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**Hypoglycemia in Diabetes:  
Epidemiology and Clinical Impact**

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**Disclosure to Participants**

Consultant: Locemia, Novo Nordisk, Lilly, Zucera  
Research Support: NIH, JDRF, Lilly

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**Outline**

- I. What is hypoglycemia and impaired awareness of hypoglycemia?
- II. How common is it in patients with diabetes?
- III. How do hypoglycemia and impaired awareness of hypoglycemia impact patients with diabetes?

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**Hypoglycemia in diabetes**

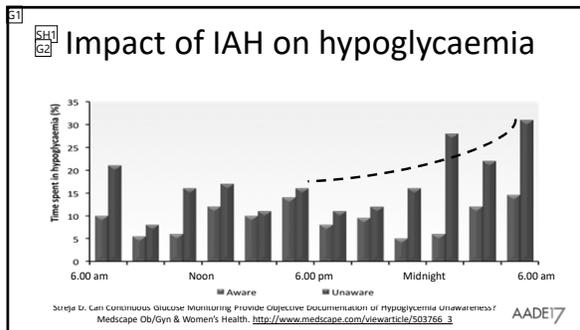
- The limiting factor in the management of diabetes
- Fear of hypoglycemia prevents patients from obtaining the reduction in microvascular risk associated with good glycemic control
- Impact can range from inconvenience, to coma, seizures, and death

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### Impaired awareness of hypoglycemia

- Recurrent hypoglycemia reduces the threshold at which the counterregulatory response is elicited; first symptom may be neuroglycopenia that requires assistance of another to treat
- Occurs in up to 25% of type 1 patients
- Occurs in 9.8% of insulin treated type 2 patients (Schopman, Diab Res Clin Prac 2010)
- Patients over 65 years often do not have typical symptoms of hypoglycemia – lightheadedness and unsteadiness not tremor and palpitations (Jaap, Diab Med 1998)

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### How common is hypoglycemia in clinical practice?

- Hypoglycemia Assessment Tool (HAT) study led by Kamlesh Khunti in UK
- Global study of 27,585 insulin treated patients from 24 countries
- On line tool designed to collect patient reported information about HG frequency and severity both in retrospect and prospectively

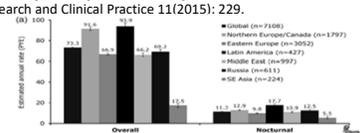
Diabetes Research and Clinical Practice 11(2015): 229.

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### Data collected prospectively over 1 month

Diabetes Research and Clinical Practice 11(2015): 229.

Type 1 diabetes  
14% had severe HG  
83% had any HG



Type 2 diabetes  
9% had severe HG  
47% had any HG

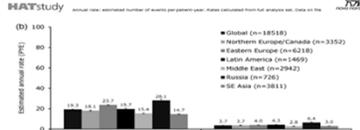


Fig. 1 – Prospective hypoglycemia rates in (a) T1D and (b) T2D were consistent across most participating countries.

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### Dead in bed syndrome

- 23 year old man with 12 yrs of T1DM
- Complicated by frequent and severe hypoglycemia
- Wore pump and CGM
- Found dead in undisturbed one morning

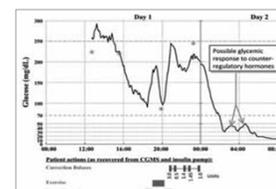


Fig. 1. Glucose levels expressed by the retrospective continuous subcutaneous glucose monitoring system (CGM) for the evening before and the morning of the patient's death. The calibrations measured and entered by the patient are represented by the 4 circles. The timing of the patient's meals, exercise, and correction insulin boluses are represented by the bars along the bottom of the graph. The precipitous decrease in glucose level after the correction doses can be observed to start just after midnight, and possible counterregulatory efforts are noted once the glucose level declined to below 20 mg/dL shortly after 2 a.m.

Tanenberg et al. Endocr Pract. 2010;16(No. 2) 245 AADE17

## Slide 8

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- G1** Note to layout: In the legend, please change "unaware" to "awareness impaired"  
Gabrielle, 11/17/2015
- SH1** while this is fine, the effect of impaired awareness on rate of severe episodes is much more important --  
6 fold increase:  
Gold AE, MacLeod KM, Frier BM: Frequency of severe hypoglycemia in patients with type I (insulin dependent) diabetes with impaired awareness of hypoglycemia. Diabetes Care 17:697-703, 1994  
Simon Heller, 11/27/2015
- G2** DEAR REVIEWERS: Kindly provide specific direction: keep this slide as is or replace it with data from the Gold study?  
Gabrielle, 11/27/2015
- 1** could slides showing impact on BG during the day and on SH both be shown? It is important  
Elizabeth Seaquist, 1/21/2016

### Mortality and hypoglycemia in type 1 diabetes

- Cause of death in 2-4% of people with type 1 diabetes (Laing et al. Diabetic Medicine 1999)
- Hypothesized to be cause of dead in bed syndrome described by Tattersall and Gill in 1991 where person < 40 years of age with 0-25 years of type 1 diabetes is found dead in undisturbed bed

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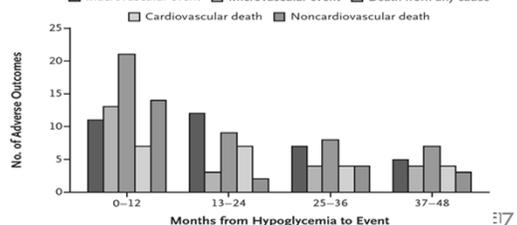
### Hypoglycemia is associated with increased risk of mortality

- In clinical trials: history of severe hypoglycemia nearly doubled risk of mortality in both ACCORD and ADVANCE
- In observational studies: Prospective clinical based study of 1000+ showed that those those with history of severe hypoglycemia at baseline had OR for mortality of 3.38 at 5 years (95% CI: 1.55-7.38, p < 0.005) (McCoy DC 2012)

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### Is hypoglycemia the cause of death in patients with history of severe hypoglycemia?

ADVANCE Trial: Relationship between severe HG and adverse events



17

Zoungas et al. NEJM 2010

### Hypoglycemia in Diabetes Mellitus as a Coronary Artery Disease Risk Factor in Patients at Elevated Vascular Risk

Leong et al J Clin Endocrinol Metab, February 2016, 101(2):659-668

- Longitudinal cohort study of 9173 DM patients without CAD before 1/1/2006 in academic primary care practice network
- 3% (285) had hypoglycemic events before 1/1/2006 identified by ICD-9 codes for ED, inpatient and outpatient visits
- Measured incident CAD through 6/30/2012

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Table 1. Baseline Characteristics Stratified by Hypoglycemia

Baseline Characteristics	No Hypoglycemia (n = 8888)	Hypoglycemia (n = 285)	P Value
Age (y), median/mean (SD)	60.6/60.67 (14.30)	59.40/58.76 (15.50)	0.3
Women, n (%)	4545 (51.36)	170 (59.65)	0.1
Non-White race/ethnicity, n (%)	2605 (29.55)	102 (35.30)	0.02
< High school education, n (%)	1267 (18.52)	39 (18.84)	0.91
Diabetes duration, median/mean years (SD)	3.70/3.30 (1.82)	4.57/3.94 (1.60)	<.001
Hypertension, n (%)	5030 (56.59)	144 (50.53)	0.04
Dyslipidemia, n (%)	5557 (62.52)	157 (55.09)	0.1
Microvascular disease, n (%)	1588 (17.83)	133 (46.62)	<.001
Renal failure, n (%)	452 (5.09)	49 (15.79)	<.001
Neuropathy, n (%)	1224 (13.74)	106 (37.19)	<.001
Retinopathy, n (%)	440 (4.95)	61 (21.40)	<.001
Dysrhythmia, n (%)	1541 (17.34)	63 (22.13)	0.4
Cerebrovascular disease, n (%)	371 (4.17)	15 (5.26)	0.37
Peripheral vascular disease, n (%)	317 (3.57)	11 (3.86)	0.79
Cancer, n (%)	459 (5.16)	22 (7.72)	0.06
Dementia, n (%)	370 (4.16)	15 (5.26)	0.36
Insulin, n (%)	2361 (26.56)	166 (58.25)	<.001
Sulfonylurea, n (%)	2979 (33.52)	94 (32.98)	0.85
= 3 noninsulin antidiabetic agents, n (%)	993 (11.28)	24 (8.42)	0.25
Medication count, median/mean (SD)	6.00/7.24 (6.24)	8.00/9.59 (7.81)	<.001
BMI (kg/m <sup>2</sup> ), median/mean (SD)	30.61/31.82 (7.51)	28.58/30.39 (7.89)	0.04
eGFR (mL/min per 1.73 m <sup>2</sup> ), median/mean (SD)	74.69/74.25 (24.33)	71.98/69.62 (27.32)	0.002
LDL (mg/dL), median/mean (SD)	88.00/92.06 (33.52)	78.00/83.30 (31.35)	<.001
HDL (mg/dL), median/mean (SD)	49.00/51.29 (15.77)	53.00/57.44 (20.08)	<.001
HbA1c (%), median/mean (SD)	7.20/7.66 (1.62)	7.50/7.95 (1.89)	0.1
Hospitalization, n (%)	1691 (19.03)	85 (29.82)	<.001
= 5% weight loss within a year	494 (5.57)	21 (7.36)	0.16
= 2 HbA1c measurements/year, n (%)	4573 (51.57)	182 (64.08)	<.001

J Clin Endocrinol Metab, February 2016, 101(2):659-668

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### Cumulative Hazards Ratios

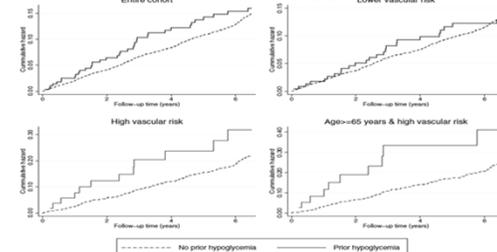


Figure 2. Cumulative hazard estimates of hypoglycemia on incident CAD in the entire cohort and in different vascular risk groups. Log rank test was statistically significant for patients age 65 years or older, high vascular risk subgroup (P = .020). Log rank tests were not statistically significant for the entire cohort, P = .450, low vascular risk group, P = .928, and high vascular risk group, P = .095.

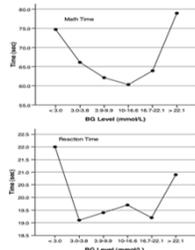
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### Effects of glycemia on cognition in school age children

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

(Gonder-Frederick et al. Diabetes Care 2009)



### Hypoglycemia and dementia risk on older patients with type 2 DM

(Whitmer et al. JAMA 2009)

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

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Table 3. Hypoglycemia and Risk of Incident Dementia\*

No. of Hypoglycemic Episodes <sup>b</sup>	No. of Dementia Cases	Adjusted for Age (Sex, Time Since DM, Race/Ethnicity, Education, Sex, and Duration of Diabetes)	Additionally Adjusted for Comorbidity <sup>c</sup>	Additionally Adjusted for 7-Year Mean HbA <sub>1c</sub> , Lowest Diabetes Treatment, and Years of Insulin Use
1 or more	250	1.58 (1.47-1.69)	1.48 (1.39-1.75)	1.44 (1.25-1.66)
2	150	1.45 (1.23-1.72)	1.29 (1.10-1.52)	1.26 (1.10-1.46)
3 or more	57	2.15 (1.64-2.81)	1.86 (1.42-2.43)	1.80 (1.37-2.36)
4 or more	43	2.92 (1.79-3.79)	2.10 (1.48-2.73)	1.94 (1.42-2.64)

Abbreviations: DM, type 2 diabetes mellitus; HbA<sub>1c</sub>, glycosylated hemoglobin.

<sup>a</sup>Analyses combined using Cox proportional hazard models.

<sup>b</sup>The 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0.

<sup>c</sup>Adjustment made using a comorbidity composite score.

Whitmer et al. JAMA 2009

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### Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes

Post hoc epidemiologic analysis of the ACCORD trial

PUNTHAKE Diabetes Care 35:787-793, 2012



Examined relationship between score on DSST and hypoglycemia risk in 2956 ACCORD-MIND participants over 20 months

Digital Symbol Substitution Test (scored as # correct in test period)

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### Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes

Post hoc epidemiologic analysis of the ACCORD trial

PUNTHAKE Diabetes Care 35:787-793, 2012

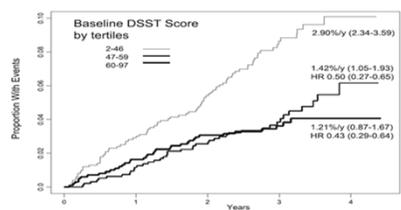


Figure 1—Kaplan-Meier curves for HbA<sub>1c</sub> according to baseline tertiles of the DSST score. Crude incidence rates and 95% CIs are shown for each group. Log-rank test P < 0.0001. HRs for the middle- and higher-score groups are with reference to the lower-DSST score group.

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### Costs of hypoglycemia

- Episode of severe hypoglycemia requiring assistance of health care provider estimated to cost \$1161 in US in 2014 (Foos et al. J Med Econ 2015)
- Between 2007 -2011, nearly 100,000 persons with diabetes were treated in emergency rooms for hypoglycemia each year at a cost exceeding \$100 million per year (Geller et al. JAMA Intern Med. 2014)

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## Fear of Hypoglycemia

- Best studied in type 1 diabetes where fear can result in increased vigilance and immobilizing distress (Martin-Nemeth, J Diab Comp 2015)
- Patients with greatest fear of hypoglycemia usually have history of severe hypoglycemia and are more anxious than patients with a lower fear of hypoglycemia
- Fear of hypoglycemia negatively impacts quality of life measures
- Fear is greatest at night and may impact sleep
- In Japan 27% of type 2 DM surveyed had high measures of fear of hypoglycemia (Sakane, J Diab Invest. 2015)

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## Conclusions

- Hypoglycemia is common in patients with diabetes
- Hypoglycemia and the fear of hypoglycemia have profound effects on the lives of patients with diabetes

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