Treatment of Type 2 Diabetes with Special Consideration to Reduce Hypoglycemia

Learning Objectives
After participating in this educational activity, participants should be able to:

1. Apply strategies to individualize glycemic targets in patients with type 2 diabetes
2. Discuss the limitations of frequently used conventional therapies for the treatment of patients with type 2 diabetes
3. Outline the risk factors and clinical consequences of hypoglycemia
4. Implement strategies to minimize hypoglycemia risk in the treatment of patients with type 2 diabetes

Activity Overview
Over 29 million people in the US have diabetes mellitus, and the figures continue to grow. Diabetes is a costly disease, both financially and personally for affected individuals. The estimated costs in 2012 were $245 billion.[1] Diabetes is the leading cause of: 1) blindness in working age adults, 2) end-stage renal disease, and 3) non-traumatic limb amputations. The impact of hyperglycemia can clearly be diminished by lowering glucose levels, but lowering

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glucose levels comes with the potential risk of hypoglycemia. This activity will focus on the risk of hypoglycemia in treated individuals with type 2 diabetes, how to individualize glycemic targets, and employ currently available glucose lowering therapies with a special consideration to their hypoglycemic risk profile.

**Case Study Steve: Question 1**

Now, let us consider the case of Steve. He is a 68 year-old obese male with type 2 diabetes diagnosed one year ago. His medical history includes cardiovascular disease with a coronary artery bypass graft (CABG) eight years ago, a cerebral vascular accident (CVA) five years ago, hypertension, and hyperlipidemia. His current medications are metformin 1000 mg twice daily, aspirin, lisinopril, atorvastatin, and atenolol. His laboratory report shows a hemoglobin A1C of 8.5%.

Which one of the following glycemic (A1C) target ranges is most appropriate for Steve?

- a) ≤6.5%
- b) <7.0%
- c) 7.0% - 8.0%
- d) <8.5%

The American Diabetes Association (ADA) recommends individualizing glycemic targets.[2] One target no longer fits everyone! Given that Steve has multiple co-morbidities, including cardiovascular disease and a history of CVA, his glycemic target should be the more conservative 7.0-8.0% to reduce the risk of hypoglycemia. Why is that the case? Well, there is now evidence, as discussed below, which demonstrates that aggressive targets can be harmful in select patient populations.

**Individualized Glycemic Targets**

Multiple clinical trials have addressed the question of: how aggressively should glucose be managed in the treatment of type 2 diabetes? The UK Prospective Diabetes Study (UKPDS) was a long-term prospective randomized controlled trial of 3,867 patients newly diagnosed with type 2 diabetes comparing intensive glycemic control to diet therapy.[3] The results of this study showed a reduction in microvascular disease and a subsequent follow up study showed a reduction in macrovascular disease and mortality.[3,4] In contrast, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, a multicenter randomized study of over 10,000 patients comparing intensive to less-intensive glycemic control using any treatment regimen demonstrated an increased risk of mortality in the more intensively treated group.[5] The cause of this increased mortality is unclear, but may have been related to hypoglycemia. The discrepant findings of these two studies demonstrate that glycemic targets must be individualized. The ACCORD study population was older, had a longer duration of diabetes, and many already had diabetes-related complications. In contrast, the UKPDS study population was comprised of younger, more recently diagnosed patients with diabetes. It is based on this body of evidence, among other studies, that the ADA recommends individualized glycemic targets. The standard A1C target recommended by the ADA is <7%, but it is appropriate to aim for a more conservative target of <8% in older patients, with a longer duration of diabetes, those with multiple co-morbidities, and/or high hypoglycemia risk (Figure 1).
Case Study Steve: Question 2
Now, let’s return to our patient Steve. True or false, Steve is at increased risk for hypoglycemia?

a) True
b) False

Steve has multiple co-morbidities including cardiovascular disease which puts him at higher risk for developing hypoglycemia. What does it mean for Steve if he develops hypoglycemia? Hypoglycemia reduces quality of life, increases the risk of medication non-adherence, increases healthcare costs, and has associated health consequences as outlined below.

Hypoglycemia Definitions and Cost
Hypoglycemia is defined in a patient with diabetes as a glucose of <70 mg/dL. In addition to the unpleasant associated symptoms such as shakiness, sweating, and tremor, hypoglycemia can cause confusion, loss of consciousness, and even death. Hypoglycemia is common not only in type 1 diabetes (an autoimmune disease that requires insulin for survival), but it is also common in type 2 diabetes. In one study, 25% of patients with type 2 diabetes had hypoglycemia frequently (daily to once per week).[6]

The risk of developing hypoglycemia goes up with certain medical conditions including cardiovascular, liver or renal disease, as well as with advanced age, longer duration of diabetes,
and irregular meal/activity schedules. Individuals with repeated episodes of hypoglycemia can develop hypoglycemia unawareness, a condition where they no longer exhibit the signs and symptoms of hypoglycemia. Hypoglycemia unawareness significantly increases the risk of developing a severe hypoglycemic episode (an episode when the person becomes unconscious or is unable to ingest carbohydrates).

Hypoglycemia has multiple, deleterious effects in the lives of individuals with diabetes. Hypoglycemia can impair quality of life, reduce work productivity, reduce patient adherence to the treatment plan, and increase average annual healthcare costs. Severe hypoglycemia is particularly concerning as it is associated with increased risk of major macrovascular events, major microvascular events, and even increased mortality.[7]

It is clear from these data that all hypoglycemia should be taken seriously. Glucose-lowering therapy should be selected with care considering the potential benefits and risks, including the risk of hypoglycemia.

**Glucose-lowering Medications**

Even with the advent of new drugs and drug classes for the treatment of diabetes, metformin remains the cornerstone of initial glucose-lowering therapy. It has a long history of use, has a low risk of hypoglycemia, and does not cause weight gain. Diabetes, however, is a progressive disease, and as such patients typically require additional therapies over time. The selection of subsequent therapies must be done thoughtfully by weighing the potential benefits of the medication with respect to the potential risks in the context of the individual patient’s circumstances.

**Case Study Steve: Question 3**

Our patient Steve is above his target hemoglobin A1C (of 7-8%). You discuss the A1C result of 8.5% with him, and the need for an additional glucose-lowering medication. You review the options and he informs you that he does not want an injectable medication.

Which one of the following medications do you add to treat his diabetes?

a) A sulfonylurea  
 b) Basal insulin  
 c) A DPP-4 inhibitor  
 d) A GLP-1 receptor agonist

Given Steve’s preference for an oral medication, a DPP-4 inhibitor is the optimal choice at this time. It carries little risk for hypoglycemia and is likely to get him down to his A1C goal of 7-8%. A GLP-1 receptor agonist also has little risk for hypoglycemia, but requires injections. Sulfonylurea or insulin therapies are less optimal choices because of the risk of hypoglycemia. Steve has known cardiovascular disease and is at particular risk for hypoglycemia-related morbidity/mortality.

**Conventional Glucose-lowering Medications**

Sulfonylureas are one of, if not the most, widely used glucose-lowering therapies. Glyburide, glipizide, and glimepiride belong to this class of drugs. Sulfonylureas stimulate insulin secretion without regard to the prevailing glucose concentration, which improves glucose control, but also significantly increases the risk for hypoglycemia, and therefore is not an ideal choice for Steve. They work effectively initially, but over time are more likely to result in treatment failure and the need for additional glucose lowering therapy.[8] This effect is likely caused by sulfonylurea-induced beta cell failure.
Thiazolidinediones (TZDs) lower glucose by improving insulin sensitivity and reducing gluconeogenesis. Rosiglitazone and pioglitazone fall under this class of drugs. The risk of hypoglycemia is low with TZDs, but other safety concerns have led the FDA to place a black box warning on rosiglitazone. Pioglitazone is available, but its use is limited due to concerns about weight gain, fluid retention, loss of bone density, and in patients with heart failure an increased risk of hospitalization due to congestive heart failure (CHF) exacerbation.

Insulin is available in multiple long-acting and short-acting formulations. Insulin can be titrated up to large doses to overcome marked insulin resistance and clearly has a significant role in treatment of type 2 diabetes. However, the disadvantages of using insulin are that insulin requires injections, is associated with weight gain, and significantly increases the risk of hypoglycemia. Steve wants to avoid injections and is at higher risk of hypoglycemia. He is also only modestly above his goal, so should be able to reach his goal with an oral agent. Therefore, insulin is not an ideal choice for Steve.

Alpha-glucosidase inhibitors and bile acid sequestrants are also treatment options, but are not commonly used due to GI side effects.

**Newer Glucose-lowering Medications**
The availability of new drugs and drug classes allow for improved individualization of glucose-lowering treatments for patients with type 2 diabetes. Below are the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines for single agent treatment of type 2 diabetes (Figure 2). The two newer agents included in green (which indicates preferred agents due to few adverse events or possible benefits) are GLP-1 receptor agonists and DPP-4 inhibitors.
Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are two drug classes with similar mechanisms of action. GLP-1-based therapies are analogs to naturally occurring GLP-1. GLP-1 is a hormone produced by the L-cells of the small intestine and is secreted in response to food consumption. DPP-4 inhibitors function by inhibiting the enzyme that breaks down GLP-1. The end result of this increase in endogenous GLP-1 levels (or exogenous GLP-1 analog levels) is glucose-dependent insulin secretion, delayed gastric emptying, and reduced glucagon secretion. The key term here is glucose-dependent insulin secretion, meaning insulin secretion is stimulated only when the glucose concentration is high. Therefore GLP-1-based therapies and DPP-4 inhibitors, when given alone, have little or no risk of inducing hypoglycemia. Other characteristics of GLP-1-based therapies to consider are:

1. They often help with weight loss, but require administration by injection
2. These agents have the potential for side effects including nausea/vomiting
3. Incretin-based therapies are typically weight neutral and are taken orally once per day
4. They rarely cause side effects

Our patient Steve prefers an oral medication and would benefit from a medication with a low risk of hypoglycemia. Therefore a DPP-4 inhibitor is an optimal choice for him.
Conclusion

Hypoglycemia is a common complication of glucose lowering therapy and is under recognized, particularly in the treatment of type 2 diabetes. The first step toward avoiding hypoglycemia is to individualize glycemic goals. For patients such as Steve who are at higher risk for hypoglycemia, a more conservative A1C goal of 7-8% is appropriate. Once an appropriate glycemic goal has been set, consider the potential risks and benefits of available glucose lowering therapies, and particularly the risk of inducing hypoglycemia, when selecting and implementing anti-hyperglycemic treatment regimens in patients with type 2 diabetes. In the case of Steve, he is best served by taking a medication with a low risk hypoglycemia, such as a DPP-4 inhibitor.
References


