Welcome & Introductions

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Ontario, Canada
WELCOME TO VANCOUVER!
ABOUT THE IHSG

Formed in 2013

16 members from around the globe

Simon Heller, Chair, UK
Stephanie Amiel, UK
Pablo Aschner, Colombia
Belinda Childs, USA
Philip Cryer, USA
Bastiaan de Galan, The Netherlands
Brian Frier, UK
Linda Gonder-Frederick, USA
Tim Jones, Australia
Kamlesh Khunti, UK
Lawrence Leiter, Canada
Yingying Luo, China
Rory McRimmon, UK
Elizabeth Seaquist, USA
Robert Vigersky, USA
Sophia Zoungas, Australia

The International Hypoglycaemia Study Group (IHSG) is supported through an unrestricted education grant from Novo Nordisk A/S and is consistent with its ongoing commitment in diabetes.

Six Degrees Academy supports the IHSG with project management, logistics and supporting tactics.
WHY HYPOGLYCEMIA MATTERS

Our Goals
WHY HYPOGLYCEMIA MATTERS

Higher incidence of hypoglycemia occurs as patients move closer to HbA1c treatment targets

Raise awareness globally across the healthcare & patient community

A better understanding can increase patient quality of life

Our goal is to improve the lives of patients with diabetes

It is an under-recognized problem that deserves increased awareness

There is a lack of understanding by both professionals and patients

Strategies & tools are needed to help physicians manage & prevent hypoglycemia
OUR OBJECTIVES THIS EVENING

1. Discuss the prevalence of hypoglycemia and how it affects patients
2. Engage with colleagues to better understand hypoglycemia
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:35 pm</td>
<td>Global Epidemiology</td>
<td>Simon Heller, BA, MB, Bchir, DM, FRCP</td>
</tr>
<tr>
<td>5:55 pm</td>
<td>Vascular Impact</td>
<td>Sophia Zoungas, MBBS, PhD, FRACP</td>
</tr>
<tr>
<td>6:15 pm</td>
<td>Hypoglycemia and the Brain</td>
<td>Elizabeth Seaquist, MD</td>
</tr>
<tr>
<td>6:35 pm</td>
<td>Technology to the Rescue</td>
<td>Robert Vigersky, MD</td>
</tr>
<tr>
<td>6:55 pm</td>
<td>Panel discussion</td>
<td>All</td>
</tr>
<tr>
<td>7:25 pm</td>
<td>Wrap-up</td>
<td>Lawrence Leiter, MD, FRCPC, FACP, FACE, FAHA</td>
</tr>
</tbody>
</table>
ALSO HERE TONIGHT...

- **Stephanie A. Amiel, BSc, MD, FRCP**, RD Lawrence Professor of Diabetic Medicine Division of Diabetes and Nutritional Sciences, King's College, London, UK

- **Pablo Aschner, MD, MSc**, Associate Professor of Endocrinology, Javeriana University School of Medicine, Director of Research, San Ignacio University Hospital, Scientific Director of the Colombian Diabetes Association, Bogota, Colombia

- **Linda Gonder-Frederick, PhD**, Associate Professor, Department of Psychiatry and Neurobehavioral Sciences Clinical Director, Behavioral Medicine Center University of Virginia Health System Charlottesville, VA, USA

- **Kamlesh Khunti, PhD, MD, FRCGP, FRCP**, Professor of Primary Care Diabetes and Vascular Medicine, University of Leicester, UK
Global Epidemiology

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
• Global epidemiology
• Epidemiology of mild & severe hypoglycemia in T1D and T2D
• Variations in different populations (e.g., adolescents, elderly)
• Geographical variations and temporal trends (if any)
• Q&A (5 minutes)
A question for you

In your practice, have you seen hypoglycemia decrease in recent years?

A. Yes, I have seen a large decrease
B. Yes, I have seen a small decrease
C. No, it has stayed the same
D. No, it has increased
In your practice, have you seen hypoglycemia decrease in recent years?

- Yes, I have seen a large decrease: 3.57%
- Yes, I have seen a small decrease: 53.57%
- No, it has stayed the same: 32.14%
- No, it has increased: 10.71%
Frequency of severe hypoglycemia in adults with type 1 diabetes

1993 – DCCT¹
0.62 (intensive) versus 0.19 (conventional) episodes*

1990s

2000 – Ter Braak²
Netherlands
Frequency* – 1.5
Proportion affected – 45%

2000s

2005 – Leiter⁴
Canada
Frequency* – 2.6
Proportion affected – 27%

2007 – UK Hypoglycaemia Study Group⁵
Frequency* – 1.1*/3.2††
Proportion affected – 22%/46%††

2010s

2012 – Kristensen⁶
Denmark
Frequency* – 1.2
Proportion affected – 31%

2004 – Pedersen-Bjergaard³
Denmark
Frequency* – 1.3
Proportion affected – 37%

HbA₁c in each trial: ¹~7% (intensive) and ~9% (conventional) over 10 years follow-up; ²Mean =7.8 ± 1.2%; ³Mean = 8.6 ± 1.3%; ⁴Most recent HbA₁c = 7.4%; ⁵Mean 7.3 1.02 and 7.3 1.16†; ⁶Mean 7.8 ± 0.73 and 7.6 ± 0.85†† at baseline and year 1, respectively; ⁷Mean = 8.0 ± 1.0% and 7.9 ± 1.0% for patients treated with long-acting insulin analogue and human insulin, respectively.

Median follow-up across all studies was between 9–12 months. *Per patient/year; † diabetes duration <5 years †† diabetes duration >15 years.

Patients with type 1 or 2 diabetes experience frequent hypoglycemic events

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

Results from the HAT study:
Hypoglycemia rates are higher than expected

HAT study
- Non-interventional, global, 6-month retrospective, 1-month prospective study of patient self-reported hypoglycemic events
- 27,585 insulin-treated patients (T1D: 8,022; T2D: 19,563)

HAT, Hypoglycaemia Assessment Tool. T1D, type 1 diabetes; T2D, type 2 diabetes.
Results from the HAT study:
Hypoglycemia rates are higher than expected

Prospective data suggest higher than expected rates of hypoglycemia in both T1D and T2D – in particular, severe events

HAT study
- Non-interventional, global, 6-month retrospective, 1-month prospective study of patient self-reported hypoglycemic events
- 27,585 insulin-treated patients (T1D: 8,022; T2D: 19,563)

HAT, Hypoglycaemia Assessment Tool. T1D, type 1 diabetes; T2D, type 2 diabetes.
Khunti et al. Diabetologia 2014;57(Suppl. 1);S201.
Severe hypoglycemia in type 1 diabetes

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

Pedersen-Bjergaard et al, DMMR 2004; 20: 479-86.
Risks of severe hypoglycemia in type 1 diabetic pregnancy according to gestational age

Risk of severe hypoglycemia in early pregnancy

- 278 women with Type 1 diabetes, traditional predictors-PH, longer duration of diabetes, increased insulin dose

Hypoglycemia 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.
Incidence of severe hypoglycemia: Adolescents

Severe hypoglycemia in children and adolescents

**Western Australia**
(1683 patients: 2000-2009)

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>Rate/100 Patient-Years</th>
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<tbody>
<tr>
<td>2000</td>
<td>18</td>
</tr>
<tr>
<td>2002</td>
<td>14</td>
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<tr>
<td>2004</td>
<td>12</td>
</tr>
<tr>
<td>2006</td>
<td>10</td>
</tr>
<tr>
<td>2008</td>
<td>8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>HbA1c (%)</th>
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<tbody>
<tr>
<td>1995</td>
<td>95</td>
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<tr>
<td>1996</td>
<td>96</td>
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<td>1997</td>
<td>97</td>
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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

---

Severe hypoglycemia vs. HbA$_{1c}$ (2010-13) in children with type 1 diabetes

Data derived from Cooper et al., *Diabetologia* 2013: 2164-70.
Proportion of elderly and younger patients with hypoglycemia at 12 months prior to treatment baseline

Relevant complications include comorbidities and diminished physiological defence to hypoglycemia

- Cognitive impairment
- Frailty
- Impaired counterregulation and diminished awareness of hypoglycemia
- Chronic renal impairment
- Impaired hepatic function
- Falls
One-third of cases were patients in nursing homes or being cared for by a home nursing service.

Survival probability curves of proportions of patients remaining free of severe hypoglycemia: Evidence from the Fremantle Diabetes Study

Edinburgh Type 2 Diabetes Study: Preceding history of severe hypoglycemia (SH) and cognitive ability


- Results of age-sensitive cognitive tests combined to derive late-life general cognitive ability factor, ‘g’
- Negative linear association between ‘g’ and frequency of SH in the year preceding cognitive testing (p < 0.0001)
- ‘SH’ group had poorer cognitive performance than ‘No SH’ group
Conclusions

- Hypoglycemia is a global problem
- Observational studies indicate risks in real life far greater than in clinical trials
- Those particularly vulnerable include children, pregnant women and the elderly
- Despite major advances in insulin delivery and technology, risks of severe hypoglycemia have not improved
- People with insulin treated diabetes require professionals to ensure that effective therapeutic interventions are made more available
Hypoglycemia: Vascular Impact

Prof Sophia Zoungas, MBBS (Hons), PhD, FRACP
Professorial Chair of Diabetes, Vascular Health and Ageing
School of Public Health and Preventive Medicine
Monash University, Clayton, Australia
Disclosures

Fellowship support: NHMRC Australia

Speakers bureau, travel or advisory board: MSD, Servier
Hypoglycemia and vascular risk

• Is there an association?
  • (type 1, type 2 diabetes and hospitalized patients)

• Is the association due to selection bias or residual confounding (marker)?

• Is the association causal?
  • (impact of severity and preconditioning)

• Landmark clinical trials and observational studies including cardiac monitoring
Which of the following is true?

- Hypoglycemia is a marker for CVD risk
- Hypoglycemia directly increases CVD risk
- Both
- Neither
Which of the following is true?

- Hypoglycemia is a marker for CVD risk: 13.16%
- Hypoglycemia directly increases CVD risk: 18.42%
- Both: 65.79%
- Neither: 2.63%
Type 2 diabetes
## Hypoglycemia in ACCORD trial\textsuperscript{1,2}

<table>
<thead>
<tr>
<th></th>
<th>Standard Therapy Group (n=5123)</th>
<th>Intensive Therapy Group (n=5128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median HbA(_{1c}) levels at 1 year, %</td>
<td>7.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Hypoglycemia requiring medical assistance, * %</td>
<td>3.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Hypoglycemia necessitating any assistance, * %</td>
<td>5.1</td>
<td>16.2</td>
</tr>
<tr>
<td>Deaths due to any cause, n (%)</td>
<td>HR 1.22 (p = 0.04)</td>
<td>203 (4)</td>
</tr>
</tbody>
</table>

*15% of hypoglycemic events did not have a documented blood glucose level.

• The risk of mortality was increased in setting of hypoglycemia in both treatment groups

• For those not reporting severe hypoglycemia mortality higher in intensive group

• For those reporting severe hypoglycemia mortality higher in standard group

ACCORD trial frequent and unrecognized hypoglycemia

- Defined by SMBG < 3.9 mmol/L (70mg/dl) in 7 days prior to clinic visit and no symptoms
- More common in intensive group
- Decreased risk of mortality in those reporting frequent and unrecognized hypoglycemia
  - All cause death (int): adjusted HR 0.93 95% CI 0.90-0.97, p<0.001
  - All cause death (stand): adjusted HR 0.98 95% CI 0.91-1.06, p=ns

ADVANCE trial

ADVANCE trial

- No increased risk in those reporting repeat severe hypoglycemia dose response (small number of participants)
- No increased risk of adverse outcomes in those reporting non-severe hypoglycemia
  - Major CV events - adjusted **OR 0.70** (95% CI 0.61-0.80)
  - All cause death - adjusted **OR 0.42** (95% CI 0.36-0.49)

• No increased risk of CV death, arrhythmic death and non-fatal MI/Stroke in those reporting non-severe hypoglycemia
• Increased risk in those reporting severe hypoglycemia
Macro- and microvascular risks in veterans

A: Cumulative incidence rate of CVD events by group. B: Cumulative incidence rate of microvascular complications by group. (Log-rank test P<0.0001 for both outcomes).

Type 1 diabetes
DCCT: Rates of severe hypoglycemia increase as HbA$_{1c}$ levels decrease

- Non-significant 41% reduction in CVD at the end of active treatment
- Significant 42% (95% CI 9% to 63%) reduction in CVD after 17 years further follow up

Squares correspond to >400 patient-years. DCCT = Diabetes Control and Complications Trial.
Eurodiab Prospective study

- 2181 patients with type 1 diabetes (nested case-control study)
- Mean age approx. 32-36 years
- No increase risk of CV events in those reporting severe hypoglycemia
  (self reported requiring assistance of third party)

<table>
<thead>
<tr>
<th>Episodes of Severe Hypoglycemia at Baseline Exam</th>
<th>Model 1 OR (95% CI)</th>
<th>Model 2 OR (95% CI)</th>
<th>Model 3 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>1-2</td>
<td>0.87 (0.55 – 1.37)</td>
<td>0.90 (0.55 – 1.48)</td>
<td>0.94 (0.57 – 1.55)</td>
</tr>
<tr>
<td>3+</td>
<td>1.09 (0.68 – 1.75)</td>
<td>1.23 (0.75 – 2.04)</td>
<td>1.33 (0.80 – 2.22)</td>
</tr>
</tbody>
</table>

In model 1, ORs were adjusted for age, sex, diabetes duration, systolic blood pressure, LDL cholesterol, AER, HbA1c, categories of smoking, and DSP. In models 2 and 3, ORs for nonfatal CVD were adjusted for numbers of nonsevere (model 2) and severe (model 3) hypoglycemic episodes at the follow-up examination, respectively. Gruden et al Diabetes Care. 2012 Jul;35(7):1598-604.
Retrospective GP cohort study

- 3260 patients with type 1 diabetes (GP database coding)
- Mean age 60±15 years
- Increased risk of CV events in those reporting severe hypoglycemia (requiring hospital admission)

Hospitalized patients
Evidence

• **NICE-SUGAR trial**
  • Critically ill patients, moderate and severe hypoglycemia a/w increased mortality, although median time to death was 7-8 days

• **AMI patients with and without known diabetes**
  • Spontaneous hypoglycemia in patients not treated with insulin a/w increased mortality while iatrogenic hypoglycemia in patients treated with insulin was not

• **ACS patients in single centre**
  • A single BG <3 mmol/l during hospitalization a/w increased risk of 2 yr mortality

• **TIMI studies**
  • Hypoglycemia on admission a/w increased risk of death or AMI at 30 days

• **DIGAMI 2 (type 2 and AMI)**
  • Hypoglycemia during hospitalization not a/w future morbidity or mortality

What may explain this association?
Selection bias

- Sampling fraction for cases and controls is related to exposure.
- Clinic/hospital based cases/controls have different exposures than population cases/controls (Berkson’s bias).
- Eg. The combination of exposure to risk and occurrence of disease increases the likelihood of being admitted to clinic/hospital.
• Severe hypoglycemia may reflect the effects of co-morbid diseases and unmeasured or incompletely quantified confounding variables

• The presence of co-morbid disease increases a patient’s vulnerability to both severe hypoglycemia and adverse clinical outcomes

• The risk factors for severe hypoglycemia and adverse CV events are shared
Multiple plausible mechanisms by which severe hypoglycemia might cause cardiovascular morbidity or mortality
CRP, C-reactive protein; IL-6, interleukin 6; VEGF, vascular endothelial growth factor.
Adapted from Desouza et al. Diabetes Care. 2010;33:1389-94
Severe hypoglycemia may cause a prolongation of QT interval in patients with type 2 diabetes

- Significant prolongation of QT interval after hypoglycemic clamps
- Increased risk of arrhythmias

NS = not significant.
Thirteen patients with type 2 diabetes taking combined insulin and glibenclamide treatment were studied during hypoglycemia; 8 participated in the euglycemic experiment clamped between 5.0 and 6.0 mmol/L. The aim was to achieve stable hypoglycemia between 2.5 and 3.0 mmol/L (45 and 54 mg/dL) during the last 60 minutes of the experiment. 1. Landstedt-Hallin L et al. J Intern Med. 1999;246:299–307.
Risk of cardiac arrhythmias with spontaneous hypoglycemia

- 25 individuals with type 2 diabetes on insulin treatment for at least 4 years
- History of CVD or risk factors for CVD
- Simultaneous CGMS and ambulatory ECG (5 days)
- Frequency of arrhythmias, HR variability and markers of cardiac repolarization compared between hypoglycemia and euglycemia matched for time of day

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>Night</th>
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<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Atrial ectopic</td>
<td>1.35</td>
<td>0.92–1.98</td>
</tr>
<tr>
<td>VPB</td>
<td>1.31</td>
<td>1.10–1.57</td>
</tr>
<tr>
<td>Complex VPB</td>
<td>1.13</td>
<td>0.78–1.65</td>
</tr>
</tbody>
</table>

IRRs and 95% CI of arrhythmias during hypoglycaemia versus euglycemia as analysed using generalized estimated equations. NA, not applicable. Elaine Chow et al. Diabetes 2014;63:1738-1747.
Abnormal QT prolongation and T-wave morphology during hypoglycemia in a single patient

• Possible that the consequences of hypoglycemia were underestimated, because
  • many hypoglycemic episodes may not be detected or recorded (especially impaired awareness) or
  • recording of hypoglycemic episodes may have occurred differently in comparator groups
• Possible physiological response varies (with severity and frequency) eg patients adapt to repeated events
• Possible other CV protective drugs taken mitigate adverse effects
Summary

• Severe hypoglycemia is associated with increased risk of vascular events (possibly Type 1)
  • Severe hypoglycemia may identify a patient vulnerable to adverse vascular events
  • Severe hypoglycemia may cause adverse vascular events
  • None of the studies to date provide evidence that clearly refutes these possibilities
Clinical implications

- Chose approaches to glucose lowering that minimize risk of severe hypoglycemia
- Ensure patients are educated about avoidance and management of hypoglycemia
- Experience of severe hypoglycemia should lead to an examination of comorbid diseases that may produce adverse outcomes
Which of the following is true?

- Hypoglycemia is a marker for CVD risk
- Hypoglycemia directly increases CVD risk
- Both
- Neither
Which of the following is true?

- Hypoglycemia is a marker for CVD risk: 17.95%
- Hypoglycemia directly increases CVD risk: 7.69%
- Both: 74.36%
- Neither: 0%
Hypoglycemia And The Brain

Elizabeth Seaquist, MD
Pennock Family Chair in Diabetes Research
Director, Division of Endocrinology and Diabetes
Department of Medicine
University of Minnesota USA

IHSG meeting 12/1/2015 Vancouver, B.C.
Disclosure

- I am a current member of the ABIM Internal Medicine Exam Committee
- To protect the integrity of Board Certification, ABIM enforces strict confidentiality and ownership of exam content
- As a member of an ABIM exam committee, I agree to keep exam information confidential
- As is true for any ABIM candidate who has taken an exam for Certification, I have signed the Pledge of Honesty in which I have agreed not to share ABIM exam questions with others
- No exam questions will be disclosed in my presentation
How does hypoglycemia affect the brain in patients with diabetes?

A. Hypoglycemia is associated with dementia
B. Hypoglycemia can cause seizures and coma
C. Hypoglycemia may alter brain development in children
D. Hypoglycemia alters glucose sensing in the brain
E. All of the above
<table>
<thead>
<tr>
<th>Statement</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Hypoglycemia is associated with dementia</td>
<td>0%</td>
</tr>
<tr>
<td>Hypoglycemia can cause seizures and coma</td>
<td>0%</td>
</tr>
<tr>
<td>Hypoglycemia may alter brain development in children</td>
<td>0%</td>
</tr>
<tr>
<td>Hypoglycemia alters glucose sensing in the brain</td>
<td>2.33%</td>
</tr>
<tr>
<td>All of the above</td>
<td>97.67%</td>
</tr>
</tbody>
</table>
How does hypoglycemia affect the brain in patients with diabetes?

**Acute hypoglycemia**
- Acute loss of consciousness
- Seizures
- Cognitive dysfunction

**Recurrent hypoglycemia**
- Cognitive dysfunction
- Structural changes
- Hypoglycemia unawareness
Effects of glycemia on cognition in school age children

- Examined 61 children with mean age of 9 years
- Children did tests on PDA just prior to pre-meal glucose testing for 4-6 weeks

Gonder-Frederick et al. *Diabetes Care* 2009.
Examined youth ages 5-16 years using standardized neurocognitive tests

117 had type 1 diabetes

✓ Categorized as having experienced 0, 1-2, or 3 more episodes of severe hypoglycemia based on family interview and medical records

58 were sibling controls without diabetes
Impact of hypoglycemia at < 5 years vs > 5 years in youth with T1DM

*P < 0.05
Hypoglycemia and dementia risk on older patients with type 2 DM

- Study included 16,667 individuals in Kaiser diabetes registry who were >55 years of age on 1/1/2003 with diagnosis of T2DM and no diagnosis of dementia or mild cognitive impairment
- Examined relationship between hypoglycemia episodes required hospitalization or ED visit between 1/1/1980-12/31/2002 and 1822 incident cases of dementia identified after 1/1/2003

### Hypoglycemia and risk of incident dementia

<table>
<thead>
<tr>
<th>No. of Hypoglycemic Episodes</th>
<th>No. of Dementia Cases</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted for Age (as time scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes</td>
</tr>
<tr>
<td>1 or more</td>
<td>250</td>
<td>1.68 (1.47 – 1.93)</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>1.45 (1.23 – 1.72)</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>2.15 (1.64 – 2.81)</td>
</tr>
<tr>
<td>3 or more</td>
<td>43</td>
<td>2.60 (1.78 – 3.79)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HbA<sub>1c</sub>, glycated hemoglobin. *Analyses combined using Cox proportional hazard models. \(^b\)*The 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0. \(^c\)*Adjustment made using a comorbidity composite scale. Whitmer et al. *JAMA* 2009.
Recurrent hypoglycemia leads to hypoglycemia associated autonomic failure
Recurrent hypoglycemia leads to hypoglycemia associated autonomic failure

Plasma glucose (mg/dl)

- Decreased insulin secretion
- Glucagon and Epinephrine secretion
- Cognitive dysfunction

Recurrent hypoglycemia leads to hypoglycemia associated autonomic failure
Risk factors for hypoglycemia in diabetes

- **Conventional risk factors – relative or absolute insulin excess**
  - Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type
  - Exogenous glucose delivery is decreased (e.g. after missed meals and during the overnight fast)
  - Glucose utilization is increased (e.g. during exercise)
  - Endogenous glucose production is decreased (e.g. after alcohol ingestion)
  - Sensitivity to insulin is increased (e.g. after weight loss, an increase in regular exercise or improved glycemic control, and in the middle of the night)
  - Insulin clearance is decreased (e.g. with renal failure)

- **Risk factors for hypoglycemia-associated autonomic failure**
  - Absolute endogenous insulin deficiency
  - A history of severe hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise, and sleep
  - Aggressive glycemic therapy *per se* (lower HbA$_1c$ levels, lower glycemic goals, or both)

Which risk factor for hypoglycemia is most common in your practice?

A. Your patients give a dose of mealtime insulin that is too much for the food they actually eat
B. Patients do not anticipate the effects of exercise on their blood sugar
C. Patients drink alcohol without eating food
D. The basal dose of insulin is too high
Which risk factors for hypoglycemia is most common in your practice?

- Your patients give a dose of mealtime insulin that is too much for the food they actually eat: 54.29%
- Patients do not anticipate the effects of exercise on their blood sugar: 22.86%
- Patients drink alcohol without eating food: 5.71%
- The basal dose of insulin is too high: 17.14%
Tools to recognize impaired awareness in your patients

Table 2—Hypoglycemia Patient Questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
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<tbody>
<tr>
<td>Name</td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>Middle</td>
</tr>
<tr>
<td>Last</td>
<td></td>
</tr>
<tr>
<td>Today’s date</td>
<td></td>
</tr>
<tr>
<td>1. To what extent can you tell by your symptoms that your blood glucose is LOW?</td>
<td>Never ___ Rarely ___ Sometimes ___ Often ___ Always</td>
</tr>
<tr>
<td>2. In a typical week, how many times will your blood glucose go below 70 mg/dL?</td>
<td>______ a week</td>
</tr>
<tr>
<td>3. When your blood glucose goes below 70 mg/dL, what is the usual reason for this?</td>
<td></td>
</tr>
<tr>
<td>4. How many times have you had a severe hypoglycemic episode (where you needed someone’s help and were unable to treat yourself)?</td>
<td>Since the last visit ______ times, In the last year ______ times</td>
</tr>
<tr>
<td>5. How many times have you had a moderate hypoglycemic episode (where you could not think clearly, properly control your body, had to stop what you were doing, but you were still able to treat yourself)?</td>
<td>Since the last visit ______ times, In the last year ______ times</td>
</tr>
<tr>
<td>6. How often do you carry a snack or glucose tablets (or gel) with you to treat low blood glucose?</td>
<td>Check one of the following: Never ___ Rarely ___ Sometimes ___ Often ___ Almost always ___</td>
</tr>
<tr>
<td>7. How LOW does your blood glucose need to go before you think you should treat it?</td>
<td>Less than ____ mg/dL</td>
</tr>
<tr>
<td>8. What and how much food or drink do you usually treat low blood glucose with?</td>
<td></td>
</tr>
<tr>
<td>9. Do you check your blood glucose before driving? Check one of the following:</td>
<td>Yes, always ___ Yes, sometimes ___ No ___</td>
</tr>
<tr>
<td>10. How LOW does your blood glucose need to go before you think you should not drive?</td>
<td>____ mg/dL</td>
</tr>
<tr>
<td>11. How many times have you had your blood glucose below 70 mg/dL while driving?</td>
<td>Since the last visit ______ times, In the last year ______ times</td>
</tr>
<tr>
<td>12. If you take insulin, do you have a glucagon emergency kit?</td>
<td>Yes___/ No ___</td>
</tr>
<tr>
<td>13. Does a spouse, relative, or other person close to you know how to administer glucagon?</td>
<td>Yes___/ No ___</td>
</tr>
</tbody>
</table>

Table 3—Hypoglycemia Provider Checklist

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>First</th>
<th>Middle</th>
<th>Last</th>
<th>Today’s date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>__</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>__</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>__</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>__</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>__</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>__</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. __Reviewed the Hypoglycemia Patient Questionnaire
2. __Questioned the patient about circumstances surrounding severe or moderate hypoglycemia
3. __Discussed strategies to avoid hypoglycemia with the patient
4. __Made medication changes where clinically appropriate
5. __Recommended carrying snack and/or glucose tablets where appropriate and provided instructions for how to use them (take 15 g glucose, wait 1.5 min, and remeasure blood glucose; repeat if hypoglycemia persists). A 1-page patient handout on treating hypoglycemia is available at http://clinical.diabetesjournals.org/content/30/1/38
6. __Prescribed glucagon if appropriate
Steps to reduce hypoglycemia

• Re-evaluate glycemic goals

• Educate patient on when to anticipate, how to recognize hypoglycemia, how to avoid hypoglycemia, and appropriate treatment of hypoglycemia

• Review insulin/secretagogue regimen, especially with respect to timing of administration and selection of dose
Improved Biomedical and Psychological Outcomes 1 Year After Structured Education in Flexible Insulin Therapy for People With Type 1 Diabetes

The U.K. DAFNE experience

- Retrospective analysis of data collected before and 1 year after attendance at 5 day DAFNE (Dose Adjusted for Normal Eating) course at one of 31 centers in UK
- 1163 eligible subjects
- Complete data available for 639 (54.9%) from 29 centers
### Hypoglycemia awareness status and severe hypoglycemia rates at enrollment and 1 year post-DAFNE

<table>
<thead>
<tr>
<th>Baseline</th>
<th>n</th>
<th>Status at 1 Year</th>
<th>SH pre-DAFNE</th>
<th>SH post-DAFNE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aware</td>
<td>Impaired</td>
<td>No Data</td>
</tr>
<tr>
<td>Aware</td>
<td>324</td>
<td>202 (62)</td>
<td>81 (25)</td>
<td>41 (13)</td>
</tr>
<tr>
<td>Impaired Awareness</td>
<td>215</td>
<td>92 (43)</td>
<td>97 (45)</td>
<td>26 (12)</td>
</tr>
<tr>
<td>All</td>
<td>539</td>
<td>294 (54)</td>
<td>178 (33)</td>
<td>67 (12)</td>
</tr>
</tbody>
</table>

Data are n (% of people in each category at baseline and follow-up, together with self-reported mean number of severe hypoglycemic (SH) episodes per subject for the year preceding DAFNE attendance and for 1st year post-DAFNE. *P<0.05 for comparison of pre- and post-DAFNE mean data.

How does hypoglycemia affect the brain in patients with diabetes?

A. Hypoglycemia is associated with dementia
B. Hypoglycemia can cause seizures and coma
C. Hypoglycemia may alter brain development in children
D. Hypoglycemia alters glucose sensing in the brain
E. All of the above
Conclusions

- Severe hypoglycemia has adverse effects on the growing brain
- ER visits for severe hypoglycemia in adults can be linked to dementia in future but cause/effect is uncertain
- Recurrent hypoglycemia leads to impaired awareness of hypoglycemia
- Clinicians need to work with patients to minimize hypoglycemia in insulin treated patients with diabetes
Technology To The Rescue

Robert A. Viggersky, MD
Professor, Uniformed Services University of the Health Sciences
Medical Director, Medtronic Diabetes
Director Emeritus, Diabetes Institute
Walter Reed National Military Medical Center
Outline

1. Impact of continuous CSII and CGM systems on the frequency and severity of hypoglycemia (including nocturnal)
   - Retrospective and real-time CGM
   - Sensor-augmented pumping
   - Artificial pancreas systems
     - Low glucose threshold suspend
     - Predictive low glucose suspend
     - Single vs. dual hormone systems

2. Impact of technology on fear of hypoglycemia

3. Do the health economics justify technology to mitigate hypoglycemia?
   - Cost of hypoglycemia
A question for you

Do you use technology to reduce the impact of hypoglycemia in your daily practice?

- Yes
- No
Do you use technology to reduce the impact of hypoglycemia in your daily practice?

- Yes: 81.08%
- No: 18.92%
Impact of continuous CSII and CGM systems on the frequency and severity of hypoglycemia (including nocturnal)

- Retrospective and real-time CGM
  - Sensor-augmented pumping
  - Artificial pancreas systems
    - Low glucose threshold suspend
    - Predictive low glucose suspend
    - Single vs. dual hormone systems

Impact of technology on fear of hypoglycemia

Do the health economics justify technology to mitigate hypoglycemia?

- Cost of hypoglycemia
(2001) Kaufman Study: Retrospective CGM captures excursions missed by BG meters

Study Design

- Study Duration: 6 months
- N: 47 pediatrics with type 1 Diabetes (A1C > 8.6%±1.6), intensive insulin therapy
- 3-day Retrospective CGM evaluation and BG Meter Readings
- Compared highs and lows identified with CGM versus BG

Outcome

191 Number of Glucose Excursions Identified

- Overall
  - Retrospective CGM: 42
  - BG Meter: 72
- Night-time
  - Retrospective CGM: 10

Retrospective CGM revealed up to 7x more night-time excursions than BG meters

(2001) Kaufman Study: Retrospective CGM helped guide bolus/basal therapy modifications

Additional Outcome

- Clinicians used CGM data to adjust and optimize therapy

Clinician Directed Change

- Basal or Long-acting Insulin: 80%
- Bolus or Rapid-acting Insulin: 70%
- Hypo treatment: 60%
- Correction Algorithm: 50%
- for Dawn Phenomenon: 40%
- for High Fat Meals: 30%
- for High Glycemic Foods: 20%

108 patients with T2D
Rates and patterns of hypoglycemia were calculated
Patient and medication factors were correlated with rates, timing, and severity of hypoglycemia

Results
49.1% had at least 1 hypoglycemic episode and 75% of them had at least 1 asymptomatic episode
CGM analysis resulted in treatment modifications in 64% of the patients

Nearly 50% of T2D patients had hypoglycemia; most of which was asymptomatic.

Table 4. Hypoglycemic Severity and Hypoglycemia Awareness in Patients with Hypoglycemic Episodes

<table>
<thead>
<tr>
<th>Hypoglycemic severity</th>
<th>n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>27 (50.9)</td>
<td>0.009a</td>
</tr>
<tr>
<td>Severe</td>
<td>11 (20.7)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>15 (28.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypoglycemia awareness</th>
<th>n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>13 (24.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>40 (75.4)</td>
<td></td>
</tr>
</tbody>
</table>

aComparison was between mild and severe hypoglycemia. There were more episodes of mild than severe hypoglycemia.

Table 6. Distribution of Patients with Hypoglycemia by Treatment Groups

<table>
<thead>
<tr>
<th>Insulin</th>
<th>n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>35 (66)</td>
<td>0.02</td>
</tr>
<tr>
<td>Noninsulin</td>
<td>18 (34)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypoglycemia-causing agents</th>
<th>n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>43 (81.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>10 (18.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of hypoglycemic agents</th>
<th>n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only 1</td>
<td>20 (37.7)</td>
<td>0.073</td>
</tr>
<tr>
<td>2 or more</td>
<td>23 (43.4)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10 (18.9)</td>
<td></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
CGM reduces A1C with no change in hypoglycemia/
reduces hypoglycemia with no change in A1C

Continuous Glucose Monitoring: Evidence and Consensus Statement for Clinical Use

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

Impact of continuous CSII and CGM systems on the frequency and severity of hypoglycemia (including nocturnal)

- Retrospective and real-time CGM
- Sensor-augmented pumping
- Artificial pancreas systems
  - Low glucose threshold suspend
  - Predictive low glucose suspend
  - Single vs. dual hormone systems

Impact of technology on fear of hypoglycemia

Do the health economics justify technology to mitigate hypoglycemia?

- Cost of hypoglycemia
Sensor-Augmented Pumping Reduces A1C without Increasing 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*

<table>
<thead>
<tr>
<th>All Patients</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>No. of events</td>
<td>32</td>
<td>27</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>

Outline

1. Impact of continuous CSII and CGM systems on the frequency and severity of hypoglycemia (including nocturnal)
   - Retrospective and real-time CGM
   - Sensor-augmented pumping
   - Artificial pancreas systems
     - Low glucose threshold suspend
     - Predictive low glucose suspend
     - Single vs. dual hormone systems

2. Impact of technology on fear of hypoglycemia

3. Do the health economics justify technology to mitigate hypoglycemia?
   - Cost of hypoglycemia
Threshold-Suspend Pumps Reduce Hypoglycemia in High Risk Patients

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

A Glycated Haemoglobin

<table>
<thead>
<tr>
<th>Threshold-Suspend Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7.26 ± 0.71</td>
<td>≤7.24 ± 0.67</td>
</tr>
<tr>
<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></th>
<th>Threshold-Suspend Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal</td>
<td>1547±2035</td>
<td>980±1200</td>
</tr>
<tr>
<td>Run-in phase</td>
<td>1406±1950</td>
<td>1568±1995</td>
</tr>
</tbody>
</table>

C Sensor Glucose <70 mg/dl

<table>
<thead>
<tr>
<th></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>Run-in phase</td>
<td>1.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Study phase</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Day and Night</td>
<td>3.7</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Percent Threshold - Suspend Group vs. Control Group

Predictive Low Glucose Management

**STOP**

Insulin delivery is suspended to reduce hypoglycemia if sensor glucose is:
- Less than 70 mg/dL above the low limit AND
- Predicted to approach the low limit in 30 minutes

**GO**

Suspended basal insulin delivery can resume if:
- The patient manually resumes OR
- Sensor glucose is above the low limit and trending upward and insulin delivery has been suspended for a minimum of 30 minutes OR
- Insulin delivery has been suspended for 2 hours

Once resumed manually or based on sensor glucose, basal insulin delivery will not be re-suspended for a minimum of 30 minutes.
Predictive Low Glucose Suspend Reduces Nocturnal Hypoglycemias over 42 Days

Predictive Low-Glucose Insulin Suspension Reduces Duration of Nocturnal Hypoglycemias in Children Without Increasing Ketosis

Bruce A. Buckingham,1 Dan Raghinaru,2 Fraser Cameron,1 B. Wayne Bequette,3 H. Peter Chase,1 David M. Maahs,3 Robert Slover,4 R. Paul Wadwa4 Darrell M. Wilson,1 Trang Ly,1 Tandy Aye,1 Irene Hramiak1,2 Cheril Larson,6 Robert Stein,7 Patricia H. Gallego,8 John Lum,7 Judy Sibayan,7 Craig Kollman,7 and Roy W. Beck,7 for the In Home Closed Loop Study Group*

Diabetes Care 2015;38:1197–1204 | DOI: 10.2337/dc14-3053

A

11-14 year olds (N=45)

B

4-10 year olds (N=36)
Recovery from predictive algorithm compared to low glucose suspend

Data on file at Medtronic (from Jan 13th 2015 to Jul 7th 2015)
MD-Logic Overnight Control for 6 Weeks of Home Use in Patients With Type 1 Diabetes: Randomized Crossover Trial

DOI: 10.2337/dc14-0835

Figure 1—Daytime comparison between the closed-loop and SAP group. Mean daytime difference between the closed-loop and SAP groups in different glucose ranges. The striped boxes represent the daytime only (between 0700 and 2300), and the dotted boxes represent the entire day comparison (0000 to 2400). Comparisons were performed using the paired nonparametric Wilcoxon sign rank test.
Dual-Hormone Artificial Pancreas System Reduces Glucose and Hypoglycemia in Adult and Adolescents

Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes

Outline

1. Impact of continuous CSII and CGM systems on the frequency and severity of hypoglycemia (including nocturnal)
   - Retrospective and real-time CGM
   - Sensor-augmented pumping
   - Artificial pancreas systems
     - Low glucose threshold suspend
     - Predictive low glucose suspend
     - Single vs. dual hormone systems

2. Impact of technology on fear of hypoglycemia

3. Do the health economics justify technology to mitigate hypoglycemia?
   - Cost of hypoglycemia
A question for you

How do you think technology can most help patients remove fear of hypoglycemia?

- Cause a reduction of emergency medical treatment
- Encourage an increase of self-monitoring of blood glucose
- Increased quality of life
- Provide an overall treatment satisfaction
- All of the above
How do you think technology can most help patients remove fear of hypoglycemia?

- Cause a reduction of emergency medical treatment: 5.88%
- Encourage an increase of self-monitoring of blood glucose: 0%
- Increased quality of life: 2.94%
- Provide an overall treatment satisfaction: 0%
- All of the above: 91.18%
CGM Reduces Fear of Hypoglycemia and Emergency Treatment

Impact of Frequent and Persistent Use of Continuous Glucose Monitoring (CGM) on Hypoglycemia Fear, Frequency of Emergency Medical Treatment, and SMBG Frequency After One Year

James J. Chamberlain, MD¹, Dana Dopita, RN, MSN, CDE¹, Emily Gilgen, RD, CD, CDE¹, and Annie Neuman, MPA, PA-C¹

---

**Figure 1:** Impact of CGM on Hypoglycemia Fear

- **During Year Prior to CGM Use**
  - Most of the Time: 20 (34.5%)
  - Frequently: 25 (43.1%)
  - Occasionally: 10 (17.2%)
  - Rarely: 3 (5.2%)
  - Never: 0 (0.0%)

- **After 1 Year of CGM Use**
  - Most of the Time: 1 (1.7%)
  - Frequently: 1 (1.7%)
  - Occasionally: 13 (22.4%)
  - Rarely: 4 (6.9%)

**Figure 2:** Mean Events per Respondent

- **During Year Prior to CGM Use**
  - 0.4 ± 0.9

- **After 1 Year of CGM Use**
  - 0.1 ± 0.3

*p=0.0013*
### Health-Related Quality of Life and Treatment Satisfaction in the Sensor-Augmented Pump Therapy for A1C Reduction 3 (STAR 3) Trial

Richard R. Rubin, Ph.D.,1,2 and Mark Peyrot, Ph.D.,1,3 for the STAR 3 Study Group*

<table>
<thead>
<tr>
<th>Measure</th>
<th>SAPT (n=166)</th>
<th>MDI (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypoglycemia Fear Survey</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia Worry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21.94</td>
<td>21.52</td>
</tr>
<tr>
<td>Week 52 Change</td>
<td>-6.36**</td>
<td>-1.87</td>
</tr>
<tr>
<td><strong>Hypoglycemia Avoidant Behavior</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>16.38</td>
<td>16.70</td>
</tr>
<tr>
<td>Week 52 Change</td>
<td>-2.30**</td>
<td>-0.52</td>
</tr>
</tbody>
</table>

*P<0.001. Diab Tech Ther 14: 143-141, 2012.

Sensor-Augmented Pumping Improves Quality of Life and Treatment Satisfaction
1. Impact of continuous CSII and CGM systems on the frequency and severity of hypoglycemia (including nocturnal)
   - Retrospective and real-time CGM
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     - Low glucose threshold suspend
     - Predictive low glucose suspend
     - Single vs. dual hormone systems

2. Impact of technology on fear of hypoglycemia

3. Do the health economics justify technology to mitigate hypoglycemia?
   - Cost of hypoglycemia
Economic Costs of Diabetes in the U.S. in 2012

$245 billion = $176 billion in direct medical costs and $69 billion in reduced productivity


*Numbers do not necessarily sum to totals because of rounding.

Table 9. Indirect Burden of Diabetes in the U.S., 2012 (in millions of dollars)

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Productivity Loss</th>
<th>Total Cost Attributable to Diabetes ($)</th>
<th>Proportion of Indirect Costs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workdays absent</td>
<td>25 million days</td>
<td>5.0</td>
<td>7%</td>
</tr>
<tr>
<td>Reduced performance at work</td>
<td>113 million days</td>
<td>20.8</td>
<td>30%</td>
</tr>
<tr>
<td>Reduced productivity days for those not in labor force</td>
<td>20 million days</td>
<td>2.7</td>
<td>4%</td>
</tr>
<tr>
<td>Reduced labor force participation due to disability</td>
<td>130 million days</td>
<td>21.6</td>
<td>31%</td>
</tr>
<tr>
<td>Mortality</td>
<td>246,000 deaths</td>
<td>18.5</td>
<td>27%</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>68.6</td>
<td>100%</td>
</tr>
</tbody>
</table>
Effect of hypoglycemia on treatment discontinuation

Having experienced ≥1 hypoglycemia event in a given 6-month interval was associated with 26% increased likelihood of antidiabetic treatment discontinuation (P<0.0001).

All cause and diabetes related annual health care costs were significantly higher in those who had moderate-severe hypoglycemia (P<0.0001).

<table>
<thead>
<tr>
<th>Annual Health Care Cost</th>
<th>Patients With Hypoglycemia (N=4860)</th>
<th>Patients Without Hypoglycemia (N=207 201)</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>A - B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Descriptive analysis, mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Total drug cost, $</th>
<th>Diabetes-related²</th>
<th>Total medical cost, $</th>
<th>Diabetes-related³</th>
<th>Total cost, $</th>
<th>Diabetes-related³</th>
</tr>
</thead>
<tbody>
<tr>
<td>All drugs</td>
<td>2725</td>
<td>691</td>
<td>11306</td>
<td>6321</td>
<td>14031</td>
<td>7012</td>
</tr>
<tr>
<td>Diabetes-related²</td>
<td>2673</td>
<td>742</td>
<td>6334</td>
<td>2523</td>
<td>9007</td>
<td>3265</td>
</tr>
<tr>
<td>Difference</td>
<td>53</td>
<td>-51</td>
<td>4972</td>
<td>3798</td>
<td>5024</td>
<td>3747</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.2394</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Based on generalized linear models, estimated mean³

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**Hypoglycemia, Treatment Discontinuation, and Costs in Patients with Type 2 Diabetes Mellitus on Oral Antidiabetic Drugs**

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Impact of continuous CSII and CGM systems on the frequency and severity of hypoglycemia (including nocturnal)

- Retrospective and real-time CGM
- Sensor-augmented pumping
- Artificial pancreas systems
  - Low glucose threshold suspend
  - Predictive low glucose suspend
  - Single vs. dual hormone systems

Impact of technology on fear of hypoglycemia

Do the health economics justify technology to mitigate hypoglycemia?

- Cost of hypoglycemia
QUESTIONS FOR OUR PANEL

Submit a question on the iPad or raise your hand to ask a question
Do we need a new classification for hypoglycemia?

Yes 88.46%
No 11.54%
Do we need separate definitions for different stakeholders such as patients, physicians, trialists, and regulators?

One size: 32.35%
Differing definitions: 67.65%
Wrap-up

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In one or two words, how do you think we can help patients manage hypoglycemia?
thank you!