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Clinical Relevance of Recent Insights in Hypoglycaemia

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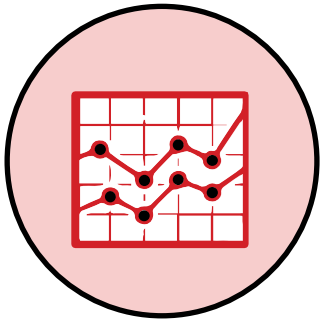
DUTCH DIABETES ACADEMY 1-12-2020

DISCLOSURES 2020
BASTIAAN DE GALAN

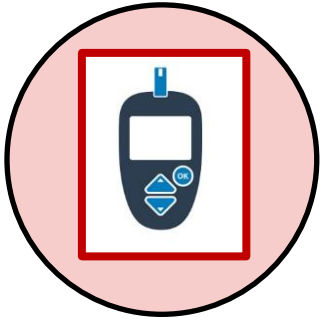
Voor bijeenkomst mogelijk relevante relaties:	Bedrijfsnamen
Sponsoring of onderzoeksgeld	• **Novo Nordisk**
Honorarium of andere (financiële) vergoeding	• **Nee**
Aandeelhouder	• **Nee**
Andere relatie, namelijk …	**Nee**

Why Hypoglycaemia Matters



Hypoglycaemia remains a common and inevitable risk of insulin (release enhancing) therapy

Hypoglycaemia is an under-recognized problem that deserves increased awareness

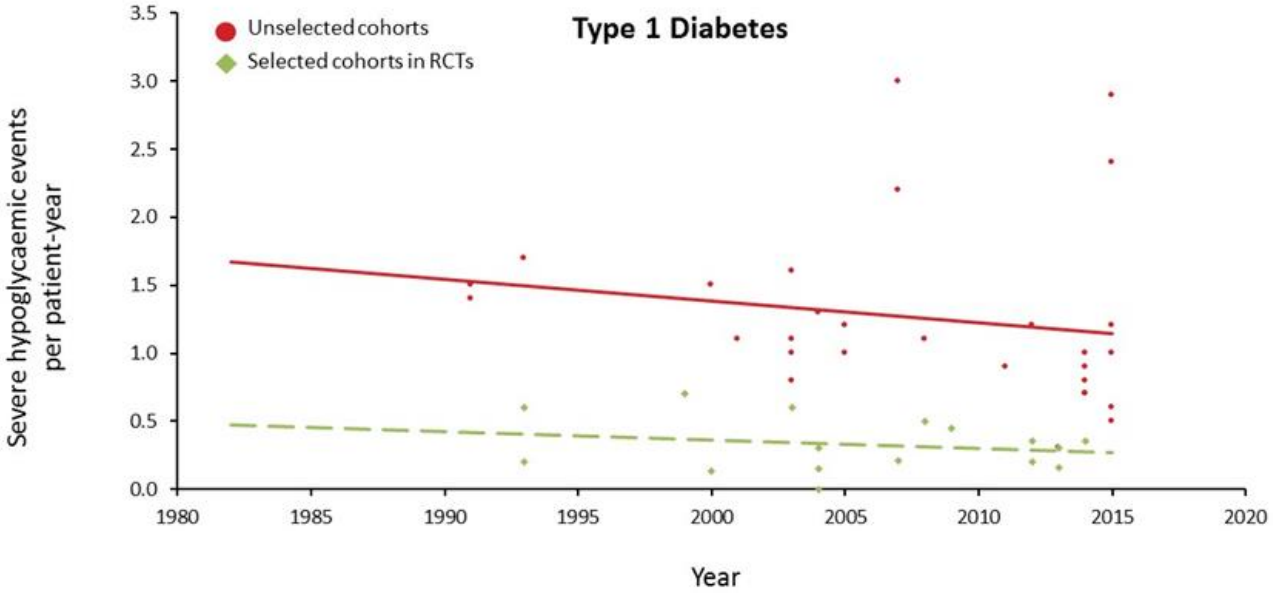


Fear and avoidance of hypoglycaemia may impair good glucose control

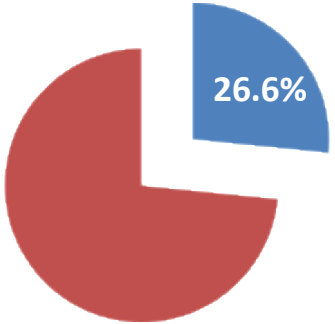
There is a lack of understanding by both professionals and patients

A better understanding can reduce its frequency and improve patient quality of life

Severe Hypoglycaemia (and IAH) in Type 1 Diabetes



Impaired awareness of hypoglycaemia in T1D (n=3293)



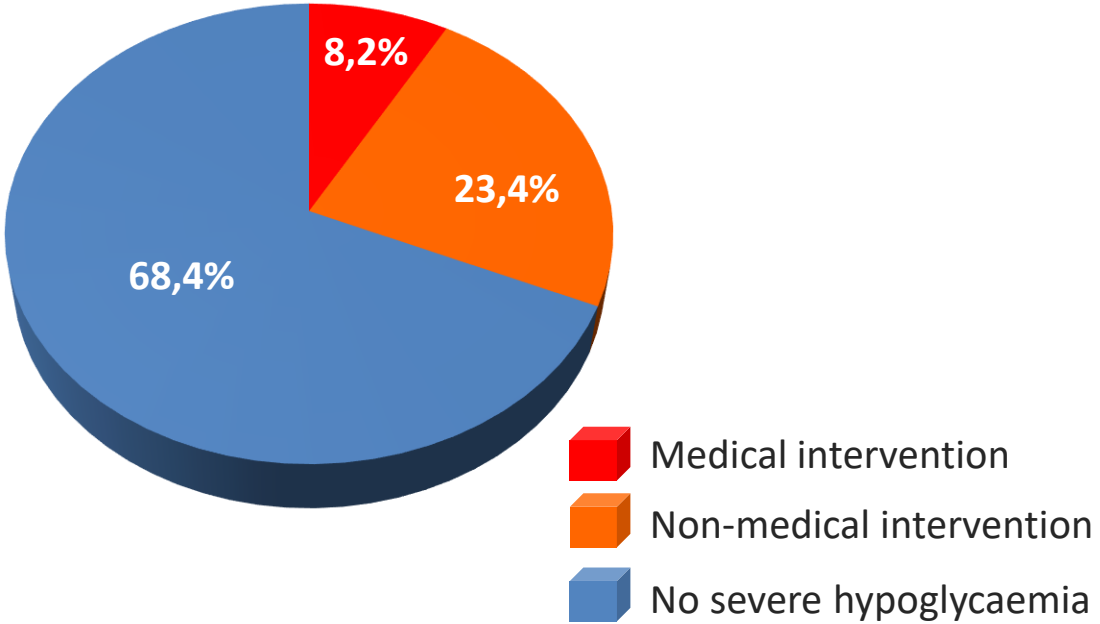
Pedersen-Bjergaard & Thorsteinsson, Curr Diab Rep 2017

Severe Hypoglycaemia in Type 2 Diabetes

Dutch Diabetes Pearl Cohort

- 7 Centres across the Netherlands
- 2350 People with type 2 diabetes on ≥1 dose of insulin
  - Basal only: 478 (20.3%)
  - Premixed: 423 (18.0%)
  - Basal-bolus: 1446 (61.5%)

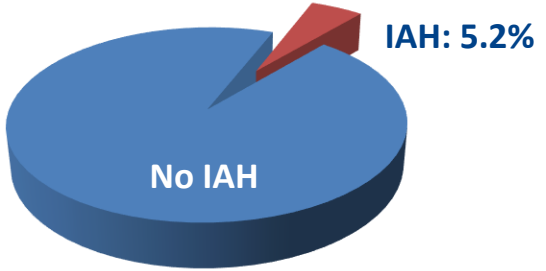
Severe hypoglycaemia in the past year



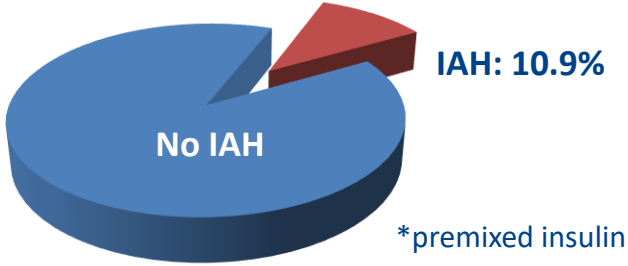
van Meijel et al., BMJ Open Diabetes Res Care 2020

Impaired awareness of hypoglycaemia in Type 2 Diabetes (n=2350)
the Dutch Diabetes Pearl Cohort

Basal only (n=478)



Complex regimen* (n=1869)



*premixed insulin or basal-bolus regimen

van Meijel et al., BMJ Open Diabetes Res Care 2020

Symptoms of hypoglycaemia that can be misinterpreted in the elderly:

- Light-headedness (heart failure, hypotension)
- Weakness, fatique (age, adverse drug effect)
- Unsteadiness (neurological condition)

Zammitt & Frier, Diabetes Care 2005;28:2948-61

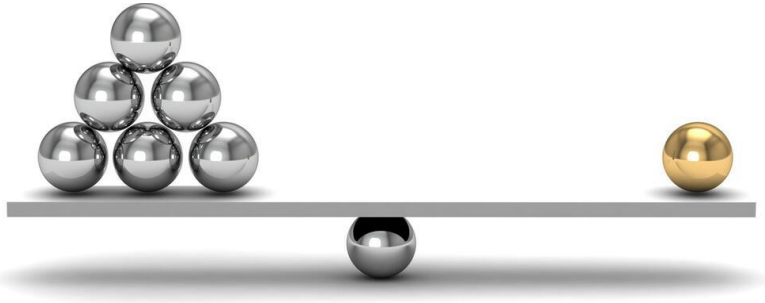
Treatment Options to Reduce the Risk of Hypoglycaemia

Insulin therapy

Other pharmacotherapy

Education

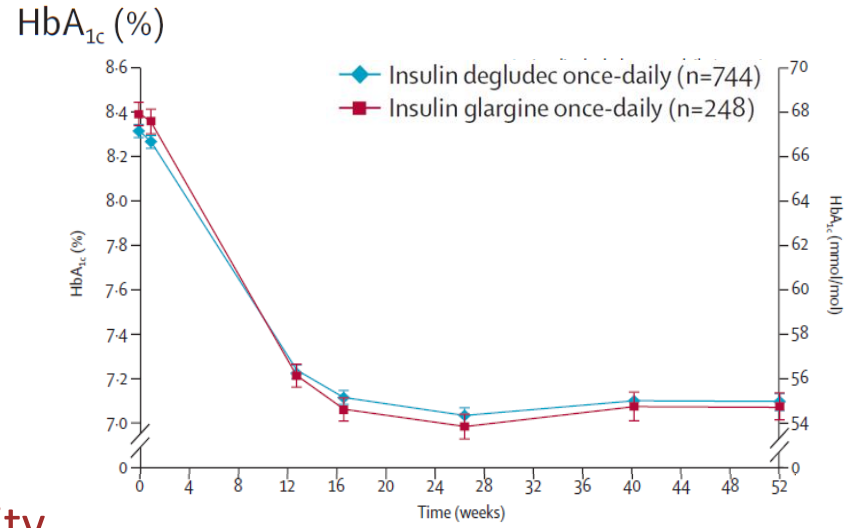
Technology



Treat-to-target in (clinical) trials

Basal insulins were systematically titrated with a treat-to-target approach to a self-measured plasma glucose concentration (SMPG) before breakfast of 3·9–<5·0 mmol/L (see appendix for details). On the

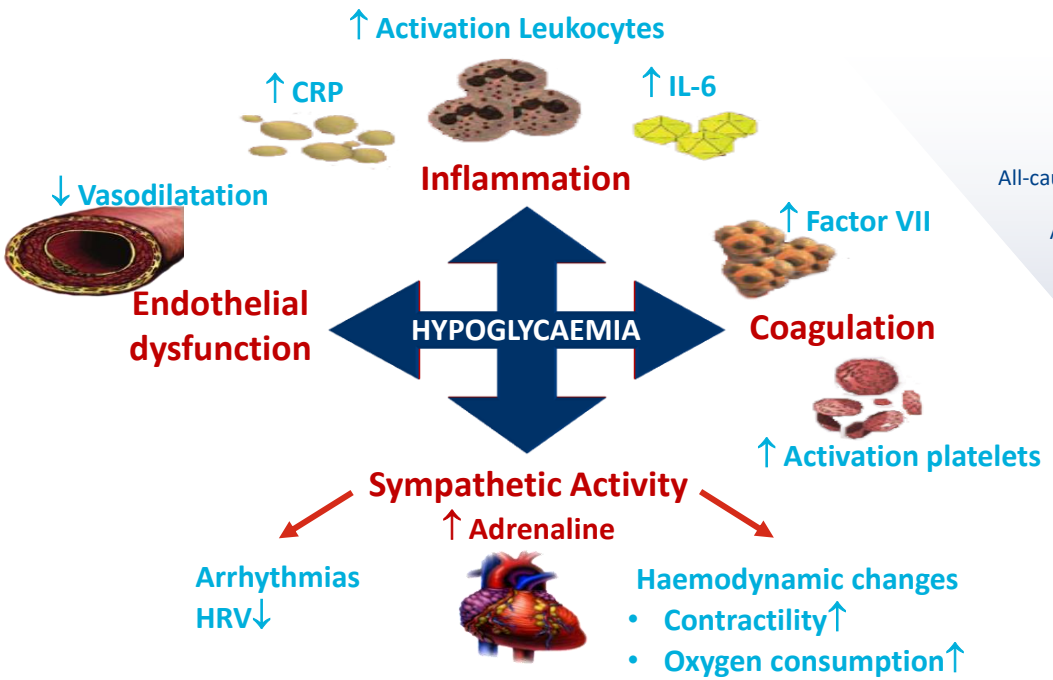
The primary endpoint was change from baseline in HbA_{1c} concentration after 52 weeks of treatment.



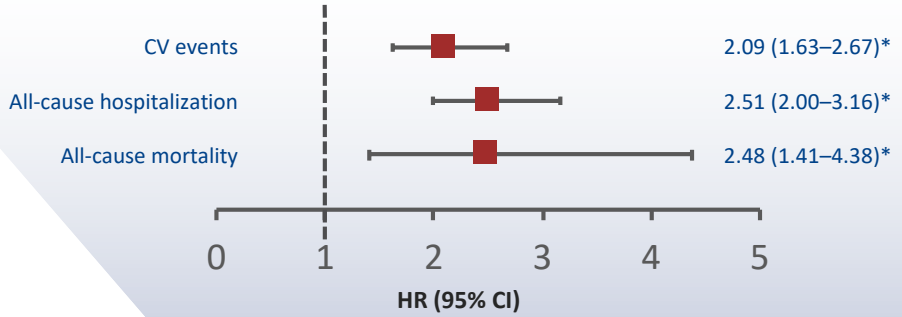
- Treat-to-target: HbA1c non-inferiority
- Hypoglycaemia as outcome parameter?

Garber et al. Lancet 2012; 379: 1498–507

Adverse Effects of Hypoglycaemia



Hypoglycaemia associated with increased risk of adverse outcomes in people with type 2 diabetes



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Frier et al. Diabetes Care 2011;34(Suppl. 2):S132–7. Hsu PF, et al. Diabetes Care 2013;36:894–900

How to Define Hypoglycaemia?

Whipple's Triad

- Low blood glucose level
- Symptoms consistent with hypoglycaemia
- Relief of symptoms when the glucose level is raised

Unresolved issues

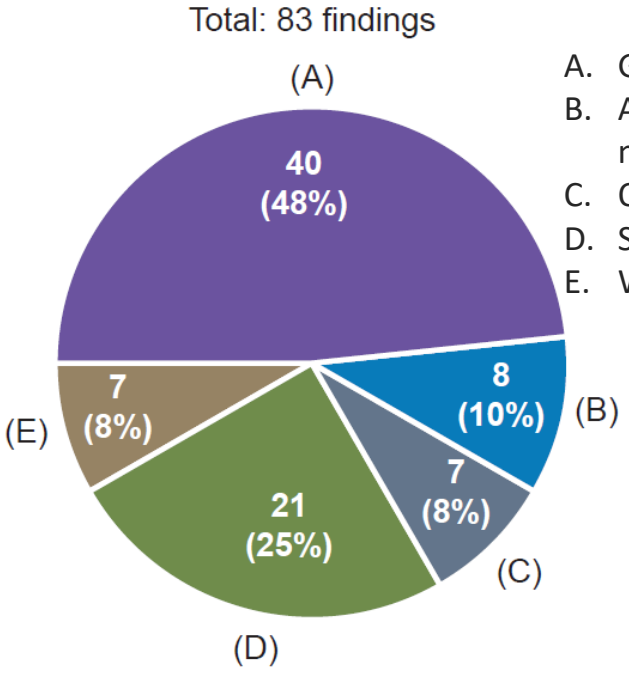
- Which glucose cut-off to use?
- Where to measure?
  - Capillary blood (conventional)
  - Interstitial fluid (CGM)
- Which symptoms are typical?
- Asymptomatic events and impaired awareness?
- Clinical relevance?
  - Physical harm
  - Decreased QoL
  - Increased costs

Whipple AO. J Internat Chir 1938;3:237-276

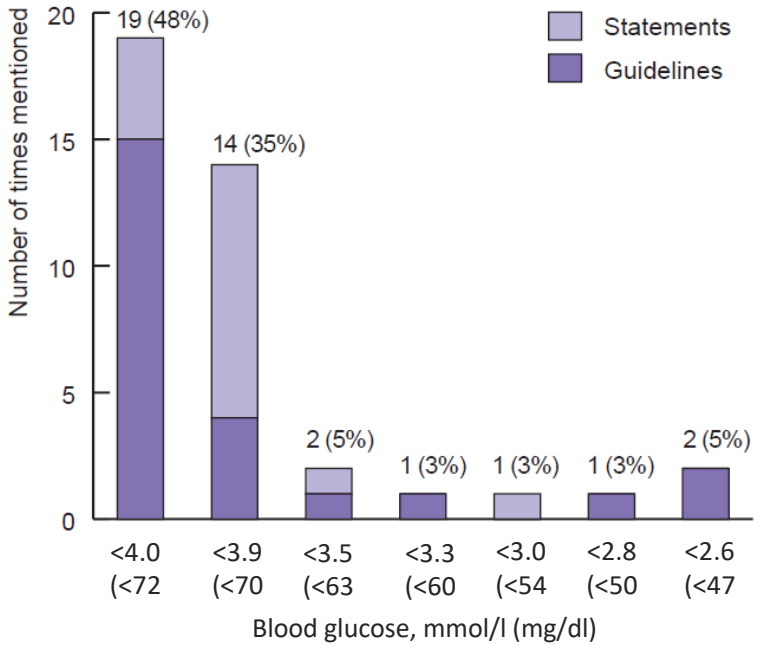
Hypoglycaemia Narrative Definitions

- ADA: "… all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm."
- WHO: "… potentially life-threatening low concentration of blood glucose…"
- NICE: "… level of blood glucose at which physiological and neurological dysfunction begins…"

Hypoglycaemia Definitions in Guidelines and Statements

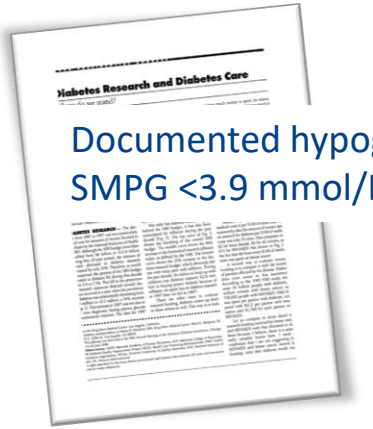


A. Glucose level
B. ADA, WHO, NICE narrative
C. Other narrative
D. Severe events
E. Whipple's triad

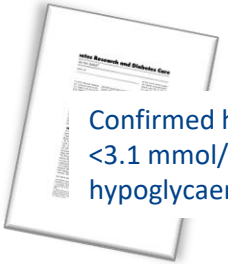


Gatschelhofer et al. 2020. Unpublished

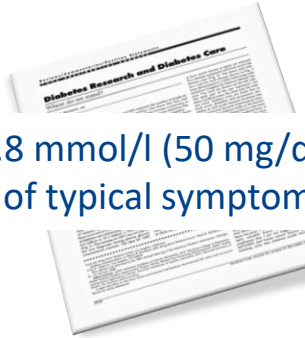
Hypoglycaemia Definitions in Trials



Documented hypoglycaemia: SMPG <3.9 mmol/L (70 mg/dl)



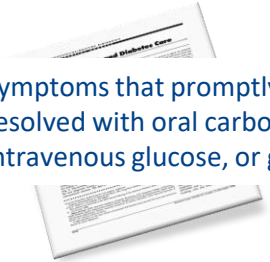
Confirmed hypoglycaemia: SMPG <3.1 mmol/l (56 mg/dl) or severe hypoglycaemia



SMPG <2.8 mmol/l (50 mg/dl) or presence of typical symptoms

Events whether confirmed by SMPG or not and whether symptomatic or asymptomatic

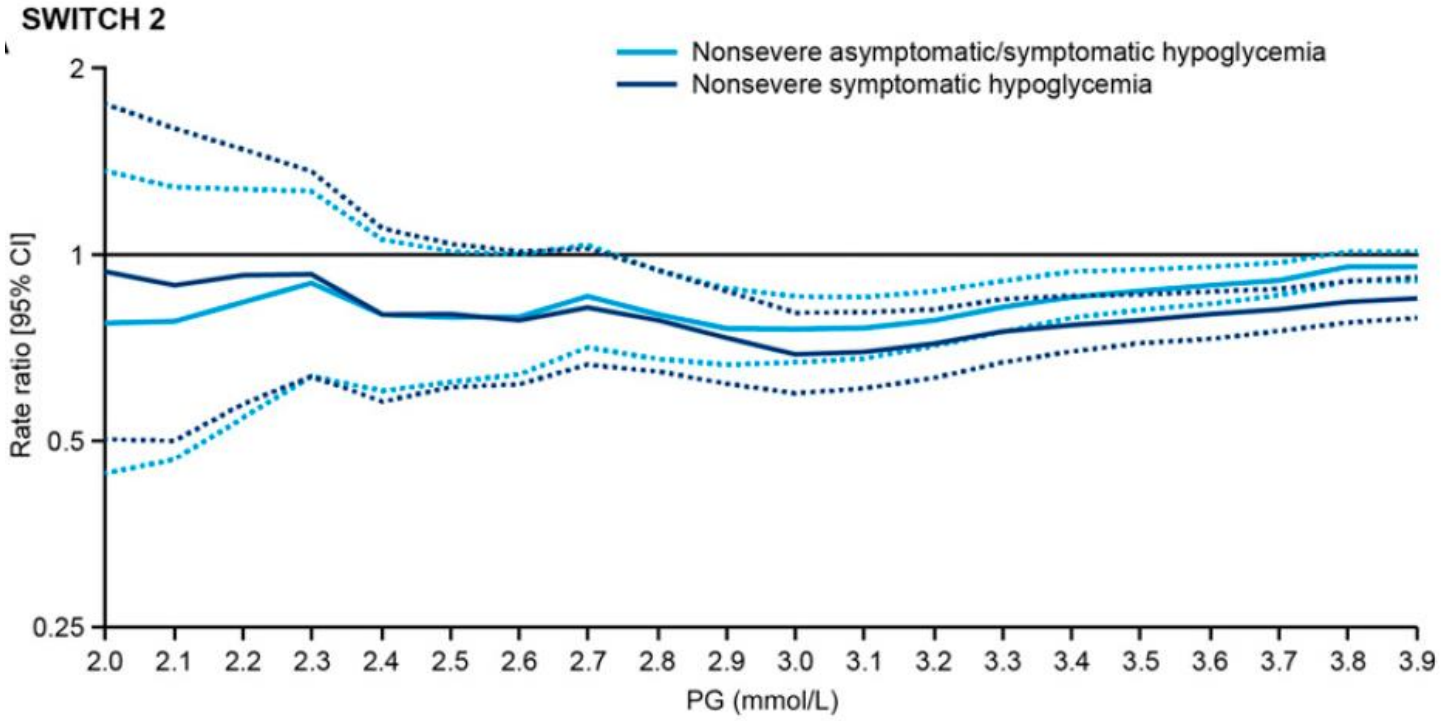
At least 2 CGM-readings ≤60 mg/dl (3.3 mmol/L) within 20 min



Symptoms that promptly resolved with oral carbohydrate, intravenous glucose, or glucagon

SMPG <3.0 mmol/L (54 mg/dl)

Impact of Glucose Cut-offs to Define Hypoglycaemia



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Heller et al. Diabetes Care 2019. doi 10.2337/dc18-2361

Hypoglycaemia in Clinical Trials

- Using different cut-offs invalidates comparing glucose-lowering strategies
- Non-severe events are usually not adjudicated and rate depend on mode and frequency of monitoring
- Clinical relevance of too high a glucose cut-off is questionable
- Severe hypoglycaemia is relatively rare
- There is a need for a level between these two ‘extremes’

Heller et al. Diabetes Care 2019. doi 10.2337/dc18-2361

IHSG Classification of Hypoglycaemia

Proposed classification for reporting hypoglycaemia in clinical trials

Level 1 ≤3.9 mmol/l (70 mg/dl)
Alert value

Level 2 <3.0 mmol/l (54 mg/dl)
Clinically important

Level 3 Cognitive decline requiring external help
Severe hypoglycaemia

International Hypoglycaemia Study Group. Diabetologia 2017;60:3-6

The Hypo-RESOLVE Project

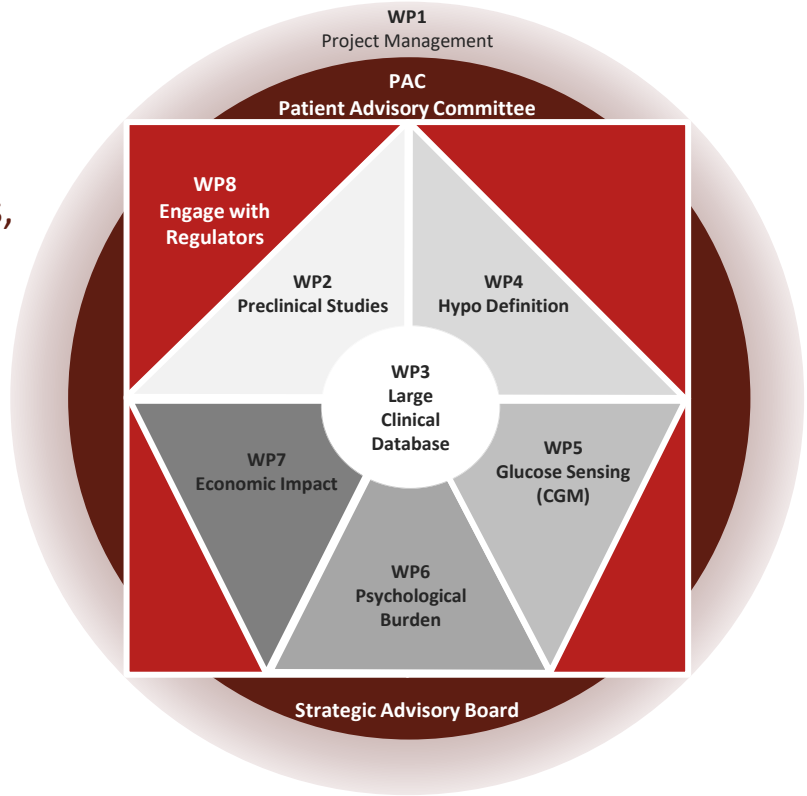
Overall objective

To reduce the burden of hypoglycaemia among patients with diabetes through better understanding (predictors, underlying mechanisms, consequences), using a comprehensive multilevel approach

05/2018-04/2022

Public-private partnership

involving 22 partners from academia, industry and patient organisations



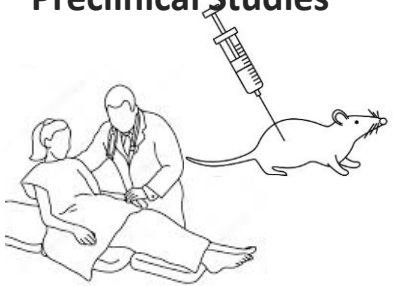
Activity in Hypo-RESOLVE

HYPO RESOLVE

Database Analyses

Predictors and consequences of hypoglycaemia

Preclinical Studies



Inflammation, cardiac/cognitive function and epigenetics

Hypo-METRICS

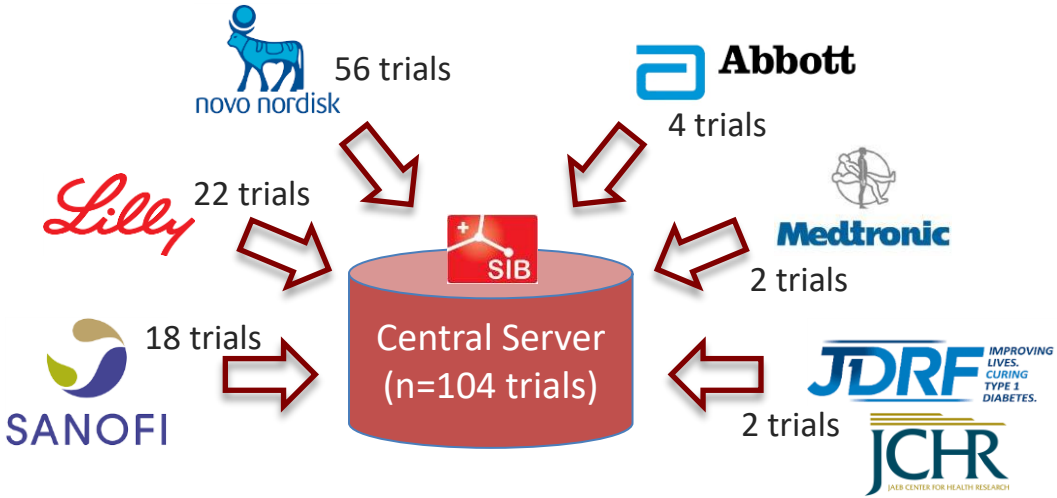
Relevance of CGM-detected Low Interstitial Glucose (LIG)

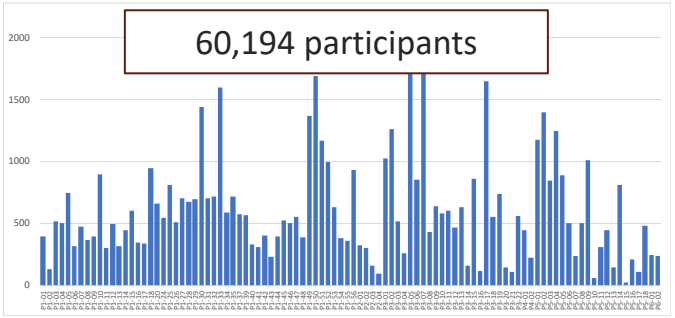
Quality of Life and Health Economics

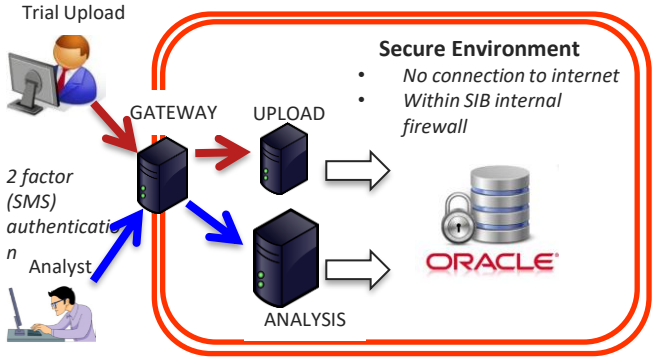
Patient-Reported Outcomes (PROs) and Costs

Robust evidence base to refine and solidify the classification of hypoglycaemia in diabetes

Construction of Hypo-RESOLVE Database

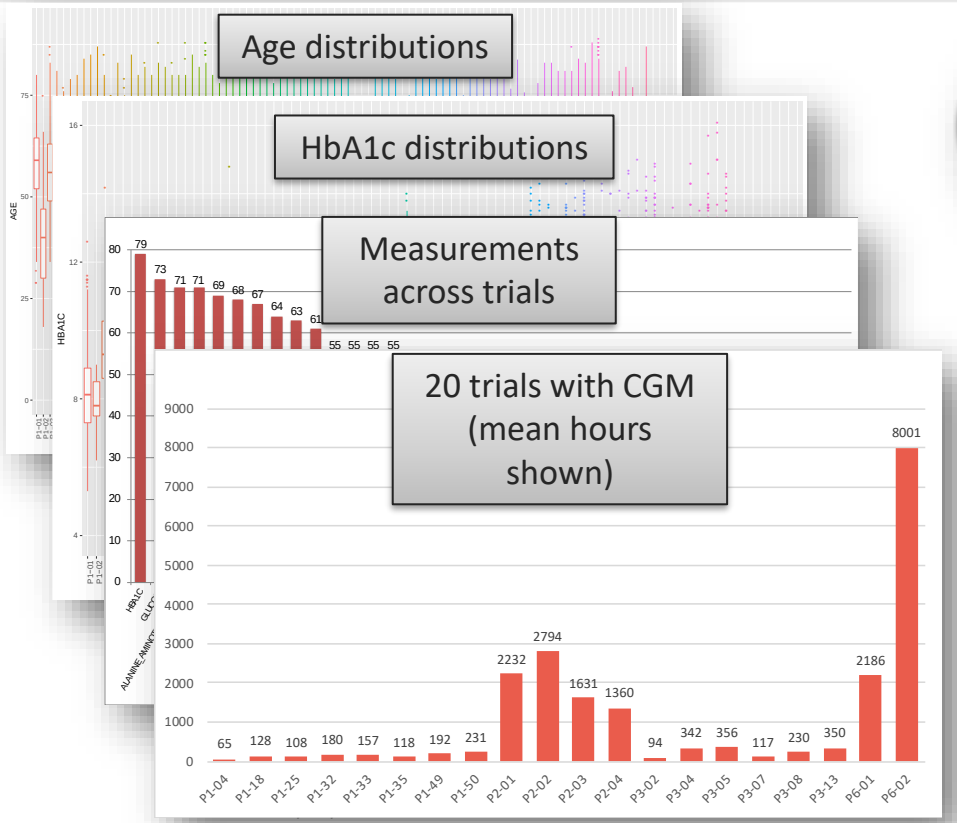


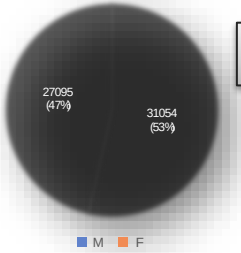




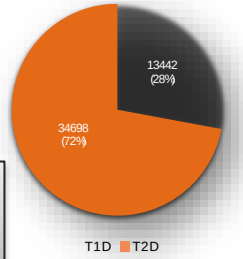
- Secure transfer through a private (VPN) connection
- Central server is protected behind a firewall

The Hypo-RESOLVE database

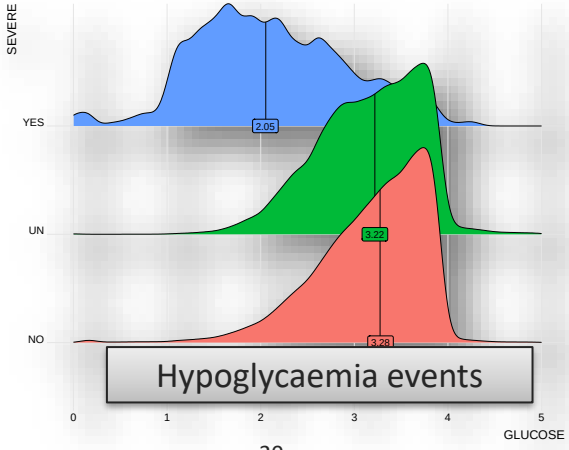




Gender



Diabetes type



Hypoglycaemia events

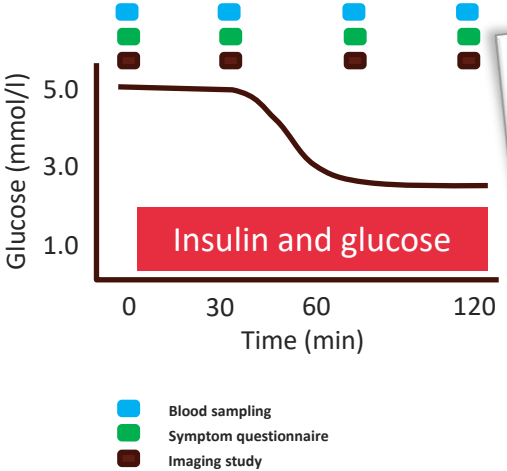
Hyperinsulinaemic hypoglycaemic clamp study

HYPO RESOLVE

Participants (n=16 each)

- T1D, aware
- T1D, impaired aware
- T1D, poor glucose control
- T2D, insulin treated
- Control groups w/out diabetes

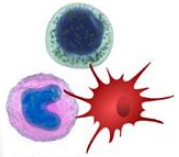
Hypoglycaemic Clamp



Follow-up (days 1, 3, 7)

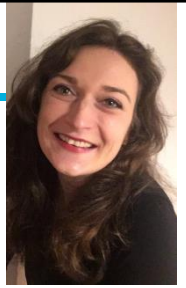
Measurements

EDTA blood:
Genome
Transcriptome
Metabolome
Circulating Mediators
Immunophenotyping



PBMC's:
Cytokines
Immunophenotyping

Urine



Hyperinsulinaemic hypoglycaemic clamp study

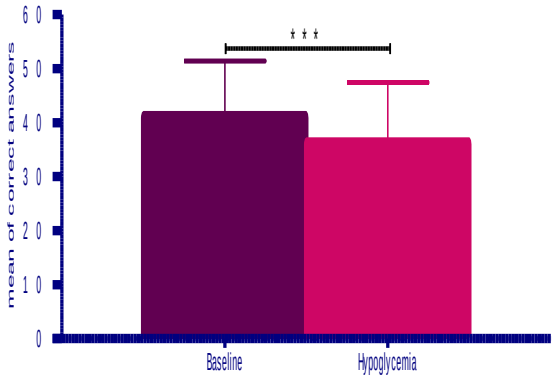
Baseline characteristics

		Type 1 diabetes				
	Healthy subjects	Poor glucose control	Normal awareness	Impaired awareness	**Type 2 diabetes**	**Total**
N (male/female)	26 (11/15)	6 (5/1)	14 (6/8)	14 (8/6)	10 (8/2)	70 (38/32)
Age (years)	47.0 ± 19.8	48.2 ± 22.0	37.4 ± 21.2	54.7 ± 13.6	62.9 ± 5.9	49.1 ± 19.1
BMI (kg/m²)	23.5 ± 3.3	27.9 ± 4.6	25.6 ± 3.2	26.2 ± 3.9	28.9 ± 3.3	25.6 ± 4.0
Duration diabetes (years)	NA	26.0 ± 11.9	17.0 ± 16.7	24.3 ± 11.6	16.5 ± 8.6	20.4 ± 13.2
HbA1c (mmol/mol)	34.5 ± 3.5	69.7 ± 2.9	54.9 ± 6.4	59.0 ± 9.1	67.4 ± 8.7	NA

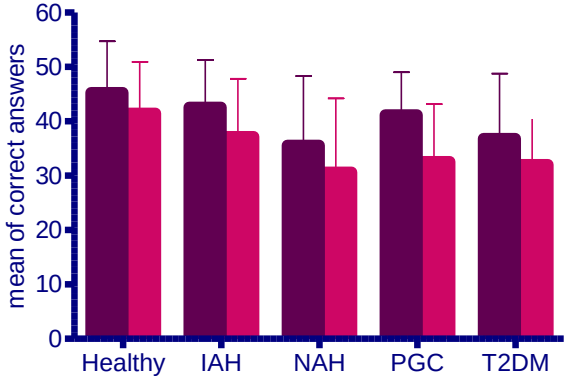
Data are shown as number or mean ± SD. NA: not applicable

Verhulst et al. Unpublished

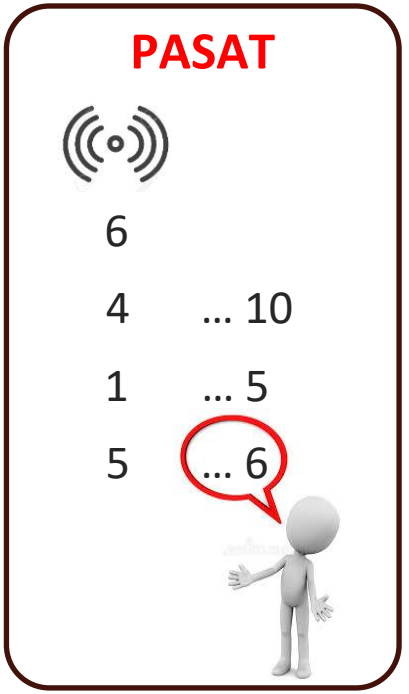
Effect of hypoglycaemia on cognitive function: *PASAT*



*	P ≤ 0.05
**	P ≤ 0.01
***	P ≤ 0.001



IAH: impaired awareness of hypoglycemia (T1DM)
NAH: normal awareness of hypoglycemia (T1DM)
PGC: poor glycemic control
T2DM: type 2 diabetes



Verhulst et al. Unpublished

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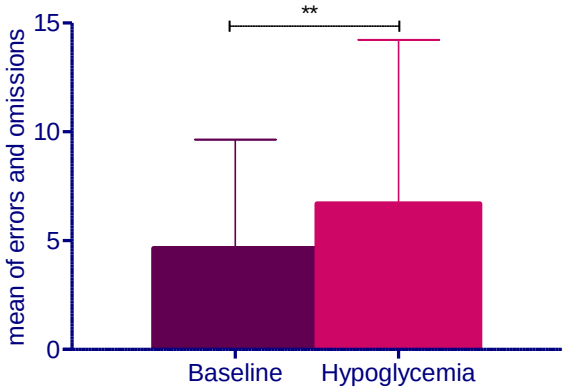
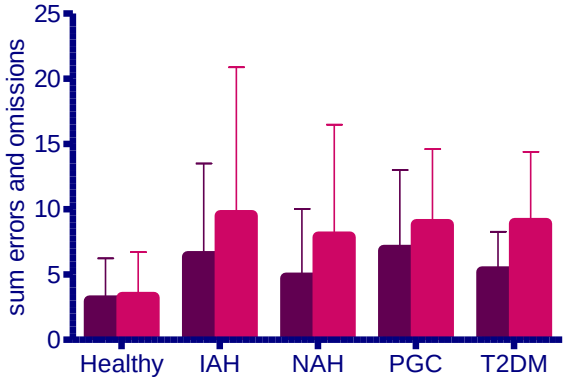
Effect of hypoglycaemia on cognitive function: *TAP*





*	P ≤ 0.05
**	P ≤ 0.01
***	P ≤ 0.001

IAH: impaired awareness of hypoglycemia (T1DM)
NAH: normal awareness of hypoglycemia (T1DM)
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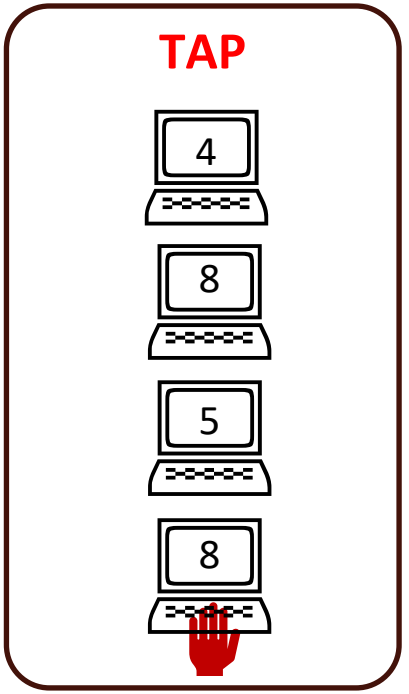

Verhulst et al. Unpublished

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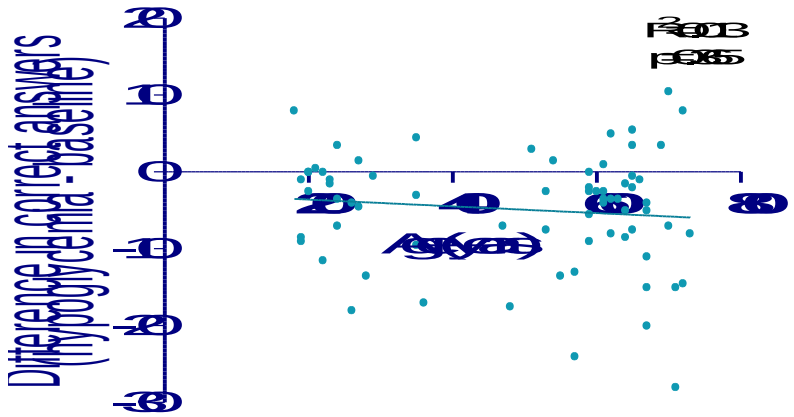
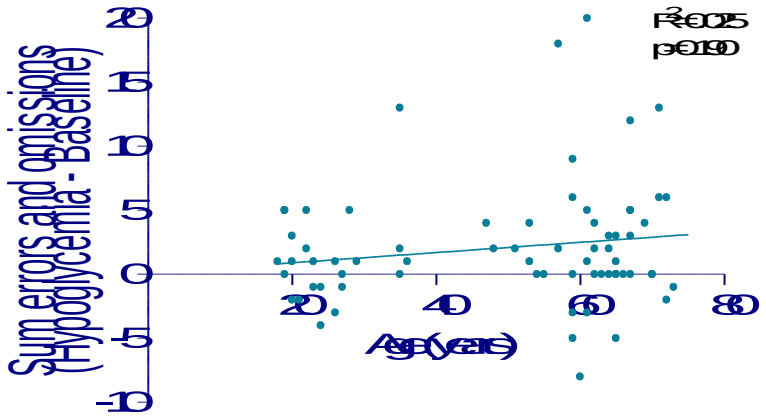
Hypoglycaemia-related cognitive dysfunction:
No effect of age

PASAT



TAP



Verhulst et al. Unpublished

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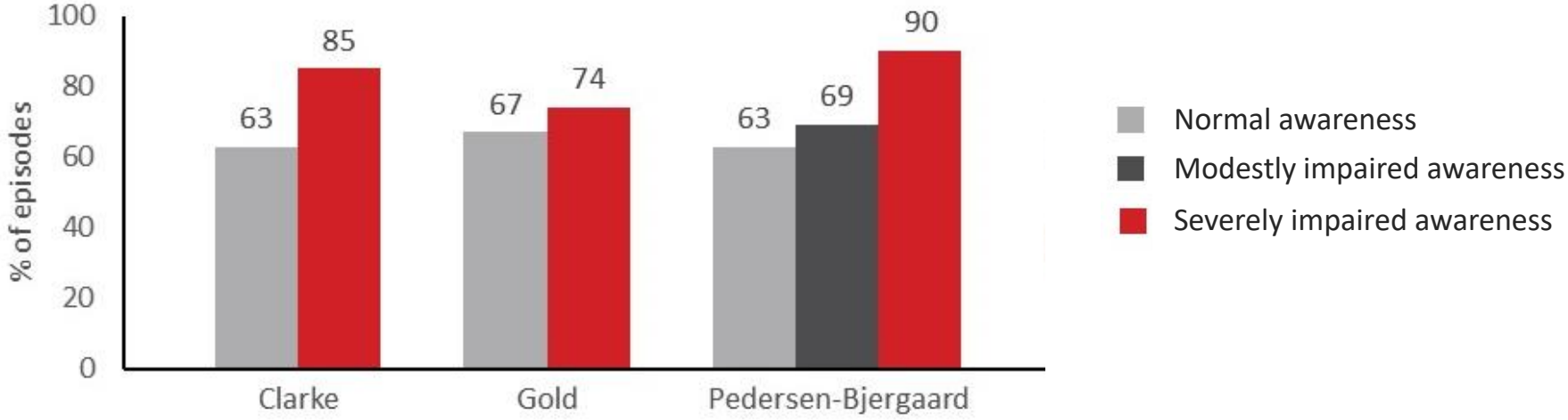
Asymptomatic Hypoglycaemia by CGM

HYPO RESOLVE

Over sixty per cent of all CGM-recorded hypoglycaemia episodes lack warning symptoms, even in people with diabetes and intact awareness



Henriksen et al, J Clin Endocrinol Metab 2018;103:2329-35

Hypo-Metrics Study: Design

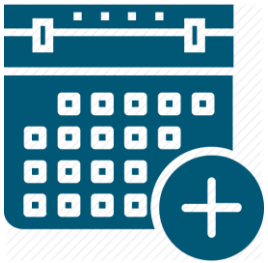
HYPOglycaemia MEasurement ThResholds for Interstitial glucose reCordingS

HYPO RESOLVE

Participants (n=600)

- T1D, aware (n=200)
- T1D, impaired aware (n=50)
- T2D, ≥2 injections/day (n=350)
- 8 centres in 5 countries

Duration of follow-up



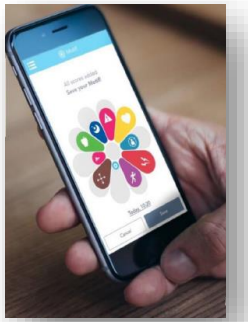
10 weeks

Blinded glucose sensor

Activity Tracking

- Sleep vs awake
- Activity
- Sleep quality

Ecological Momentary Assessments



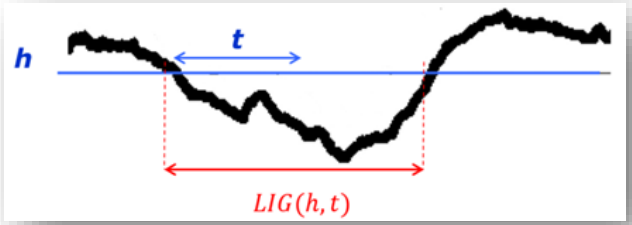
- Patient-reported outcomes
- Sleep quality (self report)
- Hypoglycaemia reporting

Hypo-Metrics Multi-Centre Study (WP5)

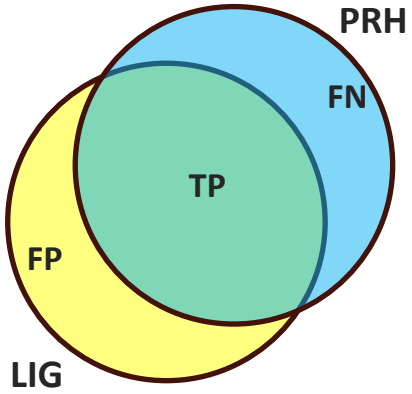
HYPOglycaemia MEasurement ThResholds for Interstitial glucose reCordingS

HYPO RESOLVE

- Objective: To determine the optimum parameters of low interstitial glucose (LIG) that best correlate with patient-reported hypoglycemia (PRH): $LIG_{PRH}(h_{opt}, t_{opt})$

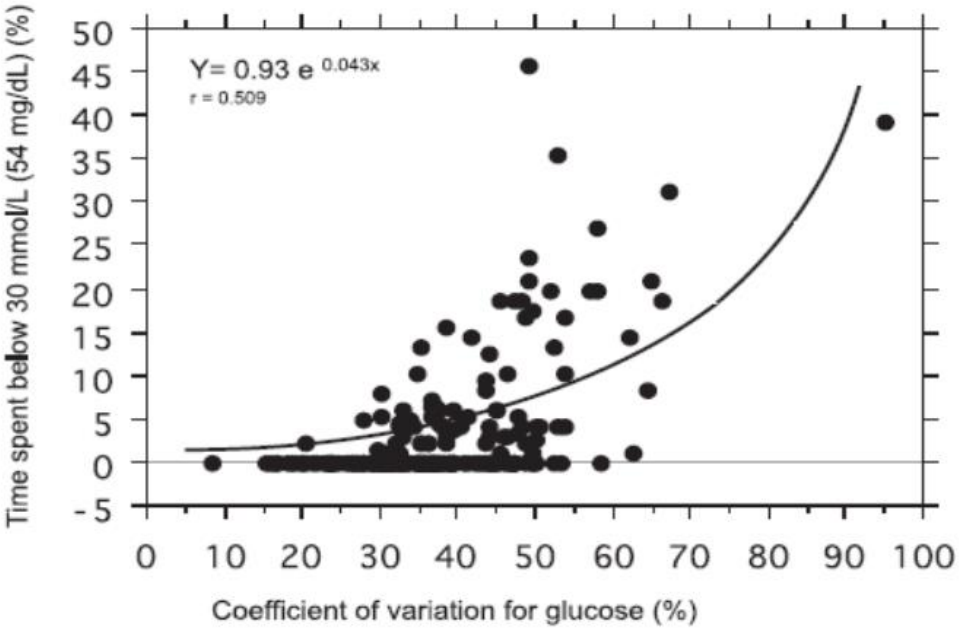


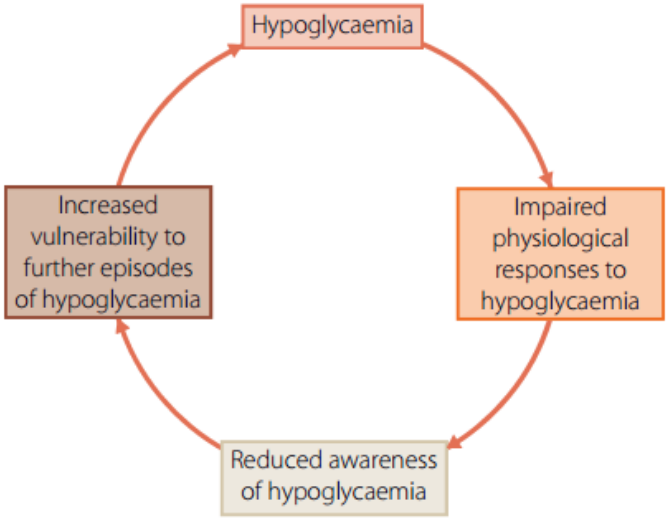
***h*:** threshold glucose value
t: time under threshold value



FP: false positive (asymptomatic LIG)
FN: false negative (CGM-missed)
TP: true positive

Glucose variability predicts hypoglycaemia (and IAH?)

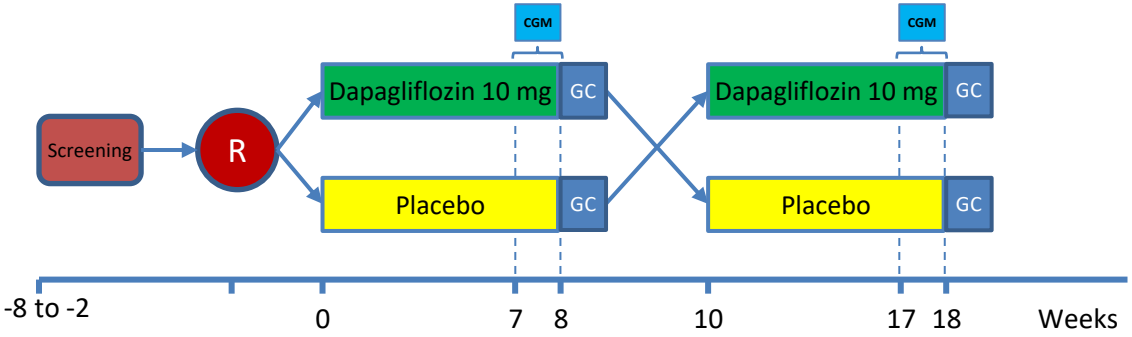




Monnier et al. Diabetes Care 2020

Effect of dapagliflozin in T1D with IAH

- N=15
- Type 1 diabetes >1 yr
- Age 18-75 yrs
- HbA1c 42-75 mmol/mol (6-9%)
- Modified Clarke score ≥3
- Exclusion : history of cardiovascular disease, ketoacidosis



- Dapagliflozin 10 mg QD vs. matched placebo for 8 weeks
- Continuous blinded glucose monitoring in final week
- Hyperinsulinaemic hypoglycaemic glucose clamp on final day

Effect on glucose metrics and body weight

	Dapagliflozin	Placebo	P-value
Change in HbA1c, mmol/mol	-4.1 ± 0.9	2.3 ± 1.4	**0.004**
Total no. of hypos (in 8 weeks)	7.0 (3.0, 19.0)	8.0 (2.0, 11.0)	0.70
Mean glucose (mmol/L)	7.6 ± 0.3	8.2 ± 0.4	0.075
Glucose variability, SD (mmol/L)	2.6 ± 0.2	3.1 ± 0.3	**0.029**
Time in range, %	72.9 ± 3.3	68.0 ± 4.2	0.19
Change in body weight, kg	-2.3 ± 0.6	-0.1 ± 0.5	**0.033**

Data are presented as mean ± SE or median (IQR)

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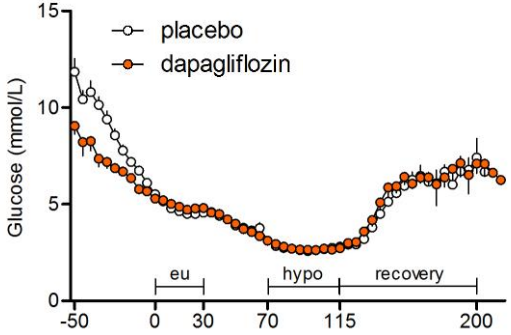
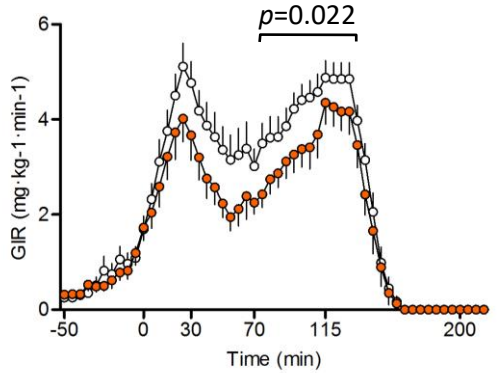
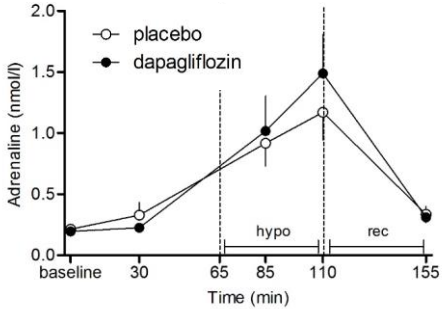
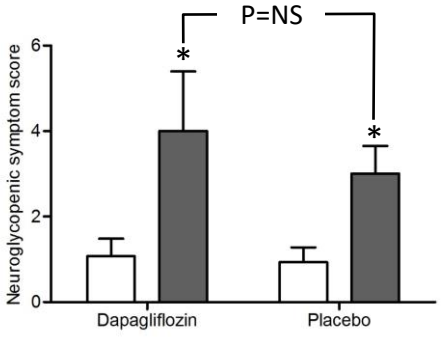
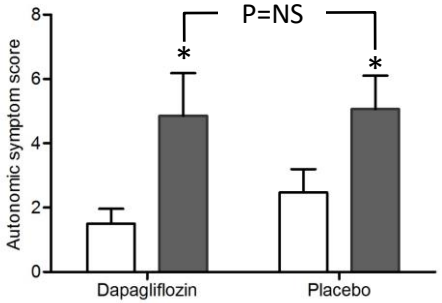
Hypoglycemic glucose clamps











euglycemia
end of hypoglycemia

*P<0.05 vs euglycemia

Van Meijel et al. 2020. Submitted

Radboudumc

Interim conclusion

- Adjunctive treatment with the SGLT-2 inhibitor dapagliflozin improves glucose variability and some components of impaired awareness of hypoglycaemia, but does not restore awareness in people with type 1 diabetes

- Yet, the (unsought) reduction in HbA1c combined with very low burden of hypoglycaemia supports the exploration of a role for SGLT-2 inhibitors in the clinical management of impaired awareness of hypoglycaemia

Take-home messages

- Hypoglycaemia remains an unmet medical need for people with diabetes
- Definitions of hypoglycaemia vary greatly among guidelines, reflecting lack of sufficient evidence
- Hypo-RESOLVE aims to increase the understanding of hypoglycaemia and to provide an evidence-based classification of hypoglycaemia
- Preliminary data on cognitive decline during hypoglycaemia support the IHSG proposed classification of hypoglycaemia
- Results from Hypo-RESOLVE are expected to inform trial design and daily clinical practice

Thank you for your attention!