# Hipoglucemia Diabética al día de hoy: Manejo y conecciones con ECV

Un evento exclusivo del Grupo Internacional para el Estudio de la hipoglucemia (IHSG)
En el Congreso de la Asociación Latinoamericana de Diabetes 2019

1 Noviembre 2019

Punta Cana, República Dominicana

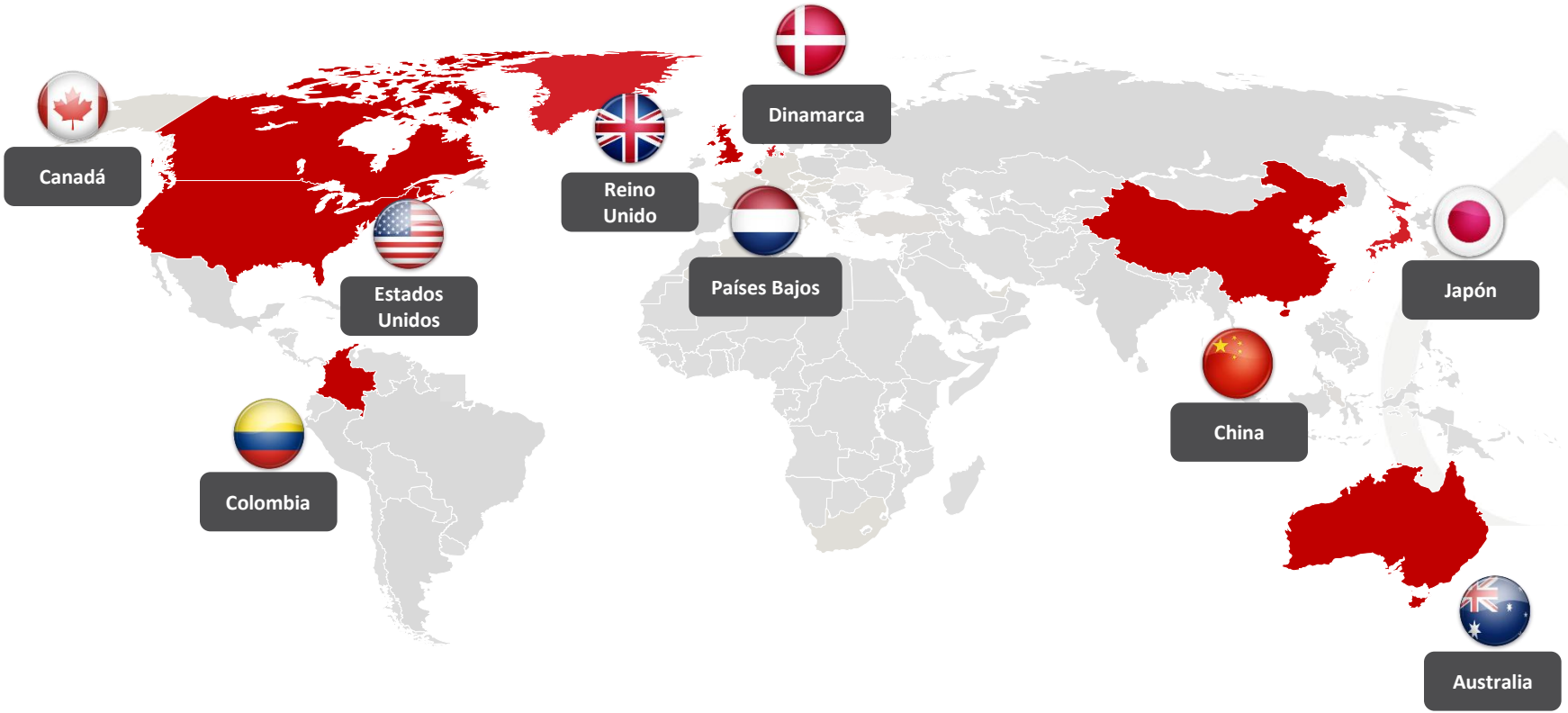
Traído para Usted por miembros del International Hypoglycaemia Study Group

IHSG

# Bienvenida del Coordinador

**Pablo Aschner, MD, MSc**
Profesor Asociado de Endocrinología,
Escuela de Medicina de la Universidad Javeriana
Asesor de investigaciones, Hospital Universitario San Ignacio
Director Científico, Asociación Colombiana de Diabetes
Bogotá, Colombia

# IHSG Alcance Global



# IHSG Miembros


Stephanie Amiel


Pablo Aschner

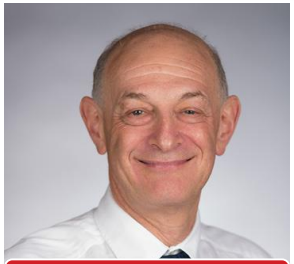

Belinda Childs


Philip Cryer


Bastiaan de Galan


Brian Frier


Linda Gonder-Frederik


Simon Heller


Tim Jones


Kamlesh Khunti


Lawrence Leiter


Yingying Luo


Munehide Matsuhisa


Rory McCrimmon


Ulrik Pedersen-Bjergaard


Elizabeth Seaquist


Sofia Zoungas

# Miren hasta dónde hemos llegado

**2013**

**ADA Chicago**
**Primera reunión**

**2014**

**EASD Viena**
**Simposio**

**2015**

**IDF Vancouver**
**Encuentro con experto**

**2016**

**Set diapositivas para educación de Profesionales de la Salud**

**Publicación sobre Clasificación de la Hipoglucemia**

**WCPD9 Atlanta Simposio**

**2017**

**Lanzamiento del sitio web del IHSG**

**EASD Lisboa Simposio**

**IDF Abu Dhabi Simposio**

**2018**

**Herramientas para Profesionales de la Salud y Pacientes**

**EASD Berlin Simposio**

**2019**

**Publicación Lancet Diabetes & Endocrinology**

**Módulo ECV e Hipoglucemia**

**Módulo Reconocimiento Hipoglucemia Alterado**

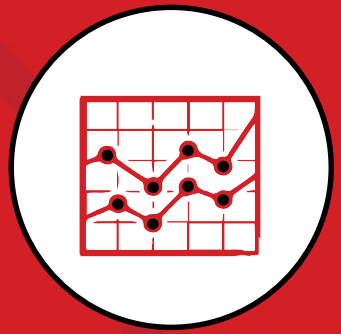
**Módulo Educando Pacientes con Diabetes y sus Cuidadores***

**ALAD Punta Cana Simposio**

**Se establece como Grupo de Estudio de la EASD**

* Módulo disponible en español

# Por qué la hipoglucemia importa



La incidencia de hipoglucemia aumenta en la medida que el paciente se acerca a las metas de $HbA_{1c}$ en el tratamiento

Es un problema no suficientemente reconocido que amerita mayor estado de alerta

Hay una falta de entendimiento tanto por los profesionales como por los pacientes

Entenderla mejor puede mejorar la calidad de vida del paciente

# Una mirada al Simposio de hoy

IHSG International HYPOGLYCAEMIA Study Group

**5:10 pm – 5:30 pm**
**La clasificación de hipoglucemia del IHSG**
Simon Heller

**5:30 pm – 5:50 pm**
**Hipoglucemia y Enfermedad Cardiovascular**
Lawrence Leiter

**5:50 pm – 6:10 pm**
**Manejando Riesgo de Hipoglucemia con Nueva Tecnología**
Elizabeth Seaquist

**6:10 pm – 6:30 pm**
**Panel P&R**
Pablo Aschner, Simon Heller,
Lawrence Leiter, Elizabeth Seaquist

El International Hypoglycaemia Study Group (IHSG) está apoyado por un grant de Novo Nordisk A/S y es consistente con su compromiso continuado con la Diabetes

# Recuerde, si Usted tiene preguntas para nuestros conferencistas….

**Usted puede someter preguntas en cualquier momento llenando la ficha de preguntas**


**Las fichas de preguntas se recogerán entre las sesiones y se responderán durante el panel de discusión**

# La clasificación de hipoglucemia del IHSG

**Simon Heller, BA, MB, Bchir, DM, FRCP**
Profesor de Diabetes Clínica
Universidad de Sheffield
Director de Investigación y Desarrollo
y Médico Consultante Honorario
Hospitales Docentes de Sheffield
NHS Foundation Trust
Sheffield, Reino Unido

# Disclosures

Advisory board member

- Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Sanofi Aventis, Zealand

Speaker’s Bureau

- Eli Lilly, Novo Nordisk

# Agenda

1. Background and history
2. Issues addressed by IHSG and others
3. Conclusions

IHSG, International Hypoglycaemia Study Group

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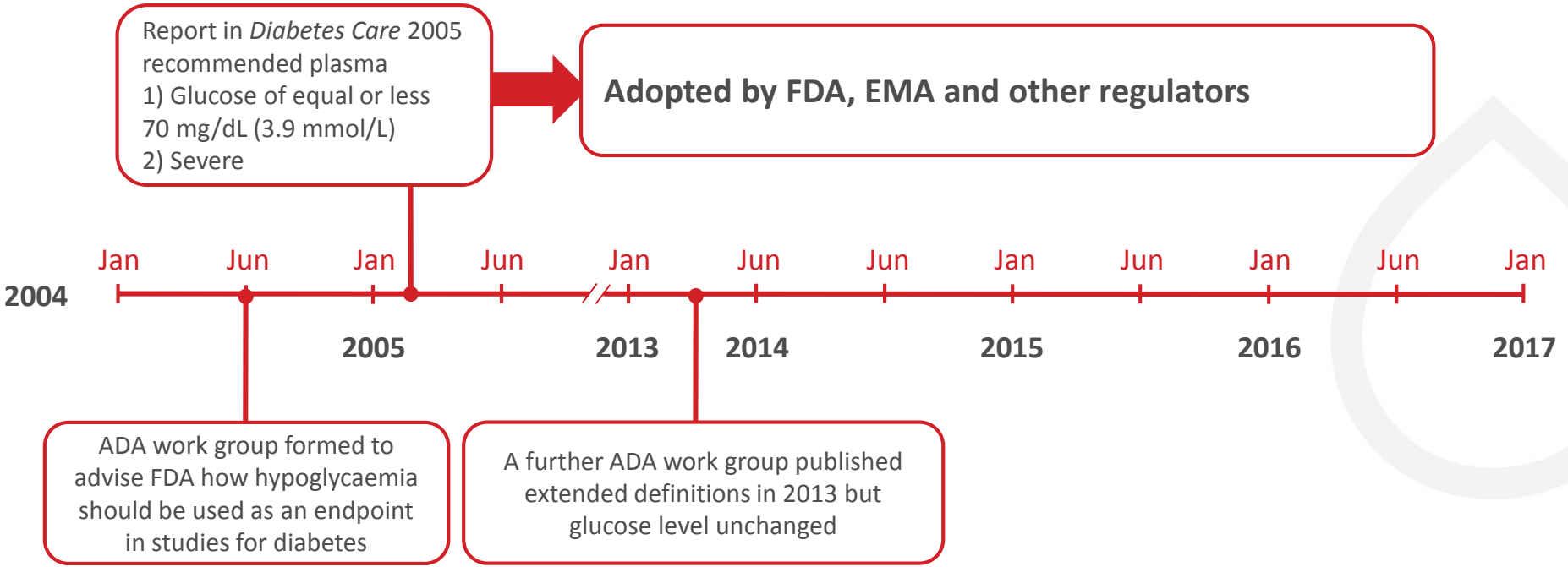
# Background




ADA, American Diabetes Association; EMA, European Medicines Agency; FDA, Food and Drug Administration.

# Definition of hypoglycaemia: View of the ADA group

**“all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm”**

ADA, American Diabetic Association; HCP, health care practitioner.
ADA W Group, *Diabetes Care* 2005;28:1245–9.

# Definition of hypoglycaemia: View of the ADA group

**The definition should apply to…**

- Clinical decisions by people with diabetes and HCPs
- Studies of diabetes drugs, devices, or management strategies

ADA, American Diabetic Association; HCP, health care practitioner.
ADA W Group, *Diabetes Care* 2005;28:1245–9.

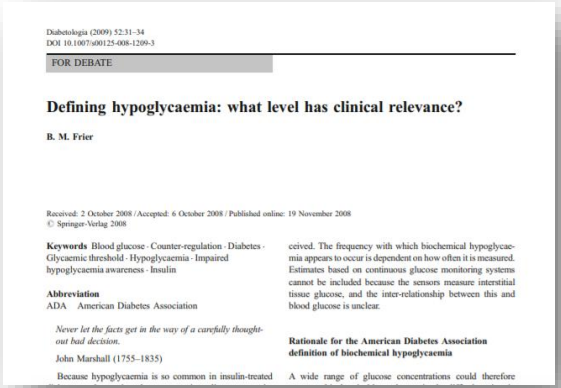
# Definition of hypoglycaemia: View of the ADA group

**and should be…**

- Free from reporting biases
- Clinically important
- Applicable to all persons with diabetes at any time of day
- Measurable by practical and widely available methods
- Reportable in a standardized fashion

ADA, American Diabetic Association; HCP, health care practitioner.
ADA W Group, *Diabetes Care* 2005;28:1245–9.

# Critique of ADA consensus



Diabetologia (2009) 52:31–34
DOI 10.1007/s00125-008-1209-3

FOR DEBATE

**Defining hypoglycaemia: what level has clinical relevance?**

B. M. Frier

Received: 2 October 2008 / Accepted: 6 October 2008 / Published online: 19 November 2008


**Keywords** Blood glucose · Counter-regulation · Diabetes · Glycaemic threshold · Hypoglycaemia · Impaired hypoglycaemia awareness · Insulin

**Abbreviation**
ADA American Diabetes Association

*Never let the facts get in the way of a carefully thought-out bad decision.*

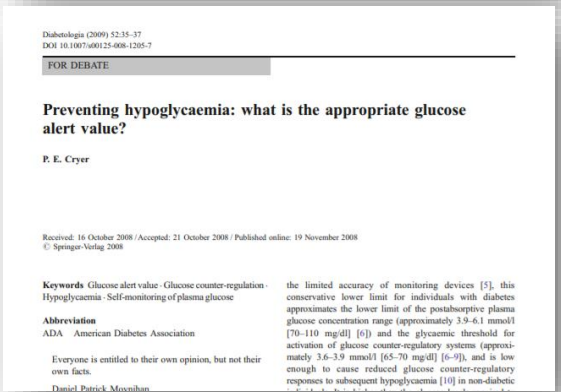
John Marshall (1755–1835)

Because hypoglycaemia is so common in insulin-treated

ceived. The frequency with which biochemical hypoglycae-mia appears to occur is dependent on how often it is measured. Estimates based on continuous glucose monitoring systems cannot be included because the sensors measure interstitial tissue glucose, and the inter-relationship between this and blood glucose is unclear.

**Rationale for the American Diabetes Association definition of biochemical hypoglycaemia**

A wide range of glucose concentrations could therefore



Diabetologia (2009) 52:35–37
DOI 10.1007/s00125-008-1205-7

FOR DEBATE

**Preventing hypoglycaemia: what is the appropriate glucose alert value?**

P. E. Cryer

Received: 16 October 2008 / Accepted: 21 October 2008 / Published online: 19 November 2008


**Keywords** Glucose alert value · Glucose counter-regulation · Hypoglycaemia · Self-monitoring of plasma glucose

**Abbreviation**
ADA American Diabetes Association

Everyone is entitled to their own opinion, but not their own facts.

Daniel Patrick Moynihan

the limited accuracy of monitoring devices [5], this conservative lower limit for individuals with diabetes approximates the lower limit of the postabsorptive plasma glucose concentration range (approximately 3.9–6.1 mmol/l [70–110 mg/dl] [6]) and the glycaemic threshold for activation of glucose counter-regulatory systems (approxi-mately 3.6–3.9 mmol/l [65–70 mg/dl] [6–9]), and is low enough to cause reduced glucose counter-regulatory responses to subsequent hypoglycaemia [10] in non-diabetic

- Plasma glucose falls to lower levels in health
- Defining hypoglycaemia as any value <3.9 mmol/L leads to overestimation of clinically significant hypoglycaemia
- Short-lived hypoglycaemia does not lead to impaired symptomatic or counterregulatory responses

## Response of the chair

- Not possible to state a single plasma glucose concentration that defines hypoglycaemia because the glycaemic thresholds… are dynamic
- Clinical practice trumps differences in methods of measurement, needs of industry
- 70 mg/dL based on potential to induce hypoglycaemia unawareness

ADA, American Diabetes Association.
Frier BM. *Diabetologia*; 2009;52:31–4; Cryer PE *Diabetologia* 2009;52:35–7.

# Classification of hypoglycaemia in diabetes

| | |
|---|---|
| Severe | Symptoms requiring active assistance of another person to treat; independent of blood glucose |
| Symptomatic | Symptoms with a measured low plasma glucose, self-treated |
| Asymptomatic | No typical symptoms but a measured low plasma glucose |
| Pseudo | Typical symptoms of hypoglycaemia with a measured plasma glucose concentration above 3.9 mmol/L |
| Probable symptomatic | Symptoms typical of hypoglycaemia are not accompanied by a plasma glucose determination |

**Definition of hypoglycaemia remained a plasma glucose of equal or less than 70 mg/dL (3.9 mmol/L)**

Seaquist ER et al. 2013;36:1384–95.

# Agenda

1. Background and history
2. **Issues addressed by IHSG and others**
3. Conclusions

IHSG, International Hypoglycaemia Study Group

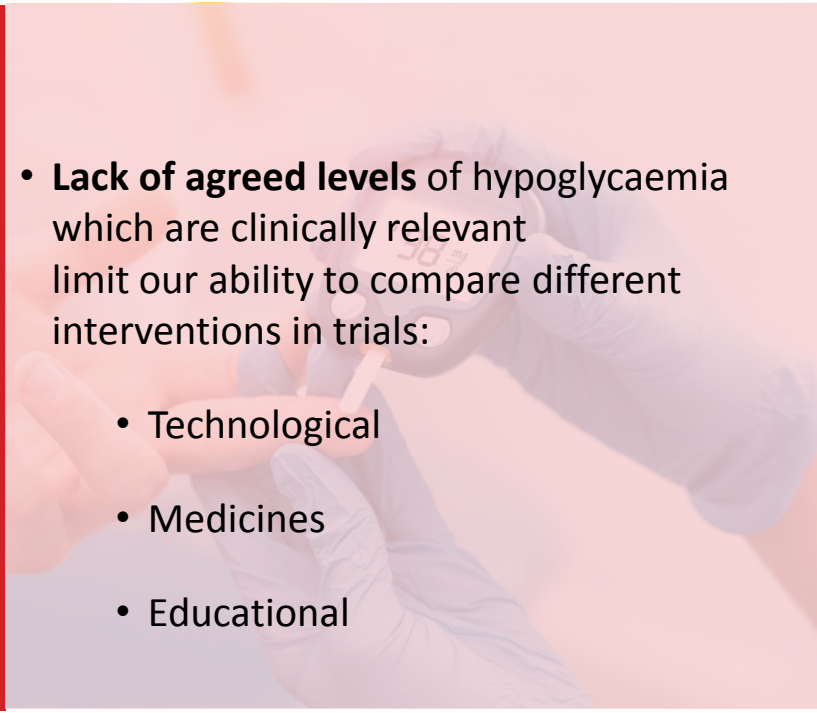
# What is the International Hypoglycaemia Study Group?

- Formed in 2013
- Global group of 15 clinicians/clinical investigators
- Purpose
  - Identify new and emerging issues and insights about hypoglycaemia
  - Formulate a comprehensive scientific communications platform to scientific understanding of hypoglycaemia and its importance as a barrier to optimal glycaemic control
  - Undertake in a variety of professional scientific communications endeavours
- Coordinated from University of Sheffield supported by grant funding from Novo Nordisk
- All activities are independent and based on decisions of the group

http://ihsgonline.com/about/goals-and-objectives/

# The IHSG addressed some limitations of the ADA definitions of hypoglycaemia

- Symptoms occur at different glucose levels
- People with impaired awareness may not have symptoms
- Asymptomatic hypoglycaemia is important and increased use of CGM means it can be captured in clinical trials



- **Lack of agreed levels** of hypoglycaemia which are clinically relevant limit our ability to compare different interventions in trials:
  - Technological
  - Medicines
  - Educational

ADA, American Diabetes Association; CGM, continuous glucose monitoring.

# The case for re-classification

**70 mg/dL level**

Highly relevant as an alert level but little evidence it impacts QoL or has health economic consequences

**Severe level**

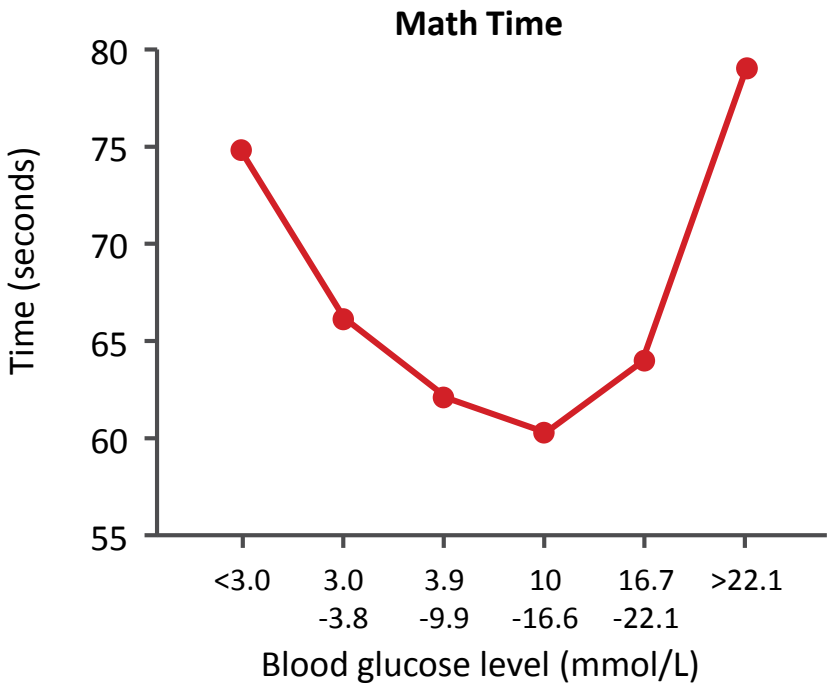
High clinical relevance but infrequent in most trials reducing power to show differences between interventions
(eg. pump trials, artificial pancreas)

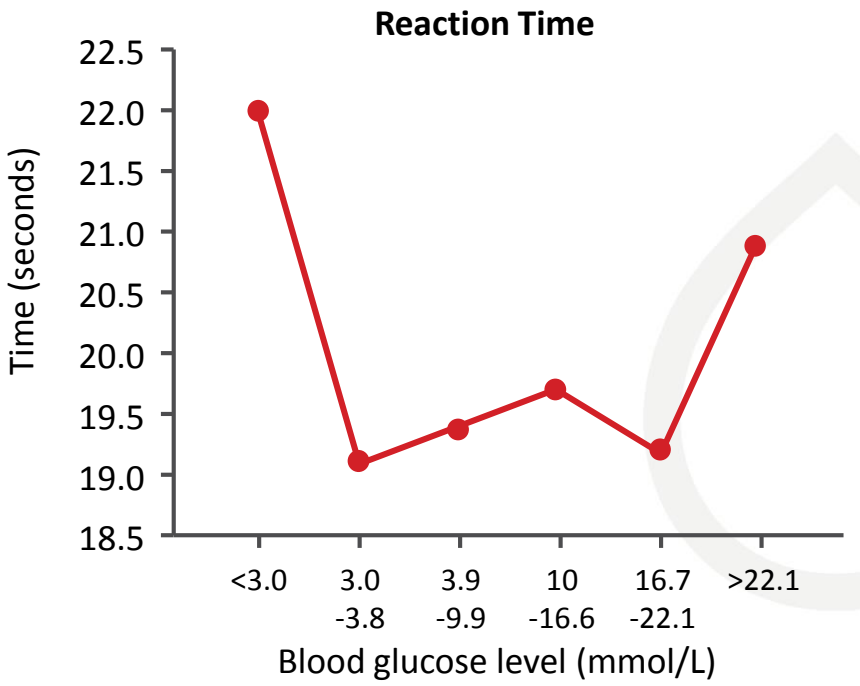
- Strong case for a third level denoting major/serious hypoglycaemia at around 50–55 mg/dL
  - Associated with impaired cognition, cardiac arrhythmias predicting mortality, impaired awareness and increased risk of severe episodes, with health economic impact
- An agreed third level would allow meaningful comparisons between different interventions and allow use of meta-analysis

QoL, quality of life.

1. IHSG. Diabetes Care. 2017;40:155–7. 2. IHSG. Diabetologia 2017;60:3–6.

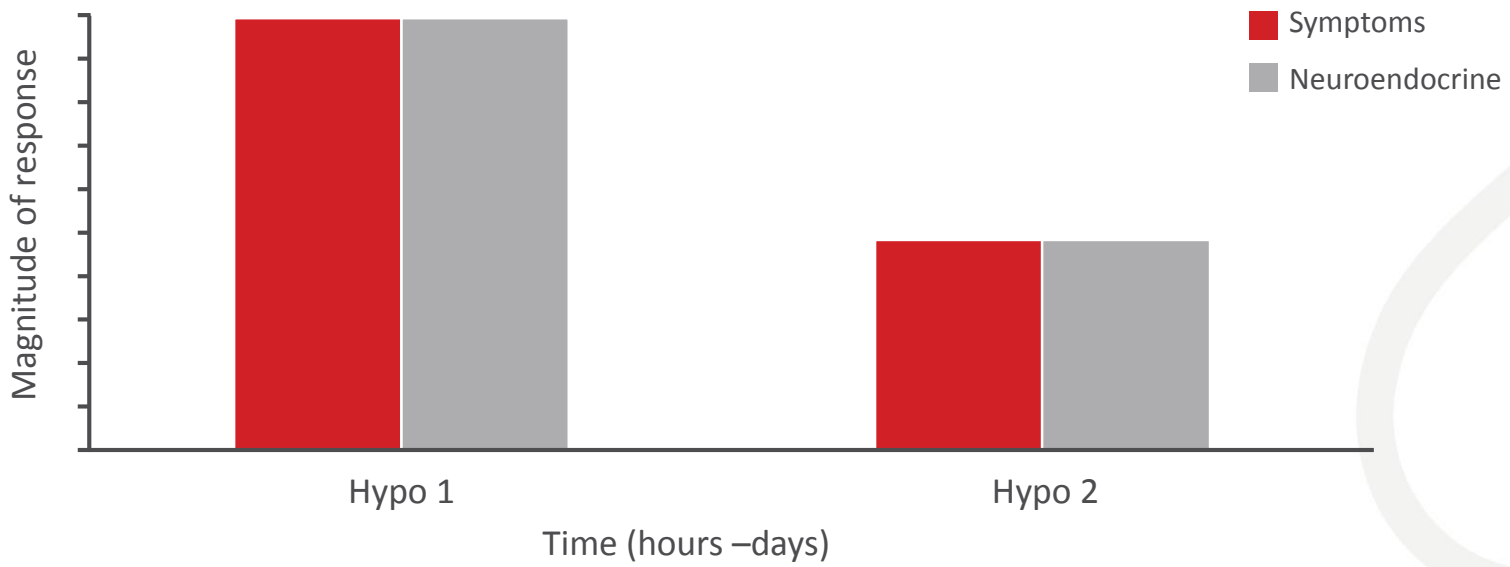
# Evidence for impaired cognitive function at <54 mg/dL




1. Gonder-Frederick LA et al. *Diabetes Care*. 2009;32:1001-1006. 2. Heller SR et al. *Lancet*. 1987;15:359-363.
3. Matyka K et al. *Diabetes Care*. 1997;20:135-141. 4. Choudhary P et al. *Diabet Med*. 2009;26:665-672.

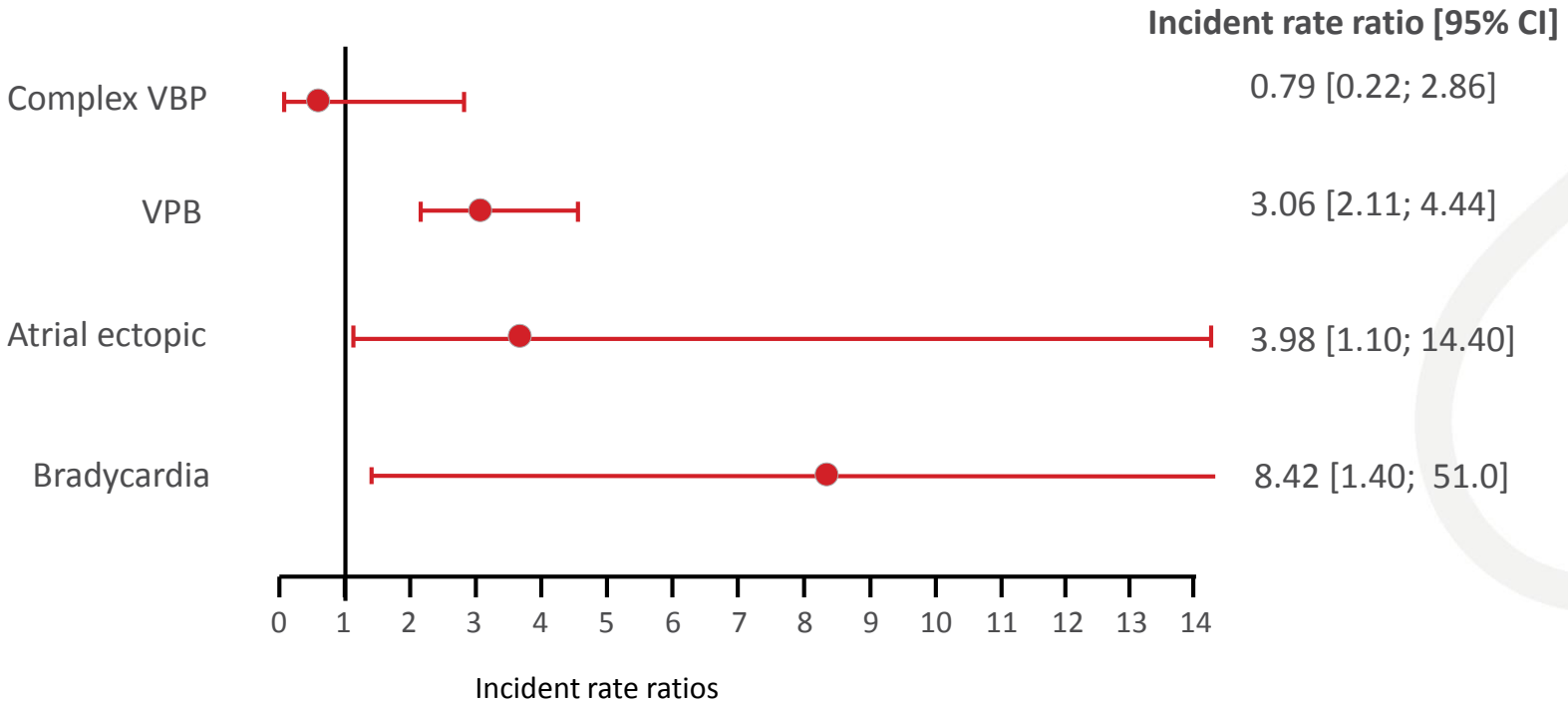
# Evidence that a glucose level of 3 mmol/L (<54 mg/dL) leads to impaired awareness of hypoglycaemia




**Studies inducing reduced awareness at <54 mg/dL (3 mmol/L)**
**2 episodes sometimes required to induce alterations in responses**

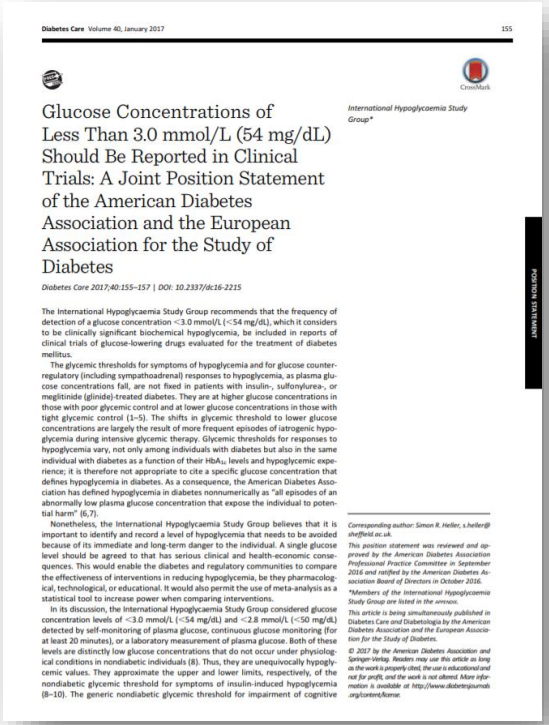
1. Heller SR, Cryer PE. *Diabetes*. 1991;40:223–6; 2. Davis MR et al. D*i*abetes. 1992;41:1335–40; 3. Mellman MJ et al. D*iabetes Care* 1994;17(3):183–8; 4. George E et al *Diabetologia* 1995;38(10):1183–90.

# Evidence for arrhythmias triggered by glucose levels “<54 mg/dL”




CI, confidence interval; VPB, ventricular premature beats.
Chow E et al. *Diabetes*. 2014;63:1738–47.

# ADA/EASD position statements



Diabetes Care Volume 40, January 2017 155

## Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

International Hypoglycaemia Study Group*

Diabetes Care 2017;40:155–157 | DOI: 10.2337/dc16-2215

The International Hypoglycaemia Study Group recommends that the frequency of detection of a glucose concentration <3.0 mmol/L (<54 mg/dL), which it considers to be clinically significant biochemical hypoglycemia, be included in reports of clinical trials of glucose-lowering drugs evaluated for the treatment of diabetes mellitus.

The glycemic thresholds for symptoms of hypoglycemia and for glucose counter-regulatory (including sympathoadrenal) responses to hypoglycemia, as plasma glucose concentrations fall, are not fixed in patients with insulin-, sulfonylurea-, or meglitinide (glinide)-treated diabetes. They are at higher glucose concentrations in those with poor glycemic control and at lower glucose concentrations in those with tight glycemic control (1–5). The shifts in glycemic threshold to lower glucose concentrations are largely the result of more frequent episodes of iatrogenic hypoglycemia during intensive glycemic therapy. Glycemic thresholds for responses to hypoglycemia vary, not only among individuals with diabetes but also in the same individual with diabetes as a function of their $HbA_{1c}$ levels and hypoglycemic experience; it is therefore not appropriate to cite a specific glucose concentration that defines hypoglycemia in diabetes. As a consequence, the American Diabetes Association has defined hypoglycemia in diabetes nonnumerically as "all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm" (6,7).

Nonetheless, the International Hypoglycaemia Study Group believes that it is important to identify and record a level of hypoglycemia that needs to be avoided because of its immediate and long-term danger to the individual. A single glucose level should be agreed to that has serious clinical and health-economic consequences. This would enable the diabetes and regulatory communities to compare the effectiveness of interventions in reducing hypoglycemia, be they pharmacological, technological, or educational. It would also permit the use of meta-analysis as a statistical tool to increase power when comparing interventions.

In its discussion, the International Hypoglycaemia Study Group considered glucose concentration levels of <3.0 mmol/L (<54 mg/dL) and <2.8 mmol/L (<50 mg/dL) detected by self-monitoring of plasma glucose, continuous glucose monitoring (for at least 20 minutes), or a laboratory measurement of plasma glucose. Both of these levels are distinctly low glucose concentrations that do not occur under physiological conditions in nondiabetic individuals (8). Thus, they are unequivocally hypoglycemic values. They approximate the upper and lower limits, respectively, of the nondiabetic glycemic threshold for symptoms of insulin-induced hypoglycemia (8–10). The generic nondiabetic glycemic threshold for impairment of cognitive

Corresponding author: Simon R. Heller, s.heller@sheffield.ac.uk.

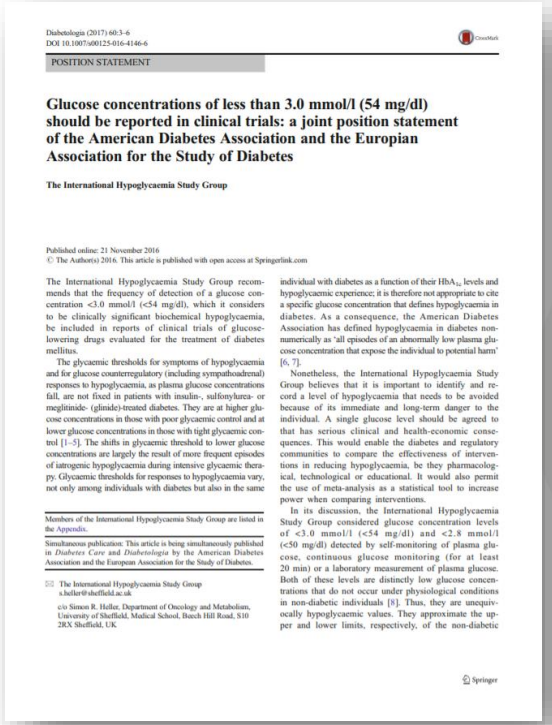
This position statement was reviewed and approved by the American Diabetes Association Professional Practice Committee in September 2016 and ratified by the American Diabetes Association Board of Directors in October 2016.

*Members of the International Hypoglycaemia Study Group are listed in the APPENDIX.

This article is being simultaneously published in Diabetes Care and Diabetologia by the American Diabetes Association and the European Association for the Study of Diabetes.







Diabetologia (2017) 60:3-6
DOI 10.1007/s00125-016-4146-6



## Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the Europian Association for the Study of Diabetes

The International Hypoglycaemia Study Group

Published online: 21 November 2016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Simultaneous publication: This article is being simultaneously published in *Diabetes Care* and *Diabetologia* by the American Diabetes Association and the European Association for the Study of Diabetes.

✉ The International Hypoglycaemia Study Group
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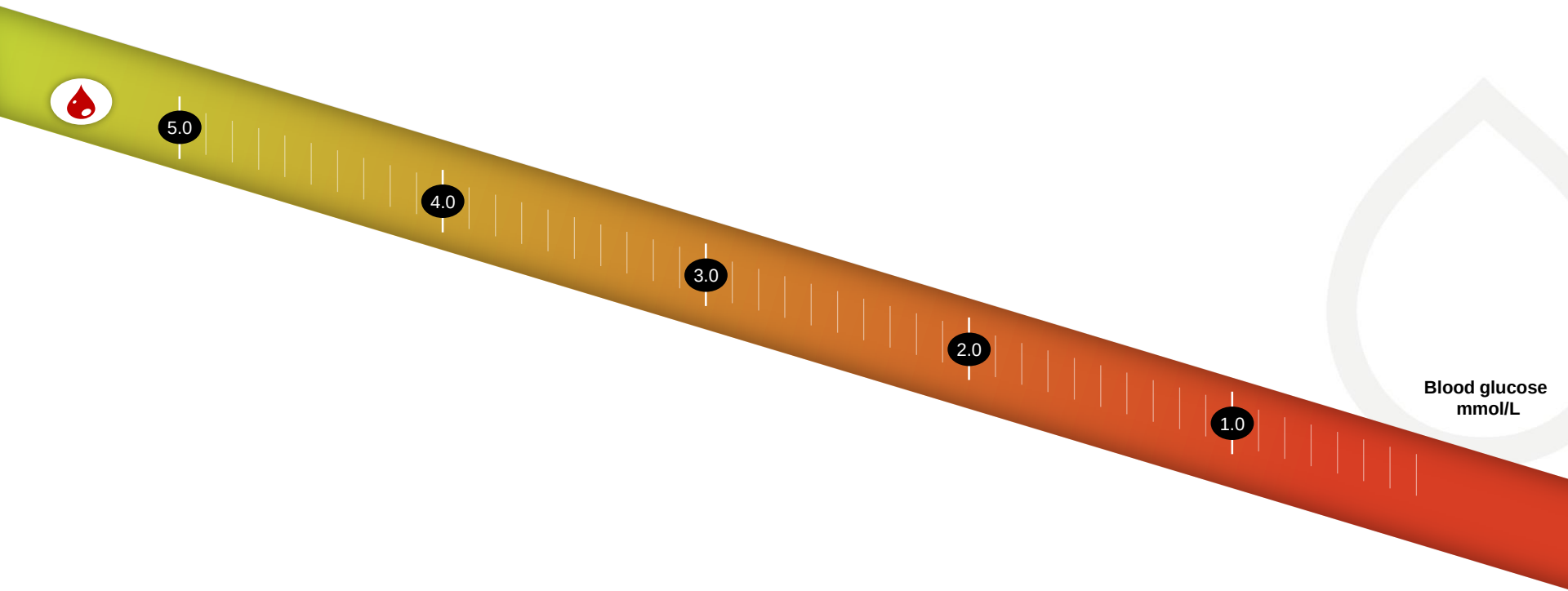
International Hypoglycaemia Study Group. *Diabetes Care* 2017; 40:155–57; International Hypoglycaemia Study Group. *Diabetologia* 2017;60:3–6.

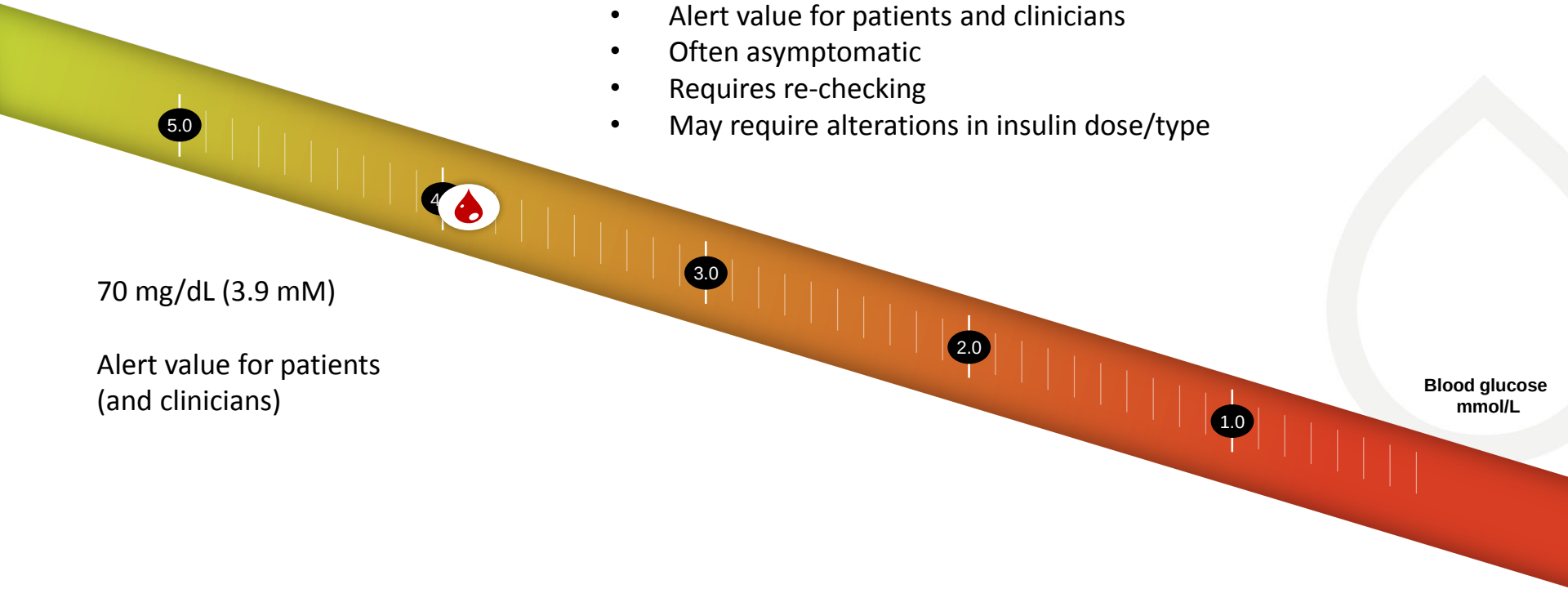
# Classifying hypoglycaemia: Level 1




International Hypoglycaemia Study Group. *Diabetes Care* 2017; 40:155–57; International Hypoglycaemia Study Group. *Diabetologia* 2017;60:3–6.

# Classifying hypoglycaemia: Level 1

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

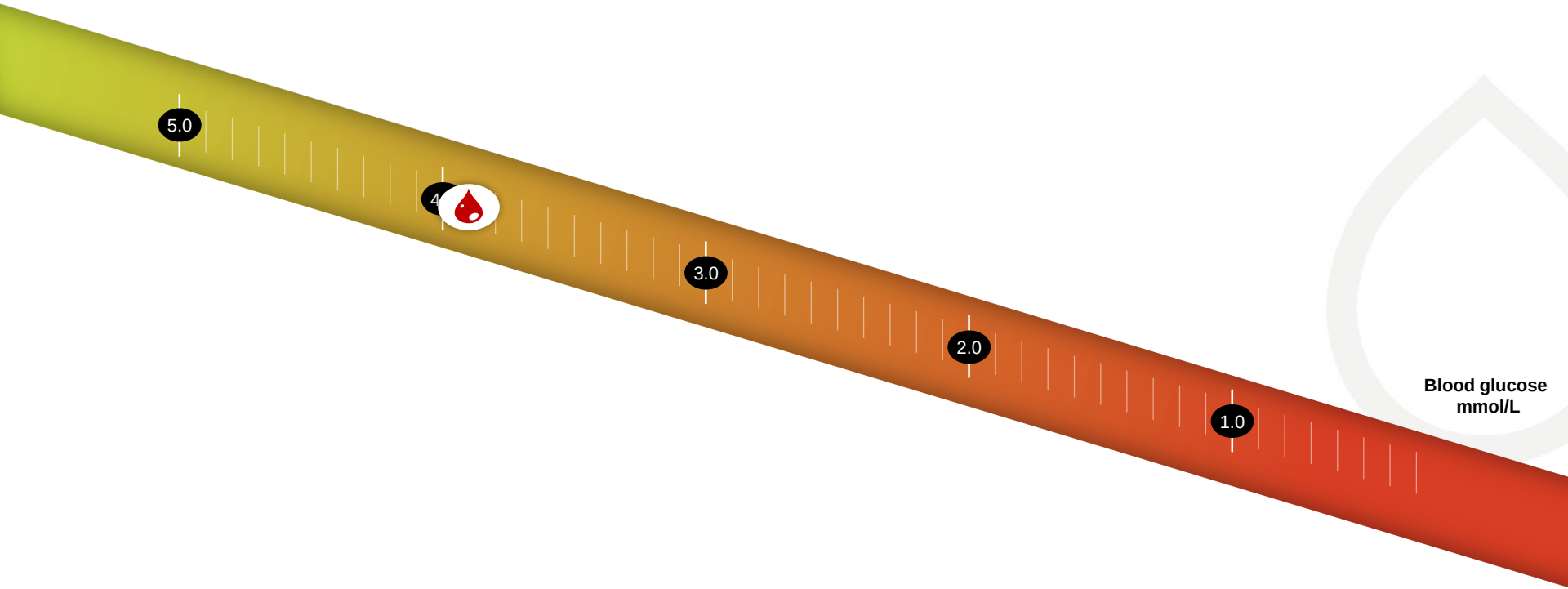



70 mg/dL (3.9 mM)

Alert value for patients
(and clinicians)

International Hypoglycaemia Study Group. *Diabetes Care* 2017; 40:155–57; International Hypoglycaemia Study Group. *Diabetologia* 2017;60:3–6.

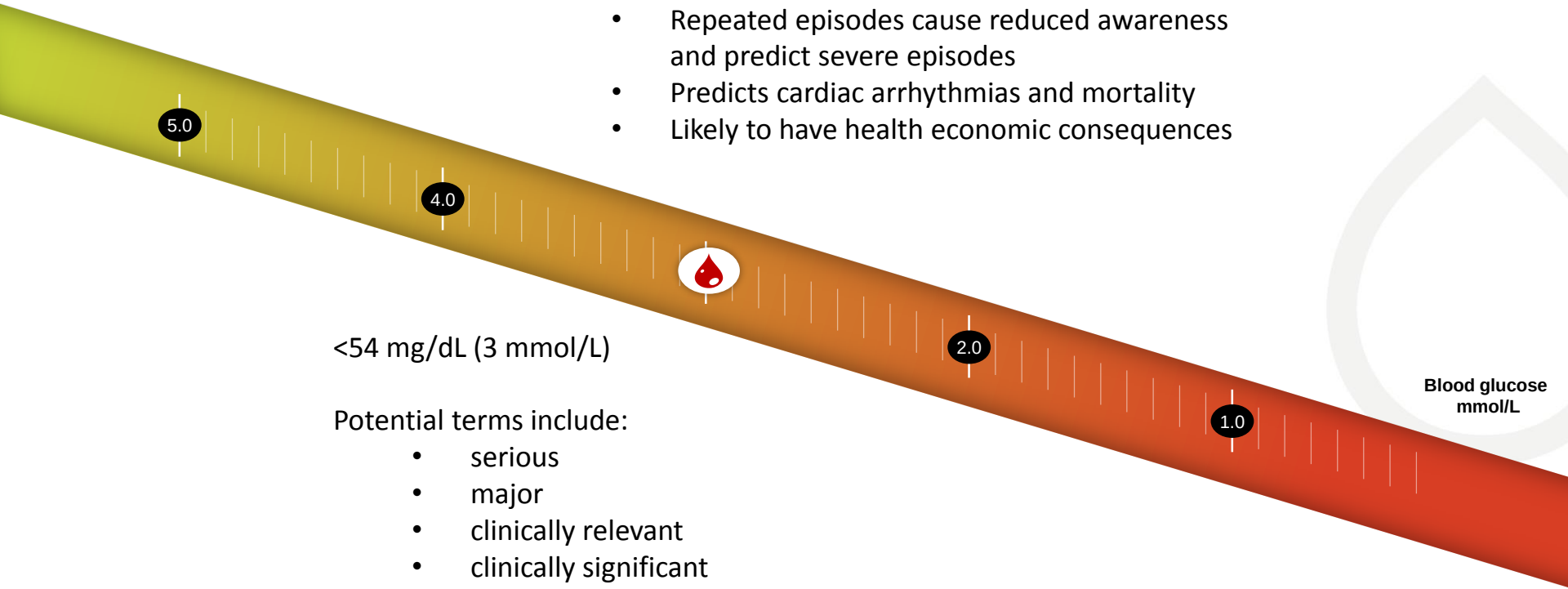
# Classifying hypoglycaemia: Level 2




International Hypoglycaemia Study Group. *Diabetes Care* 2017; 40:155–57; International Hypoglycaemia Study Group. *Diabetologia* 2017;60:3–6.

# Classifying hypoglycaemia: Level 2

- Denotes impaired cognitive function
- Repeated episodes cause reduced awareness and predict severe episodes
- Predicts cardiac arrhythmias and mortality
- Likely to have health economic consequences



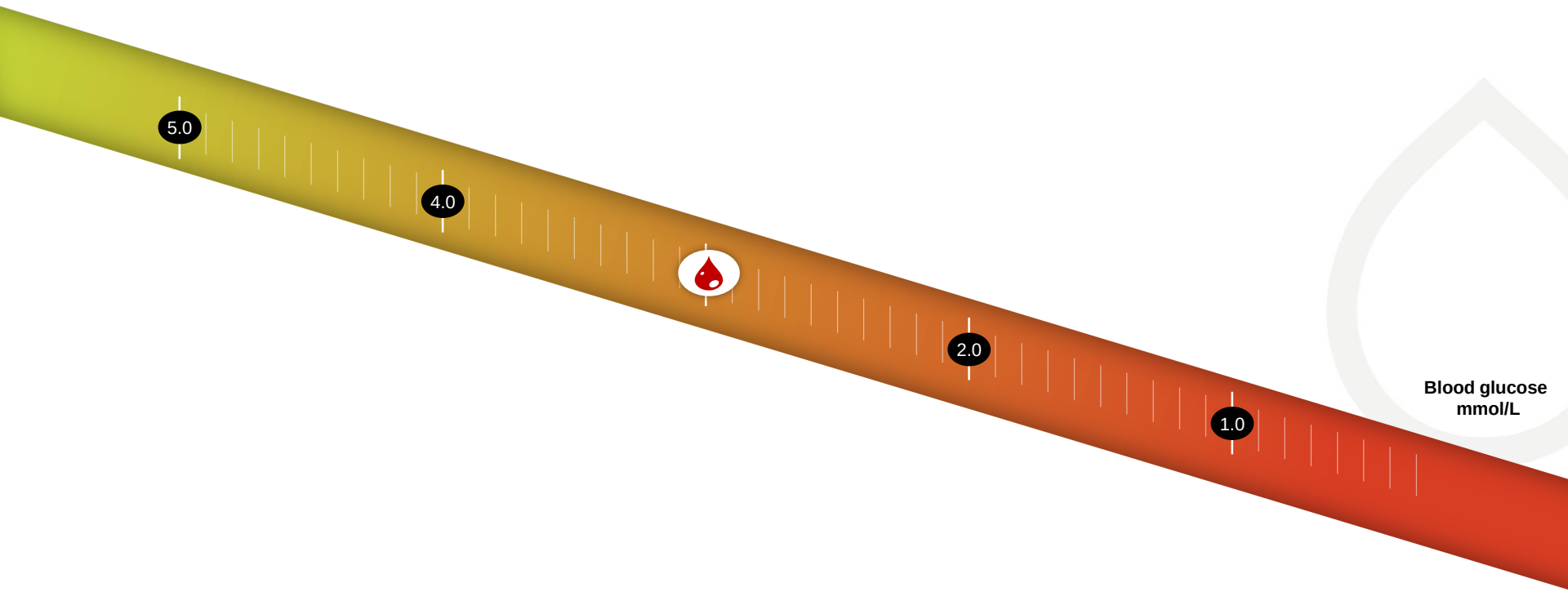

<54 mg/dL (3 mmol/L)

Potential terms include:

- serious
- major
- clinically relevant
- clinically significant

International Hypoglycaemia Study Group. *Diabetes Care* 2017; 40:155–57; International Hypoglycaemia Study Group. *Diabetologia* 2017;60:3–6.

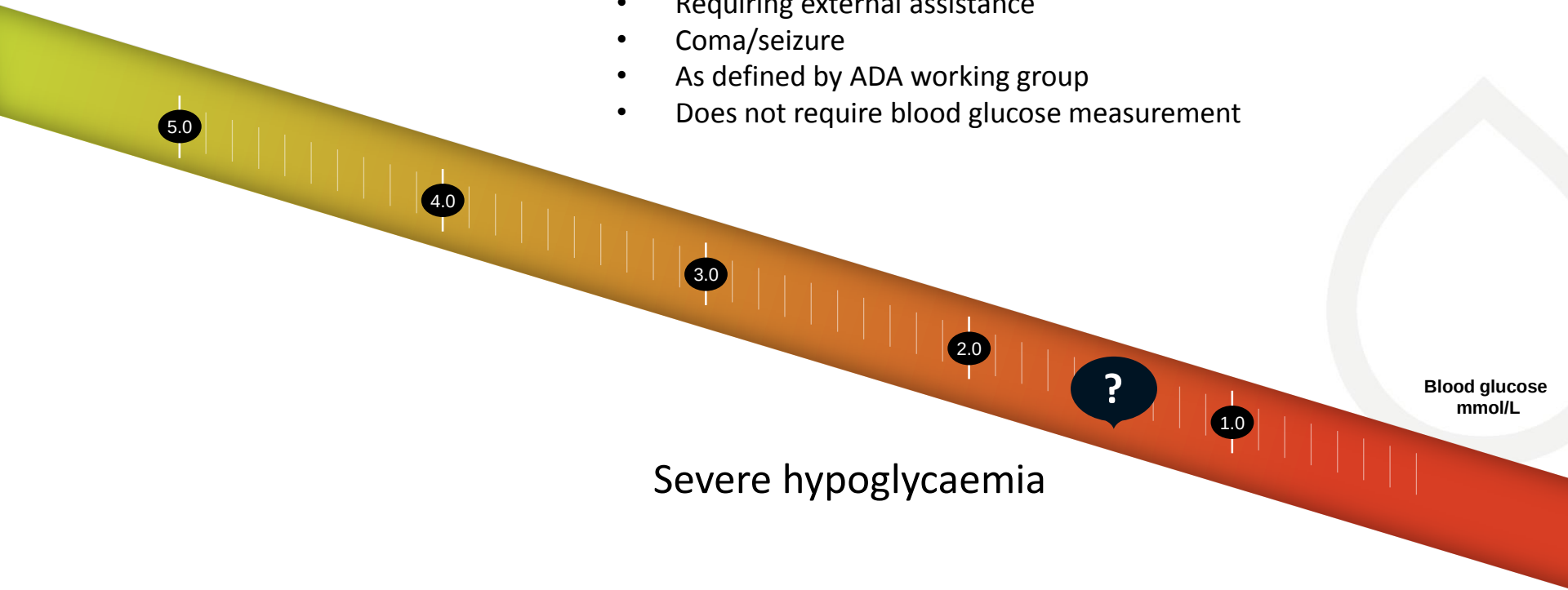
# Classifying hypoglycaemia: Level 3




ADA, American Diabetes Association.
International Hypoglycaemia Study Group. *Diabetes Care* 2017; 40:155–57; International Hypoglycaemia Study Group. *Diabetologia* 2017;60:3–6.

# Classifying hypoglycaemia: Level 3

- Severe cognitive impairment
- Requiring external assistance
- Coma/seizure
- As defined by ADA working group
- Does not require blood glucose measurement




Severe hypoglycaemia

ADA, American Diabetes Association.

International Hypoglycaemia Study Group. *Diabetes Care* 2017; 40:155–57; International Hypoglycaemia Study Group. *Diabetologia* 2017;60:3–6.

# Continuing progress

- Adopted as position statement by **ADA/EASD**
- Similar classification proposed by **JDRF** T1D Outcomes Program Statement
- Glucose level of 3.0 mmol/L (54 mg/dL) accepted by **ATTD Consensus** on continuous glucose measurement
- Classification incorporated into new **ISPAD** guidelines
- Classification included in draft **EMA** recommendations for clinical trials
  - FDA position is presently unclear

ADA, American Diabetes Association; ATTD, Advanced Technologies & Treatments for Diabetes; EASD, European Association for the Study of Diabetes; EMA European Medicnes Agency
JDRF, Juvenile Diabetes Research Foundation; ISPAD, International Society for Pediatric and Adolescent Diabetes; T1D, type 1 diabetes.

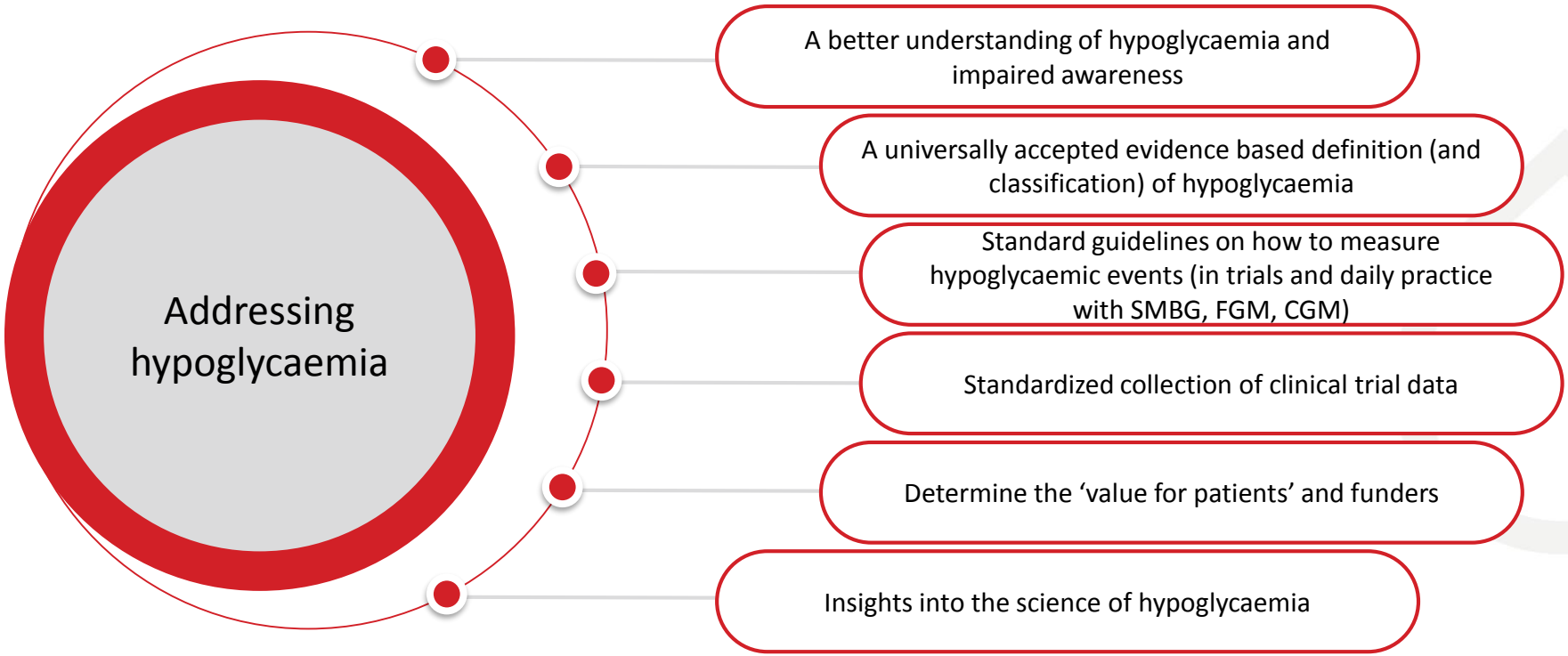
# Understanding hypoglycaemia: existing gaps

- Evidence-based data to refine hypoglycaemia classification
- Level of hypoglycaemia predicting adverse (CV) outcomes and mechanism(s) underlying this association
- Health-economic and psychological impact of non-severe and CGM-detected hypoglycaemia


CGM, continuous glucose monitoring; CV, cardiovascular.

# Bridging the gap: an IMI-2 project hypo-resolve awarded 2018

# Addressing hypoglycaemia: the focus



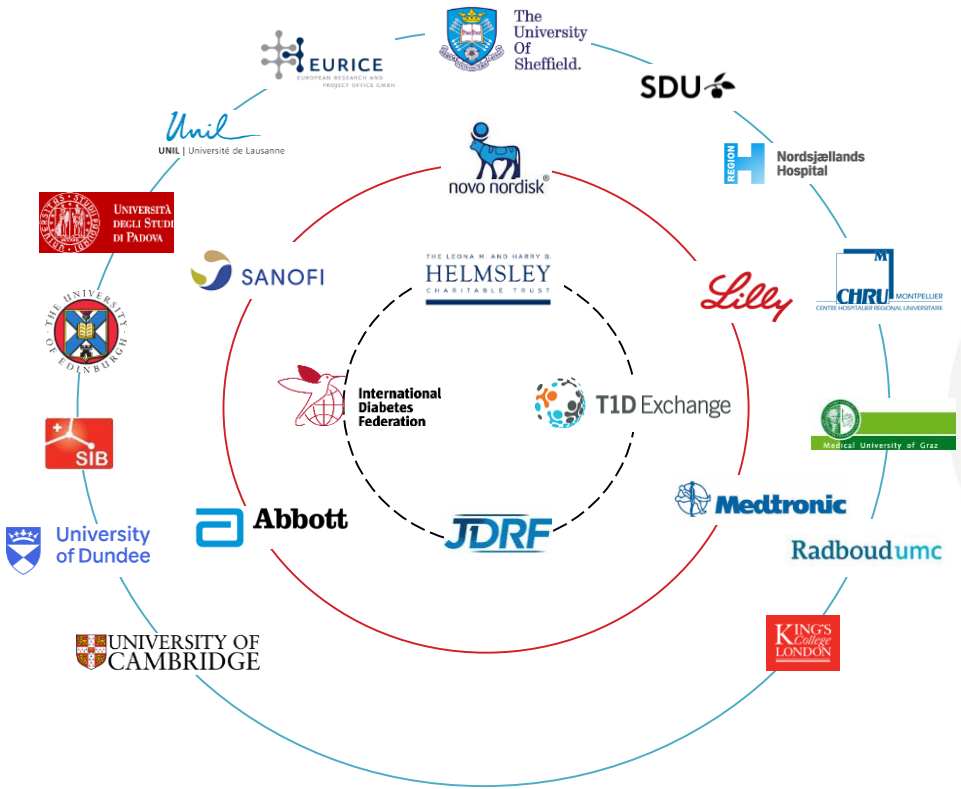

CGM, continuous glucose monitoring; FGM, flash glucose monitoring; SMBG, self-measured blood glucose.

# Hypo-RESOLVE partners

**5** industry partners

**4** associated partners

**14** academic partners



# Conclusions

- Hypoglycaemia: inevitable consequence of tight glycaemic targets involving insulin and sulphonylureas
- Study outcomes have often failed to measure the true burden of hypoglycaemia in people with diabetes
- An additional agreed glucose level of <54 mg/dl (3mmol/) will allow us to study hypoglycaemia in more depth in clinical studies
- Increasing recognition of importance of hypoglycaemia is demonstrated by the whole diabetes community working together to reduce its burden

## Recuerde, si Usted tiene preguntas para nuestros conferencistas….

**Levante su mano para que recojan su ficha de preguntas**


**Las preguntas se responderán durante el panel de discusión**

# Hipoglucemia y Enfermedad Cardiovascular

**Lawrence Leiter, MD, FRCPC, FACP, FACE, FAHA**
Director, Clínica de Lípidos
Director Asociado, Centro de Nutrición Clínica y Modificación de Factores de Riesgo
Científico Asociado, Instituto del Conocimiento Li Ka Shing
Hospital St. Michael
Toronto, Canada

# Disclosures

- Relationships with commercial interests:
  - Grants/research Support; Speakers Bureau; and/or honoraria:
    - AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, Sanofi, Servier

# Agenda

| Topic |
| --- |
| Epidemiology of hypoglycemia and CVD |
| Risk of hypoglycemia in large cardiovascular outcomes trials |
| Hypoglycemia: mediator or marker of CVD risk |
| Mechanisms of hypoglycemia-induced increased CV risk |

CV, cardiovascular; CVD, cardiovascular disease.

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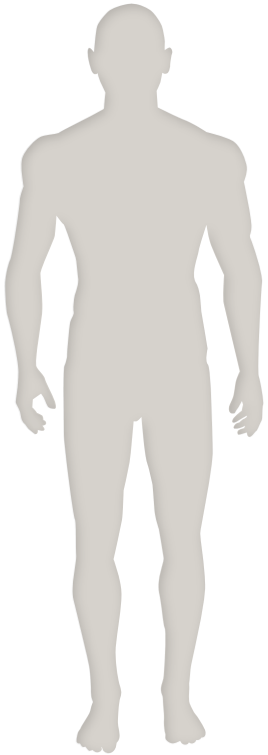
# The consequences of hypoglycemia

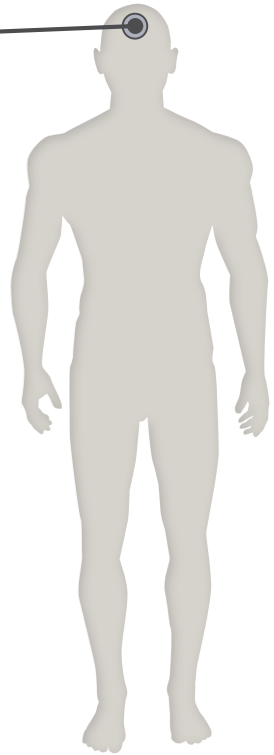


Desouza CV et al. *Diabetes Care* 2010;33:1389–94; Frier BM et al. *Diabetes Care* 2011;34(Suppl. 2):S132–S1377; Frier BM. *Nat Rev Endocrino*l 2014;10:711–22. Gjedde A et al. *Diabetes* 2015;64(Suppl. 1):A91.

# The consequences of hypoglycemia

**Brain**

Cognitive dysfunction
Hemiparesis
Seizures
Coma
Psychological (fear of hypoglycemia)



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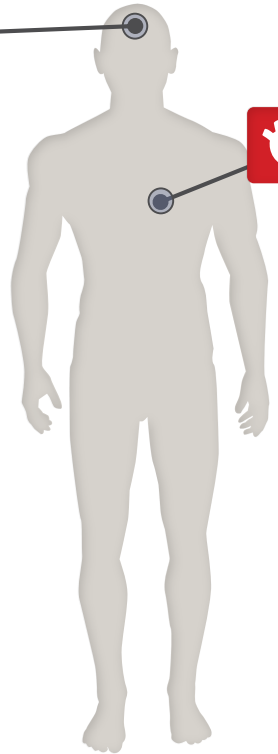

**Heart**

Myocardial infarction
Cardiac arrhythmias
Cardiac failure

Desouza CV et al. *Diabetes Care* 2010;33:1389–94; Frier BM et al. *Diabetes Care* 2011;34(Suppl. 2):S132–S1377; Frier BM. *Nat Rev Endocrinol* 2014;10:711–22. Gjedde A et al. *Diabetes* 2015;64(Suppl. 1):A91.

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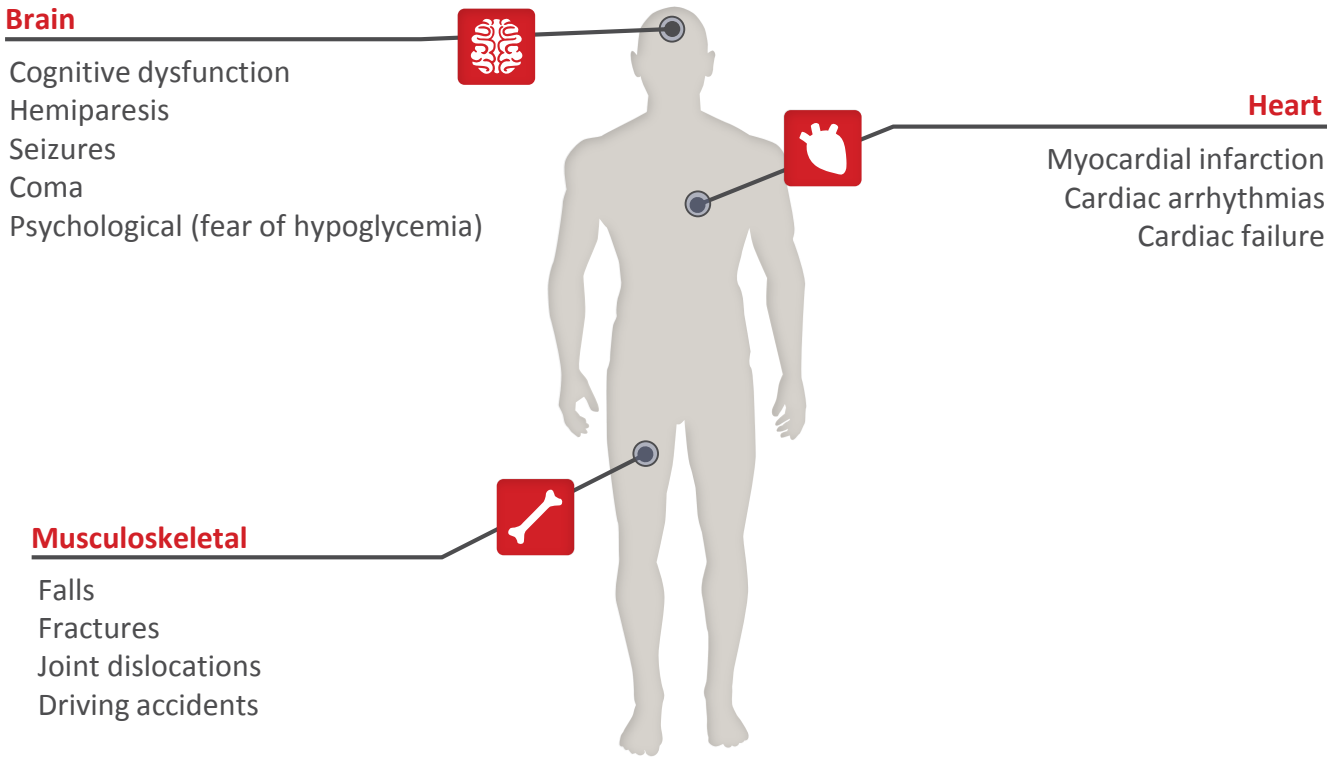


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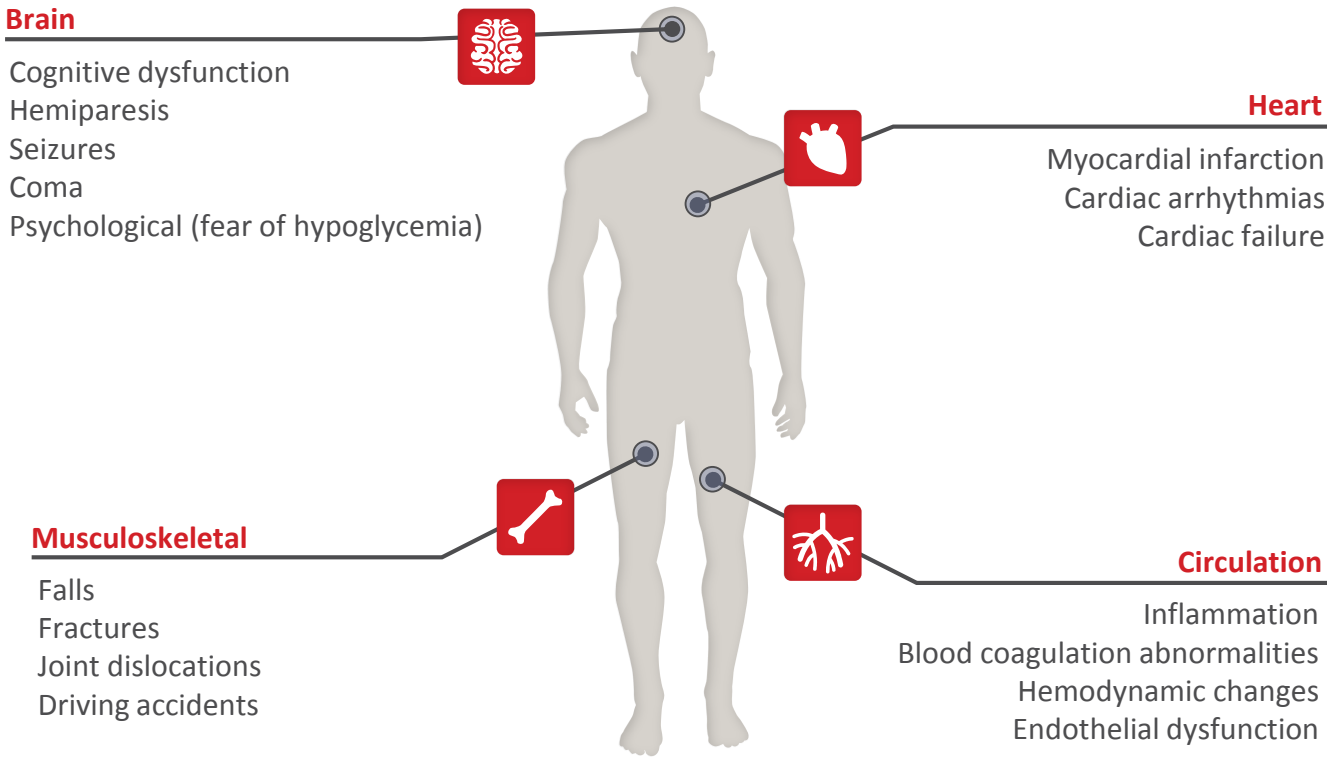


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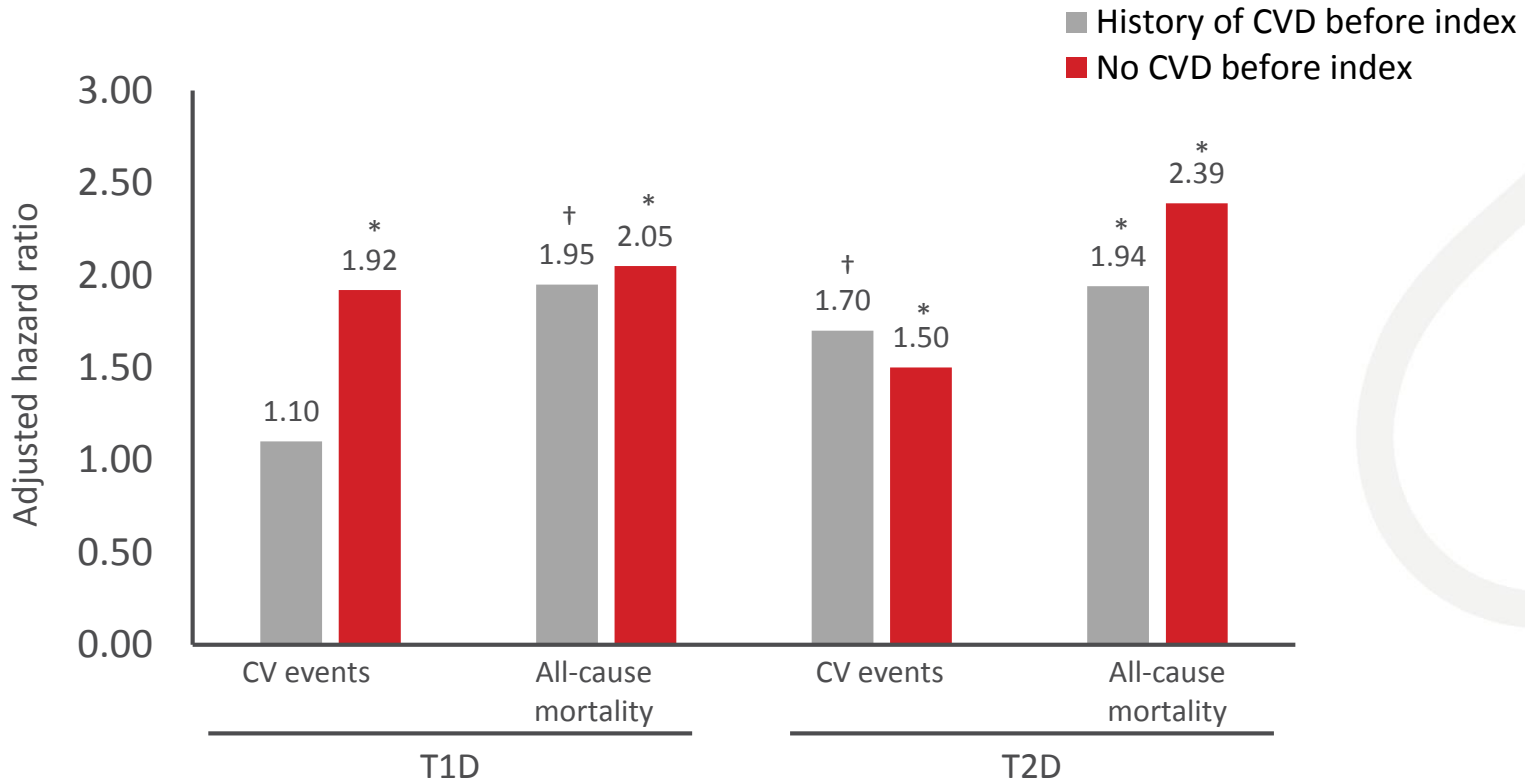
# Hypoglycemia is associated with increased CVD events and mortality in type 1 and 2 diabetes



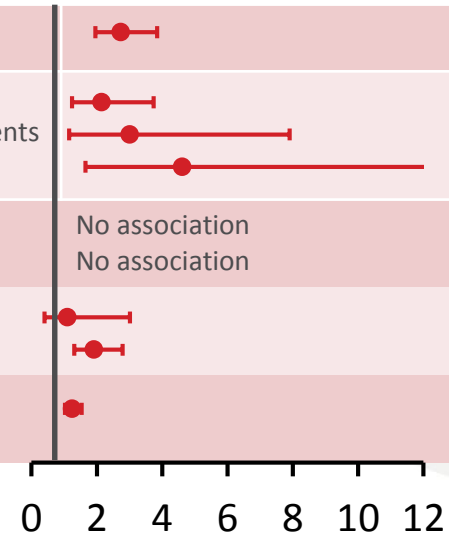

*$p$<0.001. †$p$<0.05.

Population based on the Clinical Practice Research database, including 3 260 patients with T1D and 10 422 patients with T2D. CV events defined as myocardial infarction, stroke, or CV death. HR . CV, cardiovascular; CVD, cardiovascular disease.

Khunti K et al. *Diabetes Care* 2015;38:316–22

# Epidemiological cohorts link hypoglycemia to CV events and mortality in type 1 diabetes

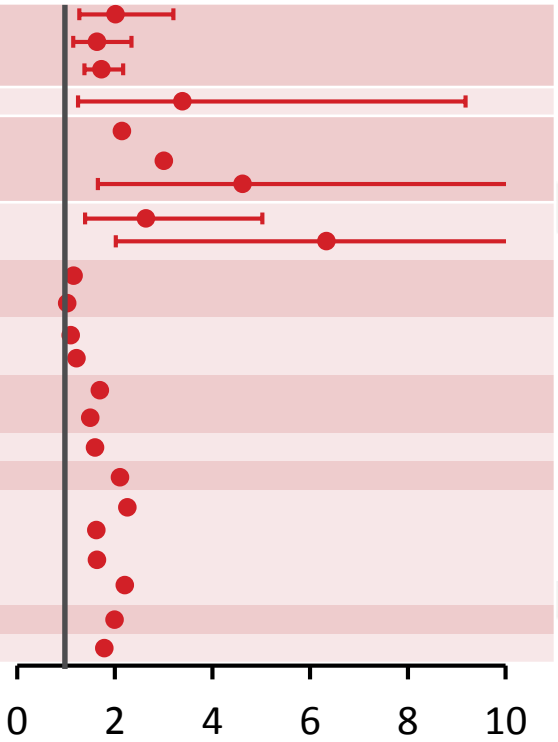
| Epidemiological cohorts | Year | Severity | Follow up | Effect | Hazard ratio |
|---|---|---|---|---|---|
| Taiwan database[1] (N=4361) | 2016 | SH | 5 years | CVD | |
| US Academic Primary Care Network[2*] (N=9173) | 2016 | Not defined | 6 years | CHD without previous CAD<br>CHD in high vascular risk patients<br>CHD in those aged ≥65 years | |
| Dutch (n=482)and Danish Cohorts (n=269)[3] | 2016 | SH | 6.5 years<br>12 years | All cause death<br>CV death | No association<br>No association |
| UK GP database[4] (N=3260) | 2015 | SH | median 5.0 years | Type 1 CVD secondary<br>Type 1 CVD | |
| Swedish Diabetes Register[5] (N=1839) | 2014 | | 5 years | All cause death | |




*Type 1 and type 2 diabetes.
ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; SH, severe hypoglycemia.
1. Lu CL et al. *Diabetes Care* 2016;39:1571–8; 2. Leong A et al. *J Clin Endocrinol Metab* 2016;101:659–68; 3. Sejling AS et al. *Diabet Med* 2016;33:77 –83; 4. Khunti K et al. *Diabetes Care* 2015;38:316 –22;
5. Lung TW et al. *Diabetes Care* 2014;37:2974–81.

# Epidemiological cohorts link hypoglycemia to CV events and mortality in type 2 diabetes

| Epidemiological cohorts | Year | Severity | Follow up | Effect |
|---|---|---|---|---|
| ARIC[1] (N-1209) | 2018 | SH | median 15.3 y | CHD<br>CV death<br>All cause death |
| Japanese database[2] (N=58223) | 2016 | SH | mean 2.3 y | CVD |
| US Academic Primary Care Network[3*] (N=9173) | 2016 | Not defined | 6 y | CHD without previous CAD<br>CHD in high vascular risk patients<br>CHD in those aged ≥65 years |
| Vincent Type 2 Diabetes Registry (Korea)[4] (N=906) | 2016 | SH | median 10.4 y | All cause death<br>CV death |
| Joint Asia Diabetes Registry[5] (N=18589) | 2016 | Mild | mean 3.9 y | CVD<br>All cause death |
| CREDIT study[6**] (N=2999) | 2016 | SH | 4·0 y | CV death<br>All cause death |
| UK GP database[7**] (N=10422) | 2015 | SH | median 4.8 y | Type 2 CVD secondary<br>Type 2 CVD |
| Scottish[8] (N=1066) | 2014 | SH | mean 4.0 y | CVD |
| German Primary Care database[9] (N=25712) | 2013 | SH | mean 2.0 y | CVD |
| Taiwan database[10] (N=2500) | 2013 | SH<br><br><br><br>Mild | 10 y | CVD<br>CHD<br>Stroke<br>CVD |
| US Veterans Network[11] (N=1522) | 2012 | SH | median 3.9 y | CVD |
| Medicare database[12] (N=860845) | 2011 | SH | mean 1 y | CVD |




*Type 1 and type 2 diabetes; **insulin treated.

ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; SH, severe hypoglycemia.

1. Lee AK et al. *Diabetes Care* 2018;41:104–11; 2. Goto A et al. *J Am Heart Assoc* 2016;5:e002875; 3. Leong A et al. *J Clin Endocrinol Metab* 2016;101:659–68; 4. Cha SA et al. *Diabetes Metab J* 2016;40:202–10; 5. Luk AO et al. *Medicine (Baltimore)* 2016;95:e5183; 6. Freemantle N et al. *Diabetes Obes Metab* 2016;18:152–8; 7. Khunti K et al. *Diabetes Care* 2015;38:316 –22; 8. Bedenis R et al. *Diabetes Care* 2014;37:3301–8; 9. Rathmann W et al. *Diabetes Obes Metab* 2013;15:55–61; 10. Hsu PF et al. *Diabetes Care* 2013; 36:894–900; 11. Zhao Y et al. *Diabetes Care* 2012;35:1126–32; 12. Johnston SS et al. *Diabetes Care* 2011;34:1164–71.

# Some studies demonstrate an association between hypoglycemia and risk of adverse outcomes in hospitalized patients

## Critically ill patients

- Intensive insulin therapy to maintain BG <110 mg/dL reduced morbidity and mortality among critically ill patients in the surgical ICU

AMI, acute myocardial infarction; BG, blood glucose; ICU, intensive care unit.

Van den Berghe G et al. *N Engl J Med* 2001;345:1359–67; Finfer S et al. *N Engl J Med* 2009;360:1283–97; NICE-SUGAR Investigators. *N Engl J Med* 2012;367:1108–18; Kosiborod M et al. *J Am Med Assoc* 2009;301:1556–64; Svensson AM et al. *Eur J Heart* 2005;26:1255–61; Pinto DS et al. *J Am Coll Cardiol* 2005;46:178–80; Mellbin LG et al. *Heart* 2009l95:721–7.

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- A single BG <3 mmol/L during hospitalization associated with increased risk of 2-year mortality

**TIMI study**

- Hypoglycemia on admission associated with increased risk of death or AMI at 30 days

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**DIGAMI 2 study (type 2 diabetes and AMI)**

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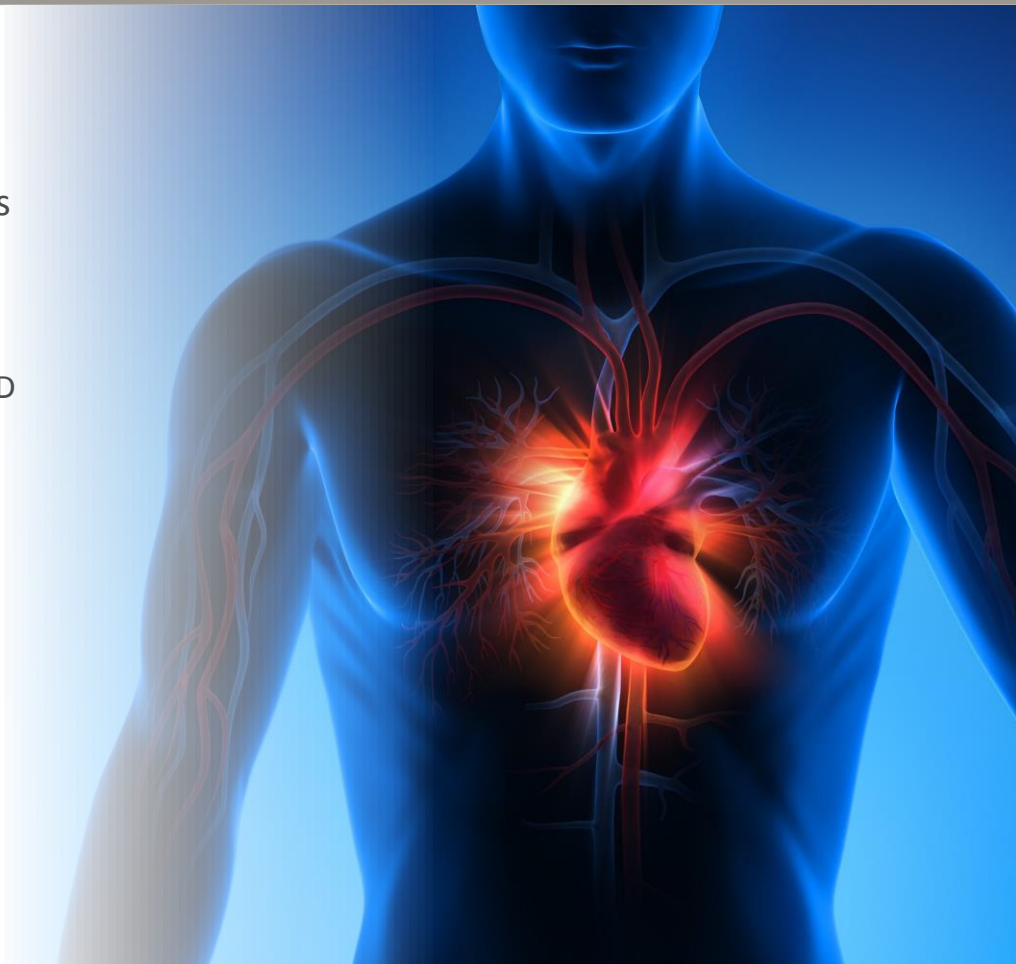
AMI, acute myocardial infarction; BG, blood glucose; ICU, intensive care unit.

Van den Berghe G et al. *N Engl J Med* 2001;345:1359–67; Finfer S et al. *N Engl J Med* 2009;360:1283–97; NICE-SUGAR Investigators. *N Engl J Med* 2012;367:1108–18; Kosiborod M et al. *J Am Med Assoc* 2009;301:1556–64; Svensson AM et al. *Eur J Heart* 2005;26:1255–61; Pinto DS et al. *J Am Coll Cardiol* 2005;46:178–80; Mellbin LG et al. *Heart* 2009l95:721–7.

# Epidemiology of hypoglycemia and CVD: Summary

- Most data from observational studies show an association between hypoglycemia (but not necessarily severe hypoglycemia) and CV events in type 1 and type 2 diabetes
  - The relationship persists over a long period: median time from first hypoglycemia to first CV event was 1.5 years in people with T1D or T2D
- Some conflicting results: clinic/hospital-based cases have different exposures than population cases
- Avoidance of severe hypoglycemia is an important consideration in selecting a glucose-lowering strategy



CV, cardiovascular events; CVD, cardiovascular disease.

# Agenda

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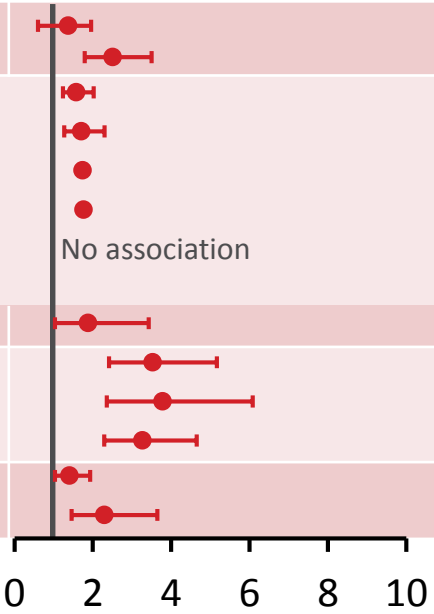
| **Risk of hypoglycemia in large cardiovascular outcomes trials** |
| Hypoglycemia: mediator or marker of CVD risk |
| Mechanisms of hypoglycemia-induced increased CV risk |

CV, cardiovascular; CVD, cardiovascular disease.

# Clinical trials linking hypoglycemia to CV events and mortality in patients with type 2 diabetes

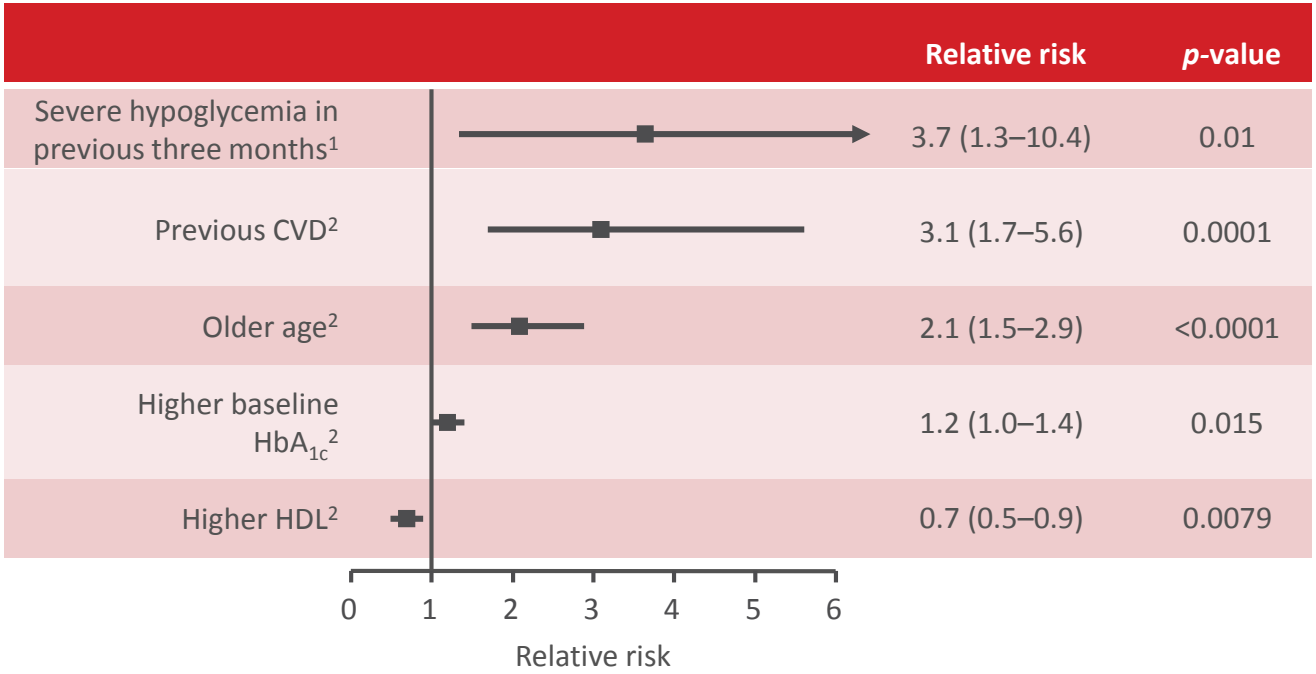
| Clinical trial cohorts | Year | Severity | Follow up | Effect size (adjusted) | Hazard ratio |
|---|---|---|---|---|---|
| DEVOTE 3[1] (N=7637) | 2018 | SH | median 2.0 y | CVD<br>All cause death | |
| ORIGIN[3] (N=12,537) | 2013 | SH<br><br><br><br>Non-severe hypoglycemia | median 6.2 y | CVD<br>CV death<br>All cause death<br>Arrhythmic death | No association |
| VADT[4] (N=1791) | 2011 | SH | median 5.6 y | CVD | |
| ADVANCE[5] (N=11,140) | 2010 | SH | median 5.0 y | CVD<br>CV death<br>All cause death | |
| ACCORD[6] (N=10,194) | 2010 | SH | mean 3.5 y | All cause death int<br>All cause death st | |




CV, cardiovascular; CVD, cardiovascular disease; int, intensive therapy; SH, severe hypoglycemia; st, standard therapy.

1. Pieber TR et al. *Diabetologia* 2018;61:58–65; 2. Heller SR et al. *Diabetes Obes Metab* 2017;19:664–71; 3. Mellbin LG et al. *Eur heart J* 2013;34:3137–44; 4. Duckworth W et al. *N Engl J Med* 2009;360:129–39; 5. Zoungas S et al. *N Engl J Med* 2010;363:1410–8; 6. Bonds DE et al. *BMJ* 2010;340:b4909.

# VADT: predictors for CV mortality



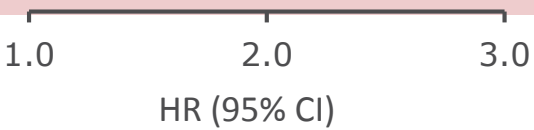

N=1791 subjects enrolled in VADT.

CVD, cardiovascular disease; $HbA_{1c}$, glycated hemoglobin; HDL, high density lipoprotein; VADT, Veterans' Affairs Diabetes Trial.

1. Davis SN et al. *Diabetes Care* 2019;42:157–63; 2. Adapted from Duckworth WC, Abraira C. Veterans Affairs Diabetes Trial. 44th EASD Annual Meeting; Rome. September 2008; Oral presentation at plenary session.

# ORIGIN: severe hypoglycemia increases risk for MACE

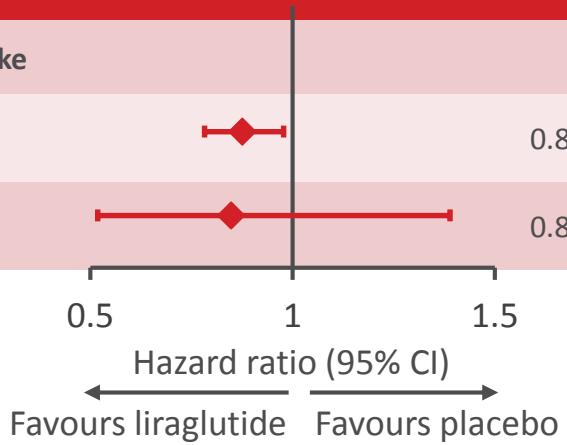
| Outcome | Adjusted HR with propensity score | *p*-value | Event rate, n/N (%)[†] |
|---|---|---|---|
| **Severe hypoglycemia** | | | |
| CV death or non-fatal MI or stroke | 1.58 (1.24–2.02) | <0.001 | 75/450 (16.7) |
| Total mortality | 1.74 (1.39–2.19) | <0.001 | 88/472 (18.6) |
| Total CV death | 1.71 (1.27–2.30) | <0.001 | 52/472 (11.0) |
| Arrhythmic death | 1.77 (1.17–2.67) | 0.007 | 28/470 (6.0) |




N=12 537 patients with dysglycemia and high CV risk.
*Primary endpoint: composite of CV death, non-fatal MI or stroke. †Participants with at least one episode of severe hypoglycemia and the listed outcome/total participants with at least one episode of severe hypoglycemia, expressed as n/N (%). N = 12,537 patients with diabetes and high CV risk.
CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Origin Trial Investigators. *Eur Heart J*. 2013;34:3137–3144.

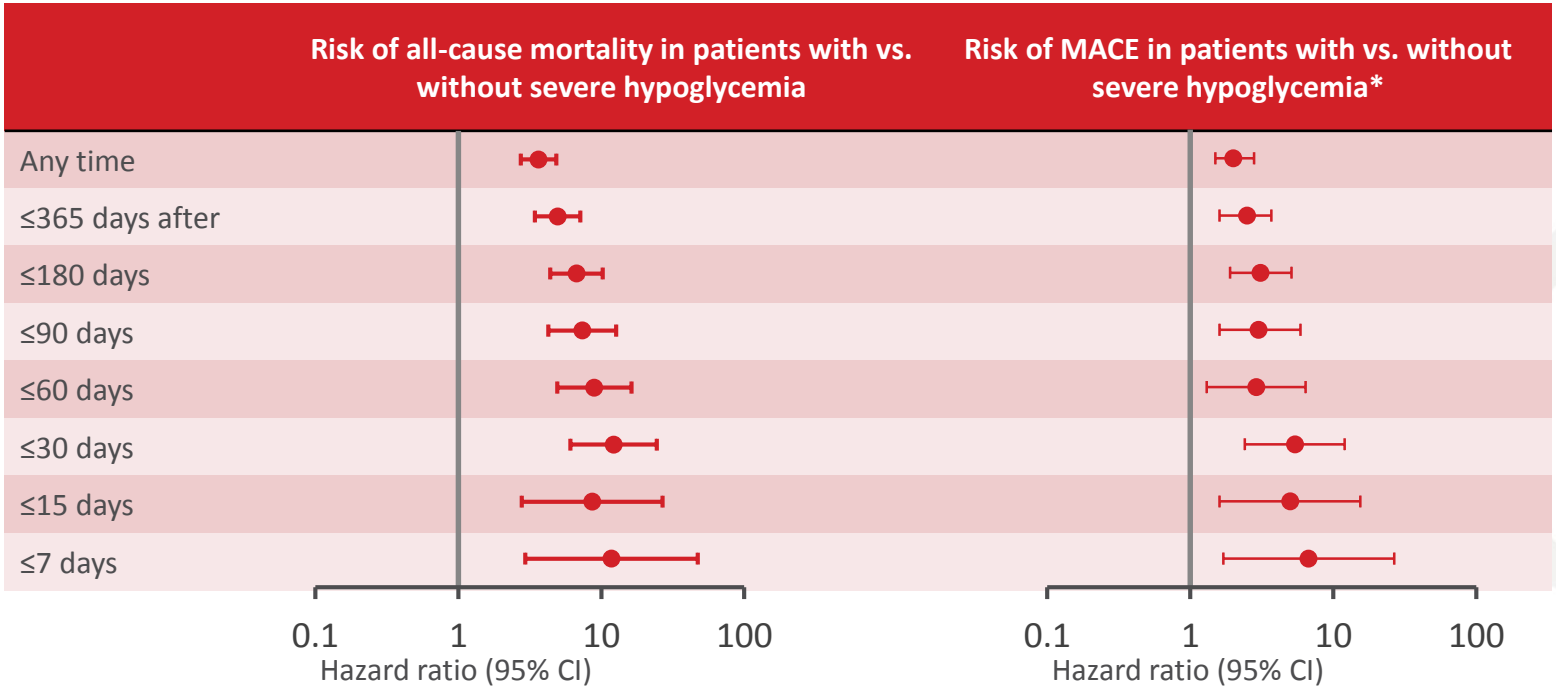
# LEADER: primary outcome by occurrence of severe hypoglycemia

| | Hazard ratio (95% CI) | Liraglutide N | Liraglutide % | Placebo N | Placebo % |
|---|---|---|---|---|---|
| **CV death, nonfatal MI or nonfatal stroke** | | | | | |
| Without severe hypoglycemia | 0.88 (0.78–0.98) | 582 | 12.8 | 654 | 14.5 |
| With severe hypoglycemia | 0.85 (0.52–1.39) | 26 | 22.8 | 40 | 26.1 |




N=9 340 patients with T2D and high CV risk. Post-hoc analysis. 'With severe hypoglycemia' is patients with one/more severe hypoglycaemic episodes (irrespective of the timing between the severe hypoglycemia and the event of interest); 'without severe hypoglycemia' is patients without severe hypoglycaemic episodes. The hazard ratios are estimated in Cox regression for each of the events of interest with an interaction between hypoglycaemic episode (with, without) and treatment.
%, proportion of patients with events; CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; N, number of patients with events.
Zinman B et al. *Diabetes Care* 2018;41:1783–91.

# LEADER: risk of all-cause mortality and cardiovascular outcomes is increased especially with shorter follow-up periods post-hypoglycemia

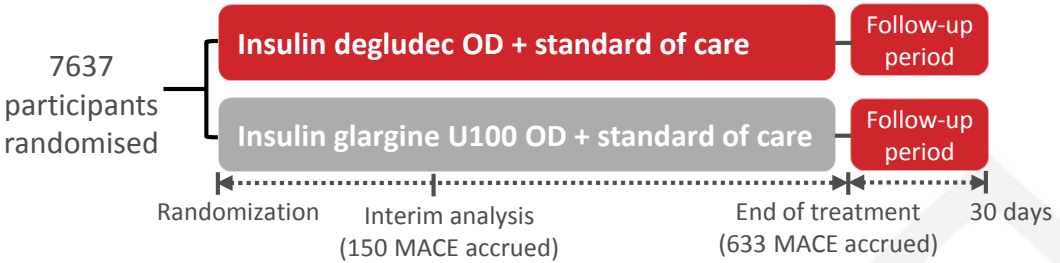



N=9 340 patients with T2D and high CV risk.
*Adjusted for concomitant insulin use during the trial.
CI, confidence interval; MACE, major adverse cardiovascular event.
Zinman B et al. *Diabetes Care* 2018;41:1783–91.

# Rate of severe hypoglycemia in DEVOTE

**Inclusion criteria:**

- Type 2 diabetes
- Current treatment with ≥1 oral or injectable antidiabetic agent(s)
- $HbA_{1c}$ ≥7.0% or <7.0% and basal insulin treatment ≥20 U/day
- High CV risk profile
  - CV or CKD and aged ≥50 years or risk factors for CV disease and aged ≥60 years




N= 7637 patients with T2D.
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular, OD, once-daily; RR, rate ratio.
Marso SP et al. *N Engl J Med* 2017;377:723–32.

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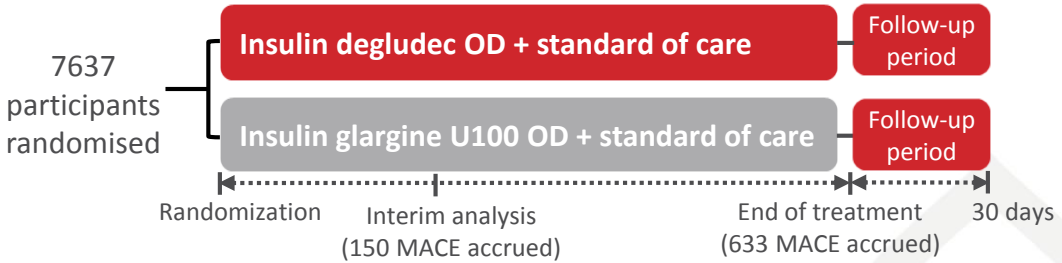
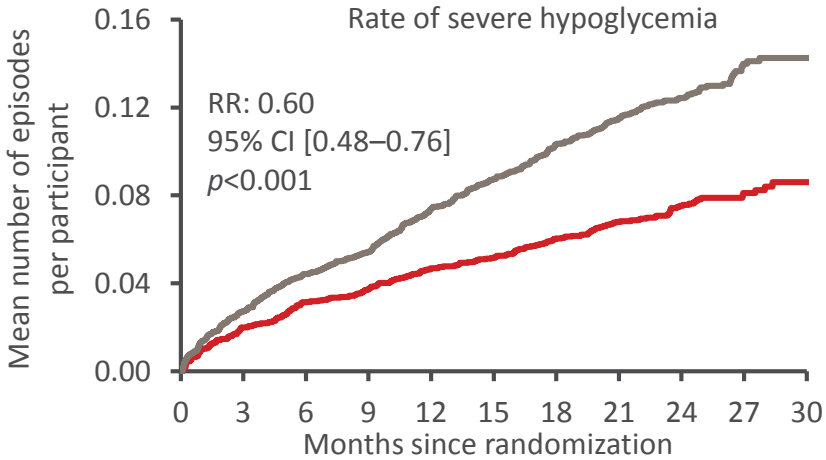
  - CV or CKD and aged ≥50 years or risk factors for CV disease and aged ≥60 years




N= 7637 patients with T2D.

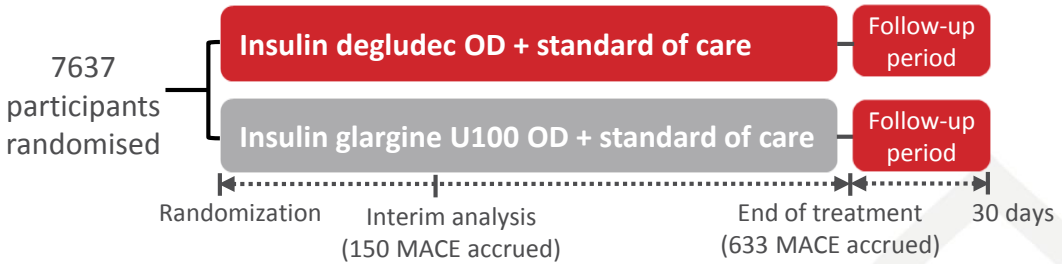
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular, OD, once-daily; RR, rate ratio.

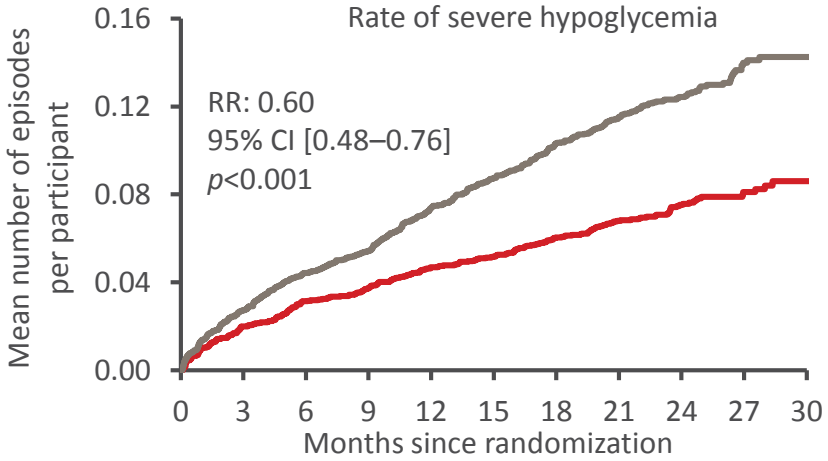
Marso SP et al. *N Engl J Med* 2017;377:723–32.

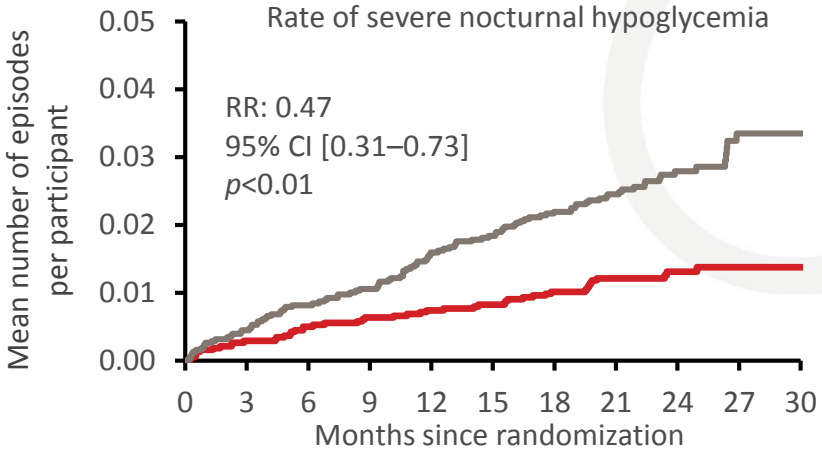
# Rate of severe hypoglycemia in DEVOTE

**Inclusion criteria:**

- Type 2 diabetes
- Current treatment with ≥1 oral or injectable antidiabetic agent(s)
- $HbA_{1c}$ ≥7.0% or <7.0% and basal insulin treatment ≥20 U/day
- High CV risk profile
  - CV or CKD and aged ≥50 years or risk factors for CV disease and aged ≥60 years



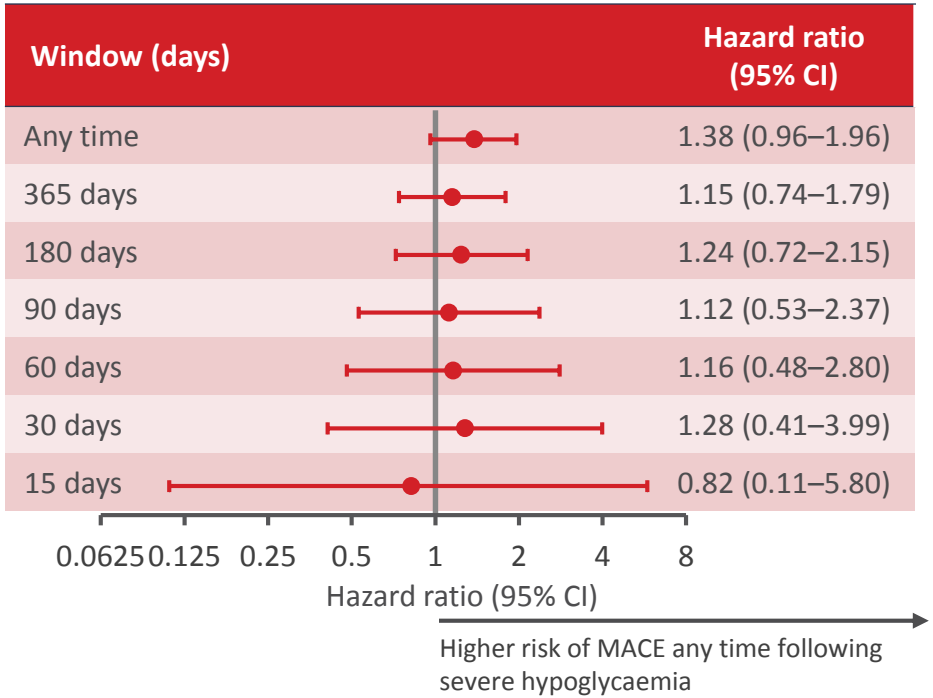

N= 7637 patients with T2D.

CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular, OD, once-daily; RR, rate ratio.

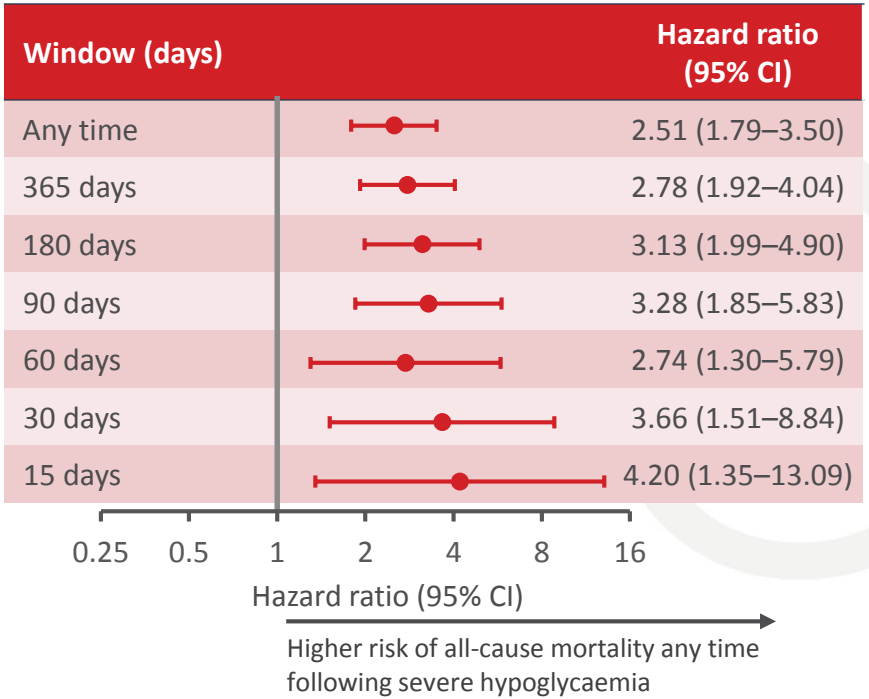
Marso SP et al. *N Engl J Med* 2017;377:723–32.

# DEVOTE 3: severe hypoglycaemia is associated with all-cause mortality with no relationship to time following hypoglycaemic event

Risk of MACE following a severe hypoglycaemic event by time period

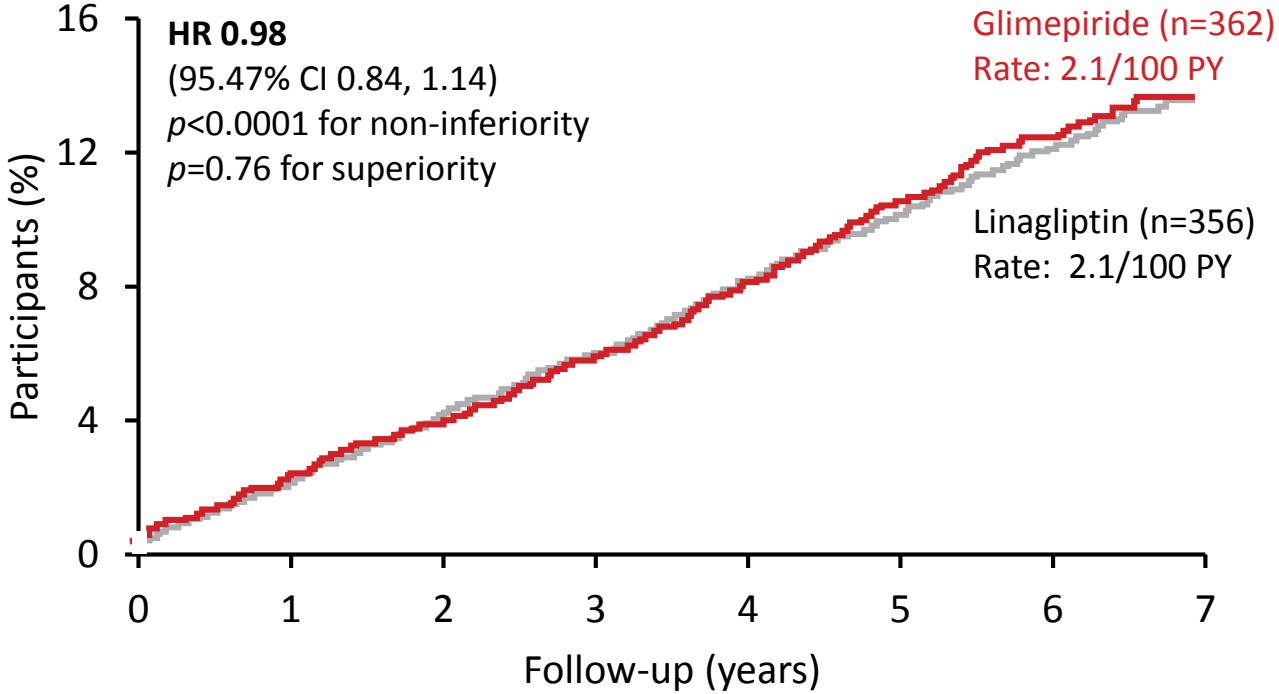



Risk of all-cause mortality following a severe hypoglycaemic event by time period



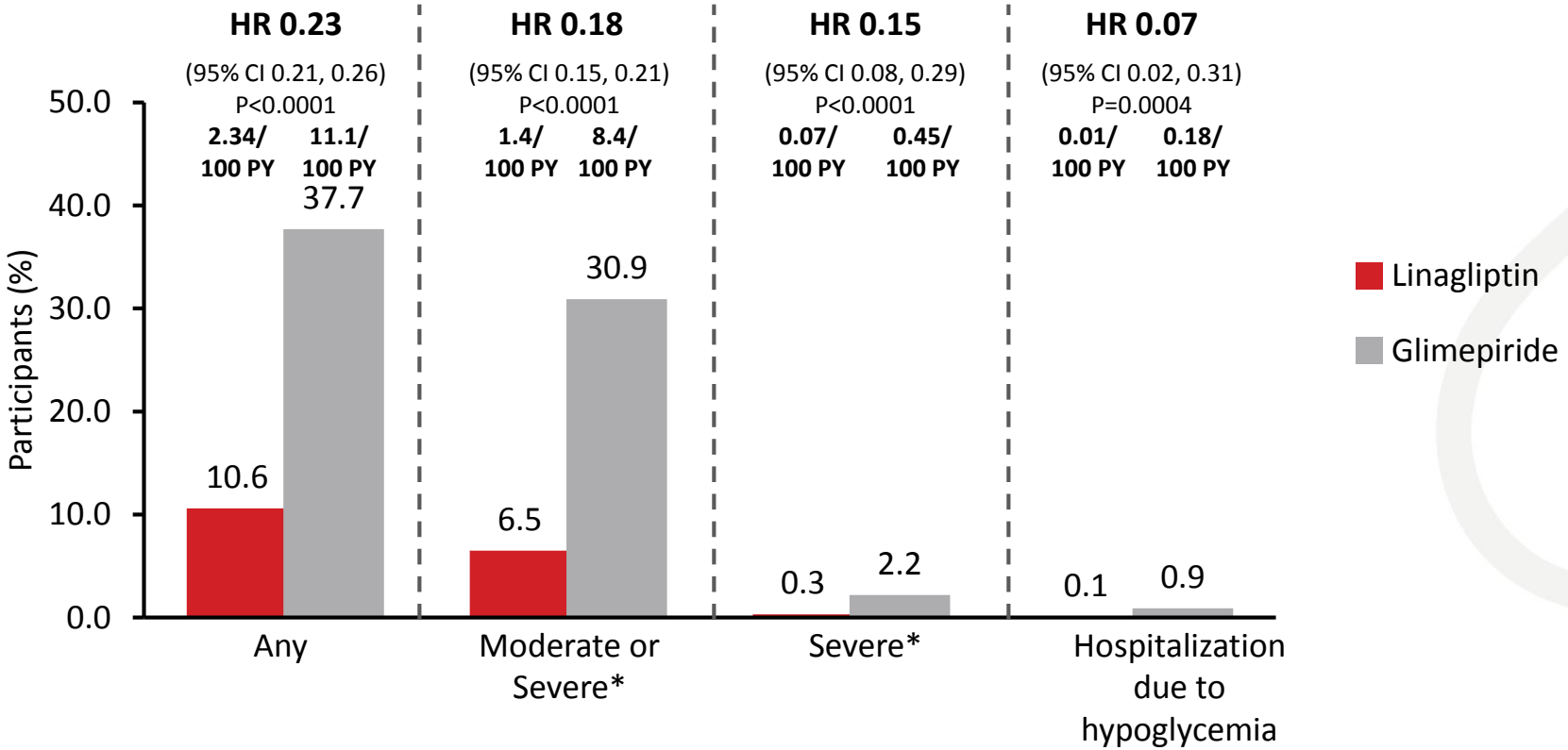

n=439 patients who experienced a severe hypoglycaemia.
CI, confidence interval; MACE, major adverse cardiovascular event.
Pieber TR et al. *Diabetologia* 2018;61:58–65.

# CAROLINA: Time to first occurrence of 3P-MACE (CV death, non-fatal MI, non-fatal stroke)




Treated set; Kaplan-Meier estimate; hazard ratio and 95% CI derived from Cox regression with factor treatment; 1-sided P value for non-inferiority and 2-sided *p*-value for superiority.
3P-MACE, 3-point major adverse CV events; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; PY, patient-years.
Presented at the ADA 79th Scientific Session, 2019, San Francisco, CA, USA.

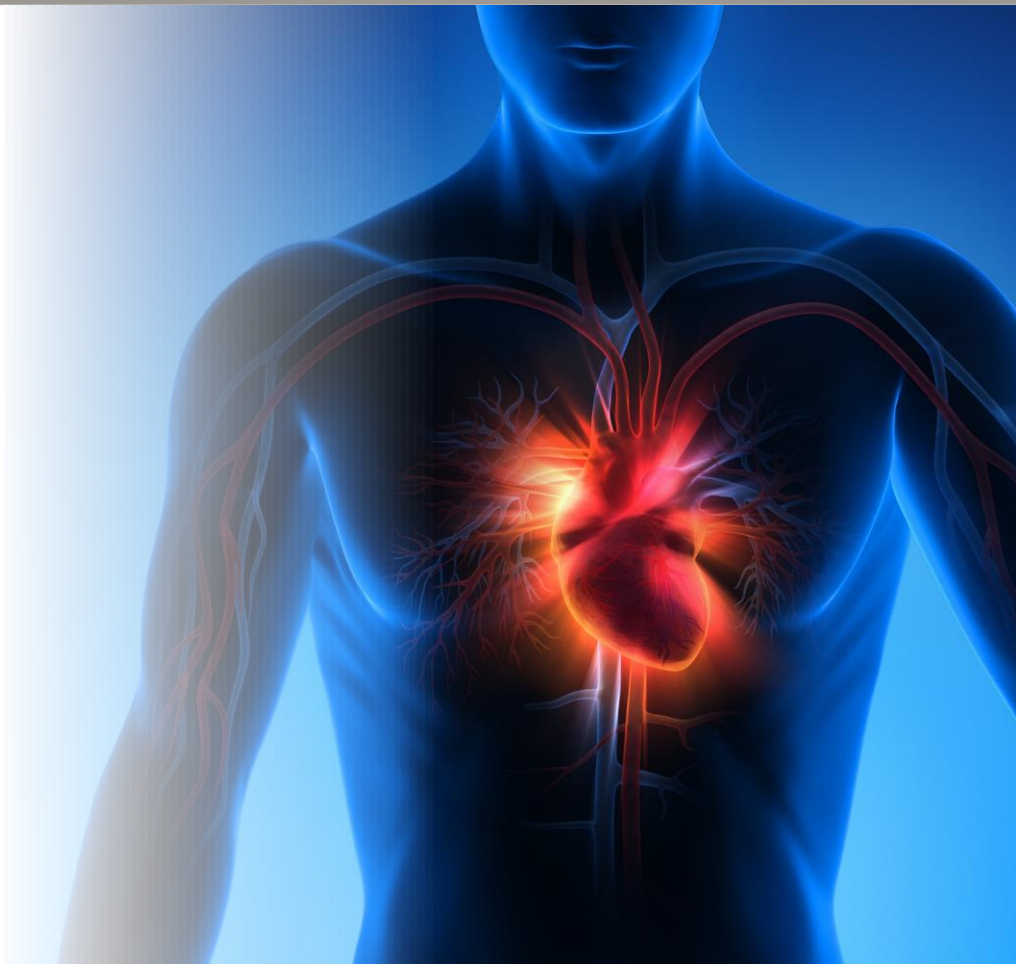
# CAROLINA: Hypoglycemia




Treated set without duplicate participants (events occurring between first study drug intake until 7 days after last permanent study drug stop. *Hypoglycemic event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.
CI, confidence interval; HR, hazard ratio; PY, patient-years.
Presented at the ADA 79th Scientific Session, 2019, San Francisco, CA, USA.

# Summary

- Most CVOTs demonstrate an association between severe hypoglycemia and CV events
- Non-severe hypoglycemia which are frequently undocumented may also have measured effects
- Evidence can be conflicting, with additional confounders and causality contributing to findings



CV, cardiovascular; CVOT, cardiovascular outcomes trial.

# Agenda

| Topic |
| --- |
| Epidemiology of hypoglycemia and CVD |
| Risk of hypoglycemia in large cardiovascular outcomes trials |
| **Hypoglycemia: mediator or marker of CVD risk** |
| Mechanisms of hypoglycemia-induced increased CV risk |

CV, cardiovascular; CVD, cardiovascular disease.

# Is severe hypoglycemia a cause or a marker of increased risk for adverse outcomes?


Zoungas S et al. *N Engl J Med* 2010;363:1410–8.

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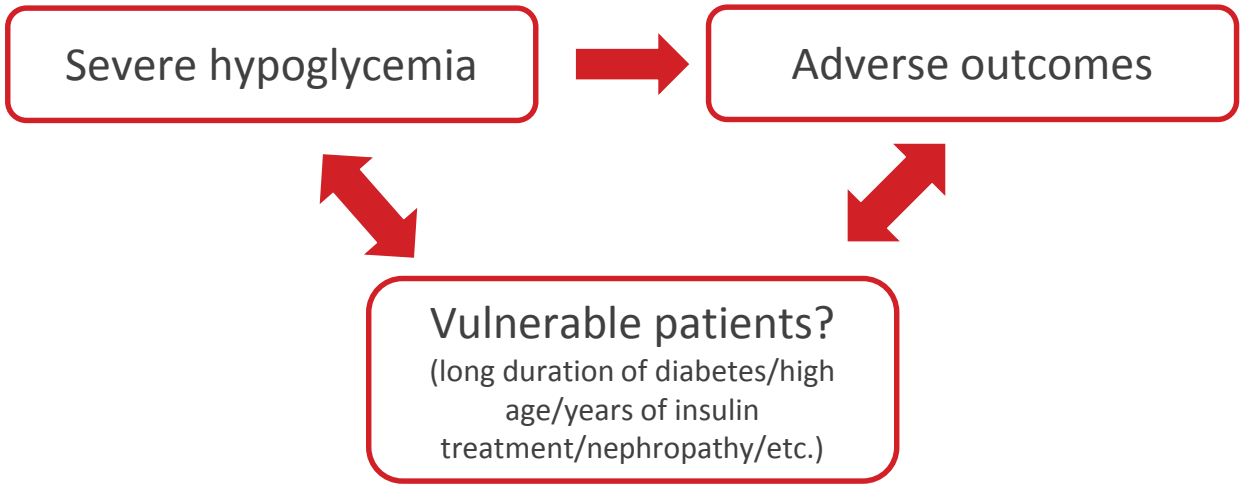
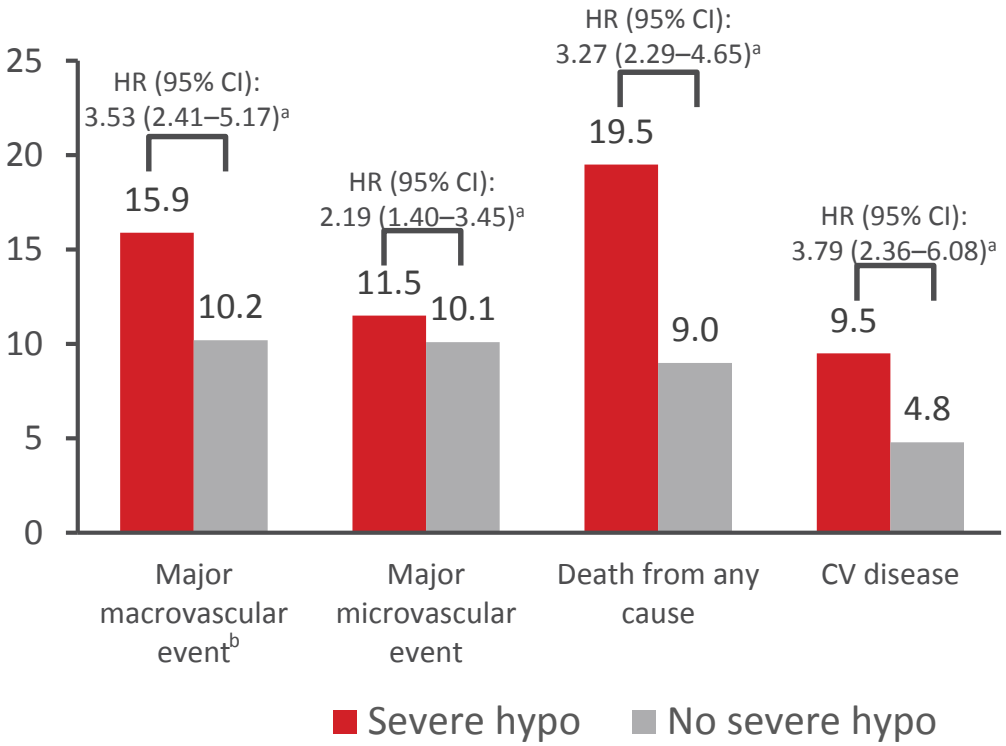



Zoungas S et al. *N Engl J Med* 2010;363:1410–8.

# ADVANCE: severe hypoglycemia is associated with increased risk of adverse outcomes




N=231 patients who had at least one severe hypoglycemia during the 5-year follow-up.
[a]Adjusted for multiple baseline covariates. [b]Primary end points. Major macrovascular event defined as CV death, nonfatal myocardial infarction, or nonfatal stroke; major microvascular event defined as new or worsening nephropathy or retinopathy.
ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; SH, severe hypoglycemia.
Zoungas S et al. *N Engl J Med*. 2010;363:1410–8.

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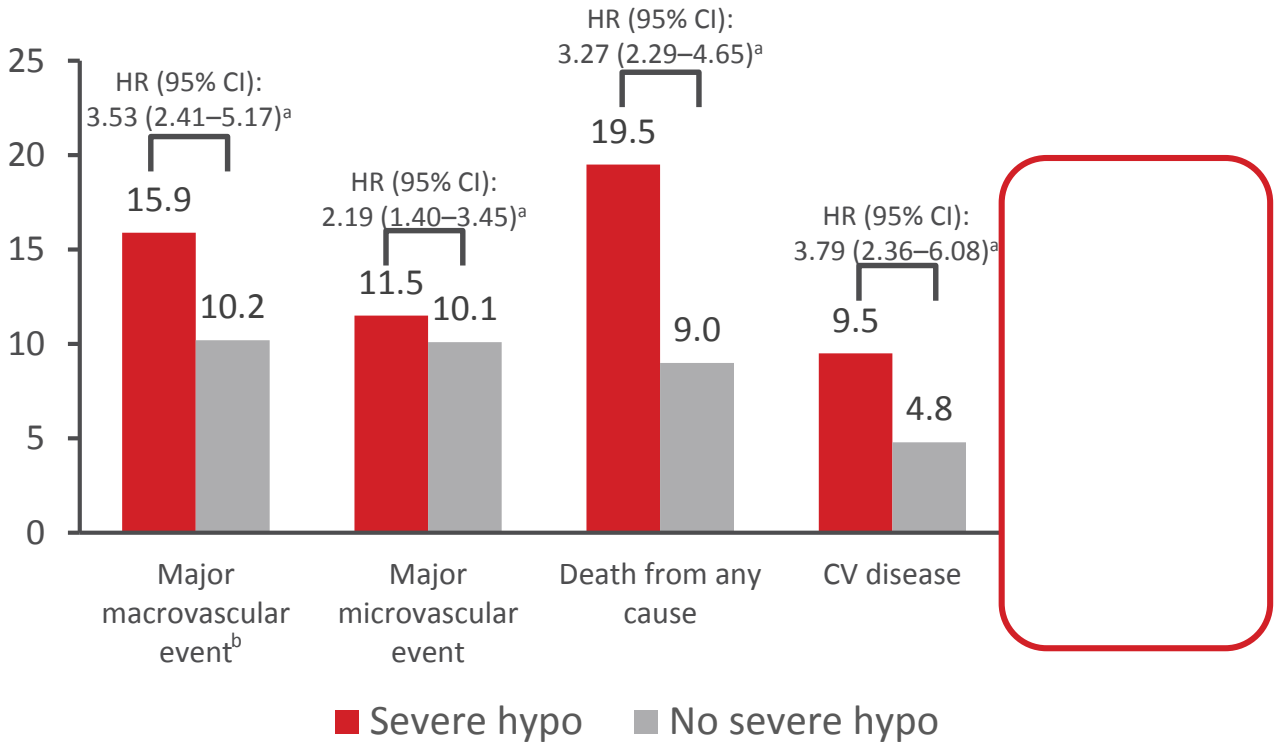


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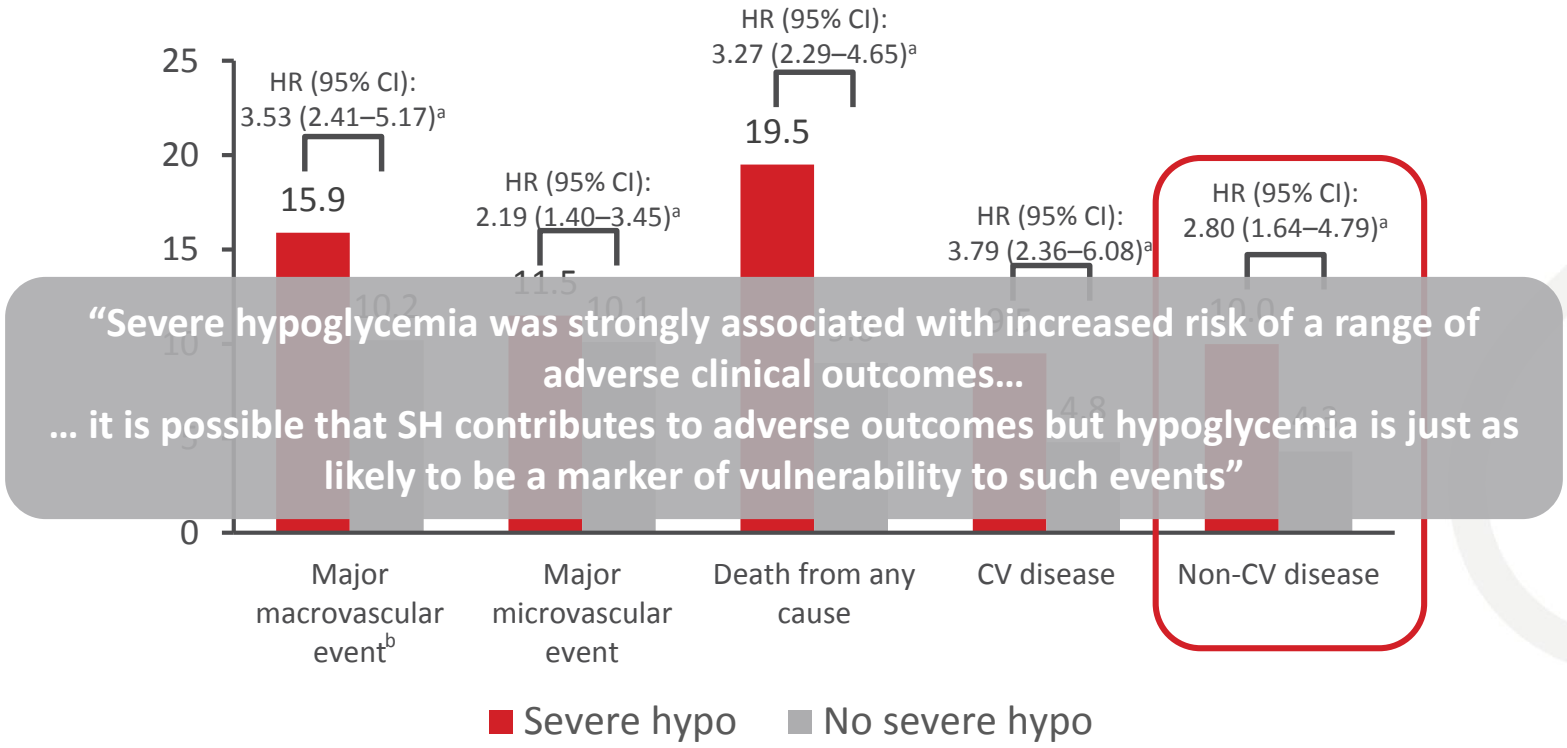
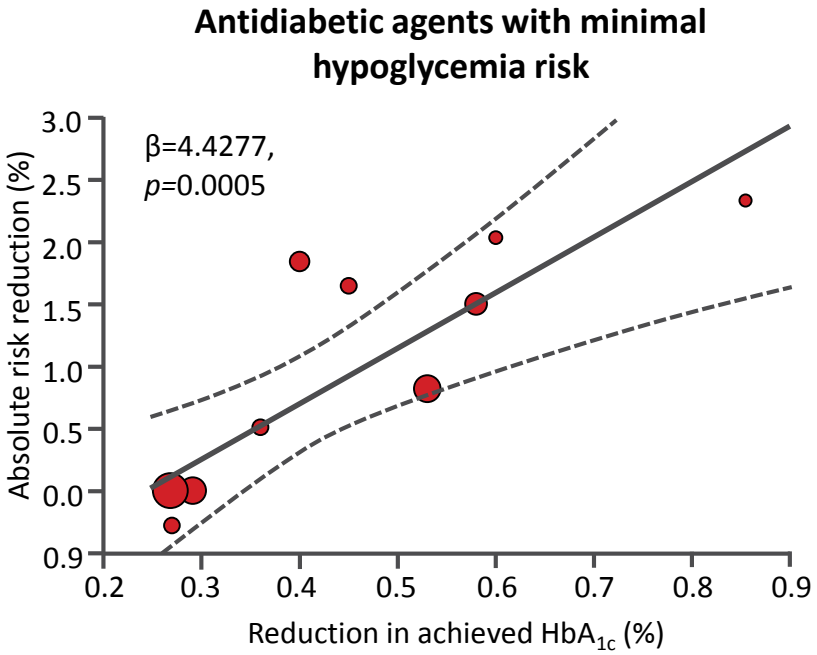
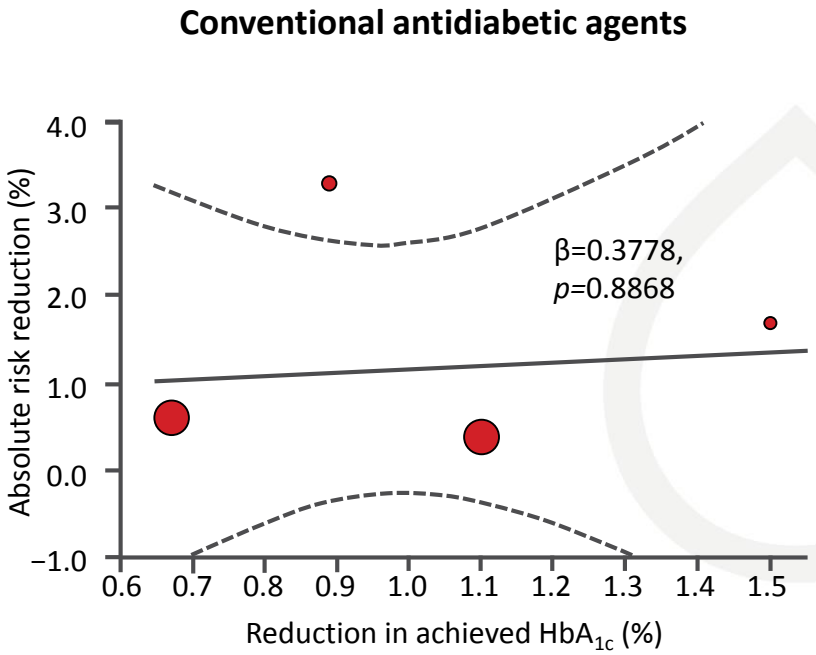



**"Severe hypoglycemia was strongly associated with increased risk of a range of adverse clinical outcomes…**
**… it is possible that SH contributes to adverse outcomes but hypoglycemia is just as likely to be a marker of vulnerability to such events"**

N=231 patients who had at least one severe hypoglycemia during the 5-year follow-up.
[a]Adjusted for multiple baseline covariates. [b]Primary end points. Major macrovascular event defined as CV death, nonfatal myocardial infarction, or nonfatal stroke; major microvascular event defined as new or worsening nephropathy or retinopathy.
ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; SH, severe hypoglycemia.
Zoungas S et al. *N Engl J Med*. 2010;363:1410–8.

# Antidiabetic agents with less hypoglycemic risk reduce the risk of MACE



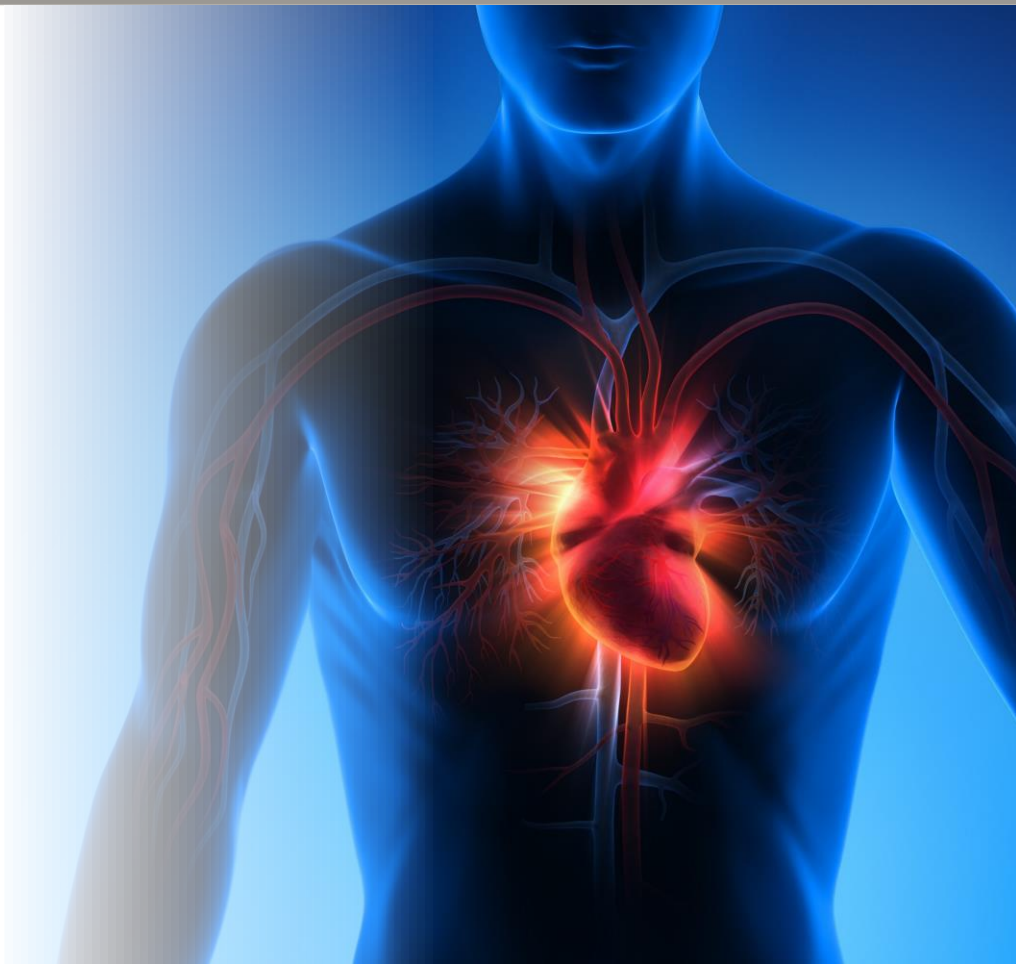

The size of the circle represents the weight of each trial and is inversely proportional to the standard error of the effect estimate. Beta coefficient depicts a change in absolute or relative effect of antihyperglycemic treatment for each 1% difference in achieved $HbA_{1c}$ between intervention and control groups.

$HbA_{1c}$, glycated haemoglobin.

Huang CJ et al. *Diabetes Obes Metab* 2018;20:2131–9.

# Summary

- Severe hypoglycemia:
  - Is associated with increased risk of vascular events
  - Identifies a patient vulnerable to adverse vascular events
  - May cause adverse vascular events
- Less severe hypoglycemia events that are unrecorded may also be contributing to risk
- Recent evidence suggests that antihyperglycemic agents that improve $HbA_{1c}$ with less hypoglycemia risk may confer risk reduction in MACE[1]



MACE, major adverse cardiovascular evemts.

1. Huang CJ et al. *Diabetes Obes Metab* 2018;20:2131–9.

# Agenda

| Topic |
| --- |
| Epidemiology of hypoglycemia and CVD |
| Risk of hypoglycemia in large cardiovascular outcomes trials |
| Hypoglycemia: mediator or marker of CVD risk |
| **Mechanisms of hypoglycemia-induced increased CV risk** |

CV, cardiovascular; CVD, cardiovascular disease.

# Endogenous neurohormonal responses


EEG, electroencephalogram.
Adapted from Frier BM. Impaired hypoglycemia awareness. In: Frier BM, Fisher M, editors, Hypoglycemia in Clinical Diabetes. 2nd edition. John Wiley & Sons, Chichester; 2007. p. 141-70.

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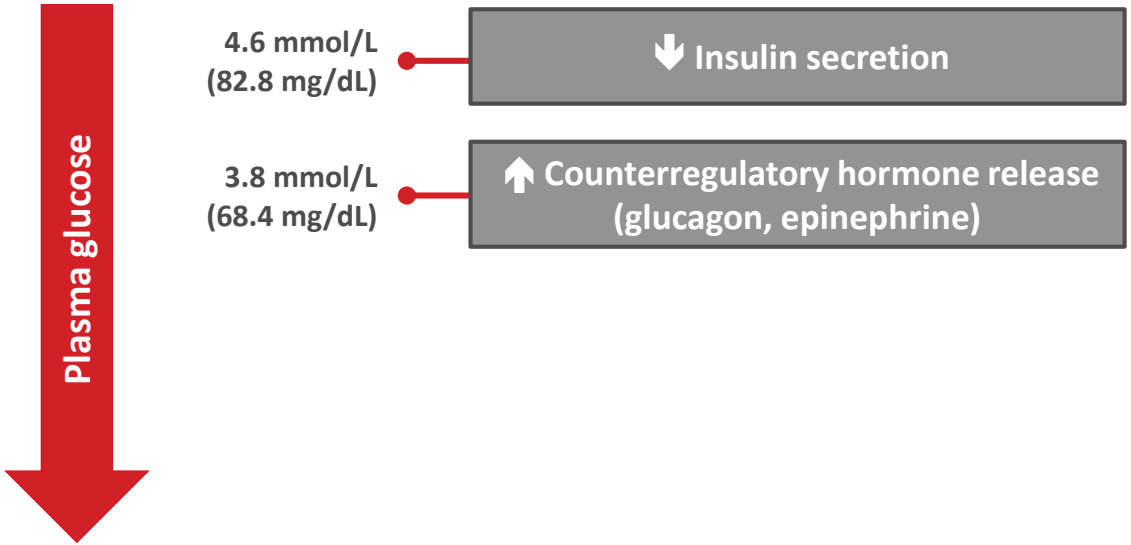


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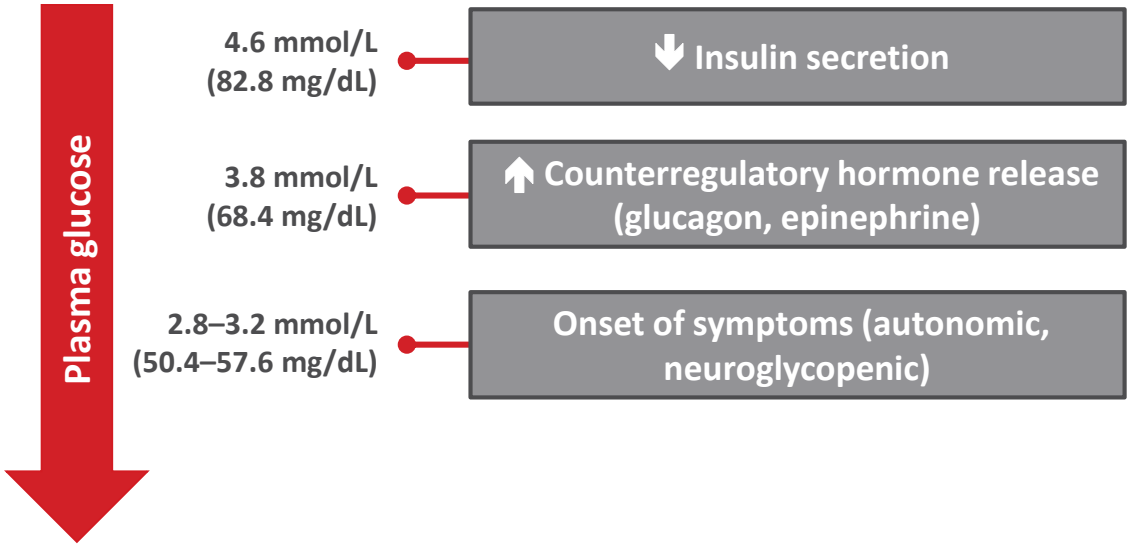


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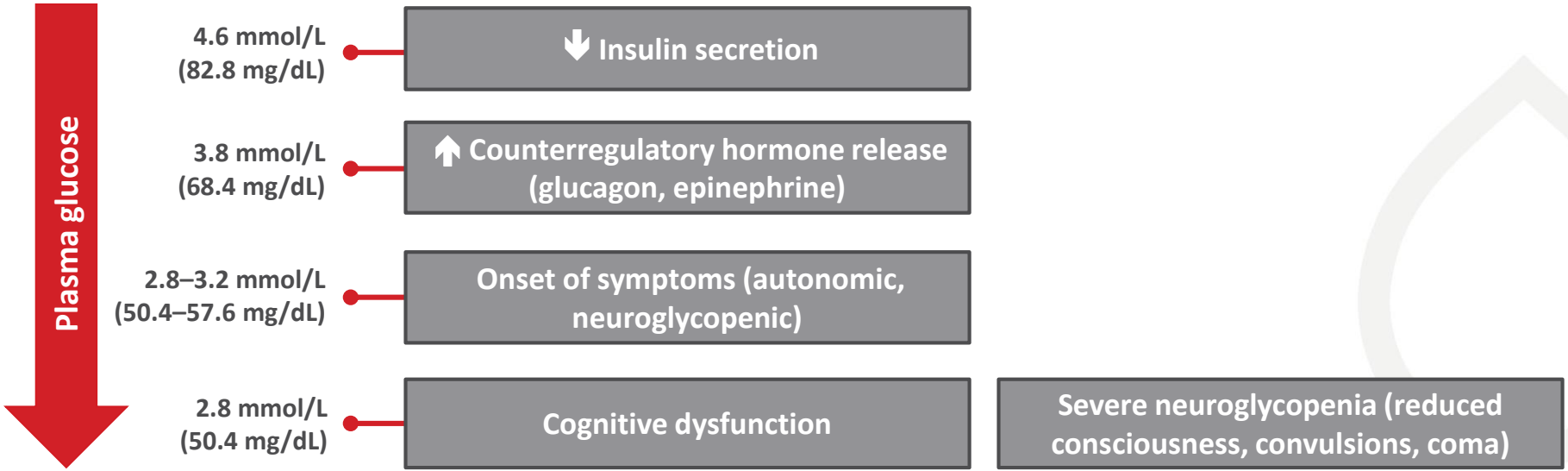


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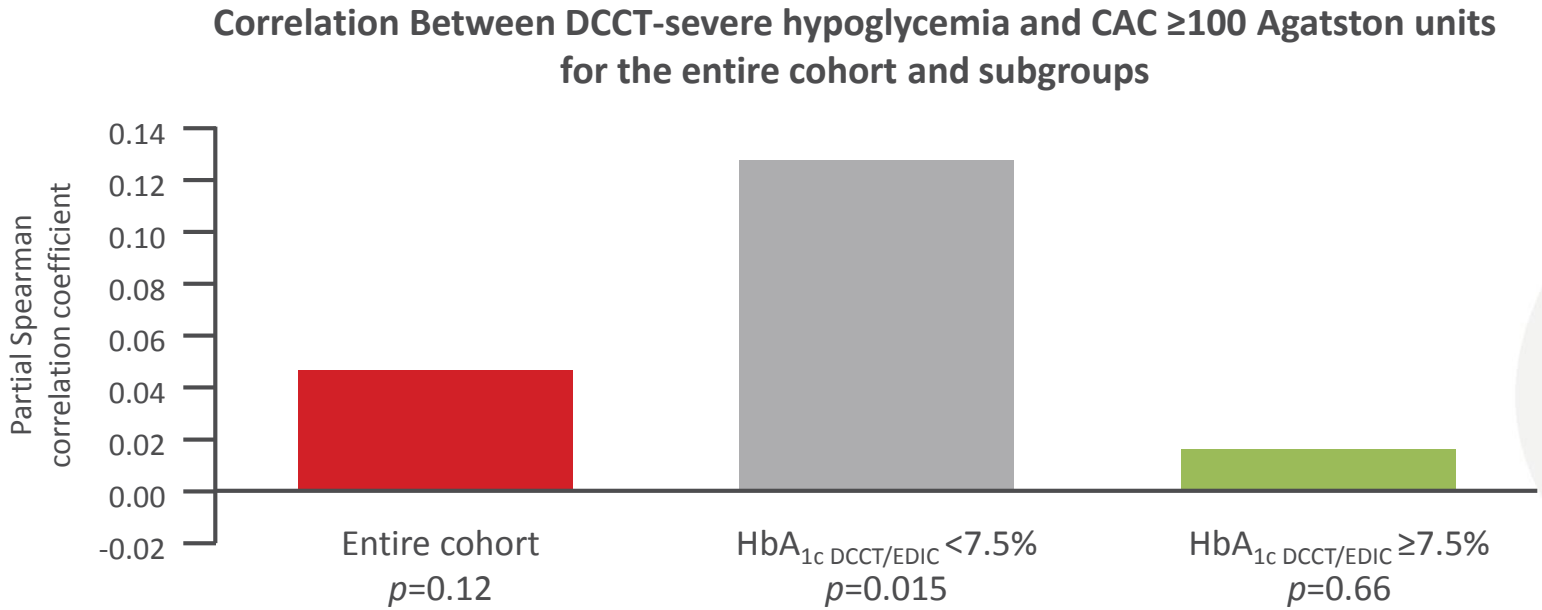
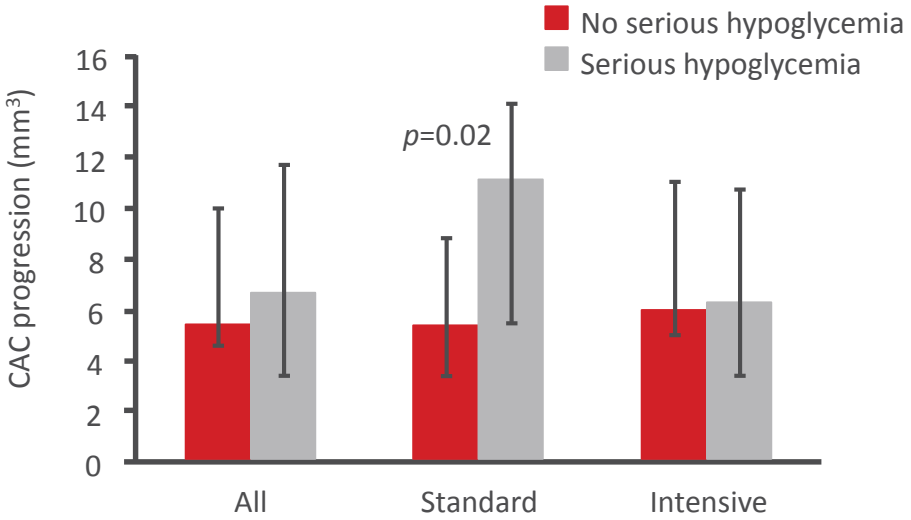
# Severe hypoglycemia and coronary artery calcification in DCCT/EDIC




N=1 205 participants form DCCT/EDIC on whom computed tomography was performed 7–9 years after the end of DCCT was performed.
CAC, coronary artery calcification; DCCT/EIDC, diabetes control and complications trial/epidemiology of diabetes interventions and complications; Entire cohort, entire DCCT-cohort
Fährmann ER et al. *Diabetes Res Clin Pract* 2015;107(2):280–9.

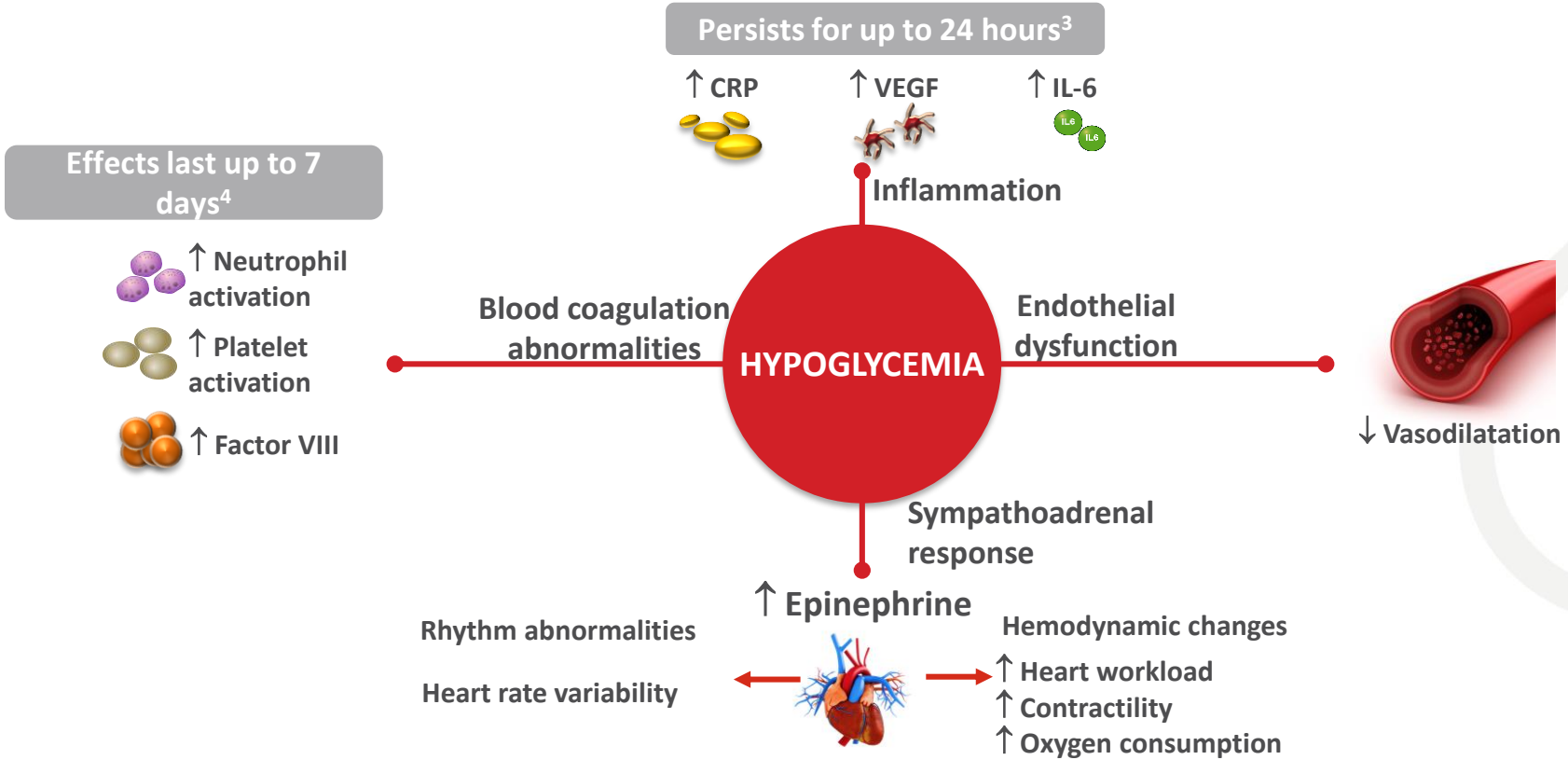
# VADT: serious hypoglycemia and progression of coronary artery calcification




- CT scans measured CAC at baseline and after ~4.5 years
- SH was more common in intensive treatment group (74%) than in standard treatment group (21%)
- In the standard group, CAC progressed (~50%) with SH in a dose-response relationship
- SH was not associated with CAC progression in the intensive group (perhaps because of a suppressed sympathoadrenal response)

N=197 patients (97 with severe hypoglycemia) from the Risk Factors, Atherosclerosis, and Clinical Events in Diabetes substudy of VADT.
CAC, coronary artery calcium; CT, computed tomography; SH, serious hypoglycemia; VADT, Veterans' Affairs Diabetes Trial.
Saremi A et al. *Diabetes Care* 2016:39;448–54.

# Multiple plausible mechanisms can explain how severe hypoglycemia may cause cardiovascular morbidity or mortality

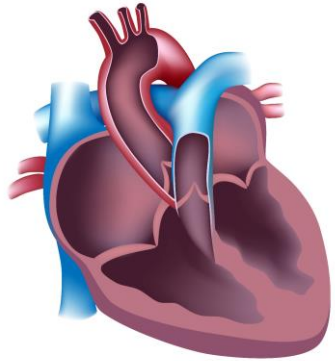



CRP, C-reactive protein; CV, cardiovascular; IL-6, interleukin-6; VEGF, vascular endothelial growth factor.

Adapted from Desouza CV et al. *Diabetes Care* 2010;33:1389–94; 2. Frier BM et al. *Diabetes Care* 2011;34 (Suppl. 2):S132–7; Wright RJ et al. *Diabetes Care* 2010;33:1591–7; Chow EYK et al. *Diabetologia* 2013;56 (Suppl. 1):S243.

# Overall conclusions

- Most data from both observational studies as well as RCTs show an association between severe hypoglycemia and both MACE and mortality

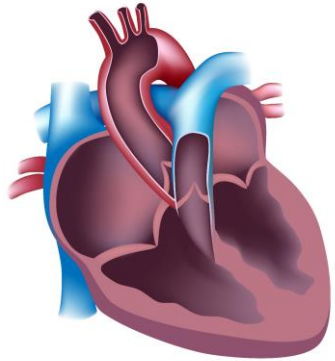



MACE, major adverse cardiovascular events; RCT, randomized controlled trial.

# Overall conclusions

- Most data from both observational studies as well as RCTs show an association between severe hypoglycemia and both MACE and mortality

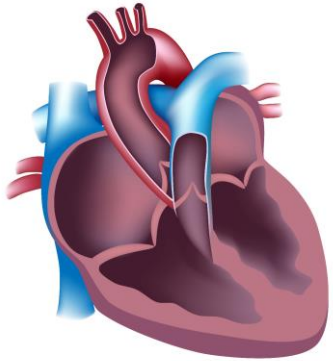
- Severe hypoglycemia may be both a mediator of adverse outcomes as well as a marker of vulnerability to such events




MACE, major adverse cardiovascular events; RCT, randomized controlled trial.

# Overall conclusions

- Most data from both observational studies as well as RCTs show an association between severe hypoglycemia and both MACE and mortality
- Severe hypoglycemia may be both a mediator of adverse outcomes as well as a marker of vulnerability to such events
- Avoidance of severe hypoglycemia must therefore be an important therapeutic goal




MACE, major adverse cardiovascular events; RCT, randomized controlled trial.

## Recuerde, si Usted tiene preguntas para nuestros conferencistas….

**Levante la mano para que recojan su ficha de preguntas**


**Las preguntas se responderán durante el panel de discusión**

# Manejando Riesgo de Hipoglucemia con Nueva Tecnología

**Elizabeth Seaquist, MD, CDE**
Profesora de Medicina y Directora,
División de Endocrinología y Diabetes,
Escuela de Medicina de la Universidad de Minnesota
Minneapolis, EUA

# Disclosures

- Eli Lilly (Advisory Board, Consultant, Research support through grants to UMN)
- Sanofi (Consultant)
- Zucara (Consultant)
- Novo Nordisk (Sponsor of the International Hypoglycemia Study Group of which I am a member)
- MannKind (Consultant)
- American Diabetes Association (Advisor)
- American Board of Internal Medicine Exam Committee (Exam Committee Member)

# Outline

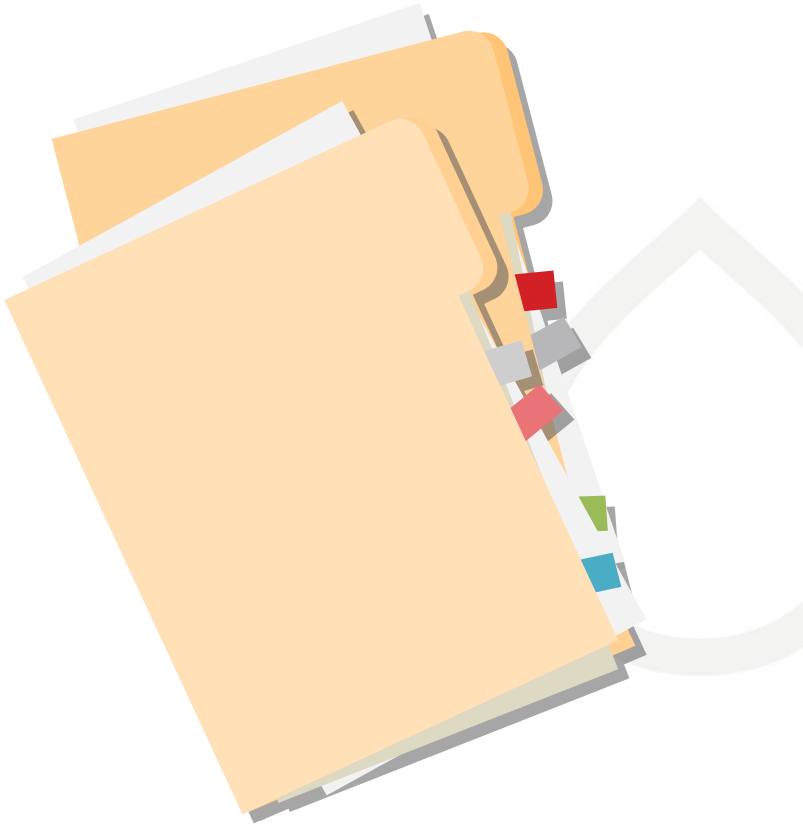
Evidence based methods to reduce hypoglycaemia in patients with diabetes

New technology and impact on hypoglycaemia

Use of new technology to prevent/reverse impaired awareness of hypoglycaemia

# Evidence based methods to reduce hypoglycaemia in T1D

- Structured education program like 5-day DAFNE (Dose Adjusted for Normal Eating) course in UK[1]
- Threshold suspend[2] or hybrid closed loop[3] pumps
- Addition of continuous glucose monitor to existing regimen[4]
- Use degludec instead of IGlar U100 as basal insulin[5]
- Islet transplantation[6]



1. Hopkins D et al. *Diabetes Care* 2012;35:1638–42; 2. Bergenstal RM et al. *N Engl J Med* 2013;369:224–32; 3. Bergenstal RM et al. *J Am Med Assoc* 2016 316:1407–8; 4. Beck RW et al. 2017;317:371–8;
5. Lane W et al. *J Am Med Assoc* 2017;318:33–44; 6. Rickels MR et al. *J Clin Endo Metab* 2016;101:4421–30

# Technology to reduce hypoglycaemia

## Low glucose suspend pump with integrated continuous glucose monitoring

# Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

N ENGL J MED 369;3 NEJM.ORG JULY 18, 2013

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*

- Randomized 247 experienced pump users to sensor augmented pump with or without low glucose suspend feature for 3 months
- $HbA_{1c}$ was the same at the end of the treatment period in both groups (7.24 ± 0.67 vs 7.14 ± 0.77%, suspend vs control)

Bergenstal RM et al. *N Engl J Med* 2013;369:224–32.

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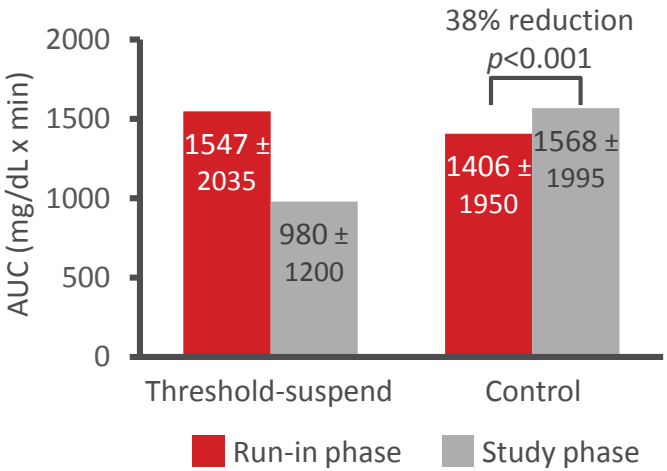
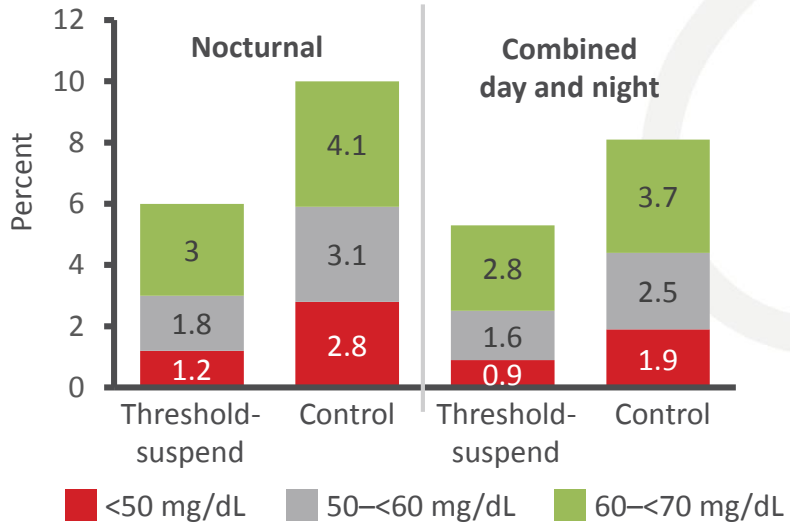
**Mean AUC for nocturnal hypoglycaemia events**




**Sensor glucose <70 mg/dL**




AUC, area under the curve.

Bergenstal RM et al. *N Engl J Med* 2013;369:224–32.

# Technology to reduce hypoglycaemia


Hybrid closed loop system

Automates rate of basal infusion

Requires manual food and correction boluses

## Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes

JAMA October 4, 2016 Volume 316, Number 13

Richard M. Bergenstal, MD
Satish Garg, MD
Stuart A. Weinzimer, MD
Bruce A. Buckingham, MD
Bruce W. Bode, MD
William V. Tamborlane, MD
Francine R. Kaufman, MD

- 124 T1D adults with history of pump use
- Study consisted of 2 week run in period and 3 month treatment period where the first 6 days were used to collect data for the algorithm
- System adjusted algorithm every midnight based on data collected
- System was in closed loop mode for 87.2% of study period
- $HbA_{1c}$ changed from 7.4% to 6.9%

Bergenstal RM et al. *J Am Med Assoc* 2016 316:1407–8.

# Glucose control, insulin usage and weight among patients using hybrid closed-loop systems

| Parameter | Run-in period | Study period |
|---|---|---|
| Sensor glucose, mean (SD) [median], mg/dL | 150.2 (22.7) [150.1] | 150.8 (13.7) [149.9] |
| Percentage of time with glucose level in range, mean (SD); median (IQR) | | |
| Sensor glucose values | | |
| >300 mg/dL | 2.3 (4.2); 1.3 (0.2–2.6) | 1.7 (1.9); 0.9 (0.5–2.1) |
| >180 mg/dL | 27.4 (13.7); 26.7 (16.0–37.2) | 24.5 (9.2); 24.1 (17.3–29.8) |
| 71-180 mg/dL | 66.7 (12.2); 67.8 (59.0–75.1) | 72.2 (8.8); 73.4 (67.7–78.4) |
| ≤70 mg/dL | 5.9 (4.1); 5.2 (3.0–7.6) | 3.3 (2.0); 2.9 (1.7–4.3) |
| ≤50 mg/dL | 1.0 (1.1); 0.6 (0.2–1.3) | 0.6 (0.6); 0.4 (0.2–0.8) |
| Sensor glucose values at night only[a] | | |
| >180 mg/dL | 26.8 (15.2); 26.4 (15.3–35.8) | 21.6 (9.9); 20.6 (13.6–28.5) |
| 71-180 mg/dL | 66.8 (14.0); 67.0 (57.6–75.2) | 75.3 (9.8); 76.4 (69.0–83.1) |
| ≤70 mg/dL | 6.4 (5.3); 5.4 (2.3–8.5) | 3.1 (2.2); 2.6 (1.7–4.2) |

Bergenstal RM et al. *J Am Med Assoc* 2016 316:1407–8.

# Glucose control, insulin usage and weight among patients using hybrid closed-loop systems

| Parameter | Run-in period | Study period |
|---|---|---|
| Sensor glucose, mean (SD) [median], mg/dL | 150.2 (22.7) [150.1] | 150.8 (13.7) [149.9] |
| Percentage of time with glucose level in range, mean (SD); median (IQR) | | |
| Sensor glucose values | | |
| >300 mg/dL | 2.3 (4.2); 1.3 (0.2–2.6) | 1.7 (1.9); 0.9 (0.5–2.1) |
| >180 mg/dL | 27.4 (13.7); 26.7 (16.0–37.2) | 24.5 (9.2); 24.1 (17.3–29.8) |
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Bergenstal RM et al. *J Am Med Assoc* 2016 316:1407–8.

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Bergenstal RM et al. *J Am Med Assoc* 2016 316:1407–8.

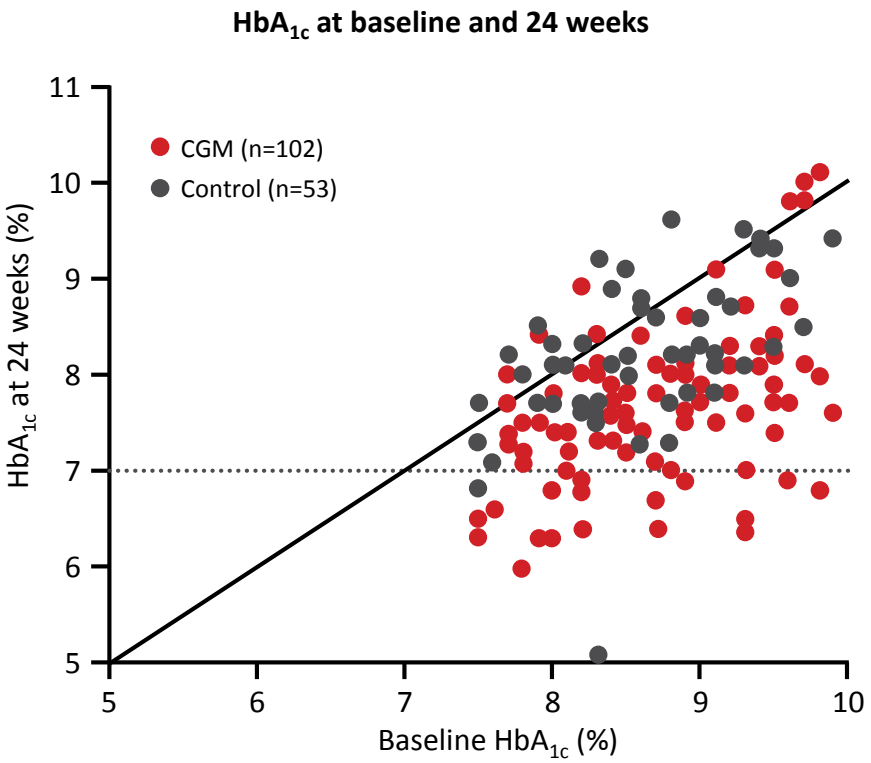
# Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections
## The DIAMOND Randomized Clinical Trial

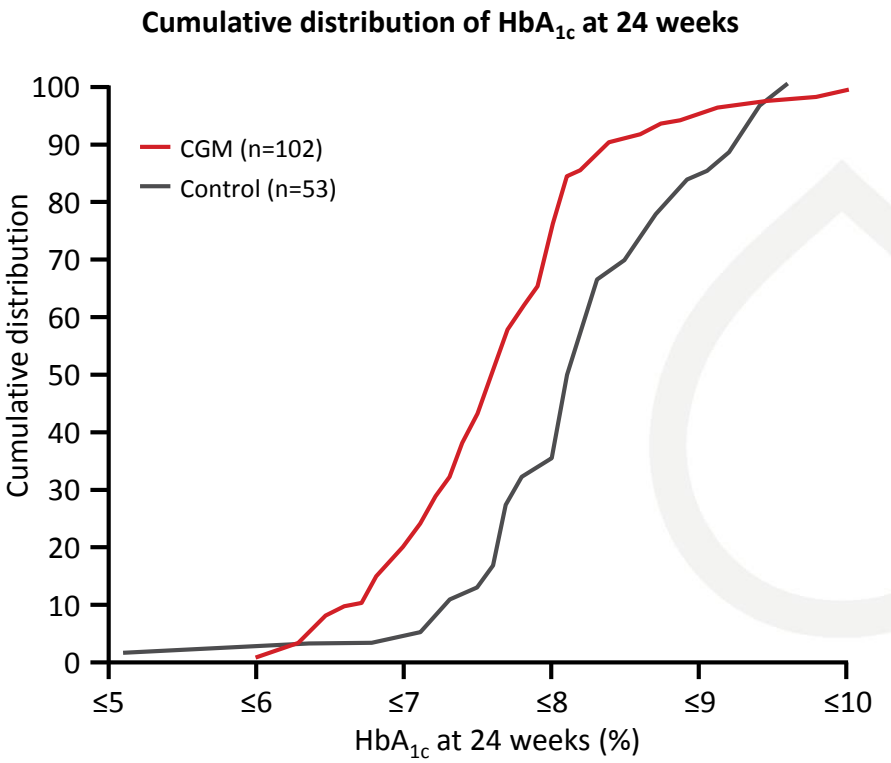
Roy W. Beck, MD, PhD; Tonya Riddlesworth, PhD; Katrina Ruedy, MSPH; Andrew Ahmann, MD; Richard Bergenstal, MD; Stacie Haller, RD, LD, CDE; Craig Kollman, PhD; Davida Kruger, MSN, APN-BC; Janet B. McGill, MD; William Polonsky, PhD; Elena Toschi, MD; Howard Wolpert, MD; David Price, MD; for the DIAMOND Study Group

- Randomized trial done 2014-16 in 24 endocrine practices in US
- Tested the impact of CGM use vs usual care on change in A1c at 24 weeks
- Enrolled adults with T1D using MDI with A1c 7.5-9.9%

CGM, continuous glucose monitoring; MDI, multiple daily injection.
Beck RW et al. 2017;317:371–8

# The DIAMOND randomized clinical trial




CGM, continuous glucose monitoring.

Beck RW et al. 2017;317:371–8

# Continuous glucose monitoring metrics

| | Baseline | | 12 and 24 weeks pooled[a] | | | |
|---|---|---|---|---|---|---|
| | CGM group (n=105) | Control group (n=53) | CGM group (n=103) | Control group (n=53) | Mean adjusted difference (99% CI)[b] | *p*-value[b] |
| Hours of data , mean (SD) | 322 (50) | 325 (51) | 301 (41) | 301 (54) | | |
| **Prespecified secondary outcomes** | | | | | | |
| Glucose variability; coefficient of variation, mean (SD), % | 42 (7) | 42 (7) | 38 (6) | 42 (7) | −4 (−6 to −2) | <0.001 |
| Minutes per day in 70–180 mg/dL range, mean (SD) | 660 (179) | 650 (170) | 736 (206) | 650 (194) | 77 (6 to 147) | 0.005 |
| **Hypoglycemia, median (IQR)** | | | | | | |
| Min per day <70 mg/dL | 65 (33 to 103) | 72 (35 to 136) | 43 (27 to 69) | 80 (36 to 111) | | 0.002 |
| Min per day <60 mg/dL | 32 (15 to 61) | 39 (15 to 78) | 20 (9 to 30) | 40 (16 to 68) | | 0.002 |
| Min per day <50 mg/dL | 13 (5 to 29) | 18 (4 to 39) | 6 (2 to 12) | 20 (4 to 42) | | 0.001 |
| **Hypoglycemia, median (IQR)** | | | | | | |
| Min per day >180 mg/dL | 687 (554 to 810) | 725 (537 to 798) | 638 (503 to 807) | 740 (625 to 854) | | 0.03 |
| Min per day >250 mg/dL | 301 (190 to 401) | 269 (184 to 383) | 223 (128 to 351) | 347 (241 to 429) | | <0.001 |
| Min per day >300 mg/dL | 129 (66 to 201) | 109 (72 to 204) | 78 (36 to 142) | 167 (89 to 226) | | <0.001 |
| **Exploratory outcome** | | | | | | |
| Mean glucose, mean (SD), mg/dL | 187 (27) | 186 (30) | 180 (27) | 189 (25) | −9 (−19 to 0) | 0.01 |
| **Post hoc outcomes, median (IQR)[c]** | | | | | | |
| Area above curve 70 mg/dL | 0.5 (0.3 to 1.1) | 0.7 (0.2 to 1.4) | 0.3 (0.2 to 0.5) | 0.7 (0.2 to 1.3) | | <0.001 |
| Area above curve 180 mg/dL | 34 (25 to 46) | 33 (26 to 45) | 27 (17 to 40) | 40 (31 to 51) | | <0.001 |

CGM, continuous glucose monitoring; IQR, interquartile range. SI conversion: to convert glucose to mmol/L, multiply the values x 0.0555. [a]Excludes 2 participants in CGM group with less than 72 hours of data. [b]Treatment group comparisons made with analysis of covariance models, adjusted for corresponding baseline value, baseline hemoglobin A1c level, and clinical site as a random effect, using pooled data from 12 and 24 weeks. Because of skewed distributions for the hypo- and hyperglycemia metrics (incl. area above the curve 70 mg/dL and area below the curve 180 mg/dL), these models were based on ranks using van der Waerden scores. P<.01 was considered significant to account for multiple comparisons (with 99% CI accordingly provided for the metrics that are approximately normally distributed). [c]Area above the glucose curve 70 mg/dL reflects both percentage and severity of glucose values in the hypoglycemic range. Area under the glucose curve 180 mg/dL is the analogous measure for hyperglycemia.

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# Continuous glucose monitoring metrics

| | Baseline | | 12 and 24 weeks pooled[a] | | | |
|---|---|---|---|---|---|---|
| | CGM group (n=105) | Control group (n=53) | CGM group (n=103) | Control group (n=53) | Mean adjusted difference (99% CI)[b] | *p*-value[b] |
| Hours of data , mean (SD) | 322 (50) | 325 (51) | 301 (41) | 301 (54) | | |
| **Prespecified secondary outcomes** | | | | | | |
| Glucose variability; coefficient of variation, mean (SD), % | 42 (7) | 42 (7) | 38 (6) | 42 (7) | −4 (−6 to −2) | <0.001 |
| Minutes per day in 70–180 mg/dL range, mean (SD) | 660 (179) | 650 (170) | 736 (206) | 650 (194) | 77 (6 to 147) | 0.005 |
| **Hypoglycemia, median (IQR)** | | | | | | |
| Min per day <70 mg/dL | 65 (33 to 103) | 72 (35 to 136) | 43 (27 to 69) | 80 (36 to 111) | | 0.002 |
| Min per day <60 mg/dL | 32 (15 to 61) | 39 (15 to 78) | 20 (9 to 30) | 40 (16 to 68) | | 0.002 |
| Min per day <50 mg/dL | 13 (5 to 29) | 18 (4 to 39) | 6 (2 to 12) | 20 (4 to 42) | | 0.001 |
| **Hypoglycemia, median (IQR)** | | | | | | |
| Min per day >180 mg/dL | 687 (554 to 810) | 725 (537 to 798) | 638 (503 to 807) | 740 (625 to 854) | | 0.03 |
| Min per day >250 mg/dL | 301 (190 to 401) | 269 (184 to 383) | 223 (128 to 351) | 347 (241 to 429) | | <0.001 |
| Min per day >300 mg/dL | 129 (66 to 201) | 109 (72 to 204) | 78 (36 to 142) | 167 (89 to 226) | | <0.001 |
| **Exploratory outcome** | | | | | | |
| Mean glucose, mean (SD), mg/dL | 187 (27) | 186 (30) | 180 (27) | 189 (25) | −9 (−19 to 0) | 0.01 |
| **Post hoc outcomes, median (IQR)[c]** | | | | | | |
| Area above curve 70 mg/dL | 0.5 (0.3 to 1.1) | 0.7 (0.2 to 1.4) | 0.3 (0.2 to 0.5) | 0.7 (0.2 to 1.3) | | <0.001 |
| Area above curve 180 mg/dL | 34 (25 to 46) | 33 (26 to 45) | 27 (17 to 40) | 40 (31 to 51) | | <0.001 |

CGM, continuous glucose monitoring; IQR, interquartile range. SI conversion: to convert glucose to mmol/L, multiply the values x 0.0555. [a]Excludes 2 participants in CGM group with less than 72 hours of data. [b]Treatment group comparisons made with analysis of covariance models, adjusted for corresponding baseline value, baseline hemoglobin A1c level, and clinical site as a random effect, using pooled data from 12 and 24 weeks. Because of skewed distributions for the hypo- and hyperglycemia metrics (incl. area above the curve 70 mg/dL and area below the curve 180 mg/dL), these models were based on ranks using van der Waerden scores. P<.01 was considered significant to account for multiple comparisons (with 99% CI accordingly provided for the metrics that are approximately normally distributed). [c]Area above the glucose curve 70 mg/dL reflects both percentage and severity of glucose values in the hypoglycemic range. Area under the glucose curve 180 mg/dL is the analogous measure for hyperglycemia.

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**Reducing Hypoglycemia in the Real World: A Retrospective Analysis of Predictive Low-Glucose Suspend Technology in an Ambulatory Insulin-Dependent Cohort**

Lars Müller, PhD,[1] Steph Habif, EdD, MS,[2] Scott Leas, BA,[2] and Eliah Aronoff-Spencer, MD, PhD[3]

- Retrospective analysis of low glucose suspend (Tandem IQ) users who uploaded 21+ days of data between 8/31/18-3/14/19
- Group A were experienced pump users who had CGM data before and after starting low glucose suspend pump
- Group B were new pump users without CGM data before low glucose suspend pump was started

CGM, continuous glucose monitoring.

Müller L et al. *Diabetes Technol Ther* 2019;21:478–84.

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Lars Müller, PhD,[1] Steph Habif, EdD, MS,[2] Scott Leas, BA,[2] and Eliah Aronoff-Spencer, MD, PhD[3]

| Cohort demographics | Overall (n=8123) | Subgroup A (n=1371) | Subgroup B (n=3563) |
|---|---|---|---|
| Mean days of use | 65 (±35) | 50 (±19) | 63 |
| Age, mean (SD) | 32.4 (±19) | 33.7 (±20) | 31.9 (±19) |
| Age, range | 6-90 | 9-87 | 6-87 |
| Under 18, n (%) | 2696 (33) | 491 (36) | 1220 (34) |
| 18-60, n (%) | 4729 (58) | 750 (55) | 2054 (58) |
| Over 60, n (%) | 698 (9) | 130 (10) | 289 (8) |
| Female, n (%) | 4211 (52) | 688 (50) | 1851 (52) |
| Type 1, n (%) | 7814 (96) | 1316 (96) | 3455 (97) |
| Type 2, n (%) | 309 (4) | 55 (4) | 108 (3) |

SD, standard deviation.

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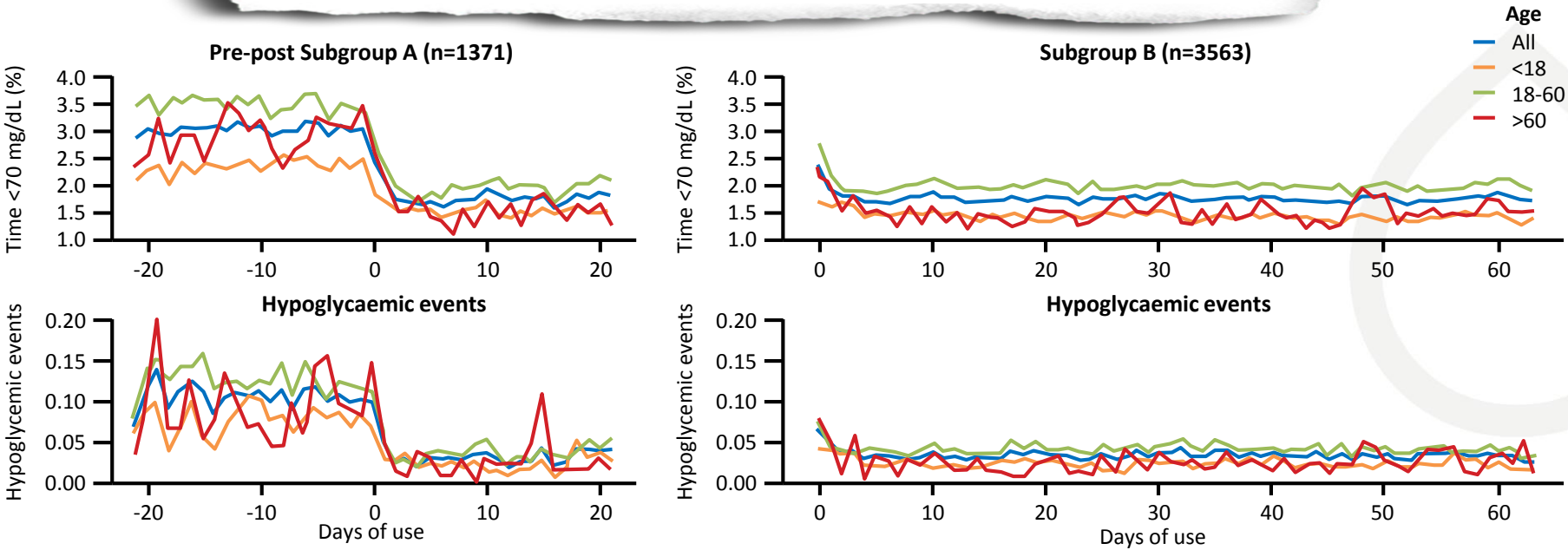



Use of LGS pump significantly reduced time <70 mg/dl (3.9 mmol/l) and number of events with BG <54 mg/dl (3 mmol/l)

LGS, low glucose suspend.

Müller L et al. *Diabetes Technol Ther* 2019;21:478–84.

# Impaired awareness of hypoglycaemia

- Impaired awareness of hypoglycaemia:[1,2,3]
  - Affects 20-25% with T1D and <10% with insulin-treated T2D[4]
  - Increases risk of severe hypoglycaemia up to 6-fold[1-3]
  - May result from >2/week hypoglycaemic events[5]

May be reversed by scrupulous avoidance of hypoglycaemia[6]

1. Gold AE et al. *Diabetes Care* 1994;17:697–703; 2. Geddes J et al. *Diabetic Med* 2008;25:501–4; 3. Pramming S et al. *Diabetic Med* 1991;8:217–22; 4. Schopman JE et al. *Diab Res Clin Pract* 2010;87:64–8; 5. Riddell M. Emerging complications: hypoglycemia/autonomic neuropathy (slide presentation); 6. Cryer PE. *Diabetes* 2011;60:24–7.

# Recovery of Hypoglycemia Awareness in T1DM: Multicenter 2 x 2 RCT comparing insulin pumps vs insulin injections, meter vs continuous glucose monitor

- 24 week study of 97 C-peptide negative patients with documented IAH
- Primary endpoint was difference in hypoglycemia unawareness as measured by Gold score
- All underwent standardized education session at baseline emphasizing:
  - Never delay treatment of hypoglycemia
  - Recognize personalized times of increased risk
  - Detect subtle symptoms
  - Confirm low blood glucose values by regular testing
- All given bolus calculator that accepted blood glucose transmissions
- Had same number of study visits and weekly phone calls

IAH, impaired awareness of hypoglycemia.
Little SA et al. *Diabetes Care* 2017;37:2114–22.

# Demographic and clinical characteristics at baseline

| | | Insulin comparison | | Monitoring comparison | |
|---|---|---|---|---|---|
| | All | MDI | CSII | SMBG | RT |
| **Site** | | | | | |
| Bournemouth | 16 (17) | 8 (16) | 8 (17) | 7 (15) | 9 (19) |
| Cambridge | 21 (22) | 11 (22) | 10 (22) | 11 (23) | 10 (21) |
| Newcastle | 22 (23) | 12 (24) | 10 (22) | 11 (23) | 11 (23) |
| Plymouth | 17 (18) | 10 (20) | 7 (15) | 9 (19) | 8 (17) |
| Sheffield | 20 (21) | 9 (18) | 11 (24) | 10 (21) | 10 (21) |
| **Baseline $HbA_{1c}$** | | | | | |
| <8% | 41 (43) | 22 (44) | 19 (41) | 21 (44) | 20 (42) |
| ≥8% | 55 (57) | 28 (56) | 27 (59) | 27 (56) | 28 (58) |
| $HbA_{1c}$ (%) | 8.2 ± 1.2 | 8.2 ± 1.3 | 8.2 ± 1.2 | 8.3 ± 1.3 | 8.2 ± 1.1 |
| $HbA_{1c}$ (mmol/mol) | 66 ± 12 | 66 ± 13 | 66 ± 12 | 67 ± 13 | 66 ± 11 |
| Age (years) | 48.6 ± 12.2 | 47.0 ± 12.3 | 50.3 ± 12.0 | 47.1 ± 11.8 | 50.1 ± 12.6 |
| Male | 35 (36) | 16 (32) | 19 (41) | 20 (42) | 15 (31) |
| Diabetes duration (years) | 28.9 ± 12.3 | 29.5 ± 12.5 | 28.2 ± 12.2 | 26.7 ± 12.1 | 31.0 ± 12.2 |
| Body weight (kg) | 74.7 ± 14.2 | 74.9 ± 13.9 | 74.5 ± 14.6 | 74.5 ± 14.6 | 75.0 ± 13.9 |
| BMI ($kg/m^2$) | 26.5 ± 4.4 | 26.7 ± 4.6 | 26.3 ± 4.4 | 26.1 ± 4.3 | 26.9 ± 4.7 |
| Insulin dose (units/kg/24 h) | 0.64 ± 0.23 | 0.63 ± 0.21 | 0.66 ± 0.26 | 0.61 ± 0.19 | 0.68 ± 0.27 |

- Annualized rate of severe hypoglycemia over preceding 6 months was 8.9/pt year
- 97% were on injections at baseline
- In injection group, glargine given at hs with second dose given in AM if evening BG >126 mg/dL (7.0 mmol/L)
- 68% had bid dosing at 24 weeks
- Blinded CGM worn for 7 days before each study visit

BG, blood glucose; CGM, continuous glucose monitoring.

Little SA et al. *Diabetes Care* 2017;37:2114–22.

# Hypoglycaemia awareness, severe hypoglycaemia, and PROs

| | Insulin comparison | | | Monitoring comparison | | |
|---|---|---|---|---|---|---|
| | MDI | CSII | *p*-value | SMBG | RT | *p*-value |
| **SH** | | | | | | |
| Annualized rate | 1.0 ± 2.1<br>0 [0–0] (n=47) | 0.6 ± 1.7<br>0 [0–0] (n=43) | 0.34 | 0.9 ± 2.1<br>0 [0–0] (n=44) | 0.8 ± 1.8<br>0 [0–0] (n=46) | 0.95<br>0.92 |
| Proportion affected (%) | 23 (n=47) | 16 (n=43) | 0.399 | 21 (n=44) | 20 (n=46) | 0.92 |
| **IAH** | | | | | | |
| Gold | 4 [3–5]<br>(2–7)<br>4.1 ± 1.6 (n=45) | 4 [3–5.5]<br>(1–7)<br>4.2 ± 1.7 (n=40) | 0.756 | 4 [3–5]<br>(1–7)<br>4.3 ± 1.6 (n=42) | 4 [3–6]<br>(1–7)<br>4.0 ± 1.7 (n=43) | 0.42 |
| Clarke | 4 [2–5]<br>(0–7)<br>3.3 ± 1.8 (n=41) | 3 [2–4]<br>(0–6)<br>3.0 ± 1.6 (n=39) | 0.305 | 3 [2–4]<br>(0–6)<br>3.3 ± 1.6 (n=39) | 3 [2–4]<br>(0–7)<br>3.1 ± 1.8 (n=41) | 0.83 |
| HypoA-Q | 9 [5.5–12]<br>(0–19)<br>8.9 ± 4.3 (n=44) | 10 [6–12.5]<br>(0–18)<br>9.4 ± 4.2 (n=40) | 0.601 | 10 [5–12]<br>(0–16)<br>9.2 ± 4.1 (n=40) | 9 [6–12]<br>(3–14)<br>9.0 ± 4.4 (n=44) | 0.83 |

- No differences found in primary endpoint between injection vs pump or meter vs continuous glucose monitor
- Both groups had a 8 unit reduction in total daily insulin dose by 24 weeks
- Higher satisfaction scores in pump group

CSII, continuous subcutaneous insulin infusion; IAH, impaired awareness of hypoglycaemia; MDI, multiple daily injections; PRO, patient-reported outcomes; RT, real-time; SH, severe hypoglycemia; SMBG, self-measured blood glucose.

Little SA et al. *Diabetes Care* 2017;37:2114–22.

*Bosi E, Choudhary P, de Valk HW, et al; SMILE Study Group.* ***Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial.*** *Lancet Diabetes Endocrinol. 2019;7:462-72.*

- 24 weeks multicenter randomized trial comparing Medtronic 670 g pump with CGM and suspend before low technology or CSII without CGM
- Subjects selected because of severe hypoglycaemia or Clarke score >4 in last 12 months
- 24-75 years, $HbA_{1c}$ 5.8–10%, no CSII for 6 months and no CGM for 3 months
- Completed 2 week run-in period
- Primary outcome was BG <3.1 mmol/L (55 mg/dL) for 20+ min

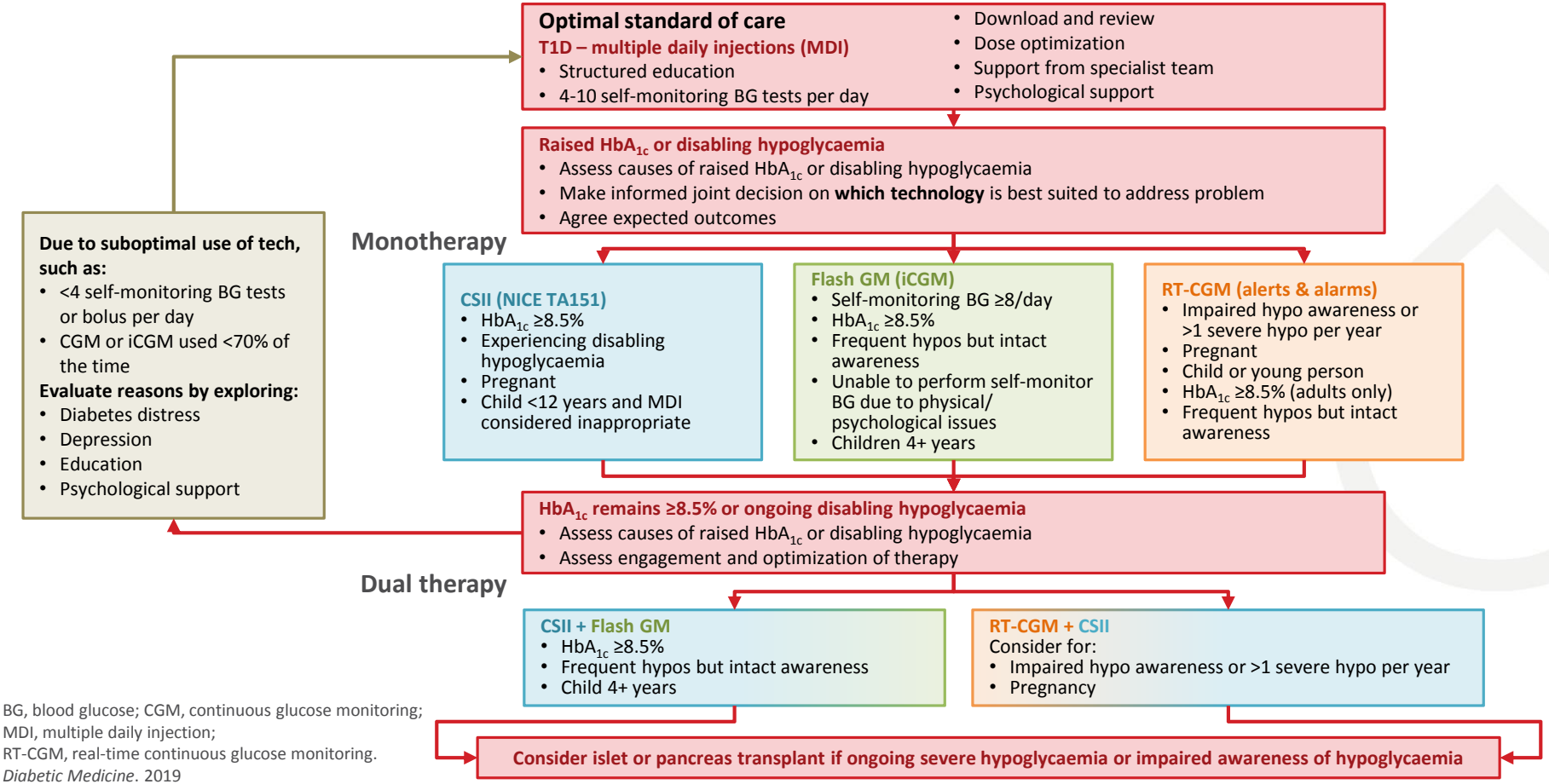
BG, blood glucose; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion.
Bosi E et al. *Lancet Diabetes Endocrinol* 2019;7:462–72.

Bosi E, Choudhary P, de Valk HW, et al; SMILE Study Group. ***Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial.*** *Lancet Diabetes Endocrinol. 2019;7:462-72.*

| **Insulin pumps with continuous glucose monitoring and suspend-before-low (CGM-SBL) technology vs pumps without CGM-SBL in high-risk T1D†** | | | | |
|---|---|---|---|---|
| **Outcomes** | **Pumps with CGM-SBL** | **Pumps without CGM-SBL** | **Difference (95% CI)** | ***p*-values** |
| Mean sensor hypoglycaemic events‡/week§ | 1.1 | 4.1 | -2.9 (-3.5 to -2.3)‖ | <0.001 |
| Time in target glucose range 70 to 180 mg/dL (3.9 to 10.0 mmol/L), %/d§ | 60% | 58% | 2.7% (0.0 to 5.4)‖ | 0.047 |
| Mean change in $HbA_{1c}$ at 24 weeks | -0.16% | -0.25% | 0.09% | 0.44 |
| Severe hypoglycemic events/100 pt-yr¶ | 8.5 | 52 | Not reported | 0.004 |

†Hb, hemoglobin; ‡Glucose ≤55 mg/dL (≤3.1 mmol/L) for >20 consecutive minutes; §Assessed over 3 two-week periods (10 to 12 weeks, 16 to 18 weeks, 22 to 24 weeks); ‖Estimated treatment effect based on repeated-measures model; ¶3.9% vs 13% of patients with ≥1 severe hypoglycemic event (P=0.079).
CGM, continuous glucose monitoring.
Bosi E et al. *Lancet Diabetes Endocrinol* 2019;7:462–72.

# Diabetes UK: Type 1 diabetes technology pathway




BG, blood glucose; CGM, continuous glucose monitoring;
MDI, multiple daily injection;
RT-CGM, real-time continuous glucose monitoring.
*Diabetic Medicine*. 2019

## Recuerde, si Usted tiene preguntas para nuestros conferencistas….

**Levante la mano para que recojan su ficha de preguntas**


**Las preguntas se responderán durante el panel de discusión**

# Panel P&R

Pablo Aschner, MD, MSc
Simon Heller, BA, MB, Bchir, DM, FRCP
Lawrence Leiter, MD, FRCPC, FACP, FACE, FAHA
Elizabeth Seaquist, MD, CDE

# Si Usted desea hacer una pregunta a nuestros conferencistas ….

1 **Use el micrófono**


2 **Llene la ficha de preguntas**


**Un resumen de todas las P&R estará disponible en IHSGonline.com después de la reunión**

# Comentarios finales

**Pablo Aschner, MD, MSc**
Profesor Asociado de Endocrinología,
Escuela de Medicina de la Universidad Javeriana
Asesor de investigaciones, Hospital Universitario San Ignacio
Director Científico, Asociación Colombiana de Diabetes
Bogotá, Colombia

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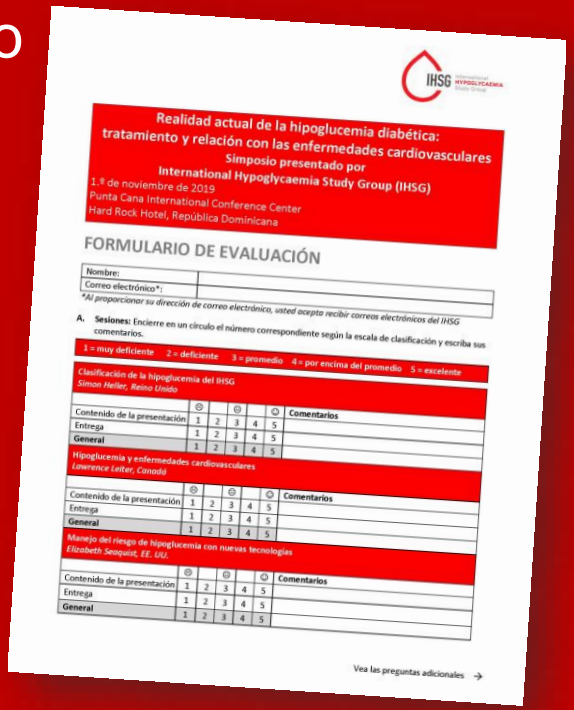

Realidad actual de la hipoglucemia diabética: tratamiento y relación con las enfermedades cardiovasculares
Simposio presentado por
International Hypoglycaemia Study Group (IHSG)
1.º de noviembre de 2019
Punta Cana International Conference Center
Hard Rock Hotel, República Dominicana

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Clasificación de la hipoglucemia del IHSG
*Simon Heller, Reino Unido*

| | ☹ | | 😐 | | ☺ | Comentarios |
|---|---|---|---|---|---|---|
| Contenido de la presentación | 1 | 2 | 3 | 4 | 5 | |
| Entrega | 1 | 2 | 3 | 4 | 5 | |
| General | 1 | 2 | 3 | 4 | 5 | |

Hipoglucemia y enfermedades cardiovasculares
*Lawrence Leiter, Canadá*

| | ☹ | | 😐 | | ☺ | Comentarios |
|---|---|---|---|---|---|---|
| Contenido de la presentación | 1 | 2 | 3 | 4 | 5 | |
| Entrega | 1 | 2 | 3 | 4 | 5 | |
| General | 1 | 2 | 3 | 4 | 5 | |

Manejo del riesgo de hipoglucemia con nuevas tecnologías
*Elizabeth Seaquist, EE. UU.*

| | ☹ | | 😐 | | ☺ | Comentarios |
|---|---|---|---|---|---|---|
| Contenido de la presentación | 1 | 2 | 3 | 4 | 5 | |
| Entrega | 1 | 2 | 3 | 4 | 5 | |
| General | 1 | 2 | 3 | 4 | 5 | |

Vea las preguntas adicionales →

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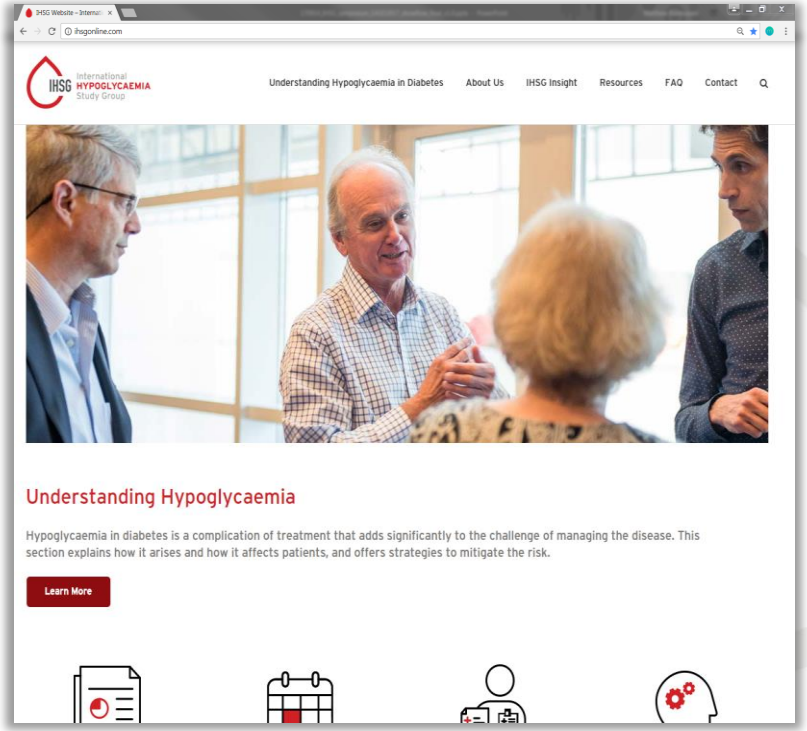


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Traducciones al Español, Francés, Hindi, Mandarin y Árabe de:

- Módulo III – Reconocimiento alterado
- Module IV – ECV

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¡Gracias!

# Hipoglucemia Diabética al día de hoy: Manejo y conecciones con ECV

Un evento exclusivo del Grupo Internacional para el Estudio de la hipoglucemia (IHSG)
En el Congreso de la Asociación Latinoamericana de Diabetes 2019

1 Noviembre 2019

Punta Cana, República Dominicana

Traído para Usted por miembros del International Hypoglycaemia Study Group

IHSG