

Hypoglycemia: A Complication When Targeting Type 2 Diabetes

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Diabetes is the Epidemic of Our Time

- 24 million Americans have diabetes
- 7.8% of adults have diabetes
- 213,000 people die each year from diabetes
- >60 million people have pre-diabetes

Diabetes increased 70% among people age 30-39 in approximately the last decade



Case Conversation

A 63 year old male is treated for T2DM for 16 years. Comorbidities include hypertension and hyperlipidemia. Medications include analogue basal insulin, metformin, ACE inhibitor, and statin

His Hgb A1C is 8.6 %.

Because of the risk of hypoglycemia and CVD risk he is concerned about trying to achieve an Hgb A1C of 6.5%

Please discuss

Risk Factors and Consequences of Hypoglycemia in Type 2 Diabetes

■ Risk factors¹

- Use of insulin secretagogues and insulin therapy
- Missed or irregular meals
- Advanced age
- Duration of diabetes
- Impaired awareness of hypoglycemia

■ Consequences^{2,3}

- Suboptimal glycemic control
- Other health effects ?

1. Amiel SA et al. *Diabet Med.* 2008;25(3):245–254.

2. Landstedt-Hallin L et al. *J Intern Med.* 1999;246(3):299–307.

3. Cryer PE. *J Clin Invest.* 2007;117(4):868–870.

OUTLINE

1. Dangers: Blunted hormonal response to hypoglycemia
(glucagon stimulation, antecedent hypoglycemia)
2. Hypoglycemia evaluation in outcome and targeted trials: UKPDS, ACCORD, VADT, 4 - T, Currie trial
3. Targeting Hgb A1C for tighter control

Characteristics of Patients at an Increased Risk of Hypoglycemia

- Are older¹
- Have a long duration of diabetes¹
- Regularly miss meals²
- Exercise²
- Take greater than the prescribed dose of their medication²

OUTLINE

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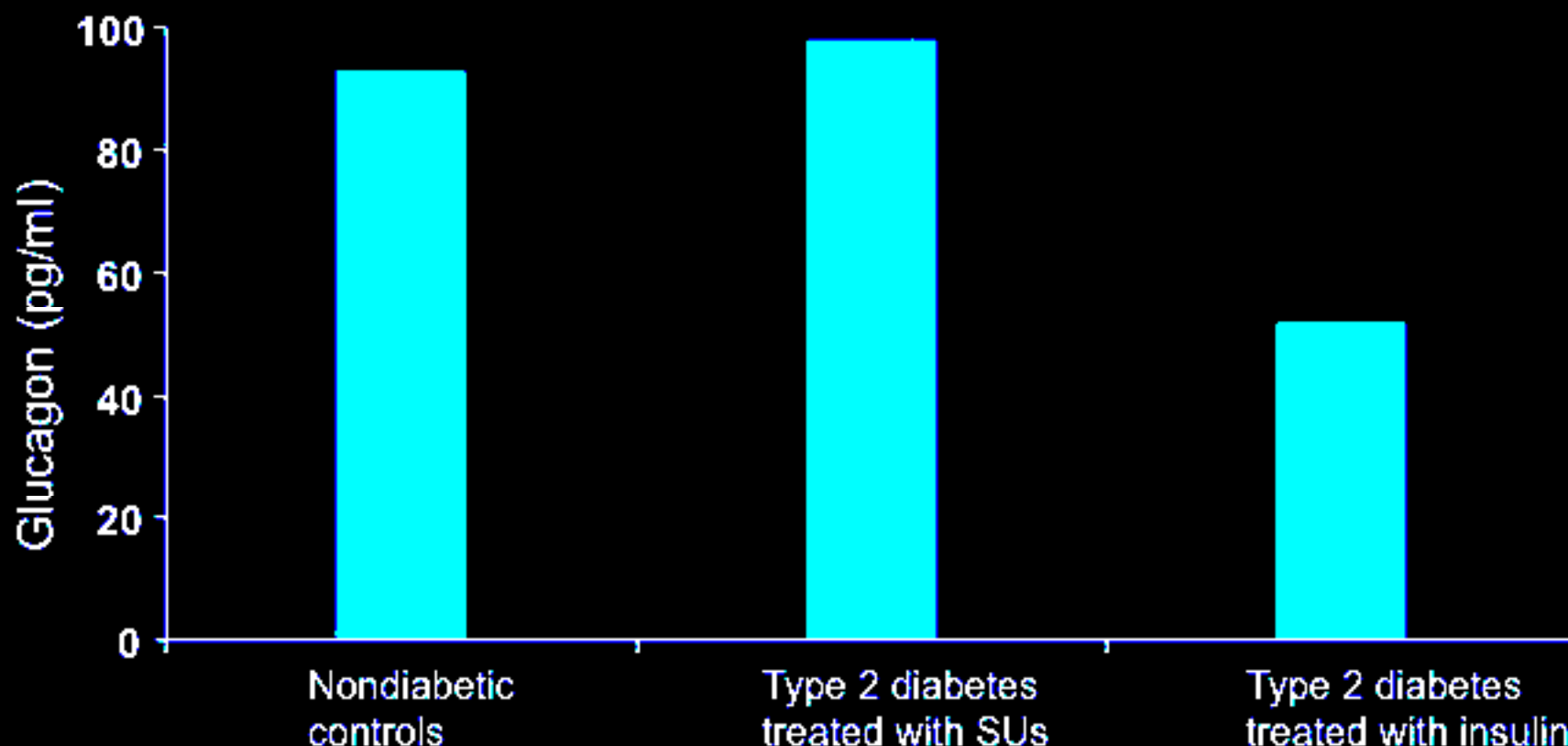
(glucagon stimulation, antecedent hypoglycemia)

2. Hypoglycemia evaluation in outcome and targeted trials: UKPDS, ACCORD, VADT, 4 T, Currie trial

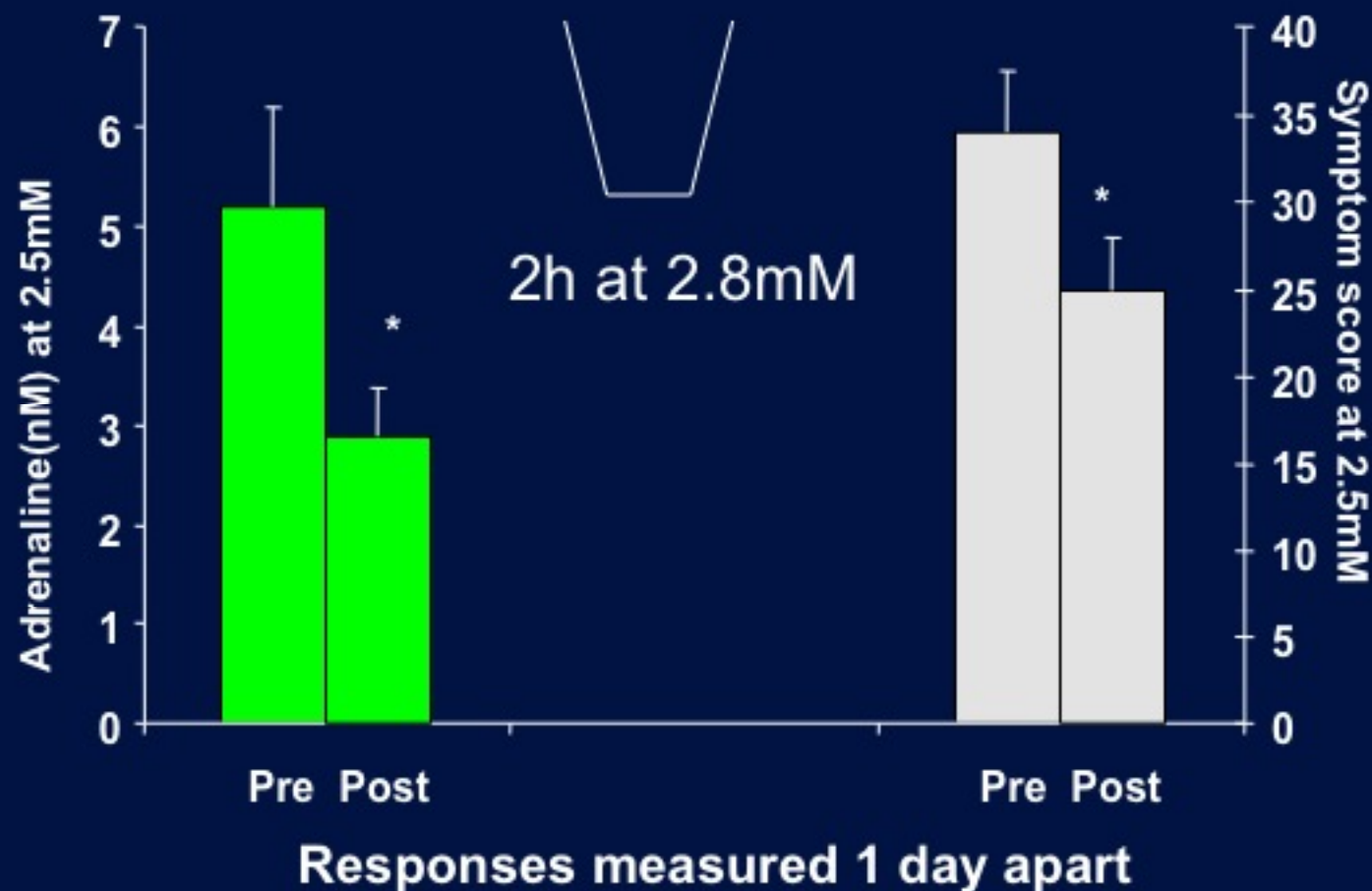
3. Targeting Hgb A1C for tighter control

The Glucagon Response to Hypoglycemia is Reduced in “More Advanced” Type 2 Diabetes

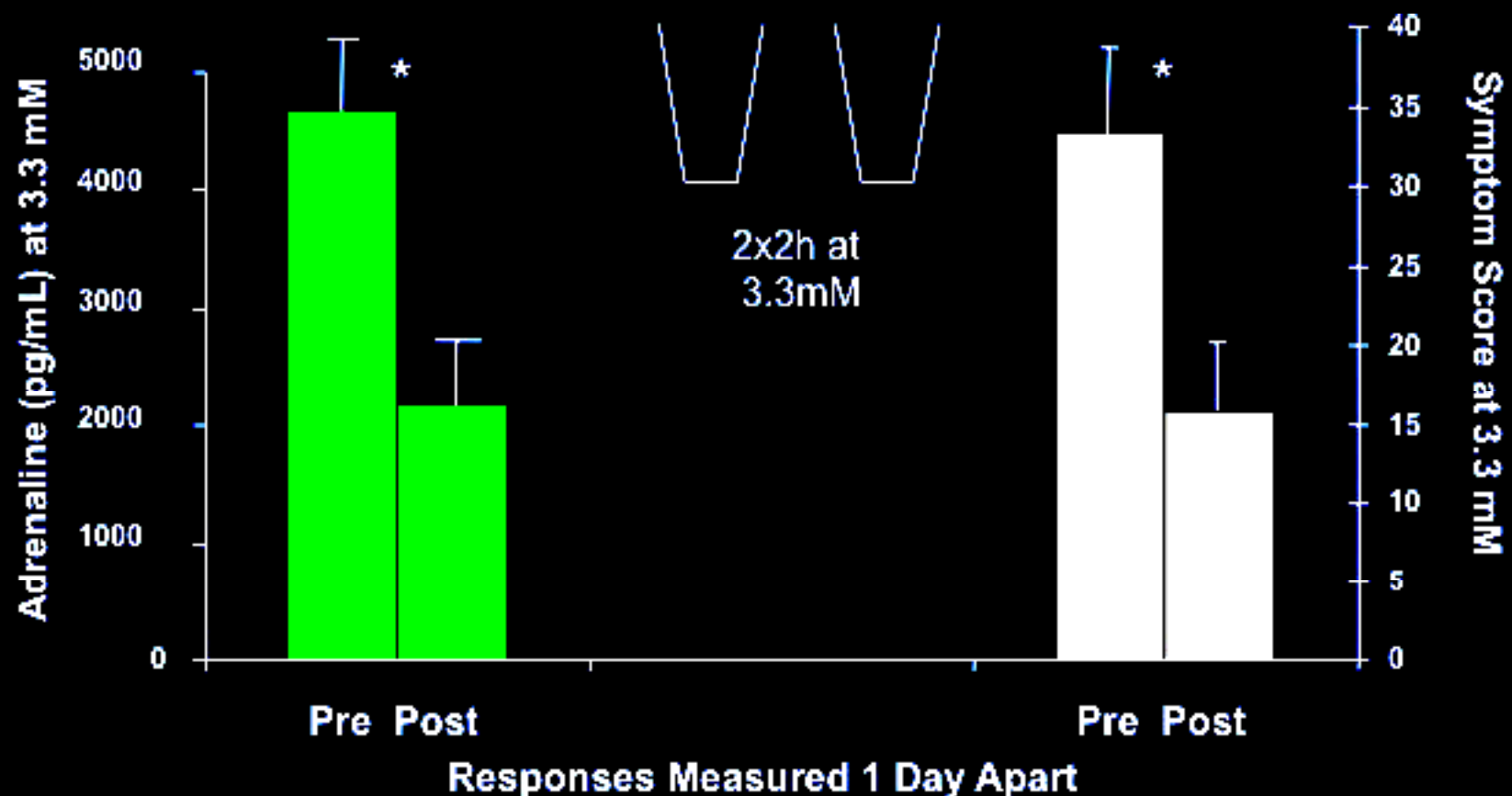
Glucagon response at plasma glucose 2.5mM



Effect of One Episode of Antecedent Hypoglycemia



Effect of Two Episodes of Antecedent Hypoglycemia in 15 patients with Type 2 diabetes (HbA1c 10.2%)



OUTLINE

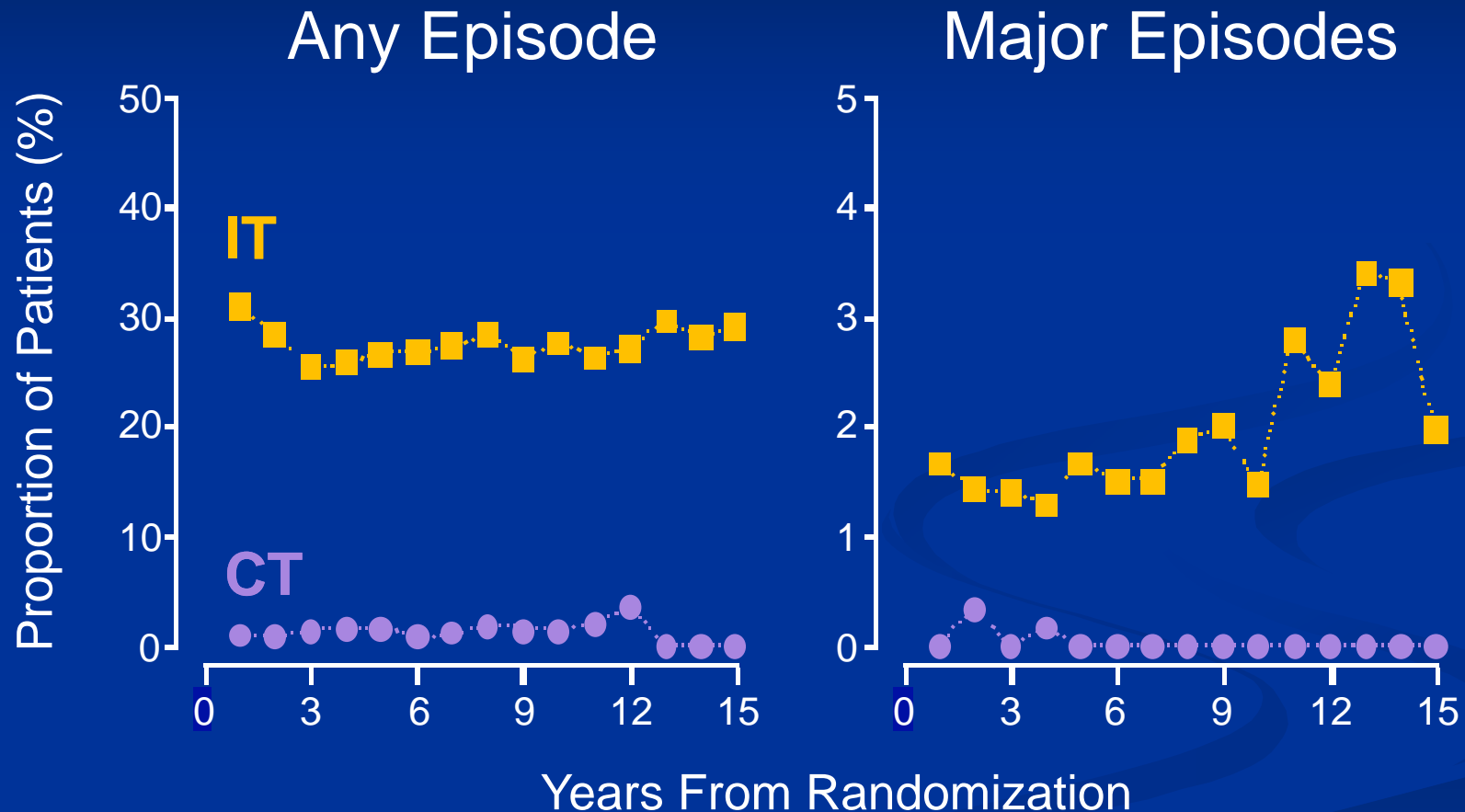
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Hypoglycemic Episodes per Annum - UKPDS



37% of patients had 2 episodes of hypoglycemia per year

The Three Current Trials

Glycemia

	ACCORD		ADVANCE		VADT	
	Intensive	Standard	Intensive	Standard	Intensive	Standard
Baseline	8.1%		7.5%		9.4%	
Final	6.4%	7.5%	6.4%	7.0%	6.9%	8.4%

ACCORD Outcomes

ADA 2009

- **Baseline** mortality predictors: $A_{1c} > 8.5\%$, ASA use, neuropathy hx
- 20% ↑ risk of death for every 1% ↑ $A_{1c} > 6\%$
 - 1% ↓ HbA1c associated with 56% ↓ adjusted mortality in intensive therapy group ($P=0.0001$); but 1% ↓ HbA_{1c} ↓ risk 14% in standard therapy group ($P=0.17$)
- $A_{1c} < 7\%$ did not explain excess deaths or predict mortality risk
- **Greater ↓ A_{1c} associated with reduced mortality; higher mortality with $A_{1c} > 7\%$**
- Of 451 deaths, 1 severe hypo, but glucose measures n/a near times of deaths for others

ACCORD Definition of a Severe Hypoglycemic Episode

- Hypoglycemia requiring medical or paramedical attention, **AND**
 - Documented blood glucose < 50 mg/dl (2.8 mmol/L), or
 - Prompt recovery with administration of oral CHO, IV glucose, or subcutaneous glucagon

Each participant's 'Glucose Diary' was reviewed at each clinic visit to identify the occurrence of one of these hypoglycemic events

What is Already Known on this Topic

- Intensive glycaemia control results in increased rates of severe hypoglycemia
- The intensive glycaemia control intervention used in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was associated with increased mortality (hypoglycemia?)

Adverse Outcomes:

Intensive vs Std	ACCORD*	ADVANCE	VADT
Severe hypoglycemia (% per yr)	3.0 vs 1.0	0.7 vs 0.4	-
Hypoglycemia requiring assistance (% per year)	4.6 vs 1.5	1.8 vs 0.6	2.3 vs 1.1
Weight gain >10 Kg	27.8 % vs 14.1%	0.0 vs -1.0	-
Weight gain (Kg) Intensive group	3.5	0.7	6.8

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT = Veterans Affairs Diabetes Trial.

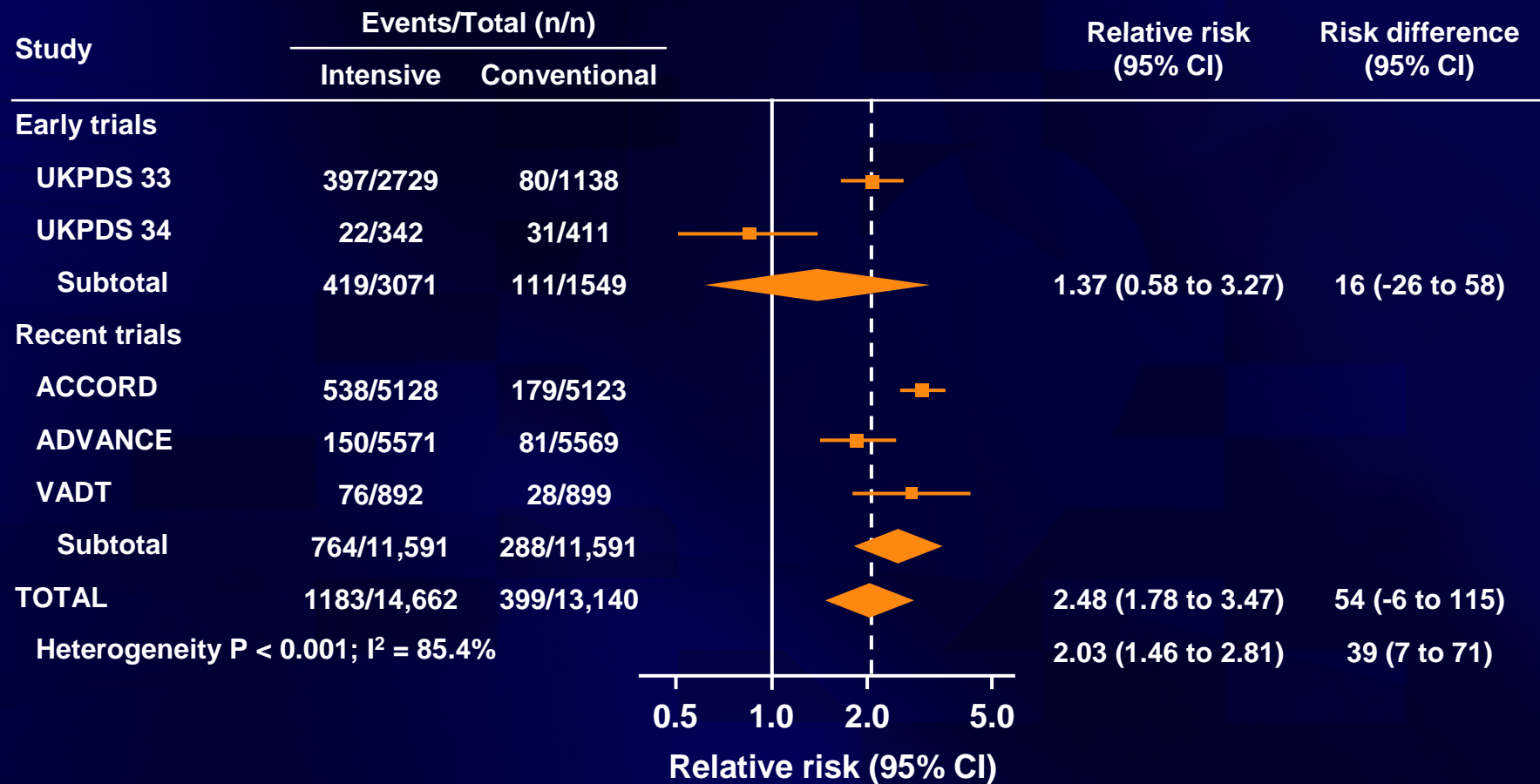
ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2557.

ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572.

VADT Study Results. ADA Scientific Session; San Francisco, CA; 2008.

Diabetes Obesity and Metabolism, 2008. In press.

Risk of severe hypoglycemia: Intensive glucose control vs standard treatment

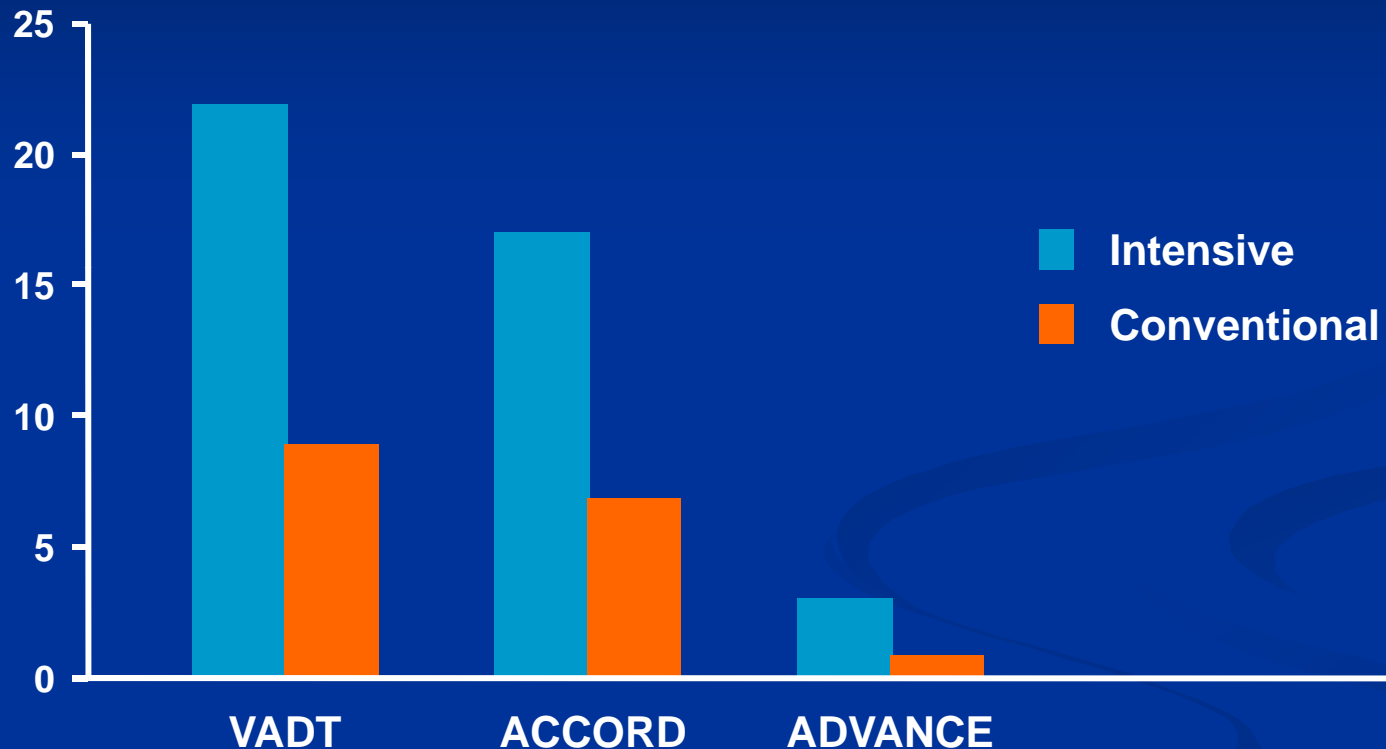


The Three Current Trials

Glycemia

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Final	6.4%	7.5%	6.4%	7.0%	6.9%	8.4%

Percent of Patients Experiencing at Least 1 Episode of Hypoglycemia In T2DM Intensification Trials



Duckworth W et al. *Diabetes Care*. 2001;24:942-945.

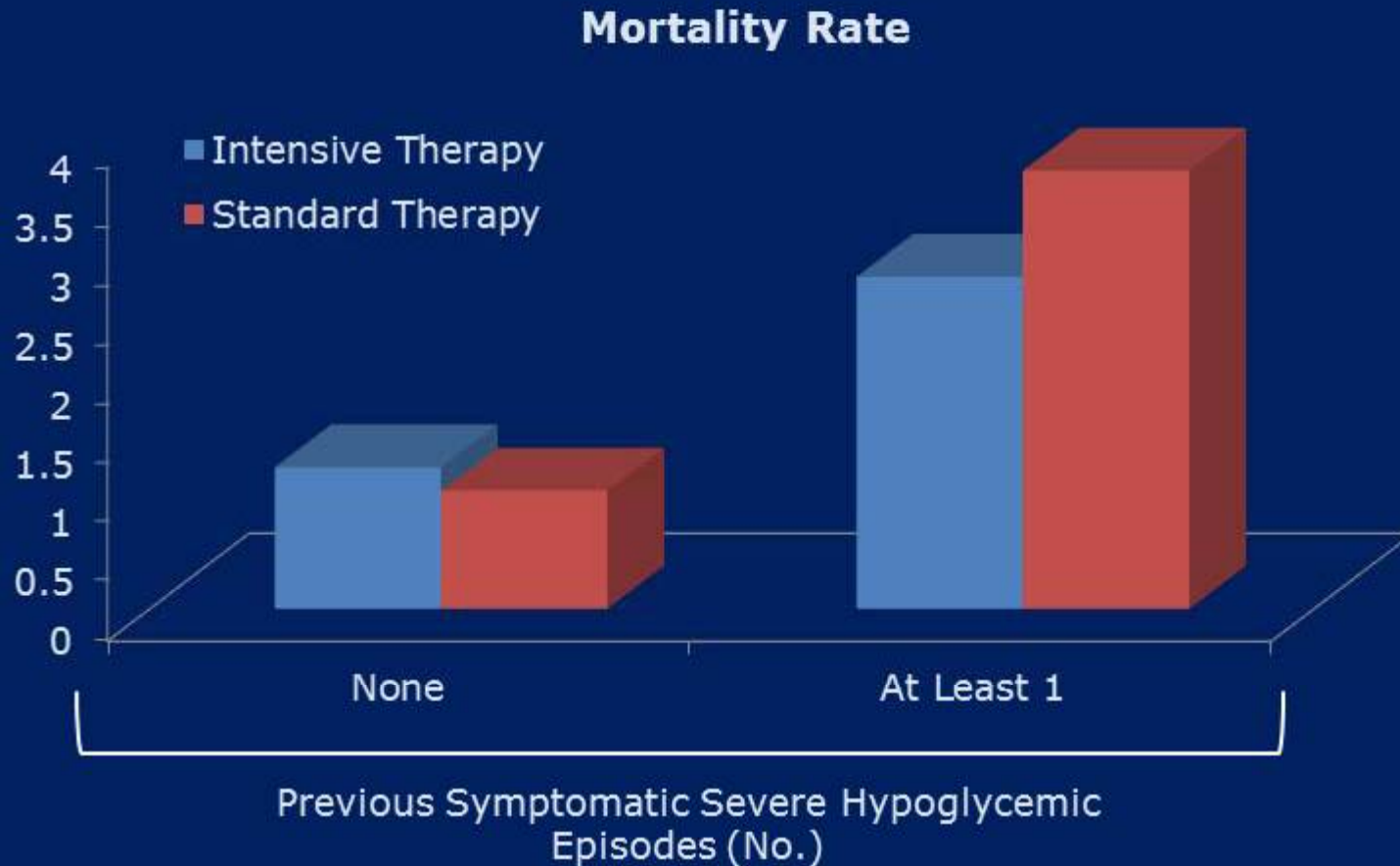
ACCORD. *N Engl J Med*. 2008;358:2545-2557.

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Mortality and episodes of hypoglycaemia among all participants and by study arm

All Participants	All Participants 451/10194 (4.40%)	Standard Group 197/5088 (3.87%)	Intensive Group 254/5106 (4.97%)
Hypoglycaemic Events requiring any assistance, medical or non medical (HA)			
No events	377/9122 (4.13)	176/4832 (3.64)	201/4090 (4.69)
At least one hypoglycaemic event	74/1072 (6.90)	21/256 (8.20)	53/816 (6.49)

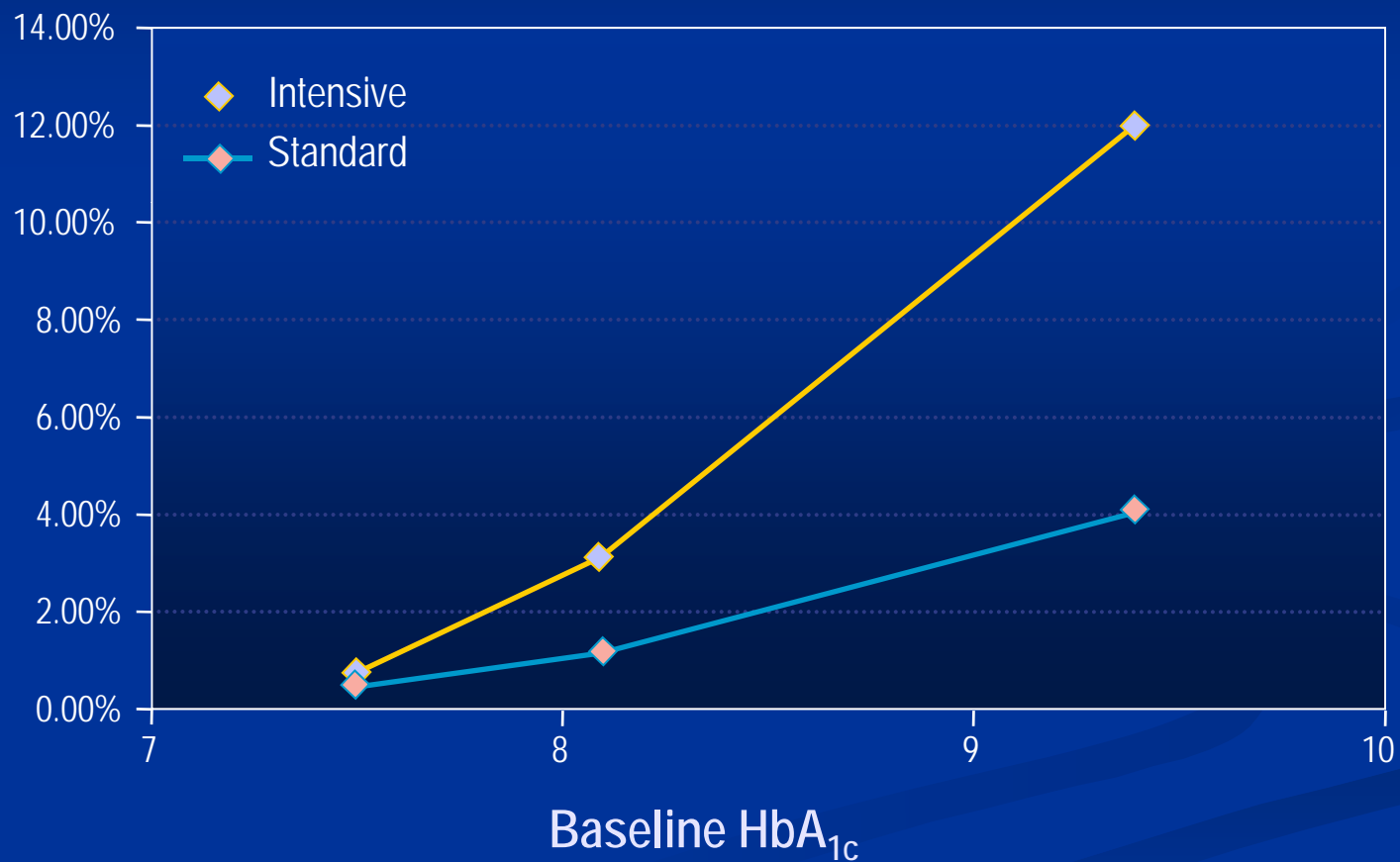
History of Symptomatic, Severe Hypoglycemia Increases Mortality Risk



$P=0.076$ between history of hypoglycemia and glycemia intervention
Bonds DE, et al: *BMJ*. 2010;340:b4909.

Severe Hypoglycemia Frequency

Intensive vs Standard Treatment



Tight Glycemic Control Controversies

Patients with lower baseline glycemia may require less glucose lowering agents- resulting in hypoglycemia –
You are already close to goal

What This Study Adds

- Patients with type 2 diabetes who experience symptomatic, severe hypoglycaemia are at increased risk of death regardless of the intensity of glucose control regardless of STD or INT groups.
- The increased risk of death seen in the ACCORD trial among participants in the intensive glycaemia control arm cannot be attributed to the increased rate of severe hypoglycaemia in intensive arm participants (Mortality greater with history of previous hypoglycemia in the STD arm over INT arm)

BMJ 2010;340:b4909

Symptomatic Severe Hypoglycemia

Tip of the Iceberg?

Symptomatic Severe

Symptomatic Non-severe

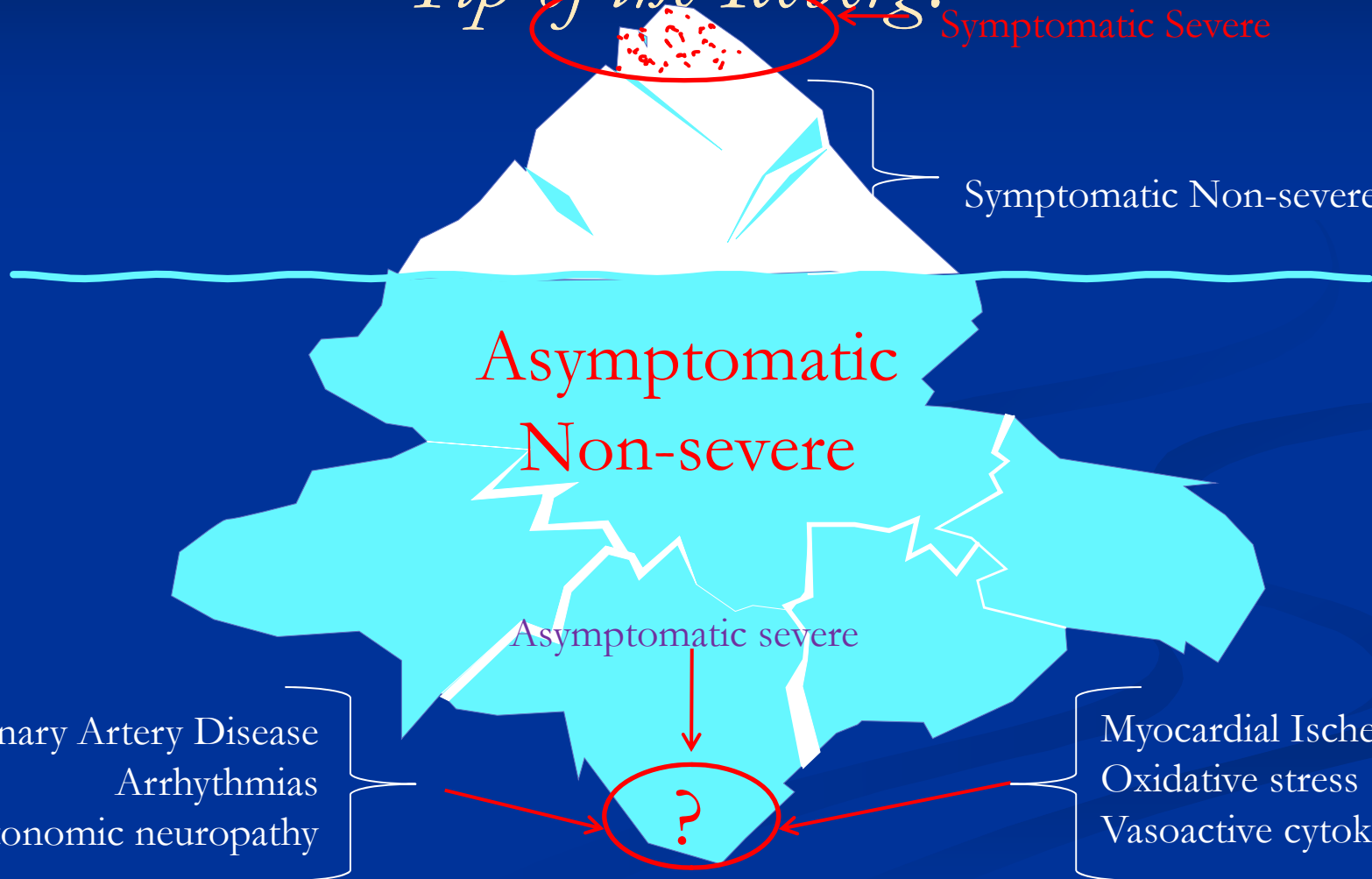
Asymptomatic Non-severe

Asymptomatic severe

Coronary Artery Disease
Arrhythmias
Autonomic neuropathy

Myocardial Ischemia
Oxidative stress
Vasoactive cytokines

?



OUTLINE

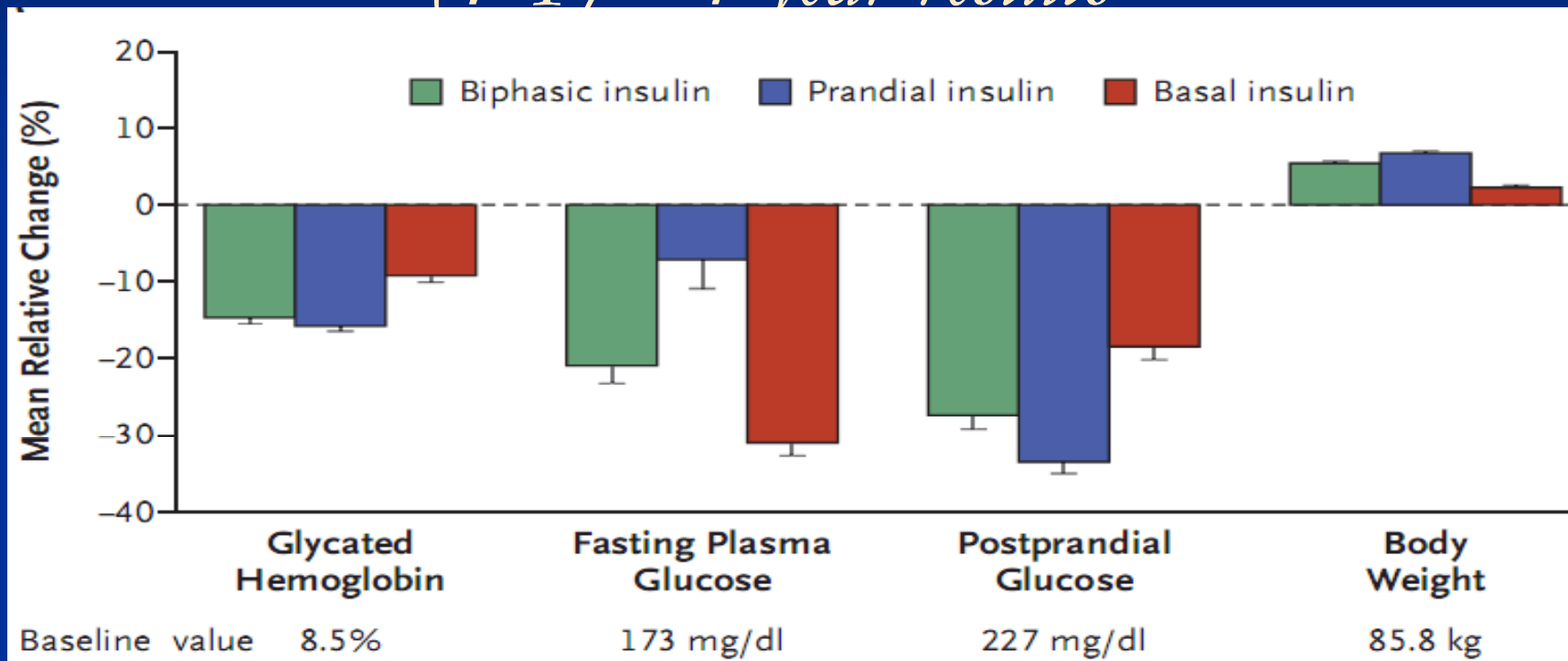
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Treating to Target in Type 2 Diabetes

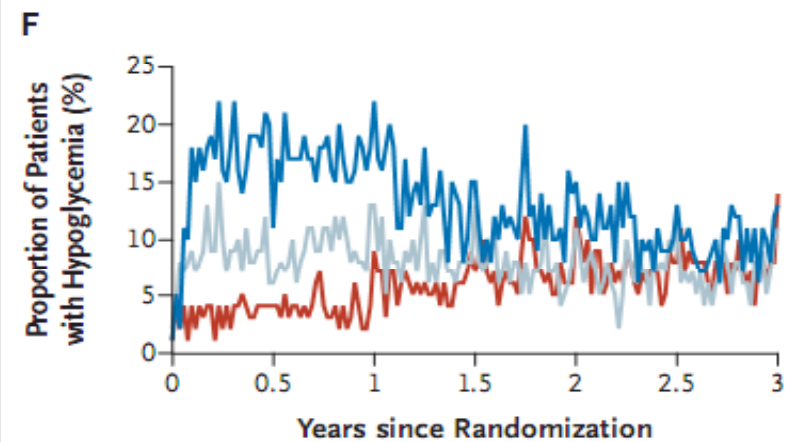
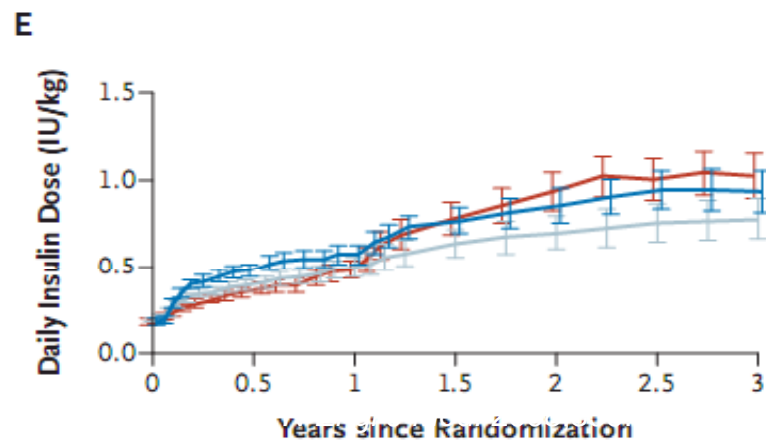
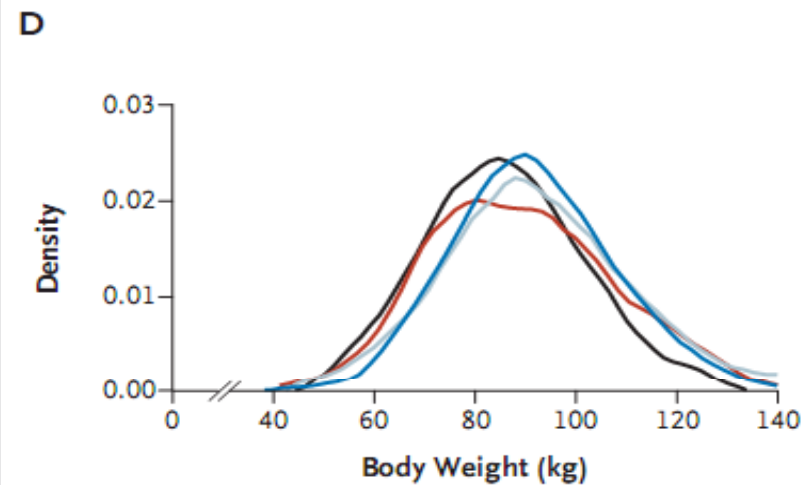
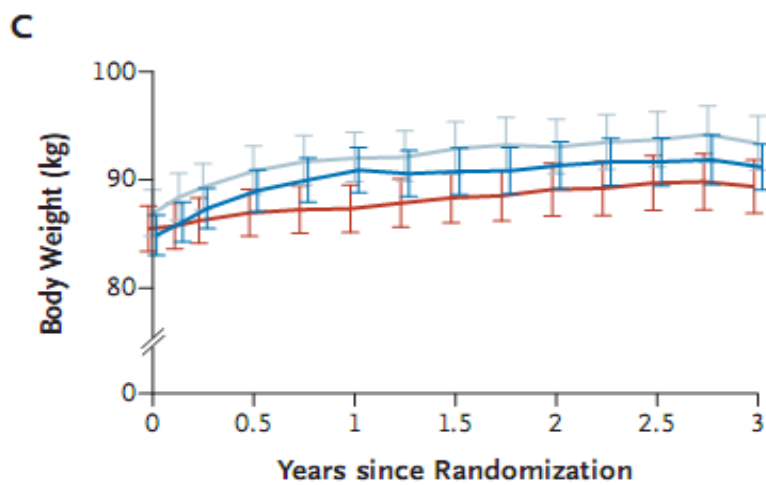
(4-T) – 1 year results



Regimens “had similar glycemic efficacy for patients with baseline $A_{1c} < 8.5\%$, but differed significantly for patient values above this level”

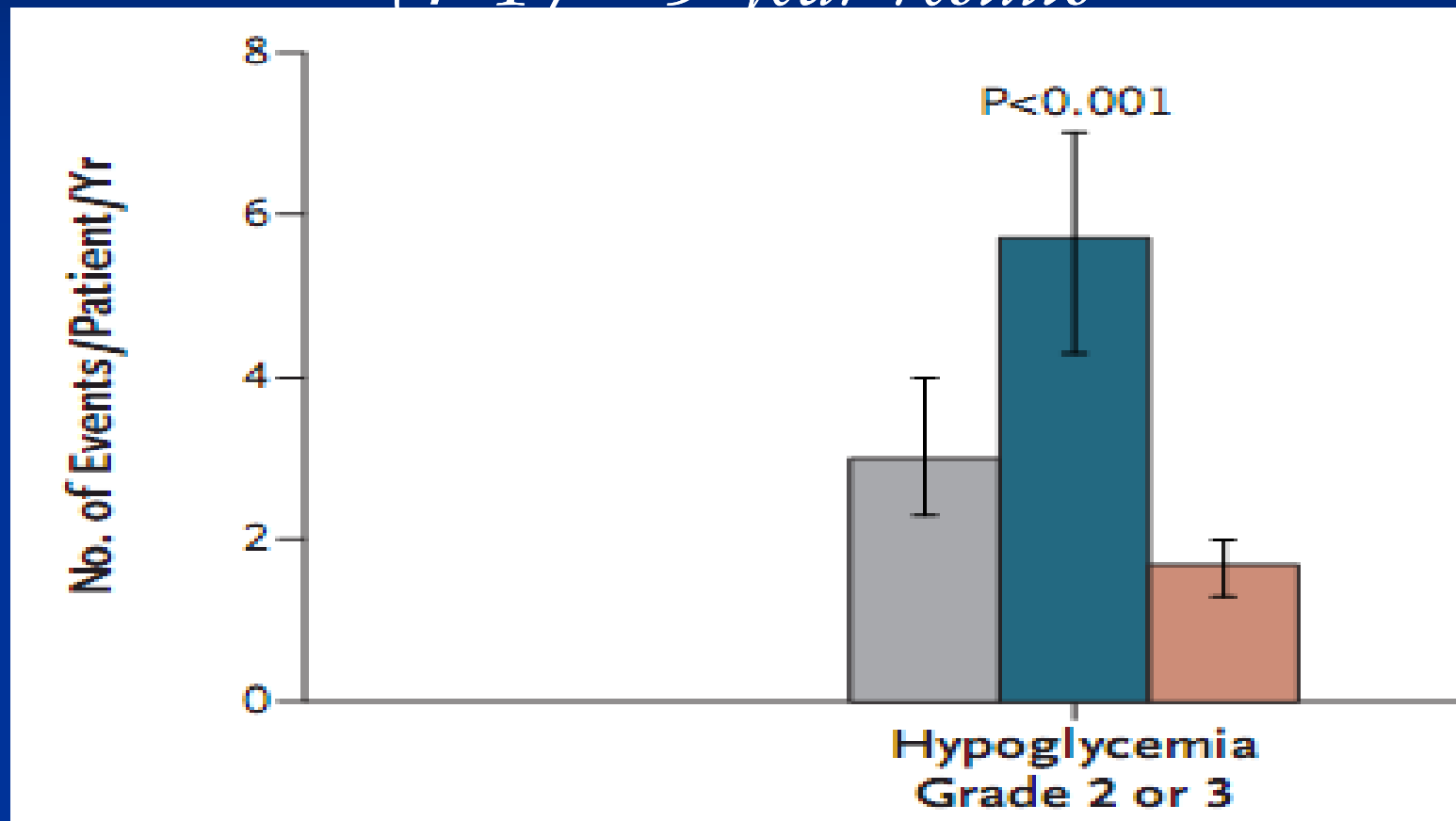
Treating to Target in Type 2 Diabetes

(4-T) – 3 year results



Treating to Target in Type 2 Diabetes

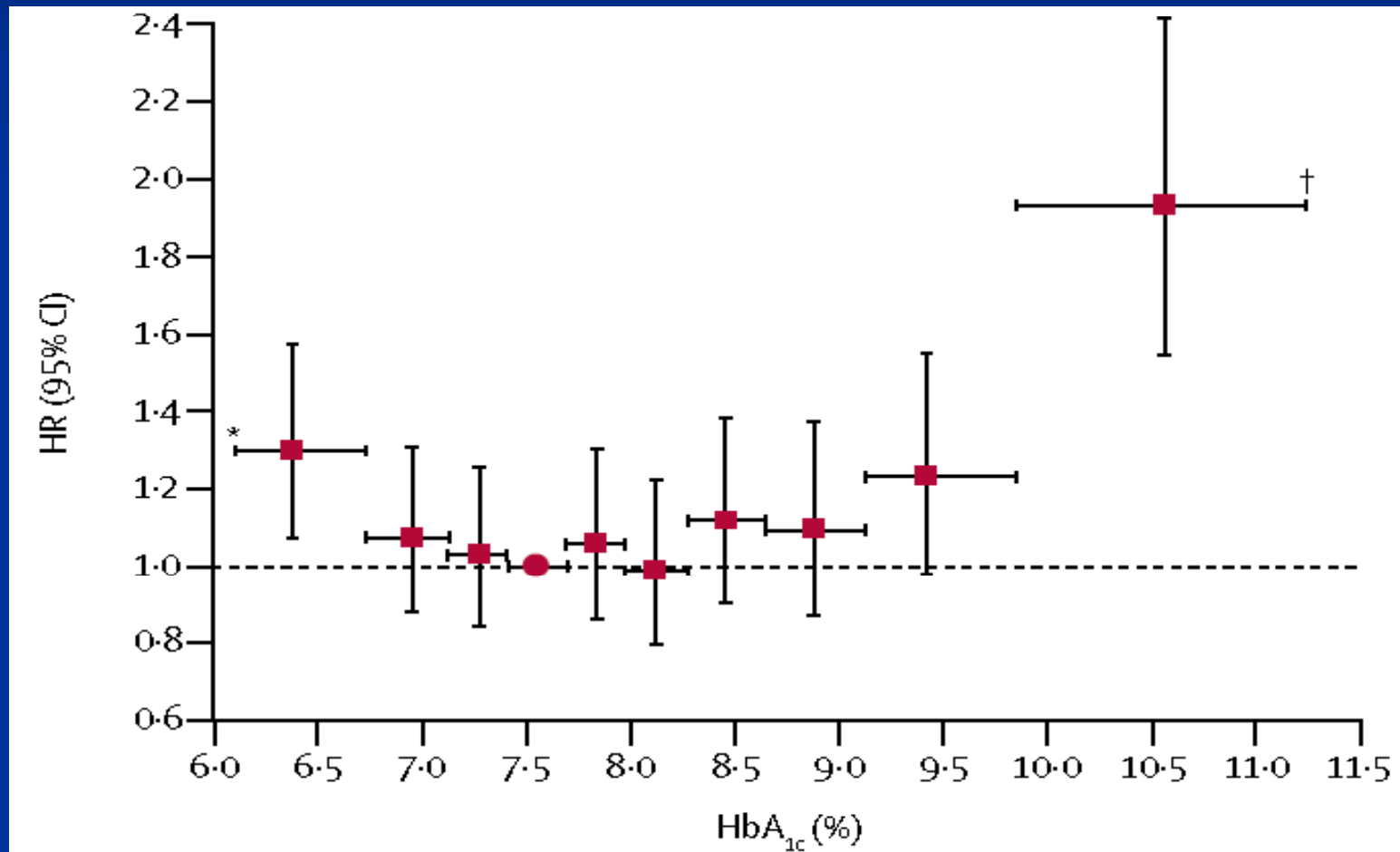
(4-T) – 3 year results



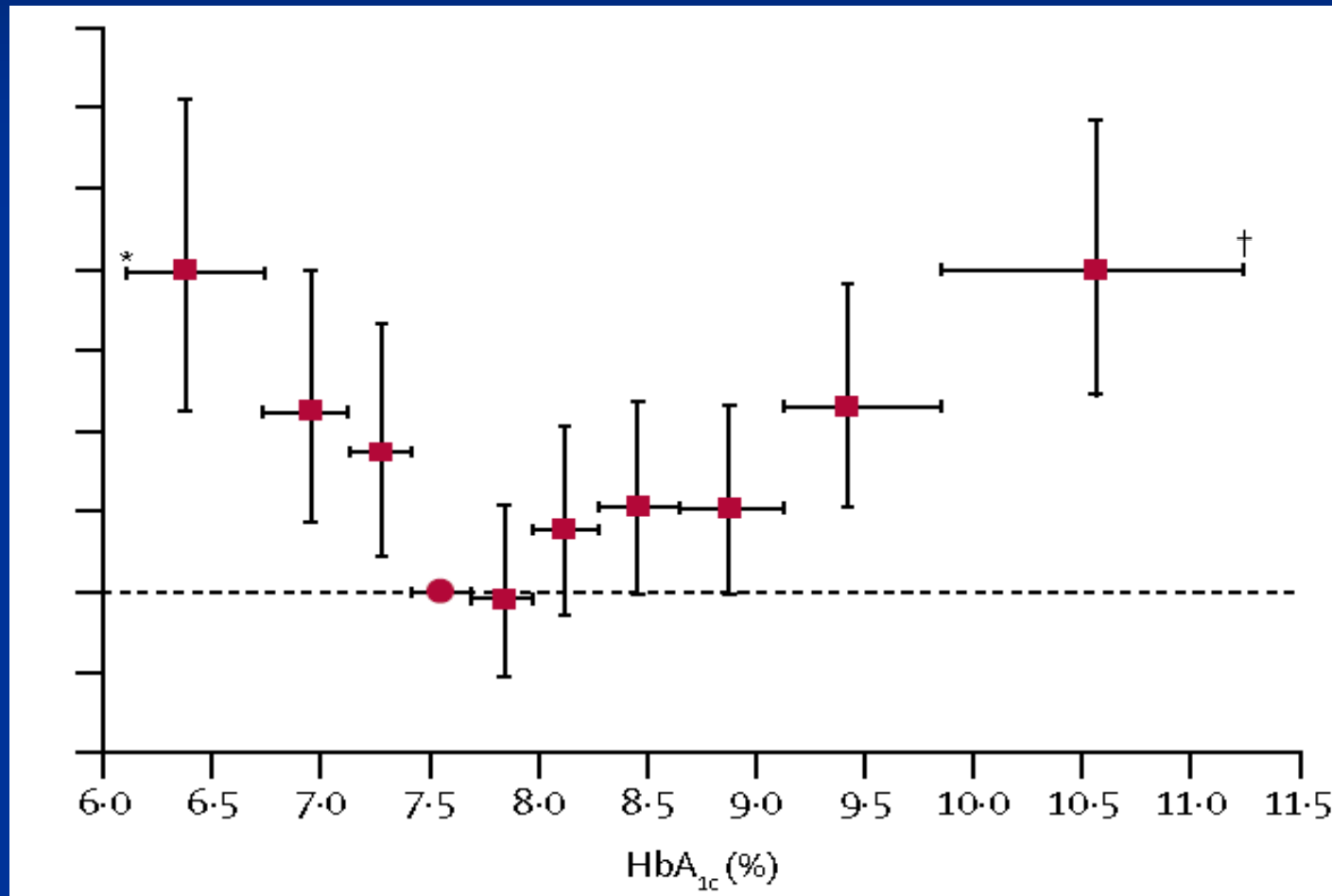
Treating to Target in Type 2 Diabetes

- Adverse Events *(4-T) – 3 year results*
- “During the study period, 19 patients died (7 in the biphasic group, 9 in the prandial group, and 3 in the basal group; $P=0.23$); of these patients, 14 died from cardiovascular disease (4 in the biphasic group, 9 in the prandial group, and 1 in the basal group; $P=0.002$). The proportion of patients with any type of serious adverse event differed among the groups, with the highest proportion in the biphasic group ($P=0.01$).”

Adverse effect of metformin-SU combination, intensification from oral monotherapy, mortality risk vs A_{1c} , n=27,965



Adverse effect of insulin intensification from oral monotherapy, mortality risk vs A_{1c} , $n=20,005$



Hypoglycemia and Other Adverse Consequences of Glucose-lowering Therapies in the Trials

- ACCORD, ADVANCE, VADT: suggestion of relationship between adverse outcome and overtreatment/hypoglycemia
- Corroborative studies: suggestion of relationship between hypoglycemia and adverse outcome
- ? A “new” paradigm: Improve glycemia without causing hypo-glycemia