# Minimizing Hypoglycemia in Diabetes

*International Hypoglycaemia Study Group**

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REVIEW

**Hypoglycemia caused by treatment with a sulfonylurea, a glinide, or insulin coupled with compromised defenses against the resulting falling plasma glucose concentrations is a problem for many people with diabetes. It is often recurrent, causes significant morbidity and occasional mortality, limits maintenance of euglycemia, and impairs physiological and behavioral defenses against subsequent hypoglycemia. Minimizing hypoglycemia includes acknowledging the problem; considering each risk factor; and applying the principles of intensive glycemic therapy, including drug selection and selective application of diabetes treatment technologies. For diabetes health-care providers treating most people with diabetes who are at risk for or are suffering from iatrogenic hypoglycemia, these principles include selecting appropriate individualized glycemic goals and providing structured patient education to reduce the incidence of hypoglycemia. This is typically combined with short-term scrupulous avoidance of hypoglycemia, which often will reverse impaired awareness of hypoglycemia. Clearly, the risk of hypoglycemia is modifiable.**

Hypoglycemia is the major limiting factor in the glycemic management of diabetes with a sulfonylurea, a glinide, or insulin (1,2). It is often recurrent, causes significant morbidity in most people with type 1 diabetes and in many with advanced type 2 diabetes (i.e., those with absolute endogenous insulin deficiency), and is sometimes fatal. Hypoglycemia limits maintenance of euglycemia over a lifetime of diabetes and, thus, generally prevents full realization of the benefits of glycemic control. It impairs defenses against subsequent falling plasma glucose concentrations and can cause impaired awareness of hypoglycemia, therefore resulting in a vicious cycle of recurrent hypoglycemia.

The problem of hypoglycemia in diabetes has been recently reviewed in detail (1,2). The intent of this article is not to reiterate that information but, rather, to summarize the relevant background and then focus on pragmatic approaches to minimizing hypoglycemia. Efforts to minimize hypoglycemia include acknowledging the problem, considering each risk factor, and applying the relevant principles of intensive glycemic therapy (3–6). The principles of intensive glycemic therapy include avoiding sulfonylureas and glinides; using more physiological insulin regimens, such as insulin analogs, when insulin is indicated; ensuring users are confident in their self-management; considering insulin treatment technologies such as continuous subcutaneous insulin infusion (CSII), continuous glucose monitoring (CGM), and CSII with CGM (ideally with suspension of insulin infusion when glucose levels fall to a selected low value) for selected patients; and closed-loop insulin or insulin and glucagon replacement or pancreas or pancreatic islet transplantation for the few patients in whom hypoglycemia persists. However, for the majority of people with diabetes who are at risk for or are suffering from iatrogenic hypoglycemia, the principles include selecting appropriate individualized glycemic

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**A complete list of the members of the International Hypoglycaemia Study Group can be found in the APPENDIX.*

goals (7,8) and providing structured patient education to reduce the incidence of hypoglycemia (9–17). This is typically coupled with short-term scrupulous avoidance of hypoglycemia and often will reverse impaired awareness of hypoglycemia (18–21).

## BACKGROUND ON HYPOGLYCEMIA IN DIABETES

### Classification and Frequency of Hypoglycemia in Diabetes

Hypoglycemia in diabetes has been defined as "all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm" (22,23). It has been classified as the following:

1. Severe hypoglycemia. An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
2. Documented symptomatic hypoglycemia. An event during which typical symptoms of hypoglycemia are accompanied by a low measured plasma glucose concentration.
3. Asymptomatic hypoglycemia. An event not accompanied by typical symptoms of hypoglycemia but with a measured low plasma glucose concentration.
4. Probable symptomatic hypoglycemia. An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that are presumed to be caused by a low plasma glucose concentration.
5. Relative (or pseudo-) hypoglycemia. An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia with a measured plasma glucose concentration that is not low.

Hypoglycemia is common in diabetes. Population-based data indicate that 30–40% of people with type 1 diabetes experience an average of one to three episodes of severe hypoglycemia each year; those with insulin-treated type 2 diabetes experience about one-third that number (24–26). The rates of any type of hypoglycemia are ~50-fold higher than those of severe hypoglycemia in both types of diabetes. As a function of treatment with a sulfonylurea, a glinide, or insulin as well as compromised physiological and behavioral defenses against falling plasma glucose concentrations (as discussed shortly), the frequency of hypoglycemia increases with the duration of diabetes (26).

Clinical hypoglycemia is a plasma glucose concentration low enough to cause symptoms and/or signs, including impaired brain functioning (27). The glycemic thresholds for symptoms and other manifestations of hypoglycemia shift to lower plasma glucose concentrations in people with well-controlled diabetes (28) and to higher plasma glucose concentrations in those with poorly controlled diabetes (28,29). Of note, both childhood and poor glycemic control shift the glycemic thresholds to higher plasma glucose concentrations in children than in adults (30). Therefore, the plasma glucose concentration at which responses occur is variable between and even within individuals, making it difficult to define a specific low plasma glucose concentration as indicative of clinical iatrogenic hypoglycemia in diabetes.

We recommend that people with diabetes treated with a sulfonylurea, a glinide, or insulin—drugs that raise circulating insulin levels even at normal or low plasma glucose concentrations—become aware of the possibility of developing hypoglycemia and take action to prevent severe hypoglycemia at a self-monitoring of plasma glucose (SMPG) concentration ≤70 mg/dL (≤3.9 mmol/L). Within the errors of glucose monitoring, that glucose alert level approximates the lower limit of the nondiabetic postabsorptive plasma glucose concentration range and the glycemic thresholds for activation of physiological glucose counterregulatory systems (31) and is low enough to reduce some of the hormonal defenses against subsequent hypoglycemia in individuals without diabetes (32).

Metformin, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors should not, and presumably do not, cause hypoglycemia when given alone or in combination with one another because they do not raise circulating insulin levels at normal or low plasma glucose concentrations. However, to the extent they lower plasma glucose concentrations, they increase the risk of hypoglycemia when given with insulin, a sulfonylurea, or a glinide.

Findings of differences in clinical associations with symptomatic and severe hypoglycemia (33) suggest that hypoglycemic events that do or do not require the assistance of another person might be considered separately. They are related because an increase in the frequency of the former predicts the occurrence of the latter (34), but an episode of severe hypoglycemia is a clinical red flag that demands action.

### Impact of Hypoglycemia

The morbidity of hypoglycemia includes an array of symptoms. Autonomic (or neurogenic) symptoms include palpitations, tremor and anxiety/arousal (which are adrenergic or catecholamine mediated), and sweating; hunger; and paresthesias (which are cholinergic or acetylcholine mediated) (35). Autonomic symptoms are largely the result of sympathetic neural rather than adrenomedullary activation (36). Neuroglycopenic symptoms include weakness, drowsiness, impaired cognition ranging from difficulty concentrating to frank confusion, incoordination, and behavioral changes. It can result in seizure, coma, and ultimately death (1,2). Clearly, hypoglycemia is associated with a lower health-related quality of life (37). People with diabetes treated with a sulfonylurea, a glinide, or insulin are at risk for hypoglycemia and must learn to detect such symptoms, interpret them as possibly indicative of hypoglycemia, document them with a plasma glucose measurement, and ingest appropriate carbohydrates to reverse the episode.

The symptoms of hypoglycemia are not specific. In addition, the patterns appear to be somewhat different in children and in elderly adults (2,38,39) who may rely more on neuroglycopenic symptoms. Evidence suggests that both children with type 1 diabetes and their parents fail to recognize 40–50% of hypoglycemic episodes (40). The very young rely on observations by their caregivers who often observe behavioral changes as a clue to hypoglycemia,

although many parents note pallor, an autonomic sign.

Although treatment of diabetes with a sulfonylurea, a glinide, or insulin is a common cause of hypoglycemia, there are other causes of low plasma glucose concentrations, including renal, hepatic, and cardiac failure; sepsis; and inanition (27). Thus, a low plasma glucose concentration in a patient not treated with such drugs, and even in some patients treated with these drugs, may well be a marker of another disorder rather than an iatrogenic cause of morbidity and mortality (41). Nonetheless, there is substantial evidence that iatrogenic hypoglycemia is sometimes fatal [reviewed in Cryer (8)].

It has been known since the discovery of insulin that hypoglycemia can cause death. There is substantial evidence of associations between hypoglycemia and mortality in diabetes. For example, severe hypoglycemia was associated with increased mortality in six randomized controlled trials of intensive glycemic therapy, two in intensive care unit (ICU) patients (42,43), and four in patients with type 2 diabetes (44–47). Although these associations do not establish a causal connection, the consistent pattern in all six trials increases the probability that hypoglycemia was the cause of some of the deaths. Furthermore, there was increased mortality in the intensive glycemic therapy arms of randomized controlled trials in ICU patients (42) and in patients with type 2 diabetes (44). Although excess mortality could have been the result of some nonglycemic aspect of the intensive therapy regimen in the patients with type 2 diabetes (44), in the ICU patients, only the glycemic goals differed (42). Finally, whereas older series indicated that 2–4% of patients with type 1 diabetes died of hypoglycemia (48–50), more recent series have indicated higher hypoglycemic mortality rates of 4% (51), 6% (52), 7% (53), and 10% (54). Indeed, hypoglycemia at the time of death of a patient with type 1 diabetes has been documented with CGM (55). Hypoglycemic mortality rates have also been reported in series of patients with type 2 diabetes (56,57). Of the evaluable deaths in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, 1% were judged as definitely or probably caused by hypoglycemia, and 9% were judged as possibly caused by hypoglycemia (57). Hypoglycemia is associated with an increased risk of cardiovascular events and all-cause mortality in insulin-treated patients with type 1 and type 2 diabetes (58). Although prolonged, profound hypoglycemia can result in brain death, and some hypoglycemic deaths are accidental or suicidal, most fatal episodes are believed to be the result of other mechanisms, such as cardiac arrhythmias (59,60).

In addition to the morbidity and mortality associated with hypoglycemia, there can also be negative consequences for emotional well-being and quality of life. Patients can develop a fear of hypoglycemia that not only decreases their quality of life but also that of their family members (61,62). Fear of hypoglycemia should be assessed by diabetes health-care providers by either survey or inquiry. An extreme level of fear may have a negative impact on diabetes management, leading, for example, to maintenance of higher-than-desirable plasma glucose levels to avoid hypoglycemia. However, awareness of the potential dangers of hypoglycemia and some level of concern are appropriate for individuals at risk. Data support that high-fear/high-risk patients would benefit most from efforts to lower the likelihood of hypoglycemia. A minority of patients have inappropriately high levels of fear when there is no history of severe hypoglycemia or an inappropriate lack of concern when there is a high risk of recurrent episodes.

### Pathophysiology of Hypoglycemia

As plasma glucose concentrations fall, the prevention or rapid correction of hypoglycemia normally involves physiological defenses (a decrease in insulin and an increase in glucagon and, in the absence of the latter, an increase in epinephrine) and a behavioral defense (carbohydrate ingestion prompted by the perception of symptoms of hypoglycemia) (31,63). Hypoglycemia in diabetes is typically the result of the interplay of therapeutic hyperinsulinemia caused by treatment with a sulfonylurea, a glinide, or insulin (all of which raise circulating insulin levels regardless of the plasma glucose concentration) and compromised physiological and behavioral defenses against the resulting falling plasma glucose concentrations (64). The compromised defenses in established type 1 diabetes and advanced type 2 diabetes (those with absolute deficiency of endogenous insulin) include loss of a decrease in insulin and loss of an increase in glucagon, both of which are probably the result of β-cell failure (64), and attenuation of an increase in epinephrine as plasma glucose concentrations fall. These cause the clinical syndrome of defective glucose counterregulation, which increases the risk of severe hypoglycemia by a factor of ≥25 (1). Attenuation of the sympathoadrenal response is believed to cause the clinical syndrome of impaired awareness of hypoglycemia, which increases the risk of severe hypoglycemia by a factor of ≥6 (1,2). Defective glucose counterregulation and impaired awareness of hypoglycemia are components of the syndrome of hypoglycemia-associated autonomic failure (HAAF) in diabetes. HAAF can be caused by recent antecedent hypoglycemia, sleep, or prior exercise, but its precise mechanisms are not known (64,65). HAAF is a dynamic syndrome distinct from diabetic autonomic neuropathy.

The clinical diagnosis of impaired awareness of hypoglycemia is based on the patient's subjective assessment (or evidence from close associates) because documentation of substantially reduced symptoms during experimental hypoglycemia, which is critical for research studies (64), is not practical clinically. Clinical scoring of symptoms has been developed (66–68). Because impaired awareness is inducible and reversible, such a classification cannot be assumed to be stable. Therefore, people with diabetes at risk for hypoglycemia by virtue of their diabetes treatment regimen should have their awareness status reviewed regularly. The fact that impaired awareness of hypoglycemia, and at least in part the attenuated sympathoadrenal response, can be reversed by as little as 2–3 weeks of scrupulous avoidance of hypoglycemia in most affected patients (18–21) provides compelling additional support for the clinical relevance of HAAF and for a portion of the therapeutic approach to the problem of hypoglycemia in diabetes, as discussed shortly.

### Risk Factors for Hypoglycemia

The risk factors for iatrogenic hypoglycemia in diabetes are those relevant to

therapeutic hyperinsulinemia and those relevant to compromised defenses against the resulting falling plasma glucose concentrations (1,2). The conventional risk factors for hypoglycemia in diabetes are based on the premise that absolute or relative therapeutic hyperinsulinemia is the sole determinant of risk and include the following:

1. Insulin (or sulfonylurea or glinide) doses are excessive, ill-timed, or of the wrong type.
2. Exogenous glucose delivery is decreased as it is after a missed or low-carbohydrate meal and during the overnight fast.
3. Endogenous glucose production is decreased as it is after alcohol ingestion.
4. Glucose utilization is increased as it is during and shortly after exercise.
5. Sensitivity to insulin is increased as it is in the middle of the night, late after exercise, and after weight loss or improved fitness.
6. Insulin clearance is decreased as it is with renal failure, hepatic failure, hypothyroidism, or, rarely, high levels of insulin-binding antibodies.

Risk factors for hypoglycemia indicative of compromised defenses against falling plasma glucose concentrations include the following situations:

1. There is absolute endogenous insulin deficiency. The frequency of hypoglycemia increases with the duration of diabetes (26) probably due to progressive endogenous insulin deficiency that develops rapidly in type 1 diabetes and more slowly in type 2 diabetes. Absolute endogenous insulin deficiency predicts loss of the glucagon response to hypoglycemia (1,64).
2. There is a history of severe hypoglycemia, impaired awareness of hypoglycemia, or both as well as a relationship of hypoglycemia to recent antecedent hypoglycemia, sleep, or exercise. These are features of HAAF in diabetes (64).
3. There is intensive glycemic therapy per se evidenced by lower glycemic goals. Although hypoglycemia can occur in patients with relatively high hemoglobin $A_{1c}$ (A1C) levels and the relationship between lower A1C levels and higher rates of severe hypoglycemia (69) is now less marked with less hypoglycemia at a given A1C level (70,71), undoubtedly due to progressive improvements in the glycemic management of diabetes, a low A1C is a risk factor for hypoglycemia during intensive therapy of diabetes [reviewed in Cryer (8)] (33,72–74). Nonetheless, as discussed shortly, structured patient education is intended to reduce both the frequency of severe hypoglycemia and the A1C level (9–17).

### Glycemic Goals in Diabetes

The selection of a glycemic goal for a person with diabetes treated with a sulfonylurea, a glinide, or insulin is a trade-off between the benefits of glycemic control (partial prevention or delay of microvascular complications and perhaps that of macrovascular complications) and the risk of recurrent morbidity, and potential mortality, of hypoglycemia (8). A reasonable individualized glycemic goal is the lowest A1C that does not cause severe hypoglycemia and preserves awareness of hypoglycemia, preferably with little or no symptomatic or even asymptomatic hypoglycemia, at a given stage in the evolution of the individual's diabetes (8). Thus, the glycemic goal should be linked not only to the level of glycemic control (i.e., the A1C) but also to the risk of hypoglycemia, specifically to the drugs used and the degree of endogenous insulin deficiency and the anticipated benefit of the targeted level of glycemic control. For example, a nondiabetic A1C would be reasonable in a patient with early type 2 diabetes who is treated effectively with lifestyle changes and/or drugs that do not cause hypoglycemia, whereas a higher A1C that is just sufficient to prevent symptoms of hyperglycemia would be reasonable in a patient who has a limited life expectancy. Action is required when a sulfonylurea, glinide, or insulin regimen causes severe hypoglycemia, impaired awareness of hypoglycemia, or an unacceptable number of symptomatic or asymptomatic hypoglycemic episodes. Actions to minimize the risk of hypoglycemia taken by the diabetes health-care provider and the person with diabetes can be expected to improve glycemic control more safely.

## MINIMIZING HYPOGLYCEMIA IN DIABETES

### General Approach to the Problem

The problem of iatrogenic hypoglycemia can be solved only if it is recognized by the diabetes health-care provider, the patient, and the caregivers. In a patient treated with a sulfonylurea, a glinide, or insulin, it is fundamental that the provider acknowledges the possibility of real, or feared, hypoglycemia and gives the patient and those close to the patient the opportunity to express their observations and thoughts. The provider must discuss with patients the frequency and timing of hypoglycemic episodes of any severity, seek evidence for asymptomatic episodes by asking whether others sometimes tell the patient that he or she is hypoglycemic and by asking close acquaintances directly, and review SMPG (and CGM) data with the patient to search for evidence of hypoglycemia.

When hypoglycemia is recognized to be a problem, the diabetes health-care provider and patient should first consider each conventional risk factor and those indicative of compromised defenses against falling plasma glucose concentrations. Sometimes, a cause of recurrent hypoglycemia can be identified and corrected.

In the absence of a simple solution, the provider must review the patient's management strategies (3–6). A detailed discussion of these strategies and their application in special populations, such as children, the elderly, and pregnant women, to particular activities, such as exercise and driving, and to specific drugs and therapeutic regimens is provided elsewhere (1,2).

In general, diabetes treatment regimens should be constructed with a view to minimizing hypoglycemia as well as hyperglycemia. Those principles relevant to minimizing hypoglycemia include drug selection, the use of insulin analogs, and the use of insulin treatment technologies as well as patient education. Discontinuing a sulfonylurea or a glinide would obviously reduce hypoglycemia and generally would require the addition of an alternative glucose-lowering medication. But sulfonylureas are both inexpensive and widely available and sometimes might be the most

practical medication. When therapy with insulin is necessary, as it is in type 1 diabetes and ultimately in most individuals with type 2 diabetes, the use of more physiological insulin regimens and genetically engineered insulin analogs reduces the frequency of at least nocturnal hypoglycemia (75,76), including severe nocturnal hypoglycemia (77).

CSII offers potential advantages over multiple daily injections (MDIs) of insulin in a basal-bolus insulin regimen, especially in type 1 diabetes, because one can vary the rate of basal insulin infusion throughout a 24-h period. CSII may be better than MDI in selected, capable, and motivated patients with hypoglycemia-prone diabetes (70,78) largely because of the premise that CSII may reduce A1C to some extent without increasing the risk of hypoglycemia. One meta-analysis concluded that compared with MDI, CSII reduces hypoglycemia, but this conclusion was based on three randomized controlled trials using an NPH or lente insulin–based MDI regimen (79); trials using insulin analog MDI comparison groups have not reported lower rates of hypoglycemia with CSII (80–82). A subsequent meta-analysis of randomized controlled trials of CSII versus MDI disclosed only a small lowering of A1C (−0.2%) with no significant difference in severe or nocturnal hypoglycemia (83). There is evidence that insulin pump bolus calculators are effective (84). Despite its conceptual attractiveness, subcutaneous CGM alone has had rather minimal effects in reducing the frequency of hypoglycemia (85–88), although studies focused on more patients with problematic hypoglycemia are needed. However, the combination of real-time CGM and CSII (sensor-augmented pump therapy) including an insulin pump programmed to suspend insulin infusion when glucose levels fall to a selected low value has been reported to reduce the frequency of severe hypoglycemia in type 1 diabetes (89–91). Based on randomized controlled trials published up to 2012, Yeh et al. (92) concluded that CSII (compared with MDI), real-time CGM (compared with SMPG), and CSII plus CGM (compared with MDI and SMPG) had not been shown to reduce the incidence of severe hypoglycemia in either type 1 or insulin-treated type 2 diabetes. Of note, one recent study (16) reported that the impact of ongoing personal support for patients with problematic hypoglycemia outweighed any benefit of CSII and CGM.

Work continues on closed-loop insulin or insulin and glucagon replacement (93,94) and on pancreas and pancreatic islet transplantation (95). When these become consistently successful, they will likely eliminate hypoglycemia.

### Structured Education Coupled With Scrupulous Avoidance of Hypoglycemia

Given documented evidence that glycemic control partially prevents or delays microvascular complications (retinopathy, nephropathy, and neuropathy) in type 1 diabetes (69) and type 2 diabetes (44,45,96,97) and might partially prevent or delay some macrovascular complications in type 1 diabetes (98) and type 2 diabetes (99), it follows that a lower A1C is in the best interest of people with diabetes if that can be achieved and maintained safely. However, when hypoglycemia becomes a problem (the regimen causes severe hypoglycemia, impaired awareness of hypoglycemia, an unacceptable number of episodes of symptomatic or asymptomatic hypoglycemia, or a combination of these), the core action for essentially all affected patients is consideration of individualized glycemic goals (7,8) and delivery of structured patient education (often reeducation) to reduce the incidence of hypoglycemia without compromising glycemic control (9–17). This is typically coupled with short-term scrupulous avoidance of hypoglycemia, which, when successful, reverses impaired awareness of hypoglycemia (18–21).

Although generally confined to observational studies, longstanding and substantial evidence shows that structured patient education on implementing flexible intensive glycemic therapy, particularly with insulin, reduces the incidence of hypoglycemia without compromising glycemic control (9–17). We would reason that it is unsafe to encourage such intensive therapy without accompanying it with high-quality education that provides sufficient knowledge of insulin actions and empowers patients with the tools to prevent and treat hypoglycemia.

In addition to basic diabetes education that includes the principles of nutrition, all people with diabetes treated with a sulfonylurea, a glinide, or insulin and not only those treated with insulin should receive structured education about hypoglycemia and how to avoid it. The therapeutic objective is to minimize the number of episodes of hypoglycemia and their severity and duration without promoting hyperglycemia and raising A1C levels. Indeed, the goal is to reduce both hypoglycemia and A1C levels. This patient education must cover a broad range of information and skills training as well as include a motivational element.

Patients need to understand the risk factors for hypoglycemia and how their particular sulfonylurea, glinide, or insulin regimen can cause hypoglycemia and when that is most likely to occur. Thus, they should be familiar with the effects

**Table 1—Recommendations of the International Hypoglycaemia Study Group**

People with diabetes treated with a sulfonylurea, a glinide, or insulin should
- Be educated about hypoglycemia.
- Treat SMPG levels ≤70 mg/dL (3.9 mmol/L) to avoid progression to clinical iatrogenic hypoglycemia.
- Regularly be queried about hypoglycemia, including the glucose level at which symptoms develop. Those developing symptoms at a glucose level <55 mg/dL (3.0 mmol/L) should be considered at risk.

When hypoglycemia becomes a problem, the diabetes health-care provider should
- Consider each conventional risk factor and those indicative of compromised glucose counterregulation.
- Avoid sulfonylureas (and glinides) if possible, using insulin analogs when insulin is required, and consider using CSII, CGM, and CSII + CGM in selected patients.
- Provide structured education and, in patients with impaired awareness of hypoglycemia, prescribe short-term scrupulous avoidance of hypoglycemia.
- Seek to achieve the lowest A1C level that does not cause severe hypoglycemia and preserves awareness of hypoglycemia with an acceptable number of less-than-severe episodes of hypoglycemia, provided that benefit from glycemic control can be anticipated.

of the dose and timing of their individual glucose-lowering drugs and the risks of missed or low-carbohydrate meals, the overnight fast, and alcohol ingestion. Patients must learn strategies to defend against the glycemic effects of planned and unanticipated exercise and the occurrence of delayed hypoglycemia after intense physical activity. In short, they need to learn to adjust their medications, meal plans, and exercise to optimize glycemic control and minimize hypoglycemia. The patient as well as the provider and caregivers must understand that episodes of hypoglycemia signal an increased likelihood of future, often more severe, hypoglycemia (34). This insight is fundamental to understanding that short-term scrupulous avoidance of hypoglycemia is key to long-term reversal of impaired awareness of hypoglycemia (18–21). In addition, a patient using CGM needs to learn how to use monitoring data to minimize hypoglycemia as well as hyperglycemia.

Patients at risk for hypoglycemia need to know the common symptoms of hypoglycemia, particularly those most meaningful to them. Being able to recognize even subtle symptoms and correctly interpret them as possibly indicative of hypoglycemia can empower the patient to take immediate action, including SMPG and ingesting carbohydrates if the value is ≤70 mg/dL (3.9 mmol/L). Consistently treating SMPG (or CGM) values below the alert value and not delaying treatment in the absence of symptoms are important. If plasma glucose testing is not practical, it is wise to treat symptoms of hypoglycemia whenever they arise and to perform SMPG as soon as possible. The patient needs to know how to treat (and not overtreat) hypoglycemia with appropriate carbohydrates and how to follow an episode with monitoring and, if indicated, regimen adjustments. Close associates, such as a spouse or partner, also need to recognize severe hypoglycemia and how to prepare and administer glucagon.

Diabetes health-care providers also should be aware that some patients, particularly those with longstanding impaired awareness of hypoglycemia, may have health beliefs that interfere with their ability to benefit from education alone and thus may benefit from psychosocial interventions to facilitate behavioral changes (14). Those beliefs range from an obsessive attachment to a very low A1C level to an overriding fear of hypoglycemia.

## CONCLUSIONS

Clinical iatrogenic hypoglycemia is a problem for many people with diabetes treated with a sulfonylurea, a glinide, or insulin. Minimizing hypoglycemia includes acknowledging the problem, considering each risk factor, and applying the principles of intensive glycemic therapy, including selecting appropriate individualized glycemic goals and providing structured patient education typically combined with short-term scrupulous avoidance of hypoglycemia. The recommendations of the International Hypoglycaemia Study Group are summarized in Table 1. The risk of hypoglycemia is modifiable and can be minimized with the methods discussed in this review.

## Appendix

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P.A. has served on scientific advisory boards and/or as a lecturer for AstraZeneca, Boehringer Ingelheim/Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, and Sanofi. B.C. had research grant support from Halozyme and Lilly to the former MidAmerica Diabetes Associates. P.E.C. has served on scientific advisory boards for Boehringer Ingelheim/Lilly, Calibrium, Merck Sharp & Dohme, Novo Nordisk, and Pfizer. B.d.G. has served on scientific advisory boards for Merck Sharp & Dohme, Novo Nordisk, and Sanofi and received research grant support from Europharma Group. S.R.H. has served on scientific advisory boards and provided consultations for which his institution has received remuneration from Lilly, Novo Nordisk, Takeda, Merck Sharp & Dohme, and Becton Dickinson and has served as a speaker for which he received remuneration from Lilly, Novo Nordisk, Boehringer Ingelheim, and Takeda. B.M.F. has served on scientific advisory boards and as a speaker for Boehringer Ingelheim, Janssen, Lilly, Merck Sharp & Dohme, Novo Nordisk, and Lilly. L.G.-F. has served as a consultant or speaker and/or has received research grant support from Abbott Diabetes Care, AstraZeneca, Dexcom, Johnson & Johnson, and Merck Sharp & Dohme. T.J. has served as a speaker for Novo Nordisk, Lilly, Medtronic, and Sanofi. K.K. has served as a consultant or speaker for AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi and has received research grant support from AstraZeneca, Boehringer Ingelheim, Lilly, Novartis, Novo Nordisk, Roche, and Sanofi. L.A.L. has served as a consultant or speaker for Abbott, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Servier, and Takeda. R.V. has served as a

consultant for Medtronic and has received research grant support from Dexcom. S.Z. has served on scientific advisory boards for Amgen, Bristol-Myers Squibb, AstraZeneca, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Takeda; has served as a speaker for Bristol-Myers Squibb, AstraZeneca, Janssen, Merck Sharp & Dohme, Servier, and Takeda; and has received research grant support from Bristol-Myers Squibb and AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

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## References


1. Cryer PE. *Hypoglycemia in Diabetes: Pathophysiology, Prevalence, and Prevention*. 2nd ed. Alexandria, VA, American Diabetes Association, 2013
2. Frier BM, Heller SR, McCrimmon RJ. *Hypoglycaemia in Clinical Diabetes*. 3rd ed. Chichester, West Sussex, Wiley Blackwell, 2014
3. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003;26:1902–1912
4. Rossetti P, Porcellati F, Bolli GB, Fanelli CG. Prevention of hypoglycemia while achieving good glycemic control in type 1 diabetes: the role of insulin analogs. Diabetes Care 2008;31 (Suppl. 2):S113–S120
5. Amiel SA. Hypoglycemia: from the laboratory to the clinic. Diabetes Care 2009;32:1364–1371
6. Graveling AJ, Frier BM. Hypoglycaemia: an overview. Prim Care Diabetes 2009;3:131–139
7. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association; European Association for the Study of Diabetes. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38:140–149
8. Cryer PE. Glycemic goals in diabetes: tradeoff between glycemic control and iatrogenic hypoglycemia. Diabetes 2014;63:2188–2195
9. Mühlhauser I, Jörgens V, Berger M, et al. Bicentric evaluation of a teaching and treatment programme for type 1 (insulin-dependent) diabetic patients: improvement of metabolic control and other measures of diabetes care for up to 22 months. Diabetologia 1983;25:470–476
10. Sämann A, Mühlhauser I, Bender R, Kloos Ch, Müller UA. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. Diabetologia 2005;48:1965–1970
11. Plank J, Köhler G, Rakovac I, et al. Long-term evaluation of a structured outpatient education programme for intensified insulin therapy in patients with type 1 diabetes: a 12-year follow-up. Diabetologia 2004;47:1370–1375
12. Crasto W, Jarvis J, Khunti K, et al. Multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: the Microalbuminuria Education and Medication Optimisation (MEMO) study. Diabetes Res Clin Pract 2011;93: 328–336
13. Hopkins D, Lawrence I, Mansell P, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 2012; 35:1638–1642
14. Leelarathna L, Little SA, Walkinshaw E, et al. Restoration of self-awareness of hypoglycemia in adults with long-standing type 1 diabetes: hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. Diabetes Care 2013;36:4063–4070
15. de Zoysa N, Rogers H, Stadler M, et al. A psychoeducational program to restore hypoglycemia awareness: the DAFNE-HART pilot study. Diabetes Care 2014;37:863–866
16. 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;37:2114–2122
17. Elliott J, Jacques RM, Kruger J, et al. Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with type 1 diabetes. Diabet Med 2014; 31:847–853
18. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993;42:1683–1689
19. Fanelli C, Pampanelli S, Epifano L, et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia 1994;37:1265–1276
20. Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet 1994;344:283–287
21. Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 1994;43:1426–1434
22. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245–1249
23. 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. Diabetes Care 2013;36:1384–1395
24. Pedersen-Bjergaard U, Pramming S, Heller SR, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev 2004;20:479–486
25. Donnelly LA, Morris AD, Frier BM, et al.; DARTS/MEMO Collaboration. Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. Diabet Med 2005;22:749–755
26. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140–1147
27. Cryer PE, Axelrod L, Grossman AB, et al.; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009;94:709–728
28. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 1988;37:901–907
29. Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 1988;318:1487–1492
30. Jones TW, Boulware SD, Kraemer DT, Caprio S, Sherwin RS, Tamborlane WV. Independent effects of youth and poor diabetes control on responses to hypoglycemia in children. Diabetes 1991;40:358–363
31. Cryer PE. The prevention and correction of hypoglycemia. In *Handbook of Physiology. Vol. II, The Endocrine Pancreas and Regulation of Metabolism*. Jefferson LS, Cherrington AD, Eds. New York, Oxford University Press, 2001, p. 1057–1092
32. Davis SN, Shavers C, Mosqueda-Garcia R, Costa F. Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. Diabetes 1997;46:1328–1335
33. ORIGIN Trial Investigators. Predictors of nonsevere and severe hypoglycemia during glucose-lowering treatment with insulin glargine or standard drugs in the ORIGIN trial. Diabetes Care 2015;38:22–28
34. Cox DJ, Gonder-Frederick L, Ritterband L, Clarke W, Kovatchev BP. Prediction of severe hypoglycemia. Diabetes Care 2007;30:1370–1373
35. Towler DA, Havlin CE, Craft S, Cryer P. Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. Diabetes 1993;42:1791–1798
36. DeRosa MA, Cryer PE. Hypoglycemia and the sympathoadrenal system: neurogenic symptoms are largely the result of sympathetic neural, rather than adrenomedullary, activation. Am J Physiol Endocrinol Metab 2004;287: E32–E41
37. Marrett E, Radican L, Davies MJ, Zhang Q. Assessment of severity and frequency of self-reported hypoglycemia on quality of life in patients with type 2 diabetes treated with oral antihyperglycemic agents: a survey study. BMC Res Notes 2011;4:251–257
38. Amin A, Lau L, Crawford S, Edwards A, Pacaud D. Prospective assessment of hypoglycemia symptoms in children and adults with type 1 diabetes. Can J Diabetes 2014;38:263–268
39. Graveling AJ, Noyes KJ, Allerhand MH, et al. Prevalence of impaired awareness of hypoglycemia and identification of predictive symptoms

in children and adolescents with type 1 diabetes. Pediatr Diabetes 2014;15:206–213
40. Gonder-Frederick L, Zrebiec J, Bauchowitz A, et al. Detection of hypoglycemia by children with type 1 diabetes 6 to 11 years of age and their parents: a field study. Pediatrics 2008;121:e489–e495
41. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
42. Finfer S, Liu B, Chittock DR, et al.; NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012;367:1108–1118
43. Macrae D, Grieve R, Allen E, et al.; CHiP Investigators. A randomized trial of hyperglycemic control in pediatric intensive care. N Engl J Med 2014;370:107–118
44. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
45. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
46. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
47. Mellbin LG, Rydén L, Riddle MC, et al.; ORIGIN Trial Investigators. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J 2013;34:3137–3144
48. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. I. Survival, causes of death, and complications. Diabetologia 1978;14:363–370
49. Tunbridge WM; Medical Services Study Group and British Diabetic Association. Factors contributing to deaths of diabetics under fifty years of age. Lancet 1981;2:569–572
50. Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, I: all-cause mortality in patients with insulin-treated diabetes mellitus. Diabet Med 1999;16:459–465
51. Patterson CC, Dahlquist G, Harjutsalo V, et al. Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetologia 2007;50:2439–2442
52. Jacobson AM, Musen G, Ryan CM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 2007;356:1842–1852
53. Feltbower RG, Bodansky HJ, Patterson CC, et al. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: results from the Yorkshire Register of Diabetes in Children and Young Adults. Diabetes Care 2008;31:922–926
54. Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006;49:298–305
55. Tanenberg RJ, Newton CA, Drake AJ. Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system. Endocr Pract 2010;16:244–248
56. Holstein A, Egberts EH. Risk of hypoglycaemia with oral antidiabetic agents in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2003;111:405–414
57. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909
58. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. Diabetes Care 2015;38:316–322
59. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–1747
60. Reno CM, Daphna-Iken D, Chen YS, VanderWeele J, Jethi K, Fisher SJ. Severe hypoglycemia-induced lethal cardiac arrhythmias are mediated by sympathoadrenal activation. Diabetes 2013;62:3570–3581
61. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. Patient Educ Couns 2007;68:10–15
62. Johnson SR, Cooper MN, Davis EA, Jones TW. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. Diabet Med 2013;30:1126–1131
63. Gerich J, Davis J, Lorenzi M, et al. Hormonal mechanisms of recovery from insulin-induced hypoglycemia in man. Am J Physiol 1979;236:E380–E385
64. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2013;369:362–372
65. Chan O, Sherwin R. Influence of VMH fuel sensing on hypoglycemic responses. Trends Endocrinol Metab 2013;24:616–624
66. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994;17:697–703
67. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 1995;18:517–522
68. Høi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B. Classification of hypoglycemia awareness in people with type 1 diabetes in clinical practice. J Diabetes Complications 2010;24:392–397
69. The Diabetes Control and Complications Trial Research Group. 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;329:977–986
70. Cooper MN, O'Connell SM, Davis EA, Jones TW. A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes. Diabetologia 2013;56:2164–2170
71. Karges B, Rosenbauer J, Kapellen T, et al. Hemoglobin A1c levels and risk of severe hypoglycemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. PLoS Med 2014;11:e1001742
72. Lipska KJ, Warton EM, Huang ES, et al. $HbA_{1c}$ and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. Diabetes Care 2013;36:3535–3542
73. Monami M, Dicembrini I, Kundisova L, Zannoni S, Nreu B, Mannucci E. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. Diabetes Obes Metab 2014;16:833–840
74. Weinstock RS, Xing D, Maahs DM, et al.; T1D Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab 2013;98:3411–3419
75. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev 2006;2:CD003287
76. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;2:CD005613
77. 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;2:553–561
78. Johnson SR, Cooper MN, Jones TW, Davis EA. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. Diabetologia 2013;56:2392–2400
79. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med 2008;25:765–774
80. Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. Diabetes Care 2004;27:1554–1558
81. Hirsch IB, Bode BW, Garg S, et al.; Insulin Aspart CSII/MDI Comparison Study Group. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care 2005;28:533–538
82. Bolli GB, Kerr D, Thomas R, et al. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion

(lispro) in type 1 diabetes: a randomized open parallel multicenter study. Diabetes Care 2009; 32:1170–1176
83. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab 2009;94:729–740
84. Ramotowska A, Golicki D, Dżygało K, Szypowska A. The effect of using the insulin pump bolus calculator compared to standard insulin dosage calculations in patients with type 1 diabetes mellitus - systematic review. Exp Clin Endocrinol Diabetes 2013;121:248–254
85. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795–800
86. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:d3805
87. Langendam M, Luijf YM, Hooft L, Devries JH, Mudde AH, Scholten RJ. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database Syst Rev 2012;1:CD008101
88. Bay C, Kristensen PL, Pedersen-Bjergaard U, Tarnow L, Thorsteinsson B. Nocturnal continuous glucose monitoring: accuracy and reliability of hypoglycemia detection in patients with type 1 diabetes at high risk of severe hypoglycemia. Diabetes Technol Ther 2013;15:371–377
89. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013; 369:224–232
90. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA 2013;310: 1240–1247
91. Maahs DM, Calhoun P, Buckingham BA, et al.; In Home Closed Loop Study Group. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. Diabetes Care 2014;37:1885–1891
92. Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157: 336–347
93. Leelarathna L, Dellweg S, Mader JK, et al.; AP@home Consortium. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. Diabetes Care 2014;37:1931–1937
94. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014;371:313–325
95. Ang M, Meyer C, Brendel MD, Bretzel RG, Linn T. Magnitude and mechanisms of glucose counterregulation following islet transplantation in patients with type 1 diabetes suffering from severe hypoglycaemic episodes. Diabetologia 2014;57:623–632
96. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
97. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–117
98. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
99. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589