Does intensive glucose control reduce the cardiovascular events and mortality in patients with type 2 diabetes?

Does intensive glucose control reduce the cardiovascular events and mortality in patients with type 2 diabetes?

Dr. Md. Shahabul Huda Chowdhury

Assistant Professor

Department of Medicine

Shaheed Suhrawardy Medical College & Hospital

Intensive glycemic control

Aggressive approach to manage blood glucose. It typically involves setting specific goals for maintaining blood glucose levels within a certain range before and after meals and attempting to achieve a quarterly hemoglobin A1c (measures average glucose over a three-month period)

Clinical studies on Intensive glycemic control

⇒ **UKPDS:** **U**nited **K**ingdom **P**rospective **D**iabetes **S**tudy

⇒ **ADVANCE:** **A**ction in **D**iabetes & **V**ascular **D**iseases: PreterA**x** & DiamicroN MR Controlled **E**valuation

⇒ **ACCORD:** **A**ction to **C**ontrol **C**ardi**O**vascular **R**isk in **D**iabetes

UKPDS

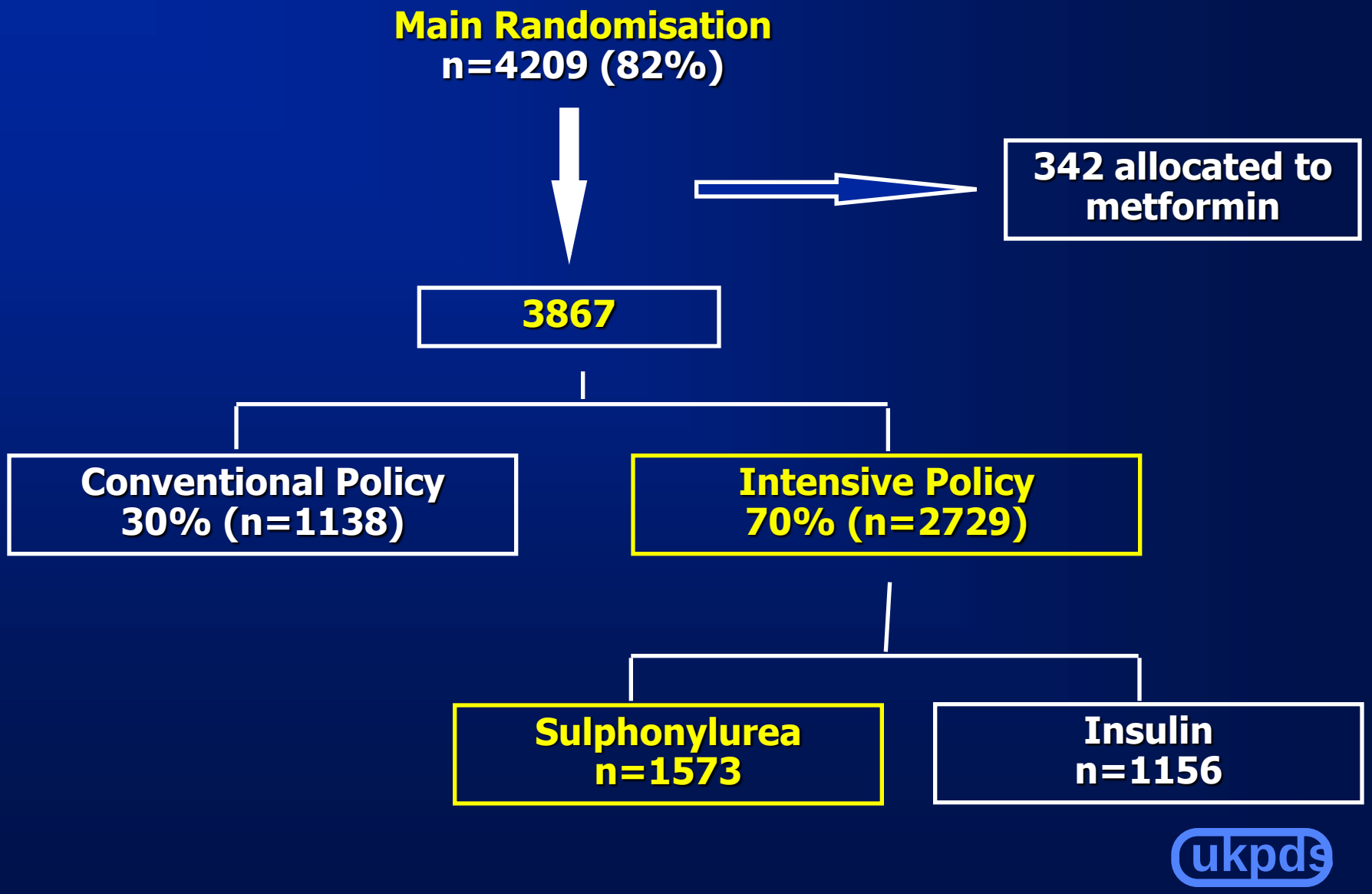
United Kingdom Prospective Diabetes Study

UK Prospective Diabetes Study: Aim

Does an intensive glucose control policy reduce the risk of complications of diabetes?

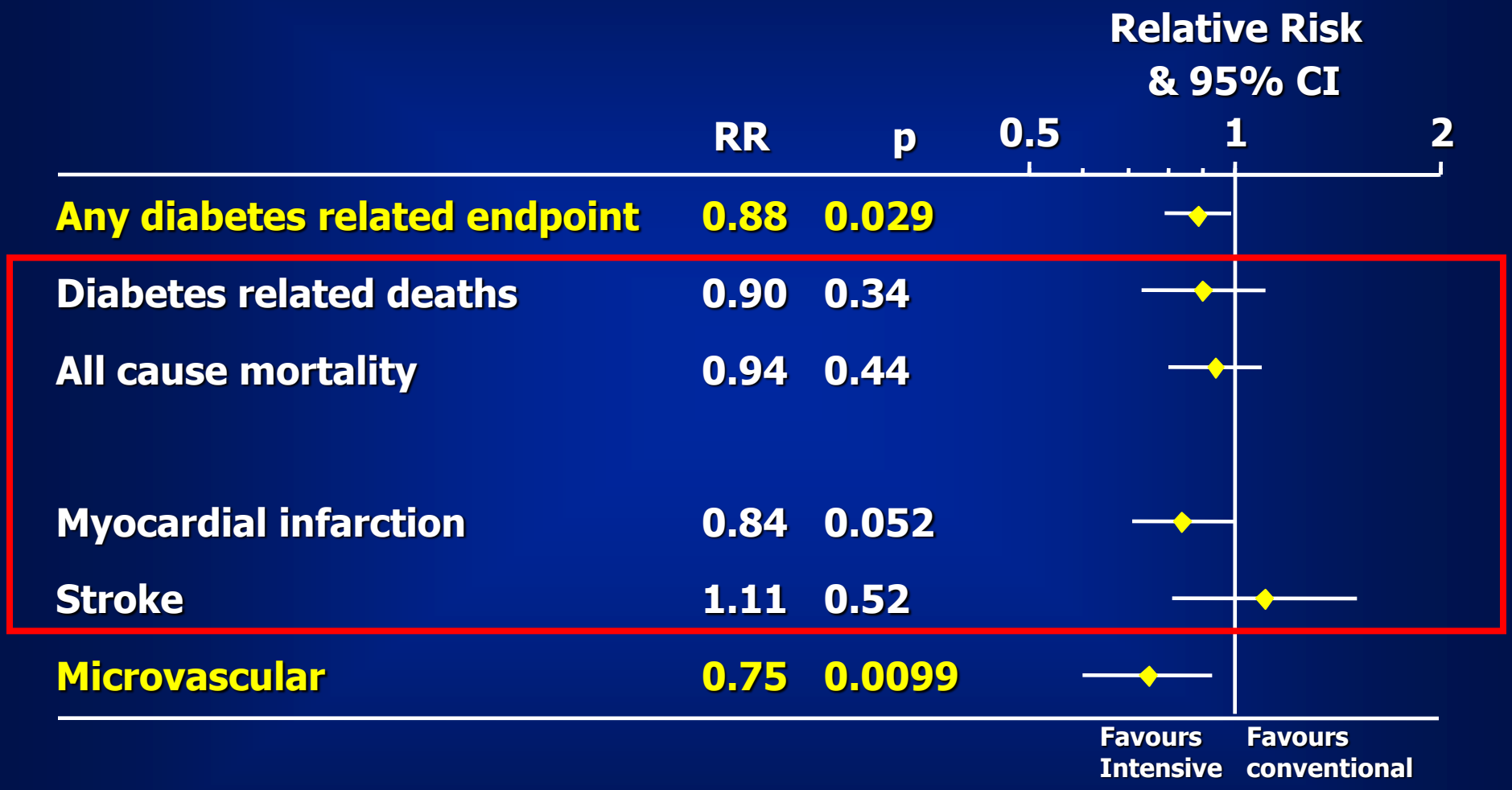
ukpds

Study Population Distribution



ukpds

Clinical Endpoints: Glucose control



Non-significant!!!

ukpds

UKPDS glucose control: Conclusion

The UKPDS has shown that intensive blood glucose control reduces the risk of diabetic complications, the greatest effect being on microvascular complications

ukpds

However…

⇒ What will happen if target is 6.5%, recommended by the International Diabetes Federation guideline?

⇒ What about the full range of patients

- Newly diagnosed+ Already under treatment
- European+ Non Europeans

To answer these questions,

ADVANCE & ACCORD were initiated

ADVANCE

Action in Diabetes & Vascular Diseases: PreterAx & DiamicroN MR Controlled Evaluation

---

ACCORD

Action to Control CardiOvascular Risk in Diabetes

The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572
The ACCORD Study Group. N Engl J Med. 2008;358:2545-2559

Both studies aimed to see effect of intensive blood glucose control on vascular outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

The ADVANCE Collaborative Group*

BACKGROUND

In patients with type 2 diabetes, the effects of intensive glucose control on vascular outcomes remain uncertain.

The Action to Control Cardiovascular Risk in Diabetes Study Group*

BACKGROUND

Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.

Nearly same baseline characteristics

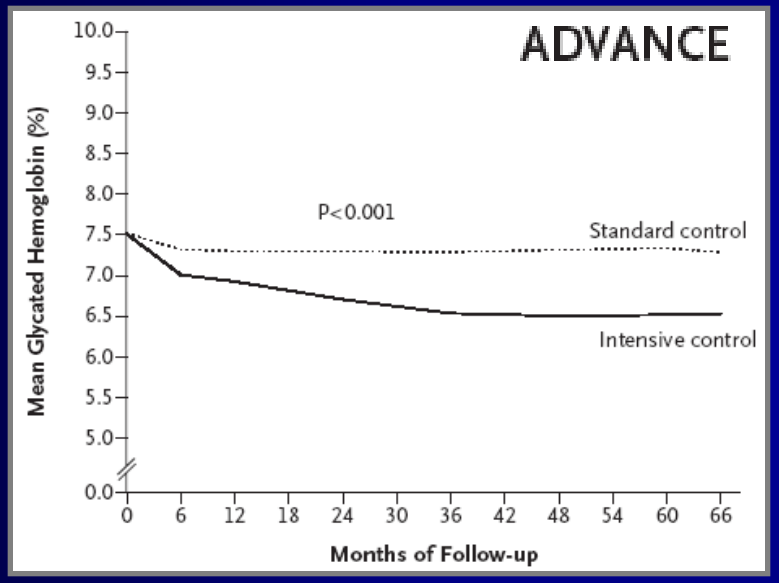
Characteristic	ACCORD	ADVANCE
Baseline data		
No. of participants	10,251	11,140
Mean age (yr)	62	66
Duration of diabetes (yr)*	10	8
Median glycated hemoglobin at baseline (%)	8.1	7.2
History of macrovascular disease (%)	35	32

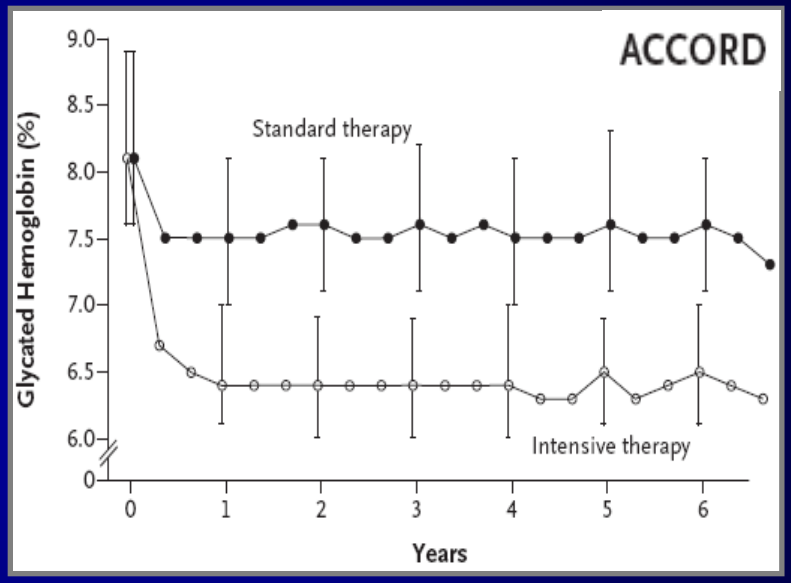
…with a major difference

The intensive arm of ADVANCE was based on Diamicron MR. Treatment had to be started with Diamicron MR, up-titrate the dose up to 4 tablets and then add other drugs to achieve 6.5% HbA1c

The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572
The ACCORD Study Group. N Engl J Med. 2008;358:2545-2559

Both ADVANCE & ACCORD achieved 6.5% HbA1c…





The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572
The ACCORD Study Group. N Engl J Med. 2008;358:2545-2559

…but with opposite cardiovascular outcome

⇒ **ADVANCE**: Reduces cardiovascular death by -12%

⇒ **ACCORD**: Increased cardiovascular death by +35%

*** ACCORD was stopped prematurely 18 months before**

The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572
The ACCORD Study Group. N Engl J Med. 2008;358:2545-2559

Probable causes behind increased death in ACCORD

⇒ Heavy use of combination therapy

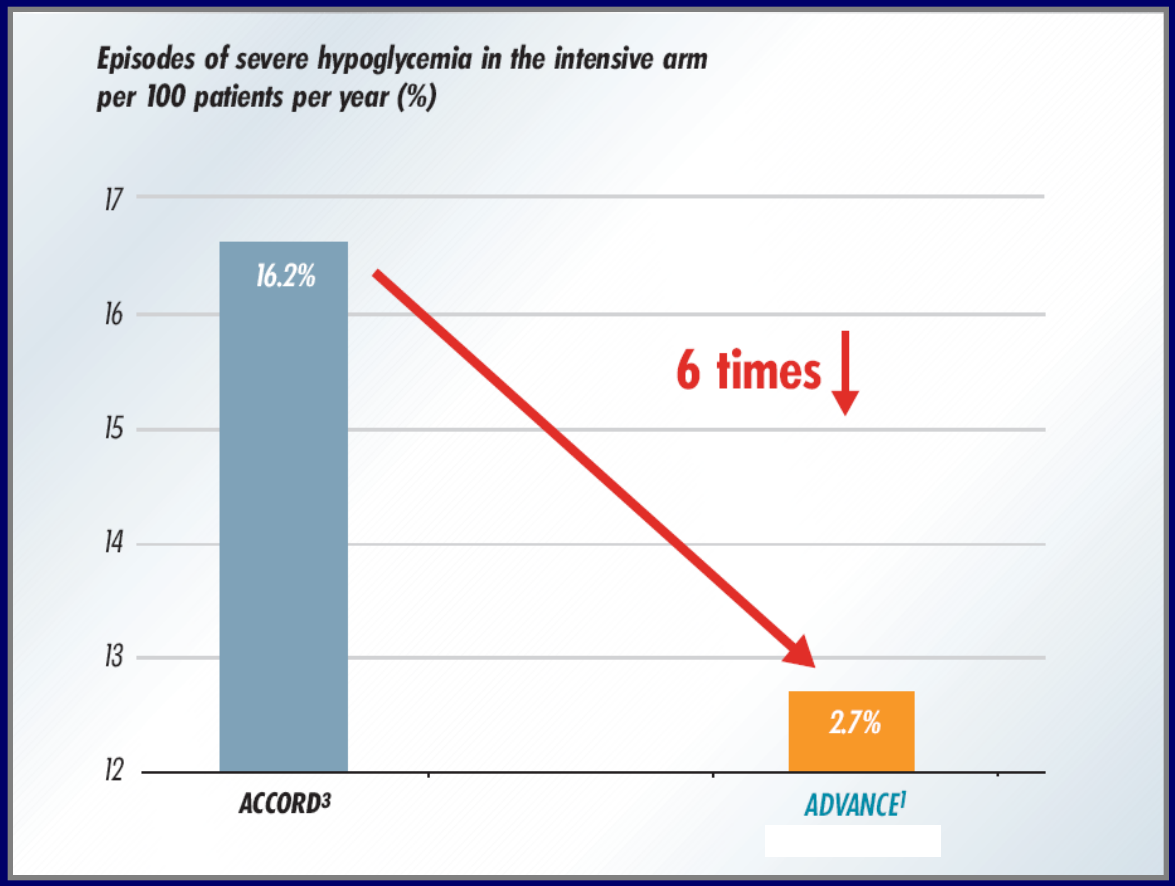
⇒ Glimepiride 78%, TZD 92%

⇒ Higher rate of severe hypoglycemia

⇒ Weight gain

The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572
The ACCORD Study Group. N Engl J Med. 2008;358:2545-2559

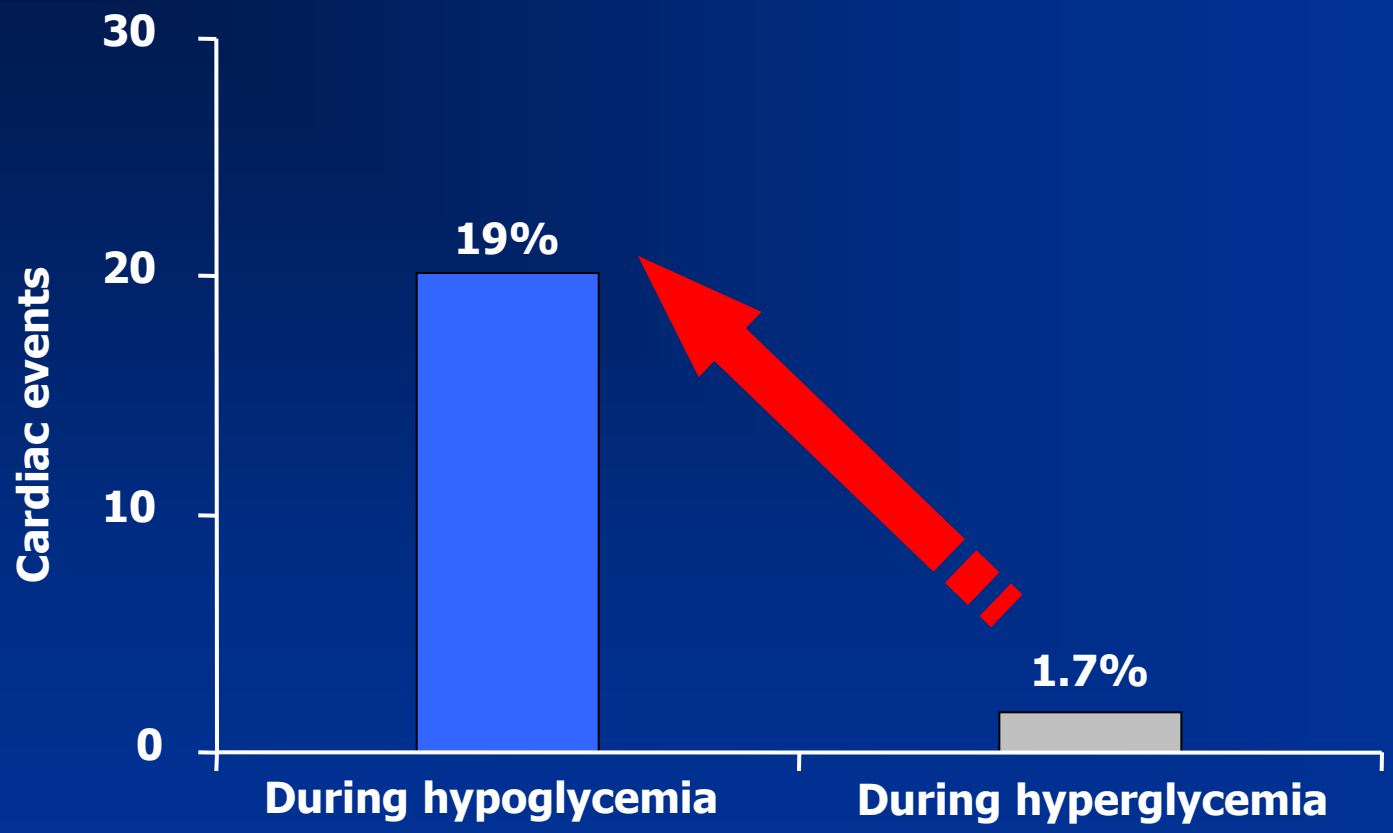
6 times less hypo in ADVANCE than ACCORD



*** Cardiac events are more during hypoglycemia**

The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572
The ACCORD Study Group. N Engl J Med. 2008;358:2545-2559

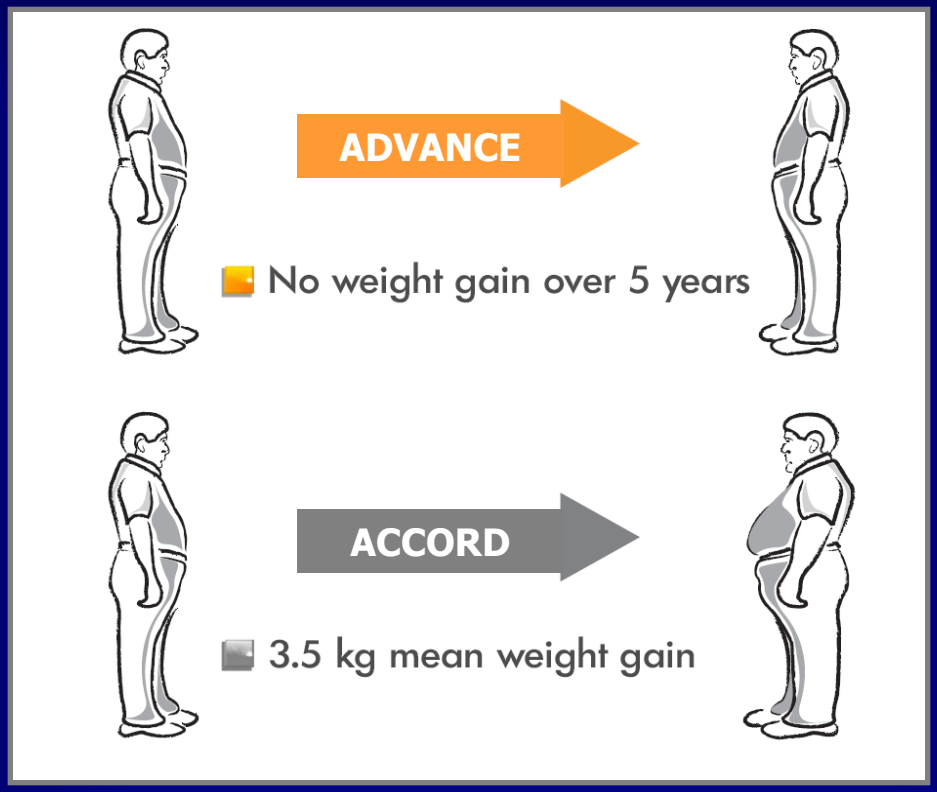
Hypoglycemia aggravates cardiac events



*** More than 10 times cardiac events during hypoglycemia**

Diab Care 2003;26:1485-9.

No weight gain in ADVANCE study



*** In ACCORD 28% patients gained more than 10 kg weight**

The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572
The ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559

One more study on Intensive glycemic control: VADT

VADT: Veterans Affairs Diabetes Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

intensive-therapy group. The primary goal of the Veterans Affairs Diabetes Trial (VADT) was to compare the effects of intensive and standard glucose control on cardiovascular events.

The primary outcome of VADT was a composite of CVD events (MI, stroke, cardiovascular death, revascularization, hospitalization for heart failure, and amputation for ischemia). During a median 5.6-year follow-up period, the cumulative incidence of the primary outcome was not significantly lower in the intensive arm (HR 0.88 [95% CI 0.74–1.05], $P = 0.12$). There were more CVD deaths in the intensive arm than in the standard arm (38 vs. 29, sudden deaths 11 vs. 4),

*** Cardiovascular death was increased by +32% using Glimepiride & TZD**

The VADT investigators *N Engl J Med*. 2009;360

Comparison: 3 recent clinical studies

ADVANCE/ ACCORD/ VADT: Baseline

	Patients	Mean age (yrs)	Duration of DM (yrs)	Median HbA_{1c}	History of CVD	BMI
ADVANCE	11,140	66	8	7.2%	32%	28
ACCORD	10,251	62	10	8.1%	35%	32
VADT	1,791	60	11.5	9.4%	40%	31

The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572
The ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559
The VADT investigators *N Engl J Med.* 2009;360

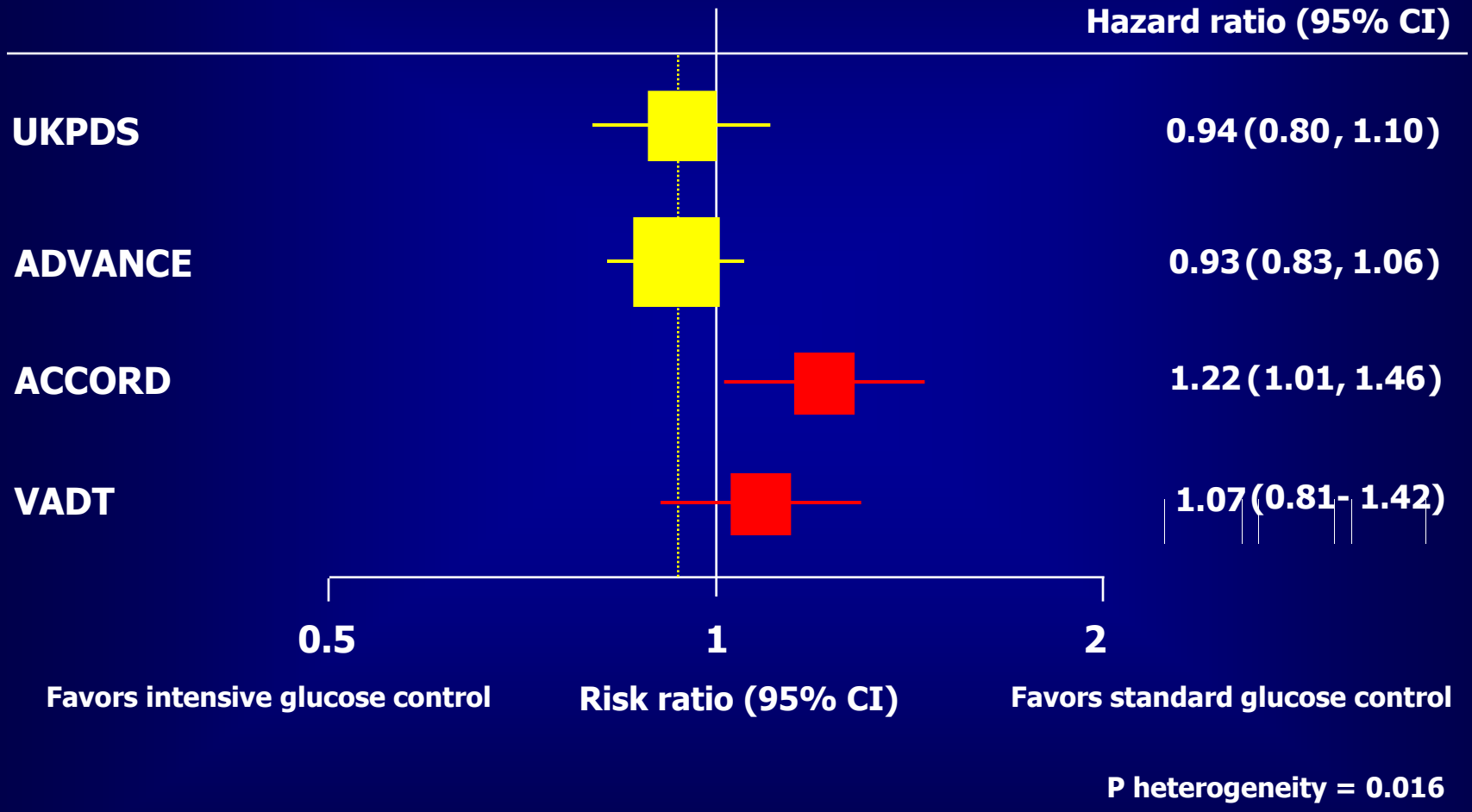
ADVANCE/ ACCORD/ VADT: Results

	HbA1c	Outcome
ADVANCE	6.5%	Reduction of CV death & mortality
ACCORD	6.5%	Increase of CV death & mortality
VADT	6.9%	Increase of CV death & mortality

*** Only ADVANCE could show positive result**

The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572
The ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559
The VADT investigators *N Engl J Med.* 2009;360

Both UKPDS & ADVANCE favors intensive BG control



*** Glimepiride was used in both VADT & ACCORD**

Even the ADA/ EASD Guideline has been changed after these findings of ADVANCE/ ACCORD/ VADT

Previous ADA/ EASD guideline 2008

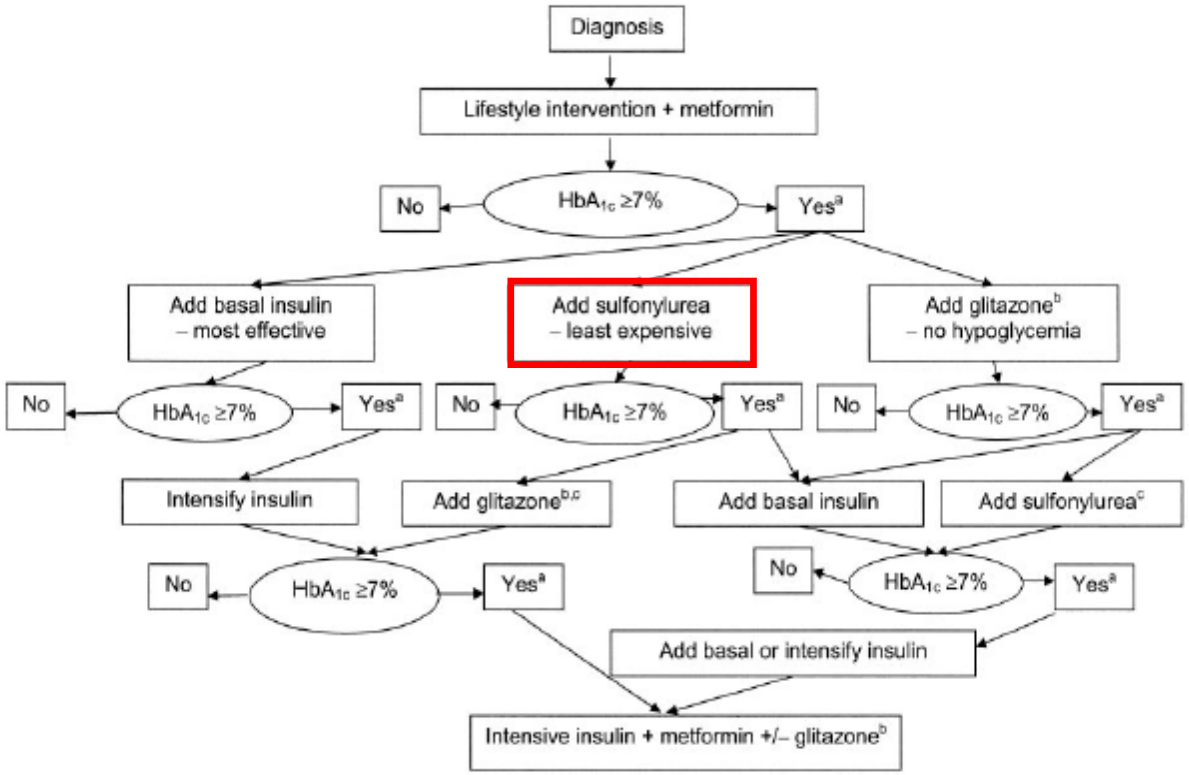


Figure 1—*Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle intervention at every visit. [a]Check A1C every 3 months until <7% and then at least every 6 months. [b]Associated with increased risk of fluid retention, CHF, and fractures. Rosiglitazone, but probably not pioglitazone, may be associated with an increased risk of myocardial infarction. [c]Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and lower expense.*

*** Sulfonylurea was not highlighted**

New ADA/ EASD consensus statement 2009

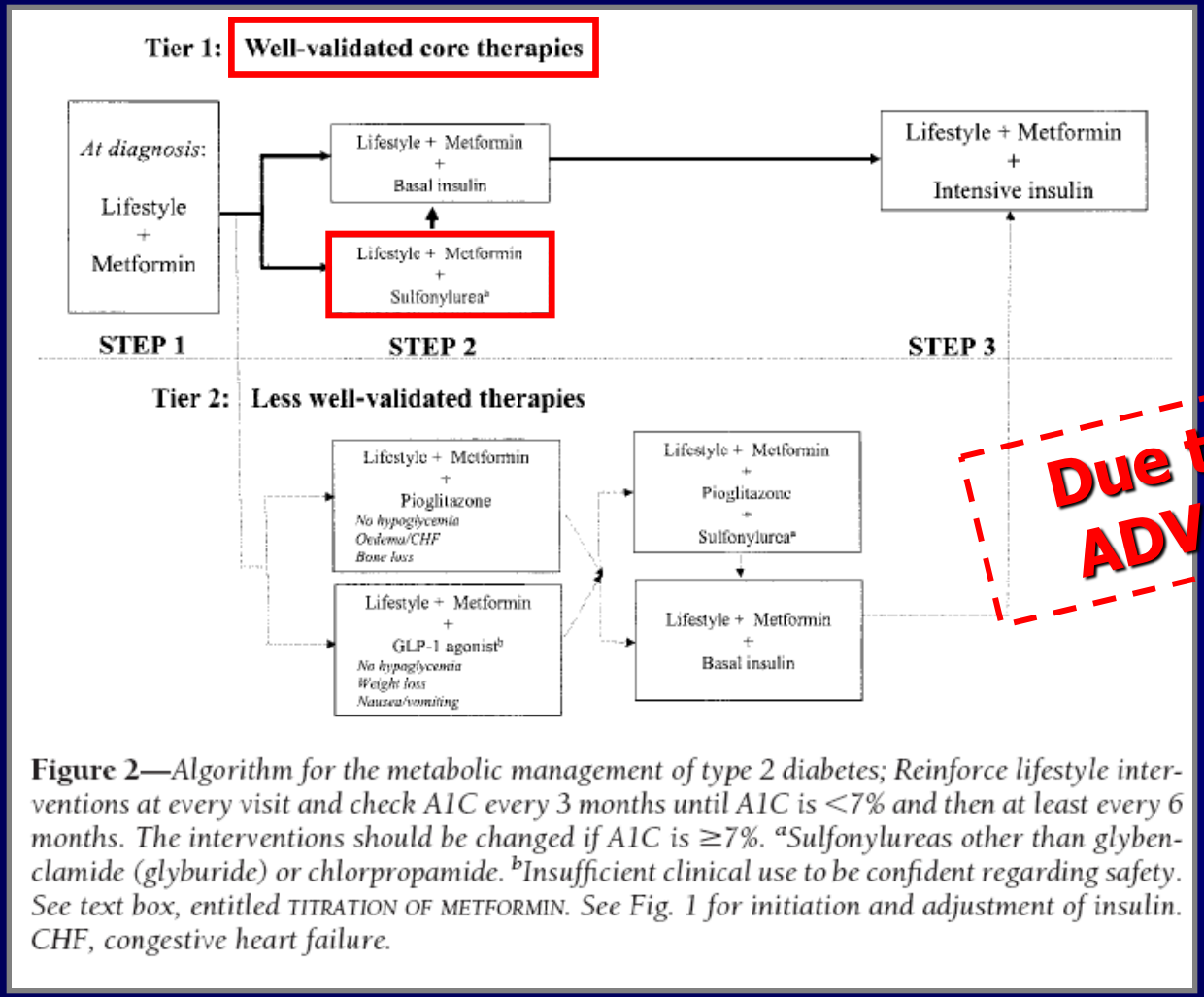


Figure 2—*Algorithm for the metabolic management of type 2 diabetes; Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is <7% and then at least every 6 months. The interventions should be changed if A1C is ≥7%. [a]Sulfonylureas other than glyburide (glybenclamide) or chlorpropamide. [b]Insufficient clinical use to be confident regarding safety. See text box, entitled TITRATION OF METFORMIN. See Fig. 1 for initiation and adjustment of insulin. CHF, congestive heart failure.*

Due to the ADVANCE

Sulfonylurea recommended as a well validated core therapy and modified release sulfonylurea should be prefered

Take home message

⇒ **Good metabolic control can reduce morbidity & mortality in type 2 diabetes**

⇒ **But, the choice of OAD is a major factor for both blood glucose control & reduction of vascular complications**

Thank You