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

IHSG

Welcome & Introduction

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University of Sheffield
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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

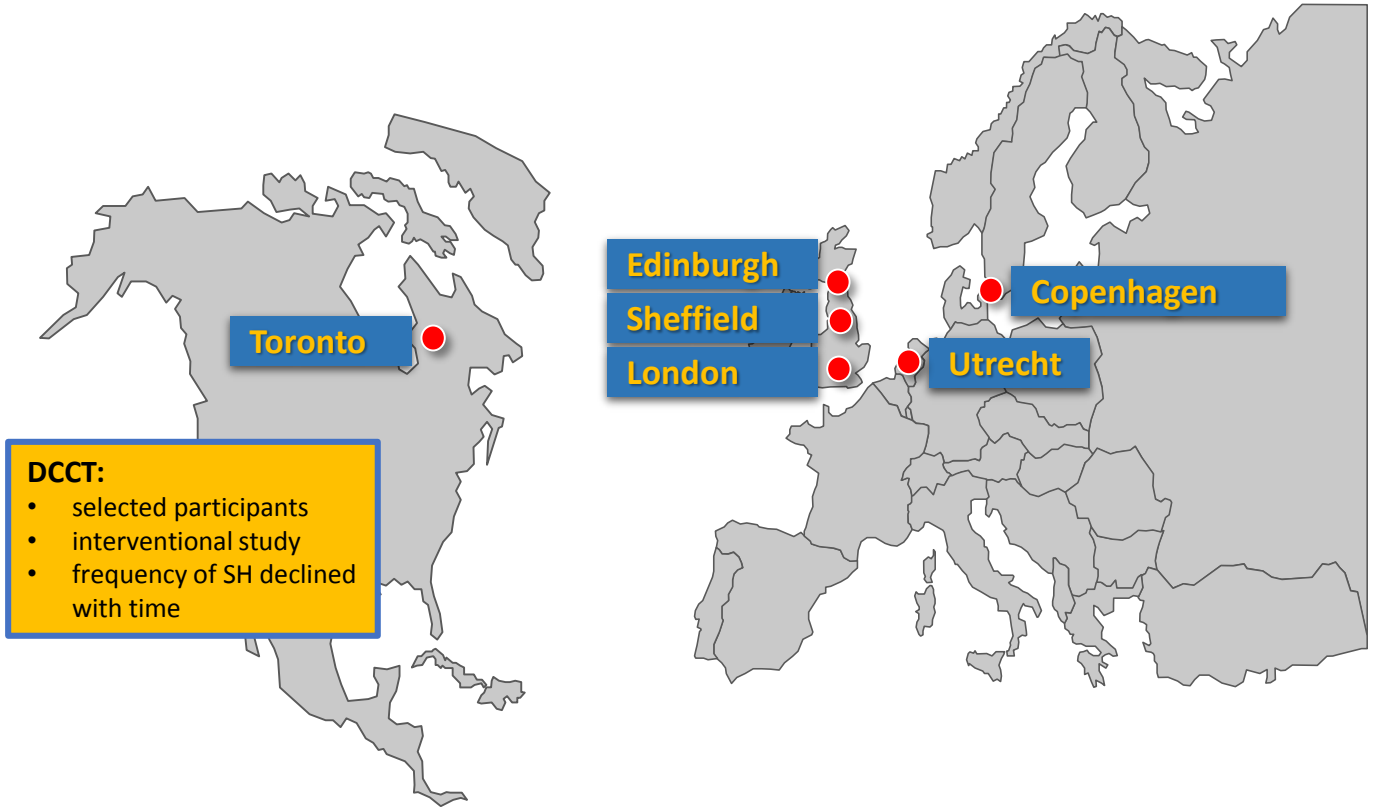
Brian M Frier,

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

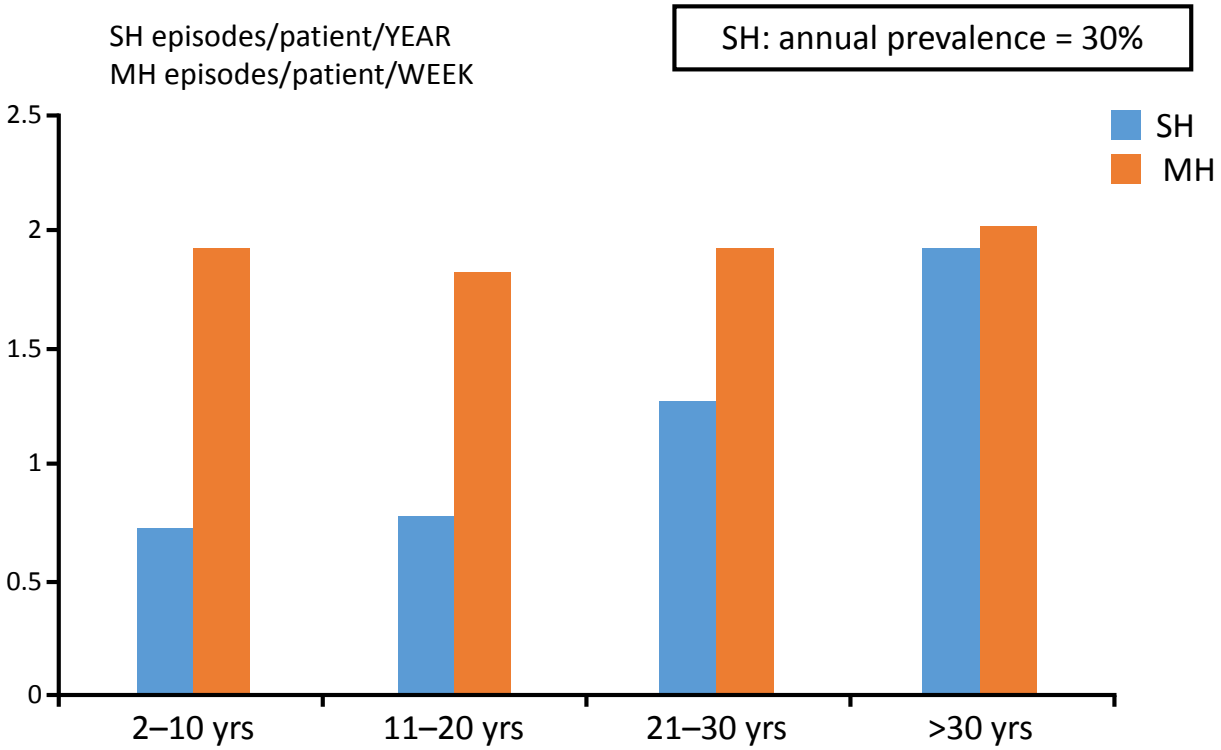
Frequency of severe hypoglycaemia: studies in unselected adult populations with type 1 diabetes



Frequency of severe hypoglycaemia in adults with type 1 diabetes

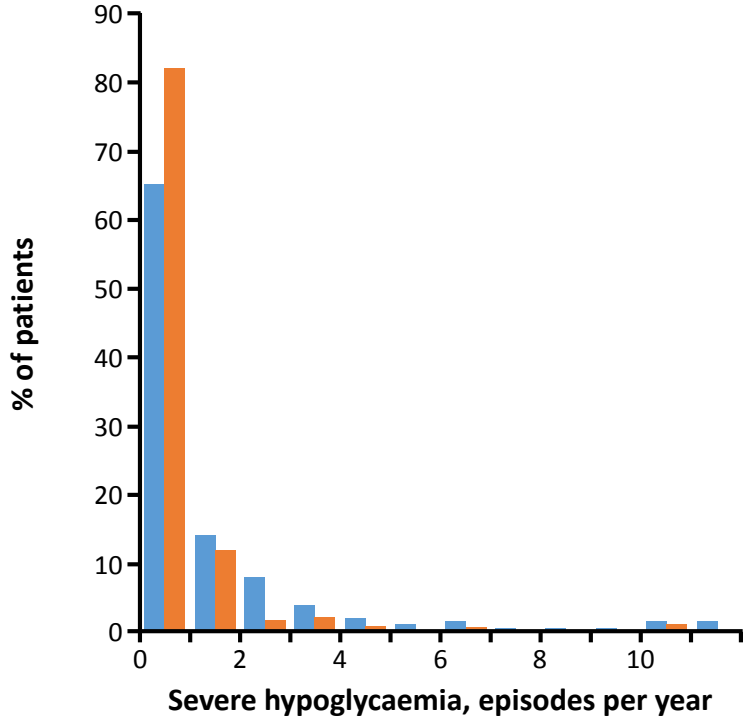
Study	Number of patients	Age (years) median (range) or mean±SD	Follow-up	Frequency (episodes/person/year)	Proportion affected (%)
MacLeod, 1993 (Scotland)	600	41 (14-79)	12 months (R)	1.6	29
ter Braak, 2000 (The Netherlands)	195	41±14	12 months (R)	1.5	41
Pedersen-Bjergaard, 2004 (Denmark)	1076	40 (18-81)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

Incidence of severe hypoglycaemia (SH) and mild hypoglycaemia (MH) in type 1 diabetes



Pedersen-Bjergaard et al (2004) DMRR 20:479

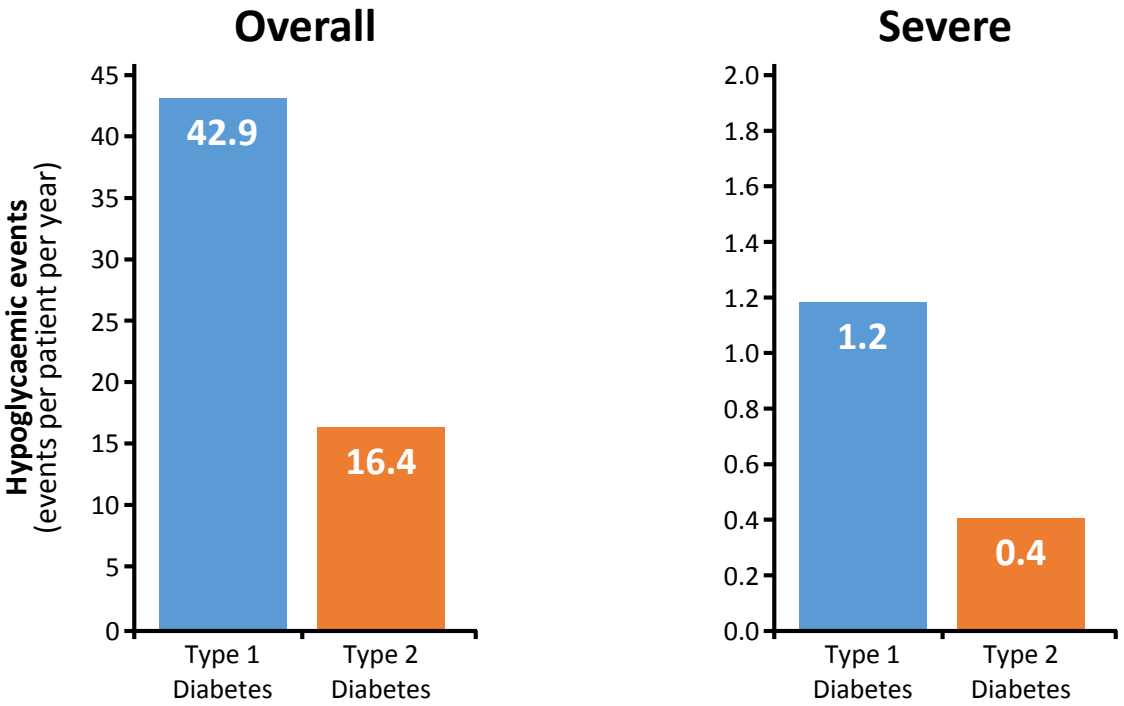
Severe hypoglycaemia in type 1 diabetes



- **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

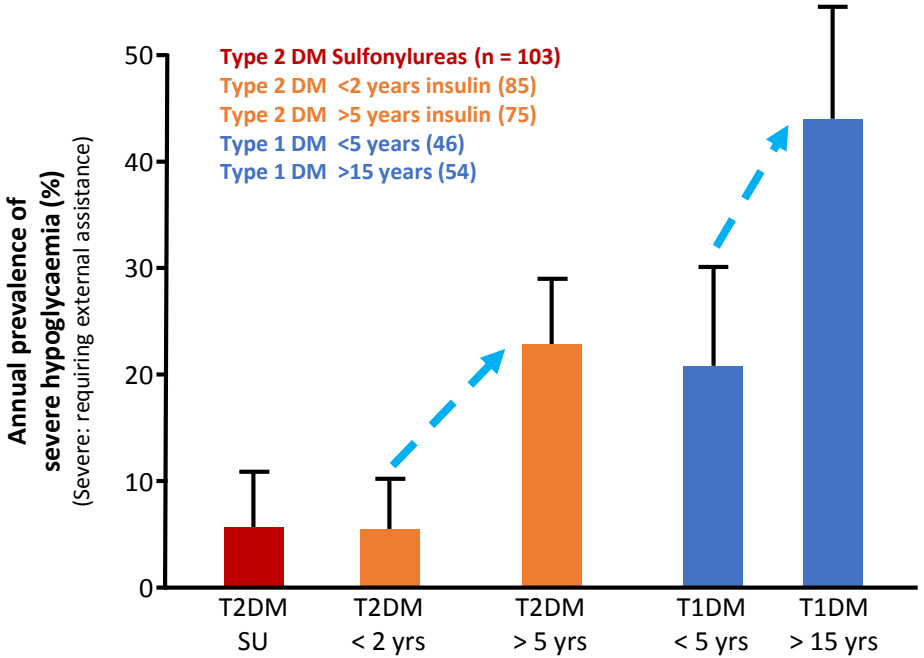
Frequency of hypoglycaemia in type 1 and insulin-treated type 2 diabetes



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

Donnelly et al. Diabet Med 2005; 22: 749–55

Frequency of severe hypoglycaemia in types 1 and 2 diabetes

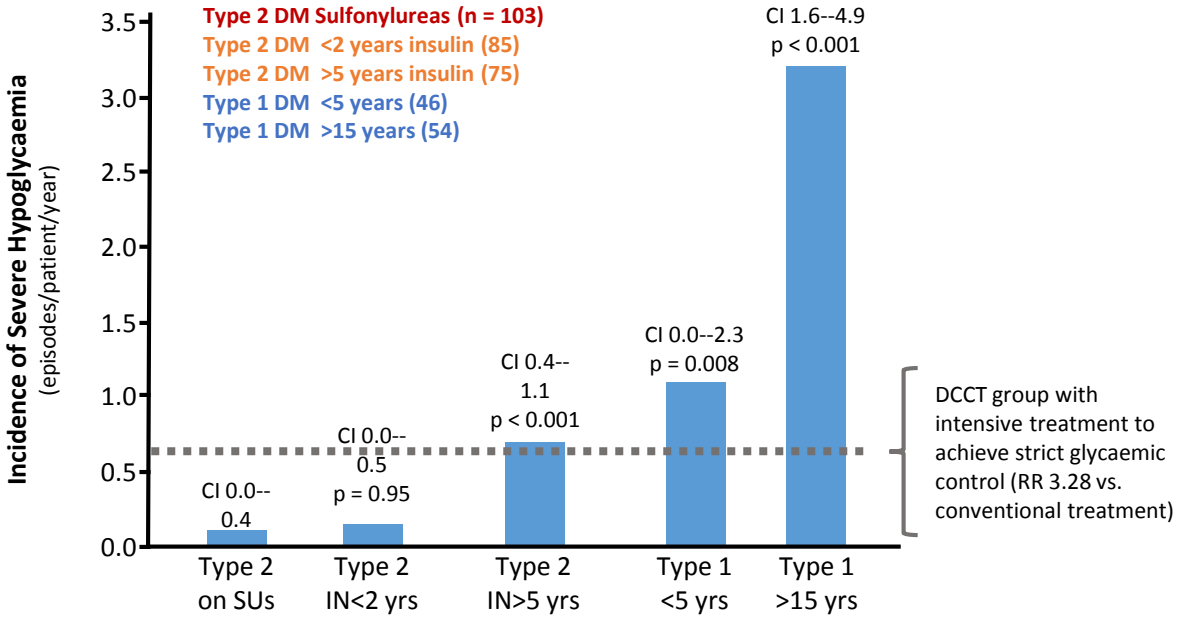


Error bars = 95% confidence intervals

Adapted from: UK Hypoglycaemia Study Group. Diabetologia 2007; 50: 1140-7

Frequency of severe hypoglycaemia in types 1 and 2 diabetes

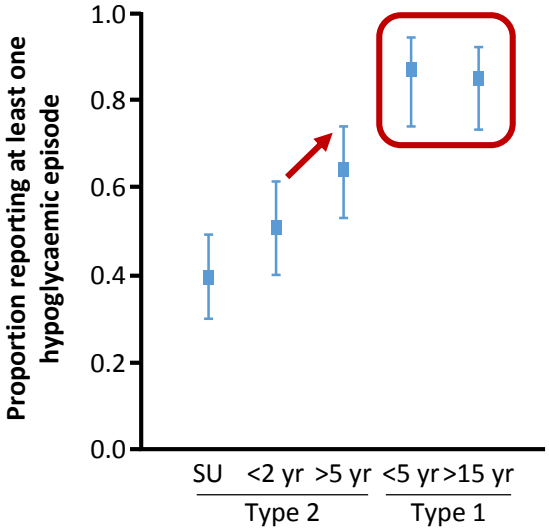
Incidence of severe hypoglycaemia



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

UK Hypoglycaemia Study Group. Diabetologia. 2007;50:1140–1147
Diabetes Control and Complications Research Group. Diabetes. 1997;46:271-286.

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



SU, sulfonylurea; T1D, type 1 diabetes; T2D, type 2 diabetes
UK Hypoglycaemia Study Group. Diabetologia 2007; 50: 1140–7

Self-reported non-severe hypoglycaemic events in Europe

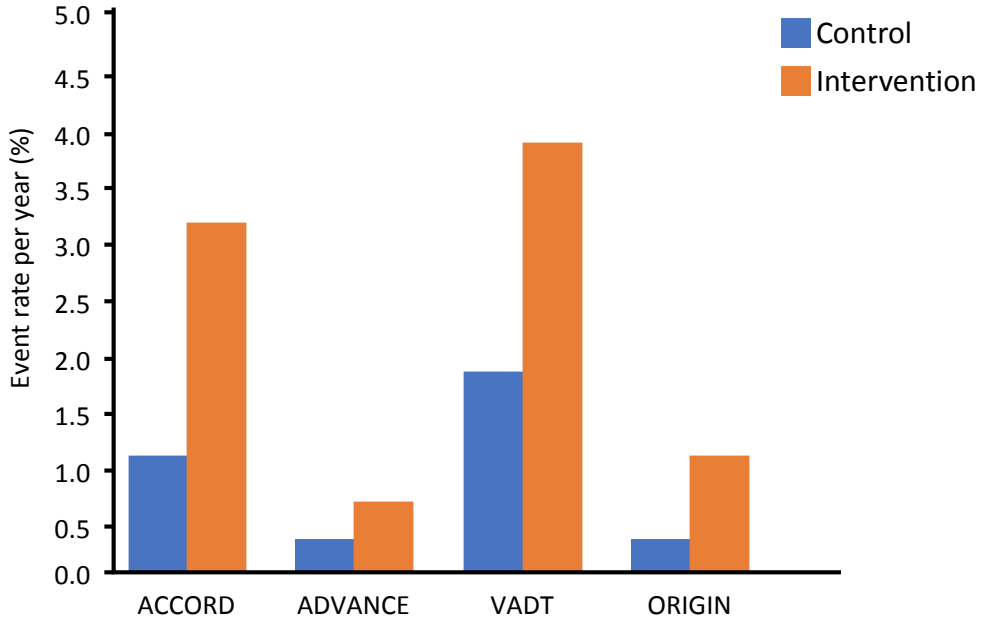
3287 adult respondents in 7 countries; questionnaire survey

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

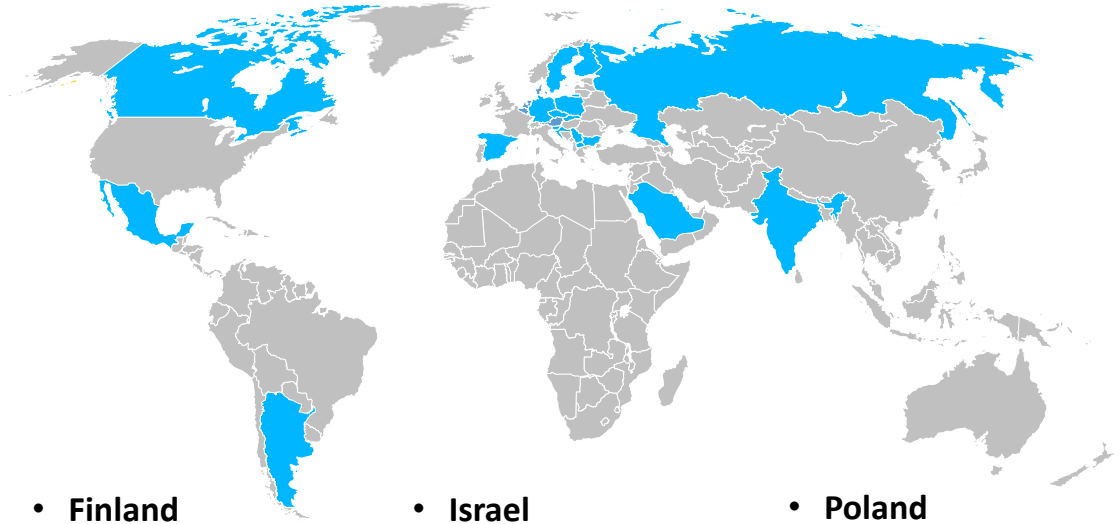
Prevalence of severe hypoglycaemia in type 2 diabetes: major endpoint trials

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



ADVANCE N Engl J Med 2008;358:2560–72; ACCORD N Engl J Med 2008;358;2545–59;
VADT N Engl J Med 2009;360:129–39
ORIGIN, N Engl J Med 2012; 367: 319–328

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

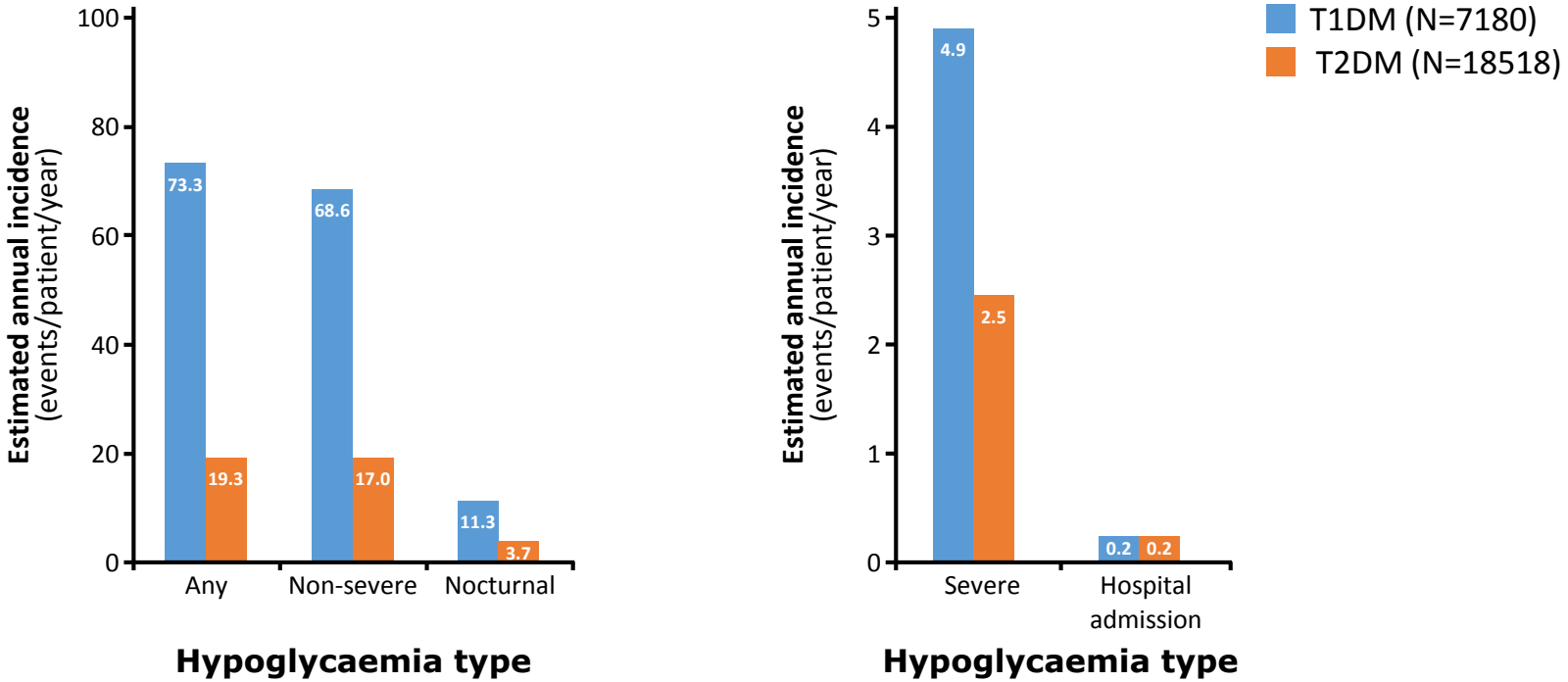
Patient self-reporting:

- 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



Annual incidence: estimated number of events per patient per year

Khunti et al (2014) Abstract at EASD, Vienna

Hypoglycaemia in children

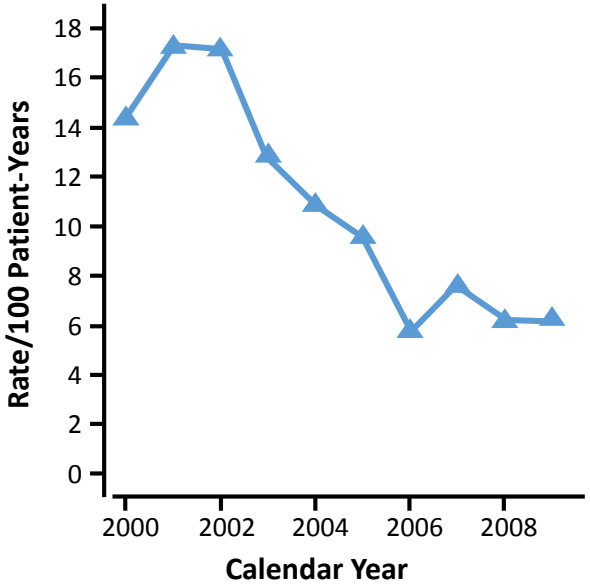
Clinical classification:

- **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

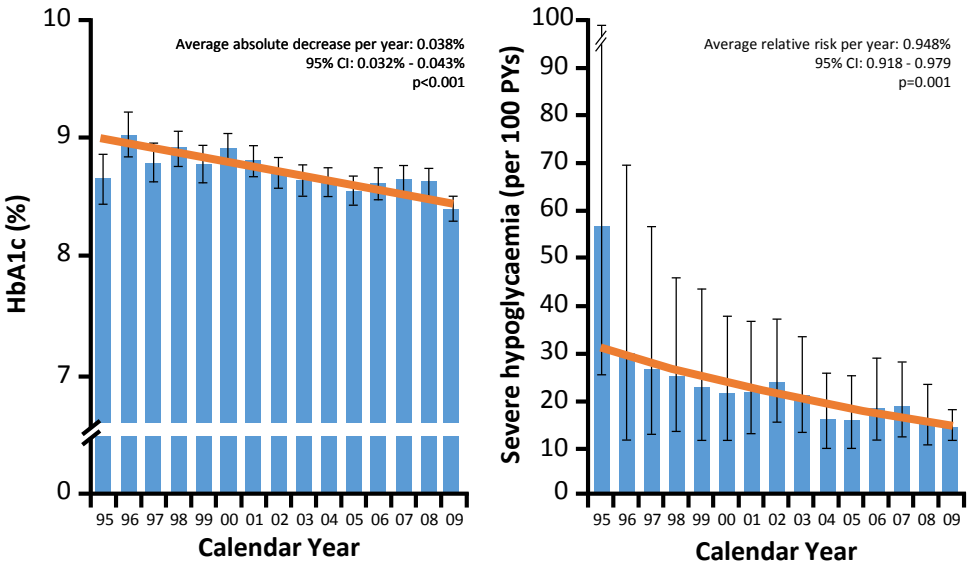
Severe hypoglycaemia in children and adolescents

Western Australia
(1683 patients: 2000-2009)



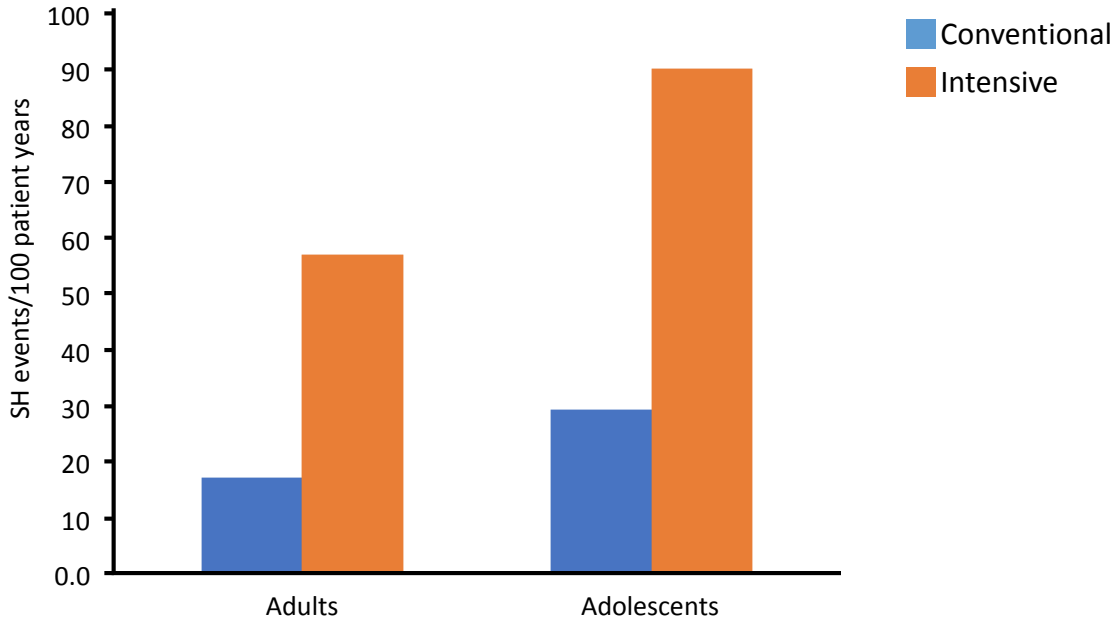
O'Connell et al., Diabetes Care 2011; 34: 2379-80

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



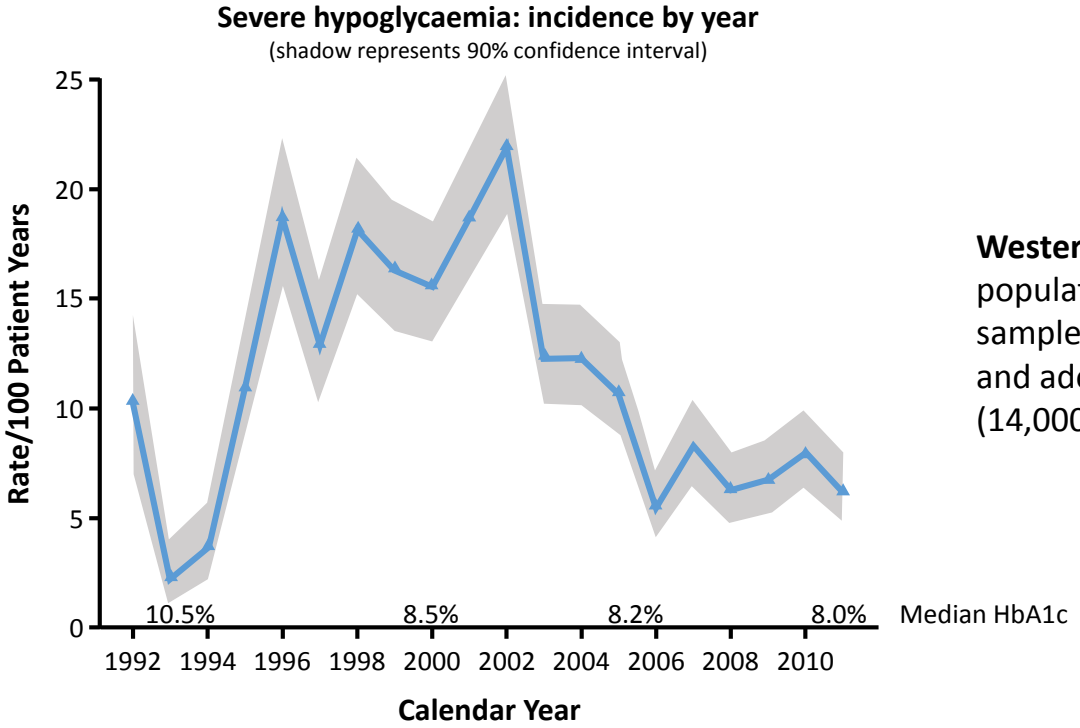
Rosenbauer et al., Diabetes Care 2012; 35: 80-86

Incidence of severe hypoglycaemia: adolescents



DCCT, J Pediatr 1994; 125: 177

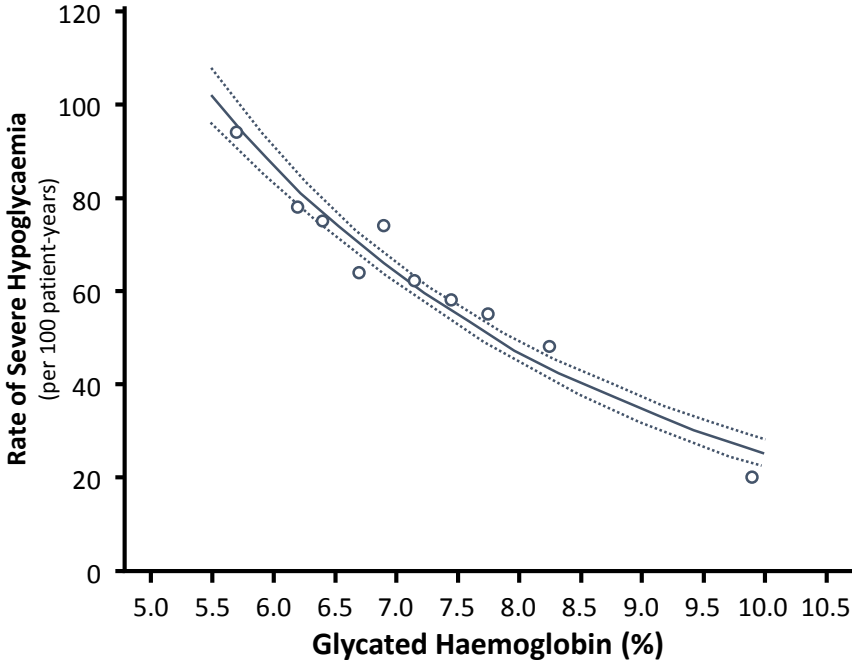
Changes in the frequencies of hypoglycaemia – induced coma and convulsions in youth with type 1 diabetes (1992-2011)



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

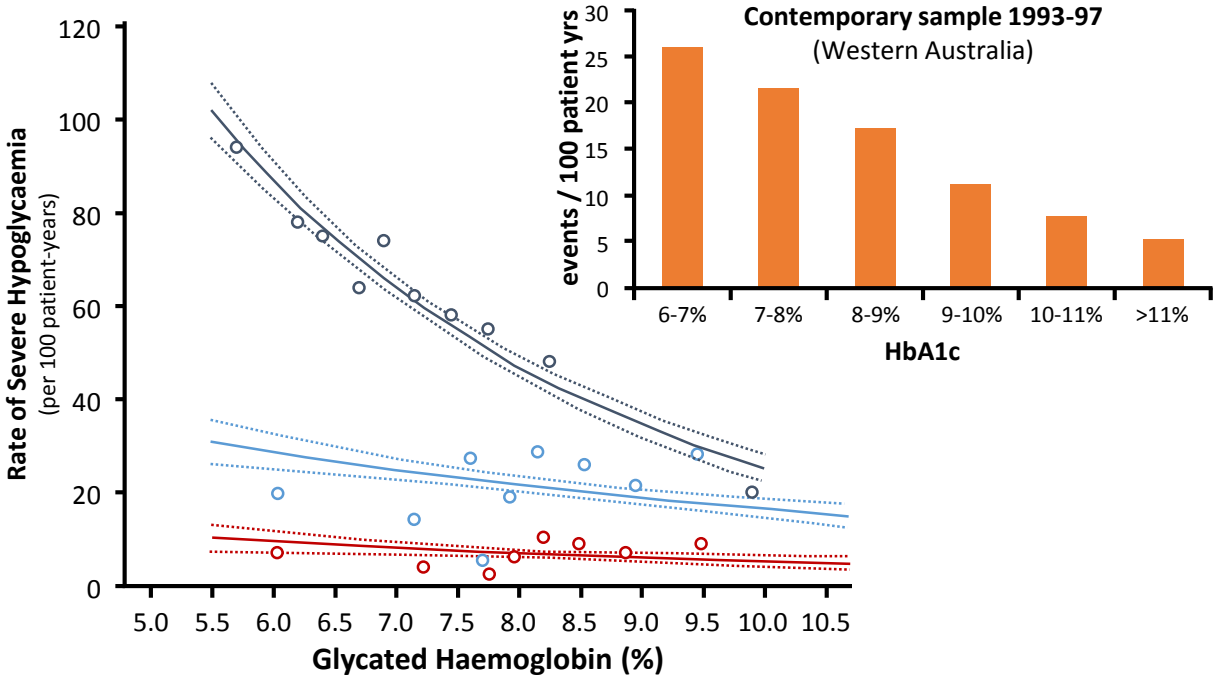
Cooper et al., Diabetologia 2013: 2164-70

DCCT: Severe hypoglycaemia vs HbA1c



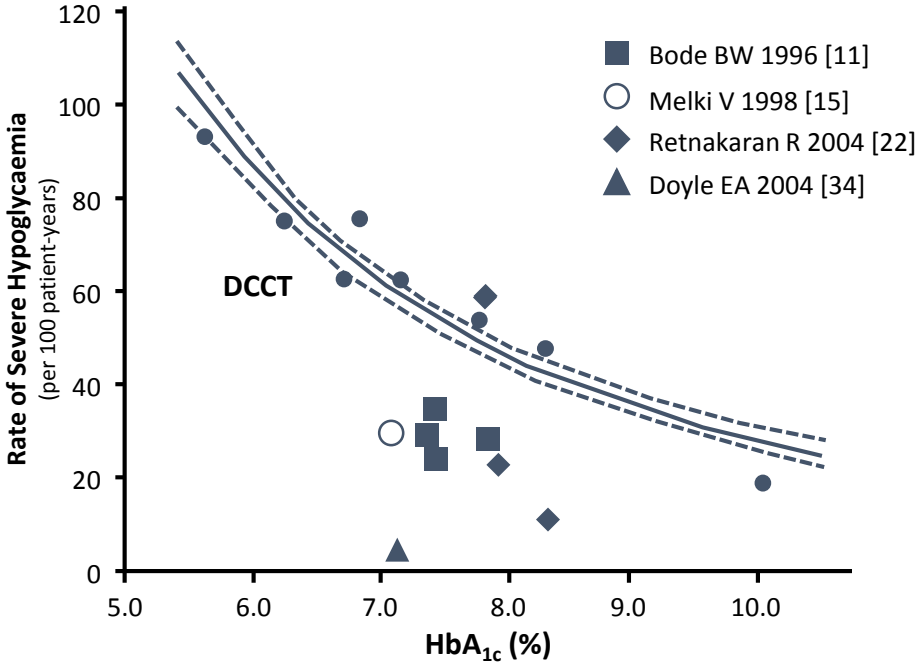
DCCT, N Engl J Med 1993; 329: 977-86

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



Data derived from Cooper et al., Diabetologia 2013: 2164-70

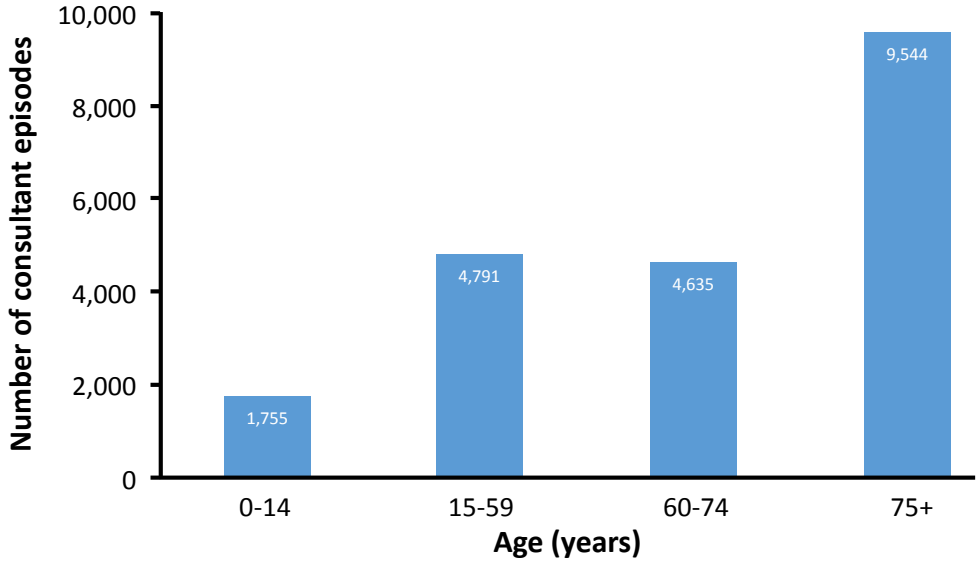
Severe hypoglycaemia vs. HbA1c in adults with type 1 diabetes treated with CSII



Hanaire et al., Diab & Metab 2008; 34: 401-23

Hospital admissions in 12 months because of hypoglycaemia (England & Wales)

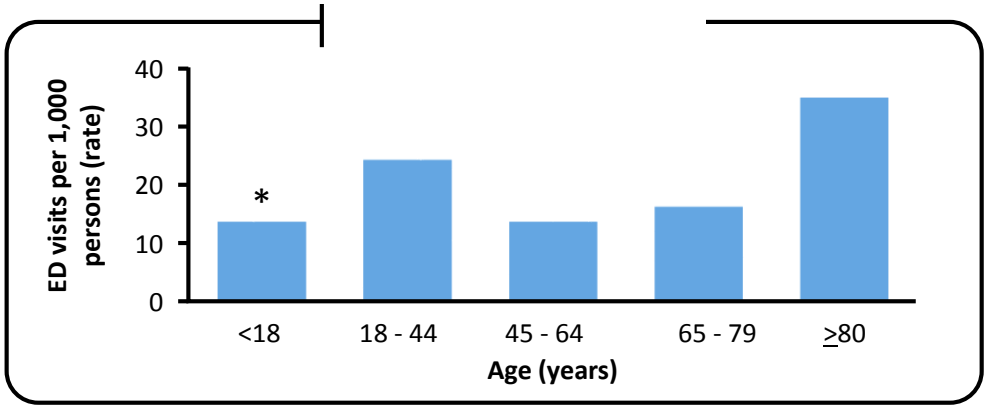
- 14,437 hospital admissions with hypoglycaemia as primary diagnosis
- Mean age: 54 years; mean length of stay: 6 days; total bed days: 76,569
- 8% had type 1 diabetes



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)

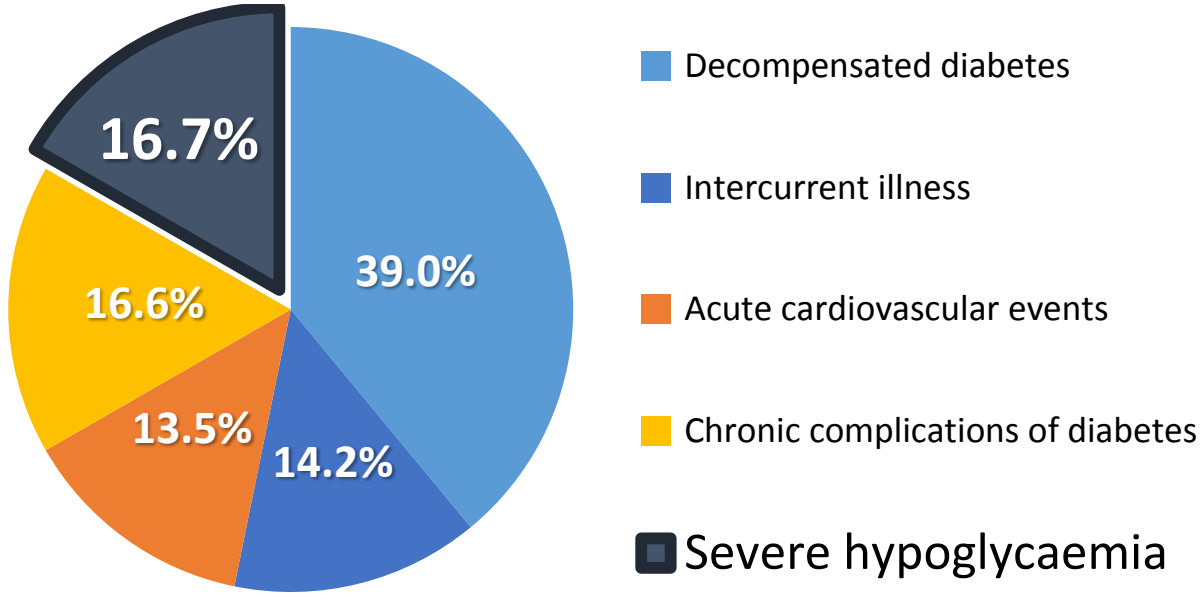


*For persons <18 years the prevalence of diagnosed diabetes was used as a proxy for national estimates of insulin treatment. ED: emergency department; OAD: oral anti-diabetes drug

Geller et al. JAMA Intern Med 2014; 174: 678-86

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

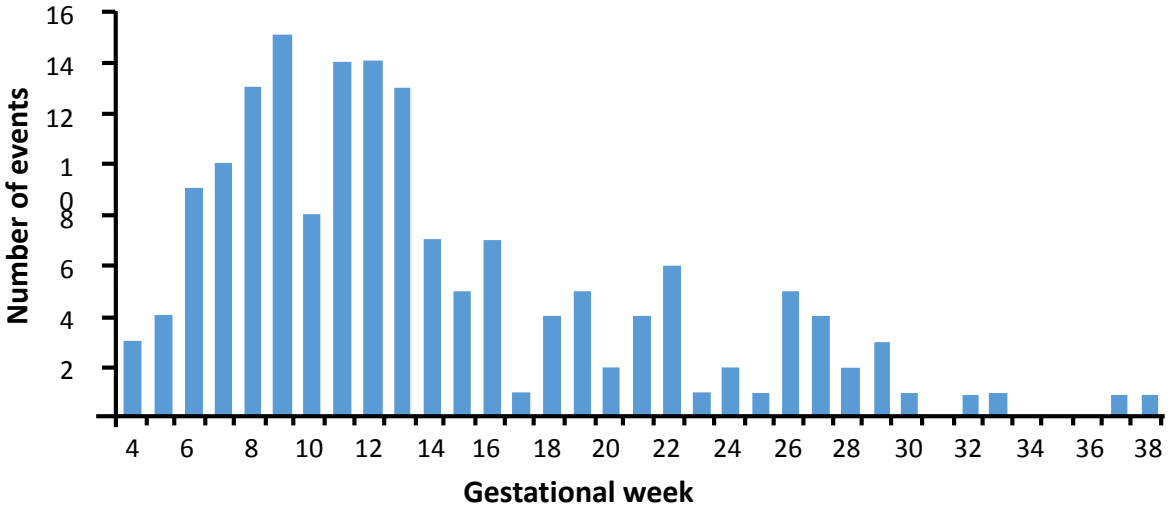
- 17% of hospital admissions were for severe hypoglycaemia



*Subjects aged 80 or over, n=591

Greco et al, Exp Clin Endocrinol Diabetes 2010; 118:215–219

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

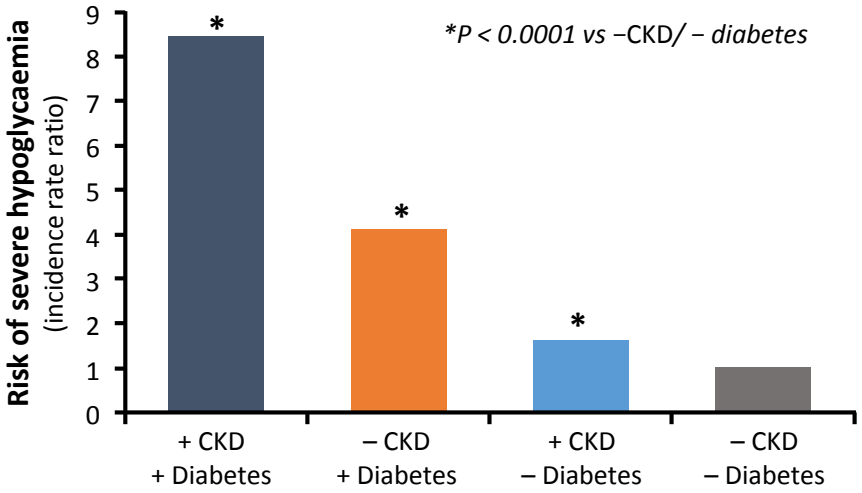


- Severe hypoglycaemia in 45%
- Incidence between 5-6 episodes/patient/year

- 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



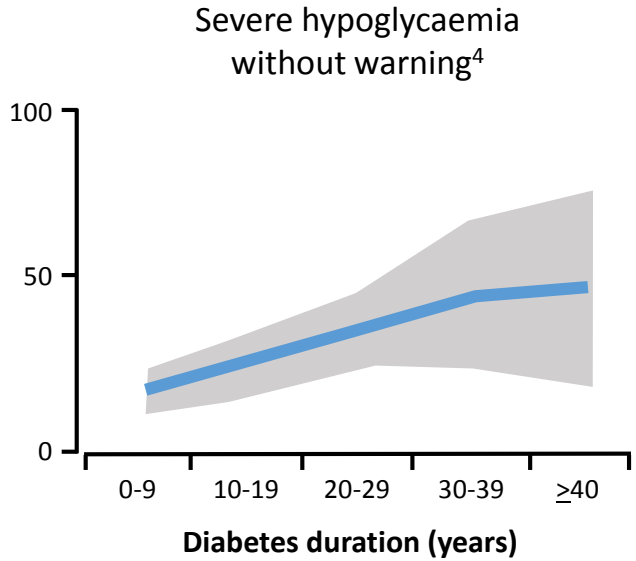
CKD: estimated glomerular flow rate: <60 ml/min per 1.73 m^2
Hypoglycaemia defined as blood glucose <50 mg/dl

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

Moen M et al. Clin J Am Soc Nephrol 2009; 4: 1121–7

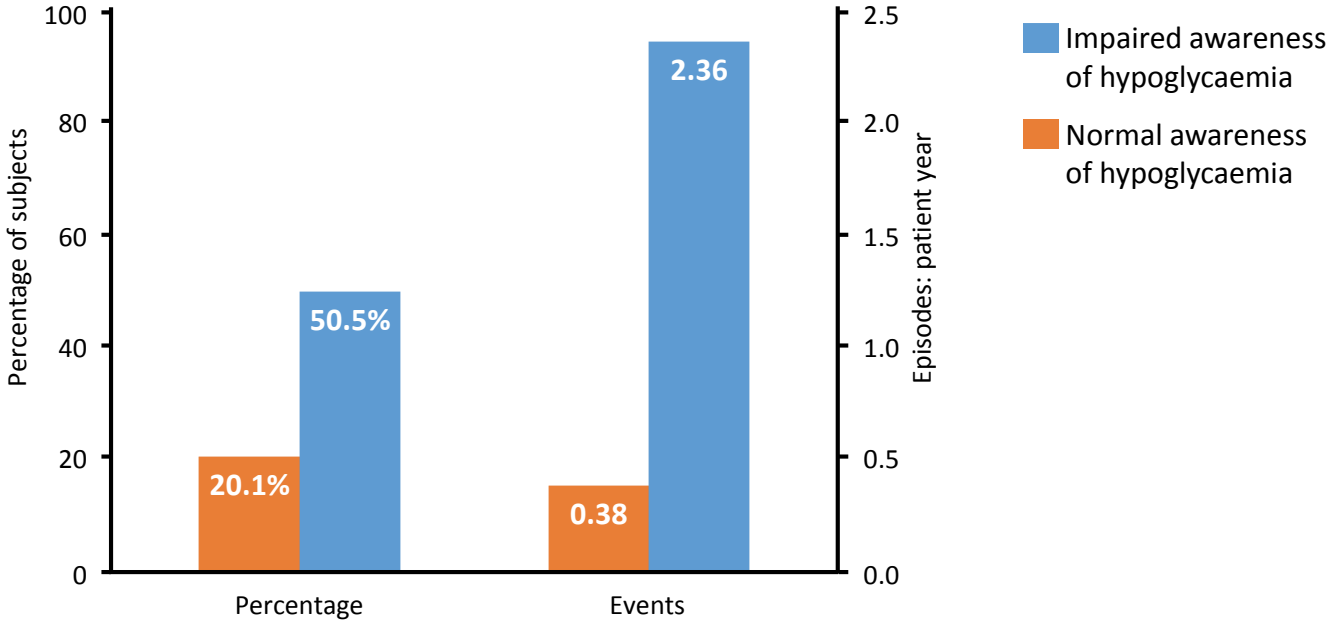
Impaired awareness of hypoglycaemia

- 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



1. Gold et al. Diabetes Care 1994;17:697-703; 2. Geddes et al. Diabetic Med 2008;25: 501–4; 3. Schopman et al. Diab Res Clin Pract 2010;87:64-8; 4. Pramming et al. Diabetic Med 1991;8:217–22

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

Geddes et al. Diabetic Med 2008;25:501-4.

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

Laing et al, (1999) Diabetic Medicine 16: 466

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

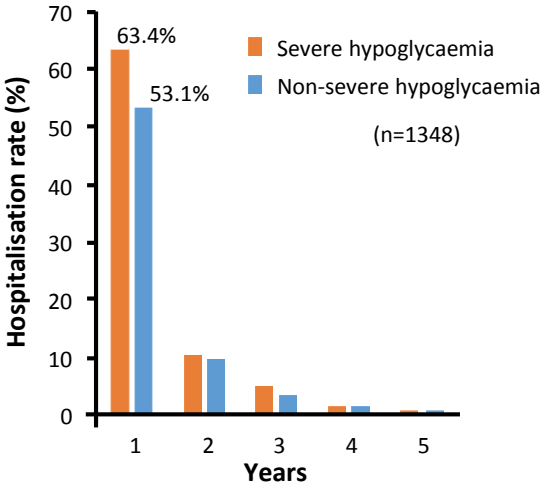
Falls, trauma, head injuries

Driving accidents

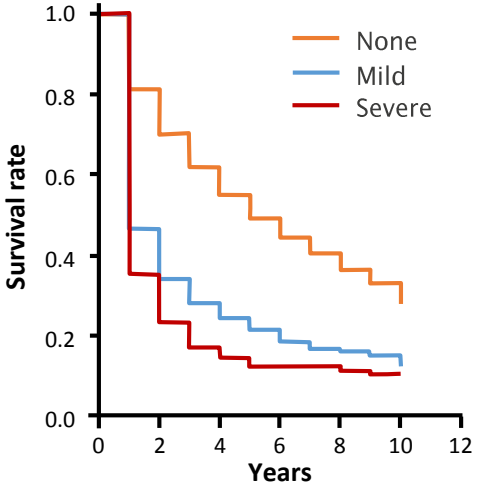
Drowning

Hospitalisation and mortality in relation to history of hypoglycaemia in type 2 diabetes

Hospitalisation rate during follow-up[1]



Survival curves for patients with hypoglycaemia and hospitalisation[1]



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

IHSG

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

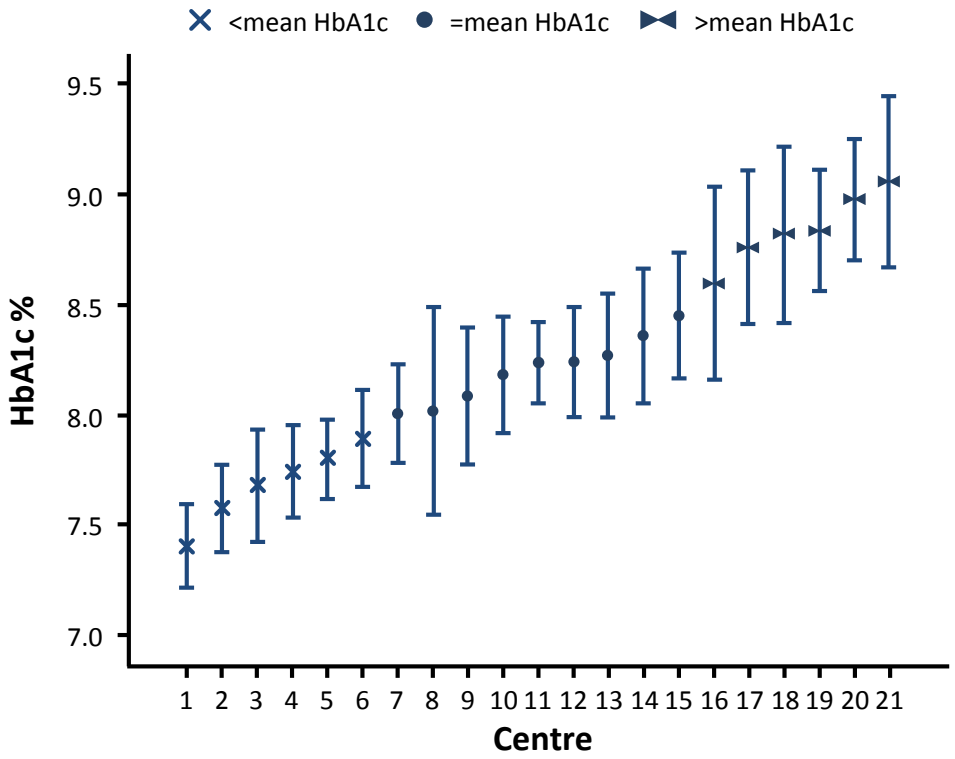
“Avoiding hypoglycaemia at all costs is crucial for some with diabetes”

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

Slomski A , JAMA 309: 2536-7, 2013

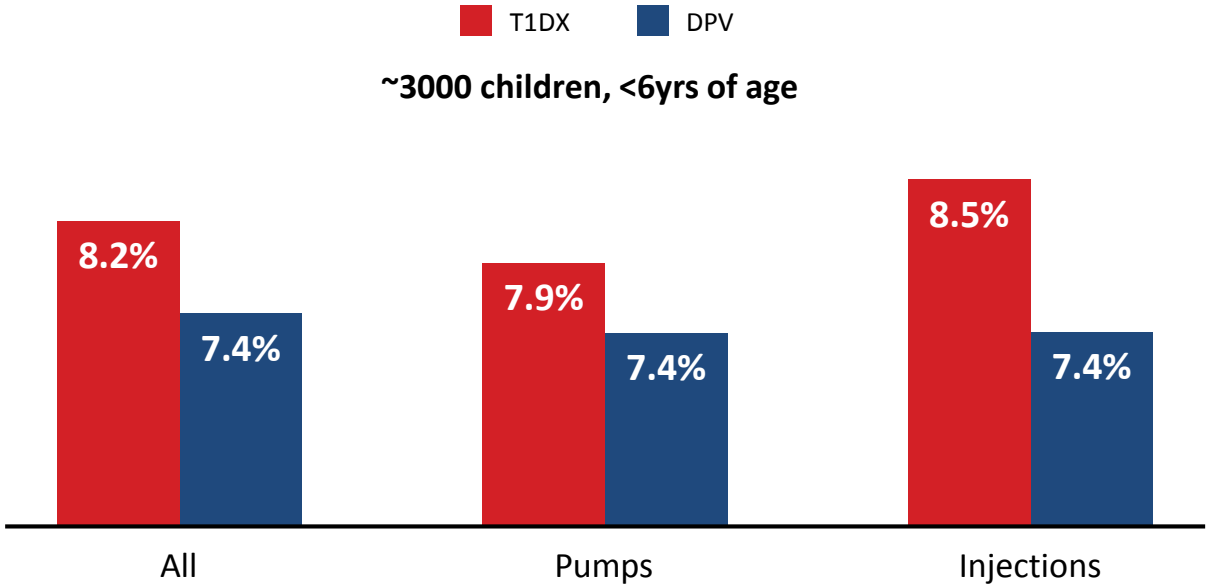
General Value of Targets

Example: Centre differences Hvidore study group, adolescents



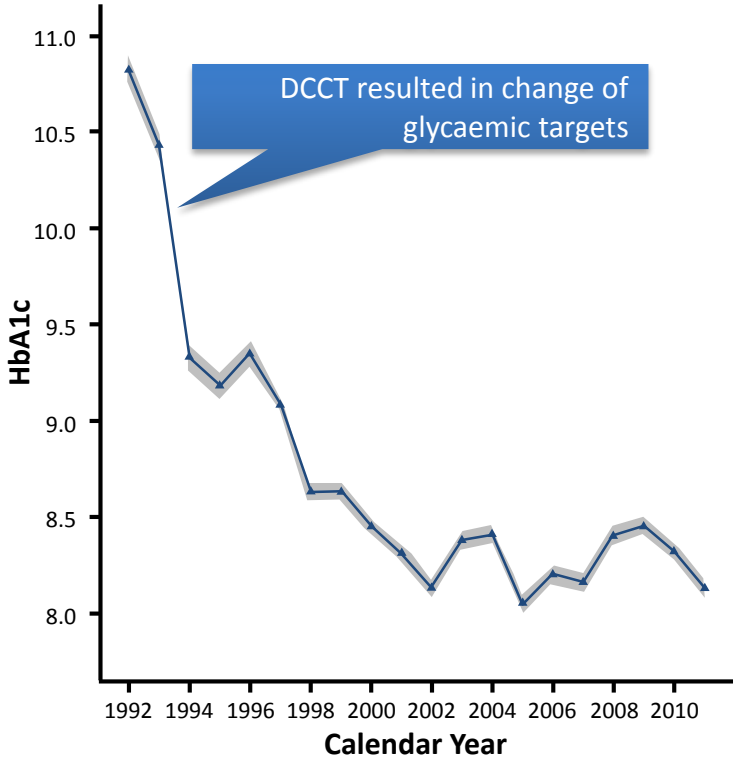
General Value of Targets:

US T1D registry vs German/Austrian dbase



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

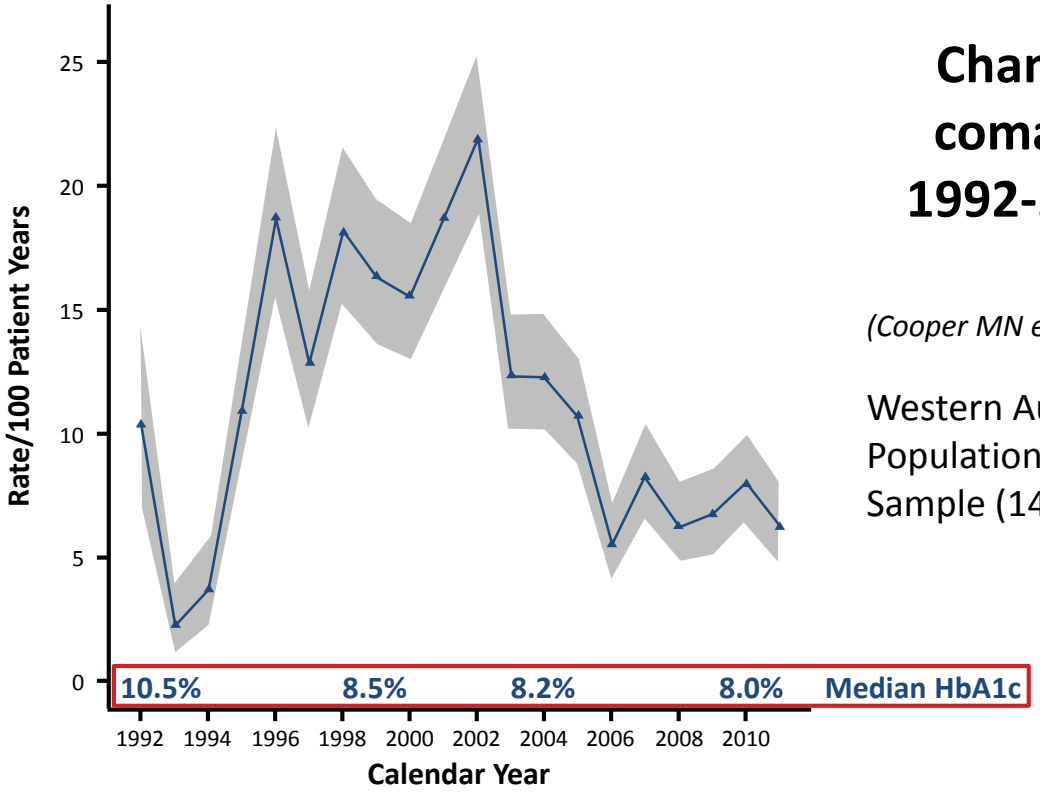
Maahs DM et al, Diabetologia 57:1578-85, 2014



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)

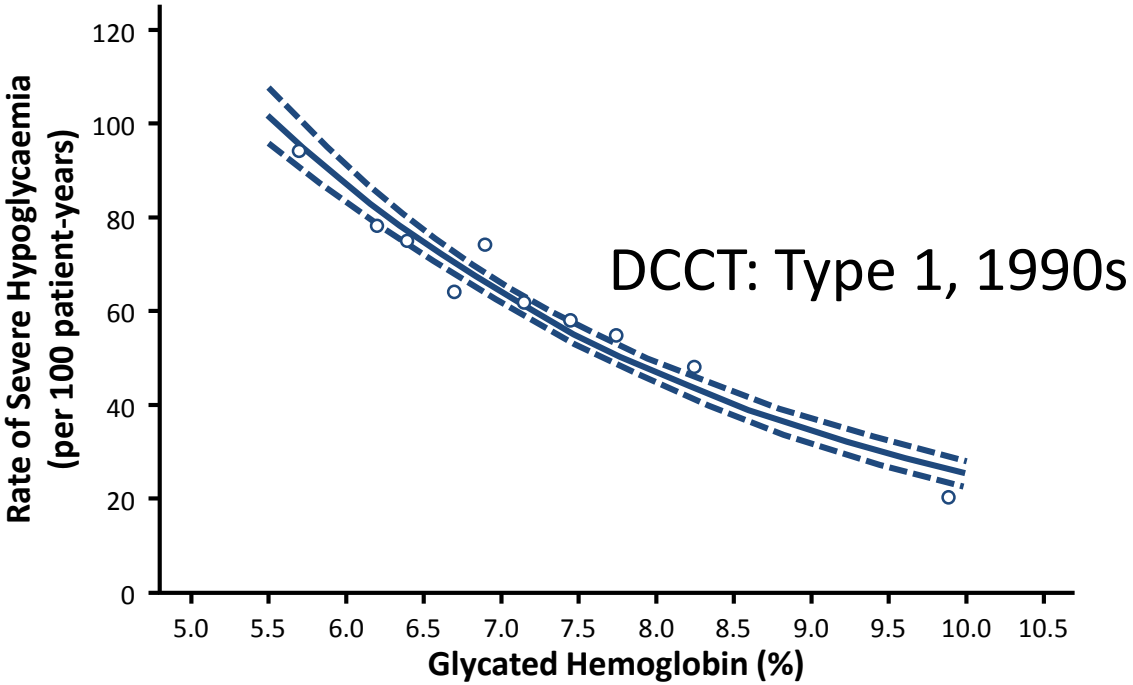
Changed pattern severe hypoglycaemia

- 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



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

Individualising Targets: considerations

1. What are the benefits of glycaemic control?

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

Individualising Targets: considerations

1. What are the benefits of glycaemic control?

    - Very old
    - Very young
    - Limited life expectancy

Individualising Targets: considerations

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

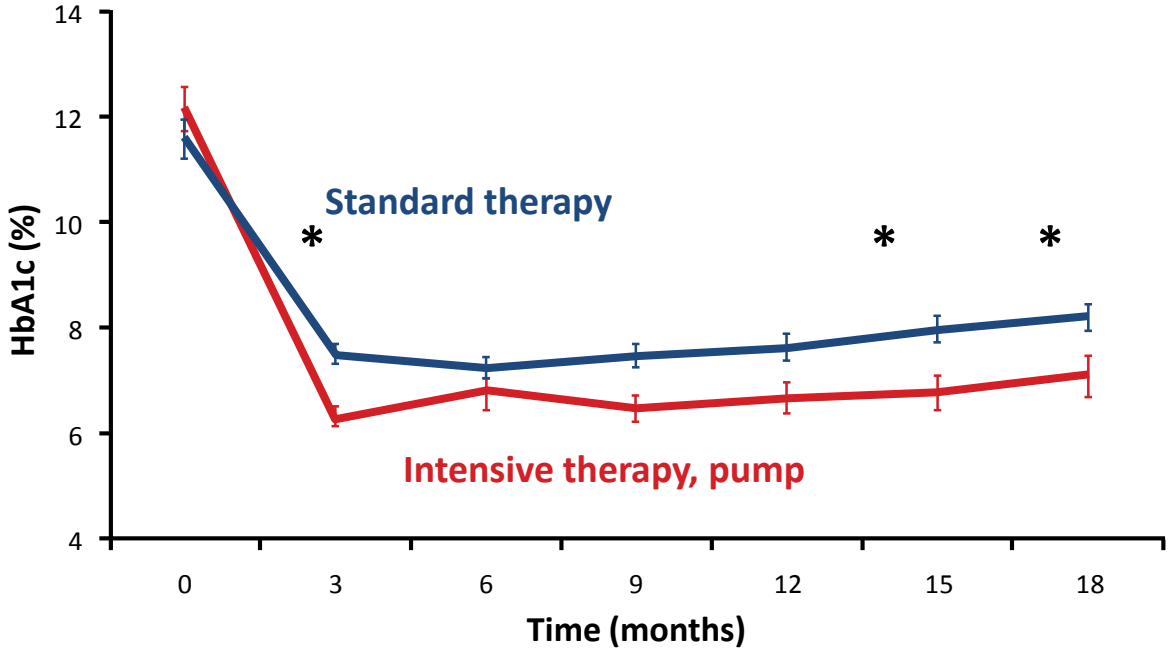
- **ACCORD**
  - Increased hypoglycaemia in intensive arm (3x)
  - Increased mortality in intensive arm (20% higher)
  - High cardiovascular risk
- **ADVANCE and VADT**
  - Hypoglycaemia associated with increased risk of mortality

Individualising Targets

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



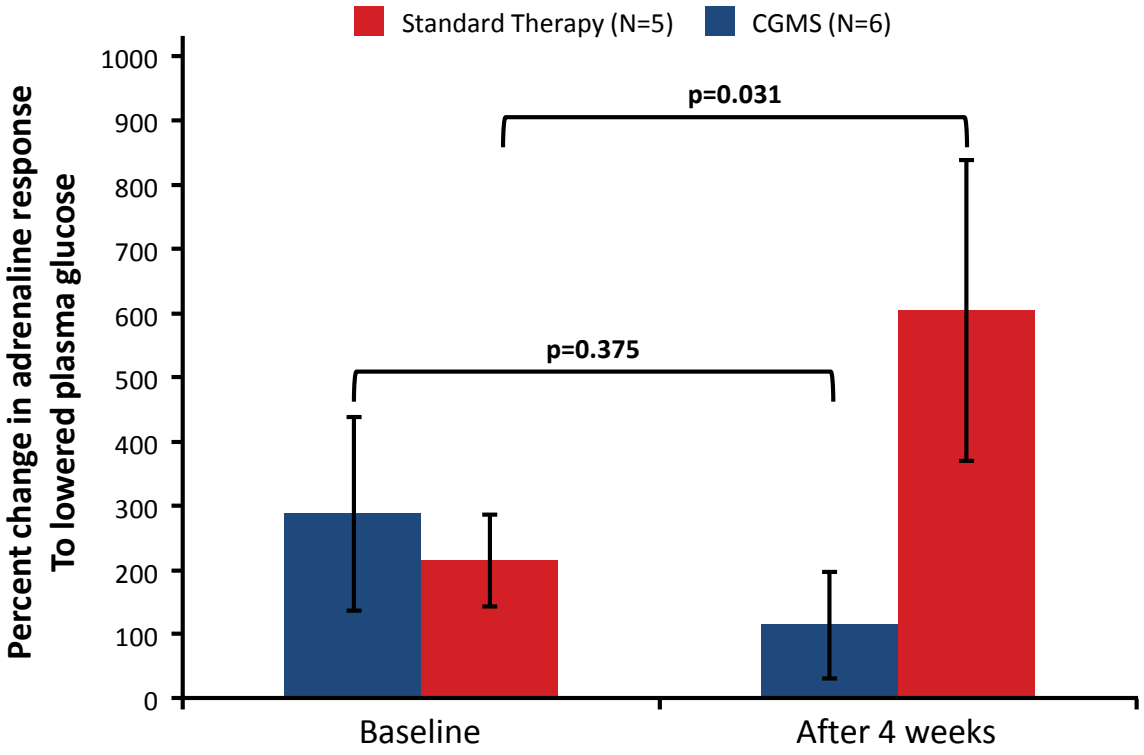
* p<0.05

Increased risk: impaired Hypoglycaemia awareness

	Total	Normal Awareness	Impaired Awareness	p value
Participants	656	465	191	
Percentage		70.90%	29.10%	
Age – years	13.48 ± 4.01	14.05 ± 3.60	10.60 ± 4.41	<0.0001
HbA1c mean	8.47 ± 1.00	8.55 ± 1.00	8.3 ± 0.96	0.006
Rate of SH – episodes/100 patient years	24.5	19.3	37.1	<0.001

T Ly et al, Diabetes Care 2009

Temporary higher targets to improve impaired awareness using CGM



Ly et al, Diabetes Care. 34(1):50-2, Jan 2011

Target Change
ADA recommendations for youth

Age	A1c Goals
<6 years	<8.5%
6-12 years	<8.0%
13-19 years	<7.5%

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

Age	Traditional A1c Goals	Current A1c Goals (2014)
<6 years	<8.5%	<7.5%
6-12 years	<8.0%	<7.5%
13-19 years	<7.5%	<7.5%

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

	HbA1c	Fasting/ Preprandial Glucose	Postprandial Glucose
ADA Guideline[1]	**<7.0%** (53 mmol/mol) **•Goals should be individualised based on factors such as age, duration of disease, co-morbidities and hypoglycaemia unawareness**	**3.9–7.2 mmol/L** (70-130 mg/dL) (preprandial)	**<10.0 mmol/L** (<180 mg/dL) (1-2 h pp)
ADA/ EASD Consensus[2]	**<7.0%** (53 mmol/mol) **•Tighter targets (6.0–6.5%) – younger, healthier** **•Looser targets (7.5–8.0%+) – older, comorbidities, hypoglycaemia prone, etc.** **•Avoidance of hypoglycaemia**	**<7.2 mmol/L** (<130 mg/dL) (preprandial)	**<10.0 mmol/L** (<180 mg/dL)
EASD/ESC Consensus[3]	**<7.0%** (53 mmol/mol) **•Target of 7.5-8.0% may be acceptable, transitioning upwards as age increases**	**<7.2 mmol/L** (<130 mg/dL)	**<9–10 mmol/L** (<160-180 mg/dL)
IDF Global Guideline[4]	**<7.0%** (53 mmol/mol) **•Lower target may be considered if easily and safely achieved** **•Higher target may be considered for people with co-morbidities or history of unacceptable hypoglycaemia**	**6.5 mmol/L** (115 mg/dL)	**9.0 mmol/L** (160 mg/dL)

1. American Diabetes Association (ADA). Diabetes Care. 2013;36(Suppl.1):S11–S66
2. Inzucchui et al. Diabetes Care. 2012;35:1364–1379
3. European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) Task Force. Eur Heart J. 2013;34:3035–3087.
4. International Diabetes Federation (IDF) Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes 2012.

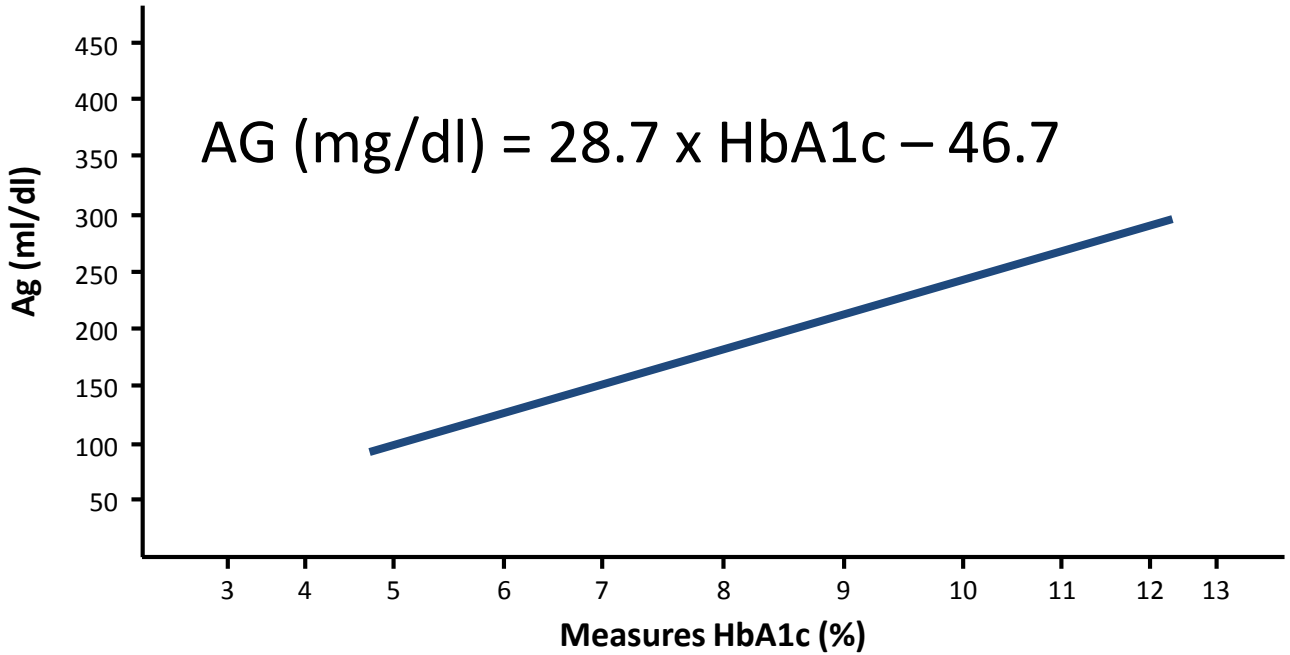
Glycaemic targets in frail elderly people

(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

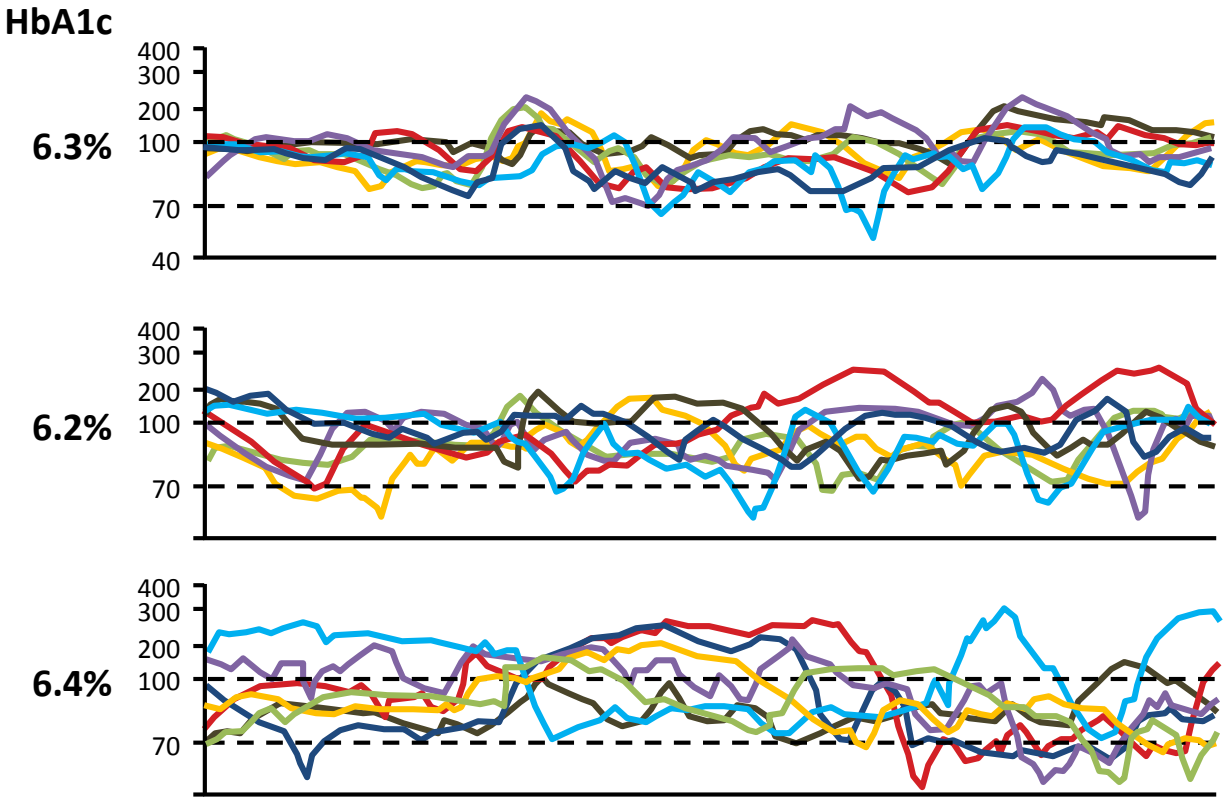


Nathan DM et al, Diabetes Care August 2008 vol. 31 no. 8 1473-1478

ADAG Study: "Translation" of HbA1c into estimated Average Glucose (eAG)

	eAG	
HbA1c (%)	(mg/dl)	(mmol/l)
5	97	5.4
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4

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

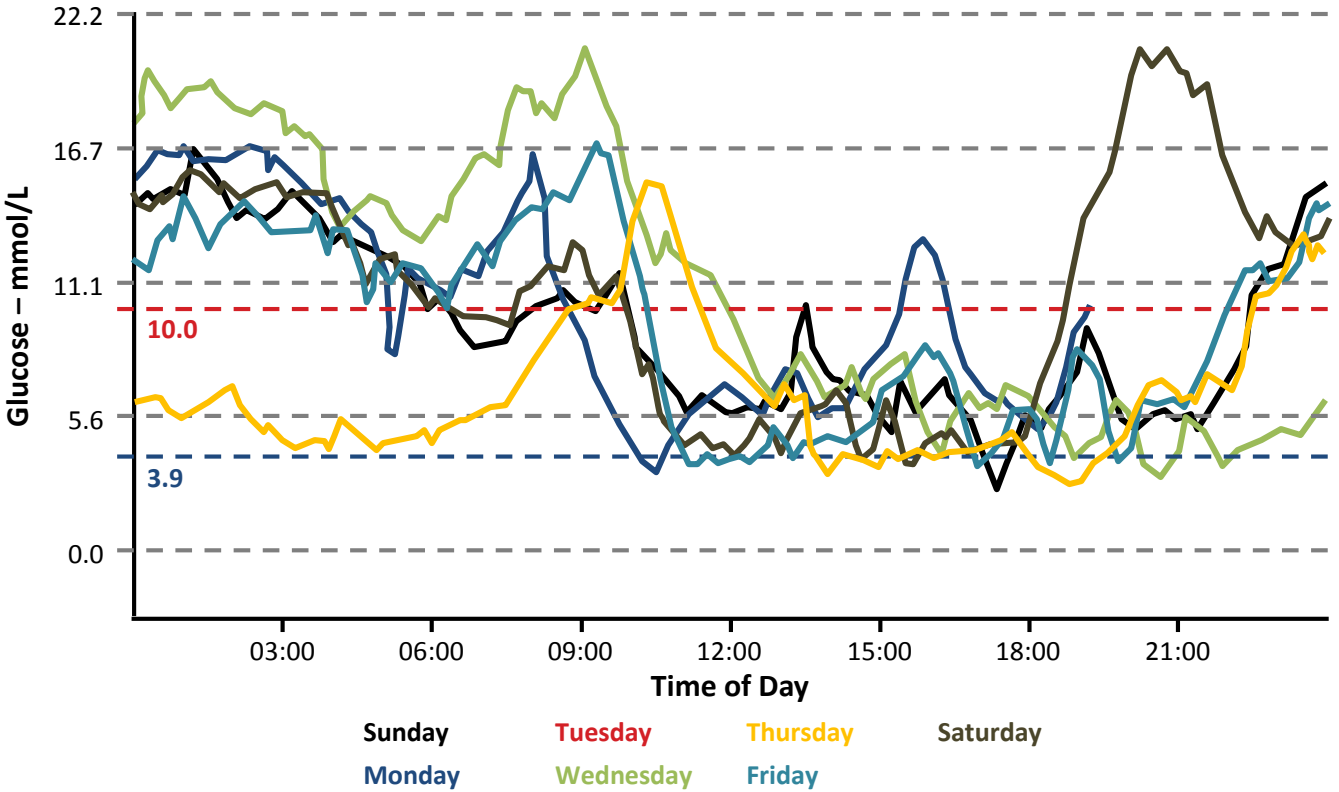

HbA1c
6.3%
400
300
200
100
70
40
6.2%
400
300
200
100
70
6.4%
400
300
200
100
70

Fear of Hypoglycaemia

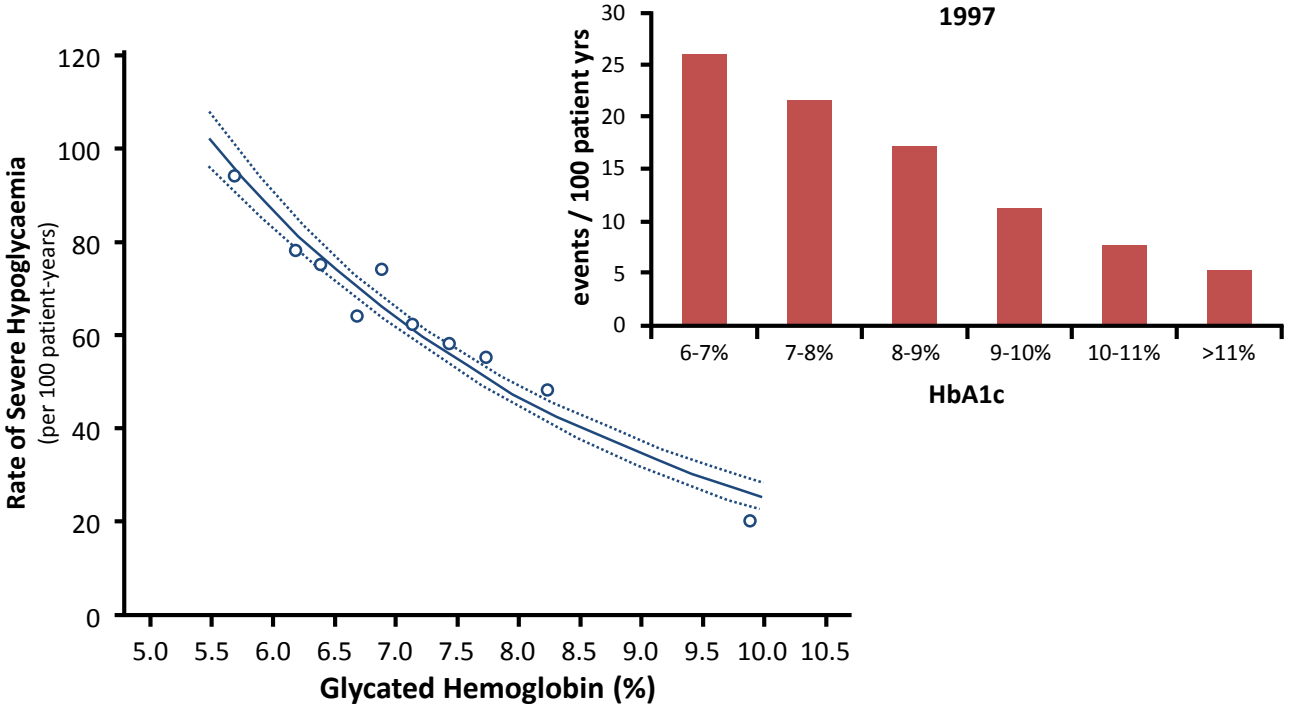
Clinician makes an assessment of a target

but

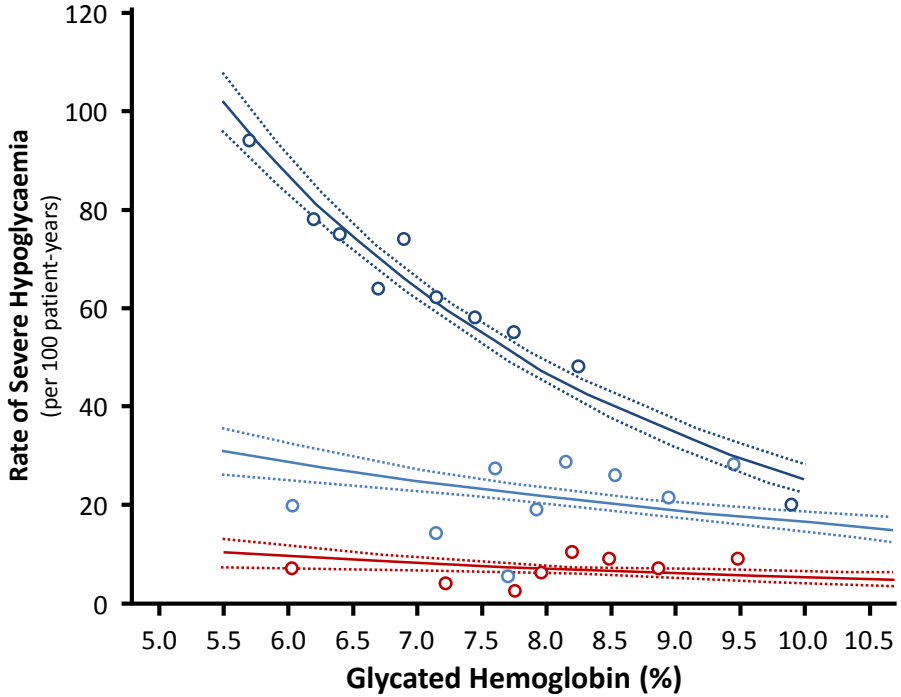
Patient may make their own assessment


22.2
16.7
11.1
10.0
5.6
3.9
0.0
Glucose – mmol/L
03:00
06:00
09:00
12:00
15:00
18:00
21:00
Time of Day
Sunday
Tuesday
Thursday
Saturday
Monday
Wednesday
Friday

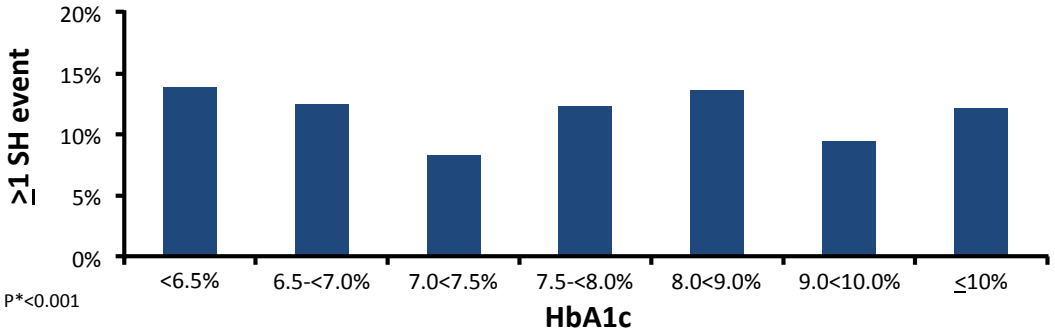
1990s: DCCT, Severe hypoglycaemia vs HbA1c



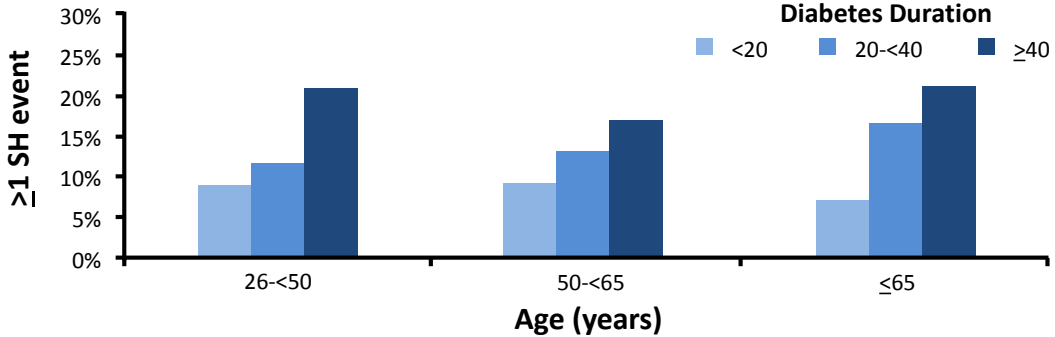
Changing relationship: all severe 2010-13



Severe hypoglycaemia
Type 1 Registry US: Adults



P*<0.001



Weinstock R, JCEM: 3411-19, 2013

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”
  - Report of a workgroup of ADA and ES, Diabetes Care; 36:1384-95, 2013

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

Even Small Medical Advances Can Mean Big Jumps In Bills

The New York Times

by Elisabeth Rosenthal, April 5th 2014

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
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- **Limitations of technology**
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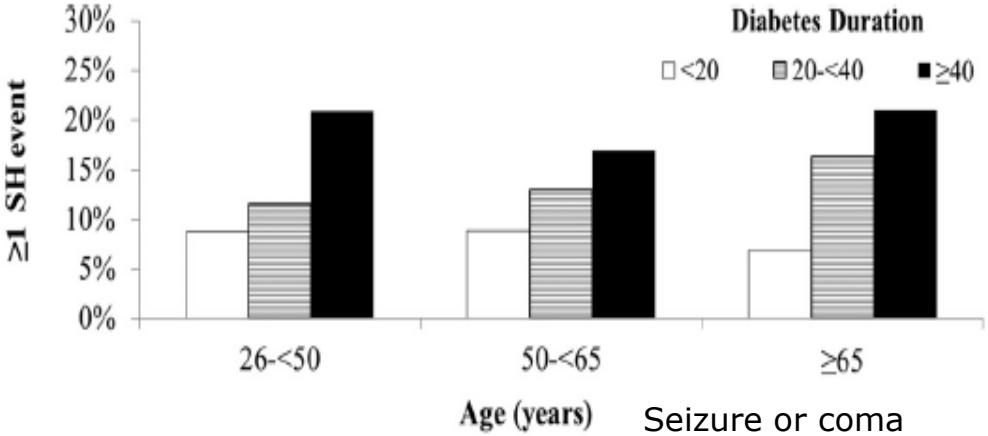
  - Real-world experiences vs. study environments
  - Inequities in access
- **Cost and cost-effectiveness**

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



Seizure or coma

J Clin Endo Metab 98: 3411–3419, 2013.

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

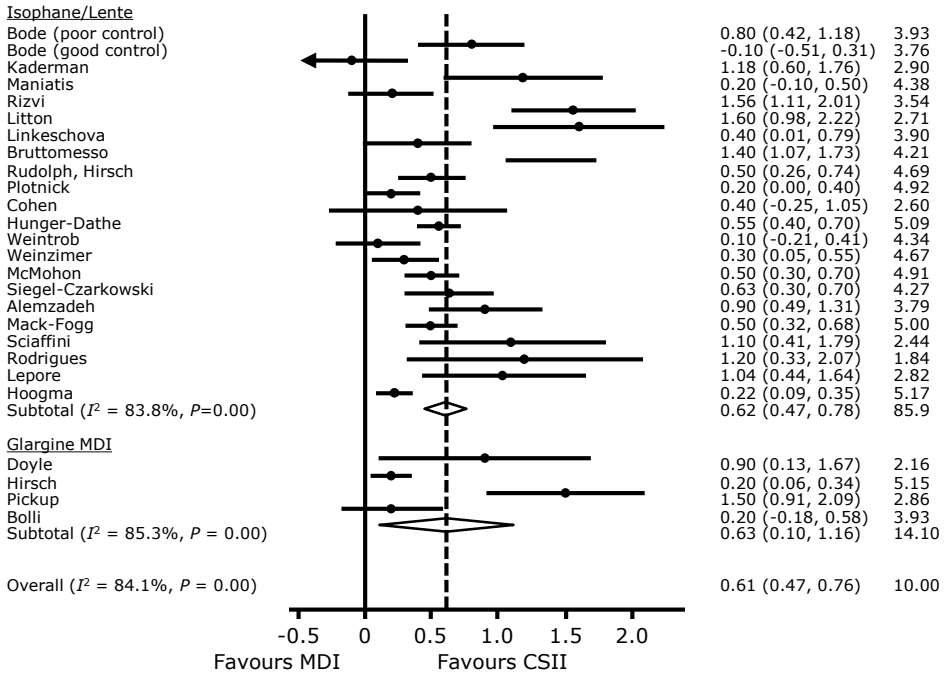


Figure 5 Forest plot of random effect meta-analysis for mean difference in HbA_{1C} (MDI vs. CDII), including sub-grouped analysis for studies using isophane/Lente insulin and those using glargine-based MDI. CI, confidence interval; SCII, continuous subcutaneous insulin infusion; HbA_{1C}, glycated haemoglobin; MDI, multiple daily injections.

Diabet. Med. 25: 765–774, 2008.

Journal of Diabetes Science and Technology
Volume 7, Issue 6, November 2013

REVIEW ARTICLE

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

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

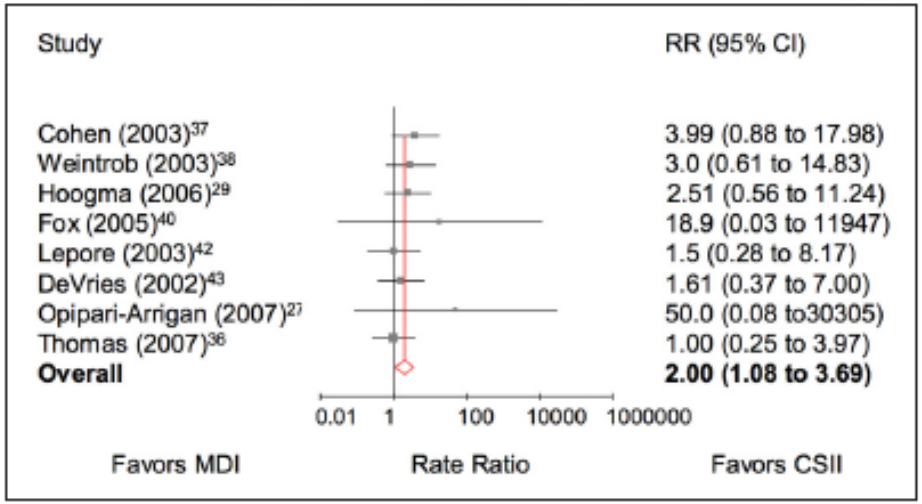


Figure 3. Decision-making random-effects meta-analysis of severe hypoglycemia RRs on MDI versus CSII. Only RCTs where the baseline population (MDI) rate of severe hypoglycemia was elevated (>18 episodes/100 patient-years) were included. CI, confidence interval.

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

Journal of Diabetes Science and Technology
Volume 6, Issue 2, March 2012

ORIGINAL ARTICLE

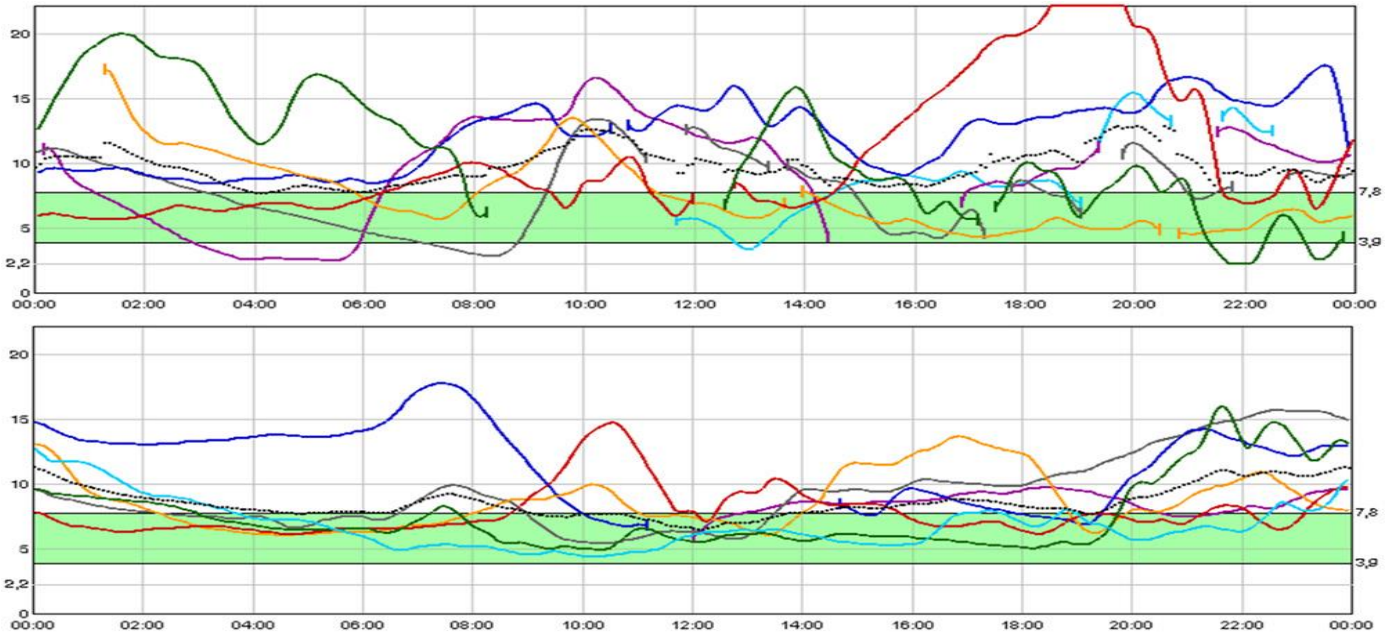
Performance of a Glucose Meter with a Built-In Automated Bolus Calculator versus Manual Bolus Calculation in Insulin-Using Subjects

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]

Insulin Dose Determinations by the Subjects[a]

All subjects		Meter		Total
		Correct	Incorrect	
Manual method	Correct	145 (35%)	8 (2%)	153 (37%)
	Incorrect	241 (59%)	15 (4%)	**256 (63%)**
Total		386 (94%)	**23 (6%)**	409

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

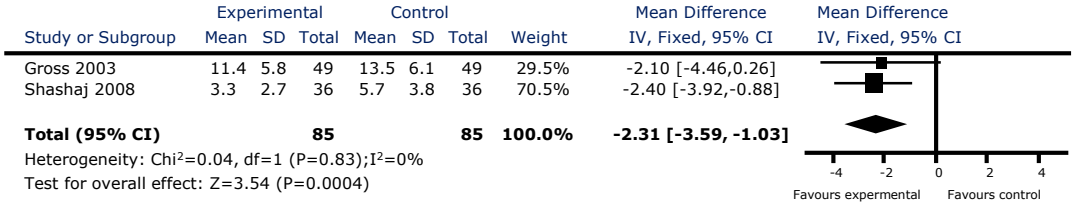
Schmidt S JDST epub May 19, 2014.

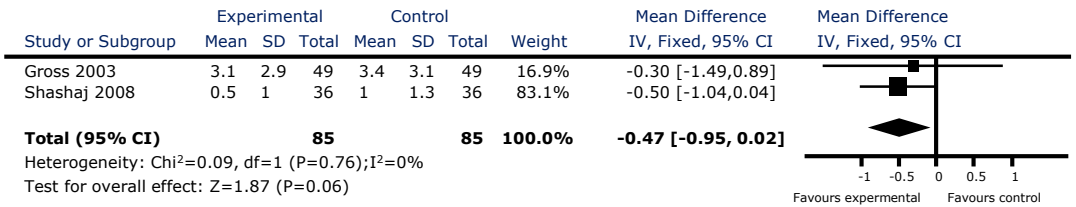
~84 Different Automatic Insulin Calculator Apps On iTunes

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. Ramotowska[1], D. Golicki[2], K. Dzygalo[1], A. SzyPowska[1]**

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





Exp Clin Endocrinol Diabetes 121: 248-254, 2013.

Journal of Diabetes Science and Technology
Volume 6, Issue 1, January 2012

ORIGINAL ARTICLE

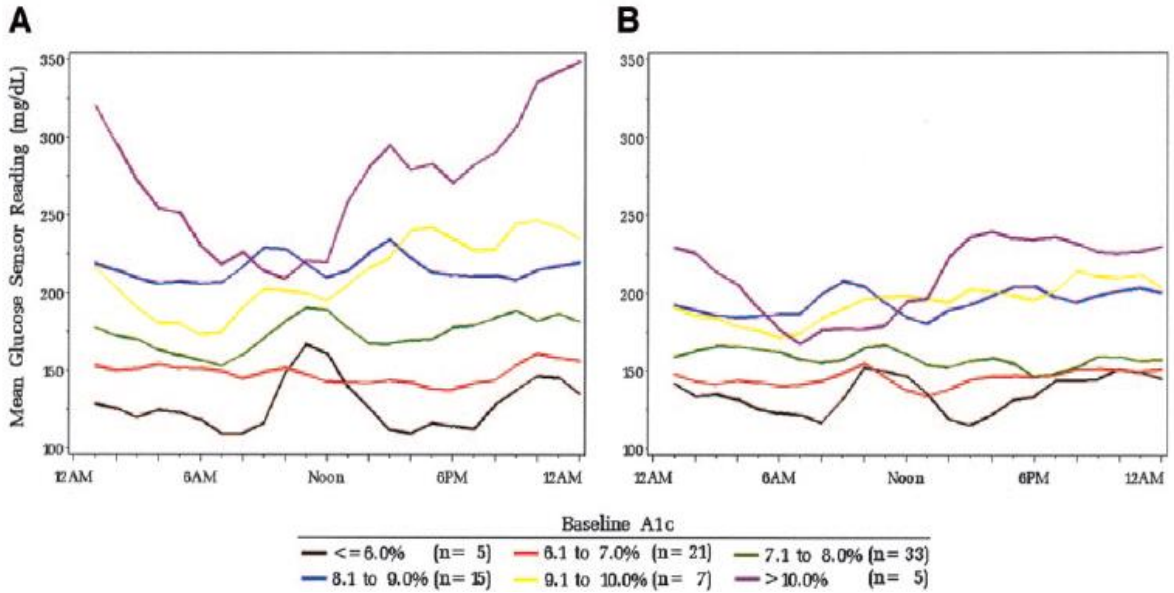
Use of an Automated Bolus Calculator Reduces Fear of Hypoglycemia and Improves Confidence in Dosage Accuracy in Patients with Type 1 Diabetes Mellitus Treated with Multiple Daily Insulin Injections

Katharine Barnard, Ph.D., C.Psychol.,[1] Christopher Parkin, M.S.,[2] Amanda Young, M.Sc.,[1] and Mansoor Ashraf, M.B.B.S.[3]

Table 2.
Perceived Improvement in Diabetes Management-Related Factors

	Significantly improved	Improved	No change	Worsened	Significantly worsened
Fear of hypoglycemia	13.0% (73)	39.0% (219)	43.0% (241)	4.8% (27)	0.2% (1)
Confidence in calculation	28.0% (157)	50.8% (285)	16.8% (94)	3.9% (22)	0.5% (3)
Ease of calculating bolus	43.7% (245)	41.2% (231)	13.2% (74)	1.8% (10)	0.2% (1)
Acting on SMBG results	27.1% (152)	54.2% (304)	16.9% (95)	1.8% (10)	0.0% (0)
Control of BG levels	20.1% (113)	53.5% (300)	23.0% (129)	3.2% (18)	0.2% (1)
Ability to achieve BG goals	13.4% (75)	53.7% (301)	30.8% (173)	2.0% (11)	0.2% (1)
Flexibility in lifestyle	20.5% (115)	42.4% (238)	35.3% (198)	1.8% (10)	0.0% (0)
Overall well-being	17.5% (98)	54.4% (305)	26.7% (150)	1.2% (7)	0.2% (1)

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

Garg S *et al. Diab Care* 29:44-50, 2006.

Journal of Diabetes Science and Technology
Volume 6, Issue 5, September 2012

ORIGINAL ARTICLE

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.,[2] Stephanie Hall, M.P.H.,[1]
Christopher Phillips, M.D., M.P.H.,[1] Ernest Alema-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]

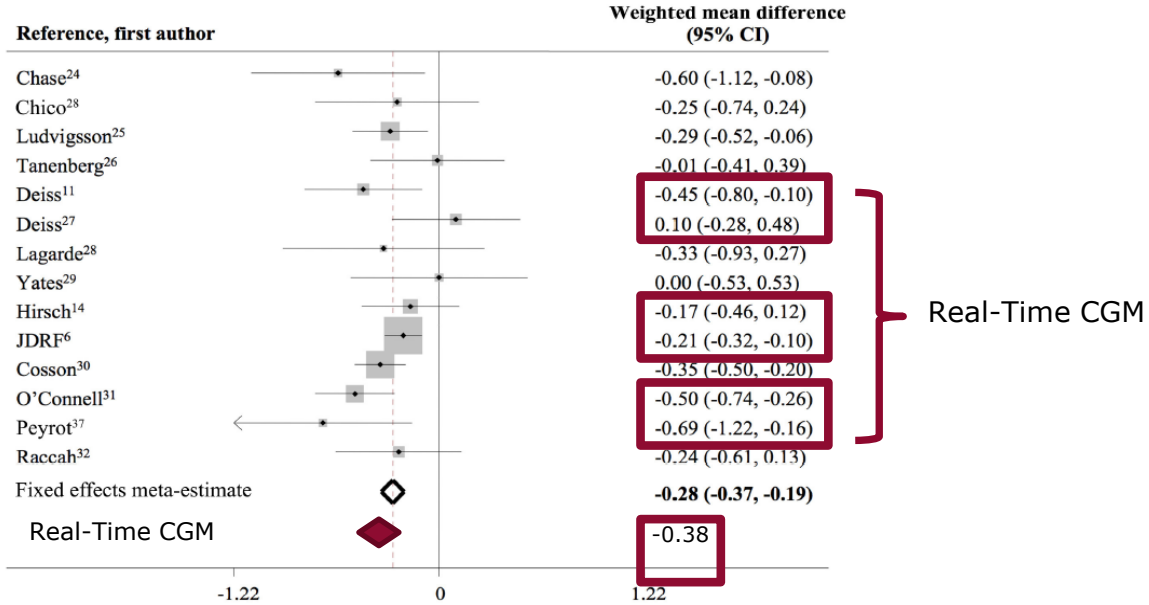
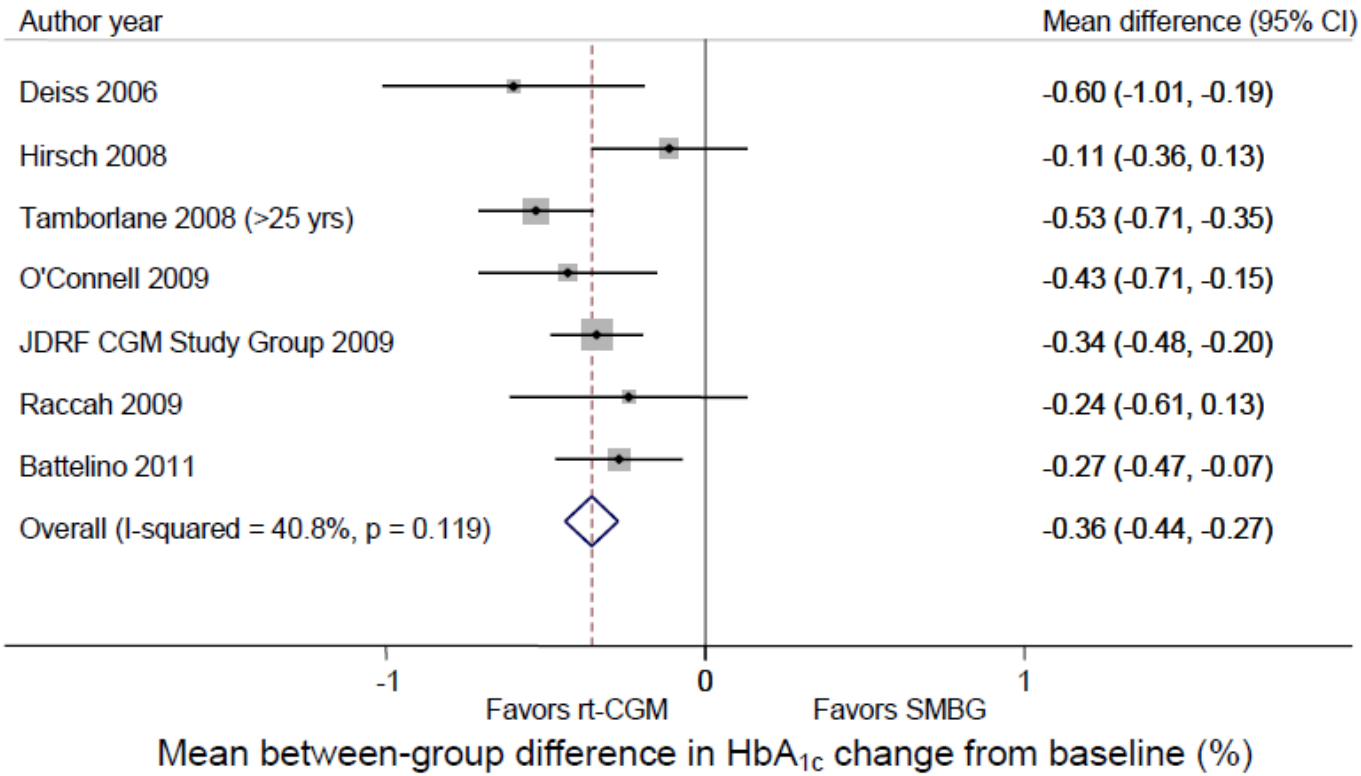
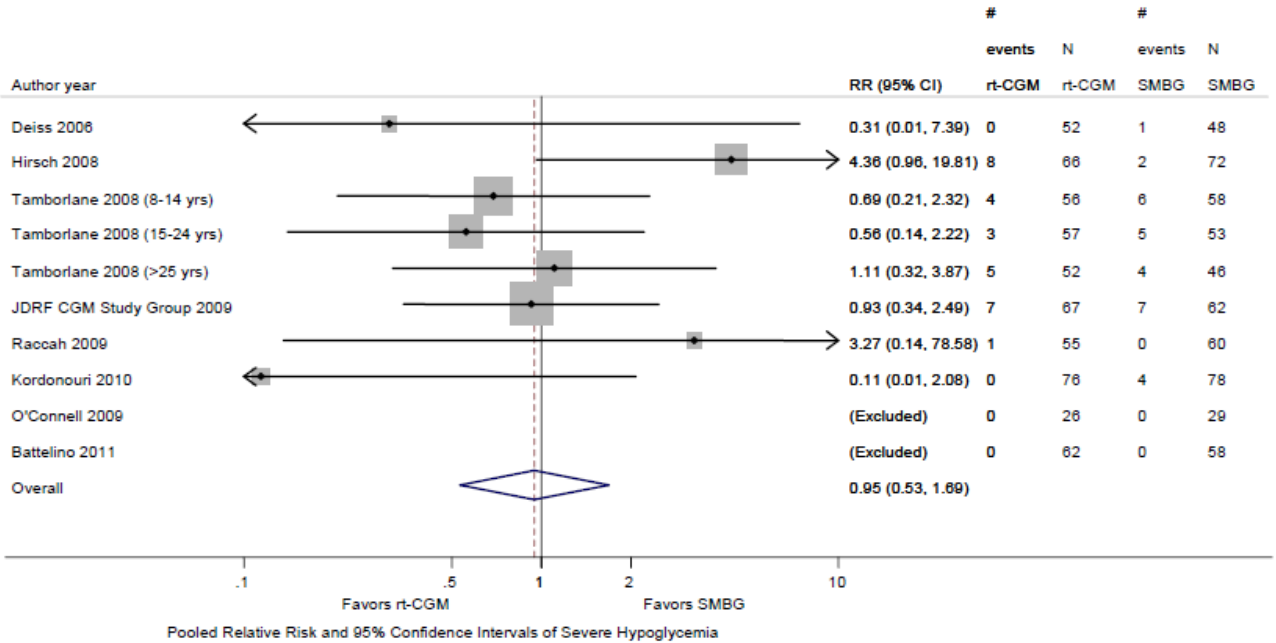


Figure 30. Between-group difference between rt-CGM and SMBG in how HbA_{1c} changed from baseline among adults with type 1 diabetes in studies where compliance was greater than 60%



Golden S. Agency for Healthcare Research and Quality Comparative Effectiveness Review Number 57 Report 12-EHC036-EF, 2012.

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.

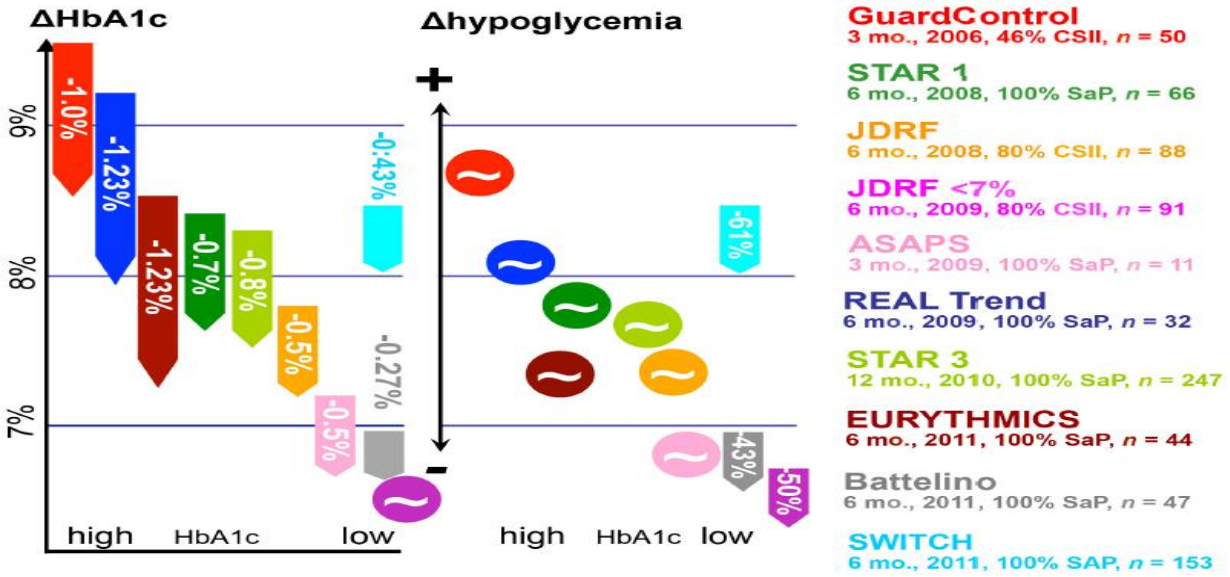
Test for heterogeneity: Q = 7.91 with 7 degrees of freedom (p = 0.34)

I-squared = 12 percent

Golden S. Agency for Healthcare Research and Quality Comparative Effectiveness Review Number 57 Report 12-EHC036-EF, 2012.

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

J Diab Sci Tech 7: 500-519, 2013.

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

Pratik Choudhary, mbbs, mrcp, mp[1,3]
Sharmin Ramasamy, mbbs, mrcp[2]
Louisa Green, bsc[3]
Geraldine Gallen, rgn[3]
Siobhan Pender, rgn[2]
Anna Brackenridge, mbbs, mrcp, md[2]
Stephanie A. Amiel, mbbs, md, frcp[1,3]
John C. Pickup, bm, dphil, frcp[1,2]

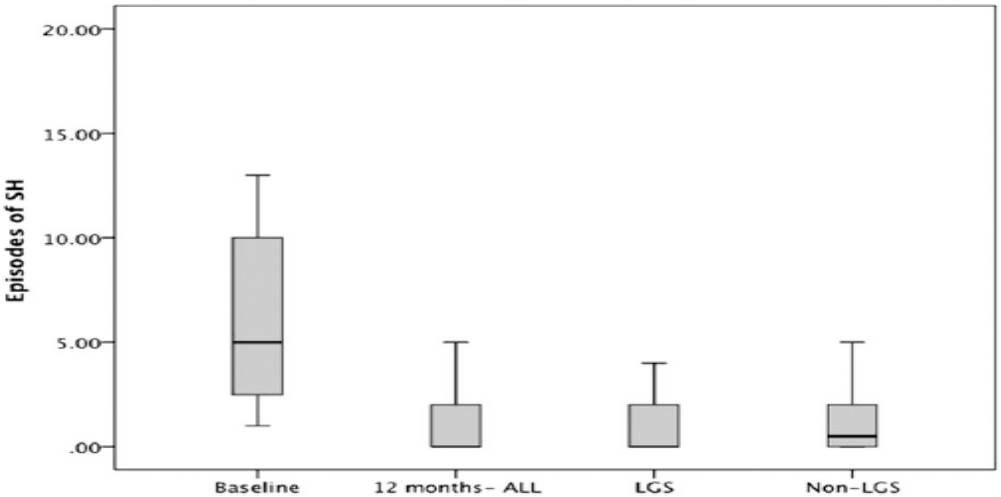
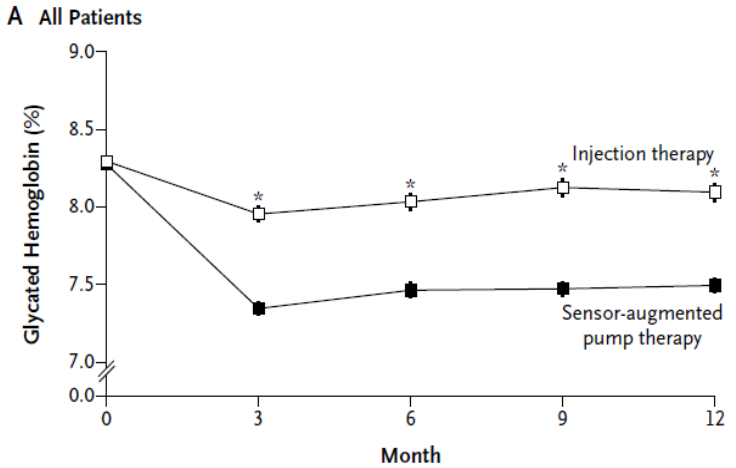


Figure 1—*Annual rates of SH, requiring third-party help at baseline and 12 months after starting CGM. Also shown are the 12-month rates divided into those treated with or without LGS. SH, severe hypoglycemia.*

Diab Care 36:4160-4162, 2013.

Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes

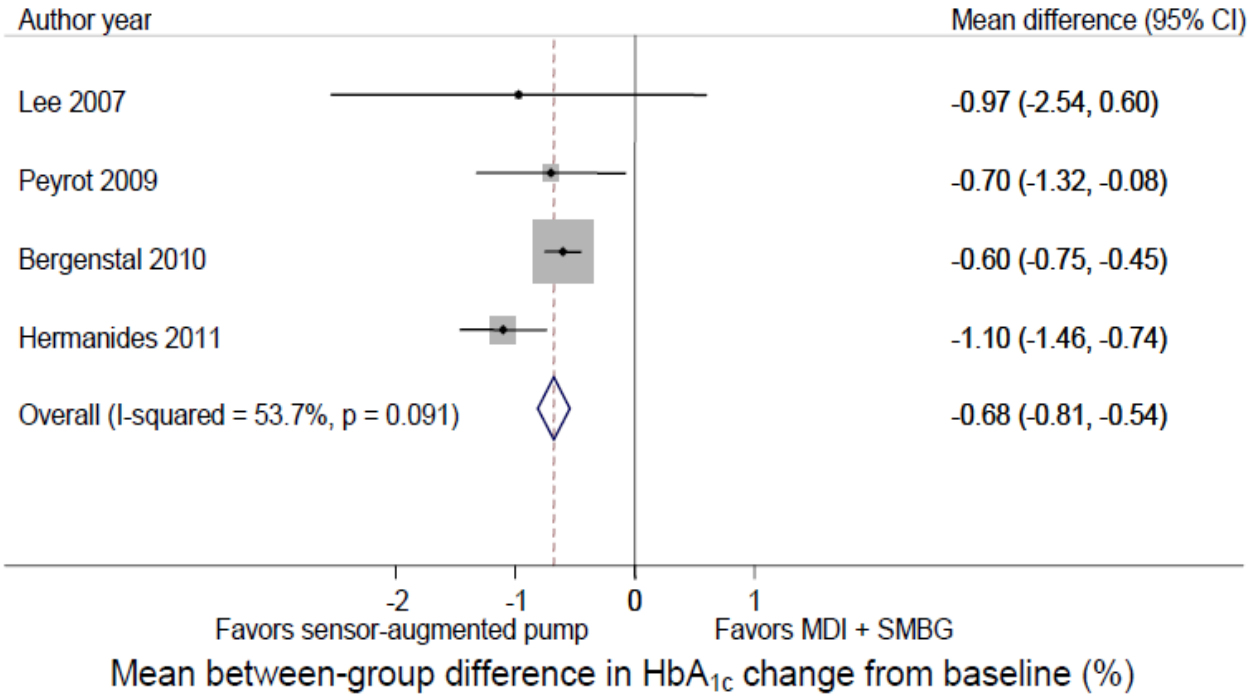
Richard M. Bergenstal, M.D., William V. Tamborlane, M.D., Andrew Ahmann, M.D., John B. Buse, M.D., Ph.D., George Dailey, M.D., Stephen N. Davis, M.D., Carol Joyce, M.D., Tim Peoples, M.A., Bruce A. Perkins, M.D., M.P.H., John B. Welsh, M.D., Ph.D., Steven M. Willi, M.D., and Michael A. Wood, M.D., for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



Variable	All Patients		
	Sensor-Augmented Pump Therapy (N=247)	Injection Therapy (N=248)	P Value
Severe hypoglycemia			
No. of events	32	27	0.58
No. of patients	21	17	
Rate per 100 person-yr	13.31	13.48	0.84

N Eng J Med 363: 311-320, 2010.

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



No difference in mild or severe hypoglycaemia

Golden S. Agency for Healthcare Research and Quality Comparative Effectiveness Review Number 57 Report 12-EHC036-EF, 2012.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

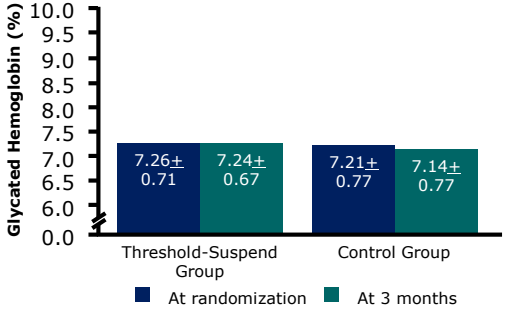
Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

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*

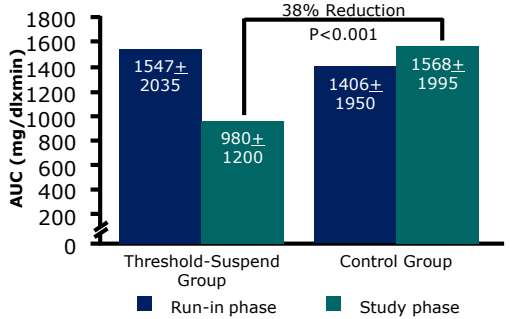
Inclusion Criteria

- 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 **≥ 80%** of the time
  - Had at **least two nocturnal hypoglycaemic** events for > 20 consecutive minutes in the absence of a pump interaction

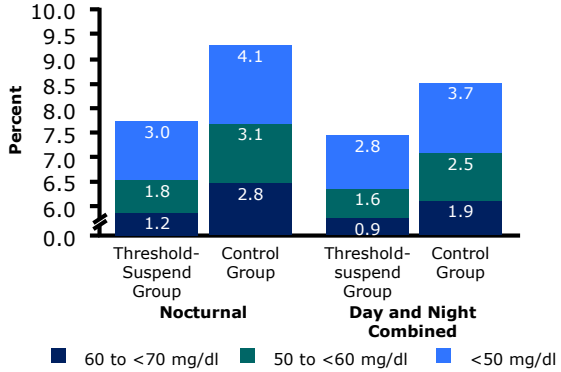
A Glycated Haemoglobin



B Mean AUC for Nocturnal Hypoglycaemic Events



C Sensor Glucose <70 mg/dl



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

*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**

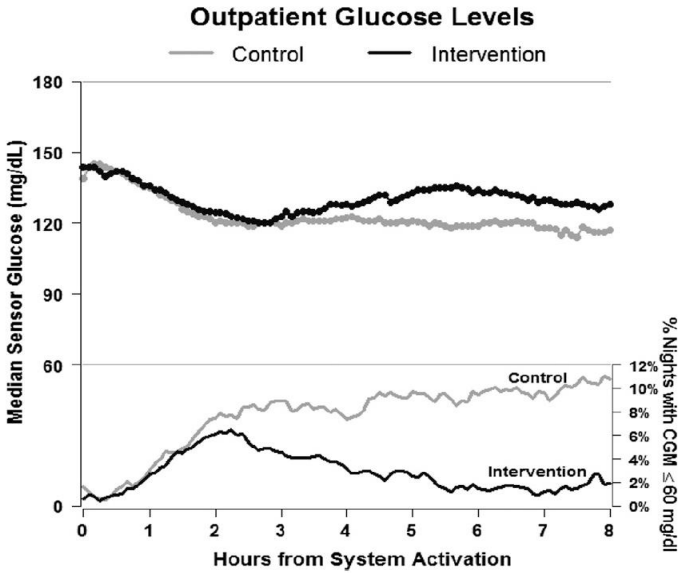
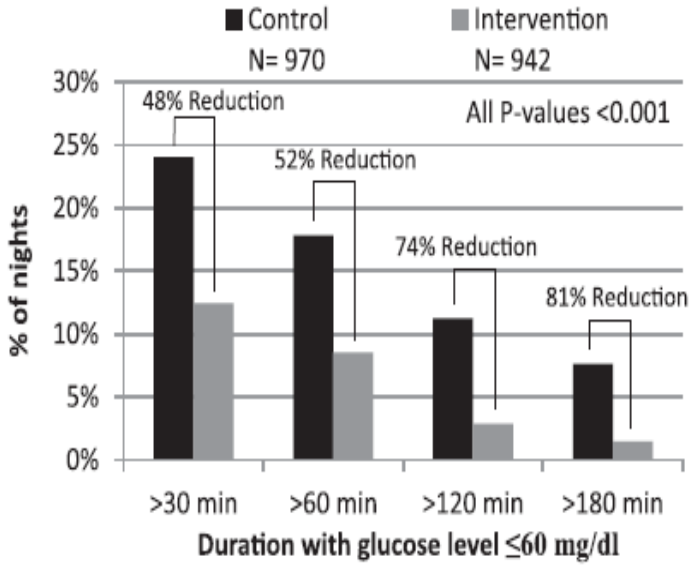
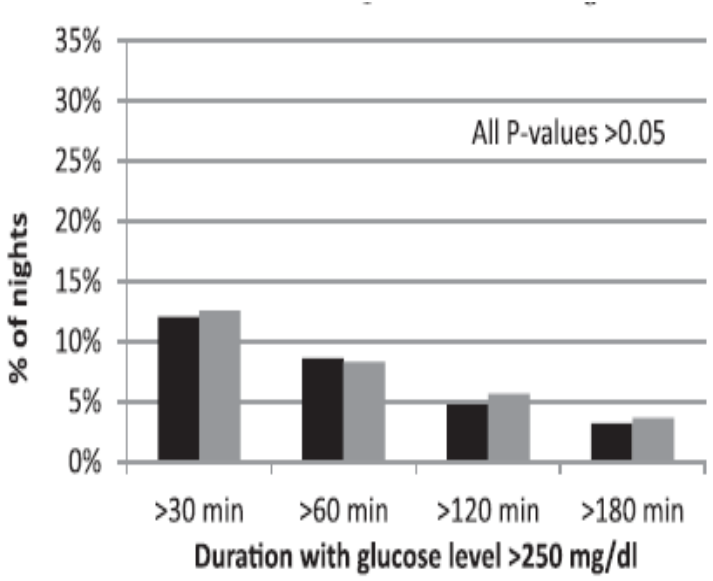


Figure 3—Sensor glucose levels overnight. The *top portion* of the figure shows the median glucose level across all nights in each treatment arm. The *bottom portion* of the figure shows the frequency of glucose level ≤60 mg/dL across all nights in each treatment arm.

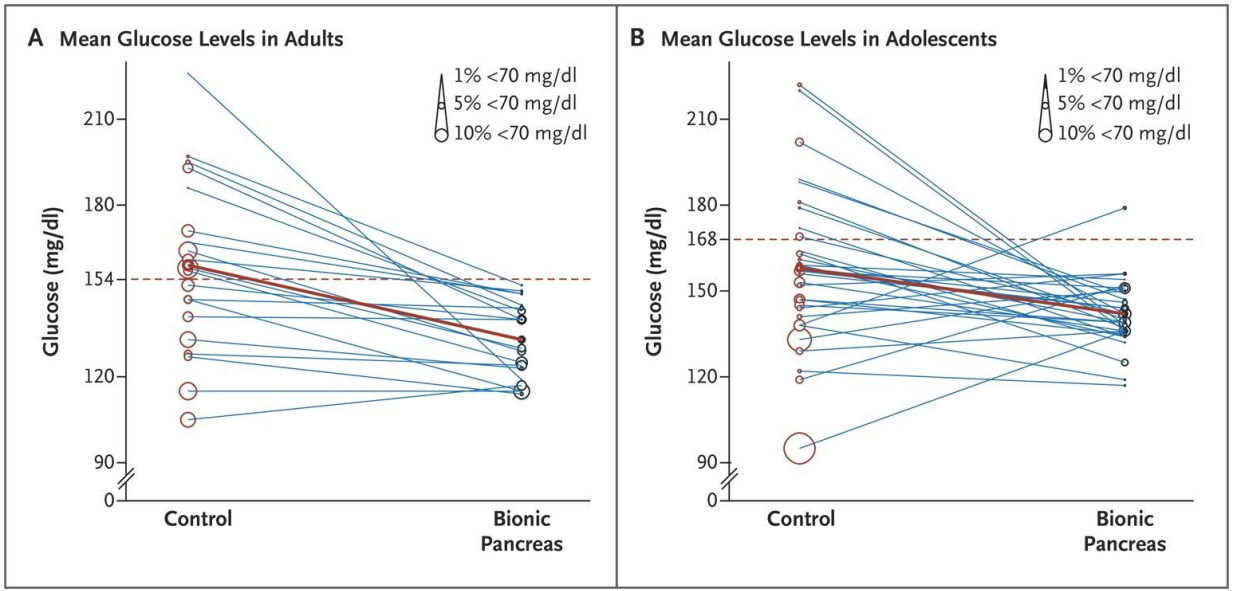
Duration of Overnight Hypoglycaemia (L) and Hyperglycaemia (R)





Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes

Steven J. Russell, M.D., Ph.D., Firas H. El-Khatib, Ph.D., Manasi Sinha, M.D., M.P.H., Kendra L. Magyar, M.S.N., N.P., Katherine McKeon, M.Eng., Laura G. Goergen, B.S.N., R.N., Courtney Balliro, B.S.N, R.N., Mallory A. Hillard, B.S., David M. Nathan, M.D., and Edward R. Damiano, Ph.D.



N Eng J Med epub July 18, 2014.

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

	Adult	Adult	P	Adolescents	Adolescents	P
	Bionic Pancreas	Control		Bionic Pancreas	Control	
Day + Night						
% of time <60 mg/dl	1.5±1.7	3.7± 3.3	<0.02	1.3± 1.7	2.2± 3.6	0.19
Nighttime Only						
% of time <60 mg/dl	0.4± 0.6	3.3± 4.9	<0.01	1.0± 1.4	1.7± 3.5	0.28

Russell S *et al. N Eng J Med* epub July 18, 2014.

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?
    _____

Who is a Successful Pumper? Someone who is:

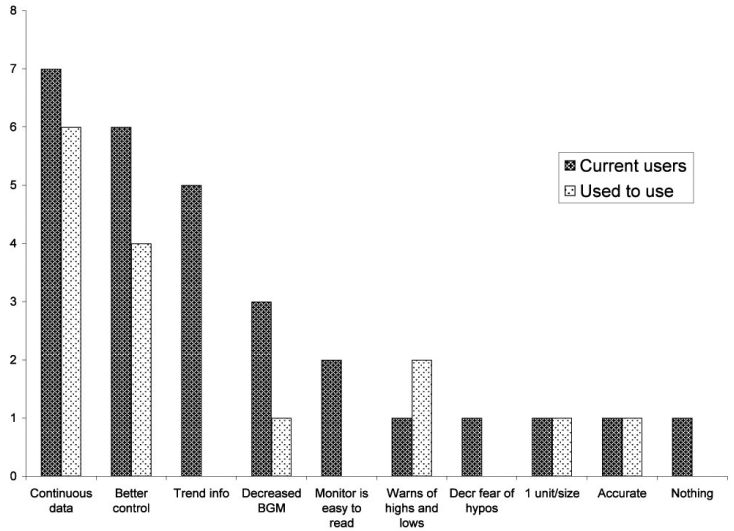
- Adherent to previous advice and keeping appointments
- Willing to do frequent BGM (≥6 times/d)
- Willing to learn and practice self management
- Capable of good problem solving
- Willing to not only ACT on their results, but ANALYZE their patterns
- Disciplined and persistent
- Willing to do the hard work
- Has a knowledgeable parent

Real-Life Utilization of Real-Time Continuous Glucose Monitoring: The Complete Picture

Neesha Ramchandani, P.N.P., C.D.E.,[1] Sandeep Arya, M.D.,[2] Svetlana Ten, M.D., C.D.E.,[3] and Sonal Bhandari, M.B.B.S., M.R.C.P.(1)[3]

Reported Comfort of Real-Time Continuous Glucose Monitoring Use

	Insertion	Wearing site	Carrying monitor
Painful, uncomfortable	38%	28%	14%
Too big, annoying, bulky, heavy	—	14%	17%
Skin irritation	—	17%	—
Adhesion problems	—	10%	—
Problem where to keep it	—	—	7%
Frightening	3%	—	—
Varies	3%	—	—
Ok	34%	28%	14%
Another monitor to carry	—	—	7%
Painless, easy, comfortable	10%	14%	10%
Monitor = pump	—	—	41%



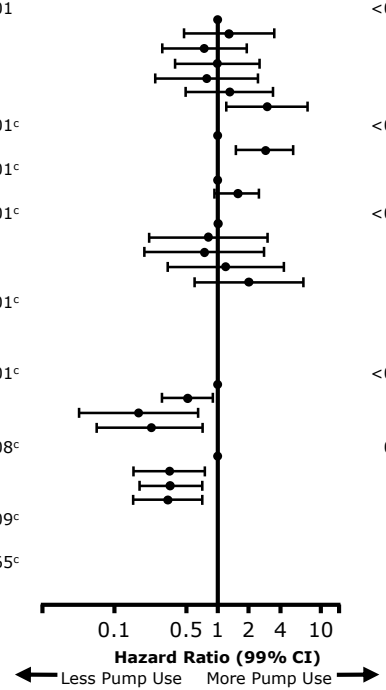
Reported beneficial features of RT-CGM

J Diab Sci Tech 5: 860-870, 2011.

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			Multivariate Analysis[g]
	N[a]	Using Pump[b]	P-Value	P-Value
Overall	**1012**	**27%**		
Clinical Center			<0.001	<0.001
A	59	18%		
B	159	20%		
C	277	20%		
D	217	23%		
E	48	26%		
F	138	35%		
G	114	59%		
Health Insurance			<0.001[c]	<0.001
Other	338	7%		
Private	652	37%		
Family Structure			<0.001[c]	0.02
Other[d]	309	13%		
Lives with Both Parents	701	33%		
Family Income			<0.001[c]	<0.001
<$25,000	99	7%		
$25,000-$49,999	130	11%		
$50,000-$74,999	111	16%		
$75,000-$99,999	95	28%		
>$100,000	239	50%		
Parent Education[e]			<0.001[c]	
High School or Less	287	15%		
AA	118	13%		
BA/BS	238	32%		
MS/MA/Professional	185	46%		
Race/Ethnicity			<0.001[c]	<0.001
White Non-Hispanic	638	36%		
Hispanic or Latino	212	14%		
Black/African American	82	5%		
Other/More than one Race	60	9%		
Age at Diagnosis (years)[f]			0.08[c]	0.001
<2	46	39%		
2-<5	149	30%		
5-<12	554	27%		
12-<19	263	24%		
DKA at Diagnosis			0.09[c]	
Yes	329	24%		
No	653	30%		
Gender			0.65[c]	
Female	507	29%		
Male	505	26%		



Diab Tech Ther 15: 929-934, 2013.

Outline

- **Types of technology**
  - Insulin delivery
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- **Cost and cost-effectiveness**

Economic Burden of Hypoglycaemia – Effect of the ACA

2010 Insured Population = 260 million

% diabetes = 7.4

diabetes = 19.2 million

Type 1

1.0 million

(100%)

Insulin-Requiring

1.0 million

(20%)

Hypo Unaware

(20%)

200,000

(8.1/yr)

Severe Hypos

1,600,000

(21%)

Hospitalization

336,000

$17,564/hosp

$5.9 billion

Type 2

18.2 million

(22%)

Insulin-Requiring

4 million

(9.8%)

Hypo Unaware

(10%)

400,000

(5.9/yr)

Severe Hypos

2.4 million

(21%)

Hospitalization

504,000

$17,564/hosp

$8.8 billion

2020 Insured Population = 320 million

% diabetes = 12

diabetes = 38.4 million

Type 1

1.2 million

(100%)

Insulin-Requiring

1.2 million

(20%)

Hypo Unaware

(20%)

240,000

(8.1/yr)

Severe Hypos

1,944,000

(21%)

Hospitalization

408,000

$17,564/hosp

$7.2 billion

Type 2

37.5 million

(22%)

Insulin-Requiring

8 million

(9.8%)

Hypo Unaware

(10%)

800,000

(5.9/yr)

Severe Hypos

4.7 million

(21%)

Hospitalization

987,000

$17,564/hosp

$17.3 billion

Economic Burden of Hypoglycaemia – Effect of the ACA

2010		2020
$14.7 billion	→	$24.5 billion

Cost-Effectiveness of CGM In Type 1 Diabetes

Author (date)	Setting/population	Cost per QALY gained
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

Cost-Effectiveness Analysis of CSII vs. MDI in Adults and Children With Type 1 Diabetes Mellitus

Study	Study objective, perspective, and data source	QALYs gained	Cost per QUALY (ICER)	Additional key findings
St. Charles et al (54)	To estimate long-term (60-year) cost-effectiveness of CSII compared with MDI in adults/children with type 1 DM US third-party payer perspective Computer simulation model (CORE Diabetes Model)	QUALY gains for CSIIvs 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, (ie, only 9 patients need to be treated with CSII to avoid 1 case of PDR)
St. Charles et al (55)	To evaluate the long-term (60-year) cost-effectiveness of CSII compared with MDI in adult patients with type 1 DM Canadian payer perspective Computer simulation model (CORE Diabetes Model)	QUALY gains for CSIIvs MDI were 0.655	**CSII: $27,265** **MDI: $23,797** **(Canadian dollars)**	…
Cummins et al (56)	Assessment report to examine the clinical and cost-effectiveness of using CSII to treat DM (type 1 DM and during pregnancy) NICE, United Kingdom Systematic review and economic evaluation (74 studies included)	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
Cohen N et al (26)	To project long-term (lifetime horizon) costs and outcomes of CSII vs MDI in adults and adolescents with type 1 DM Australian perspective Computer simulation model (CORE Diabetes Model)	QUALY gains for CSIIvs 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
Roze et al (57)	To project the long-term (60-year) costs and outcomes of CSII vs MDI in patients with type 1 DM United Kingdom; third party National Health Services perspective Computer simulation model (CORE Diabetes Model)	QUALY gains for CSIIvs 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

Grunberger *et al. Endo Pract* 2010.

Even Small Medical Advances Can Mean Big Jumps In Bills

The New York Times

by Elisabeth Rosenthal, April 5th 2014

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

King's Diabetes Research Group

KING'S HEALTH PARTNERS

Pioneering better health for all

IHSG International HYPOGLYCAEMIA Study Group

September 2014

Psychosocial aspects of hypoglycaemia

Stephanie A Amiel

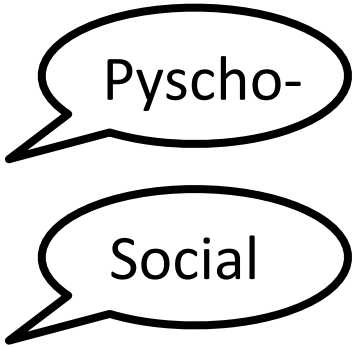
RD Lawrence Professor of Diabetic Medicine

King's College London School of Medicine

King's College Hospital NHS Foundation Trust

KING'S College LONDON

Definitions

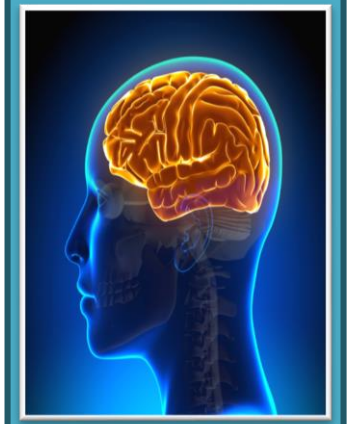


- mind
- mental

- 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

Mrs MF

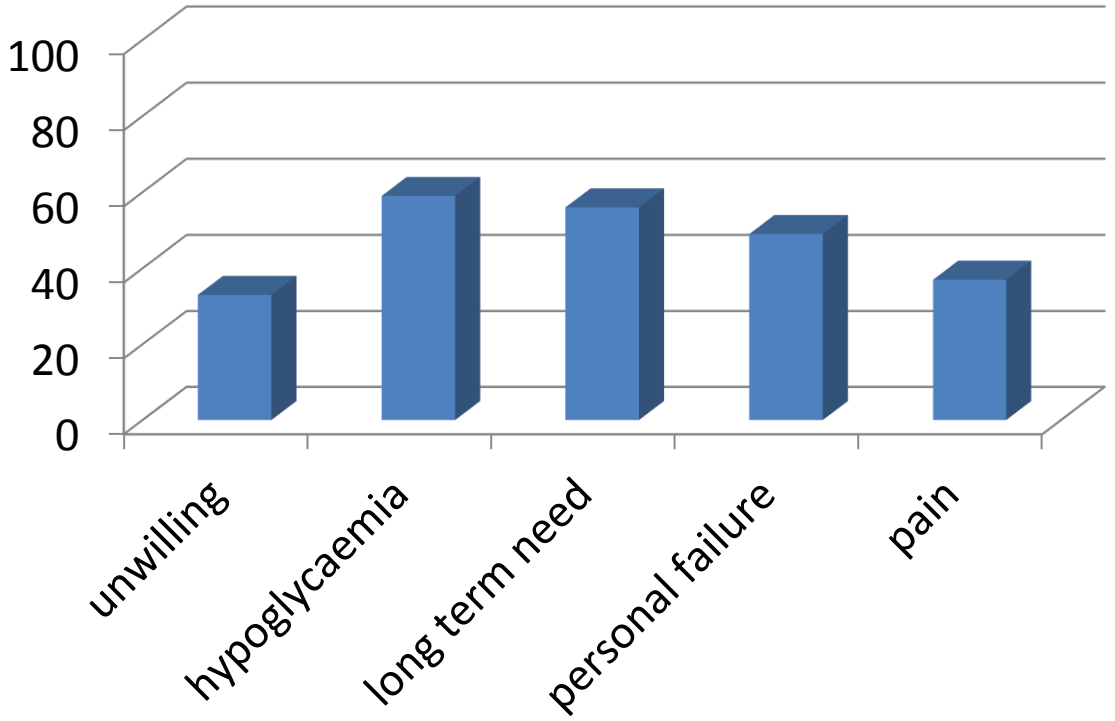
Mon	**7.00am**	**12.30pm**	**4.00pm**	**7.00pm**	**9.13pm**	**10.45pm**	
	5.8	7.1	2.8	10.1	9.1	8.1	
Tues	**6.45am**	**10.31am**		**6.45pm**	**7.15pm**		
	8.1	3.9		3.2	8.9		
Wed	**6.45am**	**10.00am**	**12.45pm**	**4.30pm**	**7.30pm**		**11.15pm**
	9.8	15.1	4.6	2.7	8.7		8.2
Thur	**7.10am**	**12.50pm**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

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

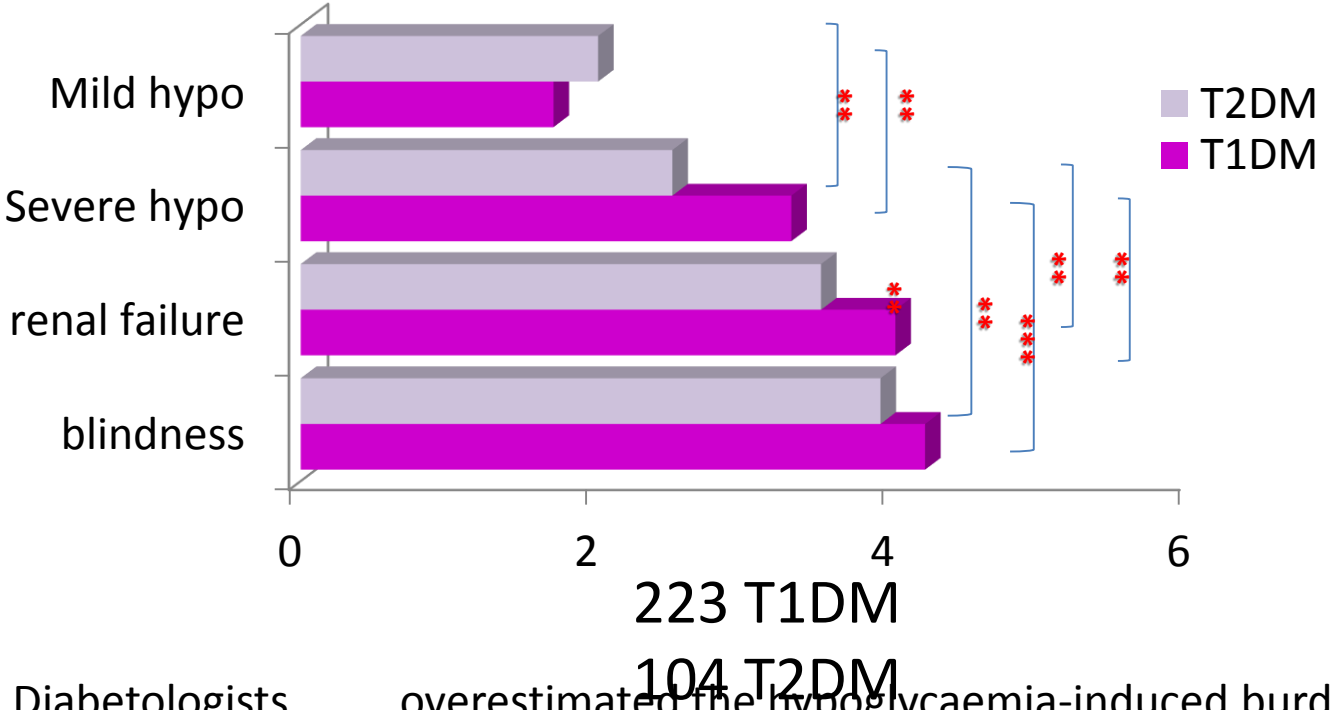
Psychological barriers to optimal treatment

100 Type 2 insulin naïve adults asked about starting insulin



Larkin M et al., Diabetes Educ. 2008;34:511-7.

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

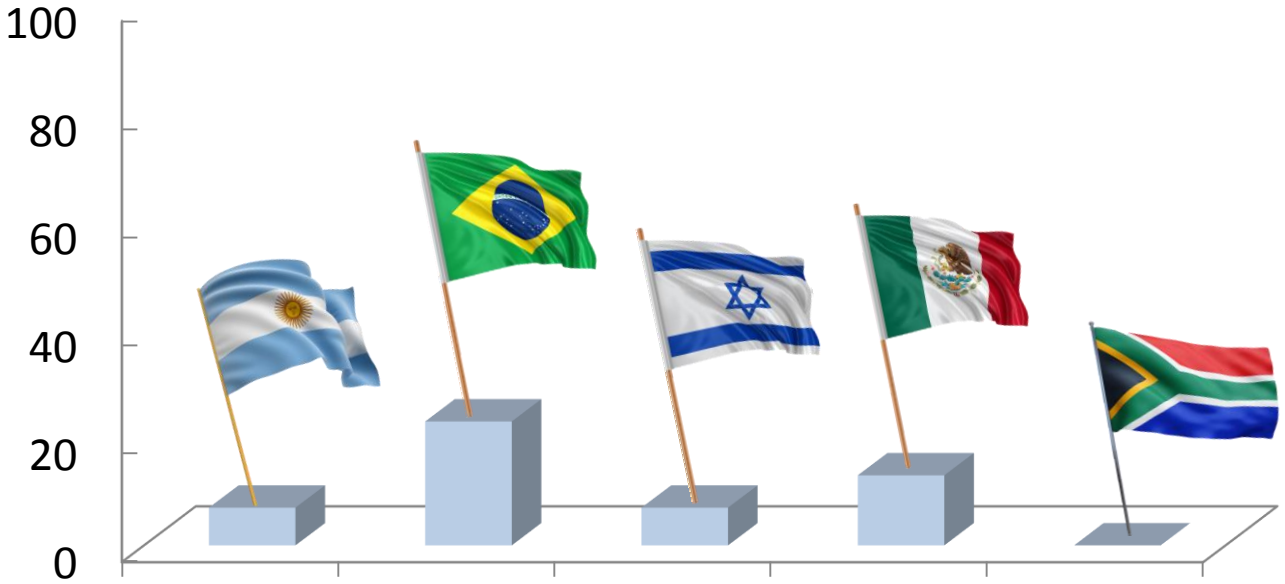
Seaquist et al., Diab Care 2013; 36:1384-1395
DAFNE curriculum
Fulcher et al., J Med Econ. 2014; 5:1-11

Non-severe hypoglycaemia

	Nocturnal	Daytime
< 1 event per week (% participants)	70	67
Cost of self treatment (€)	2.2±3.9	2.4±3.6
Increase in self tests done (%)	42	51
Contact with HCP (% participants)	39	36
Reduced doses (% participants)	38 (T1); 24 (T2)	30 (all on insulin)
Took day off work, % of participants in work	12 (n=21)	8 (n=14)
Negative impact on QoL (% participants)	28	28

Fulcher et al., J Med Econ. 2014; 5:1-11

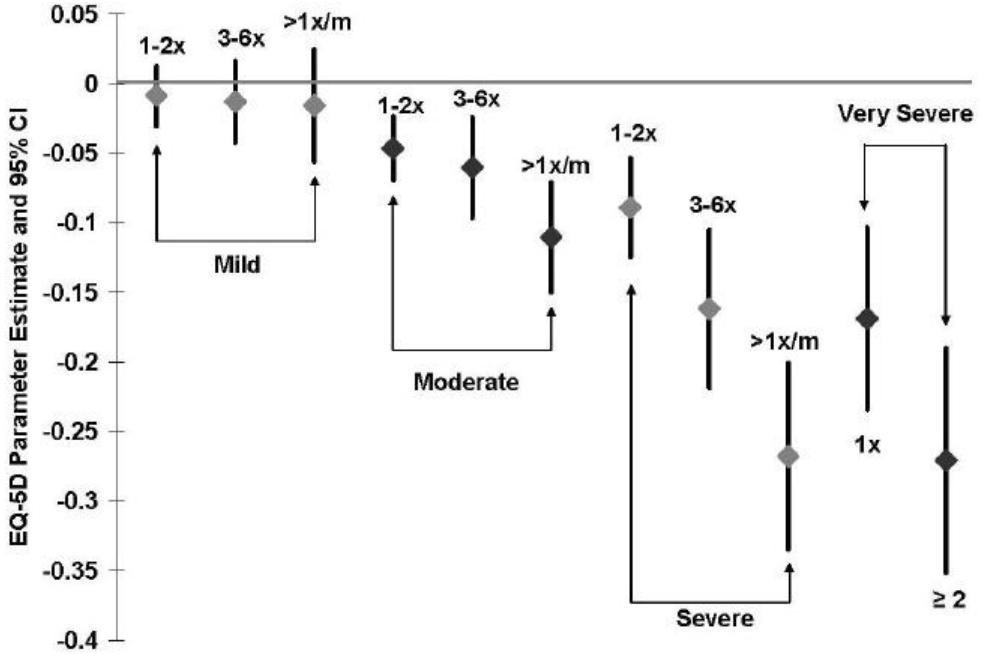
% missing a day after non-severe NH



Fulcher et al., J Med Econ. 2014; 5:1-11

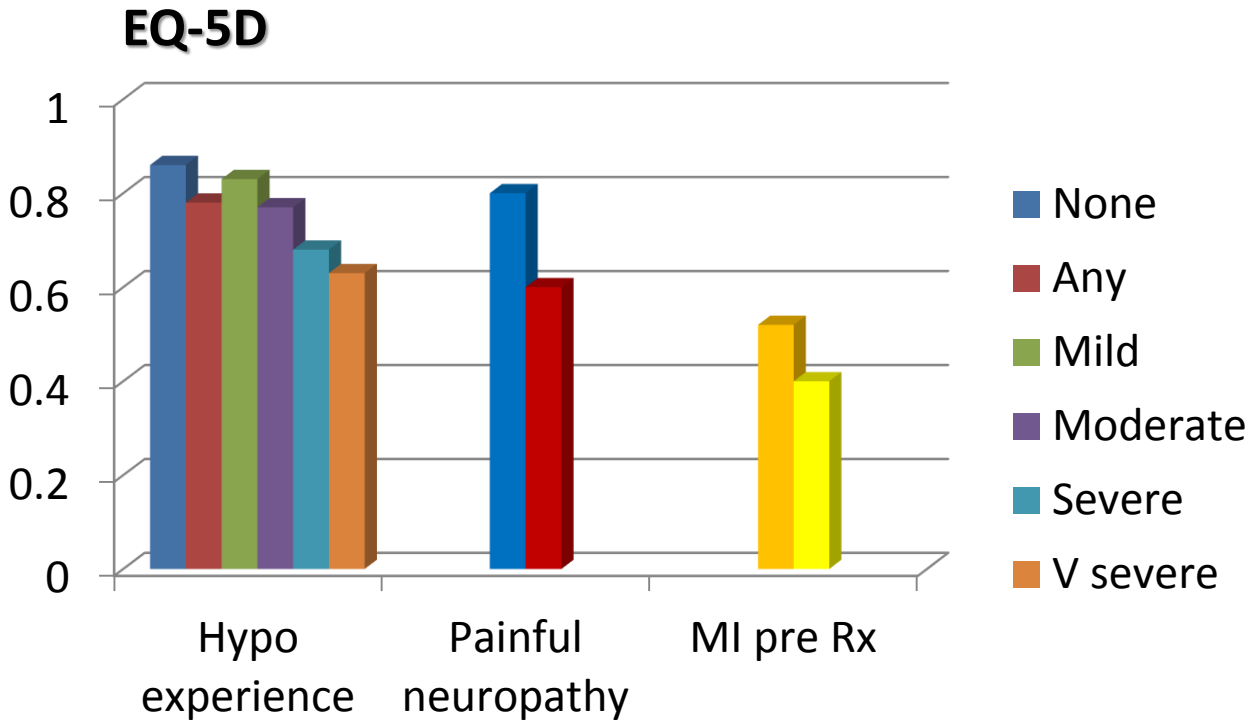
Impact of hypoglycaemia on HRQoF in 1984 T2DM on OHA

"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



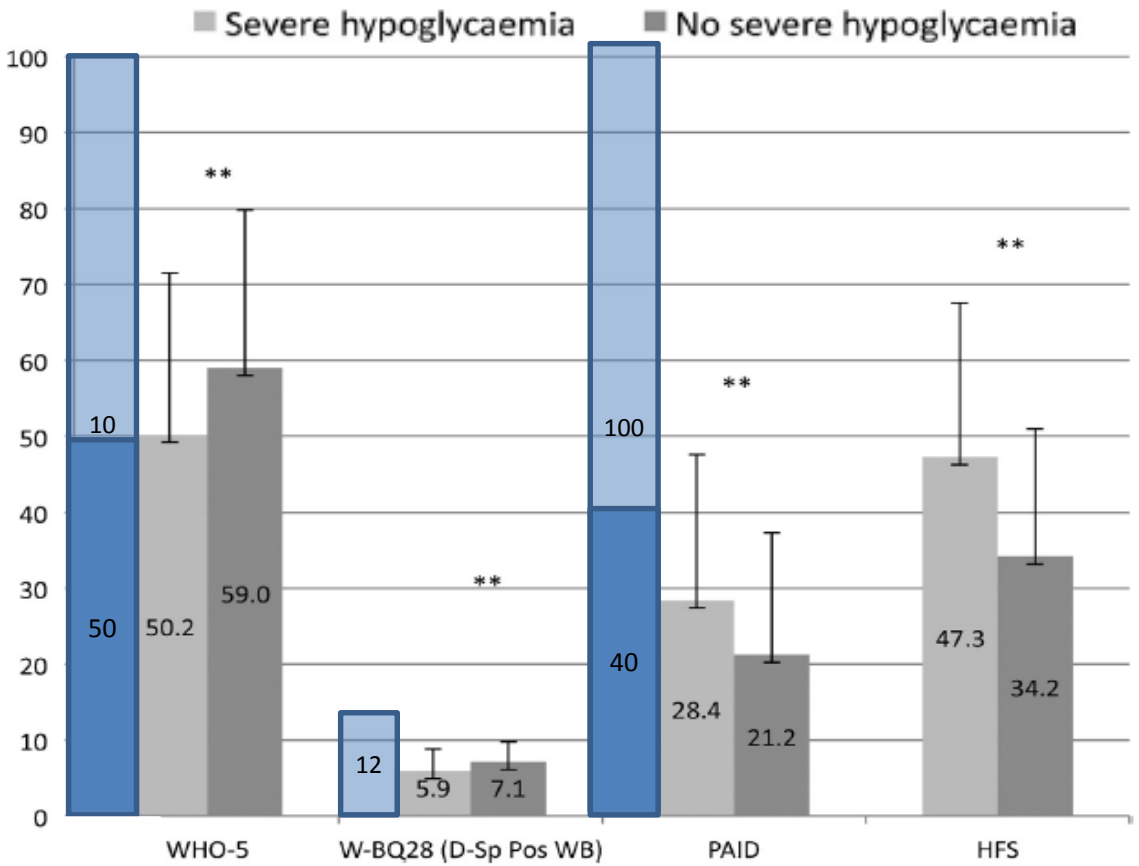
Kim et al, Diab Res Clin Pract, 2014:103:522-529
Okubu, Clin Exp Neph, 2013 and Koltowski, AJC; 2014

Severe hypoglycaemia

“requiring assistance of another person” actively to treat……..

Seaquist et al., Diab Care 2013; 36:1384-1395

Severe hypoglycaemia on QoL (T1)



Hendrieckx et al., Diab Res Clin Pract, 2014; 103: 430-436

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.

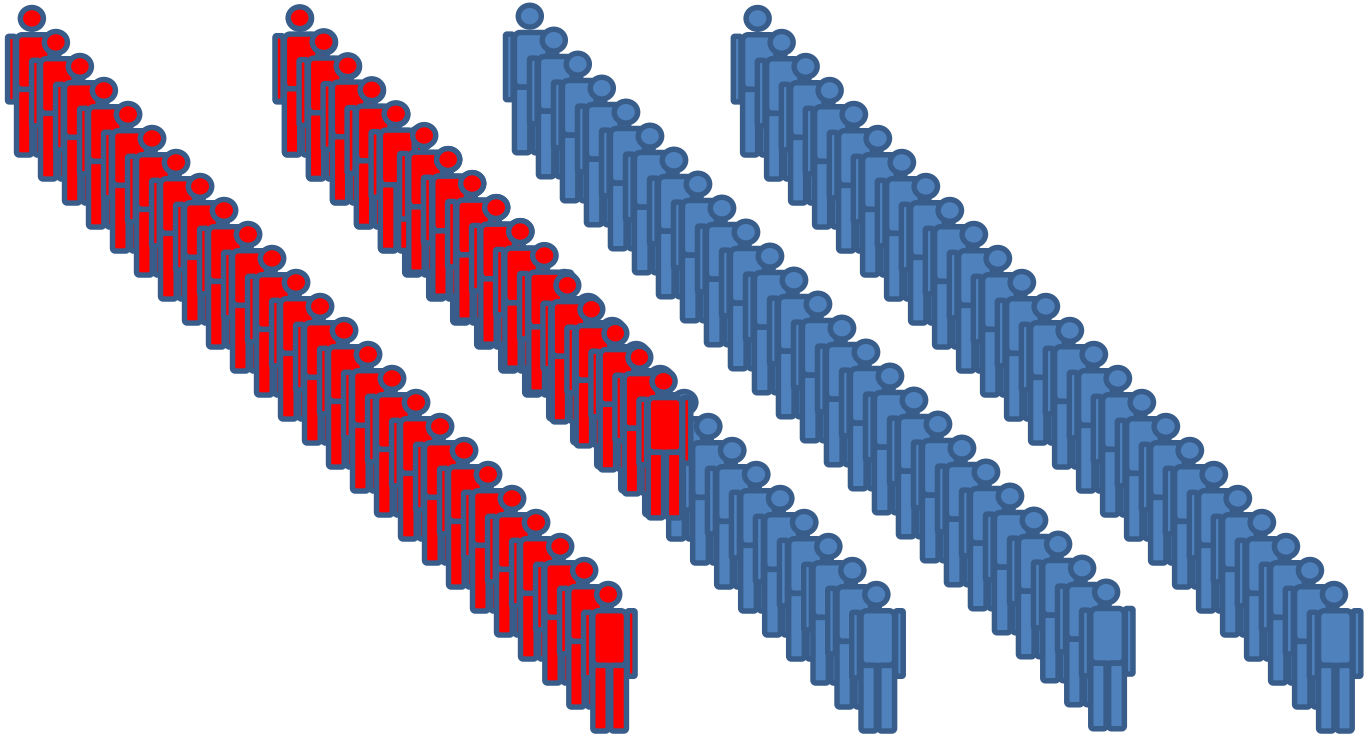
Hislop et al, Diabet. Med. 2008; 25, 91–96

Impaired awareness of hypoglycaemia

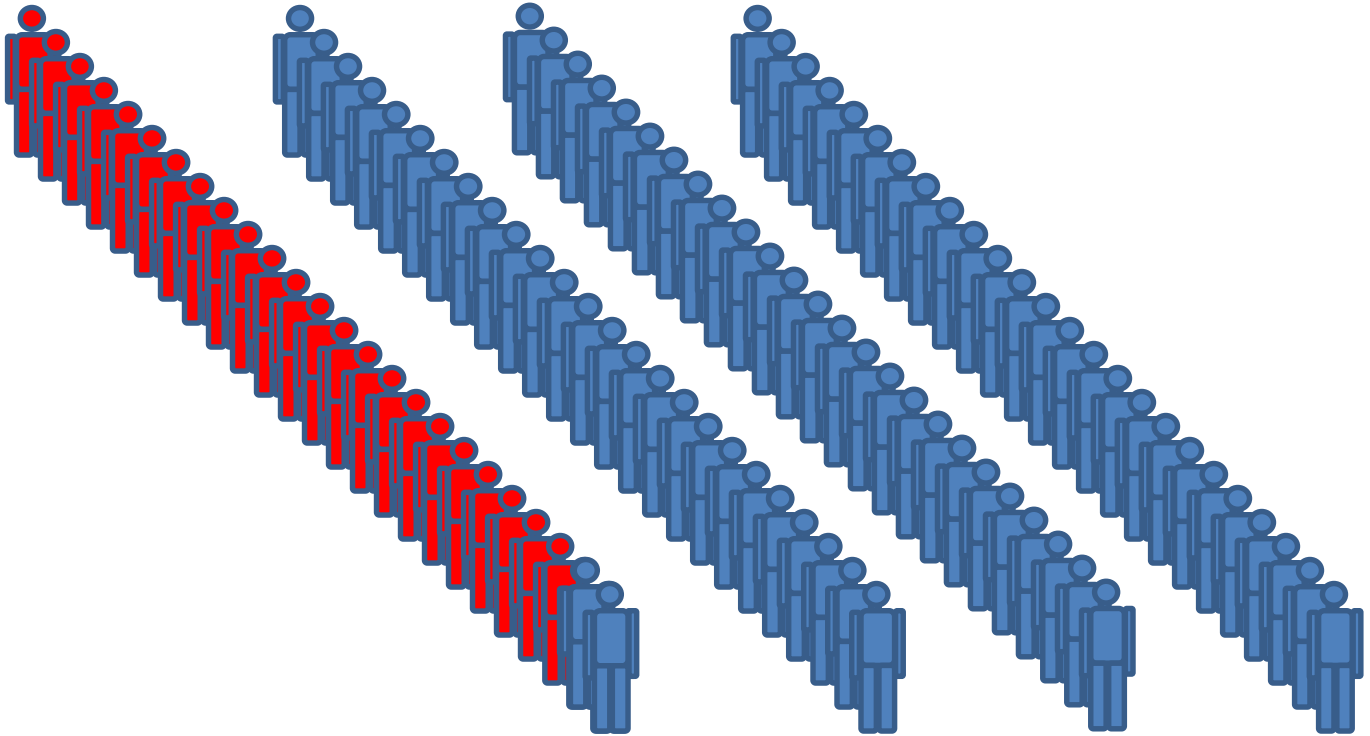
Asymptomatic: No typical symptoms but a measured low blood glucose

Seaquist et al., Diab Care 2013; 36:1384-1395

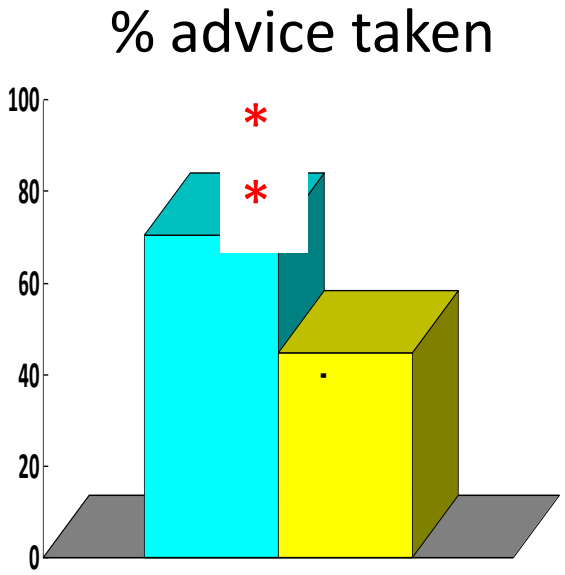
40% patients coming for DAFNE have IAH

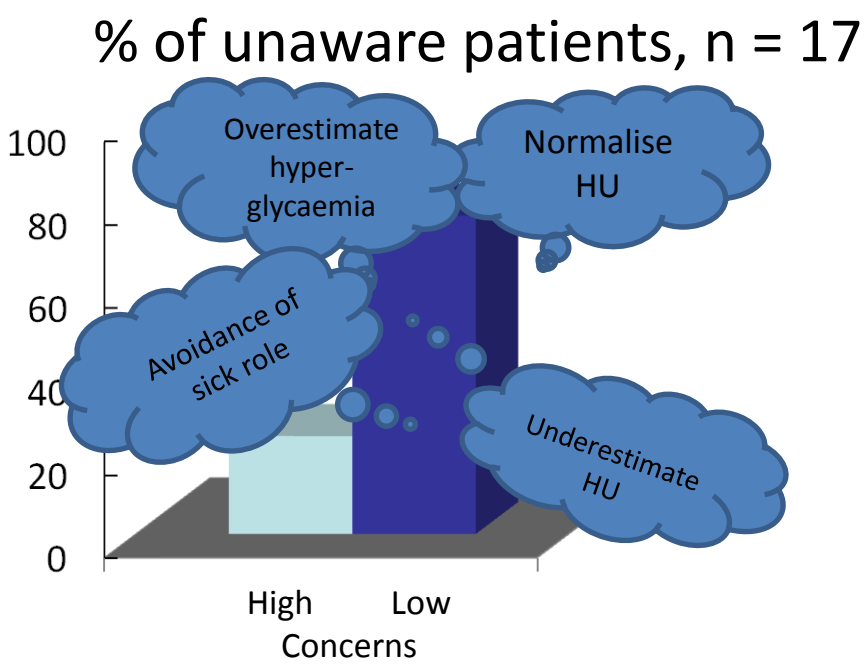


DAFNE restores awareness to 43%



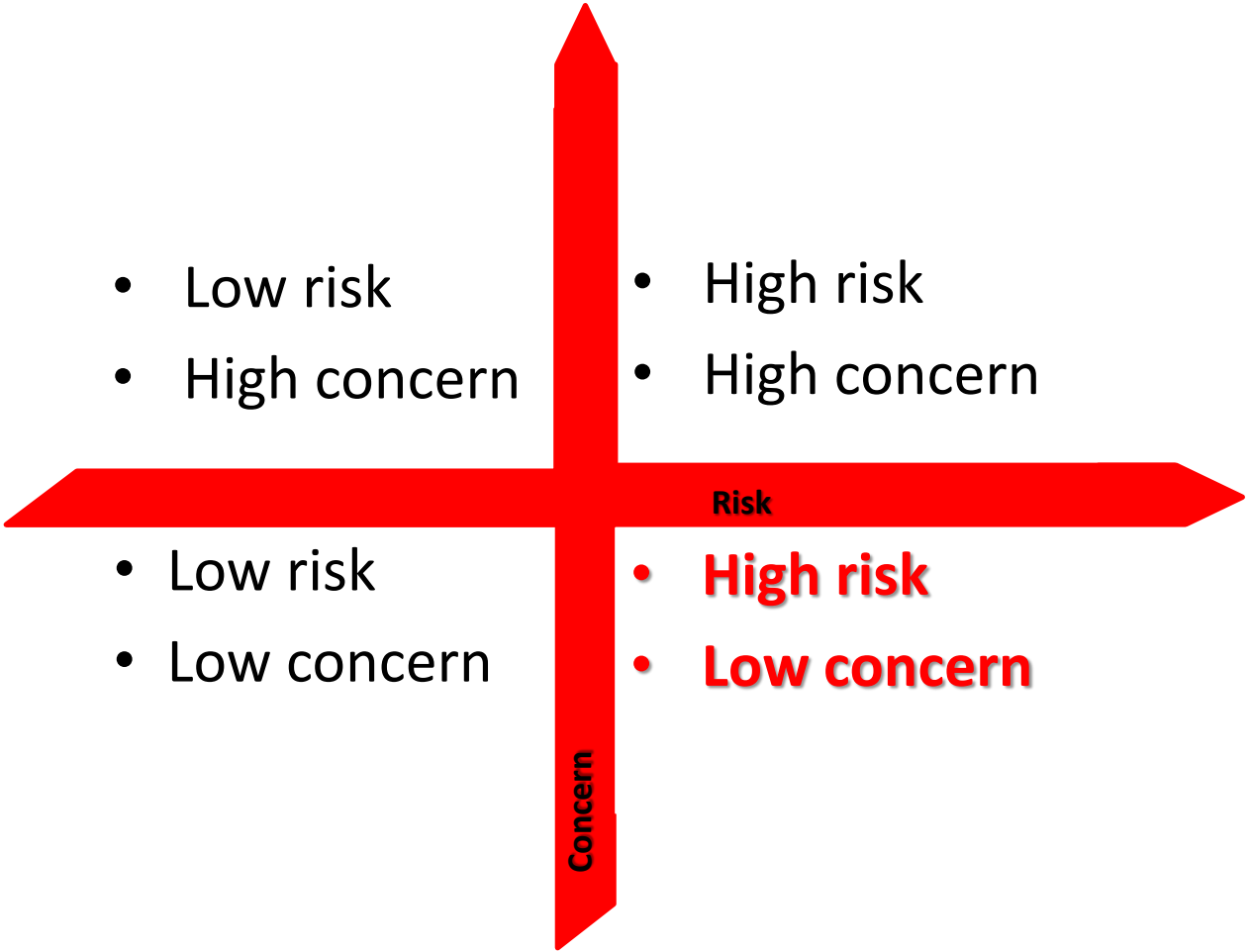
Effect of unawareness on adherence?





Smith et al., Diabetes Care. 2009 ;32:1196-8.

Rogers et al., Diabet Med. 2012;29:321-7



Linda Gonder-Frederick - unpublished

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

Rankin et al., Chronic Illn. 2013 ;10:180-191

The untold story

"…….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

Lawton et al., Diabetes Care. 2014;37:109-15

FDG PET: Effect of awareness status on hypoglycaemia responses

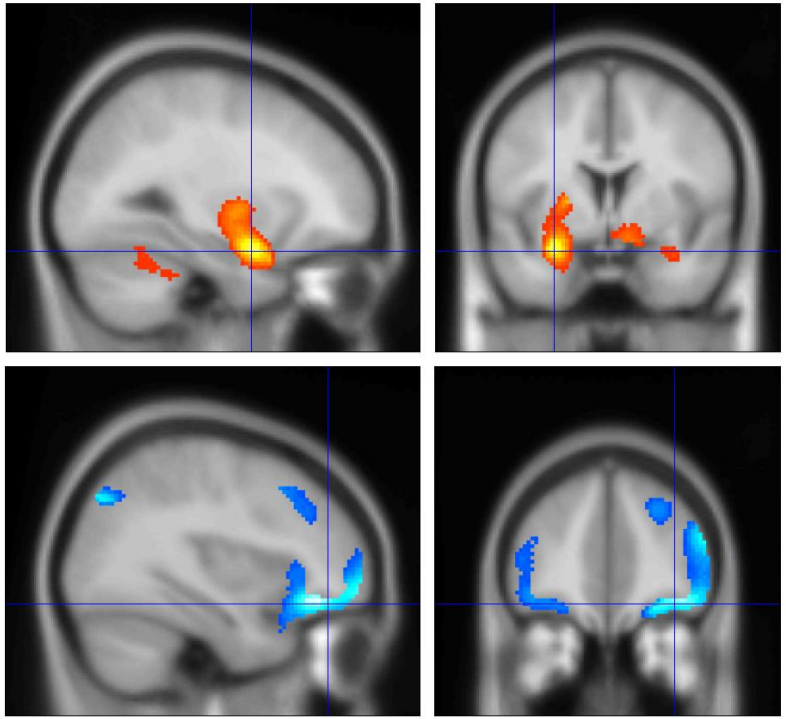
Greater Increase In aware, *P<0.05, k >100*

Symptomatic Stress Responses

Lesser fall

Hedonic Perception

Pleasure



Dunn et al, Diabetes, 2007; 56: 2766

Mrs MF

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

Unaware (*p*năwē³)

- Not aware (of)
- Not cognizant

- Ignorant (1704)
- Blind to the consequences
- Reckless (*rare*) 1817

The Shorter Oxford Dictionary

The University Of Sheffield.

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

KING'S College LONDON

King's College Hospital NHS
NHS Foundation Trust

DAFNE HART:

A psycho-educational programme

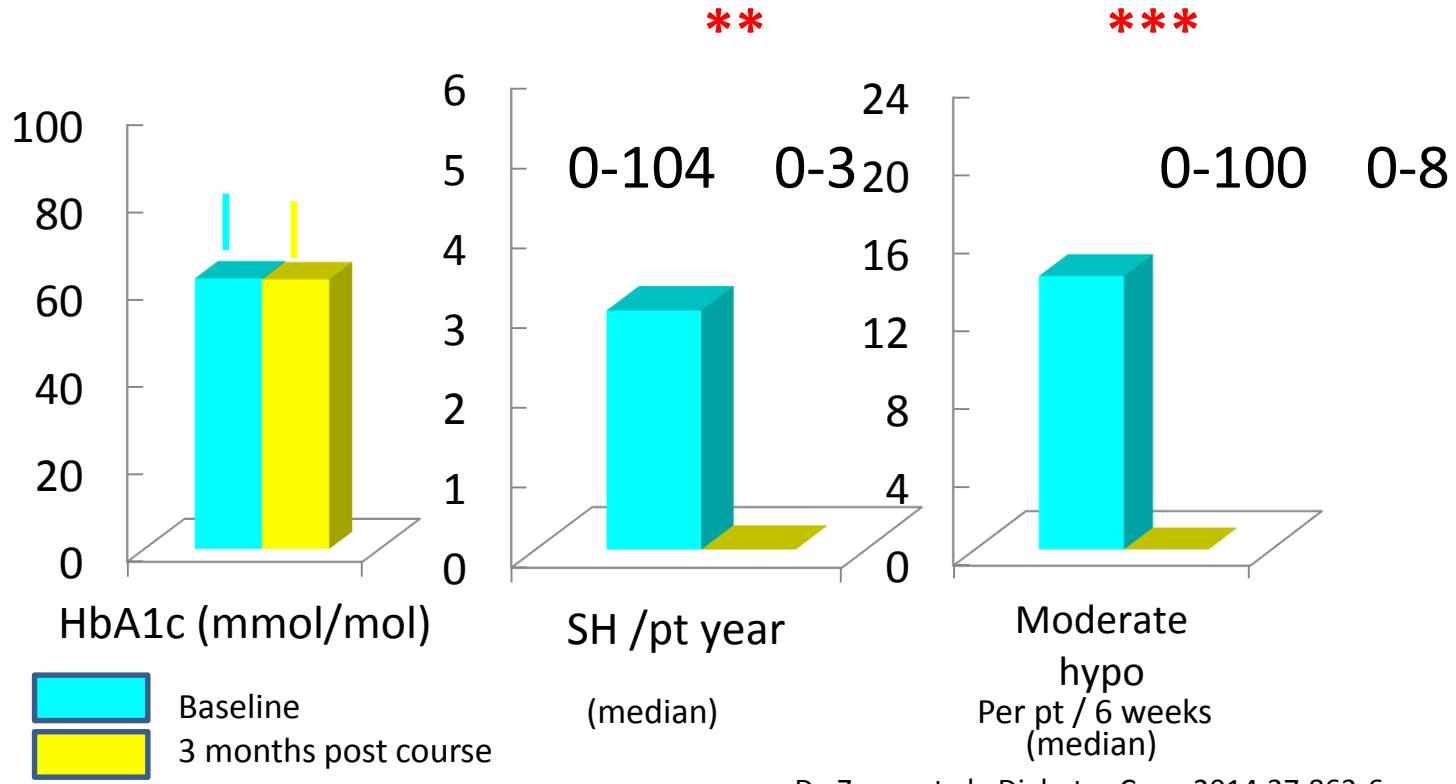
for people with T1DM and intractable problematic hypoglycaemia despite specialist support

De Zoysa, Diabetes Care, 2014

Diabetes Research Group

KING'S HEALTH PARTNERS
An Academic Health Sciences Centre for London
Pioneering better health for all

DAFNE HART: 12 month review



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

IHSG

Agenda

- 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

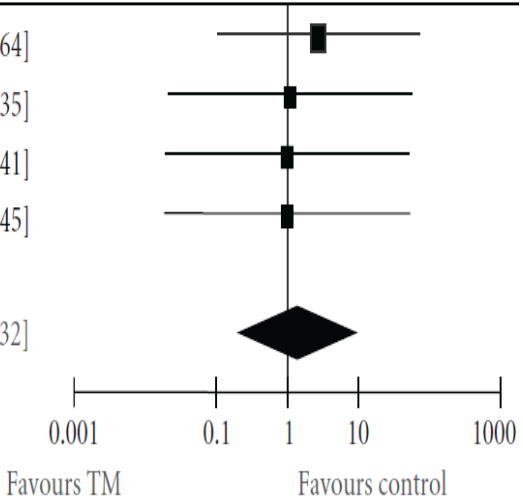
TM defined as scheduled remote transmission of BG data by telephone, fax, mobile or internet with unsolicited clinician feedback → 9 studies (568 T1D age<19 yrs) lasting 3-12 mos

Frequency of severe hypoglycemia

Study	log[odds ratio]	SE	Weight	Odds ratio Random, 95% CI
Cadario	1.02	1.68	32.6%	2.77 [0.1, 74.64]
Chase	0.09	2.02	22.5%	1.09 [0.02, 57.35]
Lawson	0	2.02	22.5%	1 [0.02, 52.41]
Rami	0	2.03	22.3%	1 [0.02, 53.45]
Total (95% CI)			100%	1.42 [0.22, 9.32]

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.24$, df = 3 ($P = .97$); $I^2 = 0\%$

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



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

Shulman RM et al. J Ped Endocrinol 2010; doi: 10.1155/2010/536957

Telemedicine for prevention of hypoglycaemia in T1D

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

Rossi MC et al. Diab Technol Ther 2013; 15:670-79

Telemedicine for prevention of hypoglycaemia in T2D

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)

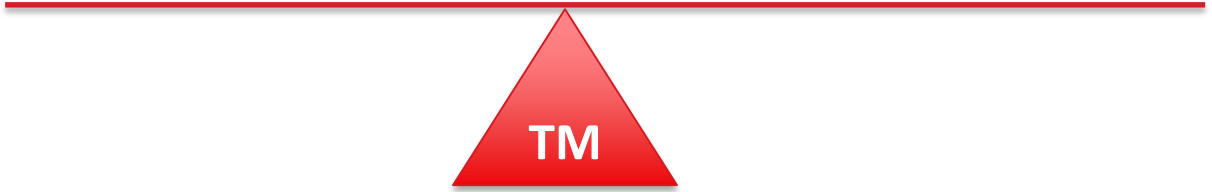
But…

- ✓ No control group
- ✓ Extra cost 9.66 USD/month per patient

Kesavadev J et al. Diab Technol Ther 2012; 14:772-76

Telemedicine for prevention of hypoglycaemia

Pro	Con
Overcomes distance barrier	Needs 24/7 personnel
Immediate problem solving	Behavioural changes are difficult
Reduces face-to-face visits	Persistence depends on“Pro-Technology” profile?
May reduce costs?	Weak evidence for benefit
Anticipates acute complications?	



P.Aschner 2014

Risk Factors for severe hypoglycaemia in T2D – Syst Rev

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)?

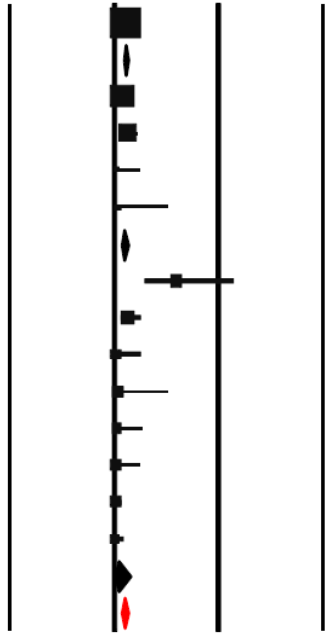
Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012

Risk Factors for severe hypoglycaemia in T2D – Syst Rev

Severe hypoglycemia rates for sulfonylurea studies*

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Holstein 2001	0.013	0.009	0.017	44 / 3489
long-term		0.013	0.009	0.017	44 / 3489
moderate-term	Matthews 2011	0.010	0.006	0.016	15 / 1546
moderate-term	Seck 2010	0.015	0.008	0.029	9 / 584
moderate-term	Garber 2011	0.002	0.000	0.031	0 / 248
moderate-term	Marre 2009	0.004	0.000	0.066	0 / 114
moderate-term		0.011	0.007	0.017	24 / 2492
short-term	UK Hypoglycemia Group	0.074	0.037	0.141	8 / 108
short-term	Arechavaleta 2011	0.015	0.008	0.031	8 / 519
short-term	Nauck 2009	0.002	0.000	0.032	0 / 242
short-term	Russell-Jones 2009	0.004	0.000	0.066	0 / 114
short-term	Chou 2008	0.002	0.000	0.034	0 / 225
short-term	Kendall 2005	0.002	0.000	0.031	0 / 247
short-term	Drouin 2004	0.001	0.000	0.009	1 / 800
short-term	Schernthaner 2004	0.001	0.000	0.009	0 / 845
short-term		0.005	0.001	0.019	17 / 3100
Overall		0.012	0.009	0.015	85 / 9081

Event rate and 95% CI



*Sulfonylurea monotherapy and combined sulfonylurea and metformin studies

Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012

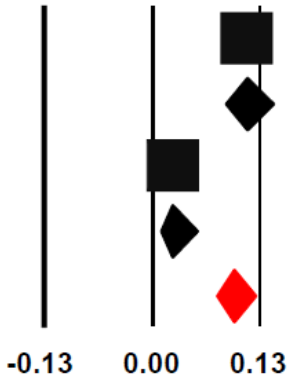
Risk Factors for severe hypoglycaemia in T2D – Syst Rev

Severe hypoglycemia event rates for NPH insulin studies

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Rosenstock 2009	0.109	0.085	0.139	55 / 504
long-term		0.109	0.085	0.139	55 / 504
short-term	Rosenstock 2001	0.023	0.010	0.051	6 / 259
short-term		0.023	0.010	0.051	6 / 259
Overall		0.093	0.073	0.118	61 / 763

Statistics for Each Study

Event rate and 95% CI



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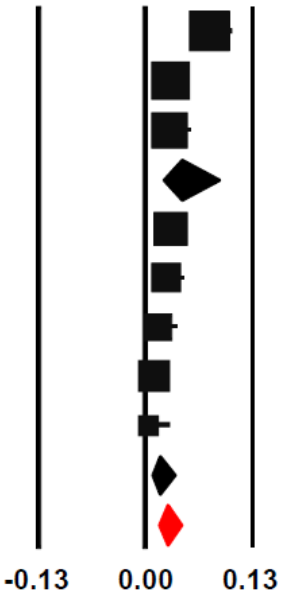
Risk Factors for severe hypoglycaemia in T2D – Syst Rev

Severe hypoglycemia event rates for insulin glargine studies*

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Rosenstock 2009	0.074	0.054	0.100	38 / 513
long-term	Buse 2011	0.029	0.016	0.050	12 / 419
long-term	Rosenstock 2008	0.027	0.014	0.054	8 / 291
long-term		0.041	0.019	0.084	58 / 1223
short-term	Kennedy 2006	0.030	0.026	0.034	228 / 7607
short-term	Riddle 2003	0.025	0.013	0.046	9 / 367
short-term	Heine 2005	0.015	0.006	0.039	4 / 267
short-term	Davies 2005	0.010	0.008	0.013	45 / 4588
short-term	Rosenstock 2001	0.004	0.001	0.027	1 / 259
short-term		0.016	0.008	0.032	288 / 13088
Overall		0.025	0.015	0.041	346 / 14311

Statistics for Each Study

Event rate and 95% CI



*Alone or added to OHAs

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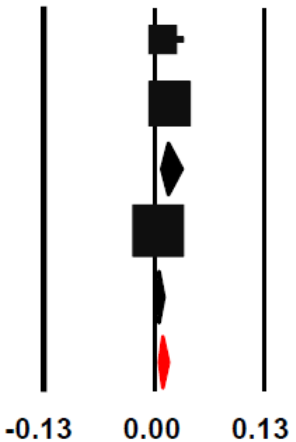
Risk Factors for severe hypoglycaemia in T2D – Syst Rev

Severe hypoglycemia event rates for insulin detemir studies

Group By Duration	Study Name	Statistics for Each Study				Event rate and 95% CI
		Event Rate	Lower Limit	Upper Limit	Total	
long-term	Holman 4T 2009	0.009	0.002	0.034	2 / 234	
long-term	Rosenstock 2008	0.017	0.007	0.041	5 / 291	
long-term		0.014	0.007	0.029	7 / 525	
moderate-term	Marre 2009	0.004	0.001	0.009	4 / 1129	
moderate-term		0.004	0.001	0.009	4 / 1129	
Overall		0.009	0.005	0.015	11 / 1154	



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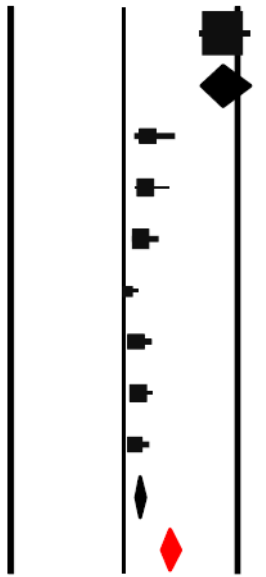
Risk Factors for severe hypoglycaemia in T2D – Syst Rev

Severe hypoglycemia event rates for NPH insulin studies*

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Rosenstock 2009	0.109	0.085	0.139	55 / 504
long-term		0.109	0.085	0.139	55 / 504
short-term	Frische 2003	0.026	0.012	0.056	6 / 232
short-term	Rosenstock 2001	0.023	0.010	0.051	6 / 259
short-term	Riddle 2003	0.018	0.009	0.037	7 / 389
short-term	Rayman (glulisine) 2007	0.004	0.001	0.018	2 / 448
short-term	Dailey (glulisine) 2004	0.014	0.006	0.030	6 / 435
short-term	Rayman (RHI) 2007	0.016	0.008	0.033	7 / 442
short-term	Dailey (RHI) 2004	0.011	0.005	0.027	5 / 441
short-term		0.016	0.012	0.022	39 / 2646
Overall		0.050	0.041	0.061	94 / 3150



*NPH insulin as either primary therapy or in combination
(Frische, sulfonylurea; Riddle oral OHAs; Rayman and Dailey, glulisine or regular insulin)

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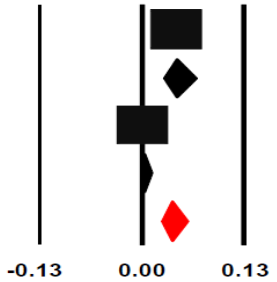
Risk Factors for severe hypoglycaemia in T2D – Syst Rev

Severe hypoglycemia event rates for insulin lispro studies

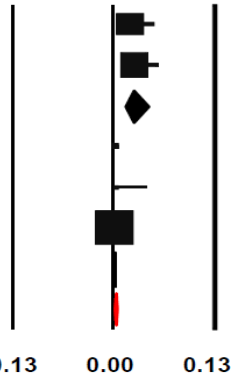
Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Buse 2011	0.042	0.027	0.064	20 / 476
long-term		0.042	0.027	0.064	20 / 476
short-term	Anderson 1997	0.001	0.000	0.010	1 / 722
short-term		0.001	0.000	0.010	1 / 722
Overall		0.036	0.023	0.054	21 / 1198



for insulin aspart studies

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Holman 4T 2009 (Prandial)	0.021	0.009	0.049	5 / 239
long-term	Holman 4T 2009 (Biphasic)	0.026	0.012	0.056	6 / 235
long-term		0.023	0.013	0.042	11 / 474
short-term	Bentrop 2011 (Biphasic)	0.002	0.000	0.007	2 / 1154
short-term	Liebl 2009 (Biphasic)	0.003	0.000	0.043	0 / 178
short-term	Valensi IMPROVE 2009 (Biphasic)	0.001	0.001	0.002	69 / 52419
short-term		0.001	0.002	0.002	71 / 53751
Overall		0.002	0.002	0.002	82 / 54225

*Subjects may also have received OHAs in addition to insulin aspart.

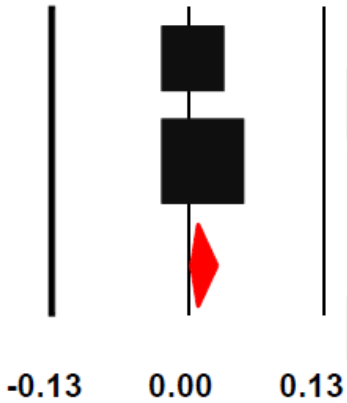


Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012

Risk Factors for severe hypoglycaemia in T2D – Syst Rev

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

Study Name	Statistics for each study				Event rate and 95% CI
	Event Rate	Lower limit	Upper limit	Total	
Rayman 2006	0.004	0.001	0.018	2 / 448	
Daily 2004	0.014	0.006	0.030	6 / 435	
	0.009	0.003	0.026	8 / 883	



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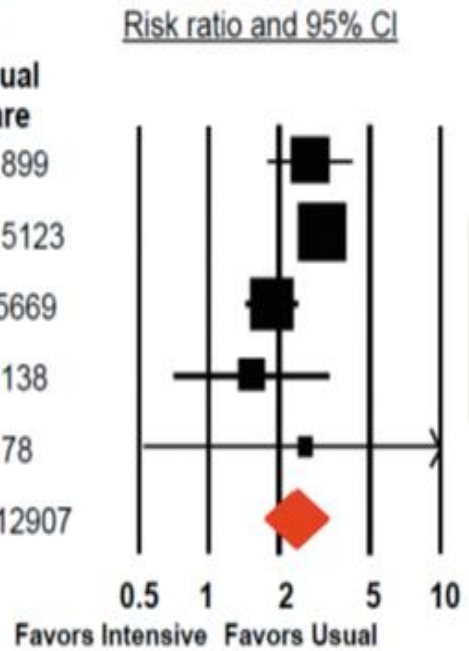
Risk Factors for severe hypoglycaemia in T2D – Syst Rev

Severe hypoglycemia events for intensive glycemic control versus usual care studies

Study name	Risk ratio	Lower limit	Upper limit	Events/Total: Intensive control	Events/Total: Usual care
VADT 2009	2.736	1.792	4.177	76 / 892	28 / 899
ACCORD 2008	3.096	2.717	3.527	849 / 5128	274 / 5123
ADVANCE 2008	1.884	1.442	2.463	150 / 5571	81 / 5669
UKPDS-33 1998	1.529	0.708	3.299	33 / 3071	8 / 1138
VA-CSDM 1995	2.600	0.520	12.993	5 / 75	2 / 78
	2.396	1.757	3.268	1113 / 14737	393 / 12907



Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012

Risk Factors for severe hypoglycaemia in T2D – Syst Rev

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

Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012

Impact of severe hypoglycaemia in T2D – Syst Rev

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

Risk Factors for severe hypoglycaemia in T2D – Syst Rev

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?

Bloomfield HE et al. VA Evidence-Based Synth Progr April 2012

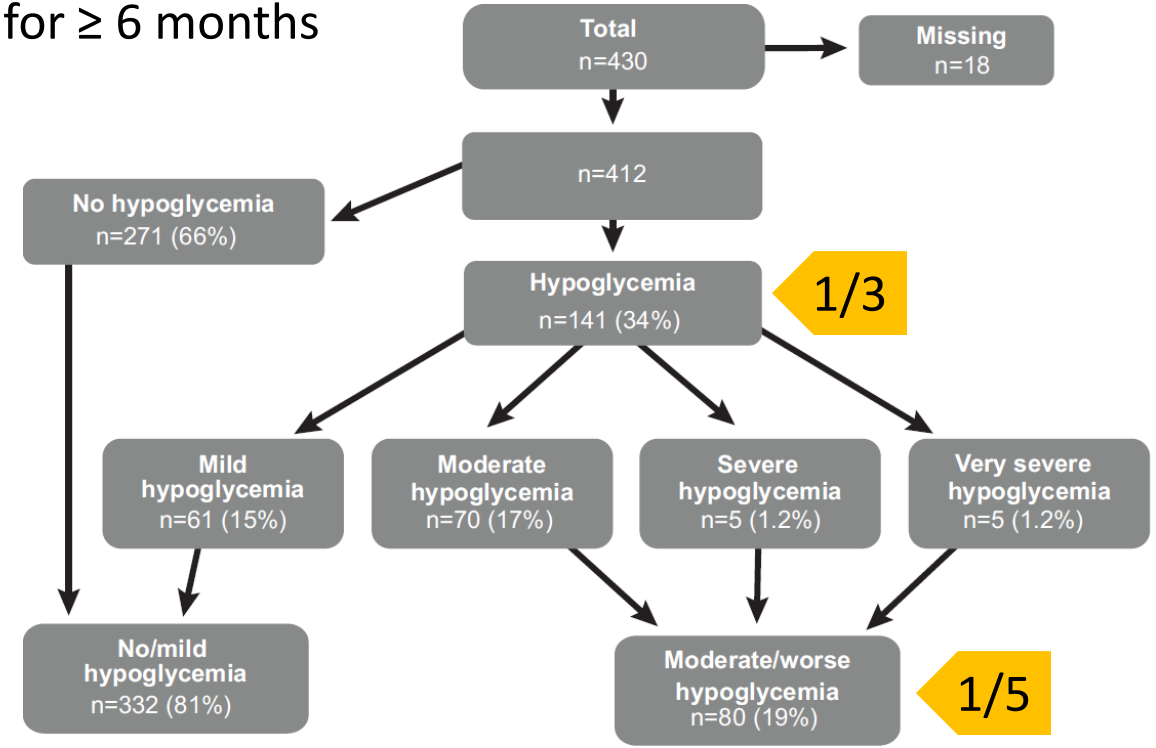
The burden of hypoglycaemia

Costs	Main cause	Source
Direct Health Care Syst Person & Family	Severe hypoglycaemia	Emergency Unit/ Hospitalisations Additional strips
Indirect State / Society/ Person&Family	Severe/Moderate hypoglycaemia, nocturnal	Absence from work, ↓ adherence, stop treatment?
Intangible Person & Family	Any, mainly nocturnal?	QOL for patient and partner

P.Aschner 2014

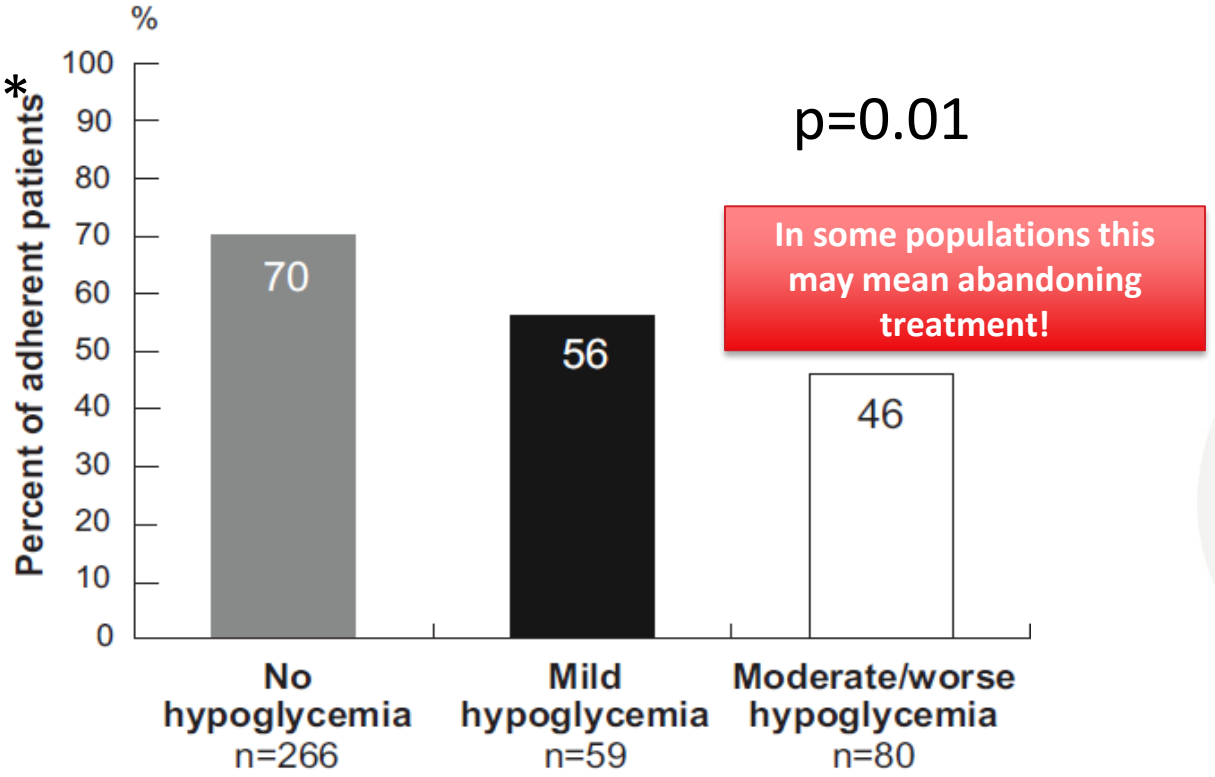
Impact of hypoglycaemia in T2D treated with MTF+SU

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



p=0.01

In some populations this may mean abandoning treatment!

*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

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

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

HbA_{1C} (mmol/L) latest value†	7.3 (0.8)	7.0 (0.8)	0.03*

Walz L et al. Pat Pref Adher 2014;8:593-601

Impact of non-severe nocturnal hypoglycaemia (NSNH)

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.

Brod M et al. Diab Obes Metab 2013;15:546-57

Impact of non-severe nocturnal hypoglycaemia (NSNH)

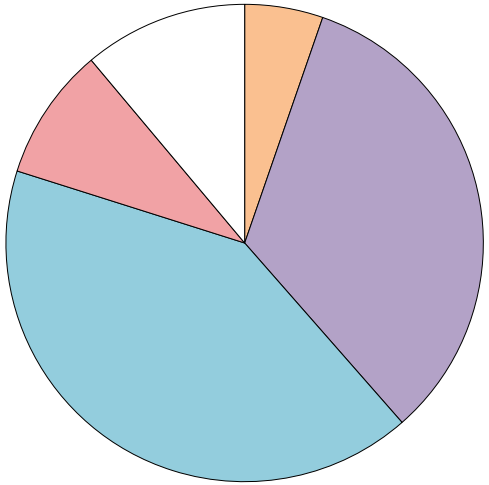
NSNH episodes	Type 2	Type 1	p
n	1416	692	
Daily	0.7%	1.2%	ns
>1 x week	7.8%	7.5%	ns
~1 x week	14.2%	19.3%	<0.01
Several x month	31.4%	33.5%	ns
1 x month	19.2%	20.3%	ns
Few x year	20.1% 286	16.6% 115	?
Very rarely	6.3%	1.4%	<0.001

Adapted from Brod M et al. Diab Obes Metab 2013;15:546-57

Impact of non-severe nocturnal hypoglycaemia (NSNH)

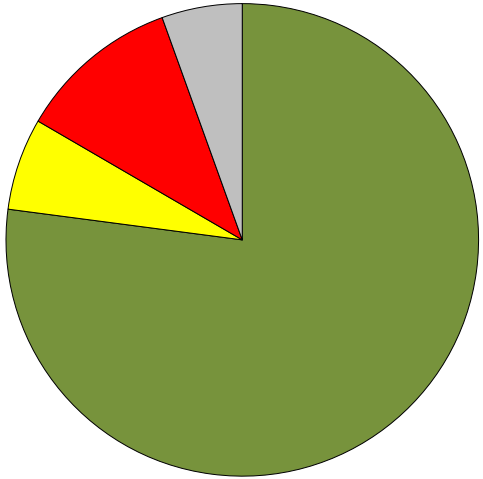
Characteristics of last NSNH episode

Time when it happened



- before MN
- MN-2 am
- 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 profesional for advice

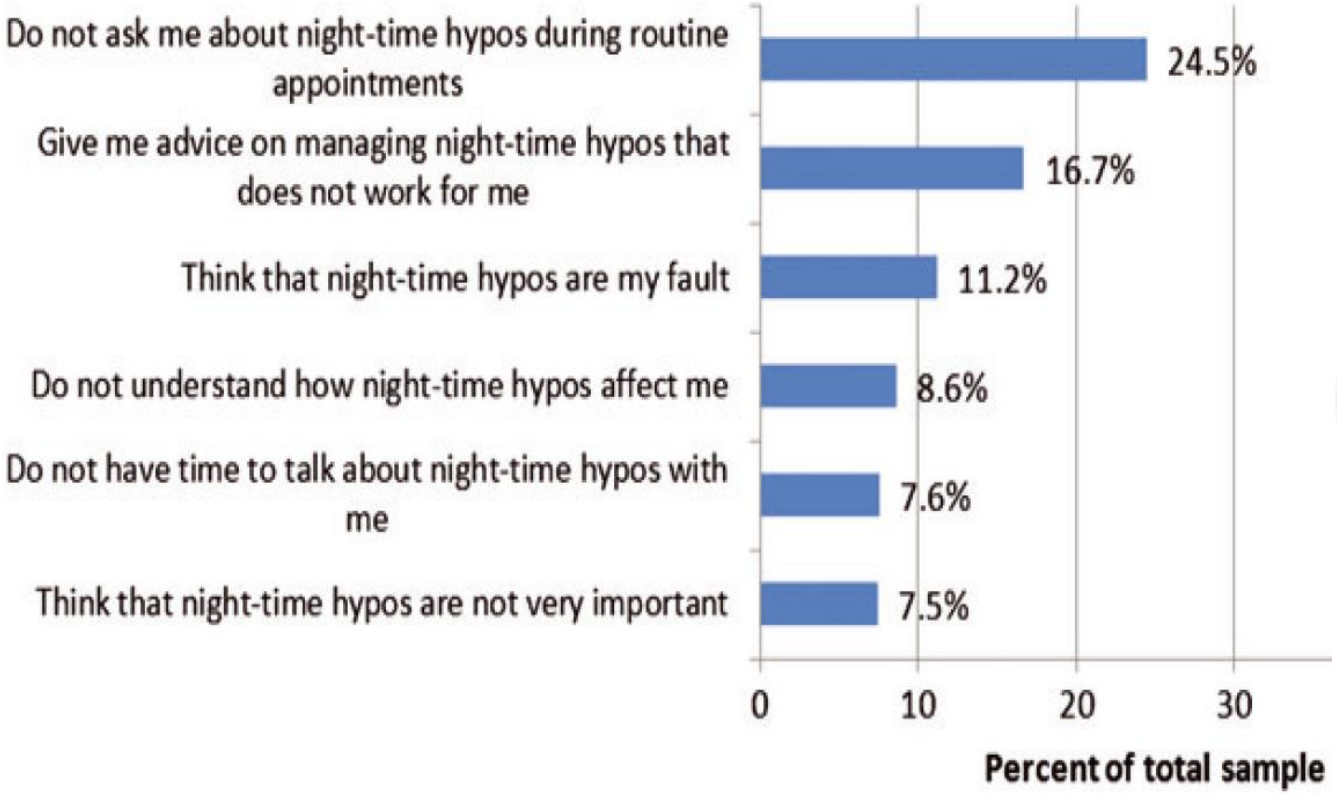
Impact on functioning and well-being

- ✓ 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



Brod M et al. Diab Obes Metab 2013;15:546-57

Global Attitude of Patients and Physicians 2 study (GAPP2)

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%).

Brod M. et al. Curr Med Res Opin 2012; 28:1947-58

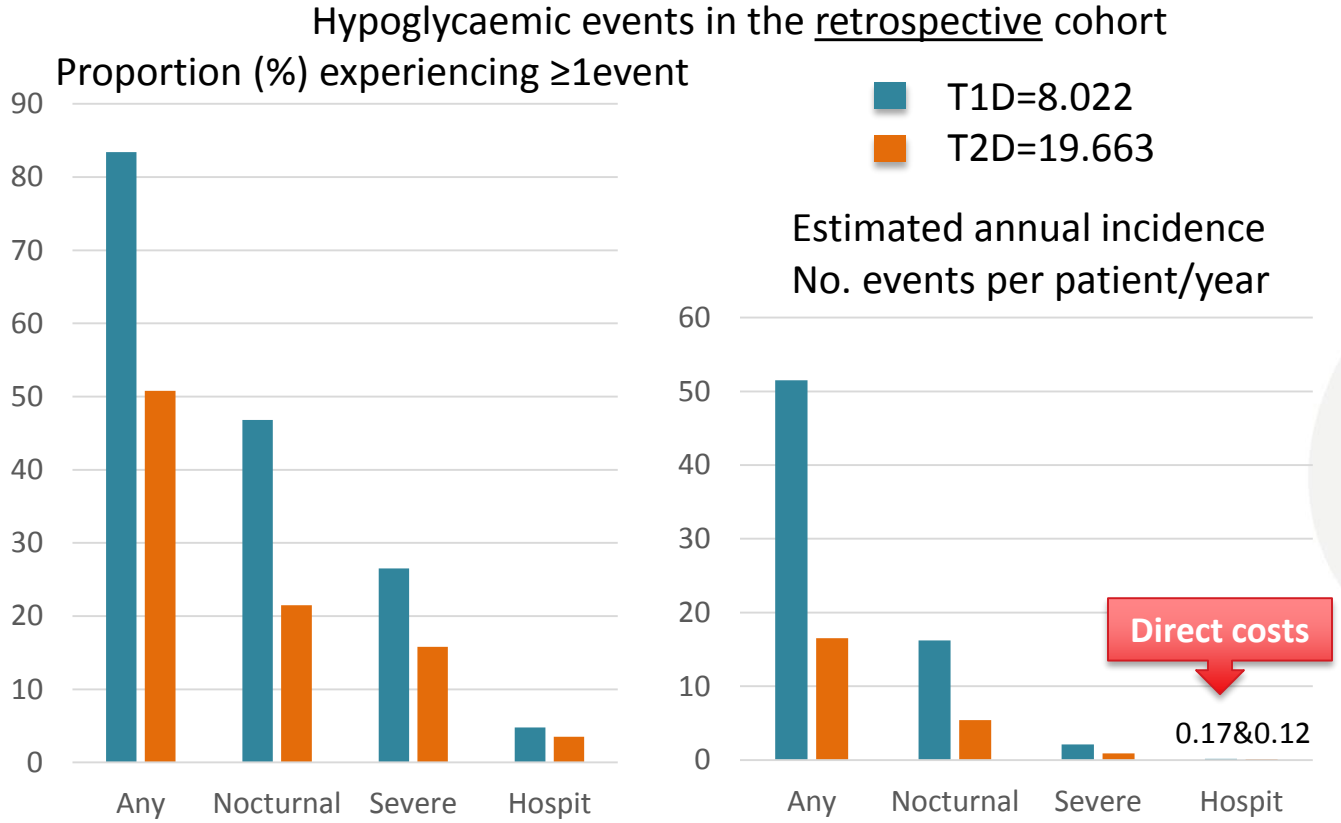
Global Attitude of Patients and Physicians 2 study (GAPP2)

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

Brod M. et al. Curr Med Res Opin 2012; 28:1947-58

Hypoglycaemia Awareness Trial (HAT)

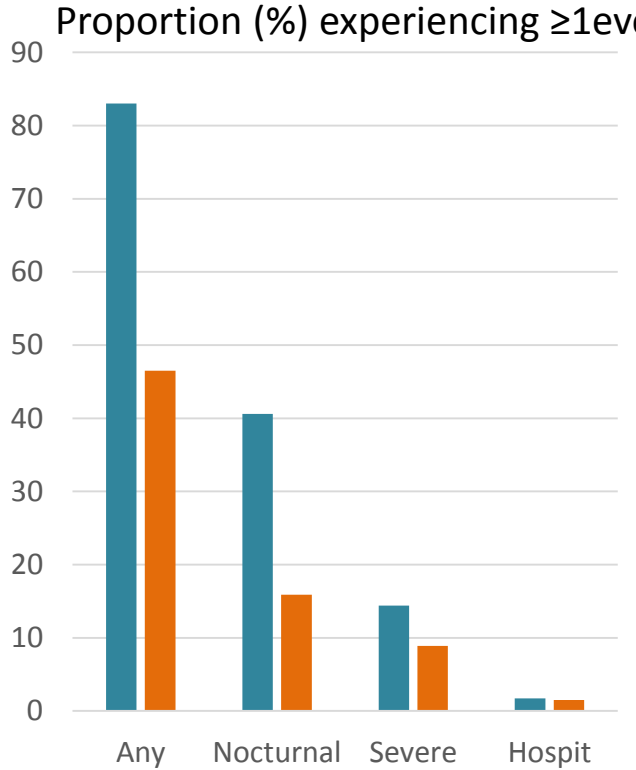


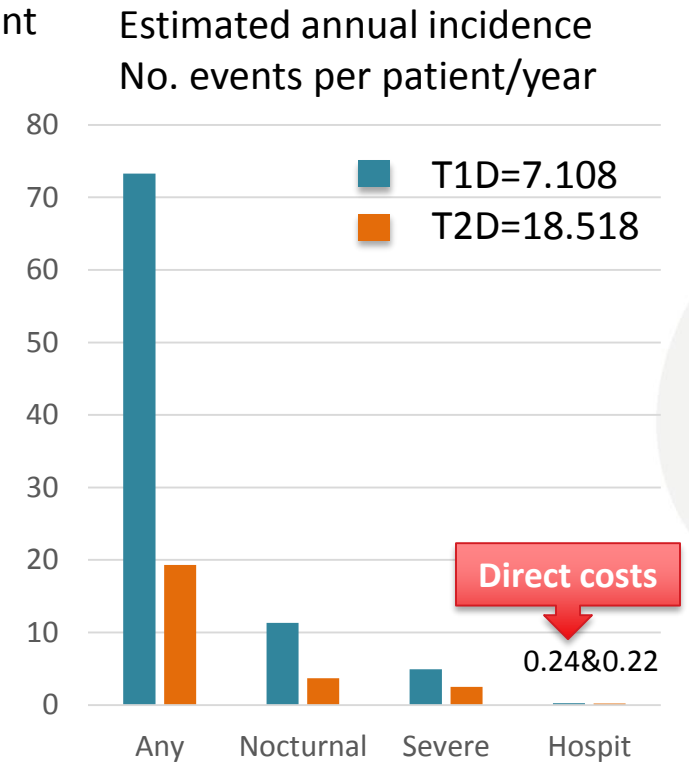
Any and nocturnal within 4 wks prior to baseline, severe and hospitalisation within 6 months

Khunti K. Personal communication

Hypoglycaemia Awareness Trial (HAT)

Hypoglycaemic events in the prospective cohort





All within 4 wks prior to baseline

Khunti K. Personal communication

The burden of hypoglycaemia

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

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

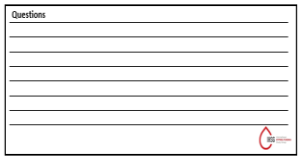
P.Aschner 2014

Thank you!

Panel Discussion

All

QUESTIONS FOR OUR PANEL



Question Cards

Microphones

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