

Hypoglycaemia and aging

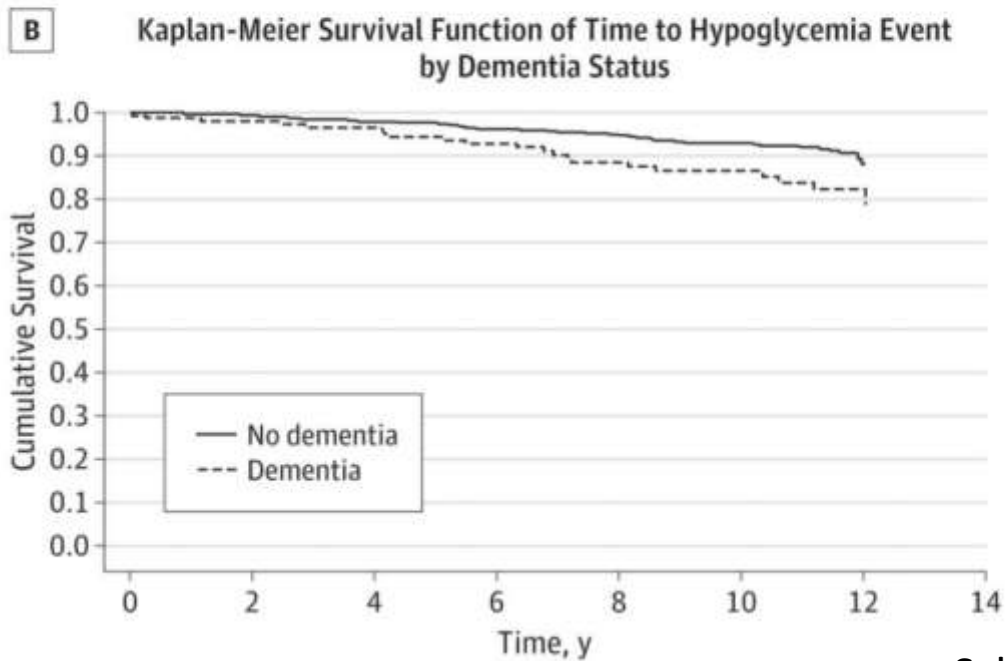
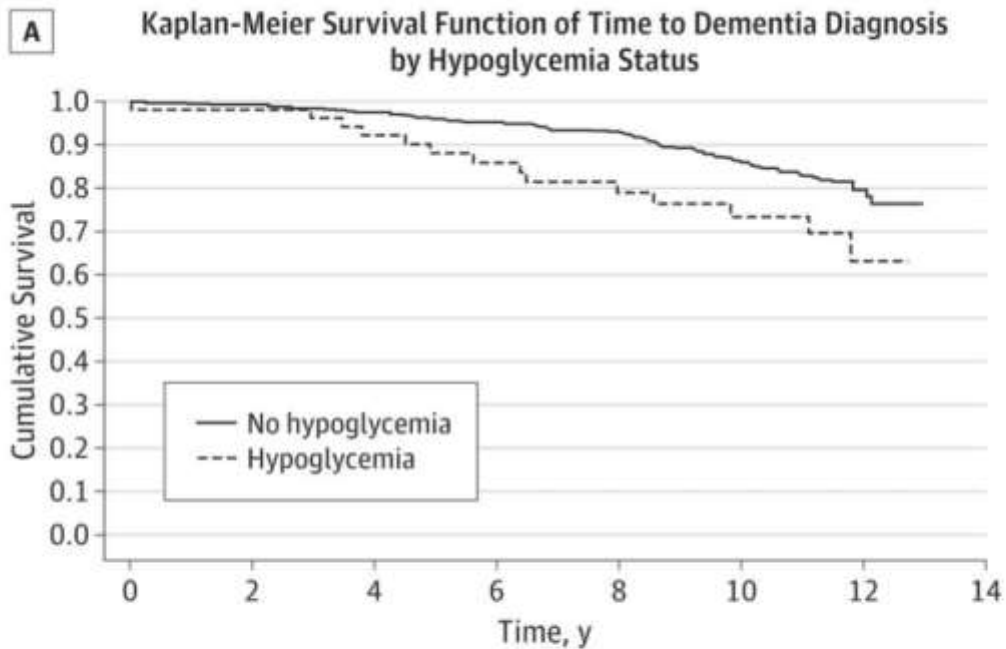
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Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus

Hypoglycemia and Risk of Incident Dementia

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



Estimates for Time to Dementia Associated With a Hypoglycemic Event

Variable	Hazard Ratio (95% CI)
Hypoglycemic event	2.09 (1.00–4.35)
Age	1.15 (1.08–1.22)
Black race/ethnicity	0.77 (0.51–1.16)
Female sex	0.78 (0.54–1.12)
Education	1.30 (0.85–1.96)
<i>APOE</i> ϵ 4 status	2.17 (1.53–3.08)
Prevalent diabetes mellitus	1.70 (1.12–2.58)
Insulin use	1.04 (0.64–1.67)
Glycated hemoglobin level	1.00 (0.85–1.17)
Baseline Mini-Mental State Examination score	0.96 (0.93–0.99)



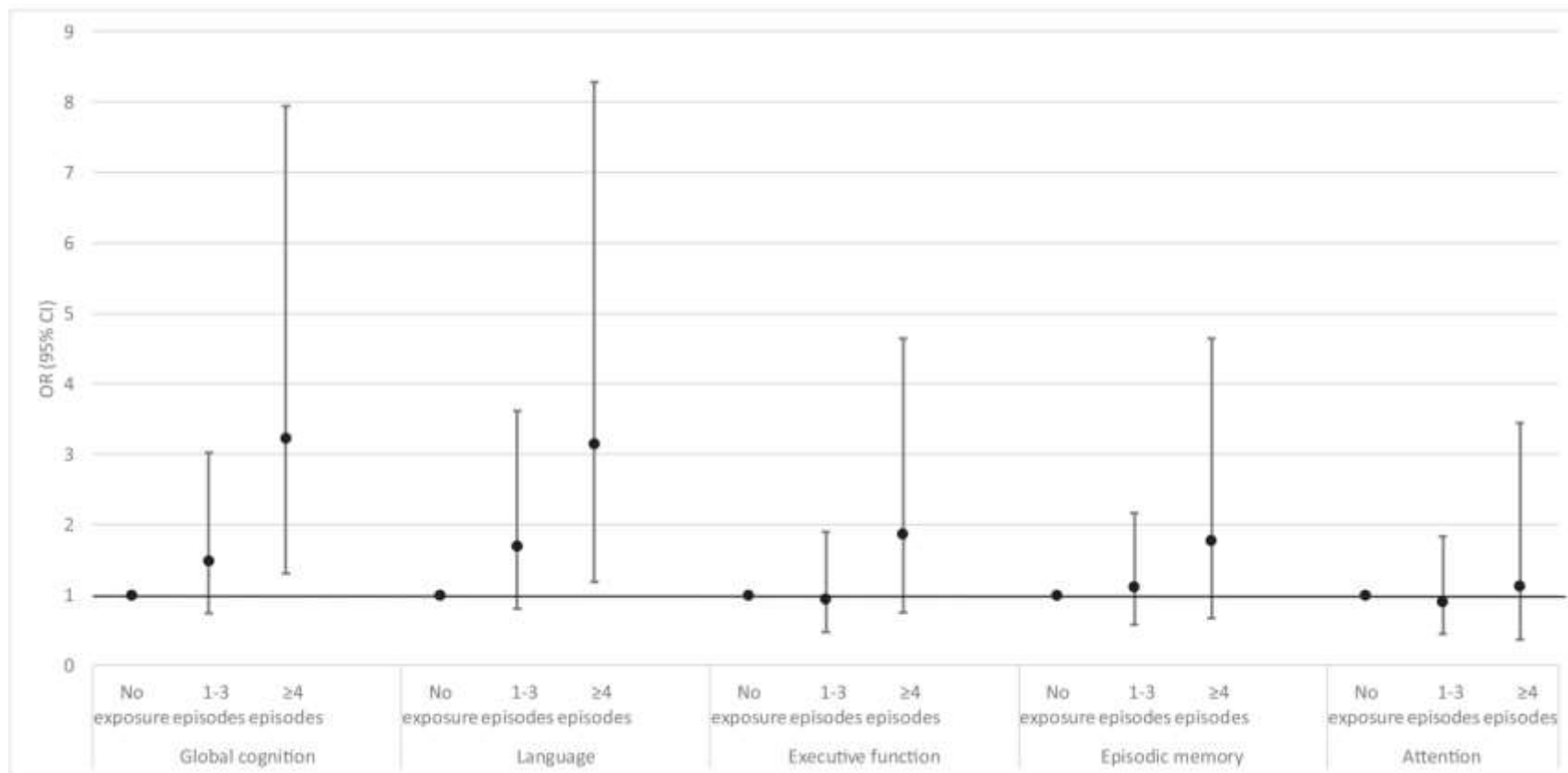
Abbreviation: APOE, apolipoprotein E.



Severe Hypoglycemia and Cognitive Function in Older Adults With Type 1 Diabetes: The Study of Longevity in Diabetes (SOLID)

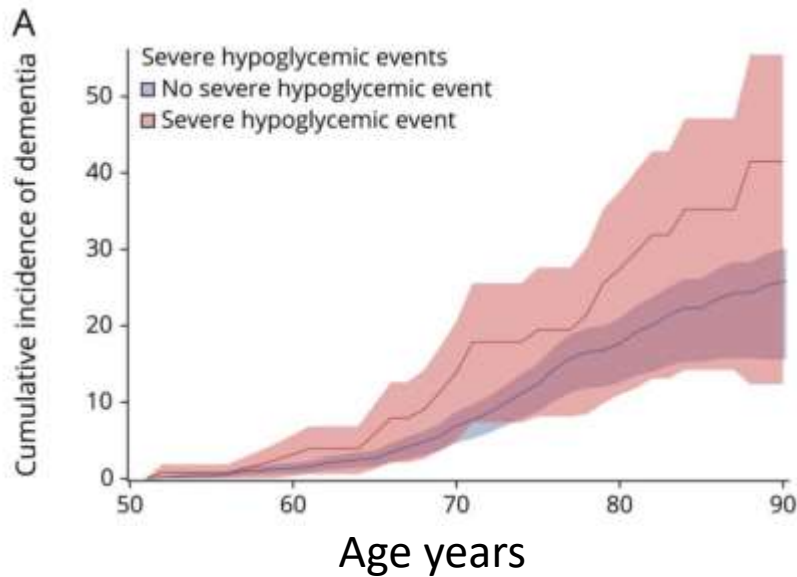
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Hypoglycemia and dementia risk in T1D

Figure Cumulative Incidence of Dementia Conditional on Dementia-Free Survival Until Age 50 Years Accounting for Competing Risk of Death



Model 1: Adjusted for age (as time scale), race, sex

Model 2: Model 1 + HbA1c

Model 3: Model 2 + depression, nephropathy, stroke

Severe glyceimic events modeled separately

Severe hypoglycemic event

No severe hypoglycemic event

Severe hypoglycemic event

Ref

1.85 (1.22, 2.80)

Ref

1.94 (1.28, 2.94)

Ref

1.75 (1.15, 2.66)

Severe hypoglycemia can result in:

- permanent neurological sequelae including neuronal cell death
- Increased platelet aggregation and fibrinogen formation
- accelerated vascular damage in the brain.
- damage to neuronal receptors in the ca-1, subiculum dentate, and granule cell areas of the hippocampus, regions critical for learning and memory

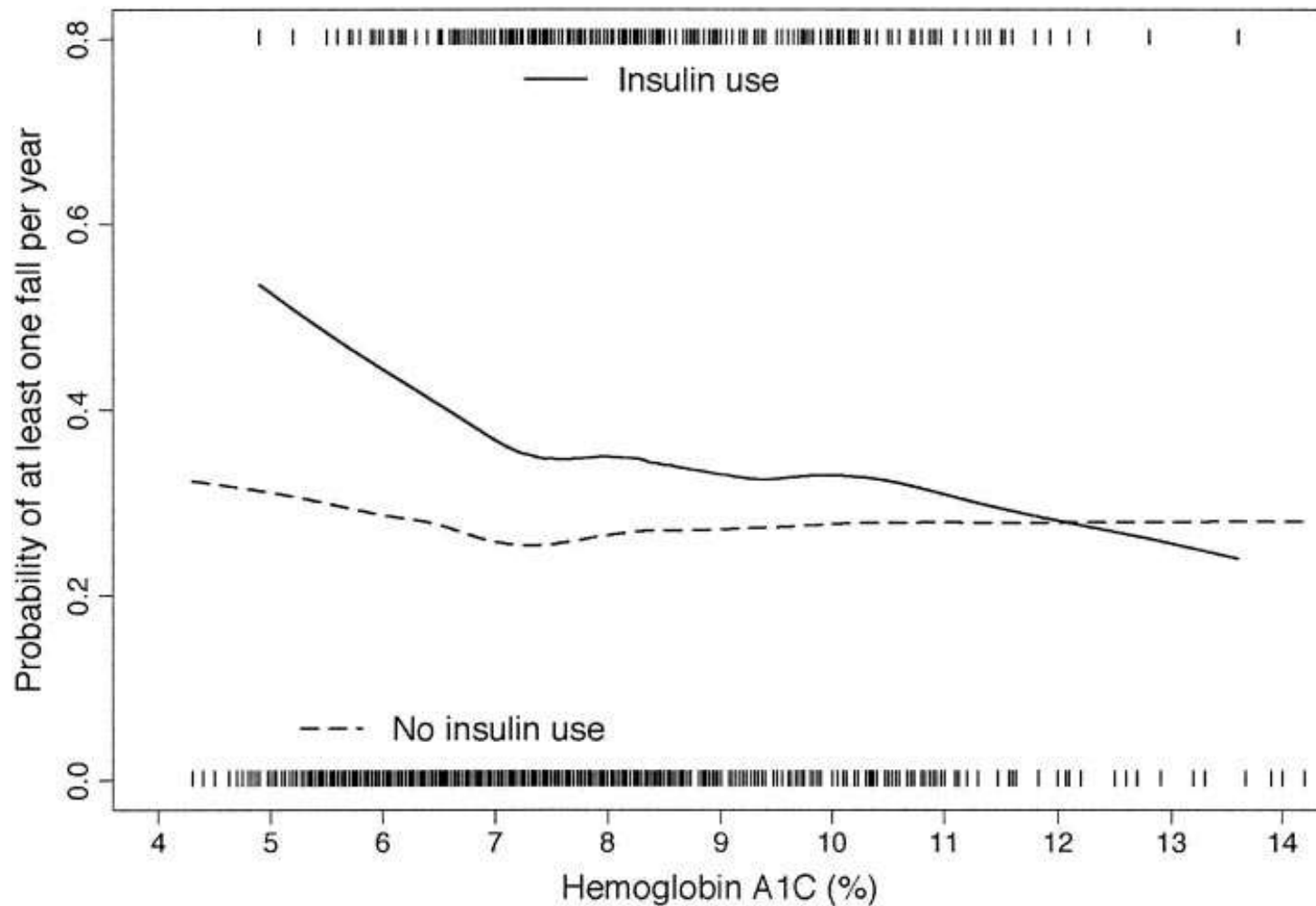
Anti-diabetic Medications and non-vertebral fractures in elderly men

Variable	HR ^a (95% CI)
Age (per 5-year increase)	1.07 (0.88, 1.29)
Race/ethnicity	
White	1.00 (reference)
Black	0.90 (0.35, 2.29)
Hispanic	3.57 (1.44, 8.87)
Asian	1.44 (0.56, 3.77)
Total hip BMD (per 1 SD decrease ^b)	1.69 (1.38, 2.06)
Fell in year before baseline (yes/no)	1.61 (1.06, 2.44)
Fasting glucose (per 1 SD increase ^c)	1.02 (0.91, 1.11)
Insulin use (yes/no)	1.62 (0.78, 3.37)
Metformin use (yes/no)	0.96 (0.60, 1.54)
Sulfonylurea use (yes/no)	1.66 (1.09, 2.51)
TZD use (yes/no)	1.18 (0.64, 2.16)

^a Adjusted for all other variables in the table. A total of 779 participants were included in the model

^b 1 SD=0.1 g/cm²

^c 1 SD=1.34 mmol/l



Diabetes-Related Complications, Glycemic Control, and Falls in Older Adults

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FOR THE HEALTH, AGING, AND BODY
COMPOSITION STUDY

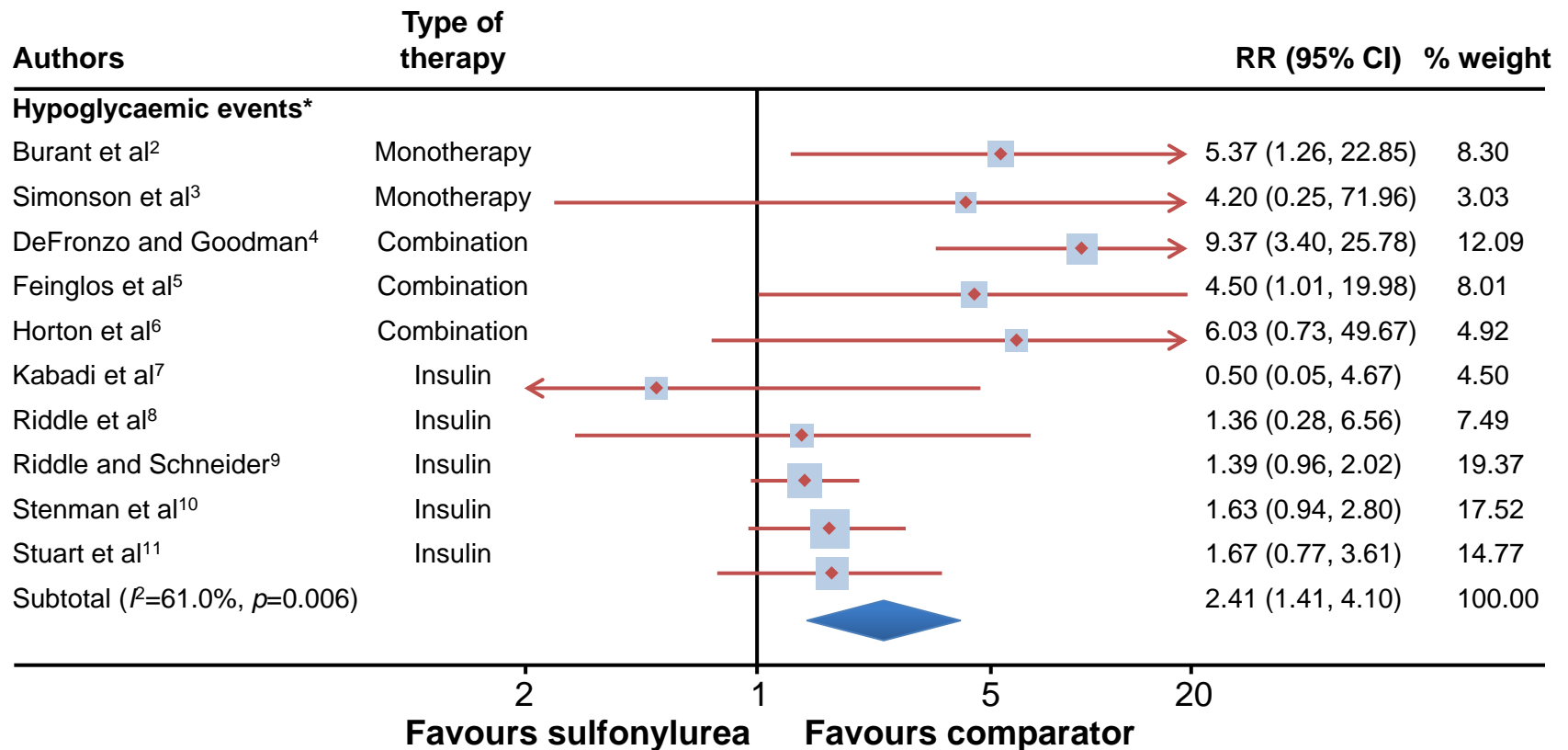
in any association between diabetes-related complications and risk of falls. Previous studies of falls among older diabetic adults were cross-sectional or had limited data characterizing glycemic control and diabetes-related complications. We used longitudinal data for diabetic participants in the Health, Aging, and

Covariates included in model	Non-insulin-treated diabetes†			Insulin-treated diabetes†		
	OR (95% CI)	Coefficient	Change in coefficient§	OR (95% CI)	Coefficient	Change in coefficient§
Age	1.53 (1.14–2.04)	0.42	—	3.98 (2.25–7.05)	1.38	—
Age + balance	1.34 (1.00–1.81)	0.30	–30%	2.98 (1.67–5.32)	1.09	–26%
Age + history of coronary heart disease	1.43 (1.06–1.92)	0.36	–16%	3.70 (2.08–6.57)	1.31	–7%
Age + history of arthritis	1.45 (1.08–1.95)	0.37	–12%	3.92 (2.21–6.95)	1.37	–1%
Age + peripheral neuropathy#	1.49 (1.11–1.99)	0.40	–6%	3.83 (2.16–6.79)	1.34	–3%
Multivariable model**	1.18 (0.87–1.60)	0.16	–61%	2.76 (1.52–5.01)	1.02	–32%

*Logistic regression models. N = 5,430. Women with missing values for any of the covariates in the multivariable model were excluded from all smaller models. †An average of more than one fall per year during follow-up. Mean follow-up time for falls was 7.2 (\pm 1.9) years. ‡Compared with women who did not report a history of diabetes. §Change in the logistic regression coefficient for diabetes compared with the coefficient in the age-adjusted model. ||Tandem walk score and tandem stand (eyes open). ¶Heart attack, angina, or congestive heart failure. #Loss of pressure sensitivity. **Adjusted for age, tandem walk score, tandem stand (eyes open), loss of pressure sensitivity, history of coronary heart disease, history of stroke, history of arthritis, history of fainting, grip strength, positive Geriatric Depression Score, near depth perception, and use of medications for sleeplessness or anxiety.

SUs result in significantly more hypoglycaemic events than other treatments

Meta-analysis of head-to-head studies¹



*Defined as either patient-reported symptoms or blood glucose levels below a threshold of 3.1–3.3mmol/l [55–60 mg/dl]

1. Hirst JA, et al. *Diabetologia* 2013;56:973-984. 2. Burant CF, et al. *Lancet* 2012;379:1403-1411. 3. Simonson DC, et al. *Diabetes Care* 1997;20:597-606. 4. DeFronzo RA, Goodman AM. *N Engl J Med* 1995;333:541-549. 5. Feinglos M, et al. *Diabetes Res Clin Pract* 2005;68:167-175. 6. Horton ES, et al. *Diabetes Care* 1998;21:1462-1469. 7. Kabadi UM, et al. *Diab Med J Brit Diabet Assoc* 1995;880-884. 8. Riddle M, et al. *Am J Med Sci* 1992;303:151-156. 9. Riddle MC, Schneider J. *Diabetes Care* 1998;21:1052-1057. 10. Stenman S, et al. *Diabetologia* 1988;31:206-213. 11. Stuart CA, et al. *Endocr Pract* 1997;3:344-348.

Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society

For patients with type 2 diabetes, sulfonylureas are the oral agents that pose the greatest risk for iatrogenic hypoglycemia and substitution with other classes of oral agents or even glucagon-like peptide 1 analogs should be considered

Severe Hypoglycemia in the TECOS trial

ITT HR (95% CI): 1.12 (0.89–1.40), p=0.33

	Sitagliptin	Placebo
	Participants with event n (%)	Participants with event n (%)
	160 (2.2%)	143 (1.9%)
Events per 100 patient-years	0.78	0.70

**Hypoglycemia requiring assistance*

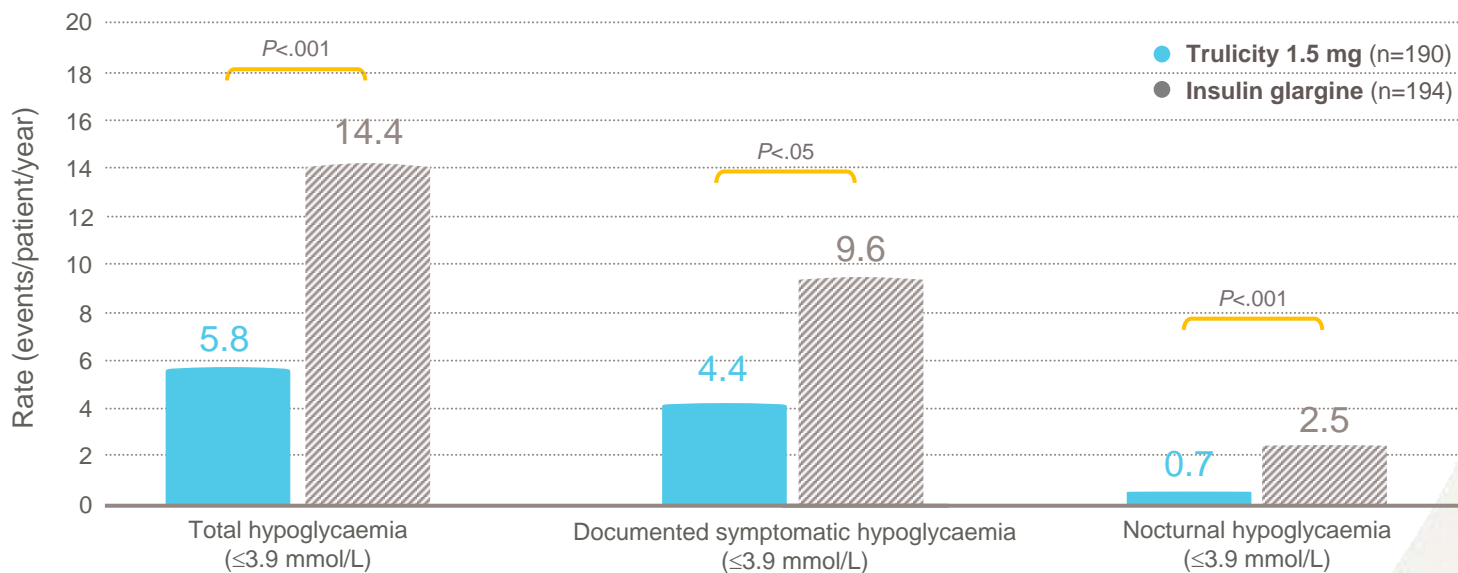
Dulaglutide- REWIND

	Dulaglutide (n=4949)	Placebo (n=4952)	Log-rank test p value
First study drug discontinuation	2092 (42.3%)	2171 (43.8%)	0.38
Acute pancreatitis*	23 (0.5%)	13 (0.3%)	0.11
Imaging and enzymes†	4 (0.1%)	3 (0.1%)	0.71
Imaging, enzymes, and symptoms‡	4 (0.1%)	3 (0.1%)	0.71
Any cancer§	351 (7.1%)	348 (7.0%)	0.98
Medullary thyroid carcinoma or C-cell hyperplasia¶	1 (<0.1%)	0	0.32
Thyroid cancer	7 (0.1%)	3 (0.1%)	0.21
Pancreatic cancer	19 (0.4%)	12 (0.2%)	0.22
Serious hepatic event	25 (0.5%)	40 (0.8%)	0.057
Serious renal or urinary event	84 (1.7%)	93 (1.9%)	0.46
Immune reactions	8 (0.2%)	20 (0.4%)	0.022
Serious gastrointestinal event	120 (2.4%)	117 (2.4%)	0.87
Supraventricular tachycardia or cardiovascular conduction disorders	216 (4.4%)	192 (3.9%)	0.26
Severe hypoglycaemia	64 (1.3%)	74 (1.5%)	0.38



⁸Gerstein HC et al. *Lancet* 2019;394:121-130.

Dulaglutide had lower rates of hypoglycaemia compared with once-daily insulin glargine through 52 weeks



- 52-week active-controlled study (AWARD-7) in patients with type 2 diabetes and moderate or severe kidney disease. Trulicity and insulin glargine groups both received concomitant insulin lispro
 - Primary endpoint was met: noninferiority of Trulicity 1.5 mg vs insulin glargine on HbA1c change from baseline to 26 weeks
 - Safety population; An additional group in this study received Trulicity 0.75 mg, which is the recommended dose for monotherapy
- AWARD = Assessment of Weekly Administration of LY2189265 in Diabetes; HbA1c = haemoglobin A1c.
Tuttle KR, et al. Presented at 53rd Annual Meeting of the European Association for the Study of Diabetes; September 11-15, 2017; Lisbon, Portugal. Oral presentation #2.

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Event	Semaglutide		Placebo	
	0.5 mg (N= 826)	1.0 mg (N= 822)	0.5 mg (N= 824)	1.0 mg (N= 825)
Severe or symptomatic hypoglycemic event**	191 (23.1)	178 (21.7)	177 (21.5)	173 (21.0)

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Table 2. Adverse Events.*

Event	Placebo (N = 2333)	Empagliflozin, 10 mg (N = 2345)	Empagliflozin, 25 mg (N = 2342)	Pooled Empagliflozin (N = 4687)
	<i>number of patients (percent)</i>			
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)

Conclusions

- Hypoglycaemia is the major factor limiting intensive control in T2D
- Can cause severe morbidity and mortality and lower health-related quality of life
- Insulin therapy and Sulphonylureas are associated with the highest risk of hypoglycaemia, both alone and in combination
- Replacement of sulphonylureas with new medications may significantly reduce the risk of hypoglycaemia