# ABCD Debate:

## Surrogate markers are of no use in evaluating treatment in diabetes

**Against the motion**

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# Surrogate marker

## Definition

1. An objective measure (laboratory measurement or physical sign) used as a *substitute* for a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives
2. Changes induced by a therapy on the surrogate marker are expected to reflect changes in the clinically meaningful endpoint



Temple RJ. In Nimmor, Tucker, eds. 1995

# Prentice criteria

1. Surrogate correlates with the true clinical outcome **--usually easy to prove**
2. Fully captures the net effect of treatment on the clinical outcome **--difficult to prove, rarely achieved**

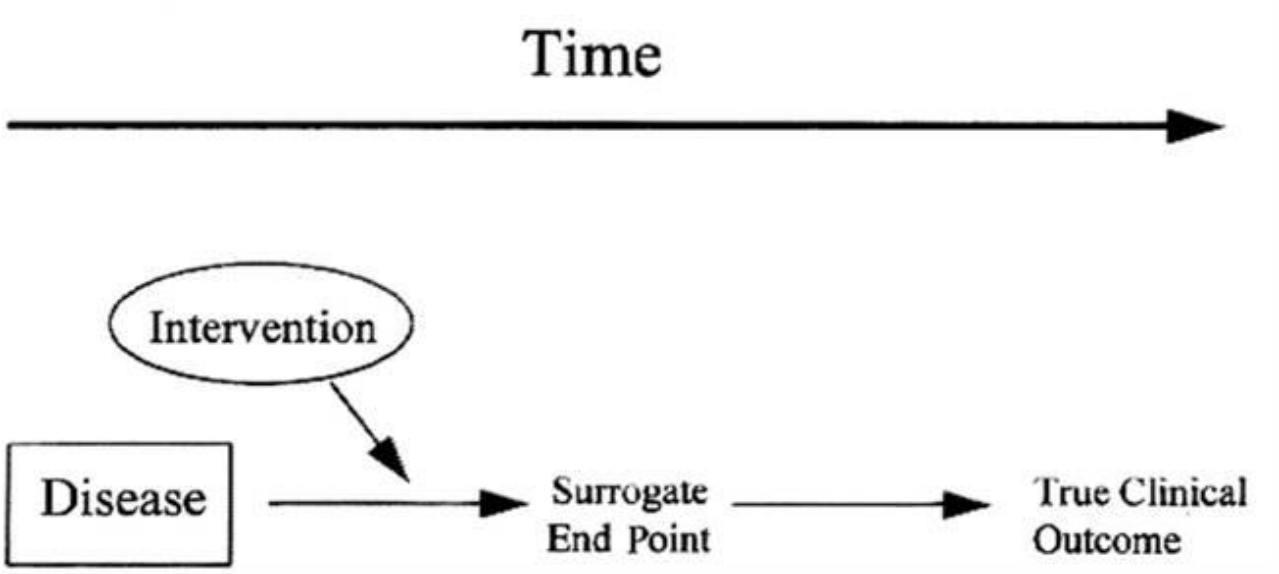


Prentice RL. Stat Med (1989). 8: 431-25

# Why use surrogate endpoints?

- Measuring the true clinical outcome is not feasible or practical
  - Time
  - Requires an invasive and/or dangerous procedure
  - Desire to intervene before an irreversible outcome
- Performing a clinical trial using the true outcome is not feasible or practical
  - Long duration of follow-up
  - Cost

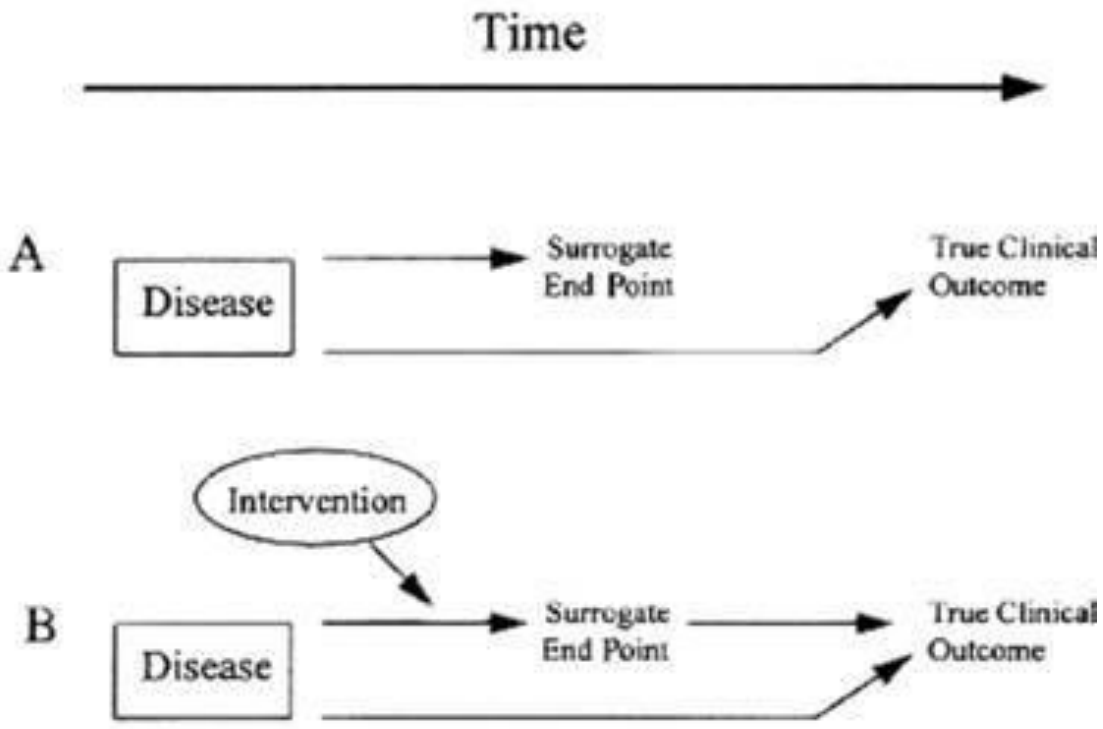
# The ideal surrogate endpoint






Fleming & DeMets. Ann Int Med (1996). 125:605-13

# Why surrogate endpoints fail



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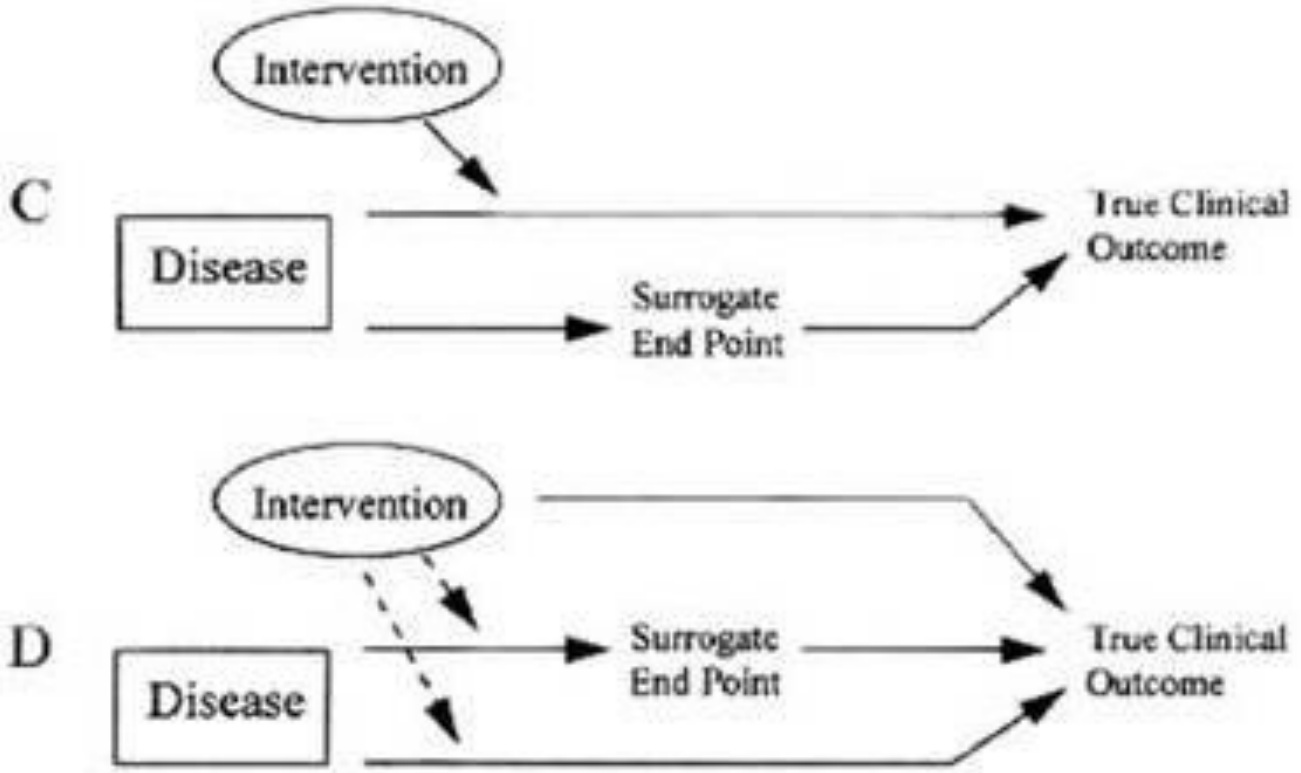
# Why surrogate endpoints fail






Fleming & DeMets. Ann Int Med (1996). 125:605-13

# Common surrogate endpoints in diabetes research

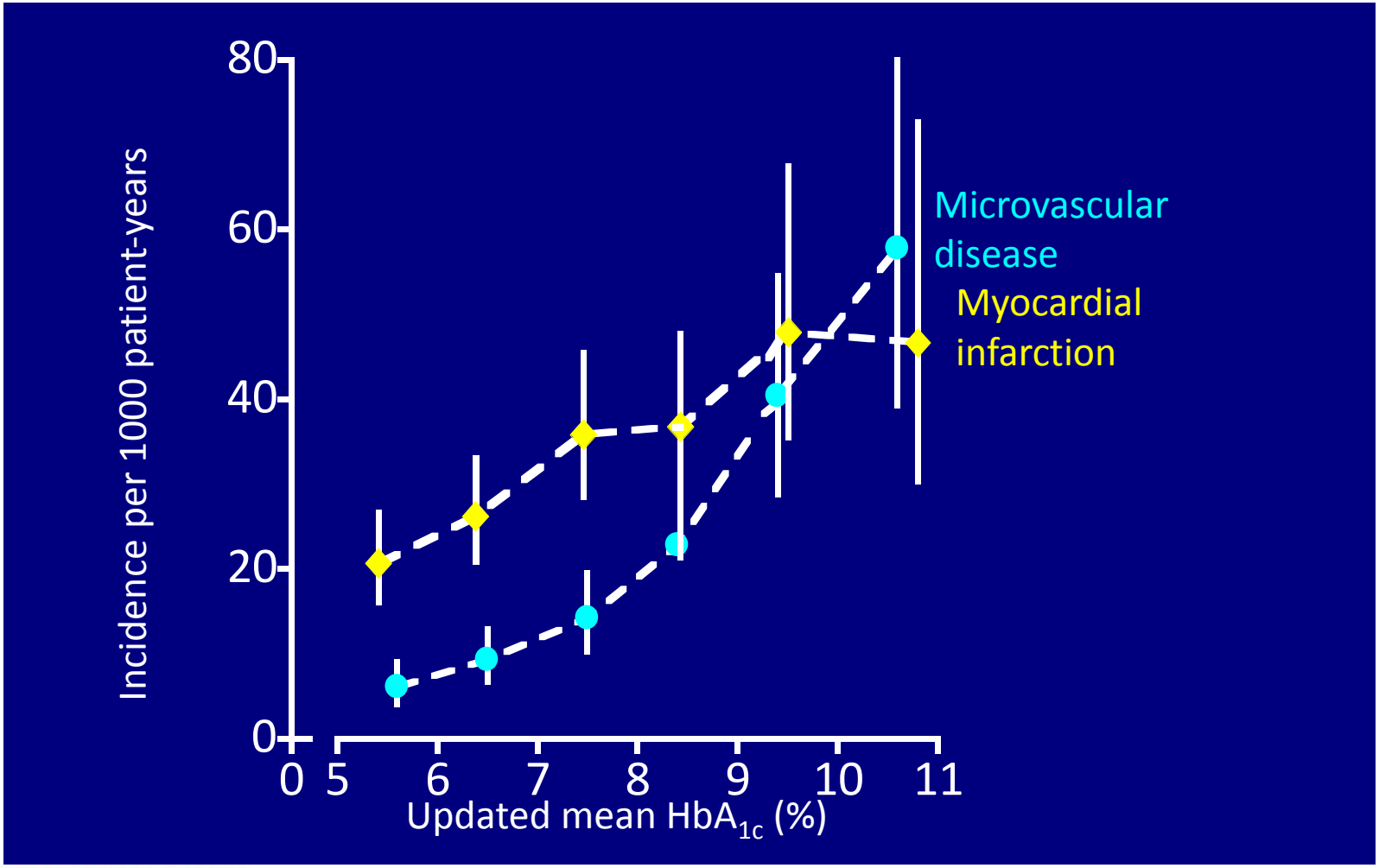
- Fasting, 2 hour post-challenge glucose values, 7-point continuous glucose monitoring
- Area under the curve (AUC) for glucose/insulin
- HOMA-S, HOMA-IR
- **HbA1c**

# HbA1c as a surrogate endpoint…for what?

- Microvascular complications
  - Decrease in vision, blindness
  - Ulcers, amputations
  - End stage renal disease
- Macrovascular complications
  - Myocardial infarction
  - Stroke
  - Unstable angina
- Death

# HbA1c and microvascular outcomes

# UKPDS:
# HbA1c and risk for complications




DIABETES TRIALS UNIT
The Oxford Centre for Diabetes, Endocrinology and Metabolism

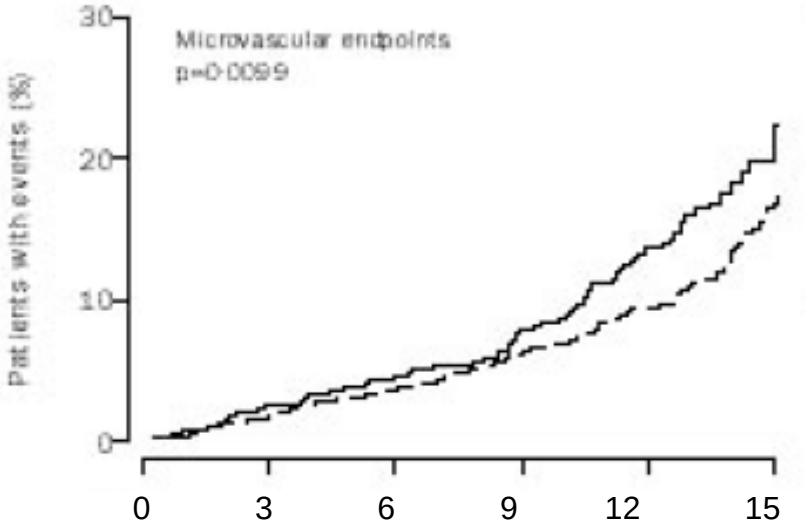
*UKPDS 35. BMJ 2000;321:405-12*

# Intensive glucose control decreases microvascular complications

## UKPDS

**Microvascular endpoints**

HR 0.75 (0.60, 0.93)
p=0.0099

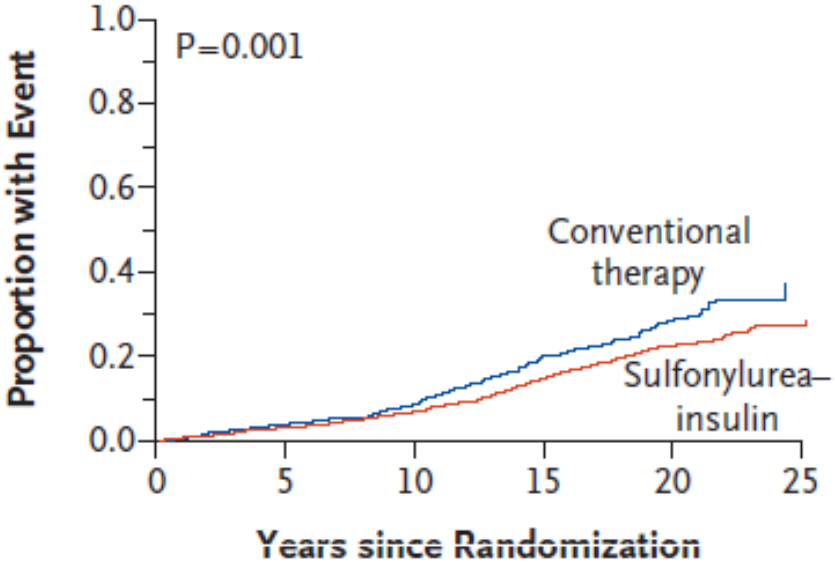



*UKPDS 33. Lancet (1998); 352:854-865*

## UKPDS-PTM

**Microvascular benefit persists**

HR 0.76 (0.64, 0.89)
p=0.001




*UKPDS 80. NEJM (2008); 359:1577-1589*

# Meta-analysis: renal outcomes after intensive glucose control

- 7 RCTs of intensive vs. conventional glucose control (Kumamoto, UKPDS, VADT, ACCORD, ADVANCE, VADT)
- Outcomes
  - Surrogate outcomes: Micro-, macroalbuminuria
  - Clinical outcomes: Cr doubling, ESRD, renal death



*Coca et al. Arch Intern Med (2012); 172: 761-769*

# Pooled risk ratios for renal endpoints

| Event | Risk Ratio (95% CI) |
|---|---|
| Microalbuminuria | **0.86 (0.76 – 0.96)** |
| Macroalbuminuria | **0.74 (0.65 – 0.85)** |
| Cr doubling | 1.06 (0.92 – 1.22) |
| ESRD | 0.69 (0.46 – 1.05) |
| Renal death | 0.99 (0.55 – 1.79) |

*BUT…interpret with caution*

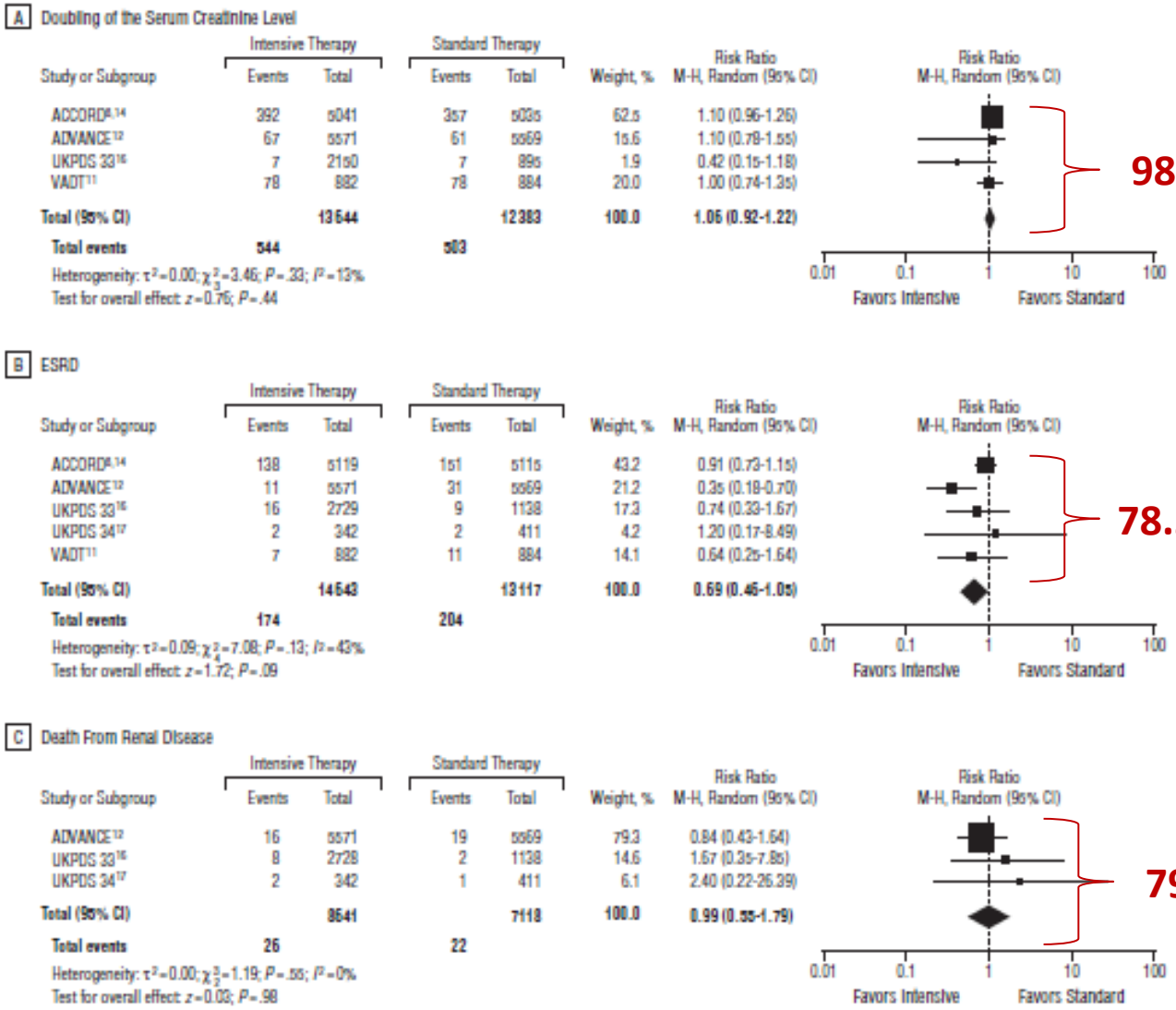


*Coca et al. Arch Intern Med (2012); 172: 761-769*

# Characteristics of included trials

| | n | Duration DM (yrs) | Duration f/u (yrs) |
|---|---|---|---|
| Kumamoto | 110 | 6.5 | 8 |
| UKPDS 33 | 3867 | 0 | 11.1 |
| UKPDS 34 | 753 | 0 | 10.7 |
| VADT Feasibility | 153 | 8 | 2 |
| ACCORD | 10251 | 10 | 5 |
| ADVANCE | 11140 | 8 | 5 |
| VADT | 1791 | 12 | 5.6 |

# Key clinical outcomes primarily influenced by shortest trials




Weight contributed by ACCORD, ADVANCE, VADT with ~5 yrs follow-up

# HbA1c and macrovascular outcomes

# Modifiable CHD Risk Factors

*Stepwise selection of major risk factors for 280 coronary artery disease events in 2,693 UKPDS patients @ 10 years*

| | | p |
|---|---|---|
| ↑ | LDL cholesterol | 0.000014 |
| ↓ | HDL cholesterol | 0.00014 |
| ↑ | Haemoglobin $A_{1c}$ | 0.0022 |
| ↑ | Systolic blood pressure | 0.0065 |
| + | Smoking | (0.056) |

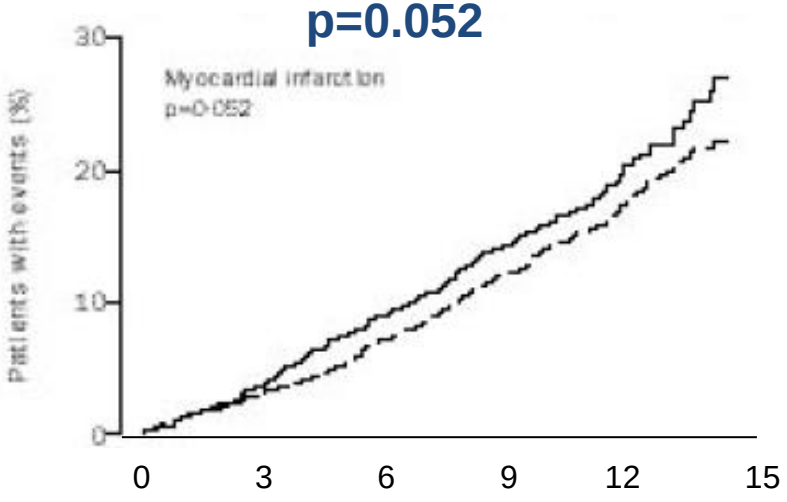
*Age and gender also major risk factors but HDL displaced triglyceride as a significant risk factor*



*UKPDS 23. BMJ 1998;316:823-8*

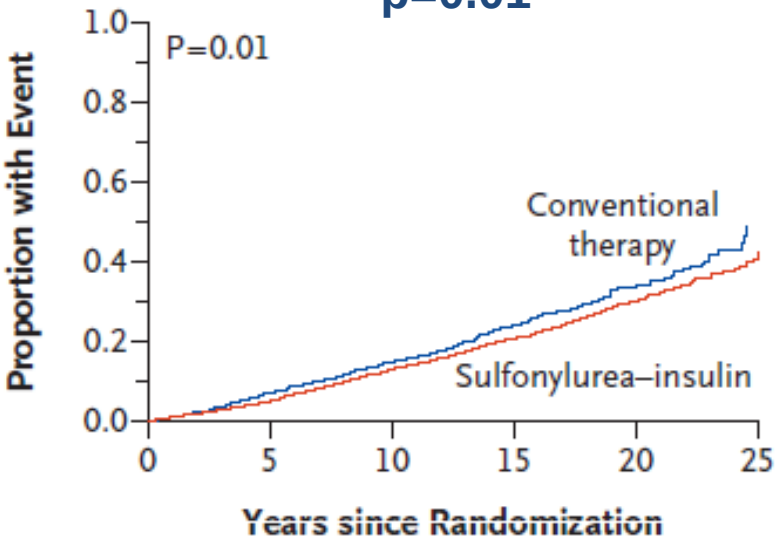
# Intensive control *may* decrease macrovascular complications

**HR 0.84 (0.71, 1.00)**
**p=0.052**



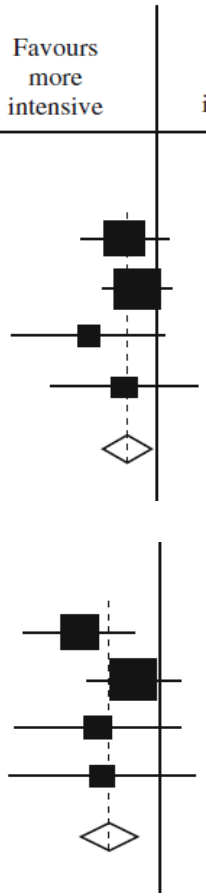

Time since Randomization (yrs)

**HR 0.85 (0.74, 0.97)**
**p=0.01**



# Meta-analysis: glucose control and macrovascular disease

| Trials | Number of events (annual event rate, %) More intensive | Number of events (annual event rate, %) Less intensive | $\Delta HbA_{1c}$ (%) | Hazard ratio (95% CI) |
|---|---|---|---|---|
| **Major cardiovascular events** | | | | |
| ACCORD | 352 (2.11) | 371 (2.29) | −1.01 | 0.90 (0.78–1.04) |
| ADVANCE | 557 (2.15) | 590 (2.28) | −0.72 | 0.94 (0.84–1.06) |
| UKPDS | 169 (1.30) | 87 (1.60) | −0.66 | 0.80 (0.62–1.04) |
| VADT | 116 (2.68) | 128 (2.98) | −1.16 | 0.90 (0.70–1.16) |
| Overall | 1,194 | 1,176 | −0.88 | 0.91 (0.84–0.99) ($Q$=1.32, $p$=0.72, $I^2$=0.0%) |
| **Myocardial infarction** | | | | |
| ACCORD | 198 (1.18) | 245 (1.51) | −1.01 | 0.77 (0.64–0.93) |
| ADVANCE | 310 (1.18) | 337 (1.28) | −0.72 | 0.92 (0.79–1.07) |
| UKPDS | 150 (1.20) | 76 (1.40) | −0.66 | 0.81 (0.62–1.07) |
| VADT | 72 (1.65) | 87 (1.99) | −1.16 | 0.83 (0.61–1.13) |
| Overall | 730 | 745 | −0.88 | 0.85 (0.76–0.94) ($Q$=2.25, $p$=0.52, $I^2$=0.0%) |

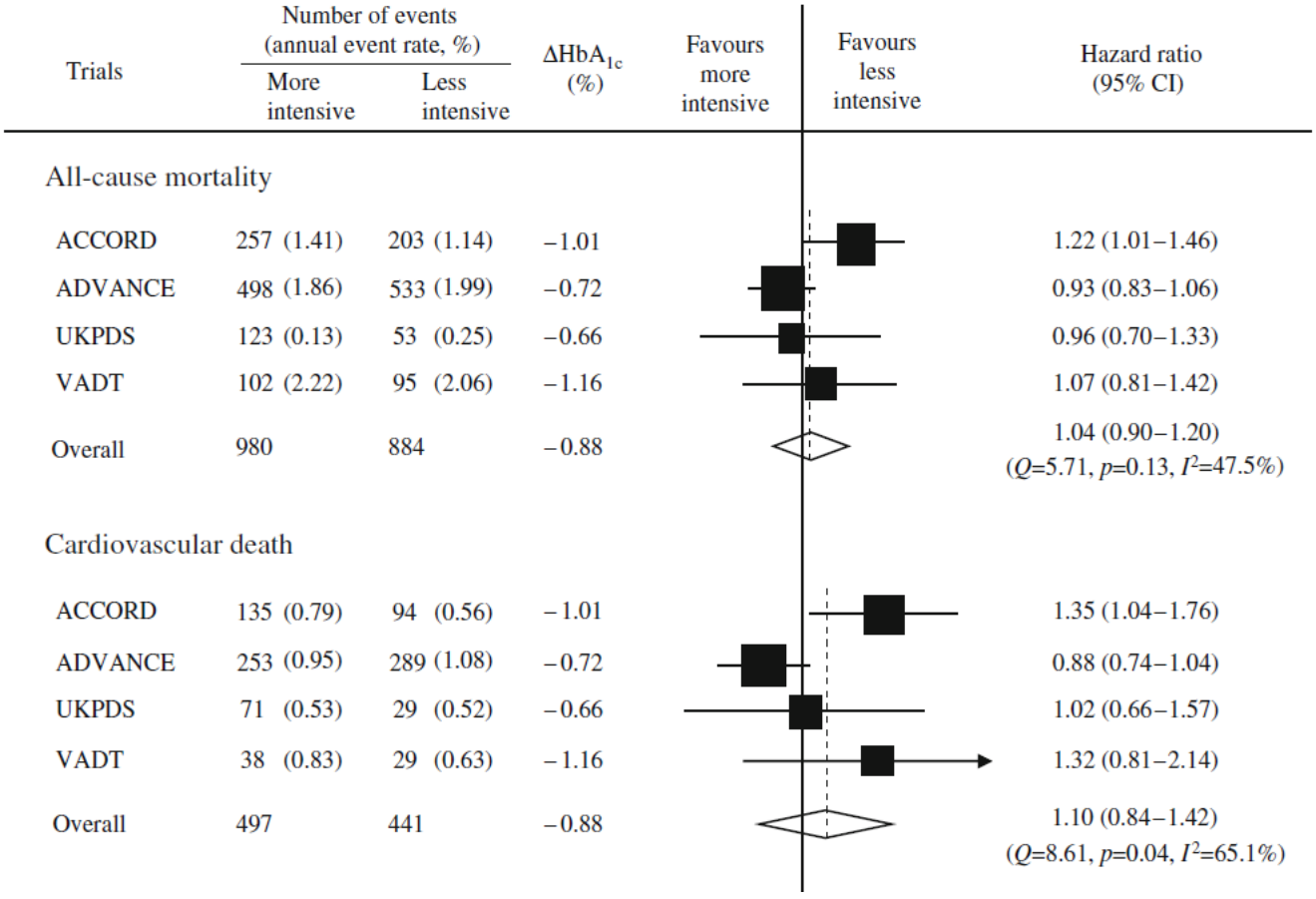



**Major CV events ↓9%**

**MI ↓15%**

*Diabetologia (2009); 52:2288-2298*

# Meta-analysis: Intensive glucose control & mortality



| Trials | Number of events (annual event rate, %) More intensive | Less intensive | $\Delta HbA_{1c}$ (%) | Favours more intensive | Favours less intensive | 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%) |

*Diabetologia* (2009); 52:2288-98

# HbA1c as a surrogate marker?

## Definition of a surrogate marker

1. An objective measure (laboratory measurement or physical sign) used as a substitute for a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives
2. Changes induced by a therapy on the surrogate marker are expected to reflect changes in the clinically meaningful endpoint

## Prentice Criteria

1. Surrogate correlates with the true clinical outcome
2. Fully captures the net effect of treatment on the clinical outcome



Temple RJ. In Nimmor, Tucker, eds. 1995

# Performance of HbA1c as a surrogate endpoint

**Important clinical outcomes**

- Microvascular complications
  - Decrease in vision, blindness
  - Ulcers, amputations
  - End stage renal disease
- Macrovascular complications
  - Myocardial infarction
  - Stroke
  - Unstable angina
- Death

- **Highly associated**
- **Therapy changes marker & outcome (causal)**
- **Prentice criteria—does not fully capture effect**

- **Weaker association**
- **Weaker impact of therapy**
- **Prentice criteria—not met**

- **Weak association**
- **No effect of therapy**
- **Prentice criteria—not met**

# Advocating rational use of HbA1c as a surrogate endpoint

- There is a role for the informed use of HbA1c for *microvascular disease*, although it does not capture the totality of risk due to multifactorial etiology
- Alone, HbA1c is not an appropriate surrogate for *macrovascular disease*—conventional risk factors are a better choice. However, HbA1c measures a small, but statistically significant effect of glucose on CV disease
- HbA1c as a surrogate should not be abandoned just because the relationships are not simple
- Measure "hard" outcomes when possible

# Conclusions

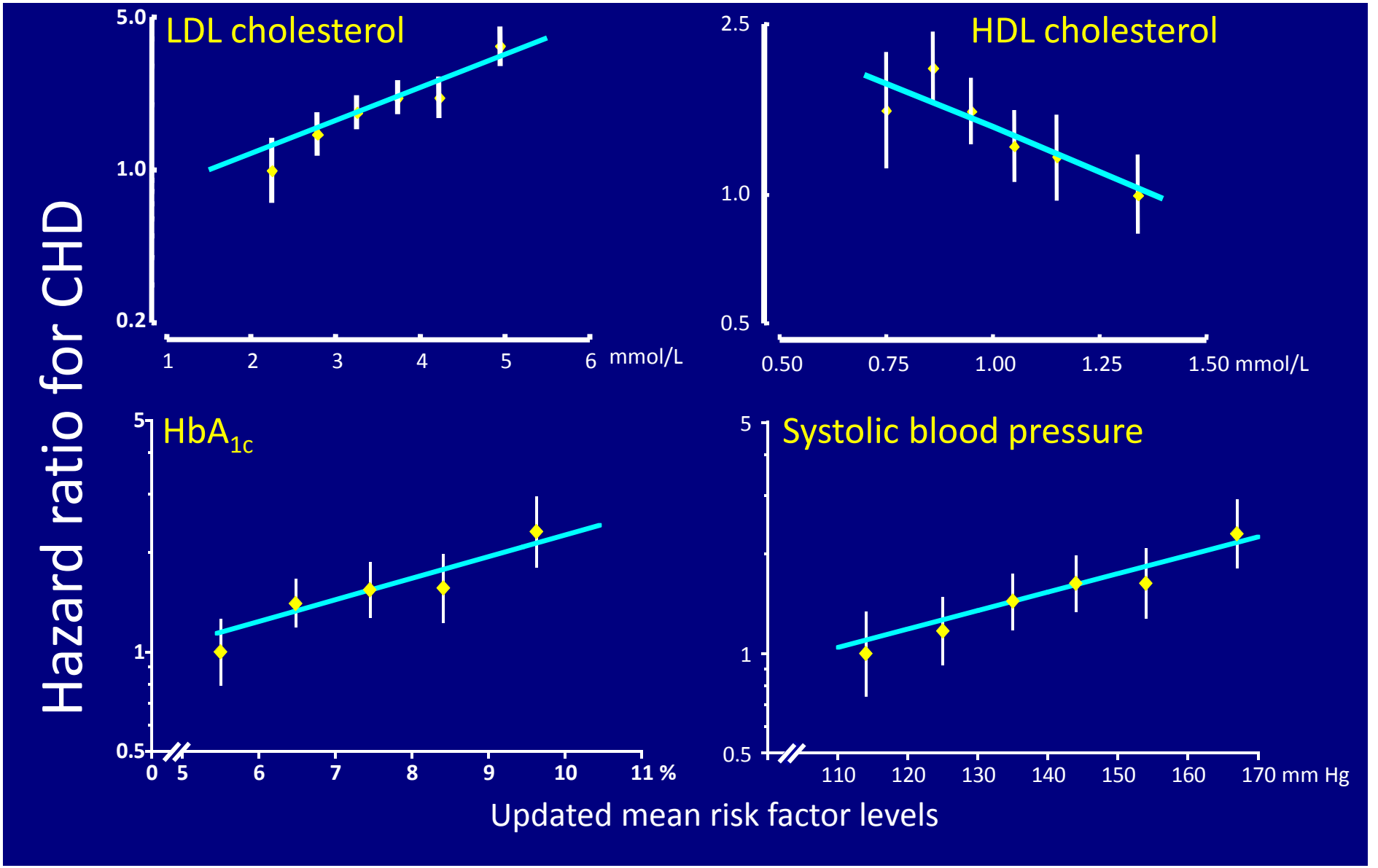
- *Surrogate endpoints DO have a role in evaluating DM therapies*

  Where long-term outcomes trials are not possible/feasible/completed

  - HbA1c measures a clinically significant relationship between glucose control and micro- and macro-vascular outcomes
  - These relationships are on the causal pathway
  - There is "pecking order" for the effect size
    - Micro>macro>death
- *Surrogate endpoints must be used judiciously and interpreted appropriately and can never fully substitute for measuring the true clinical outcome*

# THANK YOU

# CVD Risk Factors are Continuous, not Dichotomous




*UKPDS 35. BMJ 2000;321:405-412*

ukpds