Hypoglycemia in Patients With Type 2 Diabetes
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- Epidemiology and Burden of Hypoglycemia in Patients With Type 2 Diabetes
- Classification and Complications of Hypoglycemia
- Pathophysiology of Hypoglycemia in Patients With Type 2 Diabetes
- Risk Factors for Hypoglycemia
- Strategies to Prevent Hypoglycemia
- Strategies to Treat Hypoglycemia
Epidemiology and Burden of Hypoglycemia in Patients With Type 2 Diabetes
Hypoglycemia Is a Common Serious Adverse Effect of Type 2 Diabetes Therapy\textsuperscript{1}

- Reported rates of hypoglycemia vary across clinical studies due to marked differences in how hypoglycemia has been defined, measured, and reported\textsuperscript{1}
- Rates also vary based on treatment modality and patient characteristics\textsuperscript{1}
- Clinical trials (ADVANCE, ACCORD, ORIGIN, UKPDS, VADT) reported rates of severe hypoglycemia ranging from 0.3 to 12.0 per 100 person-years\textsuperscript{1}
- Below are pooled data from a meta-analysis of 46 population-based studies (N=532,542 with T2D; 1 week to 22 years’ follow-up).\textsuperscript{2}

<table>
<thead>
<tr>
<th>Hypoglycemia Level</th>
<th>Incidence per Patient-Year (95% CI)</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>19.0 (0.00-51.08)</td>
<td>0.45 (0.34-0.57)</td>
</tr>
<tr>
<td>Severe</td>
<td>0.8 (0.00-2.15)</td>
<td>0.06 (0.05-0.07)</td>
</tr>
<tr>
<td>Insulin users</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>23.3 (0.00-58.98)</td>
<td>0.52 (0.37-0.67)</td>
</tr>
<tr>
<td>Severe</td>
<td>1.1 (0.00-3.69)</td>
<td>0.21 (0.16-0.25)</td>
</tr>
</tbody>
</table>

Nearly 25% of Emergency Hospitalizations for Adverse Drug Events in Older US Adults Are Related to Antihyperglycemic Drugs

- Data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project
- Identified frequency/rates of hospitalization after emergency department and outpatient visits for adverse drug events in older adults (aged ≥65 years):
  - 5077 cases identified; 99,628 emergency hospitalizations annually
- Of all hospitalizations attributed to endocrine agents, 94.6% were for hypoglycemia
  - Of these, 66.6% involved neurologic symptoms

Economic Burden of Hypoglycemia in T2D

- Retrospective cohort study (2004-2008) using MarketScan database; N=536,581 patients aged 18-65 years with T2D¹
  - Total hypoglycemia-related costs (2008 US$) over study:
    - $52,223,675, or 0.6% of all ED, inpatient, and outpatient costs
  - Visits related to hypoglycemia accounted for:
    - 2.7% of ED costs, 0.1% of inpatient costs, 0.3% of outpatient costs

- Retrospective cohort study (2004-2015) using Optum Clinformatics Data Mart claims; N=560,503 commercially insured adults aged 19-64 years with T2D²
  - Total mean cost per-person per-visit for hypoglycemia (2016 US$):
    - $1965 (ED visits) and $11,632 (inpatient hospitalizations)


The mean cost of hypoglycemia-related medical encounters is up to 4 times higher than other diabetes-related claims¹

Mean Hypoglycemia Costs¹

- ED Visit
- Inpatient Admission
- Outpatient Visit

ED, emergency department; T2D, type 2 diabetes.
Emergency Department and Other Health Care Utilization Due to Hypoglycemia in Patients With Diabetes

- Overall incidence for ED, outpatient, and inpatient visits for hypoglycemia: 153.8 per 10,000 patient-years\(^1\)
  - Data from Optum Clinformatics Data Mart (2004-2015)\(^1\)
- 5 million ED visits (380,000 per year) for hypoglycemia in patients with diabetes; 25% resulting in hospital admission\(^2\)
- 2.4 million ED visits total for hypoglycemia in patients with diabetes (all ages); 27% resulting in hospital admission\(^3\)
- 420,320 outpatient visits for hypoglycemia\(^3\)
  - Data from NHAMCS (1993-2005)\(^2\) and NHAMCS (2005-2009)\(^3\)

Classification and Complications of Hypoglycemia
2019 American Diabetes Association and European Association for the Study of Diabetes, Definition of Hypoglycemia$^{1,2}$

<table>
<thead>
<tr>
<th>Level</th>
<th>Glycemic criteria, description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glucose $&lt;$70 mg/dL (3.9 mmol/L) and glucose $\geq$54 mg/dL (3.0 mmol/L)</td>
</tr>
<tr>
<td>2</td>
<td>Glucose $&lt;$54 mg/dL (3.0 mmol/L)</td>
</tr>
<tr>
<td>3</td>
<td>Severe event characterized by altered mental and/or physical status requiring assistance</td>
</tr>
</tbody>
</table>

Hypoglycemia: Characteristics Needed to Fulfill Whipple’s Triad

Whipple’s Triad

- Low plasma glucose levels at time of suspected hypoglycemia
- Signs and symptoms suggestive of hypoglycemia (neuroglycopenic and/or neurogenic)
- Symptom resolution with plasma glucose correction

American Diabetes Association/European Association for the Study of Diabetes Classification of Hypoglycemia and Rationale$^{1,2}$

- **Level 1:** Threshold for neuroendocrine response to falling glucose in individuals without diabetes$^{1,3}$
  - Clinically important, independent of symptom severity, as many patients experience impaired counter-regulatory response to hypoglycemia (hypoglycemia awareness)
  - Provides a margin of safety and allows time to prevent progression to a clinical hypoglycemic episode

- **Level 2:** Threshold at which neuroglycopenic symptoms begin$^1$
  - Resolution of hypoglycemic event requires immediate action

- **Level 3:** Consequences can be deadly without assistance from a third party$^1$

<table>
<thead>
<tr>
<th>Level</th>
<th>Glycemic criteria/description</th>
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<tbody>
<tr>
<td>1</td>
<td>Glucose &lt;70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)</td>
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</tr>
<tr>
<td>3</td>
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</tr>
</tbody>
</table>

Neurogenic and Neuroglycopenic Symptoms of Hypoglycemia

**Neurogenic**
- Adrenergic
  - Anxiety
  - Arousal
  - Palpitations
  - Tremor
- Cholinergic
  - Hunger
  - Paresthesias
  - Sweating

Severe and prolonged hypoglycemia can result in seizure, loss of consciousness, coma, or death.

**Neuroglycopenic**
- Behavioral changes
- Blurred vision
- Confusion
- Difficulty thinking
- Emotional lability
- Headache, dizziness
- Incoordination
- Irritability
- Weakness, fatigue
- Sensation of warmth
- Speech disturbance


[https://www.healthline.com/health/low-blood-sugar-effects-on-body#1](https://www.healthline.com/health/low-blood-sugar-effects-on-body#1)
Consequences of Hypoglycemia¹,²

<table>
<thead>
<tr>
<th>Organ/System</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Abnormal prolonged cardiac repolarization</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td></td>
<td>Sudden death</td>
</tr>
<tr>
<td>Eyes</td>
<td>Vitreous hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Worsening of retinopathy</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Brain damage, intellectual decline</td>
</tr>
<tr>
<td></td>
<td>Unusual behavior</td>
</tr>
<tr>
<td></td>
<td>Seizure, coma</td>
</tr>
<tr>
<td></td>
<td>Transient ischemic attack, stroke</td>
</tr>
<tr>
<td></td>
<td>Focal neurological lesions (rare)</td>
</tr>
<tr>
<td>Other</td>
<td>Falls</td>
</tr>
<tr>
<td></td>
<td>Accidents with injury</td>
</tr>
</tbody>
</table>

Consequences of Mild Hypoglycemia

Even mild hypoglycemia can induce defects in counter-regulatory response and lead to impaired hypoglycemia awareness\(^1\)

A prospective study of 77,611 patients with T2D from the Taiwan National Health Insurance Research Database (1998-2009)\(^2\)
- Mild hypoglycemia episodes were strongly associated with subsequent CVD hospitalization, CHD, stroke, and all-cause mortality\(^2\)

An online survey was conducted of 1404 patients with diabetes who reported non-severe hypoglycemia in the last month\(^3\)
- Lost productivity per non-severe event: $15.26 to $93.47\(^3\)
- Lost work time per month: 8.3 to 15.9 hours\(^3\)

CHD, coronary heart disease; CVD, cardiovascular disease; T2D, type 2 diabetes.

Patient Fear of Hypoglycemia (FoH)

FoH is an important limiting factor in glycemic management, and may be a significant barrier to treatment adherence.

- FoH is widespread in T1D and T2D. A survey of 15,549 patients with diabetes (96% with T2D, 4% with T1D) found 54% were anxious about risk of hypoglycemia all or most of the time.
- FoH reported by 27.7% in a survey of 355 patients with insulin-treated T2D.

Likelihood of developing FoH related to:
- History of hypoglycemia
- Length of time since first insulin treatment
- Higher blood glucose variability

FoH, fear of hypoglycemia; T1D, type 1 diabetes; T2D, type 2 diabetes.

Severe and Prolonged Hypoglycemia Increases Morbidity and Mortality

• Severe hypoglycemia can:
  - Progress to seizure, loss of consciousness, coma, or death
  - Cause acute harm to self and others, especially in the setting of falls, motor vehicle accidents, or other injuries
• Severe hypoglycemia has also been associated with mortality in ACCORD, ADVANCE, and clinical practice
• Studies have suggested a link between hypoglycemia and CVD

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CVD, cardiovascular disease.

Was Increased Mortality in ACCORD Related to Increased Hypoglycemia?

- The cause of excess mortality in the intensive treatment arm of ACCORD is unknown; however, one plausible cause was iatrogenic hypoglycemia
  - Median A1C in the intensive therapy group was intentionally and demonstrably lower than in the standard therapy group
  - Lower A1C levels associated with higher frequency of hypoglycemia in T2D
    - Prevalence of severe hypoglycemia was >3-fold higher in the intensive therapy group
  - Hypoglycemia in T2D can be fatal
    - Includes sudden, presumably cardiac arrhythmic death
  - More patients who died were in the intensive glycemic therapy group in ACCORD

A1C, glycated hemoglobin; ACCORD, Action to Control Cardiovascular Risk in Diabetes; T2D, type 2 diabetes.
Increased Mortality in the Intensive Treatment Arm in ACCORD Cannot Be Explained by Severe Hypoglycemia

- Patients with T2D who experience SH are at increased risk of death, regardless of intensity of glycemic control
- However, increased mortality rate among patients in the intensive treatment arm cannot be attributed to increased SH rate in these patients
  - Among patients who had \( \geq 1 \) SH event, mortality was lower in the intensive treatment arm
  - Among participants who had \( \geq 1 \) non-SH event, mortality was lower in the intensive treatment arm

Annual Rates of Adverse Clinical Outcomes Among Patients With Severe Hypoglycemia in ADVANCE

- Post hoc analysis of ADVANCE (RCT, N=11,140 patients with T2D)
- Examined associations between SH and risk of micro/macrovascular events and death
- Median follow-up: 5 years
- Patients assigned to receive intensive or standard glucose-lowering treatment

ADVANCE, Action in Diabetes and Vascular Disease: Preterax and DiaMicon MR Controlled Evaluation; RCT, randomized controlled trial; SH, severe hypoglycemia; T2D, type 2 diabetes.
Increased Mortality and Cardiovascular Event Risk in Patients With Severe Hypoglycemia in the Veterans Affairs Diabetes Trial

- Post hoc analysis of VADT (RCT, N=1791 veterans with T2D)
- SH associated with ↑ risk of: serious CV events ($P=0.032$); CV mortality ($P=0.012$); and total mortality ($P=0.024$)
- However, total mortality risk was relatively higher in the standard vs the intensive group ($P=0.019$)

CV, cardiovascular; RCT, randomized controlled trial; SH, severe hypoglycemia; T2D, type 2 diabetes; VADT, Veterans Affairs Diabetes Trial.

Clinical Trial Cohorts Linking Hypoglycemia to CV Risk in Patients With T2D

<table>
<thead>
<tr>
<th>Clinical Trial Cohort, Publication Year</th>
<th>Hypoglycemia Severity</th>
<th>N</th>
<th>Follow-up (years)</th>
<th>Effect Size (adjusted 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME, 2019¹</td>
<td>Severe or PG &lt;54 mg/dL</td>
<td>7020</td>
<td>Median 3.1</td>
<td>3P-MACE HR 1.03 (0.74-1.44); fatal/nonfatal stroke HR 1.00 (0.49-2.01); fatal/nonfatal MI HR 1.20 (0.75-1.93); all-cause mortality HR 1.09 (0.75-1.60); CV death HR 1.01 (0.64-1.60); non-CV death HR 1.30 (0.67-2.53); HHR HR 1.72 (1.06-2.78)</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME, 2019¹</td>
<td>Symptomatic with PG ≤70 mg/dL, any with PG &lt;55 mg/dL, or severe</td>
<td>7020</td>
<td>Median 3.1</td>
<td>3P-MACE HR 1.18 (0.90-1.55); fatal/nonfatal stroke HR 1.02 (0.57-1.85); fatal/nonfatal MI HR 1.56 (1.06-2.29); all-cause mortality HR 1.13 (0.81-1.56); CV death HR 1.06 (0.71-1.57); non-CV death HR 1.30 (0.73-2.34); HHF HR 1.91 (1.25-2.93)</td>
</tr>
<tr>
<td>DEVOTE 3, 2018³</td>
<td>Severe</td>
<td>7637</td>
<td>Median 2.0</td>
<td>CVD HR 1.38 (0.96-1.96); all-cause death HR 2.51 (1.79-3.50)</td>
</tr>
<tr>
<td>EXAMINE, 2017⁴</td>
<td>Severe</td>
<td>5380</td>
<td>Median 1.5</td>
<td>CVD HR 2.42 (1.27-4.60); CVD post-severe hypoglycemia HR 1.60 (0.80-3.20)</td>
</tr>
<tr>
<td>ORIGIN, 2013⁵</td>
<td>Severe</td>
<td>12,537</td>
<td>Median 6.2</td>
<td>CVD HR 1.58 (1.24-2.02); CV death HR 1.71 (1.27-2.30); all-cause death HR 1.74 (1.39-2.19); arrhythmic death HR 1.77 (1.17-2.67)</td>
</tr>
<tr>
<td>ORIGIN, 2013⁵</td>
<td>Non-severe</td>
<td>12,537</td>
<td>Median 6.2</td>
<td>No association</td>
</tr>
<tr>
<td>VADT, 2011⁶</td>
<td>Severe</td>
<td>1791</td>
<td>Median 5.6</td>
<td>CVD HR 1.88 (1.03-3.43)</td>
</tr>
<tr>
<td>ACCORD, 2010⁷</td>
<td>Severe</td>
<td>10,194</td>
<td>Mean 3.5</td>
<td>All-cause death HR (intensive group) 1.41 (1.03-1.93); all-cause death HR (standard group) 2.30 (1.46-3.65)</td>
</tr>
<tr>
<td>ADVANCE, 2010⁸</td>
<td>Severe</td>
<td>11,140</td>
<td>Median 5.0</td>
<td>CVD HR 3.53 (2.41-5.17); CV death HR 3.79 (2.36-6.08); all-cause death HR 3.27 (2.29-4.65)</td>
</tr>
</tbody>
</table>

3P, three-point; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CV, cardiovascular; CVD, cardiovascular disease; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events; EMPA-REG OUTCOME, (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR, hazard ratio; EXAMINE, Examination of Cardiovascular Outcomes With Alogliptin versus Standard of Care; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; ORIGIN, Outcomes Reduction With an Initial Glargine Intervention; PG, plasma glucose; VADT, Veterans Affairs Diabetes Trial; T2D, type 2 diabetes.

## Epidemiologic Cohorts Linking Hypoglycemia to CV Risk in Patients With T2D

<table>
<thead>
<tr>
<th>Epidemiological cohort, publication year</th>
<th>Hypoglycemia severity</th>
<th>N</th>
<th>Follow-up (years)</th>
<th>Effect size (adjusted 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC, 2018</td>
<td>Severe</td>
<td>1209</td>
<td>Median 15.3</td>
<td>CHD HR 2.02 (1.27-3.20); CV death HR 1.64 (1.15-2.34); all-cause death HR 1.73 (1.38-2.17)</td>
</tr>
<tr>
<td>Japanese database, 2016</td>
<td>Severe</td>
<td>58,223</td>
<td>Mean 2.3</td>
<td>CVD HR 3.39 (1.25-9.18)</td>
</tr>
<tr>
<td>Vincent T2D Registry (SK), 2016</td>
<td>Severe</td>
<td>906</td>
<td>Median 10.4</td>
<td>All-cause death HR 2.64 (1.39-5.02); CV death HR 6.34 (2.02-19.87)</td>
</tr>
<tr>
<td>Joint Asia Diabetes Registry, 2016</td>
<td>Mild</td>
<td>18,589</td>
<td>Mean 3.9</td>
<td>CVD HR 1.16 (0.94-1.43); all-cause death HR 1.03 (0.78-1.36)</td>
</tr>
<tr>
<td>CREDIT Study, 2016</td>
<td>Severe</td>
<td>2999</td>
<td>4.0*</td>
<td>CV death HR 1.10 (0.34-3.57); all-cause death HR 1.22 (0.59-2.53)</td>
</tr>
<tr>
<td>UK GP database 2015</td>
<td>Severe</td>
<td>10,422</td>
<td>Median 4.8</td>
<td>CVD secondary care HR 1.70 (1.09-2.64); CVD HR 1.50 (1.19-1.88)</td>
</tr>
<tr>
<td>Edinburgh T2D Study, 2014</td>
<td>Severe</td>
<td>1066</td>
<td>Mean 4.0</td>
<td>CVD HR 1.60 (1.13-2.26)</td>
</tr>
<tr>
<td>German primary care database, 2013</td>
<td>Severe</td>
<td>25,712</td>
<td>Mean 2.0</td>
<td>CVD HR 2.11 (1.06-4.20)</td>
</tr>
<tr>
<td>Taiwan database, 2013</td>
<td>Severe</td>
<td>2500</td>
<td>10 years*</td>
<td>CVD HR 2.26 (1.93-2.65); CHD HR 1.63 (1.28-2.08); stroke HR 1.64 (1.29-2.07); CVD HR 2.21 (1.98-2.47)</td>
</tr>
<tr>
<td>US Veterans Network, 2012</td>
<td>Severe, Mild</td>
<td>1522</td>
<td>Median 3.9</td>
<td>CVD HR 2.00 (1.63-2.44)</td>
</tr>
<tr>
<td>Medicare database, 2011</td>
<td>Severe</td>
<td>860,845</td>
<td>Mean 1.0</td>
<td>CVD HR 1.79 (1.69-1.89)</td>
</tr>
</tbody>
</table>

ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CV, cardiovascular; CREDIT, Cardiovascular Risk Evaluation in People With Type 2 Diabetes on Insulin Therapy; CVD, cardiovascular disease; GP, general practice; HR, hazard ratio; SK, South Korea; T2D, type 2 diabetes; UK, United Kingdom; US, United States.

*Type of descriptive statistic not stated

Pathophysiology of Hypoglycemia in Patients With Type 2 Diabetes
Physiologic Response to Hypoglycemia

- The brain cannot synthesize glucose and depends on circulating arterial glucose for metabolic function and survival
- When blood glucose levels fall, the body initiates counterregulatory responses to restore levels
- Limited evidence suggests counterregulatory responses to hypoglycemia are intact early in the course of T2D
  - Glucagon response is normal to modestly reduced
  - As T2D progresses and endogenous insulin production reduces, sympatheoadrenal and glucagon response to hypoglycemia become impaired

Counterregulatory response thresholds and associated symptoms in response to hypoglycemia in individuals without diabetes

<table>
<thead>
<tr>
<th>Glucose (mmol/L)</th>
<th>Inhibition of endogenous insulin</th>
<th>Glucagon and adrenaline production</th>
<th>Autonomic symptoms</th>
<th>Cognitive dysfunction</th>
<th>Neuroglycopenic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.8</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3.2</td>
<td></td>
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<tr>
<td>3.0</td>
<td></td>
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</tr>
<tr>
<td>2.8</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Counterregulatory Hormones Before and After the Administration of Regular Insulin in Normal Subjects

Plasma-Free Insulin, Glucose, Epinephrine, and Pancreatic Polypeptide Concentrations Before, During, and After Morning Hypoglycemia in Patients with T1D


Eu, euglycemia; hypo, hypoglycemia; T1D, type 1 diabetes.
Physiologic and Behavioral Defenses Against Hypoglycemia

Physiologic defenses against falling blood glucose concentrations:

↓ Pancreatic beta-cell-mediated insulin secretion

↑ Pancreatic alpha-cell-mediated glucagon secretion

↑ Adrenomedullary epinephrine secretion

These defenses are often attenuated in advanced T2D

ACh, acetylcholine; CNS, central nervous system; NE, norepinephrine; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; T2D, type 2 diabetes.
Impaired Awareness of Hypoglycemia

- Impaired awareness of hypoglycemia affects up to 10% of patients with T2D and is characterized by the loss of ability to perceive hypoglycemia onset.
  - Reduced intensity and number of symptoms
  - Change in symptom profile
- Repeated episodes of hypoglycemia are thought to attenuate autonomic response to hypoglycemia.
  - Threshold for hypoglycemia symptom activation is reset to a lower glucose level
  - Adrenaline response is diminished, contributing to counterregulatory failure
- The phenomenon of progressive counterregulatory failure and loss of awareness of symptoms of hypoglycemia is known as “hypoglycemia associated autonomic failure.”

Mechanisms of Loss of Glucagon Response

Normal physiology

- Decreased glucose
  - Beta-cells
  - Decreased insulin
  - Alpha-cells
  - Increased glucagon

- Increased glucose
  - Beta-cells
  - Increased insulin
  - Alpha-cells
  - Decreased glucagon

Pathophysiology in diabetes

- Decreased glucose
  - Beta-cells
  - No decrease in insulin
  - Alpha-cells
  - No increase in glucagon

- Increased glucose
  - Beta-cells
  - No increase in insulin
  - Alpha-cells
  - Increased glucagon

Risk Factors for Hypoglycemia
Impaired hypoglycemia awareness increases subsequent hypoglycemia risk by ~5-fold

1. Diabetes complexity
   - Diabetes duration
   - Impaired hypoglycemia awareness
   - High glycemic variability
   - Prior hypoglycemic events
     - Severe and non-severe
   - Glycemic control
     - U-shaped relationship with HbA1c
   - Fear of hypoglycemia
   - Fear of hyperglycemia

2. Multi-morbidity
   - Functional impairment, frailty
   - Comorbid health conditions:
     - Microvascular complications (autonomic, peripheral, and cardiovascular neuropathy; retinopathy), kidney disease, cardiovascular disease, heart failure, cerebrovascular disease, liver disease, lung disease, depression
   - Cognitive impairment, dementia

3. Pharmacotherapy
   - High risk medications: Insulin, sulfonylurea
   - Glucose-lowering polypharmacy
   - Non-diabetes medications
     - Example: beta blockers
   - Complex treatment regimens
   - Medication misadventures
     - Dosing errors, discordance with meals, etc.

4. Patient context and environment
   - Inadequate caregiver support or supervision
   - Food insecurity
   - Poor health literacy
   - Financial burden
   - Non-clinical or competing clinical demands
   - Fasting, either for medical tests/procedures or personal/religious reasons
     - Example: Ramadan

5. Healthcare system
   - Performance measurement, reporting, and benchmarking that focus on lowering HbA1c
   - Inadequate diabetes support/resources, including DSME and clinical monitoring
   - Payer decisions regarding DSME, glucose monitoring, drug formulary, and diabetes technologies
   - Lack of integration of patient health information, including glucose monitoring data and self-reported hypoglycemia, into clinical EHR

### Characteristics of Patients With Type 2 Diabetes at Increased Risk for Hypoglycemia

- **Older age**
- **Long duration of diabetes**
  - In UKPDS, SH rates rose after 9 years of known T2D
- **Regularly miss meals**
- **Exercise**
  - Causes excess peripheral glucose uptake
- **Use of insulin secretagogues and insulin therapy**
- **Impaired awareness of hypoglycemia**
- **Impaired drug clearance**
  - Renal impairment, hepatic failure, hypothyroidism
- **Impaired counterregulatory capacity**
  - Adrenal deficiency, growth hormone deficiency, hypopituitarism
- **Decreased endogenous glucose production**
  - Due to alcohol and/or liver failure
- **Concurrent medications**
  - Decreased renal excretion of SUs - aspirin, allopurinol
  - Displacement of SUs from albumin - aspirin, warfarin, trimethoprim
  - Decreased SU metabolism - warfarin, monoamine oxidase inhibitors
  - Insulin secretagogue activity - NSAIDs
  - Antibiotics in patients receiving sulfonylureas

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NSAIDs, nonsteroidal anti-inflammatory drugs; SH, severe hypoglycemia; SU, sulfonylurea; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.
Severe Hypoglycemia: ACCORD Study

Proportion of participants with ≥1 episode of hypoglycemia requiring medical assistance

Intensive glycemic control

Standard glycemic control

Log rank $P<0.0001$

ACCORD, Action to Control Cardiovascular Risk in Diabetes.
Severe Hypoglycemia in 3 Outcome Trials of Intensive Glucose Control in Type 2 Diabetes

Data from the ACCORD and ADVANCE trials and a subgroup analysis of the VADT, suggest that the risks of intensive glucose control outweigh its benefits in higher-risk patients.
Effect of Intensive Glucose-Lowering Treatment on Hypoglycemic Events

SH risk was more than twice as high in the intensive treatment group vs the standard treatment group.

Absolute 5-year risk increases for SH ranged from 1.9% to 6.6%.

Test for heterogeneity: $\tau^2=0.05$, $\chi^2=10.95$, df=4, $P=0.03$, $I^2=63\%$

Test for overall effect: $z=5.98$, $P<0.001$

### Insulins and Insulin Secretagogues Pose the Highest Hypoglycemia Risk in Patients With T2D

<table>
<thead>
<tr>
<th>Clinical trial cohort</th>
<th>N</th>
<th>Follow-up</th>
<th>Therapy</th>
<th>Effect size (95% CI), outcomes measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORIGIN, 2015</td>
<td>12,537</td>
<td>6.2 years (median)</td>
<td>Insulin glargine</td>
<td>4.53 (4.00-5.13), NSH HR 3.57 (2.80-4.55), SH HR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SU</td>
<td>2.07 (1.78-2.40), NSH HR 1.35 (1.07-1.70), SH HR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epidemiologic cohort</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CCHS, 2018</td>
<td>50,439</td>
<td>3.6 years (mean)</td>
<td>Insulin</td>
<td>2.77 (1.98-3.89), SH OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SU</td>
<td>2.77 (1.98-3.89), SH OR</td>
</tr>
<tr>
<td>MarketScan database, 2011</td>
<td>1339 cases 13390 controls</td>
<td>2004-2008</td>
<td>Insulin</td>
<td>2.23 (1.83-2.72), SH INPT OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SU</td>
<td>2.25 (1.93-2.63), SH INPT OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SU</td>
<td>2.50 (1.16-5.38), SH HR</td>
</tr>
</tbody>
</table>

- Some clinical and epidemiologic studies show similar hypoglycemia risk and related outcomes between insulin and SUs
- Other studies show higher hypoglycemia risk with insulin use

CCHS, Cleveland Clinic Health System; CI, confidence interval; HR, hazard ratio; INPT, inpatient admission; NSH, Non-severe hypoglycemia; OR, odds ratio; ORIGIN, Outcome Reduction With an Initial Glargine Intervention; SH, severe hypoglycemia; SU, sulfonylurea; T2D, type 2 diabetes.

Risk of Hypoglycemia With Medications Used to Treat T2D

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Monotherapy: OR (95% CI)*</th>
<th>Dual therapy (added to MET): OR (95% CI)*</th>
<th>Triple therapy (added to MET + SU): OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>1.0 (Reference)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SU</td>
<td>3.13 (2.39-4.12)</td>
<td>1.0 (Reference)</td>
<td>-</td>
</tr>
<tr>
<td>TZD</td>
<td>0.67 (0.50-0.88)</td>
<td>0.14 (0.09-0.24)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Basal insulin</td>
<td>17.9 (1.97-162)</td>
<td>0.56 (0.32-0.98)</td>
<td>0.95 (0.60-1.52)</td>
</tr>
<tr>
<td>DPP4i</td>
<td>0.69 (0.50-0.94)</td>
<td>0.12 (0.10-0.16)</td>
<td>0.87 (0.50-1.51)</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>0.63 (0.30-1.32)</td>
<td>0.12 (0.08-0.18)</td>
<td>0.86 (0.48-1.54)</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>1.06 (0.74-1.52)</td>
<td>0.19 (0.13-0.27)</td>
<td>0.60 (0.39-0.94)</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>2.16 (1.49-3.12)</td>
<td>0.55 (0.32-0.93)</td>
<td>NA</td>
</tr>
<tr>
<td>AGI</td>
<td>0.65 (0.37-1.13)</td>
<td>0.13 (0.05-0.40)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* OR >1 indicates that hypoglycemia is more likely with treatment than the reference intervention.

AGI, alpha-glucosidase inhibitor; CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; NA, not available; OR, odds ratio; RCT, randomized controlled trial; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

- Meta-analysis (N=301 RCTs) through March 2016 of T2D drugs
- Basal insulin and SU monotherapy ranked worst for avoiding hypoglycemia
- SGLT2i ranked best dual therapy option for avoiding hypoglycemia when added to MET
- GLP-1 RA ranked best triple therapy for avoiding hypoglycemia when added to MET + SU

Relative Risk for Experiencing Hypoglycemic Events: Glyburide vs Other Secretagogues

Compared with other secretagogues, glyburide was associated with a 52% greater risk of hypoglycemia (RR 1.52 [95% CI 1.21–1.92]), and with an 83% greater risk vs other sulfonylureas (1.83 [1.35–2.49]).

<table>
<thead>
<tr>
<th>Study</th>
<th>Glyburide n/N</th>
<th>Secretagogue n/N</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baba 1983</td>
<td>20/131</td>
<td>10/146</td>
<td>2.23 [1.08, 4.59]</td>
</tr>
<tr>
<td>Dills 1996</td>
<td>48/288</td>
<td>34/289</td>
<td>1.42 [0.94, 2.13]</td>
</tr>
<tr>
<td>Draeger 1996</td>
<td>74/520</td>
<td>60/524</td>
<td>1.24 [0.90, 1.71]</td>
</tr>
<tr>
<td>Haider 1976</td>
<td>2/76</td>
<td>0/80</td>
<td>5.26 [0.26, 107.81]</td>
</tr>
<tr>
<td>Hamblin 1970</td>
<td>7/50</td>
<td>2/47</td>
<td>3.29 [0.72, 15.05]</td>
</tr>
<tr>
<td>Harrower 1994</td>
<td>7/84</td>
<td>2/86</td>
<td>3.58 [0.77, 16.76]</td>
</tr>
<tr>
<td>Landgraf 1999</td>
<td>9/101</td>
<td>9/94</td>
<td>0.93 [0.39, 2.24]</td>
</tr>
<tr>
<td>Mafaury 2002</td>
<td>19/119</td>
<td>15/116</td>
<td>1.23 [0.66, 2.31]</td>
</tr>
<tr>
<td>Marbury 1999</td>
<td>37/182</td>
<td>59/362</td>
<td>1.25 [0.86, 1.81]</td>
</tr>
<tr>
<td>Rosenstock 1993</td>
<td>3/70</td>
<td>1/69</td>
<td>2.96 [0.32, 27.74]</td>
</tr>
<tr>
<td>Wolffenbuttel 1999</td>
<td>13/139</td>
<td>26/286</td>
<td>1.03 [0.55, 1.94]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2199</td>
<td>2513</td>
<td>1.52 [1.21, 1.92]</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.
Less Hypoglycemia With Insulin Glargine and Detemir Versus NPH Insulin

Data from 6 RCTs were used to model rates of hypoglycemia associated with insulin glargine vs NPH in 3656 patients with T2D.

Hypoglycemia rate (events/100 PY); association between end-of-study A1C and confirmed hypoglycemia (<65 mg/dL) during treatment with insulin glargine or NPH (P=0.021)

Relationship between confirmed hypoglycemia incidence and A1C in previous 12 weeks and at endpoint (P<0.001)

26-week RCT compared insulin detemir with NPH as add-on to OADs in 475 insulin-naïve patients with T2D.


A1C, glycated hemoglobin; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug; PY, person-years; RCT, randomized controlled trial; T2D, type 2 diabetes.
Rates of Hypoglycemia Lower With Insulin Degludec vs Insulin Glargine

- Meta-analysis of 5 T2D trials (N=3372 patients) in the iDeg development program that compared iDeg once daily to iGlar once daily¹,²
- Noninterventional US comparative effectiveness study (multiple health systems, integrated delivery networks) of insulin-naïve patients with T2D (N=4056)³

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iDeg, insulin degludec; iGlar, insulin glargine; T2D, type 2 diabetes.
Hypoglycemia Lower With Insulin Glargine U300 vs Glargine U100 in Patients With T2D Using Basal and Prandial Insulin

- Adults with T2D (N=807) using basal and mealtime insulin, randomized to Gla-300 or Gla-100
- Open-label, 6-month, parallel-group study (EDITION 1)
- No between-group difference in A1C reduction, tolerability, or safety
- Less hypoglycemia with Gla-300:
  - Hypoglycemia at any time: RR (95% CI), 0.94 (0.80, 1.11)
  - Nocturnal hypoglycemia: RR (95% CI), 0.73 (0.57, 0.92)

<table>
<thead>
<tr>
<th>Hypoglycemia at any time</th>
<th>Nocturnal hypoglycemia</th>
<th>Hypoglycemia at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Baseline to month 6</td>
<td>0.94 (0.80 to 1.11)</td>
<td>0.73 (0.57 to 0.92)</td>
</tr>
<tr>
<td>Baseline to week 8</td>
<td>0.87 (0.73 to 1.05)</td>
<td>0.70 (0.53 to 0.93)</td>
</tr>
<tr>
<td>Week 9 to month 6</td>
<td>0.98 (0.82 to 1.18)</td>
<td>0.74 (0.56 to 0.98)</td>
</tr>
</tbody>
</table>

**Documented symptomatic hypoglycemia (≤3.9 mmol/L [≤72 mg/dL])**

<table>
<thead>
<tr>
<th>Hypoglycemia at any time</th>
<th>Nocturnal hypoglycemia</th>
<th>Hypoglycemia at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Baseline to month 6</td>
<td>0.91 (0.74 to 1.12)</td>
<td>0.60 (0.46 to 0.79)</td>
</tr>
<tr>
<td>Baseline to week 8</td>
<td>0.86 (0.68 to 1.08)</td>
<td>0.67 (0.48 to 0.94)</td>
</tr>
<tr>
<td>Week 9 to month 6</td>
<td>0.95 (0.76 to 1.19)</td>
<td>0.56 (0.41 to 0.77)</td>
</tr>
</tbody>
</table>

**Severe hypoglycemia**

<table>
<thead>
<tr>
<th>Hypoglycemia at any time</th>
<th>Nocturnal hypoglycemia</th>
<th>Hypoglycemia at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Baseline to month 6</td>
<td>1.12 (0.42 to 3.00)</td>
<td>0.79 (0.28 to 2.27)</td>
</tr>
<tr>
<td>Baseline to week 8</td>
<td>0.73 (0.24 to 2.23)</td>
<td>1.49 (0.26 to 8.46)</td>
</tr>
<tr>
<td>Week 9 to month 6</td>
<td>1.30 (0.42 to 4.00)</td>
<td>0.54 (0.15 to 1.95)</td>
</tr>
</tbody>
</table>

**Confirmed (≤3.9 mmol/L [≤72 mg/dL]) or severe hypoglycemia**

<table>
<thead>
<tr>
<th>Hypoglycemia at any time</th>
<th>Nocturnal hypoglycemia</th>
<th>Hypoglycemia at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Baseline to month 6</td>
<td>0.95 (0.80 to 1.13)</td>
<td>0.75 (0.58 to 0.95)</td>
</tr>
<tr>
<td>Baseline to week 8</td>
<td>0.89 (0.74 to 1.08)</td>
<td>0.77 (0.57 to 1.02)</td>
</tr>
<tr>
<td>Week 9 to month 6</td>
<td>0.99 (0.82 to 1.19)</td>
<td>0.73 (0.55 to 0.98)</td>
</tr>
</tbody>
</table>
Hypoglycemia Lower With Insulin Glargine U300 vs Glargine U100 in Patients With T2D Using Basal Insulin and OADs

- Adults with T2D (N=811) using basal and oral antidiabetic drugs randomized to Gla-300 or Gla-100 in an open-label, 6-month study (EDITION 2)
- No between-group difference in A1C reduction, tolerability, or safety
- Less hypoglycemia with Gla-300:
  - Hypoglycemia at any time: RR (95% CI), 0.90 (0.83, 0.98)
  - Nocturnal hypoglycemia: RR (95% CI), 0.73 (0.61, 0.88)

A1C, glycated hemoglobin; CI, confidence interval; Gla-100, insulin glargine 100 units; Gla-300, insulin glargine 300 units; RR, relative risk; T2D, type 2 diabetes.

Patients With T2D Using LixiLan (FRC of iGlar + Lixisenatide) Achieved Glycemic Control Without Increased Hypoglycemia in Open-Label, Randomized Trials

LixiLan-L Trial: Patients with T2D inadequately controlled on basal insulin and metformin randomized to iGlarLixi or iGlar

LixiLan-O Trial: Patients with T2D inadequately controlled on oral agents randomized to iGlarLixi, iGlar, or Lixi

FRC, fixed-ratio combination; iGlar, insulin glargine; iGlarLixi, insulin glargine and lixisenatide; Lixi, lixisenatide; PG, plasma glucose; T2D, type 2 diabetes.

Patients Using iDegLira (FRC of Insulin Degludec + Liraglutide) Achieve Glycemic Control Without Increased Hypoglycemia

**Hypoglycemia results from the DUAL clinical trial program**
- Randomized Phase 3 safety and efficacy studies of iDegLira in patients with T2D
- Rates of confirmed hypoglycemia across studies: 1.5 to 3.5 events per PYE
- Highest rates in patients with background SU therapy

<table>
<thead>
<tr>
<th>Safety Analysis Set</th>
<th>DUAL I N=825</th>
<th>DUAL II N=199</th>
<th>DUAL III N=291</th>
<th>DUAL IV N=288</th>
<th>DUAL V N=278</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>MET pio Insulin-naive</td>
<td>Basal insulin 20-40 U daily + met SU/glinides</td>
<td>GLP-1 RA* + MET pio SU Insulin-naive</td>
<td>SU MET Insulin-naive</td>
<td>iGlar U100 20-50 U daily + MET</td>
</tr>
<tr>
<td>Confirmed hypoglycemia rates, events per PYE</td>
<td>1.8</td>
<td>1.5</td>
<td>2.8</td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia rates, events per PYE</td>
<td>0.2</td>
<td>0.2</td>
<td>0.5</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*D Liraglutide once daily/exenatide twice daily.

DUAL, Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes; FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist; iGlar, insulin glargine; MET, metformin; Pio, pioglitazone; PYE, patient year of exposure; SU, sulfonlurea; T2D, type 2 diabetes.

Hypoglycemia Risk Is Highest With Prolonged Insulin Use\textsuperscript{1}

- Observational study (9-12 months) of 383 patients with diabetes (28% with T1D, 72% with T2D)\textsuperscript{2}

<table>
<thead>
<tr>
<th>Severity of self-reported hypoglycemia</th>
<th>Mean (95% CI) rate of hypoglycemia per person-year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insulin-treated &lt;2 years</td>
</tr>
<tr>
<td>Non-severe (mild)</td>
<td>4.08 (2.5-5.8)</td>
</tr>
<tr>
<td>Severe (requiring third-party assistance)</td>
<td>0.1 (0.0-0.5)</td>
</tr>
</tbody>
</table>

- The Fremantle Diabetes Study: Longitudinal, observational, community-based cohort study (N=616 patients with T2D followed from 1998-2006)\textsuperscript{3}
  - With each additional year of insulin therapy, risk of SH requiring ambulance, ED, and hospital care increased by 42%\textsuperscript{3}

CGM Detects More Hypoglycemic Events Than Are Reported By Patients

- CGM detects more hypoglycemic events than reported by patients\(^1,2\)
  - Treating to Target in T2D Trial sub-study (N=106 insulin-dependent adults): 72-hour CGM use compared with self-reported hypoglycemia at 1 year\(^1\)
    - With glucometer, 10% reported level 2 or 3 hypoglycemia (blood glucose <56 mg/dL or requiring third-party assistance)
    - With CGM, 42% had blood glucose \(\leq 54\) mg/dL and 18% had levels \(\leq 40\) mg/dL
  - Prospective, nonblinded trial of CGM use over 5 days in insulin- and non-insulin-treated adults with T2D (N=108)\(^2\)
    - CGM detected blood glucose <70 mg/dL in 49.1% of patients over 5 days
    - Of these patients, 24.5% self-reported signs/symptoms with hypoglycemic event; 75.4% were not aware of hypoglycemia at all when detected by CGM

Strategies to Prevent Hypoglycemia
Strategies to Reduce Hypoglycemia Risk: Individualized A1C Goals and Targeted Antihyperglycemic Drug Selection

- Avoiding hypoglycemia is a critical component of T2D management
- For patients at risk, avoid low A1C targets
- Medication selection should include consideration of its hypoglycemic profile

Strategies to Reduce Hypoglycemia Risk in Patients with Type 2 Diabetes

SYSTEMS SUPPORT
- Integration of patient health information into EHR
- Patient engagement and monitoring
- Incorporation of PROs (including hypoglycemia) into clinical care
- Patient-centered care management

SOCIAL SUPPORT
- Caregiver education and engagement
- Community and social services (community health workers, food banks, meal delivery services, etc.)
- Financial assistance

CLINICAL SUPPORT
- DSME
- Hypoglycemia awareness training
- Pharmacist
- Dietician
- Social services
- Specialty diabetes care
- Diabetes technologies
- Mental health

POLICY SUPPORT
- Reimbursement for diabetes technologies, non-hypoglycemia prone medications, glucose monitoring, DSME, and social support programs
- Patient-centered performance measurement

DSME, diabetes self-management education; EHR, electronic health records; PRO, patient-reported outcomes.
ADA Algorithm for Glucose-Lowering Medication if Compelling Need to Minimize Hypoglycemia: Patients Without Established ASCVD or CKD

- Identify patient groups at highest risk for hypoglycemia
- Set and/or adjust A1C target to minimize hypoglycemia risk
- To avoid clinical inertia, reassess and modify as needed every 3-6 months

A1C, glycated hemoglobin; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones;


1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Dectedec / alargine U300 < alargine U100 / detemir < NPH insulin
Strategies to Treat Hypoglycemia
Treat Hypoglycemia With Fast-Acting Carbohydrates

- Counsel patients to treat hypoglycemia at ≤70 mg/dL alert value with fast-acting carbohydrates
- Do not use carbohydrate sources high in protein to treat or prevent hypoglycemia
  - Ingested protein may increase insulin response without increasing plasma glucose concentrations
- Treatment requires ingestion of carbohydrate- or glucose-containing foods
- Added fat may slow/prolong acute glycemic response

- Recommended sources of carbohydrates include:
  - 4 ounces of juice or non-diet soda
  - 1 tbsp of sugar, honey, or corn syrup
  - Hard candies, jelly beans, gumdrops
- Acute glycemic response correlates better with a food’s glucose content than carbohydrate content
- Pure glucose is preferred treatment, but any form of glucose-containing carbohydrate will increase blood glucose

Use of Glucagon to Treat Hypoglycemia

- Glucagon is indicated for treatment of hypoglycemia in patients unwilling or unable to ingest carbohydrates by mouth\(^1\)
- Caregivers or those in close contact with patients with T2D should receive instruction on use of glucagon kits, including kit location and appropriate timing and method of use\(^1\)
- Glucagon does not require administration from a health care professional\(^1\)
- First nasal glucagon received FDA approval in July 2019; dry powder spray formulation\(^2,3\)
  - Indicated to treat severe hypoglycemia (SH) in patients with diabetes aged ≥4 years\(^2\)
  - Alternative to administration of glucagon via injection\(^3\)

Strategies for People With Impaired Hypoglycemia Awareness

- Frequent BG monitoring (including nocturnal measurements)
- Avoid BG values <70 mg/dL (<3.9 mmol/L)
- Revise BG targets upward:
  - Preprandial target 108-216 mg/dL (6.0-12.0 mmol/L)
  - Bedtime target >144 mg/dL (>8.0 mmol/L)
  - A1C >7% (~7.5%-8%)
- Consume regular snacks between meals and at bedtime, containing unrefined carbohydrates
- Consume additional carbohydrates and/or adjust insulin dose before exercise
- Several weeks without hypoglycemia may improve counter-regulation and hypoglycemia awareness
  - Patients may benefit from short-term relaxation of glycemic targets

A1C, glycated hemoglobin; BG, blood glucose.
Management of Patients With Hypoglycemia Unawareness

• Test SMBG ≥3 times/day (typically 4-7 needed)
• May need **up to 3 times usual regimen** to exceed 100 mg/dL (ie, usual 15 grams may be increased temporarily up to 30-45 grams of dextrose)
• **Goal 1**: Avoid all hypoglycemia for 3 days
  - This is when a pattern starts to emerge in relation to therapeutic response (reduction of insulin resistance from prior hypoglycemia)
• **Goal 2**: Avoid hypoglycemia for 3 weeks
  - Associated with recovery of hypoglycemia awareness and/or counter-regulation in those without diabetic autonomic neuropathy
• In patients with diabetic autonomic neuropathy, 3-6 months are required to improve hypoglycemia awareness

SMBG, self-monitoring of blood glucose.
Summary of Hypoglycemia in T2D (1 of 2)

- Hypoglycemia has a substantial clinical and economic impact
- It manifests with neurogenic or neuroglycopenic symptoms; recurrence can lead to impaired hypoglycemia awareness
- Hypoglycemia and the fear of hypoglycemia limit patients’ ability to achieve and maintain optimal glycemic control
- Severe hypoglycemia can have serious consequences, including seizure, loss of consciousness, coma, or death; studies indicate a link between hypoglycemia and CVD
- In patients with T2D, hypoglycemia risk is highest in those treated with insulin or secretagogues (in particular, glyburide)

CVD, cardiovascular disease; T2D, type 2 diabetes.
Summary of Hypoglycemia in T2D (Part 2 of 2)

- Glycemic targets should be individualized, with hypoglycemia risk considered in both the selection of A1C target and diabetes medication
- With non-insulin agents, including newer class drugs such as DPP-4 inhibitors, SGLT-2 inhibitors and GLP1-RAs, lower glucose targets may be achievable without a significant increase in hypoglycemia risk
- Older patients, those with longer diabetes duration, strict glycemic control, impaired hypoglycemia awareness
- Hypoglycemia should be treated with fast-acting carbohydrates or glucagon; special consideration should be given to patients with impaired hypoglycemia awareness

A1C, glycated hemoglobin; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SLGT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.
Contributors

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