Minimizing Hypoglycemia Risk to Improve Cardiovascular Health

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Severe hypoglycemia is a predictor of mortality and cardiovascular events. Risk of severe hypoglycemia increases with intensive glucose control and with insulin and sulfonylurea drugs, especially in patients with chronic kidney disease.

Risk of hypoglycemia can be reduced with the use of individualized glucose targets, agents that minimize or do not cause hypoglycemia, continuous glucose monitoring, and diabetes education. This document characterizes the complex relationship between tight glycemic control, severe hypoglycemia, and cardiovascular events. It describes an individualized approach to glycemic control for patients with type 2 diabetes to reduce hypoglycemia risk and maximize cardiovascular health.

Symptoms of Hypoglycemia

SWEATING

BLURRED VISION

HEADACHE

RINGING IN THE EARS

INCREASED HEART RATE

TREMBLING

HUNGER

ANXIETY IRRITABILITY

WEAKNESS OR TIREDNESS

Hypoglycemia Risk

Hypoglycemia is classified in persons with diabetes as level 1 if glucose is between 54-69 mg/dL (inclusive), level 2 if glucose is <54 mg/dL, and level 3 for any hypoglycemic event that is characterized by altered mental or physical status requiring assistance.[1] Early symptoms of hypoglycemia typically are adrenergic (e.g., palpitations, diaphoresis, tremor, anxiety, hunger) but as the glucose drops below 50 mg/dL neuroglycopenic symptoms develop (confusion, weakness, vision changes, focal neurologic deficits, seizure, coma).

It is important to note that in elderly patients using insulin or sulfonylurea drugs, self-reported hypoglycemia was under-recognized by healthcare providers and symptoms were atypical – most commonly weakness, fatigue or feeling languid, and dizziness or lightheadedness.[2]

Hypoglycemia unawareness is characterized by the loss of early adrenergic warning symptoms, often in the setting of long-standing insulin use and antecedent hypoglycemia, and is associated with increased risk of level 3 (severe) events as shown in Figure 1.
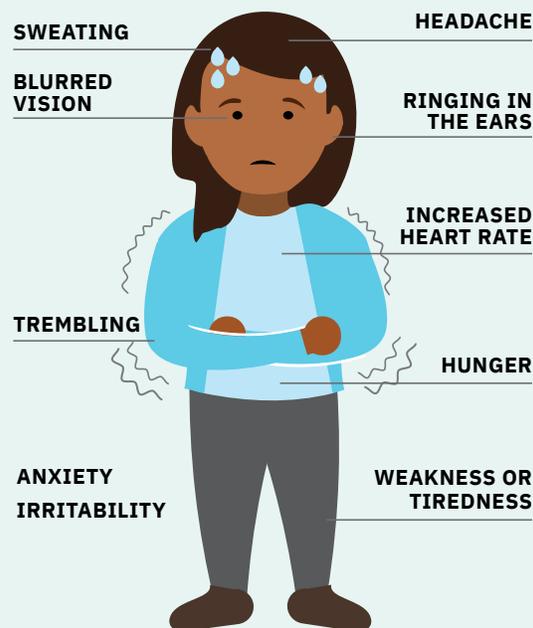
FIGURE 1

Risk Factors for Hypoglycemia

Risk factors for hypoglycemia are subdivided into multiple categories. The key factors associated with increased risk of severe hypoglycemic events include longer duration of diabetes and the use of insulin in diabetes management.[1-4]

Diabetes Complexity
- Diabetes Mellitus (DM) duration
- Duration of insulin
- Hypo unawareness
- Prior hypoglcyemia
- Comorbidity

Comorbidity
- Frailty
- Cognitive impairment
- Chronic Kidney Disease (CKD)
- Neuropathy
- Cardiovascular Disease (CVD)
- End-stage liver disease
- Depression
- Malnutrition

Pharmacotherapy
- Insulin, sulfonylurea
- Medication complexity
- Non-DM medications (beta blocker)
- Medication misadventures (dose, timing)

Environment
- Caregiver
- Food insecurity
- Poor health literacy
- Financial burden
- Competing demands
- Fasting

Health System
- A1C driven care
- Inadequate education and support
- Payor decisions
- Lack of integration between glucose monitoring and electronic medical record

Risks and Benefits of Tight Glycemic Control on Cardiovascular Health

The nature of the association between cardiovascular disease and severe hypoglycemia remains unclear, and the association may be bidirectional. Severe hypoglycemia is a predictor of mortality, and cardiovascular events are a predictor of future severe hypoglycemia.[5-7]

While severe hypoglycemia may occur at any A1C level, several trials have shown that the modest benefits of tight control (A1C target 6-6.5%) were outweighed by significant concerns over hypoglycemia. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial used the most aggressive intensive therapy (target HbA1C <6.0%) compared with standard therapy (target HbA1C 7.0-7.9%). This trial was stopped early (within four years) due to increased all-cause mortality, cardiovascular-related death, and severe hypoglycemia associated with the intensive therapy.[8] The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial[9] and Veterans Affairs Diabetes Trial (VADT)[10] also showed increased risk of hypoglycemia events with intensive glycemic control but little to no benefit on cardiovascular health. In all these trials, severe hypoglycemia was associated with a significant increase in the adjusted risks of major macrovascular events and death.[11-12] More recent studies bolster a link between hypoglycemia and cardiovascular-associated death.[13]

The potential small improvement in relative risk reduction to cardiac ischemia by tightly controlling blood sugar is outweighed by severe hypoglycemia risks in many patients, particularly the frail and/or elderly, or those with multiple complications or comorbidities who are receiving insulin or sulfonylureas. Glycemic control should be individualized for patients with type 2 diabetes in order to maximize benefits while reducing risks.

Use Individualized Glycemic Targets and Shared Decision-Making to Optimize Metabolic Profiles and A1C Targets, and to Avoid Hypoglycemia

BEST PRACTICES:

1. **Collaborate with the patient using Shared Decision-Making to set a realistic A1C and corresponding daily blood glucose target based upon the patient's health goals, psychosocial barriers, and personal preferences.[14] (Figure 2)**

   a. In patients who are using sulfonylureas, glinides, and/or insulin therapy with additional comorbidities or unacceptable hypoglycemia risk, an A1C target between 7-8% is acceptable. An A1C goal as high as 8.5% should be considered in some patients with highest hypoglycemia risk and least likelihood of benefit.

   b. Consider de-intensifying pharmacologic therapy in patients with type 2 diabetes mellitus who are frail, elderly, or who have a history of hypoglycemic unawareness, chronic kidney disease, established microvascular or macrovascular complications, or psychosocial barriers to lower A1C targets.

FIGURE 2

Patient-Centered Glycemic Management

LOW RISK	HIGH RISK
Younger	Older
Long life expectancy	Short life expectancy
Early course diabetes	Late course diabetes
No history of hypoglycemia	Antecedent hypoglycemia
No comorbidities	Comorbidities
No polypharmacy	Polypharmacy

More Aggressive   **Less Aggressive**

Brutsaert et al. Journal of Diabetes and its Complications 28 (2014) 565-572

   c. Reserve intensive glycemic management for younger patients with few comorbidities who are recently diagnosed.

   d. Whenever feasible, use diabetes treatment that does not cause hypoglycemia in combination with metformin and that also reduces cardiovascular risk (such as GLP-1 or SGLT2i agents).

2. **Considerations for prescribing sulfonylureas**

   a. Patients should be educated regarding the signs and symptoms of hypoglycemia and its appropriate treatment, and consistently questioned at follow-up regarding hypoglycemic events. The 15-15 Rule (see page 5) recommends ingesting 15 grams of carbohydrates every 15 minutes until the glucose level is >70 mg/dL.
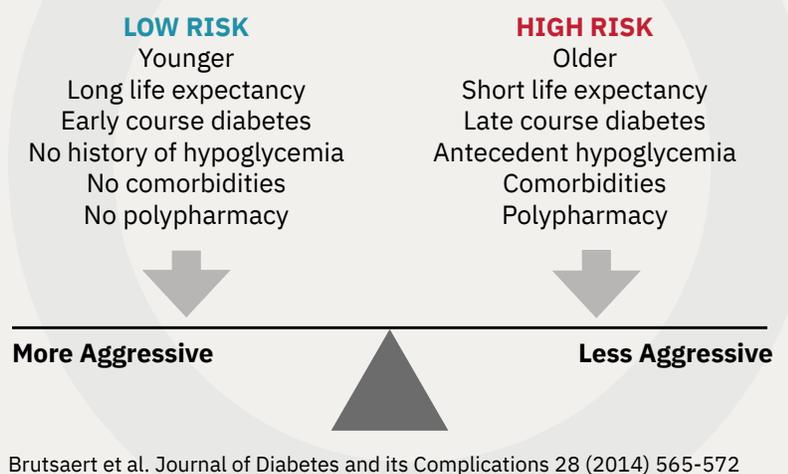
   b. Glipizide or glimepiride are preferred over glyburide secondary to glyburide's excessive hypoglycemic risk profile.

   c. Sulfonylureas should be held or reduced for patients who may be missing meals and/or engaged in heavier than normal activity.

   d. Caution should be used when combining sulfonylureas and insulin.

3. **Considerations for prescribing insulin**

   a. Patients should be educated regarding the signs and symptoms of hypoglycemia and its appropriate treatment (15-15 Rule), and consistently questioned at follow-up regarding hypoglycemic events.

   b. Patients should be encouraged to monitor glucose levels three or more times per day. Continuous glucose monitoring has been shown to reduce hypoglycemia risk and should be considered in patients receiving multiple insulin injections per day.[15]

   c. Fasting blood glucose targets with basal long or intermediate acting Neutral Protamine Hagedorn (NPH) insulins should be based upon a mutually agreeable A1C target.

   d. NPH insulin is effective and relatively inexpensive, but has an increased risk of hypoglycemia, particularly overnight compared to glargine or detemir. Hypoglycemia risk may be reduced further with the use of ultra long-acting basal insulins (degludec or glargine U300).

   e. Significant overnight drops in blood glucose from bedtime to fasting (80 points or more) with the use of basal or intermediate acting insulins may place the patient at excessive risk for hypoglycemia.

   f. Patients prescribed multiple injections of insulin per day (basal bolus insulin) are at greatest risk for hypoglycemia and should be referred to a certified diabetes care and education specialist for counseling on consistent carbohydrate meals or adjusting insulin according to meal size or carbohydrate intake.

   g. Patients should have a plan for reducing basal insulin in case of reduced oral intake (generally a reduction of at least 20-50% is appropriate).

   h. Utilize insulin sparing agents such as metformin and GLP-1 receptor agonists whenever possible in combination with insulin.

4. **Diabetes education and/or nutrition consultation referrals are indicated for patients at risk for hypoglycemia.**

   Education should include several elements:

   a. Recognition and treatment of hypoglycemia.

   b. How to adjust insulin in case of reduced intake or exercise.

   c. Consistent carbohydrate diet or flexible plan to adjust insulin dose for varying carbohydrate intake.

   d. Other risk factors for hypoglycemia, (e.g., alcohol intake).

   e. Safety while driving.

Additional Resources

Hypoglycemia Risk Score: online risk calculator intended to help identify patients at highest risk for severe hypopglycemia who might benefit from targeted interventions. https://www.mdcalc.com/hypoglycemia-risk-score

Choosing Wisely: recommendations regarding glucose monitoring are included. https://www.choosingwisely.org/clinician-lists/aafp-daily-home-glucose-monitoring-for-patients-with-type-2-diabetes/

Endocrine Society Hypoglycemia Prevention Initiative: resources and toolkits to decrease the risk of hypoglycemia through shared decision making, individualized A1C goals, and/or changes to glucose-lowering medications regimen. https://www.endocrine.org/hypoglycemia-prevention-initiative

Low Blood Sugar: patient education resource on hypoglycemia. https://www.diabetesdaily.com/learn-about-diabetes/understanding-blood-sugars/is-my-blood-sugar-normal/low-blood-sugar-hypoglycemia/

Talking with your Patients About Hypoglycemia Treatment

THE 15-15 RULE is intended to help patients understand how to quickly and adequately treat hypoglycemia without causing rebound hyperglycemia. It recommends consuming 15 grams of carbohydrate and checking blood sugar after 15 minutes. The instructions for patients are as follows:

- When you feel you are low, check your blood sugar (glucose) as soon as possible. If you are unable to check your sugar, treat yourself for low blood sugar anyway.

- If the glucose is below 70 mg/dL, eat or drink 15 grams of fast-acting carbohydrates. Examples include:
    - 3-4 glucose tablets
    - Glucose or dextrose gel (one tube typically contains 15 grams)
    - 4 ounces (½ cup) juice or regular soda
    - 1 tablespoon sugar, honey, corn syrup
    - Hard candy, jelly beans (see label for quantity)
    - If the glucose level is under 50 mg/dL, consider 15 grams of carbohydrate.

- Recheck glucose in 15 minutes. If it is still less than 70 mg/dL, repeat another 15 grams of carbohydrate. Note that the glucose level may return to normal before you feel better. It is important to avoid overtreatment.

- Once your glucose is back to normal, consider having a snack with protein or fat to help prevent recurrence. Examples include half of a peanut butter sandwich or cheese and crackers.

- Keep track of any low glucose episodes and discuss ways to prevent or address them with your health care team. If you develop any severe hypoglycemia events that result in loss of consciousness or seizure, or otherwise require another person to treat, notify your health care team immediately.

GLUCOSE TABLETS

GLUCOSE OR DEXTROSE GEL

JUICE OR SODA

HONEY, SUGAR, OR CORN SYRUP

HARD CANDY, JELLY BEANS

15 GRAMS OF CARBOHYDRATE

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