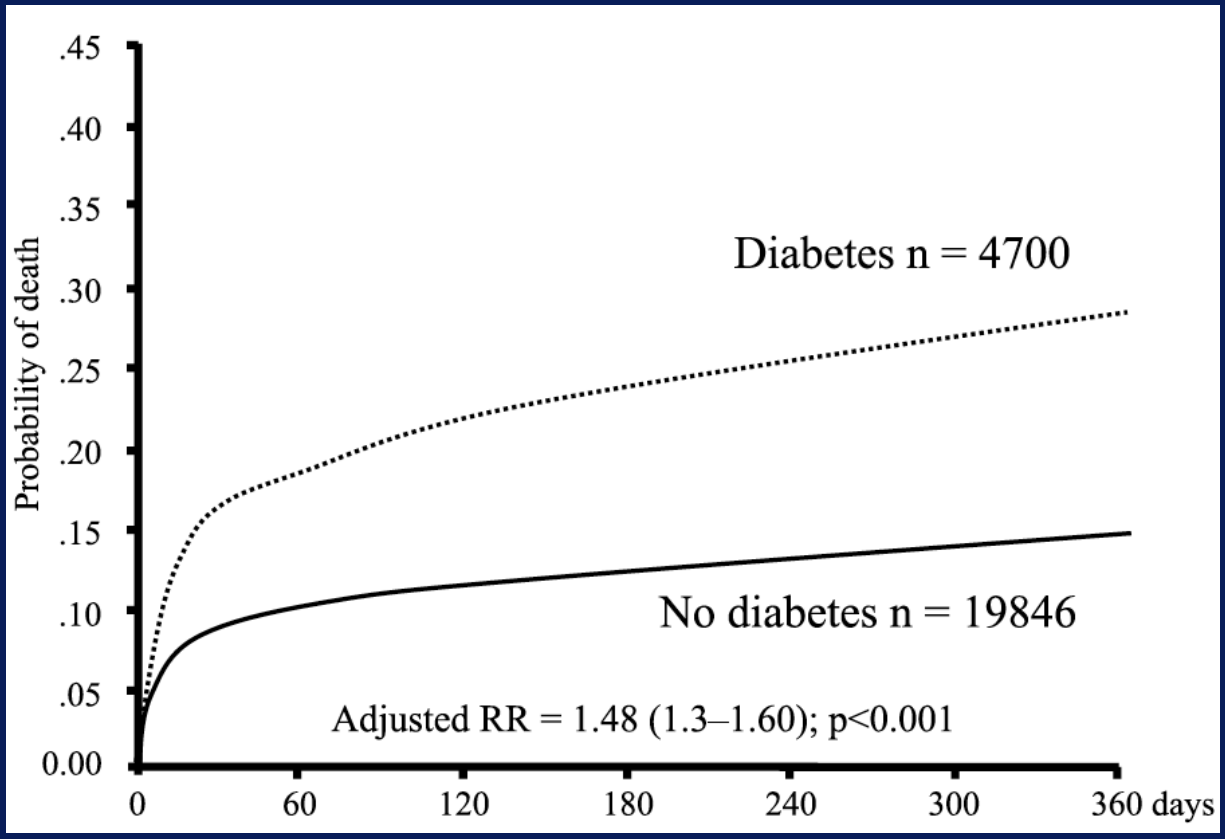
“Insulin therapy should be the treatment of choice for type 2 diabetes complicated by CHD”

Opposed by Simon Heller

University of Sheffield

Effect of diabetes over first year post MI

RIKS-HIA 1995-1998

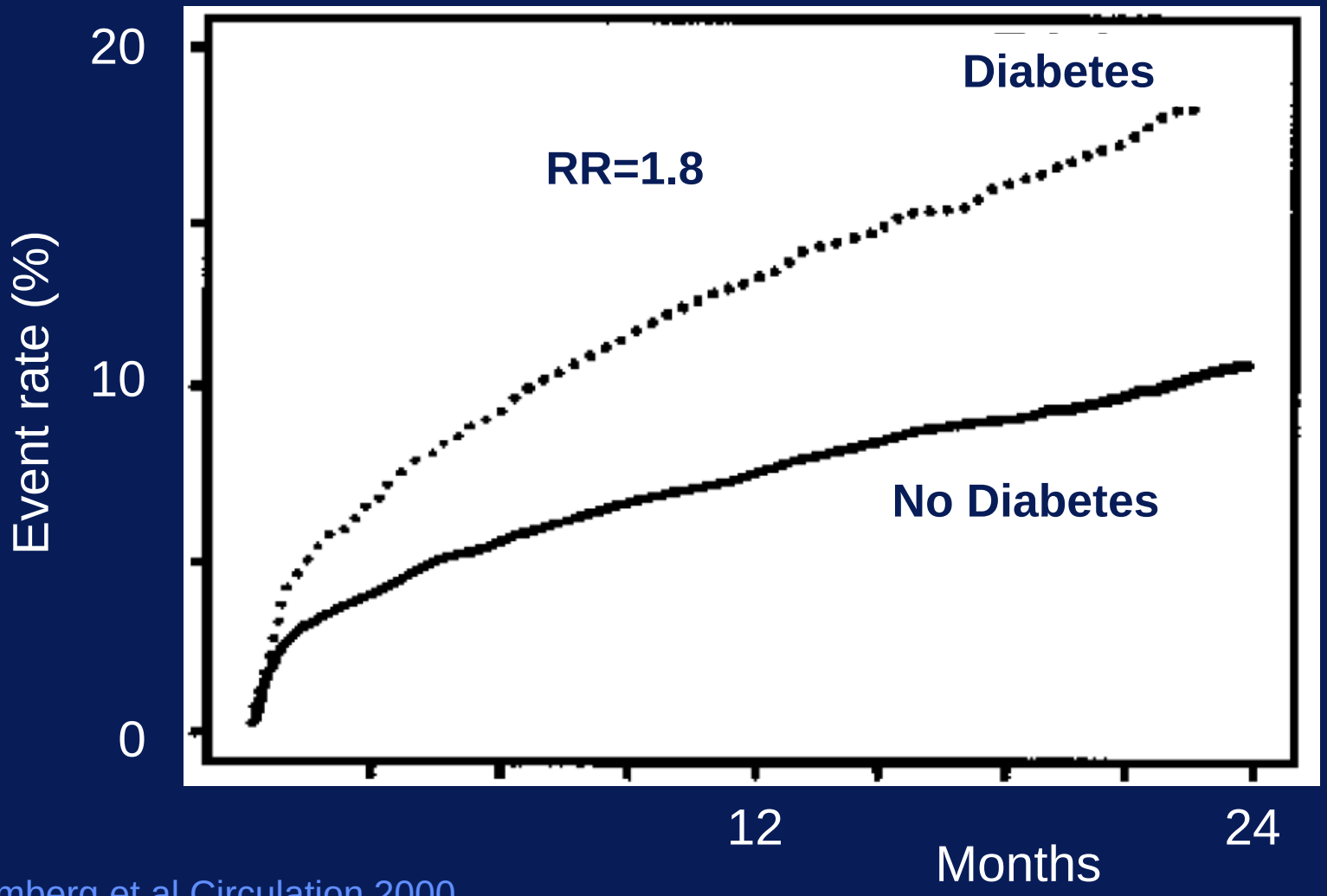


Norhammer et al Eur Ht J 2003

Total mortality after ACS

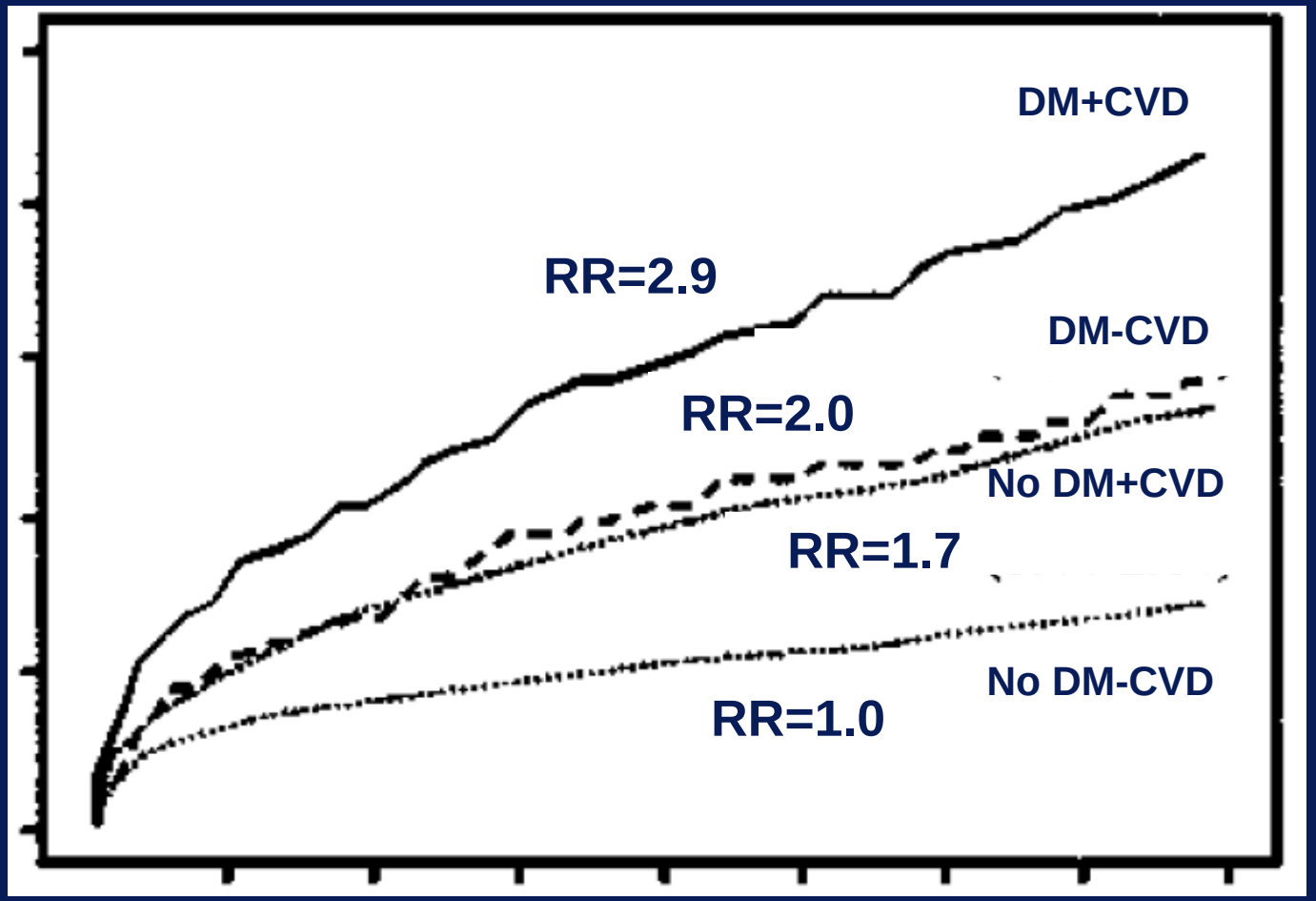
(unstable angina and non-Q-wave MI)

OASIS registry (21% of 8000 with diabetes)



Malmberg et al Circulation 2000

Total mortality after ACS according to history of CVD



Malmberg et al Circulation 2000

Carrying the motion demands positive responses to the following key questions

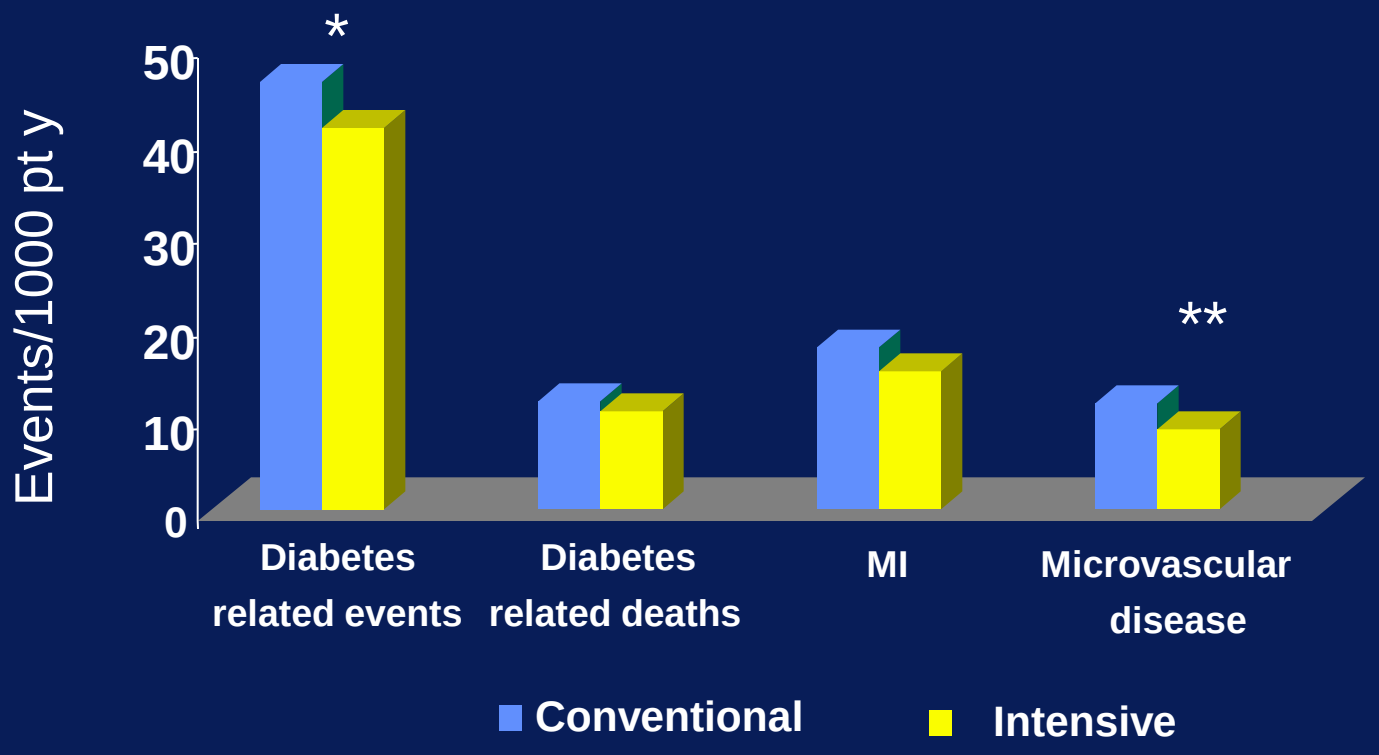
- Can the high risk of CVD
  - be usefully reduced by tighter glycaemic control?
  - be more successfully reduced by insulin compared to other agents?
- Are the benefits outweighed by the side effects?

Outline

- Insulin treatment in Type 2 diabetes
  - Evidence of benefit
  - Evidence for harm
  - Side effects
  - What do the DIGAMI trials tell us?
- Conclusions

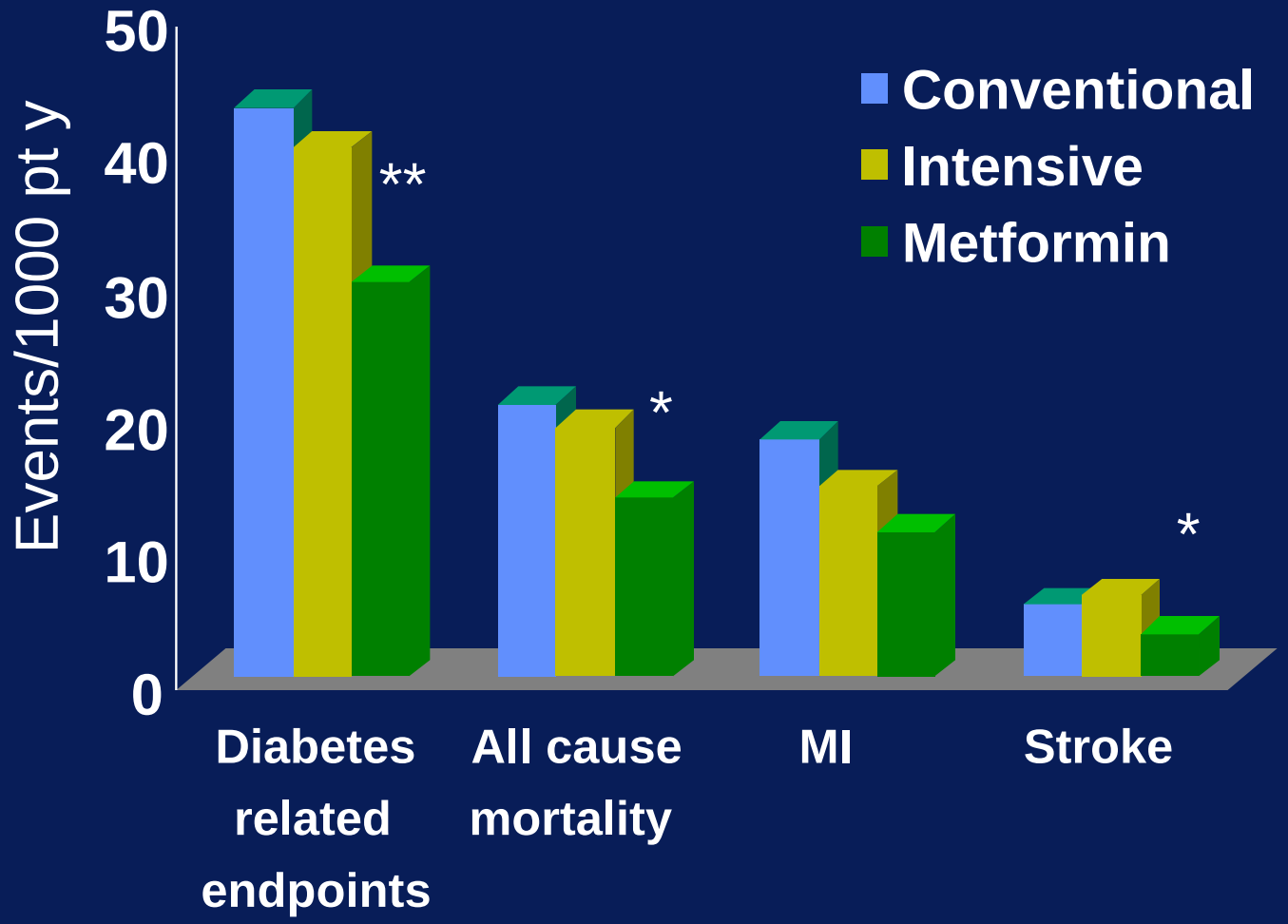
UKPDS

25% reduction in microvascular disease (mostly photocoagulation)
Complication -free interval for any diabetes event 14 vs 12.7y
Number needed to treat to prevent 1 event over 10y, 19.6 patients



The UKPDS group, Lancet, 1998

Effects of metformin in the overweight group



The UKPDS group, Lancet, 1998

Evidence for adverse effects of insulin on CVD (1)

Endogenous insulin in humans

- Raised endogenous insulin levels an independent predictor of CVD
  - Paris Prospective Study (Fontbonne et al, Int J Obes 1988)
  - Helsinki Policeman's Study (Pyorala et al Diabetes Care 2000)
  - Buselton Study (Welborn et al Diabetes Care 1979)
  - Meta-analysis showed significant albeit modest effect of insulin (Ruige et al, Circulation 1998)
- Patients with IGT (normal fasting glucose and raised insulin levels) have increased CV risk (Unwin et al, Diabet Med 2000)

Evidence for adverse effects of insulin on CVD (2)

Exogenous insulin

- Increased ET1 (Hattori et al, Metabolism, 1991)
- Increased PAI-1 (Hsueh et al, Am J Cardiol 1999)
- Insulin treated
  - rats (Stout et al, BMJ 1970)
  - chickens (Stout et al, Atherosclerosis 1973)

have increased burden of atheroslerotic plaque

Evidence for adverse effects of insulin on CVD (3)

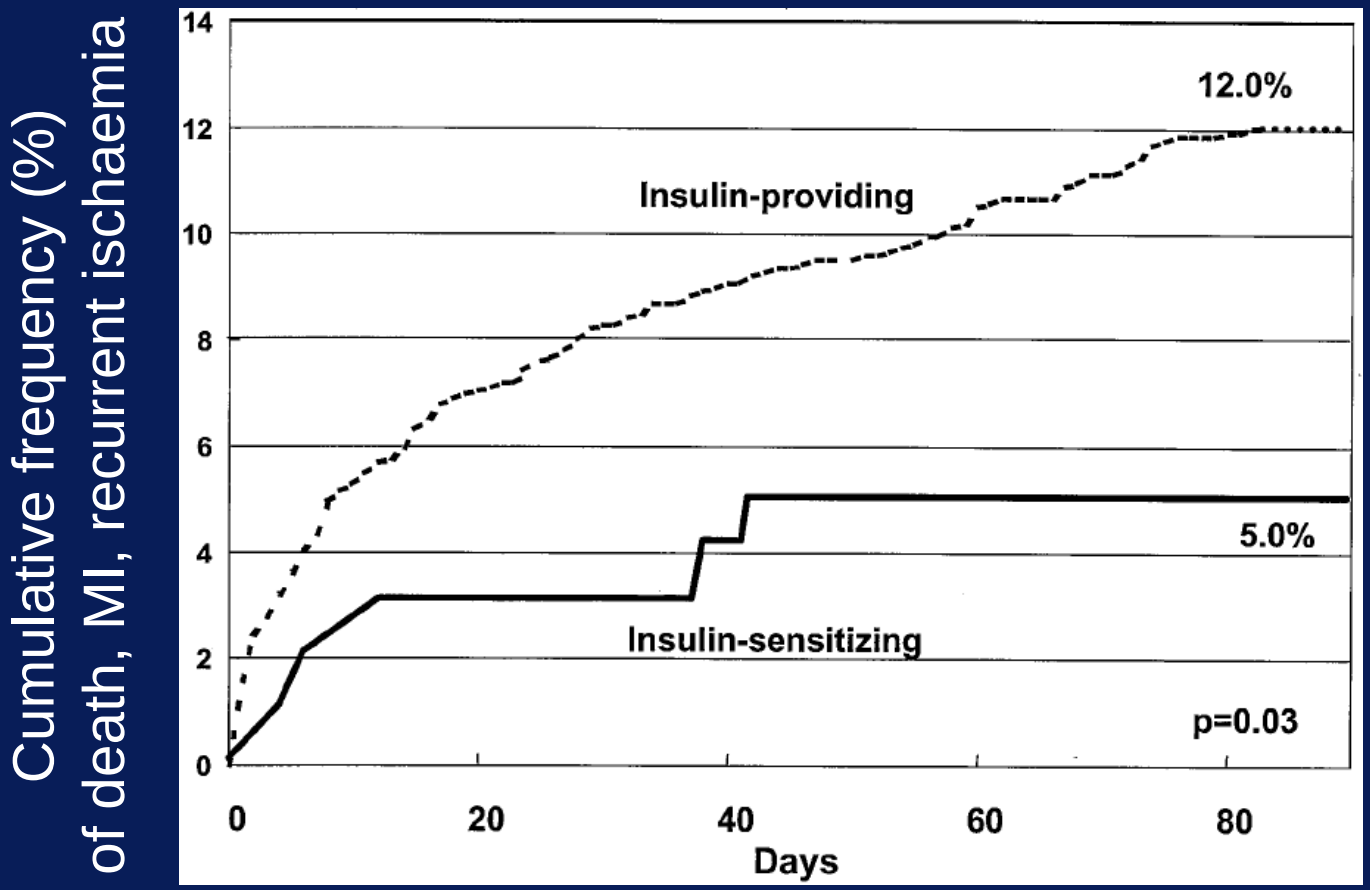
Exogenous insulin observational studies

- Observational studies show adverse effects of insulin
  - Nelson et al, Circulation 1990
  - Janka et al, Diabetes Metab 1987

but subject to considerable confounding

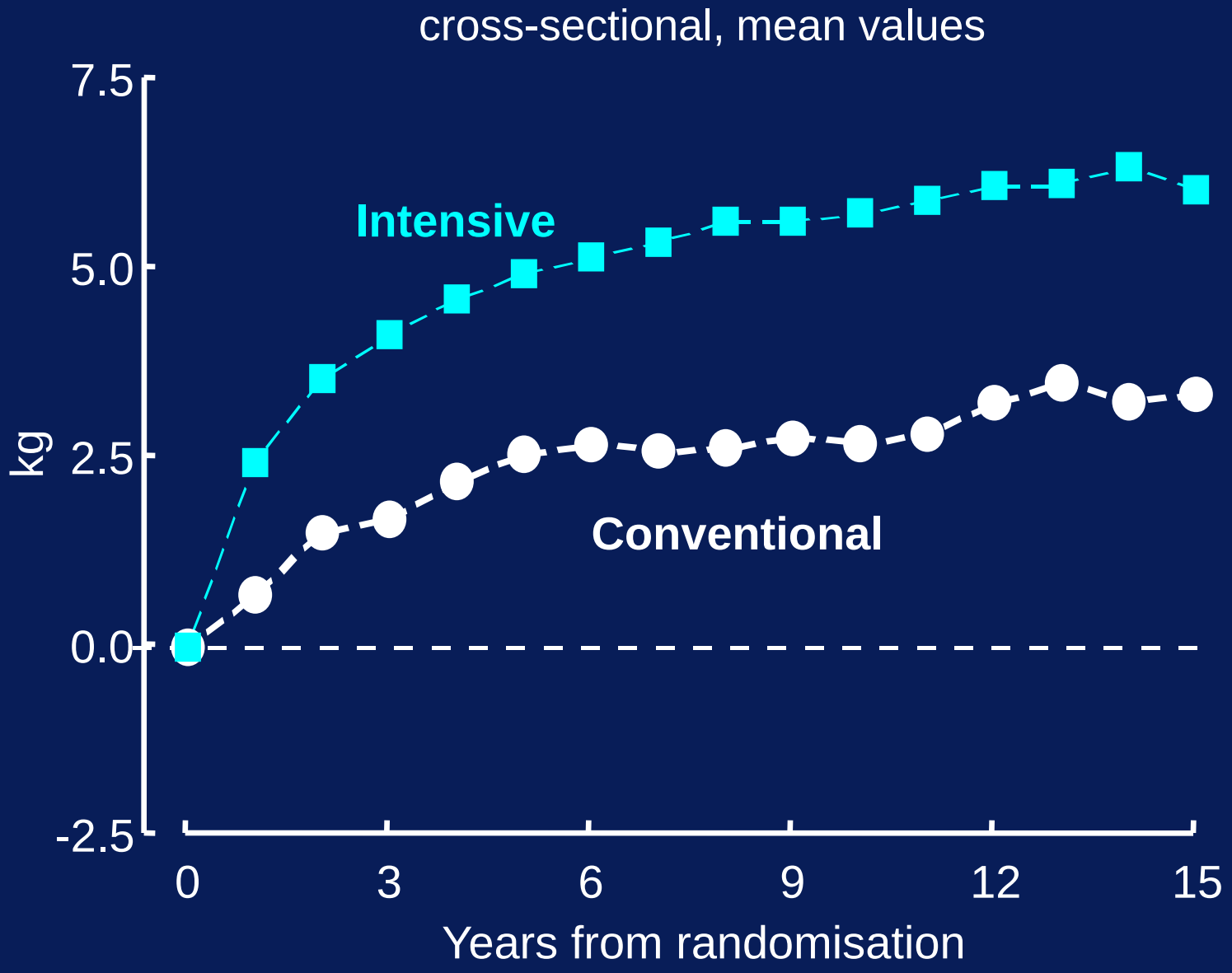
- Meta-analysis of 6 studies involving exogenous insulin showed reduction in extent of cardiovascular disease but no effect on progression or mortality (Muis et al, Diabet Med 2005)

Does blood glucose lowering therapy influence outcome in ACS?



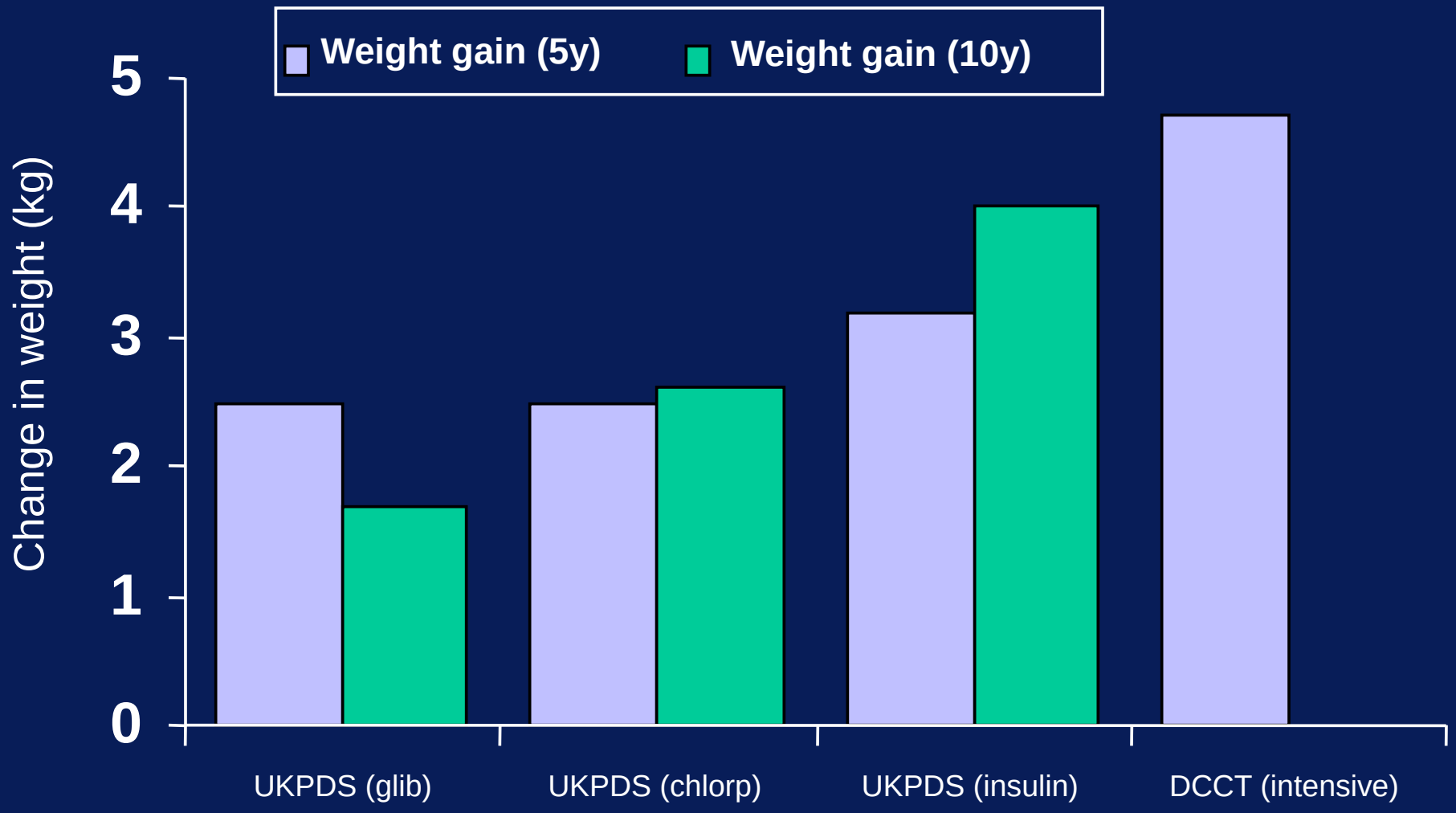
McGuire et al Am Ht J 2004

Change in Body Weight



UKPDS

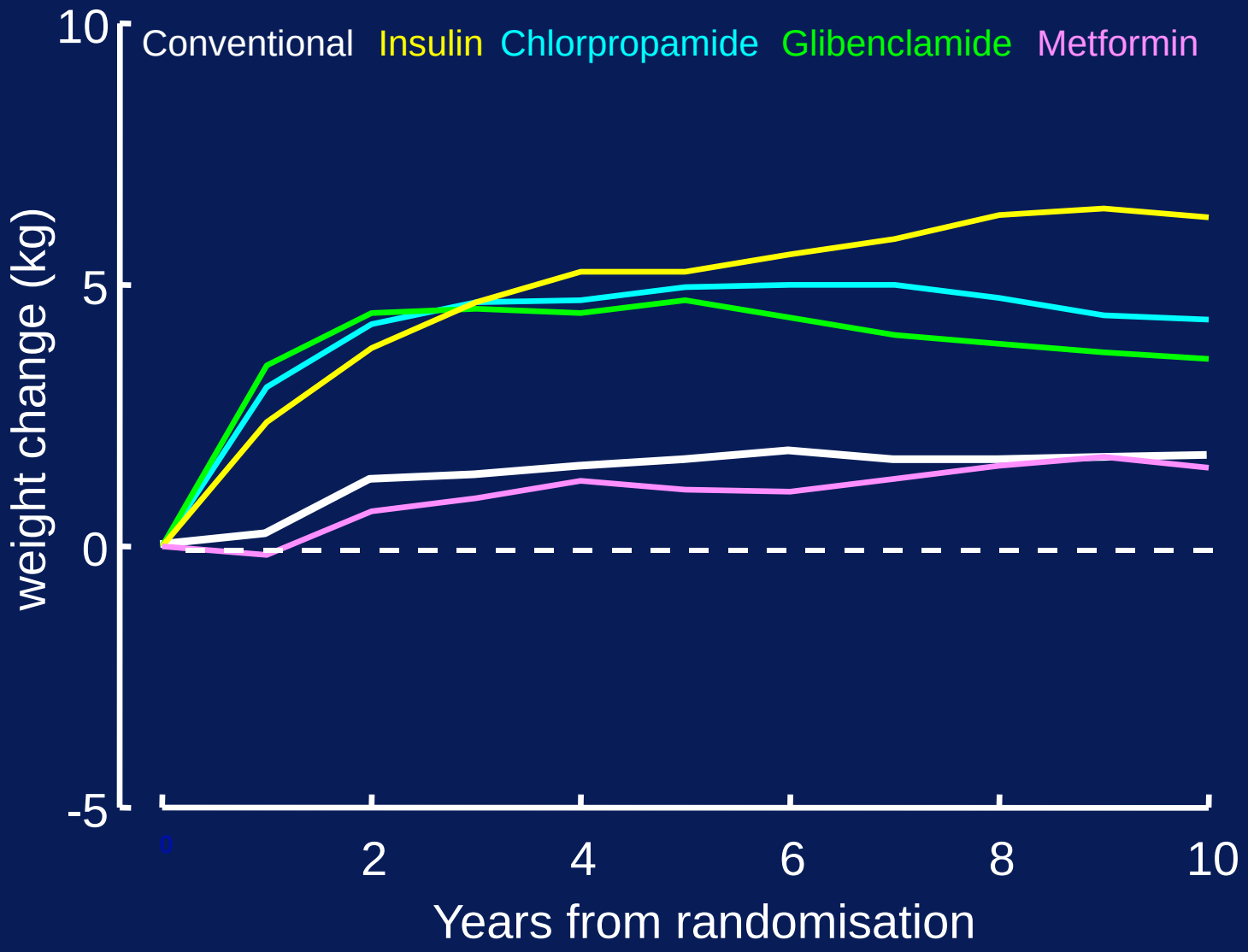
Effect of treatment on weight gain



Change in Weight

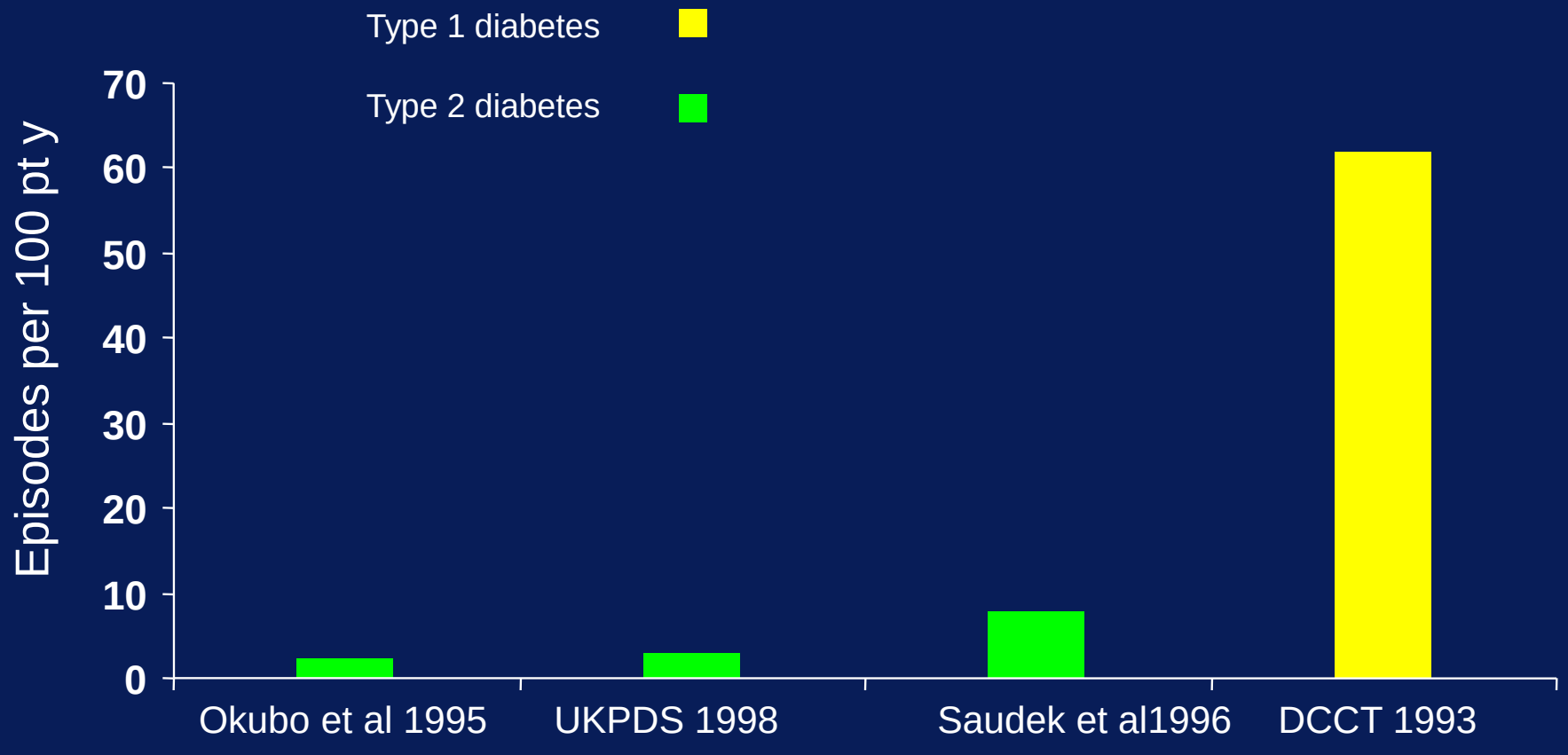
overweight patients

cohort, mean values



UKPDS

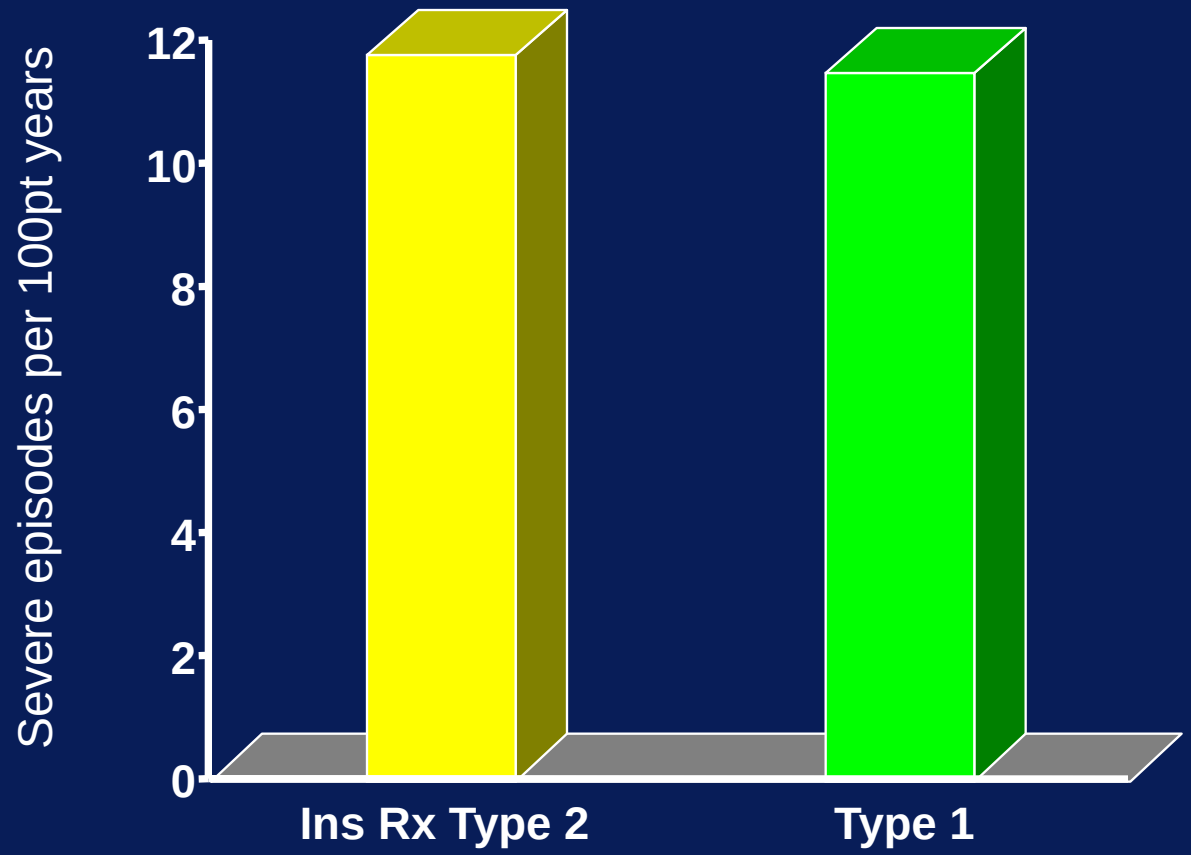
Risks of hypoglycaemia during intensive insulin therapy



Gerich Lancet 2000

Annual incidence of severe hypoglycaemia in a population based survey in Dundee

244 episodes in 160 patients, 69 Type 1 diabetes, 66 Type 2 diabetes on insulin
23 in Type 2 diabetes on sulphonylureas



Leese et al, Diabetes Care, 2003

Rationale for insulin in acute coronary syndrome in individuals with diabetes

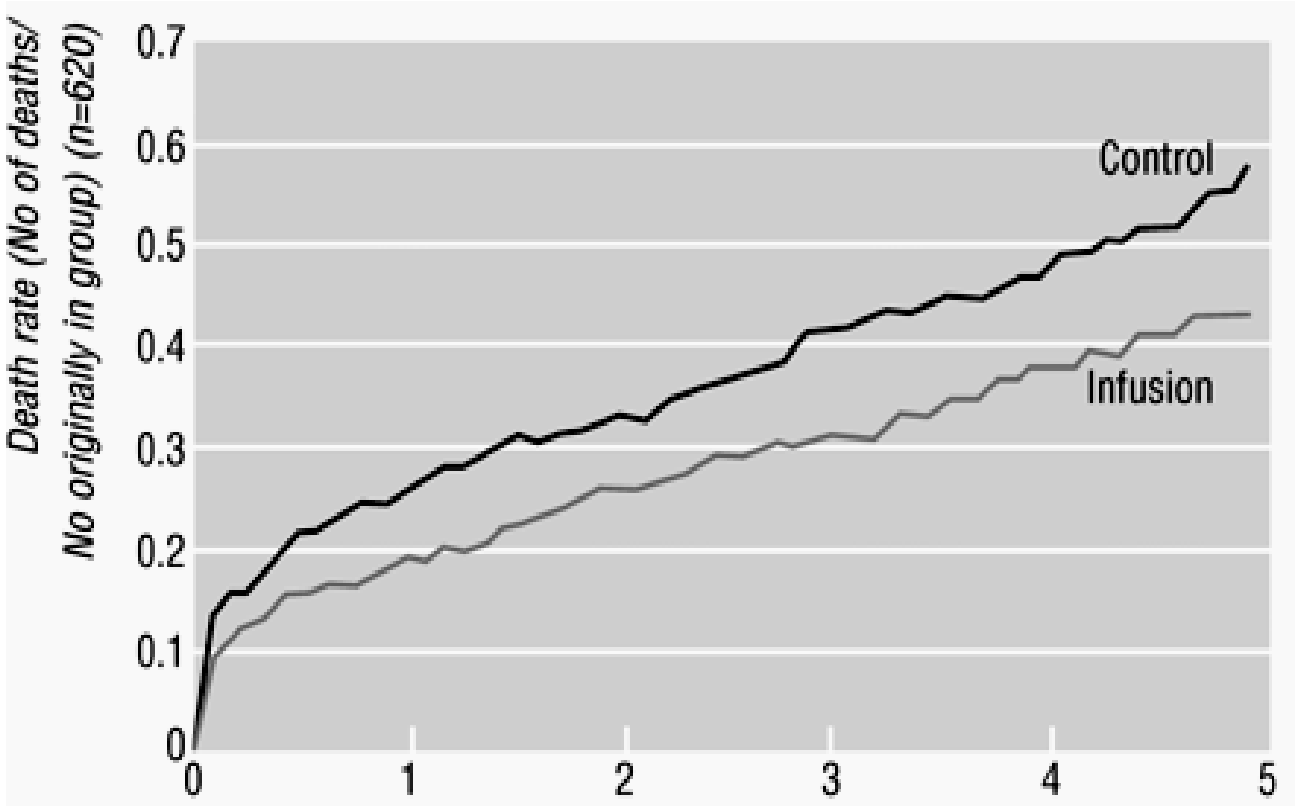
- Excess lipolysis and higher NEFA due to:
  - insulin resistance reducing glucose uptake
  - raised catecholamines
- Free radical generation, arrhythmias, reduced contractility
- Insulin/glucose infusions suppress NEFA

Scientific rationale relates to the use of insulin infusion acutely

DIGAMI

24h of high dose insulin/glucose (no K) + 3m “intensive insulin”

Absolute risk reduction 11%, Relative risk 28%, P=0.01



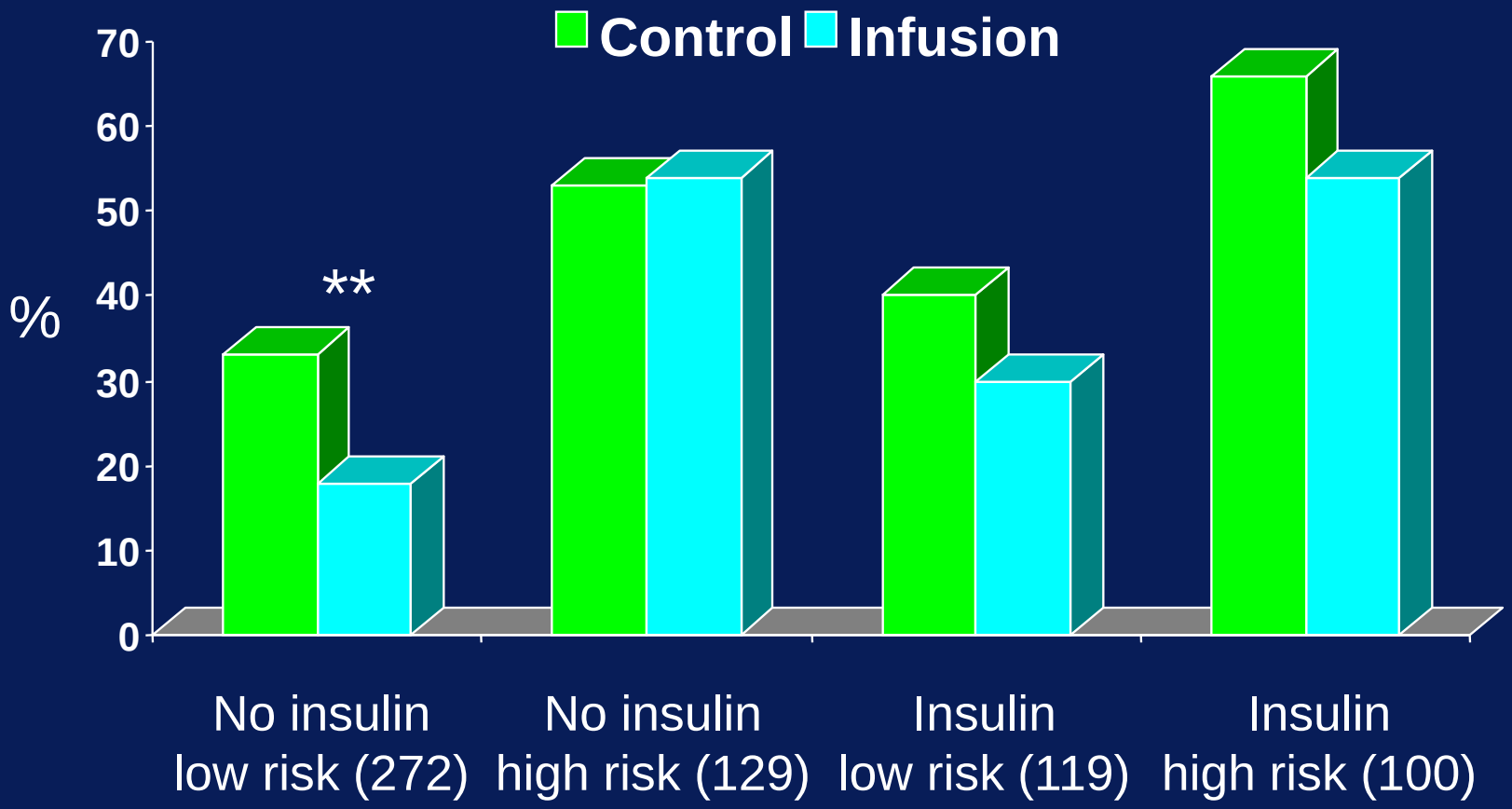
No of patients at risk

Control	314	232	187	116	58	14
Infusion	306	248	202	128	50	13

Malmberg et al BMJ 1997

DIGAMI 1

Long term mortality according to insulin and CV risk

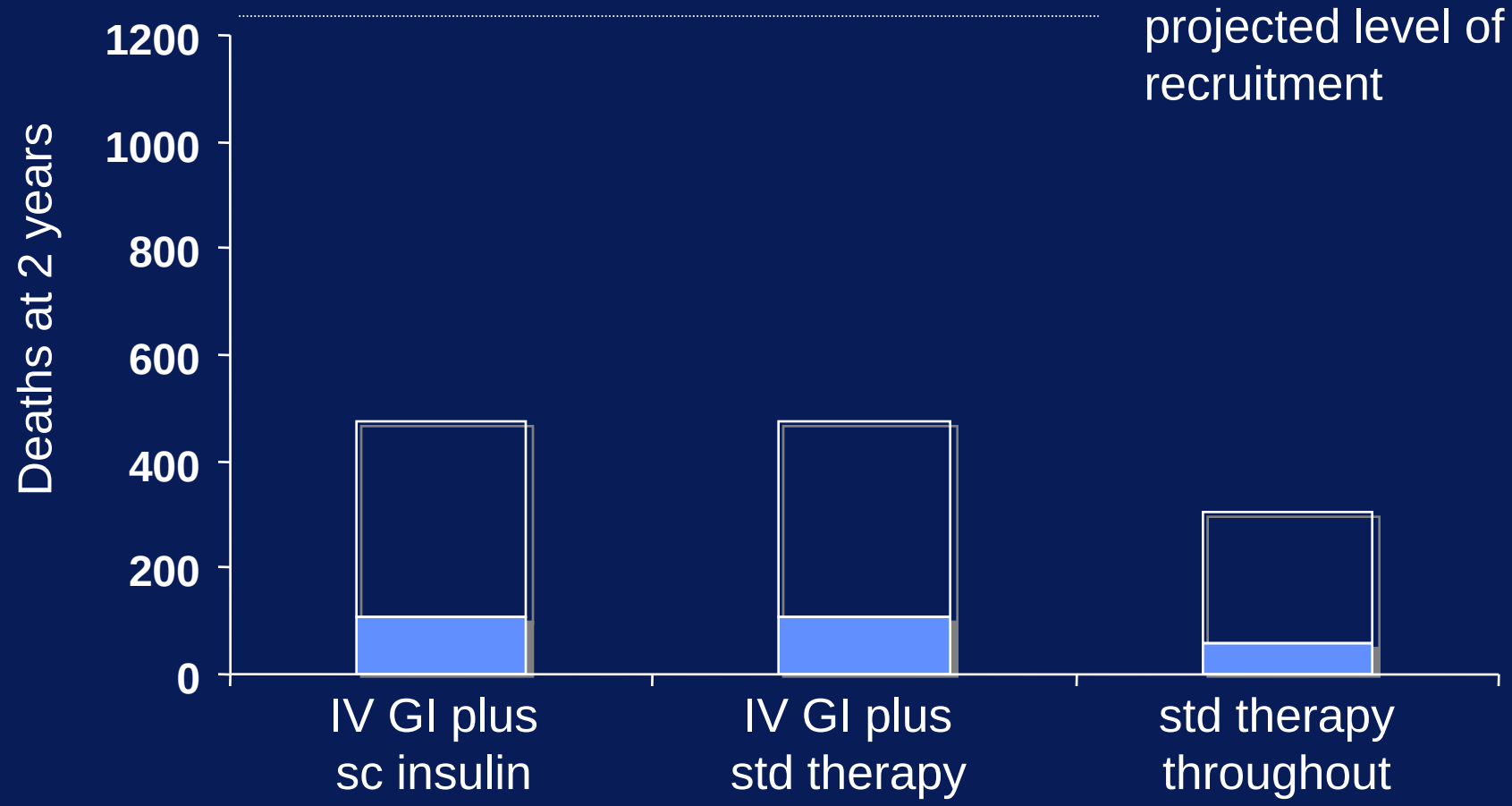


Malmberg et al BMJ 1997

Outstanding issues following DIGAMI 1

- Do insulin/glucose infusions benefit those with IGT/without diabetes post MI?
- Do insulin/glucose infusions benefit those with diabetes and non STEMI and unstable angina?
- Which component is important, acute IV infusion or 3 months intensive insulin therapy?

DIGAMI 2

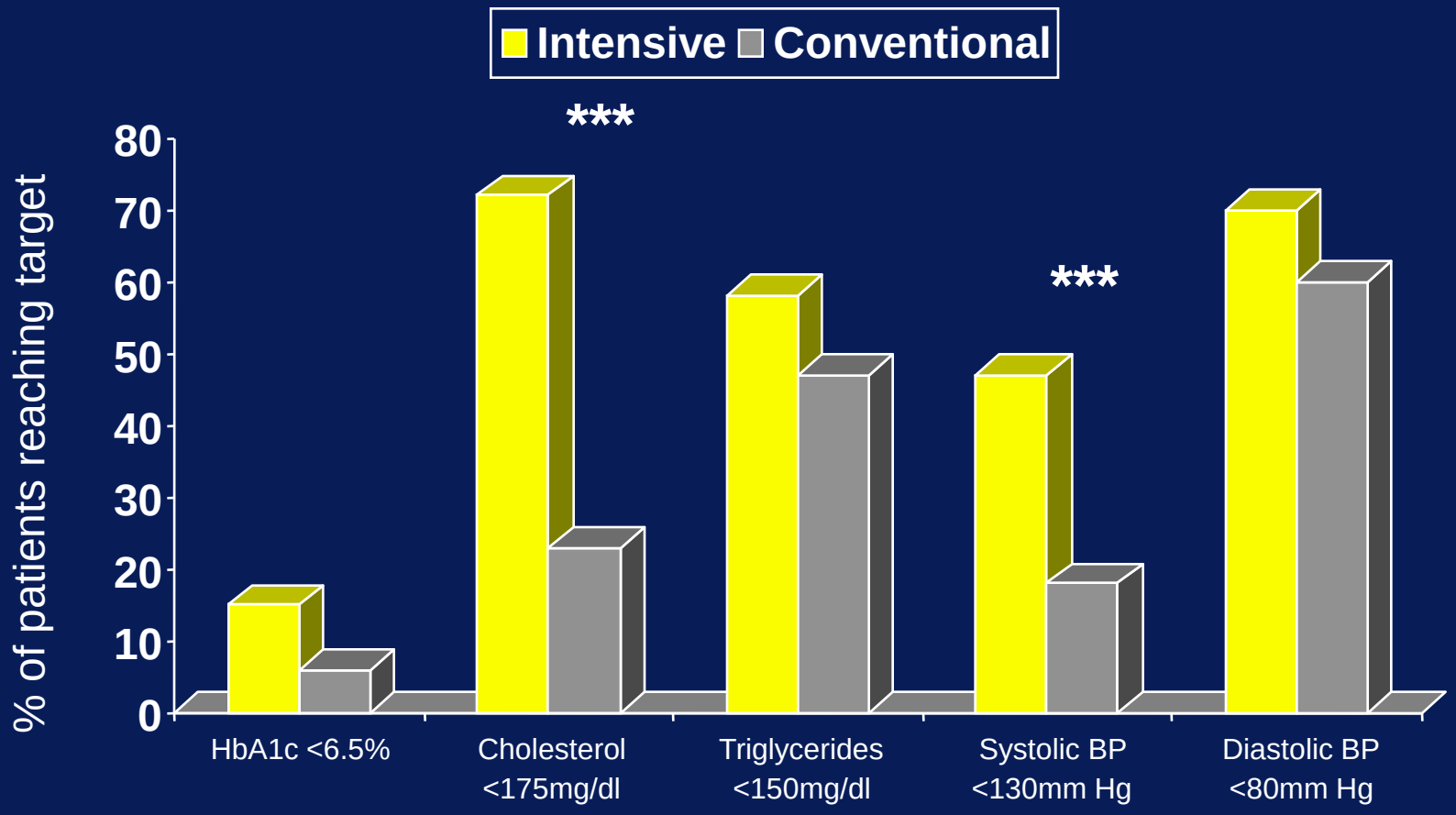

Deaths at 2 years
1200
1000
800
600
400
200
0
projected level of recruitment
IV GI plus sc insulin
IV GI plus std therapy
std therapy throughout

Outstanding issues following DIGAMI 2

- Possible reasons for negative study
  - Underpowered
  - ‘contamination’ of controls
  - Lower glucose at admission
  - Low event rate due to secondary prevention therapy
  - Less aggressive sc insulin treatment
- Reasonable to use acute IV insulin infusion without proceeding to insulin therapy unless clinically indicated

Success of treatment in Steno -2 study

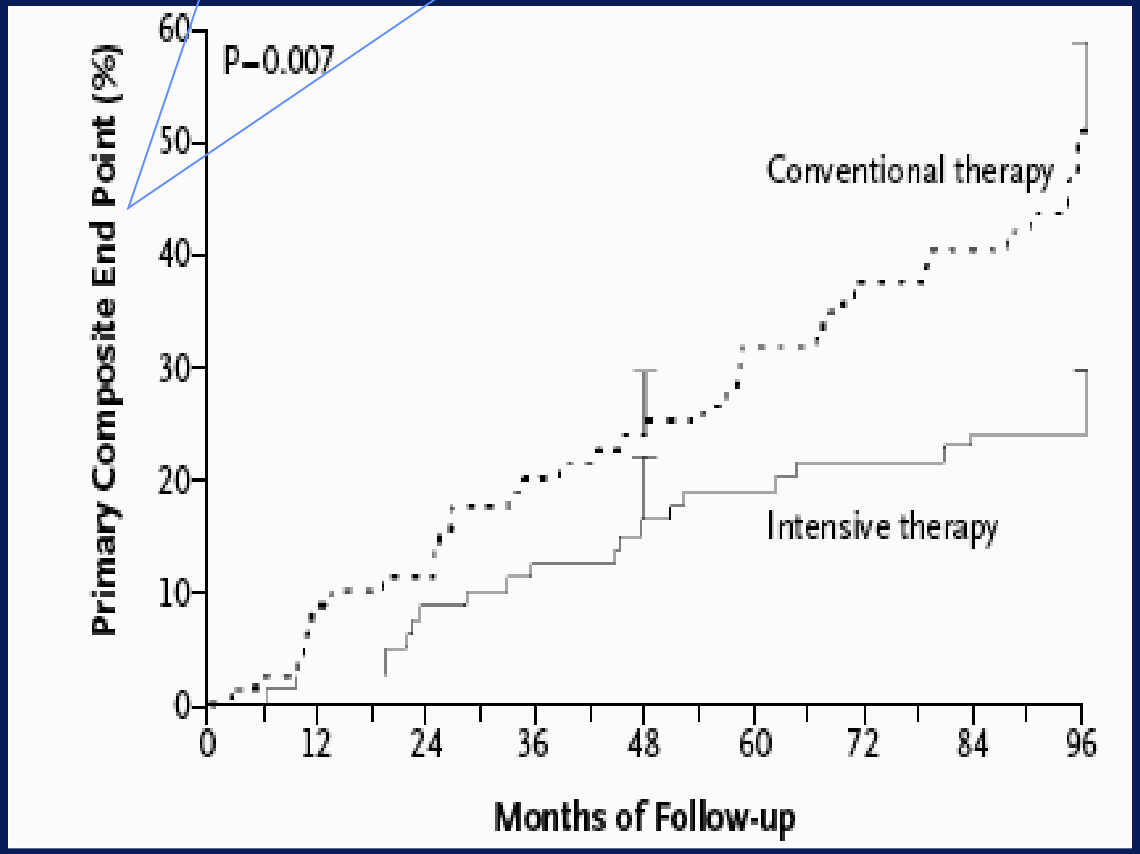
160 subjects with Type 2 diabetes and microalbuminuria randomised to intensive or conventional intervention



Gaede et al, N Engl J Med 2003

Effect of multifactorial intervention in Type 2 diabetes

CV death, MI, stroke, amputation, revascularisation



Gaede et al, N Engl J Med 2003

85 events in 35 patients in std group (44%)

33 events in 19 patients in intensive group (24%)

20% absolute risk reduction equivalent to NNT of 5

?essentially related to tight control of lipids and BP

Conclusions

- Little evidence that long-term tight glucose control involving insulin reduces CVD
- Effective lowering of lipids/BP may limit cardiovascular benefit of tight glucose control
- Side effects of hypoglycaemia and weight gain from aggressive glucose control will be unacceptable to many

The case for early insulin treatment in those with CVD has still to be made