Hypoglycemia Expert Meeting

An exclusive International Hypoglycaemia Study Group (IHSG)
event at the 2015 IDF World Diabetes Congress

December 1, 2015

Vancouver, British Columbia, Canada

Brought to you by members of the International Hypoglycaemia Study Group

IHSG

Welcome & Introductions

Lawrence A. Leiter, MD, FRCPC, FACP, FACE, FAHA
Division of Endocrinology and Metabolism,
St. Michael's Hospital
Professor of Medicine and Nutritional Sciences
University of Toronto
Ontario, Canada

WELCOME TO VANCOUVER!

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ABOUT THE IHSG

Formed in 2013

16 members from around the globe

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

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

Six Degrees Academy supports the IHSG with project management, logistics and supporting tactics

WHY HYPOGLYCEMIA MATTERS

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OUR OBJECTIVES THIS EVENING

1. Discuss the prevalence of hypoglycemia and how it affects patients
2. Engage with colleagues to better understand hypoglycemia

AGENDA

5:35 pm – Global Epidemiology	Simon Heller, BA, MB, Bchir, DM, FRCP
5:55 pm – Vascular Impact	Sophia Zoungas, MBBS, PhD, FRACP
6:15 pm – Hypoglycemia and the Brain	Elizabeth Seaquist, MD
6:35 pm – Technology to the Rescue	Robert Vigersky, MD
6:55 pm – Panel discussion	All
7:25 pm – Wrap-up	Lawrence Leiter, MD, FRCPC, FACP, FACE, FAHA

ALSO HERE TONIGHT…

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

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

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

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

Global Epidemiology

Simon Heller, BA, MB, Bchir, DM, FRCP
Professor of Clinical Diabetes
University of Sheffield
Director of Research and Development & Honorary Consultant Physician
Sheffield Teaching Hospitals Foundation Trust
Sheffield, United Kingdom

The University Of Sheffield.

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

IHSG

Outline

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

A question for you

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

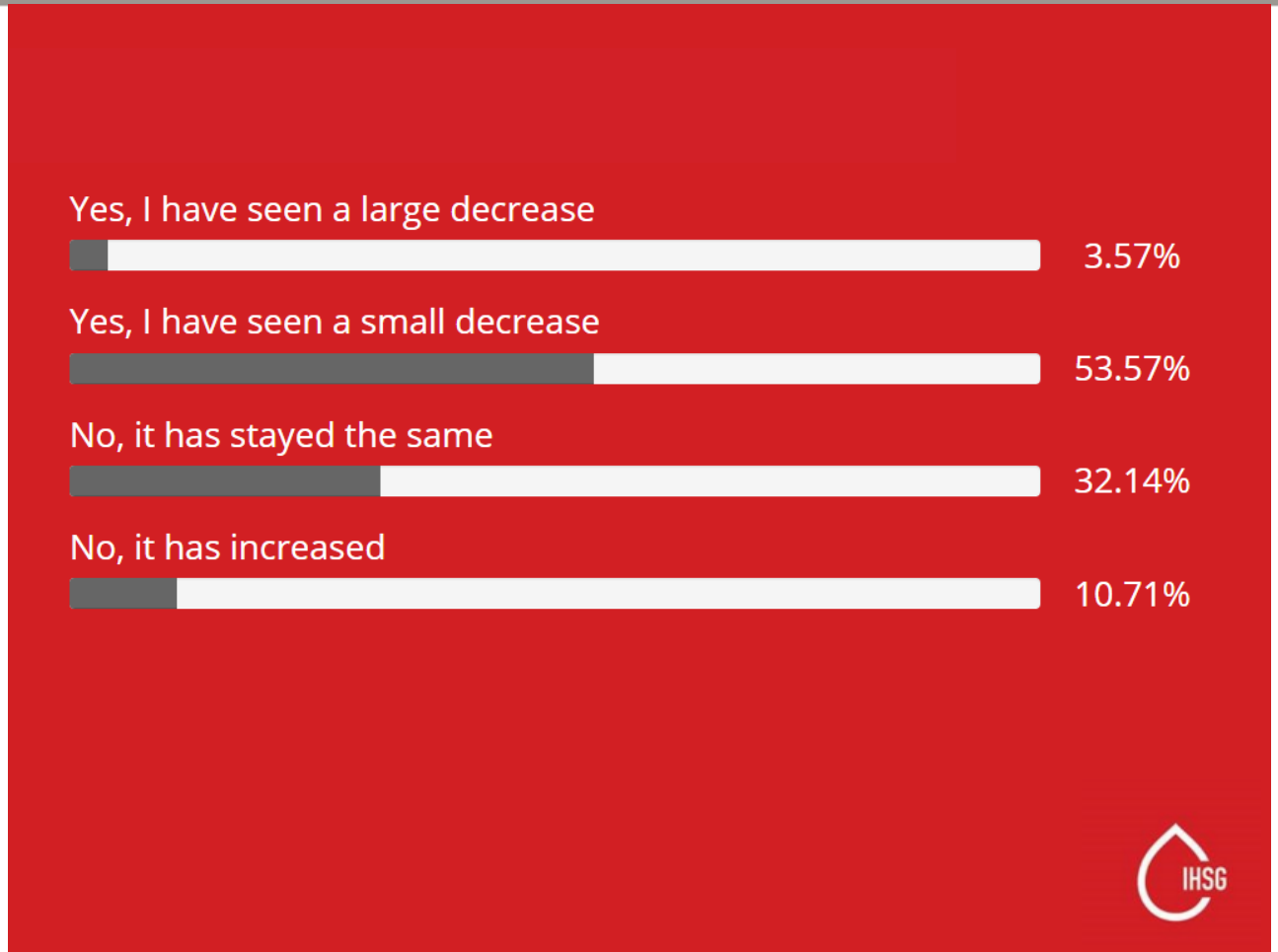
A. Yes, I have seen a large decrease

B. Yes, I have seen a small decrease

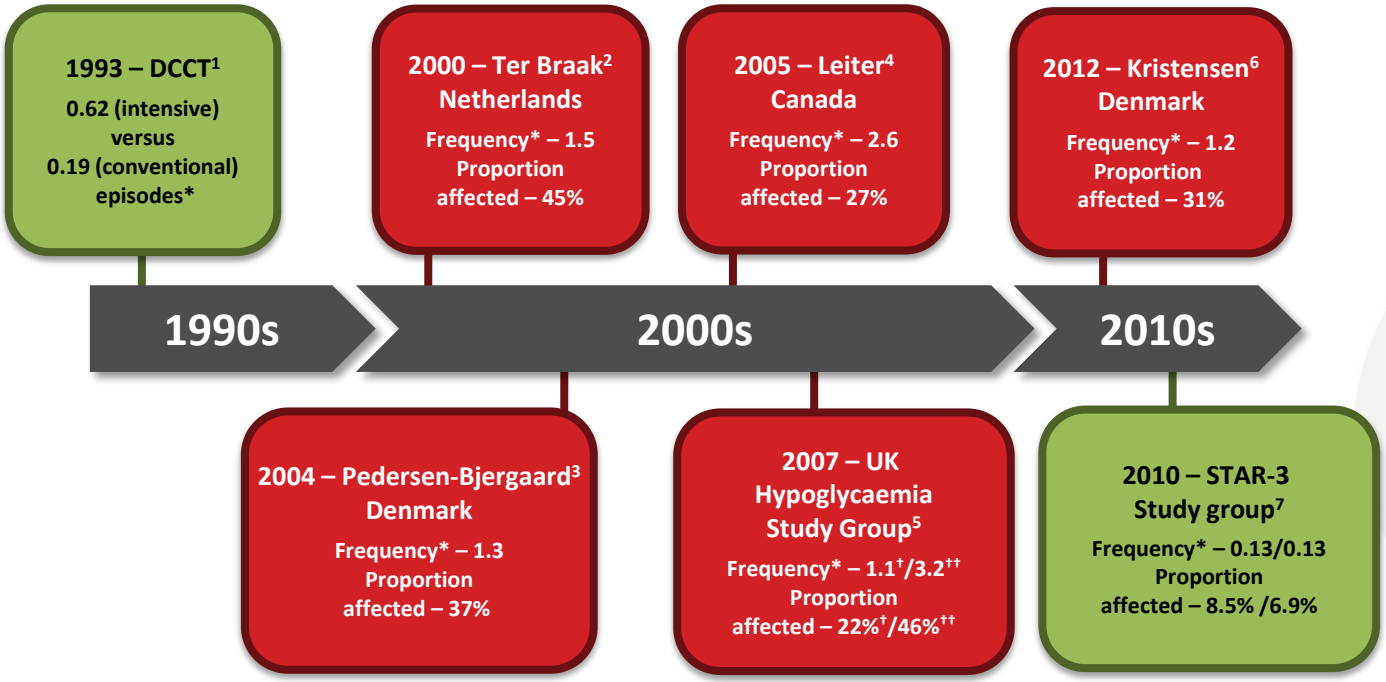
C. No, it has stayed the same

D. No, it has increased

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



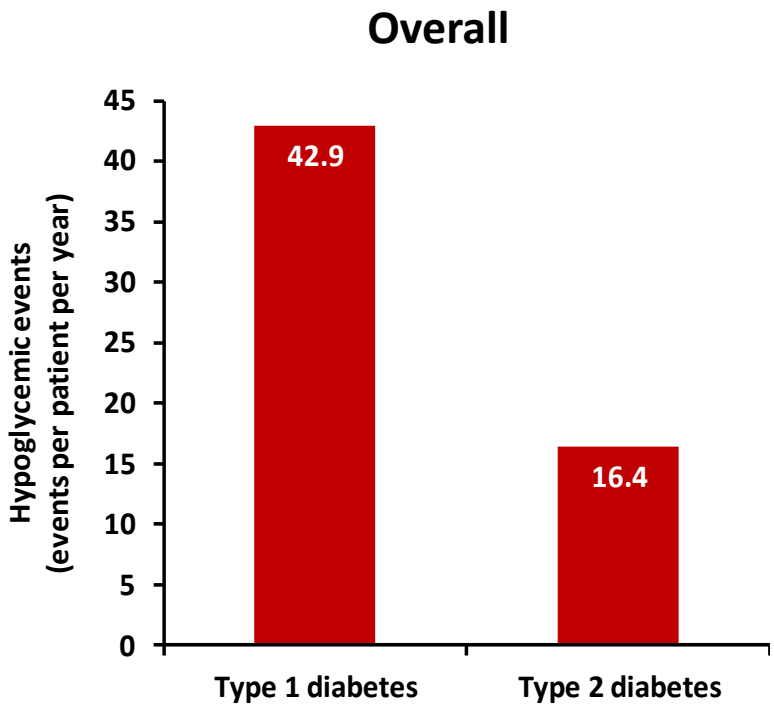
Frequency of severe hypoglycemia in adults with type 1 diabetes

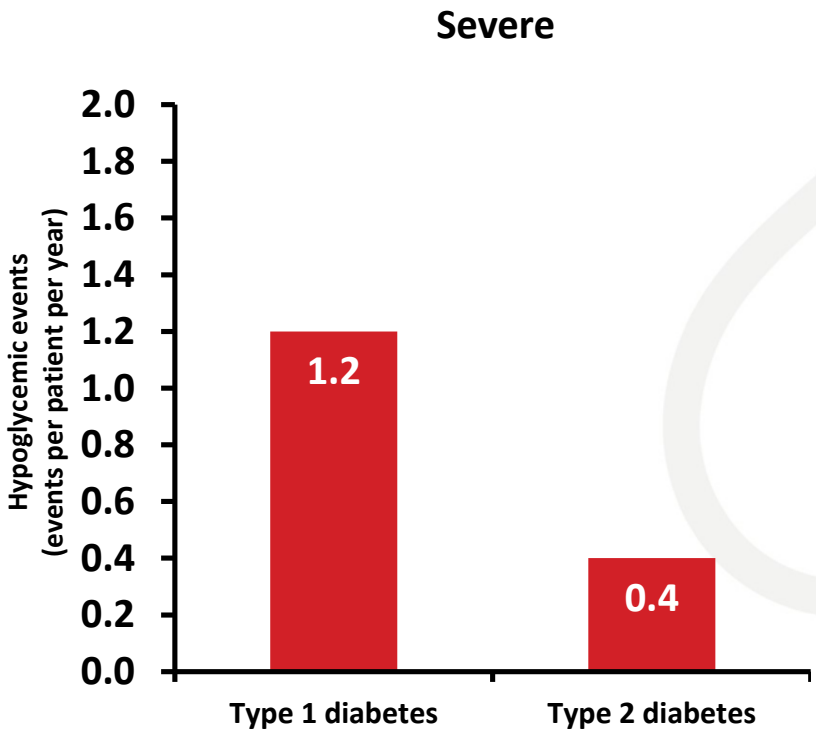


HbA_{1c} in each trial: [1]~7% (intensive) and ~9% (conventional) over 10 years follow-up; [2]Mean =7.8 ± 1.2%; [3]Mean = 8.6 ± 1.3%; [4]Most recent HbA_{1c} = 7.4%; [5]Mean 7.3 1.02 and 7.3 1.16†; 7.8 ± 0.73 and 7.6 ± 0.85†† at baseline and year 1, respectively; [6]Mean = 8.0 ± 1.0% and 7.9 ± 1.0% for patients treated with long-acting insulin analogue and human insulin, respectively.
Median follow-up across all studies was between 9–12 months. *Per patient/year; † diabetes duration <5 years †† diabetes duration >15 years.

[1]The DCCT Research Group *NEJM*; [2]Ter Braak et al. *Diabetes Care* 2000; [3]Pedersen-Bjergaard et al. *Diabetes Metab Res Rev*; [4]Leiter et al. *Can J Diabetes* 2005; [5]UK Hypoglycaemia Study Group *Diabetologia* 2007; [6]Kristensen et al. *Diabetes Res Clin Pract* 2012; [7]Davis et al. *Diabetes Technol Ther* 2010;12:249–255.

Patients with type 1 or 2 diabetes experience frequent hypoglycemic events



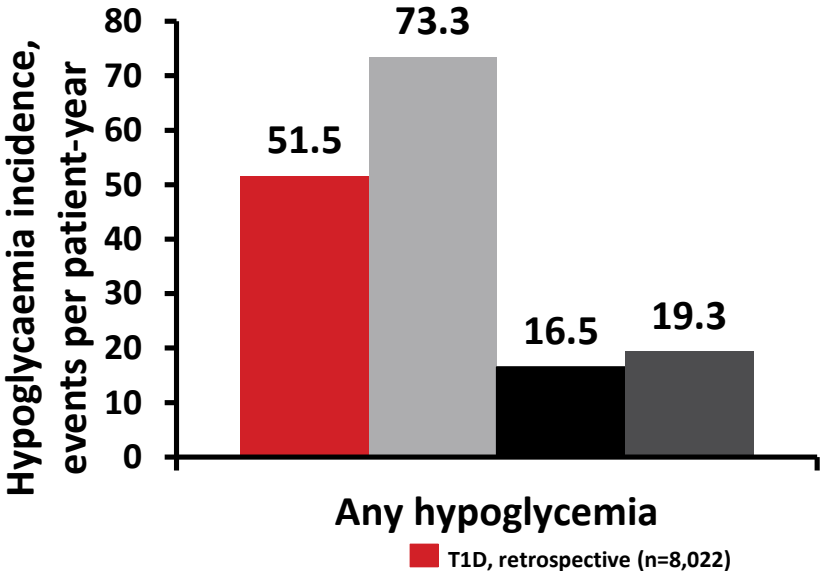


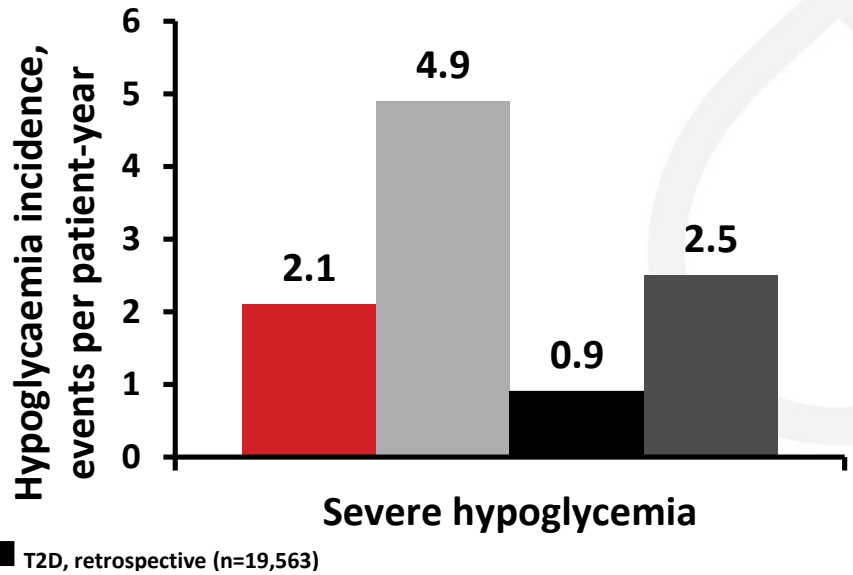
Severe hypoglycaemia was defined as any episode requiring third-party assistance.
Donnelly et al. *Diabet Med* 2005;22:749–55.

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

HAT study

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





HAT, Hypoglycaemia Assessment Tool. T1D, type 1 diabetes; T2D, type 2 diabetes.

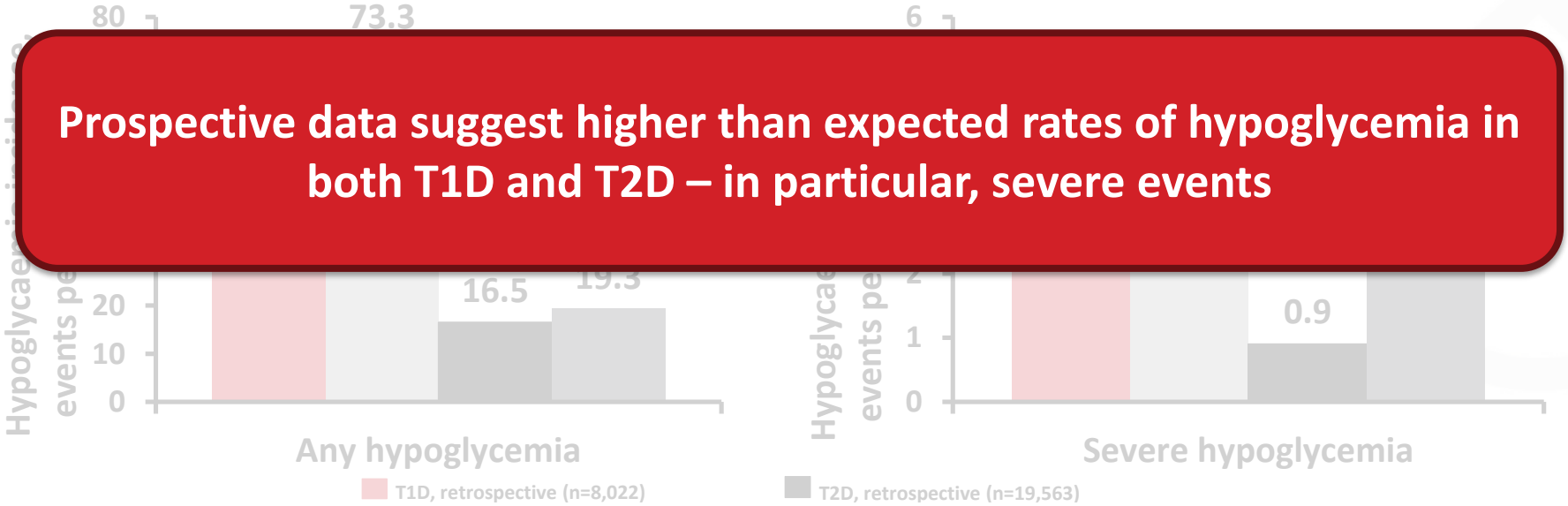
Khunti et al. *Diabetologia* 2014;57(Suppl. 1);S201.

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

HAT study

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

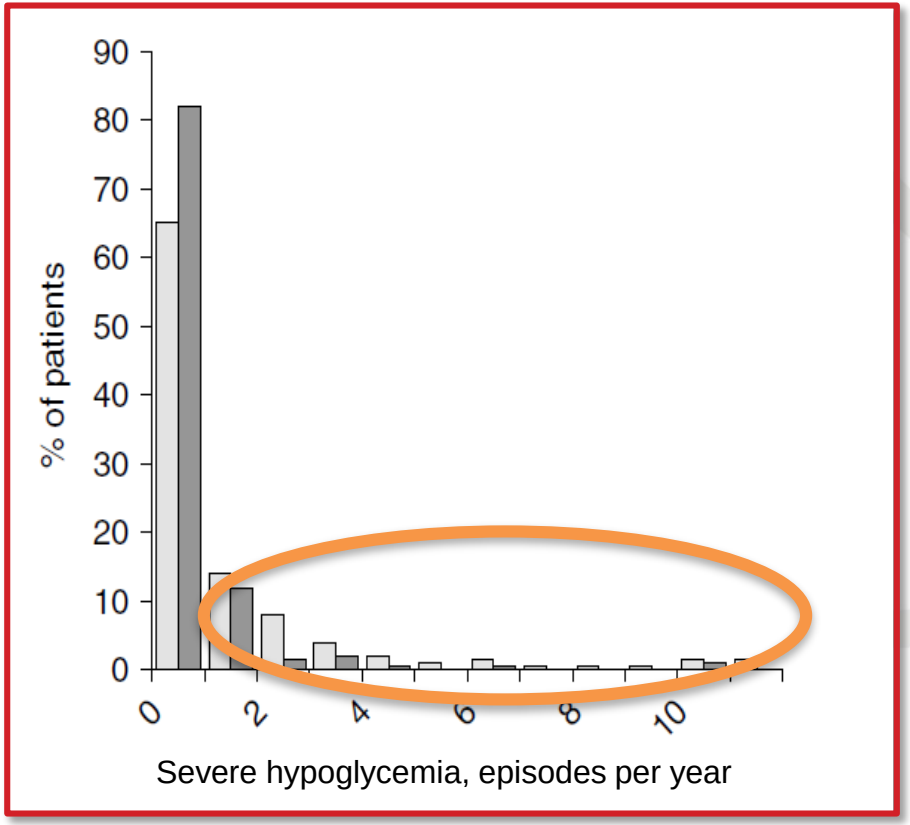
Prospective data suggest higher than expected rates of hypoglycemia in both T1D and T2D – in particular, severe events



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

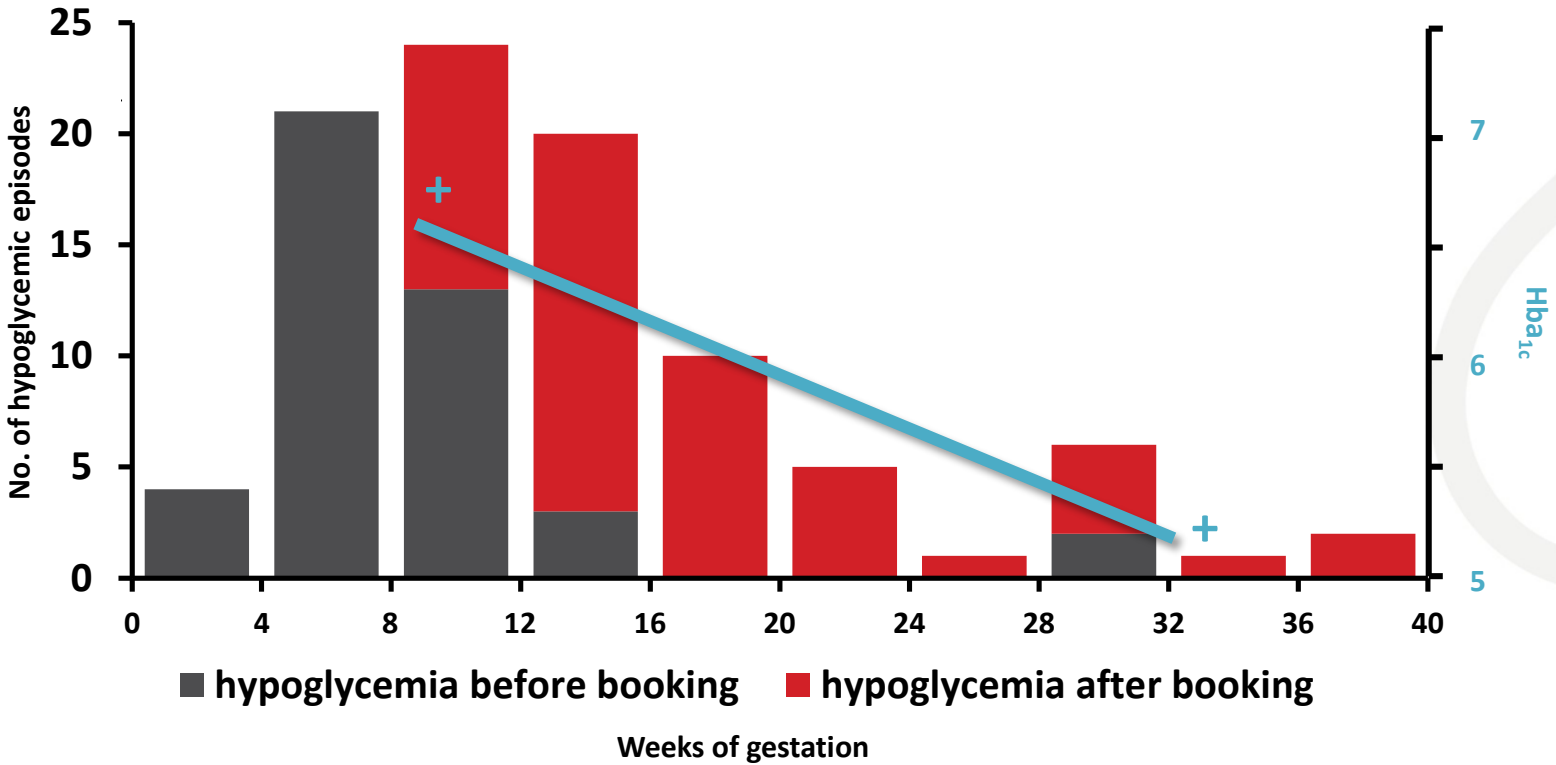
Severe hypoglycemia in type 1 diabetes

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



Pedersen-Bjergaard et al, *DMMR* 2004; 20: 479-86.

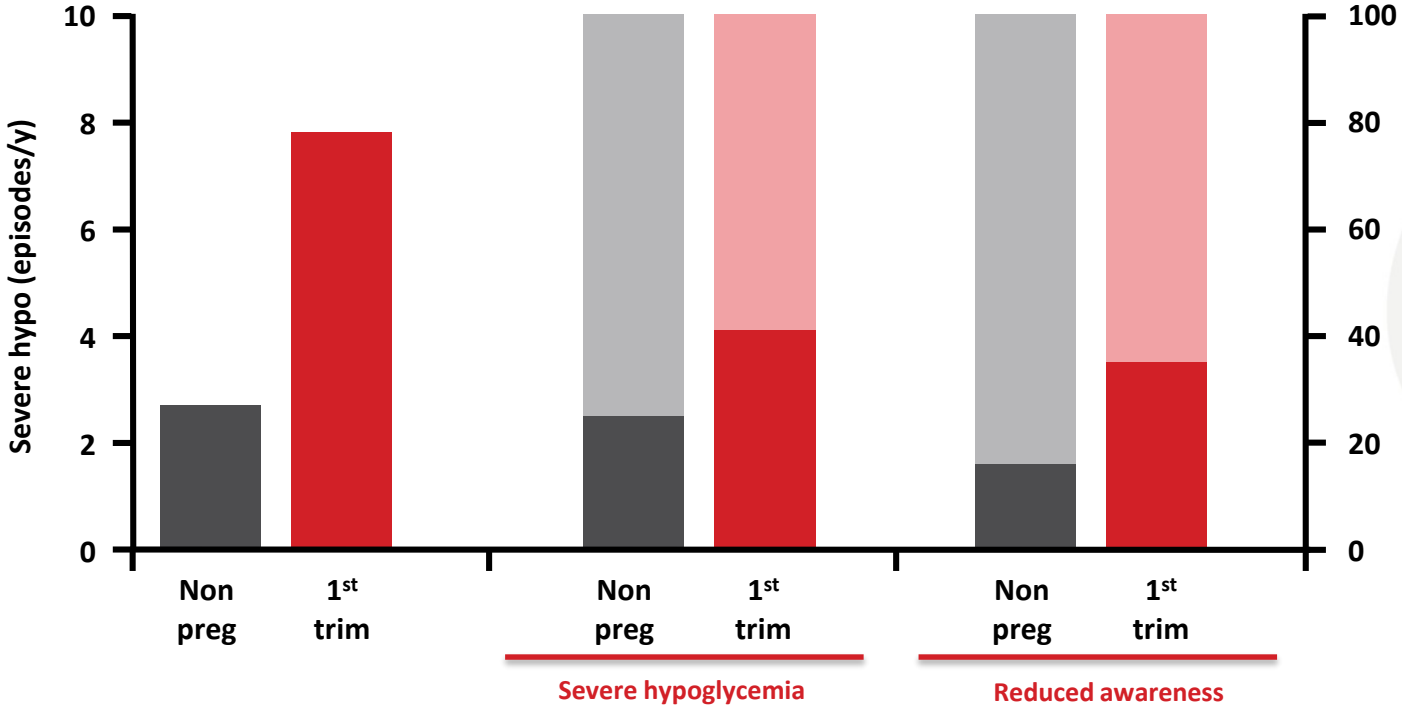
Risks of severe hypoglycemia in type 1 diabetic pregnancy according to gestational age



Kimmerle et al *Diabetes Care* 1992.

Risk of severe hypoglycemia in early pregnancy

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



Evers et al, *Diabetes Care*, 2002.

Hypoglycemia in children

Clinical classification:

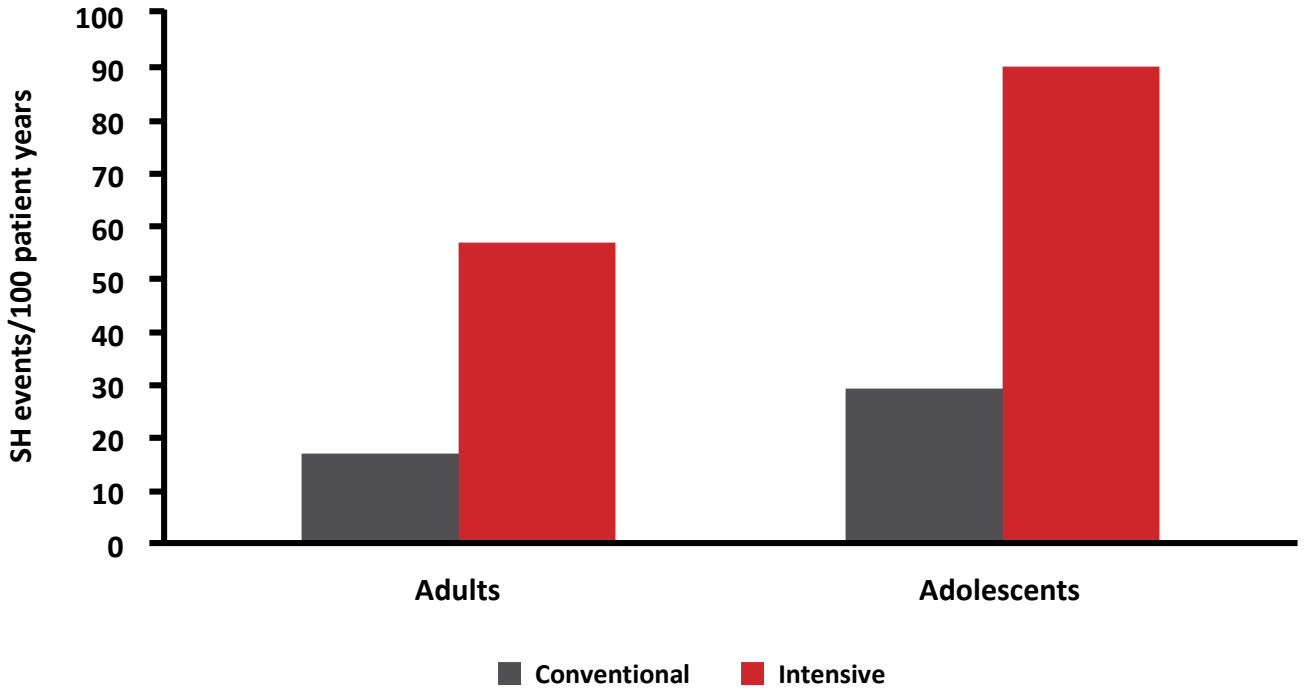
MILD Episodes not requiring external assistance (self-treated), or easily reversed by glucose or food

MODERATE Episodes requiring external assistance (with carbohydrate)

SEVERE Episodes causing coma/convulsions, or requiring parenteral therapy

Davis et al., *Diabetes Care*, 1997; 20: 22-25.

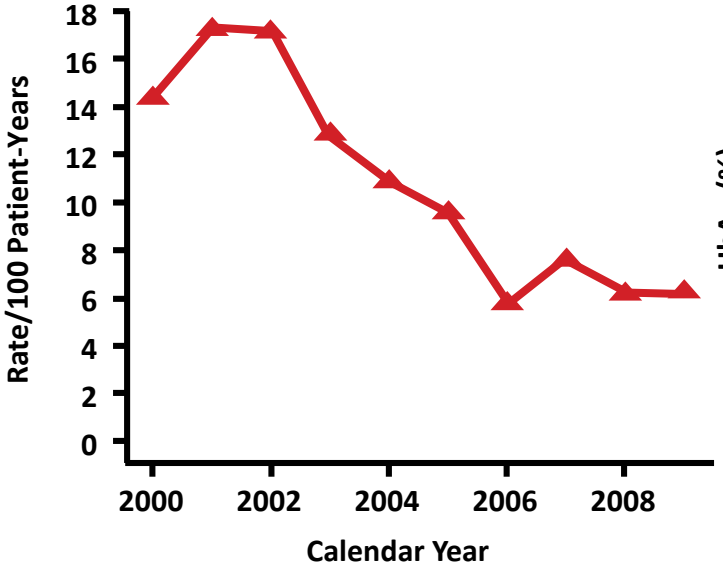
Incidence of severe hypoglycemia: Adolescents



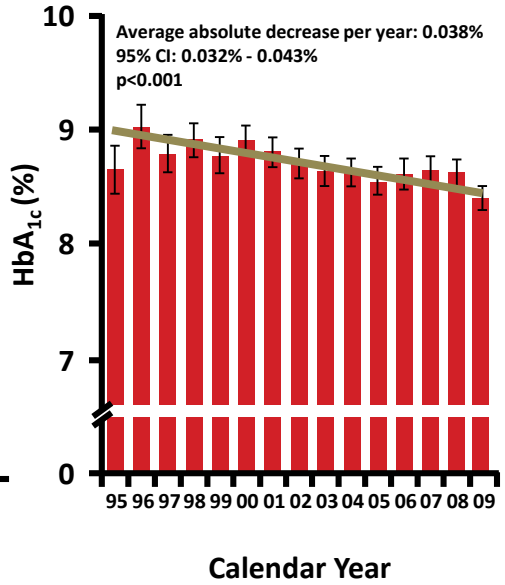
DCCT, J Pediatr 1994; 125: 177.

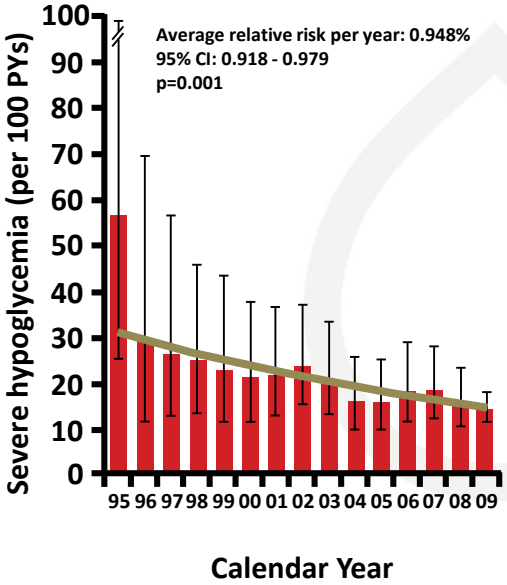
Severe hypoglycemia in children and adolescents

Western Australia
(1683 patients: 2000-2009)



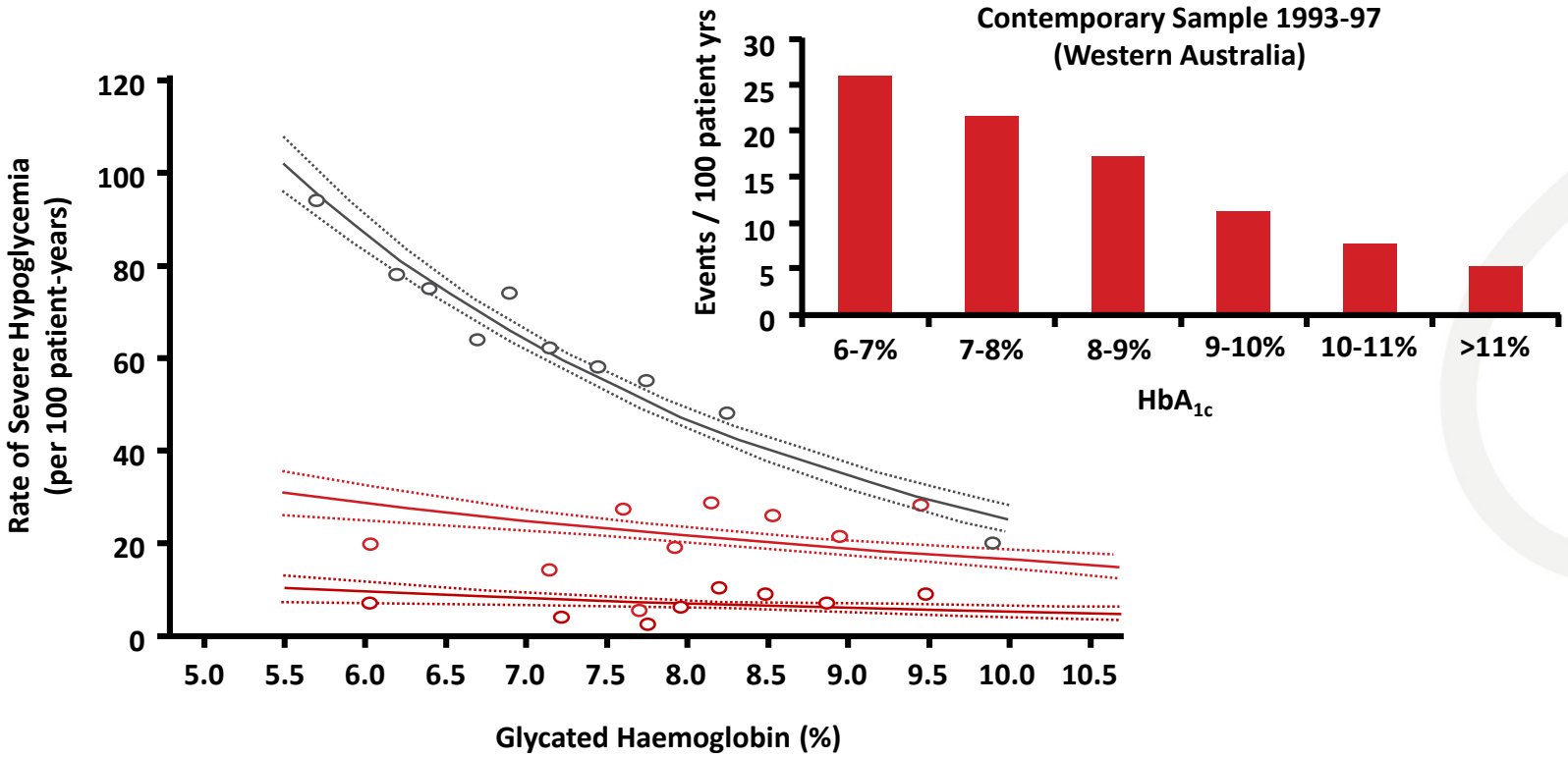
Germany & Austria
(30,700 patients: 1995-2009)





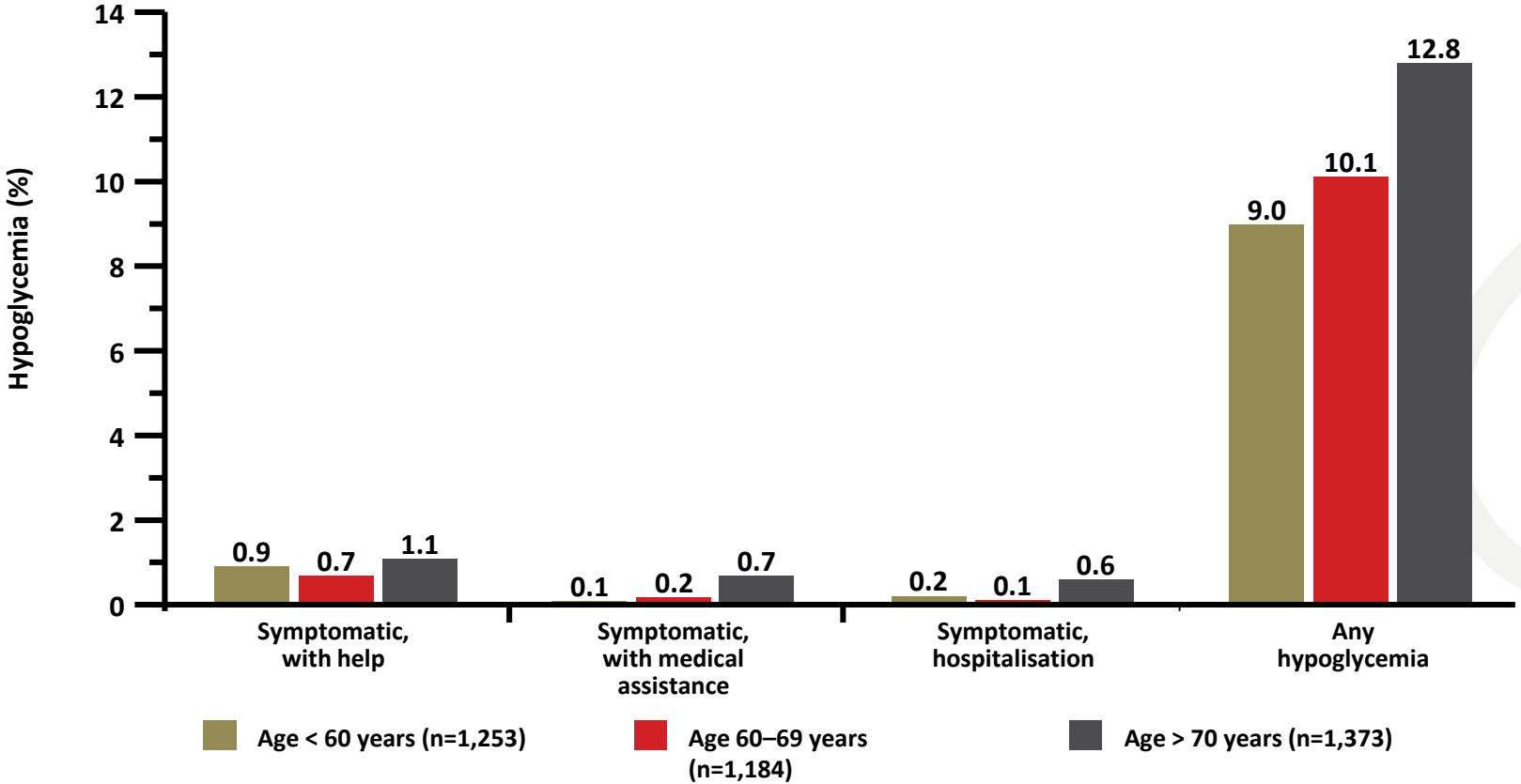
O'Connell et al., *Diabetes Care* 2011; 34: 2379-80. Rosenbauer et al., *Diabetes Care* 2012; 35: 80-86.

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



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

Proportion of elderly and younger patients with hypoglycemia at 12 months prior to treatment baseline

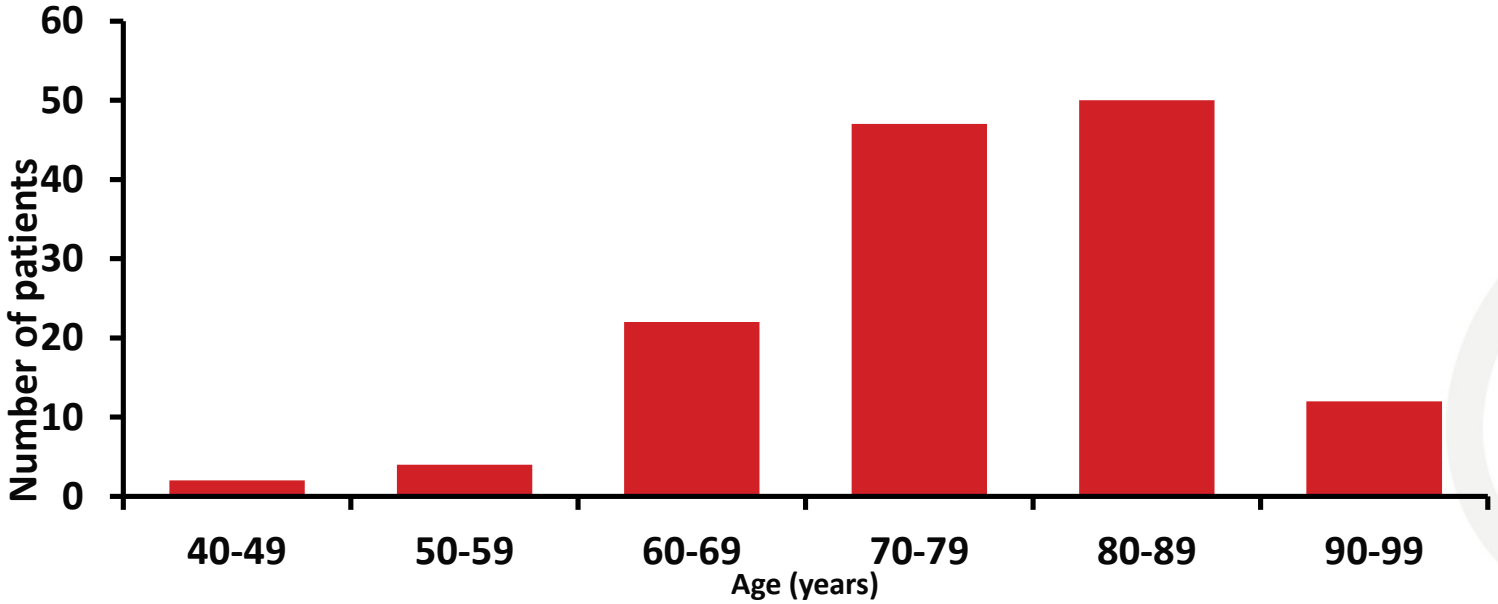


Data from a prospective, observational registry. Bramlage P, et al. *Cardiovasc Diabetol* 2012;11:122.

Relevant complications include comorbidities and diminished physiological defence to hypoglycemia

- Cognitive impairment
- Frailty
- Impaired counterregulation and diminished awareness of hypoglycemia
- Chronic renal impairment
- Impaired hepatic function
- Falls

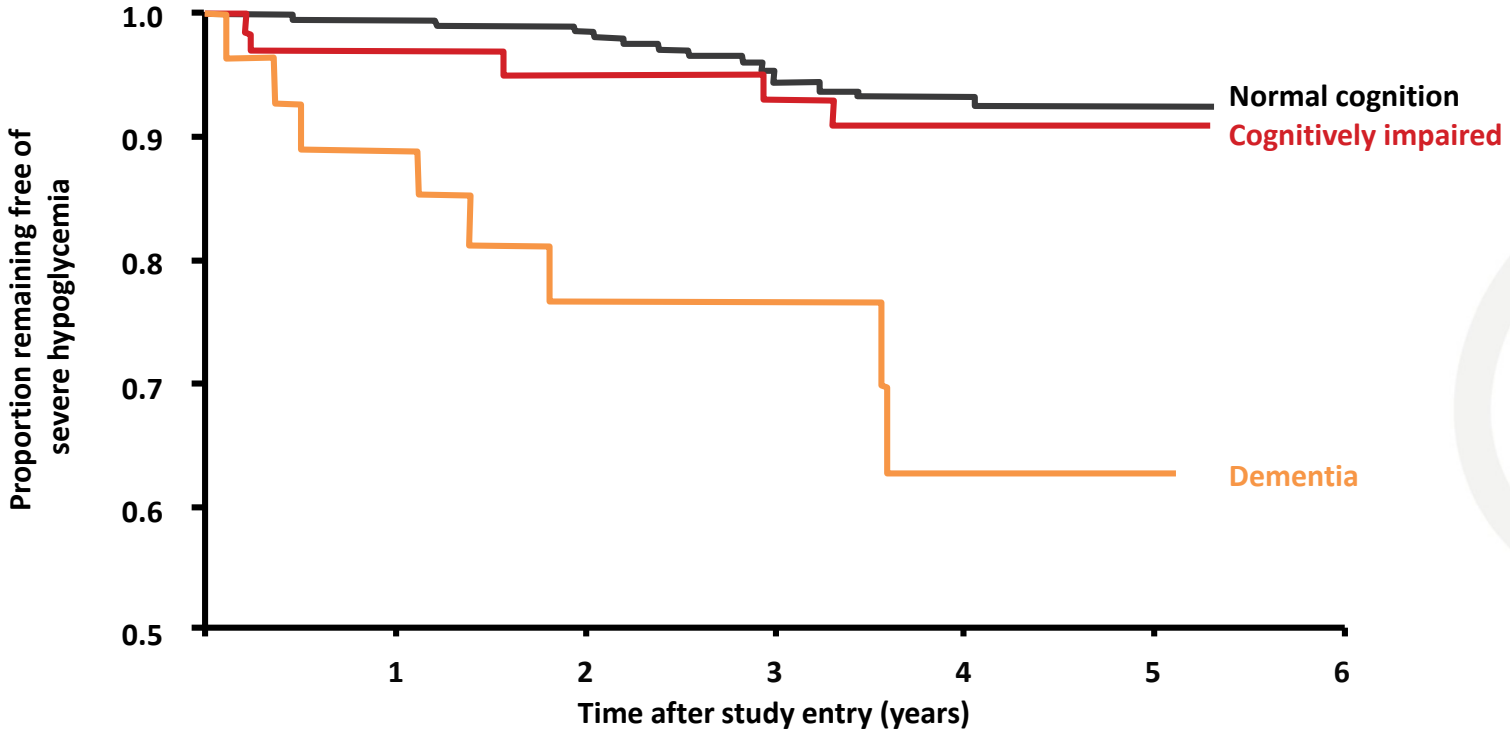
Age distribution of patients with type 2 diabetes with SU-induced hypoglycemia (n = 139)



One-third of cases were patients in nursing homes or being cared for by a home nursing service

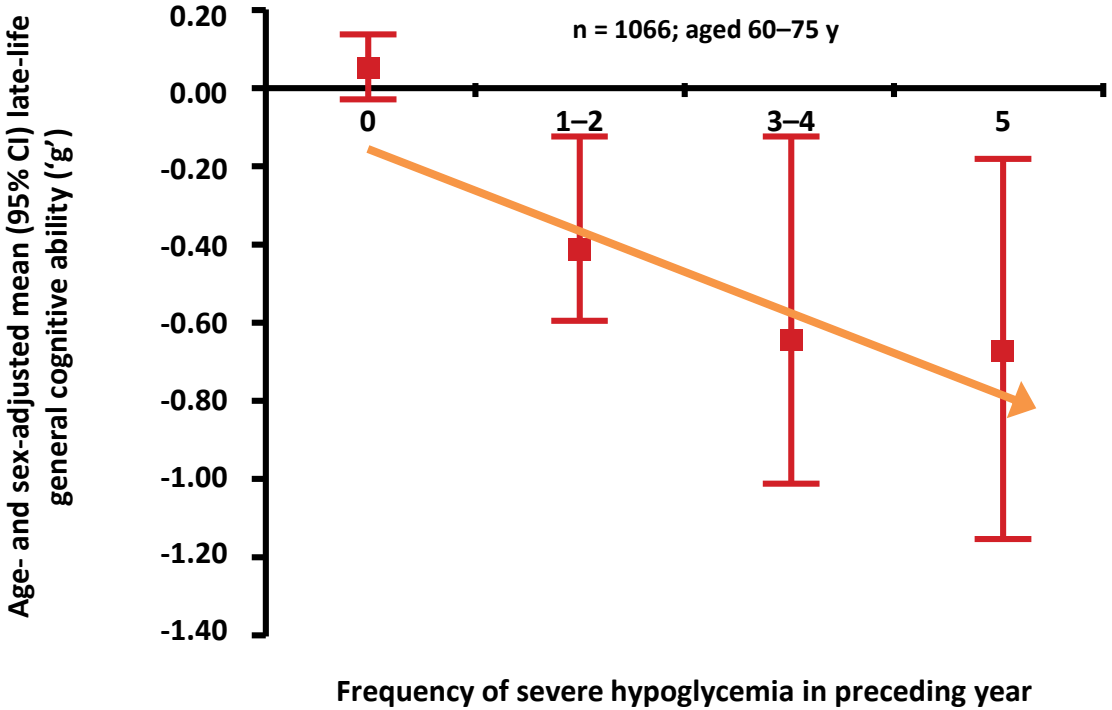
Holstein A, et al. *Expert Opin Drug Saf.* 2010;9:675–681.

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



Bruce, et al. *Diabetologia* 2009;52(9):1808–1815.

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



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

Aung PP, et al. *Diabet Med.* 2012;29:293–302.

Conclusions

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

Hypoglycemia: Vascular Impact

Prof Sophia Zoungas, MBBS (Hons), PhD, FRACP

Professorial Chair of Diabetes, Vascular Health and Ageing
School of Public Health and Preventive Medicine
Monash University, Clayton, Australia

MONASH University

THE GEORGE INSTITUTE for Global Health

IHSG

Disclosures

Fellowship support: NHMRC Australia

Speakers bureau, travel or advisory board: MSD, Servier

Outline

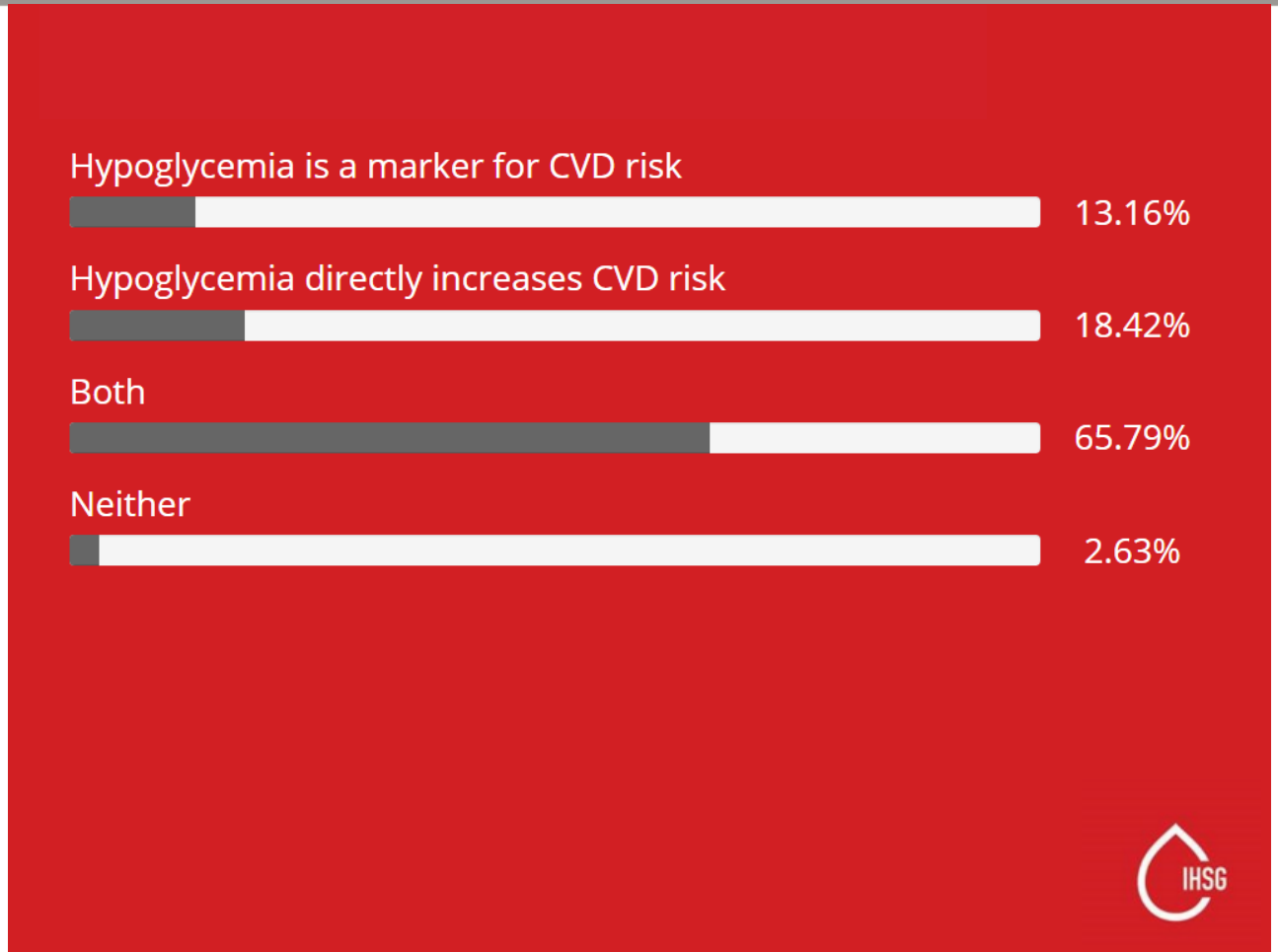
Hypoglycemia and vascular risk

- Is there an association?
  - (type 1, type 2 diabetes and hospitalized patients)
- Is the association due to selection bias or residual confounding (marker)?
- Is the association causal?
  - (impact of severity and preconditioning)
- Landmark clinical trials and observational studies including cardiac monitoring

Which of the following is true?

- Hypoglycemia is a marker for CVD risk
- Hypoglycemia directly increases CVD risk
- Both
- Neither

Which of the following is true?



Type 2 diabetes

Hypoglycemia in ACCORD trial[1,2]

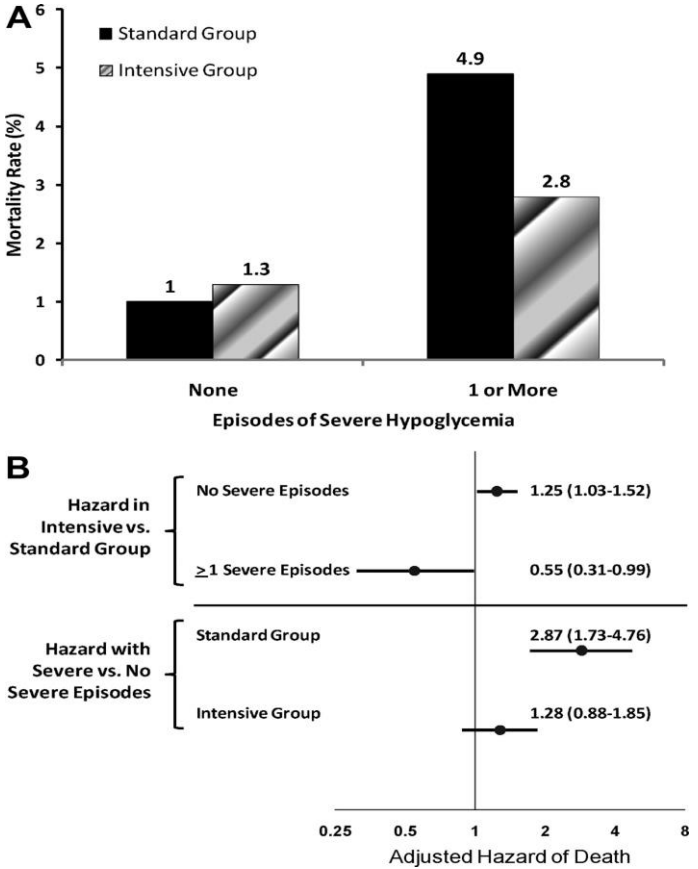
	Standard Therapy Group (n=5123)	Intensive Therapy Group (n=5128)
Median HbA_{1c} levels at 1 year, %	7.5	6.4
Hypoglycemia requiring medical assistance,* %	3.5	10.5
Hypoglycemia necessitating any assistance,* %	5.1	16.2
Deaths due to any cause, n (%) HR 1.22 p= 0.04	203 (4)	257 (5)

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

1. ACCORD Study Group et al. *N Engl J Med*. 2008;358:2545–2559.
2. Bonds DE et al. *Am J Card*. 2007;99(12A):80i–89i.

ACCORD trial annualized mortality rates and risks by randomized group

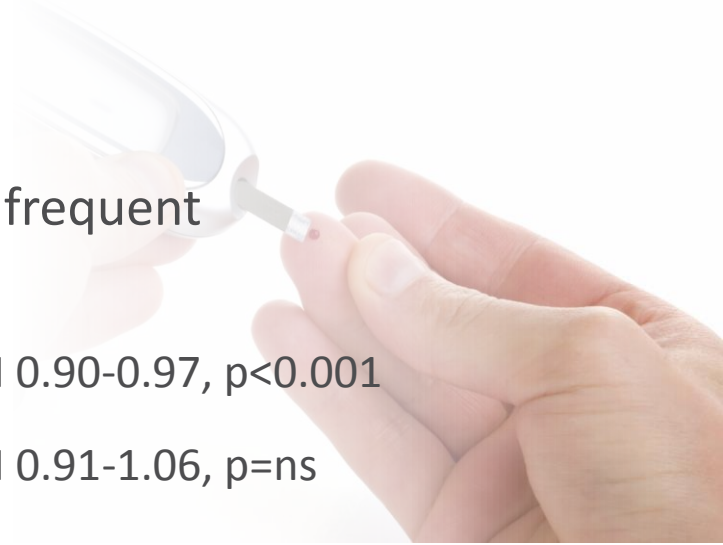
- The risk of mortality was increased in setting of hypoglycemia in both treatment groups
- For those not reporting severe hypoglycemia mortality higher in intensive group
- For those reporting severe hypoglycemia mortality higher in standard group



Yakubovich N , Gerstein H *C Circulation* 2011;123:342-348.

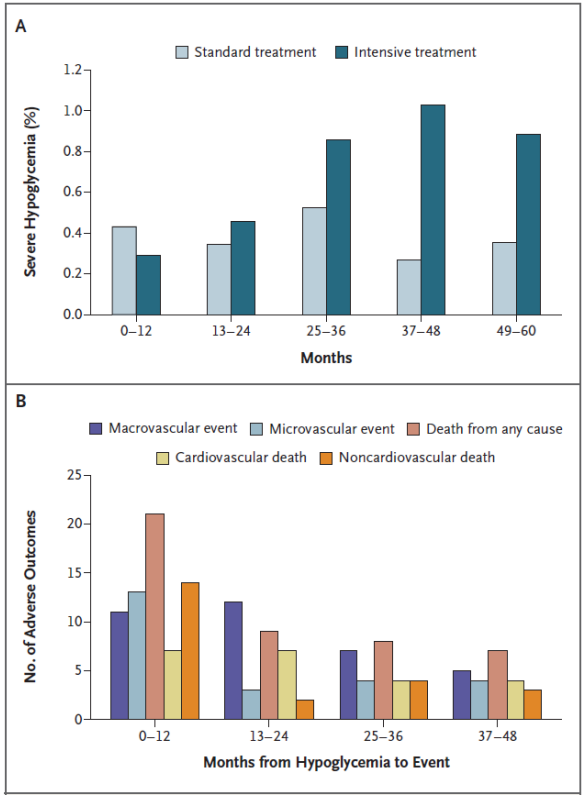
ACCORD trial frequent and unrecognized hypoglycemia

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



Seaquest et al. *Diabetes Care*. 2012 Feb;35(2):409-14.

ADVANCE trial



Events	Severe Hypoglycemia (N=231)	No Severe Hypoglycemia (N=10,909)	Hazard Ratio (95% CI)
	no. of patients with events (%)		
Major macrovascular events	33 (15.9)	1114 (10.2)	
Unadjusted model			4.05 (2.86–5.74)
Adjusted model			3.53 (2.41–5.17)
Major microvascular events	24 (11.5)	1107 (10.1)	
Unadjusted model			2.39 (1.60–3.59)
Adjusted model			2.19 (1.40–3.45)
Death from any cause	45 (19.5)	986 (9.0)	
Unadjusted model			4.86 (3.60–6.57)
Adjusted model			3.27 (2.29–4.65)
Cardiovascular disease	22 (9.5)	520 (4.8)	
Unadjusted model			4.87 (3.17–7.49)
Adjusted model			3.79 (2.36–6.08)
Noncardiovascular disease	23 (10.0)	466 (4.3)	
Unadjusted model			4.82 (3.16–7.35)
Adjusted model			2.80 (1.64–4.79)
Respiratory system events	18 (8.5)	656 (6.0)	
Unadjusted model			3.23 (2.02–5.17)
Adjusted model			2.46 (1.43–4.23)
Digestive system events	20 (9.6)	867 (7.9)	
Unadjusted model			2.97 (1.90–4.63)
Adjusted model			2.20 (1.31–3.72)
Diseases of the skin	6 (2.7)	146 (1.3)	
Unadjusted model			5.02 (2.20–11.40)
Adjusted model			4.73 (1.96–11.40)
Cancer	5 (2.2)	149 (1.4)	
Unadjusted model			3.44 (1.40–8.42)
Adjusted model			2.11 (0.65–6.82)

Zoungas S et al. *N Engl J Med*. 2010;363:1410–1418.

ADVANCE trial

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

Zoungas S et al. *N Engl J Med*. 2010;363:1410–1418.

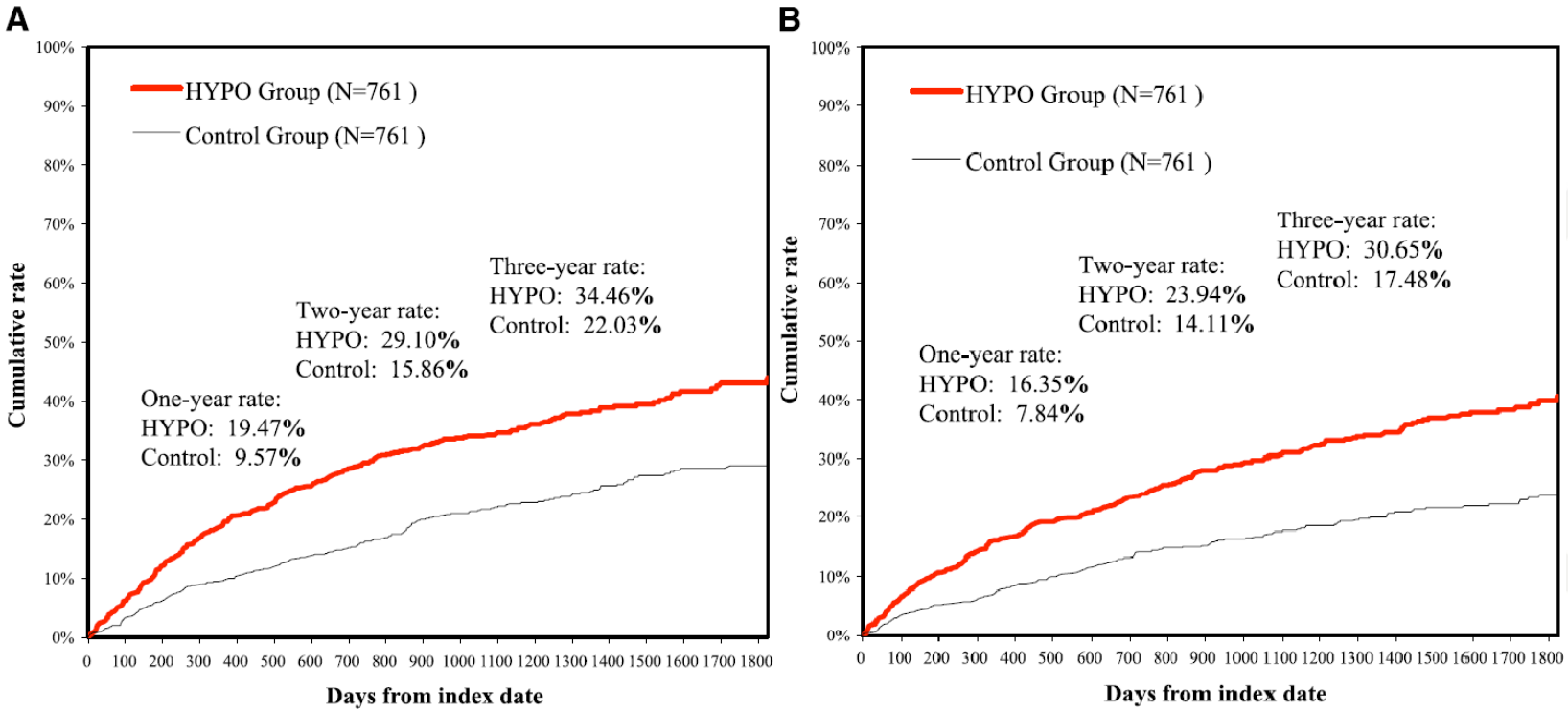
ORIGIN trial

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

Outcome	Unadjusted hazard	*P*-value	Adjusted hazard with propensity score	*P*-value
Non-severe hypoglycaemia				
CV death or non-fatal MI or stroke	1.10 (0.98–1.23)	0.115	1.00 (0.88–1.12)	0.947
Mortality	1.21 (1.08–1.35)	<0.001	1.12 (0.99–1.26)	0.066
Cardiovascular death	1.16 (1.00–1.34)	0.049	1.03 (0.88–1.20)	0.688
Arrhythmic death	1.19 (0.97–1.47)	0.091	1.10 (0.88–1.36)	0.403
Severe hypoglycaemia				
CV death or non-fatal MI or stroke	1.77 (1.39–2.25)	<0.001	1.58 (1.24–2.02)	<0.001
Total mortality	2.05 (1.65–2.55)	<0.001	1.74 (1.39–2.19)	<0.001
Cardiovascular death	2.02 (1.52–2.69)	<0.001	1.71 (1.27–2.30)	<0.001
Arrhythmic death	2.14 (1.43–3.18)	<0.001	1.77 (1.17–2.67)	0.007
Severe nocturnal hypoglycaemia				
CV death or non-fatal MI or stroke	1.88 (1.18–3.00)	0.008	1.64 (1.01–2.65)	0.044
Total mortality	1.95 (1.25–3.04)	0.003	1.64 (1.04–2.58)	0.033
Cardiovascular death	1.99 (1.13–3.53)	0.019	1.61 (0.89–2.93)	0.116
Arrhythmic death	2.04 (0.91–4.57)	0.083	1.79 (0.80–4.02)	0.155

Mellbin LG, et al. *Eur Heart J.* 2013;34(40):3137-3144.

Macro- and microvascular risks in veterans

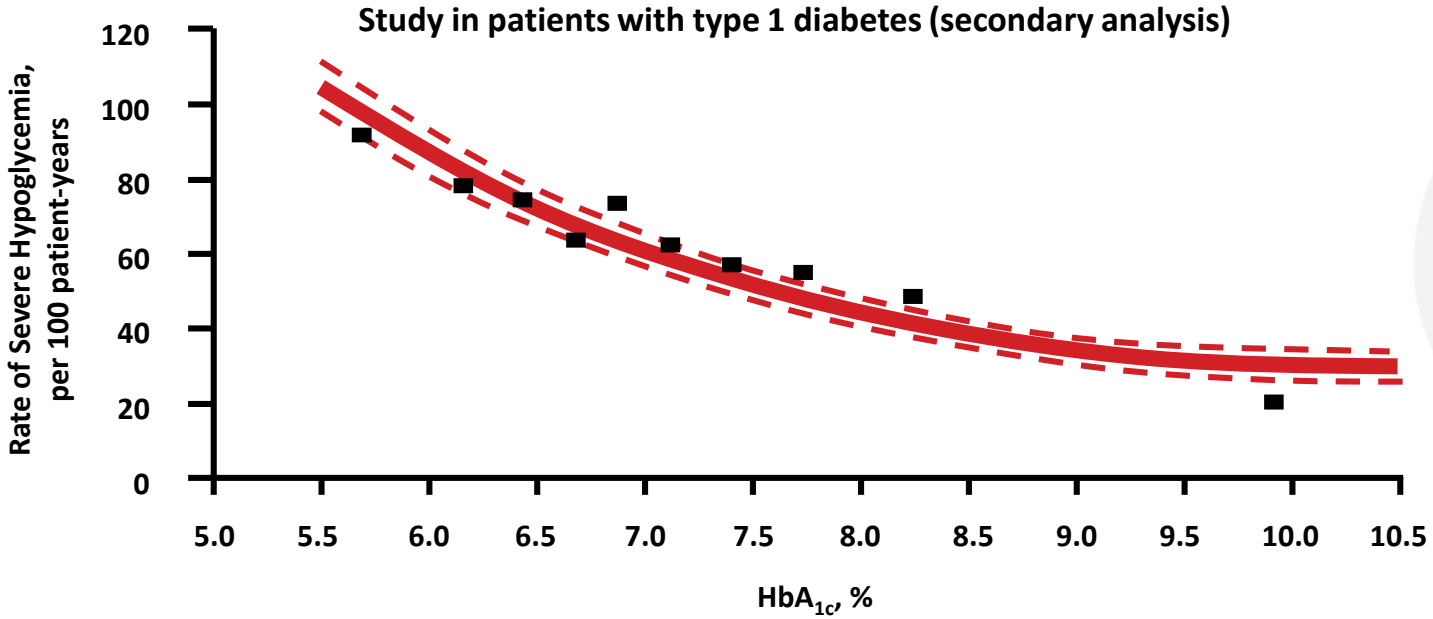


A: Cumulative incidence rate of CVD events by group. B: Cumulative incidence rate of microvascular complications by group. (Log-rank test P<0.0001 for both outcomes).
Zhao Y, et al. *Diabetes Care*. 2012;35(5):1126-1132.

Type 1 diabetes

DCCT: Rates of severe hypoglycemia increase as HbA_{1c} levels decrease

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



Squares correspond to >400 patient-years. DCCT = Diabetes Control and Complications Trial.
DCCT Research Group. *N Engl J Med.* 1993;329(14):977–986.

Eurodiab Prospective study

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

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

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

Retrospective GP cohort study

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

		Population	Unadjusted incidence rates (per 1,000 person-years)	Unadjusted HR (CPRD plus HES)	Adjusted HR	
					CPRD plus HES	CPRD
Type 1 diabetes	CV events	History of CVD before index (*n* = 298, events = 54)	45.6 (33.4, 57.8)	1.44 (0.56, 3.69)	1.10 (0.40, 3.01)	0.81 (0.23, 2.84)
		No CVD before index (*n* = 2,962, events = 209)	13.3 (11.5, 15.1)	1.99* (1.38, 2.87)	1.92* (1.32, 2.79)	1.73† (1.13, 2.65)
	All-cause mortality	History of CVD before index (*n* = 298, deaths = 113)	85.0 (69.3, 100.7)	2.83* (1.74, 4.62)	1.95† (1.14, 3.35)	1.53 (0.80, 2.90)
		No CVD before index (*n* = 2,962, deaths = 641)	39.5 (36.4, 42.6)	2.69* (2.23, 3.24)	2.05* (1.69, 2.49)	1.62* (1.28, 2.05)

Khunti et al *Diabetes Care* 2015;38:316–322.

Hospitalized patients

Evidence

- NICE-SUGAR trial
  - Critically ill patients, moderate and severe hypoglycemia a/w increased mortality, although median time to death was 7-8 days[1]
- AMI patients with and without known diabetes
  - Spontaneous hypoglycemia in patients not treated with insulin a/w increased mortality while iatrogenic hypoglycemia in patients treated with insulin was not[2]
- ACS patients in single centre
  - A single BG <3 mmol/l during hospitalization a/w increased risk of 2 yr mortality[3]
- TIMI studies
  - Hypoglycemia on admission a/w increased risk of death or AMI at 30 days[4]
- DIGAMI 2 (type 2 and AMI)
  - Hypoglycemia during hospitalization not a/w future morbidity or mortality[5]

1. NICE-SUGAR investigators *NEJM* 2009 and 2012. 2. Kosiborod M et al. *JAMA.* 2009. 3. Svensson et al. *Eur Heart J.* 2005. 4. Pinto et al. *JACC* 2005. 5. Mellbin LG, et al. *Heart*. 2009.

What may explain this association?

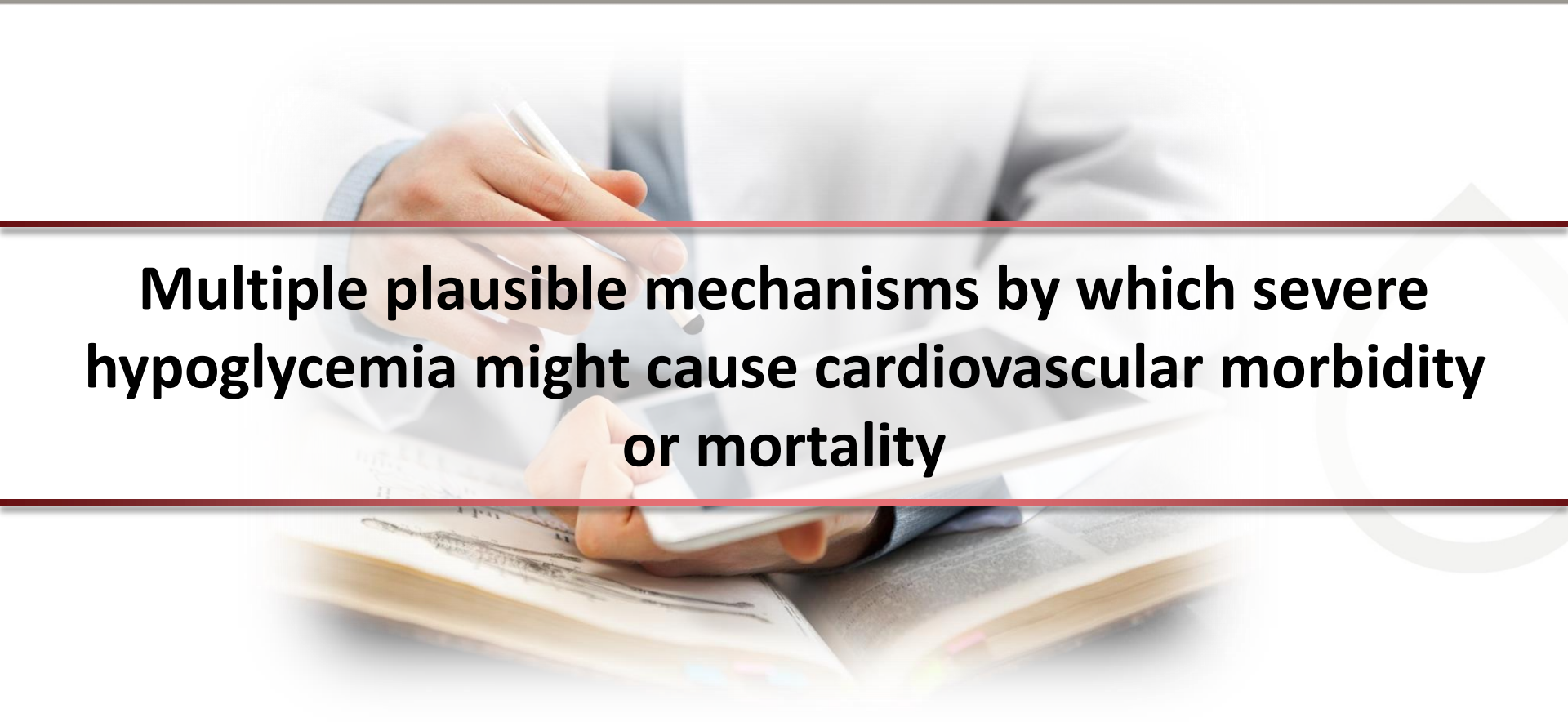
Selection bias

- Sampling fraction for cases and controls is related to exposure
- Clinic/hospital based cases/controls have different exposures than population cases/controls (Berkson's bias)
- Eg. The combination of exposure to risk and occurrence of disease increases the likelihood of being admitted to clinic/hospital

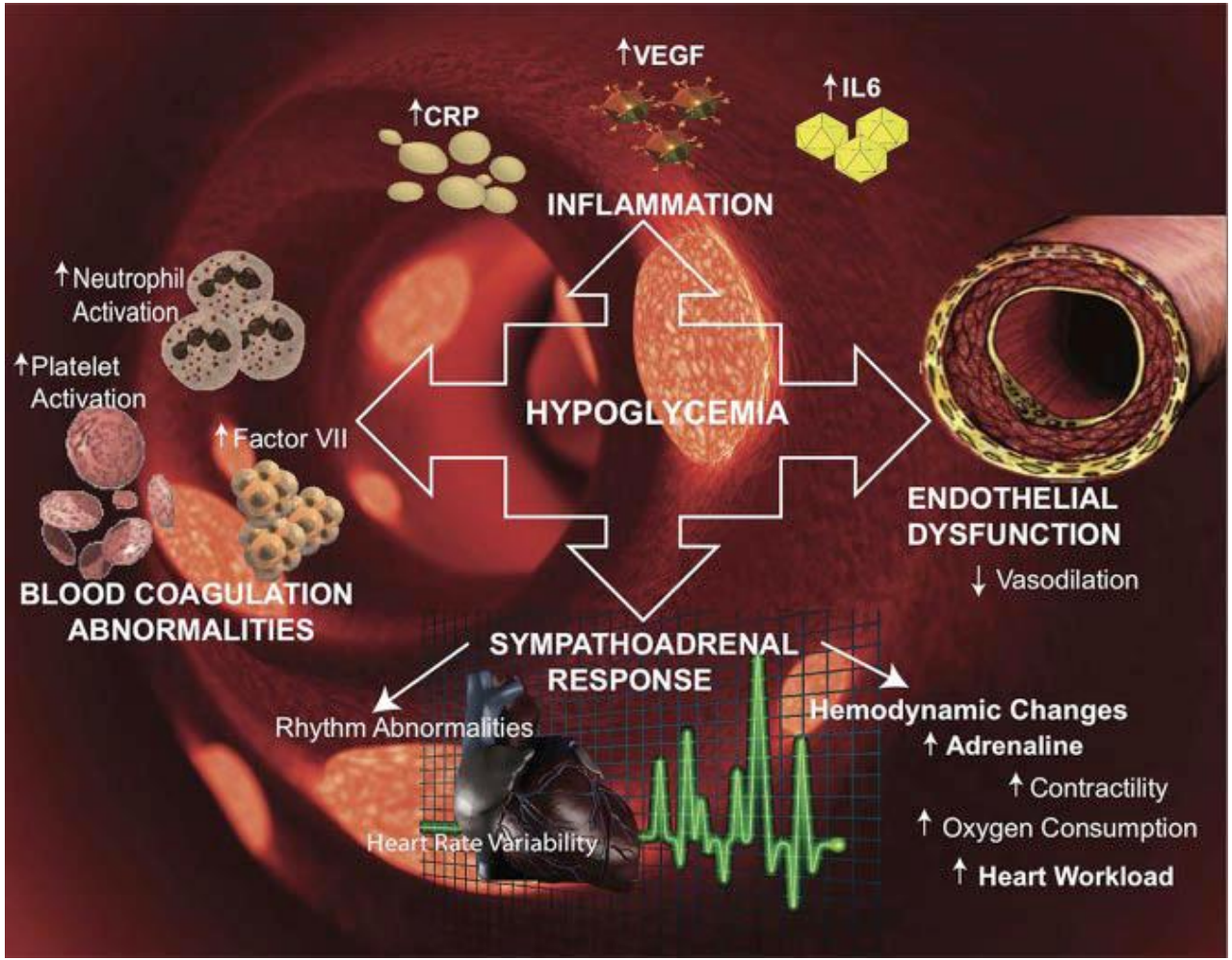
Marker of risk?

- Severe hypoglycemia may reflect the effects of co-morbid diseases and unmeasured or incompletely quantified confounding variables
- The presence of co-morbid disease increases a patient's vulnerability to both severe hypoglycemia and adverse clinical outcomes
- The risk factors for severe hypoglycemia and adverse CV events are shared

Direct cause?

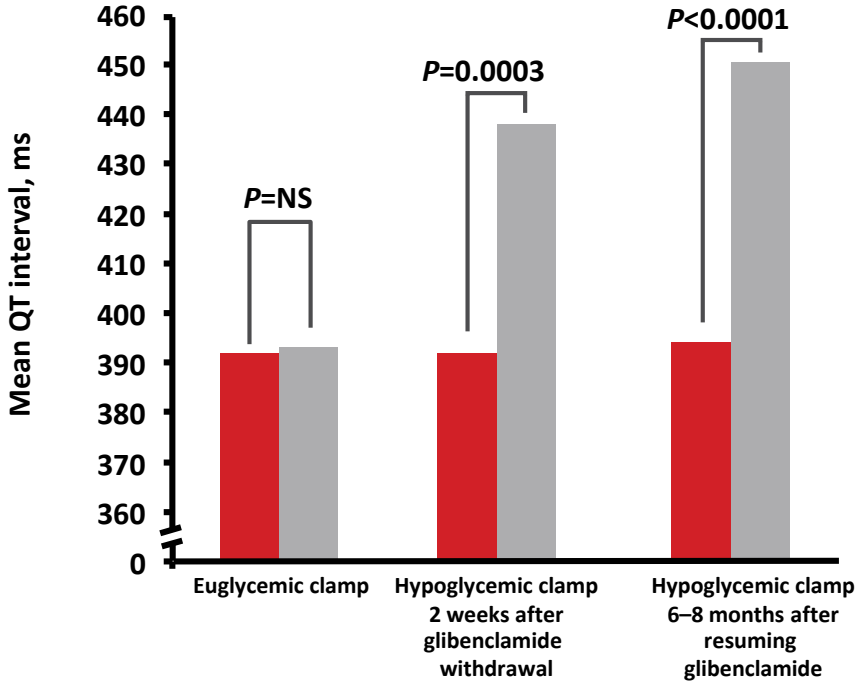


Multiple plausible mechanisms by which severe hypoglycemia might cause cardiovascular morbidity or mortality



CRP, C-reactive protein; IL-6, interleukin 6; VEGF, vascular endothelial growth factor.
Adapted from Desouza et al. Diabetes Care. 2010;33:1389-94

Severe hypoglycemia may cause a prolongation of QT interval in patients with type 2 diabetes[1]



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

NS = not significant.

Thirteen patients with type 2 diabetes taking combined insulin and glibenclamide treatment were studied during hypoglycemia; 8 participated in the euglycemic experiment clamped between 5.0 and 6.0 mmol/L. The aim was to achieve stable hypoglycemia between 2.5 and 3.0 mmol/L (45 and 54 mg/dL) during the last 60 minutes of the experiment. 1. Landstedt-Hallin L et al. *J Intern Med*. 1999;246:299–307.

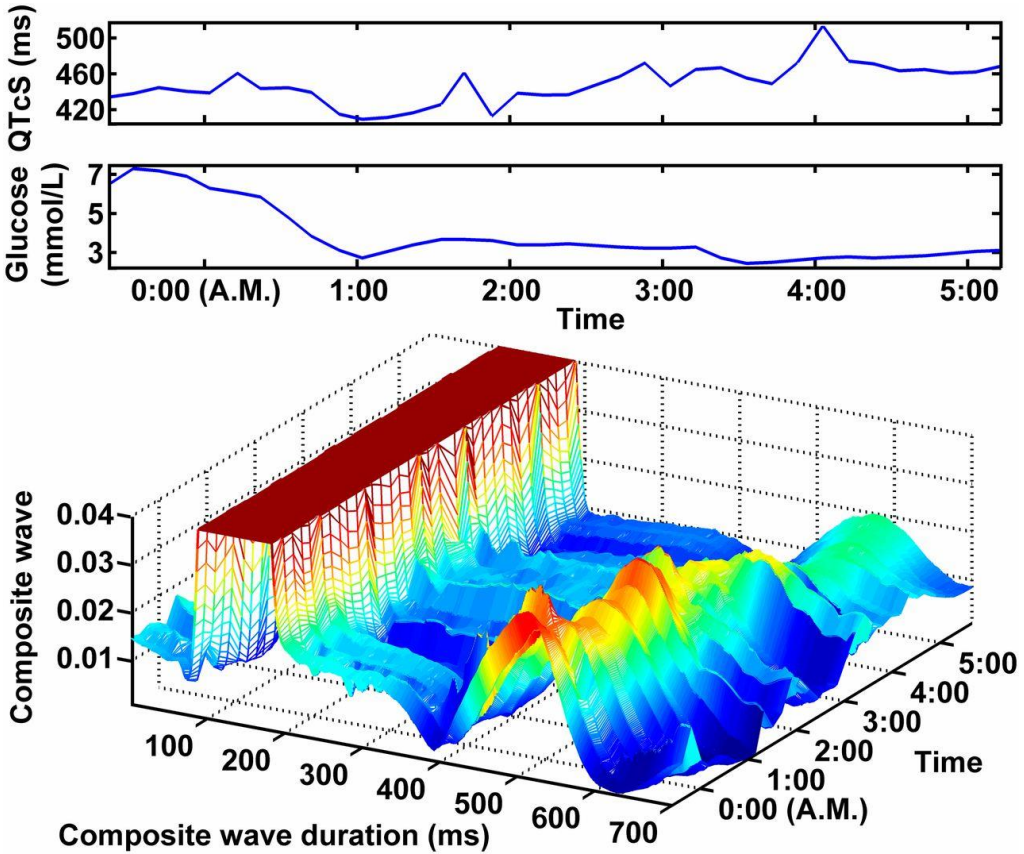
Risk of cardiac arrythmias with spontaneous hypoglycemia

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

	Day			Night		
	IRR	95% CI	*P*	IRR	95% CI	*P*
Bradycardia	NA	NA	NA	8.42	1.40–51.0	0.02
Atrial ectopic	1.35	0.92–1.98	0.13	3.98	1.10–14.40	0.04
VPB	1.31	1.10–1.57	<0.01	3.06	2.11–4.44	<0.01
Complex VPB	1.13	0.78–1.65	0.52	0.79	0.22–2.86	0.72

IRRs and 95% CI of arrhythmias during hypoglycaemia versus euglycemia as analysed using generalized estimated equations. NA, not applicable.
Elaine Chow et al. *Diabetes* 2014;63:1738-1747.

Abnormal QT prolongation and T-wave morphology during hypoglycemia in a single patient



Elaine Chow et al. *Diabetes* 2014;63:1738-1747.

Other considerations

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

Summary

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

Clinical implications

Chose approaches to glucose lowering that minimize risk of severe hypoglycemia

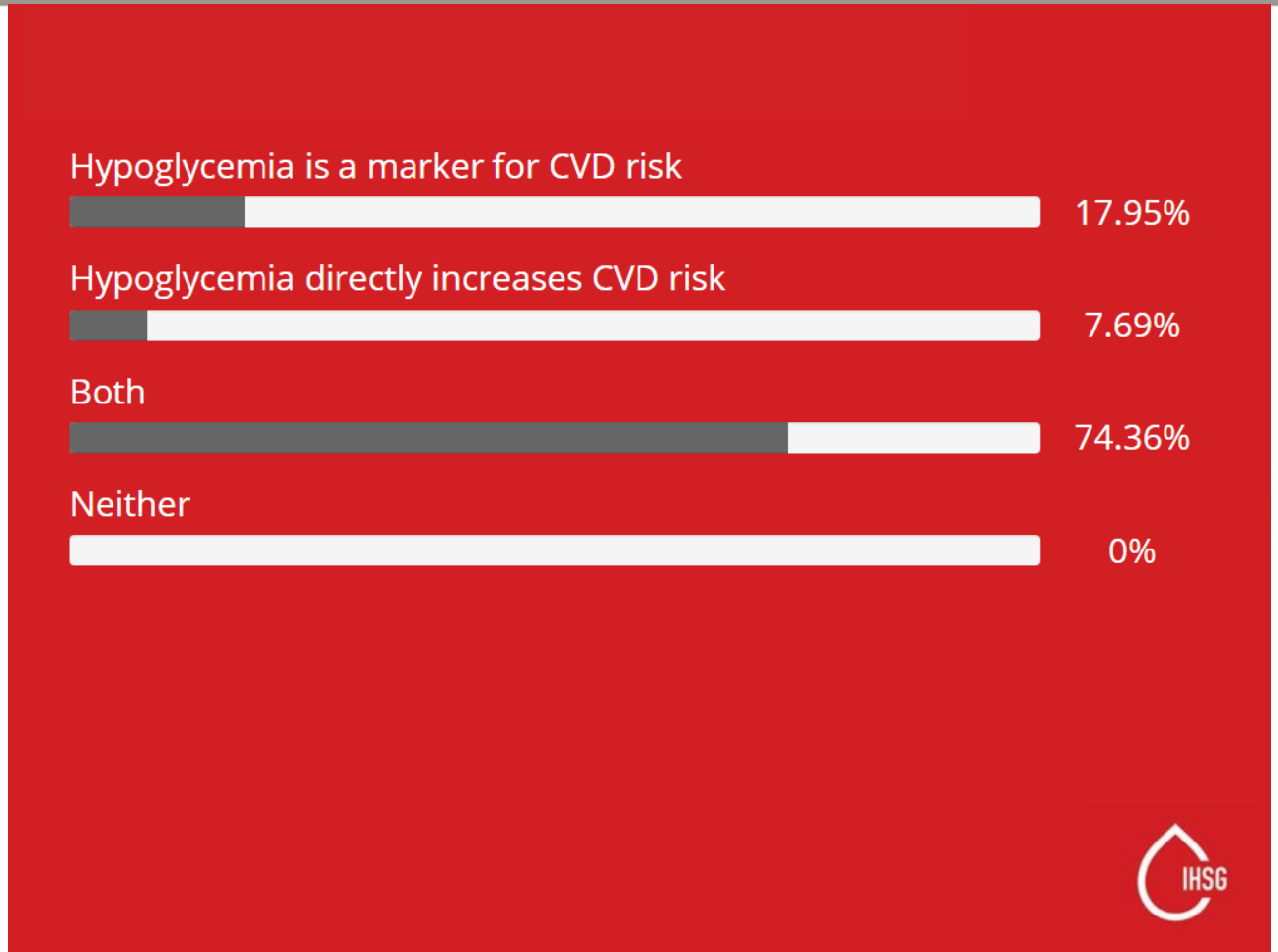
Ensure patients are educated about avoidance and management of hypoglycemia

Experience of severe hypoglycemia should lead to an examination of comorbid diseases that may produce adverse outcomes

Which of the following is true?

- Hypoglycemia is a marker for CVD risk
- Hypoglycemia directly increases CVD risk
- Both
- Neither

Which of the following is true?



Hypoglycemia And The Brain

Elizabeth Seaquist, MD

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Department of Medicine
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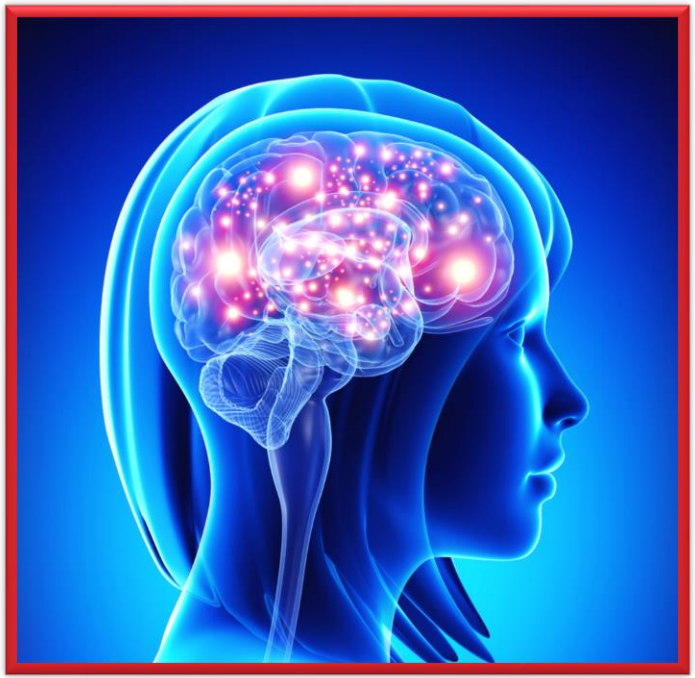
IHSG meeting 12/1/2015 Vancouver, B.C.

IHSG

Disclosure

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

How does hypoglycemia affect the brain in patients with diabetes?



A. Hypoglycemia is associated with dementia

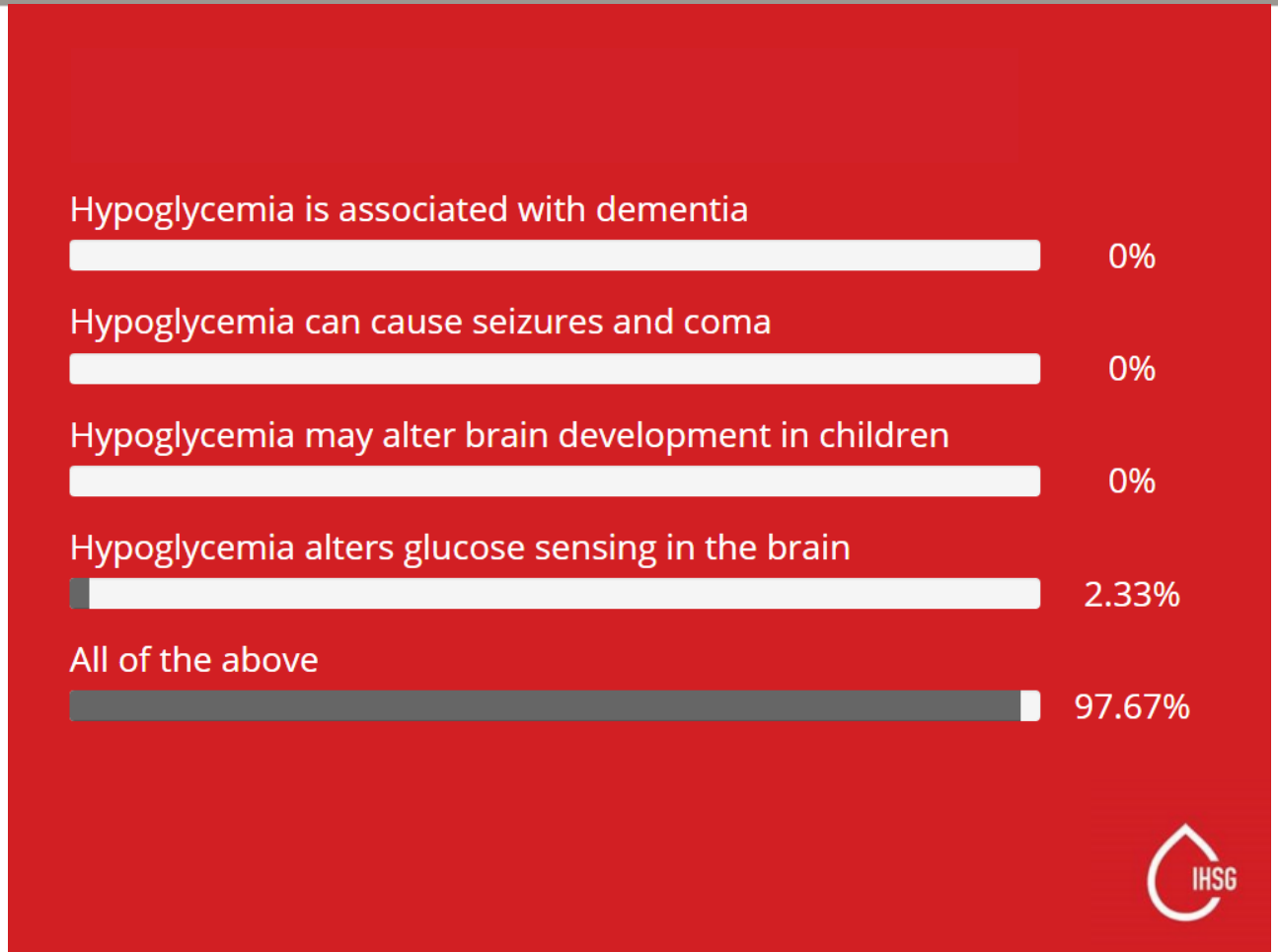
B. Hypoglycemia can cause seizures and coma

C. Hypoglycemia may alter brain development in children

D. Hypoglycemia alters glucose sensing in the brain

E. All of the above

How does hypoglycemia affect the brain in patients with diabetes?



How does hypoglycemia affect the brain in patients with diabetes?

Acute hypoglycemia

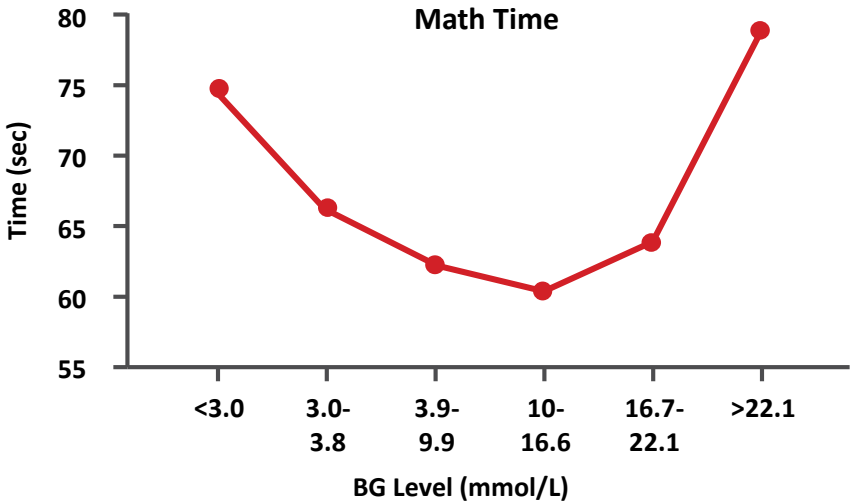
- Acute loss of consciousness
- Seizures
- Cognitive dysfunction

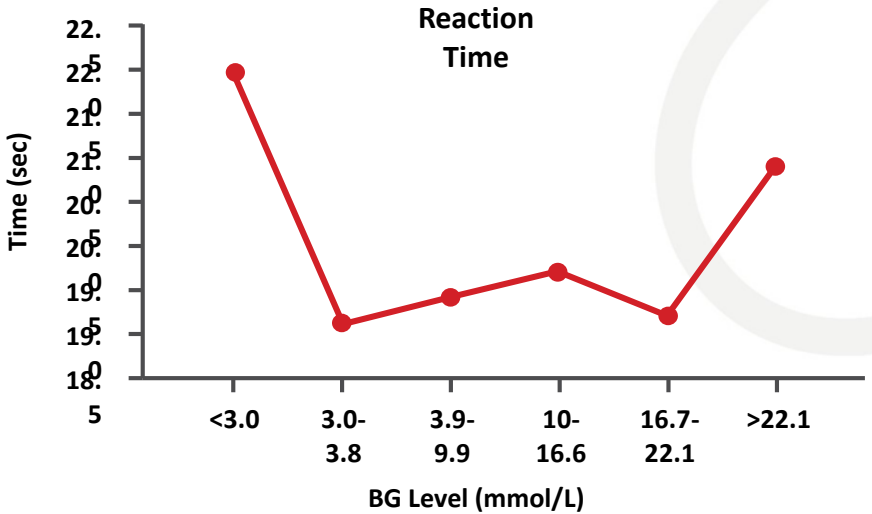
Recurrent hypoglycemia

- Cognitive dysfunction
- Structural changes
- Hypoglycemia unawareness

Effects of glycemia on cognition in school age children

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





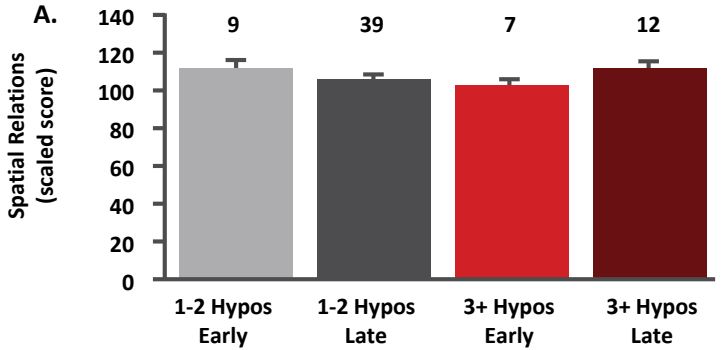
Gonder-Frederick et al. *Diabetes Care* 2009.

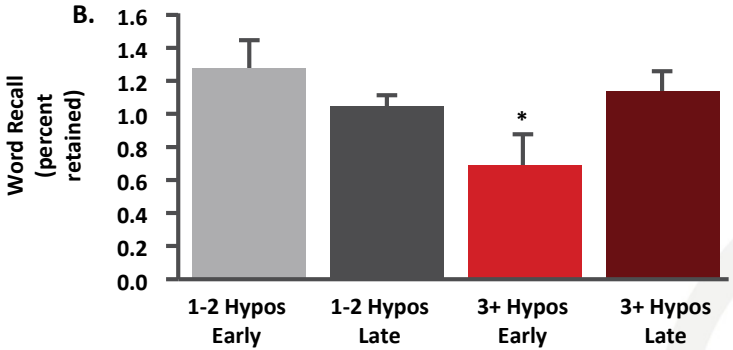
Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus

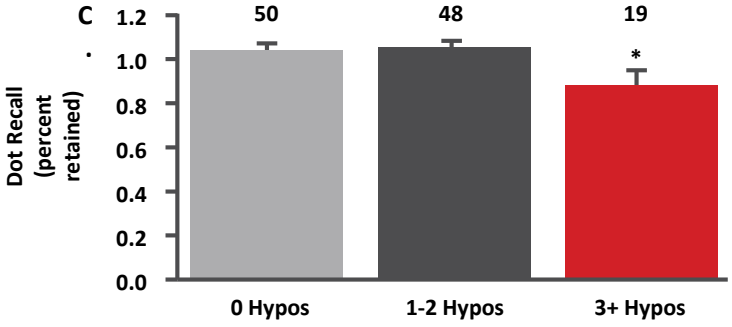
Perantie, et al. *Pediatric Diabetes* 2008.

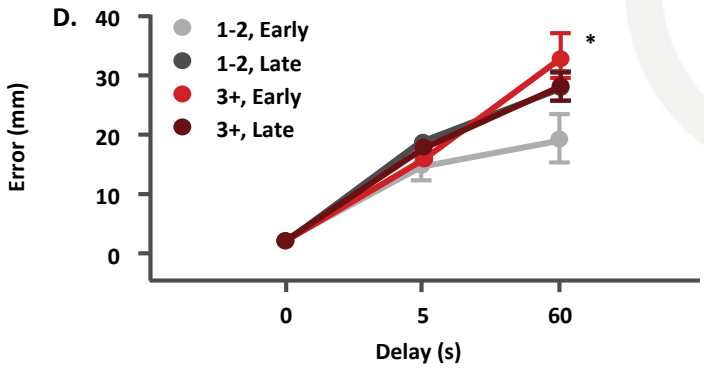
- Examined youth ages 5-16 years using standardized neurocognitive tests
- 117 had type 1 diabetes
  - ✓ Categorized as having experienced 0, 1-2, or 3 more episodes of severe hypoglycemia based on family interview and medical records
- 58 were sibling controls without diabetes

Impact of hypoglycemia at < 5 years vs > 5 years in youth with T1DM









*P< 0.05

Perantie, et al. *Pediatric Diabetes* 2008: 9:87-95.

Hypoglycemia and dementia risk on older patients with type 2 DM

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

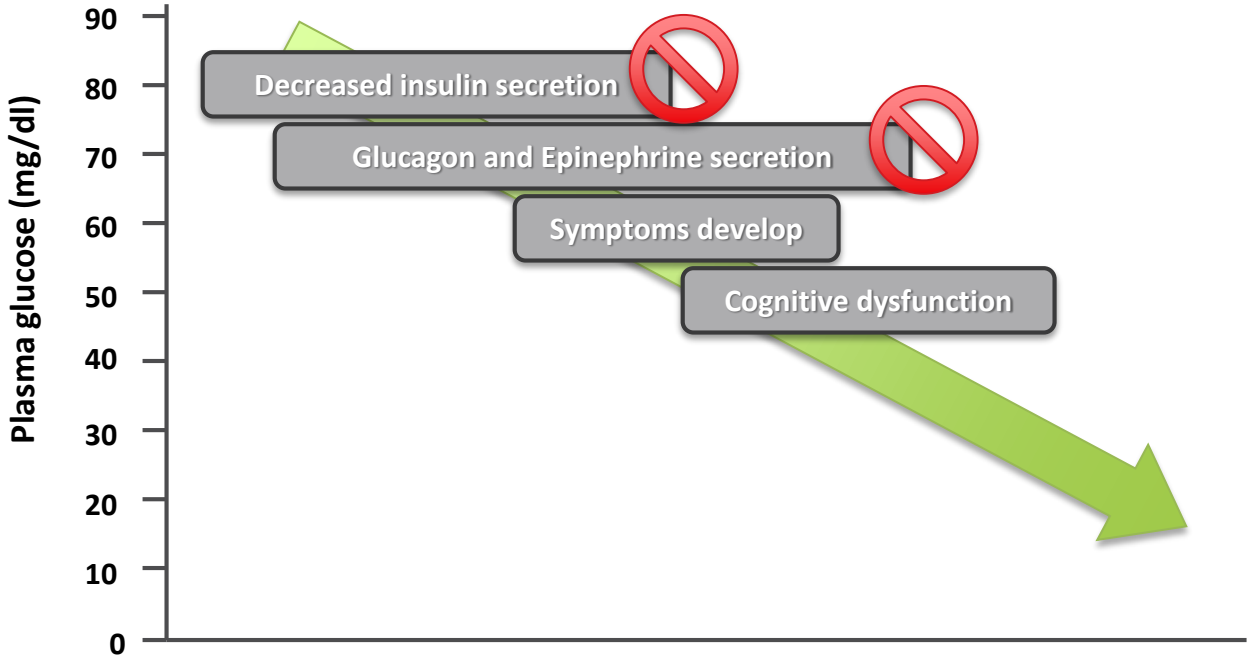
Whitmer et al. *JAMA* 2009.

Hypoglycemia and risk of incident dementia[a]

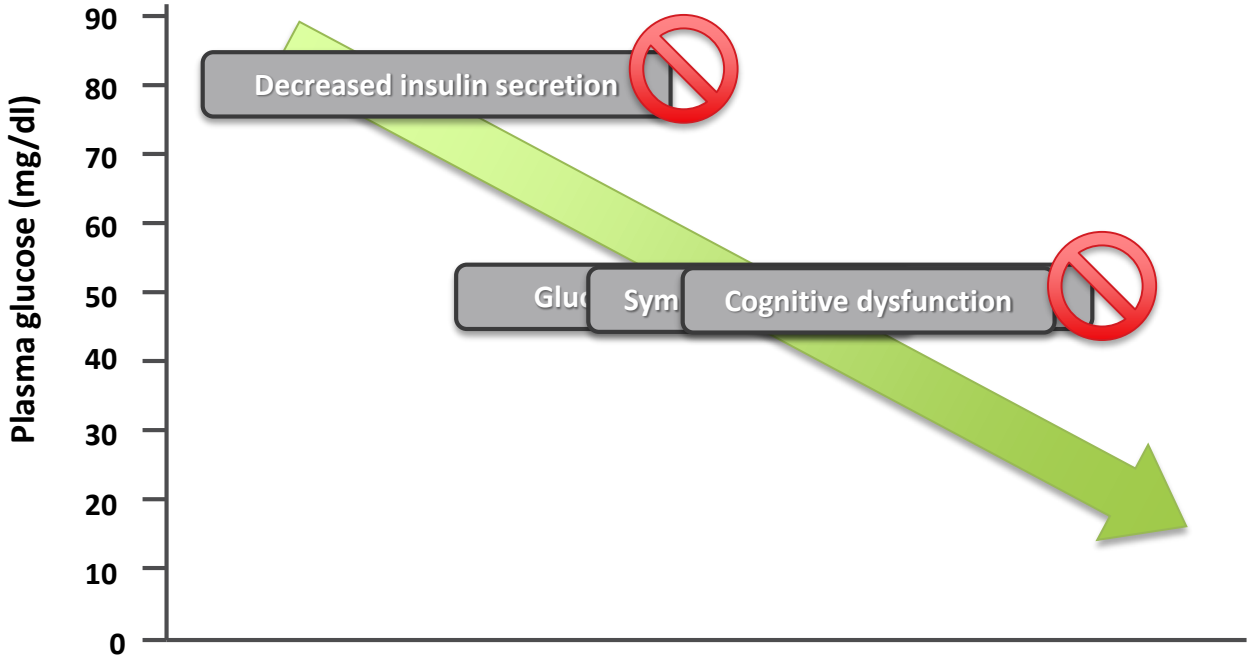
No. of Hypoglycemic Episodes[b]	No. of Dementia Cases	Hazard Ratio (95% Confidence Interval)		
		Adjusted for Age (as time scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes	Additionally Adjusted for Comorbidities[c]	Additionally Adjusted for 7-Year Mean HbA_{1c} Level, Diabetes Treatment, and Years of Insulin Use
1 or more	250	1.68 (1.47 – 1.93)	1.48 (1.29 – 1.70)	1.44 (1.25 – 1.66)
1	150	1.45 (1.23 – 1.72)	1.29 (1.10 – 1.53)	1.26 (1.10 – 1.49)
2	57	2.15 (1.64 – 2.81)	1.86 (1.42 – 2.43)	1.80 (1.37 – 2.36)
3 or more	43	2.60 (1.78 – 3.79)	2.10 (1.48 – 2.73)	1.94 (1.42 – 2.64)

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin. [a]Analyses combined using Cox proportional hazard models. [b]The 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0. [c]Adjustment made using a comorbidity composite scale.
Whitmer et al. *JAMA* 2009.

Recurrent hypoglycemia leads to hypoglycemia associated autonomic failure



Recurrent hypoglycemia leads to hypoglycemia associated autonomic failure



Risk factors for hypoglycemia in diabetes

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

- **Risk factors for hypoglycemia-associated autonomic failure**
  - Absolute endogenous insulin deficiency
  - A history of severe hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise, and sleep
  - Aggressive glycemic therapy *per se* (lower HbA_{1c} levels, lower glycemic goals, or both)

Cryer et al. *JCEM* 2009.

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

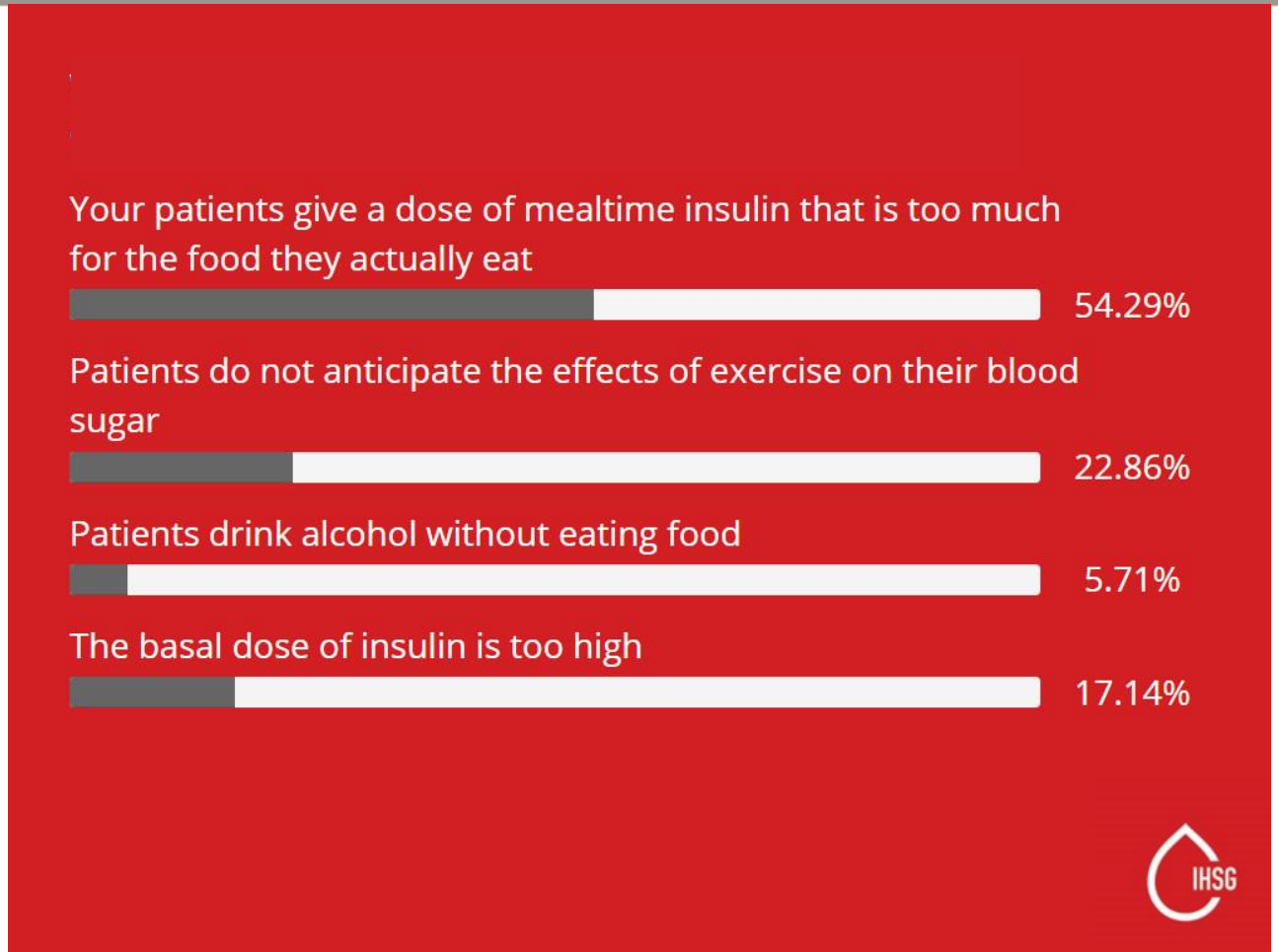
A. Your patients give a dose of mealtime insulin that is too much for the food they actually eat

B. Patients do not anticipate the effects of exercise on their blood sugar

C. Patients drink alcohol without eating food

D. The basal dose of insulin is too high

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



Tools to recognize impaired awareness in your patients

Table 2—*Hypoglycemia Patient Questionnaire*

Name _____
First Middle Last
Today's date _____

1. To what extent can you tell by your symptoms that your blood glucose is LOW?
____ Never ____ Rarely ____ Sometimes ____ Often ____ Always

2. In a typical week, how many times will your blood glucose go below 70 mg/dL?
_____ a week

3. When your blood glucose goes below 70 mg/dL, what is the usual reason for this?
_____

4. How many times have you had a severe hypoglycemic episode (where you needed someone's help and were unable to treat yourself)?
Since the last visit ____ times
In the last year ____ times

5. How many times have you had a moderate hypoglycemic episode (where you could not think clearly, properly control your body, had to stop what you were doing, but you were still able to treat yourself)?
Since the last visit ____ times
In the last year _____ times

6. How often do you carry a snack or glucose tablets (or gel) with you to treat low blood glucose? Check one of the following:
Never ___ Rarely ___ Sometimes___ Often___ Almost always___

7. How LOW does your blood glucose need to go before you think you should treat it?
Less than ____mg/dL

8. What and how much food or drink do you usually treat low blood glucose with?
_____

9. Do you check your blood glucose before driving? Check one of the following:
Yes, always___ Yes, sometimes ___ No___

10. How LOW does your blood glucose need to go before you think you should not drive?
____mg/dL

11. How many times have you had your blood glucose below 70 mg/dL while driving?
Since the last visit ____ times
In the last year _____ times

12. If you take insulin, do you have a glucagon emergency kit?
Yes___/ No ___

13. Does a spouse, relative, or other person close to you know how to administer glucagon?
Yes___/ No ___

Seaquist E. R. et al. *Diabetes Care* 2013;36:1384-1395.

Tools to recognize impaired awareness in your patients

Table 3—*Hypoglycemia Provider Checklist*

Name _____
First Middle Last

Today's date _____

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

Seaquist E. R. et al. *Diabetes Care* 2013;36:1384-1395.

Steps to reduce hypoglycemia

- Re-evaluate glycemic goals
- Educate patient on when to anticipate, how to recognize hypoglycemia, how to avoid hypoglycemia, and appropriate treatment of hypoglycemia
- Review insulin/secretagogue regimen, especially with respect to timing of administration and selection of dose

Improved Biomedical and Psychological Outcomes 1 Year After Structured Education in Flexible Insulin Therapy for People With Type 1 Diabetes

The U.K. DAFNE experience

David Hopkins, FRCP[1]
Ian Lawrence, FRCP[2]
Peter Mansell, MD[3]
Gillian Thompson, BSC[4]
Stephanie Amiel, MD[5]
Michael Campbell, PHD[6]
Simon Heller, MD[7]

Diabetes Care, 35:1638-1642, 2012.

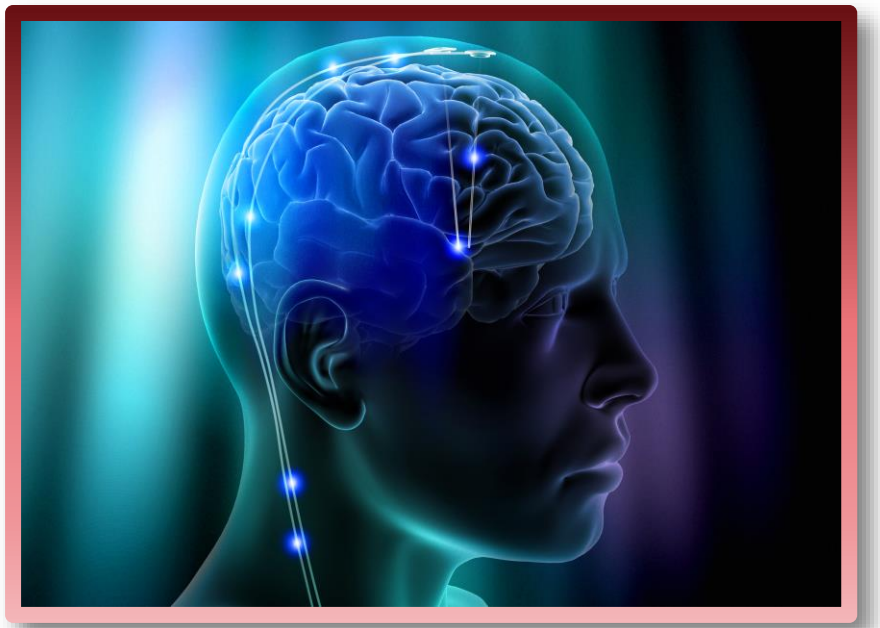
- Retrospective analysis of data collected before and 1 year after attendance at 5 day DAFNE (Dose Adjusted for Normal Eating) course at one of 31 centers in UK
- 1163 eligible subjects
- Complete data available for 639 (54.9%) from 29 centers

Hypoglycemia awareness status and severe hypoglycemia rates at enrollment and 1 year post-DAFNE

Baseline	n	Status at 1 Year			SH pre-DAFNE		SH post-DAFNE	
		Aware	Impaired	No Data	Mean	SD	Mean	SD
Aware	324	202 (62)	81 (25)	41 (13)	0.87	3.99	0.35*	1.63
Impaired Awareness	215	92 (43)	97 (45)	26 (12)	3.6	13.6	1.3*	5.9
All	539	294 (54)	178 (33)	67 (12)	1.7	8.5	0.6*	3.7

Data are *n* (%) of people in each category at baseline and follow-up, together with self-reported mean number of severe hypoglycemic (SH) episodes per subject for the year preceding DAFNE attendance and for 1st year post-DAFNE. *$P<0.05$ for comparison of pre- and post-DAFNE mean data.
Diabetes Care 35:1638-1642, 2012.

How does hypoglycemia affect the brain in patients with diabetes?



A. Hypoglycemia is associated with dementia

B. Hypoglycemia can cause seizures and coma

C. Hypoglycemia may alter brain development in children

D. Hypoglycemia alters glucose sensing in the brain

E. All of the above

Conclusions

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

Technology To The Rescue

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

Outline

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

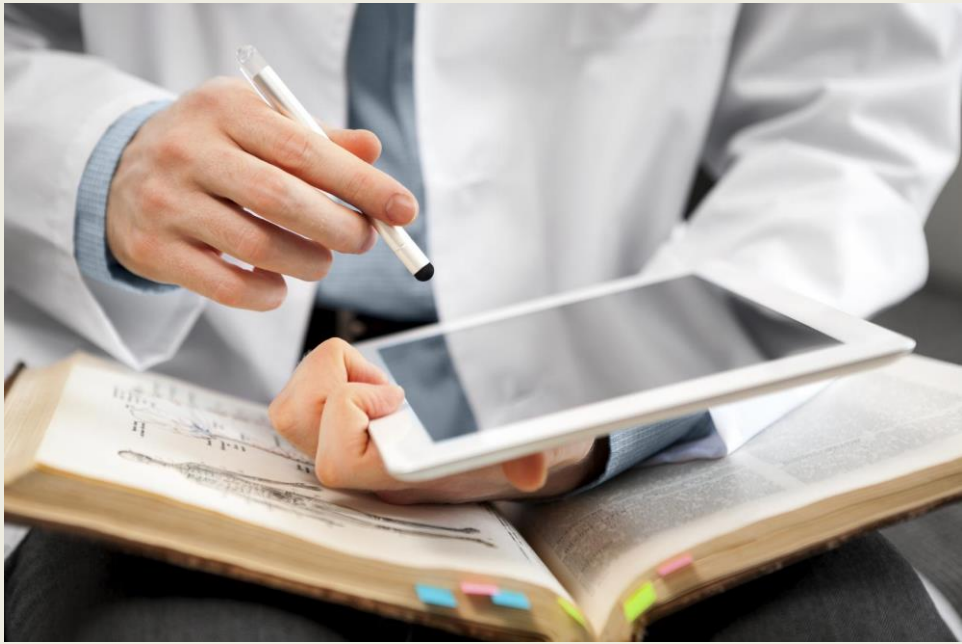
2. Impact of technology on fear of hypoglycemia

3. Do the health economics justify technology to mitigate hypoglycemia?
   - Cost of hypoglycemia

A question for you

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

- Yes
- No



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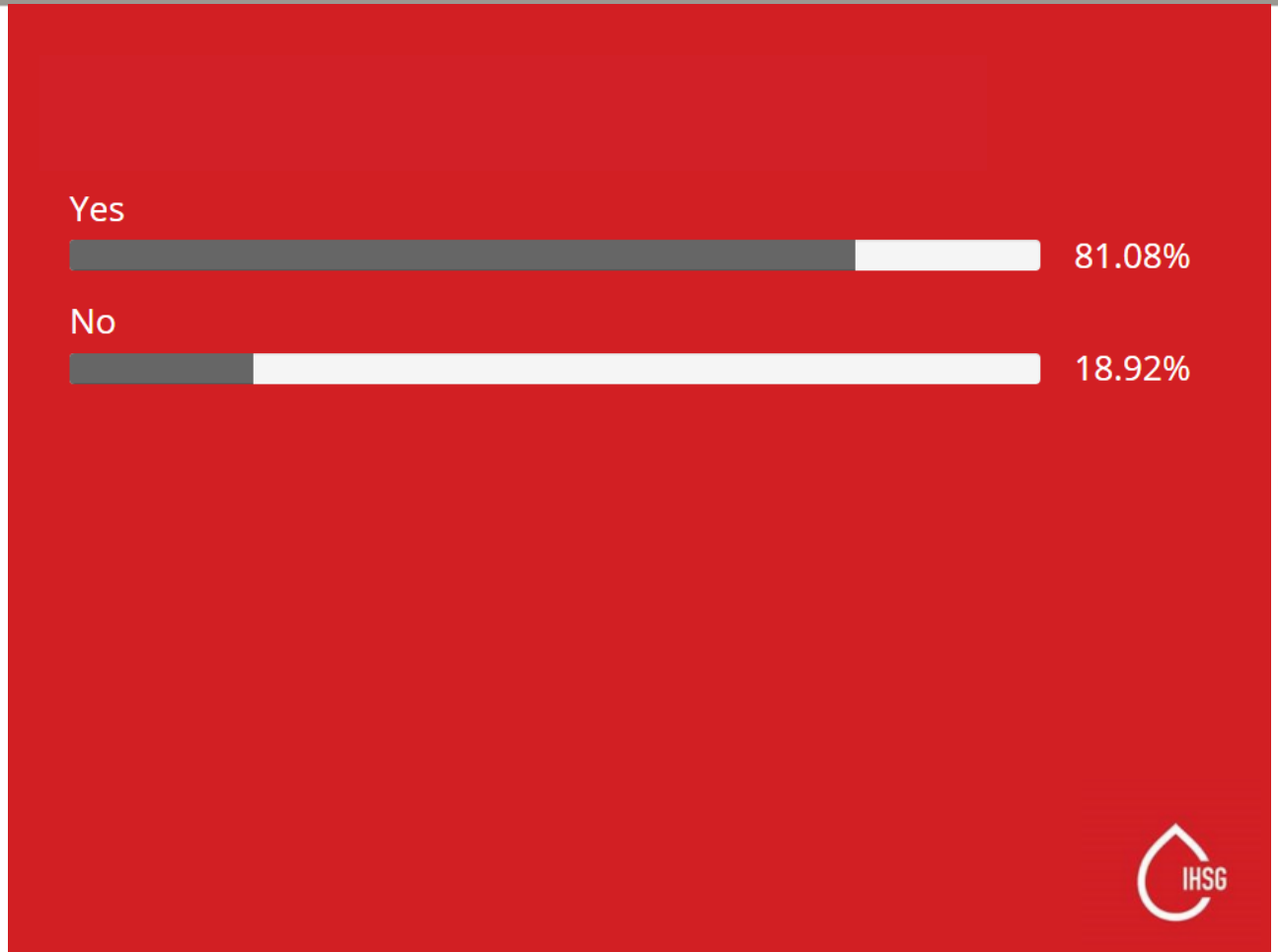

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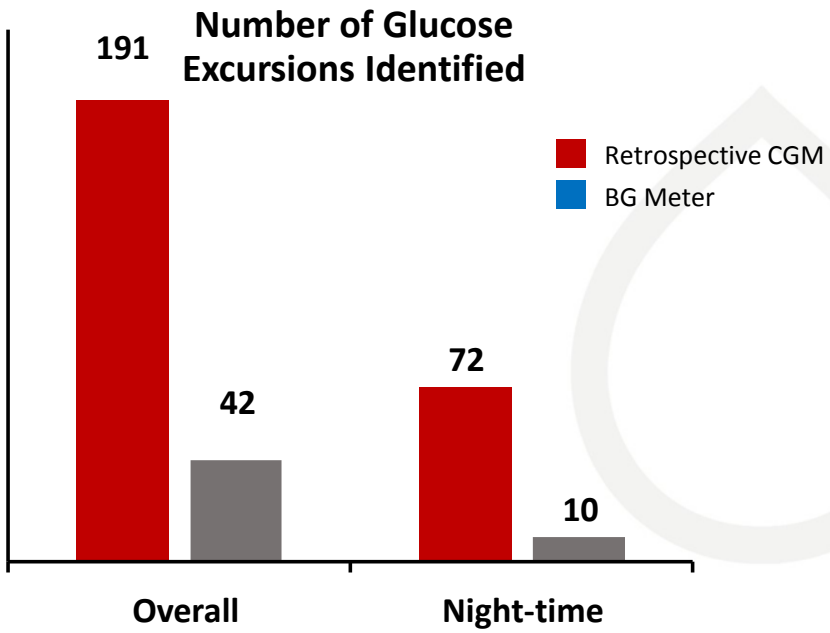
(2001) Kaufman Study:
Retrospective CGM captures excursions missed by BG meters

Study Design

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

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

Outcome

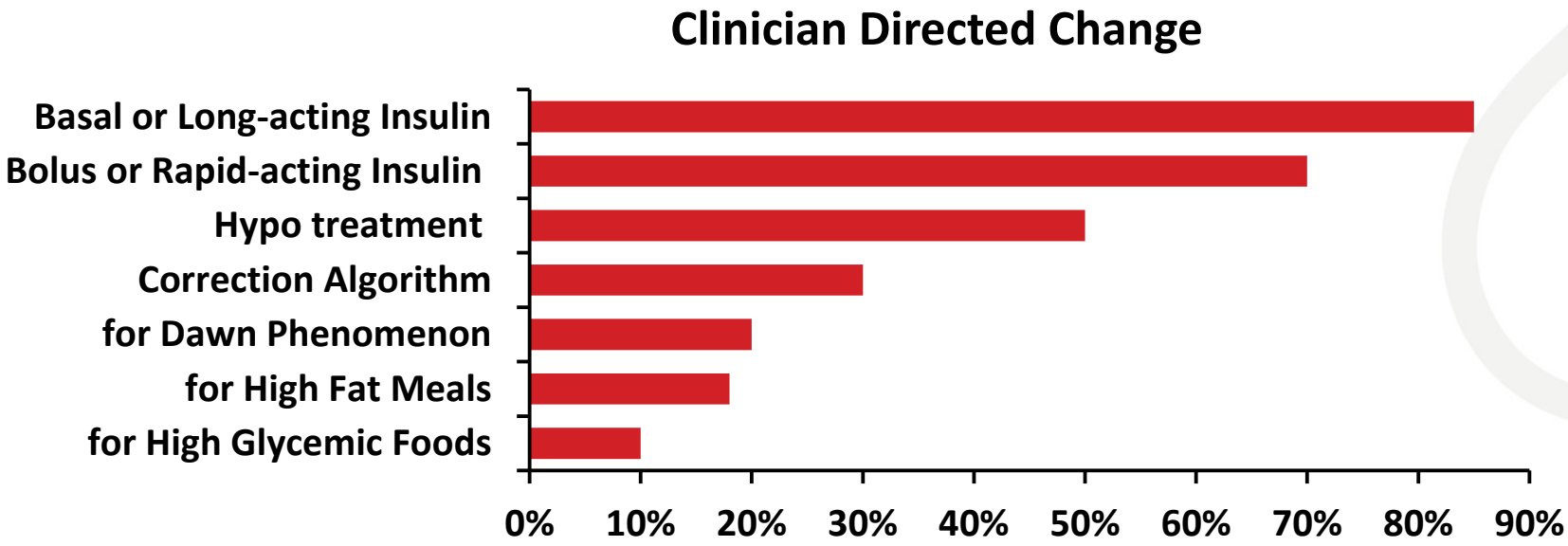


Kaufman F, et. al. *Diabetes Care*. 2001;24(12):2030-4.

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

Additional Outcome

- Clinicians used CGM data to adjust and optimize therapy



Kaufman F, et. al. *Diabetes Care*. 2001;24(12):2030-4.

(2015) Gehlaut Study

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

Results

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

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

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

	n (%)	*P* value
Hypoglycemic severity		
Mild	27 (50.9)	0.009[a]
Severe	11 (20.7)	
Both	15 (28.3)	
Hypoglycemia awareness		
Yes	13 (24.5)	<0.001
No	40 (75.4)	

[a]Comparison was between mild and severe hypoglycemia.
There were more episodes of mild than severe hypoglycemia.

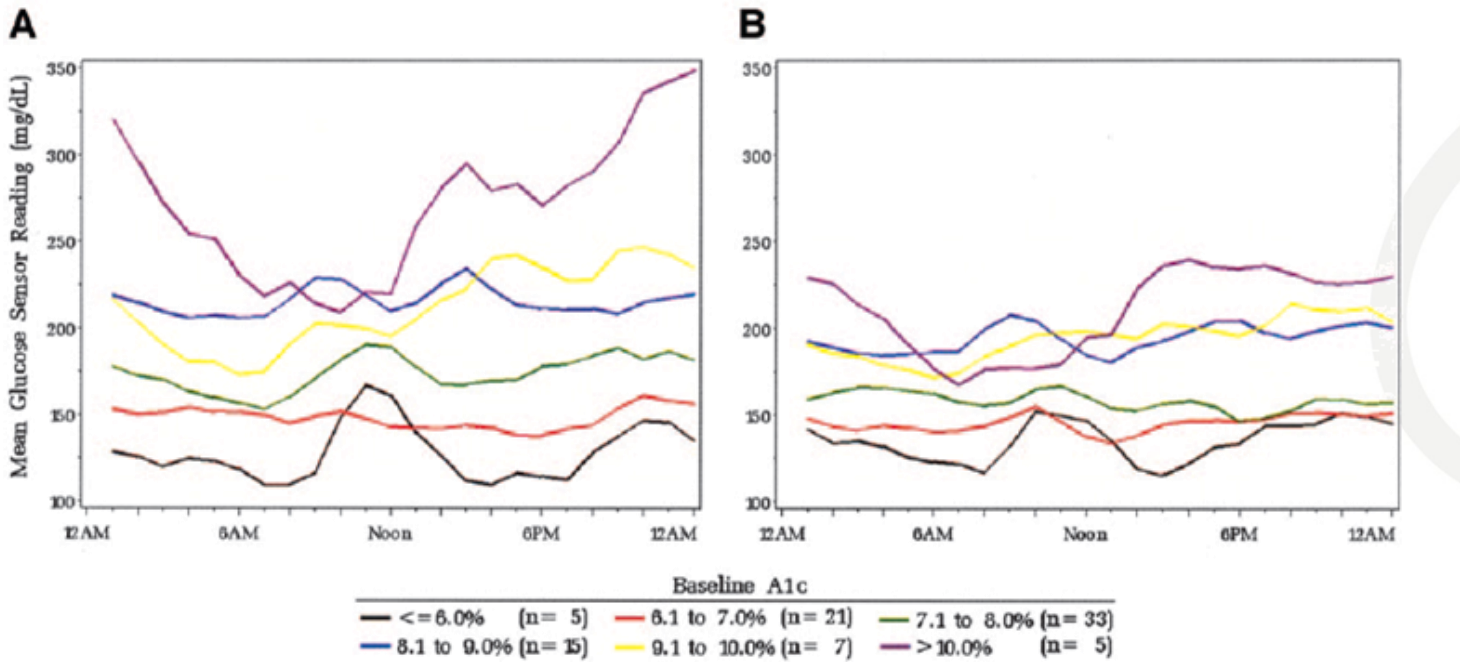
Table 6. Distribution of Patients with Hypoglycemia by Treatment Groups

	n (%)	*P* value
Insulin		
Insulin	35 (66)	0.02
Noninsulin	18 (34)	
Hypoglycemia-causing agents		
Yes	43 (81.1)	<0.001
No	10 (18.9)	
No. of hypoglycemic agents		
Only 1	20 (37.7)	0.073
2 or more	23 (43.4)	
None	10 (18.9)	

Gehlaut R, et al. Hypoglycemia in type 2 diabetes- More common than you think. *J Diabetes Sci Technol*. 2015; (ahead of print).

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

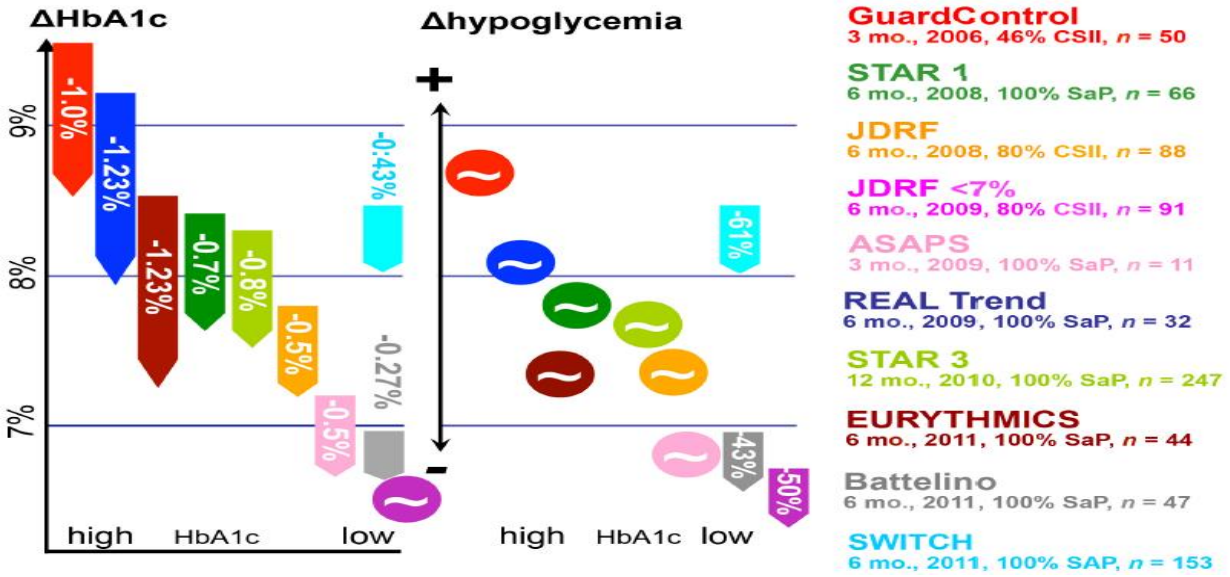


Garg S et al. *Diab Care* 29:44-50, 2006.

CGM reduces A1C with no change in hypoglycemia/ reduces hypoglycemia with no change in A1C

Continuous Glucose Monitoring: Evidence and Consensus Statement for Clinical Use

Andreas Liebl, M.D.,[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.

Outline

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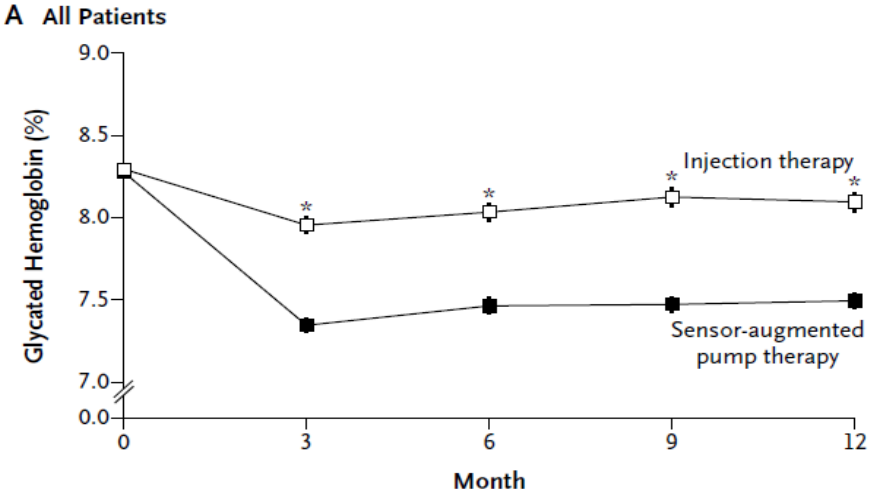
2. Impact of technology on fear of hypoglycemia
3. Do the health economics justify technology to mitigate hypoglycemia?
   - Cost of hypoglycemia

Sensor-Augmented Pumping Reduces A1C without Increasing Hypoglycemia

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

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



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.

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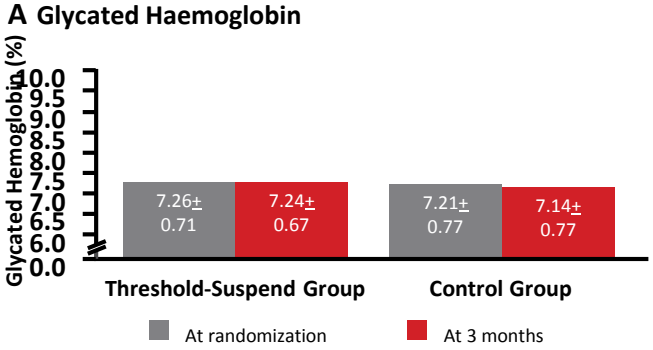
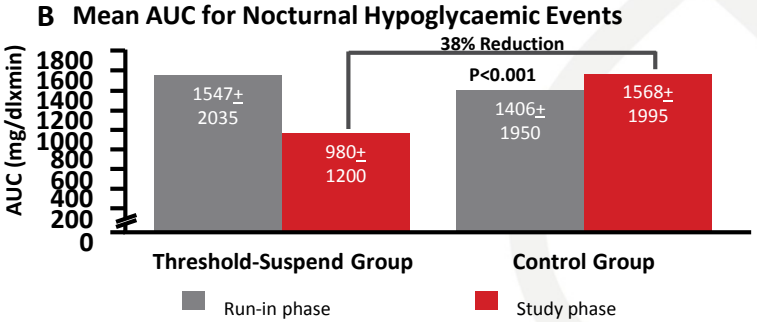
3. Do the health economics justify technology to mitigate hypoglycemia?
   - Cost of hypoglycemia

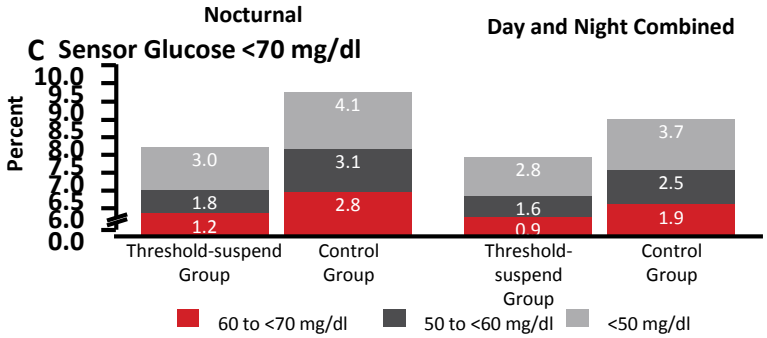
Threshold-Suspend Pumps Reduce Hypoglycemia in High Risk Patients

Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

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







N Eng J Med 369:224–232, 2013.

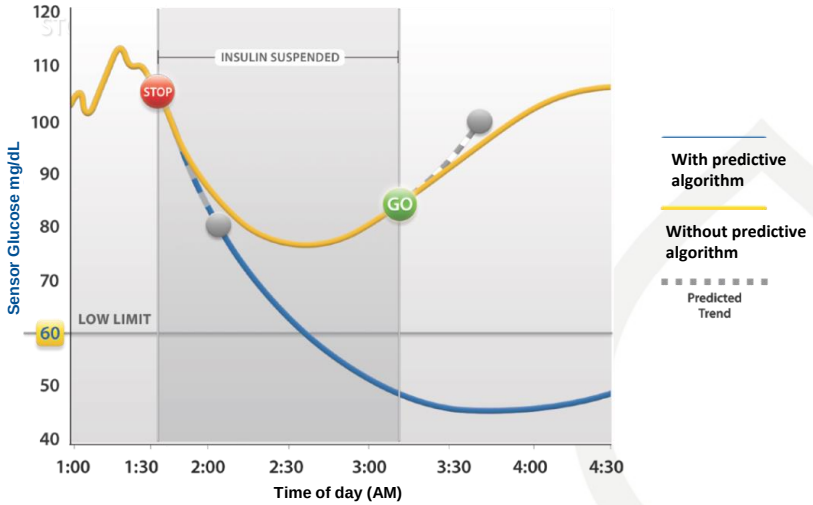
Predictive Low Glucose Management

Insulin delivery is suspended to reduce hypoglycemia if sensor glucose is:

- Less than 70 mg/dL above the low limit AND
- Predicted to approach the low limit in 30 minutes

Suspended basal insulin delivery can resume if:

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



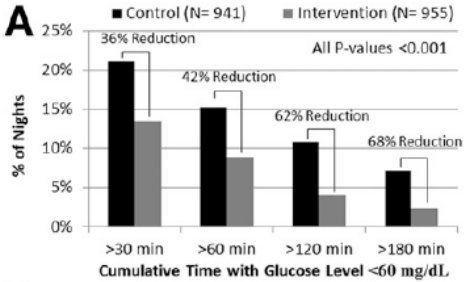
Once resumed manually or based on sensor glucose, basal insulin delivery will not be re-suspended for a minimum of 30 minutes.

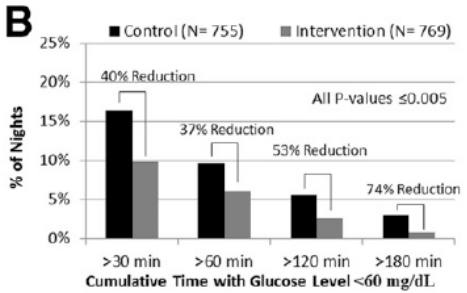
Predictive Low Glucose Suspend Reduces Nocturnal Hypoglycemia over 42 Days

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

*Bruce A. Buckingham,[1] Dan Raghinaru,[2] Fraser Cameron,[3] B. Wayne Bequette,[3] H. Peter Chase,[4] David M. Maahs,[4] Robert Slover,[4] R. Paul Wadwa,[4] Darrell M. Wilson,[1] Trang Ly,[1] Tandy Aye,[1] Irene Hramiak,[5] Cheril Clarson,[6] Robert Stein,[6] Patricia H. Gallego,[6] John Lum,[2] Judy Sibayan,[2] Craig Kollman,[2] and Roy W. Beck,[2] for the In Home Closed Loop Study Group**

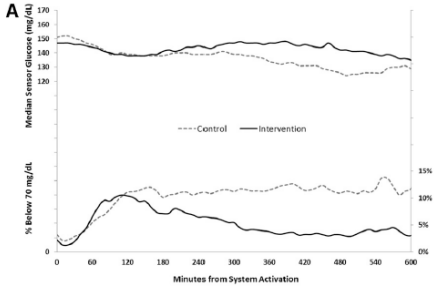
Diabetes Care 2015;38:1197–1204 | DOI: 10.2337/dc14-3053

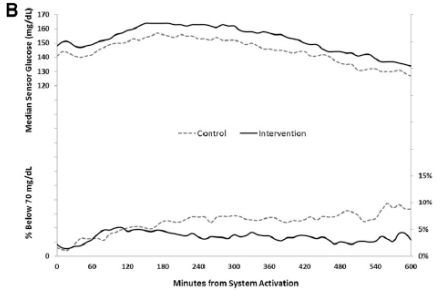




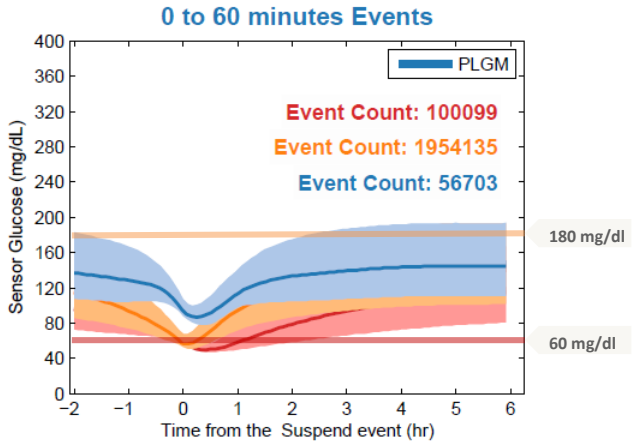
11-14 year olds
(N=45)

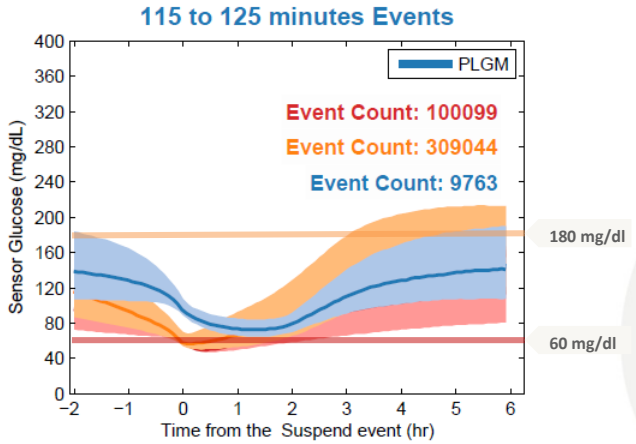
4-10 year olds
(N=36)





Recovery from predictive algorithm compared to low glucose suspend





Data on file at Medtronic (from Jan 13th 2015 to Jul 7th 2015)

Fully Closed Loop Improves Glycemic Control Compared to Sensor-Augmented Pump

MD-Logic Overnight Control for 6 Weeks of Home Use in Patients With Type 1 Diabetes: Randomized Crossover Trial

Revital Nimri,[1] Ido Muller,[1] Eran Atlas,[1] Shahar Miller,[1] Aviel Fogel,[1] Natasa Bratina,[2] Olga Kordonouri,[3] Tadej Battelino,[2,4] Thomas Danne,[3] and Moshe Phillip[1,5]

DOI: 10.2337/dc14-0835

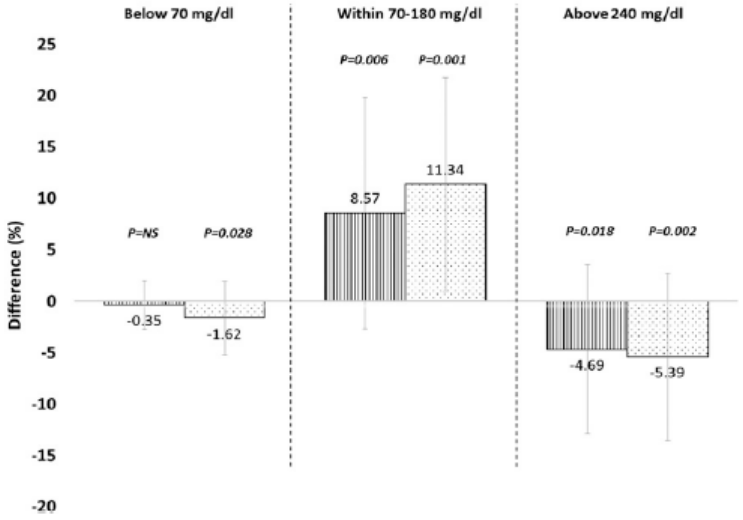
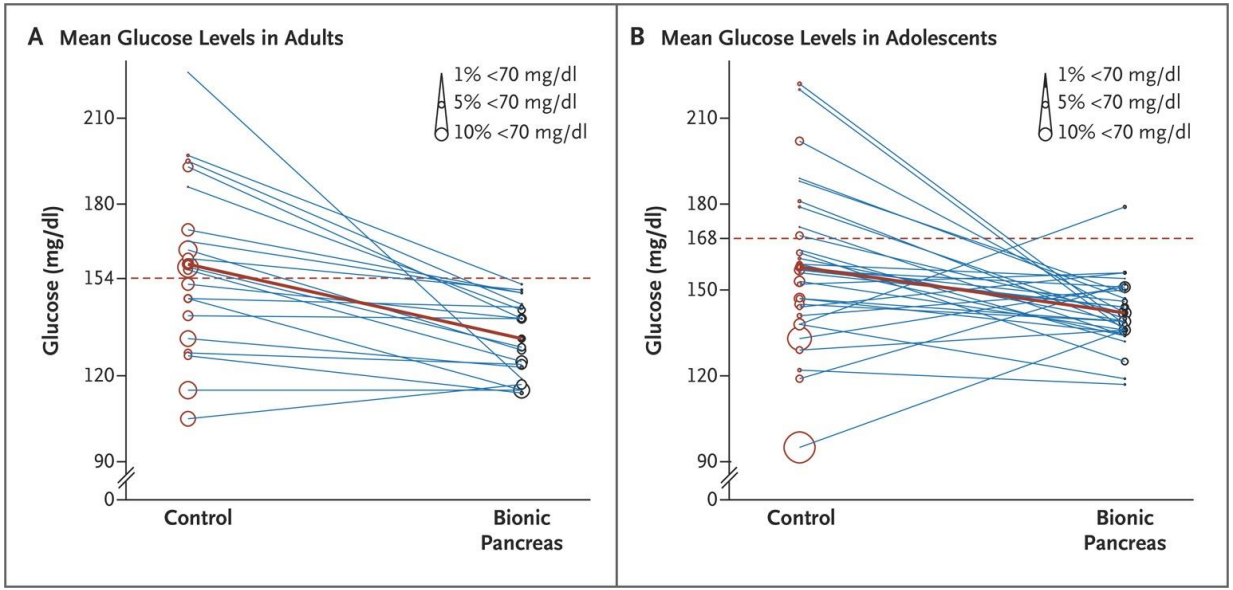


Figure 1—Daytime comparison between the closed-loop and SAP group. Mean daytime difference between the closed-loop and SAP groups in different glucose ranges. The striped boxes represent the daytime only (between 0700 and 2300), and the dotted boxes represent the entire day comparison (0000 to 2400).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

Dual-Hormone Artificial Pancreas System Reduces Glucose and Hypoglycemia in Adult and Adolescents

Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes

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.

Outline

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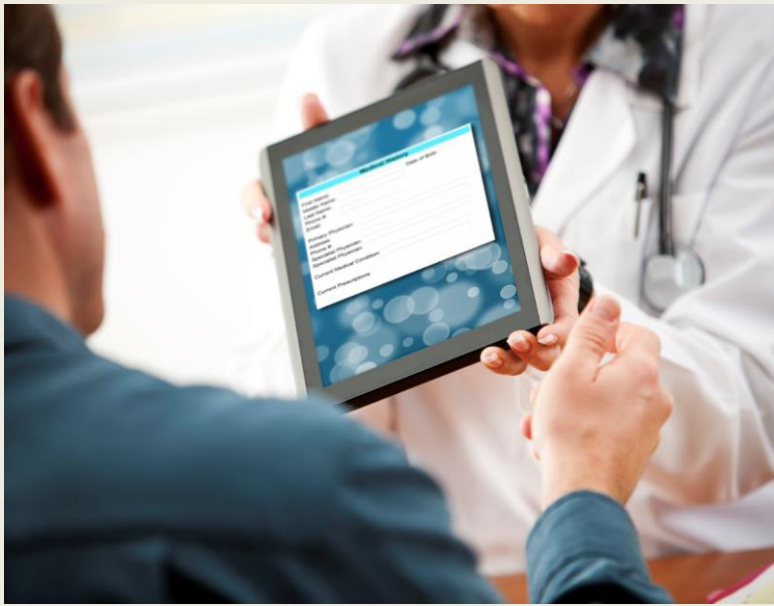
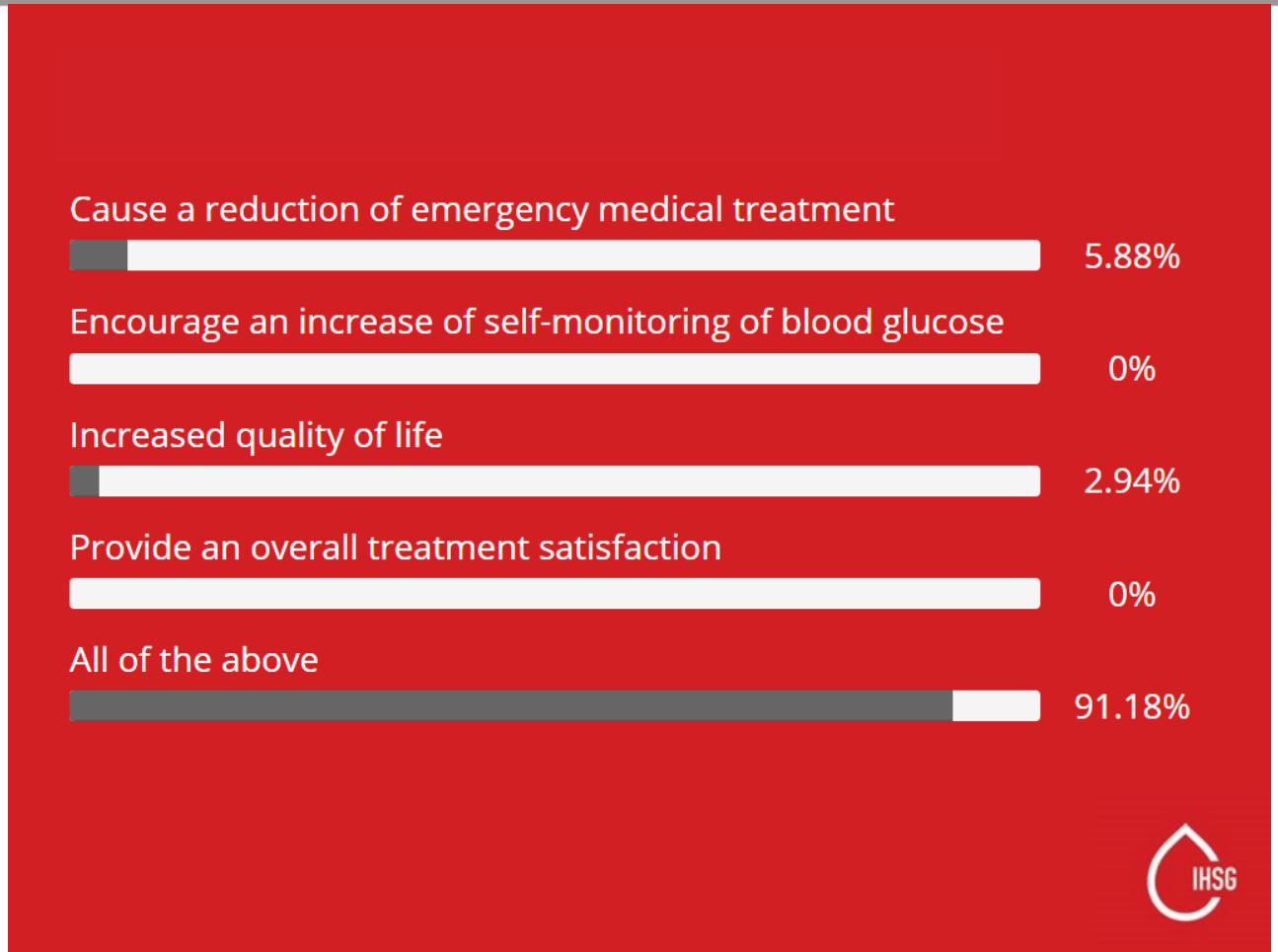
A question for you

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

- Cause a reduction of emergency medical treatment
- Encourage an increase of self-monitoring of blood glucose
- Increased quality of life
- Provide an overall treatment satisfaction
- All of the above



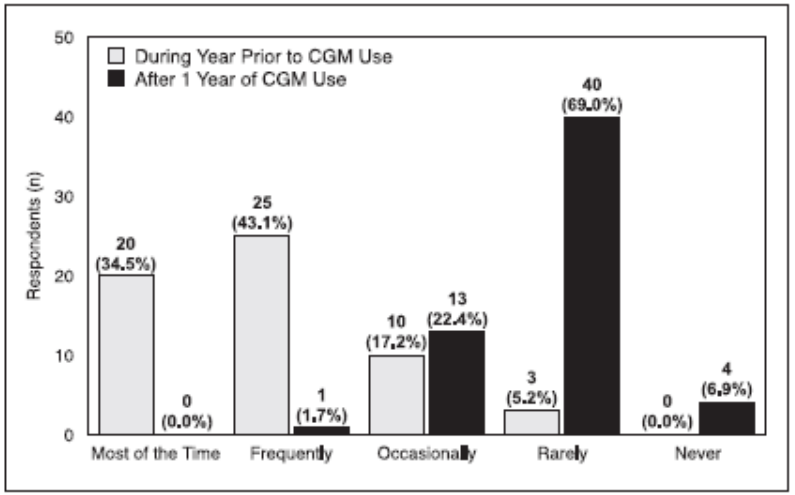
How do you think technology can most help patients remove fear of hypoglycemia?

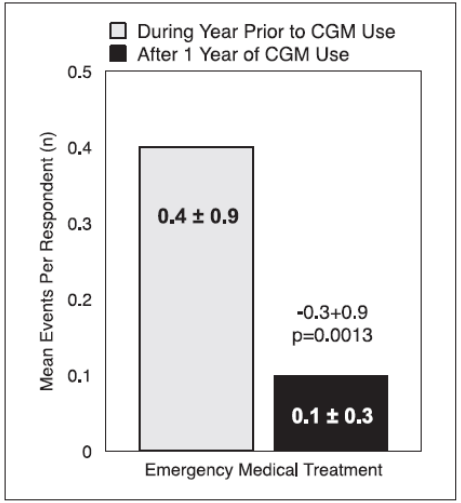


CGM Reduces Fear of Hypoglycemia and Emergency Treatment

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

James J. Chamberlain, MD[1], Dana Dopita, RN, MSN, CDE[1], Emily Gilgen, RD, CD, CDE[1], and Annie Neuman, MPA, PA-C[1]





J Diab Sci Tech ePub Sept 9, 2015.

Sensor-Augmented Pumping Improves Quality of Life and Treatment Satisfaction

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

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

Adult		
Measure	**SAPT (n=166)**	**MDI (n=168)**
Hypoglycemia Fear Survey		
Hypoglycemia Worry		
Baseline	21.94	21.52
Week 52 Change	-6.36**	-1.87
Hypoglycemia Avoidant Behavior		
Baseline	16.38	16.70
Week 52 Change	-2.30**	-0.52

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

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SCIENTIFIC STATEMENT

Economic Costs of Diabetes in the U.S. in 2012

AMERICAN DIABETES ASSOCIATION

Diab Care 2013

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

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

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

Data sources: analyses of the NHIS (2009-2011), CPS (2011), CDC mortality data, and the U.S. Census Bureau population estimates for 2010 and 2012.
*Numbers do not necessarily sum to totals because of rounding.

Effect of hypoglycemia on treatment discontinuation

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

Morgan Bron, PharmD, MS[1]
Maryna Marynchenko, MBA[2]
Hongbo Yang, PhD[3]
Andrew P. Yu, PhD[4]
Eric Q. Wu, PhD[5]

[1]Principal Scientist, Takeda Pharmaceuticals International, Inc., Deerfield, IL; [2]Associate, Analysis Group, Inc., Boston, MA; [3]Associate, Analysis Group, Inc., Boston, MA; [4]Manager, Analysis Group, Inc., Boston, MA; [5]Managing Principal, Analysis Group, Inc., Boston, MA

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

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

Annual Health Care Cost[1]	Patients With Hypoglycemia (N=4860)	Patients Without Hypoglycemia (N=207 201)	Difference	*P* value
	A	B	A - B	A vs. B
Descriptive analysis, mean (SD)				
Total drug cost, $				
All drugs	2725	2673	53	<0.2394[a]
Diabetes-related[2]	691	742	-51	<0.0001
Total medical cost, $				
Any cause	11306	6334	4972	<0.0001[a]
Diabetes-related[3]	6321	2523	3798	<0.0001[a]
Total cost, $				
Any cause	14031	9007	5024	<0.0001[a]
Diabetes-related	7012	3265	3747	<0.0001[a]
Based on generalized linear models, estimated mean[4]				

Postgrad Med 124:124-132, 2012

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QUESTIONS FOR OUR PANEL

Submit a question on the iPad or raise your hand to ask a question

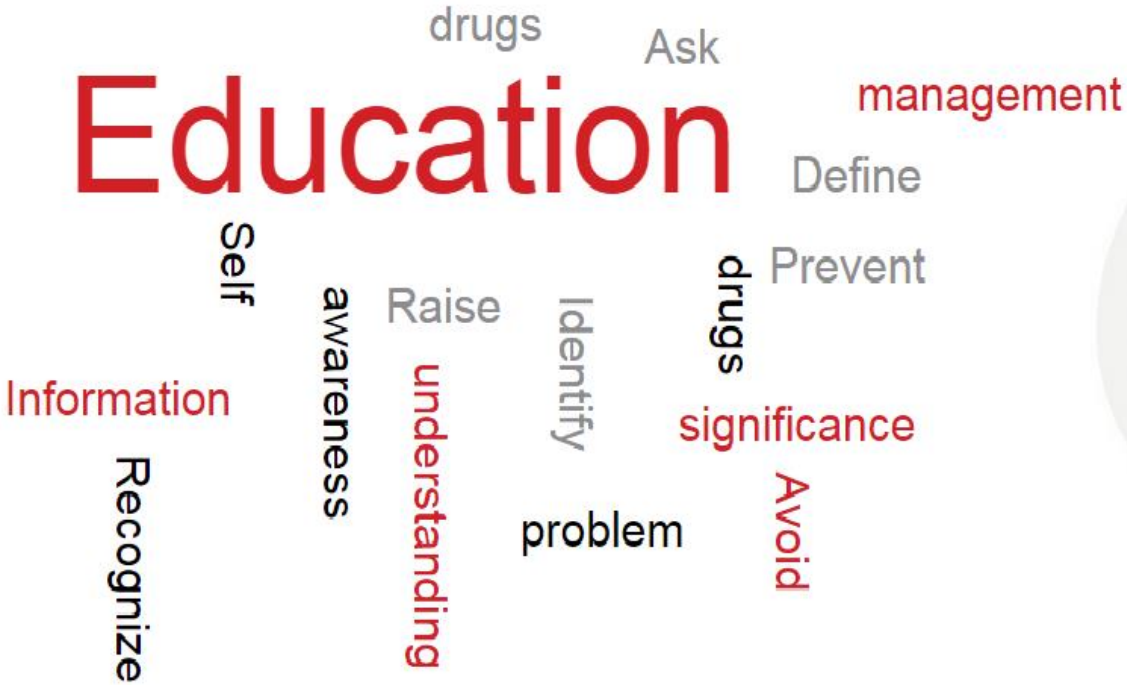
Do we need a new classification for hypoglycemia?

Do we need separate definitions for different stakeholders such as patients, physicians, trialists, and regulators?

Wrap-up

Lawrence A. Leiter, MD, FRCPC, FACP, FACE, FAHA
Division of Endocrinology and Metabolism,
St. Michael's Hospital.
Professor of Medicine and Nutritional Sciences
University of Toronto
Ontario, Canada

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




thank you!