Hypoglycemia in Diabetes: Why it matters and what to do about it
An educational presentation of the International Hypoglycaemia Study Group
Audience poll

1. How often do you assess your patients for hypoglycemia?
   a) Every visit
   b) Every year
   c) Rarely or never

2. How knowledgeable are you about addressing hypoglycemia risk factors?
   (scale from 1 to 7, with 7 = most confident)

3. How do you usually deal with patients with problematic hypoglycemia?
   a) discuss hypoglycemia prevention/management with the patient
   b) refer the patient to a diabetes education specialist
   c) review the patient’s lifestyle/treatment and implement changes as needed
Outline

1. How intensively should glucose be lowered?
2. Hypoglycemia classification
3. Prevalence and risk factors
4. Impact on body and mind
5. Prevention strategies
6. Treatment strategies

+ Case Study & Quiz Questions
In general:
• Hypoglycemia is common in insulin-treated diabetes, but may also occur in people on oral medications, especially sulfonylureas/glinides.
Which of the following might have contributed to Doug’s hypoglycemic episodes?

- a) Peripheral neuropathy
- b) Alcohol consumption
- c) Use of sulfonylureas
- d) Having long standing diabetes but not using insulin

**Answer: b and c**

- Many alcohol-containing drinks contain carbohydrate and can cause initial hyperglycemia. However, alcohol also inhibits gluconeogenesis, which becomes the main source of endogenous glucose about 8 hours after a meal. Therefore, there is increased risk of hypoglycemia the morning after significant alcohol intake if there has not been food intake.\(^1\) Alcohol consumption can also interfere with the ability to perceive hypoglycemia symptoms and features of inebriation can be confused with those of hypoglycemia.

- Use of sulfonylureas (SUs) is a known risk factor for hypoglycemia. Glibenclamide causes more hypoglycemia than other SUs.\(^2\)

**References:**
The association between hypoglycemia and level of glucose control is not as strong or predictable as previously supposed.
Intensive glucose control: modest but significant CV benefits (T2D data)


**Speaker Notes:**
While the microvascular benefits of earlier intensive glycemic control have been repeatedly demonstrated, there is less concordance on whether glycemic control with antihyperglycemic agents influences CV morbidity and mortality.1-5

The landmark ACCORD, ADVANCE, UKPDS and VADT trials examined glycemic control in subjects with T2D at high cardiovascular risk. These trials independently failed to demonstrate a reduction in overall CV events when tight glycemic control was achieved with conventional antihyperglycemic agents.1-4

However, the UKPDS post-trial monitoring program5 revealed that earlier glycemic control vs. conventional therapy was associated with significant relative risk reductions for myocardial infarction (15%, P=0.014) and all-cause mortality (12%, P=0.007).

This meta-analysis by Turnbull and colleagues6 suggests that intensive glycemic control affords a modest but significant CV benefit (specifically MACE and MI) in the short-to-medium term, although all-cause and cardiovascular mortality are not benefited.

Extension data from the VADT group demonstrate the long-term benefits of intensive glucose lowering7 are discussed in slide 10. The difference in glycateated hemoglobin levels between the intensive-therapy group and the standard-therapy group averaged 1.5
percentage points during the trial (median level, 6.9% vs. 8.4%) and declined to 0.2 to 0.3 percentage points by 3 years after the trial ended. Over a median follow-up of 9.8 years, the intensive-therapy group had a significantly lower risk of the primary outcome than did the standard-therapy group (hazard ratio, 0.83; 95% confidence interval [CI], 0.70 to 0.99; P=0.04), with an absolute reduction in risk of 8.6 major cardiovascular events per 1000 person-years, but did not have reduced cardiovascular mortality (hazard ratio, 0.88; 95% CI, 0.64 to 1.20; P=0.42). No reduction in total mortality was evident (hazard ratio in the intensive-therapy group, 1.05; 95% CI, 0.89 to 1.25; P=0.54; median follow-up, 11.8 years).

References:
This slide shows the HbA1c achieved and the rate of development of microvascular complications in the intensive and conventional treatment arms of the DCCT trial and the EDIC follow-up (which involved patients with T1D). In these trials, intensive glucose control significantly reduced the incidence of microvascular complications (retinopathy, nephropathy, neuropathy).
HbA1c reflects long-term average glucose control. Two patients may have the same HbA1c, but have markedly different patterns of short-term glycemic variability (and thus vulnerability to hypoglycemia).
This definition arose from discussions prior to, and during, the June 9, 2016 IHSG meeting. The “alert value” and “serious biochemical” categories can be used to inform clinical care and (at investigators’ discretion) in clinical trials.

As hypoglycemia symptoms vary widely, a single definition for hypoglycemia may not be realistic or useful.

**Note:** Paediatric diabetes and hypoglycemia present unique challenges. Children with diabetes should be referred to appropriate specialists.

**Resource**
The symptoms listed are the most commonly reported symptoms by a large group of young adults with type 1 diabetes and classified in groups using Factor Analysis. There are many other symptoms associated with hypoglycemia, and the nature of the symptoms varies with age.

It should be noted that patients who have poor glycemic control with an elevated HbA1c may experience symptoms of hypoglycemia at levels > 3.9 mmol/L (70 mg/dl).
These data were obtained in a prospective study of people with diabetes allocated to each treatment group according to the treatment they were prescribed by their usual diabetes care team. Insulin treatment for people with type 2 diabetes did not include people on basal insulin replacement only. The patients in this study had good glycemic control at recruitment (HbA1c <8%).
Disregarding or undertreating non-severe hypoglycemia may also increase the risk of severe hypoglycemia.
Repeated long-term exposure to nocturnal hypoglycemia can alter the glucose thresholds for hormonal secretion, generation of symptoms and onset of cognitive impairment, leading to counterregulatory deficiencies, impaired awareness of hypoglycemia, and hypoglycemia-associated autonomic failure.

Note: A low fasting glucose in the morning raises the index of suspicion for nocturnal hypoglycemia during the previous night.

A U.S. Medicare study found advanced age, recent hospitalization and polypharmacy to be the most important predictors of severe hypoglycemia.

Impaired renal function is known to increased the risk of hypoglycemia.

Hypoglycemia can have both a short-term impact (e.g., falls, driving mishaps) and a cumulative impact. Over the long term, hypoglycemia increases the risk of cardiovascular and cognitive impairment.

The ACCORD and VADT trials have found a significant association between hypoglycemia and mortality. Seaquist E et al. Diabetes Care 2012;35:409. (However, mortality in ACCORD was higher in subjects in the standard treatment group with a history of severe hypoglycemia than in the intensive group.) One conclusion to be drawn is that intensive therapy may not achieve its purpose – avoidance of mortality and morbidity from diabetes complications – unless hypoglycemia risk can be managed.

Hypoglycemia also has an impact on hospitalisation. In one study, the hospitalisation rate during the first year of follow-up was 53.1% for mild hypoglycemia and 63.4% for severe hypoglycemia. Hsu et al. Diabetes Care 2013; 36: 894.
Some, but not all, studies have also shown an effect of hypoglycemia on work performance.

**Severe** hypoglycemia has a QOL impact comparable to that of moderately painful neuropathy and approaching that of a myocardial infarction.

Hypoglycemia may also cause anxiety in caregivers.
Adherence was defined as always taking medications as prescribed. More than half of subjects with moderate or worse hypoglycemia did not adhere to their regimens, indicating that hypoglycemia can make certain populations compromise their treatment.

Poorly adherent patients may not report their lack of adherence and/or may not return to consult their original physician.

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Impaired awareness of hypoglycemia can be defined as a reduced ability to perceive the onset of hypoglycemia in advance of cognitive impairment.

Regular episodes of hypoglycemia can lead to a re-setting of the glycemic threshold for symptom generation to a lower value. The resultant IAH (at glucose values higher than the new threshold) can substantially affect quality of life:

- Increased reliance on others
- Increased blood testing
- Loss of employment
- Loss of driving licence
- Family stress

Impaired awareness of hypoglycemia:
- Affects 20-25% with T1D and about 10% with insulin-treated T2D
- Increases risk of severe hypoglycemia up to 6-fold
- May result from > 2 episodes of hypoglycemia per week

May be reversed by scrupulous avoidance of hypoglycemia

Some pediatric studies have shown similar effects.
• Doug, 67, had some hypoglycemia while on metformin + glimepiride; 6 months ago his HbA1c rose to 7.7% (61 mmol/mol) after years of good glucose control.
• He began insulin therapy with basal insulin to improve his glucose control.
• His most recent HbA1c was 7.1% (54 mmol/mol).
• He reports several episodes of hypoglycemia over the past 6 months, two of them severe.
• His awareness of hypoglycemia has diminished (he only has symptoms at blood glucose < 3 mmol/L) and his relatives often have to tell him when his blood glucose is low.

The combination of insulin plus sulfonylurea increases the risk of hypoglycemia; it may not have been the most appropriate therapeutic choice for Doug.
• Age, comorbidities, and use of alcohol add to the risk.
• Greater frequency of hypoglycemia may reduce Doug’s awareness.
Answer: [b or c] and/or d

- A relaxed HbA1c target may be appropriate for people with advanced disease, complications, and limited life expectancy. Doug has not reached this end-stage yet, so it would be premature to raise his target.
- While temporarily increasing HbA1c targets can help restore awareness of hypoglycemia, it may be possible to reduce Doug’s hypoglycemia risk by changing his therapy. Considerations include:
  - There are newer basal insulin agents that have a lower risk of causing hypoglycemia.
  - Stopping insulin is an option to consider; it may be possible to manage Doug’s HbA1C with a combination of other antihyperglycemic agents.
  - Suitable replacements for the sulfonylurea include GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors, none of which are associated with significant hypoglycemia.
In theory, the glycemic goal should be the same as for someone without diabetes; in practice, the goal should be the lowest value that can be achieved without doing more harm (including causing hypoglycemia) than benefit.

The risk of hypoglycemia must be balanced against the risk of hyperglycemia: uncontrolled plasma glucose can lead to CV damage.
Note: In practice, many people with diabetes achieve a HbA1C target about 1% over their target, so relaxing targets is a strategy to be used with great caution. Further, patients may not be aware of the significance of A1C in relation to their day-to-day glucose control. The physician, nurse, and/or dietitian needs to convey and clarify this information to patients.
• Patients in older age-groups are especially vulnerable to hypoglycemia.
• Age-related impairment in counterregulatory glucagon response has been described in elderly patients with diabetes and symptoms change with advancing age.
• Careful education regarding the symptoms and treatment of hypoglycemia, with regular reinforcement, is extremely important in this age group.
• If SUs are to be used, use short-acting agents preferentially.
• Consider changes in dietary habits (e.g., inadequate diet) that often occur in the elderly.

The ADA/Endocrine Society Working Group has developed a patient questionnaire to help clinicians learn how often the patient is experiencing symptomatic and asymptomatic hypoglycemia, ensure the patient is aware of how to appropriately treat hypoglycemia, and remind both parties of the risks associated with driving while hypoglycemic. [See Table 2 in reference below.]

**Reference**
In some regions, DPP-4 inhibitors may not be reimbursed in combination with insulin, so an alternative strategy might be preferable (e.g., stopping the SU and relaxing the glycemic target).

In a case such as Doug’s, every effort to lose weight should be encouraged.
Answer: b and c

- Increasing carbohydrate consumption would be counterproductive to Doug’s goal of losing weight.
- The fact that his HbA1C has gone down to 6.9% is encouraging and suggests that he may be able to maintain good glycemic control with the right mix of agents.
- Discontinuation of insulin (which appears to be causing his hypoglycemic episodes) is an appropriate strategy to consider.
- If insulin is discontinued, it is appropriate to replace the DPP-4 inhibitor with a GLP-1 agonist, which are more effective glucose-lowering agents than DPP-4 inhibitors and are associated with little to no hypoglycemia.
- Doug is probably not a good candidate for an insulin pump because his motivation and capacity to follow treatment are limited. Ideal pump users are highly motivated, have wide and unpredictable glycemic excursions, have frequent severe hypoglycemia, and feel that diabetes management is interfering with work, school, or family obligations.

Sulfonylureas are the oral glucose-lowering medication class associated with the greatest risk of hypoglycemia.
People requiring insulin or those treated with sulfonylureas/glinides need to be aware of potential delayed effects of physical activity on glucose levels – in particular delayed hypoglycemia 6–12 hours after cessation of the activity.
When possible, insulin should be avoided in hypoglycemia-prone people with T2D. Alternatives to prandial insulin include DPP-4 inhibitors and SGLT-2 inhibitors.

Glucose patterns to watch for:
- Glucose > 10% lower than target
- Postprandial hypoglycemia
- Extra hypoglycemia on school/work days
- Extra hypoglycemia on days off
- Extra hypoglycemia on exercise days
Note: Current CSII and CGM experience is with T1D.

In the CSII vs. MDI meta-analysis, the greatest reduction occurred in those with most severe hypoglycemia on MDI and those with the longest duration of diabetes. But these were in patients who were hypoglycemia prone.

Some evidence also suggests that the use of sensor-augmented insulin-pump therapy with the threshold-suspend feature may reduce nocturnal hypoglycemia, without increasing HbA1c values. (Bergenstal RM et al. NEJM 2013;369:224.)

Not all CGM studies have shown a reduction in hypoglycemia.
Quiz question

Characteristics of suitable CSII (insulin pump) candidates may include:

- Significant dawn phenomenon
- Preference for less frequent blood glucose monitoring
- Willingness to monitor blood glucose several times a day
- Inability or unwillingness to perform frequent MDI
- Predictable lifestyle
- Erratic lifestyle

CSII – continuous subcutaneous insulin injection; MDI = multiple daily injections

Answer: a, c and f

The Consensus Statement by the American Association of Clinical Endocrinologists/American College of Endocrinology Insulin Pump Management Task Force includes substantial dawn phenomenon, willingness to perform MDI and monitor blood glucose frequently, and erratic lifestyle among the characteristics of good insulin candidates.
Examples of 15 g fast-acting carbohydrates:
• 4 ounces of juice or soda (regular, not diet)
• 8 ounces of skim milk
• 5–6 candies or sweets

The choice of carbohydrates may vary depending on geographical region and ethnic population.

If an insulin injection is due, it should not be omitted, but the dose may need to be adjusted.
For IV glucose, the concentration is generally 10 to 20%. A 50% solution should be avoided unless a central line is in place.

Family members/caregivers should be educated on how and when to administer glucagon.

In unconscious patients:
- With IV access: treat with 10-25 mg IV glucose for 3 minutes
- Without IV access: treat with 1 mg glucagon subcutaneously or intramuscularly
- Adrenaline is not effective and should not be administered
When driving, people with diabetes should:
• Ensure they have fast-acting glucose and test strips with them
• Have regular snacks and rests
• Avoid alcohol

Patients need to be aware of driving regulations in people with diabetes, which differ from country to country.

Physicians should discuss driving issues individually with patients.
It is probable that Doug will require insulin again at some point in the future. It would be useful to prepare him for this eventuality.
Key takeaways

- Hypoglycemia is a significant clinical outcome with potentially serious short- and long-term effects
- Hypoglycemia may occur in T1D or T2D, including in patients not on insulin
- Benefits of intensive glucose control need to be balanced against risks
- Glycemic targets may be relaxed in some populations at high risk of hypoglycemia
- Frequent glucose monitoring and medication adjustments may help reduce the risk of hypoglycemic episodes
- Education about hypoglycemia prevention strategies may help patients reduce the risk
Thank you