Super-Tight Glucose Control: Why, When and How?

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Outline

- Glucose control and vascular risk
- Does improving control reduce vascular risk?
- Does super tight control reduce risk further?
- Does it matter how we improve control?
- Does one size fit all?
- Targets / game plan
- Is it all about glucose anyway?

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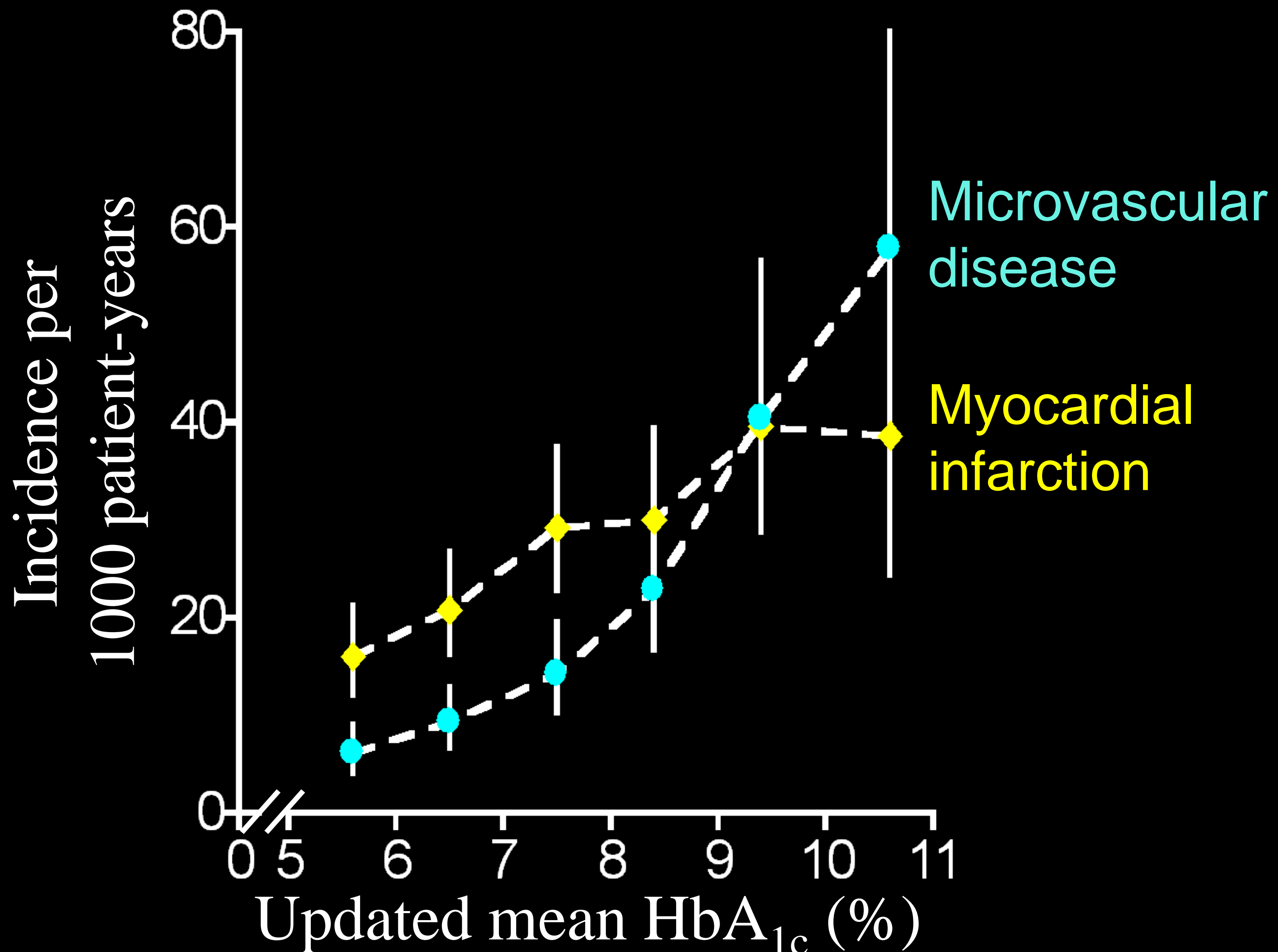
HbA$_{1c}$ and Vascular Risk



UKPDS 35. BMJ 2000; 321: 405-12

HbA_{1c} and Vascular Risk

- Strong association between HbA_{1c} and microvascular risk, particularly when $HbA_{1c} > 7.5$ %
- Strong association between HbA_{1c} and macrovascular risk, but increases less steeply when $HbA_{1c} > 7.5$ %

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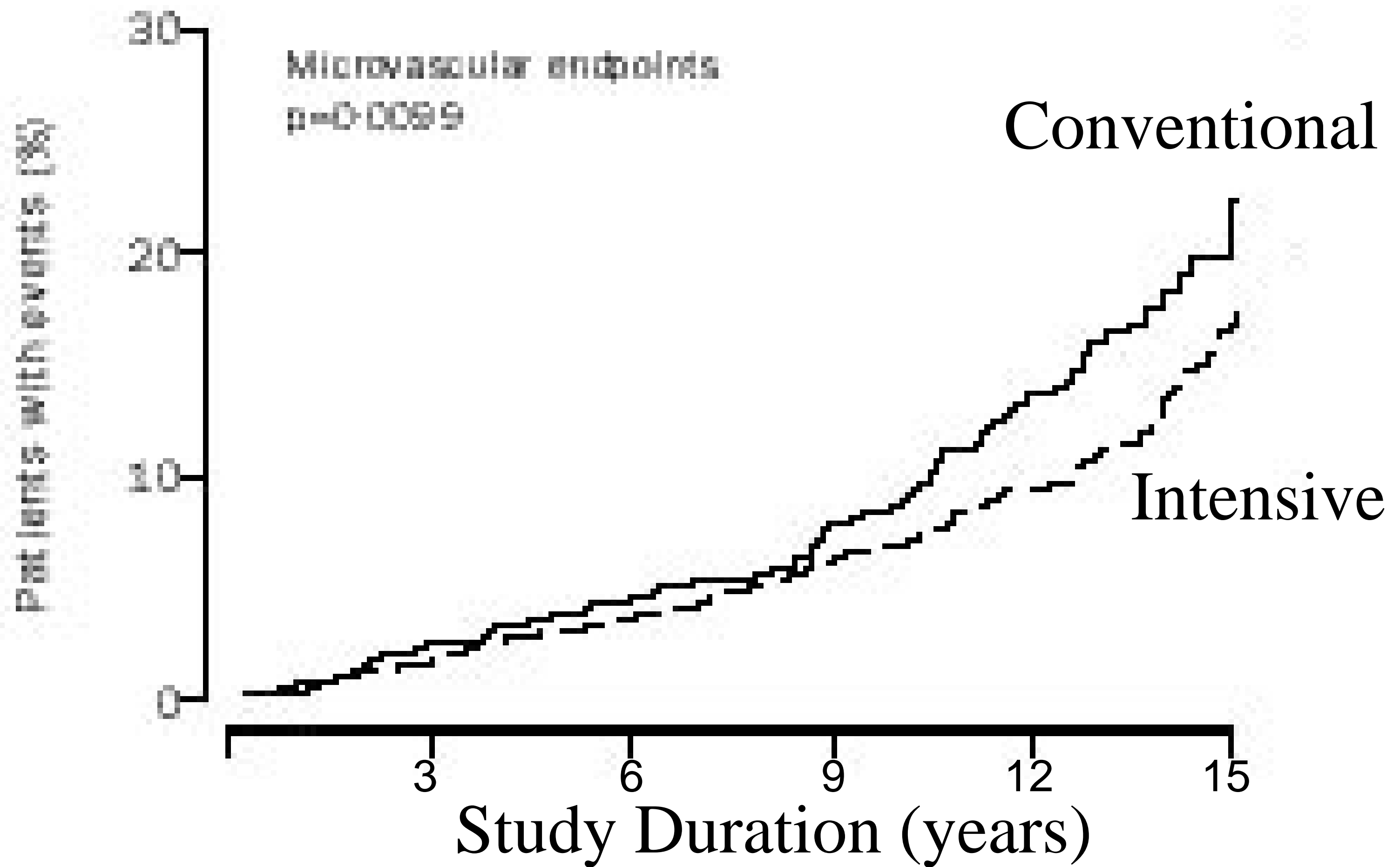
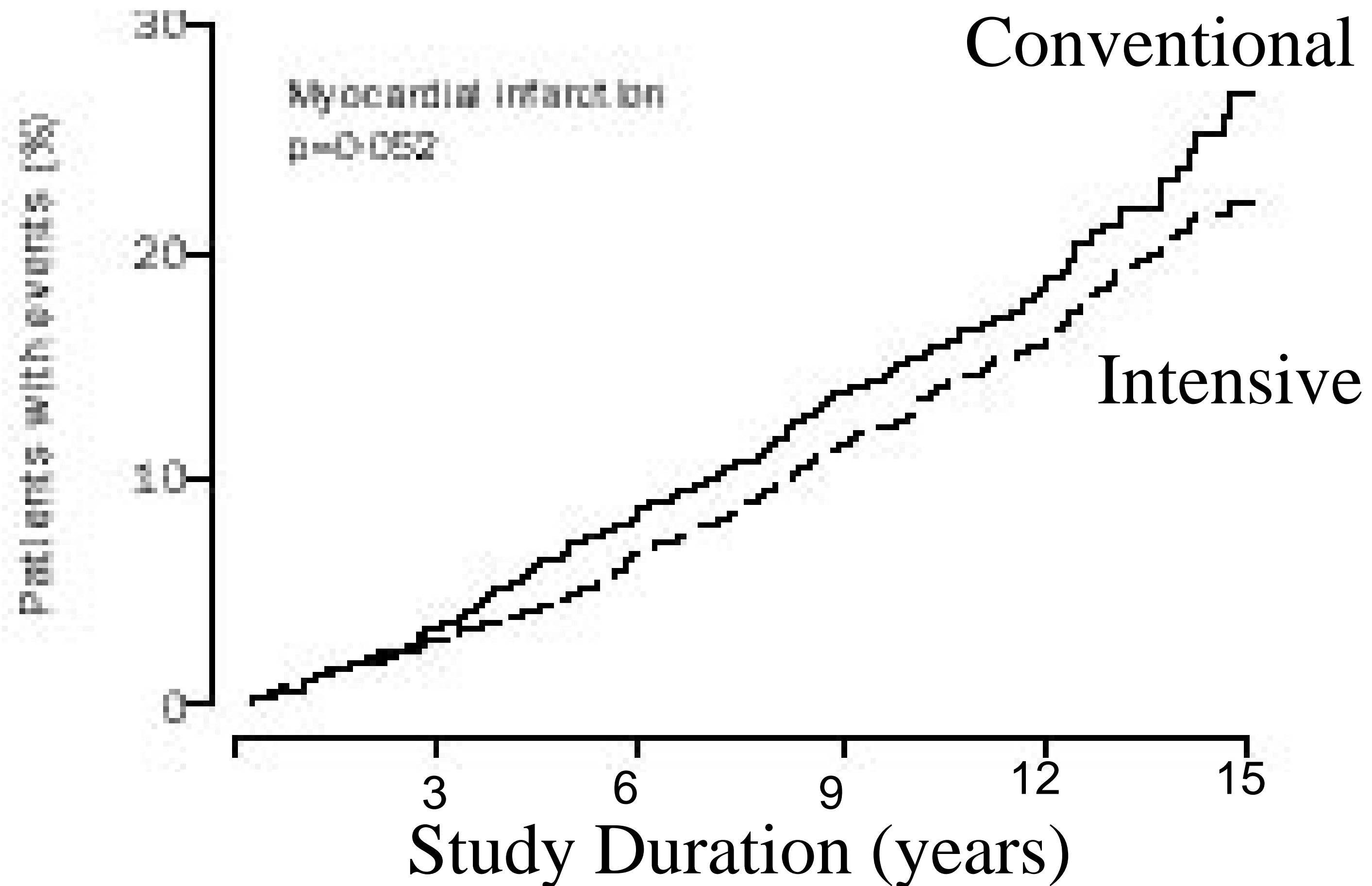
Glucose Control and Microvascular Risk UKPDS



Glucose Control and Myocardial Infarction



Improving Glucose Control and Vascular Risk - UKPDS

From diagnosis of diabetes, mean HbA_{1c} of 7.0 rather than 7.9 % over 10 years, using metformin / sulphonylurea / insulin, leads to:

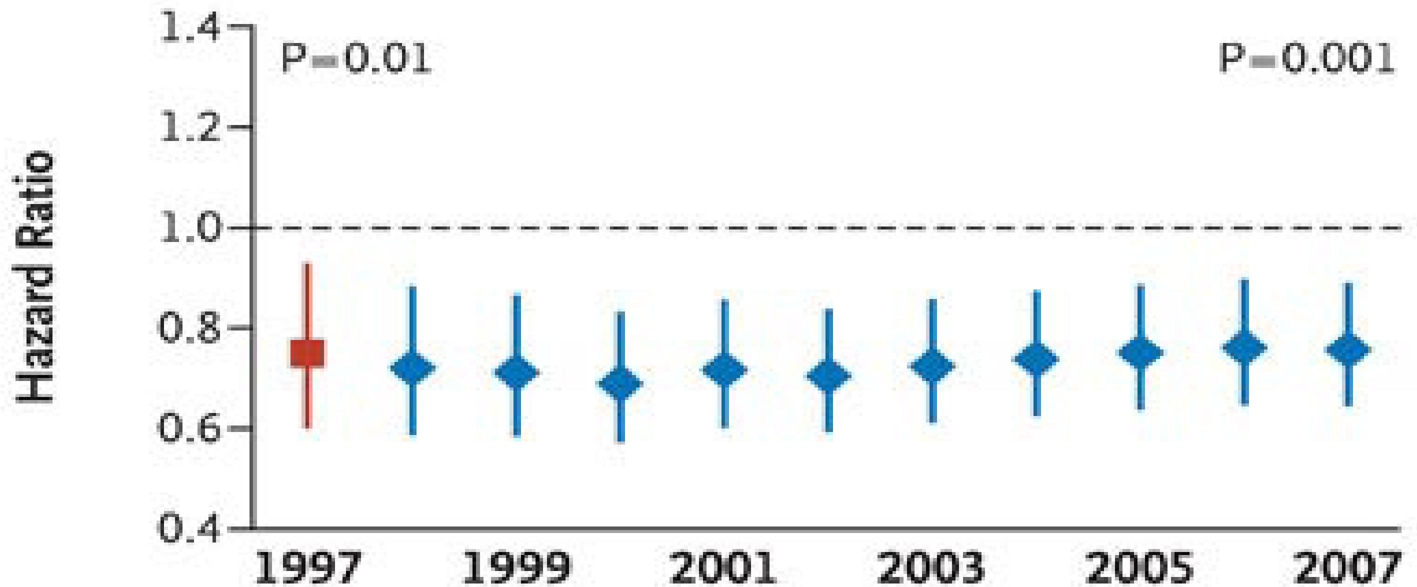
- Significant reduction in microvascular events
- No significant reduction in macrovascular events (except – obese people on metformin)
- More hypoglycaemia and more weight gain

Hence the general HbA_{1c} target of 7.0 %

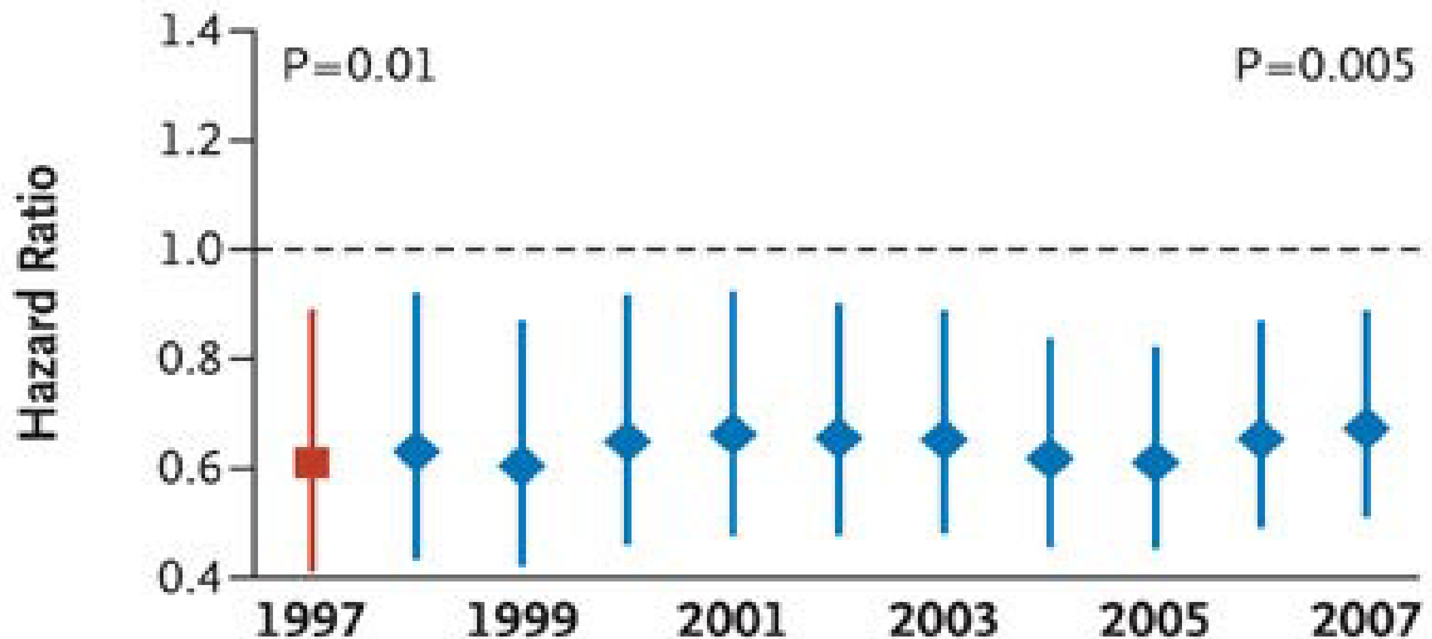
UKPDS Open Follow-Up

- Diabetes management in routine clinics, with usual clinical care
- HbA_{1c} in the previously intensive and conventional groups similar after first year
- HbA_{1c} ~8.0 %

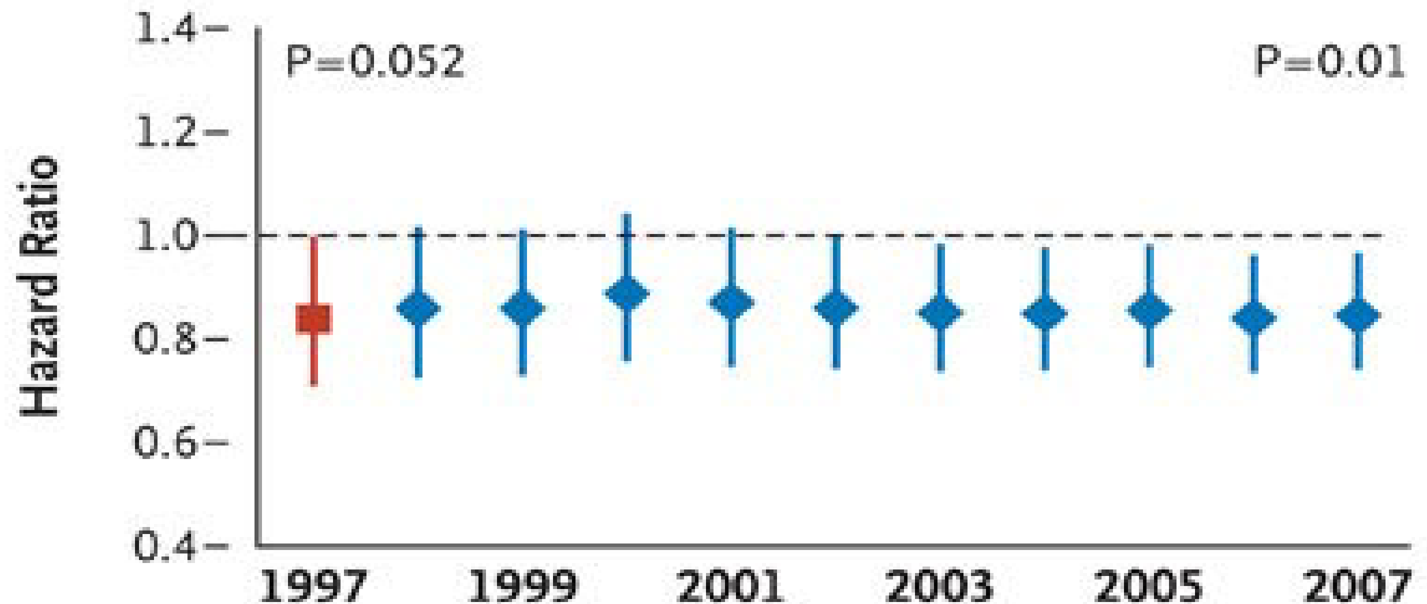
UKPDS Open Follow-Up
Microvascular Risk – SU / Insulin



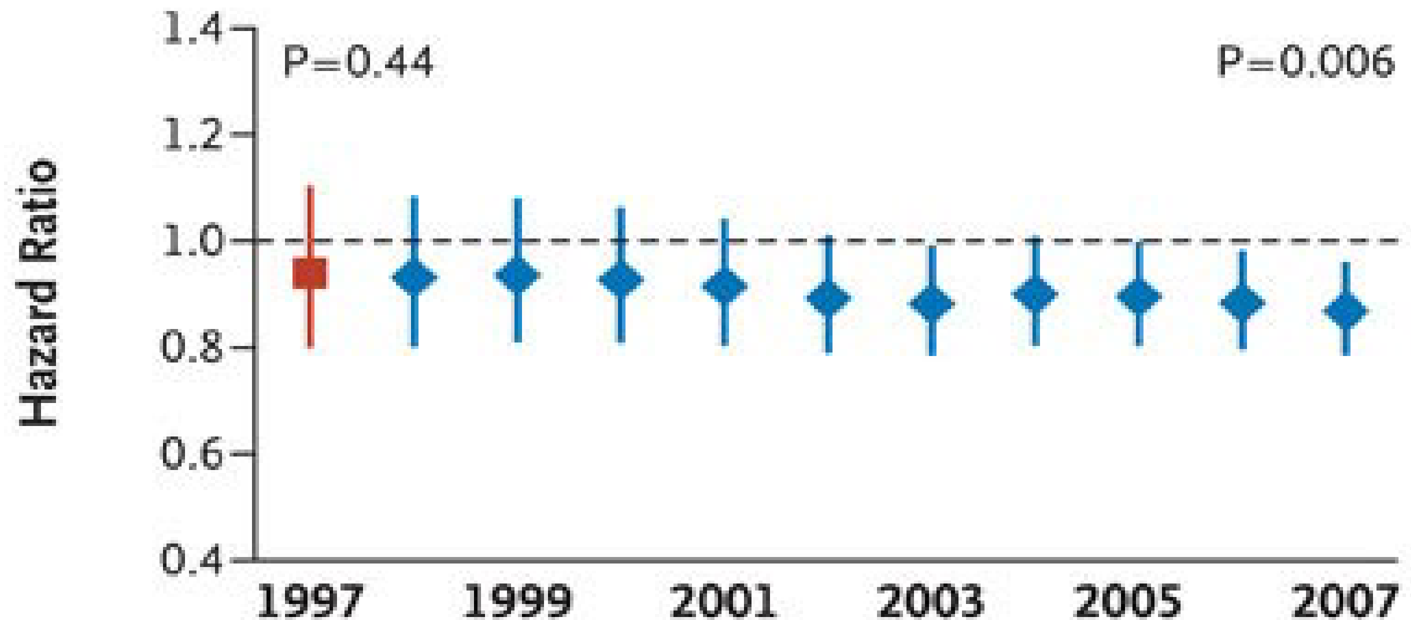
UKPDS Open Follow-Up
Metformin and Macrovascular Risk



UKPDS Follow-Up
SU/Insulin and Macrovascular Risk



UKPDS Follow-Up
SU/Insulin and All Cause Death



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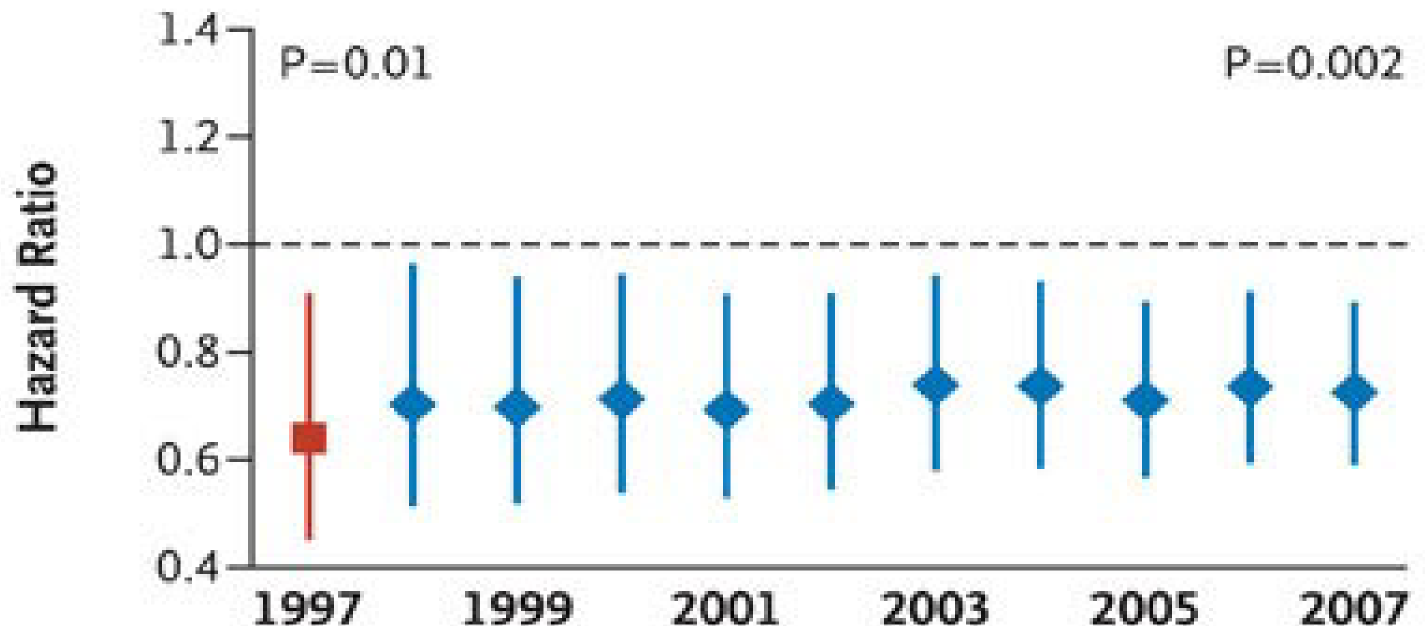

Long Term Glucose Control and Vascular Risk

- Sustained good glucose control (metformin / SU / insulin) over a very prolonged time reduces both micro- and macro-vascular risk
- "Metabolic memory" – prior period of tight control has prolonged benefits beyond the actual period of good control

  epigenetics?

- It is really hard to sustain HbA_{1c} of 7.0 % with increasing duration diabetes

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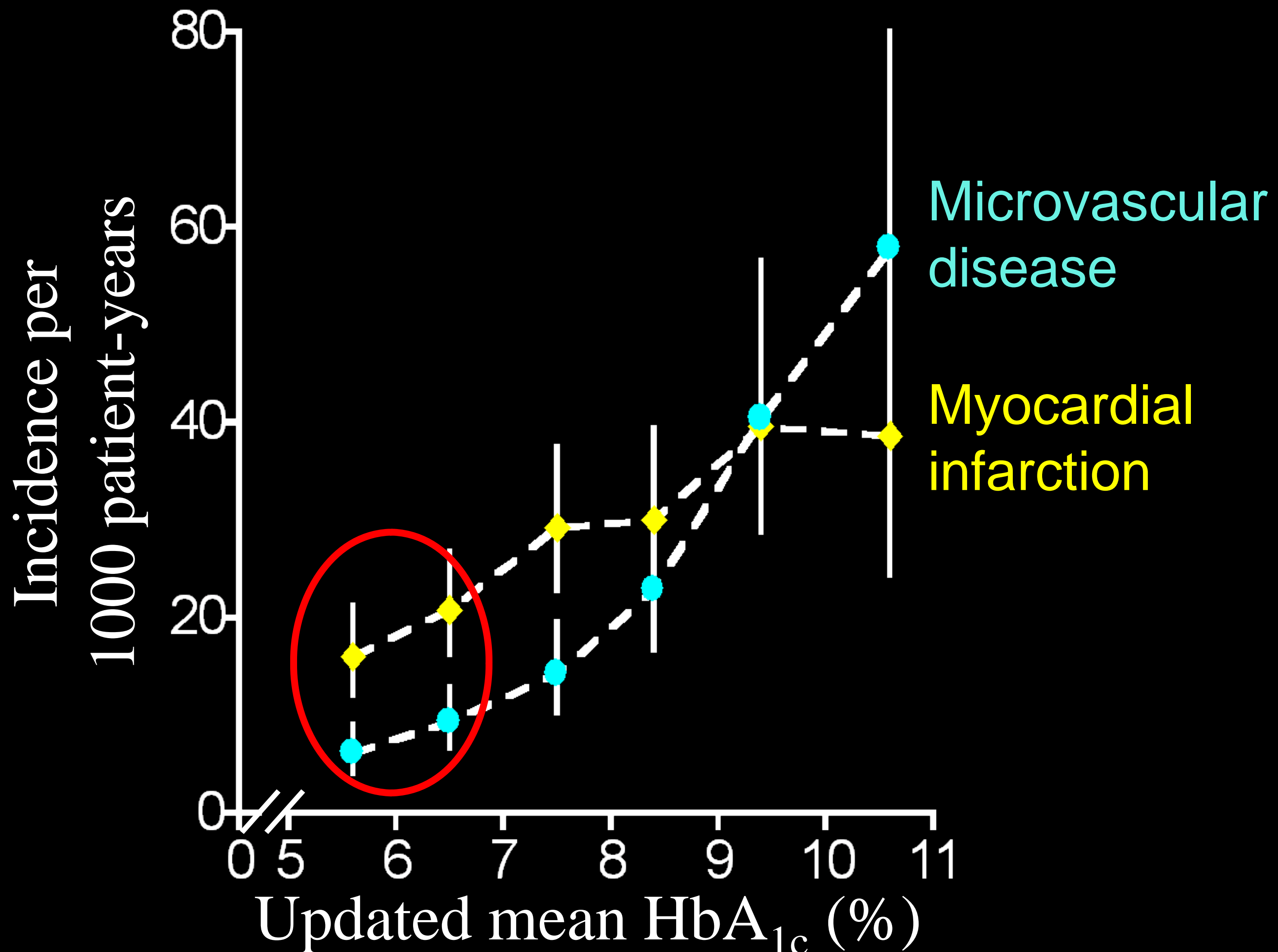
HbA$_{1c}$ and Vascular Risk



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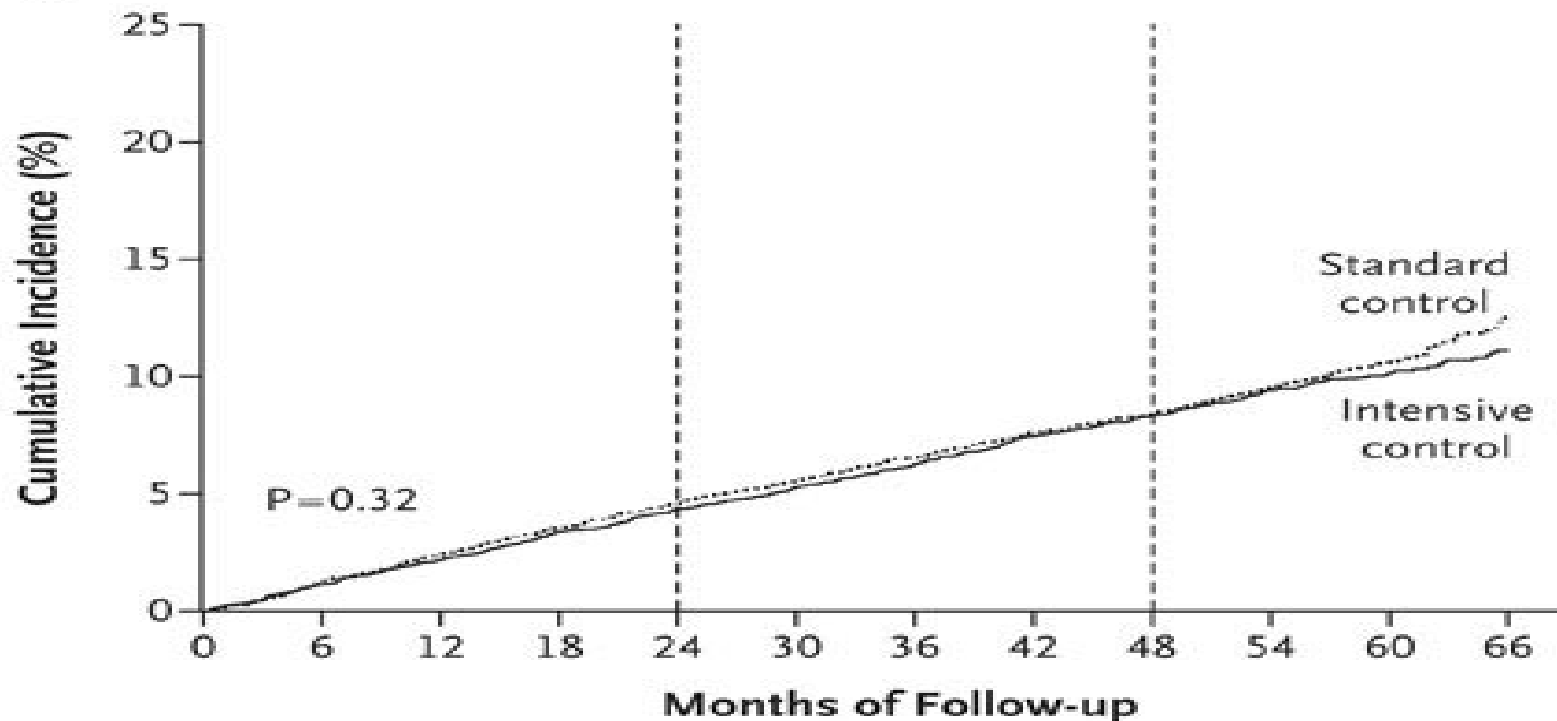
Glucose Control – Epidemiological Data

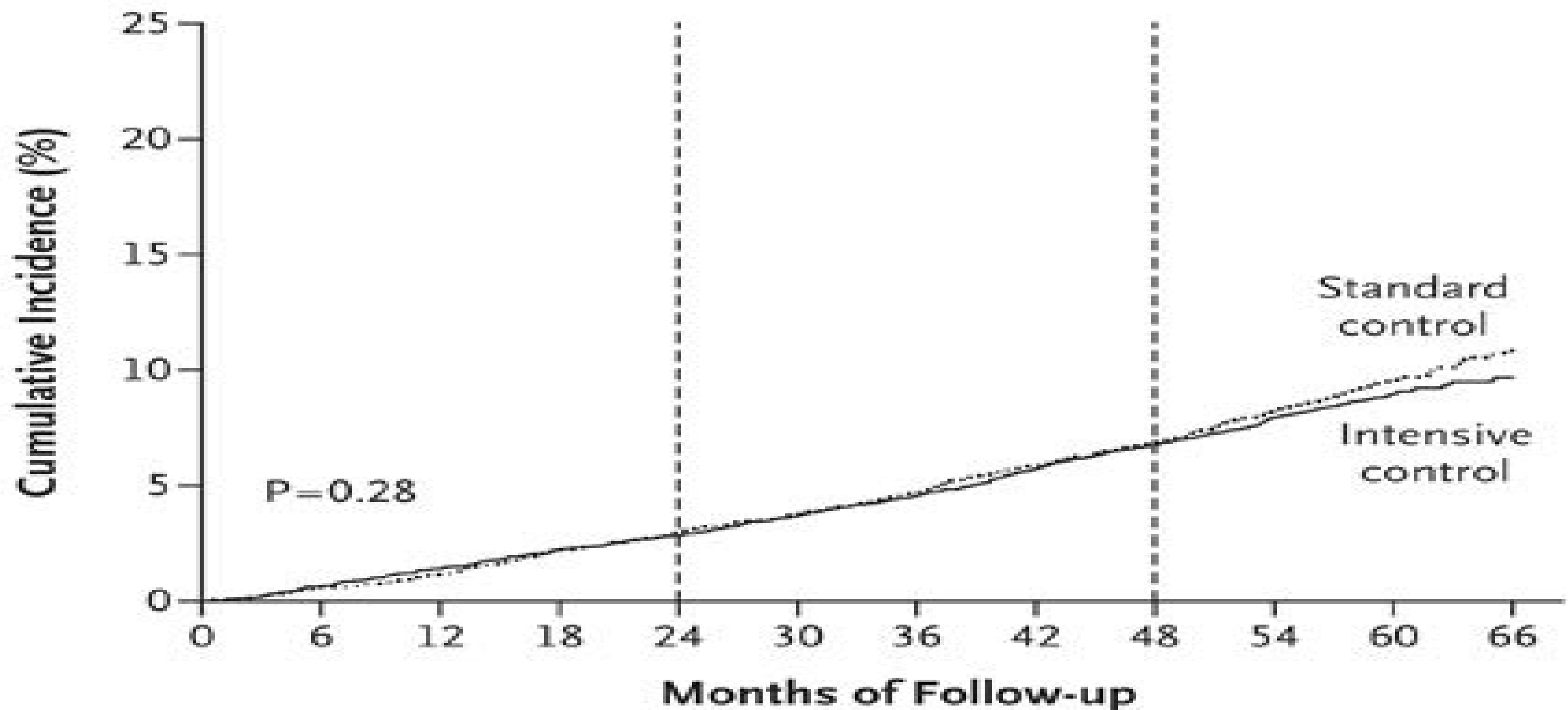
- The lower the HbA_{1c}, the lower the risk of micro- and macro-vascular events – even down into the “non-diabetic” range
- So would reducing HbA_{1c} <7.0 % give even better outcomes?
- Hence – ACCORD, VADT, ADVANCE:

  Does super-tight glucose control improve outcomes?

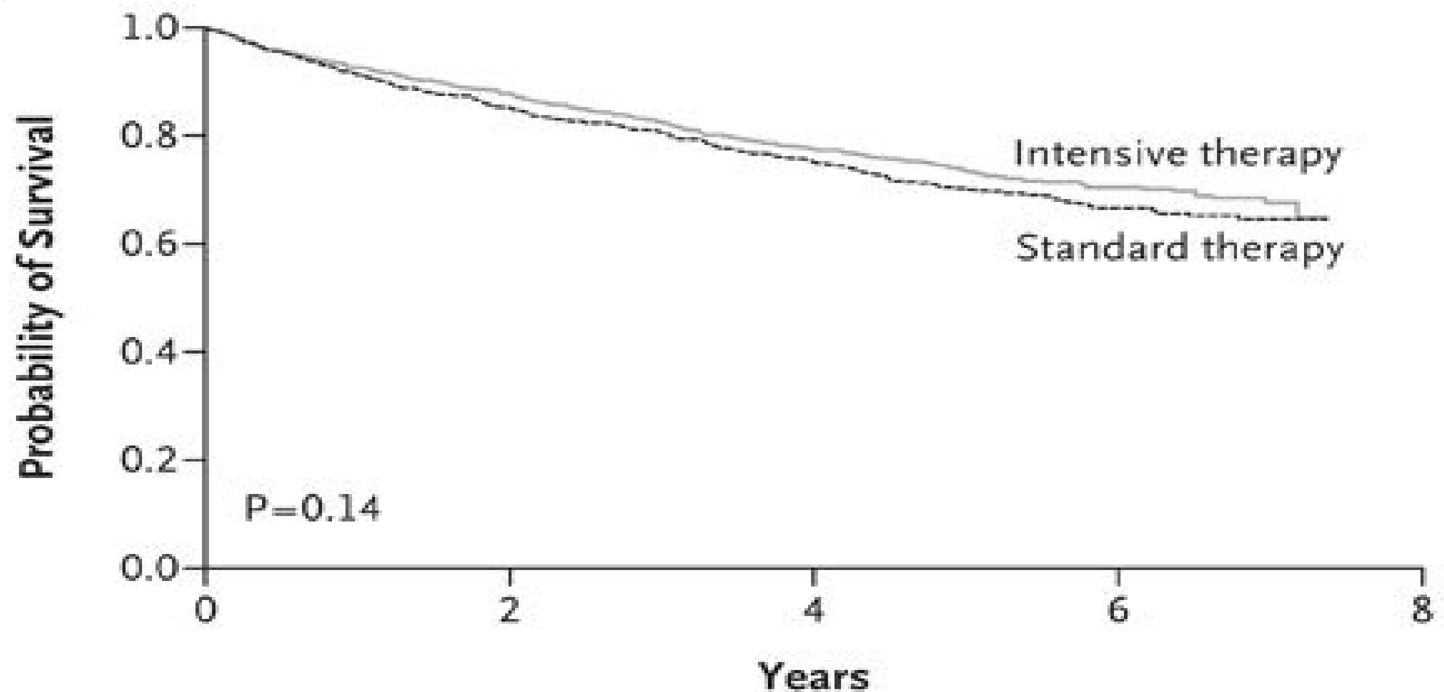
ADVANCE
Major Macrovascular Events



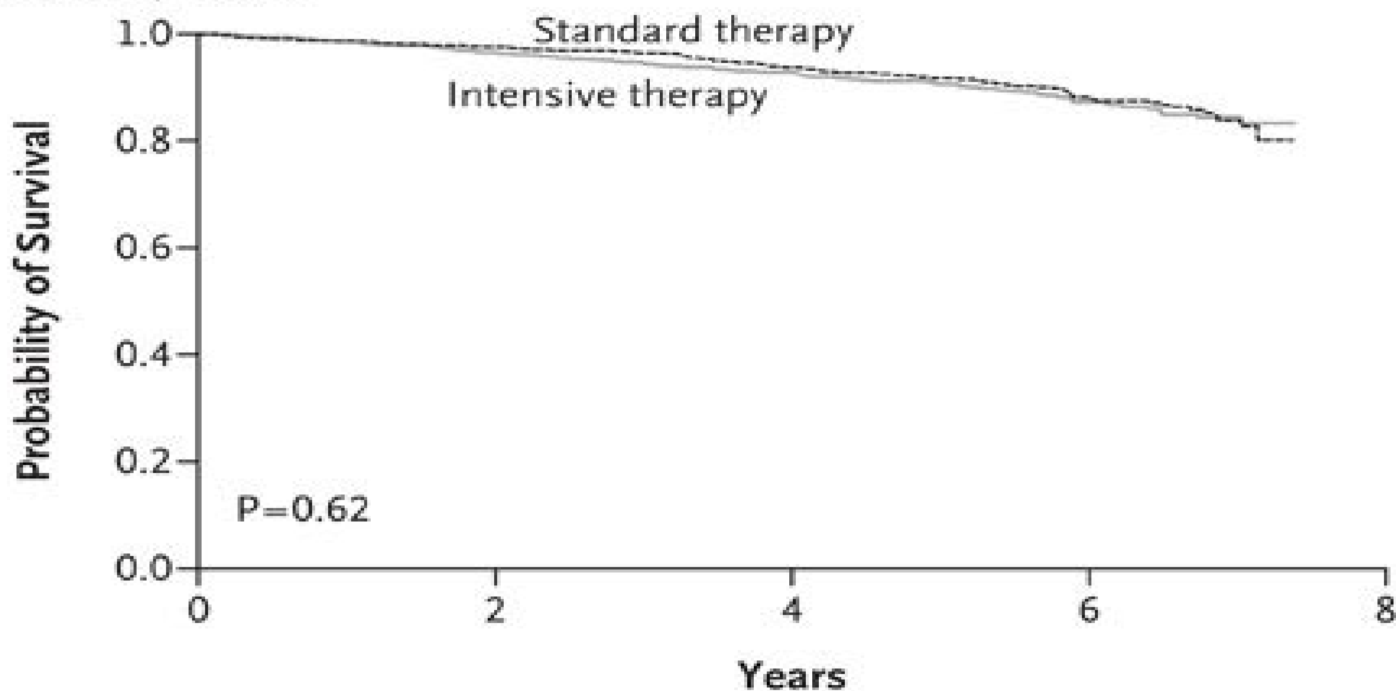
ADVANCE
All Cause Death



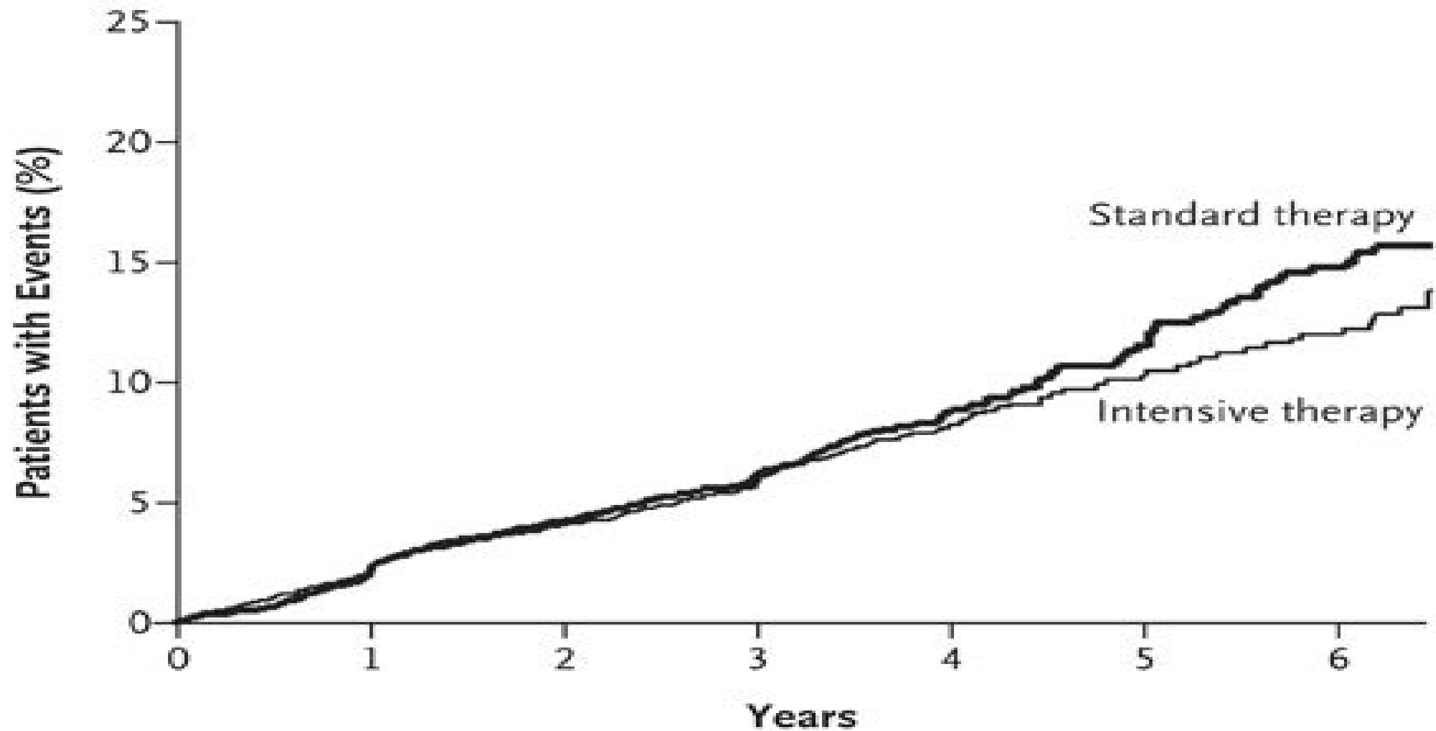
VADT
Major Macrovascular Events



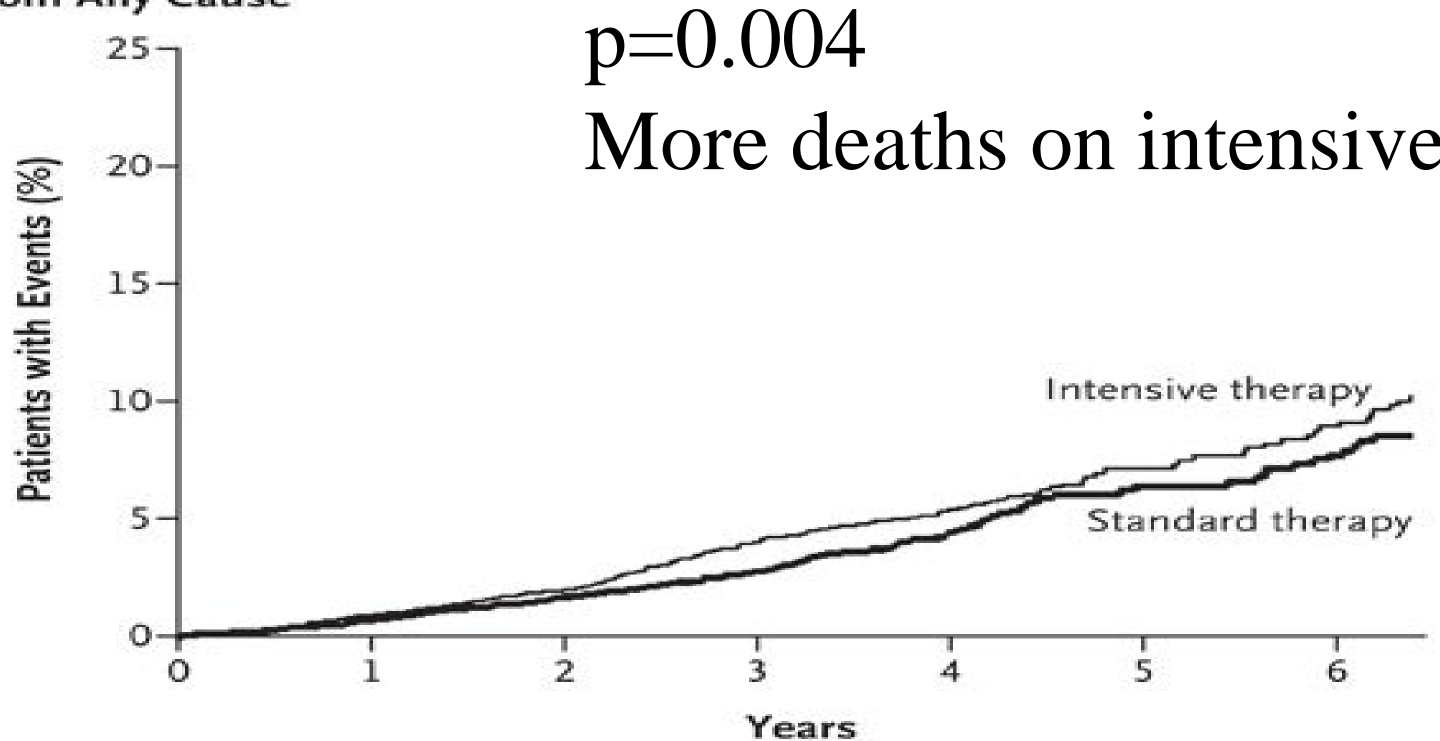
VADT
All Cause Deaths



ACCORD
Major Macrovascular Events



ACCORD
All Cause Deaths



"Super-Tight" Glucose Control

- Reduction in microvascular events
- No apparent benefit on macrovascular outcomes – events or deaths
- No apparent benefit on all-cause mortality/ suggestion of an increase

    hypoglycaemia *per se*? (severe – x2)

    hypoglycaemia as a marker of frailty?

    one / combination of agents used?

Why the discrepancy with UKPDS?

Participant Entry Characteristics

	UKPDS	ACCORD	ADVANCE	VADT
Age (y)	54	62	66	60.4
Duration (y)	0	10	8	11.5
CVD entry	?	35 %	32 %	40 %
Entry HbA_{1c} (%)	7.1 / 6.2	8.1	7.5	9.4
Achieved HbA_{1c} (%)	7.0	6.4	6.4	6.9
Agents used	M/SU/In	Any	Glic MR +	Any

Glucose Control and Vascular Risk

- Maintaining tight control (HbA_{1c} ~7.0 %) from diagnosis using metformin / SU / insulin reduces CVD risk over 15-20 years
- (Rapidly) improving glucose control in people with duration diabetes >10 years and with/at very high risk of CVD has no CVD benefit (but reduces microvascular risk)
- Achieving HbA_{1c} <7.0 % may be harmful

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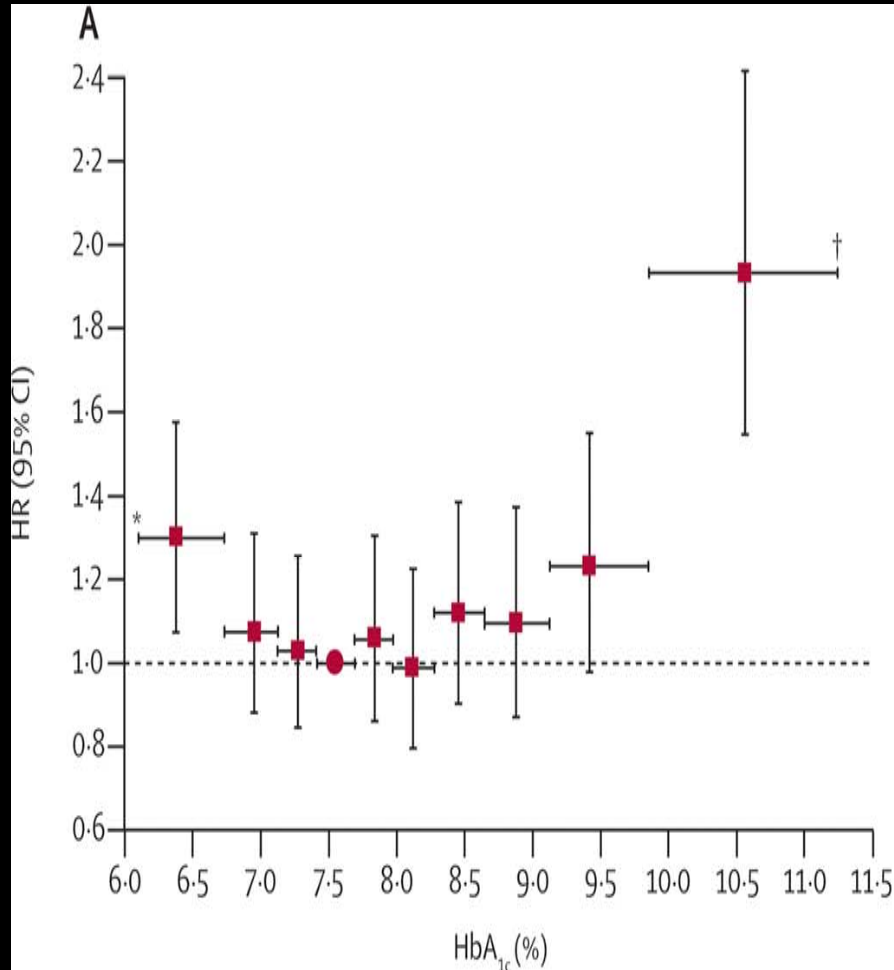
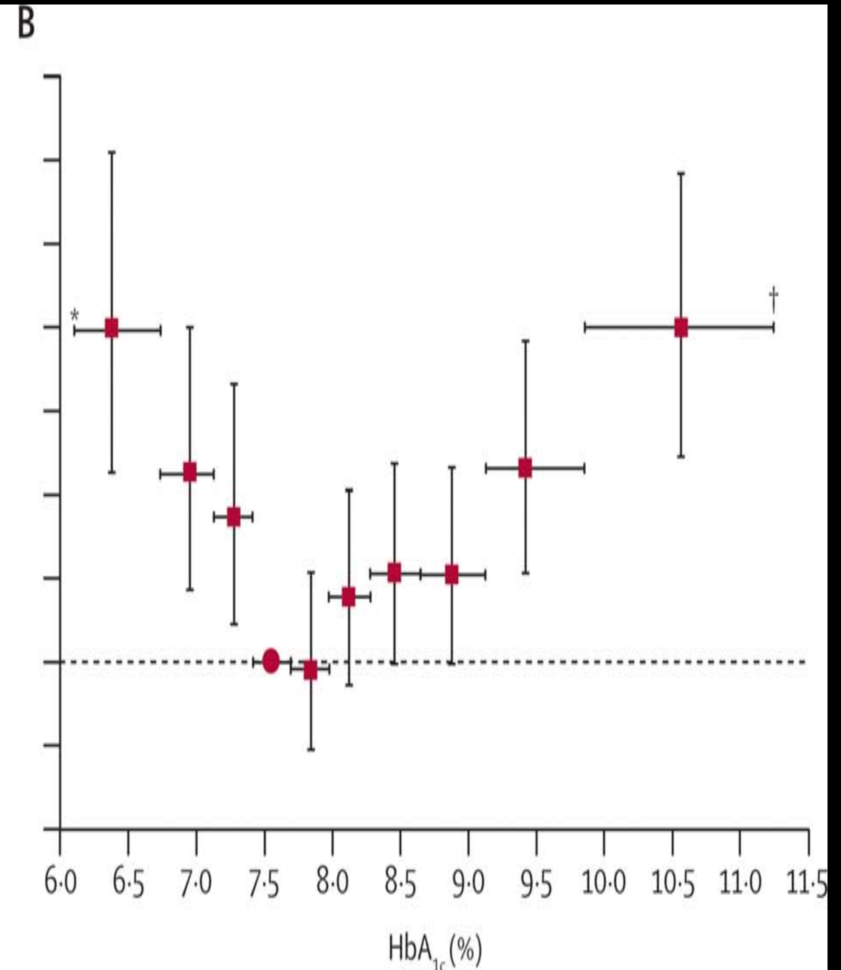
GP Research Data Base
All Cause Mortality and HbA_{1c}



Metformin+SU



Insulin Based

Participant Characteristics

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Duration (y)	0	10	8	11.5
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Newer Agents

- Thiazolidenediones (pioglitazone)
- Incretins

    GLP-1 analogues (exenatide, liraglutide)

    DPPV inhibitors (sitagliptin, saxagliptin)

- SGLT2 inhibitors – block reabsorption of glucose by renal tubules

    glycosuria, lower blood glucose, weight loss

    urinary infection +++

    ~500 ml volume deplete

Newer Agents – Risk / Benefits

- Added benefit of no hypoglycaemia, unless used with SU / insulin
- Added benefit of weight loss (GLP1 analogues)
- Known side effects

  fractures, oedema with pioglitazone

  nausea, (pancreatitis?) with GLP1
- Long-term side effects - ????

Newer Agents – Risk / Benefits

- Reduce HbA_{1c} by ~1.0 % (Pio, GLP1 analogues) or ~0.6 % (DPPV inhibitors)
- No evidence of macrovascular harm or benefit specifically associated with newer agents in ADOPT, ACCORD, VADT (but low power)
- Assumption of proportional reduction in microvascular risk
- CVD risk?

Newer Agents – Should We Use?

- When hypoglycaemia problematic (occupation, ???very frail)
- Really won’t have insulin
- When weight problematic?

- Do we really know when / how to use them?

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Exenatide

Mr P	Mr R
Duration 8 years	Duration 10 years
HbA_{1c} 8.6 % on max met/SU	HbA_{1c} 8.3 % on max met/SU
BMI 36.4 kg/m^2	BMI 35.9 kg/m^2
Commenced exenatide	Commenced exenatide

On Exenatide

Mr P		Mr R	
Weight	HbA_{1c}	Weight	HbA_{1c}
114.6	8.6 (SU halved)	119.0	8.3 (SU halved)
110.2	7.8	118.3	9.8 (SU max)
107.1	7.0 (SU stopped)	119.3	9.0
102.8	6.5	117.9	8.9
98	6.2	120.0	9.3

Why the different response?

Using The Newer Agents

- Type 2 diabetes is NOT one disease
- One size does not fit all
- Need to be able to choose the best management for individual person – currently difficult clinically

- Three - six month trial of new agent, then:
  - Review HbA_{1c}, weight and side effects
  - Stop / continue as indicated

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Marshall's Game Plan for Type 2 Diabetes Diagnosed Today

- Concentrate efforts in new diagnoses
- Diagnose early (UKPDS – HbA_{1c} <7.0%)
- Hit hard for first 10 years – HbA_{1c} <7.0 % (UKPDS – benefits seem to outweigh risks)
- Escalate therapy as soon as HbA_{1c} >7.0 %
- Usually, lifestyle then metformin, then add SU, then insulin

  (UKPDS – micro- and macrovascular benefit; known good long-term safety record; cheap)

Marshall's Game Plan for Type 2 Diabetes Diagnosed Today

After 10 years or earlier if severe CVD/frail:

- Less tight control – HbA_{1c} 7.0 – 8.0 % (ACCORD / ADVANCE / VADT / Epidemiology: Microvascular risk still quite low; no evidence of CVD benefit/possibly increased mortality at lower level)
- The benefits of the first 10 years of really tight control will persist for the second 10 years (UKPDS follow-up; metabolic memory)

Marshall's Game Plan for Established Longer Duration Type 2 Diabetes

Have we missed the boat?

- Be wary of reducing HbA_{1c} too quickly / below 7.5 %
- Be wary of hypoglycaemia – SUs, insulin
- Weigh up the risk / benefit ratio very carefully, especially for newer agents
- Much more individualisation

target HbA_{1c} drugs used

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It’s Not All About Glucose!

Lipids

No smoking

Blood pressure

Weight

Glucose

Better to have some improvement in all risk factors than big improvement in only one!