How Big (Hypoglycemia) Is an Issue in Type 1 Diabetes

J. Hans DeVries
Academic Medical Center at the University of Amsterdam
Keystone, CO, 20 July 2013
Disclosures

- CGM: Dexcom, Medtronic, Roche Diagnostics
At the conclusion of this presentation, the participant should be able to:

- Summarize frequency details of hypoglycemia in Type 1 diabetes
- Summarize the impact of Continuous Glucose Monitoring on the occurrence of severe hypoglycemia in Type 1 diabetes
Contents

• Epidemiology of hypoglycemia
• Causes of hypoglycemia
• Hypoglycemia and Mortality
• Consequences of hypoglycemia
• Can Continuous Glucose Monitoring diminish hypoglycemia?
Skewed distribution

Pedersen-Bjergaard, Diabetes Metab Res Rev 2004
### Epidemiology mild hypoglycemia < 3.0 mmol/l

<table>
<thead>
<tr>
<th>Mild hypoglycemia</th>
<th>% with ≥ 1 hypo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 tablets</td>
<td>39 (30 to 49)</td>
</tr>
<tr>
<td>Type 2 insulin &lt;2 year</td>
<td>51 (40 to 61)</td>
</tr>
<tr>
<td>Type 2 insulin &gt;5 year</td>
<td>64 (53 to 74)</td>
</tr>
<tr>
<td>Type 1 &lt; 5 year</td>
<td>87 (74 to 94)</td>
</tr>
<tr>
<td>Type 1 &gt;15 year</td>
<td>85 (73 to 92)</td>
</tr>
</tbody>
</table>
Epidemiology severe hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>% with $\geq 1$ hypo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 tablets</td>
<td>7 (3 to 13)</td>
</tr>
<tr>
<td>Type 2 insulin &lt;2 year</td>
<td>7 (3 to 13)</td>
</tr>
<tr>
<td>Type 2 insulin &gt;2 year</td>
<td>25 (19 to 36)</td>
</tr>
<tr>
<td>Type 1 &lt;5 year</td>
<td>22 (12 to 36)</td>
</tr>
<tr>
<td>Type 1 &gt;15 year</td>
<td>46 (34 to 59)</td>
</tr>
</tbody>
</table>

Causes of hypoglycemia

- **Situational risk factors**
  - Missed meal, alcohol
  - Exercise, sexual activity
  - Sleep

- **Chronic risk factors**
  - Frequent hypoglycemia
  - Strict glycemic control
  - Impaired awareness of hypoglycemia
  - Decreased insulin clearance (e.g. renal failure)
  - Peak action long-acting insulin, delayed action human/rapid-acting insulin
Strict glycemic control

Adapted from DCCT Research Group. 1996
Impaired awareness of hypoglycemia
frequency of severe hypoglycemia

Geddes, Diabet Med, 2008
Defective glucose contraregulation

- Normal
- <1 month diabetes
- 1-5 years diabetes
- >15 years diabetes

Boli et al, Diabetes 1983
Nocturnal Hypoglycaemia in Type 1 Diabetes: Is it important?

- It does not wake up People with T1 Diabetes
Which part of mortality in type 1 diabetes is due to hypoglycemia?

- Varies from 7.5 to 10% in registries with 10 to 25 yrs follow up.

Skrivarhaug, *Diabetologia* 2006;
Feltbower *Diabetes Care* 2008
Hypoglycemia prolongs QTc time, lowers K$^+$

Murphy, *Diabetologia* 2004;47:1940
Increased mortality associated with severe hypoglycemia

- N=1,020 (20% T1)
- 7.5% reported severe hypo
- 5 year follow-up
- Mortality: OR 3.4 after correction, double without correction

McCoy, *Diabetes Care* 2012;35:1897-901
Hypoglycemia and mortality at the ICU

Macroalbuminuria predicts severe hypoglycemia in Type 2 diabetes

- N=1,217
- 10 year follow-up
- 12.6% experienced Severe Hypo
- Univariate risk factors: age, duration of diabetes, insulin use, sulfonylurea use, macroalbuminuria
- Multivariate: duration of diabetes, macroalbuminuria

Yun *Diabetes Care* 2013
Effects of Treatment Group on Changes in Cognition (problem solving, learning, memory, etc)

A Original Treatment Assignment

Change in z Score

Intensive treatment

Conventional treatment

Cognitive Domain

Effects of Severe Hypoglycaemia on Changes in Cognition

B Number of Severe Hypoglycemic Events

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Change in z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No episodes</td>
<td>1-5 Episodes</td>
</tr>
</tbody>
</table>

Effects of Glycated Hemoglobin on Changes in Cognition

C Degree of Metabolic Control

- Glycated hemoglobin, <7.4%
- Glycated hemoglobin, ≥7.4% and ≤8.8%
- Glycated hemoglobin, >8.8%

Change in z Score

Cognitive Domain

- Psychomotor efficiency
- Motor speed

P = 0.001

P < 0.001

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• Can technology diminish hypoglycemia?
Pump therapy; DeVries to Fatourechi

Fatourechi JCEM 09; reply DeVries online
CGM reduces time in hypoglycemia

Battelino, Diabetes Care 2011

P=0.03
Minor hypo reduced by Low Glucose Suspend

<table>
<thead>
<tr>
<th></th>
<th>LGS off</th>
<th>LGS on</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Glucose (mg/dL)</td>
<td>145</td>
<td>148</td>
<td>NS</td>
</tr>
<tr>
<td>AUC &gt; 140 mg/dL (mg/dL x day)</td>
<td>25</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>AUC &lt; 70 mg/dL</td>
<td>0.76</td>
<td>0.53</td>
<td>0.05</td>
</tr>
<tr>
<td>Time &lt; 70 mg/dL (min)</td>
<td>101</td>
<td>58</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Cochrane Metanalysis
Real-Time CGM, Severe Hypo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CGM n/N</th>
<th>SBGM n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirsch 2008</td>
<td>8/66</td>
<td>3/72</td>
<td></td>
<td>16.2 %</td>
</tr>
<tr>
<td>Juvenile 2008</td>
<td>5/56</td>
<td>7/58</td>
<td></td>
<td>22.7 %</td>
</tr>
<tr>
<td>Juvenile 2008</td>
<td>5/52</td>
<td>4/46</td>
<td></td>
<td>17.0 %</td>
</tr>
<tr>
<td>Juvenile 2008</td>
<td>3/57</td>
<td>5/53</td>
<td></td>
<td>14.0 %</td>
</tr>
<tr>
<td>Juvenile 2009</td>
<td>7/67</td>
<td>7/62</td>
<td></td>
<td>27.4 %</td>
</tr>
<tr>
<td>Raccab 2009</td>
<td>1/46</td>
<td>0/54</td>
<td></td>
<td>2.7 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>344</strong></td>
<td><strong>345</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
</tr>
</tbody>
</table>

Total events: 29 (CGM), 26 (SBGM)
Heterogeneity: $\tau^2 = 0.0$; $\text{Chi}^2 = 4.25$, df = 5 ($P = 0.51$); $I^2 = 0.0$
Test for overall effect: $Z = 0.20$ ($P = 0.84$)

Langendam, Luijf, *Cochrane Database Syst Rev* 2012; jan 18:CD008101
Why? Insufficient accuracy

- Frequent sampling during glucose peak
- Frequent sampling during glucose nadir
- sc insulin + 5U
- Breakfast

Night (22:00–8:00): sampling every 30 minutes
Results

MAD per glucose range

<table>
<thead>
<tr>
<th>Glucose (mmol/l)</th>
<th>MAD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3.9</td>
<td>25</td>
</tr>
<tr>
<td>3.9-10.0</td>
<td>15</td>
</tr>
<tr>
<td>≥10.0</td>
<td>10</td>
</tr>
</tbody>
</table>

CRC: Overall Accuracy

<table>
<thead>
<tr>
<th>CGM System</th>
<th>MARD (%)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>16.5</td>
<td>14.3</td>
</tr>
<tr>
<td>Dexcom</td>
<td>20.5</td>
<td>18.2</td>
</tr>
<tr>
<td>Medtronic</td>
<td>16.4</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Overall p<0.001
Abbott vs Dexcom p<0.001
Medtronic vs Dexcom p<0.001
Medtronic vs Abbott NS

Luijf, DT&T 2013 Epub ahead of print
18 T1 patients, 2 x 9 days in-house study

- MARD 16.7%
- MARD in hypo 38.8%
- Positive predictive value for hypo alarm 42%
- False alert rate 53.3%
- Sensitivity for hypoglycaemia 37.5%

Sensor alarm fails at moment of need

Longer historic perspective

- Dexcom STS; MARD 21.0%
- Dexcom G4Platinum; MARD 13%

Garg Diabetes Care 2006
Christiansen, DT&T, online first
Roche prototype CGM sensor

- MARD: 9.2%

JDST 2013
CONTINUOUS GLUCOSE MONITORING REDUCES SEVERE HYPOGLYCAEMIA IN THOSE WITH HYPOGLYCAEMIA UNAWARENESS: RESULTS OF A CLINICAL AUDIT

P. Choudhary¹, L. Green², A. Cox², G. Galler², H. Rogers², D. Hopkins², S.A. Amiel²

¹Diabetes, King's College London, ²Diabetes, King's College Hospital, London, UK
CGM in Impaired Hypoglycemia Awareness

95 children & adults with type 1 DM and Impaired Hypoglycemia Awareness

randomised to:
- Sensor Augmented Pump with Low Glucose Suspend
- Pump alone

26 weeks

Severe Hypoglycemia

Sec: HbA1c, Fear of Hypo

Ly TT, ADA 13, 228-OR
Severe Hypo / 100 pt years

A1c unchanged 7.4%

Ly TT, ADA 13, 228-OR

Fear for Hypo & Hypo Unawareness Score reduced
Conclusions

• Hypoglycemia is the limiting factor in the treatment of type 1 diabetes
• Technology helps to prevent hypoglycemia