Insulin Leadership Summit

THE FUTURE OF TYPE 2 DIABETES IN PRIMARY CARE FROM SANOFI-AVENTIS

Starting Insulin sooner rather than later in type 2 diabetes

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Outline

- Having diabetes increases risks
- Treating diabetes decreases risks
- Multi-factorial treatment
- We may have reached a limit
- Challenge is now getting good care to all

Relationship of glucose, total cholesterol and systolic BP with CVD

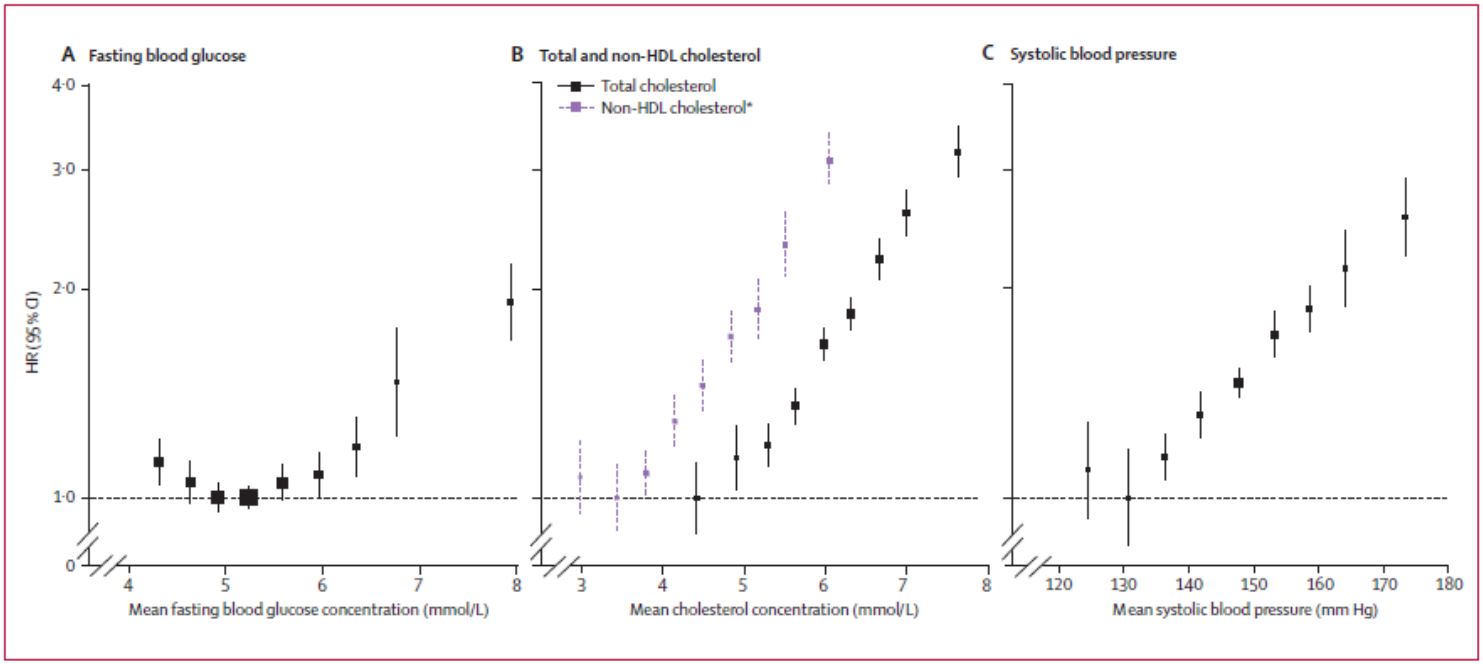


***Figure 6*: Comparison of hazard ratios (HRs) for coronary heart disease by long-term average concentrations of fasting blood glucose concentration, total (and non-HDL) cholesterol, and systolic blood pressure, in a common set of participants**

Analyses were done in participants with no known history of diabetes at baseline. Analyses of fasting blood glucose concentration, total cholesterol, and systolic blood pressure were based on 140 624 participants (10 667 cases). For fasting blood glucose, participants were classified into groups of baseline fasting concentrations, as described in figure 4. For the other factors presented, participants were classified according to baseline values as follows: total cholesterol, <4·5, 4·5–5·1, 5·1–5·7, 5·7–6·3, 6·3–6·9, 6·9–7·5, 7·5–8·1, 8·1–8·7, ≥8·7 mmol/L; non-HDL cholesterol, <3, 3–3·6, 3·6–4·2, 4·2–4·8, 4·8–5·4, 5·4–6·0, 6·0–6·6, 6·6–7·2, ≥7·2 mmol/L; systolic blood pressure: <110, 110–120, 120–130, 130–140, 140–150, 150–160, 160–170, 170–180, ≥180 mm Hg). These categories approximately correspond to those used for fasting blood glucose concentration (ie, increments of half the SD of each factor). HRs were adjusted, where appropriate, for age, smoking status, BMI, systolic blood pressure, total cholesterol and fasting blood glucose, and stratified, where appropriate, by sex and trial arm. HRs were plotted against the mean value in each group. Long-term average values were calculated with information from serial measurements. The reference group for each factor is the category with the lowest HR. *Analyses of non-HDL cholesterol were based on a subset of 71 224 participants (4290 cases).

The Emerging Risk Factors Collaboration, Lancet, 2010

Diabetes a vascular risk marker

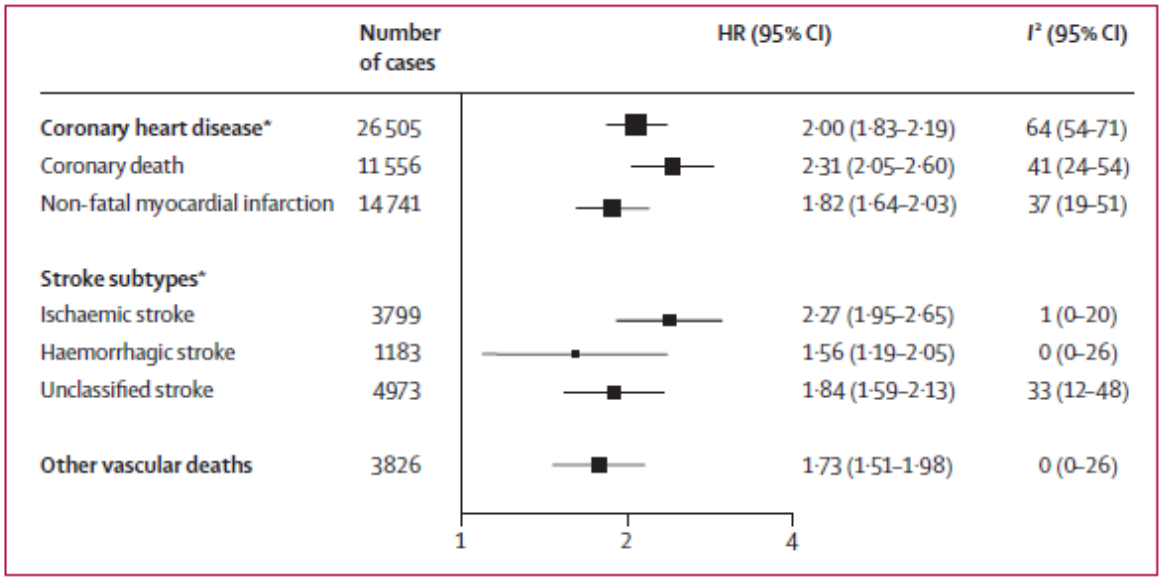


***Figure 1*: Hazard ratios (HRs) for vascular outcomes in people with versus those without diabetes at baseline**
Analyses were based on 530 083 participants. HRs were adjusted for age, smoking status, body-mass index, and systolic blood pressure, and, where appropriate, stratified by sex and trial arm. 208 coronary heart disease outcomes that contributed to the grand total could not contribute to the subtotals of coronary death or non-fatal myocardial infarction because there were fewer than 11 cases of these coronary disease subtypes in some studies. *Includes both fatal and non-fatal events.

The Emerging Risk Factors Collaboration, Lancet, 2010

CVD risk is a continuum
with respect to “glycaemia”

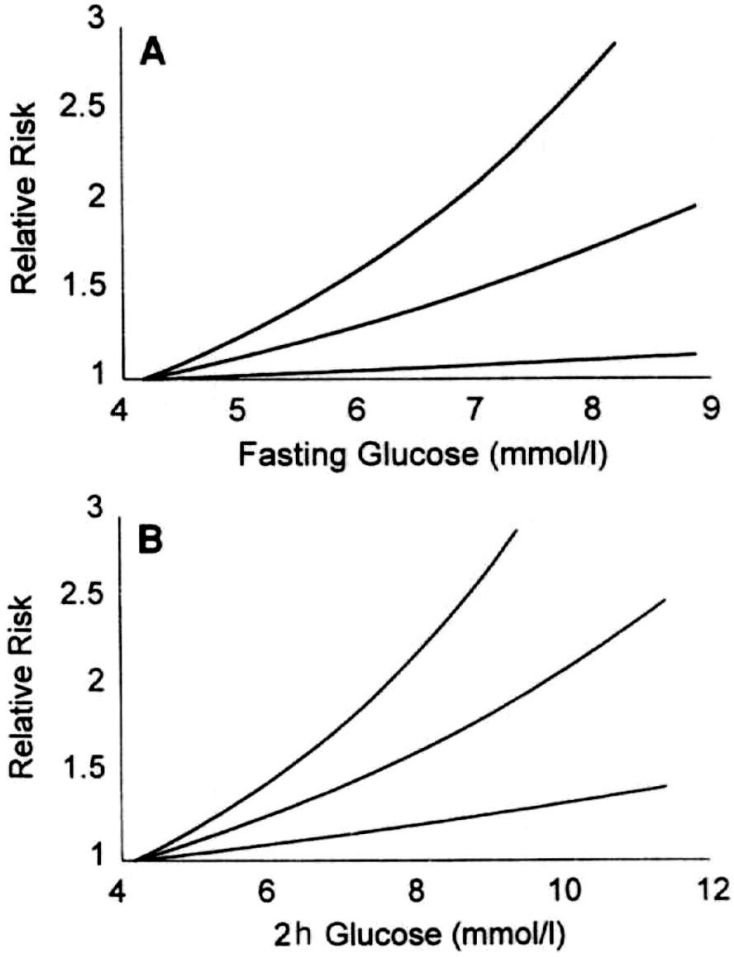
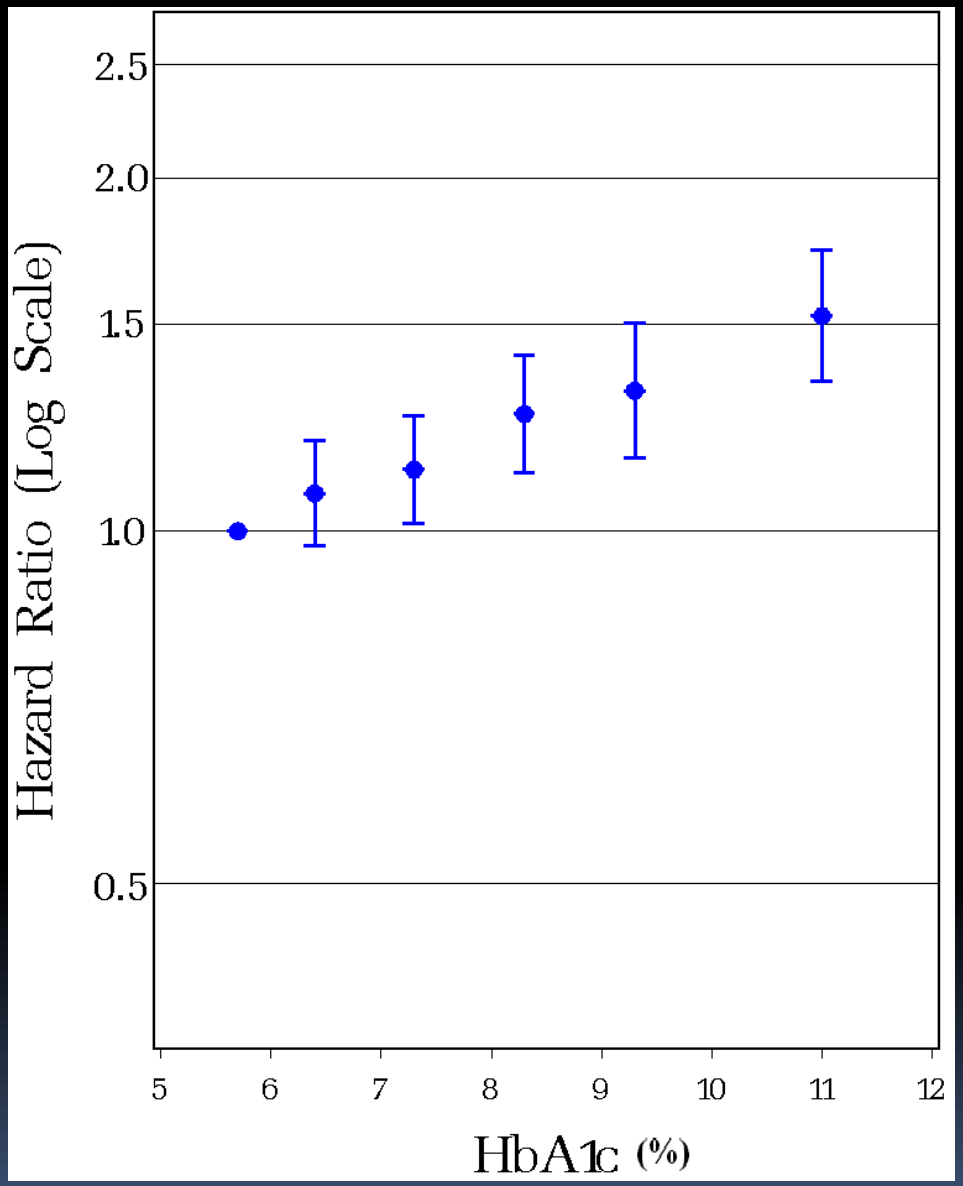


Figure 3—*The curves and 95% CIs (within which the curve lies) generated from the model and the combined β-coefficient for fasting (A), and 2-h postprandial (B) glucose values are displayed (relative risk = exp(β × (glucose – 4.2)/4.2).*

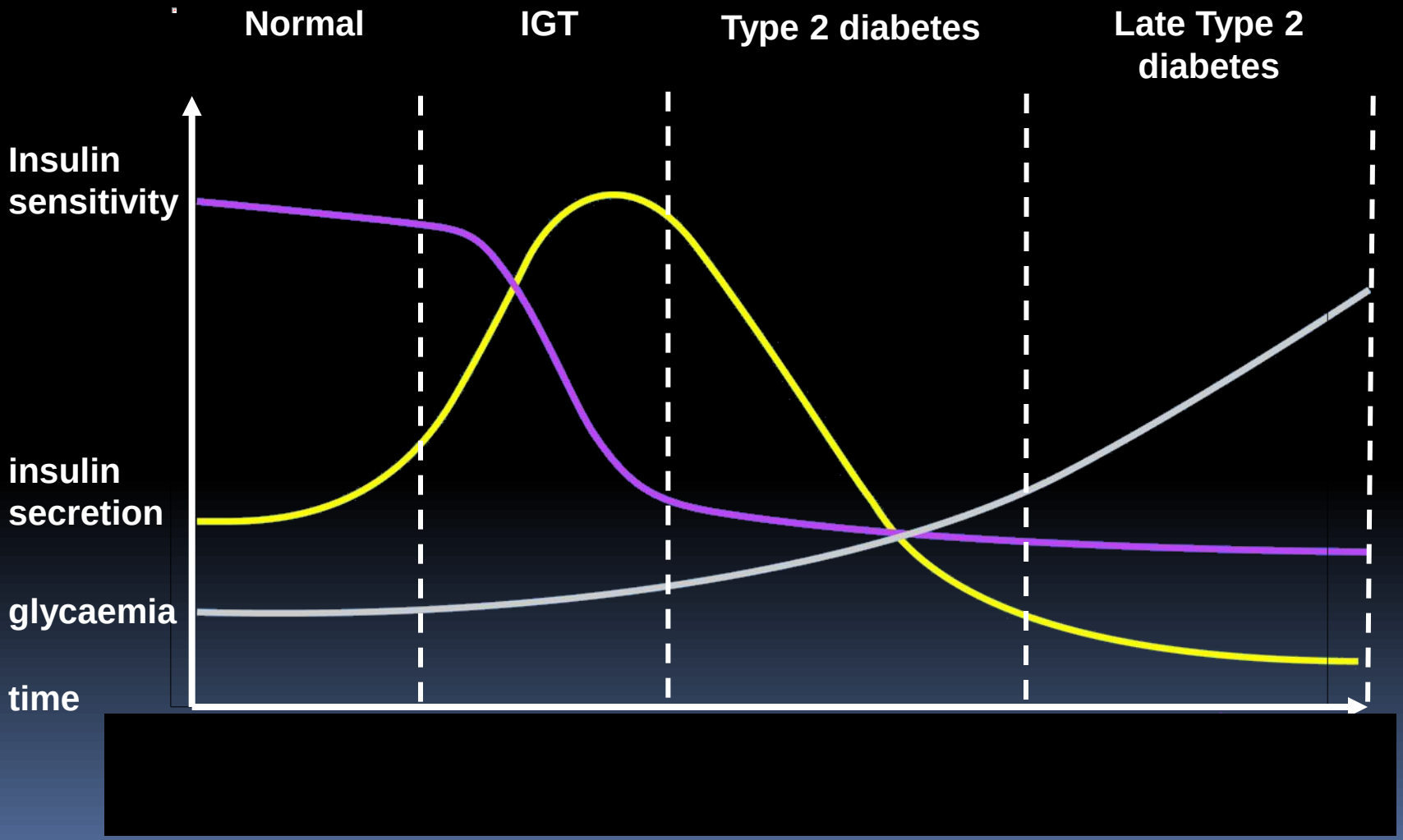
Coutinho et al, Diabetes Care, 1999



48,444 people with type 2 diabetes, no previous CVD, follow up after Get Checked

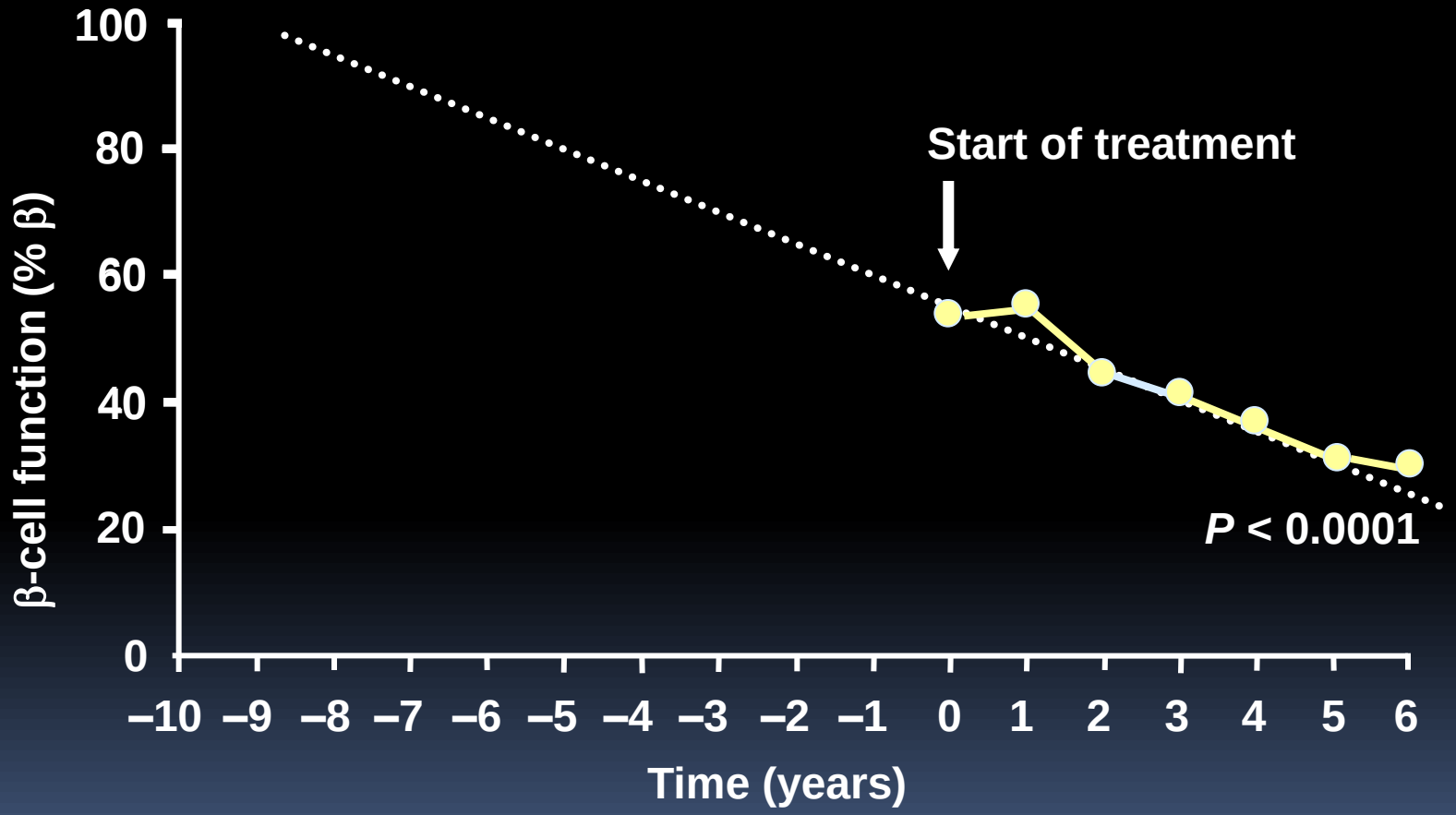
Elley, Kenealy et al, Diabetic Medicine, 2008

Type 2 Diabetes is a Progressive Disease



Adapted from Bailey CJ *et al*. *Int J Clin Pract* 2004; **58**: 867–876.

The UKPDS demonstrated progressive decline of β-cell function over time



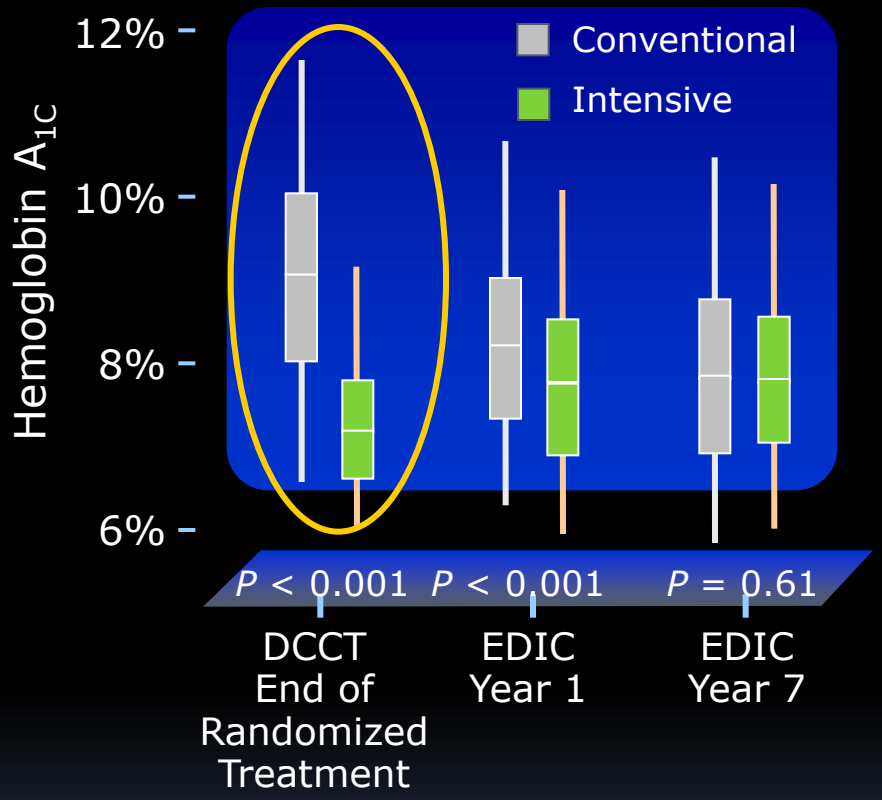
HOMA model, diet-treated
n = 376

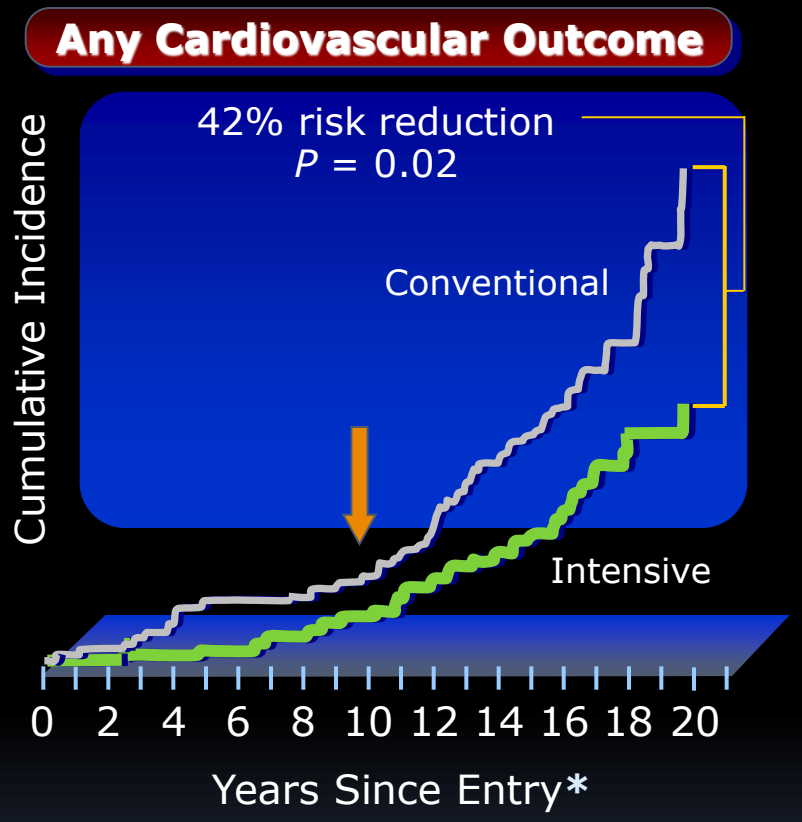
Adapted from Holman RR. *Diabetes Res Clin Pract* 1998; 40 (Suppl):S21–S25.

But, does glucose control prevent CVD?

How long does the investment take to pay the dividend?

Legacy Effect of Earlier Glucose Control





* Diabetes Control and Complications Trial (DCCT) ended and Epidemiology of Diabetes Interventions and Complications (EDIC) began in year 10 (1993). 1441 patients, mean follow-up: 17 years.

DCCT/EDIC Research Group. *JAMA*. 2002

Nathan DM, et al. *N Engl J Med*. 2005

Note: Type 1 diabetes

UKPDS, Type 2 Diabetes, 10.7 yr trial

plus data after median 8.5 years post-trial follow-up

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

RRR = Relative Risk Reduction, P = Log Rank

UK Prospective Diabetes Study (UKPDS) Group. *The Lancet* 1998; **352**:837–853.

Metformin

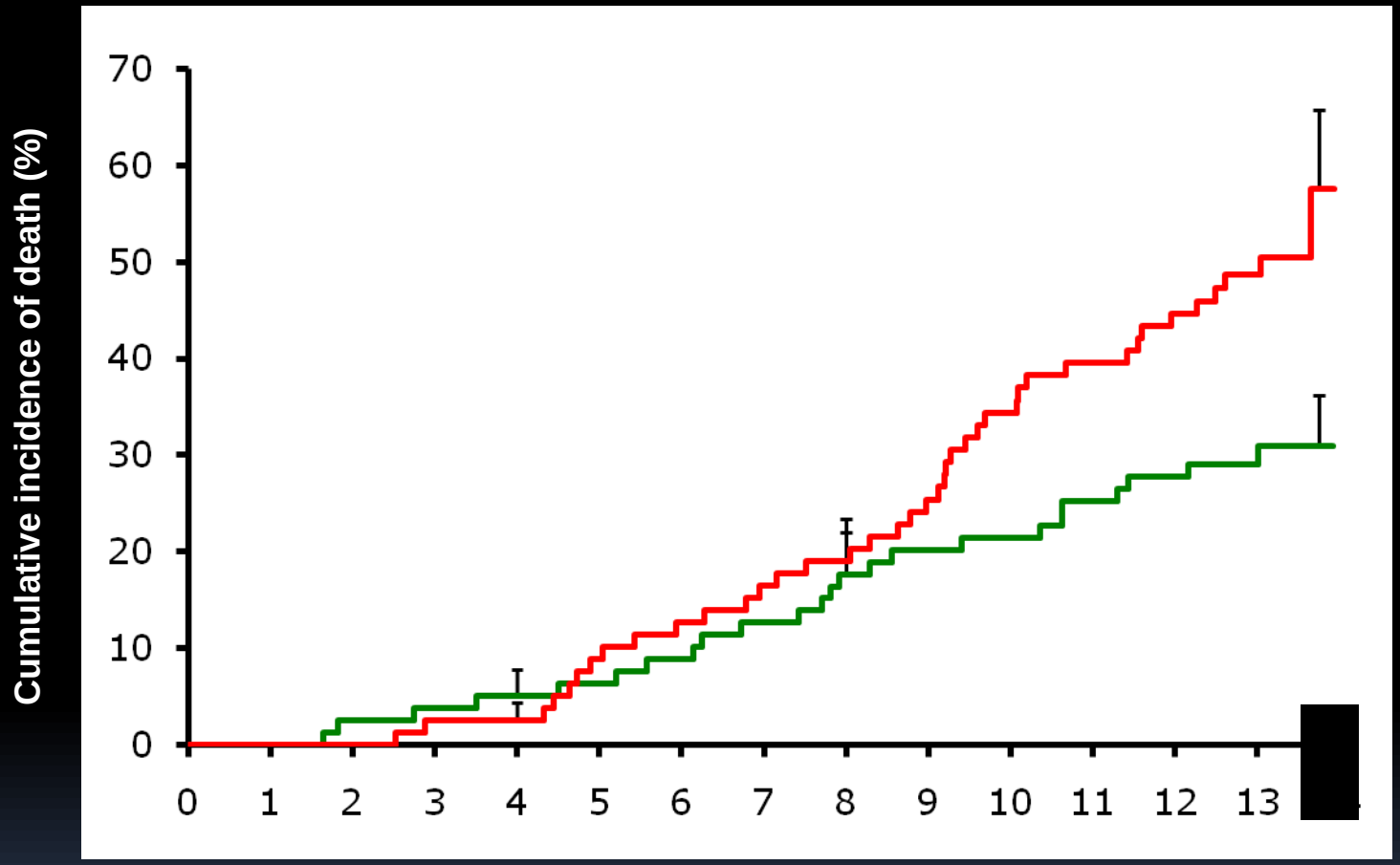
Overweight group (>120% ideal) on metformin

- *lower HbA1c levels (7.4% v 8.0%)*
- *32% reduction in diabetic complications*
- *42% reduction in diabetes-related deaths*
- *36% reduction in deaths from all causes*

Don't throw out metformin

UKPDS 34, Lancet, 1998

Steno-2 Post Trial: Mortality of any cause

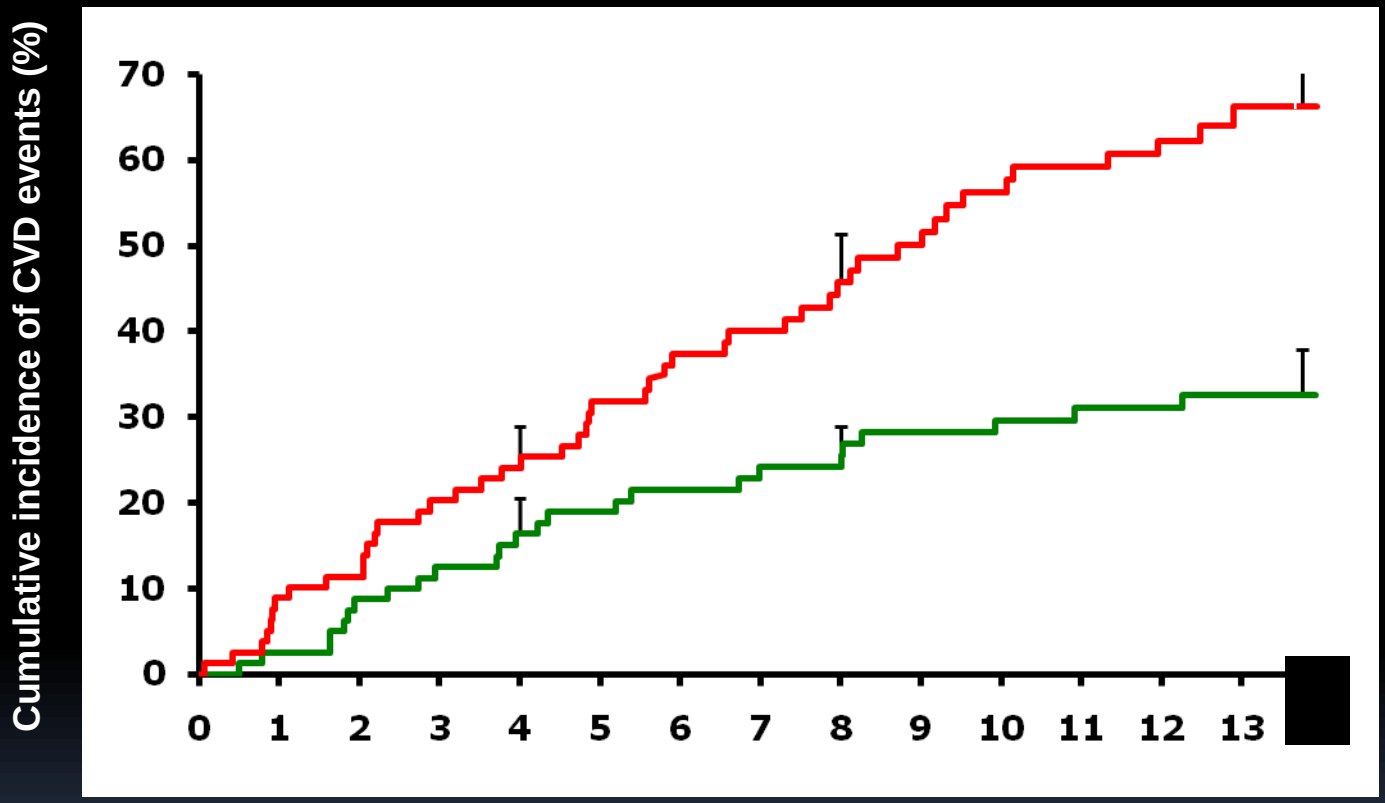


160 patients, type 2 diabetes and microalbuminuria, RCT mean treatment 7.8 years, mean follow up 13.3 years. Treatment with ACE, aspirin, target bp <130 / < 80, HbA1c < 6.5%, total cholesterol < 4.5mmol/L, triglyceride < 1.7 mmol/L

Gaede et al. NEJM 2008

Steno-2 Post Trial: Any CVD events

Cumulative incidence of patients with a major CVD event during follow-up



Numbers at risk								
Conventional	80	70	60	46	38	29	25	14
Intensive	80	72	65	61	56	50	47	31

Gaede et al. NEJM 2008

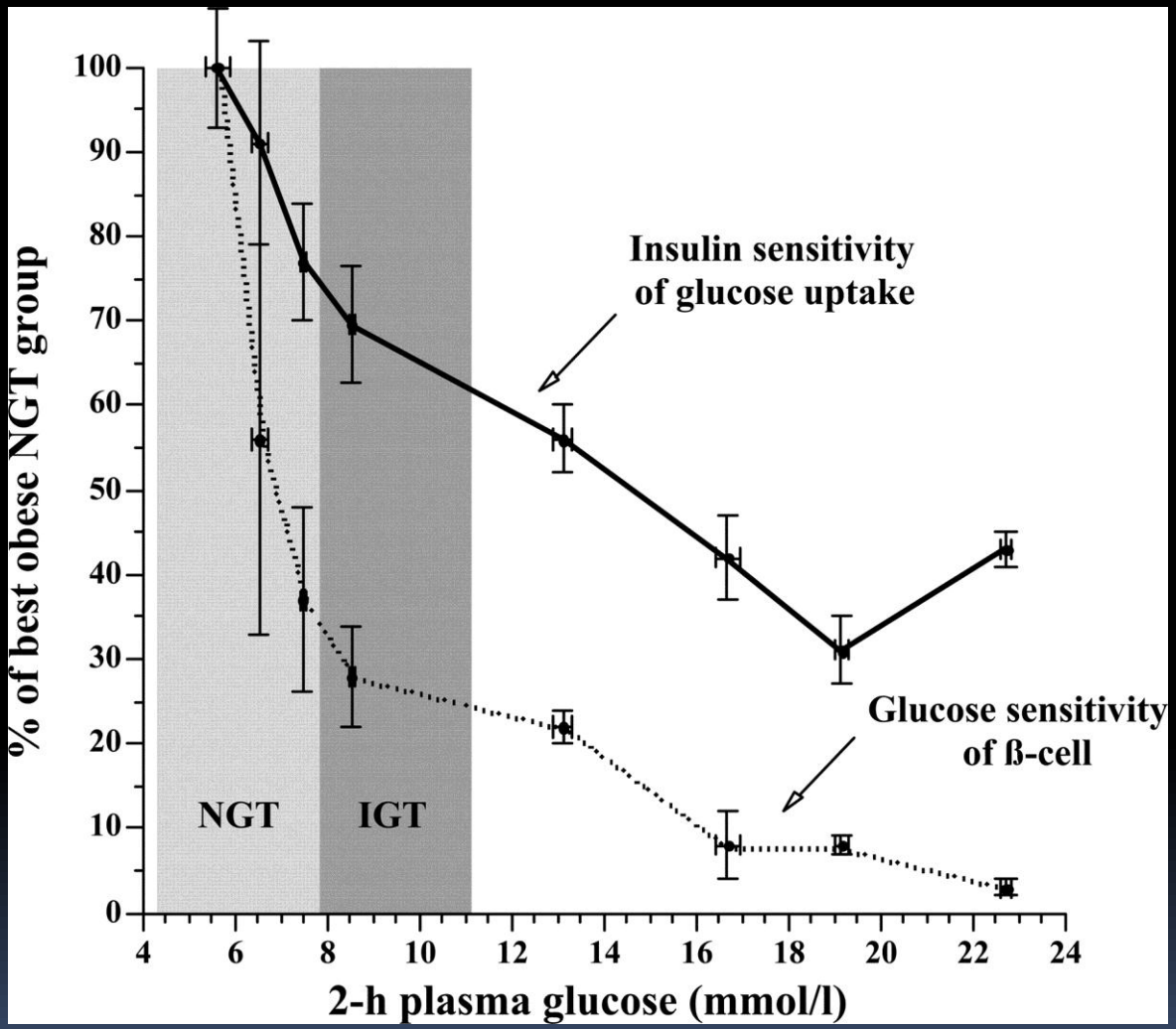
How many of you have been in the same practice for 10 years of more?

Both Genetics and Environment Affect Risk of Type 2 Diabetes

	Pima US	Pima Mexico	Other Mexicans
Diabetes prevalence	37.5%	8.0%	2.5%
Obesity	69.3%	13.2%	17.7%
Physical activity	7.6	27.4	27.1 h/wk

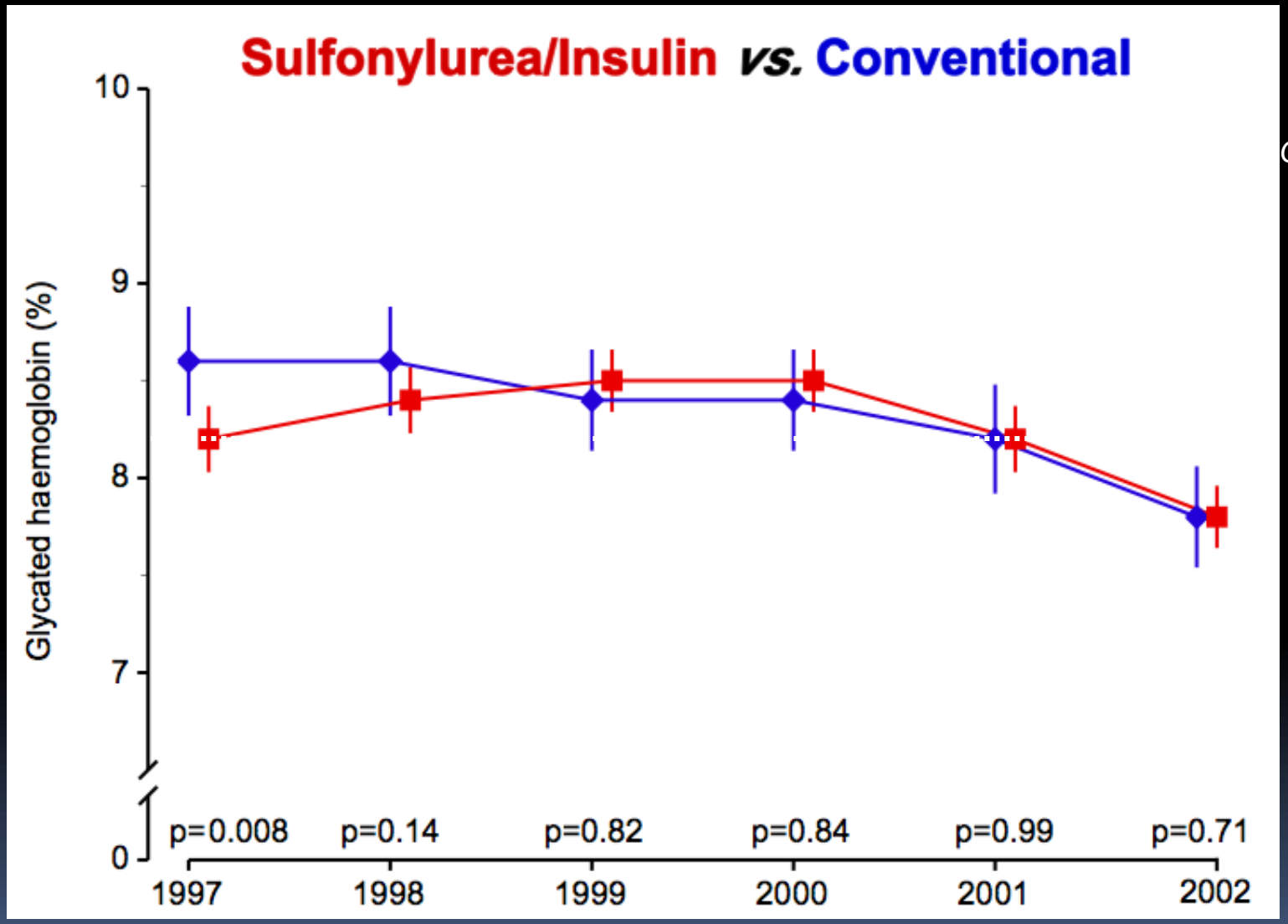
Schulz et al *Diab Care* 2006; 29: 1866.

β-cell glucose sensitivity and insulin sensitivity against 2-h plasma glucose concentration in obese NGT tertiles, IGT, and T2DM quartiles



Ferrannini, E. et al. J Clin Endocrinol Metab 2005;90:493-500

UKPDS Post-Trial Changes in HbA_{1c}



CI)

HbA_{1c} target

- Accord trial 7.5% v 6.4%

Terminated early for excess deaths in intensive group

- Advance trial 7.3% v 6.5%

No reduction of CV events

- VADT trial 8.4% v 6.9%

No reduction of CV events

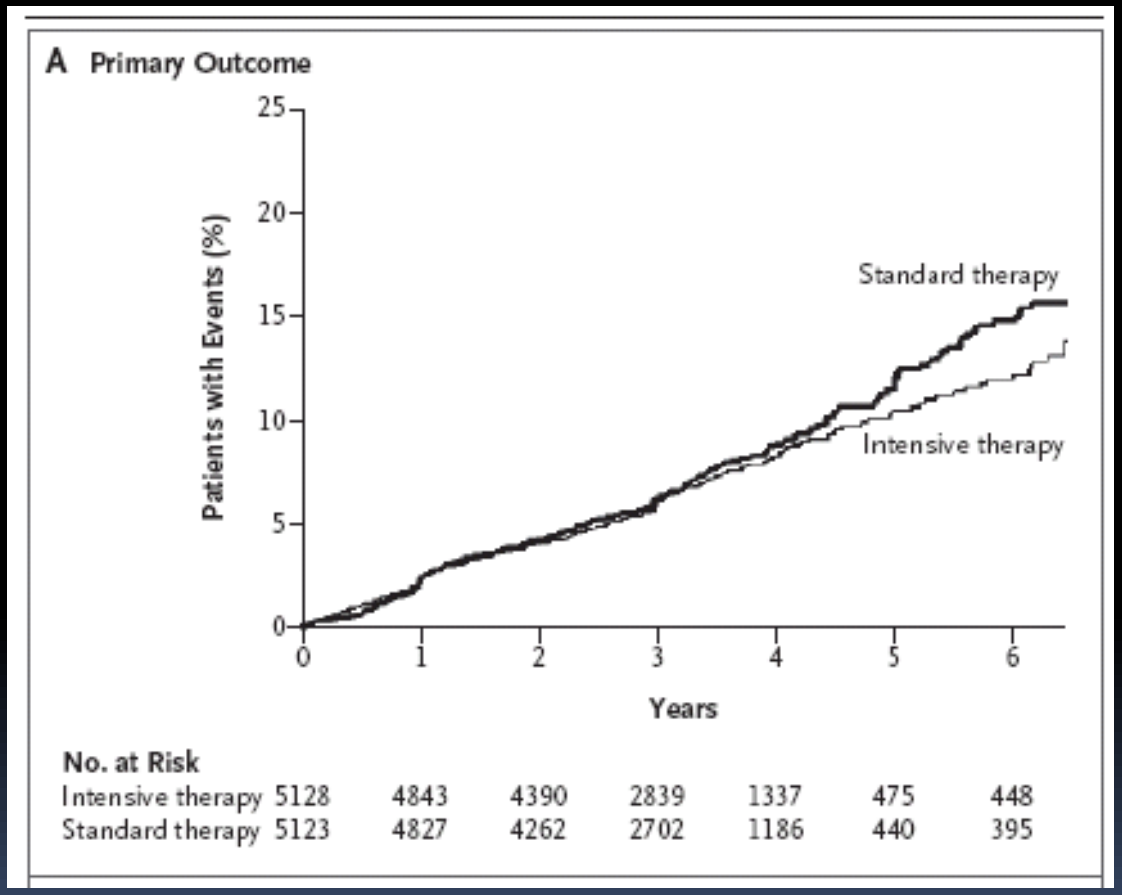
Accord

The Action to Control Cardiovascular Risk in Diabetes Study Group

- N=10,000
  - 1/3 already on insulin
  - 1/3 prevalent CVD events
  - Age 62
  - Diabetes for 10 years
  - HbA1c 8.3

Strategy of (ultra) intensive glycaemic control aiming for HbA1c 6 (achieved 6.3)

Accord June 2008

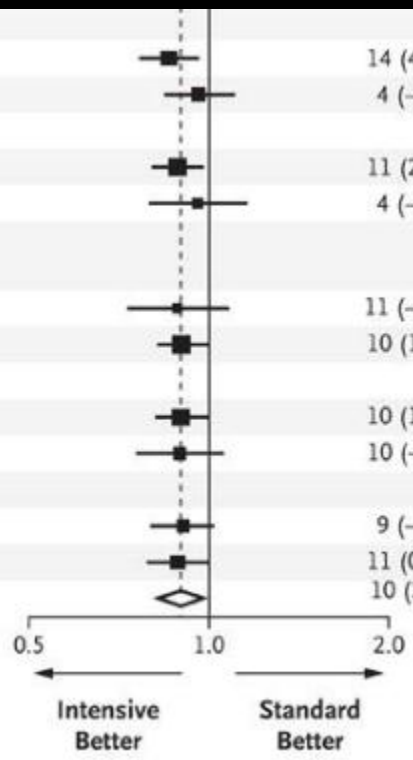


352 vs 371 events

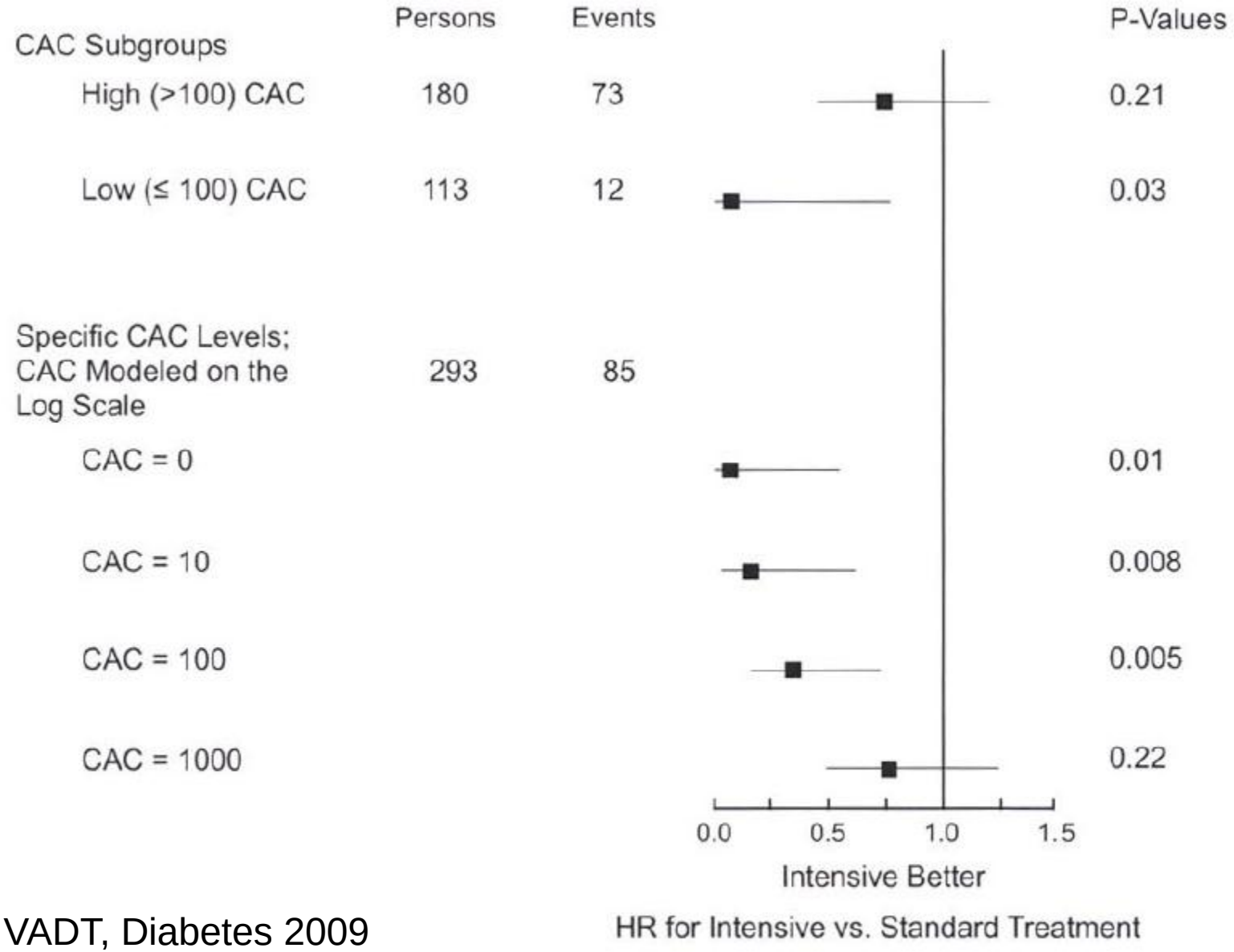
HR 0.9 (0.78-1.04, p=0.16)

primary outcome was the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes.

History of macrovascular disease				
No	0.67 (0.63 to 0.70)	591 (15.6)	678 (18.0)	14 (4 to 23)
Yes	0.67 (0.62 to 0.72)	418 (23.3)	438 (24.4)	4 (−10 to 16)
History of microvascular disease				
No	0.65 (0.62 to 0.68)	799 (16.0)	892 (17.9)	11 (2 to 19)
Yes	0.79 (0.69 to 0.90)	210 (36.8)	224 (38.4)	4 (−16 to 21)
Treatment with any blood-pressure–lowering drugs				
No	0.75 (0.69 to 0.81)	199 (14.3)	222 (16.0)	11 (−7 to 27)
Yes	0.64 (0.61 to 0.67)	810 (19.4)	894 (21.4)	10 (1 to 18)
Treatment with statins				
No	0.70 (0.66 to 0.73)	746 (18.6)	815 (20.5)	10 (1 to 19)
Yes	0.60 (0.55 to 0.65)	263 (16.9)	301 (18.9)	10 (−6 to 24)
Treatment with antiplatelet drugs				
No	0.70 (0.66 to 0.74)	485 (16.4)	541 (18.1)	9 (−2 to 20)
Yes	0.63 (0.59 to 0.67)	524 (20.0)	575 (22.3)	11 (0 to 21)
Overall	0.67 (0.64 to 0.70)	1009 (18.1)	1116 (20.0)	10 (2 to 18)



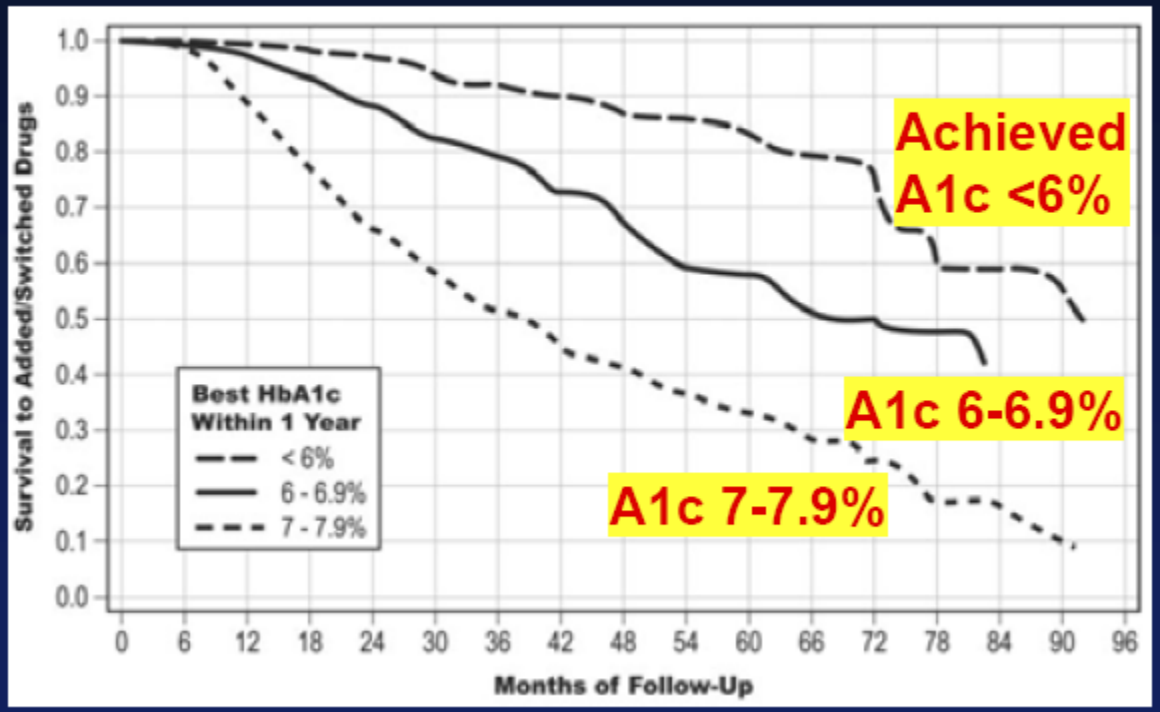
Accord, NEJM 2008



Reaven, VADT, Diabetes 2009

FIG. 3. HRs (95% CI) for effect of treatment (intensive vs. standard) in multivariable-adjusted models. Boxes represent HRs, and lines indic 95% CI. *P* values indicate the significance of treatment effect in the indicated models. The treatment effect was estimated for high- and low-C subgroups separately (upper portion of figure) or for specific CAC scores (lower portion of figure) within a multivariable model includ log(CAC + 1) as a continuous variable, treatment, and the calcium-treatment interaction effect. Multivariable models included age, ethnic diabetes duration, history of hypertension, history of smoking, prior CVD history, total and HDL cholesterol, and A1C as covariates.

Get to A1c <6% = Stable for Years



Nichols, *Diabetes Care* 2006; 29: 504

We may be reaching the limits of what can be achieved with current medications

As ‘usual care’ improves, becomes more and more difficult to show an advantage from a new regimen

There are some things we cannot change or prevent

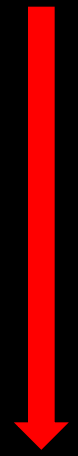
The challenge becomes delivering this best-practice, early, to everyone

Everyone includes the people with whom we don’t currently engage well

We are also reaching the limits of what we can achieve with the way we currently organise care

Multi-factorial care, in roughly this order or importance

Smoking
Blood pressure
ACE inhibitors (nephropathy)
Statins
Aspirin
Systematic care
Patient understanding and ability to self-manage
Glucose control
Feet, eyes, kidneys, nerves
Depression, anxiety, prognosis, expectations



Order varies between starting points and endpoints

All of these

Starting insulin has a special place amongst the barriers to care in that the reasons for not starting insulin are not the same as the reasons for not doing other things

US, 342 doctors
and 2003 patients looked after continuously by same doctor

Doctor's target HbA1c	Patients' actual HbA1c
Fast ≤ 6.1 mmol/L	7.0% +/- 1.6
Fast > 7.8 mmol/L	7.8% +/- 1.8

★ Set Targets

Belfiglio et al, Diabetes Care, 2001

"Clinical inertia is due to at least three problems:

overestimation of care provided

use of "soft" reasons to avoid intensification of therapy

lack of education, training, and practice organization aimed at achieving therapeutic goals

Physicians will need to build into their practice a system of reminders and performance feedback to ensure necessary care."

★ Work to meet Targets

Phillips et al, Annals of Internal Medicine, 2001

"While physicians privately acknowledge their doubts about the benefits of glycaemic control, or even the possibility of losing weight, they often end up blaming their patients for poor compliance or negative outcomes."

Loewe et al, Social Science & Medicine, 1998

Doctors attribute more of positive and less of the negative outcomes to medical control.

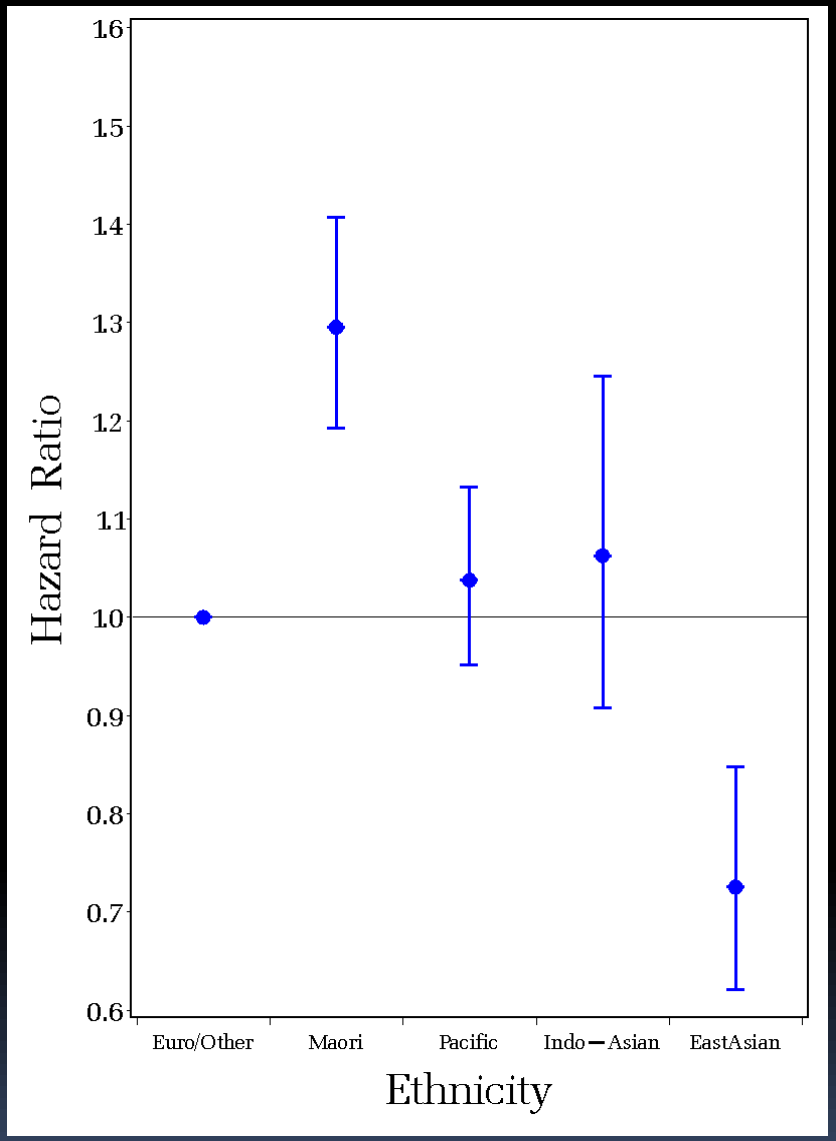
Gillespie BJClinPsych, 1988

"Patient and provider resistance to insulin therapy is substantial, and for providers it is part of a larger pattern of reluctance to prescribe blood glucose-lowering medication. Interventions to facilitate timely initiation of insulin therapy will need to address factors associated with this resistance."

Peyrot et al, Diabetes Care, 2005

Whether we can or whether we cannot achieve our targets partly depends on how hard we try, how we organise care, how well we engage patients

I think we have to be careful not to blame the patient for not achieving goals!

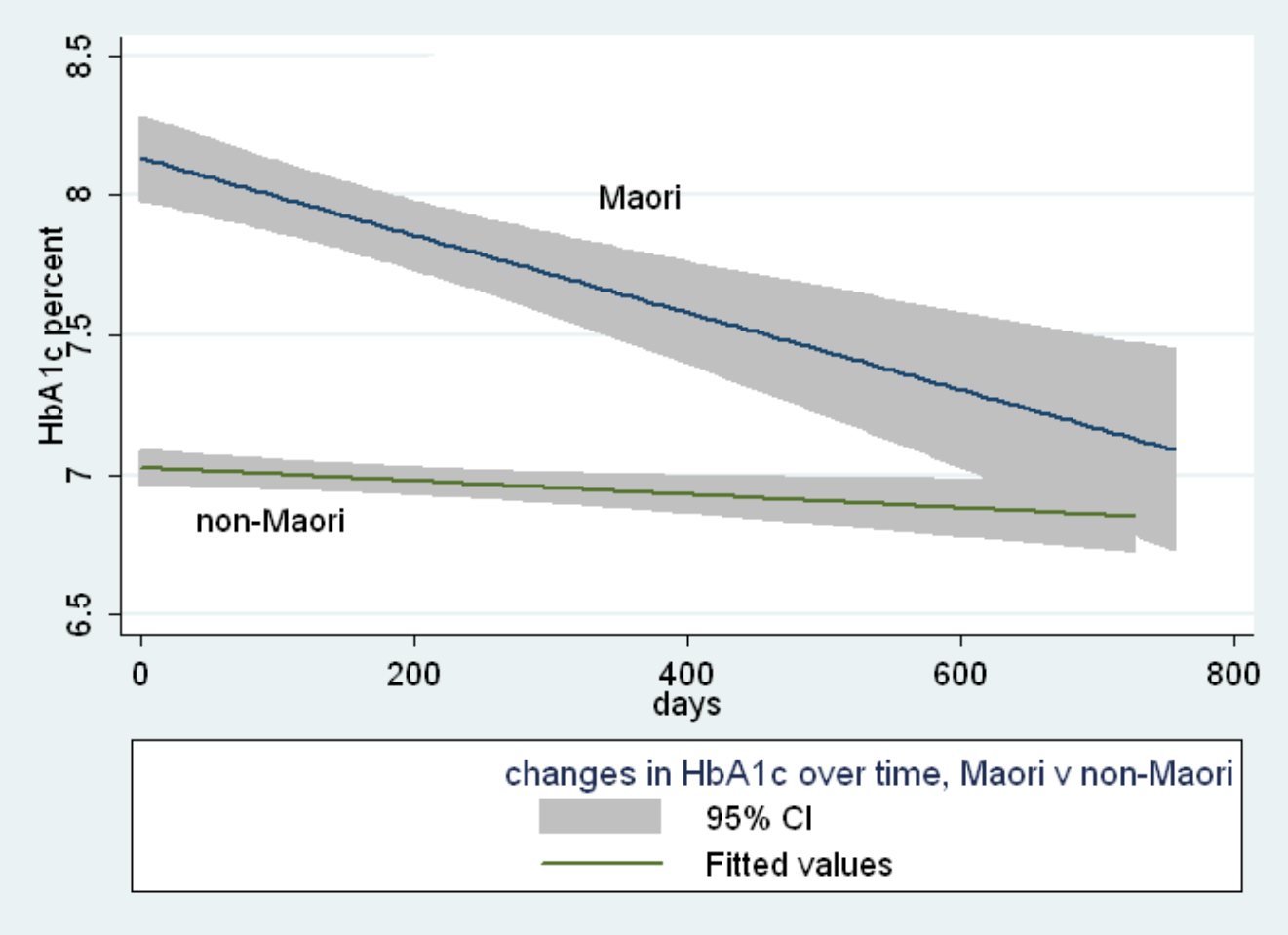


48,444 people with type 2 diabetes, no previous CVD, follow up after Get Checked

★ Equal treatment may not be enough

Kenealy et al, Diabetic Medicine, 2008

With systematic care … We can do it … Graph shows 'effect' of being Maori ***after*** removing the effect of everything else that lowers glucose



Kenealy et al 2010

Engaging patients

- Diabetes Tracking Study
- ~~Smart answers~~
- Smart questions
  - What do you already about diabetes?
  - When you were diagnosed – tell me the story
  - How did you feel about it?
  - How did your family react?
  - How do you see your future?
  - What horror stories do you worry about?
  - What scares you about insulin?