HYPOGLYCEMIA IN DIABETES

Sue Pedersen, MD, FRCPC
Specialist in Endocrinology & Metabolism
C-ENDO Endocrinology Centre, Calgary

Rocky Mountain GIM Conference
Banff, AB
November 23, 2012
Disclosures: Sue Pedersen, MD, FRCPC

- Research trials: Novo Nordisk, Boehringer Ingelheim, Sanofi Aventis, Eli Lilly, Astra Zeneca, BMS, J&J

- Speaking honoraria: Sanofi, Novo Nordisk, Merck, BMS, Eli Lilly, Astra Zeneca, Roche

- Advisory Boards: Merck, Novo Nordisk, BMS

- Stocks: none

- Slides: some are personal; some have been drawn from slide decks provided by: Novo Nordisk, Merck, Medtronic, BMS, Eli Lilly
Objectives

- To examine prevalence and consequences of hypoglycemia in the diabetic patient
- To review risk factors for hypoglycemia
- To discuss strategies to minimize the incidence of hypoglycemia
Question

Which color of food, plate, and tablecloth results in the lowest calorie intake?

a) red plate, red food, white cloth
b) white plate, red food, red cloth
c) white plate, red food, white cloth
d) red plate, white food, white cloth
HYPOGLYCEMIA: PREVALENCE
Hypoglycemia is under-recognized

- Patients often underreport hypoglycemia
  - Fear of losing licence/employability
  - Some think it’s a ‘normal part’ of having diabetes
  - Patient may be hypoglycemia unaware

- Physicians don’t ask about it enough
Minor hypoglycemia occurs frequently and may be under-reported

Proportion of patients with asymptomatic hypoglycemia as measured by continued glucose monitoring systems:

- **63%**
  - type 1 diabetes

- **47%**
  - type 2 diabetes

- **83%**
  - type 2 diabetes

- **74%**
  - of these were nocturnal

- **54%**
  - of these were nocturnal

---

Hypoglycemia is common among patients on insulin therapy

Hypoglycemic events per patient per year as recorded over a one-month period

Hypoglycemia risk increases with the intensification of therapy

For all therapies, the significance of differences between levels is $p<0.0001$

Proportion of patients experiencing severe hypoglycemia increases as duration of diabetes increases.

Insulin-treated patients

Proportion experiencing ≥1 episode of severe hypoglycemia over 9–12 months

HYPOGLYCEMIA: CONSEQUENCES
Severe hypoglycemia increases the risk for adverse outcomes

Hazard ratios represent the risk of an adverse cardiovascular outcome or death among patients reporting severe hypoglycemia (<2.8 mmol/L)* as compared with those not reporting severe hypoglycemia

<table>
<thead>
<tr>
<th>Clinical Outcome and Interval After Hypoglycemia</th>
<th>Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvascular events</td>
<td>2.07 (1.32-3.26)‡</td>
</tr>
<tr>
<td>Macrovascular events</td>
<td>3.45 (2.34-5.08)‡</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>3.30 (2.31-4.72)‡</td>
</tr>
<tr>
<td>Death from non-CV cause</td>
<td>2.86 (1.67-4.90)‡</td>
</tr>
<tr>
<td>Death from CV cause</td>
<td>3.78 (2.34-6.11)‡</td>
</tr>
</tbody>
</table>

*Severe hypoglycemia is defined as blood glucose <2.8 mmol per litre with transient dysfunction of the CNS, without other apparent cause, during which the patient was unable to administer treatment (requiring help from another person).
†Adjusted for multiple covariates: sex, duration of diabetes, treatment assignment, presence or absence of a history of macrovascular disease, presence or absence of a history of microvascular disease, and smoking status at baseline. Time-dependent covariates during follow-up included age; level of glycated hemoglobin; body mass index; creatinine level; ratio of urinary albumin to creatinine; systolic blood pressure; use or nonuse of sulfonylurea, metformin, thiazolidinedione, insulin, or any other diabetes drug; and use or nonuse of antihypertensive agents.
‡p<0.001.
CI=confidence interval.
Pathophysiologic Cardiovascular Consequences of Hypoglycemia

CRP=C-reactive protein; IL-6=interleukin 6; VEGF=vascular endothelial growth factor.

Minor hypoglycemia is significant and can impact patients’ lives

<table>
<thead>
<tr>
<th>Lifestyle changes</th>
<th>Type 1 n=193</th>
<th>Type 2 n=97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ate extra food</td>
<td>66.8%</td>
<td>62.9%</td>
</tr>
<tr>
<td>Had greater fear of future hypoglycemia</td>
<td>37.8%</td>
<td>29.9%</td>
</tr>
<tr>
<td>Went home from school, work, activities</td>
<td>6.7%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Stayed home the next day</td>
<td>1.6%</td>
<td>9.3%**</td>
</tr>
</tbody>
</table>

*p<0.001, **p<0.01

Patients rank fear of severe hypoglycemia as highly as fear of developing serious chronic complications.

Impact of non-severe hypoglycemic events on productivity

- Non-severe hypoglycemic events* cost the individual an estimated 1,939.06 – 2,986.28 US$ per year
  - Absenteeism or lost time from work
  - Reduced productivity while at work
  - Out-of-pocket expenses (e.g. extra groceries, extra test strips and lancets, transportation services)

Brod M et al.  Value in Health (in press)
HYPOGLYCEMIA: RISK FACTORS
Thresholds for hypoglycemia vary with age*

Blood glucose concentration (mmol/L)

**Men aged 23 ± 2 years**

- Hypoglycemic awareness
- Greater reaction time for corrective action
- Onset of cognitive dysfunction

**Men aged 65 ± 3 years**

- Hypoglycemic awareness
- Onset of cognitive dysfunction
- Less reaction time for corrective action

*Based on data in nondiabetic patients with no family history of diabetes.

Figure adapted from Zammit NN, Frier BM. *Diabetes Care*. 2005;28(12):2948-61.
Relationship between severe hypoglycemia and HbA1c

Severe hypoglycemia correlated to poor control in intensively treated patients

Miller ME BMJ. 2010;340:b5444.
Risk factors for hypoglycemia

- Older age
- Long duration of diabetes
- Prior episode of severe hypoglycemia
- DM meds used:
  - Type of insulin
  - Non-insulin medications
- Glycemic control – too tight, or very poor
- Hypoglycemia unawareness
- Delayed/smaller/missed meal
- Alcohol
- Exercise
- Renal dysfunction
- Other meds: eg nonselective beta blockers
What’s the ideal A1c?

• 35 yo man, T2DM x4 years, metformin 1g bid
• 75yo woman, T2DM x17 years, on metformin and glyburide
• 55yo man, T2DM x10 years, on metformin and DPP-4 inhibitor
STRATEGIES TO MINIMIZE HYPOGLYCEMIA
## Type 2 diabetes therapies

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Hypo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase</td>
<td>Acarbose (GlucoBay)</td>
<td>No</td>
</tr>
<tr>
<td>Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin (Glucophage)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Linaglaptin (Trajenta)</td>
<td>No</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Saxagliptin (Onglyza)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Sitaglptin (Januvia)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Exenatide (Byetta)</td>
<td>No</td>
</tr>
<tr>
<td>GLP-1R Agonists</td>
<td>Liraglutide (Victoza)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Gliclazide (Diamicron)</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride (Amaryl)</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Glyburide (Diabeta)</td>
<td>+++</td>
</tr>
</tbody>
</table>

### Hypoglycemia in ADOPT (patients with new-onset diabetes)

- **Thiazolidinedione**: 9.8%
- **Metformin**: 11.6%
- **Sulfonylurea**: 38.7%

**Hypothesis**: PS0.01 vs. Thiazolidinedione

SU mechanism of action

SUs promote insulin release from pancreatic β-cells by binding to SU receptors and closing ATP-sensitive potassium ($K_{ATP}$) channels.
$K_{\text{ATP}}$ channels are located in various excitable cell types

- In addition to pancreatic $\beta$-cells, $K_{\text{ATP}}$ channels are located in other excitable cell types such as:
  - Cardiac myocytes
  - Vascular smooth muscle cells
  - Skeletal muscle cells
  - Neurons

SUs may block ischemic preconditioning

- The preconditioned myocardium is more resistant to ischemic insult\(^1\)
- SUs close cardiac \(K_{\text{ATP}}\) channels, potentially blocking ischemic preconditioning and resulting in a large infarct\(^1\)
- The clinical relevance of the effects of SUs on cardiac \(K_{\text{ATP}}\) channels remains to be proven\(^2\)

Certain sulfonylureas may increase mortality and CV morbidity

In a Danish study of 107,806 patients, monotherapy with certain commonly used sulfonylureas (glimepiride, glibenclamide, glipizide, and tolbutamide) appeared to be associated with increased mortality and CV risk vs metformin in both patients with and without previous MI.

No Previous MI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hazard Ratio (95% CI)</th>
<th>HR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1.32 (1.24–1.40)</td>
<td></td>
</tr>
<tr>
<td>Gliclazide</td>
<td>1.05 (0.94–1.16)</td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>1.19 (1.11–1.28)</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>1.27 (1.17–1.38)</td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>1.28 (1.17–1.39)</td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.97 (0.81–1.15)</td>
<td></td>
</tr>
</tbody>
</table>

Previous MI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hazard Ratio (95% CI)</th>
<th>HR(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.30 (1.11–1.51)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>0.90 (0.68–1.20)</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>1.47 (1.22–1.76)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>1.53 (1.23–1.89)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glipizide</td>
<td>1.47 (1.17–1.84)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>1.29 (0.86–1.94)</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Repaglinide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


CV, cardiovascular; MI, myocardial infarction.
Increased mortality with SU may be dose related

In a Canadian retrospective cohort study of patients with newly diagnosed T2DM (n=12,272), first- or second-generation sulfonylurea monotherapy was associated with increased mortality in a dose-related manner.

<table>
<thead>
<tr>
<th>Drug mono-therapy group</th>
<th>Lower (higher) daily dose</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation sulfonylurea&lt;sup&gt;a&lt;/sup&gt;, n = 120</td>
<td>42.4 (86.5)</td>
<td>2.07</td>
</tr>
<tr>
<td>Glyburide sulfonylurea, n = 4138</td>
<td>53.4 (70.2)</td>
<td>1.32, 1.29</td>
</tr>
<tr>
<td>Metformin, n = 1537</td>
<td>41.5 (37.6)</td>
<td>0.92, 0.96, 0.84</td>
</tr>
</tbody>
</table>

<sup>a</sup>Either chlorpropamide or tolbutamide.


T2DM, type 2 diabetes mellitus.
SU tissue selectivity: *in vitro* studies

<table>
<thead>
<tr>
<th>SU</th>
<th>Tissue Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliclazide</td>
<td>Pancreas-selective</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Pancreas-selective</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Partial pancreas-selective</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Non-selective</td>
</tr>
<tr>
<td>Glyburide (glibenclamide)</td>
<td>Non-selective</td>
</tr>
</tbody>
</table>

- Non-selective SUs may inhibit ischemic preconditioning, possibly translating into increased CV risk

GLP-1 actions are glucose-dependent in patients with T2DM

![Graph showing glucose, insulin, and glucagon levels during infusion.](image)

*mmol/l  
Fasting glucose

*pmol/l  
Insulin

*pmol/l  
Glucagon

*p<0.05  
n=10

DPP-4 Inhibitors: Current safety analysis – cardiovascular events

No increased risk of CV events was observed in patients randomly treated with DPP-4 inhibitors.

Risk ratio for major CV events: 1 - 5

<table>
<thead>
<tr>
<th></th>
<th>DPP-4 inhibitor better</th>
<th>Comparator better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin⁵,†</td>
<td>0.21</td>
<td>0.63</td>
</tr>
<tr>
<td>Linagliptin¹</td>
<td>0.15</td>
<td>0.34</td>
</tr>
<tr>
<td>Saxagliptin⁴</td>
<td>0.23</td>
<td>0.42</td>
</tr>
<tr>
<td>Sitagliptin²</td>
<td>0.41</td>
<td>0.68</td>
</tr>
<tr>
<td>Vildagliptin³,†</td>
<td>0.62</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Total patients in analysis:
- Alogliptin: 3,489
- Linagliptin: 5,239
- Saxagliptin: 4,607
- Sitagliptin: 10,246
- Vildagliptin: 10,988

Primary endpoint:
- Non-fatal MI, non-fatal stroke, CV death
- CV death, MI, stroke, hospitalisation due to angina pectoris
- MI, stroke, CV death
- Med DRA terms for MACE
- Acute coronary syndrome, transient ischaemic attack, stroke, CV death

Comments:
- Pre-specified/Independent adjudication
- Pre-specified/Independent adjudication
- Pre-specified/Independent adjudication
- No formal adjudication
- Pre-specified/Independent adjudication

References:
Exenatide bid: RRs and 95% CIs Were Consistent Across Multiple Methods of Analysis

<table>
<thead>
<tr>
<th>Endpoint/Method</th>
<th>RR (95% CI)</th>
<th>Exenatide Better</th>
<th>Comparator Better</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary MACE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (Mantel-Haenszel)</td>
<td>0.70 (0.38, 1.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (Cox)</td>
<td>0.71 (0.36, 1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (Andersen-Gill)</td>
<td>0.69 (0.39, 1.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (Pooled)</td>
<td>0.78 (0.42, 1.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (Shuster)</td>
<td>0.53 (0.21, 1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary CV endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (Mantel-Haenszel)</td>
<td>0.69 (0.46, 1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (Cox)</td>
<td>0.68 (0.44, 1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (Andersen-Gill)</td>
<td>0.69 (0.47, 1.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (Pooled)</td>
<td>0.77 (0.51, 1.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (Shuster)</td>
<td>0.44 (0.22, 0.86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Liraglutide: Adjudicated MACE

<table>
<thead>
<tr>
<th>SMQ Type</th>
<th>IR</th>
<th>95% CI</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMQ, Broad</td>
<td>0.73</td>
<td>(0.38; 1.41)</td>
<td>39</td>
</tr>
<tr>
<td>SMQ, Narrow</td>
<td>0.73</td>
<td>(0.38; 1.41)</td>
<td>39</td>
</tr>
<tr>
<td>Custom</td>
<td>0.72</td>
<td>(0.35; 1.50)</td>
<td>31</td>
</tr>
</tbody>
</table>

What Type of Insulin to Use?

Analogue insulin more closely matches physiologic insulin profiles. A long-acting insulin analogue (detemir, glargine)* may be considered as an alternative to NPH as the basal insulin. Rapid-acting insulin analogues should be considered over regular insulin.

*Grade B, Level 2 (17-20) (to reduce the risk of hypoglycemia) Grade B, Level 2 (50), for detemir; Grade C, Level 3 (51), for glargine.

Short acting analogs vs Regular

- Little (T1) to no (T2) significant effect on HbA1C
- Benefit to reduce severe hypos in T1DM
- QOL improvements: more convenient, flexible and with less need for snacks
- No hard outcome data

Singh SR et al CMAJ 2009;180:385-397
Long acting analogs

- Meta analyses of poor quality, and mostly short term studies
- Glycemic control: little benefit compared to conventional insulin (N or NPH)
- Benefit to reduce hypoglycemia and improve QOL
- Hard outcome data is needed
- Consider whether overnight coverage vs 24h basal coverage is needed

Singh SR et al CMAJ 2009;180:385-397
Characteristics of an ideal basal insulin:

- Flat, peakless time-action profile
- Continuous insulin action over a 24 h period
- Low variability for a predictable metabolic effect

## Duration of action of basal insulins

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Duration of Action</th>
<th>Administration Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>Up to 12 hour duration</td>
<td>2 to 3 times daily</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>Up to 24 hour duration</td>
<td>1 to 2 times daily</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td></td>
<td>Any time of day, same time daily</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>42 hour duration of action</td>
<td>1 time daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any time of day, with possibility to change time daily, if needed</td>
</tr>
</tbody>
</table>
T2DM: A1C over time

Mean ± SEM; FAS; LOCF
Comparisons: Estimates adjusted for multiple covariates

In the following results presentations, p-values are shown for results that show statistically significant differences, and not for results that are statistically insignificant

T2DM: Confirmed hypoglycemia

SAS Comparisons: Estimates adjusted for multiple covariates

T2DM: Nocturnal confirmed hypoglycemia

SAS
Comparisons: Estimates adjusted for multiple covariates

# T2DM: Hypoglycemic episodes

<table>
<thead>
<tr>
<th>Estimated rates of hypoglycemia (events/patient yr)</th>
<th>IDeg (n=753)</th>
<th>IGlar (n=251)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe*</td>
<td>0.06</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Overall Confirmed</td>
<td>11.09</td>
<td>13.63</td>
<td>0.82 [0.69-0.99]</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>1.39</td>
<td>1.84</td>
<td>0.75 [0.58-0.99]</td>
</tr>
</tbody>
</table>

*Insufficient episodes for statistical assessment.
Rate: rate of hypoglycaemia in episodes per patient-year
RR: rate ratio for IDeg OD/IGlar OD

### T1DM: Hypoglycemic episodes

<table>
<thead>
<tr>
<th>Estimated rates of hypoglycemia (events/patient yr)</th>
<th>IDeg (n=472)</th>
<th>IGlar (n=154)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycemia</td>
<td>0.21</td>
<td>0.16</td>
<td>1.38 [0.72-2.64]</td>
</tr>
<tr>
<td>Overall confirmed hypoglycemia</td>
<td>42.54</td>
<td>40.18</td>
<td>1.07 [0.89-1.28]</td>
</tr>
<tr>
<td>Diurnal confirmed hypoglycemia</td>
<td>36.09</td>
<td>32.82</td>
<td>1.11 [0.91-1.34]</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>4.41</td>
<td>5.86</td>
<td>0.75 [0.59-0.96] *</td>
</tr>
</tbody>
</table>

Flexible timing of dose schedule

Meneghini L et al. ADA 2011;35-LB (NN1250-3668).
Key findings through 26 weeks:
Flexible dosing of insulin degludec vs. once-daily insulin glargine (type 1)

<table>
<thead>
<tr>
<th></th>
<th>A1C</th>
<th>FPG</th>
<th>Nocturnal hypoglycemia rate</th>
<th>Confirmed hypoglycemia rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin degludec (FLEX)</td>
<td>-0.4%</td>
<td>-1.3 mmol/L</td>
<td>623</td>
<td>8238</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>-0.6%</td>
<td>-1.3 mmol/L</td>
<td>996</td>
<td>7973</td>
</tr>
<tr>
<td>Treatment difference [95% CI]</td>
<td>0.17 [0.04-0.30]</td>
<td>Treatment difference [95% CI]</td>
<td>-0.05 [-0.85-0.76]</td>
<td>Treatment ratio [95% CI]</td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td><strong>Comparable</strong></td>
<td><strong>Comparable</strong></td>
<td><strong>40% risk reduction</strong></td>
<td><strong>Comparable</strong></td>
</tr>
</tbody>
</table>

All in comparison with insulin glargine; Red box indicates statistical significance; hypoglycemia rates presented as rates per 100 patient years of exposure; Russell-Jones et al. ADA 2012. 348-OR.; Mathieu et al. ADA 2012. Abstract 2162-PO.
### Key findings through 26 weeks: Flexible dosing of insulin degludec vs. once-daily insulin glargine (type 2)

<table>
<thead>
<tr>
<th></th>
<th>A1C</th>
<th>FPG</th>
<th>Nocturnal hypoglycemia rate</th>
<th>Confirmed hypoglycemia rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin degludec (FLEX)</strong></td>
<td>-1.2%</td>
<td>-3.2 mmol/L</td>
<td>63</td>
<td>364</td>
</tr>
<tr>
<td><strong>Insulin glargine</strong></td>
<td>-1.2%</td>
<td>-2.8 mmol/L</td>
<td>75</td>
<td>348</td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td>Comparable</td>
<td><strong>Degludec statistically better</strong></td>
<td><strong>23% risk reduction</strong></td>
<td>Comparable</td>
</tr>
</tbody>
</table>

All in comparison with insulin glargine; Red box indicates statistical significance; hypoglycemia rates presented as rates per 100 patient years of exposure; Meneghini L et al. ADA 2011;35-LB (NN1250-3668).
Summary – Degludec

• Longer acting basal insulin than currently available basal insulin analogues

• Lower risk of hypoglycemia, particularly nocturnal

• Allows more flexibility in dosing regimen
**SGLT-2 Inhibitors**

- **SGLT2**: up to ~90%* of glucose is reabsorbed from the S1/S2 segments.
- **SGLT1**: ~10%* of glucose is reabsorbed from the S3 segment.
- *Based on animal data.

Glipizide vs Dapagliflozin: A1C

Mean baseline HbA$_{1c}$ 7.72%

<table>
<thead>
<tr>
<th>Change in HbA$_{1c}$ (%)‡</th>
<th>Dapagliflozin* + metformin (n=400)</th>
<th>Glipizide† + metformin (n=401)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.4</td>
<td>-0.52</td>
<td>-0.52</td>
</tr>
<tr>
<td>-0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-inferior mean difference, 0.0%; 95% CI −0.11% to 0.11%

**Glipizide vs Dapagliflozin: Change in Body Weight**

- **Dapagliflozin + metformin (n=400)**
  - Difference: -4.7 kg
  - 95% CI: -5.1 to -4.2
  - p<0.0001

- **Glipizide + metformin (n=401)**

**Weight change (kg)**

- **Dapagliflozin**
  - Mean change: -3.2 kg
- **Glipizide**
  - Mean change: 1.4 kg

**Proportion of patients with weight reduction ≥5%†**

- **Dapagliflozin**
  - 33.3%
- **Glipizide**
  - 2.5%

*Data are adjusted mean change from baseline

†Data are adjusted percent

Glipizide vs Dapagliflozin: Hypoglycemia by 52 Weeks

- Proportion of patients with ≥1 episode of hypoglycemia by 52 weeks*

  - **Dapagliflozin + metformin** (n=400): 3.5%
  - **Glipizide metformin** (n=401): 40.8%

  *Data are adjusted percent

Pump therapy with continued glucose monitoring is an emerging, effective option

Impact on A1C of insulin pump therapy with CGM and SMBG vs. insulin pump therapy and SMBG alone

No increased risk of major hypoglycemia noted with insulin pump therapy + continued glucose monitoring

Emerging closed loop external pancreas technology

Median time spent in normal glucose range:
- 85% overnight closed-loop session
- vs. 27% homecare open-loop session

Hypoglycemia:
No hypoglycemia occurred during closed-loop session.
In development:
Glucose-responsive basal insulins

- Basal insulin that **releases insulin in response to glucose levels**

- **Automatically adjusts** to unanticipated changes in blood glucose levels (i.e. during illness, exercise, etc.)

- **Potential advantages:**
  - Improved control of prandial glucose excursions
  - Adjustment to early morning increase in hepatic
  - Lower risk of hypoglycemia and hyperglycemia due to fever, exercise, stress, etc.

- **Proof-of-concept demonstrated in vitro and in vivo**

CONCLUSIONS

• Hypoglycemia is frequent, often overlooked, and is associated with adverse outcomes

• Risk factors for hypoglycemia should be considered when selecting the best treatment option for our patient

• Several strategies exist to minimize the risk of hypoglycemia, with new developments on the horizon
Question

Which color of food, plate, and tablecloth results in the lowest calorie intake?

a) red plate, red food, white cloth
b) white plate, red food, red cloth
c) white plate, red food, white cloth
d) red plate, white food, white cloth
Obesity Surgery to Treat Type 2 Diabetes?

>> THURSDAY, AUGUST 30, 2012

THANK YOU!