Effective Initiation and Treatment With Basal Insulin in People With Type 2 Diabetes: Focus on Mitigating Hypoglycemia in Patients at Increased Risk: Executive Summary

John Anderson, Scott Urquhart, Geralyn Spollett, and Paresh Dandona

Many people with type 2 diabetes are treated with insulin with the goal of achieving a specific A1C target. The most prominent risk for people on insulin therapy is hypoglycemia. When basal insulin analogs are used appropriately, the risk of hypoglycemia can be reduced while still achieving individualized glycemic goals.

In a series of short videos now available on the *Clinical Diabetes* website, the authors discuss approaches to optimizing basal insulin initiation and treatment in people with type 2 diabetes, including those at high risk such as individuals with renal impairment and older adults, with a focus on reaching A1C goals while mitigating the risk for hypoglycemia.

This article is intended to briefly summarize those discussions. The videos below are also available on a landing page along with short biographies of the authors at https://clinical.diabetesjournals.org/content/basal-insulin-videos.

Video Summaries

Introduction (Video 1)

Video 1. Introduction. Available at https://bcove.video/2Q2Rb9b.

Approximately 50% of people with type 2 diabetes have poorly controlled disease and are vulnerable to long-term micro- and macrovascular complications (1). As type 2 diabetes progresses, many patients will require insulin to maintain glycemic control. The appropriate use of insulin requires a balance between the need for tight glucose control and the potential risk for hypoglycemia. Definitions of hypoglycemia have evolved over time, and the American Diabetes Association (ADA) now uses a three-level classification of hypoglycemia severity (2). Mitigating the risk for hypoglycemia is crucial to the successful treatment of people with type 2 diabetes. In the following series of videos, the authors discuss the use of available insulin formulations in the context of hypoglycemia risk.

Basal Insulin Therapy—Balancing Glycemic Control With Risk for Hypoglycemia (Video 2)

Video 2. Basal Insulin Therapy—Balancing Glycemic Control With Risk for Hypoglycemia. Available at https://bcove.video/3h3Y85h.

The achievement of tight glycemic control reduces micro- and macrovascular complications, and adherence to treatment improves quality of life and decreases health care costs (3–9). The authors discuss the association between A1C reduction and microvascular complications, as reported in the UK Prospective Diabetes Study (9).

Using insulin therapies to achieve tight glycemic control can place people at risk for hypoglycemia. The importance of educating patients on how to avoid hypoglycemia while maintaining glycemic control is also highlighted, including teaching patients how to appropriately titrate insulin. People with diabetes should also be encouraged to monitor their blood glucose levels, particularly while titrating their antidiabetic therapies, and to communicate their results to their health care providers (HCPs).

Fear of hypoglycemia on the part of either the patient or the HCP can affect treatment decisions and adherence to therapy (10).

Corresponding author: John Anderson, JohnAnderson1@hcahealthcare.com

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The authors review published evidence from a retrospective cohort study demonstrating that, in patients with type 2 diabetes, improved adherence to insulin treatment reduces the likelihood of emergency room visits and hospitalizations resulting from hypoglycemia (11).

Major advances in the development of insulin therapies have occurred throughout the past century, from the discovery of insulin in 1921 (12) to the recent development of the second-generation basal insulin analogs insulin glargine 300 units/mL (Gla-300) and insulin degludec (IDeg). Both of these basal insulin formulations enable more effective glycemic control and provide stable and predictable insulin levels throughout a period of at least 24 hours, with a lower risk for hypoglycemia (13).

Identifying and Managing Patients at Increased Risk for Hypoglycemia (Video 3)

It is crucial to identify people who are at elevated risk for developing hypoglycemia, including those for whom a long duration of type 2 diabetes or complexity of their treatments can impair the ability to perceive hypoglycemia (14). The presence of certain comorbidities such as chronic kidney disease (CKD) and cardiovascular disease (CVD) in people with type 2 diabetes can predispose them to developing hypoglycemia (14). The authors explain that people with CKD and those who are undergoing dialysis are particularly vulnerable because the half-life of insulin is markedly protracted in this population.

Video 3. Identifying and Managing Patients at Increased Risk for Hypoglycemia. Available at https://bcove.video/32whg7M.

Some medications can increase the risk for developing hypoglycemia, and others can mask its symptoms. The authors review several important considerations for managing hypoglycemia risk, including medical nutrition therapy, appropriate selection of glycemic targets, hypoglycemia awareness, patient–HCP communication, and blood glucose monitoring (2,15). For people receiving basal insulin, it is important to provide a clear titration schedule and to both optimize and simplify the treatment regimen as appropriate (1,16). The authors emphasize that the appropriate selection of basal insulin is important in achieving predictable, stable glycemic control.

Differences Between First- and Second-Generation Basal Insulin Therapies (Video 4)

As the development of insulin formulations has evolved from NPH through first-generation basal insulin analogs (insulin glargine 100 units/mL [Gla-100] and insulin detemir) and then to second-generation basal insulin analogs (Gla-300 and IDeg), clinicians now have access to basal insulins with much more stable and prolonged pharmacokinetic profiles and with a lower risk of hypoglycemia (12,17–19). The authors discuss the importance of reducing the risk for hypoglycemia and note that emergency room visits and hospitalizations as a result of hypoglycemia can incur large costs (20) and are largely preventable.

Video 4. Differences Between First- and Second-Generation Basal Insulin Therapies. Available at https://bcove.video/39etT9f.

The authors also explain the differences between randomized controlled trials (RCTs) and real-world studies that assess drug effects in people in everyday clinical practice and comprise a broader group of participants, including those at high risk or who may otherwise be excluded from RCTs because of various comorbidities.

The authors summarize the results of the retrospective real-world DELIVER-2 study (n = 6,033) that demonstrated cost savings of $1,439/year per patient associated with a reduction in all hypoglycemia-related health care resource utilization when switching from the patients' current insulin to Gla-300 versus switching to another basal insulin analog (21). They also review results of the randomized, pragmatic real-world ACHIEVE Control trial (n = 3,304), which showed superiority with Gla-300 versus first-generation basal insulin analogs for achievement of a 6-month composite end point of HEDIS (Healthcare Effectiveness Data and Information Set) A1C target attainment without documented symptomatic (≤70 mg/dL) or severe (defined as ADA level 3) hypoglycemia at any time of day (22). The authors note that, across several RCTs and real-world studies of people with type 2 diabetes and increased risk for hypoglycemia (e.g., those ≥65 years of age, with renal impairment, or with CVD) lower rates of hypoglycemia were seen with second-generation basal insulin analogs (Gla-300 and IDeg) versus first-generation basal insulin analogs (23–27) and were

consistent with results from RCTs in the overall population with type 2 diabetes.

The authors conclude this video by summarizing results from RCTs such as the EDITION meta-analysis (n = 2,737) that evaluated Gla-100 versus Gla-300 and showed a consistent benefit of Gla-300 with regard to hypoglycemia risk (28). The authors also discuss the results of the BEGIN research program (n = 3,386), which evaluated IDeg versus Gla-100 and showed a benefit of IDeg with regard to nocturnal hypoglycemia, but not to overall incidence of hypoglycemia (28).

Comparison of Second-Generation Basal Insulin Analogs (Video 5)

Although both Gla-300 and IDeg provide stable insulin concentrations for more than 24 hours, they have unique mechanistic differences; Gla-300 is released freely into the circulation from microprecipitates, whereas IDeg, once injected, forms large multihexameric complexes in the subcutaneous tissue and binds to albumin in circulation (29–33).

Video 5. Comparison of Second-Generation Basal Insulin Analogs. Available at https://bcove.video/3915xiS.

Few studies have compared the efficacy and safety of Gla-300 and IDeg in insulin-naive patients. The authors discuss the results from the BRIGHT RCT (n = 929), which demonstrated similar efficacy and safety of Gla-300 and IDeg throughout 24 weeks, with a lower risk of hypoglycemia with Gla-300 during the initial 12-week titration period versus IDeg (34). In the real-world DELIVER Naïve D study (n = 1,276), the efficacy and safety of Gla-300 and IDeg, including risks of hypoglycemia, were generally comparable (35). In the CONFIRM study (n = 4,056), a lower risk of pre- versus post-treatment hypoglycemia was seen with IDeg than with Gla-300 (36), although the rate of hypoglycemia at baseline between the two groups was not balanced.

Studies comparing the efficacy and safety of IDeg and Gla-300 in people at increased risk for developing hypoglycemia have also been conducted. For example, in the CONCLUDE trial (n = 1,609), a similar risk of hypoglycemia was observed with IDeg and Gla-300 (37). The authors review a subgroup analysis of the BRIGHT trial (n = 929) in patients with type 2 diabetes and renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m^2), which showed greater reductions in A1C with Gla-300 than with IDeg, with similar rates of hypoglycemia (38). Although the results of these subgroup analyses are informative, further studies are needed to confirm them.

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