disability that may reduce ability to respond to low blood glucose
- Individuals with impaired awareness of hypoglycemia
- Individuals with a longer duration of diabetes (including those using insulin for ≥5 y)
- Individuals who use alcohol
- Individuals with eating disorders
- Individuals with irregular eating schedules
- Individuals that are fasting for religious or cultural reasons
- Individuals with a history of untreated pituitary, adrenal, or thyroid insufficiency

Source: Adapted from American Diabetes Association Professional Practice Committee. *Diabetes Care*, 2022; 45(Suppl. 1): S46–S59.

The 2009 Evaluation and Management of Adult Hypoglycemic Disorders Endocrine Society Clinical Practice Guideline included individuals with and without diabetes mellitus (14). That guideline made 7 recommendations involving people living with diabetes, and these focused on defining the glucose level (or change in glucose level) at which hypoglycemia should be addressed, identifying those at highest risk for hypoglycemia, managing impaired awareness of hypoglycemia (IAH), and preventing and treating hypoglycemia. Since the development of those clinical practice guidelines, substantial changes have been made both in how hypoglycemia is defined and how it is clinically measured. A 2018 consensus statement developed by 8 separate organizations, including the Endocrine Society, defined 3 levels of hypoglycemia (15). This statement was developed specifically with individuals with T1D in mind and also aimed to standardize common definitions such as hyperglycemia, time in range (TIR), and diabetic ketoacidosis (DKA). The 3 levels of hypoglycemia were determined using known physiologic thresholds for counter-regulatory responses as well as plasma glucose concentrations when both neuroglycopenic and neurogenic symptoms appear (Table 2). Future clinical trials that include hypoglycemia as an outcome will use these definitions and practicing clinicians should be aware of them.

Continuous glucose monitoring (CGM) systems have become much more commonly used in individuals with T1D and with T2D, which are able to both identify and predict clinically significant episodes of hypoglycemia requiring adjustment in therapy that may otherwise be missed (16). Further, algorithm-driven insulin pumps (ADIPs) are now available that can reduce the risk for hypoglycemia (17). With the increased use of these technologies, questions regarding their use in the inpatient setting have become an important area for study (18). Since the publication of the last guidelines, new formulations of glucagon are now available, and inpatient glycemic surveillance and management programs have been developed that use data from electronic health records (EHRs) to reduce the risk for inpatient hypoglycemia.

Given these considerable advancements in the field, an updated guideline focused solely on diabetes-related hypoglycemia was needed. The Endocrine Society convened a guideline development panel to review all published data and to make pertinent recommendations focused on hypoglycemia in people living with diabetes. The purpose of this guideline is to address updates in the field of diabetes-related hypoglycemia, in those with either T1D or T2D, both in adults

Table 2. Definitions of levels of hypoglycemia

Level 1	Glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L). This level of hypoglycemia should alert patients that they may need to ingest carbohydrate to prevent progressive hypoglycemia.
Level 2	Glucose <54 mg/dL (3.0 mmol/L). This level of hypoglycemia is associated with increased risk for cognitive dysfunction and mortality.
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance. This level of hypoglycemia is life-threatening and requires emergent treatment typically with glucagon.

Source: Adapted from Agiostratidou, G, et al. *Diabetes Care*, 2017; 40(12): 1622–1630.

and in children, and in the outpatient and inpatient settings. The guideline is targeted to all health care professionals (HCPs) involved in the care of people with diabetes who are at risk for developing hypoglycemia as well as other key stakeholders including hospital systems, insurance organizations, and others that provide and regulate resources used in diagnosing, predicting, and managing hypoglycemia in people with diabetes. Topics that are addressed with respect to reducing the risk for and predicting the development of hypoglycemia include the use of CGM both in the inpatient and outpatient settings, ADIP therapy, and inpatient glycemic management programs leveraging EHR data. The guideline addresses the benefits and costs associated with both long-acting (basal) and rapid-acting analog insulins with respect to hypoglycemia as well as the benefits of a structured program of patient education in reducing risk for hypoglycemia. Finally, this guideline addresses the use of newer glucagon formulations in the treatment of acute hypoglycemia.

Most of the studies reviewed in developing the recommendations in this guideline included individuals with T1D or T2D at risk for hypoglycemia. Although these populations make up the majority of people living with diabetes and are the target population for this guideline, others with diabetes are at risk for hypoglycemia and would benefit from these recommendations. These include those with monogenic forms of diabetes, diabetes in pregnancy, diseases involving the exocrine pancreas (eg, cystic fibrosis and hemochromatosis), those with drug-related hyperglycemia (including those taking glucocorticoids), and those with diabetes following pancreatic surgery. Hospitalized individuals with hyperglycemia who may temporarily require insulin, and are therefore at risk for hypoglycemia, may also benefit from these recommendations.

Definitions of Terms Used in This Clinical Guideline

1. Real-time continuous glucose monitoring: Real-time CGM involves the use of devices that measure interstitial glucose every 1 to 5 minutes and automatically transmit these data to a device, such as a receiver, smart phone, or an insulin pump, providing real-time feedback for the user (19). The latest versions of these devices come equipped with alerts that can aid the user in making real-time adjustments in their diabetes therapy, including in insulin dosing.

2. Intermittently scanned continuous glucose monitoring: Intermittently scanned CGM involves devices that measure interstitial glucose every 1 to 5 minutes and transmit these data to a device, such as a receiver or smart phone, providing feedback for the user (19). Unlike real-time CGM, intermittently scanned CGM requires that the user purposefully scan their sensor to obtain information and older technology may not provide predictive alerts. Those that provide predictive alerts are preferred as they can identify and prevent hypoglycemia.

3. Algorithm-driven insulin pump therapy: ADIP therapy involves the use of an insulin pump combined with a CGM device, which then allows for changes in basal insulin delivery based on an individual's real-time glycemic data. The changes in insulin dose are based on mathematical algorithms programmed into the insulin pump. These devices are also referred to as "sensor-driven" or "sensor-augmented insulin pump therapy." Devices termed "*hybrid*" or "*hybrid closed-loop systems*" provide changes to basal insulin and may deliver mini-correction boluses in response to hyperglycemia but require the user to give an insulin bolus with meals. All of these terms are found in the medical literature, including in the studies identified for these guidelines. ADIP is the term used to refer to all currently available forms of automated insulin delivery through devices in this guideline.

4. Personal continuous glucose monitoring: Personal CGM is a tool for persons with diabetes to use in real time to assist them in making both short- and long-term adjustments in their therapeutic management.

5. Professional continuous glucose monitoring: Professional CGM is a diagnostic tool used for the short-term investigation of an individual's glycemic profile to determine glycemic patterns, to assist with therapeutic management. It is typically placed by a member of the individual's diabetes care team, and data are later collected for interpretation.

6. Inpatient glycemic surveillance and management programs: Inpatient glycemic surveillance and management programs vary greatly but for this guideline we included systems that collect real-time glycemic data from the EHR (including fingerstick data, laboratory-drawn data, and possibly CGM data if available) into a database that can be readily analyzed for pertinent patterns and/or generate clinical decision support to guide insulin dose adjustment. We included systems that allow for daily reports (eg, stoplight/traffic light charts) designed to help trained hospital staff to identify patients who require changes in their clinical management to avoid both hypoglycemia and hyperglycemia. These systems contrast with paper-charting that cannot directly interface with the EHR (20).

7. Structured diabetes education: Structured diabetes education actively engages the person with diabetes through methods including hands-on training and exercises and group meetings as they develop their health care goals and learn how to manage their condition. Structured education differs from didactic education in that the person with diabetes is actively involved in their education, vs merely having information given to them as passive learners (21). Structured diabetes education programs include education surrounding stress management, healthy eating and physical activity, medication use and glucose monitoring, and problem solving (22). It also involves teaching risk reduction, including those risks related to hypoglycemia. Structured education can be provided via digital health approaches, such as telehealth and virtual classes.

Question 1. *Should continuous glucose monitoring vs self-monitoring of blood glucose be used for people with type 1 diabetes receiving multiple daily injections?*

Background

Most individuals with T1D do not meet recommended glycemic targets (23, 24). Previous clinical trials showing the benefit of CGM in the management of T1D predominantly have included adults using insulin pumps (25–27), despite the fact that most adults with T1D administer insulin by

injection ([28], [29]). Compared to insulin pump users, a smaller proportion of individuals who inject insulin use CGM ([30]). Randomized controlled trials (RCTs) in children have not consistently shown improvement in glycemic control (as measured by glycated hemoglobin levels and reduced hypoglycemia with the use of CGM ([25], [31]).

Recommendation 1

We recommend continuous glucose monitoring (CGM) rather than self-monitoring of blood glucose (SMBG) by fingerstick for patients with type 1 diabetes (T1D) receiving multiple daily injections (MDIs). (1⊕⊕OO)

Remarks

- Comprehensive patient education on how to use and troubleshoot CGM devices and interpret these data is critically important for maximum benefit and successful outcomes.
- SMBG continues to be necessary to validate or confirm CGM values; eg, when symptoms do not match sensor glucose values and during the sensor warm-up period. Therefore, patients using CGM must continue to have access to SMBG.

Summary of Evidence

The evidence-to-decision (EtD) framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/7BmuC_MXtPU.

Benefits and Harms

The systematic review (SR) included 10 RCTs that compared real-time CGM vs SMBG ([2], [32–41]). One of these studies ([34]) included 2 cohorts: 1 with pregnant patients with T1D and 1 with patients with T1D planning pregnancy. We analyzed these 2 populations separately from the rest of the studies.

In the nonpregnant population, CGM may reduce the proportion of patients with glucose less than 54 mg/dL (3.0 mmol/L) (odds ratio [OR] 0.15; 95% CI, 0.05 to 0.41; low-certainty evidence), likely reduces episodes of severe hypoglycemia (incidence rate ratio [IRR] 0.39; 95% CI, 0.18 to 0.85; moderate-certainty evidence), and likely increases the percentage of TIR 70 to 180 mg/dL (3.9 to 10.0 mmol/L) (mean difference [MD] 5.20; 95% CI, 3.10 to 7.29; moderate-certainty evidence). The evidence suggests there was no difference in the incidence of episodes of glucose less than 54 mg/dL (3.0 mmol/L) (very low-certainty evidence), seizures (very low-certainty evidence), time below 70 mg/dL (3.9 mmol/L) (low-certainty evidence), or time below 54 mg/dL (3.0 mmol/L) (low-certainty evidence), or in HbA$_{1c}$ level (very low-certainty evidence), but the evidence is uncertain.

In pregnant patients, CGM likely decreases the time below 54 mg/dL (3.0 mmol/L) (MD −1.00; 95% CI, −1.60 to −0.41, moderate-certainty evidence) and may increase the percentage of TIR 70 to 180 mg/dL (3.9-10.0 mmol/L) (MD 7.00; 95% CI, 2.57 to 11.43, low-certainty evidence), and the evidence suggests there was no difference in time below 70 mg/dL (3.9 mmol/L) (low-certainty evidence). In the population planning pregnancy, CGM may reduce time below 54 mg/dL (3.0 mmol/L) (MD 1.00; 95% CI, 0.20 to 1.80, low-certainty

evidence), and the evidence suggests there was no difference in episodes of severe hypoglycemia (very low-certainty evidence), time below 70 mg/dL (3.9 mmol/L) (low-certainty evidence), or the percentage of TIR 70 to 180 mg/dL (3.9 to 10.0 mmol/L) (very low-certainty evidence). Of note, though our systematic review used TIR as 70 to 180 mg/dL (3.9 to 10.0 mmol/L) for all individuals, the accepted TIR for pregnancy is lower (63 to 140 mg/dL [3.5 to 7.8 mmol/L]) ([42]).

Other Evidence-to-Decision Criteria and Considerations

Panel members placed a high value on the benefits of CGM use and less on its insignificant undesirable effects. Although not a prioritized outcome, panel members noted that contact dermatitis from the sensor adhesive affects a minority of those using CGM, and various strategies may ameliorate this adverse effect. Some individuals (especially adolescents) do not want a medical device attached to their bodies. Alerts and alarms are annoying, embarrassing, and disruptive, and glucose values every 1 to 5 minutes (288 values per day) may be overwhelming. These issues can be mitigated by proper training and education. Also, alarm thresholds can be customized to minimize their effect (eg, a person with poor glucose control can have the high threshold set at 300 mg/dL [16.6 mmol/L] or higher, whereas the person with well-controlled diabetes may choose a high threshold of 200 mg/dL [11.1 mmol/L]).

Real-time and intermittently scanned CGM are both available, though not all technologies have predictive alerts. The panel noted that for people with T1D, real-time CGM and intermittently scanned CGM with predictive alerts are preferred to intermittently scanned CGM without alerts for monitoring and detection of hypoglycemia, especially during sleep. Certain CGM systems require fingerstick blood glucose (BG) values to calibrate the device. SMBG continues to be necessary during the sensor warm-up period, to validate questionable CGM values, and when the sensor malfunctions or the sensor signal is lost.

Studies that included children and adolescents were ineligible for inclusion in our literature review because they included participants who used insulin pumps. For example, a recent RCT examined the effect of CGM on glycemic control in adolescents and young adults (ages 14 to 24 years) with T1D ([43]). Participants were randomly assigned to CGM or usual care using a BG meter for monitoring: Of the participants randomly assigned to CGM and SMBG, 49% and 59%, respectively, used a pump. Use of CGM resulted in a small but significant improvement in glycemic control over 26 weeks.

Cost of CGM systems and SMBG varies considerably depending on the specific device used and, for SMBG, the daily frequency of BG measurements. The effect on health equity would be significantly influenced by access, insurance coverage, and out-of-pocket cost for CGM. Cost for the user is moderate with insurance coverage and much larger without coverage. The panel noted that available data do not reflect newer versions of CGM. It is relatively easy to compare direct annual costs of CGM and SMBG; however, it is much more challenging to measure long-term cost-effectiveness, which would include reduction of episodes of severe hypoglycemia and attendant costs (transport by ambulance, evaluation and treatment in an ED, hospitalization), effect on improved

glycemic control, and resulting reduction of long-term complications and improved long-term health and productivity.

Comprehensive patient education on the proper use of the devices and how to interpret these data is essential for optimal use and outcomes.

Justification for the Recommendation

The panel justified a strong recommendation despite the low quality of evidence, based on recognition that iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes and is a major concern for individuals with diabetes and for their family members (44, 45). Use of CGM is recommended for anyone with T1D and even more strongly for individuals with IAH, fear of hypoglycemia, and for young children who have functional hypoglycemia unawareness (whose parents often do not sleep well owing to fear of nocturnal hypoglycemia). Avoiding hypoglycemia is a priority as it increases the risk of repeated and more serious hypoglycemia (loss of consciousness or seizures) and is associated with increased instability of glucose control; poor QOL; diabetes distress; potentially serious injury when driving or operating hazardous machinery; damage to the brain and heart; and, rarely, death.

Trend arrows showing the direction and rate of change of glucose levels enable the CGM user to predict the glucose level in the next 30 to 60 minutes and make better-informed management decisions (46, 47). This information was not captured in published studies. Earlier versions of CGM required multiple daily calibrations, and management decisions could not be based on glucose values obtained from CGM (a confirmatory fingerstick BG measurement was required). The acceptability of newer CGM systems has improved owing to their greater accuracy, longer duration of use, and either no calibration or less frequent calibration required than earlier CGM systems that are now obsolete. This is reflected in increased use of CGM across all ages and most especially in young children (48, 49).

Research Considerations

- The importance of reducing hypoglycemia in those individuals with T1D using MDIs at high risk for hypoglycemia via the use of CGM emphasizes the need for further research. A proposed area for future research is evaluating hypoglycemia-related outcomes via the use of newer CGM devices.
- Future studies should also continue to incorporate patient-oriented outcomes (ie, QOL, medication adherence, etc).

Question 2. Should real-time continuous glucose monitoring and algortihm-driven insulin pumps vs multiple daily injections with self-monitoring of blood glucose three or more times daily be used for people with type 1 diabetes?

Background

With the publication of the Diabetes Control and Complication Trial (50), the use of MDIs with SMBG 3 or more times daily became the preferred diabetes management regimen because of the benefit it demonstrated in reducing microvascular complications in adults and adolescents with T1D. Since then, the best approaches to achieving optimal

glycemic control without hypoglycemia have evolved as new insulins and technologies have become available. Over the last decade, rapid and successive improvements in the devices have made it possible to continuously monitor BG levels without performing multiple daily fingersticks and to use this information to modify insulin administration in real time.

Recommendation 2

We suggest using real-time continuous glucose monitoring (CGM) and algorithm-driven insulin pumps (ADIPs) rather than multiple daily injections (MDIs) with self-monitoring of blood glucose (SMBG) three or more times daily for adults and children with type 1 diabetes (T1D). (2⊕⊕OO)

Remark

Fingerstick blood glucose (BG) monitoring may still be necessary to validate or confirm CGM values; therefore, with respect to use and insurance coverage, there will be times when SMBG must be used.

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/qyRYH8PFfcs.

Benefits and Harms

The SR did not find any studies that compared real-time CGM and ADIPs with MDIs with SMBG 3 or more times daily in any population (41). The lack of this evidence makes it impossible to directly define the relative benefits and harms of the 2 approaches. The use of CGM has significantly reduced hypoglycemia and improved glycemic control in patients with T1D, regardless of how insulin is administered (see recommendation 1 to use CGM rather than SMBG). As CGM is incorporated into ADIP systems, we may safely assume that these systems at a minimum will have moderate benefits in people with T1D in reducing risk of hypoglycemia.

Numerous studies have shown improved overall glycemic control of T1D with either less hypoglycemia or no worsening of hypoglycemia using ADIP therapy (51). The evidence from CGM data reviewed in recommendation 1 provides support for improved avoidance of both high and low uncontrolled glycemic levels. It seems likely from available data that newer ADIPs may provide greater safety and effectiveness when compared with insulin pump therapy that did not use an algorithm. Model predicted control algorithm pumps with a dedicated safety system seem to be the most effective, and algorithms using Fuzzy Logic systems seem promising (52).

Other Evidence-to-Decision Criteria and Considerations

The latest ADIP technologies generated much enthusiasm among the panelists with regard to the individuals with diabetes that they treat. Use of such devices to manage T1D

will likely improve overall glycemic control. The panelists noted that using real-time CGM and ADIPs is associated with a greater immediate cost than using MDIs with SMBG in most settings. However, over the long term, it is possible that individuals using such devices will experience fewer costs because of a reduction in severe hypoglycemia and long-term complications. Because ADIPs reduce insulin administration to prevent hypoglycemia, they may reduce diabetes distress and the fear of hypoglycemia in those with T1D.

The panelists noted that ADIPs are associated with less time below 70 mg/dL (3.9 mmol/L) and higher overnight and 24-hour period glycemic TIRs and thus may be preferable over MDIs with SMBG (53). Benefits were seen in studies with children and adults. The panel noted that the studies were using mostly algorithms and equipment now considered out of date and that the main limitations of the available research evidence were related to inconsistency in outcome reporting, small sample size, and short follow-up duration of individual trials.

Justification for the Recommendation

Because evidence is lacking to demonstrate the relative benefits and harms of using real-time CGM and ADIPs vs MDIs with SMBG, the panelists relied on the evidence used to support the recommendation of using CGM vs SMBG in recommendation 1 to justify their recommendation. In addition, panelists were influenced by the opinions their patients have expressed about the benefits of using real-time CGM and ADIPs in managing their diabetes.

Research Considerations

The advancements in technology both for CGM and for insulin pump therapy emphasize the need for further research. Proposed areas for future research include:

1. Comparing the available ADIPs
2. Including measures of patient-centered outcomes such as ease of use, diabetes distress, and fear of hypoglycemia in studies involving ADIP systems

Question 3. ***Should professional or personal real-time continuous glucose monitoring vs no continuous glucose monitoring be used for people with type 2 diabetes in the outpatient setting who take insulin and/or sulfonylureas and are at high risk for hypoglycemia?***

Background

SMBG helps those with diabetes reach their glycemic targets and alone can improve HbA_{1c} in the outpatient setting. Intensification of T2D therapy leads to hypoglycemia, which is a feared complication and an important barrier to improved glycemic management (54, 55). Hypoglycemia can be both recognized and unrecognized, and individuals with IAH are at high risk for recurrent episodes. Hypoglycemia increases hospitalizations and health care usage, while also worsening diabetes distress, glycemic control, and QOL. Outpatient use of CGM reduces both hypoglycemia and the fear of hypoglycemia, as extrapolated from studies in T1D. Consider also those at risk for hypoglycemia, including individuals outlined in Table 1. The panel also identified those individuals requiring enteral feeding with hyperglycemia and those with

steroid-related hyperglycemia as potentially benefitting from CGM.

Recommendation 3

We suggest real-time continuous glucose monitoring (CGM) be used rather than no continuous glucose monitoring (CGM) for outpatients with type 2 diabetes (T2D) who take insulin and/or sulfonylureas (SUs) and are at risk for hypoglycemia. (2⊕OOO)

Remarks

- Professional CGM is a diagnostic tool used for the short-term investigation of an individual's glycemic profile to determine glycemic patterns and to assist with therapeutic management.
- Personal CGM is a tool for patients to use in real time at home to assist the patient and their health care professionals (HCPs) in making both short- and long-term adjustments in their therapeutic management.

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/aOeKMkoV4SY.

Benefits and Harms

The SR included 6 RCTs (55–59) that compared the use of professional or personal real-time CGM in patients with T2D vs not using CGM (41). The use of CGM probably reduces HbA_{1c} (MD −0.20; 95% CI, −0.34 to −0.05; moderate certainty), and, compared to the baseline values, patients who used CGM likely spent less percentage of their time below 70 mg/dL (3.9 mmol/L) (MD −0.57; 95% CI, −0.99 to −0.14; moderate-certainty evidence). The evidence suggests there was no difference between those using and those not using CGM with regard to the proportion of patients with glucose lower than 70 mg/dL (3.9 mmol/L) (very low-certainty evidence), or less than 54 mg/dL (3.0 mmol/L) (very low-certainty evidence), the number of episodes per patient of glucose less than 70 mg/dL (3.9 mmol/L) (very low-certainty evidence), less than 54 mg/dL (3.0 mmol/L) (low-certainty evidence), or less than 40 mg/dL (2.2 mmol/L) (low-certainty evidence), time spent below 70 mg/dL (3.9 mmol/L) (low-certainty evidence), or TIR 70 to 180 mg/dL (3.9 to 10.0 mmol/L) (low-certainty evidence). Compared to the baseline values, the evidence suggests there was no difference in TIR 70 to 180 mg/dL (3.9 to 10.0 mmol/L) when initiating CGM (very low-certainty evidence), but the evidence is very uncertain. Three of the included studies reported no severe hypoglycemia events during their study period (56–58). One study reported one episode of myocardial infarction (MI) in the CGM group (56).

Other Evidence-to-Decision Criteria and Considerations

The panel noted that patient-related factors are important in the outpatient use of CGMs (60–63). Some individuals with diabetes may be intimidated by technology or may not feel

comfortable with having a device on their body (64, 65). Those using CGM often raise concerns about CGM alerts being bothersome to them, including in the work setting, and may also be disruptive for their family members (66, 67). Many of the data available regarding individual comfort and concerns regarding use of CGM come from studies involving people with T1D. However, many of the concerns regarding CGM use will be similar between those with T1D and those with T2D.

The panel identified that, in the SR, the costs of hypoglycemia (including ambulance calls, ED visits, and hospitalizations for severe hypoglycemia) were not compared with the costs of CGM devices. There may be a group of individuals with diabetes for whom substantial cost savings are possible, including those with IAH as well as those patients with comorbidities that place them at high risk for hypoglycemia (68–70).

T2D is more common in individuals with low socioeconomic status as well as in minorities, many of whom are uninsured or underinsured (71, 72). The current health insurance landscape makes obtaining a CGM device difficult, if not impossible, for these people. Individuals with private insurance will most likely have greater access to CGM use. CGMs differ in costs, and it is not clear from studies which device would be best recommended for a certain patient group. The acquisition of and reimbursement for devices from insurers, patient education and data report generation, and electronic medical record integration need to be simplified and standardized. The panel also noted that often a caregiver applies the CGM and assists the person with diabetes in its use. Therefore, it is important that anyone involved in using the CGM receive appropriate and adequate education (73). Barriers to the use of CGM devices may be overcome by ensuring that all involved receive this education.

The panel noted that individuals with diabetes and their providers both typically favor the use of CGM. Data also suggest that the intervention is likely acceptable to key stakeholders. The panel noted that there may be considerable barriers for initiation of CGM in T2D due to the resource-heavy nature of the intervention, and that future research should determine what barriers exist both in primary care and subspecialist settings, and methods for overcoming those barriers. The panel noted that CGMs support virtual care and remote patient monitoring, which is becoming more widespread with the availability of telehealth services (74–76).

Justification for the Recommendation

The panel justified a conditional recommendation due to the importance of reducing outpatient hypoglycemia in those with T2D but recognized the indirectness of the evidence and the broader population included in the studies vs those only at high risk for hypoglycemia, including specific subgroups. There is also concern about the resources necessary and the uncertainty about the cost and coverage of CGM, although both are slowly improving. Therefore, there is very low certainty of the evidence. The panel noted there was very little evidence for the use of personal or professional CGM in individuals taking SUs. However, the benefits of reducing hypoglycemia were felt to be important enough that the conditional recommendation, on very low certainty evidence, was made.

Implementation Considerations

The panel noted that while SUs and insulin were the focus for this recommendation, other medications including the meglitinides, are also associated with an increased risk for hypoglycemia and individuals taking these medications would also likely benefit from the use of personal or professional CGM.

Research Considerations

The importance of reducing hypoglycemia in outpatients with T2D with the use of CGM emphasizes the need for further research. Proposed areas for future research include the following:

1. Developing new, simpler devices that will be acceptable to individuals with diabetes and HCPs and that integrate ambulatory glucose data directly into outpatient medical records
2. Evaluating hypoglycemia reduction as the major outcome of outpatient CGM use in T2D and evaluating its effect on patient outcomes, complications, and cost
3. Evaluating hypoglycemia outcomes with newer available devices that have predictive alerts or warnings regarding pending hypoglycemia

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Question 4. Should initiation of continuous glucose monitoring in the inpatient setting vs not using continuous glucose monitoring be used for select people at high risk for hypoglycemia?

Background

Hypoglycemia is a limiting factor for glucose management and occurs frequently in high-risk hospitalized patients with T1D and T2D. Contributing factors for hypoglycemia are multifactorial and include patient, treatment, and institutional process factors (77). Hospitalized patients may not consistently experience symptoms of hypoglycemia (78). Intermittent POC-BG monitoring, which is the current method for checking inpatient glucose levels, is time-consuming and not desirable to patients. In contrast, CGMs measure interstitial glucose levels every 1 to 5 minutes via scanning of device and are helpful in the outpatient setting to warn of impending hypoglycemia and can be similarly used in the hospital setting. Several studies have demonstrated the detection of hypoglycemia (especially nocturnal) and asymptomatic hypoglycemia by CGM that was missed with traditional POC-BG testing (79, 80).

Recommendation 4

We suggest initiation of continuous glucose monitoring (CGM) in the inpatient setting for select inpatients at high risk for hypoglycemia. (2⊕OOO)

Remarks

- This should be performed via a hybrid approach in which CGM use is combined with periodic point-of-care blood glucose (POC-BG) testing to validate the accuracy of CGM.
- Inpatient CGM use is not currently approved by the US Food and Drug Administration (FDA) but currently has enforcement discretion. It has been used in hospitals recently with emergency use authorization during the COVID-19 pandemic.

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/tYzX0tRdowc.

Benefits and Harms

The SR included 6 studies, 4 RCTs (81–84), and 2 observational studies (85, 86) that evaluated the effect of initiation of CGM in the inpatient setting (41). The focus of these studies was more on accuracy of CGM data in the hospital and less on the benefits of CGM utilization in the hospital specifically hypoglycemia reduction.

The initiation of CGM in the inpatient setting likely results in a large reduction in the occurrence of episodes of glucose less than 54 mg/dL (3.0 mmol/L) (OR 0.11; 95% CI, 0.03 to 0.37; moderate-certainty evidence) and likely reduces the percentage of time spent below 54 mg/dL (3.0 mmol/L) (MD −0.57; 95% CI, −1.02 to −0.11; moderate-certainty evidence). The evidence suggests there was no difference in the occurrence of episodes of glucose less than 70 mg/dL (3.9 mmol/L) (very low–certainty evidence), proportion of patients with glucose less than 54 mg/dL (3.0 mmol/L) (very low-certainty evidence), time below 70 mg/dL (3.9 mmol/L) (low-certainty evidence), or TIR 70 to 180 mg/dL (3.9 to 10.0 mmol/L) (very low-certainty evidence), but the evidence is uncertain.

Only 1 RCT examined the frequency of severe hypoglycemia, seizures, loss of consciousness, and mortality, but did not observe any events (82). Similarly, 2 observational studies did not observe any episodes of severe hypoglycemia (85, 86). These single-arm studies found that the proportion of patients with glucose less than 70 mg/dL (3.9 mmol/L) and less than 54 mg/dL (3.0 mmol/L) detected by CGM was higher compared with POC-BG testing ($P = .001$ and $P = .001$, respectively). This suggests CGM detects more hypoglycemia than POC-BG.

Table 3. Candidate inpatients at high risk for hypoglycemia for the initiation of inpatient continuous glucose monitoring

- Those with impaired awareness of hypoglycemia
- Individuals age 65 years and older
- Individuals with a BMI $\leq$ 27 kg/mg^2
- Those with T1D, who often have variable glycemic control
- Those requiring high-dose steroids, or tapering off steroids
- Those requiring parenteral nutrition or enteral nutrition, who may be at risk for hypoglycemia if the dietary source of glucose is discontinued/changed/interrupted
- Those isolated for a contagious disease (eg, COVID-19), as CGM may assist with reducing health care personnel exposure and the need for personal protective equipment
- Individuals with chronic kidney disease (stages 3-5) and/or liver disease or critical illness, given their higher propensity for hypoglycemia
- Individuals with comorbid conditions that might increase their risk for hypoglycemia including a history of cerebrovascular accident, active malignancy, congestive heart failure, pancreatic disorders, or infection
- Individuals with a history of preadmission hypoglycemia or hypoglycemia during recent/current admission

Abbreviations: BMI, body mass index; T1D, type 1 diabetes; CGM, continuous glucose monitoring.

Table 4. Elements needed for initiation of personal continuous glucose monitoring in the inpatient setting

Engagement, training, and education of nursing personnel and other health care providers

Patient education regarding care of the device and how to respond to alerts for high or low BG

Purchase of equipment (eg, sensors, transmitters, receivers)

Expertise from health care professionals knowledgeable in this technology

Oversight and guidance for CGM use

Integration of CGM data with hospital electronic medical record

Clarity of assigned responsibility for interpreting and acting on CGM data

Source: Adapted from Galindo RJ et al. *J Diabetes Sci Technol*, 2020; (14)4 (87). © Diabetes Technology Society
Abbreviations: BG, blood glucose; CGM, continuous glucose monitoring.

Other Evidence-to-Decision Criteria and Considerations

The panel identified individuals with diabetes who would especially benefit from initiation of CGM in the hospital (Table 3), including those with characteristics shown in Table 1. The panel also delineated the elements needed for initiation of CGM in the inpatient setting, shown in Table 4. Inpatients without diabetes who may be at high risk for hypoglycemia may also include those with significantly poor nutrition (with low glycogen stores), fulminant renal and liver failure, and sepsis, as well as those with a need for insulin therapy due to illness severity and enteral or parenteral feeding (88). The panel also identified those patients with steroid-related hyperglycemia as individuals who might benefit from inpatient CGM. CGM may not be accurate in their initial warm-up period, although this time is getting shorter with newer devices. Inpatient CGM use may not be appropriate for individuals for whom there are concerns regarding each CGM's accuracy. These include those patients with hypotension and vasoconstriction (including those who are severely dehydrated, volume depleted, or requiring vasopressor therapy), patients who are edematous or with anasarca, and patients with DKA and/or severe hyperglycemia. Clinicians must consider substances known to interfere with CGM accuracy, including high-dose vitamin C and hydroxyurea. Patients with extremes of both hyperglycemia and hypoglycemia should have their CGM results corroborated with POC-BG checks. The panel noted that having a system to integrate CGM data with the EHR system in the inpatient setting is a difficult yet crucial process and needs to be addressed. The panel noted that the focus of the recommendation is on the use of CGM for hospital care and not necessarily to continue the CGM use after discharge.

Justification for the Recommendation

The panel justified a recommendation in favor of initiating CGM use in the inpatient setting for select inpatients at high risk for hypoglycemia, based on very low-certainty evidence. High value was placed on acceptability by HCPs and patients. Although resource requirements may be large, effect on improved resource utilization and cost-effectiveness is not known (eg, considering potential savings).

Implementation Considerations

- The panel noted that prior to initiating CGM use in the hospital, there needs to be an adequate framework and resources, including staff that are trained in CGM devices who can aid in their management. An appropriate security and privacy data infrastructure will need to ensure patient data safety with inpatient use of these devices.
- The panel also noted there must be guidelines and processes for when the CGM device must be removed for imaging and surgical procedures in the hospital.
- This recommendation does not apply to situations in which CGM may not be accurate, including in patients with extensive skin infection, hypoperfusion, or hypovolemia and those receiving vasoactive or pressor therapy. Some medications can cause inaccurate CGM readings (eg, acetaminophen more than 4 g/day, dopamine, heparin, vitamin C, hydroxyurea).

Research Considerations

The importance of reducing hypoglycemia in inpatients with diabetes by using CGM emphasizes the need for further research. Proposed areas for future research include the following:

1. Evaluating accuracy and safety of initiating CGM devices in different patient populations to define inpatients at high risk for hypoglycemia who would benefit from its use
2. Evaluating whether inpatient CGM should be used for determining insulin dosing (currently, hospitals require POC-BG checks to dose insulin for patients wearing their own CGMs when hospitalized)

Comments

- Hospital teams need to monitor future changes in FDA approval for inpatient CGM (which currently has emergency use authorization due to the COVID-19 pandemic).
- Expanding CGM use successfully in the hospital will require substantial resource utilization and support in areas of HCP education of devices with clear protocols, process maps, and documentation guidelines.

Question 5. Should continuation of personal continuous glucose monitoring in the inpatient setting vs discontinuation of continuous glucose monitoring be used for people at high risk for hypoglycemia who are already using it?

Background

The increasing use of CGM devices in the outpatient setting has led to significant improvements in glycemic control and decreased glucose variability. These devices are not currently approved for inpatient use, but emerging data have led to increasing interest in incorporating CGM in the hospital setting. Individuals with diabetes (and their families) frequently express dissatisfaction and anxiety with discontinuation of their personal CGM in the inpatient setting.

> ### Recommendation 5
>
> We suggest continuation of personal continuous glucose monitoring (CGM) in the inpatient setting with or without algorithm-driven insulin pump (ADIP) therapy rather than discontinuation. (2⊕OOO)

> ### Remarks
>
> - This should be performed via a hybrid approach in which CGM use is combined with periodic point-of-care blood glucose (POC-BG) testing to validate the accuracy of CGM.
> - Inpatient CGM use is not currently approved by the US Food and Drug Administration (FDA) but currently has enforcement discretion. It has been used in hospitals recently with emergency use authorization during the COVID-19 pandemic.

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/Xi4rwJwcO_o.

Benefits and Harms

The SR found no research evidence comparing continuation of personal CGM in the inpatient setting with the comparator of discontinuation of personal CGM (41).

The panel recommendation considered the indirect evidence from research identified in recommendation 4 that focused on the benefits and harms of initiating CGM in adult inpatients at risk for hypoglycemia. Based on low-certainty evidence that there may be a higher detection rate of hypoglycemia, lower percentage time spent with hypoglycemia and hyperglycemia, and likely lower mean BG (moderate-level certainty) with the use of CGM in patients at high risk for hypoglycemia, the panel found that CGM use is probably favored over POC-BG testing alone. See recommendation 4 for a more detailed summary of those findings.

Based on this indirect evidence of moderate desirable effects and small undesirable effects, the panel recommended continuation of personal CGM in the inpatient setting rather than discontinuation for inpatients who are already using personal CGM.

Other Evidence-to-Decision Criteria and Considerations

Panel members placed a high value on the moderate benefits that may occur with CGM use, especially avoidance of hypoglycemia, over insignificant negative effects. Hypoglycemia is common in the hospital setting, and several studies have demonstrated the detection of symptomatic hypoglycemia and asymptomatic hypoglycemia by CGM that was missed by traditional POC-BG testing (82, 84–86). Patients with personal CGM are very likely to want to continue to use their personal CGM in an inpatient setting. Indeed, anecdotally, patients and their families are often anxious or dissatisfied if hospital policy requires their discontinuation.

The accuracy of CGM devices when compared to POC-BG measurements in the inpatient setting has been demonstrated as moderate to good in several RCT and non-RCT studies in the inpatient setting (85, 86, 89). The lower accuracy of CGM at extremes of glycemic excursion events introduces a potential for inappropriate therapeutic interventions; however, this risk is mitigated when hospitals implement processes to obtain confirmatory laboratory or bedside POC-BG values prior to adjustments in insulin or other glucose-modifying therapies.

The acceptability of CGM depends in part on the resources needed to deploy this intervention (Table 4). For those continuing personal CGM in the hospital, the staff will also need to identify and document the preexisting CGM and presence or absence of a subcutaneous insulin pump. There will need to be a process to ensure that the personal CGM is in working order, and health care personnel will need to receive education about the different types of devices that patients may bring in (eg, CGMs with and without predictive alerts). Hospitals will need to consider costs associated with training of personnel who will be using these devices as well as increased costs that could occur with integration into the EHR, repeated sensor malfunctions, or need for removal and replacement in patients undergoing magnetic resonance imaging or other radiologic procedures (82, 90). However, there are potential cost savings attributable to reductions in nurse time for performing POC-BG testing, reducing hypoglycemia events, and lowering laboratory costs for verifying POC-BG measures (91). A recent study found that transmission of information from CGM devices to a nursing station with alerts for upward or downward trends in sensor glucose values could reduce time with glucose values out of desired range (83). We note that the costs for continuing personal CGM in the inpatient setting is less than the cost of starting CGM de novo.

Overall, the panel determined that the feasibility of introducing CGM for noncritically ill patients at high risk for hypoglycemia will vary by institution, depending on the resources available to support the effort. Successful implementation requires that protocols, education, and EHR changes reinforce several crucial aspects of care, including appropriate patient selection, verification that the personal CGM is functioning properly, and education regarding the different CGM devices available (88, 92).

Justification for the Recommendation

The balance of effects probably favors continuation of CGM use in the inpatient setting for those patients who are already using personal CGM, based on very low-certainty and indirect evidence. The panel placed high value on acceptability by HCPs and patients (and their families) and a high value on prevention of hypoglycemia. Although resource requirements may be large, cost-effectiveness was not known (eg, considering potential savings). CGM has become the standard of care for pediatric T1D in the ambulatory setting. Patients and their families rely on CGM to feel safe, particularly at night. Patient and family dissatisfaction with discontinuing a CGM already in use in the ambulatory setting was therefore taken into account by the panel. The panel also notes that during the COVID-19 pandemic, the use of CGM increased to minimize contact with patients and reduce sleep interruption.

Implementation Considerations

- CGM glucose values alone should not be used to guide adjustments in clinical care. CGM readings should always be confirmed with laboratory or bedside POC-BG monitoring prior to adjustments in insulin or other glucose-modifying therapies.
- This recommendation does not apply to situations in which CGM may not be accurate, including in patients with extensive skin infection, hypoperfusion, or hypovolemia and those receiving vasoactive or pressor therapy. Some medications can cause inaccurate CGM readings (eg, acetaminophen more than 4 g/day, dopamine, heparin, vitamin C, hydroxyurea).
- This recommendation does not apply to patients who are unwilling or unable to follow hospital CGM protocols or to patients with contraindications, such as those undergoing magnetic resonance imaging. Individuals should be encouraged to bring their own CGM supplies to the hospital for their personal use.

Research Considerations

The importance of reducing hypoglycemia in inpatients with diabetes via the use of personal CGM emphasizes the need for further research. Proposed areas for future research include the following:

1. Evaluating the accuracy and safety of continuing these devices in surgical areas and critical care units
2. Identifying patient selection criteria for continuation of personal CGM
3. Evaluating the use of CGM devices in combination with ADIPs
4. Gauging nurse satisfaction and level of confidence with continuing personal CGM devices

Comments

- The panel acknowledges that recruitment for RCTs for continuation of personal CGMs vs discontinuation may be problematic, given the reluctance of individuals with diabetes and their families to discontinue personal CGM owing to their perception that it confers safety from serious hypoglycemic events.
- Hospital teams need to monitor future changes in FDA approval for inpatient CGM (which currently has emergency use authorization due to the COVID-19 pandemic).
- Hypoglycemia adverse drug event reporting involving continued use of personal CGM in the inpatient setting needs to be examined carefully on an ongoing basis.

Question 6. Should inpatient glycemic surveillance and management programs leveraging electronic health record data vs standard care be used for hospitalized people at risk for hypoglycemia?

Background

Several academic and community-based hospitals have developed computerized glycemic surveillance and management programs that are integrated with their EHRs (93).

These programs include data from the EHR (including fingerstick BG data, laboratory-measured BG data, and CGM data if available) and put this information into a database that can be readily analyzed for pertinent patterns. These data can be compiled into reports that allow for coordination of glycemic management in real time by multiple patient care team members including nursing staff, hospitalists, and consulting endocrinologists who can make changes to a given patient's diabetes-related therapies in real time to reduce the risk for hypoglycemia. It also allows for the creation of hospital-based teams whose role is to evaluate patient glycemic trends, including hypoglycemia, leading to hospital-wide interventions to reduce adverse glycemic outcomes.

Recommendation 6

We recommend that inpatient glycemic surveillance and management programs leveraging electronic health record (EHR) data be used for inpatients at risk for hypoglycemia. (1⊕OOO)

Remarks

- The panel defined leveraging EHR data as specific hospital staff using glycemic data collected within the EHR (from all admitted patients) to identify those at risk for and those having hypoglycemic and hyperglycemic episodes to develop mechanisms for managing and mitigating these adverse outcomes. Standard care is lack of such a program.
- EHR data leveraged includes patterns of glycemia with proactive alerts for high and for low trends, so that hypoglycemia and severe hyperglycemia can be identified in a systematic fashion. Staff can then intervene on these trends (eg, adjusting insulin infusion rates) to avoid unwanted outcomes (repeat hypoglycemia, glycemic variability, etc).

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/ZkhlYmdz66c.

Benefits and Harms

The SR identified 1 RCT and 8 nonrandomized studies to address this question (41). The use of a glycemic management program may result in fewer patients with glucose less than 70 mg/dL (3.9 mmol/L) (OR 0.55; 95% CI, 0.39 to 0.77), corresponding to 75 fewer (95% CI, from 105 fewer to 37 fewer) patients with glucose less than 70 mg/dL (3.9 mmol/L) per 1000 patients (low-certainty evidence) (94–98). Computerized glycemic management programs may reduce episodes of glucose less than 70 mg/dL (3.9 mmol/L) per patient (MD −0.40; 95% CI, −0.79 to −0.01) (very low-certainty evidence), but (99) may result in fewer patients with severe hypoglycemia (OR 0.11; 95% CI, 0.03 to 0.34), corresponding to 30 fewer patients (95% CI, from 32 fewer to 22 fewer) per 1000 patients (very low-certainty evidence) (94, 95, 98), but the evidence is very uncertain. Data from the single RCT demonstrated that computerized glycemic management programs likely led to more TIR (glucose 60 to 180 mg/dL [3.3 to 10.0 mmol/L]) (MD 3.30; 95% CI, 3.22 to 3.38) compared with those randomly assigned to standard of care (moderate-certainty evidence) (100). The evidence suggests there were no differences in total number of episodes of glucose less than 70 mg/dL (3.9 mmol/L) or less than 54 mg/dL (3.0 mmol/L), and no difference was found in mortality, although these data were of very-low certainty (96, 97, 99, 100).

Other Evidence-to-Decision Criteria and Considerations

The panel members determined that this recommendation addressed a high-priority problem—that of inpatient hypoglycemia. Hypoglycemia is dangerous and costly as well as associated with significant adverse outcomes and increased hospital length of stay (LOS) with poor recovery and increased mortality (101–104). Patients who are admitted to the hospital often have IAH and may have acute medical conditions or require therapeutics that further impair hypoglycemia awareness (101). The panel noted that the Centers for Medicaid and Medicare (CMS) will include hypoglycemia as a priority quality measure in the inpatient setting beginning in 2023, with potential financial penalties for institutions with excessive rates of hypoglycemia.

The panel appreciated that the inpatient setting includes a very heterogeneous population at risk for hypoglycemia but agreed that all patients and HCPs would value hypoglycemia avoidance and its complications. They noted that patients and their caregivers in the hospital are often fearful of iatrogenic hypoglycemia and value its reduction (105, 106). The panel also appreciated that computerized glycemic surveillance and management programs can be very costly with high resource requirements. Staff training can be very time-intensive, and repeated education is required. For an inpatient glycemic surveillance and management program to work well, there must be integration between glucometers throughout the hospital, the main laboratory, and the EHR, so that daily reports can be easily created and made available to hospital staff. Staff must be trained to interpret and troubleshoot the program, and nursing staff and other clinical staff must be trained in how to make pertinent clinical management changes in a timely manner based on review of data received. These requirements may be very difficult to satisfy for a smaller hospital system with fewer resources and a lower volume of patients with diabetes. However, the panel felt that if the intervention led to substantial reductions in hypoglycemia episodes and hospital LOS, costs may overall balance out (107–109). The panel also noted that inpatient hyperglycemia and its management can predispose patients to developing hypoglycemia and noted that hyperglycemia and hypoglycemia should preferably be addressed using the same glycemic surveillance and management program.

The staff involved in such a program may depend on the type of hospital, and may include diabetes educators, nurses, pharmacists, and advanced practitioners including nurse practitioners and physician assistants/associates. The panel raised concerns about equity, and as mentioned, while most hospital systems have basic standardized protocols geared toward treating hypoglycemia, not all systems have the resources to purchase and use a computerized glycemic surveillance and management program. The panel is hopeful that hospital systems will prioritize funding for such programs once inpatient

Table 5. Currently available insulin preparations

Preparations	Currently available
Prandial or correctional insulin preparations	
Very rapid-acting insulins	Faster aspart
	Lispro-aabc
Rapid-acting insulins	Aspart
	Glulisine
	Lispro[a]
Short-acting insulin	Regular insulin
Basal insulin preparations	
Intermediate-acting insulin	NPH
Long-acting insulins	Glargine[b]
	Detemir
	Degludec[a]

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Abbreviation: NPH, neutral protamine Hagedorn.
[a]Available in U100 and U200 preparations.
[b]Available in U100 and U300 preparations.

hypoglycemia becomes one of the electronic clinical quality measures that hospitals can choose for reporting to CMS.

Justification for the Recommendation

The panel agreed that the high-value desirable anticipated effects of using an inpatient glycemic surveillance and management program that leverages EHR data to rapidly identify and reduce hypoglycemia in hospitalized patients warranted a strong recommendation, although they acknowledged this was based on very low-certainty evidence. The panel determined that cost and hospital personnel time considerations were the primary concerns regarding the use of such a program and noted that costs and benefits may differ in different health care settings. However, the panel noted that the anticipated substantial reductions in inpatient hypoglycemia would lead to overall reductions in costly hospital LOS and hypoglycemia-related adverse effects.

Research Considerations

The importance of reducing hypoglycemia in the inpatient setting in at-risk patients by using inpatient glycemic management programs emphasizes the need for further research. Proposed areas for future research include the following:

1. Implementing methods for inpatient glycemic surveillance and management programs, including integrating CGM data into EHR
2. Evaluating inpatient glycemic surveillance and management programs to better define appropriate quality measures

Question 7. Should long-acting insulin analogs vs human insulin be used for people on basal insulin therapy who are at high risk for hypoglycemia?

Background

Insulin-related hypoglycemia is common, leading to an estimated 100 000 annual emergency room visits in the United States alone (110). Everyone with T1D, and an estimated 20% to 30% of individuals with T2D, will require insulin management during the course of their lifetime, and the majority of these individuals will require basal insulin therapy (111). With the global increases in prevalence both of T1D and T2D, it is expected that the percentage of individuals with diabetes using basal insulin will increase in the coming years. Any therapeutic intervention that may reduce an individual's risk for hypoglycemia should be a priority. This question addresses whether long-acting insulin analogs have advantages over human neutral protamine Hagedorn (NPH) insulin with respect to reducing hypoglycemia in individuals with diabetes at high risk for hypoglycemia (Table 5).

Recommendation 7

We suggest long-acting insulin analogs be used rather than human neutral protamine Hagedorn (NPH) insulin for adult and pediatric outpatients on basal insulin therapy who are at high risk for hypoglycemia. (2⊕OOO)

Remarks

- Patients who are at high risk for hypoglycemia are defined as those with a history of severe hypoglycemia (requiring assistance to manage), impaired awareness of hypoglycemia (IAH), and/or medical conditions that predispose them to severe hypoglycemia including renal and hepatic dysfunction.
- The panel placed high value on reducing severe hypoglycemia and found moderate-certainty evidence for severe hypoglycemia reduction as an outcome in those using long-acting analog insulins vs NPH insulin. However, the panel acknowledges that most studies of long-acting analog insulins do not assess for significant adverse effects (including cardiovascular outcomes) and that many studies were designed to demonstrate noninferiority of analog insulin compared with human NPH insulin.

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/JvDJ63I_Who.

Benefits and Harms

The SR identified 41 RCTs that compared long-acting insulin analogs with NPH insulin and that addressed this question (41). The use of long-acting insulin analogs likely results in a lower proportion of patients with mild-to-moderate hypoglycemia (OR 0.79; 95% CI, 0.66 to 0.96), corresponding to 57 fewer patients per 1000 (95% CI, 102 fewer to 10 fewer), compared with human NPH insulin (moderate-certainty evidence) (113–118). Long-acting insulin analogs also likely result in a lower proportion of patients with severe hypoglycemia (OR 0.71; 95% CI, 0.59 to 0.85), corresponding to 27 fewer patients per 1000 (95% CI, 38 fewer to 14 fewer) (moderate-certainty evidence) (114–116, 118–136). Long-acting analogs may result in more TIR (defined as glucose 70-180 mg/dL [3.9 to 10.0 mmol/L]) (MD 7.10; 95% CI, 3.57 to 10.53; low-

certainty evidence) (137, 138). Those taking long-acting insulin analogs may have a lower HbA$_{1c}$ compared with those taking human NPH insulin (MD −0.14; 95% CI, −0.24 to −0.04; low-certainty evidence) when comparing values at follow-up (113–121, 123, 126, 128, 129, 132, 133, 135–149). Long-acting insulin analogs may also result in a lower HbA$_{1c}$ compared with human NPH insulin when comparing values to baseline (MD −0.10; 95% CI, −0.19 to −0.01; low-certainty evidence) (113–121, 123, 125–130, 132–151). Of note, the panel placed a high value on the reduction of severe hypoglycemia as an outcome and noted that the hypoglycemia associated with basal insulin often occurs at night, a particularly worrisome event for patients. Also, analog insulins are longer acting and can often be dosed once per day, and flexibility in timing of dosing may be preferred by patients. The panel also noted that older studies included in the SR may have had different definitions for severe hypoglycemia and varying use (or no use) of CGM.

The evidence suggests there were no differences between those patients taking long-acting insulin analogs compared with those taking human NPH insulin with respect to asymptomatic hypoglycemia, glucose less than 70 mg/dL (3.9 mmol/L) regardless of symptoms, episodes of severe hypoglycemia, percentage of time spent below 70 mg/dL (3.9 mmol/L), episodes of seizures or loss of consciousness, patients with MI or stroke, and mortality; however, the evidence for these outcomes was low or very-low certainty (41). The panel noted that most studies were of short duration (less than 1 year) and that adverse event outcomes including MI, seizure, stroke, and death were rare, and thus placed lower value on these outcomes. The panel also noted that most trials of longer duration that included severe hypoglycemia as an outcome were not designed to capture these rare adverse events and that original studies were designed as noninferiority trials for drug approval.

Other Evidence-to-Decision Criteria and Considerations

The panel placed high value on reducing hypoglycemia, noting that hypoglycemia leads to individuals with diabetes (and parents of children with T1D) feeling fearful, which affects their daily lives and potentially leads to medication nonadherence. Individuals with diabetes experiencing more significant symptoms of hypoglycemia report having poorer medication adherence and are more likely to report being less satisfied with their medical care (152). Further, hypoglycemia often leads to changes in an individual's social functioning and may be associated with increased absenteeism from work (153). However, not all people have the same degree of concern regarding hypoglycemia, especially mild-to-moderate hypoglycemia. This variability in how individuals tolerate hypoglycemia may affect their opinions regarding the use of analog vs human NPH basal insulin. Specifically, if individuals are more willing to tolerate hypoglycemia, they may not be more willing to pay more for more costly analog insulins.

Long-acting analog basal insulins may be cost-effective for individuals with T1D or T2D, but this is likely dependent on patient characteristics as well as specific analog insulin characteristics. The panel noted that the long-term costs of hypoglycemia are not insignificant in relation to the costs of long-acting insulin analogs. By reducing the risk for severe hypoglycemia, insulin analogs may reduce costly ED visits and hospitalizations (154). Reductions in hypoglycemia associated with insulin analogs may also encourage insulin adherence, with resulting reductions in expensive comorbid complications of diabetes. Data from retrospective analyses conducted in the United States, Canada, and Europe have demonstrated that analog basal insulins are cost-effective when assessed by cost per quality-adjusted life year (QALY) (154–160). These studies included people with T1D and T2D. However, not all cost-effectiveness analyses have been in favor of analog basal insulins, with SRs showing considerable variation in cost-effectiveness between studies (161–163). It is important to note that more information is needed regarding the cost-effectiveness of the newer long-acting analog basal insulins, including U300 glargine and insulin degludec, as most studies available compare these newer insulins to other available analog insulins (eg, glargine and detemir) and not to human NPH insulin (Table 5).

The panel recognized that individuals' socioeconomic status would affect their ability to pay for analog insulins, which are more expensive than human NPH insulin. For those who do not have health insurance or are underinsured, costs for analog insulins may be substantial. Also, access to analog insulins may vary in different health care settings, including in international settings. The panel acknowledged that this is a rapidly changing issue, as less expensive biosimilar insulins are now readily available (164, 165).

Justification for the Recommendation

The panel felt that if cost were not a consideration, long-acting basal analog insulins would be preferred by most people with diabetes and their HCPs given their association with less severe hypoglycemia and favorable pharmacodynamic characteristics. However, insulin analogs may not be acceptable to health systems (including insurance companies) given costs. Nevertheless, there are potential cost-savings downstream including expected reductions in health care usage (related to hypoglycemia and diabetes comorbidities), given improved medication adherence and improved glucose control. The panel noted that in pediatric populations the standard of care for individuals using MDIs to manage their diabetes is to use a once-daily long-acting analog for basal insulin. NPH insulin requires at least twice daily dosing, (some intensive regimens use 3 NPH doses daily), which is generally not preferred by those with diabetes or their caregivers.

The panel placed high value on reducing severe hypoglycemia and found moderate-certainty evidence for severe hypoglycemia reduction as an outcome in those using long-acting insulin analogs vs human NPH insulin. However, the panel acknowledged that most studies of long-acting insulin analogs did not assess for significant adverse events (including cardiovascular outcomes), and that many studies were designed to demonstrate noninferiority of analog insulin compared with human NPH insulin. The panel also noted that there may be individuals for whom NPH insulin is preferred because of its pharmacokinetic profile. This includes individuals taking glucocorticoids and those using enteral feeding.

The panel determined that cost considerations were the primary concern regarding the use of insulin analogs, especially in underinsured and uninsured people in the United States. They acknowledged that this may differ by country. The panel felt that acceptability favored long-acting insulin analogs given their ease of use (ie, once-daily dosing).

Research Considerations

The importance of reducing hypoglycemia via the use of long-acting insulin analogs emphasizes the need for further research. Proposed areas for future research include the following:

1. Analyzing TIR using real-time CGM to determine a more accurate incidence of hypoglycemia
2. Evaluating the rates of hypoglycemia with newer long-acting analog insulins, including biosimilar insulins
3. Evaluating costs and cost-effectiveness of different insulins

Question 8. Should rapid-acting analogs vs regular (short-acting) human insulin be used for people on basal-bolus therapy who are at high risk for hypoglycemia?

Background

Hypoglycemia is common, affecting almost two-thirds of people with diabetes, with an additional 7.5% reporting severe hypoglycemia (166). Individuals reporting severe hypoglycemia are more than 3 times more likely to die within 5 years compared with those without severe hypoglycemia (95% CI, 1.5 to 7.4; $P = .005$). Hypoglycemia is also associated with increased diabetes-related distress and affects the ability to work and medication adherence. Interventions that reduce the occurrence of and risk for hypoglycemia should be prioritized. This question addressed whether rapid-acting insulin analogs have advantages over human regular (short-acting) insulin with respect to reducing hypoglycemia in those who are at high risk for low blood glucose levels (Table 5).

Recommendation 8

We suggest that rapid-acting insulin analogs be used rather than regular (short-acting) human insulins for adult and pediatric patients on basal-bolus insulin therapy who are at high risk for hypoglycemia. (2⊕OOO)

Remarks

- Patients who are at high risk for hypoglycemia are defined as those with a history of severe hypoglycemia (requiring assistance to manage), impaired awareness of hypoglycemia (IAH), and/or medical conditions that predispose them to severe hypoglycemia including renal and hepatic dysfunction.
- The panel placed high value on reducing severe hypoglycemia and found moderate-certainty evidence for reduction of mild-to-moderate and severe hypoglycemia as an outcome in those using rapid-acting analog insulins vs regular (short-acting) insulin. However, the panel acknowledges that many studies were designed to demonstrate noninferiority of analog insulin compared with human regular (short-acting) insulin. Also, many of the data available for review demonstrating reductions in hypoglycemia were in adults with type 1 diabetes (T1D); very few data were available regarding the pediatric population.

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/jBgJgTG5VlQ.

Benefits and Harms

The SR identified 50 RCTs that compared rapid-acting insulin analogs with regular (short-acting) insulin and addressed this question (41). The use of rapid-acting insulin analogs likely results in fewer episodes of severe hypoglycemia (IRR 0.74; 95% CI, 0.65 to 0.86) compared with human insulin (moderate-certainty evidence) (145, 167–180). Rapid-acting insulin analogs may result in lower values of HbA_{1c} at follow-up when compared with human insulin (when studied < 3 years) (MD −0.08; 95% CI, −0.13 to −0.03) (low-certainty evidence), though the difference was of limited clinical relevance, and there were serious concerns regarding risk of bias and inconsistency of results between the trials (114, 119, 145, 167–172, 174, 176–205).

Of note, rapid-acting insulin analogs likely result in more patients having mild-to-moderate hypoglycemia (defined as glucose less than 70 mg/dL [3.9 mmol/L]) compared with those taking human insulin (OR 1.33; 95% CI, 1.09 to 1.61) (moderate-certainty evidence) (174, 180, 186, 198, 206). This difference corresponded to 59 more patients (95% CI, from 19 more to 94 more) per 1000 patients using rapid-acting analog insulin having mild-to-moderate hypoglycemia compared with those patients using human insulin. The panel noted that many people with diabetes taking insulin are most concerned about severe hypoglycemia but viewed mild-to-moderate hypoglycemia as a necessary and acceptable risk to maintain desirable control of glycemia.

The evidence suggests there were no differences between those patients taking rapid-acting insulin analogs compared with those taking human insulin with respect to episodes of glucose less than 50 mg/dL (2.8 mmol/L), mild-to-moderate hypoglycemia, patients with asymptomatic hypoglycemia, symptomatic hypoglycemia, episodes of symptomatic hypoglycemia, patients with glucose less than 70 mg/dL (3.9 mmol/L) regardless of symptoms, patients with severe hypoglycemia, patients in a coma, and mortality, but the available evidence for these outcomes was of low or very-low certainty (41).

Other Evidence-to-Decision Criteria and Considerations

The panel members determined that this recommendation addressed a high-value issue for people with diabetes—that of insulin-related hypoglycemia in individuals taking rapid-acting or human short-acting insulin. Those with diabetes experiencing more significant symptoms of hypoglycemia report having poorer diabetes medication adherence and are also more likely to miss work (152, 153). However, the panel also acknowledged that ability to tolerate symptomatic hypoglycemia likely differs among people with diabetes, and that individuals may also differ in their ability to tolerate the consequences of hypoglycemia (eg, some may be more willing to accept mild-to-moderate hypoglycemia if it means they will achieve a HbA_{1c} closer to their target, while others, such as the parents of young children, may be less willing to tolerate any degree of hypoglycemia).

The panel also acknowledged that the costs of using rapid-acting insulin analog vs human insulin will depend on

several patient-related factors, including their insurance status and economic stability (employment, income, expenses, etc). Rapid-acting insulin analogs may be cost prohibitive in uninsured and underinsured populations. Nevertheless, the panel felt that, especially when considering costs at a population-level, with reductions in the costs related to treating episodes of severe hypoglycemia (eg, ED visits and hospitalizations), rapid-acting insulin may be more cost-effective in those with both T1D and T2D when compared with human insulin and reviewed supportive data. The panel noted that individuals with diabetes are often afraid to initiate or adjust insulin therapy given concerns regarding hypoglycemia, which can lead to the development of costly comorbid complications with associated hospital visits (154). The fewer hypoglycemic events described with analog insulins may be associated with more insulin adherence, which would be cost-saving in the long term. Data from Canada, Japan, and Europe have demonstrated that rapid-acting insulin analogs are often cost-effective when compared with regular insulin, although there was considerable variability in cost savings in these studies, including differences based on type of diabetes (T1D or T2D) and type of rapid-acting analog insulin (insulin aspart vs insulin lispro) (161, 207–209). For example, in a study evaluating the cost-effectiveness of rapid-acting insulin analogs in Canada, the authors found that insulin aspart was cost-effective compared with regular insulin, but only in those with T1D, and the study found that insulin lispro was not cost-effective in patients with either T1D or T2D (161). In a separate study evaluating the cost-effectiveness of insulin aspart in different European countries in individuals with T2D, the authors found substantial variability in cost savings, with insulin aspart being cost-effective in Sweden and Spain but not Italy or Poland (209). The panel also highlighted that more low-cost options are being made available for rapid-acting insulin analogs and that studies evaluating the cost-effectiveness of these new insulins, as well as some of the new faster-acting insulin analogs (eg, faster-acting insulin aspart and insulin lispro-aabc), are needed.

Although the panel could not find specific clinical trials evaluating analog insulins and their effect on health equity, a number of reviews exist that discuss this topic more generally (164, 165). The panel noted that the higher out-of-pocket costs of rapid-acting insulin analogs would have significant effects for the underinsured and uninsured in the United States as well as in underserved populations in other countries. The panel noted opportunities to increase health equity globally with expanded medical insurance to individuals in need and with improved coverage for insulin analogs.

The panel noted that individuals may find paying for rapid-acting insulin analogs more acceptable if they are associated with both lower risks for nocturnal hypoglycemia and less insulin-associated weight gain. The panel also noted that individuals may be more willing to use rapid-acting insulin analogs given their improved pharmacodynamic profiles, specifically their more physiologic (and thus healthful) onset and offset of action compared with human insulin. The panel felt that physicians and other HCPs would likely accept higher costs of analog insulins if they were more effective in reducing hypoglycemia, but that health systems (including health insurance companies, hospital formularies, etc) might not find these costs to be acceptable.

Justification for the Recommendation

The panel agreed that, based on very low-certainty evidence, the use of rapid-acting insulin analogs be used rather than regular insulin for adult and pediatric individuals with diabetes on basal-bolus insulin therapy who are at high risk for hypoglycemia. The panel placed high value on reducing severe hypoglycemia and found moderate-certainty evidence for mild-to-moderate and severe hypoglycemia reduction as an outcome in those using rapid-acting insulin analogs vs human insulin. However, the panel acknowledged that many of the studies included in their review were designed to demonstrate noninferiority of analog insulins compared with human insulin, that many of the data available for review demonstrating reductions in hypoglycemia were in individuals with T1D, and that very few data were available regarding pediatric populations. The panel inferred that those with T2D would equally benefit from the reduction in hypoglycemia seen in those with T1D. The panel also noted that the standard of care for children and adolescents using multiple injections of insulin is for the use of rapid-acting insulin analogs rather than human regular insulin. The panel determined that cost considerations were the primary concern regarding the use of insulin analogs, especially in the underinsured and uninsured individuals in the United States and acknowledged that this may differ by country.

Research Considerations

The importance of reducing hypoglycemia via the use of rapid-acting insulin analogs emphasizes the need for further research. Proposed areas for future research include the following:

1. Analyzing glucose TIR using real-time CGM to help determine the true incidence of hypoglycemia
2. Evaluating rates of hypoglycemia and cost-effectiveness with newer rapid-acting analog insulins, including biosimilar insulins
3. Evaluating rapid-acting insulin analogs in pediatric populations and in people with T2D (the panel noted that, although additional trials may be difficult as rapid-acting insulin analogs are already FDA approved, these trials are needed)

Question 9. Should a structured program of patient education with follow-up vs unstructured advice be used for people receiving insulin therapy who are at high risk of hypoglycemia?

Background

Most people receiving insulin therapy are at risk for hypoglycemia. As a result of repeated hypoglycemia, they are at high risk for IAH and hypoglycemia-associated autonomic failure. Studies using CGM both in T1D and T2D have identified that serious hypoglycemia occurs in many individuals with diabetes. In 6 studies including individuals with T1D, most participants had serious hypoglycemia, with a majority having multiple episodes per week, including episodes that were not associated with symptoms (2, 33, 39, 210–212). Studies of people with T2D have also demonstrated that hypoglycemia is common, especially in those who are taking insulin (213–215). Studies have identified level 2 hypoglycemia in patients both with good and poor glycemic control and in patients both with T2D and renal dysfunction (Table 2). Studies in which a structured program of patient education aimed to

help individuals at high risk for hypoglycemia have demonstrated both reductions in the frequency of hypoglycemia and a 30% improvement in the recognition of hypoglycemia symptoms ([216], [217]). Given the high costs and morbidity associated with hypoglycemia, an educational program that helps to reduce hypoglycemia favorably affects patient care.

Recommendation 9

We recommend that a structured program of patient education over unstructured advice be used for adult and pediatric outpatients with type 1 diabetes (T1D) or type 2 diabetes (T2D) receiving insulin therapy. (1⊕⊕OO)

Remarks

- Structured education on how to avoid repeated hypoglycemia is critical, and this education should be performed by experienced diabetes clinicians. Moreover, insurance coverage for education should be available for all insulin-using patients.
- The recommendation is not intended to limit structured education only to those on insulin therapy; for example, patients using sulfonylureas (SUs) and meglitinides are also at risk for hypoglycemia, and the recommendation also applies to this patient population.

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/7QaF1GWXxRg.

Benefits and Harms

The SR identified 19 studies, 10 RCTs, and 9 nonrandomized comparative trials that compared structured counseling vs no structured counseling ([41]). Participation in a structured program of patient education may reduce the number of episodes of severe hypoglycemia (OR 0.25; 95% CI, 0.13 to 0.47; low-certainty evidence) and HbA_{1c} at follow-up in randomized (MD −0.35; 95% CI, −0.50 to −0.20; moderate-certainty evidence) and nonrandomized studies (MD −0.34; 95% CI, −0.40 to −0.29; very low–certainty evidence). Structured educational programs may result in less percentage of time with glucose less than 54 mg/dL (3.0 mmol/L) (MD −2.8; 95% CI, −2.4 to −3.2; very low-certainty evidence), but the evidence is very uncertain. There may be no differences in the proportion of patients with glucose less than 70 mg/dL (3.9 mmol/L) or percentage of time spent in the 70 to 180 mg/dL (3.9 to 10.0 mmol/L) range or below 70 mg/dL (3.9 mmol/L) (low-certainty evidence). The evidence also suggests there were no differences found in the proportion of patients having severe hypoglycemia or death (very low-certainty evidence), but it is very uncertain. Overall, the panel felt there were moderate desirable effects favoring the intervention and trivial undesirable effects, which was the basis for the panel's strong recommendation despite low-certainty evidence, placing high value on the outcome of severe hypoglycemia, which was considered a life-threatening situation for people with diabetes.

Table 6. Elements for a structured diabetes education program in those at risk for hypoglycemia

Education should be provided by individuals with specific training in providing the program, including, but not limited to, diabetes educators, nurses, and dieticians.	
Education can be provided both in one-on-one and group sessions.	
The education program should include active, hands-on learning modalities, with discussions and exercises aimed at instructing participants in the risk factors associated with and management strategies for reducing and treating hypoglycemia.	
Key elements of the program	Avoiding delay of hypoglycemia treatment
	Knowing optimal treatments for hypoglycemia
	Recognizing individual's particular risk factors for hypoglycemia
	Improving individual's ability to recognize subtler symptoms of hypoglycemia
	Focusing on methods for reducing nocturnal hypoglycemia

Note: Structured diabetes education programs that teach the basics regarding insulin management and diet have been shown to improve HbA_{1c} while reducing severe hypoglycemia and also to reduce psychologic distress ([216], [219], [220]). Structured educational programs that focus on reducing hypoglycemia episodes by having participants focus on internal and external cues of hypoglycemia (eg, physical symptoms, mood changes, food intake, physical activity) have also been shown to reduce episodes of severe hypoglycemia and to improve awareness of hypoglycemia in those who have IAH ([221–225]).

Other Evidence-to-Decision Criteria and Considerations

The reduction of hypoglycemia was considered a high priority for individuals both with T1D and T2D; therefore, a structured diabetes education program that includes hypoglycemia and its prevention is a priority, especially for people with diabetes using insulin. The panel noted that reducing hypoglycemia is a high-value outcome, and experiencing hypoglycemia results in increased diabetes distress ([218]). The panel discussed that there may be variability in how people prioritize hypoglycemia relative to their personal glycemic targets. For example, some people with diabetes may accept hypoglycemia as a side effect of "tight" glycemia management, whereas others with IAH may not attribute their symptoms to hypoglycemia and feel they are able to remain functional even at low glucose levels. However, the panel agreed that hypoglycemia is always an unwanted outcome, and it should be avoided whenever possible in all people with diabetes.

The panel considered additional elements such as duration of the education program and number of educational sessions ([Table 6]). The type of education each individual receives should be personalized and based on their availability, and it should address language barriers and cultural components ([226–228]). The panel discussed the possible unintentional consequence of people with diabetes not receiving sufficient education and the effect of cost of education or insurance coverage limitations for these individuals ([229], [230]). The panel noted that, in the United States, accredited programs from the American Diabetes Association or the Association for Clinical Diabetes and Education Specialists allow institutions to receive reimbursement for the education services provided ([231]). The panel emphasized that structured diabetes education programs should be a continuum and that the individual's

needs should be reevaluated as their educational needs change over time. This would include the education needed to initiate technology associated with preventing hypoglycemia (eg, insulin pumps and CGMs).

The panel viewed the use of multiple educational formats as important, such as online tools, telehealth, on-demand tools, and interactive apps as options for structured programs, in addition to in-person classes, all with a goal of improving access. The panel felt it was particularly important to offer structured education during each patient life transition, such as from pediatric to young adult care or to older adult settings or based on clinical conditions (including those that increase risk for hypoglycemia such as liver or renal disease). In particular, for the pediatric population, the panel felt that implementation of a structured education program should allow for reeducating at appropriate developmental stages and especially in transition from pediatric to adult care (continuum of education program).

Justification for the Recommendation

Overall, the panel determined that these data supported a strong recommendation for structured education for reducing hypoglycemia for people both with T1D and with T2D, although this recommendation was based on low-certainty evidence. The evidence suggests structured education results in fewer episodes of severe hypoglycemia and better glycemic control and few undesirable effects. The panel felt that individuals with diabetes and their caregivers would strongly value the benefits seen with structured education.

Research Considerations

The importance of structured education about hypoglycemia in people with diabetes emphasizes the need for further research. Proposed areas for future research include the following:

1. Evaluating the benefits of structured education in patients with T2D who are receiving medications other than insulin that increase the risk for hypoglycemia (eg, SUs and meglitinides)
2. Comparing group vs individual structured education programs
3. Evaluating the effects of structured education programs for reducing hypoglycemia in diverse populations
4. Evaluating outcomes regarding who provides the education, duration of the education, virtual vs in-person programs, and involvement of patient partners and family in the education program

Question 10.   *Should glucagon preparations that do not have to be reconstituted vs preparations that do have to be reconstituted be used for people with severe hypoglycemia?*

Background

Severe hypoglycemia is a common acute complication of insulin therapy in individuals with T1D and T2D, and SUs and meglitinides used for the treatment of T2D can also cause severe hypoglycemia. Prolonged severe hypoglycemia is associated with neurologic and cardiovascular complications and may cause coma and death. Severe hypoglycemia is a frequent

Table 7. **Currently available glucagon preparations**

Glucagon: emergency kit, with powder and diluent   Nasal glucagon
Glucagon (stable liquid): autoinjector, prefilled syringe
Dasiglucagon: autoinjector, prefilled syringe

cause of costly ED visits and use of emergency medical services (EMS) [232–237]. Despite its well-established efficacy as the primary treatment for acute, severe hypoglycemia, glucagon is underprescribed and underutilized [238, 239]. Injectable glucagon can rapidly reverse hypoglycemia; however, prior to the advent of nasal and stable liquid glucagon preparations, glucagon administration required a multistep procedure to reconstitute lyophilized glucagon powder before it was injected. A consequence of this complex administration includes frequent failure to administer full therapeutic doses in treated patients. This leads to emergency medical treatment and/or admission to a hospital. The high rate of failure to administer the full, correct dose by untrained and even trained individuals makes this an exigent issue.

> ### Recommendation 10
>
> We recommend that glucagon preparations that do not have to be reconstituted over glucagon preparations that do have to be reconstituted (ie, available as a powder and diluent) be used for outpatients with severe hypoglycemia. (1⊕OOO)

Summary of Evidence

The EtD framework with a detailed summary of the evidence can be found online at https://guidelines.gradepro.org/profile/PsNW-5ankRw.

Benefits and Harms

The SR identified 7 RCTs and 2 nonrandomized pre-post studies that compared glucagon preparations that do not have to be reconstituted to glucagon preparations that do have to be reconstituted (Table 7). All RCTs were included in the meta-analysis, whereas the nonrandomized studies were reported narratively (41). Time to recovery from hypoglycemia may be longer with the preparations that did not require reconstitution (MD 2.22 minutes; 95% CI, 1.09 to 3.36; low-certainty evidence), whereas the proportion of patients who recovered from hypoglycemia and whose neuroglycopenic symptoms cleared may not be different (very low-certainty evidence), but the evidence is very uncertain. Nasal adverse events (IRR 5.51; 95% CI, 1.91 to 15.90; moderate-certainty evidence) and ophthalmologic adverse events (IRR 6.21; 95% CI, 1.84 to 20.91; moderate-certainty evidence) were likely more frequent with preparations that did not need to be reconstituted. Two studies reported that most patients (66.6% to 71.1%) recovered from a moderate hypoglycemic event 15 minutes after using nasal glucagon (low-certainty evidence) (240, 241).

Other Evidence-to-Decision Criteria and Considerations

The panel noted that hypoglycemia and the use of glucagon are priorities for all individuals with diabetes who are at risk for hypoglycemia, as hypoglycemia is common and costly. Ease of glucagon administration is important because family and friends are typically who administers the glucagon. Newer glucagon preparations can be easily delivered by the intranasal route or by autoinjectors with stable glucagon that are easy and intuitive to administer, and education of family, friends, and colleagues in how to administer the glucagon is critical.

All the available glucagon formulations have roughly equivalent efficacy (if properly administered) and there are only insignificant differences with respect to adverse effects and cost. Panel members placed a very high value on the availability and use of readily administered glucagon by trained or untrained bystanders.

Studies were conducted in a controlled clinical setting in which mild-to-moderate hypoglycemia was induced and glucagon was administered by a nurse, which is an indirect setting for outpatient use. The panel noted that this setting would not be representative of the real world in which severe hypoglycemia necessitating glucagon administration occurs spontaneously and often during the night. Glucagon is typically administered by a nontrained family member or other third party in a stressful, high-anxiety state.

The panel evaluated potential cost savings associated with newer glucagon formulations. A cost-effective modeling study suggested that nasal glucagon would reduce the costs associated with treating episodes of severe hypoglycemia (242). A second modeling study found that stable liquid glucagon rescue pens and prefilled syringes were predicted to be associated with significant annual cost savings (243).

The panel placed high value on ease of glucagon administration. Studies of nasal glucagon have shown that caregivers find it easy to administer and that it is less intimidating than injectable glucagon both in adult and pediatric populations (240, 241, 244). Studies evaluating the use of glucagon autoinjectors have also shown them to be easier to use than traditional glucagon formulations that require reconstitution (245, 246).

The panel highlighted implementation considerations for pediatric populations, as nasal glucagon is approved for ages 4 years and older, dasiglucagon (stable liquid glucagon) has FDA approval for ages 6 years and older, and liquid stable glucagon is approved for ages 2 years and older. This relates to the age of children included in the trials that led to FDA approval. The clinician managing a child with T1D younger than age 6 years must decide whether to use standard glucagon or prescribe a newer formulation off label.

Justification for the Recommendation

The panel justified a strong recommendation despite the low quality of evidence, based on the recognition that severe hypoglycemia is a major life-threatening concern for individuals with diabetes and for their family members. The benefits of a rapid treatment that is intuitive and easy to use is felt to be a critical resource for family members and others who will typically use such treatment. The panel discussed that there was noninferiority between those forms of glucagon requiring reconstitution and those not requiring reconstitution, with negligible differences in desirable effects. Noninferiority, however, is relevant only once the glucagon is given in full dosage.

Implementation Considerations

- Glucagon preparations that do not have to be reconstituted should be prescribed for all patients with diabetes who use insulin or insulin secretagogues (SUs, meglitinides).
- Family members, coworkers, friends, roommates, school personnel, coaches, etc should be instructed on when and how to administer glucagon.
- When glucagon preparations that do not have to be reconstituted are not available, family members, coworkers, friends, roommates, school personnel, coaches, etc should be instructed on when and how to administer those glucagon preparations that require reconstitution.
- Ready-to-use glucagon formulations should be available for use by EMS and in medical offices, schools, airports, and other pertinent locations.

Research Consideration

The importance of treating acute severe hypoglycemia with glucagon emphasizes the need for further research. A proposed area for future research is analyzing how often new glucagon preparations are used and their effect on resource utilization (eg, EMS, hospitalization, and evaluation of potential savings).

Methods of Development of Evidence-Based Clinical Practice Guidelines

This guideline was developed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (247). A detailed description of the Endocrine Society guideline development program can be found online at https://www.endocrine.org/clinical-practice-guidelines/methodology. This methodology includes the use of EtD frameworks to ensure all important criteria are considered when making recommendations (248, 249). The process was facilitated by the GRADEpro Guideline Development Tool (GRADEpro GDT) (250). This GDP consisted of 7 content experts representing the following specialties: endocrinology, pediatric endocrinology, hospital medicine, and pharmacy. A patient representative was also included on the panel. Members were identified by the Endocrine Society Board of Directors and the Clinical Guidelines Committee (CGC) and were vetted according to the conflict-of-interest policy for clinical practice guidelines, which can be found online at: https://www.endocrine.org/-/media/endocrine/files/cpg/methodology-page-refresh/conflict_of_interest_cpg_final.pdf (251). This was adhered to throughout the guideline process to manage and mitigate conflicts of interest. Detailed disclosures of panel members and the management strategies implemented during the development process can be found in Appendix A. In addition, the group included a clinical practice guideline (CPG) methodologist from the Mayo Evidence-Based Practice Center, who led the team that conducted the SRs and meta-analyses, and a methodologist from the McMaster University GRADE Centre, who advised on methodology and moderated the application of the EtD framework and development of the recommendations. All members of the GDP

Table 8. Grading of Recommendations Assessment, Development and Evaluation classification of guideline recommendations

Certainty of evidence	Interpretation
High⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate⊕⊕⊕O	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low⊕⊕OO	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low⊕OOO	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Source: Reprinted with permission from Schünemann HJ, Brożek J, Guyatt GH, Oxman AD. GRADE Handbook. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. https://gdt.gradepro.org/app/handbook/handbook.html#h.9rdbelsnu4iy. Accessed March 2, 2022 (255).

underwent training in guideline participation and GRADE methods led by MacGRADE Centre methodologists and informed by the Guideline Participant Tool (252).

GDP members were assigned to lead support to the SR team and present evidence to the GDP for each guideline question. The questions addressed in this guideline were prioritized from an extensive list of potential questions through a survey and discussion; 10 questions were identified as most important. The Mayo Evidence-Based Practice Center conducted a systematic review for each question and produced GRADE evidence profiles that summarized the body of evidence for each question

and the certainty of the evidence (41). The systematic searches for evidence were conducted on July 2020 and updated in April 2022. In parallel to the development of the evidence summaries, the GDP members searched for and summarized research evidence for other EtD criteria, such as patients' values and preferences, feasibility, acceptability, costs/resource use, cost-effectiveness, and health equity. Research evidence summaries noted in the EtD frameworks were compiled using standardized terminology templates for clarity and consistency (253). During a series of video conferences, the GDP judged the balance of benefits and harms, in addition to the other EtD criteria, to determine the direction and strength of the recommendation (Tables 8 and 9) (253, 254).

The draft recommendations were posted publicly for external peer review and were reviewed internally by Endocrine Society members, the Society's CGC, representatives of any cosponsoring organizations, a representative of the board of directors, and an expert reviewer. Revisions to the guideline were made based on submitted comments and approved by the CGC, the expert reviewer, and the board of directors. Finally, the guideline manuscript was reviewed before publication by the *Journal of Clinical Endocrinology and Metabolism*'s publisher's reviewer.

This guideline will be reviewed annually to assess the state of the evidence and determine if there are any developments that would warrant an update to the guideline.

Acknowledgments

Table 9. Grading of Recommendations Assessment, Development and Evaluation strength of recommendation classifications and interpretation

Strength of recommendation	Criteria	Interpretation by patients	Interpretation by health care providers	Interpretation by policy makers
1—Strong recommendation for or against	Desirable consequences CLEARLY OUTWEIGH the undesirable consequences in most settings (or vice versa)	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
2—Conditional recommendation for or against	Desirable consequences PROBABLY OUTWEIGH undesirable consequences in most settings (or vice versa)	The majority of individuals in this situation would want the suggested course of action, but many would not.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.

Source: Data from Schünemann HJ, et al. *Blood Adv.* 2018, Nov 27;2(22):3198–3225 (256).

Appendix A. Guideline Development Panel (GDP) makeup, roles, conflicts, and management plans

Role	Name	Relevant COI?	Representative
Chair	Anthony McCall	No	
Co-Chair	David Lieb	No	AACE
Members			
	Roma Gianchandani	No	
	Heide MacMaster	No	
	Gregory Maynard	No	SHM
	Elizabeth Seaquist	Yes	ADA
	Joseph Wolfsdorf	Yes	PES
	Robin Fein Wright	No	
Methodologists	M. Hassan Murad	No	
	Wojtek Wiercioch	No	

Disclaimer

The Endocrine Society's clinical practice guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The guidelines should not be considered as an all-encompassing approach to patient care and not inclusive of all proper approaches or methods, or exclusive of others.

Summary

- Total number of GDP members = 10
- Percentage of total GDP members with relevant (or potentially relevant) COI = 20%

Individual Disclosures, Conflicts, and Management Strategies

Chairs

Chair: Anthony L. McCall, MD, PhD
Cornell University, NY, USA
Expertise: Adult endocrinology

The guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances. THE ENDOCRINE SOCIETY MAKES EVERY EFFORT TO PRESENT ACCURATE AND RELIABLE INFORMATION. THIS PUBLICATION IS PROVIDED "AS IS" AND THE SOCIETY MAKES NO WARRANTY, EXPRESS OR IMPLIED, REGARDING THE ACCURACY AND RELIABILITY OF THESE GUIDELINES AND SPECIFICALLY EXCLUDES ANY WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR USE OR PURPOSE, TITLE, OR NONINFRINGEMENT OF THIRD PARTY RIGHTS. THE SOCIETY, ITS OFFICERS, DIRECTORS, MEMBERS, EMPLOYEES, AND AGENTS SHALL NOT BE LIABLE FOR DIRECT, INDIRECT, SPECIAL, INCIDENTAL, OR CONSEQUENTIAL DAMAGES, INCLUDING THE INTERRUPTION OF BUSINESS, LOSS OF PROFITS, OR OTHER MONETARY DAMAGES, REGARDLESS OF WHETHER SUCH DAMAGES COULD HAVE BEEN FORESEEN OR PREVENTED, RELATED TO THIS PUBLICATION OR THE USE OF OR RELIANCE ON THE INFORMATION CONTAINED HEREIN.

Disclosures (2019-2022):

- National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases: Primary Investigator for study on diabetes disparities
- Endocrine Society: Editorial Board (no compensation)

Open Payments Database: https://openpayments data.cms.gov/physician/478255

Assessment and Management

- No relevant conflicts in 12 months prior to selection.

- On reassessment in 2020, Dr McCall had an Open Payments database entry for 2019 from Eli Lilly for $4820 Associated Research Funding payment made to UVA on March 27, 2019 re Trulicity ("The effect of dulaglutide on major cardiovascular events in patients with type 2 diabetes—researching cardiovascular events with a weekly incretin in diabetes—REWIND"). Lilly terminated this study circa 2013, when Dr McCall was still at University of Virginia. Thus, Dr McCall was not site principal investigator (PI) for this study after 2013. Lilly temporarily reopened the study circa 2019 (after Dr McCall had left University of Virginia) because it had not determined the long-term effects for recruited patients. The recruited patients were called and vital status was ascertained. UVA received a payment (as the study was in debt), which was attributed to Dr McCall. Dr McCall received no direct payments. It is difficult to construe this as a currently-relevant relationship. He continued as a conflict of interest (COI)-free member.
- No management required.

Co-Chair: David C. Lieb, MD
Eastern Virginia Medical School, VA, USA
Expertise: Adult endocrinology
Nominated by AACE

Disclosures (2019-2022):

- American Association of Clinical Endocrinology (AACE): Education Oversight Committee Chair; Vice Chair Annual Meeting; Clinical Congress Program Committee; Co-Chair Annual Meeting Abstract Section Subcommittee; Clinical Practice Guidelines Oversight Committee Member
- Association of Program Directors in Diabetes, Endocrinology and Metabolism (APDEM): Leadership Council Member
- Board of Directors for the Mid-Atlantic Society of Endocrinologists: Secretary, Treasurer (uncompensated)
- ACGME milestones working group: (costs of travel, lodging, dinner covered)
- ADA Hampton Roads: Leadership Board (no compensation)
- NovoNordisk (Novo Nordisk manufactures and markets Ozempic [semaglutide], Fiasp [insulin aspart], Victoza [liraglutide], Tresiba [insulin degludec], Levemir [insulin detemir], Xultophy [insulin degludec + liraglutide], Novolog [insulin aspart], NovoLog Mix 70/30 [insulin aspart protamine and insulin aspart], Novolin 70/30 [human NPH + regular insulin], Novolin N [human NPH insulin], Novolin R [human regular insulin], Prandin [repaglinide], and GlucaGen HypoKit [glucagon].): Site

Co-Investigator (no compensation)

Open Payments Database: https://openpayments data.cms.gov/physician/73782

Assessment and Management

- Dr Lieb's relationship with NovoNordisk relates to the SELECT trial, which involves Ozempic (semaglutide, Novo Nordisk) in a nondiabetic, obese population at high risk for cardiovascular outcomes. Dr Lieb's endocrine chief is site PI for the SELECT study at EVMS, and his endocrine chief's expectation is that faculty members would help perform examinations on potential participants, review study labs, etc. Because of this, Dr Lieb is listed as a site Co-I. He attended an investigator meeting that Novo held in Orlando, Florida, USA. To be a good divisional citizen, he would periodically conduct physical examinations, review labs, and obtain informed consents. However, Dr Lieb will not receive any payments or salary support for this, and he will not be acknowledged in any way for his participation. The GDP chairs and the CGC chair judged this to be a nonrelevant relationship and concluded that Dr Lieb could still participate as a COI-free member.
- No industry relationships relevant to this CPG.
- No management required.

Roma Gianchandani, MD
University of Michigan, MI, USA
Expertise: Adult endocrinology

Disclosures (2019-2022):

- Biomed Central Editorial Board

Open Payments Database: https://openpayments data.cms.gov/physician/371886

Assessment and Management:

- No industry relationships relevant to this CPG.
- No management required.

Heidemarie MacMaster, PharmD, CDE
Lahey Clinic, MA, USA
Expertise: Clinical pharmacy, diabetes education

Disclosures (2019-2022):

- American Diabetes Association: Member
- American Association of Diabetes Educators: Member
- American College of Clinical Pharmacy/Endocrine Subcommittee: Member

- Massachusetts College of Pharmacy: volunteer faculty

Open Payments Database: N/A

Assessment and Management:

- No industry relationships relevant to this CPG.
- No management required.

Gregory A. Maynard, MD, MS, MHM
UC Davis, CA, USA
Expertise: General internal medicine (hospitalist)
Nominated by Society of Hospital Medicine

Disclosures (2019-2022):

- Society of Hospital Medicine and Professional Society for Hospitalists: Consultant on glycemic control and glucometrics
- Arjo Inc: Consultant

Open Payments Database: https://openpayments data.cms.gov/physician/1140413

Assessment and Management:

- No industry relationships relevant to this CPG.
- No management required.

M. Hassan Murad, MD
Mayo Clinic, MN, USA
Expertise: Clinical practice guideline methodology

Disclosures (2019-2022):

- Society for Vascular Surgery: methodology consultant
- American Society of Hematology: methodology consultant
- CHEST: methodology consultant
- World Health Organization: methodology consultant
- Evidence Foundation: board member

Open Payments Database: no entries

Assessment and Management:

- No industry relationships relevant to this CPG.
- No management required.

Elizabeth Seaquist, MD
University of Minnesota, MN, USA
Expertise: Adult endocrinology
Nominated by American Diabetes Association

Disclosures (2019-2022):

- ADA: Past President of Medicine and Science (2014), Advisor, Heritage Council, grant recipient, award recipient (Banting Medal for service)
- JDRF: (grant recipient and grant reviewer)
- Eli Lilly (Eli Lilly markets Baqsimi [glucagon], Basaglar [glargine insulin], Glucagon for injection, Glyxambi [empagliflozin/linagliptin], Humalog [lispro, 50/50, 75/25, U200], Humulin [R, N, U500, 70/30], Jardiance [empagliflozin], Jentadueto [linagliptin/metformin], Jentadueto XR [linagliptin/ metformin ER], Synjardy [empagliflozin/metformin], Synjardy XR [empagliflozin/metformin ER], Trajenta [linagliptin], Trulicity [dulaglitide].): Site PI on CVOT using dulaglutide; PI on investigator-initiated study using U500 insulin; site PI and consultant for study of nasal glucagon
- Eli Lilly Diabetes Care: Advisory Board
- Sanofi (Sanofi manufactures and markets Adlyxin [lixisenatide], Lantus [glargine], Toujeo [glargine U-300], Apidra [glulisine], Admelog [lispro], Siliqua [glargine + lixisenatide], Amaryl [glimepiride].): Leadership for educational event on diabetes and CVD
- Zucara Therapeutics (Zucara is developing a somatostatin type 2 receptor antagonist as a treatment for treated patients with DM.): Consultant (regarding a somatostatin agonist in development)
- Novo Nordisk (Novo Nordisk manufactures and markets Ozempic [semaglutide], Fiasp [insulin aspart], Victoza [liraglutide], Tresiba [insulin degludec], Levemir [insulin detemir], Xultophy [insulin degludec + liraglutide], Novolog [insulin aspart], NovoLog Mix 70/30 [insulin aspart protamine and insulin aspart], Novolin 70/30 [human NPH + regular insulin], Novolin N [human NPH insulin], Novolin R [human regular insulin], Prandin [repaglinide], and GlucaGen HypoKit [glucagon].): Advisor, International Hypoglycaemia Study Group member
- MannKind (MannKind markets Afrezza [inhaled insulin].): Advisor (related to Afrezza [inhaled insulin])
- National Institutes of Health: PI for brain glucose metabolism study
- George Washington University (subcontract of National Institutes of Health grant): PI for comparative effectiveness trial in diabetes
- Romania Diabetes Association: Speaker on hypoglycemia
- University of Colorado: Speaker on hypoglycemia
- University of Montreal: Speaker on brain glucose metabolism
- University of Toronto: Speaker on impaired awareness of hypoglycemia
- Six Degrees (From Dr Seaquist: "Six degrees is a firm that organizes medical meetings. They have been doing the administrative work for the International Hypoglycemia Study Group that now has morphed into an interest group at the European Association for the Study of Diabetes.

Table A PICO Questions Vis-a-Vis Potential WC Member Conflicts

PICO question	GDP members with potentially pertinent conflicts related to PICO
1. Should CGM vs SMBG be used for people with T1D receiving multiple daily injections?	None
2. Should real-time CGM and algorithm-driven insulin pumps vs multiple daily injections with SMBG 3 or more times daily be used for people with T1D?	None
3. Should professional or personal real time CGM vs no CGM be used for people with T2D in the outpatient setting who take insulin and/or SUs and are at risk for hypoglycemia?	None
4. Should initiation of CGM in the inpatient setting vs not using CGM be used for select people at high risk for hypoglycemia?	None
5. Should continuation of personal CGM in the inpatient setting vs discontinuation of CGM be used for people at high risk for hypoglycemia who are already using it?	None
6. Should inpatient glycemic surveillance and management programs leveraging EHR data vs standard care be used for hospitalized people at risk for hypoglycemia?	None
7. Should long-acting insulin analogs vs human insulin (NPH) be used for people on basal insulin therapy who are at high risk for hypoglycemia?	Seaquist
8. Should rapid-acting insulin analogs vs regular (short-acting) human insulin be used for people on basal bolus therapy who are at high risk for hypoglycemia?	Seaquist
9. Should a structured program of patient education with follow-up vs unstructured advice be used for people receiving insulin therapy and who are at high risk of hypoglycemia?	None
10. Should glucagon preparations that do not have to be reconstituted vs preparations that do have to be reconstituted be used for people with severe hypoglycemia?	Seaquist

In the past they were supported by an unrestricted educational grant to the University of Sheffield from Novo Nordisk, but now have several such grants from other partners. I don't remember all but I know Novo and Abbott contribute."): Speaker on hypoglycemia
- American Board of Internal Medicine (ABIM): Speaker on diabetes

Open Payments Database: https://openpayments data.cms.gov/physician/187760

Assessment and Management:

- Dr Seaquist has industry relationships relevant to this CPG.
- Dr Seaquist was allowed to participate in the GDP because she is a renowned expert in this area, and she was nominated by American Diabetes Association.
- Divestment: Dr Seaquist divested from the Eli Lilly Diabetes Care Advisory Board prior to CPG initiation and was not to speak on behalf of any pharmaceutical or technology companies or participate on any advisory boards at least until CPG publication.
- COI management: Dr Seaquist's industry relationships are relevant to various diabetes treatments, some of which may be associated with lower risk of hypoglycemia (Eli Lilly, Sanofi, Novo Nordisk, MannKind); and hypoglycemia treatments (glucagon [Lilly, Novo Nordisk], somatostatin type 2 receptor antagonist [Zucara]).
  - Dr Seaquist was not involved in systematic reviews for PICO questions directly related to the aforementioned considerations.

- Dr Seaquist was not involved in determining the strength and direction of a recommendation directly related to the aforementioned considerations.
- Dr Seaquist did not vote on matters directly related to the aforementioned considerations.
- Dr Seaquist did not draft guideline sections directly related to the aforementioned considerations.
- All GDP participants were made aware of Dr Seaquist's potentially relevant industry relationships.

Wojtek Wiercioch, MSc, PhD
McMaster University GRADE Centre, Hamilton, ONT, Canada
Expertise: Clinical practice guideline methodology

Disclosures (2019-2022): None

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No COI management required.

Joseph I. Wolfsdorf, MBBCh
Boston Children's Hospital/Harvard Medical School, Boston, MA, USA
Expertise: Pediatric endocrinology
Disclosures (2019-2022):
- Xeris Pharmaceuticals (Xeris markets glucagon [GVOKE] and is evaluating stable, liquid glucagon

as a combination therapy inside a physiological, closed-loop, bihormonal artificial pancreas. Xeris also has pramlintide-insulin preparation on phase 2 trials according to its website. From Dr Wolfsdorf September 2020: "I served on the DSMB for a clinical trial of parenteral glucagon for treatment of congenital hyperinsulinism. The trial was terminated. The total amount I received, including travel expenses and honorarium was $3625."):Consultant fee for Data Safety and Monitoring Board (study of stable form of glucagon for treatment of congenital hyperinsulinism) (terminated 2019)

- UpToDate: Editorial board, pediatric diabetes and hypoglycemia in children
- Ultragenyx: Data Safety Monitoring Board on gene therapy for type 1 glycogen storage disease; Chair Central Independent Committee for study on gene transfer in patients with glycogen storage disease

Open Payments Database: https://openpayments data.cms.gov/physician/1263559

Assessment and Management:

- Dr Wolfsdorf had industry relationships relevant to this CPG (Xeris).
- Dr Wolfsdorf was allowed to participate in the GDP because he is a renowned expert in the area of hypoglycemia, and since the Pediatric Endocrine Society (PES) nominated him.
- Divestment: None required.
- COI management: The relationship with Xeris was judged to be sufficiently low risk (ie, it seems rather implausible that his participation on the Xeris DSMB will inappropriately influence his work on the guideline), so no COI management was required.

Robin Fein Wright, LCSW
Patient representative

Disclosures (2019-2022):

- DiabetesSisters (DiabetesSisters is a 501(c)(3) nonprofit organization whose mission is to improve the health and quality of life of women with diabetes, and to advocate on their behalf (https://diabetessisters.org/about-us): Facilitator for support groups for T1D and T2D

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No COI management required.

NOTES ON PRIOR PANEL MEMBERS:

1. An individual with no relevant conflicts of interest was appointed as chair at the outset of guideline development but given an inability to attend conference calls, they were asked to step down from the Guideline Development Panel in June 2020, prior to any significant progress on the guideline.
2. An individual with the following relevant relationships was appointed to the panel:
   (a) Roche (Roche markets glucose monitoring systems, namely Accu-Chek products [360 diabetes management software, Aviva Expert meter, Aviva meter, Aviva Nano meter, Combo system, Compact Plus system, Connect diabetes management system, FastClix lancing device, Lancing Devices for Professionals, Smart Pix device reader model 2, Softclix Lancet Device].): Speaker
   (b) Novo Nordisk[2]: International Hypoglycaemia Study Group member
   (c) Insulet (The Insulet Corporation produces and markets the Omnipod Insulin Pump, a tubeless closed-loop insulin pump.): Data Safety Monitoring Board for patch pump hybrid closed loop. These relationships were assessed and managed as relevant to PICOs 1, 2, 3,4, 5, 7, 8, and 10.

   This individual's participation on the panel ended in November 2020, prior to the completion of evidence reviews or any other significant work on the guideline.
3. An individual with the following relevant relationships was appointed to the panel:
   (a) Dexcom (Dexcom manufactures and markets continuous glucose monitors.): Consultant, Speaker
   (b) Medtronic (Medtronic manufactures and markets insulin pumps, continuous glucose monitors, and an automated, closed-loop insulin delivery system [MiniMed 670G].) : Consultant
   (c) Novo Nordisk (Novo Nordisk manufactures and markets Ozempic [semaglutide], Fiasp [insulin aspart], Victoza [liraglutide], Tresiba [insulin degludec], Levemir [insulin detemir], Xultophy [insulin degludec + liraglutide], Novolog [insulin aspart], NovoLog Mix 70/30 [insulin aspart protamine and insulin aspart], Novolin 70/30 [human NPH + regular insulin], Novolin N [human NPH insulin], Novolin R [human regular insulin], Prandin [repaglinide], and GlucaGen HypoKit [glucagon].): Clinical Advisory Board Member
   (d) Study PI for pharma sponsored trials (all payments to Northwestern University): Dexcom, Novo Nordisk, AstraZeneca (AstraZeneca markets Bydureon [exenatide]; Byetta [exenatide]; Farxiga/Forxiga [dapagliflozin]; Komboglyze [saxagliptin and metformin HCl]; Kombiglyze XR [saxagliptin and metformin XR]; Onglyza [saxagliptin]; Qtern [dapagliflozin and saxagliptin]; Symlin [pramlintide acetate]; Xigduo [dapagliflozin and metformin HCI]; Xigduo XR [dapagliflozin and metformin HCI extended-release].) UK, Eli Lilly (Eli Lilly markets Baqsimi [glucagon], Basaglar [glargine insulin], Glucagon for injection, Glyxambi [empagliflozin/linagliptin], Humalog [lispro, 50/50, 75/25, U200], Humulin [R, N, U500, 70/30], Jardiance [empagliflozin], Jentadueto [linagliptin/metformin], Jentadueto XR [linagliptin/metformin ER], Synjardy [empagliflozin/metformin], Synjardy XR [empagliflozin/

metformin ER], Trajenta [linagliptin], Trulicity [dulaglitide].), Insulet (The Insulet Corporation produces and markets the Omnipod Insulin Pump - a tubeless closed-loop insulin pump), and Bristol-Myers Squibb (Glucophage [metformin], Glucophage XR [metformin ER], Glucovance [glyburide/metformin].) These relationships were assessed and managed as relevant to PICOs 1, 2, 3, 4, 5, 7, 8, and 10.

During the development of this guideline, it came to the attention of the CGC chair that this individual had taken on new relationships and participated in marketing activities, in violation of the COI policy. This individual was asked not to continue these activities or take on any new relationships, but at that time and due to competing priorities, they chose to resign from the panel in October 2021.

4. An individual with no relevant conflicts of interest was appointed to the panel, but during the development of the guideline, it came to the attention of the CGC chair that they participated on an advisory board for Dexcom. Although no payment was accepted, it still posed a relevant COI that was in violation of Endocrine Society policy. This individual resigned from the panel in November 2021. No judgments were made or recommendations drafted during the period between their participation on the advisory board and their departure from the panel, so no mitigation was necessary.

References

1. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Metab*. 2013;98(5):1845-1859.
2. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *Lancet*. 2018;391(10128):1367-1377.
3. American Diabetes Association Professional Practice Committee; Draznin B, Aroda VR, Bakris G, et al. 4. Comprehensive medical evaluation and assessment of comorbidities: *Standards of Medical Care in Diabetes–2022. Diabetes Care*. 2022;45(Suppl 1):S46-S59.
4. Jensen MV, Broadley M, Speight J, et al. The impact of hypoglycaemia in children and adolescents with type 1 diabetes on parental quality of life and related outcomes: a systematic review. *Pediatr Diabetes*. 2022;23(3):390–405.
5. Lake A, Arthur A, Byrne C, Davenport K, Yamamoto JM, Murphy HR. The effect of hypoglycaemia during hospital admission on health-related outcomes for people with diabetes: a systematic review and meta-analysis. *Diabet Med*. 2019;36(11):1349-1359.
6. Li P, Geng Z, Ladage VP, Wu J, Lorincz I, Doshi JA. Early hypoglycaemia and adherence after basal insulin initiation in a nationally representative sample of Medicare beneficiaries with type 2 diabetes. *Diabetes Obes Metab*. 2019;21(11):2486-2495.
7. Chatwin H, Broadley M, Valdersdorf Jensen M, et al. 'Never again will I be carefree': a qualitative study of the impact of hypoglycemia on quality of life among adults with type 1 diabetes. *BMJ Open Diabetes Res Care*. 2021;9(1):e002322.
8. Wu C, Ge YL, Zhang XY, et al. The influence of hypoglycemia on the specific quality of life in type 2 diabetes mellitus: a comparative cross-sectional study of diabetics with and without hypoglycemia in Xi'an, China. *Health Qual Life Outcomes*. 2021;19(1):151.
9. McCoy RG, Lipska KJ, Van Houten HK, Shah ND. Association of cumulative multimorbidity, glycemic control, and medication use with hypoglycemia-related emergency department visits and hospitalizations among adults with diabetes. *JAMA Netw Open*. 2020;3(1):e1919099.
10. Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. *Value Health*. 2011;14(5):665-671.
11. Kurani SS, Heien HC, Sangaralingham LR, et al. Association of area-level socioeconomic deprivation with hypoglycemic and hyperglycemic crises in US adults with diabetes. *JAMA Netw Open*. 2022;5(1):e2143597.
12. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. *Diabetes Care*. 2020;44(1):258-279.
13. Karter AJ, Lipska KJ, O'Connor PJ, et al; SUPREME-DM Study Group. High rates of severe hypoglycemia among African American patients with diabetes: the Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME-DM) network. *J Diabetes Complications*. 2017;31(5):869-873.
14. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94(3):709-728.
15. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA$_{1c}$ for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, the Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D exchange. *Diabetes Care*. 2017;40(12):1622-1630.
16. Hermanns N, Heinemann L, Freckmann G, Waldenmaier D, Ehrmann D. Impact of CGM on the management of hypoglycemia problems: overview and secondary analysis of the HypoDE Study. *J Diabetes Sci Technol*. 2019;13(4):636-644.
17. Steineck I, Ranjan A, Nørgaard K, Schmidt S. Sensor-augmented insulin pumps and hypoglycemia prevention in type 1 diabetes. *J Diabetes Sci Technol*. 2017;11(1):50-58.
18. Galindo RJ, Umpierrez GE, Rushakoff RJ, et al. Continuous glucose monitors and automated insulin dosing systems in the hospital consensus guideline. *J Diabetes Sci Technol*. 2020;14(6):1035-1064.
19. Edelman SV, Argento NB, Pettus J, Hirsch IB. Clinical implications of real-time and intermittently scanned continuous glucose monitoring. *Diabetes Care*. 2018;41(11):2265-2274.
20. Gray J, Roseleur J, Edney L, Karnon J; Southern Adelaide Local Health Network's Hypoglycaemia Clinical Working Group. Pragmatic review of interventions to prevent inpatient hypoglycaemia. *Diabet Med*. 2022;39(2):e14737.
21. Lawton J, Rankin D. How do structured education programmes work? An ethnographic investigation of the Dose Adjustment for Normal Eating (DAFNE) programme for type 1 diabetes patients in the UK. *Soc Sci Med*. 2010;71(3):486-493.
22. Association of Diabetes Care and Education Specialists; Kolb L. An effective model of diabetes care and education: the ADCES7 self-care behaviors. *Sci Diabetes Self Manag Care*. 2021;47(1):30-53.
23. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. *Diabetes Technol Ther*. 2019;21(2):66-72.
24. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2021;44(11):2589-2625.

25. Tamborlane WV, Beck RW, Bode BW, *et al*. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008;359(14):1464-1476.

26. Bergenstal RM, Tamborlane WV, Ahmann A, *et al*. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med*. 2010;363(4):311-320.

27. Battelino T, Conget I, Olsen B, *et al*; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia*. 2012;55(12):3155-3162.

28. Grunberger G, Abelseth JM, Bailey TS, *et al*. Consensus statement by the American Association of Clinical Endocrinologists/American College of Endocrinology insulin pump management task force. *Endocr Pract*. 2014;20(5):463-489.

29. Pickup J. Insulin pumps. *Int J Clin Pract Suppl*. 2011;65(S170):16-19.

30. Foster NC, Miller KM, Tamborlane WV, Bergenstal RM, Beck RW; T1D Exchange Clinic Network. Continuous glucose monitoring in patients with type 1 diabetes using insulin injections. *Diabetes Care*. 2016;39(6):e81-e82.

31. DiMeglio LA, Kanapka LG, DeSalvo DJ, *et al*; SENCE Study Group. Time spent outside of target glucose range for young children with type 1 diabetes: a continuous glucose monitor study. *Diabet Med*. 2020;37(8):1308-1315.

32. Beck RW, Riddlesworth T, Ruedy K, *et al*; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA*. 2017;317(4):371-378.

33. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet*. 2016;388(10057):2254-2263.

34. Feig DS, Donovan LE, Corcoy R, *et al*; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet*. 2017;390(10110):2347-2359.

35. Lind M, Polonsky W, Hirsch IB, *et al*. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. *JAMA*. 2017;317(4):379-387.

36. Ólafsdóttir AF, Polonsky W, Bolinder J, *et al*. A randomized clinical trial of the effect of continuous glucose monitoring on nocturnal hypoglycemia, daytime hypoglycemia, glycemic variability, and hypoglycemia confidence in persons with type 1 diabetes treated with multiple daily insulin injections (GOLD-3). *Diabetes Technol Ther*. 2018;20(4):274-284.

37. Oskarsson P, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R, Bolinder J. Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial. *Diabetologia*. 2018;61(3):539-550.

38. Pratley RE, Kanapka LG, Rickels MR, *et al*; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study Group. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. *JAMA*. 2020;323(23):2397-2406.

39. Riddlesworth T, Price D, Cohen N, Beck RW. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. *Diabetes Ther*. 2017;8(4):947-951.

40. Ahmadi SS, Westman K, Pivodic A, *et al*. The association between HbA_{1c} and time in hypoglycemia during CGM and self-monitoring of blood glucose in people with type 1 diabetes and multiple daily insulin injections: a randomized clinical trial (GOLD-4). *Diabetes Care*. 2020;43(9):2017-2024.

41. Murad M. Endocrine society technical review on hypoglycemia in high-risk individuals with diabetes. *J Clin Endocrinol Metab*. 2023;108(3).

42. Murphy HR. Continuous glucose monitoring targets in type 1 diabetes pregnancy: every 5% time in range matters. *Diabetologia*. 2019;62(7):1123-1128.

43. Laffel LM, Kanapka LG, Beck RW, *et al*; CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group; CDE10. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: a randomized clinical trial. *JAMA*. 2020;323(23):2388-2396.

44. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008;57(12):3169-3176.

45. Cryer PE. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. *Diabetes*. 2014;63(7):2188-2195.

46. Aleppo G, Laffel LM, Ahmann AJ, *et al*. A practical approach to using trend arrows on the Dexcom G5 CGM system for the management of adults with diabetes. *J Endocr Soc*. 2017;1(12):1445-1460.

47. Laffel LM, Aleppo G, Buckingham BA, *et al*. A practical approach to using trend arrows on the Dexcom G5 CGM system to manage children and adolescents with diabetes. *J Endocr Soc*. 2017;1(12):1461-1476.

48. Miller KM, Hermann J, Foster N, *et al*; T1D Exchange and DPV Registries. Longitudinal changes in continuous glucose monitoring use among individuals with type 1 diabetes: international comparison in the German and Austrian DPV and U.S. T1D Exchange registries. *Diabetes Care*. 2020;43(1):e1-e2.

49. Cardona-Hernandez R, Schwandt A, Alkandari H, *et al*; SWEET Study Group. Glycemic outcome associated with insulin pump and glucose sensor use in children and adolescents with type 1 diabetes. Data from the International Pediatric Registry SWEET. *Diabetes Care*. 2021;44(5):1176-1184.

50. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986.

51. Fuchs J, Hovorka R. Closed-loop control in insulin pumps for type-1 diabetes mellitus: safety and efficacy. *Expert Rev Med Devices*. 2020;17(7):707-720.

52. Brown SA, Kovatchev BP, Raghinaru D, *et al*; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med*. 2019;381-(18):1707-1717.

53. Bekiari E, Kitsios K, Thabit H, *et al*. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. *BMJ*. 2018;361(8149):k1310.

54. Ajjan RA, Abougila K, Bellary S, *et al*. Sensor and software use for the glycaemic management of insulin-treated type 1 and type 2 diabetes patients. *Diab Vasc Dis Res*. 2016;13(3):211-219.

55. Ajjan RA, Jackson N, Thomson SA. Reduction in HbA1c using professional flash glucose monitoring in insulin-treated type 2 diabetes patients managed in primary and secondary care settings: a pilot, multicentre, randomised controlled trial. *Diab Vasc Dis Res*. 2019;16(4):385-395.

56. Beck RW, Riddlesworth TD, Ruedy K, *et al*. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections. *Ann Intern Med*. 2017;167(6):365.

57. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther*. 2017;8(1):55-73.

58. Yaron M, Roitman E, Aharon-Hananel G, *et al*. Effect of flash glucose monitoring technology on glycemic control and treatment

satisfaction in patients with type 2 diabetes. *Diabetes Care.* 2019;42(7):1178-1184.

59. Yeoh E, Lim BK, Fun S, *et al.* Efficacy of self-monitoring of blood glucose versus retrospective continuous glucose monitoring in improving glycaemic control in diabetic kidney disease patients. *Nephrology.* 2018;23(3):264-268.

60. Tansey M, Laffel L, Cheng J, *et al.* Satisfaction with continuous glucose monitoring in adults and youths with type 1 diabetes. *Diabet Med.* 2011;28(9):1118-1122.

61. Schmidt S, Duun-Henriksen AK, Nørgaard K. Psychosocial factors and adherence to continuous glucose monitoring in type 1 diabetes. *J Diabetes Sci Technol.* 2012;6(4):986-987.

62. Ritholz MD, Atakov-Castillo A, Beste M, *et al.* Psychosocial factors associated with use of continuous glucose monitoring. *Diabet Med.* 2010;27(9):1060-1065.

63. Pickup JC, Ford Holloway M, Samsi K. Real-time continuous glucose monitoring in type 1 diabetes: a qualitative framework analysis of patient narratives. *Diabetes Care.* 2015;38(4):544-550.

64. Health Quality Ontario. Continuous monitoring of glucose for type 1 diabetes: a health technology assessment. *Ont Health Technol Assess Ser.* 2018;18(2):1-160.

65. Lawton J, Blackburn M, Allen J, *et al.* Patients' and caregivers' experiences of using continuous glucose monitoring to support diabetes self-management: qualitative study. *BMC Endocr Disord.* 2018;18(1):12.

66. Hilliard ME, Levy W, Anderson BJ, *et al.* Benefits and barriers of continuous glucose monitoring in young children with type 1 diabetes. *Diabetes Technol Ther.* 2019;21(9):493-498.

67. Shivers JP, Mackowiak L, Anhalt H, Zisser H. "Turn it off!": diabetes device alarm fatigue considerations for the present and the future. *J Diabetes Sci Technol.* 2013;7(3):789-794.

68. van Beers CAJ, DeVries JH, Kleijer SJ, *et al.* Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. *Lancet Diabetes Endocrinol.* 2016;4(11):893-902.

69. Wang F, Wang D, Lu XL, Sun XM, Duan BH. Continuous glucose monitoring in diabetes patients with chronic kidney disease on dialysis: a meta-analysis. *Minerva Endocrinol.* 2022;47(3):325-333.

70. Honda F, Hiramatsu A, Hyogo H, *et al.* Evaluation of glycemic variability in chronic liver disease patients with type 2 diabetes mellitus using continuous glucose monitoring. *PLoS One.* 2018;13(4):e0195028.

71. Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: A systematic review and meta-analysis. *Int J Epidemiol.* 2011;40(3):804-818.

72. Cheng YJ, Kanaya AM, Araneta MRG, *et al.* Prevalence of diabetes by race and ethnicity in the United States, 2011-2016. *JAMA.* 2019;322(24):2389-2398.

73. Heinemann L, Klonoff DC. An opportunity to increase the benefit of CGM usage: the need to train the patients adequately. *J Diabetes Sci Technol.* 2020;14(6):983-986.

74. Carlson AL, Martens TW, Johnson L, Criego AB. Continuous glucose monitoring integration for remote diabetes management: virtual diabetes care with case studies. *Diabetes Technol Ther.* 2021;23(S3):S56-S65.

75. Majithia AR, Kusiak CM, Armento Lee A, *et al.* Glycemic outcomes in adults with type 2 diabetes participating in a continuous glucose monitor-driven virtual diabetes clinic: prospective trial. *J Med Internet Res.* 2020;22(8):e21778.

76. da Silva Negreiros FD, de Araujo AL, Mattos SM, *et al.* Digital technologies in the care of people with diabetes during the COVID-19 pandemic: a scoping review. *Rev Esc Enferm USP.* 2021;55:e20210295.

77. Cruz P. Inpatient hypoglycemia: the challenge remains. *J Diabetes Sci Technol.* 2020;14(3):560-566.

78. Hulkower RD, Pollack RM, Zonszein J. Understanding hypoglycemia in hospitalized patients. *Diabetes Manag (Lond).* 2014;4(2):165-176.

79. Zick R, Petersen B, Richter M, Haug C. Comparison of continuous blood glucose measurement with conventional documentation of hypoglycemia in patients with type 2 diabetes on multiple daily insulin injection therapy. *Diabetes Technol Ther.* 2007;9(6):483-492.

80. Pazos-Couselo M, García-López JM, González-Rodríguez M, *et al.* High incidence of hypoglycemia in stable insulin-treated type 2 diabetes mellitus: continuous glucose monitoring vs. self-monitored blood glucose. Observational prospective study. *Can J Diabetes.* 2015;39(5):428-433.

81. Gu W, Liu Y, Chen Y, *et al.* Multicentre randomized controlled trial with sensor-augmented pump vs multiple daily injections in hospitalized patients with type 2 diabetes in China: time to reach target glucose. *Diabetes Metab.* 2017;43(4):359-363.

82. Levitt DL, Spanakis EK, Ryan KA, Silver KD. Insulin pump and continuous glucose monitor initiation in hospitalized patients with type 2 diabetes mellitus. *Diabetes Technol Ther.* 2018;20(1):32-38.

83. Singh LG, Satyarengga M, Marcano I, *et al.* Reducing inpatient hypoglycemia in the general wards using real-time continuous glucose monitoring: the glucose telemetry system, a randomized clinical trial. *Diabetes Care.* 2020;43(11):2736-2743.

84. Singh LG, Levitt DL, Satyarengga M, *et al.* Continuous glucose monitoring in general wards for prevention of hypoglycemia: results from the Glucose Telemetry System Pilot Study. *J Diabetes Sci Technol.* 2020;14(4):783-790.

85. Galindo RJ, Migdal AL, Davis GM, *et al.* Comparison of the FreeStyle libre pro flash continuous glucose monitoring (CGM) system and point-of-care capillary glucose testing (POC) in hospitalized patients with type 2 diabetes (T2D) treated with basal-bolus insulin regimen. *Diabetes Care.* 2020;43(11):2730-2735.

86. Gómez AM, Umpierrez GE, Muñoz OM, *et al.* Continuous glucose monitoring versus capillary point-of-care testing for inpatient glycemic control in type 2 diabetes patients hospitalized in the general ward and treated with a basal bolus insulin regimen. *J Diabetes Sci Technol.* 2015;10(2):325-329.

87. Galindo RJ, Aleppo G, Klonoff DC, Spanakis EK, Agarwal S, Vellanki P, Olson DE, Umpierrez GE, Davis GM, Pasquel FJ. Implementation of continuous glucose monitoring in the hospital: emergent considerations for remote glucose monitoring during the COVID-19 pandemic. *J Diabetes Sci Technol.* 2020;4:822-832.

88. Pratiwi C, Mokoagow MI, Made Kshanti IA, Soewondo P. The risk factors of inpatient hypoglycemia: a systematic review. *Heliyon.* 2020;6(5):e03913.

89. de Adana MSR, Colomo N, Maldonado-Araque C, *et al.* Randomized clinical trial of the efficacy and safety of insulin glargine vs. NPH insulin as basal insulin for the treatment of glucocorticoid induced hyperglycemia using continuous glucose monitoring in hospitalized patients with type 2 diabetes and respiratory disease. *Diabetes Res Clin Pract.* 2015;110(2):158-165.

90. Schaupp L, Donsa K, Neubauer KM, *et al.* Taking a closer look—continuous glucose monitoring in non-critically ill hospitalized patients with type 2 diabetes mellitus under basal-bolus insulin therapy. *Diabetes Technol Ther.* 2015;17(9):611-618.

91. van Steen SC, Rijkenberg S, Limpens J, van der Voort PH, Hermanides J, DeVries JH. The clinical benefits and accuracy of continuous glucose monitoring systems in critically ill patients—a systematic scoping review. *Sensors (Basel).* 2017;17(1):146.

92. Faulds ER, Jones L, McNett M, *et al.* Facilitators and barriers to nursing implementation of continuous glucose monitoring (CGM) in critically ill patients with COVID-19. *Endocr Pract.* 2021;27(4):354-361.

93. Alamri N, Seley JJ. Evaluation of several electronic glycemic management systems. *J Diabetes Sci Technol.* 2018;12(1):60-62.

94. Aloi J, Bode BW, Ullal J, *et al.* Comparison of an electronic glycemic management system versus provider-managed

subcutaneous basal bolus insulin therapy in the hospital setting. *J Diabetes Sci Technol*. 2017;11(1):12-16.

95. Defayette AA, Voigt LM, Zammit KT, Nadler JN, Kersten BP. Evaluation of a computerized insulin dosing tool for the treatment of diabetic ketoacidosis. *J Pharm Pract*. 2020;33(6):768-773.

96. Edholm K, Lappé K, Kukhareva P, et al. Reducing diabetic ketoacidosis intensive care unit admissions through an electronic health record-driven, standardized care pathway. *J Healthc Qual*. 2020;42(5):e66-e74.

97. Groysman AY, Peragallo-Dittko V, Islam S, Klek S. Safety and efficacy of glucostabilizer in the management of diabetic ketoacidosis. *Endocr Pract*. 2020;26(6):627-633.

98. Ullal J, Aloi JA, Reyes-Umpierrez D, et al. Comparison of computer-guided versus standard insulin infusion regimens in patients with diabetic ketoacidosis. *J Diabetes Sci Technol*. 2018;12(1):39-46.

99. Rabinovich M, Grahl J, Durr E, et al. Risk of hypoglycemia during insulin infusion directed by paper protocol versus electronic glycemic management system in critically ill patients at a large academic medical center. *J Diabetes Sci Technol*. 2018;12(1):47-52.

100. Schnipper JL, Liang CL, Ndumele CD, Pendergrass ML. Effects of a computerized order set on the inpatient management of hyperglycemia: a cluster-randomized controlled trial. *Endocr Pract*. 2010;16(2):209-218.

101. Umpierrez G, Korytkowski M. Diabetic emergencies—ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nat Rev Endocrinol*. 2016;12(4):222-232.

102. Khazai NB, Hamdy O. Inpatient diabetes management in the twenty-first century. *Endocrinol Metab Clin North Am*. 2016;45(4):875-894.

103. Johnston LE, Kirby JL, Downs EA, et al; Virginia Interdisciplinary Cardiothoracic Outcomes Research (VICTOR) Center. Postoperative hypoglycemia is associated with worse outcomes after cardiac operations. *Ann Thorac Surg*. 2017;103(2):526-532.

104. Badawi O, Waite MD, Fuhrman SA, Zuckerman IH. Association between intensive care unit-acquired dysglycemia and in-hospital mortality. *Crit Care Med*. 2012;40(12):3180-3188.

105. Carey M, Boucai L, Zonszein J. Impact of hypoglycemia in hospitalized patients. *Curr Diab Rep*. 2013;13(1):107-113.

106. Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care*. 2009;32(7):1153-1157.

107. Varlamov EV, Kulaga ME, Khosla A, Prime DL, Rennert NJ. Hypoglycemia in the hospital: systems-based approach to recognition, treatment, and prevention. *Hosp Pract 1995*. 2014;42(4):163-172.

108. Newsom R, Patty C, Camarena E, et al. Safely converting an entire academic medical center from sliding scale to basal bolus insulin via implementation of the eGlycemic management system. *J Diabetes Sci Technol*. 2018;12(1):53-59.

109. Cardona S, Pasquel FJ, Fayfman M, et al. Hospitalization costs and clinical outcomes in CABG patients treated with intensive insulin therapy. *J Diabetes Complications*. 2017;31(4):742-747.

110. Geller AI, Shehab N, Lovegrove MC, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. *JAMA Intern Med*. 2014;174(5):678-686.

111. Garg SK, Rewers AH, Akturk HK. Ever-Increasing insulin-requiring patients globally. *Diabetes Technol Ther*. 2018;20(S2):S21-S24.

112. Korytkowski MT, Muniyappa R, Antinori-Lent K, Donihi AC, Drincic AT, Hirsch IB, Luger A, McDonnell ME, Murad MH, Nielsen C, Pegg C, Rushakoff RJ, Santesso N, Umpierrez GE. Management of hyperglycemia in hospitalized adult patients in non-critical care settings: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2022;107(8):2101-2128.

113. Danne T, Philotheou A, Goldman D, et al. A randomized trial comparing the rate of hypoglycemia—assessed using continuous glucose monitoring–in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). *Pediatr Diabetes*. 2013;14(8):593-601.

114. Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia*. 2004;47(4):622-629.

115. Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall MA, Ludvigsson J. Insulin detemir compared with NPH insulin in children and adolescents with type 1 diabetes. *Diabet Med*. 2007;24(1):27-34.

116. Rosenstock J, Fonseca V, McGill JB, et al. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. *Diabetologia*. 2009;52(9):1778-1788.

117. Rostami P, Setoodeh A, Rabbani A, Nakhaei-Moghadam M, Najmi-Varzaneh F, Rezaei N. A randomized clinical trial of insulin glargine and aspart, compared to NPH and regular insulin in children with type 1 diabetes mellitus. *Iran J Pediatr*. 2014;24(2):173-178.

118. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Insulin analogues in children with type 1 diabetes: a 52-week randomized clinical trial. *Diabet Med*. 2013;30(2):216-225.

119. Ashwell SG, Amiel SA, Bilous RW, et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. *Diabet Med*. 2006;23(3):285-292.

120. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to neutral protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. *Diabet Med*. 2008;25(4):442-449.

121. Bolli GB, Songini M, Trovati M, et al. Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with type 1 diabetes. *Nutr Metab Cardiovasc Dis*. 2009;19(8):571-579.

122. Chase HP, Arslanian S, White NH, Tamborlane WV. Insulin glargine versus intermediate-acting insulin as the basal component of multiple daily injection regimens for adolescents with type 1 diabetes mellitus. *J Pediatr*. 2008;153(4):547-553.

123. De Leeuw I, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab*. 2005;7(1):73-82.

124. Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. *Diabetes Care*. 2001;24(2):296-301.

125. Hershon KS, Blevins TC, Mayo CA, Rosskamp R. Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes. *Endocr Pract*. 2004;10(1):10-17.

126. Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. *Diabetes Care*. 2004;27(5):1081-1087.

127. Home PD, Rosskamp R, Forjanic-Klapproth J, Dressler A, European Insulin Glargine Study Group. A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes. *Diabetes Metab Res Rev*. 2005;21(6):545-553.

128. Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. *Diabet Med*. 2005;22(7):850-857.

129. Raskin P, Klaff L, Bergenstal R, Hallé JP, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care*. 2000;23(11):1666-1671.

130. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care*. 2000;23(5):639-643.

131. Rosak C, Jung R, Hofmann U. Insulin glargine maintains equivalent glycemic control and better lipometabolic control than NPH insulin in type 1 diabetes patients who missed a meal. *Horm Metab Res*. 2008;40(8):544-548.

132. Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care*. 2001;24(4):631-636.

133. Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. *Clin Ther*. 2004;26(5):724-736.

134. Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K; Pediatric Study Group of Insulin Glargine. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2002;15(4):369-376.

135. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. *Diabetes Technol Ther*. 2004;6(5):579-588.

136. Vague P, Selam J-L, Skeie S, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care*. 2003;26(3):590-596.

137. Betonico CC, Titan SMO, Lira A, et al. Insulin glargine U100 improved glycemic control and reduced nocturnal hypoglycemia in patients with type 2 diabetes mellitus and chronic kidney disease stages 3 and 4. *Clin Ther*. 2019;41(10):2008-2020.e3.

138. Radman M, Jurisić D, Ljutić D, Jerković R, Kovacić N, Hozo IS. Assessing glycemia in type 1 diabetic patients using a microdialysis system for continuous glucose monitoring. *Ann Saudi Med*. 2007;27(3):166-170.

139. Chatterjee S, Jarvis-Kay J, Rengarajan T, Lawrence IG, McNally PG, Davies MJ. Glargine versus NPH insulin: efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes —the Glargine and Aspart Study (GLASS) a randomised crossover study. *Diabetes Res Clin Pract*. 2007;77(2):215-222.

140. Fulcher GR, Gilbert RE, Yue DK. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. *Intern Med J*. 2005;35(9):536-542.

141. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2005;7(1):56-64.

142. Hassan K, Rodriguez LM, Johnson SE, Tadlock S, Heptulla RA. A randomized, controlled trial comparing twice-a-day insulin glargine mixed with rapid-acting insulin analogs versus standard neutral protamine Hagedorn (NPH) therapy in newly diagnosed type 1 diabetes. *Pediatrics*. 2008;121(3):e466-e472.

143. Kølendorf K, Ross GP, Pavlic-Renar I, et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in type 1 diabetes. *Diabet Med*. 2006;23(7):729-735.

144. Montañana CF, Herrero CH, Fernández MR. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight type 2 diabetes patients—the PREDICTIVETM BMI clinical trial. *Diabet Med*. 2008;25(8):916-923.

145. Murphy NP, Keane SM, Ong KK, et al. Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care*. 2003;26(3):799-804.

146. Porcellati F, Rossetti P, Pampanelli S, et al. Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med*. 2004;21(11):1213-1220.

147. Rossetti P, Pampanelli S, Fanelli C, et al. Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. *Diabetes Care*. 2003;26(5):1490-1496.

148. Yokoyama H, Tada J, Kamikawa F, Kanno S, Yokota Y, Kuramitsu M. Efficacy of conversion from bedtime NPH insulin to morning insulin glargine in type 2 diabetic patients on basal-prandial insulin therapy. *Diabetes Res Clin Pract*. 2006;73(1):35-40.

149. Zachariah S, Sheldon B, Shojaee-Moradie F, et al. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. *Diabetes Care*. 2011;34(7):1487-1491.

150. Berard L, Cameron B, Woo V, Stewart J. Replacing insulin glargine with Neutral Protamine Hagedorn (NPH) insulin in a subpopulation of study subjects in the Action to Control Cardiovascular Risk in Diabetes (ACCORD): effects on blood glucose levels, hypoglycemia and patient satisfaction. *Can J Diabetes*. 2015;39(4):296-301.

151. Rosenstock J, Park G, Zimmerman J, U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. *Diabetes Care*. 2000;23(8):1137-1142.

152. Walz L, Pettersson B, Rosenqvist U, Deleskog A, Journath G, Wändell P. Impact of symptomatic hypoglycemia on medication adherence, patient satisfaction with treatment, and glycemic control in patients with type 2 diabetes. *Patient Prefer Adherence*. 2014;8(30):593-601.

153. Haluzik M, Kretowski A, Strojek K, et al. Perspectives of patients with insulin-treated type 1 and type 2 diabetes on hypoglycemia: results of the HAT observational study in Central and Eastern European countries. *Diabetes Ther*. 2018;9(2):727-741.

154. Brixner DI, McAdam-Marx C. Cost-effectiveness of insulin analogs. *Am J Manag Care*. 2008;14(11):766-775.

155. Idris I, Gordon J, Tilling C, Vora J. A cost comparison of long-acting insulin analogs vs NPH insulin-based treatment in patients with type 2 diabetes using routinely collected primary care data from the UK. *J Med Econ*. 2015;18(4):273-282.

156. Brändle M, Azoulay M, Greiner RA. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. *Int J Clin Pharmacol Ther*. 2011;49(3):217-230.

157. Gschwend MH, Aagren M, Valentine WJ. Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. *J Med Econ*. 2009;12(2):114-123.

158. Morales C, de Luis D, de Arellano AR, Ferrario MG, Lizán L. Cost-effectiveness analysis of insulin detemir compared to neutral protamine Hagedorn (NPH) in patients with type 1 and type 2 diabetes mellitus in Spain. *Diabetes Ther*. 2015;6(4):593-610.

159. Pfohl M, Schädlich PK, Dippel FW, Koltermann KC. Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. *J Med Econ*. 2012;15(Suppl 2):14-27.

160. Grima DT, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. *Pharmacoeconomics*. 2007;25(3):253-266.

161. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. *CMAJ*. 2009;180(4):400-407.

162. Tricco AC, Ashoor HM, Antony J, *et al*. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ*. 2014;349(7977):g5459.

163. Hagenmeyer EG, Koltermann KC, Dippel FW, Schädlich PK. Health economic evaluations comparing insulin glargine with NPH insulin in patients with type 1 diabetes: a systematic review. *Cost Eff Resour Alloc*. 2011;9(1):15.

164. Haire-Joshu D, Hill-Briggs F. The next generation of diabetes translation: a path to health equity. *Annu Rev Public Health*. 2019;40(1):391-410.

165. Cefalu WT, Dawes DE, Gavlak G, *et al*; Insulin Access and Affordability Working Group. Insulin Access and Affordability Working Group: conclusions and recommendations. *Diabetes Care*. 2018;41(6):1299-1311.

166. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care*. 2012;35(9):1897-1901.

167. Chen JW, Lauritzen T, Bojesen A, Christiansen JS. Multiple mealtime administration of biphasic insulin aspart 30 versus traditional basal-bolus human insulin treatment in patients with type 1 diabetes. *Diabetes Obes Metab*. 2006;8(6):682-689.

168. Ciofetta M, Lalli C, Del Sindaco P, *et al*. Contribution of postprandial versus interprandial blood glucose to HbA1c in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care*. 1999;22(5):795-800.

169. Ferguson SC, Strachan MW, Janes JM, Frier BM. Severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia: a comparative study of insulin lispro and regular human insulin. *Diabetes Metab Res Rev*. 2001;17(4):285-291.

170. Heller SR, Colagiuri S, Vaaler S, *et al*. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with type 1 diabetes. *Diabet Med*. 2004;21(7):769-775.

171. Heller SR, Amiel SA, Mansell P. Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. U.K. Lispro Study Group. *Diabetes Care*. 1999;22(10):1607-1611.

172. Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson JH. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. The Benelux-UK Insulin Lispro Study Group. *Diabetes Care*. 1997;20(12):1827-1832.

173. Home PD, Lindholm A, Hylleberg B, Round P. Improved glycemic control with insulin aspart: A multicenter randomized double-blind crossover trial in type 1 diabetic patients. UK Insulin Aspart Study Group. *Diabetes Care*. 1998;21(11):1904-1909.

174. Home PD, Lindholm A, Riis A, European Insulin Aspart Study Group. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med*. 2000;17(11):762-770.

175. Jacobs MA, Keulen ET, Kanc K, *et al*. Metabolic efficacy of preprandial administration of Lys(B28), Pro(B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. *Diabetes Care*. 1997;20(8):1279-1286.

176. Lalli C, Ciofetta M, Del Sindaco P, *et al*. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. *Diabetes Care*. 1999;22(3):468-477.

177. Pańkowska E, Nazim J, Szalecki M, Urban M. Equal metabolic control but superior caregiver treatment satisfaction with insulin aspart in preschool children. *Diabetes Technol Ther*. 2010;12(5):413-418.

178. Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, *et al*. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. *Lancet Diabetes Endocrinol*. 2014;2(7):553-561.

179. Persson B, Swahn ML, Hjertberg R, *et al*. Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Res Clin Pract*. 2002;58(2):115-121.

180. Tamás G, Marre M, Astorga R, Dedov I, Jacobsen J, Lindholm A; Insulin Aspart Study Group. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. *Diabetes Res Clin Pract*. 2001;54(2):105-114.

181. Anderson JH Jr, Brunelle RL, Keohane P, *et al*. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. *Arch Intern Med*. 1997;157(11):1249-1255.

182. Anderson JH Jr, Brunelle RL, Koivisto VA, *et al*. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. *Diabetes*. 1997;46(2):265-270.

183. Anderson JH Jr, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. *Clin Ther*. 1997;19(1):62-72.

184. Annuzzi G, Del Prato S, Arcari R, *et al*. Preprandial combination of lispro and NPH insulin improves overall blood glucose control in type 1 diabetic patients: a multicenter randomized crossover trial. *Nutr Metab Cardiovasc Dis*. 2001;11(3):168-175.

185. Bastyr EJ, Huang Y, Brunelle RL, Vignati L, Cox DJ, Kotsanos JG. Factors associated with nocturnal hypoglycaemia among patients with type 2 diabetes new to insulin therapy: experience with insulin lispro. *Diabetes Obes Metab*. 2000;2(1):39-46.

186. Brunetti P, Muggeo M, Cattin L, *et al*. Incidence of severe nocturnal hypoglycemia in patients with type 1 diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargine. *Nutr Metab Cardiovasc Dis*. 2010;20(7):519-526.

187. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2004;27(10):2363-2368.

188. Daniels AR, Bruce R, McGregor L. Lispro insulin as premeal therapy in type 1 diabetes: comparison with Humulin R. *N Z Med J*. 1997;110(1056):435-438.

189. Deeb LC, Holcombe JH, Brunelle R, *et al*. Insulin lispro lowers postprandial glucose in prepubertal children with diabetes. *Pediatrics*. 2001;108(5):1175-1179.

190. DeVries JH, Lindholm A, Jacobsen JL, Heine RJ, Home PD, Tri-Continental Insulin Aspart Study Group. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with type 1 diabetes. *Diabet Med*. 2003;20(4):312-318.

191. Fairchild JM, Ambler GR, Genoud-Lawton CH, *et al*. Insulin lispro versus regular insulin in children with type 1 diabetes on twice daily insulin. *Pediatr Diabetes*. 2000;1(3):135-141.

192. Ford-Adams ME, Murphy NP, Moore EJ, *et al*. Insulin lispro: a potential role in preventing nocturnal hypoglycaemia in young children with diabetes mellitus. *Diabet Med*. 2003;20(8):656-660.

193. Gale EA. A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with type 1 diabetes on intensified insulin therapy. The UK Trial Group. *Diabet Med*. 2000;17(3):209-214.

194. Garg SK, Carmain JA, Braddy KC, *et al*. Pre-meal insulin analogue insulin lispro vs Humulin R insulin treatment in young subjects with type 1 diabetes. *Diabet Med*. 1996;13(1):47-52.

195. Garg SK, Rosenstock J, Ways K. Optimized basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human

insulin in combination with basal insulin glargine. *Endocr Pract.* 2005;11(1):11-17.

196. Heller S, Damm P, Mersebach H, *et al.* Hypoglycemia in type 1 diabetic pregnancy: role of preconception insulin aspart treatment in a randomized study. *Diabetes Care.* 2010;33(3):473-477.

197. Holcombe JH, Zalani S, Arora VK, Mast CJ; Lispro in Adolescents Study Group. Comparison of insulin lispro with regular human insulin for the treatment of type 1 diabetes in adolescents. *Clin Ther.* 2002;24(4):629-638.

198. Home PD, Hallgren P, Usadel KH, *et al.* Pre-meal insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. *Diabetes Res Clin Pract.* 2006;71(2):131-139.

199. Jansson PA, Ebeling P, Smith U, *et al.* Improved glycemic control can be better maintained with insulin lispro than with human regular insulin. *Diab Nutr Metab.* 1998;11(3):194-199.

200. Kristensen PL, Tarnow L, Bay C, *et al.* Comparing effects of insulin analogues and human insulin on nocturnal glycaemia in hypoglycaemia-prone people with type 1 diabetes. *Diabet Med.* 2017;34(5):625-631.

201. Provenzano C, Vero R, Oliva A, *et al.* Lispro insulin in type 1 diabetic patients on a Mediterranean or normal diet: a randomized, cross-over comparative study with regular insulin. *Diabetes Nutr Metab.* 2001;14(3):133-139.

202. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care.* 2000;23(5):583-588.

203. Raslová K, Bogoev M, Raz I, Leth G, Gall MA, Hâncu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract.* 2004;66(2):193-201.

204. Rayman G, Profozic V, Middle M. Insulin glulisine imparts effective glycaemic control in patients with type 2 diabetes. *Diabetes Res Clin Pract.* 2007;76(2):304-312.

205. Valle D, Santoro D, Bates P, Scarpa L; Italian Multicentre Lispro Study Group. Italian Multicentre study of intensive therapy with insulin lispro in 1184 patients with type 1 diabetes. *Diabetes Nutr Metab.* 2001;14(3):126-132.

206. Mora PF, Sutton DR, Gore A, *et al.* Efficacy, safety and cost-effectiveness comparison between U-100 human regular insulin and rapid acting insulin when delivered by V-Go wearable insulin delivery device in type 2 diabetes. *BMJ Open Diabetes Res Care.* 2020;8(2):e001832.

207. Pollock RF, Valentine WJ, Pilgaard T, Nishimura H. The cost effectiveness of rapid-acting insulin aspart compared with human insulin in type 2 diabetes patients: an analysis from the Japanese third-party payer perspective. *J Med Econ.* 2011;14(1):36-46.

208. Reviriego J, Gomis R, Marañés JP, Ricart W, Hudson P, Sacristán JA. Cost of severe hypoglycaemia in patients with type 1 diabetes in Spain and the cost-effectiveness of insulin lispro compared with regular human insulin in preventing severe hypoglycaemia. *Int J Clin Pract.* 2008;62(7):1026-1032.

209. Palmer JL, Goodall G, Nielsen S, *et al.* Cost-effectiveness of insulin aspart versus human soluble insulin in type 2 diabetes in four European countries: subgroup analyses from the PREDICTIVE study. *Curr Med Res Opin.* 2008;24(5):1417-1428.

210. Agesen RM, Kristensen PL, Beck-Nielsen H, *et al.* Effect of insulin analogs on frequency of non-severe hypoglycemia in patients with type 1 diabetes prone to severe hypoglycemia: much higher rates detected by continuous glucose monitoring than by self-monitoring of blood glucose—the HypoAna trial. *Diabetes Technol Ther.* 2018;20(3):247-256.

211. Forlenza GP, Li Z, Buckingham BA, *et al.* Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. *Diabetes Care.* 2018;41(10): 2155-2161.

212. Bosi E, Choudhary P, de Valk HW, *et al*; SMILE Study Group. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial. *Lancet Diabetes Endocrinol.* 2019;7(6):462-472.

213. Munshi MN, Segal AR, Suhl E, *et al.* Frequent hypoglycemia among elderly patients with poor glycemic control. *Arch Intern Med.* 2011;171(4):362-364.

214. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Use of flash glucose-sensing technology for 12 months as a replacement for blood glucose monitoring in insulin-treated type 2 diabetes. *Diabetes Ther.* 2017;8(3):573-586.

215. Ahmad I, Zelnick LR, Batacchi Z, *et al.* Hypoglycemia in people with type 2 diabetes and CKD. *Clin J Am Soc Nephrol.* 2019;14(6):844-853.

216. Iqbal A, Heller SR. The role of structured education in the management of hypoglycaemia. *Diabetologia.* 2018;61(4):751-760.

217. Little SA, Leelarathna L, Walkinshaw E, *et al.* Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2×2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). *Diabetes Care.* 2014;37(8):2114-2122.

218. Perrin NE, Davies MJ, Robertson N, Snoek FJ, Khunti K. The prevalence of diabetes-specific emotional distress in people with type 2 diabetes: a systematic review and meta-analysis. *Diabet Med.* 2017;34(11):1508-1520.

219. Pieber TR, Brunner GA, Schnedl WJ, Schattenberg S, Kaufmann P, Krejs GJ. Evaluation of a structured outpatient group education program for intensive insulin therapy. *Diabetes Care.* 1995;18(5):625-630.

220. Elliott J, Rankin D, Jacques RM, *et al*; NIHR DAFNE Research Study Group. A cluster randomized controlled non-inferiority trial of 5-day Dose Adjustment for Normal Eating (DAFNE) training delivered over 1 week versus 5-day DAFNE training delivered over 5 weeks: the DAFNE 5×1-day trial. *Diabet Med.* 2015;32(3): 391-398.

221. Little SA, Speight J, Leelarathna L, *et al.* Sustained reduction in severe hypoglycemia in adults with type 1 diabetes complicated by impaired awareness of hypoglycemia: two-year follow-up in the HypoCOMPaSS randomized clinical trial. *Diabetes Care.* 2018;41(8):1600-1607.

222. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care.* 2001;24(4):637-642.

223. Cox DJ, Kovatchev B, Koev D, *et al.* Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. *Int J Behav Med.* 2004;11(4):212-218.

224. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. Long-term effect of an education program (HyPOS) on the incidence of severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care.* 2010;33(3):e36.

225. de Zoysa N, Rogers H, Stadler M, *et al.* A psychoeducational program to restore hypoglycemia awareness: the DAFNE-HART pilot study. *Diabetes Care.* 2014;37(3):863-866.

226. Cunningham AT, Crittendon DR, White N, Mills GD, Diaz V, LaNoue MD. The effect of diabetes self-management education on HbA1c and quality of life in African-Americans: a systematic review and meta-analysis. *BMC Health Serv Res.* 2018;18(1):367.

227. Ricci-Cabello I, Ruiz-Pérez I, Rojas-García A, Pastor G, Rodríguez-Barranco M, Gonçalves DC. Characteristics and effectiveness of diabetes self-management educational programs targeted to racial/ethnic minority groups: a systematic review, meta-analysis and meta-regression. *BMC Endocr Disord.* 2014;14:60.

228. Tourkmani AM, Abdelhay O, Alharbi TJ, *et al.* Impact of Ramadan-focused diabetes education on hypoglycemia risk and metabolic control for patients with type 2 diabetes mellitus: a systematic review. *Int J Clin Pract.* 2021;75(3):e13817.

229. Lian JX, McGhee SM, Chau J, Wong CKH, Lam CLK, Wong WCW. Systematic review on the cost-effectiveness of self-

management education programme for type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2017;127:21-34.

230. Teljeur C, Moran PS, Walshe S, *et al*. Economic evaluation of chronic disease self-management for people with diabetes: a systematic review. *Diabet Med*. 2017;34(8):1040-1049.

231. American Diabetes Association Professional Practice Committee; Draznin B, Aroda VR, Bakris G, *et al*. 5. Facilitating behavior change and well-being to improve health outcomes: *Standards of Medical Care in Diabetes–2022. Diabetes Care*. 2022;45(Suppl 1):S60-S82.

232. Wang J, Geiss LS, Williams DE, Gregg EW. Trends in emergency department visit rates for hypoglycemia and hyperglycemic crisis among adults with diabetes, United States, 2006-2011. *PLoS One*. 2015;10(8):e0134917.

233. Zhao Y, Shi Q, Wang Y, Fonseca V, Shi L. Economic burden of hypoglycemia: utilization of emergency department and outpatient services in the United States (2005-2009). *J Med Econ*. 2016;19(9):852-857.

234. Foos V, Varol N, Curtis BH, *et al*. Economic impact of severe and non-severe hypoglycemia in patients with type 1 and type 2 diabetes in the United States. *J Med Econ*. 2015;18(6):420-432.

235. Basu S, Berkowitz SA, Seligman H. The monthly cycle of hypoglycemia: an observational claims-based study of emergency room visits, hospital admissions, and costs in a commercially insured population. *Med Care*. 2017;55(7):639-645.

236. Parsaik AK, Carter RE, Pattan V, *et al*. Population-based study of severe hypoglycemia requiring emergency medical service assistance reveals unique findings. *J Diabetes Sci Technol*. 2012;6(1):65-73.

237. Moffet HH, Warton EM, Siegel L, Sporer K, Lipska KJ, Karter AJ. Hypoglycemia patients and transport by EMS in Alameda County, 2013-15. *Prehosp Emerg Care*. 2017;21(6):767-772.

238. Kahn PA, Wagner NE, Gabbay RA. Underutilization of glucagon in the prehospital setting. *Ann Intern Med*. 2018;168(8):603-604.

239. Mitchell BD, He X, Sturdy IM, Cagle AP, Settles JA. Glucagon prescription patterns in patients with either type 1 or 2 diabetes with newly prescribed insulin. *Endocr Pract*. 2016;22(2):123-135.

240. Deeb LC, Dulude H, Guzman CB, *et al*. A phase 3 multicenter, open-label, prospective study designed to evaluate the effectiveness and ease of use of nasal glucagon in the treatment of moderate and severe hypoglycemia in children and adolescents with type 1 diabetes in the home or school setting. *Pediatr Diabetes*. 2018;19(5):1007-1013.

241. Seaquist ER, Dulude H, Zhang XM, *et al*. Prospective study evaluating the use of nasal glucagon for the treatment of moderate to severe hypoglycaemia in adults with type 1 diabetes in a real-world setting. *Diabetes Obes Metab*. 2018;20(5):1316-1320.

242. Pohlmann J, Mitchell BD, Bajpai S, Osumili B, Valentine WJ. Nasal glucagon versus injectable glucagon for severe hypoglycemia: a cost-offset and budget impact analysis. *J Diabetes Sci Technol*. 2019;13(5):910-918.

243. Leinwand B, Johnsrud M, Nguyen A, Meyer J, Johnson K. A ready-to-use liquid glucagon for treatment of severe hypoglycemia demonstrates reduced healthcare payer costs in a budget impact model. *J Med Econ*. 2020;23(7):744-750.

244. Yale JF, Dulude H, Egeth M, *et al*. Faster use and fewer failures with needle-free nasal glucagon versus injectable glucagon in severe hypoglycemia rescue: a simulation study. *Diabetes Technol Ther*. 2017;19(7):423-432.

245. Valentine V, Newswanger B, Prestrelski S, Andre AD, Garibaldi M. Human factors usability and validation studies of a glucagon autoinjector in a simulated severe hypoglycemia rescue situation. *Diabetes Technol Ther*. 2019;21(9):522-530.

246. Newswanger B, Prestrelski S, Andre AD. Human factors studies of a prefilled syringe with stable liquid glucagon in a simulated severe hypoglycemia rescue situation. *Expert Opin Drug Deliv*. 2019;16(9):1015-1025.

247. Swiglo BA, Murad MH, Schünemann HJ, *et al*. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab*. 2008;93(3):666-673.

248. Alonso-Coello P, Schünemann HJ, Moberg J, *et al*; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *Gac Sanit*. 2018;32(2):166.e1-166.e10.

249. Alonso-Coello P, Oxman AD, Moberg J, *et al*; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *Gac Sanit*. 2018;32(2):167.e1-167.e10.

250. GRADEPro software: GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. https://www.gradepro.org/. Accessed Aug 5, 2019.

251. Endocrine Society. Conflict of Interest Policy & Procedures for Endocrine Society Clincal Practice Guidelines. 2019, https://www.endocrine.org/-/media/endocrine/files/cpg/methodology-page-refresh/conflict_of_interest_cpg_final.pdf. Accessed August 5, 2019.

252. Piggott T, Baldeh T, Akl EA, *et al*. Supporting effective participation in health guideline development groups: the guideline participant tool. *J Clin Epidemiol*. 2021;130(February):42-48.

253. Piggott T, Baldeh T, Dietl B, *et al*. Standardized wording to improve efficiency and clarity of GRADE EtD frameworks in health guidelines. *J Clin Epidemiol*. 2022;146:106-122.

254. Andrews J, Guyatt G, Oxman AD, *et al*. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66(7):719-725.

255. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group; 2013.

256. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, Lansing J, Balduzzi S, Darzi A, Morgano GP, Neumann I, Nieuwlaat R, Yepes-Nuñez JJ, Zhang Y, Wiercioch W. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood advances*. 2018;2(22):3198-3225.