Treatment-induced hypoglycemia presents a significant limiting factor in diabetes management. Since the first applications of insulin to diabetes management, most treatments that lower glucose have been associated with significant risks of hypoglycemia. There have, however, been some improvements in these risks with more recently developed treatments. Advances in temporal profile and predictability of insulin preparations, and treatments using novel mechanisms that either augment insulin availability only with concurrent hyperglycemia, or that induce glucose lowering entirely independently of insulin availability or action, have provided important advances in our capacity to treat diabetes while reducing treatment-related hypoglycemia. Similarly, advances in glucose monitoring methodologies have provided unprecedented availability of tools that allow our patients to be aware of hypoglycemia and therefore allow superior near-term and long-term management of diabetes while minimizing the incidence and impact of hypoglycemia. We will review clinical data evaluating these new tools and medications from the perspective of improving hypoglycemia in diabetes management, and consider strategies for implementation of these tools in routine clinical practice.

References:

2. Murphy NP, Keane SM, Ong KK, Ford-Adams M, Edge JA, Acrini CL, Dunger DB. Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. Diabetes Care 2003;26:799-804
7. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 2010;303:1410-8
13. Investigators OT. Predictors of nonsevere and severe hypoglycemia during glucose-lowering treatment with insulin glargine or standard drugs in the ORIGIN trial. Diabetes Care 2015;38:22-8
HYPOGLYCEMIA: CHALLENGES AND STRATEGIES

Outline
- Definition and clinical scope
- Sources of Hypoglycemia
- Does Efficacy == Hypoglycemia?
  - Old medicines
  - New medicines
- Strategies for avoiding hypoglycemia
  - Modern Insulin
  - Medication choices
  - Technology
  - (Strategies for minimizing variability)

Definitions
- Superficially, this is easy – ‘low’ glucose
- ADA 3.9 mmol/L (70 mg/dL)
- EASD 3.0 mmol/L (54 mg/dL)
- Intentionally chosen to be pragmatic, above usual symptom thresholds
- ADA/Endo Society Workgroup
  - Severe Hypoglycemia – Requires assistance, any glucose level, neurologic recovery with treatment
  - Documented Symptomatic Hypoglycemia – Typical symptoms with measured glucose ≤ 70 mg/dL (3.9 mmol/L)
  - Asymptomatic Hypoglycemia – Measured glucose ≤ 70 mg/dL without symptoms
  - Probable Asymptomatic Hypoglycemia – Typical symptoms with circumstances suggesting glucose ≤ 70 mg/dL but without a measurement
  - Pseudohypoglycemia – Typical symptoms with a measured glucose >70 mg/dL

Determinants of Prevalence
- Measurement method
  - Precision/accuracy – system and user features
  - Handheld glucometers are less accurate at lower glucose values (±10 mg/dL)
  - Adrenergic response to hypoglycemia can cause digital vasoconstriction
- Ascertainment
  - Timing in relation to food/treatment/symptoms
  - Availability of a measurement tool
  - Hypoglycemia unawareness
  - Mode of therapy and fidelity of application of therapy
  - Aggressiveness of targeting low HbA1c
  - Use of insulin

Implications
- Rates
  - Type 1: 115-320 events per 100 patient-years
  - Type 2: 35-70 events per 100 patient-years
- Cognitive Dysfunction
  - Children – Acute/Near term deficits; developmental delay
  - Adults – ACCORD-MIND
    - Higher A1c associated with worse cognition
    - No association between more intensive vs control and worse progression
    - Rosiglitazone but not insulin associated with higher rates of progression
    - Depression associated with higher rates of progression
    - No difference in rates of brain shrinkage between treatment groups
- Mortality
  - 4-10% of deaths in Type 1 DM attributable to hypoglycemia
  - Type 2 – Magnification of CVD and All-cause Mortality

Presenter Disclosure Information
In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Kieren J Mather, MD
Research Support:
NIH, Novo Nordisk, Merck, Sanofi, Abbott
Employee: n/a
Board Member/Advisory Panel: n/a
Stock/Shareholder: n/a
Consultant: n/a
Other: n/a
Hypoglycemia Has A Significant Effect on Mortality

- ADVANCE study analysis – SU plus others versus guideline
- Severe hypoglycemia = gluc < 2.8 mM (50 mg/dL) or otherwise unexplained symptoms, REQUIRING HELP
- Increased rate with SU targeting lower A1c; 2.7% vs 1.5%
- Increased rate of macrovascular event, death, others (HR ~2.9)

Zoungas 2010 NEJM

Special Populations

- Elderly
  - Poor cognition predisposes to hypoglycemia
  - Renal dysfunction alters risks related to medicines
  - β-blockers interfere with hypoglycemia awareness and counter-regulatory response
  - Age-related impairment in counter-regulatory response
- Pregnant
  - Physiologically lower values in all women, lower targets in DM
- Hospitalized patients
  - Systematic use of known poor treatment approaches
  - Targets have been debatable, and vary by unit and clinical circumstance
  - Severe hypoglycemia extends duration of stay and costs

Punthakee 2012, Seaquist 2013

Other factors

- Adverse effects on quality of life
  - Fear of hypoglycemia
  - Dependency and loss of control
  - Driving and hypoglycemia
- Treatment targets and treatment inertia
  - Aggressive targets and hypoglycemia avoidance are in conflict
  - Physician may be reluctant to be aggressive
  - Patient may be reluctant, or complicate their management by over-use of avoidance or correction strategies

Sources of Hypoglycemia

- Carbohydrate/Insulin mismatch
  - Insulin
  - Secretagogues
- Failure of counter-regulation
  - Cortisol deficiency
  - Glucagon suppression
    - (GH, catechol deficiency)
    - Hepatic synthetic dysfunction
- Consumption/Paraneoplastic
  - Big IGF-II

Approaches to Hypoglycemia Avoidance

- Patient Education
  - How the medicines work, which ones are more likely to cause it
  - What other factors to consider
    - Exercise/exertion
    - Skipped meal
    - Alcohol use without carbohydrates
- Dietary Interventions
  - Matching meal content to insulin
    - Carb balance and consistency; carb counting for dosing
    - Timing
    - Rescue carbs
- Exercise management
  - Exercise is encouraged but can drastically alter glucose
  - Monitoring before (during) and after; pre-treat or post treat

Glucose Monitoring

- Self-blood glucose monitoring
  - Meters
  - Sensors
  - Smart phone apps
  - What frequency is appropriate to the treatment regimen?
- Clinical surveillance
  - Review the record/meter output
    - Are there too many hypoglycemia events?
    - Are the events symptomatic?
    - Are the events explained or unexplained?
    - What if there is no record?
Trading Efficacy for Hypoglycemia?

- Old medicines – Hypoglycemia-limited dosing
  - Insulin
  - Secretagogues
  - Sulfonylureas
  - Glinides

- Newer medicines can separate efficacy from hypoglycemia
  - Glucose-dependent insulin secretion (and some alpha cell effects)
  - GLP-1 mimetics
  - DPP4 inhibitors
  - Insulin-independent glucose lowering
    - Metformin
    - Thiazolidinediones
    - SGLT-2 inhibitors (emerging evidence for alpha cell effects)
    - α-glucosidase inhibitors
    - Central dopamine agonist

Hypoglycemia Unawareness is Reversible

Table 1 - Approach to re-educate recognition of hypoglycemia in patients with HLA-A

<table>
<thead>
<tr>
<th>Description</th>
<th>Treatment</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Metformin plus:</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin 50 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride 2 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride 6 mg/d</td>
<td></td>
</tr>
<tr>
<td>Odds ratio of hypoglycemia</td>
<td>OR 0.006 (!)</td>
<td></td>
</tr>
</tbody>
</table>

Ahren 2014

Hypoglycemia with sulfonylurea

- N=3059 randomized
- Metformin plus: Vildagliptin 50 mg/d
- Glimepiride 2 mg/d
- Glimepiride 8 mg/d
- Odds ratio of hypoglycemia OR 0.006 (!)

Ahren 2014

Hypoglycemia with α-glucosidase inhibitors

- Nateglinide versus acarbose in Korean participants
- N=58, randomized crossover
- Equal improvements in glycemic control in both periods
- No severe hypoglycemia: Any hypoglycemia n=3 acarbose vs 5 nateglinide
- Variability data from 7-point SBGM

Kim 2011

Hypoglycemia with DPP4 inhibitors

- Park 2012

Hypoglycemia with PPARgamma agonists

- Belcher 2005
**Hypoglycemia with GLP-1 mimetics**

Meta-analysis comparing efficacy and safety of GLP-1 vs Sitagliptin

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of studies</th>
<th>Kaplan-Meier</th>
<th>Incidence of hypoglycemia</th>
<th>Incidence of any hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 2014</td>
<td>1</td>
<td></td>
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</tr>
</tbody>
</table>

**Hypoglycemia with SGLT2 inhibitors**

- Dapagliflozin development program
  - Monotherapy OR 0.48 [0.18 – 1.39] against other agents
- Empagliflozin development program
  - Monotherapy and add-on therapy; not different from comparators
  - Except study against glimepiride with Odds Ratio of ‘any’ hypoglycemia 0.1 [0.07 – 0.16], p<0.0001
- Canagliflozin add-on to metformin 4% vs 6% sitagliptin

**Hypoglycemia with initial combo therapy**

- Initial triple therapy metformin+pioglitazone+exenatide versus conventional sequential therapy metformin/SU/glargine

**Hypoglycemia frequency**

- ‘Any’ hypoglycemia 46% conventional vs 14% triple
- 2.2 vs 0.31 events per participant-year

**Latest Meta-analysis**

- Network meta-analysis of agents added to metformin

SGLT2 inhibitors no detectable increase in hypoglycemia as monotherapy or added to other orals (point estimates below 1, wide confidence intervals)

**Meta-analysis – Non-Insulin Agents added to Metformin**

Phung 2010 JAMA
Strategies – Medication Choices

- α-glucosidase inhibitors (acarbose, voglibose) – **Neutral**
  - Alone, or as add-on
  - In elderly
- PPARgamma agonists/TZD - **Neutral**
  - As add-on to metformin
  - As part of initial combination therapy metformin/pioglitazone
  - Lower rates of hypoglycemia 14% than sequential metformin+SU+glargine
- DPP4 inhibitor – **Neutral**
  - Superior to SU; not different from GLP-1 mimetic
- GLP-1 mimetics – **Neutral**
  - Superior to NPH; not different from DPP4i or TZD
- SGLT2 inhibitors – **Neutral**
  - Alone or as add-on to metformin
  - Superior to SU; comparable to DPP4, TZD

Glargine is superior to NPH

- Glucose Control
- Hypoglycemia

Detemir versus NPH

Degludec Versus Glargine

Strategies – Improve Insulin Timing

- Peakless long-acting
  - **Glargine u-100, u-300**
  - Treat To Target trial U-100 glarg vs NPH added to oral agents, targeting A1c <7%. 27% vs 33% hypoglycemia (1 yr study Type 2 DM)
  - Similar overall result in a 5 yr study in Type 2 DM with odds ratio 0.74 for any hypoglycemia
  - U-300 vs U-100 glargine still fewer hypoglycemia events in Type 1 DM (rate ratio 0.69)
- **Detemir**
  - Studied as added therapy to oral agents plus liraglutide, no difference in hypoglycemia versus placebo
  - 55% lower hypoglycemia rates than NPH
- **Degludec**
  - Treat to Target degludec vs U-100 glarg added to OHA, targeting A1c <7%. 0.25 vs 0.38 episode hypoglycemia per year patient exposure
  - CGM study comparing degludec and U-100 glargine found reduced overall variability and reduced overall hypoglycemia time

Strategies – Technology

- **Insulin pumps**
  - Superior tool for matching needs and timing, in particular allowing different basals across the day
- **Glucose sensors (Continuous Glucose Monitor)**
  - Better tool for catching hypoglycemia events (trends, thresholds)
  - Improved response time
  - Improved diagnostics
- **Sensor-augmented pumps** – A whole step improvement
  - Sensor-augmented pump versus MDI insulin – better control, no increase in hypoglycemia events
  - Threshold-suspend versus usual sensor plus pump systems gave 31% reduction in hypoglycemia events
- **Closed-loop systems**
  - Insulin-only: Better control, lower variability, AND 50% fewer hypoglycemia events
  - Dual Hormone: Small N, short duration studies so far but very promising.
**Important Caveats in Evaluating This Literature**

- No unified definition of hypoglycemia endpoints
  - All/Minor/Severe
  - Selfreport
  - Record-keeping systems
  - Very different parameters available with CGM

- No uniform study design for measuring hypoglycemia while achieving a particular primary goal (HbA1c)

- No uniform approach to comparing hypoglycemia 'rate'
  - Absolute rates within the study time frame
  - Odds ratios of events, rate ratios of events

**Distinguishing Hypoglycemia and Variability**

- Poor control
  - Many high glucose values
  - Numerous low glucose values
  - High variability

- Variability without lows?
  - Variability without highs?

- Sensor/CGM data is opening the door to assessing these various parameters of control

- Some are arguing for incorporating these newer measures as part of the overall assessment of an agent's efficacy/safety

**Summary**

- Hypoglycemia is an important factor that limits our approach to treatment in diabetes

- Hypoglycemia has a personal burden and important clinical implications for patients

- Strategies for hypoglycemia avoidance include
  - Patient education
  - Glucose monitoring
  - Dietary interventions
  - Exercise management
  - Medication selection
  - Technological options

**References 1**


**References 2**


References 3


