Diabetic Hypoglycemia: Questions and Controversies

Presented by the
International Hypoglycaemia Study Group (IHSG)
at the
9th World Congress on Prevention of Diabetes and its Complications

December 3, 2016
Atlanta, Georgia, USA

Brought to you by members of the International Hypoglycaemia Study Group

IHSG

Welcome & Introductions

Elizabeth Seaquist, MD, CDE
Professor of Medicine, Pennock Family Chair in Diabetes Research
Director, Division of Endocrinology and Diabetes
Department of Medicine, University of Minnesota
2014 President of Medicine and Science
American Diabetes Association
Minneapolis, MN, USA

WELCOME TO ATLANTA!

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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

OUR OBJECTIVE THIS MORNING

To highlight important but lesser-known aspects of hypoglycemia

AGENDA

8:05 am

Hypoglycemia Classification

Simon Heller

8:15 am

Impaired Awareness of Hypoglycemia

Stephanie Amiel

8:30 am

Fear of Hypoglycemia

Linda Gonder-Frederick

8:45 am

Panel Q&A Session

All

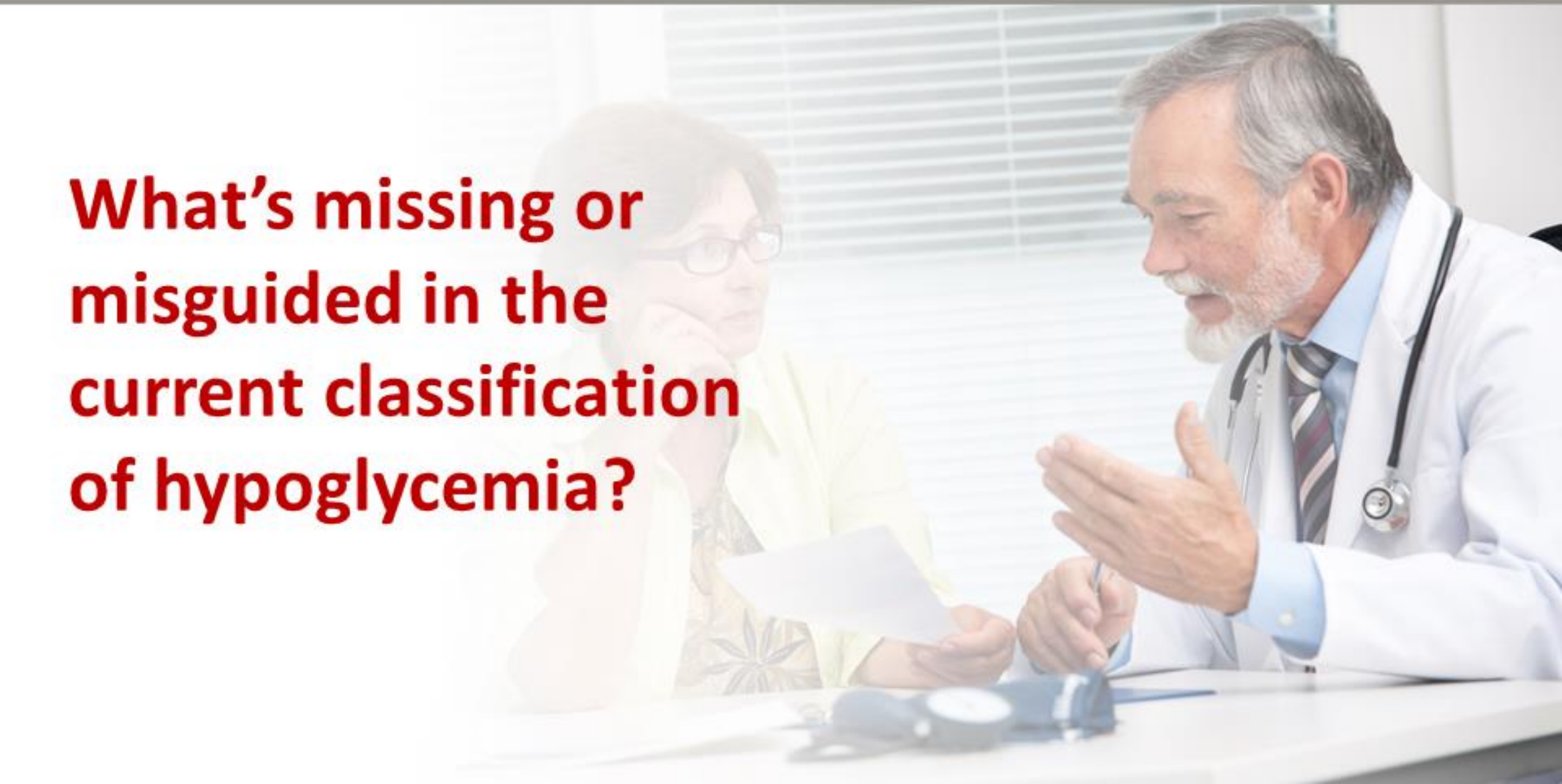
Hypoglycemia Classification

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, UK

Presenter Disclosure

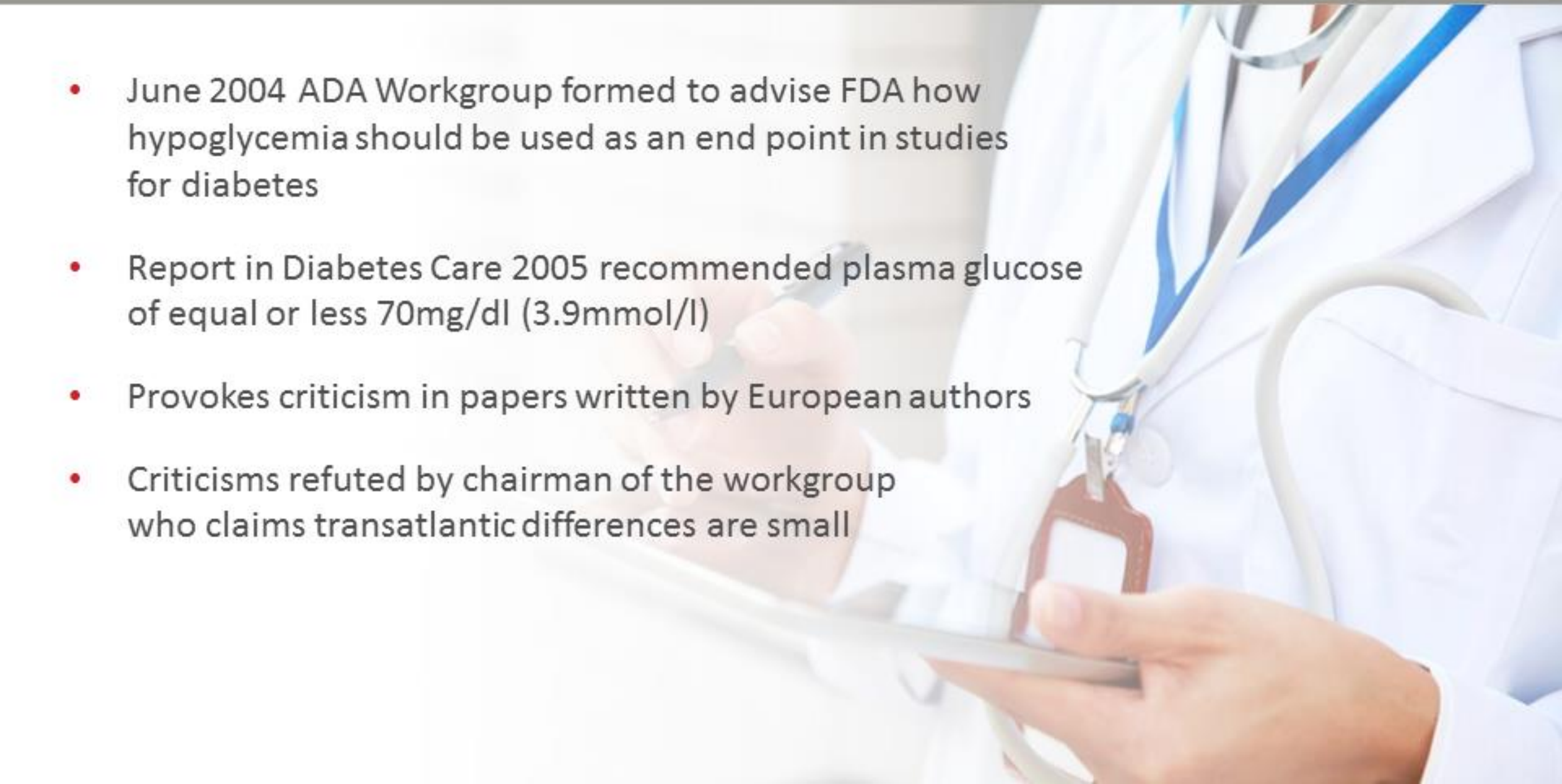
- **Advisory Board Member:** Eli Lilly, Novo Nordisk, Sanofi Aventis, Takeda
- **Consultant:** Eli Lilly, Novo Nordisk, Takeda, Boeringher Ingelheim
- **Research Support:** Medtronic
- **Speaker's Bureau:** Eli Lilly, Novo Nordisk, Sanofi Aventis, Takeda, AstraZeneca, Johnson & Johnson

What's missing or misguided in the current classification of hypoglycemia?



Background

- June 2004 ADA Workgroup formed to advise FDA how hypoglycemia should be used as an end point in studies for diabetes
- Report in Diabetes Care 2005 recommended plasma glucose of equal or less 70mg/dl (3.9mmol/l)
- Provokes criticism in papers written by European authors
- Criticisms refuted by chairman of the workgroup who claims transatlantic differences are small



What did the ADA group actually say?

Addressed 3 questions:

1. How should hypoglycemia be defined?
2. How should hypoglycemia be reported?
3. What constitutes a meaningful reduction in hypoglycemia?

View of the ADA working group

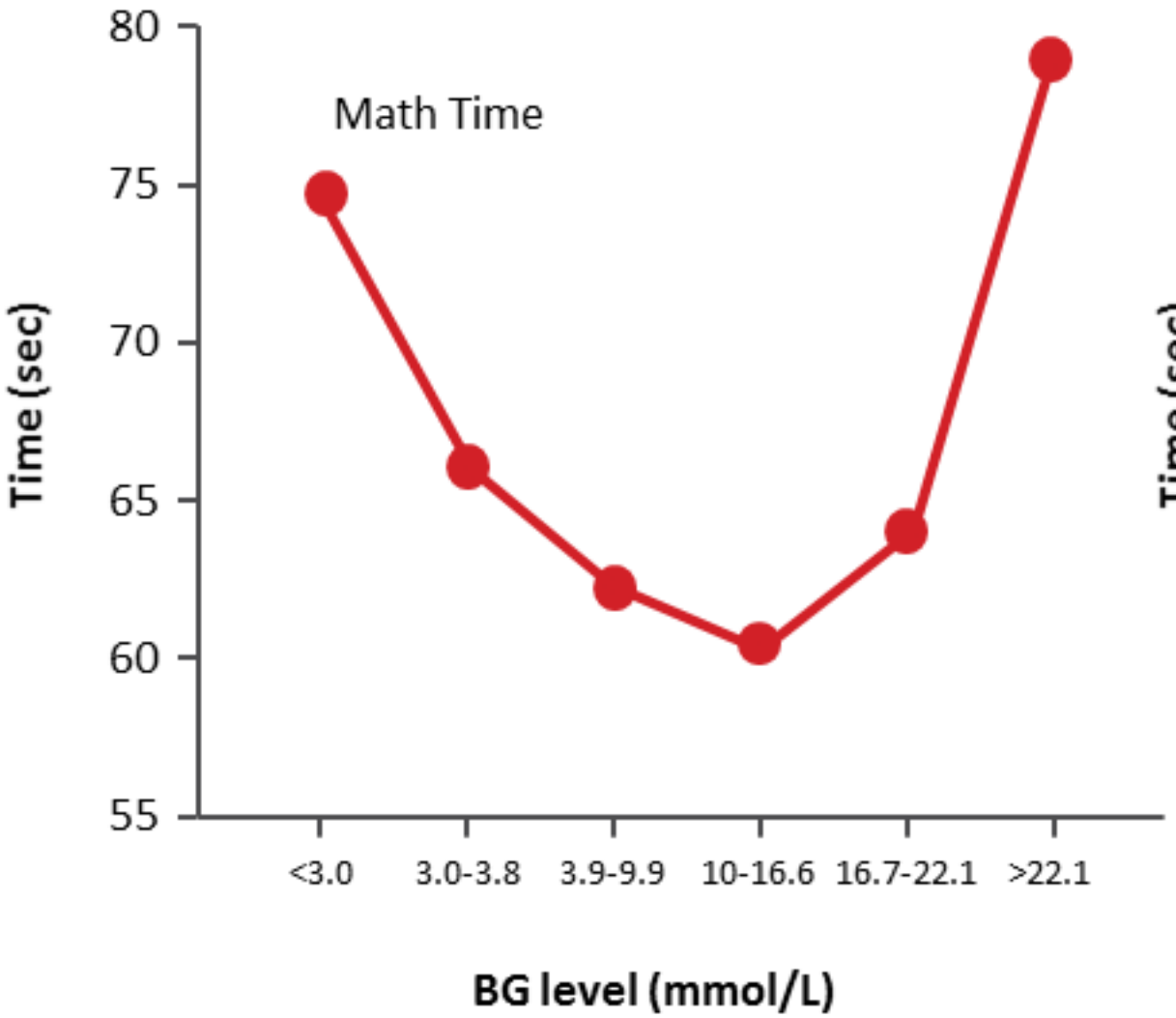
- **The definition should apply to:**
  - clinical decisions by people with diabetes and HCPs
  - studies of diabetes drugs, devices, or management strategies
- **And should be:**
  - free from reporting biases
  - clinically important
  - applicable to all persons with diabetes
  - applicable to any time of day
  - measurable by practical and widely available methods,
  - reportable in a standardized fashion

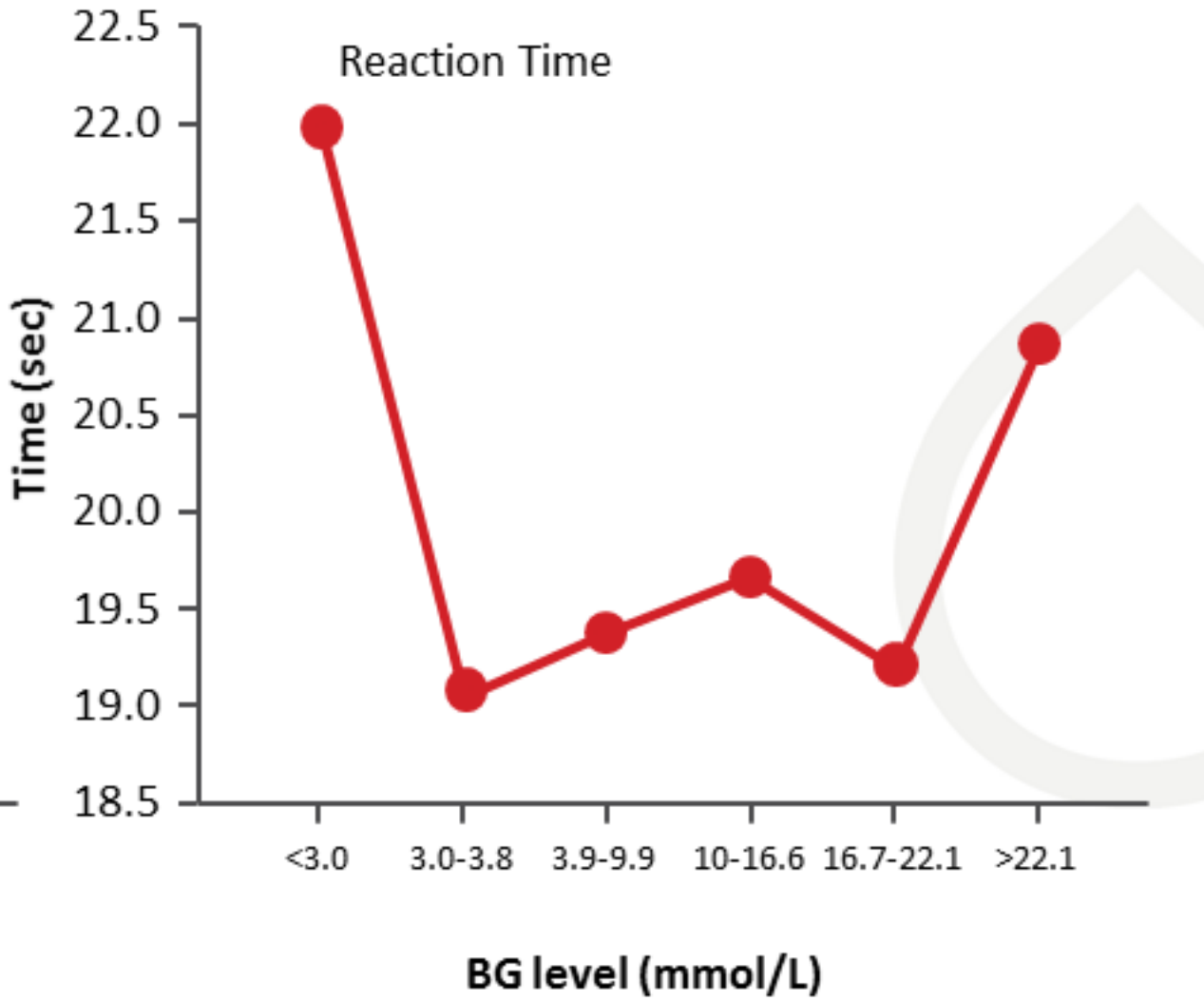
ADA W Group, *Diabetes Care* 2005.

Hypoglycemia: An outcome critically relevant to patients

- Predicts serious morbidity and mortality
- Limitations of traditional definitions:
  - Symptoms occur at different glucose levels
  - People with impaired awareness may not have symptoms
  - Some asymptomatic hypoglycemia is clinically relevant
- Severe – often uncommon in many trials leading to insufficient statistical power to compare interventions
- Current classification doesn't capture all significant hypoglycemia
  - real-world prevalence is higher than clinical-trial prevalence
  - 70mg/dl (3.9mM) is not usually associated with morbidity
- *Strong* case for third agreed level denoting major/serious hypoglycemia at around 50-55mg/dl

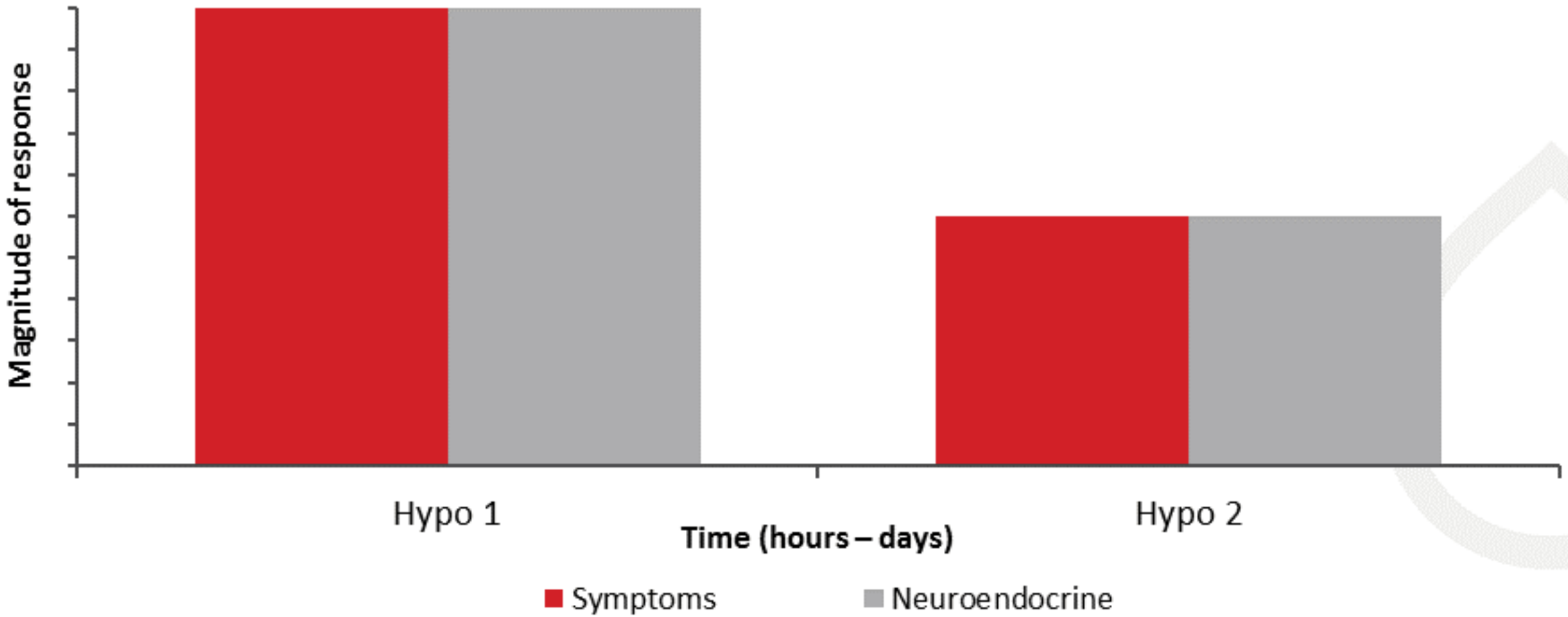
Evidence for impaired cognitive function 3 mmol/L < 54mg/dl





Gonder-Frederick et al, *Diabetes Care* 2009. Heller et al *Lancet* 1987. Matyka et al *Diabetes Care* 1997. Choudhary et al *Diabet Med* 2009.

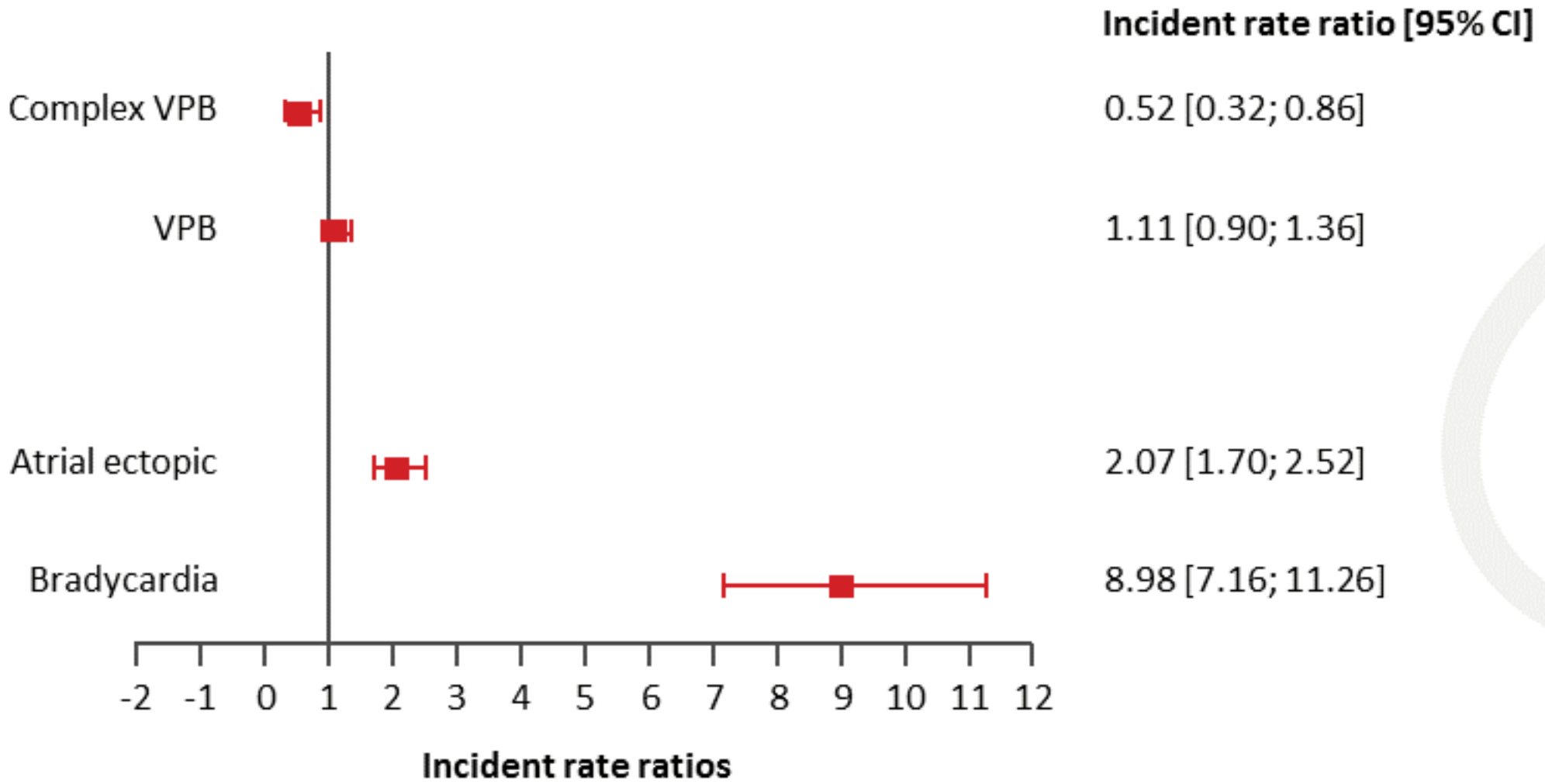
Evidence that a glucose level of <54mg/dl leads to impaired awareness of hypoglycemia



Studies inducing reduced awareness at <54mg/dl (3mmol/l)

Heller & Cryer 1991. Davis et al 1992. Mellman et al 1994. Robinson et al 1995.

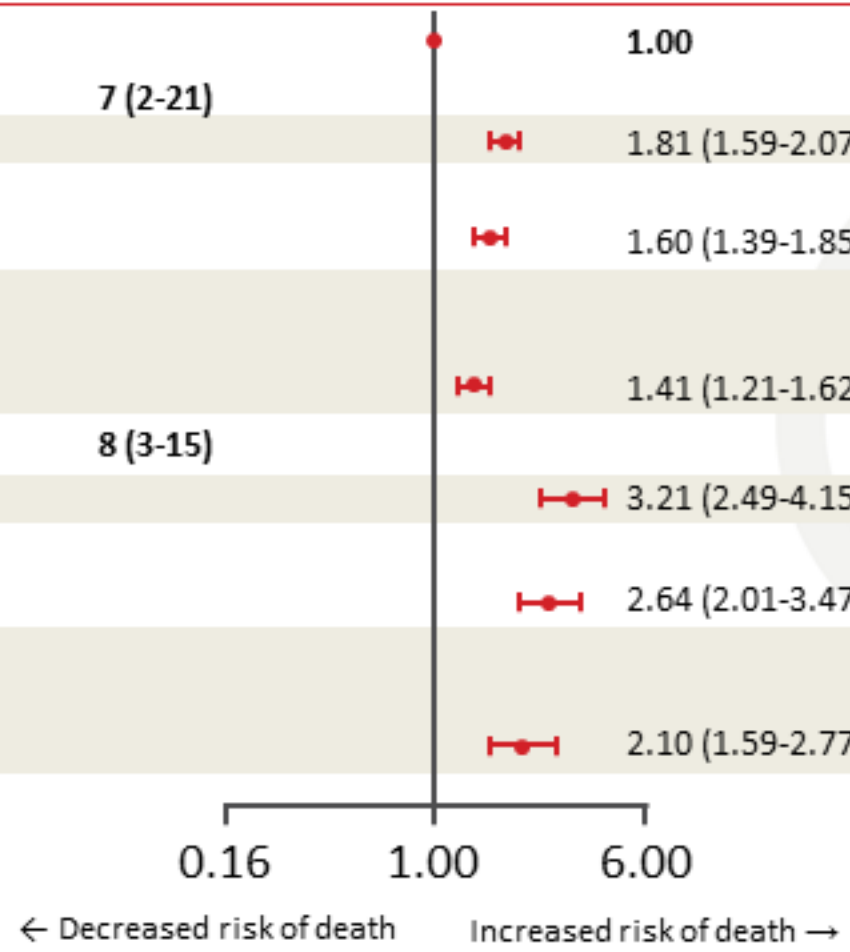
Evidence for arrhythmias triggered by glucose levels <54mg/dl



Chow et al *Diabetes* 2014. Pistrosch F. et al *Acta Diabetologica* 1015.

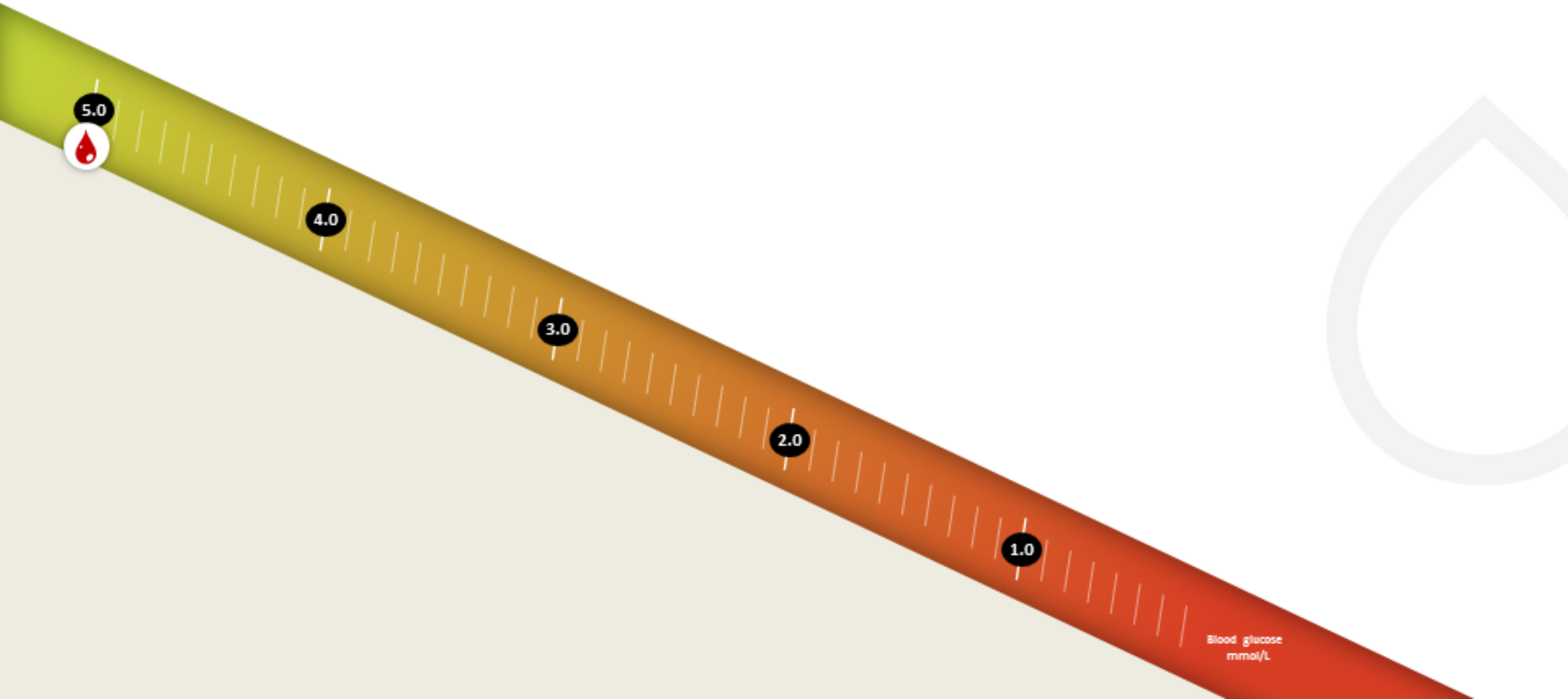
Evidence for increased mortality associated with glucose levels <55mg/dl

Subgroup	Deaths no.	Population no.	Median Time from Randomization to Hypoglycemia (IQR) days	Median Time from Hypoglycemia to Death (IQR) days	Hazard Ratio (95% CI)	P Value
No hypoglycemia	**726**	**3089**			**1.00**	
Moderate hypoglycemia	**774**	**2714**	**1 (0-2)**	**7 (2-21)**		
Stratified by treatment					1.81 (1.59-2.07)	<0.001
Stratified by treatment & adjusted for baseline characteristics					1.60 (1.39-1.85)	<0.001
Stratified by treatment & adjusted for baseline & post-randomization characteristics					1.41 (1.21-1.62)	<0.001
Severe hypoglycemia	**79**	**223**	**4 (2-9)**	**8 (3-15)**		
Stratified by treatment					3.21 (2.49-4.15)	<0.001
Stratified by treatment & adjusted for baseline characteristics					2.64 (2.01-3.47)	<0.001
Stratified by treatment & adjusted for baseline & post-randomization characteristics					2.10 (1.59-2.77)	<0.001



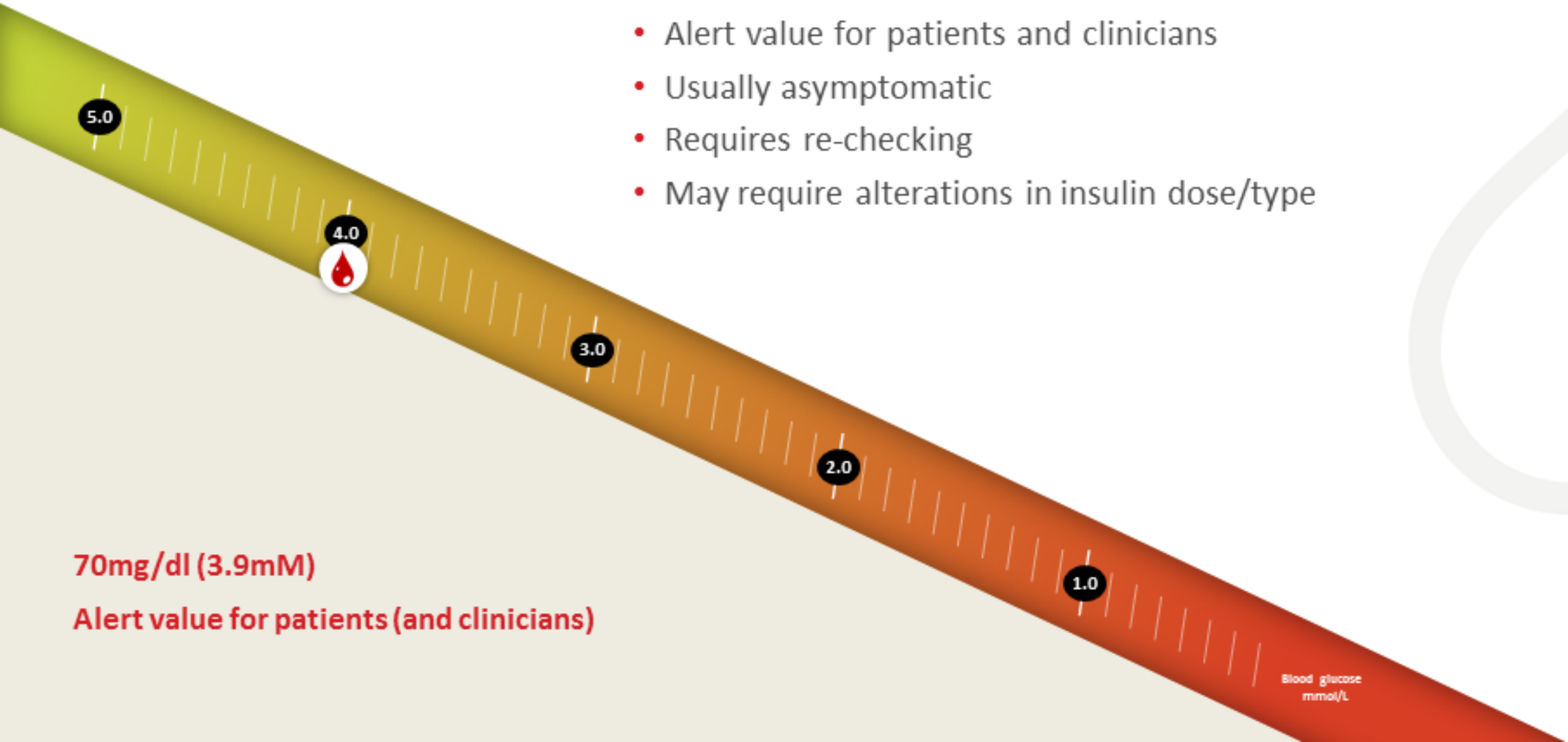
NICE-SUGAR *NEJM* 2013.

Classifying hypoglycemia in clinical trials – Level 1



Classifying hypoglycemia in clinical trials – Level 1

- Alert value for patients and clinicians
- Usually asymptomatic
- Requires re-checking
- May require alterations in insulin dose/type

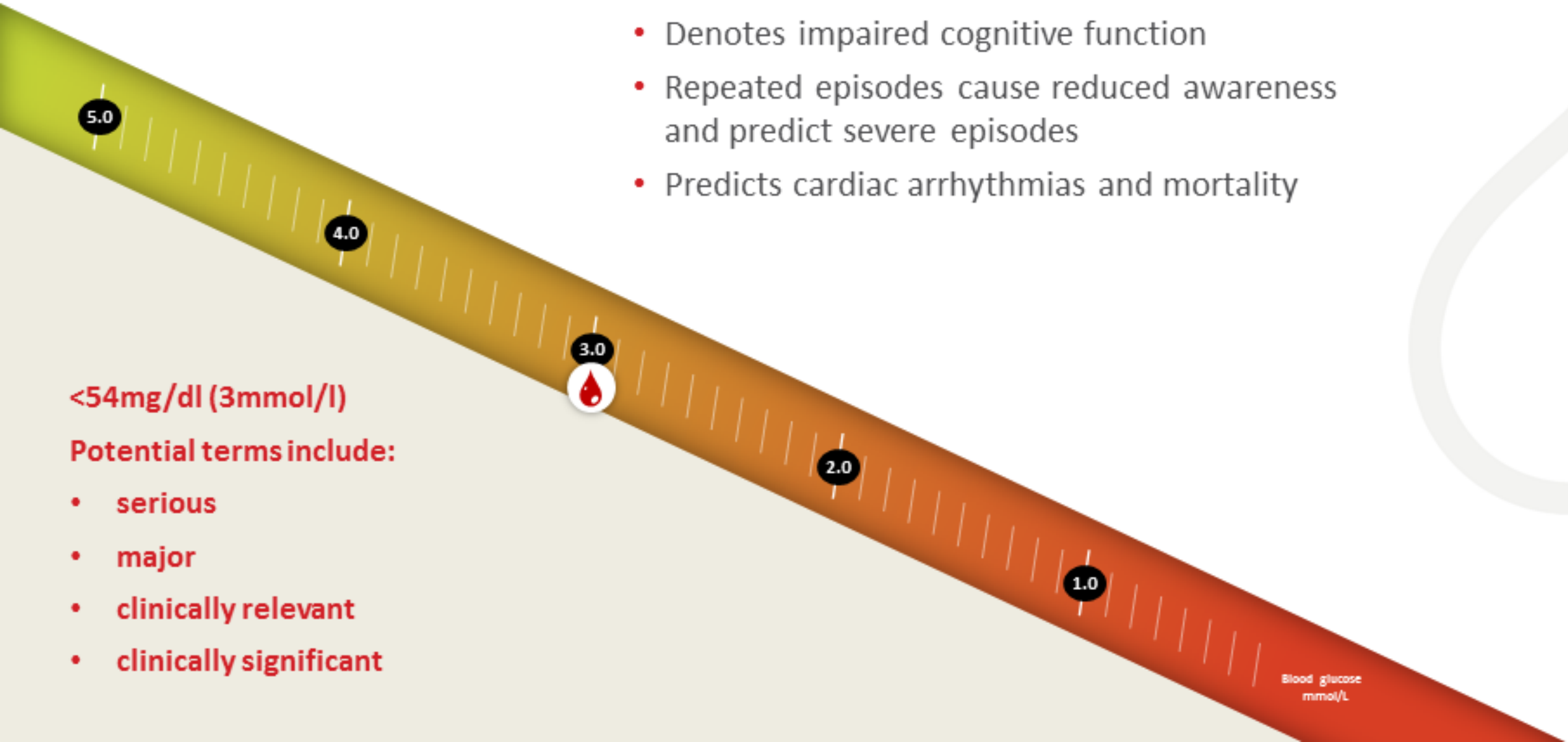


70mg/dl (3.9mM)

Alert value for patients (and clinicians)

Classifying hypoglycemia in clinical trials – Level 2

- Denotes impaired cognitive function
- Repeated episodes cause reduced awareness and predict severe episodes
- Predicts cardiac arrhythmias and mortality



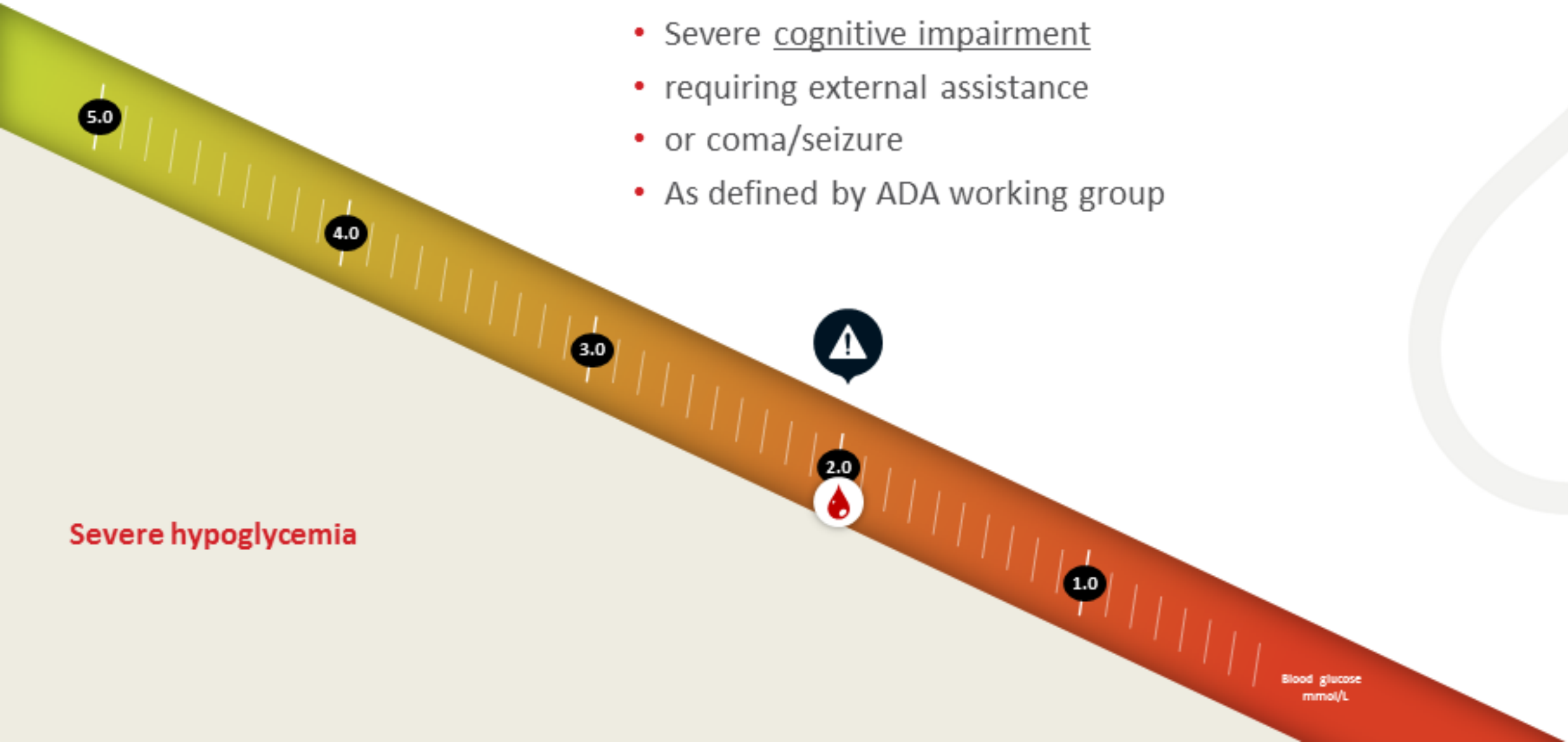
<54mg/dl (3mmol/l)

Potential terms include:

- **serious**
- **major**
- **clinically relevant**
- **clinically significant**

Classifying hypoglycemia in clinical trials – Level 3

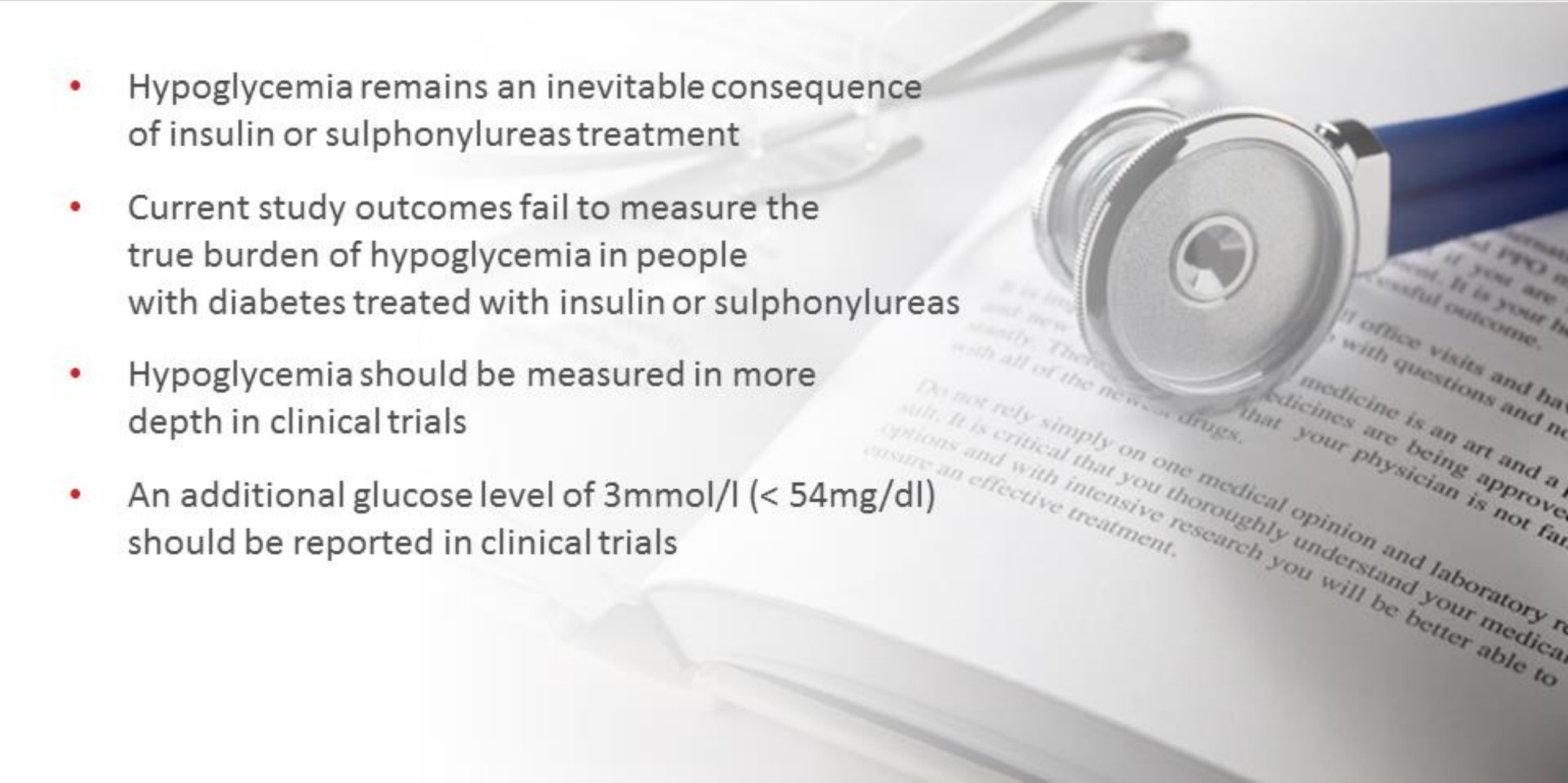
- Severe cognitive impairment
- requiring external assistance
- or coma/seizure
- As defined by ADA working group



Severe hypoglycemia

Conclusions

- Hypoglycemia remains an inevitable consequence of insulin or sulphonylureas treatment
- Current study outcomes fail to measure the true burden of hypoglycemia in people with diabetes treated with insulin or sulphonylureas
- Hypoglycemia should be measured in more depth in clinical trials
- An additional glucose level of 3mmol/l (< 54mg/dl) should be reported in clinical trials



Impaired Awareness of Hypoglycemia

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

Presenter Disclosure

- **Advisory Board Member:** Medtronic, Novo Nordisk

The meaning of impaired awareness

Mrs. MF

	7.00am	12.30pm	4.00pm	7.00pm	9.13pm	10.45pm	
Monday	5.8	7.1	2.8	10.1	9.1	8.1	

The meaning of impaired awareness

Mrs. MF

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	8.1	3.9		3.2	8.9		
Wednesday	**6.45am**	**10.00am**	**12.45pm**	**4.30pm**	**7.30pm**		**11.15pm**
	9.8	15.1	4.6	2.7	8.7		8.2

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Thursday	**7.10am**	**12.50pm**					
	4.6	6.7					

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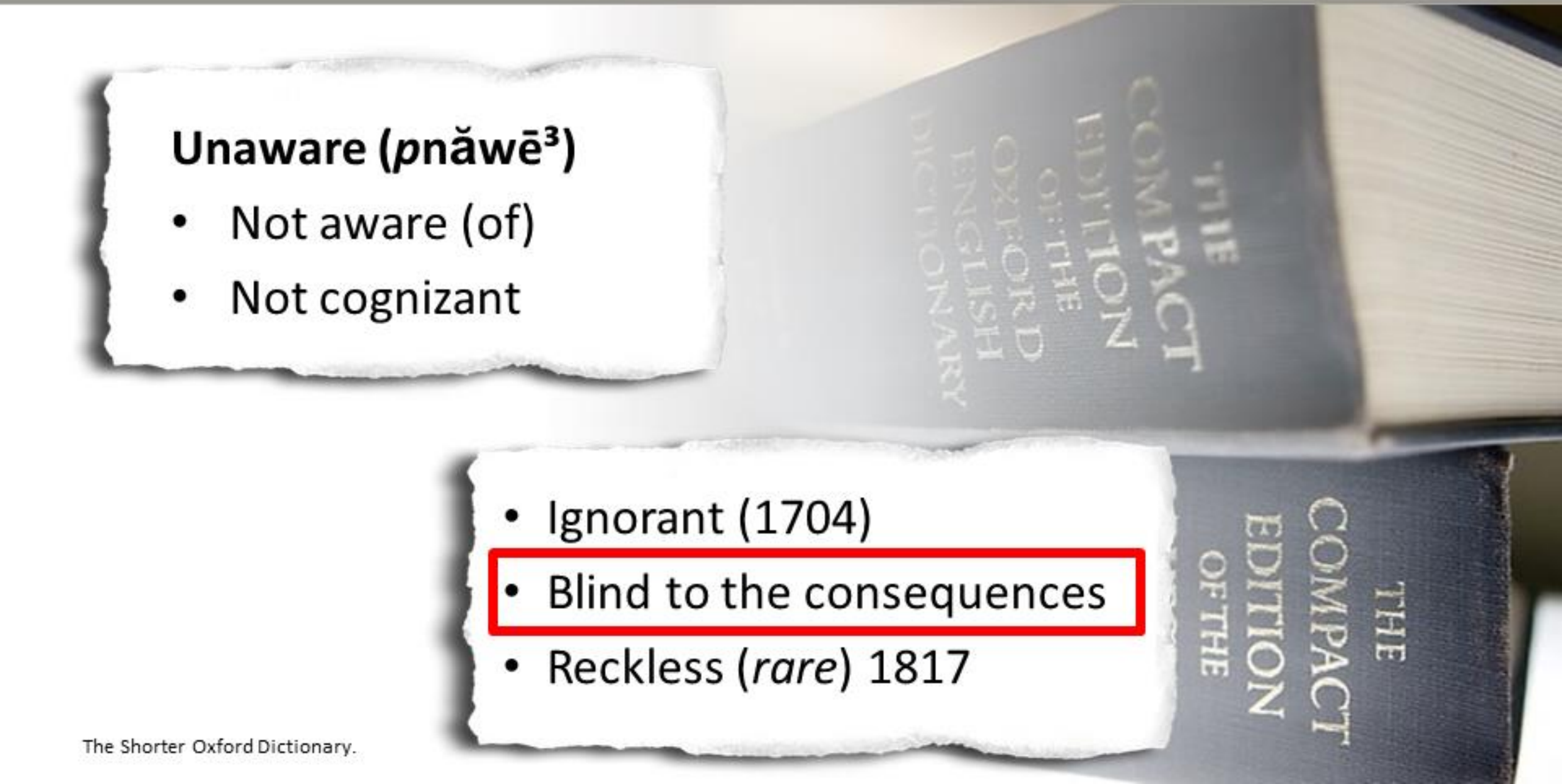
Thursday	**7.10am**	**12.50pm**			**7.15pm**		
	4.6	6.7			10.1		
Friday	**7.45am**	**12.40pm**		**3.30pm**			
	6.9	11.1		2.9			

Dictionary definitions:

Unaware (*p*năwē³)

- Not aware (of)
- Not cognizant



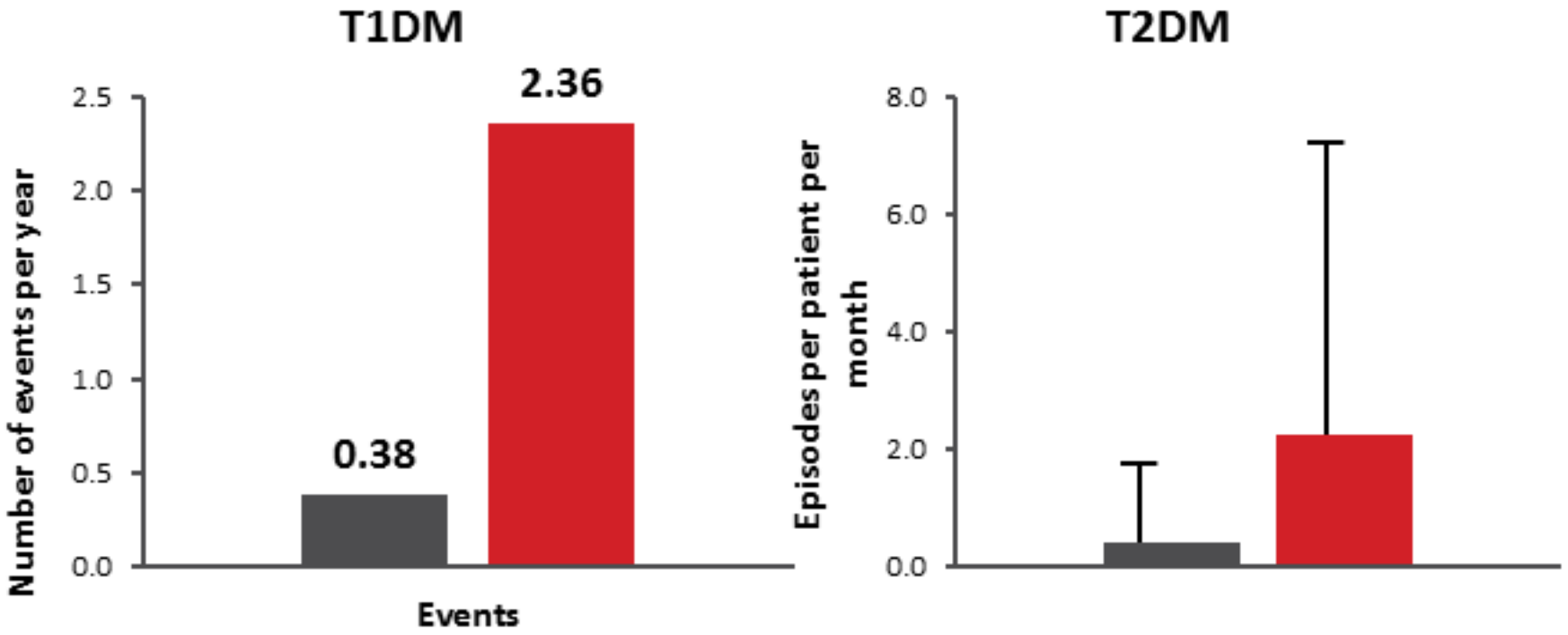
- Ignorant (1704)
- Blind to the consequences
- Reckless (*rare*) 1817

The Shorter Oxford Dictionary.

The identification of impaired awareness

"Do you know when you[illegible]s are commencing?"

Always aware	1	2	3	4	6	7	Never aware



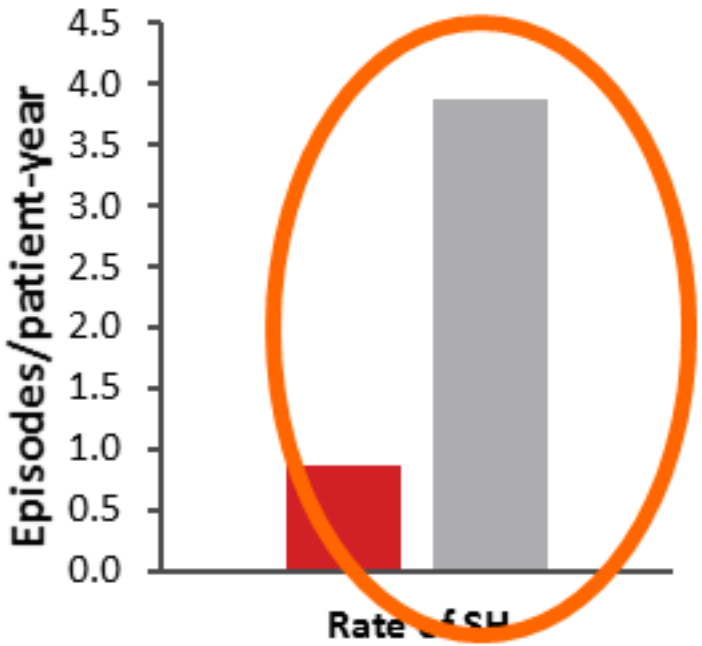
Geddes et al., 2008.
Schopman et al., 2010.

The identification of impaired awareness

Do your symptoms of hypoglycemia usually occur at a blood glucose level of:

- Greater than/equal to 3 mmol/l (54 mg/dl)
- Less than 3 mmol/l (54 mg/dl)
- Do not feel symptoms

DAFNE



Hopkins et al., 2012;35:1638.
Pedersen-Bjergaard et al., 2004.

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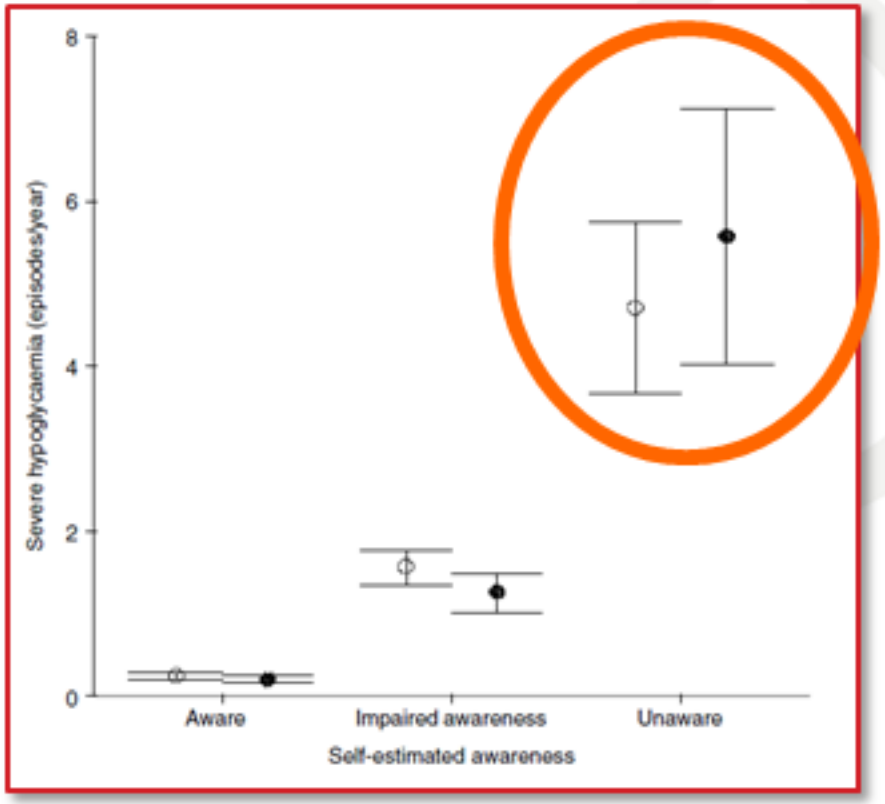
DAFNE

Do you have symptoms, when you have a hypo?

- 'always' = aware
- 'usually' = impaired awareness
- 'occasionally' or 'never' = unaware



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The identification of impaired awareness

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"Do you know when your hypos are commencing?"

Always aware	1	2	3	4	5	6	7	Never aware

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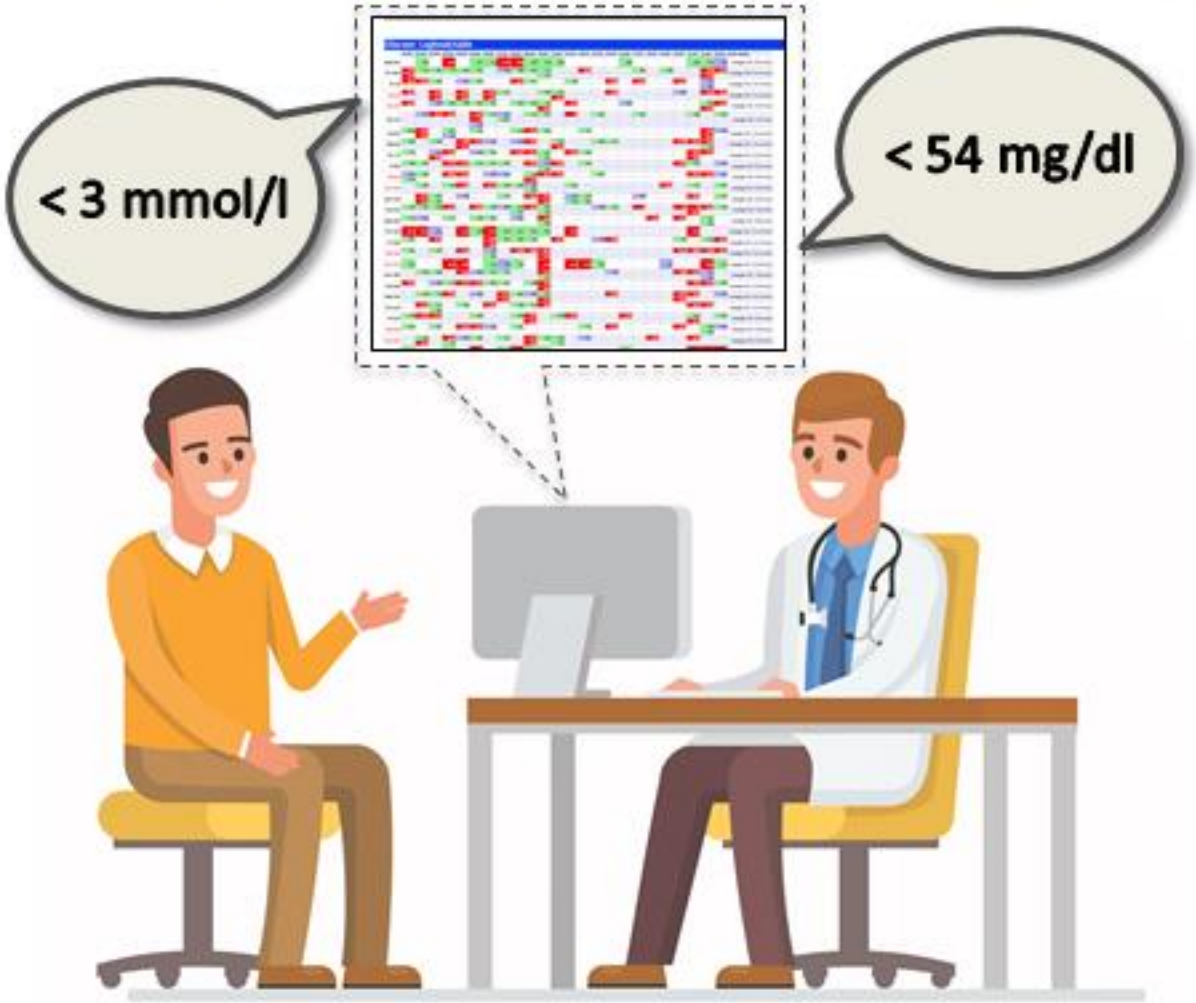
The identification of impaired awareness

Step 2: Review the records



Step 3: Ask the family

The ADA checklist

- 15-item patient questionnaire
- Health care provider check-list

Table 3—*Hypoglycemia Provider Checklist*

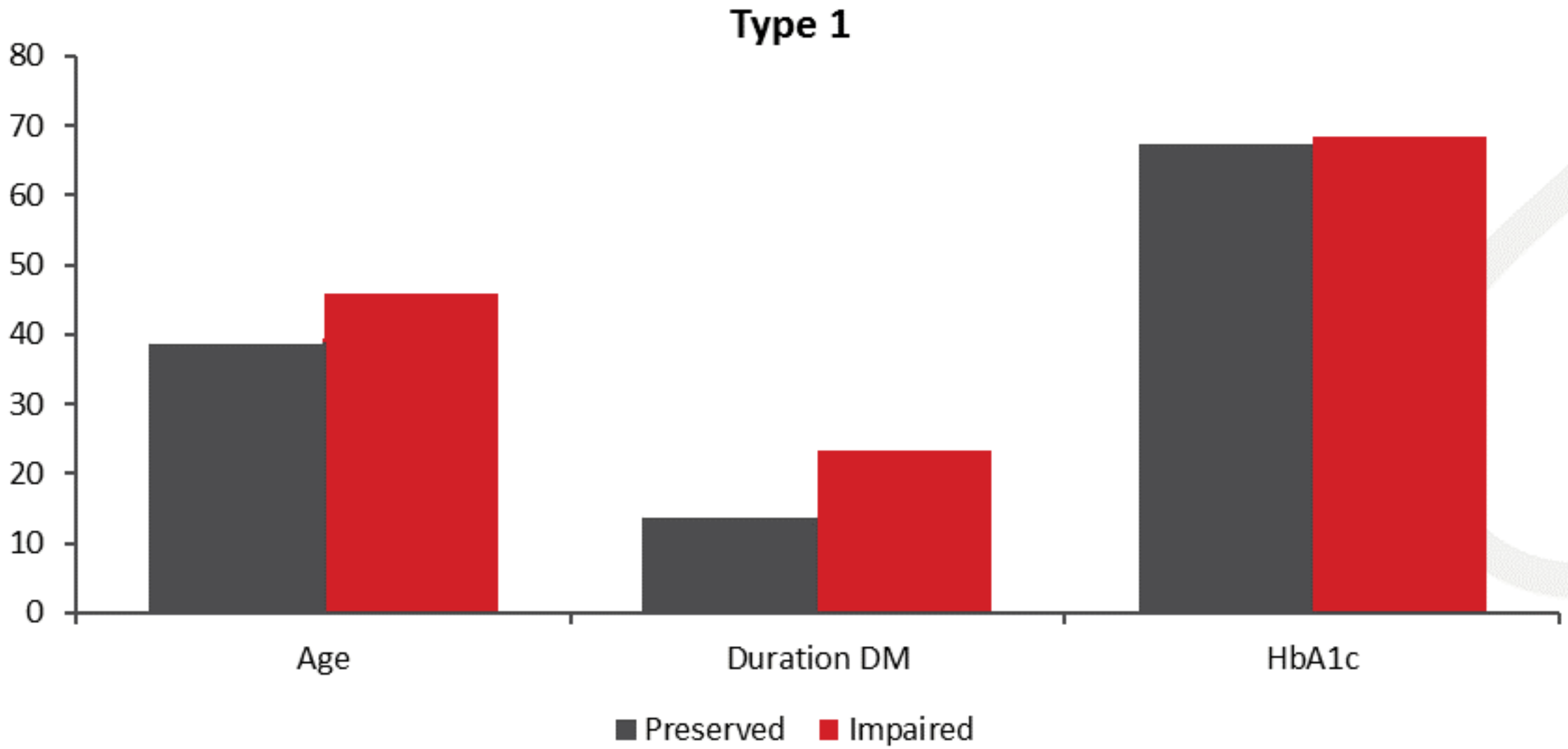
Name _____
First Middle Last

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
6. __ Prescribed glucagon if appropriate

Seaquist et al., *Diabetes Care*, 2102.

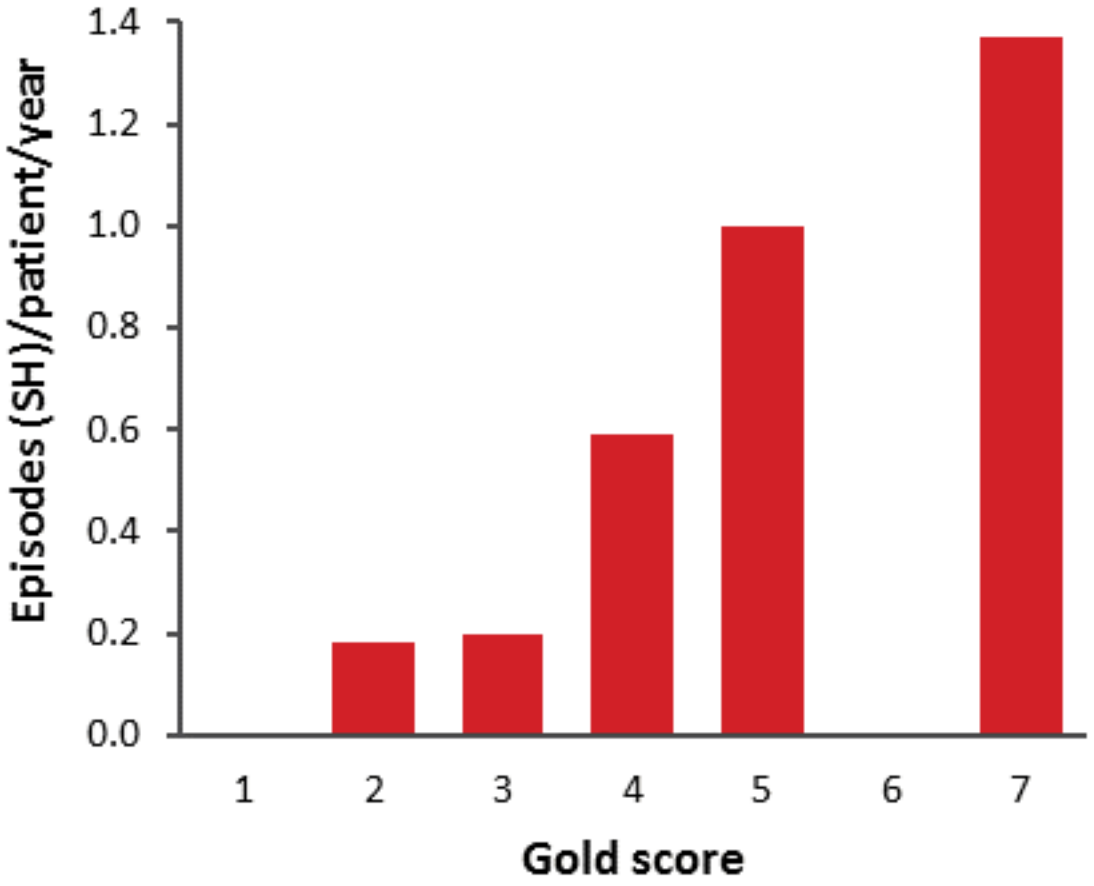
Who is at risk?



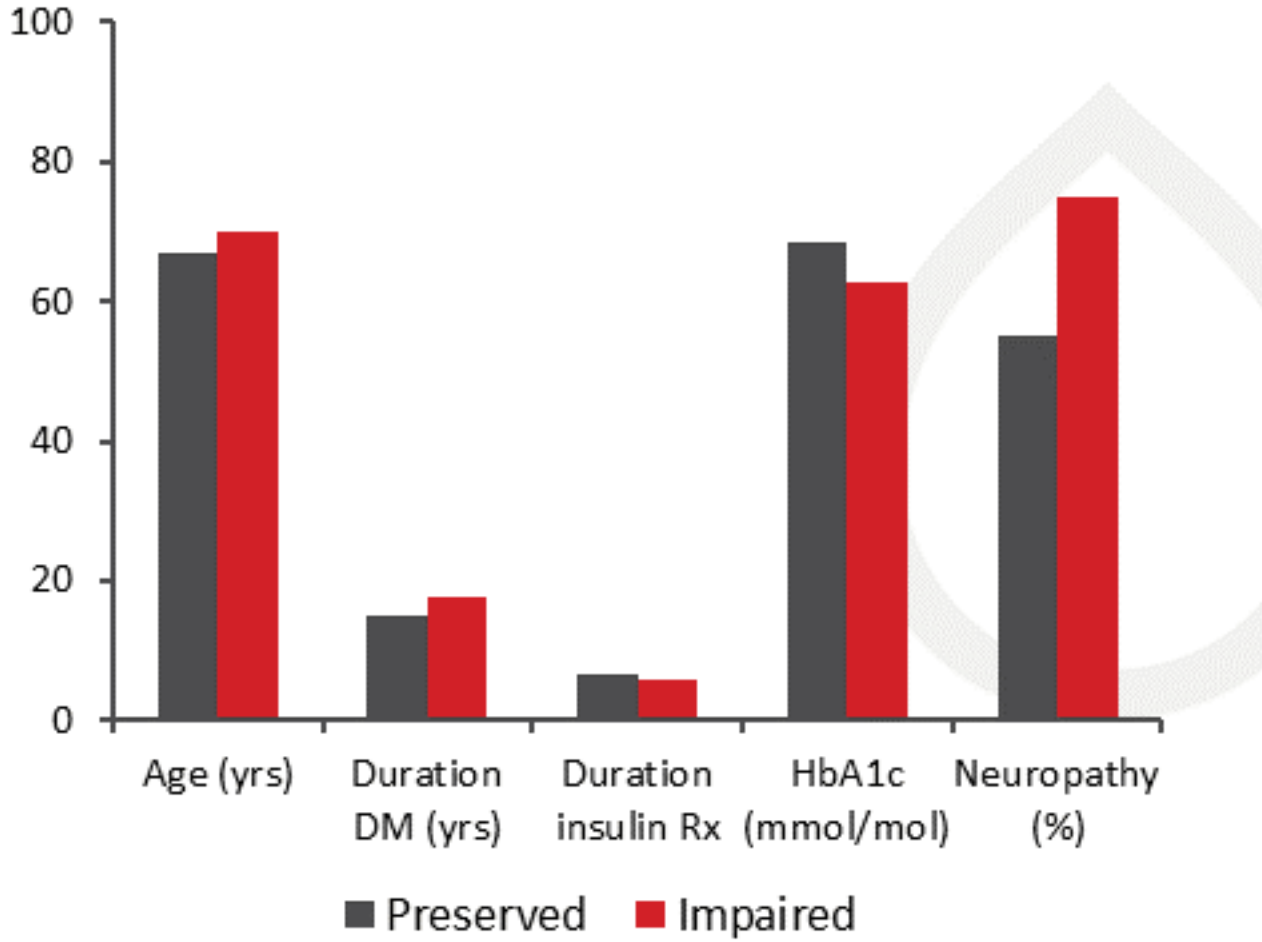
Geddes et al., *Diabet. Med*. 2008 25, 501–504.

And in type 2…

Awareness of hypoglycemia



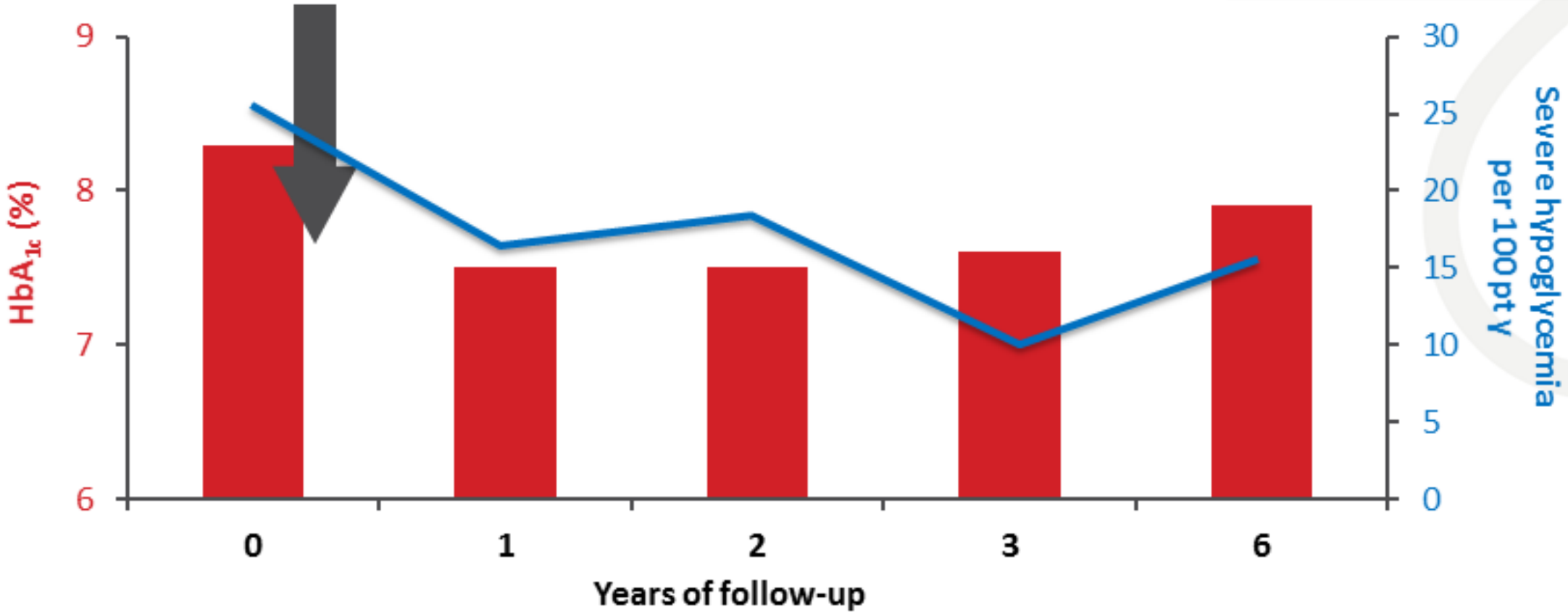
But no differences in …



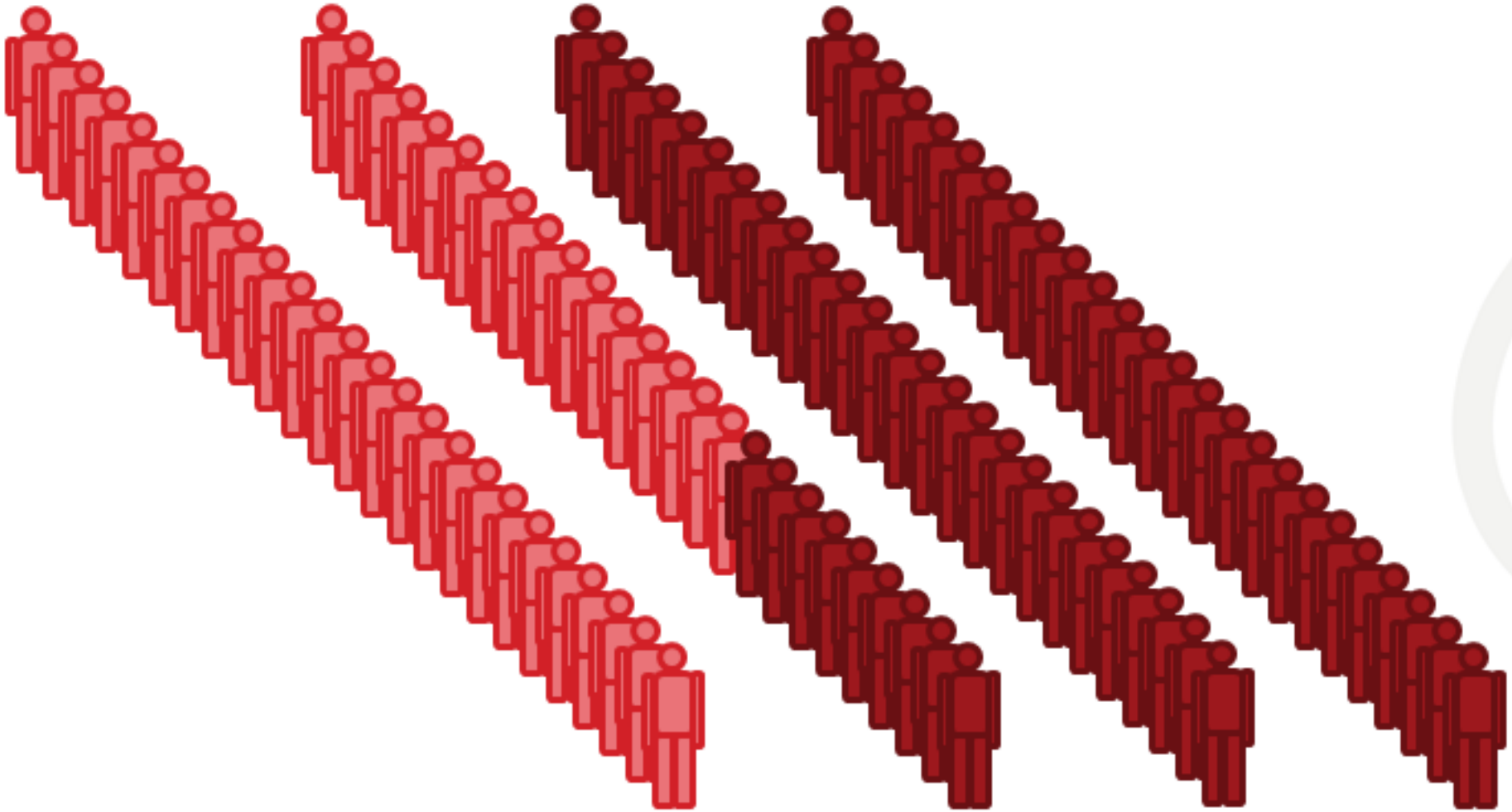
Schopman et al., *Diab Res Clin Pract* 2010; 87:6 4 – 68.

Structured education in flexible intensive insulin therapy

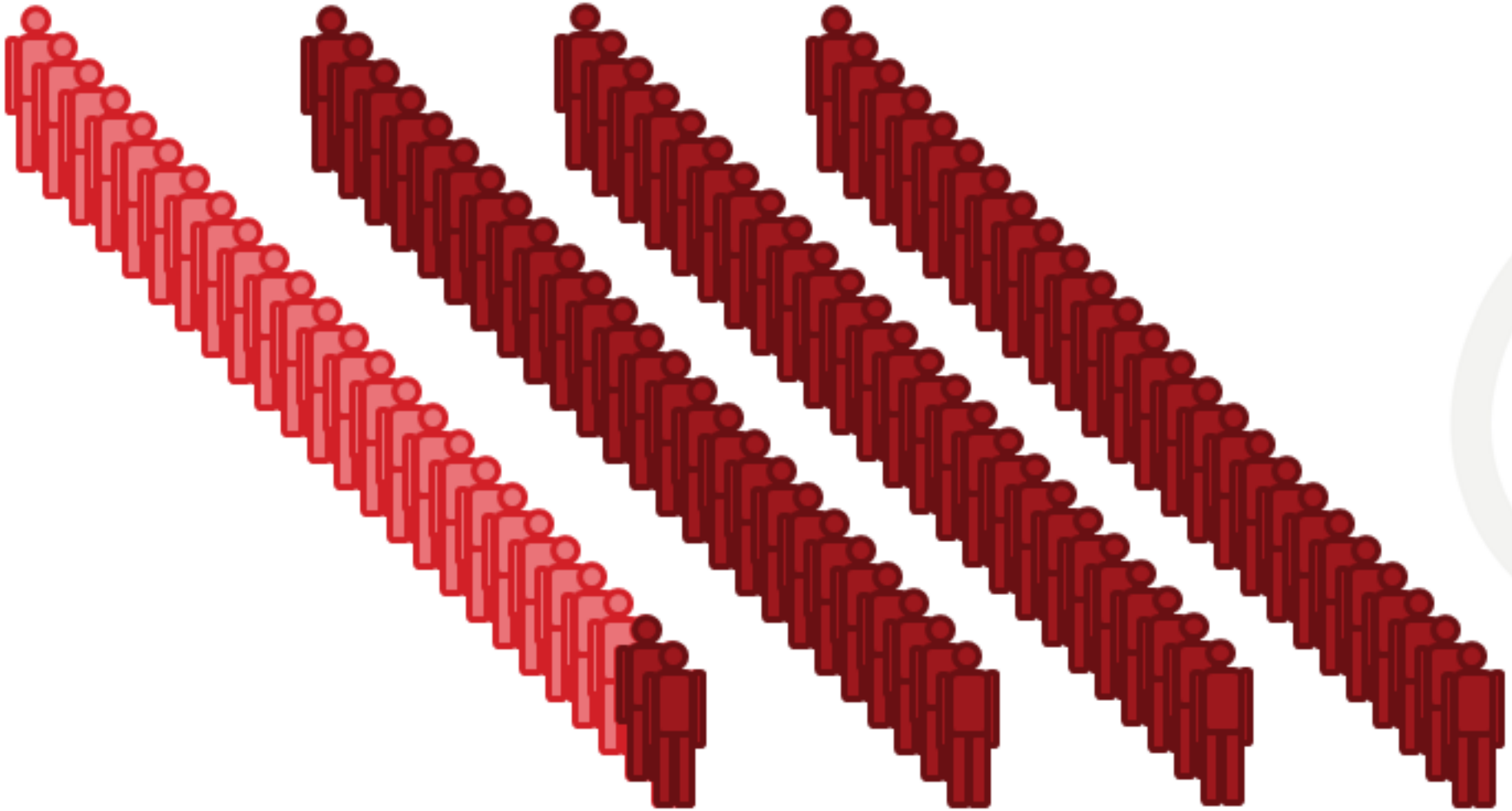
DAFNE **Type 1 Diabetes:** Less guesswork. More freedom. Better health.



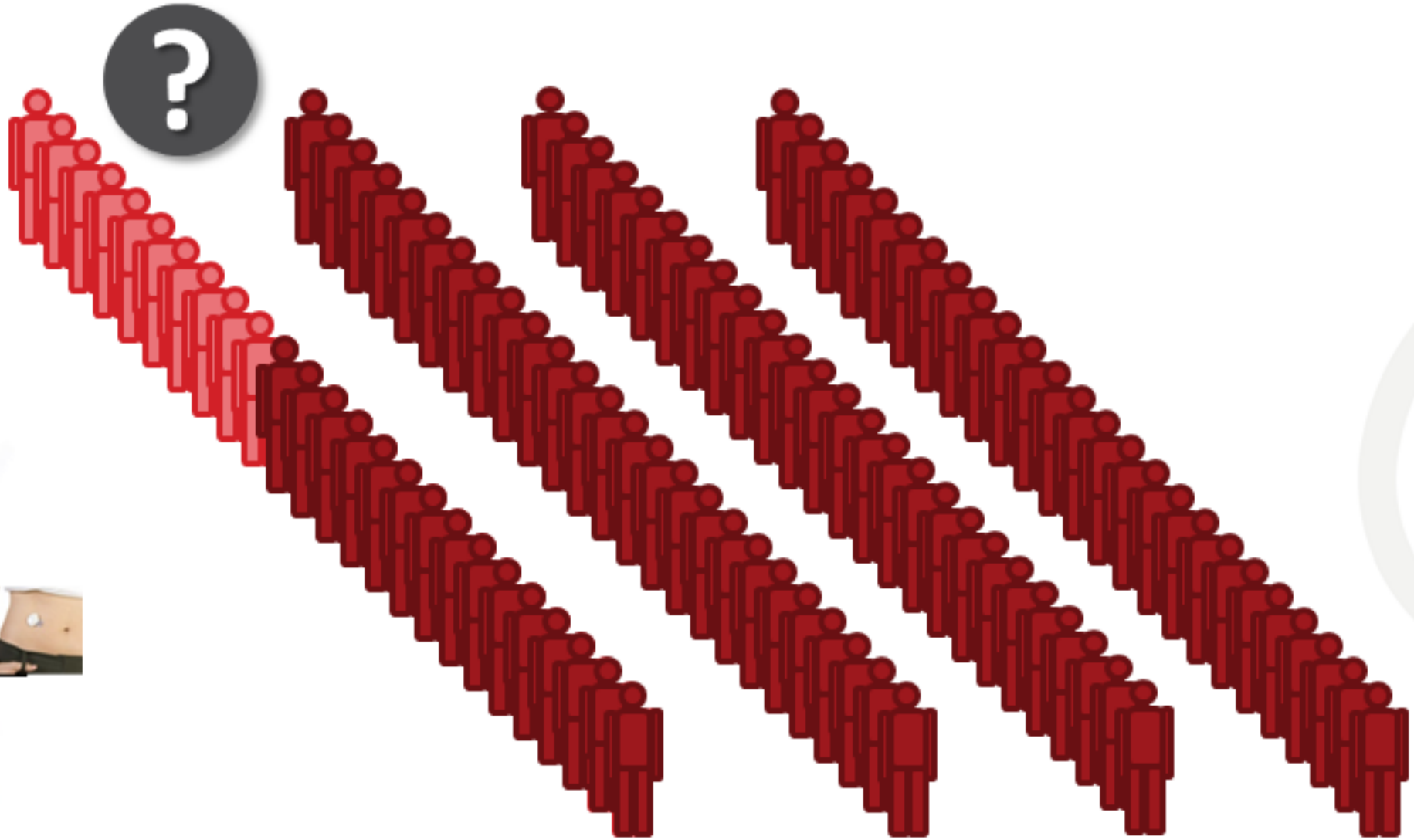
40% of people coming to structured education had IAH

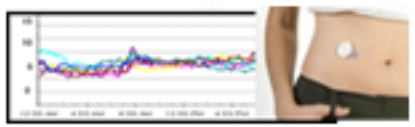


Structured education restores awareness to 43%



Technology can help some of the rest





UKITC
UK Islet Transplant Consortium

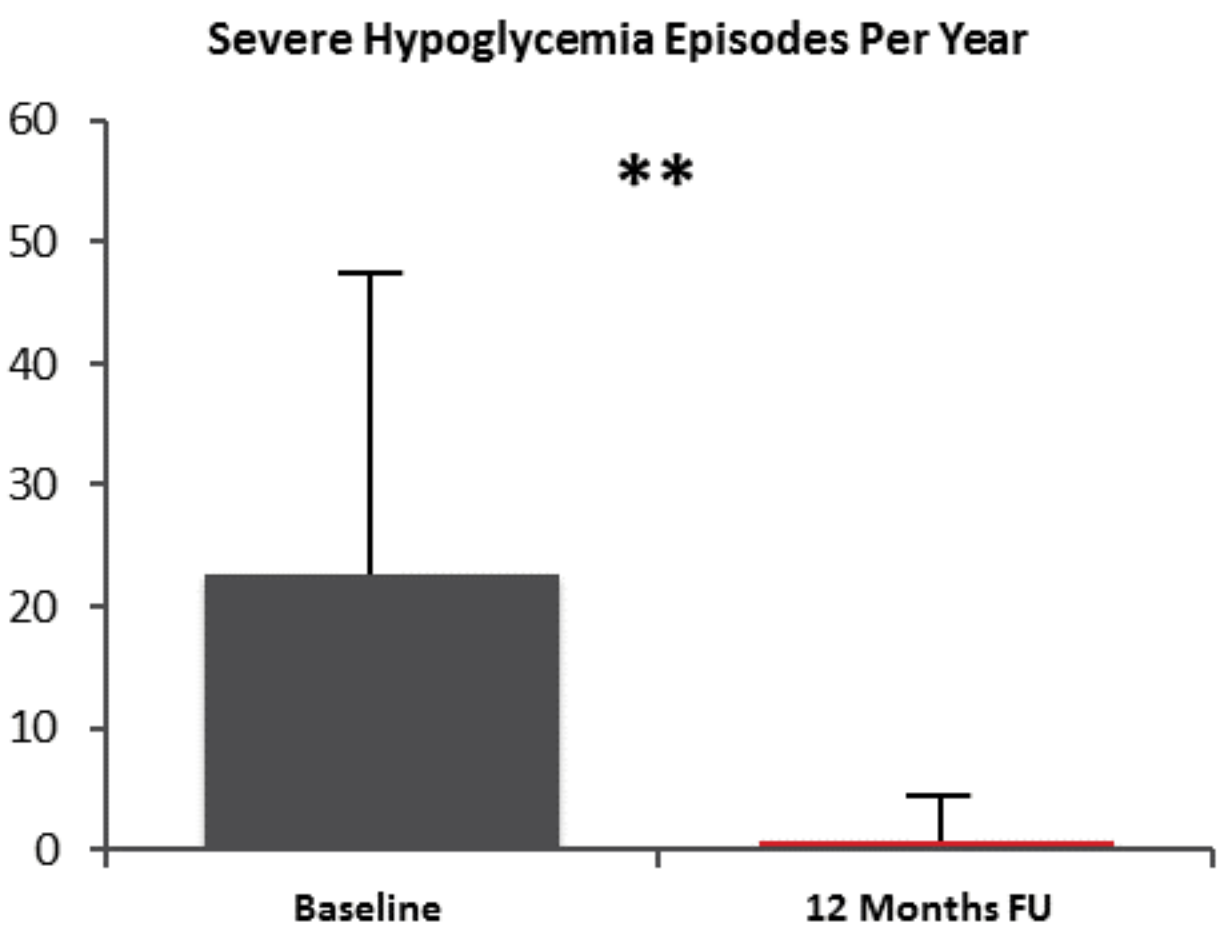
‘Thinking traps’

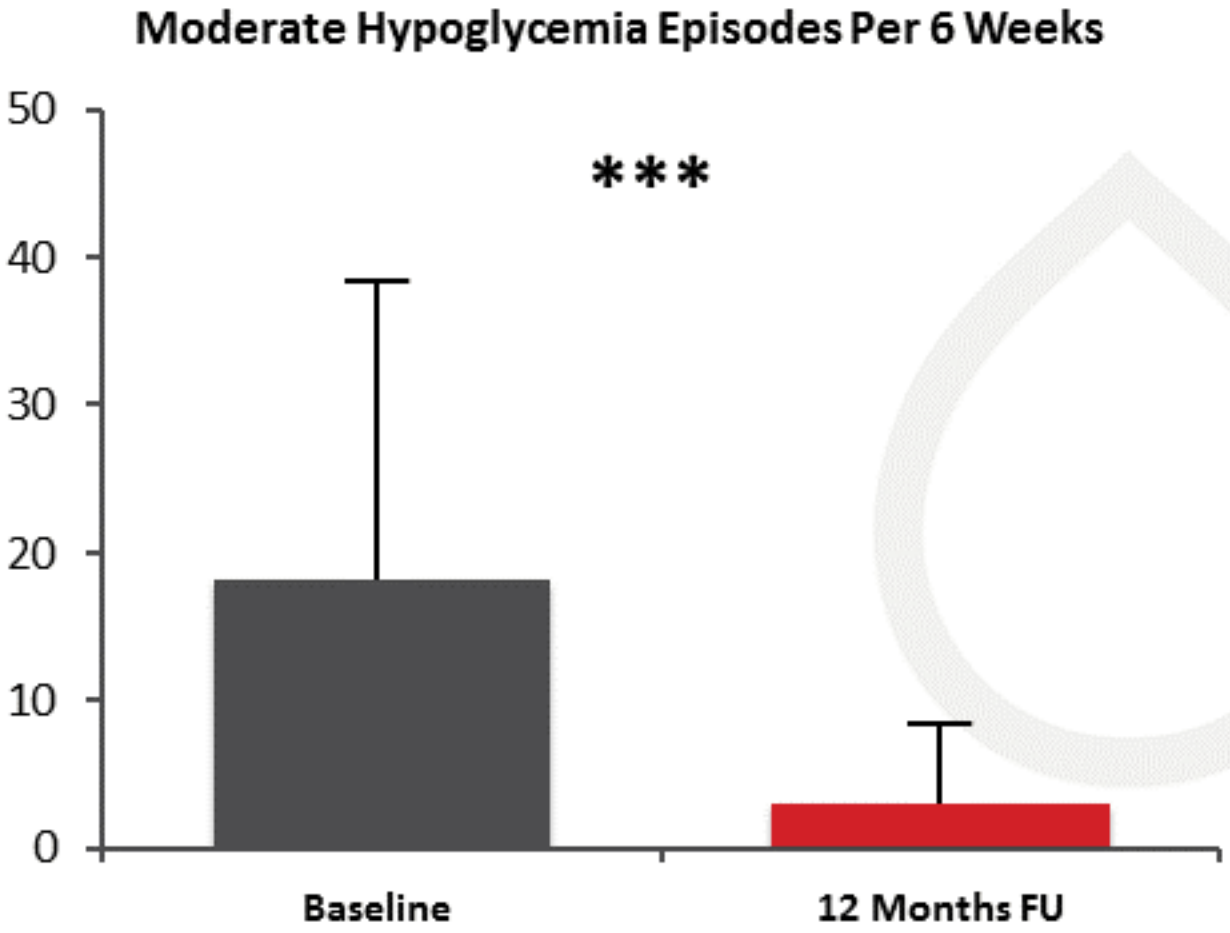
“I’ll be ok”
“It’ll (SH) never happen to me”

“I need to avoid going high at any cost”
“I will ruin my diabetes control”

“I don’t want to make a fuss”
“I should just get on with it”

Impact of DAFNE HART on hypoglycemia





Mean ± SD, paired t-tests, n=20. De Zoysa, *Diabetes Care*. 2013 Dec 6. [Epub ahead of print].

Summary and conclusions

- Impaired awareness of hypoglycemia identifies people at risk for severe episodes
- It is easy to diagnose
- Avoidance of exposure to < 3 mmol/l (54 mg/dl) restores awareness
- This can be achieved through a pathway of education, medications with low risk of hypoglycemia, pumps and sensors, transplantation
- For some, addressing beliefs and cognitions around hypoglycemia may be key

Fear of Hypoglycemia

Linda Gonder-Frederick, Ph.D.

Associate Professor
Department of Psychiatry and Neurobehavioral Sciences
University of Virginia, Charlottesville, Virginia

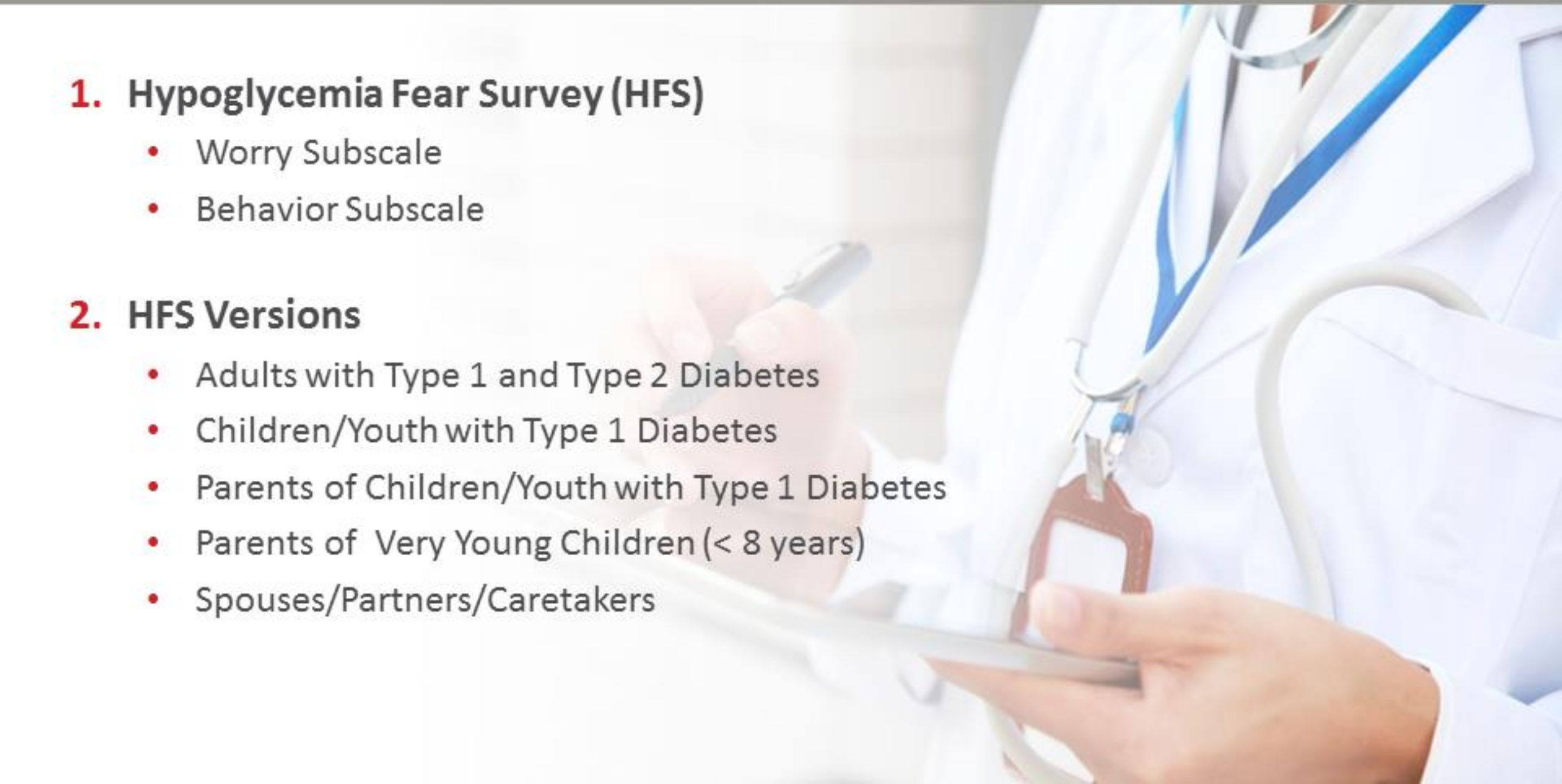
Disclosures

- Linda Gonder-Frederick has been a consultant for, received research funding/ support from, and served on advisory boards for:
  - Abbot Laboratories
  - AstraZeneca plc
  - Dexcom Inc.
  - Johnson & Johnson Services, Inc.
  - Merck & Co., Inc.
- The Hypoglycemia Fear Survey (HFS) is licensed to pharmaceutical companies and other for-profit organizations. These licensing fees are used to sponsor research on the problem of hypoglycemia and fear of hypoglycemia.

Defining and Measuring Fear of Hypoglycemia

1. **Hypoglycemia Fear Survey (HFS)**
   - Worry Subscale
   - Behavior Subscale

2. **HFS Versions**
   - Adults with Type 1 and Type 2 Diabetes
   - Children/Youth with Type 1 Diabetes
   - Parents of Children/Youth with Type 1 Diabetes
   - Parents of Very Young Children (< 8 years)
   - Spouses/Partners/Caretakers



A Global Issue

Fear of Hypoglycemia Occurs in Individuals Living with Diabetes and Their Families/Loved Ones Across Countries and Cultures

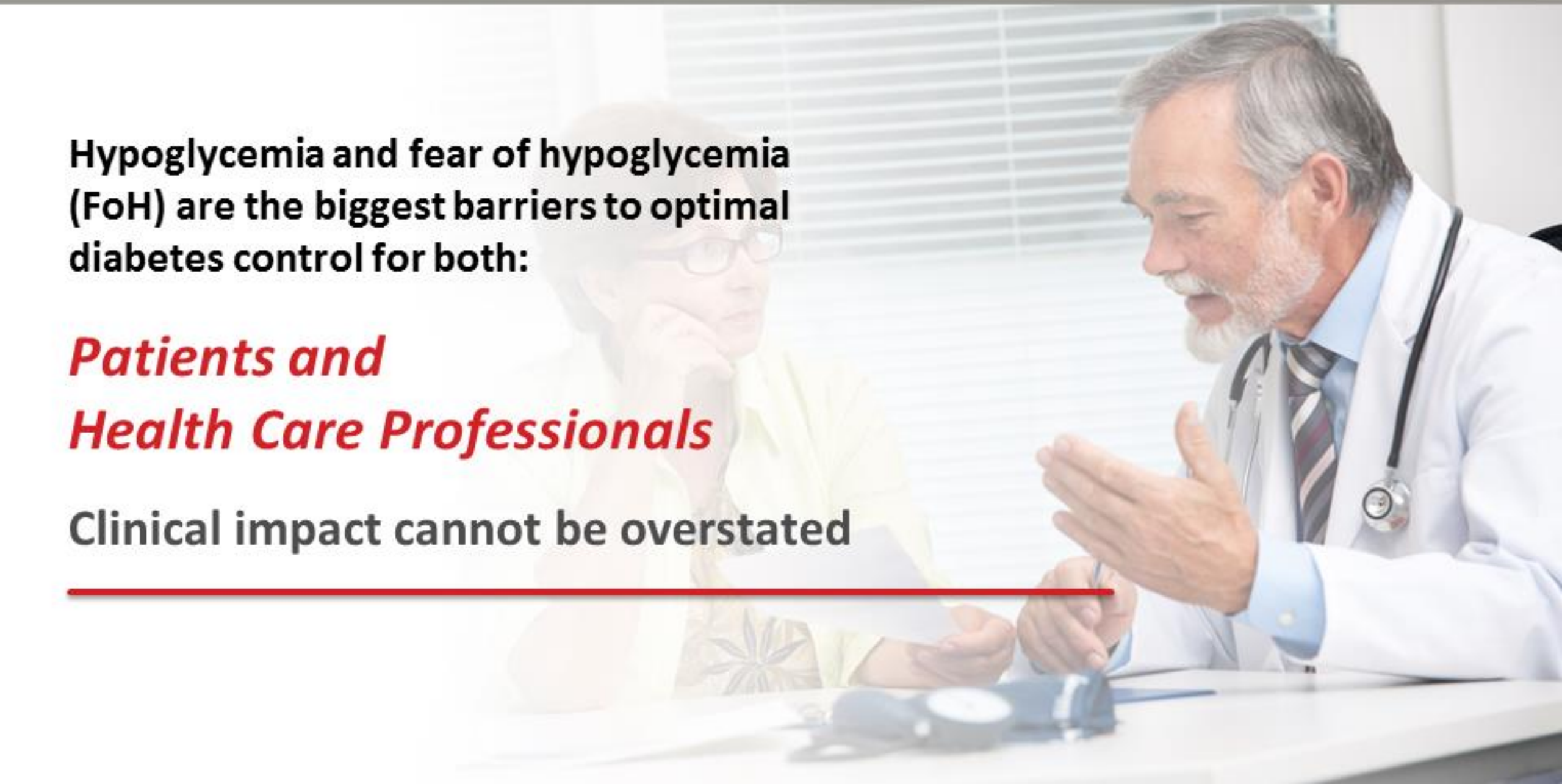
Predictors of Fear of Hypoglycemia

Impact of Fear of Hypoglycemia

Hypoglycemia and fear of hypoglycemia (FoH) are the biggest barriers to optimal diabetes control for both:

Patients and
Health Care Professionals

Clinical impact cannot be overstated



Impact of Fear of Hypoglycemia On Quality of Life

- Increased Anxiety and Depression
- Reduced Diabetes Self-Efficacy
- Restriction of Normal Activities (travel)
- Relationship Conflict and Tension

Impact of Fear of Hypoglycemia On Diabetes Management & Control

Willingness to Use or Prescribe Insulin

Barrier to Exercise and Physical Activity

Maintaining Higher Blood Glucose Levels to Reduce Fear

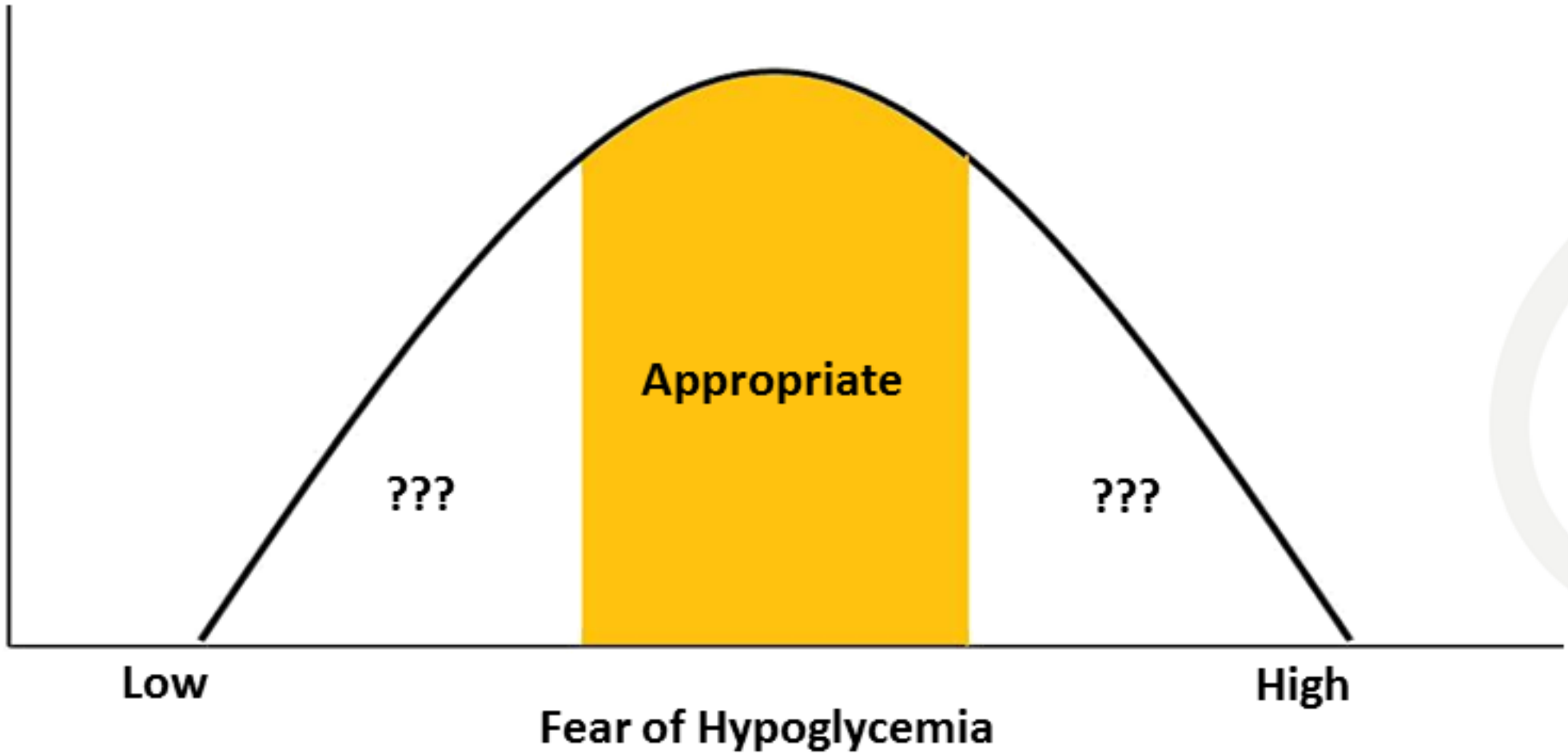
Impact of Fear of Hypoglycemia On Families/Significant Others

- **Parents of children with T1D:**
  - Generally experience more FoH than adults with diabetes
  - Especially if their child has a history of seizure or unconsciousness due to hypos
- **Non-diabetic Spouses and Partners**
  - Typically experience higher levels of FoH than their loved ones with diabetes

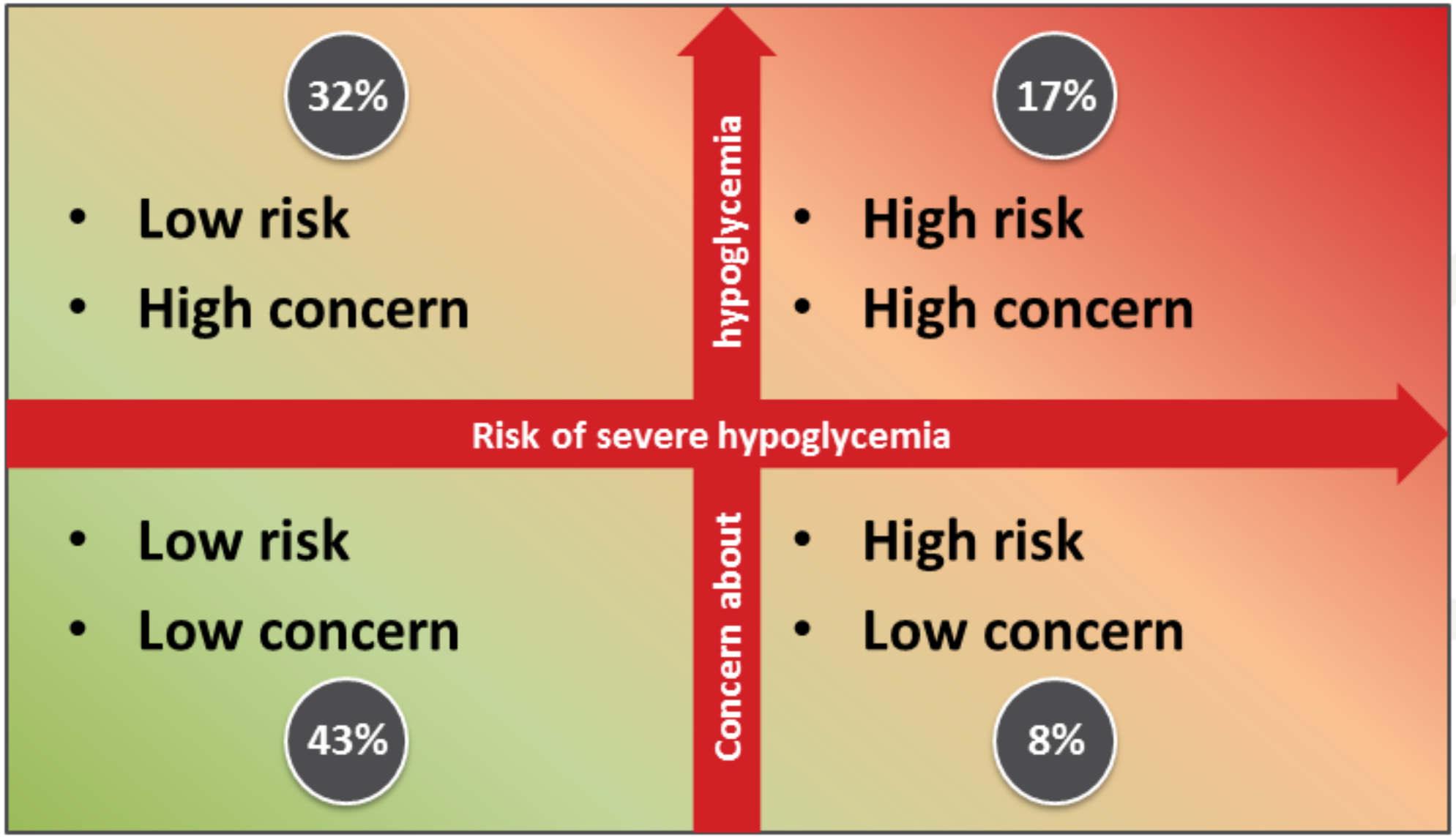
Consistency In Findings Across Countries and Cultures

U.S., Netherlands, U.K., China, Turkey, Iran, Norway, Germany, Slovenia, Australia, Saudi Arabia, Canada, Spain, and Sweden

Some Fear of Hypoglycemia Is Adaptive

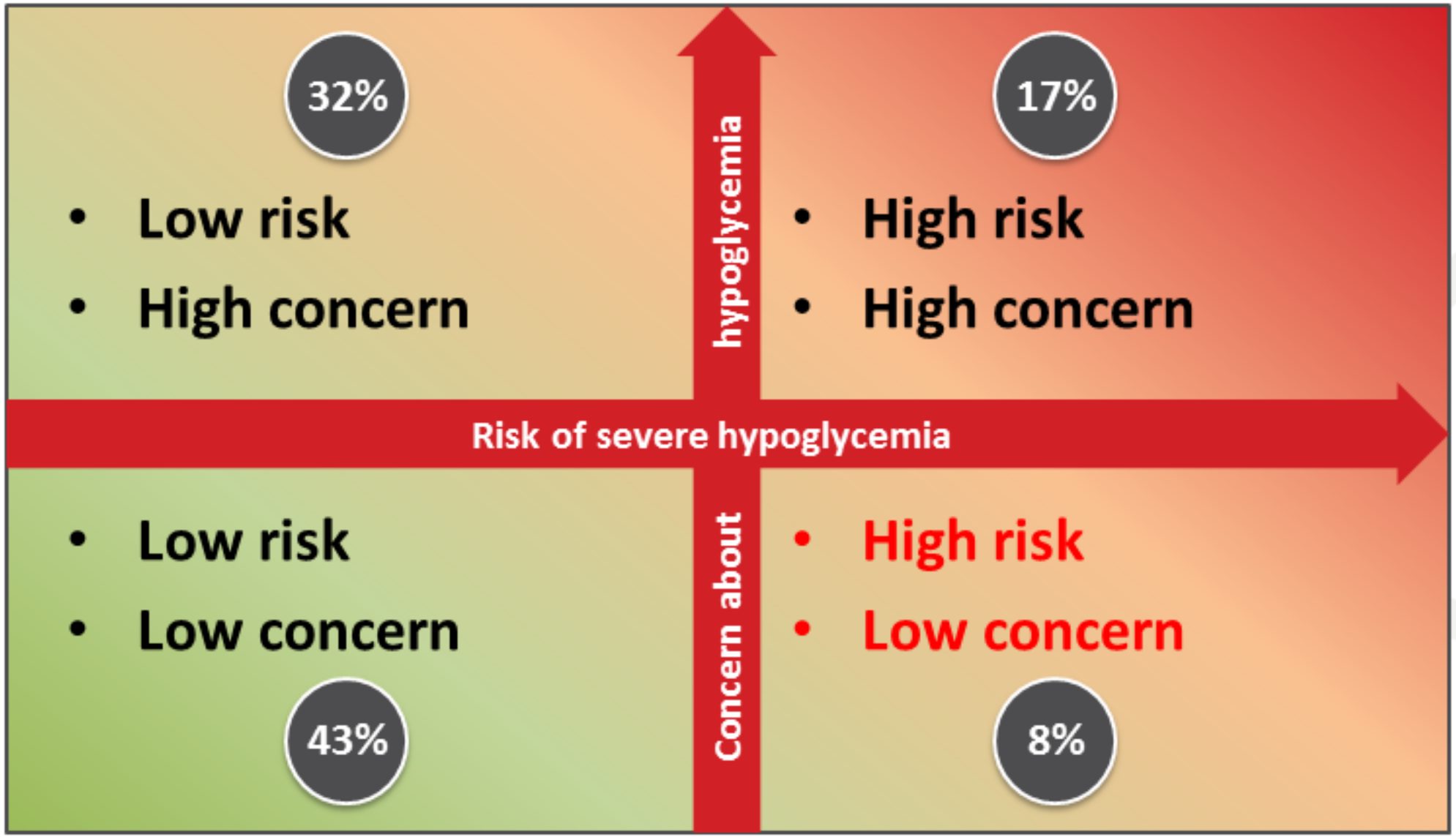


Fear of Hypoglycemia Is Not A Linear Construct



N = 469 people with T1; Mean HbA_{1c} 61 mmol/mol. Anderbro et al. *Acta Diabetol*, 2015.

Fear of Hypoglycemia Is Not A Linear Construct



N = 469 people with T1; Mean HbA_{1c} 61 mmol/mol. Anderbro et al. *Acta Diabetol*, 2015.

Interventions For Fear of Hypoglycemia

- Medical
- Educational
- Psychobehavioral
- Technological

Clinical Implications: Patient Education

- A randomized control trial (n = 249, age 2-18 years)

- After 24 months, episodes of SH decreased from 42% to 25%
- No Δ in HbA_{1c}
- Cost < 10€

1. Nordfeldt S, Johansson C, Carlsson E, Hammersjo J. Persistant effects of a pedagogical device targeted and preventing severe hypoglycemia: A randomized, controlled study. *Acta Paediatrica*, 2005, 94, 1395 – 1401.

Clinical Implications: The "Technology Solution"

Insulin Pump (CSII)

Continuous Glucose Monitor (CGM)

Sensor Augmented Pump (SAP)

Low Glucose Suspend (LGS)

Predictive LGS

Clinical implications

Assess the frequency and severity of episodes

and

Indicators of problematic FoH

- Impact of quality of life
- Emotional implications
- The impact on diabetes self-care


Thank you!

Panel Q&A Session

QUESTIONS FOR OUR PANEL

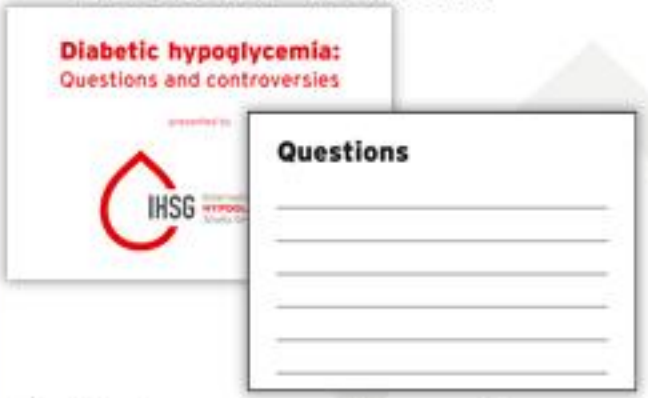
Question?

1. Raise your hand

2. Ask your question live

OR

1. Write it down



2. Raise your hand to have it collected

Evaluation and Coming soon…

Please take a moment to complete the evaluation form for today's meeting

Coming soon…

- CME slide presentation
- Physician and patient tools
- IHSG website

Learn about these and other IHSG initiatives by signing up for our **website mailing list** via the evaluation form

спасибо

谢谢

GRACIAS

THANK YOU

ありがとうございました

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