IHSG education module:
Impaired Awareness

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Impaired awareness of hypoglycaemia

- Defined as a diminished ability to perceive the onset of acute hypoglycaemia
- Affects 25–40% people with longstanding T1D and 10% with insulin-requiring T2D
- Clinical assessment should be based on subjective experience when awake
- Syndrome may include reduced symptom intensity and number, altered symptom profile, and/or failure to interpret symptoms
- Increases risk of severe hypoglycaemia
- Other frequently used terms:
  - Reduced awareness
  - Unawareness

Symptoms of hypoglycaemia

- Symptoms are age-specific and idiosyncratic
- Symptoms vary within individuals between hypoglycaemia events
- Symptoms of hypo- and hyper-glycaemia overlap
- Symptoms change over time
- An individual’s beliefs about symptoms are unreliable and inconsistent
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Hypoglycaemia produces neuroglycopenia and causes activation of autonomic system: common symptoms in young adults

**Neuroglycopenic symptoms**
- Confusion
- Drowsiness
- Speech difficulty
- Odd behaviour

**Autonomic symptoms**
- Sweating
- Tremor
- Pounding heart
- Hunger
- Anxiety

**Non-specific symptoms**
- Headache
- Nausea

### Physiology of glucose counterregulation

As plasma glucose levels fall, the prevention or correction of clinical hypoglycaemia involves...

**Physiological defences:**
1. ↓ Insulin
2. ↑ Glucagon
3. ↑ Adrenaline
4. ↑ Sympathetic activation and noradrenaline
5. ↑ Cortisol and growth hormone

**Behavioural defence:**
Carbohydrate ingestion prompted largely by autonomic symptoms

These data on the levels at which responses to a falling plasma glucose concentration start have been acquired by inducing controlled slow-fall hypoglycaemia using an insulin clamp technique. Hyperinsulinaemia is created by infusion of intravenous insulin and the glucose profile created by the investigator using frequent bedside plasma glucose measurements and an adjustable intravenous glucose infusion.\(^1,2\) Cognitive disruption or coma may occur at higher glucose levels.

In insulin-treated diabetes, the ability to reduce circulating insulin in response to falling plasma glucose is lost. In insulin-deficient diabetes, the ability to release glucagon in response to a falling plasma glucose is lost, and is thought to relate to loss of a signal of declining insulin secretion from the beta cell to the glucagon-secreting alpha cell. Thus, the first line of defence becomes the adrenaline and sympathetic responses and the generation and perception of symptoms of hypoglycaemia associated with the autonomic activation. Cognitive impairment is detectable on formal testing as plasma glucose concentrations fall below 3 mmol/L (54 mg/dL). This has been found in experimental hypoglycaemia and in hypoglycaemia in free-living individuals with type 1 diabetes.
In people with impaired awareness of hypoglycaemia, the counterregulatory responses to hypoglycaemia shifts to a lower glucose concentration than in people with intact awareness, and lower than the 3 mmol/L (54 mg/dL) at which cognitive dysfunction is first evident. The magnitude of the stress responses is also much reduced. This is associated with a loss of symptoms of hypoglycaemia – the person experiencing the hypoglycaemia has impaired subjective awareness of the state.
Recent antecedent hypoglycaemia, as well as sleep and prior exercise, shifts the glycaemic thresholds for sympathoadrenal responses – including the epinephrine and neurogenic symptom responses – to lower plasma glucose concentrations.

Hypoglycaemia blunts warning symptoms to subsequent episodes in non-diabetic people

- Antecedent hypoglycaemia reduces hypoglycaemic warning symptoms the following day\(^1\)
- At least 30-minutes of hypoglycaemia are required for blunting of warning symptoms\(^2\)

Hypoglycaemia (2.4 mmol/L) was induced in 10 non-diabetic adults on the morning after:

- Euglycaemic during night (control study)
- 2 hours of asymptomatic hypoglycaemia during night (plasma glucose: 2.4 mmol/L)

Asymptomatic nocturnal hypoglycaemia increased the threshold and reduced the magnitude of autonomic and neuroglycopenic symptoms, counterregulatory hormone responses and cognitive dysfunction during hypoglycaemia.
Hypoglycaemia (2.4 mmol/L) was induced in 10 non-diabetic adults on the morning after:
- Euglycaemic during night (control study)
- 2 hours of asymptomatic hypoglycaemia during night (plasma glucose: 2.4 mmol/L)
- Asymptomatic nocturnal hypoglycaemia increased the threshold and reduced the magnitude of autonomic and neuroglycopenic symptoms, counterregulatory hormone responses and cognitive dysfunction during hypoglycaemia.
Abnormal attitudes and behaviour in relation to hypoglycaemia in people with IAH

Many people with IAH are resistant to:
- Behavioural changes to avoid or manage hypoglycaemia\(^1,2\)
- Recommended changes in therapy (e.g. reduction in insulin doses)\(^3\)

People with IAH have unique cortical responses to hypoglycaemia\(^4\), affecting:
- Drive to eat
- Emotional salience
- Aversion
- Recall

IAH may be attributed to habituation to hypoglycaemia

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IAH, impaired awareness of hypoglycaemia.
People with T1D and impaired awareness of hypoglycaemia gave semi-structured interviews exploring perceptions and experiences of their condition. Responses fell into either high or low concern groups. Respondents within the high concern group reported hypoglycaemic events as frightening, disabling and socially embarrassing. They realised that action was needed to regain awareness prevent, minimise or eradicate impaired awareness.
People with T1D and impaired awareness of hypoglycaemia gave semi-structured interviews exploring perceptions and experiences of their condition. Responses fell into either high or low concern groups. Respondents within the high concern group reported hypoglycaemic events as frightening, disabling and socially embarrassing. They realised that action was needed to regain awareness prevent, minimise or eradicate impaired awareness.
The majority of patients were less concerned or motivated to address impaired awareness. Reasons for low concern could be grouped into 4 categories:

A: Respondents viewed hypoglycaemia as a normal part of having diabetes. Some respondents had not experienced hypoglycaemia in at least 10 years prior to the survey, so were categorised as A1.

B: Respondents underestimated the effects of hypoglycaemia, felt they could function with blood glucose ‘3 mmol/L, or believed that a severe hypoglycaemic event would not happen to them.

C: Respondents believed that treating asymptomatic hypoglycaemia was a bother, and did not want to be overly cautious in managing their diabetes.

D: Respondents were more concerned about being hyperglycaemic, emphasizing anxiety to developing complications associated with hyperglycaemia.
Characteristics of patients with type 1 diabetes and impaired awareness of hypoglycaemia*

Impaired awareness of hypoglycaemia
n=17

Different patients with varying levels of motivation to regain awareness may require different interventions to help them avoid future hypoglycaemia

Category A: Normalise IAH
Category B: Underestimate IAH
Category C: Avoid “sick role”
Category D: Overestimate impact of high glucose

Category A1**: as aversive Want to regain their awareness

**Told they experience symptoms of hypoglycaemia before blood glucose fell below 1.8 mmol/L**. **Patients in category A1 had not experienced any severe hypoglycaemia for at least 10 years prior to the study despite continuing to have impaired awareness of hypoglycaemia.**

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These are some of the tools and resources that can be used to gauge awareness of hypoglycaemia.
Awareness of hypoglycaemia: clinical assessment

Patient history
- Have the warning symptoms changed?
  - Character
  - Intensity
  - Glucose threshold
  - Frequency
- Severe hypoglycaemia?
- Asymptomatic hypoglycaemia (below 3 mmol/L)?
- Can others recognise the patient’s low glucose before them?
  - Physician can verify with relatives if possible
The Gold and Pedersen-Bjergaard scores are quick to administer and proven to associate with risk of severe hypoglycaemia, but are subjective.

The DAFNE tool is more objective by asking for a glucose concentration below which the person is aware of hypoglycaemia.

The Clarke score, Hypo Awareness Questionnaire and HYPO score all require scoring by the health care professional, but give additional information. The Clarke score includes frequency of severe hypoglycaemic episodes and thus measures more than awareness alone.
### Awareness of hypoglycaemia awareness: impact of scores

- **Gold score >4 (=impaired awareness)²**: 6-fold increase in severe hypoglycaemia in type 1 diabetes; 17-fold increase in insulin-requiring type 2 diabetes
- **Pedersen-Bjergaard score defines awareness, impaired awareness and unawareness²,³**: with 3–6 and 9–20-fold increase in risk for severe hypoglycaemia in type 1 diabetes
- **DAFNE hypoglycaemia awareness rating (symptoms perceived at <3 mmol/L (54 mg/dL or not at all = impaired awareness)³**: 4-fold increase in severe hypoglycaemia in type 1 diabetes
- **Clarke score >4 (= reduced awareness)⁴**: 6-fold increase in severe hypoglycaemia in type 1 diabetes

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Note that the terminology varies between methods. Impaired awareness in the Gold classification is comparable to unawareness in the Pedersen-Bjergaard score and reduced awareness in the Clarke score.
The figure shows glucose variability over the course of 24 hours, for one week of CGM. Each line color represents a single day. The green range denotes the normal glycaemic range, while the red area denotes hypoglycaemia. Over the course of the week, multiple hypoglycaemic episodes can be observed.
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Clinically significant impaired or reduced awareness or un awareness:

- Affects 13–28% of people with T1D
- Affects 6–10% of people with insulin-treated T2D
- Increases with long duration of diabetes
The data described a cross-sectional Danish-British multicentre survey of 1076 consecutive adult patients with clinical type 1 diabetes who completed a detailed questionnaire on hypoglycaemia and related issues. The rate of severe hypoglycaemia in the preceding year was 1.3 episodes/patient-year and episodes were reported by 36.7% of subjects. The distribution was highly skewed with 5% of subjects accounting for 54% of all episodes. Most patients with multiple events of severe hypoglycaemia had impaired awareness. Impaired awareness was the strongest measurable factor predicting risk of recurrent severe hypoglycaemia.
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66 patients collected 7-point diurnal blood glucose profiles at home on three consecutive days and then once-weekly for 3 weeks. Patients indicated whether they felt hypoglycaemic at sampling times and collected extra samples if they felt hypoglycaemic at any time during the study period. The graph at right depicts the BG concentration at which the patient felt hypoglycaemic.

- At a blood glucose concentration <2mM, 75% of patients did not experience symptoms of hypoglycaemia. At a concentration <3mM, 85% did not experience symptoms, suggesting that symptomatic hypoglycaemia is an unreliable indicator of biochemical hypoglycaemia.
153 patients with T1DM were monitored with CGM for 7 days and recorded hypoglycaemic symptoms. A total of 74% of all episodes were asymptomatic. Higher fractions of asymptomatic hypoglycaemia in patients with impaired awareness.
19 patients with type 1 diabetes with normal hypoglycaemia awareness were matched for age, sex, duration of diabetes and glycaemic control with 19 patients with impaired awareness of hypoglycaemia.

Frequency of severe hypoglycaemia in the preceding year was estimated retrospectively.

Capillary blood glucose was monitored prospectively four times daily, over a 4-week period.

All blood glucose values <3 mmol/L were recorded and classified by symptom response.

![IAH, asymptomatic (silent) and severe hypoglycaemia in type 1 diabetes](image-url)
A questionnaire including the three methods was filled in by 372 outpatients with type 1 diabetes [43% women, age 51±14 years (mean±SD)], duration of diabetes 24±13 years, and HbA1c 8.2±1.0%)

All three methods for assessment of hypoglycaemia awareness are feasible in clinical practice since the degree of awareness is associated with risk of severe hypoglycaemia.
518 people with type 1 diabetes were recruited by random selection over a 2-year period. Participants completed a questionnaire documenting baseline characteristics and assessment of their awareness status using the Gold scoring method. The number of episodes of severe hypoglycaemia they had experienced in the preceding year was recorded retrospectively.
Data were obtained from 122 people with insulin-treated T2D. IAH was assessed using the Gold scoring system. Previous exposure to severe hypoglycaemia (events requiring external assistance) was estimated retrospectively for the year preceding the study.
• It can be difficult to dissociate the impact of impaired awareness of hypoglycaemia from that of having had severe episodes.
• This study involved 38 people with type 1 diabetes who had a Gold Score>4, three or more episodes of blood glucose levels of <3mmol/L (54 mg/dl) without detecting symptoms in 2 weeks of blood glucose results and at least one episode of severe hypoglycaemia, defined as requiring third party assistance in the last 2 years.
It is often not easy to distinguish the impact of impaired awareness of hypoglycaemia on the family from that of severe episodes of hypoglycaemia but in the above study, researchers spoke to relatives of people with family members who had been recruited into a study by virtue of having type 1 diabetes and impaired awareness and Gold score $\geq 4$. 

Impact of impaired awareness on family members

- High concern/worry/anxiety
- Curtailing own lifestyle through need to monitor and/or treat person with diabetes
- Resentment of supervisory role
- Fear of personal injury while trying to treat a severe episode
- Distress over manifestations of cognitive impairment and abnormal behaviours
- Exhaustion
- Sleep disturbance
- Frustration, resentment, ambivalence and guilt

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The incidence of IAH in children with T1DM in Western Australia was determined via a questionnaire in a study conducted by Dr. Patricia Gallego. Children and adolescents with type 1 diabetes aged between 6 months and 19 years and diabetes duration of at least 6 months, attending paediatric diabetes clinics at Princess Margaret Hospital were eligible to participate in the study.
IAH was defined as patients having a Clarke score ≥4.
The incidence of hypoglycaemia unawareness was very high at 29% in this population and in this group. The rate of severe hypoglycaemic events was almost double compared to children with normal awareness.

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<thead>
<tr>
<th></th>
<th>Total</th>
<th>Normal awareness</th>
<th>Impaired awareness</th>
<th>p-value</th>
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<tr>
<td>Participants</td>
<td>656</td>
<td>465</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td></td>
<td>70.9%</td>
<td>29.1%</td>
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<td>Age (years)</td>
<td>13.5 ± 4.0</td>
<td>14.1 ± 3.6</td>
<td>10.6 ± 4.4</td>
<td>&lt;0.0001</td>
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<td>HbA1c (mean)</td>
<td>8.5 ± 1.0</td>
<td>8.6 ± 1.0</td>
<td>8.3 ± 1.0</td>
<td>0.006</td>
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<td>Rate of SH, episodes/100 patient-years</td>
<td>24.5</td>
<td>19.3</td>
<td>37.1</td>
<td>&lt;0.0001</td>
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SH, severe hypoglycaemia.
Questionnaires were completed by 98 children with T1D (mean age 10.6 years) and their parent(s), and hospital admission data for the previous year were collected. Awareness of hypoglycaemia was assessed using ‘Clarke’ or ‘Gold’ scoring systems. For 4 weeks, participants performed routine blood glucose measurements and completed questionnaires after each episode of hypoglycaemia. The Gold questionnaire classified a greater proportion of the participants as having IAH than the 'Clarke' questionnaire.
# Prevalence of IAH in young people with type 1 diabetes

<table>
<thead>
<tr>
<th>Year</th>
<th>Region</th>
<th>N</th>
<th>Age group</th>
<th>Questionnaires</th>
<th>IAH (%)</th>
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<td>1998</td>
<td>Hungary¹</td>
<td>130</td>
<td>3–17 years</td>
<td>Onset of hypo</td>
<td>37</td>
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<tr>
<td>2002</td>
<td>Perth²</td>
<td>656</td>
<td>6 months–19 years</td>
<td>Modified Clarke</td>
<td>29</td>
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<tr>
<td>2009/10</td>
<td>Perth³</td>
<td>196</td>
<td>8–18 years</td>
<td>Modified Clarke</td>
<td>19</td>
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<tr>
<td>2014</td>
<td>Edinburgh⁴</td>
<td>98</td>
<td>Children &amp; adolescents</td>
<td>Clarke</td>
<td>10</td>
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IAH, Impaired awareness of hypoglycaemia.
Prevalence of IAH was significantly lower in the 2015 cohort compared to 2002. Note that the reduction in severe hypoglycaemia may be attributed to increased use of insulin analogues, insulin pump therapy, improved diabetes education, or more effective glycaemic control.
Severe hypoglycaemia in children has consequences in their parents or caregivers.
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Previous studies have shown that the symptoms associated with hypoglycaemia are common in the elderly population. Additionally, normal glycaemic thresholds for symptom generation or cognitive impairment in the younger population are shifted downwards in the elderly.
Comorbidities from other diseases associated with the elderly population increase the difficulty in recognizing hypoglycaemia in elderly populations due to overlapping symptoms.
The elderly population faces different consequences of hypoglycaemia than in the younger population.

- Increased risk of falls
- Reduced ability to perform activities of daily living
- Increased risk of fear and anxiety
- Loss of independence
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In this study, responses to experimentally induced hypoglycaemia (left) were measured in 12 people with type 1 diabetes and recurrent severe hypoglycaemia before and after avoidance of exposure to measured plasma glucose of under 3 mmol/L for at least 3 weeks. In all, adrenaline and symptom responses were restored. Six had intensively treated type 1 diabetes, six had problematic hypoglycaemia as part of generally looser diabetes self-management but all showed the improvement. Outside the setting of research, not all were able to maintain the benefit, achieved by investigator-driven insulin dose adjustments during the trial. This study was conducted in the pre-DAFNE era in the UK.
Proper management is required to balance avoidance of hypoglycaemia and risk of future episodes. Improper management techniques can promote an increase in hypoglycaemia risk.

**Discuss common behavioural factors increasing risk of hypoglycaemia with insulin**

- Post-meal insulin injection
- Failure to adjust insulin regimen for exercise or increased alcohol intake
- Over-enthusiastic correction regimens
  - eg, within two hours of a meal or earlier correction dose
A number of strategies can be employed to manage IAH and hypoglycaemia. Frequent episodes of hypoglycaemia are associated with IAH. Thus, reversal or avoidance of hypoglycaemia can reduce IAH.

Educational programs including those listed can also improve IAH. Careful monitoring of blood glucose, especially during high-risk activities, can be employed and bolstered through the use of technology such as CGM.
Glycaemic management of impaired awareness of hypoglycaemia in type 1 diabetes

- Reinforce lower limit of desirable glucose range
- Insulin analogues:
  - Lower frequency of severe hypoglycaemia in high-risk patients
  - Less nocturnal hypoglycaemia
- Real-time CGM: fewer episodes of severe hypoglycaemia but IAH unchanged
- CSII: meta-analysis showed less severe hypoglycaemia
- CSII with insulin suspension:
  - Reduces frequency of hypoglycaemia
- Whole pancreas and islet cell transplantation:
  - Symptomatic awareness can be restored
  - Severe hypoglycaemia can be eradicated

CGM, continuous glucose monitoring; CSII, continuous subcutaneous infusion; IAH, impaired awareness of hypoglycaemia.
Glycaemic management of IAH in type 2 diabetes

With SU treatment:
- Consider if glycaemic target is too low
- Shift to other OAD without hypoglycaemic potential or GLP-1RA

With insulin therapy
- Revise glycaemic targets
- Insulin analogues
- CGM
- CSII?

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; GLP-1RA, glucagon-like peptide-1 receptor agonist.
IAH, impaired assessment of hypoglycaemia; OAD, oral anti-diabetic drug; SU, sulphonylureas.
A pathway for individuals with impaired hypoglycaemia awareness?

Exclusion or treatment of comorbidities

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion.
### A pathway for individuals with impaired hypoglycaemia awareness?

- **Exclusion or treatment of comorbidities**
- **Review/support from experienced physician, diabetes nurse/dietitian**

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CGLM, continuous glucose monitoring; CII, continuous subcutaneous insulin infusion.
## A pathway for individuals with impaired hypoglycaemia awareness?

- **Exclusion or treatment of comorbidities**
- **Review/support from experienced physician, diabetes nurse/dietitian**
- **Structured training in insulin self management using basal insulin analogues**

**CGM**: continuous glucose monitoring; **CSI**: continuous subcutaneous insulin infusion.
## A pathway for individuals with impaired hypoglycaemia awareness?

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<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Exclusion or treatment of comorbidities</td>
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<tr>
<td>2</td>
<td>Review/support from experienced physician, diabetes nurse/dietitian</td>
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<td>3</td>
<td>Structured training in insulin self management using basal insulin analogues</td>
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<td>4</td>
<td>CGM/CSII</td>
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CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion.
A pathway for individuals with impaired hypoglycaemia awareness?

- Exclusion or treatment of comorbidities
- Review/support from experienced physician, diabetes nurse/dietitian
- Structured training in insulin self management using basal insulin analogues
- CGM/CSII
- Addressing major psychological issues in individuals with impaired awareness of hypoglycaemia

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion.
A pathway for individuals with impaired hypoglycaemia awareness?

- Exclusion or treatment of comorbidities
- Review/support from experienced physician, diabetes nurse/dietitian
- Structured training in insulin self management using basal insulin analogues
- CGM/CSII
- Addressing major psychological issues in individuals with impaired awareness of hypoglycaemia
- Islet cell/pancreas transplantation?

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion.
IAH management with continuous glucose monitoring

Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial

Articles

Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial

Articles

All participants wore a masked rtCGM system for 28 days and were randomly assigned to 26 weeks of unmasked rtCGM or to the control group (continuing SMBG).

Block randomisation with 1:1 allocation was done centrally, with the study site as the stratifying variable.

Masking of participants and study sites was not possible. Control participants wore a masked rtCGM system during the follow-up phase (weeks 22–26).

149 participants were randomly assigned (n=74 to the control group; n=75 to the rtCGM group) and 141 completed the follow-up phase (n=66 in the control group, n=75 in the rtCGM group).
The mean number of hypoglycaemic events per 28 days among participants in the rtCGM group was reduced from 10.8 (SD 10.0) to 3.5 (4.7).

Reductions among control participants were negligible (from 14.4 (12.4) to 13.7 (11.6)).

Incidence of hypoglycaemic events decreased by 72% for participants in the rtCGM group (incidence rate ratio 0.28 [95% CI 0.20–0.39], p<0.0001.

rtCGM reduces the number of hypoglycaemic events in people with T1D and IAH

[Graph showing mean number of hypoglycaemic episodes per 28 days for SMBG and rtCGM at baseline and follow-up, with reductions indicated.]
Patients were randomly assigned to either 16 weeks of CGM followed by 12 weeks of washout and 16 weeks of SMBG, or 16 weeks of SMBG followed by 12 weeks of washout and 16 weeks of CGM (where the SMBG phase was the control).
During the CGM phase, patients used a real-time CGM system consisting of a Paradigm Veo system with a MiniLink transmitter and an Enlite glucose sensor (Medtronic, CA, USA). During the SMBG phase, patients were equipped with a masked CGM device, consisting of an iPro 2 continuous glucose monitor and an Enlite glucose sensor, which does not display real-time glucose values. The number of SMBG measurements per day and SMBG systems were not standardised between patients, to mimic real-life conditions.
Secondary outcome: severe hypoglycaemia

*Mean difference: \(9.8\%\) between CGM and SMBG.