



HbA1c and diabetic complications

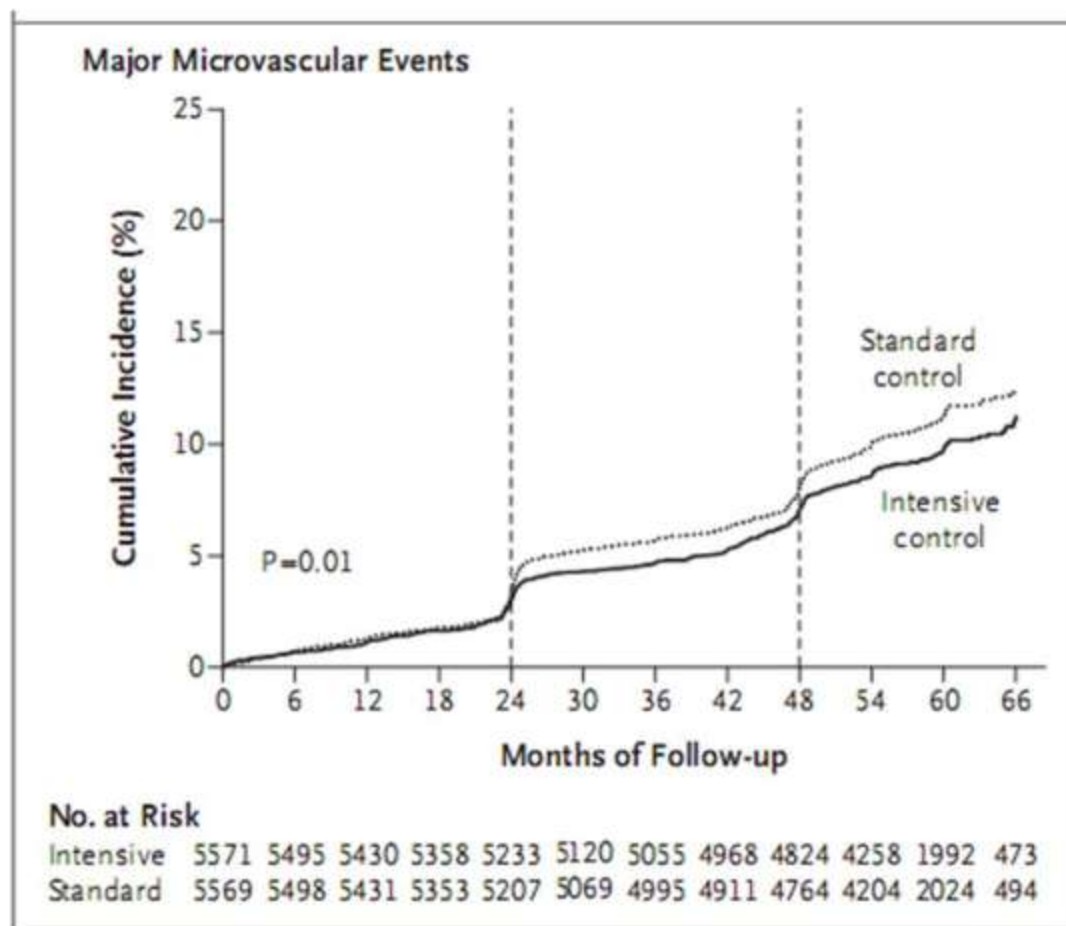


UKPDS

Risk reduction over 10 years

Any diabetes-related endpoint	12%	$P = 0.029$
Microvascular endpoints	25%	$P = 0.0099$
Myocardial infarction	16%	$P = 0.052$
Cataract extraction	24%	$P = 0.046$
Retinopathy at 12 years	21%	$P = 0.015$
Microalbuminuria at 12 years	33%	$P = 0.000054$

ADVANCE trial



ADVANCE Study Group.
N Engl J Med 2008;358:2532-45.



HbA1c and microvascular disease



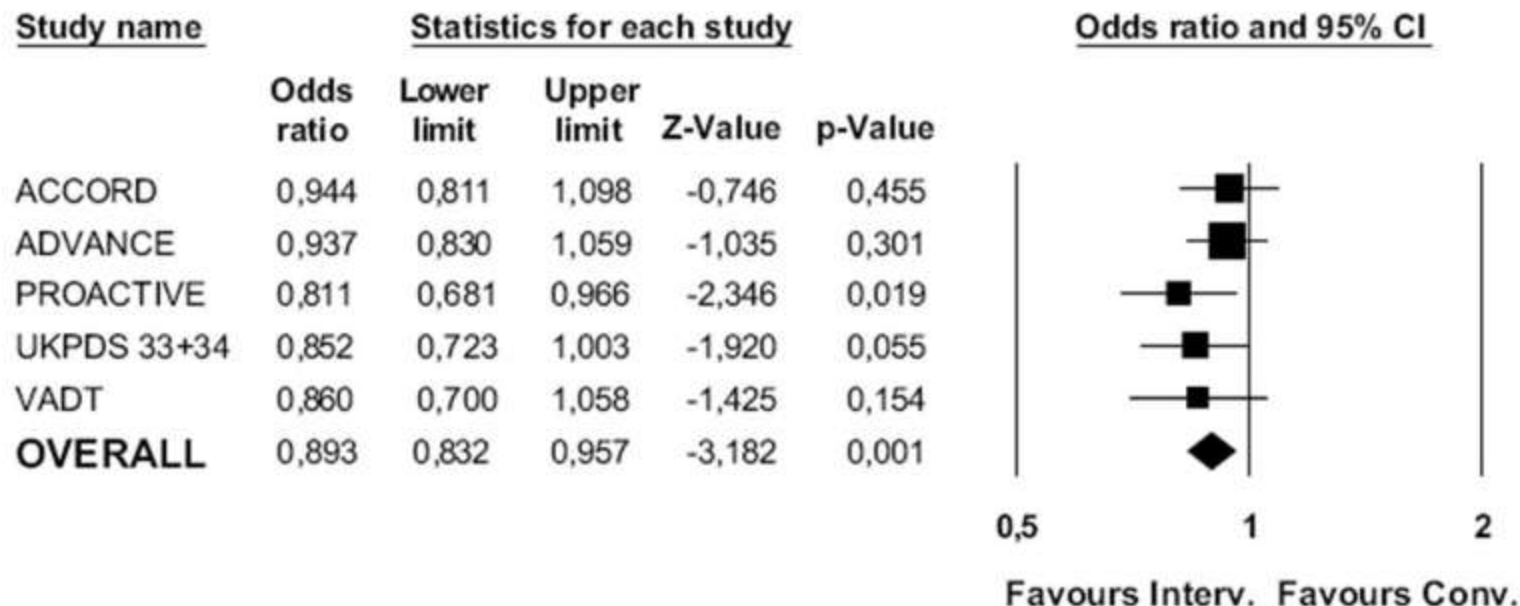
ADVANCE trial

Characteristic	Mean Glycated Hemoglobin Reduction during Follow-up (95% CI) <i>percent</i>	Intensive Control (N=5571) <i>number of patients (percent)</i>	Standard Control (N=5569)	Hazard Ratio (95% CI)	Relative Risk Reduction (95% CI) <i>percent</i>
Age					
<65 yr	0.70 (0.65 to 0.75)	367 (16.1)	421 (18.7)		14 (1 to 25)
≥65 yr	0.70 (0.65 to 0.75)	642 (19.5)	695 (21.0)		8 (-3 to 17)

ADVANCE Study Group.
N Engl J Med 2008;358:2532-45.

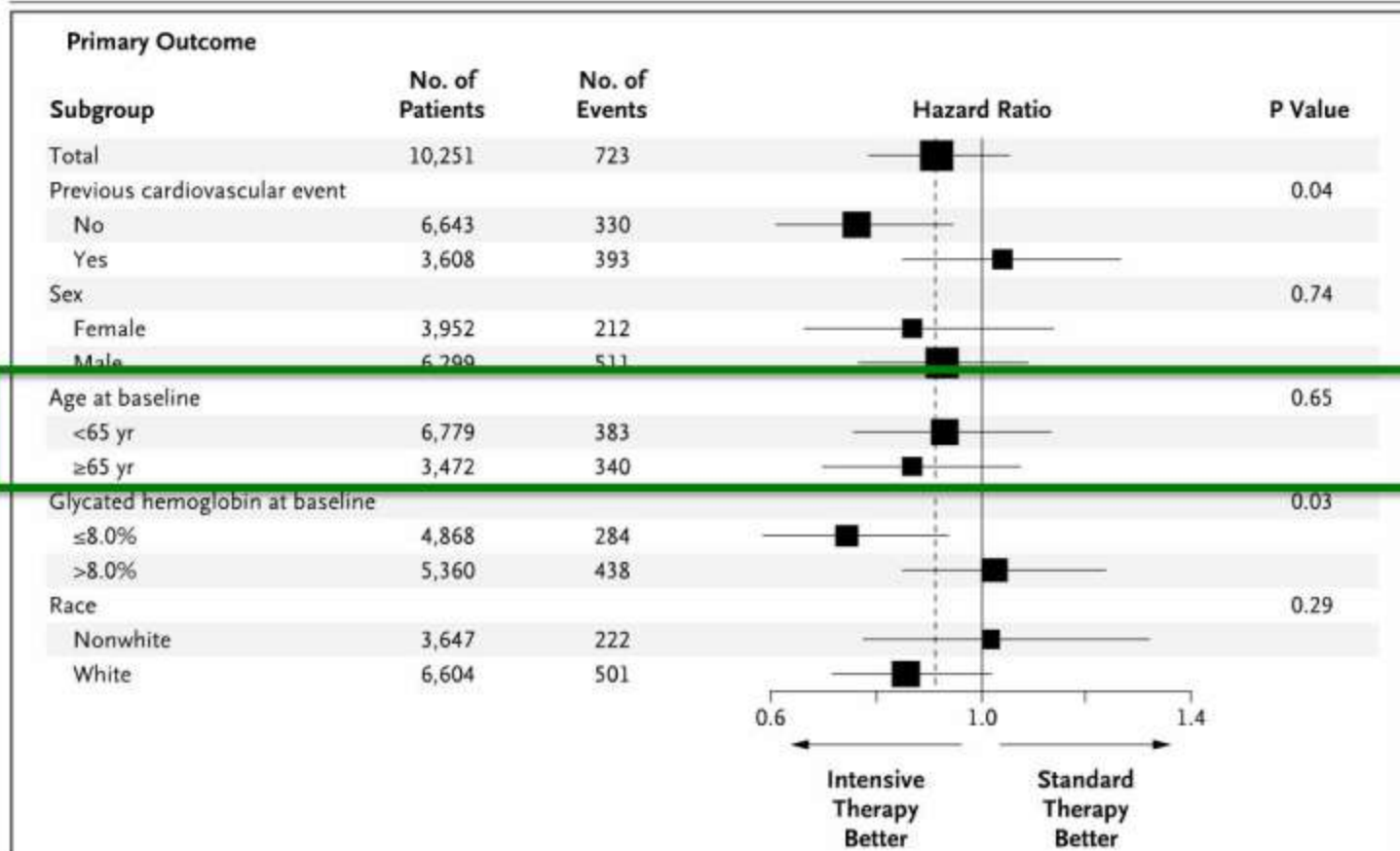
Meta-analysis of large-scale RCTs

Cardiovascular events



HbA1c and macrovascular disease

ACCORD trial





HbA1c in advanced age



Reduced life expectancy (smaller benefit)

Reduced functional benefit for avoidance of some microvascular complications

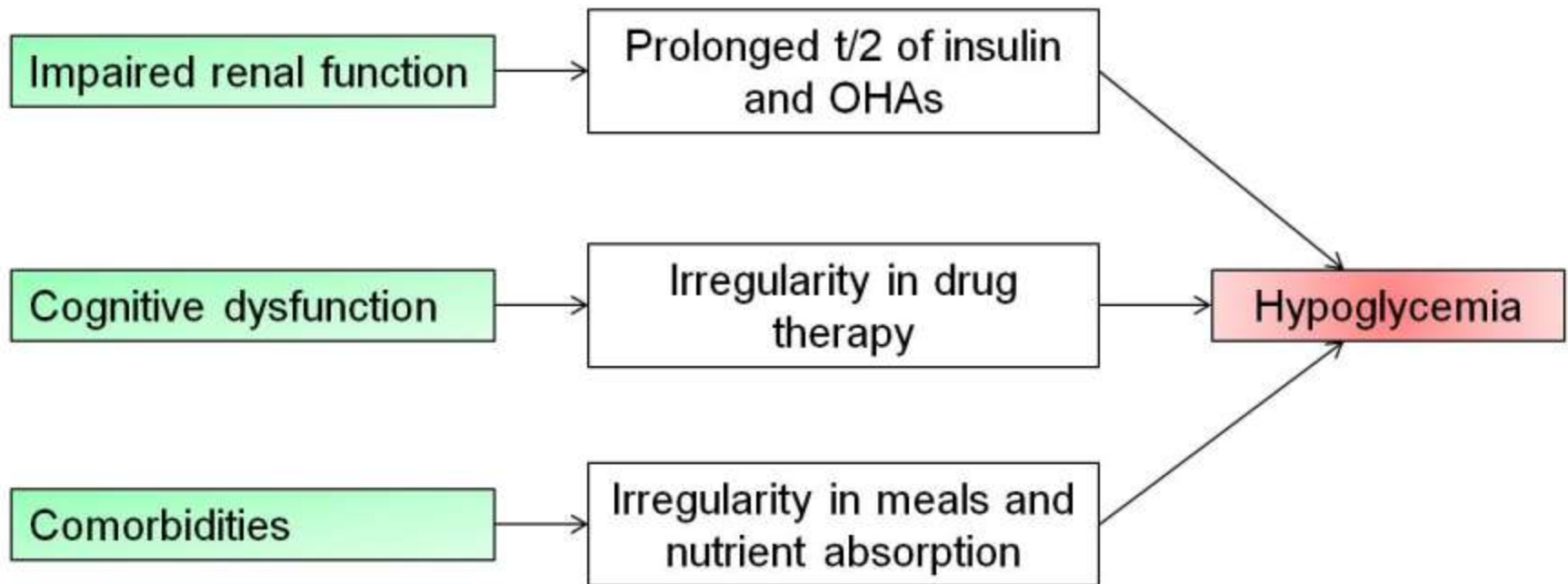
Greater risk of hypoglycemia

Greater risk of consequences from hypoglycemia

Impact of some therapies on patients' autonomy

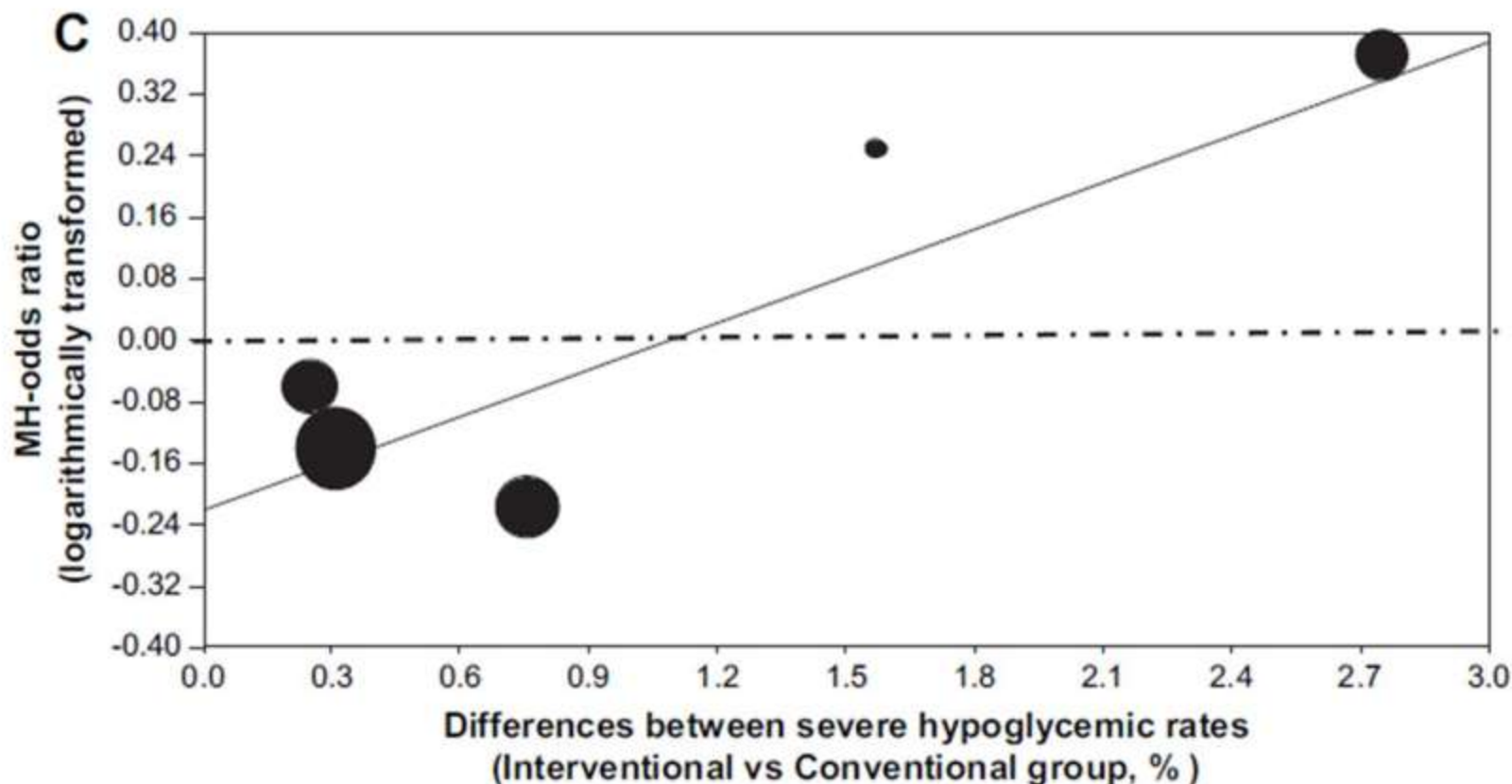


Hypoglycemic risk in aging T2DM



Glycemic control and CV mortality

Meta-analysis of large-scale RCTs



Mannucci E, Monami M, Lamanna C, Marchionni N.
Nutr Metab Cardiovasc Dis 2009;19:604-612.



Hypoglycemia and falls

A cohort study



Population with type 2 diabetes and nature of accident	Hazard ratio (95% CI)	Predicted incidence rate per 10000 person-years (95% CI)	
		Hypoglycaemia	No hypoglycaemia
Age <65 years			
Any accident	1.35 (1.14, 1.61)*	138.5 (114.1, 162.9)	102.8 (90.3, 115.3)
Accidental fall	1.17 (0.88, 1.57)	42.7 (30.4, 55.1)	36.4 (29.5, 43.4)
Motor vehicle accident	2.31 (1.44, 3.70)*	23.9 (12.4, 35.5)	10.4 (6.3, 14.4)
Other accident	1.43 (1.13, 1.81)*	76.0 (57.2, 94.7)	53.1 (43.7, 62.5)
Age ≥65 years			
Any accident	1.46 (1.18, 1.80)*	135.5 (108.0, 162.9)	92.9 (78.9, 106.9)
Accidental fall	1.52 (1.18, 1.95)*	78.9 (58.3, 99.4)	52.0 (41.4, 62.6)
Motor vehicle accident	0.79 (0.26, 2.38)	4.7 (0.0, 9.7)	6.0 (2.6, 9.4)
Other accident	1.23 (0.82, 1.85)	38.0 (23.6, 52.3)	30.8 (23.1, 38.6)

Diabetes therapy and fractures

A case-control study

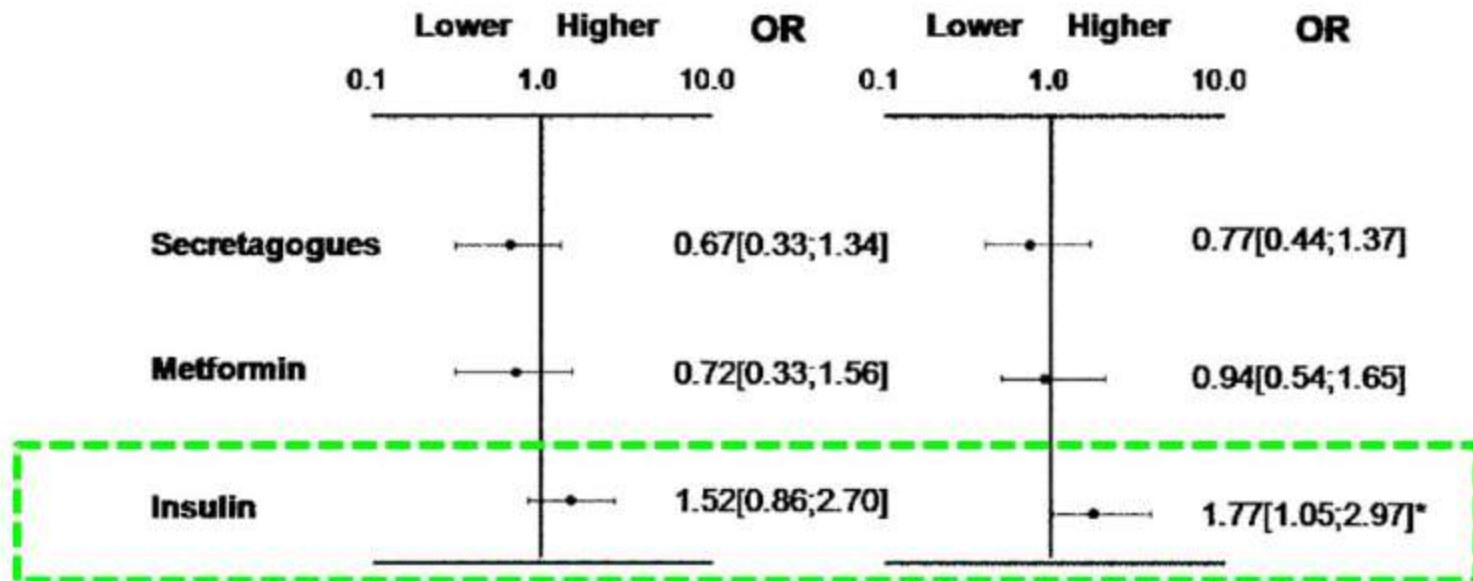


Figure 1—Adjusted ORs, with 95% CI, for bone fractures of exposure to different hypoglycemic drugs in a logistic regression model. Left panel: Exposure for at least 36 months (mean \pm SD 67.6 \pm 22.3, 66.0 \pm 21.5, and 60.2 \pm 18.3 months for secretagogues, metformin, and insulin, respectively). Right panel: Exposure at index date. Data are presented on a logarithmic scale. *P < 0.05.



All-cause mortality in population

Relationship with HbA1c



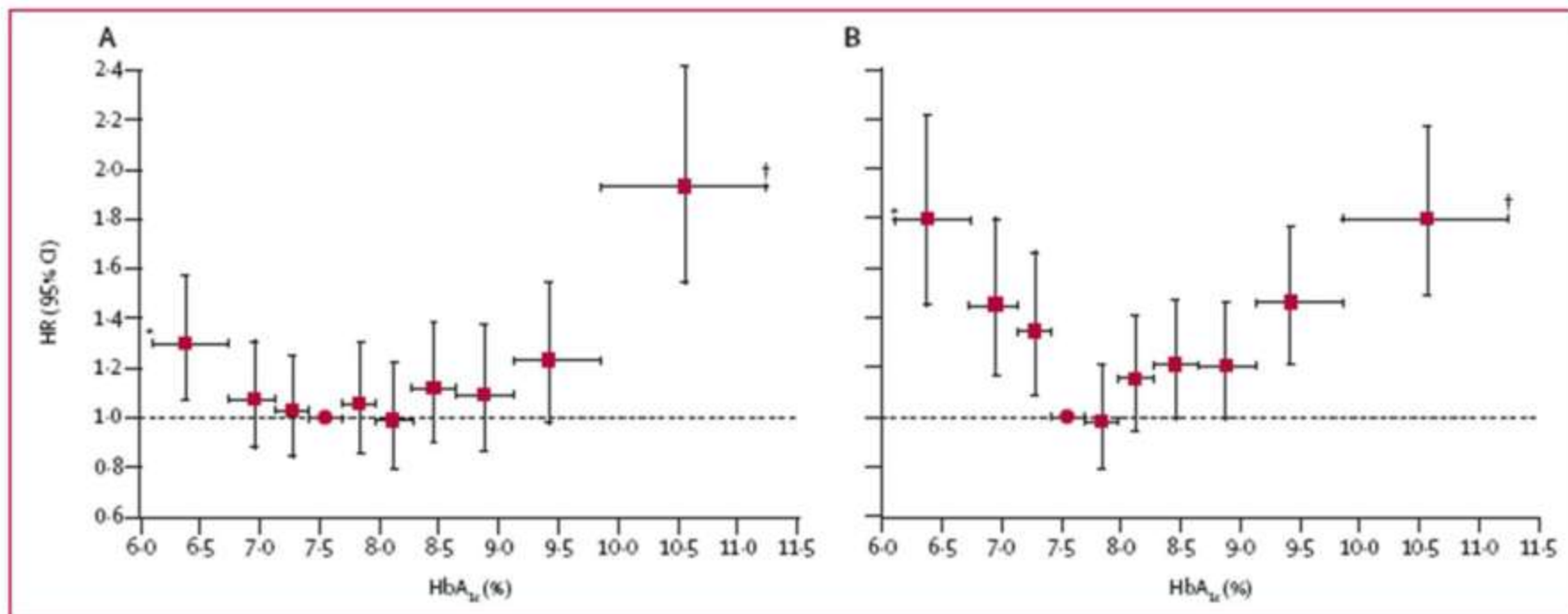
Death from any cause

Glycated hemoglobin category — hazard ratio (95% CI)

<5.0%	1.43 (1.17–1.74)
5.0 to <5.5% (reference)	1.00
5.5 to <6.0%	1.34 (1.18–1.52)
6.0 to <6.5%	1.92 (1.63–2.27)
≥6.5%	1.92 (1.54–2.40)

All-cause mortality in T2DM

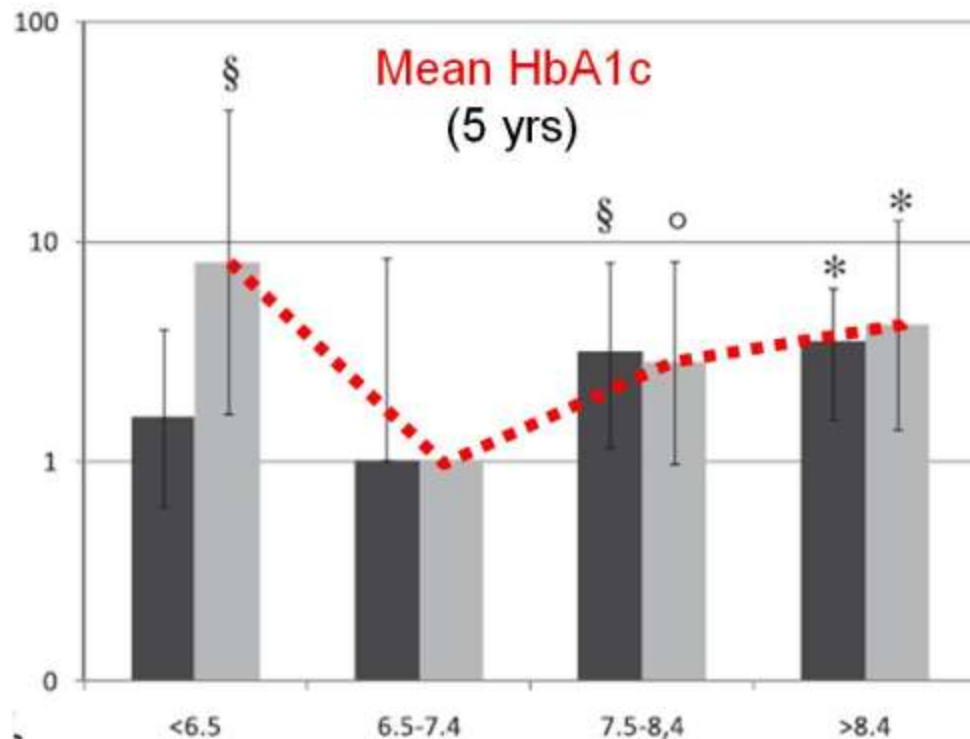
Relationship with HbA1c





All-cause mortality in T2DM

Relationship with HbA1c



■ Non-insulin treated patients
■ Insulin treated patients

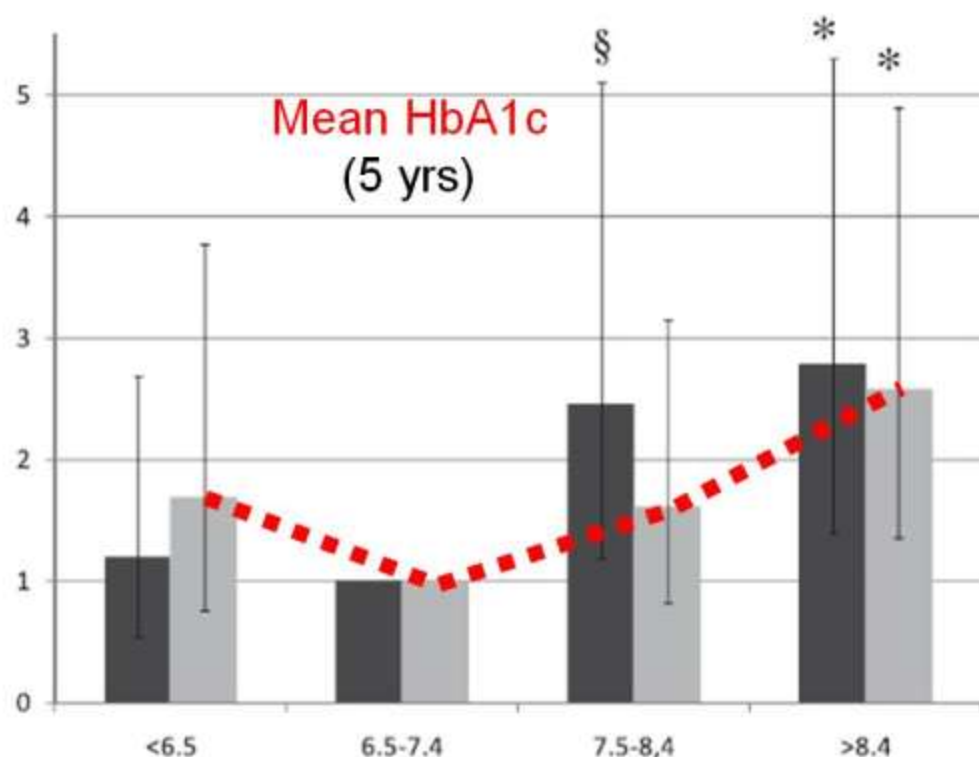
mean follow-up of 5.7 ± 3.5 years

Survivors	Dead
427 (44.0)	427 (47.8)



All-cause mortality in T2DM

Relationship with HbA1c



Age <71 yrs
Age ≥71 yrs

mean follow-up of 5.7 ± 3.5 years

Survivors	Dead
427 (44.0)	427 (47.8)

- Obiettivi di compenso glicemico meno stringenti (HbA_{1c} 7-8%) dovrebbero essere perseguiti in pazienti con diabete di lunga durata > 10 anni soprattutto con precedenti di CVD o una lunga storia di inadeguato compenso glicemico o fragili per età e/o comorbidità. L'approccio terapeutico deve essere tale da prevenire le ipoglicemie. (**Livello della prova VI, Forza della raccomandazione B**)



Advanced age or frailty?



Comorbidity

Renal function

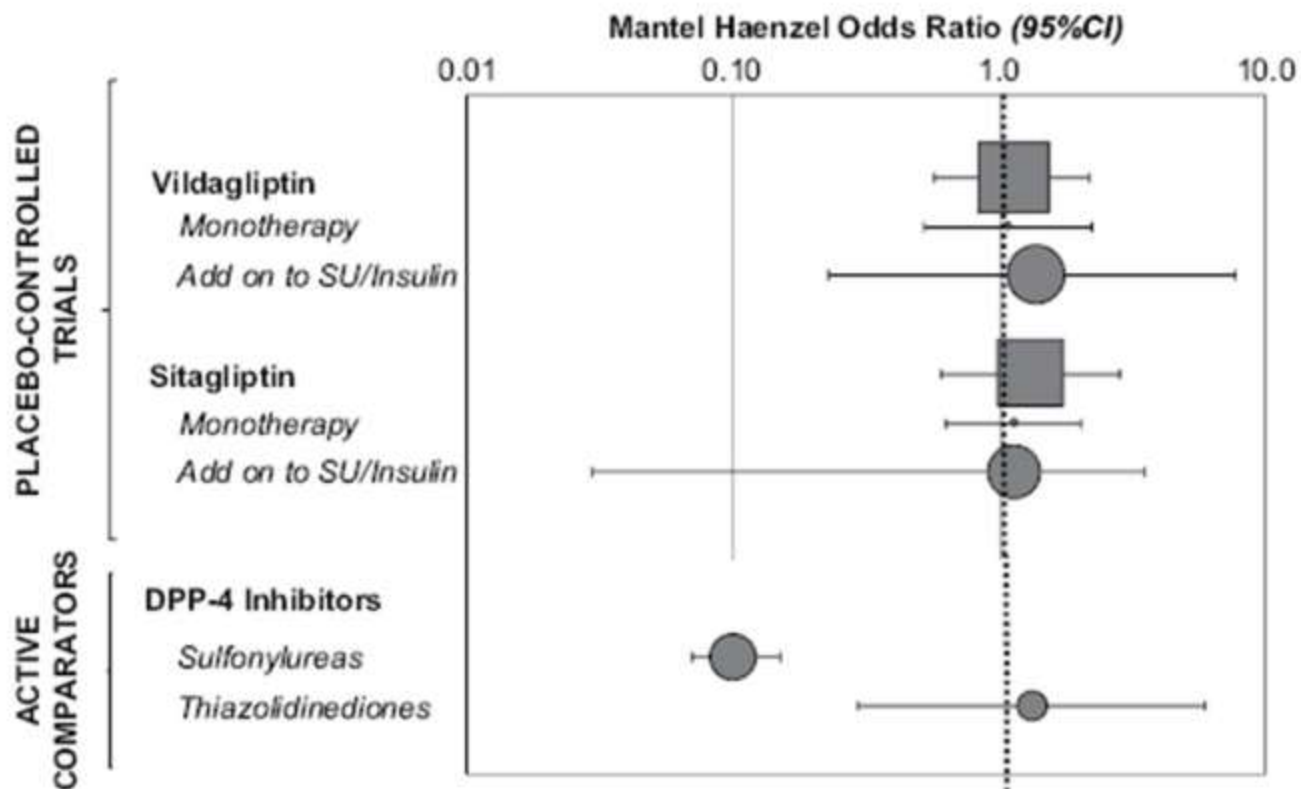
Cognitive function

Duration of diabetes

Autonomy and social support

DPP4i and hypoglycemia

Meta-analysis of RCTs



Mantel–Haenzel odds ratio (with 95% CI) for any hypoglycemia (logarithmic scale).

Monami M, Iacomelli I, Marchionni N, Mannucci E.
Nutr Metab Cardiovasc Dis, 2009



Diabetes drugs



Not inducing hypos

Metformin

DPP4 inhibitors

GLP-1 receptor agonists

Thiazolidinediones

AGI

SGLT-2 inhibitors

Inducing hypos

Insulin

Sulfonylureas

Glinides



Diabetes drugs and hypos



Mode of administration

Oral

Metformin

DPP4 inhibitors

Sulfonylureas

Glinides

Thiazolidinediones

AGI

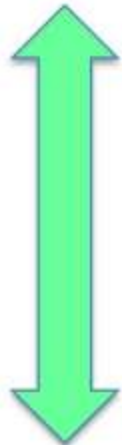
SGLT-2 inhibitors

Injectable

Insulin

GLP-1 receptor agonists

THERAPEUTIC TARGET



PATIENT'S
CHARACTERISTICS:
Age
Comorbidity
Life expectancy
Frailty
...



ACTION THRESHOLD

A paradigm shift?

THERAPEUTIC TARGET



PATIENT'S CHARACTERISTICS:
Age
Comorbidity
Life expectancy
Frailty
...

≠

ACTION THRESHOLD



ENVIRONMENT:
Social support
Healthcare organization
...

DRUG FEATURES:
Hypoglycemic risk
Other side effects
Contraindications
Mode of administration
...



Conclusions (for now)



- It is reasonable to adopt higher therapeutic targets in patients with reduced life expectancy, comorbidities, long duration of diabetes, frailty
- The action threshold (i.e., HbA1c level at which a new drug should be added) can be higher than the therapeutic target, depending on the characteristics of the drug (hypoglycemic risk, other side effects, mode of administration)
- Social support and organization of healthcare can be an issue
- Age per se is not relevant



What is still missing



A larger number of trials in advanced age (and/or larger subgroups of elderly patients in trials)

Studies on the effect of improved metabolic control on cognitive function

RCTs to assess the possibility of preventing disability through a more accurate glycemic control