



Landmark Clinical Trials

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Polling Question

Which of the following is not considered a landmark trial in diabetes?

A. DPP-DPPOS

B. DCCT-EDIC

C. DMIT-35

D. UKPDS

What's a Landmark Clinical Trial?

land·mark
/ˈlan(d)ˌmärk/
n.

1. a prominent or well-known object in or feature of a particular landscape

2. an important or unique decision, event, fact, discovery, etc.

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Some Landmark Trials …

- **United Kingdom Prospective Diabetes Study** (UKPDS)=>UKPDS-PTM
- **Diabetes Control and Complications Trial** (DCCT)=>EDIC
- **Diabetes Prevention Program** (DPP)=>DPPOS
- **Action to Control Cardiovascular Risk in Diabetes** (ACCORD)=>ACCORDION
- **Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation** (ADVANCE)=>ADVANCE-ON
- **Veterans Affairs Diabetes Trial** (VADT)

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United Kingdom Prospective Diabetes Study

(UKPDS)=>UKPDS-PTM

UK Prospective Diabetes Study

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

ukpds

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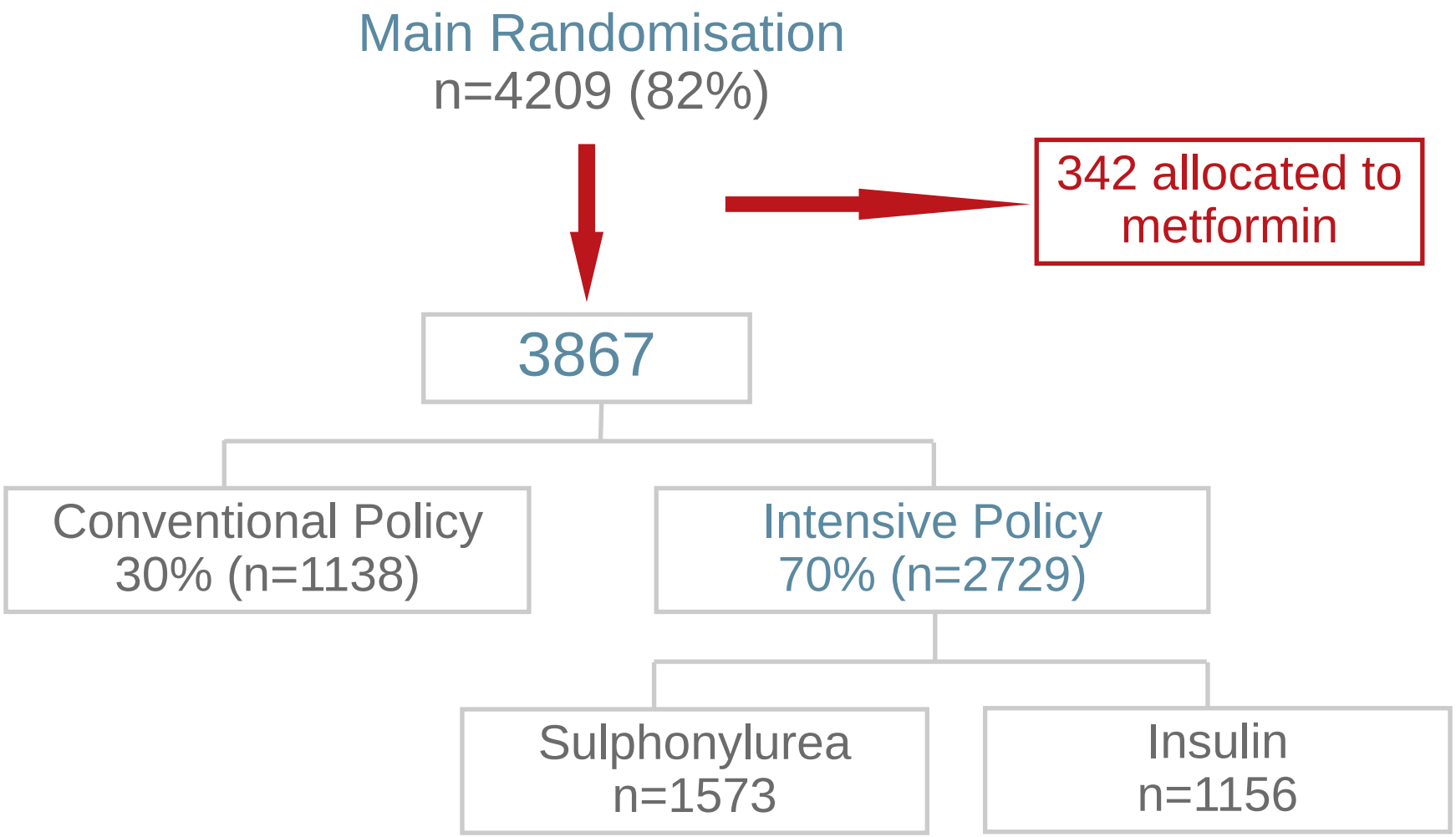
Randomisation of Treatment Policies



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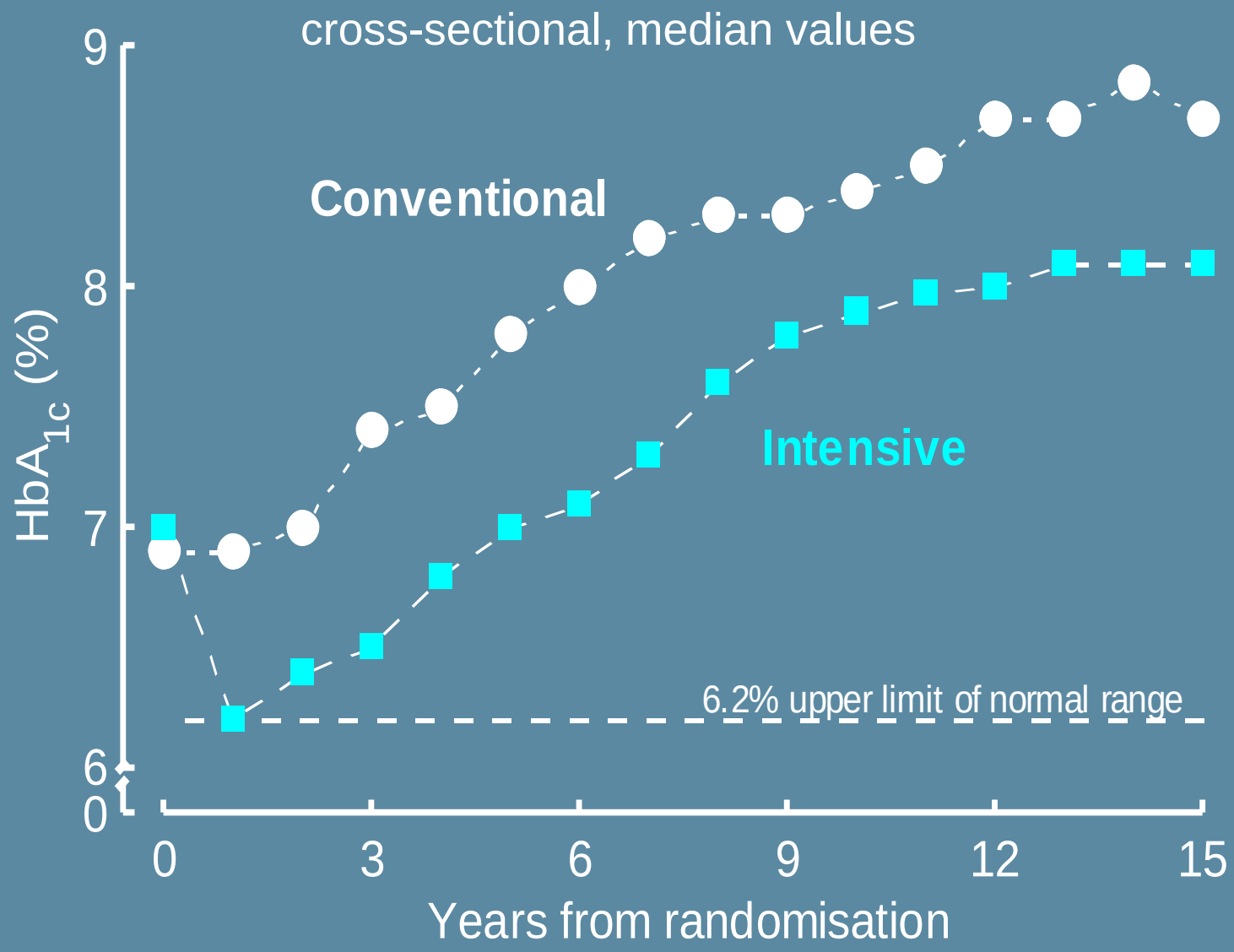
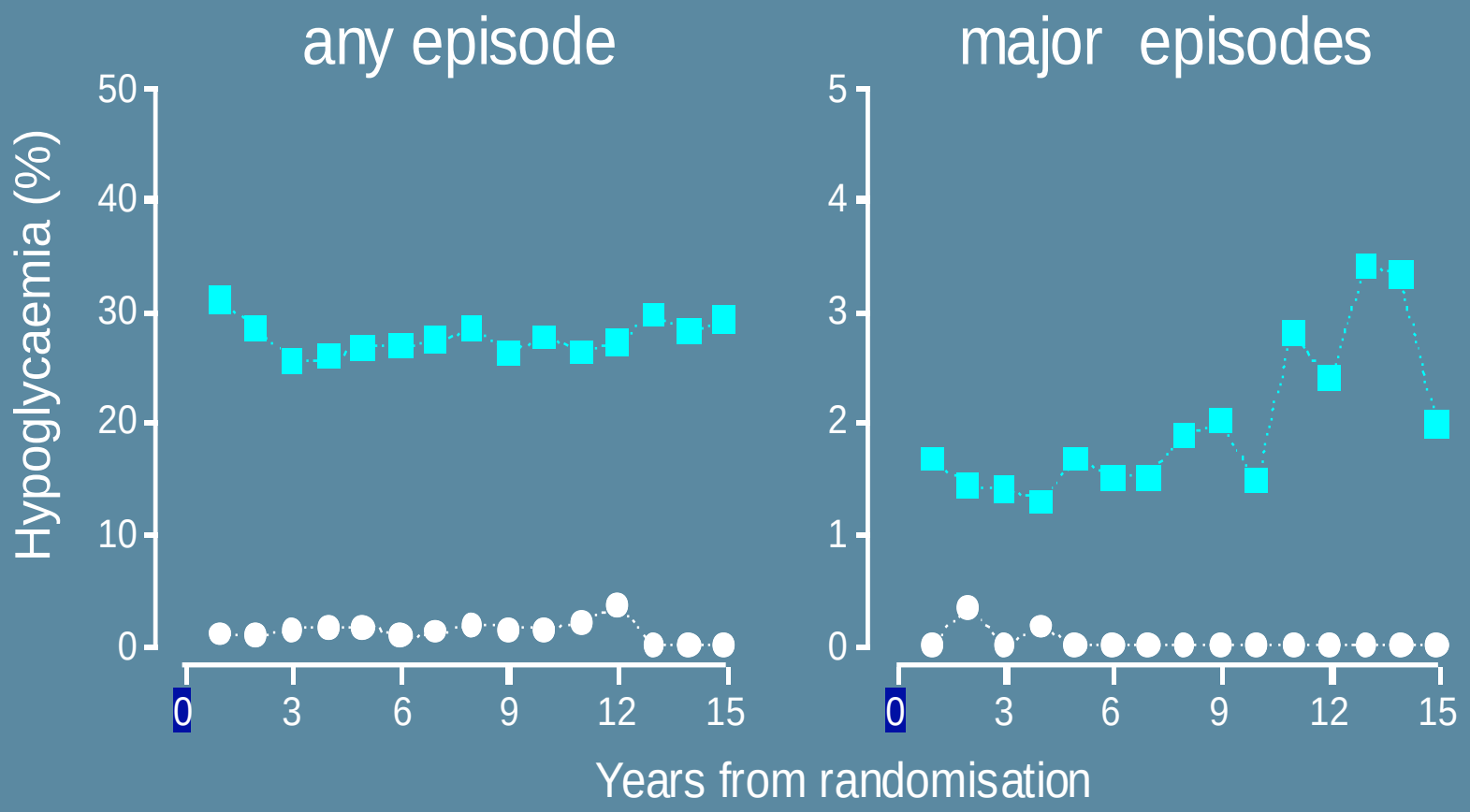
HbA1c


cross-sectional, median values
Conventional
Intensive
6.2% upper limit of normal range
HbA1c (%)
9
8
7
6
0
0
3
6
9
12
15
Years from randomisation

Hypoglycaemic episodes per annum

Actual Therapy Analysis



Glucose Control Study Summary

The intensive glucose control policy maintained a lower HbA1c by mean 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

12% for any diabetes related endpoint
25% for microvascular endpoints
16% for myocardial infarction
24% for cataract extraction
21% for retinopathy at twelve years
33% for albuminuria at twelve years

All results are statistically significantly different from results seen in the ‘conventional’ policy patients

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Blood Pressure Control Study Summary

The ‘tight’ blood pressure control arm resulted in a mean BP of 144/82 (use of ACEI or β-blocker) compared with the ‘less tight’ control BP of 154/87

24% for any diabetes related endpoint
32% for deaths related to diabetes
18% for all cause mortality
21% for myocardial infarction
44% for stroke
49% for peripheral vascular disease
37% for microvascular endpoints

All results are statistically significantly different from results seen in the ‘conventional’ policy patients

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Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:* *P:*	12% 0.029	**9%** **0.040**
Microvascular disease	*RRR:* *P:*	25% 0.0099	**24%** **0.001**
Myocardial infarction	*RRR:* *P:*	16% 0.052	**15%** **0.014**
All-cause mortality	*RRR:* *P:*	6% 0.44	**13%** **0.007**

RRR = Relative Risk Reduction, P = Log Rank

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Legacy Effect of Earlier Metformin Therapy

After median 8.5 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:* *P:*	32% 0.0023	**21%** **0.013**
Microvascular disease	*RRR:* *P:*	29% 0.19	**16%** **0.31**
Myocardial infarction	*RRR:* *P:*	39% 0.010	**33%** **0.005**
All-cause mortality	*RRR:* *P:*	36% 0.011	**27%** **0.002**

RRR = Relative Risk Reduction, P = Log Rank

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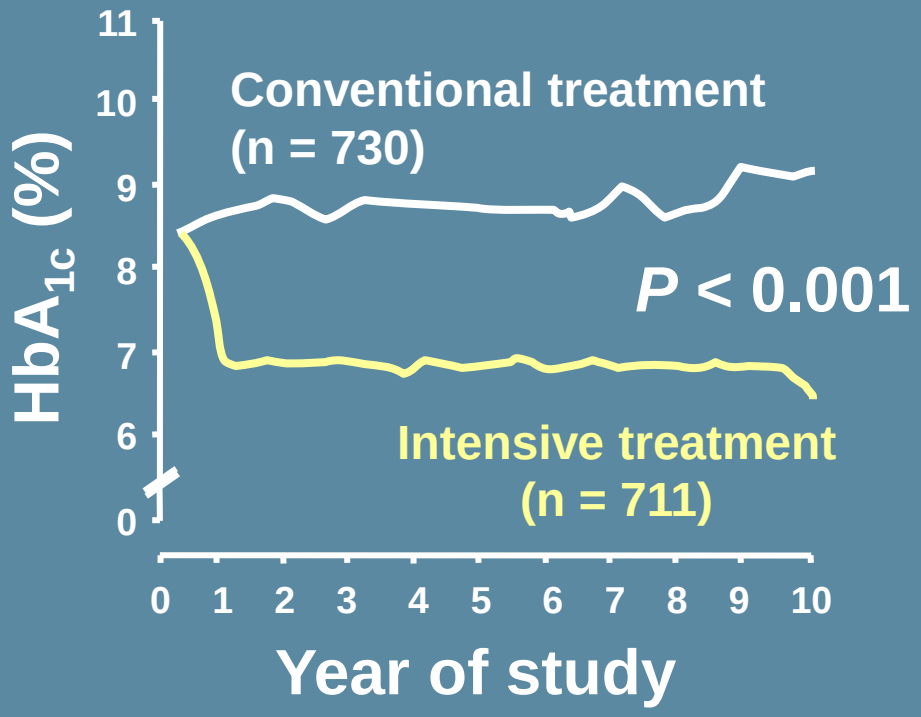
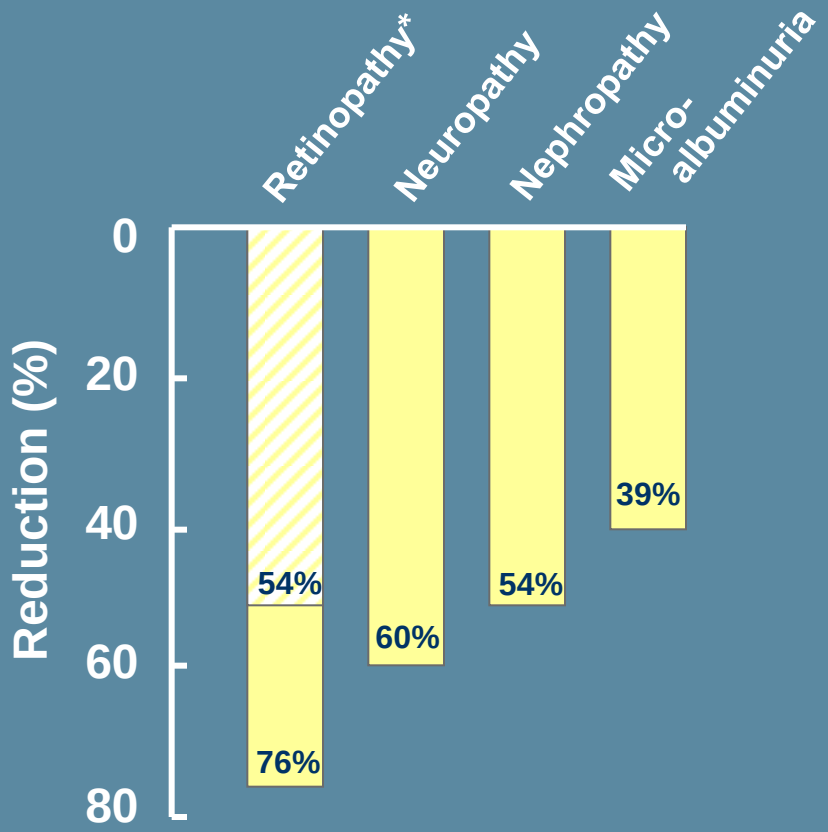
Diabetes Control and Complications Trial (DCCT)=>EDIC

DCCT: intensive control reduces complications in type 1 diabetes

Conventional versus intensive insulin therapy (n = 1,441)



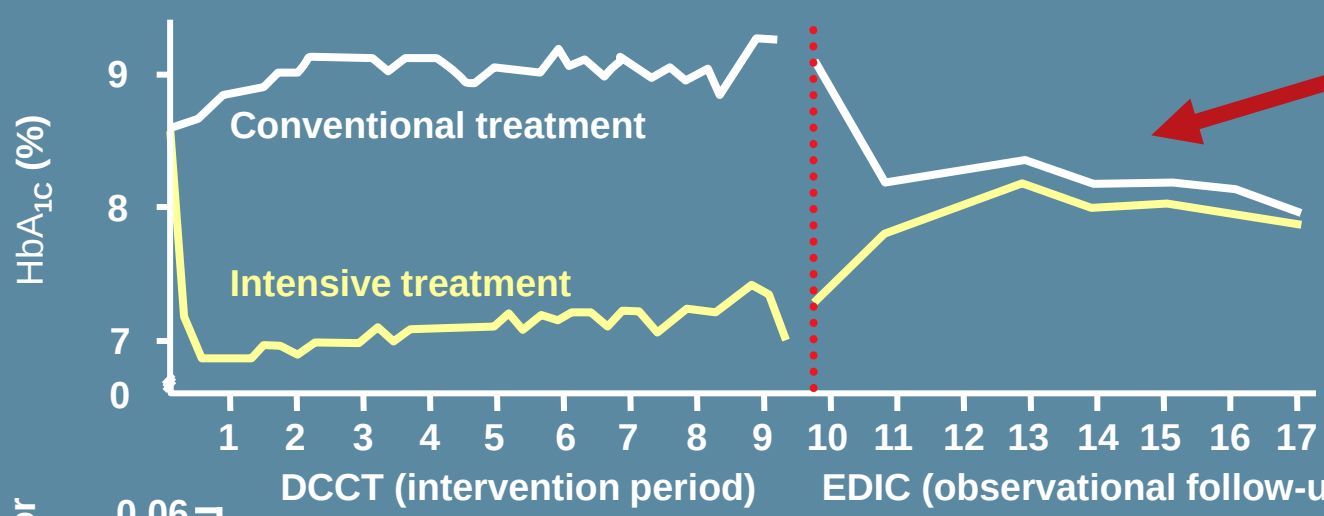


*Subdivided to primary and secondary prevention of retinopathy. Age 27 years, HbA1c 8.8%. Insulin dose (U/kg/d) 0.62 (primary), 0.71 (secondary).

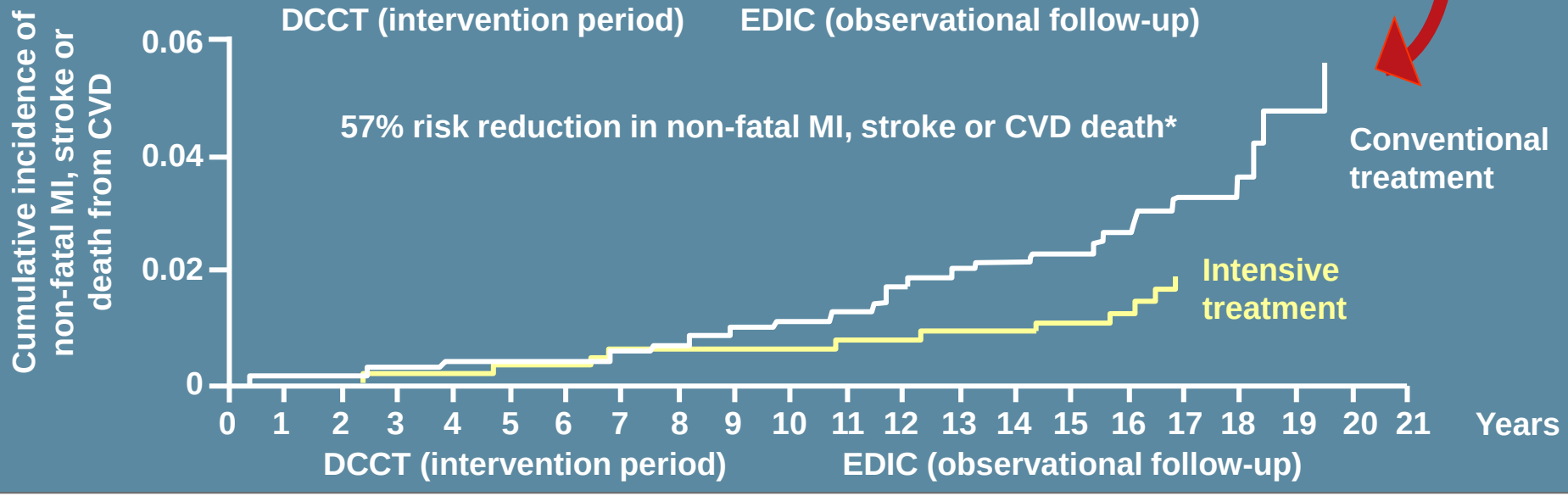
DCCT Research Group. *N Engl J Med* 1993; 329:977–986.

The Global Partnership for Effective Diabetes Management
CONTROL TO GOAL

DCCT/EDIC: long-term follow-up and legacy effect



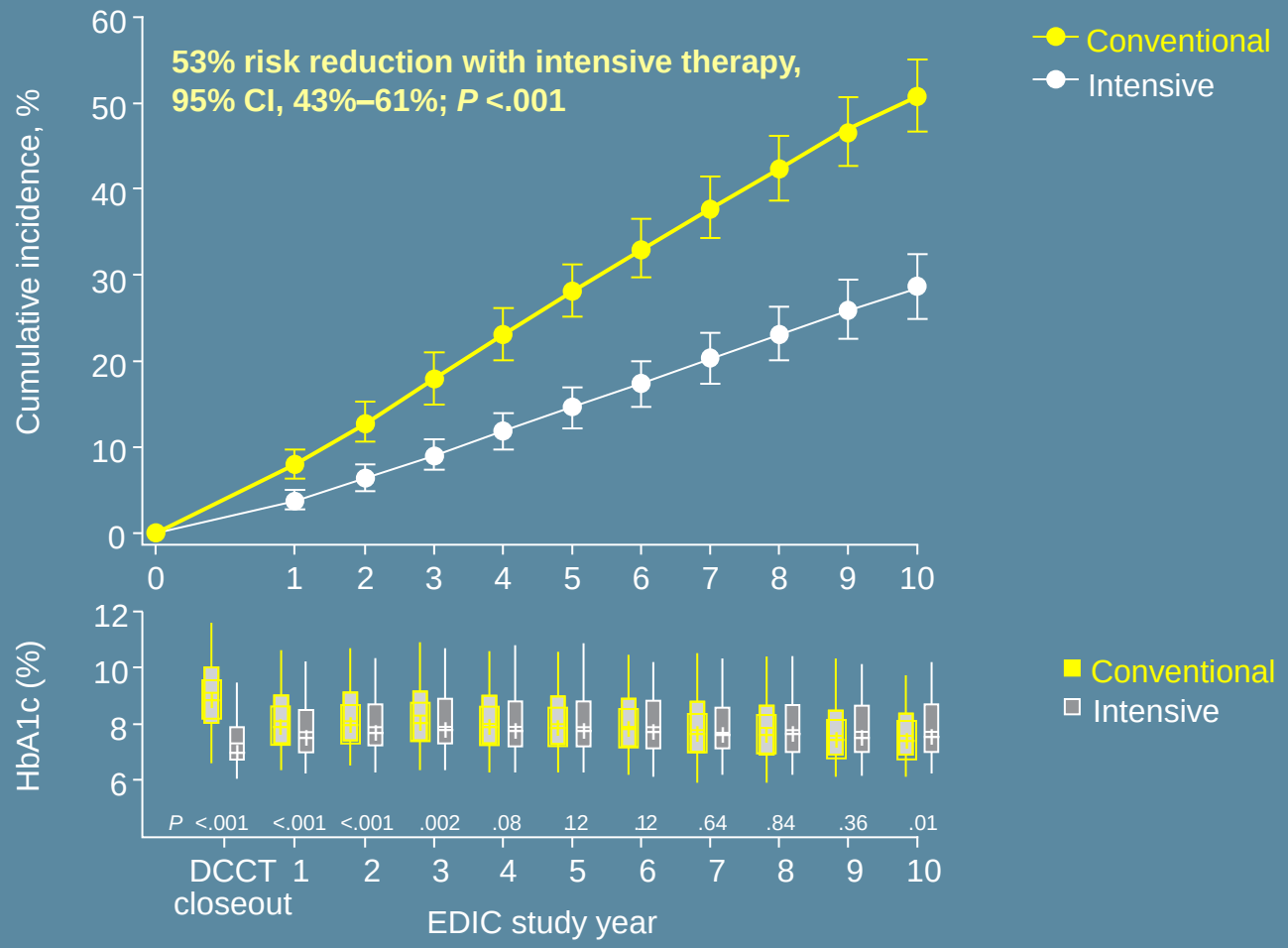
Glucose similar BUT CV events still higher



*Intensive vs conventional treatment.

DCCT Research Group. *N Engl J Med* 1993; 329:977–986.
Nathan DM, et al. *N Engl J Med* 2005; 353:2643–2653

Cumulative incidence of retinopathy over 10 years in EDIC following DCCT: the ‘legacy effect’



Error bars are 95% CI. N = 1211

White NH, et al. *Arch Ophthalmol* 2008; 126:1707–1715.

Diabetes Prevention Program (DPP)=>DPPOS

Polling Question

When intervening to prevent diabetes in a person with pre-diabetes, which of the following is the best indicator of long term success?

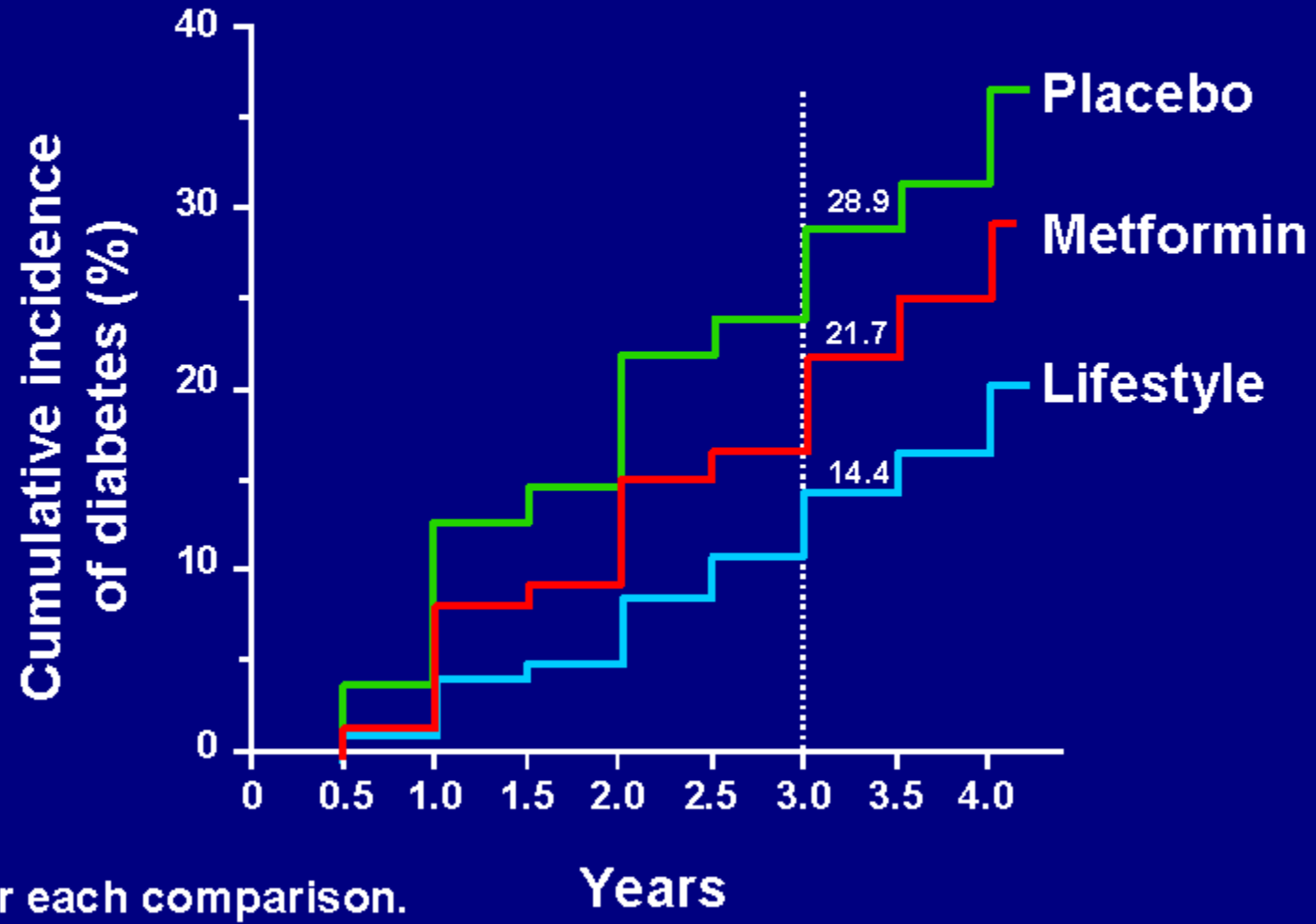
A. Insulin doses under 0.5U/kg

B. Stable dose of sulfonylurea agents

C. Weight gain of less than 5 kg

D. Return to normal glucose tolerance at least once

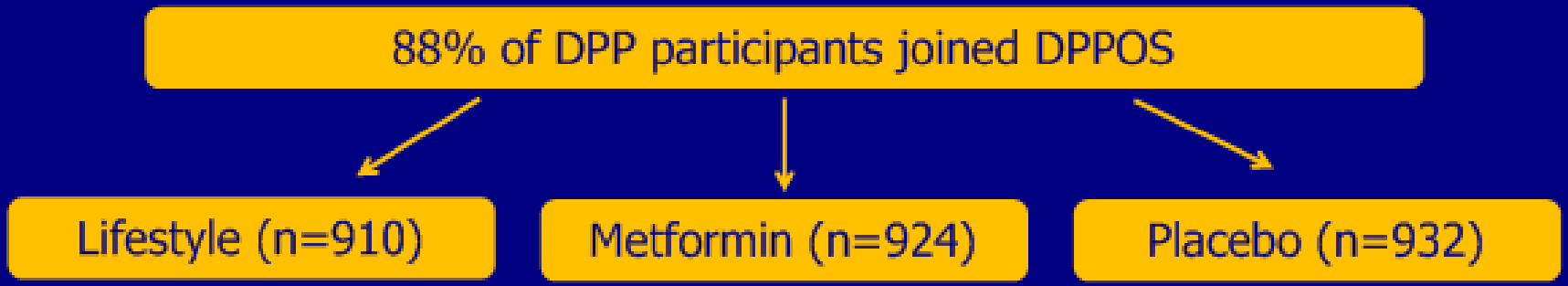
US DPP: Incidence of Type 2 Diabetes With Different Interventions



P<0.001 for each comparison.

Diabetes Prevention Program Research Group. *N Engl J Med.* 2002;346:393-403.

DPPOS Maintenance: Years 5-10



- Interventions for participants who developed diabetes
  - Glucose testing within 6 wks to confirm diagnosis
  - Received 1 hr of individual counseling
  - Encouraged to monitor glucose levels once daily
  - Maintained in original treatment groups

DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study

DPPOS Substudy: Effect of Regression from Prediabetes to NGR on Diabetes Risk

72% (n=1,990 of total 2,671)
of subjects in DPPOS included in analysis

- Lifestyle (n=736)
- Metformin (n=647)
- Placebo (n=607)

- Objective: quantify and predict diabetes risk reduction during DPPOS
- Examined participants who regressed to NGR* at least once on yearly OGTT during the DPP and never met criteria for diabetes diagnosis
- Those who regressed to NGR were compared with those who maintained prediabetes state† with and without stratification by previous DPP treatment group
- Included subjects had persistent prediabetes or restoration of NGR over 5.7 years of follow-up in DPPOS; any patient who progressed to diabetes during DPPOS was excluded

NGR=normal glucose regulation
*Defined as FPG <5.6 mmol/L and 2-hr glucose <7.8 mmol/L
†Defined as FPG 5.6-6.9 mmol/L and 2-hr glucose 7.8-11.0 mmol/L, or both, on yearly OGTT during DPP; never met criteria for diabetes diagnosis
DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study

DPPOS Substudy: Additional Outcomes

Effects on diabetes risk in DPPOS

Adverse

- Increased weight loss during DPP (HR, 1.26; 95% CI, 1.15-1.39; *P*<0.0001)
- Increased BMI at beginning of DPPOS (HR, 1.14; 95% CI, 1.05-1.25; *P*=0.0021)

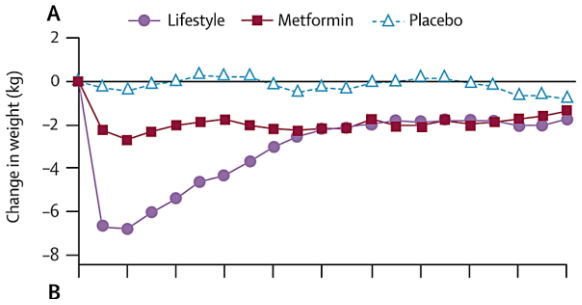
Protective

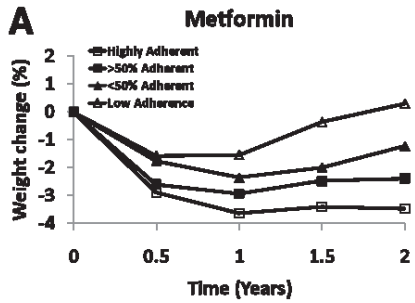
- Higher beta-cell function (HR, 0.80; 95% CI, 0.71-0.89; *P*<0.0001)
- Insulin sensitivity (HR, 0.83; 95% CI, 0.74-0.94; *P*=0.0001)

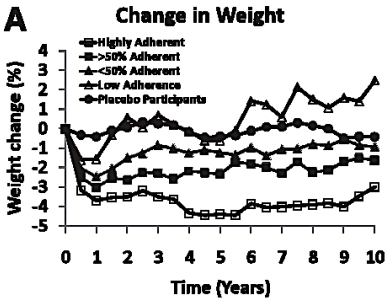
- Previous DPP treatment group assignment did not have an effect on risk reduction in DPPOS among those who attained NGR
- Participants who consistently stayed in a prediabetes state during DPP had increased diabetes risk despite intensive lifestyle intervention (HR, 1.31; 95% CI, 1.03-1.68; *P*=0.0304) and a lower chance of achieving NGR (OR, 0.59; 95% CI, 0.42-0.82; *P*=0.0014) vs placebo in DPPOS

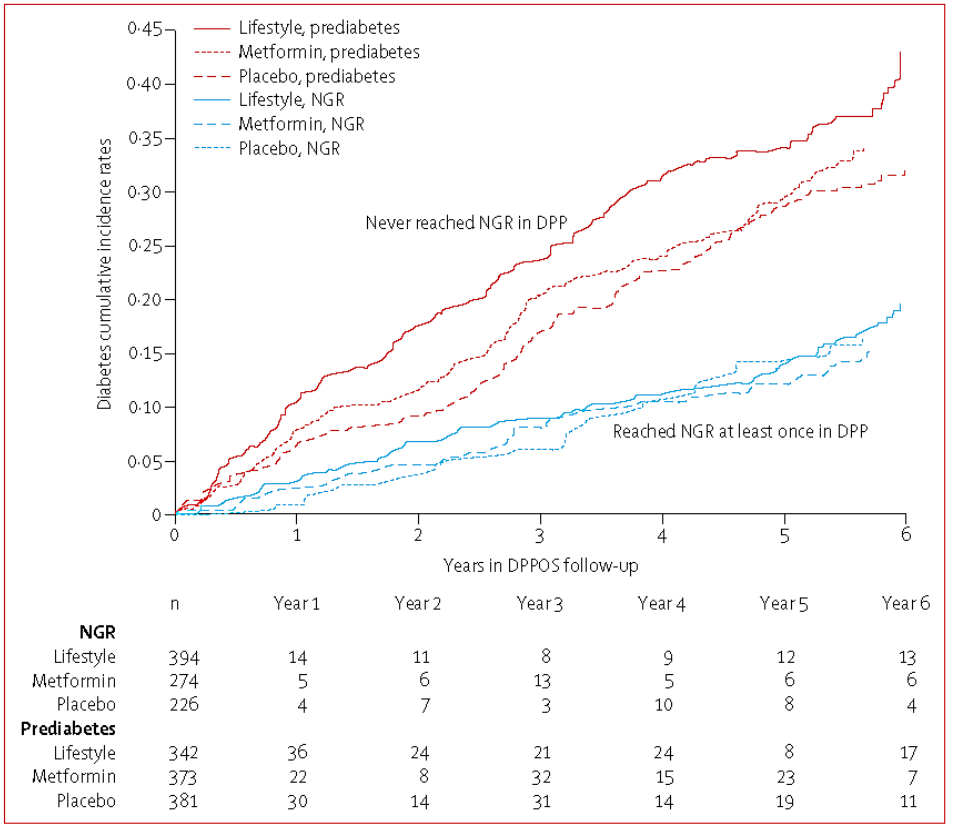
NGR=normal glucose regulation
DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study

DPPOS and weight loss









	n	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
NGR							
Lifestyle	394	14	11	8	9	12	13
Metformin	274	5	6	13	5	6	6
Placebo	226	4	7	3	10	8	4
Prediabetes							
Lifestyle	342	36	24	21	24	8	17
Metformin	373	22	8	32	15	23	7
Placebo	381	30	14	31	14	19	11

Figure 3: Diabetes cumulative incidence rates during DPPOS in participants who attained normal glucose regulation at least once during DPP compared with those who consistently had prediabetes, stratified by treatment group in DPP

DPP=Diabetes Prevention Program. DPPOS=Diabetes Prevention Program Outcomes Study. NGR=normal glucose regulation.

DPPRG-Lancet 2009;374:1677. DPPRG-Diabetes Care 2012;35:731.
Perreault L, et al Lancet 2012;379:2243

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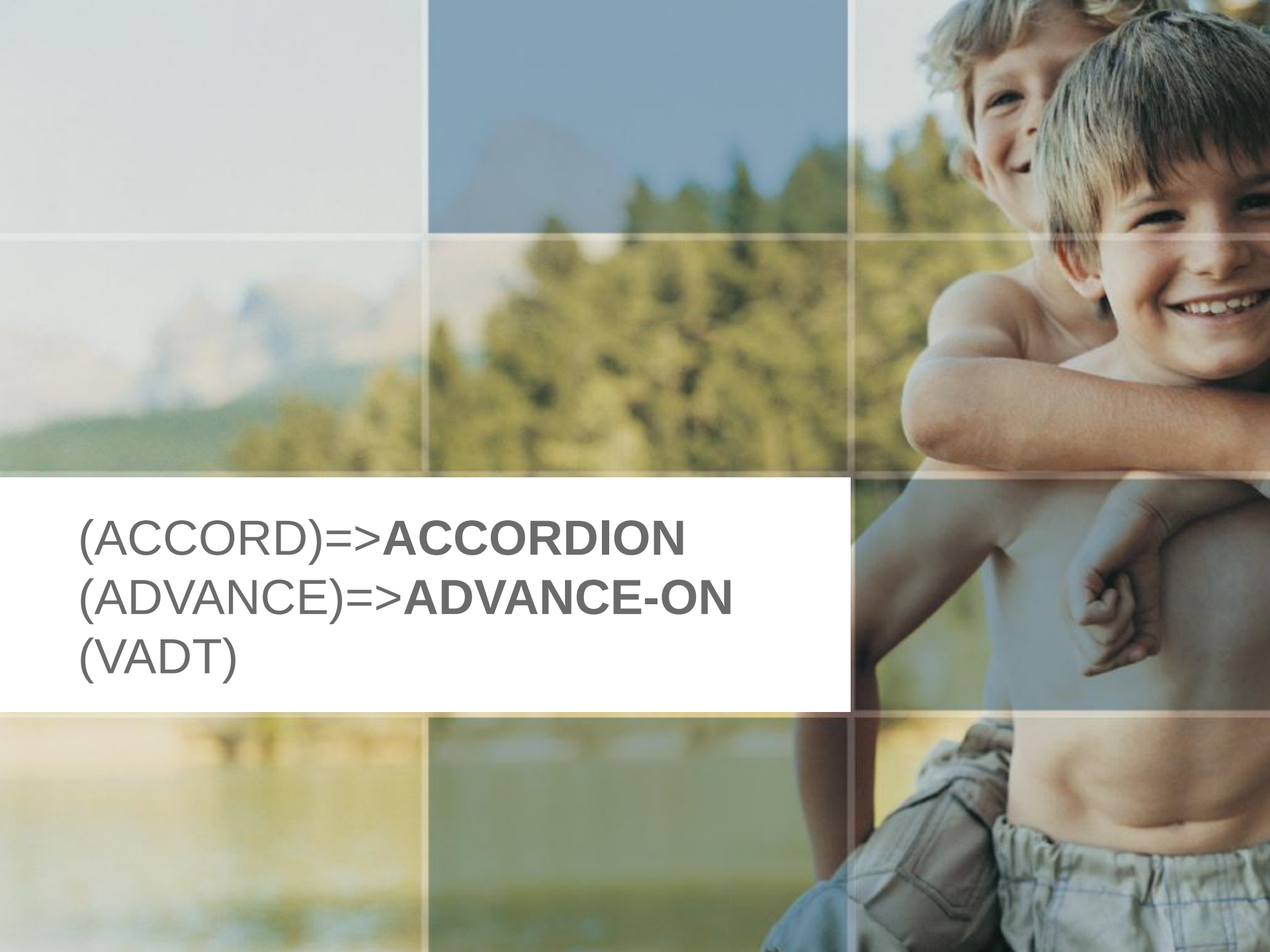

(ACCORD)=>**ACCORDION**
(ADVANCE)=>**ADVANCE-ON**
(VADT)

Polling Question

Which of the following were associated with increased mortality in the ACCORD trial?

A. older age, male sex, longer diabetes duration

B. history of cardiovascular disease, heart failure, higher HbA1c

C. serum creatinine and urine albumin/creatinine ratio

D. all the above

Macrovascular Trials in Type 2 Diabetes
(ACCORD, ADVANCE, VADT)

Table 1 Key characteristics of trials and length of follow-up

Trial name	Trial acronym	Year reported	Number	Design	Glycaemic control comparison	Entry criteria	Median follow-up (years)
The Action to Control Cardiovascular Risk in Diabetes Study	ACCORD	2008	10,251	Randomised, double 2×2 factorial	Intensive (target HbA_{1c} <6%) vs standard (target HbA_{1c} 7–7.9%)	Type 2 diabetes, HbA_{1c} ≥7.5%, 40–79 years or 55–79 years[a]	3.4[b]
Action in Diabetes and Vascular Disease: Preterax[g] + Diamicron Modified Release Controlled Evaluation	ADVANCE	2008	11,140	Randomised, 2×2 factorial	Intensive (target HbA_{1c} ≤6.5%) vs standard (target HbA_{1c} >6.5%)	Diagnosis of type 2 diabetes at ≥30 years, ≥55 years[c]	4.9
UK Prospective Diabetes Study	UKPDS	1998	3,867	Randomised	Intensive (target FPG <6 mmol/l) vs conventional (best achievable FPG with diet alone)	Newly diagnosed type 2 diabetes, 25–65 years old[d]	5.0[e]
Veterans Affairs Diabetes Trial	VADT	2008	1,791	Randomised	Intensive (target absolute reduction 1.5%) vs standard	Poorly controlled type 2 diabetes, military veterans[f]	5.6

Turnbull FM, et al.. Diabetologia 2009;52;2288

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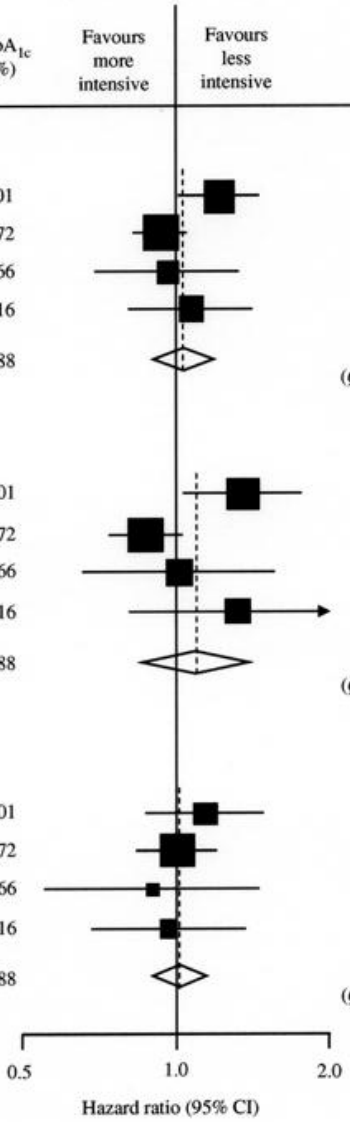
Macrovascular Trial Outcomes

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA$_{1c}$ (%)	Hazard ratio (95% CI)
All-cause mortality				
ACCORD	257 (1.41)	203 (1.14)	−1.01	1.22 (1.01–1.46)
ADVANCE	498 (1.86)	533 (1.99)	−0.72	0.93 (0.83–1.06)
UKPDS	123 (0.13)	53 (0.25)	−0.66	0.96 (0.70–1.33)
VADT	102 (2.22)	95 (2.06)	−1.16	1.07 (0.81–1.42)
Overall	980	884	−0.88	1.04 (0.90–1.20) (Q=5.71, p=0.13, I^2=47.5%)
Cardiovascular death				
ACCORD	135 (0.79)	94 (0.56)	−1.01	1.35 (1.04–1.76)
ADVANCE	253 (0.95)	289 (1.08)	−0.72	0.88 (0.74–1.04)
UKPDS	71 (0.53)	29 (0.52)	−0.66	1.02 (0.66–1.57)
VADT	38 (0.83)	29 (0.63)	−1.16	1.32 (0.81–2.14)
Overall	497	441	−0.88	1.10 (0.84–1.42) (Q=8.61, p=0.04, I^2=65.1%)
Non-cardiovascular death				
ACCORD	115 (0.63)	98 (0.55)	−1.01	1.14 (0.87–1.49)
ADVANCE	245 (0.92)	244 (0.91)	−0.72	1.00 (0.84–1.20)
UKPDS	52 (0.39)	24 (0.43)	−0.66	0.90 (0.55–1.46)
VADT	64 (1.40)	66 (1.43)	−1.16	0.97 (0.69–1.36)
Overall	476	432	−0.88	1.02 (0.89–1.18) (Q=0.99, p=0.80, I^2=0.0%)



Turnbull FM, et al.. Diabetologia 2009;52;2288

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Summary:

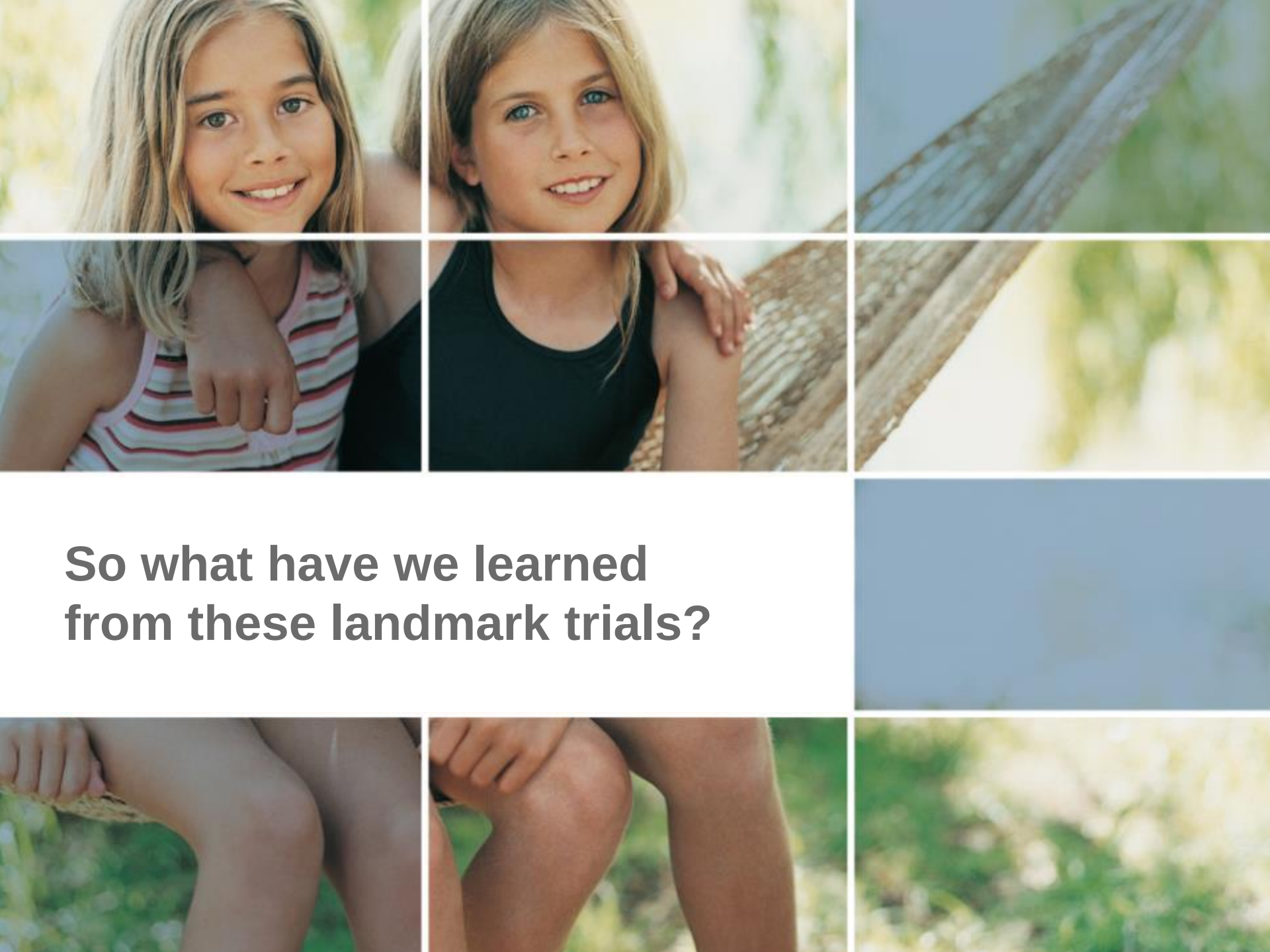
ACCORD, ADVANCE, UKPDS, VADT

- A meta-analysis of ACCORD, ADVANCE, UKPDS, and VADT (total 27,049 participants with 2,370 major vascular events) showed a significant 9% reduction in these events, driven by a 15% reduction in myocardial infarction, with non-significant 10 and 4% increases in cardiovascular and total mortality, respectively.

- Hypoglycemia rates were 2.5-fold more common with intensive treatment.

- There was heterogeneity between the trials, with ADVANCE suggesting a reduction in cardiovascular mortality, the UKPDS being neutral, and ACCORD and VADT having trends to increased CV mortality in the initial trial data. In the meta-analysis, those with no history of macrovascular disease had a significant 16% reduction in CVD, but there was no CV benefit in those with such a history.

Travert F, Woodward M. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298
Boomgarden ZT, Cardiovascular disease and glycemic treatment. Diabetes Care 2010;33:e134-e139



So what have we learned from these landmark trials?

Landmark Trials

- **Type 2 diabetes can be prevented (?delayed) in individuals with pre-diabetes by lifestyle modifications or metformin.**
- **In people with pre-diabetes, getting them back to normal glucose tolerance is key to preventing diabetes, and weight loss is pivotal in that goal.**
- **Diabetes complications can be dramatically lowered in people with type 1 and type 2 diabetes by intensive insulin therapy with lasting 'legacy' effects over at least 20 years.**

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Landmark Trials

- **Tight glycemic control with insulin is associated with significant increases in hypoglycemia.**
- **In people with type 2 diabetes and cardiovascular risk, early insulin seems not to have adverse CV outcomes (although hypoglycemia is more common).**
- **In people with type 2 diabetes who have had long duration diabetes and have existing CV complications, there is a risk to trying to go too low in glucose (A1C) levels. Individualize targets!**

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Thank You

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