

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?

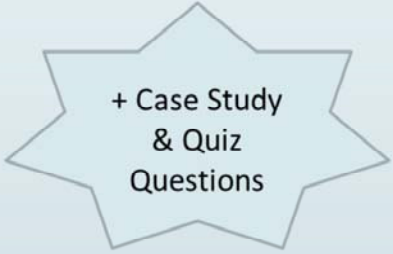
(scale from 1 to 7, with 7 = most confident)

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

Meet Doug

- Doug, 67, has had type 2 diabetes for 9 years. He has vascular disease and some peripheral neuropathy.
- His BMI is 34 kg/m²
- A retired truck driver, he occasionally drives his grandchildren to school.
- He drinks beer most evenings.
- He has been on metformin and the sulfonylurea (SU) glimepiride for several years.
- His HbA1c has recently risen to 7.7% (61 mmol/mol).
- In the last year he has reported several episodes of non-severe hypoglycemia.



BMI = Body Mass Index

In general:

- Hypoglycemia is common in insulin-treated diabetes, but may also occur in people on oral medications, especially sulfonylureas/glinides.

Question

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:

1. Childs BP et al. *Clinical Diabetes* 2012;30:28.
2. Gangji AS et al. *Diabetes Care* 2007;30:389.

Glucose control and hypoglycemia

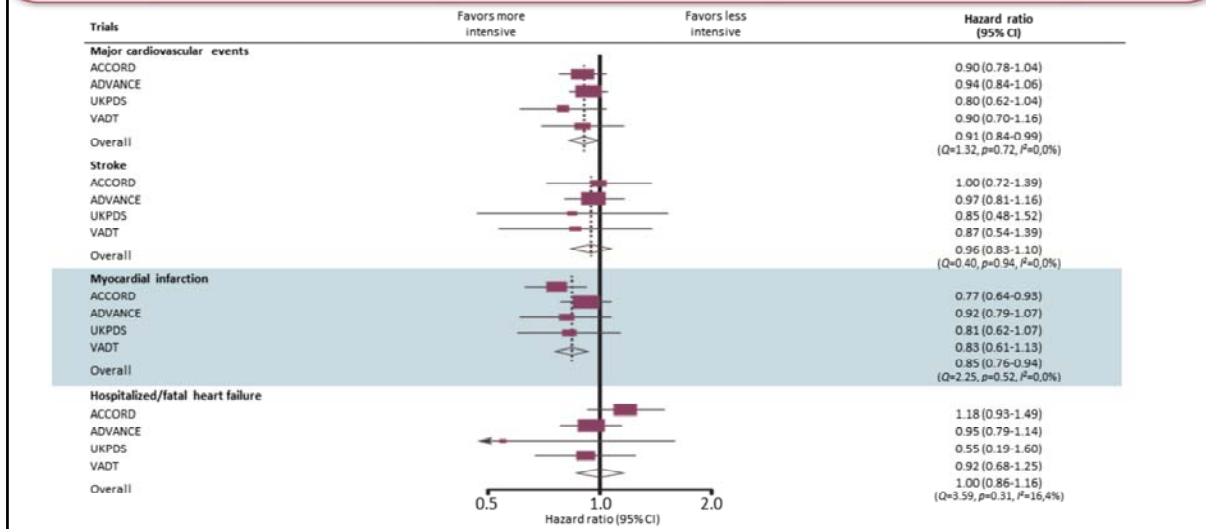
- Strict glycaemic control has well-documented benefits
- Hypoglycemia can occur at all levels of glucose control in Type 2 diabetes¹
- Intensifying treatment may increase the risk of hypoglycemia



1. Lipska KJ et al. Diabetes Care 2013;36:3535.

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)



Adapted from Turnbull FM et al. *Diabetologia*. 2009;52:2288-98; Hayward RA, et al. *NEJM* 2015;372:2197-206.

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.

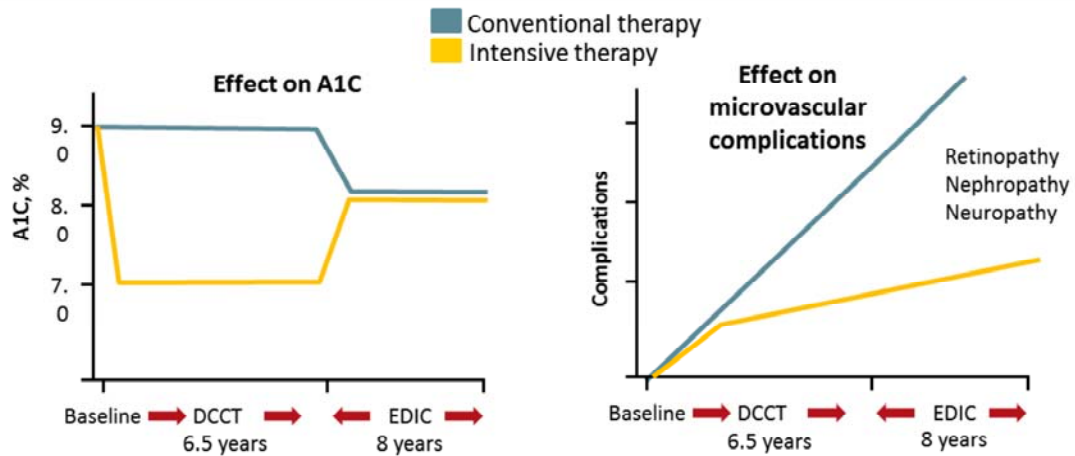
Extension data from the VADT group demonstrate the long-term benefits of intensive glucose lowering⁷ are discussed in slide 10. The difference in glycated hemoglobin levels between the intensive-therapy group and the standard-therapy group averaged 1.5

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:

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352(9131):837-53.
2. The ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011; 364(9):818-28.
3. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008; 358(24):2560-72.
4. 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(2):129-39.
5. Holman RR, Paul SK, Bethel MA, et al. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359(15):1577-89.
6. Control Group, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*. 2009;52(11):2288-98.
7. Hayward RA, Reaven PD, Wiitala WL, et al; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;372(23):2197-206.

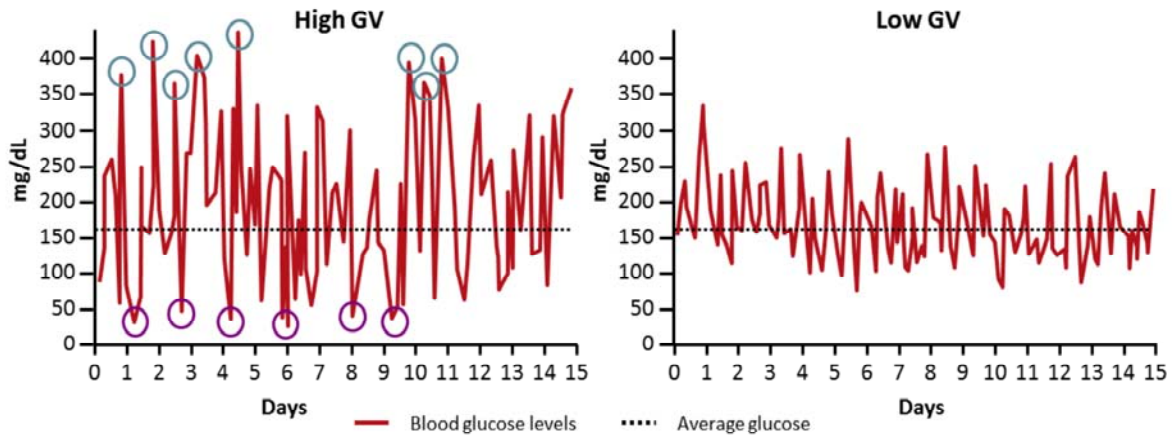
Intensive glucose control in T1D: DCCT/EDIC



DCCT/EDIC research group. NEJM 2000;342:381.

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 vs glucose variability (GV)



15-day glucose traces of two subjects who had identical HbA_{1c} of 8.0% but different degrees of GV.

Kovatchev B, Cobelli C. Glucose Variability: Timing, Risk Analysis and Relationship to Hypoglycemia in Diabetes. *Diabetes Care* 2016; 502:510.

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).

International Hypoglycaemia Study Group (IHSG) classification of hypoglycemia

Alert value

Plasma glucose
< 3.9 mmol/L
(70 mg/dL) and
no symptoms

Non-severe vs. severe symptomatic:

- Non-severe: Patient has symptoms but can self-treat and cognitive function is mildly impaired
- Severe: Patient has symptoms and cognitive function markedly impaired

Serious biochemical

Plasma glucose
< 3.0 mmol/L
(54 mg/dL)

Seaquist ER et al. ADA/Endocrine Society consensus report on hypoglycemia. Diabetes Care 2013;36:1384.

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

Frier BM. Hypoglycemia in diabetes mellitus: epidemiology and clinical implications. Nature Reviews Endocrinology 2014;10:711.

Common hypoglycemia symptoms

1. Development of symptoms

Autonomic	Neuroglycopenic	Non-specific
<ul style="list-style-type: none">• Trembling• Pounding heart• Sweating• Anxiety• Hunger	<ul style="list-style-type: none">• Difficulty concentrating• Confusion• Weakness• Drowsiness, dizziness• Vision changes• Difficulty speaking	<ul style="list-style-type: none">• Nausea• Headache

2. Low blood glucose (< 3.9 mmol/l or 70 mg/dL)

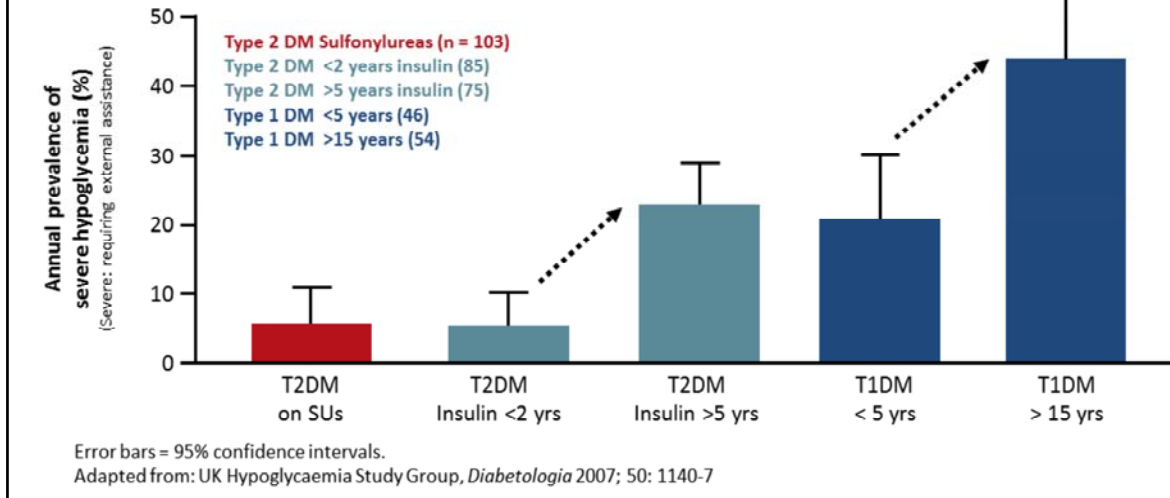
3. Response to treatment with carbohydrate

1. Seaquist ER et al. ADA/Endocrine Society consensus report on hypoglycemia. Diabetes Care 2013;36:1384.
2. McAulay V et al. Diabet Med 2001;18:690. 3. Deary IJ et al. Diabetologia 1993;36:771.

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).

Prevalence of severe hypoglycemia in types 1 and 2 diabetes



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%).

Risk factors for severe hypoglycemia

T1D

- History of severe episodes
- Intensive insulin therapy
- Long duration of diabetes
- Renal impairment
- Impaired awareness of hypoglycemia
- Extremes of age

T2D (on insulin or SUs)

- Advancing age
- Intensive glucose-lowering therapy
- Cognitive impairment
- Depression
- Aggressive treatment of glycemia
- Impaired awareness of hypoglycemia
- Duration of MDI insulin therapy
- Renal impairment and other comorbidities

1. IHSG. Diabetes Care 2015;38:1583.

2. Gerstein HC et al (ORIGIN trial investigators). Diabetes Care 2015;38.:22.

3. Lipska KJ et al. Diabetes Care 2013;36:3535.

SU = sulfonylurea

MDI = multiple daily injections

Disregarding or undertreating non-severe hypoglycemia may also increase the risk of severe hypoglycemia.

Possible causes of nocturnal hypoglycemia

Insulin-related	Other
<ul style="list-style-type: none">• Use of NPH (isophane) in the evening• Dose of basal insulin too high (e.g. increased to correct high glucose levels on waking)• Too much rapid-acting insulin to correct high glucose or cover bedtime snacks• Premix or regular insulin before dinner	<ul style="list-style-type: none">• Use of long-acting insulin secretagogues (SUs, glinides)• Earlier physical activity, especially strenuous• Alcohol consumption• Low blood glucose (< 6 mmol/L or 108 mg/dL) at bedtime²• Inadequate consumption of carbohydrate for the evening meal and/or bedtime snack

1. Schneider G. Diabetes self-management. January 24, 2012. <http://www.diabetesselfmanagement.com/managing-diabetes/blood-glucose-management/exorcising-the-specter-of-nighttime-hypoglycemia/>

2. Chapter on nocturnal hypoglycaemia in Hypoglycaemia in Clinical Diabetes 2014, 3rd edition. Frier BM et al, Eds.

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.

Reference: Edelman SV, Blose JS. Diabetes Educ 2014;40:269.

Quiz question

Which of the following is/are known to increase the risk of hypoglycemia in older people?

- a) Polypharmacy
- b) Impaired renal function
- c) Reduced weight
- d) Recent hospitalization
- e) Peripheral vascular disease



Answer: a, b and d

- 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.

Reference: Shorr RI et al. Arch Intern Med 1997;157:1681.

Acute consequences of hypoglycemia

Brain

Coma, Seizures,
Cognitive dysfunction,
Mood change,
Psychological effects

Cardiovascular

Myocardial ischemia,
Cardiac arrhythmias

Physical injuries

Falls, Accidents,
Fractures, Dislocations,
Driving mishaps

Increased  mortality

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.

Impact of non-severe hypoglycemia

- Reduced quality of life in both T1D and T2D^{1,2}
- May cause fear of hypoglycemia
- May cause psychological morbidity³



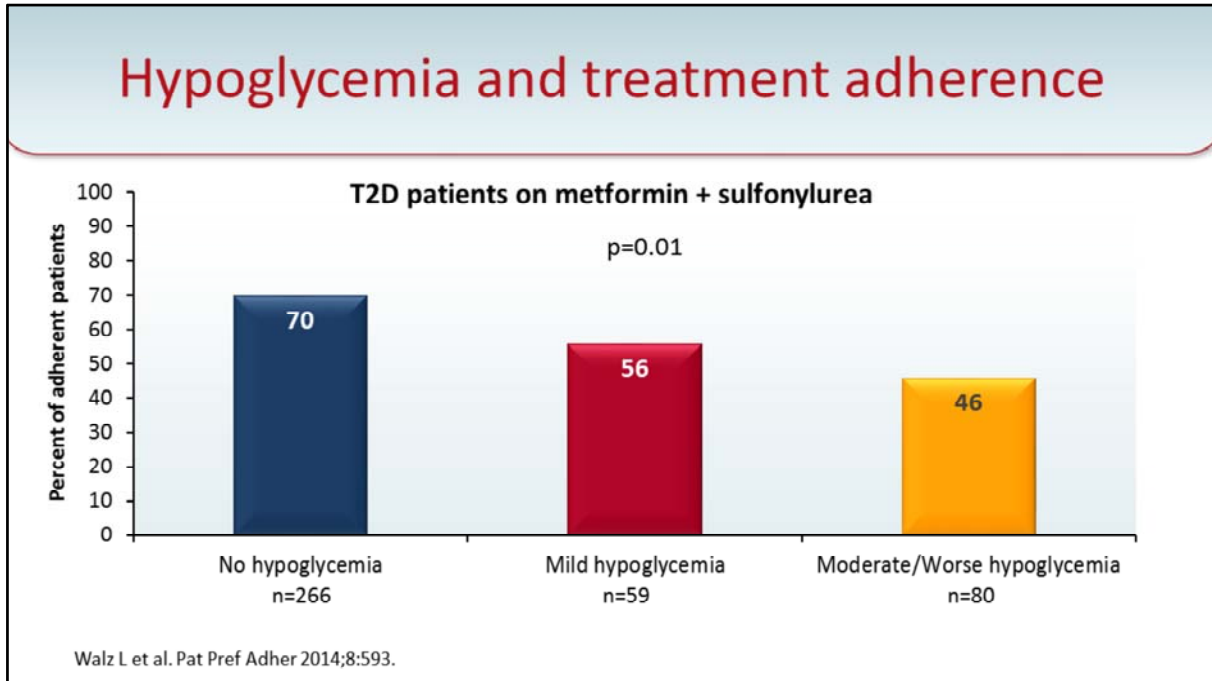
1. Fidler C et al. J Med Econ 2011;14:646.
2. Rombopoulos G et al. Hormones (Athens) 2013;12:550.
3. Barendse S et al. Diabet Med 2012; 29: 293.

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.

Hypoglycemia and treatment adherence



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.

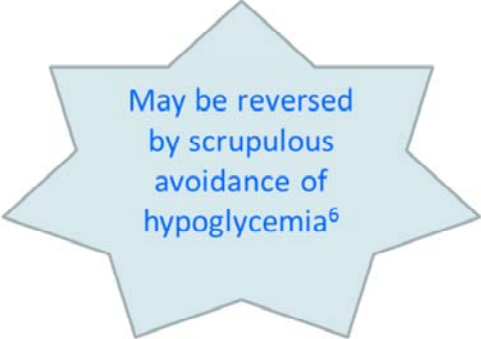
Permission information from primary source: <<Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed.>> See

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4011898/figure/f2-ppa-8-593/>

Impaired Awareness of Hypoglycemia (IAH)

Impaired awareness of hypoglycemia:

- Affects 20-25% with T1D and about 10% with insulin-treated T2D¹
- Increases risk of severe hypoglycemia up to 6-fold²⁻⁴
- May result from > 2 episodes of hypoglycemia per week⁵



May be reversed
by scrupulous
avoidance of
hypoglycemia⁶

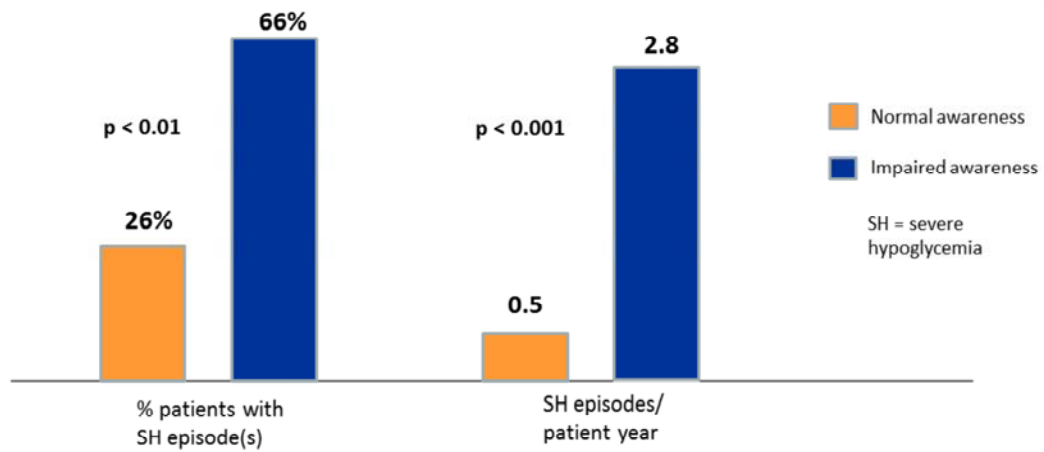
1. Schopman et al. Diab Res Clin Pract 2010;87:64. 2. Gold et al. Diabetes Care 1994;17:697. 3. Geddes et al. Diabetic Med 2008;25:501.
4. Pramming et al. Diabetic Med 1991;8:217. 5. Riddell M. Emerging complications: hypoglycemia/autonomic neuropathy (slide presentation). American Diabetes Association Clinical Guidelines for the Transition of Care in Young Adults with Type 1 Diabetes Position Statement Conference. Available at <http://docslide.us/documents/emerging-complications-hypoglycemia-autonomic-neuropathy-michael-riddell.html>
6. Cryer PE. Elimination of hypoglycemia from the lives of people affected by diabetes. Diabetes 2011;60:24-27.

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

Impact of IAH on severe hypoglycemia



Gold AE et al. Frequency of Severe Hypoglycemia in Patients With Type I Diabetes With Impaired Awareness of Hypoglycemia. Diabetes Care 1994;7:697-703.

Some pediatric studies have shown similar effects.

Revisit Doug

- 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.



Previous status: T2D, BMI 34, metformin, glimepiride

- 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.

Q&A

What would be the best course(s) of action for Doug?

- a) Relax his HbA1c target
- b) Switch his basal insulin to another product
- c) Stop insulin
- d) Replace the sulfonylurea with an agent from another class



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.

What is a reasonable glycemic goal?

"The lowest A1C that does not cause severe hypoglycemia and preserves awareness of hypoglycemia."

Cryer PE. Diabetes 2014;63:2188

"The lowest HbA1c that does not cause severe hypoglycemia, preserves awareness of hypoglycemia and results in an acceptable number of documented episodes of symptomatic hypoglycemia"

Report of a workgroup of ADA and ES, Diabetes Care 2013; 36:1384

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.

Hypoglycemia and glucose targets

Type 1 diabetes

- Aim for lowest HbA1c not associated with frequent hypoglycemia
- It may sometimes be appropriate to relax targets in patients with advanced disease, complications, or limited life expectancy
- In such patients, aim for glucose levels low enough to minimize symptoms of hyperglycemia

Type 2 diabetes

- Aim for lowest HbA1c not associated with frequent hypoglycemia
- HbA1c < 7.0% (53 mmol/mol) is usually appropriate for recent-onset disease
- It may sometimes be appropriate to relax targets (e.g. severe complications, advanced co-morbidities, cognitive impairment, limited life expectancy, unacceptable hypoglycemia from stringent control)

1. Seaquist ER et al. ADA/Endocrine Society consensus report on hypoglycemia. Diabetes Care 2013;36:1384.
2. Global guideline for type 2 diabetes. International Diabetes Federation 2012.

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.

Less stringent targets in frail elderly may be appropriate

A1c < 7.5% (58 mmol/mol)	A1c < 8% (64 mmol/mol)	A1c < 8.5% (69 mmol/mol)
Complicated regimens should be simplified		
<ul style="list-style-type: none"> • Few comorbidities • Good physical function • Preserved cognitive function 	<ul style="list-style-type: none"> • Multiple chronic illnesses • Mild cognitive impairment • Risk of falls and hypoglycemia 	<ul style="list-style-type: none"> • End-stage chronic illness • Moderate-to-severe cognitive impairment • In long-term care



1. Kirkman MS et al. Diabetes in older adults. Diabetes Care 2012;35:2650.
2. Seaquist ER et al. ADA/Endocrine Society consensus report on hypoglycemia. Diabetes Care 2013;36:1384.

- 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.

Reference: Seaquist ER et al. ADA/Endocrine Society consensus report on hypoglycemia. Diabetes Care 2013;36:1384.

Screening for risk of severe hypoglycemia

Screening should be based on established risk factors:

- Low HbA1c; high pre-treatment HbA1c in T2D
- Long duration of diabetes
- A history of previous hypoglycemia
- Impaired awareness of hypoglycemia (IAH)*
- Recent episodes of severe hypoglycemia
- Daily insulin dosage > 0.85 U/kg/day
- Physically active (e.g., athlete)



* **Clinical tip:** In people with IAH, blood glucose monitoring records reveal many low values, without hypoglycemia symptoms being experienced.

1. IHSG. Diabetes Care 2015;38:1583.
2. Gerstein HC et al (ORIGIN trial investigators). Diabetes Care 2015;38.:22.
3. Canadian Diabetes Association 2013 clinical practice guidelines. Chapter 14: Hypoglycemia. Can J Diabet 2013;A3.
4. ISPAD Guidelines 2014. Pediatric Diabetes 2014; 15 (Suppl 20).

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

Seaquist ER et al. ADA/Endocrine Society consensus report on hypoglycemia. Diabetes Care 2013;36:1384.

Revisit Doug

- Doug continued on basal insulin, and his sulfonylurea was replaced with a DPP-4 inhibitor.
- He has reduced his carbohydrate intake and takes daily walks in an attempt to lose weight; his BMI has gone down to 32 kg/m².
- His latest HbA1c was 6.9% (52 mmol/mol).
- He continues to have IAH and hypoglycemic episodes, including one while driving.



Previous status: T2D,
BMI 34, metformin,
glimepiride, basal insulin

IAH = impaired awareness of hypoglycemia

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.

Q&A

What management strategy(ies) might you recommend at this juncture?

- a) Increase carbohydrate consumption
- b) Replace the DPP4-inhibitor with a GLP-1 agonist
- c) Stop insulin
- d) Adjust insulin dose to match his carbohydrate consumption
- e) Change to using an insulin pump



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.

Reference: Kim SM. Insulin pumps. <http://emedicine.medscape.com/article/2139073-overview>

Strategies to prevent hypoglycemia¹

Patient education

- Discuss hypoglycemia risk factors and treatment with patients on insulin or sulfonylureas/glinides
- Educate patients and caregivers on how to recognize and treat hypoglycemia
- Instruct patients to report hypo episodes to their doctor/educator
- Consider enrolling patients with frequent hypoglycemia in a blood glucose awareness training program



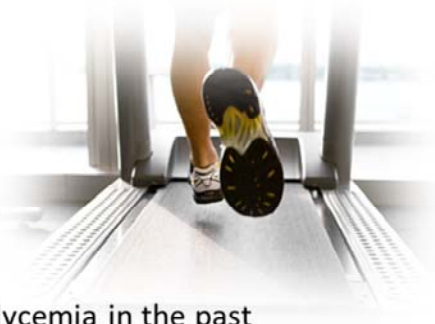
IHSG. Diabetes Care 2015;38:1583.

Sulfonylureas are the oral glucose-lowering medication class associated with the greatest risk of hypoglycemia.

Strategies to prevent hypoglycemia

Diet and exercise

- Follow a predictable eating plan, including carbohydrate counting
- Monitor glucose before and after exercise
- Eat pre-exercise snacks if blood glucose levels are low/declining
- Modify physical activity that has led to hypoglycemia in the past
- Avoid alcohol, especially on an empty stomach



Seaquist ER et al. ADA/Endocrine Society consensus report on hypoglycemia. Diabetes Care 2013;36:1384.

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.

Strategies to prevent hypoglycemia

Glucose and medication monitoring

- If on sulfonylureas (for T2D), consider changing to another drug class
- If add-on to basal insulin is needed, consider alternatives to prandial insulin
- If on basal-bolus insulin, check blood glucose before each meal every day
- Ensure medication is dosed correctly
- Consider insulin adjustments:
 - Regular/soluble insulin → rapid-acting insulin
 - NPH/isophane → insulin analogues
 - Adjusting insulin in relation to exercise



1. Diamant M, et al. Diabetes Care 2014;37:2763–2773. 2. Eng C et al. Lancet 2014;384:2228. 3. McIntyre HD et al. Med J Aust 2010; 192:637. 3. The management of Type 2 Diabetes. NICE guidelines 2009, updated 2014. Accessed at www.guidance.nice.org.uk/cg87

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

Technology to reduce hypoglycemia (T1D)

- Meta-analysis of CSII studies:¹ Severe hypoglycemia in T1D occurs less than with MDI (rate ratio 4.19)
- CGM studies:² Significant reduction in hypoglycemia in two studies (-43% and -61%)
- Low-glucose suspend feature reduces nocturnal hypoglycemia³

CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections.
CGM = continuous glucose monitoring.

1. Pickup JC, Sutton AJ. Diabet Med. 2008;25:765.

2. Liebl A et al.. J Diab Sci Tech 2013;7:500.

3. Bergenstal RM et al. NEJM 2013;369:224.



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:

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



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

Grunberger G et al. Consensus Statement by the AACE/ACE insulin pump management task force. Endocr Pract 2014;20:463-489.

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.

Treatment for hypoglycemia

- 1 **Recognize** symptoms so they can be treated as soon as they occur
- 2 **Confirm the need for treatment** if possible (blood glucose <3.9 mmol/L (70 mg/dL) is the alert value)
- 3 **Treat** with 15 g fast-acting carbohydrate to relieve symptoms
- 4 **Retest** in 15 minutes to ensure blood glucose > 4.0 mmol/L (72 mg/dL) and re-treat (see above) if needed
- 5 **Eat** a long-acting carbohydrate to prevent recurrence of symptoms

Cryer PE. Management of hypoglycemia during treatment of diabetes mellitus. UpToDate review, last updated May 15, 2014. Canadian Diabetes Association 2013 clinical practice guidelines. Chapter 14: Hypoglycaemia. Can J Diabet 2013;A3.

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.

Treating severe hypoglycemia in conscious person

- 1 Treat** with 20 g fast-acting carbohydrate to relieve symptoms
- 2 Retest** in 15 min. to ensure blood glucose > 4.0 mmol/L (72 mg/dL) and re-treat with 15 g more carbohydrate if needed. If in hospital and glucose < 4.0 mmol/L (72 mg/dL) after 45 minutes, consider IV glucose
- 3 Eat** usual snack or meal due at that time of day or a snack with 15 g carbohydrate plus protein

The hospital management of hypoglycaemia in adults with diabetes mellitus. NHS [U.K.] guidelines 2010.
Canadian Diabetes Association 2013 clinical practice guidelines. Chapter 14: Hypoglycaemia. Can J Diabet 2013;A3.

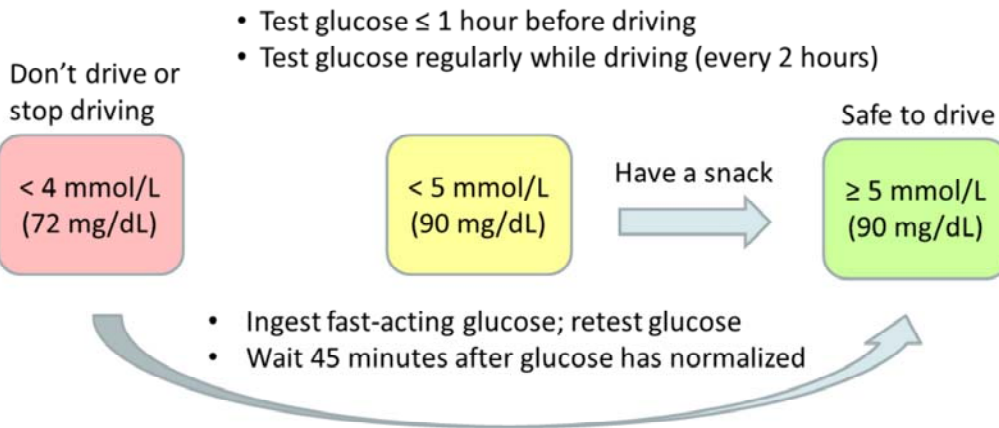
For IV glucose, the concentration is generally 10 to 20%. A 50% solution should be avoided unless a central line is in place.

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

Hypoglycemia and driving: prevention & treatment



Graveling AJ, Frier BM. Driving and Diabetes. Clin Diabet Endocrinol DOI 10.1186/s40842-015-0007-3.

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.

Revisit Doug: management strategy

- Doug's basal insulin was stopped, which eliminated his hypoglycemic episodes.
- His DPP-4 agent was replaced with a GLP-1 agonist.
- His HbA1c has remained stable at 6.9% to 7.2%.
- With support from a dietitian, he committed to a healthy eating program and lost 5 kg over 6 months.
- In the absence of hypoglycemic episodes, his awareness of hypoglycemia was gradually restored.



Previous status: T2D,
BMI 32, metformin, DPP-4
inhibitor, basal insulin

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

