Current Developments in Diabetic Hypoglycemia

A Symposium on the occasion of the 50th Annual Meeting of the European Association for the Study of Diabetes

15 September 2014
Vienna, Austria

Brought to you by members of the International Hypoglycaemia Study Group
Welcome & Introduction

Simon Heller, BA, MB, Bchir, DM, FRCP
Professor of Clinical Diabetes
University of Sheffield
Director of Research and Development & Honorary Consultant Physician
Sheffield Teaching Hospitals Foundation Trust
Sheffield, United Kingdom
WELCOME TO VIENNA!
The International Hypoglycaemia Study Group (IHSG) is supported through an unrestricted education grant by Novo Nordisk A/S and is consistent with its ongoing commitment in diabetes.
ABOUT THE IHSG

Formed in 2013

15 members from around the globe

Our goal is to improve the scientific understanding of hypoglycaemia, as well as its importance as a barrier to optimal glycaemic control by means of raising awareness

Simon Heller, Chair, UK
Belinda Childs, USA
Brian Frier, UK
Kamlesh Khunti, UK
Rory McCrimmon, UK

Stephanie Amiel, UK
Philip Cryer, USA
Linda Gonder-Frederick, USA
Lawrence Leiter, Canada
Robert Vigersky, USA

Pablo Aschner, Columbia
Bastiaan de Galan, Netherlands
Tim Jones, Australia
Yingying Luo, China
Sophia Zoungas, Australia
WHY HYPOGLYCAEMIA MATTERS

• Higher incidence of hypoglycaemia occurs as patients move closer to HbA1c treatment targets
• It is an under-recognised problem that deserves increased awareness
• There is a lack of understanding by both professionals and patients
• A better understanding can increase patient quality of life
AGENDA

10:10 – Hypoglycaemia Epidemiology & Natural History
Brian Frier, MD, FRCPE

10:35 – Glycaemic Targets in Hypoglycaemia
Tim Jones, MD, DCH, FRACP

11:00 – Advances in Technology
Robert Vigersky, MD, FACP

11:25 – Psychosocial Aspects of Hypoglycaemia
Stephanie Amiel, BSc, MD, FRCP

11:50 – What’s New in Hypoglycaemia Education
Pablo Aschner, MD, MSc

12:15 – Panel Discussion
All
Hypoglycaemia: epidemiology and natural history

Brian M Frier,
Edinburgh, Scotland
Hypoglycaemia epidemiology: how to identify and record?

• Precise *definitions* are required for “mild”, “severe” and “nocturnal” episodes

• *Prospective* recording is essential for accurate assessment

• Severe hypoglycaemia (requiring external help) should ideally document confirmatory *account from witness*

• Restriction of severe hypoglycaemia to *coma* (events requiring parenteral therapy) provides a more robust measure - but will identify fewer episodes

• Data from clinical trials are *not* indicative of exposure in normal life; free-living, *unselected diabetic populations* should be studied to quantify everyday exposure
Frequency of severe hypoglycaemia: studies in unselected adult populations with type 1 diabetes

DCCT:
- selected participants
- interventional study
- frequency of SH declined with time
## Frequency of severe hypoglycaemia in adults with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Age (years) median (range) or mean±SD</th>
<th>Follow-up</th>
<th>Frequency (episodes/person/year)</th>
<th>Proportion affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacLeod, 1993 (Scotland)</td>
<td>600</td>
<td>41 (14-79)</td>
<td>12 months (R)</td>
<td>1.6</td>
<td>29</td>
</tr>
<tr>
<td>ter Braak, 2000 (The Netherlands)</td>
<td>195</td>
<td>41±14</td>
<td>12 months (R)</td>
<td>1.5</td>
<td>41</td>
</tr>
<tr>
<td>Pedersen-Bjergaard, 2004 (Denmark)</td>
<td>1076</td>
<td>40 (18-81)</td>
<td>12 months (R)</td>
<td>1.3</td>
<td>37</td>
</tr>
<tr>
<td>Leiter, 2005 (Canada)</td>
<td>202</td>
<td>44±12</td>
<td>12 months (R)</td>
<td>2.6</td>
<td>27</td>
</tr>
<tr>
<td>UK Hypoglycaemia Study Group, 2007 (United Kingdom)</td>
<td>100 (46 &lt;5 years; 54 &gt;15 years)</td>
<td>&lt;5y: 41±13 &gt;15y: 53±10</td>
<td>9–12 months (P)</td>
<td>1.1 3.2</td>
<td>22 46</td>
</tr>
<tr>
<td>Kristensen, 2012 (Denmark)</td>
<td>3813</td>
<td>48±15</td>
<td>12 months (R)</td>
<td>1.2</td>
<td>31</td>
</tr>
</tbody>
</table>
Incidence of severe hypoglycaemia (SH) and mild hypoglycaemia (MH) in type 1 diabetes

SH: annual prevalence = 30%

<table>
<thead>
<tr>
<th>Age Group</th>
<th>SH episodes/patient/YEAR</th>
<th>MH episodes/patient/WEEK</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–10 yrs</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>11–20 yrs</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>21–30 yrs</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt;30 yrs</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Severe hypoglycaemia in type 1 diabetes

- **Incidence**: 1.3 episodes/patient/year
- **Prevalence**: 37%
- Distribution of severe hypoglycaemic events was skewed in type 1 diabetes (n=1049; blue bars)
  - 54% of events affected 5% of subjects;
  - 69% of events affected 10% of subjects
- 209 subjects (orange bars) were selected as having same characteristics as DCCT cohort

*Pedersen-Bjergaard et al, DMMR 2004; 20: 479-86*
Frequency of hypoglycaemia in type 1 and insulin-treated type 2 diabetes

Severe hypoglycaemia was defined as any episode requiring third-party assistance.

Frequency of severe hypoglycaemia in types 1 and 2 diabetes

- **Type 2 DM Sulfonylureas (n = 103)**
  - Type 2 DM <2 years insulin (85)
  - Type 2 DM >5 years insulin (75)

- **Type 1 DM**
  - <5 years (46)
  - >15 years (54)

Error bars = 95% confidence intervals

Adapted from: UK Hypoglycaemia Study Group. Diabetologia 2007; 50: 1140-7
Frequency of severe hypoglycaemia in types 1 and 2 diabetes

Incidence of severe hypoglycaemia

- **Type 2 DM Sulfonylureas (n = 103)**
  - Type 2 DM <2 years insulin (85)
  - Type 2 DM >5 years insulin (75)
  - Type 1 DM <5 years (46)
  - Type 1 DM >15 years (54)

**Incidence of Severe Hypoglycaemia (episodes/patient/year)**

- Type 2 on SUs: CI 0.0--0.4, p = 0.95
- Type 2 IN<2 yrs: CI 0.0--0.5, p > 0.001
- Type 2 IN>5 yrs: CI 0.4--1.1, p > 0.001
- Type 1 <5 yrs: CI 0.0--2.3, p = 0.008
- Type 1 >15 yrs: CI 1.6--4.9, p < 0.001

SU = sulfonylureas; IN = insulin; CI = 95% confidence interval; p values in relation to the type-2 group treated with SUs

**DCCT group with intensive treatment to achieve strict glycaemic control (RR 3.28 vs. conventional treatment)**

**UK Hypoglycaemia Study Group. Diabetologia. 2007;50:1140–1147**

Frequency of non-severe hypoglycaemia in types 1 and 2 diabetes

Self-reported non-severe hypoglycaemic events in Europe

3287 adult respondents in 7 countries; questionnaire survey
Type 1 diabetes: 1.8 episodes/patient/week
Type 2 diabetes: 0.4-0.7 episodes/patient/week

Ostenson et al., Diabetic Med 2014; 31: 92-101

SU, sulfonylurea; T1D, type 1 diabetes; T2D, type 2 diabetes
Prevalence of severe hypoglycaemia in type 2 diabetes: major endpoint trials

Intensive therapy contributes to an increased risk of hypoglycaemia by 2–3-fold, particularly in advanced type 2 diabetes.

Event rate per year (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>1.0</td>
<td>3.5</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>VADT</td>
<td>1.5</td>
<td>4.0</td>
</tr>
<tr>
<td>ORIGIN</td>
<td>1.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Hypoglycaemia Amongst insulin-Treated patients with diabetes (HAT) Study: participating countries

- Finland
- Sweden
- Denmark
- Netherlands
- Germany
- Austria
- India
- Russia
- Israel
- Lebanon
- Argentina
- Malaysia
- Mexico
- Saudi Arabia
- Slovakia
- Slovenia
- Poland
- Serbia
- Bulgaria
- Canada
- Croatia
- Hungary
- Romania
- Czech Republic
HAT study: to quantify the ‘real-world’ frequency of hypoglycaemia in people with type 1 and type 2 diabetes

To determine the percentage of patients experiencing at least 1 hypoglycaemic event during the period of observation in insulin-treated patients with type 1 and type 2 diabetes

Patient self-reporting:

• Awareness of hypoglycaemia
• Fear of hypoglycaemia
• Experience with hypoglycaemia

Assess impact of hypoglycaemic events on patient productivity, healthcare utilisation and Quality of Life

Khunti et al (2014), Abstract at EASD, Vienna
HAT study: estimated rate of hypoglycaemia

### Hypoglycaemia type

<table>
<thead>
<tr>
<th>Hypoglycaemia type</th>
<th>Estimated annual incidence (events/patient/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>73.3</td>
</tr>
<tr>
<td>Non-severe</td>
<td>68.6</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>11.3</td>
</tr>
<tr>
<td>Severe</td>
<td>4.9</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>2.5</td>
</tr>
</tbody>
</table>

#### Baseline vs 4 weeks

- **Baseline**: 73.3, 68.6, 11.3
- **4 weeks**: 19.3, 17.0, 3.7

**T1DM (N=7180)** vs **T2DM (N=18518)**

Annual incidence: estimated number of events per patient per year

*Khunti et al (2014) Abstract at EASD, Vienna*
Hypoglycaemia in children

Clinical classification:

• **MILD** Episodes not requiring external assistance (self-treated), or easily reversed by glucose or food

• **MODERATE** Episodes requiring external assistance (with carbohydrate)

• **SEVERE** Episodes causing coma/convulsions, or requiring parenteral therapy

*Davis et al., Diabetes Care, 1997; 20: 22-25*
Severe hypoglycaemia in children and adolescents

Western Australia
(1683 patients: 2000-2009)

Germany & Austria
(30,700 patients: 1995-2009)

Average absolute decrease per year: 0.038%
95% CI: 0.032% - 0.043%
p<0.001

Average relative risk per year: 0.948%
95% CI: 0.918 - 0.979
p=0.001

O’Connell et al., Diabetes Care 2011; 34: 2379-80

Rosenbauer et al., Diabetes Care 2012; 35: 80-86
Incidence of severe hypoglycaemia: adolescents

DCCT, J Pediatr 1994; 125:177
Changes in the frequencies of hypoglycaemia – induced coma and convulsions in youth with type 1 diabetes (1992-2011)

Severe hypoglycaemia: incidence by year
(shadow represents 90% confidence interval)

Western Australia: population-based sample of 1770 children and adolescents (14,000 patient years)

Cooper et al., Diabetologia 2013: 2164-70
DCCT: Severe hypoglycaemia vs HbA1c

Rate of Severe Hypoglycaemia (per 100 patient-years)

Glycated Haemoglobin (%)

Severe hypoglycaemia vs. HbA1c (2010-13) in children with type 1 diabetes

Contemporary sample 1993-97
(Western Australia)

Glycated Haemoglobin (%)

Rate of Severe Hypoglycaemia
(per 100 patient-years)

Data derived from Cooper et al., Diabetologia 2013: 2164-70
Severe hypoglycaemia vs. HbA1c in adults with type 1 diabetes treated with CSII

Rate of Severe Hypoglycaemia (per 100 patient-years)

- Retnakaran R 2004 [22]
- Doyle EA 2004 [34]

Hanaire et al., Diab & Metab 2008; 34: 401-23
Hospital admissions in 12 months because of hypoglycaemia (England & Wales)

- 14,437 hospital admissions with hypoglycaemia as primary diagnosis
- Mean age: 54 years; mean length of stay: 6 days; total bed days: 76,569
- 8% had type 1 diabetes

Source: HES online: Primary diagnosis – 4 character table (2009/10)
Available at http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=215
Hospital emergency treatment for insulin-related hypoglycaemia is most frequent in the elderly (USA)

- Emergency Dept visits and hospital admissions for hypoglycaemia (2007-2011) - based on 8,100 cases in 63 hospitals in the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project
  - Number of patients in USA using insulin or OADs was estimated from the National Health Interview Survey (NHIS)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>ED visits per 1,000 persons (rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>*</td>
</tr>
<tr>
<td>18 - 44</td>
<td></td>
</tr>
<tr>
<td>45 - 64</td>
<td></td>
</tr>
<tr>
<td>65 - 79</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td></td>
</tr>
</tbody>
</table>

*For persons <18 years the prevalence of diagnosed diabetes was used as a proxy for national estimates of insulin treatment. ED: emergency department; OAD: oral anti-diabetes drug

Causes of hospital admissions of elderly* patients with type 2 diabetes

- 17% of hospital admissions were for severe hypoglycaemia

```
- Decompensated diabetes: 39.0%
- Intercurrent illness: 14.2%
- Acute cardiovascular events: 13.5%
- Chronic complications of diabetes: 16.6%
- Severe hypoglycaemia: 16.7%
```

*Subjects aged 80 or over, n=591

Pregnancy in 108 women with type 1 diabetes: frequency of hypoglycaemia

- Severe hypoglycaemia in 45%
- Incidence between 5-6 episodes/patient/year
- Frequency highest in 1st trimester
- Events mainly occur during sleep
- Breastfeeding provokes postpartum hypoglycaemia

Adapted from Nielsen et al., Diabetes Care 2008; 31: 9-14
Severe hypoglycaemia: Chronic Kidney Disease (CKD) + type 2 diabetes

Risk of severe hypoglycaemia (glucose <50 mg/dl) increases with declining renal function in patients with type 2 diabetes.

CKD: estimated glomerular flow rate: <60 ml/min per 1.73 m²
Hypoglycaemia defined as blood glucose <50 mg/dl

Risk of severe hypoglycaemia (glucose <50 mg/dl) increases with declining renal function in patients with type 2 diabetes

Impaired awareness of hypoglycaemia

- Affects 20–25% of adults with type 1 diabetes\(^1,2\); <10% of insulin-treated type 2 diabetes\(^3\)
- Risk of severe hypoglycaemia is 3 to 6 fold greater\(^1,2\)
- Spectrum of severity – may be reversible
- No international consensus on definition

---

Impaired Awareness of Hypoglycaemia (IAH): severe hypoglycaemia in type 1 diabetes

Annual prevalence and incidence of severe hypoglycaemia in people with type 1 diabetes with IAH

Morbidity of hypoglycaemia in diabetes

**Brain**
- Coma, seizures
- Cognitive dysfunction
- Psychological effects

**Cardiovascular**
- Myocardial ischaemia
- Cardiac arrhythmias

**Musculoskeletal**
- Falls, accidents
- Fractures, dislocations
- Driving mishaps
Mortality associated with hypoglycaemia in type 1 diabetes

• Acute metabolic complications (DKA and hypoglycaemia) are the commonest cause of excess death in those aged < 30 years

• In British Diabetic Association Cohort Study (n=23,752; type 1 diabetes onset <30 years), in those aged 20-49 years, hypoglycaemia caused:
  • 18% of male deaths
  • 6% of female deaths

• How hypoglycaemia caused death was not reported

Mortality and hypoglycaemia in diabetes: potential causes

**Brain**
- Prolonged coma – brain death
- Seizures
- Stroke: infarction, haemorrhage

**Cardiovascular**
- Myocardial ischaemia and infarction
- Cardiac arrhythmias
- Cardiac failure

**Accidental**
- Falls, trauma, head injuries
- Driving accidents
- Drowning
Hospitalisation and mortality in relation to history of hypoglycaemia in type 2 diabetes

The hospitalisation rate during the follow-up period was 53.1% for mild hypoglycaemia and 63.4% for severe hypoglycaemia, and occurred during the first year.

Hsu et al., Diabetes Care 2013; 36: 894-900
Summary: epidemiology and natural history of hypoglycaemia

- Severe hypoglycaemia is common in insulin-treated diabetes.
- Severe hypoglycaemia is more common in type 1 diabetes than in insulin-treated type 2 diabetes.
- The frequency of severe hypoglycaemia increases with duration of insulin therapy in type 2 diabetes.
- The frequency of severe hypoglycaemia in children appears to be falling but is an increasing problem in the elderly.
- Hypoglycaemia is associated with serious morbidity and significant mortality.
Glycaemic Targets in Hypoglycaemia

Tim Jones, MD, DCH, FRACP
Clinical Professor, School of Paediatrics & Child Health
Telethon Institute of Child Health Research
University of Western Australia
Head, Department Endocrinology and Diabetes
Princess Margaret Hospital
Perth, Australia
Glycaemic Targets in Hypoglycaemia

• Value of targets in diabetes management
• Targets in hypoglycaemia
  – Rationale
  – Limitations
• Individualising targets
• Clinical approach to hypoglycaemia prevention
• Special groups and clinical syndromes
• HbA1c vs glucose values
• Changing relationship between hypoglycaemia and glycaemic control
“Avoiding hypoglycaemia at all costs is crucial for some with diabetes”

“steer a course that helps avoid hypoglycaemia by setting individualised treatment targets”

Slomski A, JAMA 309: 2536-7, 2013
General Value of Targets
Example: Centre differences Hvidore study group, adolescents

<mean HbA1c  =mean HbA1c  >mean HbA1c
General Value of Targets:
US T1D registry vs German/Austrian dbase

Target HbA1c:
- **US**: <8.5%
- **German/Austrian**: <7.5%

~3000 children, <6yrs of age

---

Maahs DM et al, Diabetologia 57:1578-85, 2014
Improved Glycaemic Control since DCCT

West Australian Cohort:
- >16,000 patient years
- Population based
Changes in the rate of coma and convulsions 1992-2011 in youth with TD1M

(Cooper MN et al Diabetologia 2164-70 2013)

Western Australia
Population-based Sample (14,000 pt yrs)
• Research and improved understanding of counterregulation and hypoglycaemia precipitants
• More physiological insulin delivery through pumps and insulin analogs
• Increased glucose monitoring
• **Patient Education**
Glycaemic Targets and Hypoglycaemia
Benefits of optimal glycaemic control
vs.
Risks of adverse consequences from hypoglycaemia
Contingent on this relationship

DCCT: Type 1, 1990s

i.e. that intensive therapy with lower glucose targets is associated with increased hypoglycaemia
The Equation

1. Benefits of glycaemic control

2. Adverse consequences from hypoglycaemia

3. The relationship between HbA1c and risk of hypoglycaemia
1. What are the benefits of glycaemic control?

- Microvascular complications
  - DCCT, UKPDS, etc
  - Type 1 and 2

- Macrovascular complications
1. What are the benefits of glycaemic control?

- Very old
- Very young
- Limited life expectancy
2. What are the risks of adverse consequences from hypoglycaemia for that individual?

- Frail aged
- Macrovascular disease
- Very young
- Occupation
Hypoglycaemia Impact

- Severe hypoglycaemia:
  - morbidity, mortality, economic

- Symptomatic:
  - quality of life

- Impaired hypoglycaemia awareness
  - 25% (3 to 5 x risk of severe events)

- Excessive fear of hypoglycaemia
  - patients and caregivers
  - clinicians
  - quality of life
Intensive therapy and mortality

• ACCORD
  – Increased hypoglycaemia in intensive arm (3x)
  – Increased mortality in intensive arm (20% higher)
  – High cardiovascular risk

• ADVANCE and VADT
  – Hypoglycaemia associated with increased risk of mortality
3. What is the risk of significant hypoglycaemia for that individual?

- Not on therapies associated with hypoglycaemia
- Impaired awareness of hypoglycaemia
- Age associated differences
- Diabetes duration
- New onset Type 1
Intensive Therapy From Diagnosis

![Graph showing HbA1c levels over time for standard therapy and intensive therapy, pump. The graph indicates a significant difference with * p<0.05.](image-url)
### Increased risk: impaired Hypoglycaemia awareness

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Normal Awareness</th>
<th>Impaired Awareness</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>656</td>
<td>465</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td><strong>Percentage</strong></td>
<td></td>
<td>70.90%</td>
<td>29.10%</td>
<td></td>
</tr>
<tr>
<td><strong>Age – years</strong></td>
<td>13.48 ± 4.01</td>
<td>14.05 ± 3.60</td>
<td>10.60 ± 4.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>HbA1c mean</strong></td>
<td>8.47 ± 1.00</td>
<td>8.55 ± 1.00</td>
<td>8.3 ± 0.96</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Rate of SH – episodes/100 patient years</strong></td>
<td>24.5</td>
<td>19.3</td>
<td>37.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Temporary higher targets to improve impaired awareness using CGM

Percent change in adrenaline response to lowered plasma glucose

Baseline
After 4 weeks

Standard Therapy (N=5)  CGMS (N=6)

p=0.031

p=0.375
Target Change
ADA recommendations for youth

<table>
<thead>
<tr>
<th>Age</th>
<th>A1c Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 years</td>
<td>&lt;8.5%</td>
</tr>
<tr>
<td>6-12 years</td>
<td>&lt;8.0%</td>
</tr>
<tr>
<td>13-19 years</td>
<td>&lt;7.5%</td>
</tr>
</tbody>
</table>

Basis:

1. Uncertain benefit of tight control in very young, “clock ticking” hypothesis
2. Concern over susceptibility of developing brain to hypoglycaemic insult
3. High rates of severe hypoglycaemia in younger children
## Target Change
 ADA recommendations for youth 2014

<table>
<thead>
<tr>
<th>Age</th>
<th>Traditional A1c Goals</th>
<th>Current A1c Goals (2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 years</td>
<td>&lt;8.5%</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>6-12 years</td>
<td>&lt;8.0%</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>13-19 years</td>
<td>&lt;7.5%</td>
<td>&lt;7.5%</td>
</tr>
</tbody>
</table>

Rationale for change:

1. Benefits tighter glycaemic control in childhood confirmed
2. Risk of having significant hypoglycaemia reduced and relationship to A1c weaker
3. Reassuring data concerning the risk of long term adverse consequences of hypoglycaemia

Chiang et al, *Diabetes Care* 2014; 37:2034-2054
T1D through the lifespan: a position statement of the ADA
Less stringent

- History of severe hypoglycaemia
- Reduced hypoglycaemia awareness
- Limited life expectancy
- Advanced complications
- Extensive comorbid conditions
- High risk of adverse consequences of hypoglycaemia
# Guidelines for glycaemic targets for treatment of T2DM

<table>
<thead>
<tr>
<th>ADA Guideline&lt;sup&gt;1&lt;/sup&gt;</th>
<th>HbA1c</th>
<th>Fasting/ Preprandial Glucose</th>
<th>Postprandial Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;7.0% (53 mmol/mol)</strong></td>
<td></td>
<td><strong>3.9–7.2 mmol/L</strong> (70–130 mg/dL)</td>
<td><strong>&lt;10.0 mmol/L</strong> (&lt;180 mg/dL) (1–2 h pp)</td>
</tr>
<tr>
<td>• Goals should be individualised based on factors such as age, duration of disease, co-morbidities and hypoglycaemia unawareness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADA/EASD Consensus&lt;sup&gt;2&lt;/sup&gt;</th>
<th>HbA1c</th>
<th>Fasting/ Preprandial Glucose</th>
<th>Postprandial Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;7.0% (53 mmol/mol)</strong>&lt;br&gt;• Tighter targets (6.0–6.5%) – younger, healthier&lt;br&gt;• Looser targets (7.5–8.0%+) – older, comorbidities, hypoglycaemia prone, etc.&lt;br&gt;• Avoidance of hypoglycaemia</td>
<td><strong>&lt;7.2 mmol/L</strong> (&lt;130 mg/dL) (preprandial)</td>
<td><strong>&lt;10.0 mmol/L</strong> (&lt;180 mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EASD/ESC Consensus&lt;sup&gt;3&lt;/sup&gt;</th>
<th>HbA1c</th>
<th>Fasting/ Preprandial Glucose</th>
<th>Postprandial Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;7.0% (53 mmol/mol)</strong>&lt;br&gt;• Target of 7.5–8.0% may be acceptable, transitioning upwards as age increases</td>
<td><strong>&lt;7.2 mmol/L</strong> (&lt;130 mg/dL)</td>
<td><strong>&lt;9–10 mmol/L</strong> (&lt;160–180 mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IDF Global Guideline&lt;sup&gt;4&lt;/sup&gt;</th>
<th>HbA1c</th>
<th>Fasting/ Preprandial Glucose</th>
<th>Postprandial Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;7.0% (53 mmol/mol)</strong>&lt;br&gt;• Lower target may be considered if easily and safely achieved&lt;br&gt;• Higher target may be considered for people with co-morbidities or history of unacceptable hypoglycaemia</td>
<td><strong>6.5 mmol/L</strong> (115 mg/dL)</td>
<td><strong>9.0 mmol/L</strong> (160 mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

Glycaemic targets in frail elderly people
(ADA & American Geriatrics Society)

- **HbA1c <7.5 % (58 mmol/mol)**
  - Very few co-morbidities
  - Preserved cognitive and physical function

- **HbA1c <8.0 % (64 mmol/mol)**
  - Multiple chronic illnesses
  - Mild cognitive impairment
  - Risk of falls and hypoglycaemia

- **HbA1c <8.5 % (69 mmol/mol)**
  - End-stage chronic illness
  - Moderate to severe cognitive impairment
  - In long-term care

Kirkman et al. *Diabetes Care* 2012; 35: 2650
Targets: HbA1c vs Glucose levels

AG (mg/dl) = 28.7 x HbA1c – 46.7

Nathan DM et al, Diabetes Care August 2008 vol. 31 no. 8 1473-1478
ADAG Study: “Translation” of HbA1c into estimated Average Glucose (eAG)

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>(mg/dl)</th>
<th>(mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>97</td>
<td>5.4</td>
</tr>
<tr>
<td>6</td>
<td>126</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
<td>8.6</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
<td>10.2</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
<td>11.8</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Nathan DM et al, Diabetes Care August 2008 vol. 31 no. 8 1473-1478
Fear of Hypoglycaemia

Clinician makes an assessment of a target

but

Patient may make their own assessment
1990s: DCCT, Severe hypoglycaemia vs HbA1c

Rate of Severe Hypoglycaemia (per 100 patient-years)

Glycated Hemoglobin (%)

HbA1c

1997

events / 100 patient yrs

6-7%  7-8%  8-9%  9-10%  10-11%  >11%

0  5  10  15  20  25  30

5.0  5.5  6.0  6.5  7.0  7.5  8.0  8.5  9.0  9.5  10.0  10.5
Changing relationship:
all severe 2010-13

Rate of Severe Hypoglycaemia
(per 100 patient-years)

Glycated Hemoglobin (%)
Severe hypoglycaemia
Type 1 Registry US: Adults


<table>
<thead>
<tr>
<th>HbA1c</th>
<th>&gt;1 SH event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.5%</td>
<td>15%</td>
</tr>
<tr>
<td>6.5-&lt;7.0%</td>
<td>10%</td>
</tr>
<tr>
<td>7.0-&lt;7.5%</td>
<td>10%</td>
</tr>
<tr>
<td>7.5-&lt;8.0%</td>
<td>10%</td>
</tr>
<tr>
<td>8.0-&lt;9.0%</td>
<td>15%</td>
</tr>
<tr>
<td>9.0-&lt;10.0%</td>
<td>10%</td>
</tr>
<tr>
<td>≤10%</td>
<td>15%</td>
</tr>
</tbody>
</table>

P*<0.001

<table>
<thead>
<tr>
<th>Diabetes Duration</th>
<th>&gt;1 SH event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>10%</td>
</tr>
<tr>
<td>20-&lt;40</td>
<td>15%</td>
</tr>
<tr>
<td>≥40</td>
<td>20%</td>
</tr>
</tbody>
</table>

Summary: Glycaemic Targets

• A reasonable individualised glycaemic goal: “The lowest A1C that does not cause severe hypoglycaemia and preserves awareness of hypoglycaemia.”
  – Cryer PE, Diabetes; 63:2188-2195, 2014

• “The lowest HbA1c that does not cause severe hypoglycaemia, preserves awareness of hypoglycaemia and results in an acceptable number documented episodes of symptomatic hypoglycaemia”
Clinical approach to hypoglycaemia

- Recognise that avoidance of hypoglycaemia is a key outcome in diabetic care as well as optimal HbA1c
- Identify: risk factors for hypoglycaemia:
  - Conventional risk factors for hypoglycaemia
  - Risk factors for reduced hypoglycaemia awareness and HAAF
- Patient and clinician education around intensive glycaemic therapy
  - Insulin, monitoring, risk factors, prevention etc
- Technologies
Advances in Technology: Successes and Limitations in Mitigating Hypoglycaemic Risk

Robert A. Vigersky, M.D.
Professor, Uniformed Services University of the Health Sciences
Director, Diabetes Institute
Walter Reed National Military Medical Center
Diabetes technologies and therapies are overpriced, offer little value, and place an unjust burden on the US healthcare system.

“That captive audience of Type 1 diabetics has spawned lines of high-priced gadgets and disposable accouterments, borrowing business models from technology companies like Apple”.

Is this true?
Outline

- **Types of technology**
  - Insulin delivery
    - Pumps
    - Bolus calculators
  - Continuous glucose monitors
  - Sensor-augmented pumps including low threshold suspend systems
  - Closed loop systems
- **Limitations of technology**
  - Management of patient expectations
  - Importance of patient engagement
  - Real-world experiences vs. study environments
  - Inequities in access
- **Cost and cost-effectiveness**
Outline

- **Types of technology**
  - Insulin delivery
    - Pumps
    - Bolus calculators
  - Continuous glucose monitors
  - Sensor-augmented pumps including low threshold suspend systems
  - Closed loop systems

- **Limitations of technology**
  - Management of patient expectations
  - Importance of patient engagement
  - Real-world experiences vs. study environments
  - Inequities in access

- **Cost and cost-effectiveness**
Severe Hypoglycemia and Diabetic Ketoacidosis in Adults With Type 1 Diabetes: Results From the T1D Exchange Clinic Registry

Ruth S. Weinstock, Dongyuan Xing, David M. Maahs, Aaron Michels, Michael R. Rickels, Anne L. Peters, Richard M. Bergenstal, Breanne Harris, Stephanie N. DuBose, Kellee M. Miller, and Roy W. Beck, for the T1D Exchange Clinic Network

Severe Hypoglycaemia and Glycaemic Control In Type 1 Diabetes: Meta-analysis of Multiple Daily Insulin Injections Compared With Continuous Subcutaneous Insulin Infusion

J.C. Pickup and A.J. Sutton*, Metabolic Unit, King’s College London School of Medicine, Guy’s Hospital, London and *Department of Health Sciences, University of Leicester, Leicester, UK

Figure 5 Forest plot of random effect meta-analysis for mean difference in HbA1c (MDI vs. CSII), including sub-grouped analysis for studies using isophane/Lente insulin and those using glargine-based MDI. CI, confidence interval; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin; MDI, multiple daily injections. 

The Evidence Base for Diabetes Technology: Appropriate and Inappropriate Meta-Analysis

John C. Pickup, B.M., D.Phil.

Figure 3. Decision-making random-effects meta-analysis of severe hypoglycemia RR s on MDI versus CSII. Only RCTs where the baseline population (MDI) rate of severe hypoglycemia was elevated (>18 episodes/100 patient-years) were included. CI, confidence interval.
Components of Current Automated Bolus Calculators

**Factors Considered:**
- Target glucose level
- Current glucose level
- Insulin-carbohydrate ratio
- Active insulin on board
- Grams of carbohydrate
- Insulin sensitivity factor

**Factors Not Considered:**
- Glycaemic index of meal
- Effect of fat and protein content of a mixed meal on rates of nutrient absorption and glucose excursions
- Variable rates of gastric emptying
- Variable rates of insulin absorption depending on injection site
- Life-event impact on post-meal excursion
- Renal status
Performance of a Glucose Meter with a Built-In Automated Bolus Calculator versus Manual Bolus Calculation in Insulin-Using Subjects

Allen Sussman, M.D.,1 Elizabeth J. Taylor, M.S., C.D.E.,2 Mona Patel, B.S.,3 Jeanne Ward, B.S.,3 Shridhara Alva, Ph.D.,3 Andrew Lawrence, B.Sc.,3 and Ronald Ng, Ph.D.3

<table>
<thead>
<tr>
<th>All subjects</th>
<th>Meter</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correct</td>
<td>Incorrect</td>
</tr>
<tr>
<td>Manual method</td>
<td>Correct</td>
<td>145 (35%)</td>
</tr>
<tr>
<td></td>
<td>Incorrect</td>
<td>241 (59%)</td>
</tr>
<tr>
<td>Total</td>
<td>386 (94%)</td>
<td>23 (6%)</td>
</tr>
</tbody>
</table>
Carbohydrate Counting and Bolus Calculators

6 days of masked CGM before (upper panel) and after (lower panel) introduction of carbohydrate counting and an automated bolus calculator

Schmidt S JDST epub May 19, 2014.
The Effect of using the Insulin Pump Bolus Calculator Compared to Standard Insulin Dosage Calculations in Patients with Type 1 Diabetes Mellitus – Systematic Review

Authors: A. Ramotowska¹, D. Golicki², K. Dzygalo¹, A. SzyPowska¹

Affiliations: ¹Department of Paediatrics, Medical University of Warsaw, Warsaw, Poland.
²HealthQuest, Warsaw, Poland.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Gross 2003</td>
<td>11.4</td>
<td>5.8</td>
<td>49</td>
<td>13.5</td>
</tr>
<tr>
<td>Shashaj 2008</td>
<td>3.3</td>
<td>2.7</td>
<td>36</td>
<td>5.7</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>85</td>
<td>100.0%</td>
<td>-2.31 [-3.59, -1.03]</td>
<td>-0.47 [-0.95, 0.02]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi²=0.04, df=1 (P=0.83); I²=0%
Test for overall effect: Z=3.54 (P=0.0004)

### Table 2.
Perceived Improvement in Diabetes Management-Related Factors

<table>
<thead>
<tr>
<th></th>
<th>Significantly Improved</th>
<th>Improved</th>
<th>No change</th>
<th>Worsened</th>
<th>Significantly worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of hypoglycemia</td>
<td>13.0% (73)</td>
<td>39.0% (219)</td>
<td>43.0% (241)</td>
<td>4.8% (27)</td>
<td>0.2% (1)</td>
</tr>
<tr>
<td>Confidence in calculation</td>
<td>28.0% (157)</td>
<td>50.8% (285)</td>
<td>16.8% (94)</td>
<td>3.9% (22)</td>
<td>0.5% (3)</td>
</tr>
<tr>
<td>Ease of calculating bolus</td>
<td>43.7% (245)</td>
<td>41.2% (231)</td>
<td>13.2% (74)</td>
<td>1.8% (10)</td>
<td>0.2% (1)</td>
</tr>
<tr>
<td>Acting on SMBG results</td>
<td>27.1% (152)</td>
<td>54.2% (304)</td>
<td>16.9% (95)</td>
<td>1.8% (10)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Control of BG levels</td>
<td>20.1% (113)</td>
<td>53.5% (300)</td>
<td>23.0% (120)</td>
<td>3.2% (18)</td>
<td>0.2% (1)</td>
</tr>
<tr>
<td>Ability to achieve BG goals</td>
<td>13.4% (75)</td>
<td>53.7% (301)</td>
<td>30.8% (173)</td>
<td>2.0% (11)</td>
<td>0.2% (1)</td>
</tr>
<tr>
<td>Flexibility in lifestyle</td>
<td>20.5% (115)</td>
<td>42.4% (238)</td>
<td>35.3% (198)</td>
<td>1.8% (10)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Overall well-being</td>
<td>17.5% (98)</td>
<td>54.4% (305)</td>
<td>26.7% (150)</td>
<td>1.2% (7)</td>
<td>0.2% (1)</td>
</tr>
</tbody>
</table>
Improvement in Glycaemic Excursions with a Transcutaneous, Real-time Continuous Glucose Sensor

Modal Day Under Masked (A) and Unmasked Conditions (B) According to Baseline A1C

Comparative Analysis of the Efficacy of Continuous Glucose Monitoring and Self-Monitoring of Blood Glucose in Type 1 Diabetes Mellitus

Baraka Floyd, M.D., M.Sc.1 Prakash Chandra, M.D., M.P.H.2 Stephanie Hall, M.P.H.1
Christopher Phillips, M.D., M.P.H.1 Ernest Atunna-Mensah, Ph.D.1 Gregory Strayhorn, M.D., Ph.D.1
Elizabeth O. Ofili, M.D., M.P.H.1 and Guillermo E. Umpierrez, M.D.2

<table>
<thead>
<tr>
<th>Reference, first author</th>
<th>Weighted mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chase24</td>
<td>-0.60 (-1.12, -0.08)</td>
</tr>
<tr>
<td>Chico21</td>
<td>-0.25 (-0.74, 0.24)</td>
</tr>
<tr>
<td>Ludvigsson25</td>
<td>-0.29 (-0.52, -0.06)</td>
</tr>
<tr>
<td>Tanenberg26</td>
<td>-0.01 (-0.41, 0.39)</td>
</tr>
<tr>
<td>Deiss11</td>
<td>-0.45 (-0.80, -0.10)</td>
</tr>
<tr>
<td>Deiss27</td>
<td>0.10 (-0.28, 0.48)</td>
</tr>
<tr>
<td>Lagarde38</td>
<td>-0.33 (-0.93, 0.27)</td>
</tr>
<tr>
<td>Yates29</td>
<td>0.00 (-0.53, 0.53)</td>
</tr>
<tr>
<td>Hirsch14</td>
<td>-0.17 (-0.46, 0.12)</td>
</tr>
<tr>
<td>JDRF16</td>
<td>-0.21 (-0.32, -0.10)</td>
</tr>
<tr>
<td>Cosson50</td>
<td>-0.35 (-0.50, -0.20)</td>
</tr>
<tr>
<td>O’Connell11</td>
<td>-0.50 (-0.74, -0.26)</td>
</tr>
<tr>
<td>Peyrot57</td>
<td>-0.69 (-1.22, -0.16)</td>
</tr>
<tr>
<td>Raccah32</td>
<td>-0.24 (-0.61, 0.13)</td>
</tr>
<tr>
<td>Fixed effects meta-estimate</td>
<td>-0.28 (-0.37, -0.19)</td>
</tr>
</tbody>
</table>

Real-Time CGM
Figure 30. Between-group difference between rt-CGM and SMBG in how HbA₁c changed from baseline among adults with type 1 diabetes in studies where compliance was greater than 60%.

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deiss 2006</td>
<td>-0.60 (-1.01, -0.19)</td>
</tr>
<tr>
<td>Hirsch 2008</td>
<td>-0.11 (-0.36, 0.13)</td>
</tr>
<tr>
<td>Tamborlane 2008 (&gt;25 yrs)</td>
<td>-0.53 (-0.71, -0.35)</td>
</tr>
<tr>
<td>O'Connell 2009</td>
<td>-0.43 (-0.71, -0.15)</td>
</tr>
<tr>
<td>JDRF CGM Study Group 2009</td>
<td>-0.34 (-0.48, -0.20)</td>
</tr>
<tr>
<td>Raccach 2009</td>
<td>-0.24 (-0.61, 0.13)</td>
</tr>
<tr>
<td>Battelino 2011</td>
<td>-0.27 (-0.47, -0.07)</td>
</tr>
<tr>
<td>Overall (I-squared = 40.8%, p = 0.119)</td>
<td>-0.36 (-0.44, -0.27)</td>
</tr>
</tbody>
</table>
Figure 33. Pooled relative risk of severe hypoglycemia in rt-CGM versus SMBG interventions among patients with type 1 diabetes

CI = confidence interval, RR = relative risk, rt-CGM = real-time continuous glucose monitor, SMBG = self monitoring of blood glucose
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

Test for heterogeneity: Q = 7.91 with 7 degrees of freedom (p = 0.34)
I-squared = 12 percent
Continuous Glucose Monitoring: Evidence and Consensus Statement for Clinical Use

Andreas Liebl, M.D.,1 Helmut R. Henrichs, M.D.,2 Lutz Heinemann, Ph.D.,3 Guido Freckmann, M.D.,4 Eberhard Biermann, M.D.,5 and Andreas Thomas, Ph.D.,6 for the Continuous Glucose Monitoring Working Group of the Working Group Diabetes Technology of the German Diabetes Association

GuardControl
3 mo., 2006, 46% CSII, n = 50

STAR 1
6 mo., 2008, 100% SaP, n = 66

JDRF
6 mo., 2008, 80% CSII, n = 88

JDRF <7%
6 mo., 2009, 80% CSII, n = 91

ASAPS
3 mo., 2009, 100% SaP, n = 11

REAL Trend
6 mo., 2009, 100% SaP, n = 32

STAR 3
12 mo., 2010, 100% SaP, n = 247

EURYTHMICs
6 mo., 2011, 100% SaP, n = 44

Battelino
6 mo., 2011, 100% SaP, n = 47

SWITCH
6 mo., 2011, 100% SAP, n = 153

Real-Time Continuous Glucose Monitoring Significantly Reduces Severe Hypoglycemia in Hypoglycemia-Unaware Patients With Type 1 Diabetes

Paule Choudhary, MBBS, MD, PhD1,3
Soleiman Rahalidar, MBBS, MD1
Louisa Green, BSc
Girardelle Gallen, RGN3

Sethna Pender, BSc2
Anna Blackford, MBBS, MD, PhD2
Stefanie A. Amiel, MBBS, MD, FRCP3,4
John C. Pickup, FMedSci, FRCP1,2

Figure 1—Annual rates of severe hypoglycemia (SH) requiring third-party help at baseline and 12 months after starting continuous glucose monitoring (CGM). Also shown are the 12-month rates divided into those treated with or without CGM. SH, severe hypoglycemia.
Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes

Richard M. Bergenstal, M.D., William V. Tamborlane, M.D., Andrew Ahmann, M.D., John B. Buse, M.D., Ph.D., George Dailey, M.D., Stephen N. Davis, M.D., Carol Joyce, M.D., Tim Peoples, M.A., Bruce A. Perkins, M.D., M.P.H., John B. Welsh, M.D., Ph.D., Steven M. Willi, M.D., and Michael A. Wood, M.D., for the STAR 3 Study Group*

A All Patients

Variable

<table>
<thead>
<tr>
<th></th>
<th>Sensor-Augmented Pump Therapy (N = 247)</th>
<th>Injection Therapy (N = 248)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>32</td>
<td>27</td>
<td>0.58</td>
</tr>
<tr>
<td>No. of patients</td>
<td>21</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Rate per 100 person-yr</td>
<td>13.31</td>
<td>13.48</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Figure 35. Between-group difference between sensor-augmented pumps and MDI/SMBG in how HbA1c changed from baseline among patients with type 1 diabetes

<table>
<thead>
<tr>
<th>Author year</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee 2007</td>
<td>-0.97 (-2.54, 0.60)</td>
</tr>
<tr>
<td>Peyrot 2009</td>
<td>-0.70 (-1.32, -0.08)</td>
</tr>
<tr>
<td>Bergenstal 2010</td>
<td>-0.60 (-0.75, -0.45)</td>
</tr>
<tr>
<td>Hermanides 2011</td>
<td>-1.10 (-1.46, -0.74)</td>
</tr>
<tr>
<td>Overall (I-squared = 53.7%, p = 0.091)</td>
<td>-0.68 (-0.81, -0.54)</td>
</tr>
</tbody>
</table>

No difference in mild or severe hypoglycaemia
Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group*
Inclusion Criteria

- 16 to 70 years of age
- Type 1 diabetes of at least 2 years’ duration
- Glycated haemoglobin value of 5.8% to 10.0%
- Used insulin-pump therapy for more than 6 months
- During run-in:
  - Wore sensors $\geq 80\%$ of the time
  - Had at least two nocturnal hypoglycaemic events for $>20$ consecutive minutes in the absence of a pump interaction
A Glycated Haemoglobin

<table>
<thead>
<tr>
<th>Glycated Haemoglobin (%)</th>
<th>Threshold-Suspend Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>At randomization</td>
<td>7.26±0.71</td>
<td>7.24±0.67</td>
</tr>
<tr>
<td>At 3 months</td>
<td>7.21±0.77</td>
<td>7.14±0.77</td>
</tr>
</tbody>
</table>

B Mean AUC for Nocturnal Hypoglycaemic Events

<table>
<thead>
<tr>
<th>AUC (mg/dl/min)</th>
<th>Threshold-Suspend Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in phase</td>
<td>1547±2035</td>
<td>980±1200</td>
</tr>
<tr>
<td>Study phase</td>
<td>1406±1950</td>
<td>1568±1995</td>
</tr>
</tbody>
</table>

P<0.001 38% Reduction

C Sensor Glucose <70 mg/dl

<table>
<thead>
<tr>
<th>Percent</th>
<th>Threshold-Suspend Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal</td>
<td>3.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Day and Night Combined</td>
<td>3.7</td>
<td>3.1</td>
</tr>
</tbody>
</table>
David M. Maahs,1 Peter Calhoun,2 Bruce A. Buckingham,3 H. Peter Chase,1 Irene Hramiak,4 John Lum,2 Fraser Cameron,5 B. Wayne Bequette,5 Tandy Aye,3 Terri Paul,4 Robert Slover,1 R. Paul Wadwa,1 Darrell M. Wilson,3 Craig Kollman,2 and Roy W. Beck,2 for the In Home Closed Loop Study Group* .

A Randomized Trial of a Home System to Reduce Nocturnal Hypoglycemia in Type 1 Diabetes

Diabetes Care 2014;37:1885–1891 | DOI: 10.2337/dc13-2159

Figure 3—Sensor glucose levels overnight. The top portion of the figure shows the median glucose level across all nights in each treatment arm. The bottom portion of the figure shows the frequency of glucose level ≤80 mg/dL across all nights in each treatment arm.
Duration of Overnight Hypoglycaemia (L) and Hyperglycaemia (R)

Control
N= 970

Intervention
N= 942

48% Reduction
All P-values <0.001

52% Reduction

74% Reduction

81% Reduction

% of nights

Duration with glucose level ≤60 mg/dl

>30 min
>60 min
>120 min
>180 min

% of nights

Duration with glucose level >250 mg/dl

All P-values >0.05
Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes


A Mean Glucose Levels in Adults

B Mean Glucose Levels in Adolescents

% of Time Spent In Hypoglycaemic Range In Adults and Adolescents On the Bionic Pancreas

<table>
<thead>
<tr>
<th></th>
<th>Adult Bionic Pancreas</th>
<th>Adult Control</th>
<th>P</th>
<th>Adolescents Bionic Pancreas</th>
<th>Adolescents Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day + Night</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of time &lt;60 mg/dl</td>
<td>1.5±1.7</td>
<td>3.7±3.3</td>
<td>&lt;0.02</td>
<td>1.3±1.7</td>
<td>2.2±3.6</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Nighttime Only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of time &lt;60 mg/dl</td>
<td>0.4±0.6</td>
<td>3.3±4.9</td>
<td>&lt;0.01</td>
<td>1.0±1.4</td>
<td>1.7±3.5</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Outline

• **Types of technology**
  • Insulin delivery
    • Pumps
    • Bolus calculators
  • Continuous glucose monitors
  • Sensor-augmented pumps including low threshold suspend systems
  • Closed loop systems

• **Limitations of technology**
  • Management of patient expectations
  • Importance of patient engagement
  • Real-world experiences vs. study environments
  • Inequities in access

• **Cost and cost-effectiveness**
Motivation

1. On a 1 to 7 scale, how interested are you in using a pump?
   not interested 1 2 3 4 5 6 7 very interested

2. How motivated are you to control your glucose levels?
   not motivated 1 2 3 4 5 6 7 very motivated

3. Are you willing to check more often, and keep/download records if needed?
   □ yes  □ no  □ maybe

4. How likely is it that you can control your glucoses day-to-day?
   not likely 1 2 3 4 5 6 7 very likely

5. How convenient will a pump be in your daily life?
   not too 1 2 3 4 5 6 7 very

6. How likely is it that better glucose control will improve your health?
   not likely 1 2 3 4 5 6 7 very likely

7. How comfortable are you about having diabetes (discuss with friends, check glucose in front of others, use an insulin pen or syringe in public?
   not very 1 2 3 4 5 6 7 very

8. Will others accept you if you wear a pump?
   not at all 1 2 3 4 5 6 7 totally □ I’ll hide it

9. How excited are you about adapting new technology to control your diabetes?
   not very 1 2 3 4 5 6 7 very

10. Have you considered or discussed with others situations that might make wearing a pump inconvenient, such as athletics, work environment, etc.?
    □ yes  □ no  □ not yet  □ Which situations may present problems?

11. Who can you rely on for support if pump problems arise?

Walsh J. Pumping Insulin, 2013.
Who is a Successful Pumper? Someone who is:

• Adherent to previous advice and keeping appointments
• Willing to do frequent BGM (≥6 times/d)
• Willing to learn and practice self management
• Capable of good problem solving
• Willing to not only ACT on their results, but ANALYZE their patterns
• Disciplined and persistent
• Willing to do the hard work
• Has a knowledgeable parent
Real-Life Utilization of Real-Time Continuous Glucose Monitoring: The Complete Picture


Reported Comfort of Real-Time Continuous Glucose Monitoring Use

<table>
<thead>
<tr>
<th>Feature</th>
<th>Insertion</th>
<th>Wearing site</th>
<th>Carrying monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful, uncomfortable</td>
<td>38%</td>
<td>28%</td>
<td>14%</td>
</tr>
<tr>
<td>Too big, annoying, bulky, heavy</td>
<td>—</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>—</td>
<td>17%</td>
<td>—</td>
</tr>
<tr>
<td>Adhesion problems</td>
<td>—</td>
<td>10%</td>
<td>—</td>
</tr>
<tr>
<td>Problem where to keep it</td>
<td>—</td>
<td>—</td>
<td>7%</td>
</tr>
<tr>
<td>Frightening</td>
<td>3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Varies</td>
<td>3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ok</td>
<td>34%</td>
<td>28%</td>
<td>14%</td>
</tr>
<tr>
<td>Another monitor to carry</td>
<td>—</td>
<td>—</td>
<td>7%</td>
</tr>
<tr>
<td>Painless, easy, comfortable</td>
<td>10%</td>
<td>14%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Reported beneficial features of RT-CGM

Race, socioeconomic status, and treatment center are associated with insulin pump therapy in youth in the first year following diagnosis of Type 1 Diabetes

Maria H. Lin, MD,1 Crystal G. Connor, MS, MPH,2 Katrina J. Ruedy, MSPH,2 Roy W. Beck, MD, PhD,2 Craig Kollman, PhD,2 Bruce Buckingham, MD,3 Maria J. Redondo, MD,4 Desmond Schatz, MD,5 Heidi Haro, BS,6 Joyce M. Lee, MD, MPH,7,8 William V. Tamborlane, MD,9 and Jamie R. Wood, MD,1 for the Pediatric Diabetes Consortium*

Univariate Analysis

<table>
<thead>
<tr>
<th>Overall</th>
<th>N</th>
<th>Using Pump</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Center</td>
<td>1012</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A</td>
<td>59</td>
<td>18%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B</td>
<td>159</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C</td>
<td>277</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D</td>
<td>217</td>
<td>23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E</td>
<td>48</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>F</td>
<td>138</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G</td>
<td>114</td>
<td>59%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Health Insurance</td>
<td>Other</td>
<td>338</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Private</td>
<td>652</td>
<td>37%</td>
</tr>
<tr>
<td>Family Structure</td>
<td>Other</td>
<td>309</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Lives with Both Parents</td>
<td>701</td>
<td>33%</td>
</tr>
<tr>
<td>Family Income</td>
<td>&lt;$25,000</td>
<td>99</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>$25,000-$49,999</td>
<td>130</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>$50,000-$74,999</td>
<td>111</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>$75,000-$99,999</td>
<td>95</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>&gt;$100,000</td>
<td>239</td>
<td>50%</td>
</tr>
<tr>
<td>Parent Education</td>
<td>High School or Less</td>
<td>197</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>128</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>BA/BS</td>
<td>238</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>MS/MA/Professional</td>
<td>185</td>
<td>46%</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>White Non-Hispanic</td>
<td>638</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>Hispanic or Latino</td>
<td>212</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Black/African American</td>
<td>82</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Other/More than one Race</td>
<td>60</td>
<td>9%</td>
</tr>
<tr>
<td>Age at Diagnosis (years)</td>
<td>&lt;2</td>
<td>46</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>2-&lt;5</td>
<td>149</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>5-&lt;12</td>
<td>554</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>12-&lt;19</td>
<td>263</td>
<td>24%</td>
</tr>
<tr>
<td>DKA at Diagnosis</td>
<td>Yes</td>
<td>329</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>653</td>
<td>30%</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>507</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>505</td>
<td>26%</td>
</tr>
</tbody>
</table>

Multivariate Analysis

| Clinical Center | P-Value |
| A | <0.001 |
| B | <0.001 |
| C | <0.001 |
| D | <0.001 |
| E | <0.001 |
| F | <0.001 |
| G | <0.001 |

Outline

- **Types of technology**
  - Insulin delivery
    - Pumps
    - Bolus calculators
  - Continuous glucose monitors
  - Sensor-augmented pumps including low threshold suspend systems
  - Closed loop systems

- **Limitations of technology**
  - Management of patient expectations
  - Importance of patient engagement
  - Real-world experiences vs. study environments
  - Inequities in access

- **Cost and cost-effectiveness**
# Economic Burden of Hypoglycaemia – Effect of the ACA

<table>
<thead>
<tr>
<th>Year</th>
<th>Insured Population</th>
<th>% Diabetes</th>
<th># Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>260 million</td>
<td>7.4%</td>
<td>19.2 million</td>
</tr>
<tr>
<td>2020</td>
<td>320 million</td>
<td>12%</td>
<td>38.4 million</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-Requiring</td>
<td></td>
</tr>
<tr>
<td>1.0 million (100%)</td>
<td>18.2 million (22%)</td>
</tr>
<tr>
<td>Hypo Unaware</td>
<td></td>
</tr>
<tr>
<td>200,000 (8.1/yr)</td>
<td>400,000 (5.9/yr)</td>
</tr>
<tr>
<td>Severe Hypos</td>
<td></td>
</tr>
<tr>
<td>1,600,000 (21%)</td>
<td>2.4 million (21%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>336,000</td>
<td>504,000</td>
</tr>
<tr>
<td>$17,564/hosp</td>
<td>$17,564/hosp</td>
</tr>
<tr>
<td>$5.9 billion</td>
<td>$8.8 billion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin-Requiring</td>
<td></td>
</tr>
<tr>
<td>1.2 million (100%)</td>
<td>37.5 million (22%)</td>
</tr>
<tr>
<td>Hypo Unaware</td>
<td></td>
</tr>
<tr>
<td>240,000 (8.1/yr)</td>
<td>800,000 (5.9/yr)</td>
</tr>
<tr>
<td>Severe Hypos</td>
<td></td>
</tr>
<tr>
<td>1,944,000 (21%)</td>
<td>4.7 million (21%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>408,000</td>
<td>987,000</td>
</tr>
<tr>
<td>$17,564/hosp</td>
<td>$17,564/hosp</td>
</tr>
<tr>
<td>$7.2 billion</td>
<td>$17.3 billion</td>
</tr>
</tbody>
</table>

- **Hospitalization Cost**: $17,564/hosp
- **Total Cost**: $5.9 billion ($7.2 billion) for Type 1, $8.8 billion ($17.3 billion) for Type 2
Economic Burden of Hypoglycaemia – Effect of the ACA

2010: $14.7 billion  →  2020: $24.5 billion
## Cost-Effectiveness of CGM In Type 1 Diabetes

<table>
<thead>
<tr>
<th>Author (date)</th>
<th>Setting/population</th>
<th>Cost per QALY gained</th>
</tr>
</thead>
</table>
| **Huang et al.**  
*Diab Care 33:1269, 2010* | T1DM, Juvenile Diabetes Research Foundation-CGM trials, CGM vs. SMBG, 2 cohorts: 1) A1C < 7%, all ages; and 2) A1C >/= 7.0% and >/= 25 years of age | When considering immediate QoL benefit: $98,679 for A1C >/= 7.0% cohort and $78,943 for A1C < 7% cohort |
| **McQueen et al.**  
*Cost Eff Resour Alloc 9: 13, 2011* | T1DM, intensive insulin therapy with CGM (+ SMBG) vs. intensive insulin therapy with SMBG only, US | Using their individualized model: $45,033 |
| **Ly et al.**  
*Value in Health*  
e-pub July 15, 2014 | T1DM, Sensor-augmented pump with low glucose suspend in hypoglycaemic unaware patients | Over 6 months, cost per QALY gained is Australian $40,908 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Study objective, perspective, and data source</th>
<th>QALYs gained</th>
<th>Cost per QUALY (ICER)</th>
<th>Additional key findings</th>
</tr>
</thead>
</table>
| St. Charles et al   | To estimate long-term (60-year) cost-effectiveness of CSII compared with MDI in adults/children with type 1 DM | QUALY gains for CSII vs MDI were 0.262                                         | CSII: $16,992  
MDI: $27,195                                                                 | Improved glycaemic control from CSII reduced incidence of DM complications including PDR, ESRD, PVD  
The NNT for PDR was 9, (i.e., only 9 patients need to be treated with CSII to avoid 1 case of PDR)                                               |
| (54)                | US third-party payer perspective  
Computer simulation model (CORE Diabetes Model)                                                                    |                                                                               |                                                                                      |                                                                                                                                                      |
| St. Charles et al   | To evaluate the long-term (60-year) cost-effectiveness of CSII compared with MDI in adult patients with type 1 DM | QUALY gains for CSII vs MDI were 0.655                                         | CSII: $27,265  
MDI: $23,797 (Canadian dollars)                                                   |                                                                                                                                                      |
| (55)                | Canadian payer perspective  
Computer simulation model (CORE Diabetes Model)                                                                    |                                                                               |                                                                                      |                                                                                                                                                      |
| Cummins et al       | Assessment report to examine the clinical and cost-effectiveness of using CSII to treat DM (type 1 DM and during pregnancy) | N/A                                                                            | N/A                                                                                  | CSII is cost-effective for type 1 DM in both children and adults  
No evidence that CSII is better than MDI in pregnancy                                                                                           |
| (56)                | NICE, United Kingdom  
Systematic review and economic evaluation (74 studies included)                                                   |                                                                               |                                                                                      |                                                                                                                                                      |
| Cohen N et al       | To project long-term (lifetime horizon) costs and outcomes of CSII vs MDI in adults and adolescents with type 1 DM | QUALY gains for CSII vs MDI were 0.467 (adults) and 0.560 (adolescents)        | CSII: A$74,147 (adults); A$74,661 (adolescents)                                       | Authors indicated that CSII represents good value for most scenarios studied                                                                                                                                 |
| (26)                | Australian perspective  
Computer simulation model (CORE Diabetes Model)                                                                    |                                                                               |                                                                                      |                                                                                                                                                      |
| Roze et al          | To project the long-term (60-year) costs and outcomes of CSII vs MDI in patients with type 1 DM                | QUALY gains for CSII vs MDI were 0.76                                         | CSII: £80 511  
MDI: £61 104 (variance = £25 648/QUALY gained with CSII)                           | Improvements in glycaemic control with CSII vs MDI led to a reduced incidence of DM-related complications  
For patients with type 1 DM, CSII represents good value based on current United Kingdom standards                                           |
| (57)                | United Kingdom; third party National Health Services perspective  
Computer simulation model (CORE Diabetes Model)                                                                    |                                                                               |                                                                                      |                                                                                                                                                      |
Diabetes technologies and therapies are overpriced, offer little value, and place an unjust burden on the US healthcare system.

“That captive audience of Type 1 diabetics has spawned lines of high-priced gadgets and disposable accouterments, borrowing business models from technology companies like Apple”.

Accumulating evidence suggests that it is not. Future studies will be needed to validate the cost and cost-effectiveness of technologic approaches to reducing hypoglycaemia and A1C.
Thanks
Psychosocial Aspects of Hypoglycaemia

Stephanie A Amiel
RD Lawrence Professor of Diabetic Medicine
King’s College London School of Medicine
London, United Kingdom
Psychosocial aspects of hypoglycaemia

Stephanie A Amiel
RD Lawrence Professor of Diabetic Medicine
King’s College London School of Medicine
Definitions

Pyscho-
• mind
• mental

Social
• capable of being associated to others (1)
• marked by geniality (4); sympathetic (4b)
• consisting.....of persons associated ... in friendly intercourse (5c)
• living, or disposed to live, in ...communities desirous of enjoying the ....company of others (6)

Shorter Oxford English Dictionary, 3rd edition
Consequences of Hypoglycaemia

**Brain**
- Coma, seizures
- Cognitive dysfunction
- Psychological effects
- Fear of hypoglycaemia

**Cardiovascular**
- Myocardial ischaemia
- Cardiac arrhythmias

**Musculoskeletal**
- Falls, accidents
- Fractures, dislocations
- Driving mishaps
- Loss of privileges

**Death**
<table>
<thead>
<tr>
<th></th>
<th>7.00am</th>
<th>12.30pm</th>
<th>4.00pm</th>
<th>7.00pm</th>
<th>9.13pm</th>
<th>10.45pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon</td>
<td>5.8</td>
<td>7.1</td>
<td>2.8</td>
<td>10.1</td>
<td>9.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Tues</td>
<td>6.45am</td>
<td>10.31am</td>
<td>6.45pm</td>
<td>7.15pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.1</td>
<td>3.9</td>
<td>3.2</td>
<td>8.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wed</td>
<td>6.45am</td>
<td>10.00am</td>
<td>12.45pm</td>
<td>4.30pm</td>
<td>7.30pm</td>
<td>11.15pm</td>
</tr>
<tr>
<td></td>
<td>9.8</td>
<td>15.1</td>
<td>4.6</td>
<td>2.7</td>
<td>8.7</td>
<td>8.2</td>
</tr>
<tr>
<td>Thur</td>
<td>7.10am</td>
<td>12.50pm</td>
<td></td>
<td></td>
<td>7.15pm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.6</td>
<td>6.7</td>
<td></td>
<td></td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Fri</td>
<td>7.45am</td>
<td>12.40pm</td>
<td>3.30pm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.9</td>
<td>11.1</td>
<td>2.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Synopsis

• Psycho-social impact of
  – Non-severe hypoglycaemia
  – Hypoglycaemia unawareness
  – Severe hypoglycaemia

• On
  – The person with diabetes
  – The health economy
  – The families of the person with diabetes
Psychological barriers to optimal treatment

100 Type 2 insulin naïve adults asked about starting insulin

unwilling  hypoglycaemia  long term need  personal failure  pain

Fear of hypoglycaemia

- Diabetologists overestimated the hypoglycaemia-induced burden and anxiety.
- < ¼ patients decreased doses; increased intake and < 1/8 ate extra

Banke Petersen Eur Diabetes Nursing 2007; 4: 113–118
Bohme et al., Diabetes Metab. 2013;39:63-70
Non-severe hypoglycaemia

Documented symptomatic:
Symptoms with a measured low blood glucose

“≤ 2 episodes per week”

• 2 on-line or face-to face surveys
• 300 patients per survey
• Self reported diabetes (21-22% T1)
• Non-severe hypoglycaemia in the past month

Seaquist et al., Diab Care 2013; 36:1384-1395
DAFNE curriculum
Fulcher et al., J Med Econ. 2014; 5:1-11
<table>
<thead>
<tr>
<th></th>
<th>Nocturnal</th>
<th>Daytime</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 event per week (% participants)</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Cost of self treatment (€)</td>
<td>2.2±3.9</td>
<td>2.4±3.6</td>
</tr>
<tr>
<td>Increase in self tests done (%)</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>Contact with HCP (% participants)</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>Reduced doses (% participants)</td>
<td>38 (T1); 24 (T2)</td>
<td>30 (all on insulin)</td>
</tr>
<tr>
<td>Took day off work, % of participants in work</td>
<td>12 (n=21)</td>
<td>8 (n=14)</td>
</tr>
<tr>
<td>Negative impact on QoL (% participants)</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>

Fulcher et al., J Med Econ. 2014; 5:1-11
% missing a day after non-severe NH

Fulcher et al., J Med Econ. 2014; 5:1-11
Impact of hypoglycaemia on HRQoF in 1984 T2DM on OHA

“Symptoms” rated as
Mild (46%)
Moderate (37%)
Severe (13%)
Very severe (4%)

Marrett et al., BMC Res Notes.2011;4:251
Impact of hypoglycaemia on QoL

EQ-5D

Hypo experience | Painful neuropathy | MI pre Rx

Severe hypoglycaemia

“requiring assistance of another person” actively to treat........
Severe hypoglycaemia on QoL (T1)
SH in young adults

• 92 people, T1 DM, age 18-28 yrs
• CES-D depressive symptoms
  • < 16 not depressed (64.8%)
  • ≥ 23 severe depression (23.1%)
• ASR
  • Not distressed (60-68%)
  • ≥ 60 = psychological distress (18-30%)

Greater CES-D scores in those with
≥ 4 SH per month vs 0.

Impaired awareness of hypoglycaemia

Asymptomatic: No typical symptoms but a measured low blood glucose

Seaquist et al., Diab Care 2013; 36:1384-1395
40% patients coming for DAFNE have IAH
DAFNE restores awareness to 43%
Effect of unawareness on adherence?

% of unaware patients, n = 17

- Overestimate hyperglycaemia
- Normalise HU
- Avoidance of sick role
- Underestimate HU

Visit 1 – 4

- Hypo aware
- Hypo unaware

Rogers et al., Diabet Med. 2012;29:321-7
Loss of awareness of hypoglycaemia

DAFNE HART
24 people with IAH and SH

...run a bath (of)......practically boiling water. ..... when I got in, apparently, I started screaming ... my then husband came in and ...rescued me... things like that are really, really scary

...passed out while walking in the snow...I ..am paralysed and can’t move

- Reliance on others
- Increased blood testing
- Loss of employment
- Loss of driving

Rankin et al., Chronic Illn. 2013 ;10:180-191
“.......I feel guilty. I’m not the kind of character that finds joy in mothering another adult that I loved and respected as a male, you know, responsible being. I’m not, I want a proper partner.........”

Partner of man with type 1 diabetes and hypoglycaemia unawareness

FDG PET: Effect of awareness status on hypoglycaemia responses

Greater Increase
In aware, $P<0.05$, $k>100$

Symptomatic Stress Responses

Lesser fall
Hedonic Perception
Pleasure

Dunn et al, Diabetes, 2007; 56: 2766
<table>
<thead>
<tr>
<th></th>
<th>7.00am</th>
<th>12.30pm</th>
<th>4.00pm</th>
<th>7.00pm</th>
<th>9.13pm</th>
<th>10.45pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon</td>
<td>5.8</td>
<td>7.1</td>
<td>2.8</td>
<td>10.1</td>
<td>9.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Tues</td>
<td>6.45am</td>
<td>10.31am</td>
<td>6.45pm</td>
<td>7.15pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.1</td>
<td>3.9</td>
<td>3.2</td>
<td>8.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wed</td>
<td>6.45am</td>
<td>10.00am</td>
<td>12.45pm</td>
<td>4.30pm</td>
<td>7.30pm</td>
<td>11.15pm</td>
</tr>
<tr>
<td></td>
<td>9.8</td>
<td>15.1</td>
<td>4.6</td>
<td>2.7</td>
<td>8.7</td>
<td>8.2</td>
</tr>
<tr>
<td>Thur</td>
<td>7.10pm</td>
<td>12.50pm</td>
<td></td>
<td></td>
<td>7.15pm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.6</td>
<td>6.7</td>
<td></td>
<td></td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Fri</td>
<td>7.45am</td>
<td>12.40pm</td>
<td>3.30pm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.9</td>
<td>11.1</td>
<td>2.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Unaware (pnǔwē³)**
- Not aware (of)
- Not cognizant

- Ignorant (1704)
- Blind to the consequences
- Reckless (*rare*) 1817
DAFNE HART: A psycho-educational programme for people with T1DM and intractable problematic hypoglycaemia despite specialist support

De Zoysa, Diabetes Care, 2014
DAFNE HART: 12 month review

HbA1c (mmol/mol)

SH /pt year

Moderate hypo
Per pt / 6 weeks

Baseline
3 months post course

**

***

De Zoysa et al., Diabetes Care. 2014;37:863-6
Summary & Conclusions

• There are significant psycho-social impacts of severe hypoglycaemia and impaired awareness of hypoglycaemia – for people with diabetes and their families

• The psychological effects create barriers to hypoglycaemia avoidance

• These must be tackled directly
What’s new in hypoglycaemia education
Focus on type 2 diabetes

Pablo Aschner MD.MSc.
Professor of Endocrinology, Javeriana University
Scientific Director, Colombian Diabetes Association
Bogotá, Colombia

Potential conflicts of interest:
Advisory boards/lectures for AstraZeneca, BMS, Lilly, GSK, Jansen, MSD, Novartis, y Sanofi
• Reducing the impact of hypoglycaemia – Role of telemedicine
• Risk factors for hypoglycaemia in patients with Type 2 Diabetes (T2D)
• Impact of hypoglycaemia in patients with Type 2 Diabetes (T2D)
• The burden of hypoglycaemia in patients with Type 2 Diabetes (T2D)
• Recommendations
Telemedicine for prevention of hypoglycaemia in T1D Meta-analysis

TM defined as scheduled remote transmission of BG data by telephone, fax, mobile or internet with unsolicited clinician feedback → 9 studies (568 T1D age<19 yrs) lasting 3-12 mos

**Frequency of severe hypoglycemia**

<table>
<thead>
<tr>
<th>Study</th>
<th>log[odds ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Random, 95% CI</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadario</td>
<td>1.02</td>
<td>1.68</td>
<td>32.6%</td>
<td>2.77 [0.1, 74.64]</td>
<td></td>
</tr>
<tr>
<td>Chase</td>
<td>0.09</td>
<td>2.02</td>
<td>22.5%</td>
<td>1.09 [0.02, 57.35]</td>
<td></td>
</tr>
<tr>
<td>Lawson</td>
<td>0</td>
<td>2.02</td>
<td>22.5%</td>
<td>1 [0.02, 52.41]</td>
<td></td>
</tr>
<tr>
<td>Rami</td>
<td>0</td>
<td>2.03</td>
<td>22.3%</td>
<td>1 [0.02, 53.45]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100% 1.42 [0.22, 9.32]

Heterogeneity: Tau² = 0; Chi² = 0.24, df = 3 (P = .97); I² = 0%

Test for overall effect: Z = 0.37 (P = .71)

Difference in HbA1c -0.12 (95%CI -0.35 to 0.11)

127 T1D on basal-bolus (glargine-glulisine) randomized to “Diabetes Interactive Diary” (CHO/Bolus calculator with pat/MD communic. via short messages) vs. usual education on CHO counting. Mean age 37 yrs, mean duration 16 yrs.

Benefits
- Lower risk of moderate/severe hypoglycaemia (↓86%)
- Improved “percieved frequency of hyperglycaemic episodes” (DTSQ)
- Improved “social relations” and “fear of hypoglycaemia” in diabetes specific QOL scale

But...
- Almost 12% drop-out
- Not more effective in reducing HbA1c

Retrospective cohort of 1,000 T2D (mean age 53 years) regularly reporting SMBG and adjusting doses using the Diabetes Tele Managing System (DTMS). They had on average 17 DTMS follow-ups and reported 66,745 SMBGs over 6 months. 79% were on insulin±OAD (Rest on OAD only)

Benefits
✓ Reduced HbA1c from 8.5±1.4% to 6.3±0.6%  (p<0.0001)
✓ 84% reported no hypoglycaemia and rate of SMBG values <70mg/dl was 0.04 per pat. per month (considered low)

But...
✓ No control group
✓ Extra cost 9.66 USD/month per patient
Telemedicine for prevention of hypoglycaemia

Pro
Overcomes distance barrier
Immediate problem solving
Reduces face-to-face visits
May reduce costs?
Anticipates acute complications?

Con
Needs 24/7 personnel
Behavioural changes are difficult
Persistence depends on “Pro-Technology” profile?
Weak evidence for benefit
Systematic Review of 127 references

Key Question #1: What is the incidence of severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents?

Key Question #2: What are the risk factors for severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., demographics, co-morbidities, diabetes treatment regimen, other medication use, goal and achieved HbA1c)?

Key Question #3: What is the effect of severe hypoglycemia on other outcomes in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., quality of life, mortality, morbidity, utilization)?
### Severe hypoglycemia rates for sulfonylurea studies*

<table>
<thead>
<tr>
<th>Group By Duration</th>
<th>Study Name</th>
<th>Event Rate</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>long-term</td>
<td>Holstein 2001</td>
<td>0.013</td>
<td>0.009</td>
<td>0.017</td>
<td>44 / 3489</td>
</tr>
<tr>
<td>long-term</td>
<td>Matthews 2011</td>
<td>0.010</td>
<td>0.006</td>
<td>0.016</td>
<td>15 / 1546</td>
</tr>
<tr>
<td>moderate-term</td>
<td>Seck 2010</td>
<td>0.015</td>
<td>0.008</td>
<td>0.029</td>
<td>9 / 584</td>
</tr>
<tr>
<td>moderate-term</td>
<td>Garber 2011</td>
<td>0.002</td>
<td>0.000</td>
<td>0.031</td>
<td>0 / 248</td>
</tr>
<tr>
<td>moderate-term</td>
<td>Marre 2009</td>
<td>0.004</td>
<td>0.000</td>
<td>0.066</td>
<td>0 / 114</td>
</tr>
<tr>
<td>moderate-term</td>
<td></td>
<td>0.011</td>
<td>0.007</td>
<td>0.017</td>
<td>24 / 2492</td>
</tr>
<tr>
<td>short-term</td>
<td>UK Hypoglycemia Group</td>
<td>0.074</td>
<td>0.037</td>
<td>0.141</td>
<td>8 / 108</td>
</tr>
<tr>
<td>short-term</td>
<td>Arechavaleta 2011</td>
<td>0.015</td>
<td>0.008</td>
<td>0.031</td>
<td>8 / 519</td>
</tr>
<tr>
<td>short-term</td>
<td>Nauck 2009</td>
<td>0.002</td>
<td>0.000</td>
<td>0.032</td>
<td>0 / 242</td>
</tr>
<tr>
<td>short-term</td>
<td>Russell-Jones 2009</td>
<td>0.004</td>
<td>0.000</td>
<td>0.066</td>
<td>0 / 114</td>
</tr>
<tr>
<td>short-term</td>
<td>Chou 2008</td>
<td>0.002</td>
<td>0.000</td>
<td>0.034</td>
<td>0 / 225</td>
</tr>
<tr>
<td>short-term</td>
<td>Kendall 2005</td>
<td>0.002</td>
<td>0.000</td>
<td>0.031</td>
<td>0 / 247</td>
</tr>
<tr>
<td>short-term</td>
<td>Drouin 2004</td>
<td>0.001</td>
<td>0.000</td>
<td>0.009</td>
<td>1 / 800</td>
</tr>
<tr>
<td>short-term</td>
<td>Schernthaner 2004</td>
<td>0.001</td>
<td>0.000</td>
<td>0.009</td>
<td>0 / 845</td>
</tr>
<tr>
<td>short-term</td>
<td>Overall</td>
<td>0.012</td>
<td>0.009</td>
<td>0.015</td>
<td>85 / 9081</td>
</tr>
</tbody>
</table>

*Sulfonylurea monotherapy and combined sulfonylurea and metformin studies

Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012
### Severe hypoglycemia event rates for NPH insulin studies

<table>
<thead>
<tr>
<th>Group Duration</th>
<th>Study Name</th>
<th>Statistics for Each Study</th>
<th>Event rate and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Event Rate</td>
<td>Lower Limit</td>
</tr>
<tr>
<td>long-term</td>
<td>Rosenstock 2009</td>
<td>0.109</td>
<td>0.085</td>
</tr>
<tr>
<td>long-term</td>
<td></td>
<td>0.109</td>
<td>0.085</td>
</tr>
<tr>
<td>short-term</td>
<td>Rosenstock 2001</td>
<td>0.023</td>
<td>0.010</td>
</tr>
<tr>
<td>short-term</td>
<td></td>
<td>0.023</td>
<td>0.010</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.093</td>
<td>0.073</td>
</tr>
</tbody>
</table>

Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012
## Severe hypoglycemia event rates for insulin glargine studies*

<table>
<thead>
<tr>
<th>Group By Duration</th>
<th>Study Name</th>
<th>Statistics for Each Study</th>
<th>Event Rate</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>long-term</td>
<td>Rosenstock 2009</td>
<td></td>
<td>0.074</td>
<td>0.054</td>
<td>0.100</td>
<td>38 / 513</td>
</tr>
<tr>
<td>long-term</td>
<td>Buse 2011</td>
<td></td>
<td>0.029</td>
<td>0.016</td>
<td>0.050</td>
<td>12 / 419</td>
</tr>
<tr>
<td>long-term</td>
<td>Rosenstock 2008</td>
<td></td>
<td>0.027</td>
<td>0.014</td>
<td>0.054</td>
<td>8 / 291</td>
</tr>
<tr>
<td>long-term</td>
<td></td>
<td></td>
<td>0.041</td>
<td>0.019</td>
<td>0.084</td>
<td>58 / 1223</td>
</tr>
<tr>
<td>short-term</td>
<td>Kennedy 2006</td>
<td></td>
<td>0.030</td>
<td>0.026</td>
<td>0.034</td>
<td>228 / 7607</td>
</tr>
<tr>
<td>short-term</td>
<td>Riddle 2003</td>
<td></td>
<td>0.025</td>
<td>0.013</td>
<td>0.046</td>
<td>9 / 367</td>
</tr>
<tr>
<td>short-term</td>
<td>Heine 2005</td>
<td></td>
<td>0.015</td>
<td>0.008</td>
<td>0.039</td>
<td>4 / 267</td>
</tr>
<tr>
<td>short-term</td>
<td>Davies 2005</td>
<td></td>
<td>0.010</td>
<td>0.008</td>
<td>0.013</td>
<td>45 / 4588</td>
</tr>
<tr>
<td>short-term</td>
<td>Rosenstock 2001</td>
<td></td>
<td>0.004</td>
<td>0.001</td>
<td>0.027</td>
<td>1 / 259</td>
</tr>
<tr>
<td>short-term</td>
<td></td>
<td></td>
<td>0.016</td>
<td>0.008</td>
<td>0.032</td>
<td>288 / 13088</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.025</td>
<td>0.015</td>
<td>0.041</td>
<td>346 / 14311</td>
</tr>
</tbody>
</table>

*Alone or added to OHAs

---

Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012
### Severe hypoglycemia event rates for insulin detemir studies

<table>
<thead>
<tr>
<th>Group By Duration</th>
<th>Study Name</th>
<th>Statistics for Each Study</th>
<th>Event rate and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Event Rate</td>
<td>Lower Limit</td>
</tr>
<tr>
<td>long-term</td>
<td>Holman 4T 2009</td>
<td>0.009</td>
<td>0.002</td>
</tr>
<tr>
<td>long-term</td>
<td>Rosenstock 2008</td>
<td>0.017</td>
<td>0.007</td>
</tr>
<tr>
<td>long-term</td>
<td></td>
<td>0.014</td>
<td>0.007</td>
</tr>
<tr>
<td>moderate-term</td>
<td>Marre 2009</td>
<td>0.004</td>
<td>0.001</td>
</tr>
<tr>
<td>moderate-term</td>
<td></td>
<td>0.004</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.009</td>
<td>0.005</td>
</tr>
</tbody>
</table>
### Severe hypoglycemia event rates for NPH insulin studies*

<table>
<thead>
<tr>
<th>Group By Duration</th>
<th>Study Name</th>
<th>Statistics for Each Study</th>
<th>Event rate and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>long-term</td>
<td>Rosenstock 2009</td>
<td>0.109 0.085 0.139</td>
<td>55 / 504</td>
</tr>
<tr>
<td>long-term</td>
<td></td>
<td>0.109 0.085 0.139</td>
<td>55 / 504</td>
</tr>
<tr>
<td>short-term</td>
<td>Frische 2003</td>
<td>0.026 0.012 0.056</td>
<td>6 / 232</td>
</tr>
<tr>
<td>short-term</td>
<td>Rosenstock 2001</td>
<td>0.023 0.010 0.051</td>
<td>6 / 259</td>
</tr>
<tr>
<td>short-term</td>
<td>Riddle 2003</td>
<td>0.018 0.009 0.037</td>
<td>7 / 389</td>
</tr>
<tr>
<td>short-term</td>
<td>Rayman (glulisine) 2007</td>
<td>0.004 0.001 0.018</td>
<td>2 / 448</td>
</tr>
<tr>
<td>short-term</td>
<td>Dailey (glulisine) 2004</td>
<td>0.014 0.006 0.030</td>
<td>6 / 435</td>
</tr>
<tr>
<td>short-term</td>
<td>Rayman (RHI) 2007</td>
<td>0.016 0.008 0.033</td>
<td>7 / 442</td>
</tr>
<tr>
<td>short-term</td>
<td>Dailey (RHI) 2004</td>
<td>0.011 0.005 0.027</td>
<td>5 / 441</td>
</tr>
<tr>
<td>short-term</td>
<td></td>
<td>0.016 0.012 0.022</td>
<td>39 / 2646</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.050 0.041 0.061</td>
<td>94 / 3150</td>
</tr>
</tbody>
</table>

*NPH insulin as either primary therapy or in combination (Frische, sulfonylurea; Riddle oral OHAs; Rayman and Dailey, glulisine or regular insulin)
**Risk Factors for severe hypoglycaemia in T2D – Syst Rev**

### Severe hypoglycemia event rates for insulin lispro studies

<table>
<thead>
<tr>
<th>Group By Duration</th>
<th>Study Name</th>
<th>Statistics for Each Study</th>
<th>Event rate and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>long-term</td>
<td>Buse 2011</td>
<td>Event Rate: 0.042, Lower Limit: 0.027, Upper Limit: 0.064</td>
<td>Total: 20 / 476</td>
</tr>
<tr>
<td>long-term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short-term</td>
<td>Anderson 1997</td>
<td>Event Rate: 0.001, Lower Limit: 0.000, Upper Limit: 0.010</td>
<td>Total: 1 / 722</td>
</tr>
<tr>
<td>short-term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>Event Rate: 0.036, Lower Limit: 0.023, Upper Limit: 0.054</td>
<td>Total: 21 / 1198</td>
</tr>
</tbody>
</table>

### for insulin aspart studies

<table>
<thead>
<tr>
<th>Group By Duration</th>
<th>Study Name</th>
<th>Statistics for Each Study</th>
<th>Event rate and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>long-term</td>
<td>Holman 4T 2009 (Prandial)</td>
<td>Event Rate: 0.021, Lower Limit: 0.009, Upper Limit: 0.049</td>
<td>Total: 5 / 239</td>
</tr>
<tr>
<td>long-term</td>
<td>Holman 4T 2009 (Biphasic)</td>
<td>Event Rate: 0.026, Lower Limit: 0.012, Upper Limit: 0.056</td>
<td>Total: 6 / 235</td>
</tr>
<tr>
<td>long-term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short-term</td>
<td>Bentrop 2011 (Biphasic)</td>
<td>Event Rate: 0.002, Lower Limit: 0.000, Upper Limit: 0.007</td>
<td>Total: 2 / 1154</td>
</tr>
<tr>
<td>short-term</td>
<td>Liebl 2009 (Biphasic)</td>
<td>Event Rate: 0.003, Lower Limit: 0.000, Upper Limit: 0.043</td>
<td>Total: 0 / 178</td>
</tr>
<tr>
<td>short-term</td>
<td>Valensi IMPROVE 2009 (Biphasic)</td>
<td>Event Rate: 0.001, Lower Limit: 0.001, Upper Limit: 0.002</td>
<td>Total: 69 / 52419</td>
</tr>
<tr>
<td>short-term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>Event Rate: 0.002, Lower Limit: 0.002, Upper Limit: 0.002</td>
<td>Total: 82 / 54225</td>
</tr>
</tbody>
</table>

*Subjects may also have received OHAs in addition to insulin aspart.*
# Risk Factors for severe hypoglycaemia in T2D – Syst Rev

## Severe hypoglycemia event rates for insulin glulisine (+NPH insulin) short-term (26 wks) studies

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Event Rate</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rayman 2006</td>
<td>0.004</td>
<td>0.001</td>
<td>0.018</td>
<td>2 / 448</td>
</tr>
<tr>
<td>Daily 2004</td>
<td>0.014</td>
<td>0.006</td>
<td>0.030</td>
<td>6 / 435</td>
</tr>
<tr>
<td></td>
<td>0.009</td>
<td>0.003</td>
<td>0.026</td>
<td>8 / 883</td>
</tr>
</tbody>
</table>

Event rate and 95% CI:

-0.13 0.00 0.13

---

Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012
Severe hypoglycemia events for intensive glycemic control versus usual care studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Intensive control</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>VADT 2009</td>
<td>2.736</td>
<td>1.792</td>
<td>4.177</td>
<td>76 / 892</td>
<td>28 / 899</td>
</tr>
<tr>
<td>ACCORD 2008</td>
<td>3.096</td>
<td>2.717</td>
<td>3.527</td>
<td>849 / 5128</td>
<td>274 / 5123</td>
</tr>
<tr>
<td>ADVANCE 2008</td>
<td>1.884</td>
<td>1.442</td>
<td>2.463</td>
<td>150 / 5571</td>
<td>81 / 5669</td>
</tr>
<tr>
<td>UKPDS-33 1998</td>
<td>1.529</td>
<td>0.708</td>
<td>3.299</td>
<td>33 / 3071</td>
<td>8 / 1138</td>
</tr>
<tr>
<td>VA-CSDM 1995</td>
<td>2.600</td>
<td>0.520</td>
<td>12.993</td>
<td>5 / 75</td>
<td>2 / 78</td>
</tr>
</tbody>
</table>

Risk ratio and 95% CI
Factors most consistently associated with risk of severe hypoglycaemia include:

- Intensive glycaemic control
- History of hypoglycaemia
- Renal insufficiency
- History of microvascular complications
- Longer diabetes duration
- Lower education level
- African-American race
- History of dementia
- Higher age and lower BMI in 2 largest studies
Patients who had experienced severe hypoglycaemia had an increased risk of:

- Long-term mortality (not short-term)
- Neurological events (other than non-fatal stroke)
- Hospital and emergency department utilization
- Decreased QOL

Limited evidence suggests that:

- Non-fatal MI and stroke - unlikely consequences
- Mixed findings for cognitive decline and dementia
- Few reports on motor vehicle accidents
- More likely to miss days at work

Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012
Overall incidence of severe hypoglycaemia was < 1% for:

- Metformin monotherapy
- GLP-1 analogs
- DPP-4 inhibitors
- Glinides
- Thiazolidinediones
- Insulin detemir

Would treatment with these drugs be cost-effective?
### The burden of hypoglycaemia

<table>
<thead>
<tr>
<th>Costs</th>
<th>Main cause</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct</strong></td>
<td><strong>Severe hypoglycaemia</strong></td>
<td>Emergency Unit/Hospitalisations Additional strips</td>
</tr>
<tr>
<td>Health Care Syst Person &amp; Family</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indirect</strong></td>
<td><strong>Severe/Moderate hypoglycaemia, nocturnal</strong></td>
<td>Absence from work, ↓ adherence, stop treatment?</td>
</tr>
<tr>
<td><strong>Intangible</strong></td>
<td><strong>Any, mainly nocturnal?</strong></td>
<td>QOL for patient and partner</td>
</tr>
</tbody>
</table>
Impact of hypoglycaemia in T2D treated with MTF+SU

Cross-sectional, multicenter study in 430 consecutive primary health care Swedish patients on stable doses of metformin and SU for ≥ 6 months

Walz L et al. Pat Pref Adher 2014;8:593-601
Impact of hypoglycaemia in T2D treated with MTF+SU

*always taking medications exactly as prescribed
(from 3 quest. on antihyperglyc. medication included in self-report adherence and barriers questionnaire)

Walz L et al. Pat Pref Adher 2014;8:593-601
Impact of hypoglycaemia in T2D treated with MTF+SU

Treatment Satisfaction Questionnaire for Medication (TSQM) scores

<table>
<thead>
<tr>
<th>TSQM dimension</th>
<th>All patients (n=430)</th>
<th>No/mild (n=332)</th>
<th>Moderate/worse (n=80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness (0–100)</td>
<td>69.7±10.9</td>
<td>70.3±10.8</td>
<td>67.7±11.2</td>
<td>0.029*</td>
</tr>
<tr>
<td>Side effects (0–100)</td>
<td>92.9±16.2</td>
<td>94.4±14.0</td>
<td>87.1±21.8</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Convenience (0–100)</td>
<td>75.1±12.0</td>
<td>75.6±12.1</td>
<td>73.9±11.6</td>
<td>0.081</td>
</tr>
<tr>
<td>Global satisfaction (0–100)</td>
<td>70.3±16.1</td>
<td>71.2±16.2</td>
<td>67.0±16.0</td>
<td>0.036*</td>
</tr>
</tbody>
</table>

*P-values are age-adjusted; missing patients are excluded; data are expressed as the mean and standard deviation. *P<0.05.

HbA1c (mmol/L) latest value

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.3 (0.8)</td>
</tr>
<tr>
<td></td>
<td>7.0 (0.8)</td>
</tr>
<tr>
<td></td>
<td>0.03*</td>
</tr>
</tbody>
</table>

Walz L et al. Pat Pref Adher 2014;8:593-601
20-min survey assessing the impact of non-severe nocturnal hypoglycaemia (NSNH) episodes was administered to patients > 18 yrs with self-reported diabetes via internet in 9 Countries (USA, UK, Germany, Canada, France, Italy, Spain, Netherlands, Sweden)

20.212 were screened and 2.108 who had experienced at least 1 NSNHE in the last month were eligible. 74.2% were on insulin and 67.2% had T2D.
# Impact of non-severe nocturnal hypoglycaemia (NSNH)

<table>
<thead>
<tr>
<th>NSNH episodes</th>
<th>Type 2</th>
<th>Type 1</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1416</td>
<td>692</td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>0.7%</td>
<td>1.2%</td>
<td>ns</td>
</tr>
<tr>
<td>&gt;1 x week</td>
<td>7.8%</td>
<td>7.5%</td>
<td>ns</td>
</tr>
<tr>
<td>~1 x week</td>
<td>14.2%</td>
<td>19.3%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Several x month</td>
<td>31.4%</td>
<td>33.5%</td>
<td>ns</td>
</tr>
<tr>
<td>1 x month</td>
<td>19.2%</td>
<td>20.3%</td>
<td>ns</td>
</tr>
<tr>
<td>Few x year</td>
<td>20.1% 286</td>
<td>16.6% 115</td>
<td>?</td>
</tr>
<tr>
<td>Very rarely</td>
<td>6.3%</td>
<td>1.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adapted from Brod M et al. Diab Obes Metab 2013;15:546-57
Impact of non-severe nocturnal hypoglycaemia (NSNH)

Characteristics of last NSNH episode

Time when it happened
- before MN
- 2 - 4 am
- 4 - 6 am
- missing

Status when it happened
- woke by symp
- woke by other
- no symp
- woke to check

Adapted from Brod M et al. Diab Obes Metab 2013;15:546-57
Impact of non-severe nocturnal hypoglycaemia (NSNH)

Impact of NSNHE on diabetes management
✓ 3.6 ± 6.6 extra BGM tests in the next week
✓ 15.8% decrease in insulin dose lasting for 3.6 ± 5.9 days
✓ 14.8% contacted a health care professional for advice

Impact on functioning and well-being
✓ For those who woke up it took ~ 1hr to go back to sleep
✓ ~60% indicated that bed-partner also woke up
✓ 79.3% reported impact on overall functioning next day (felt emotionally low, decreased or avoided driving, had difficulty concentrating, decreased household chores or errands, restricted social activities).
✓ 70.4% felt tired or fatigued next day

Adapted from Brod M et al. Diab Obes Metab 2013;15:546-57
Impact of non-severe nocturnal hypoglycaemia (NSNH)

Health care provider interactions

- Do not ask me about night-time hypos during routine appointments: 24.5%
- Give me advice on managing night-time hypos that does not work for me: 16.7%
- Think that night-time hypos are my fault: 11.2%
- Do not understand how night-time hypos affect me: 8.6%
- Do not have time to talk about night-time hypos with me: 7.6%
- Think that night-time hypos are not very important: 7.5%

Online multinational cross-sectional study of 3,042 T2D patients currently treated with basal insulin, and 1,222 healthcare professionals involved in the care of such patients → 36% of patients had experienced self-treated hypoglycaemia during the previous 30 days.

In response patients reported:
- ✓ missing (7%), reducing (11%) or mis-timing (4%) basal insulin doses
- ✓ increasing the level of glucose monitoring (40%) or utilising healthcare resources (7%).
Online multinational cross-sectional study of 3,042 T2D patients currently treated with basal insulin, and 1,222 healthcare professionals involved in the care of such patients → 36% of patients had experienced self-treated hypoglycaemia during the previous 30 days.

✓ Nocturnal events worried significantly more patients than diurnal (42% vs. 23%, p < 0.001).
✓ Most prescribers (76%) believed that insulin analogues minimised the risk of nocturnal hypoglycaemia when compared to NPH insulin.
Hypoglycaemia Awareness Trial (HAT)

Hypoglycaemic events in the retrospective cohort

Proportion (%) experiencing ≥1 event

- T1D=8.022
- T2D=19.663

Estimated annual incidence
No. events per patient/year

Any and nocturnal within 4 wks prior to baseline, severe and hospitalisation within 6 months

Direct costs

0.17&0.12

Khunti K. Personal communication
Hypoglycaemia Awareness Trial (HAT)

Hypoglycaemic events in the prospective cohort

**Proportion (%) experiencing ≥1 event**

- Any: [Graph Data]
- Nocturnal: [Graph Data]
- Severe: [Graph Data]
- Hospit: [Graph Data]

**Estimated annual incidence**

- No. events per patient/year
  - T1D = 7.108
  - T2D = 18.518

**Direct costs**

- 0.24 & 0.22

All within 4 wks prior to baseline

Khunti K. Personal communication
The burden of hypoglycaemia

<table>
<thead>
<tr>
<th>Costs</th>
<th>Main cause</th>
<th>Source</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td>Severe hypoglycaemia</td>
<td>Emergency Unit/Hospitalisations</td>
<td>Low</td>
</tr>
<tr>
<td>Health Care Syst Person &amp; Family</td>
<td>Additional strips</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect</td>
<td>Severe/Moderate hypoglycaemia, nocturnal</td>
<td>Absence from work, ↓ adherence, stop treatment?</td>
<td>Moderate</td>
</tr>
<tr>
<td>State / Society/ Person&amp;Family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intangible</td>
<td>Any, mainly nocturnal?</td>
<td>QOL for patient and partner</td>
<td>High</td>
</tr>
<tr>
<td>Person &amp; Family</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Difficult to demonstrate cost-effectiveness of treatments that do not cause hypoglycaemia
Prevention of hypoglycaemia in T2D

Patients require instructions on the recognition and management of hypoglycaemia at the time of the first prescription

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>
| Treatment with  
✓ Sulfonylurea  
✓ Glinide  
✓ Insulin  
✓ Any combination including any of the above | Treatment with  
✓ Metformin  
✓ Thiazolidinediones  
✓ Alpha-glucosidase inhibitors*  
✓ DPP-4 inhibitor  
✓ GLP-1 receptor agonist  
✓ SGLT-2 inhibitor  
✓ Any combination involving only those mentioned above |

*hypoglycaemia in patients taking alpha-glucosidase inhibitors must be treated with glucose or dextrose (monosaccharide)

P.Aschner 2014
Absence of hypoglycaemia as a target in T2D

- Hypoglycaemia is not only a safety issue (underestimated in patients with type 2 diabetes)
- RCT should include hypoglycaemia in a composite endpoint for efficacy: proportion of patients reaching glucose control (e.g. HbA1c < 7%) without hypoglycaemia
Thank you!
Panel Discussion
QUESTIONS FOR OUR PANEL

Simon Heller, BA, MB, Bchir, DM, FRCP
Brian Frier, MD, FRCPE
Tim Jones, MD, DCH, FRACP
Robert Vigersky, MD, FACP
Stephanie Amiel, BSc, MD, FRCP
Pablo Aschner, MD, MSc

Question Cards

Microphones