Diabetes – the Basics

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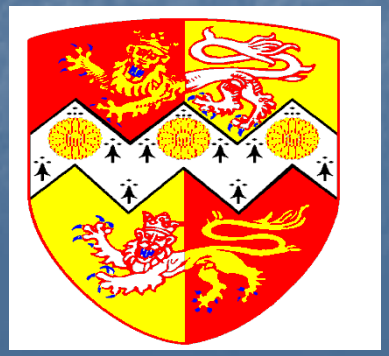
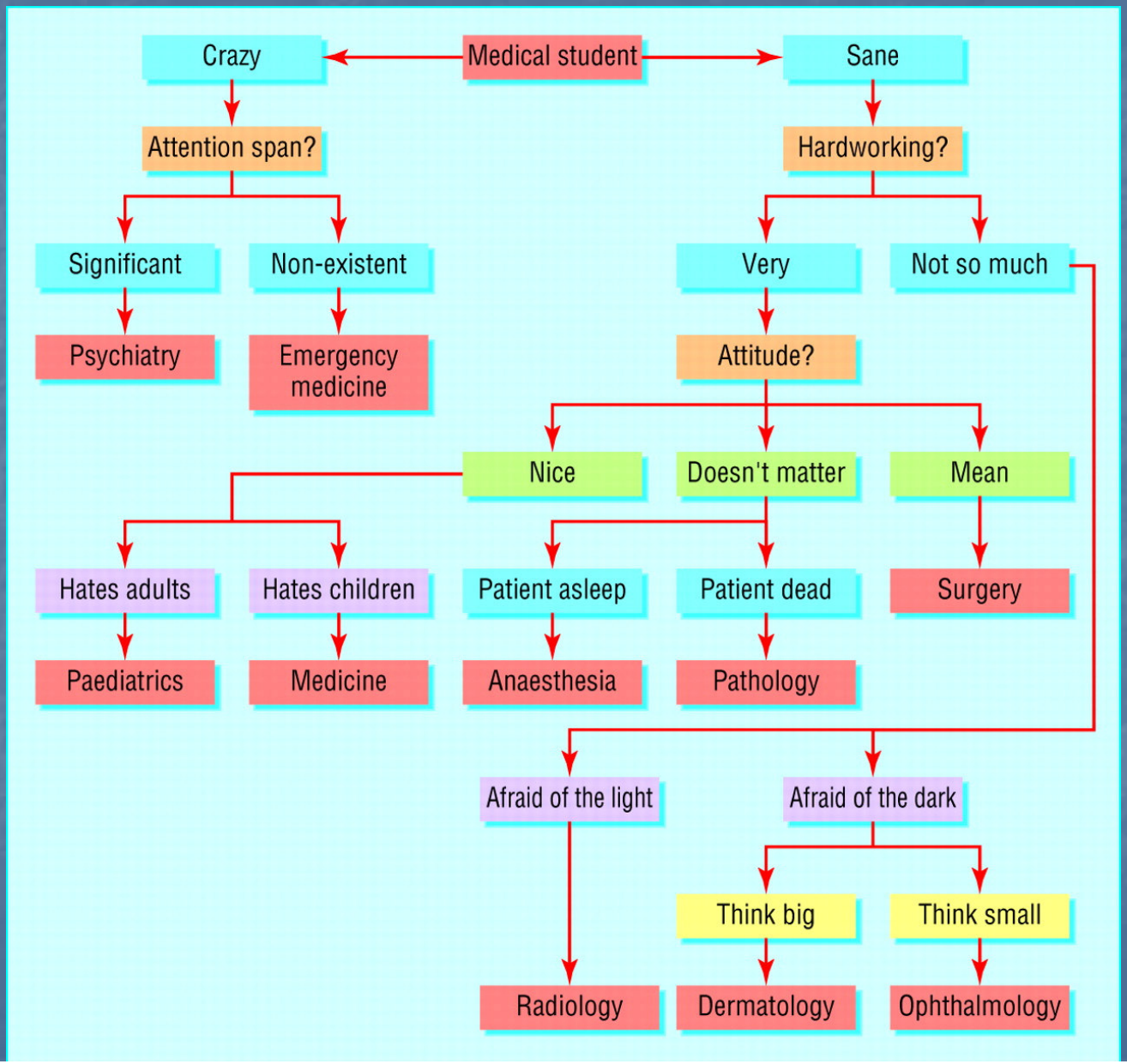


What Kind of Doctor do You Want to Be?



Veysman BMJ 2005;331:1529

Who is From One of These Places?

- Asia
- Africa
- North or South America
- Australia or Polynesia
- Europe

Why is This Important?

- Most of you are from a genetically susceptible population
- Many of you may know someone with diabetes
- You may be the person they turn to for advice

Why is it Important?

- Diabetes has an impact on almost every branch of medicine
- More than 10% of inpatients have diabetes
- It is becoming more prevalent
- The global economic burden of diabetes is enormous

The Impact of Diabetes in the UK

- The prevalence of people with known diabetes increased in one health district from 2.3 to 3.4% between 1996 and 2005, while the proportion known to have diabetic complications fell from half to one third
- Glucose-lowering therapies and test strips accounted for 6.9% of the total UK drug bill in 2008
- Adjusted costs for these prescriptions rose (in England) from £290m in 2000 to £591m in 2008
- Insulin accounted for 48.4% of these costs and test strips for a further 23.6%

Gale EAM Diabetic Medicine 2010;27(9):973-976

The Impact of Diabetes in the UK

- The glitazones accounted for 11.7% of scripts by cost, but 2.8% by volume. Metformin accounted for 10.7% by cost, but 52.8% by volume
- Use of insulin secretagogues (mainly sulphonylureas), fell from 16.2 to 3.7% by cost between 2000 and 2008 and from 33.7 to 19.5% by volume
- Patients with Type 1 diabetes had a mean HbA1c of 8.8% in 2000 as against 8.7% in 2008. Insulin-treated patients with Type 2 diabetes had an HbA1c of 8.5% in 2000 as against 8.4% in 2008

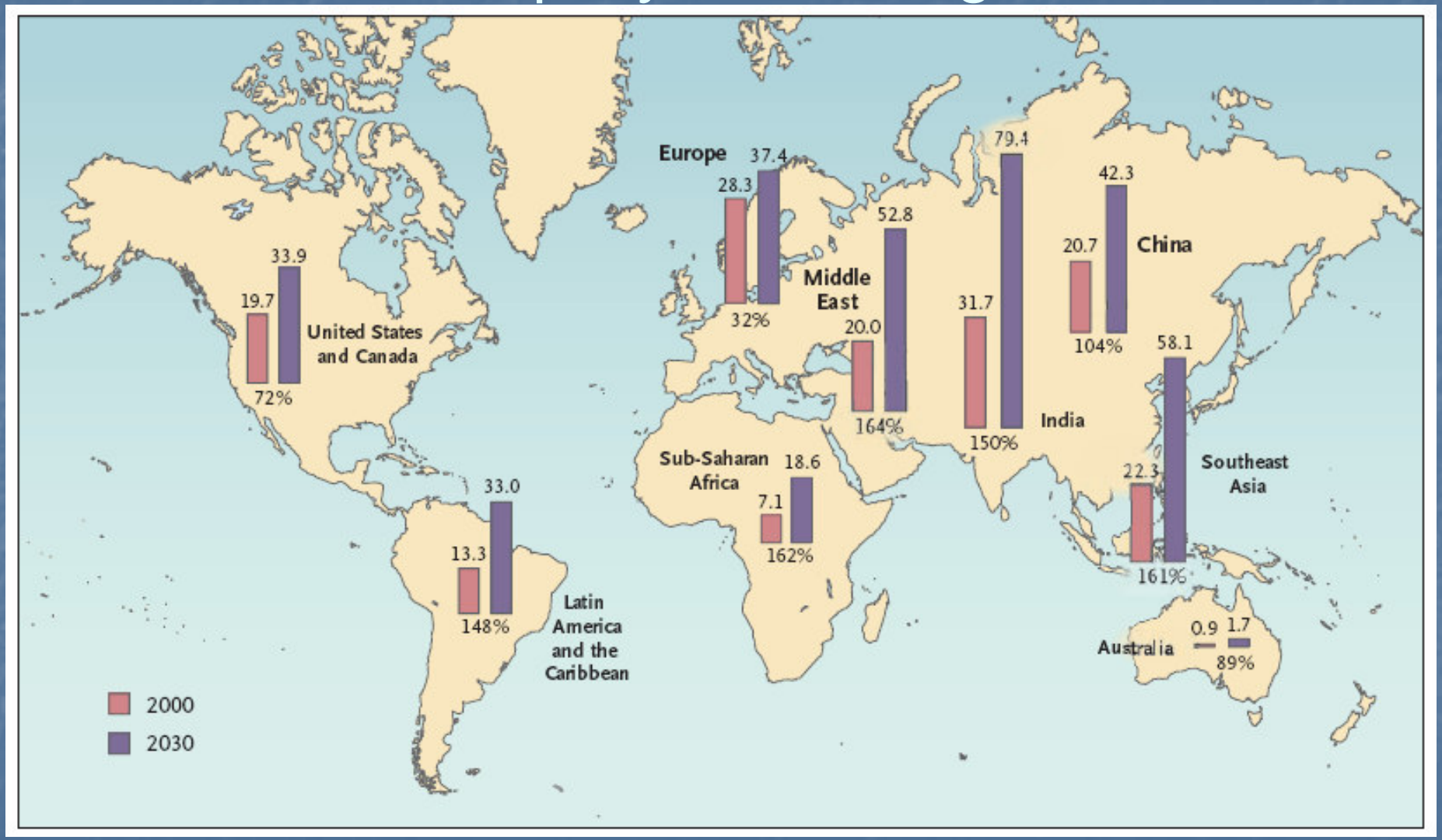
Gale EAM Diabetic Medicine 2010;27(9):973-976

The Impact of Diabetes in the UK

- Reductions in HbA1c were seen in some treatment groups and may reflect earlier diagnosis and / or more aggressive escalation of therapy
- Systolic blood pressure fell by approximately 8 mmHg (5%) in those with Type 2 diabetes and total cholesterol fell from 5.6 to 4.2 mmol/l (25%) over the same period
- The costs for acute hospital care for diabetes rose from 8.7 to 12.3% of revenue between 1994 and 2004

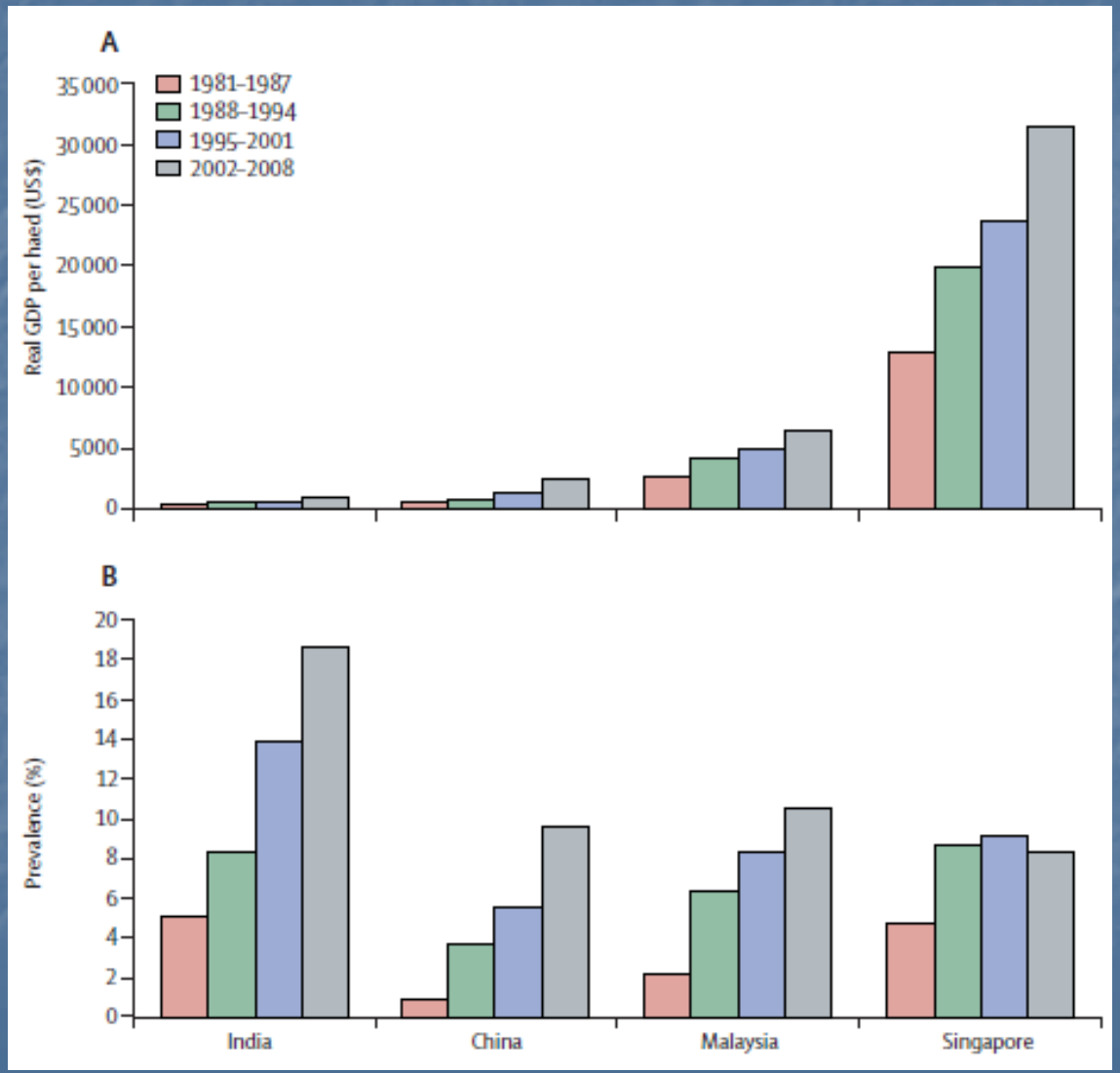
Gale EAM Diabetic Medicine 2010;27(9):973-976

The Incidence Of Type 2 Diabetes Is Rapidly Increasing



Millions of cases of diabetes in 2000 and estimate of 2030 and percentage change shown

What's the Problem in Asia?



Ramachandran A et al Lancet 2010;375(9712):408-418

Some Definitions

- Type 1
- Type 2
- Others (not mentioned any more)

How is the Diagnosis Made (1)?

Glucose criteria (mmol/L)			
	*Fasting**	*Random*	*OGTT (2 hr value)*
Diabetes mellitus	≥ 7.0	≥ 11.1**	≥ 11.1
Impaired fasting glucose	5.6 – 6.9		
Impaired glucose tolerance			7.9 – 11.0
Normal	≤ 5.5		≤ 7.8

* includes fasting value on OGTT (oral glucose tolerance test) or no calorie intake for ≥8 hours.
** with classic symptoms or hyperglycaemic crisis.

Davies PH et al Brit J Diab Vasc Dis 2010;10(6):261-264

How is the Diagnosis Made (2)?

HbA_{1c} criteria: IFCC assay[11]		
	DCCT aligned – HbA_{1c} (%)	IFCC- HbA_{1c} (mmol/mol)
Diabetes mellitus	≥ 6.5	≥ 48
Pre-diabetes	5.7 – 6.4	39-47
Normal	≤ 5.6	≤ 38

Please note the above values may not apply in the following clinical circumstances

- **Abnormal red cell turnover conditions:** such as anaemias from haemolysis, spherocytosis or iron deficiency (such as in pregnancy)
- **Haemoglobinopathies:** certain ones will affect diagnostic criteria (eg HbS, HbC, HbF, HbE). With Sickle cell trait, specific HbA_{1c} assays will overcome this problem.
- **Rapid onset diabetes:** such as most Type 1 diabetes mellitus and some Type 2: the HbA_{1c} can be within the normal range despite marked hyperglycaemia
- **Near patient testing:** using current HbA_{1c} tests are not deemed to be sufficiently accurate for diagnosis
- In these and other cases where there is doubt as to the use of HbA_{1c}, the glucose criteria below must be used. Renal failure concerns can be overcome if specific assays are used.

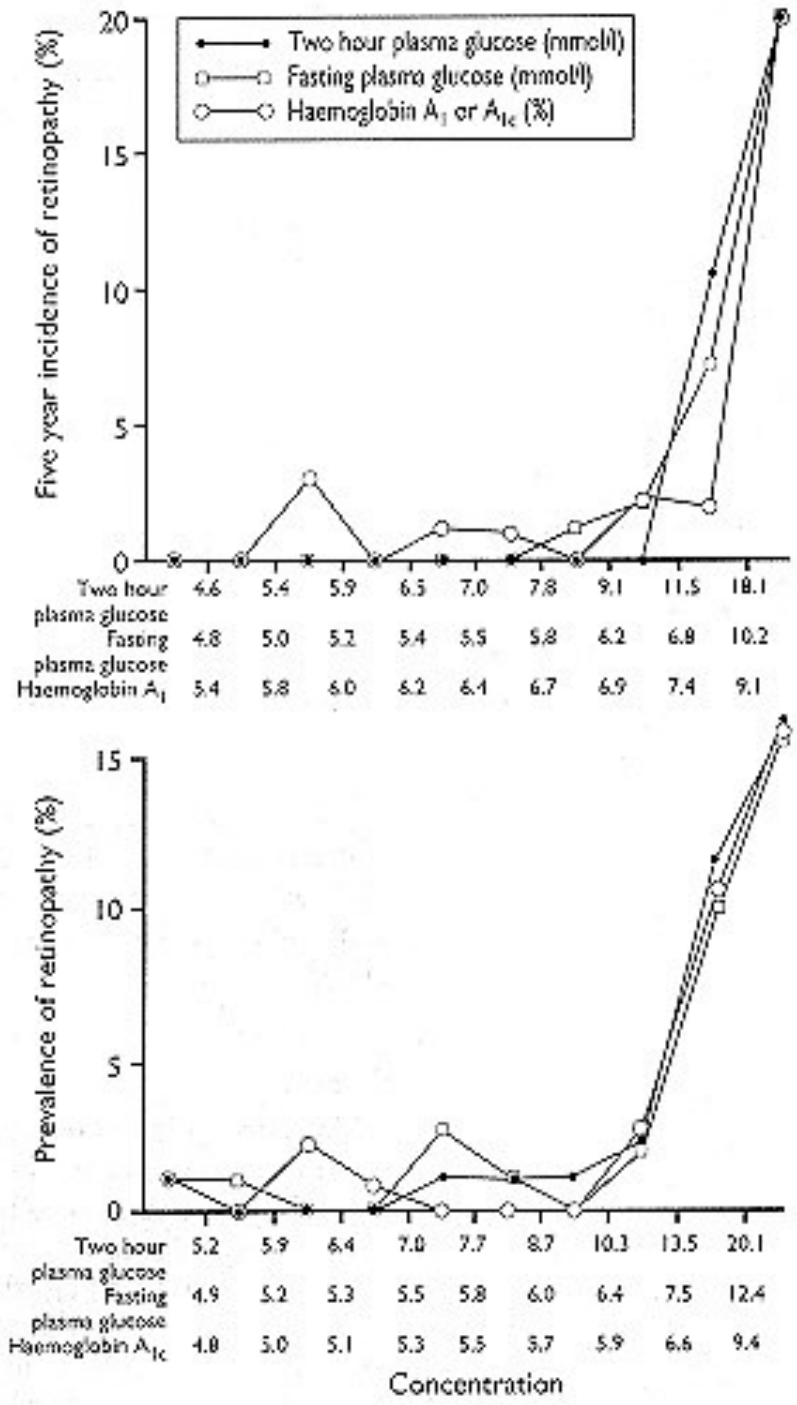
Davies PH et al Brit J Diab Vasc Dis 2010;10(6):261-264

How is the Diagnosis Made (3)?

Diagnosis of Diabetes Mellitus: Summary of ADA criteria[12] *Any one criterion is sufficient even if others normal*
1: HbA_{1c}: ≥ 6.5% (≥ 48 mmol/mol) using an IFCC standardised assay
2: Fasting glucose: ≥ 7.0 mmol/L
3: OGTT 2 hour value: ≥ 11.1 mmol/L
4: Random glucose ≥ 11.1 mmol/L with classic symptoms or hyperglycaemic crisis.
In the absence of classic symptoms or hyperglycaemic crisis, criteria 1 - 3 need repeating.

So, in summary, making the diagnosis of diabetes is not as straightforward as it used to be

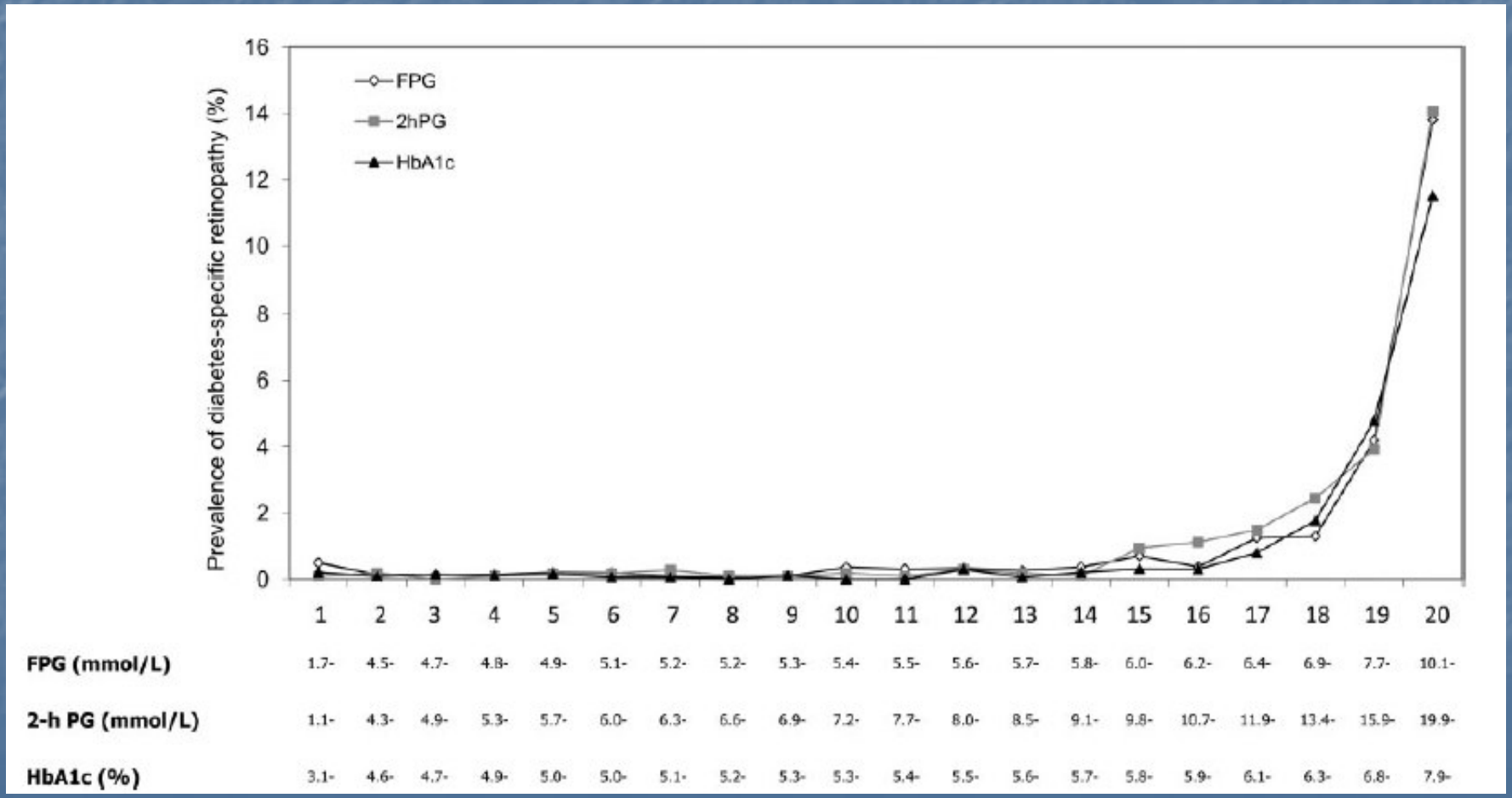
Davies PH et al Brit J Diab Vasc Dis 2010;10(6):261-264



Why Those Numbers?

McCance D et al BMJ 1994; 308(6940):1323-8

Remarkably Similar to More Recent Data



Colagiuri S et al Diabetes Care 2011;34(1):145-150

Two Main Types

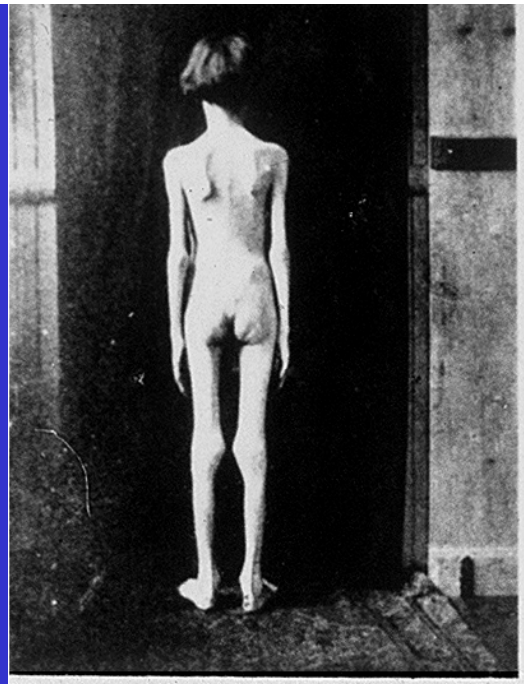
- Type 1
  - Autoimmune destruction of the β cells of the Islets of Langerhans in the pancreas. This leads to an absolute insulin deficiency. Insulin treatment is therefore mandatory
  - Previously known as IDDM or juvenile onset diabetes

Two Main Types

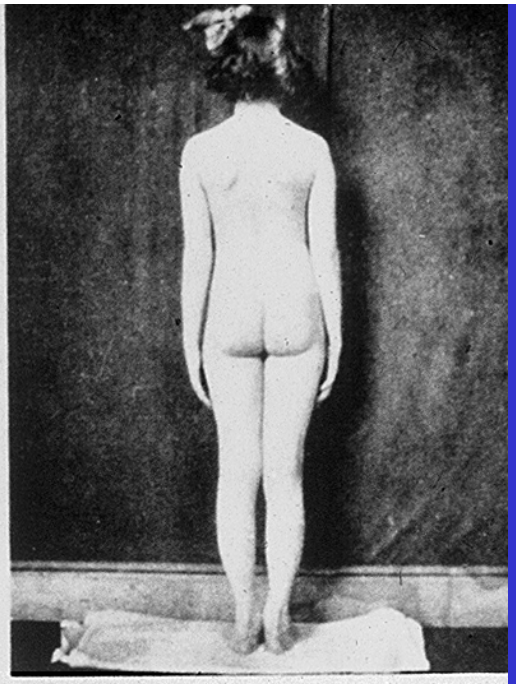
- Type 2
  - Impaired insulin action (insulin resistance) and eventually, impaired insulin secretion as well
  - Usually treated with oral medication initially, then may move onto insulin
  - Formerly known as NIDDM or maturity onset diabetes

Clinical Features

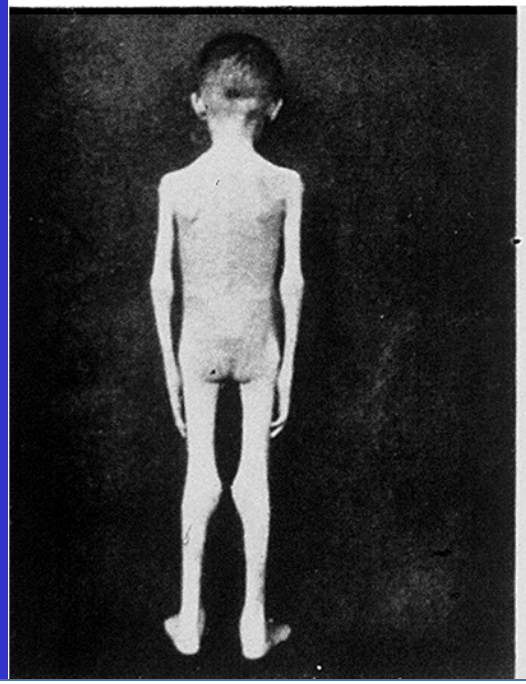
	Type 1	Type 2
Age at Onset (years)	< 40	> 40
Duration of Symptoms	Days or Weeks	Years
Body Weight	Normal or Low	Normal or High
Ketones	Yes	No
Insulin Mandatory?	Yes	No
Autoantibodies	Yes	No
Complications at Diagnosis	No	Up to 20%
Family History?	No	Yes
Other Autoimmune Diseases?	Yes	No
Percentage of cases	10%	90%

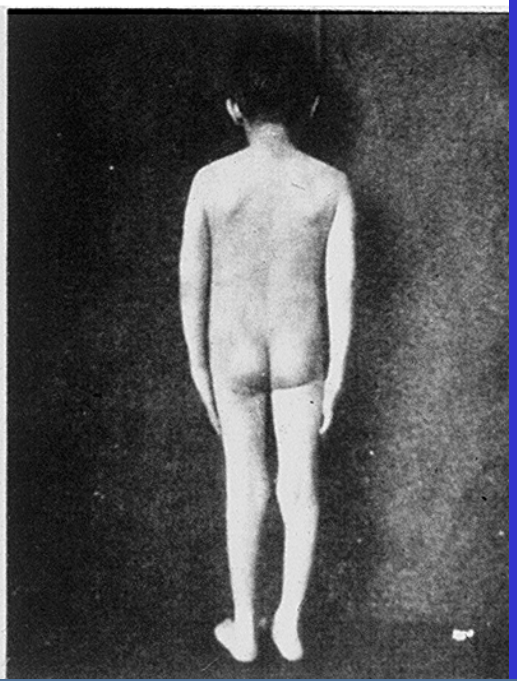


Case VI Before Insulin

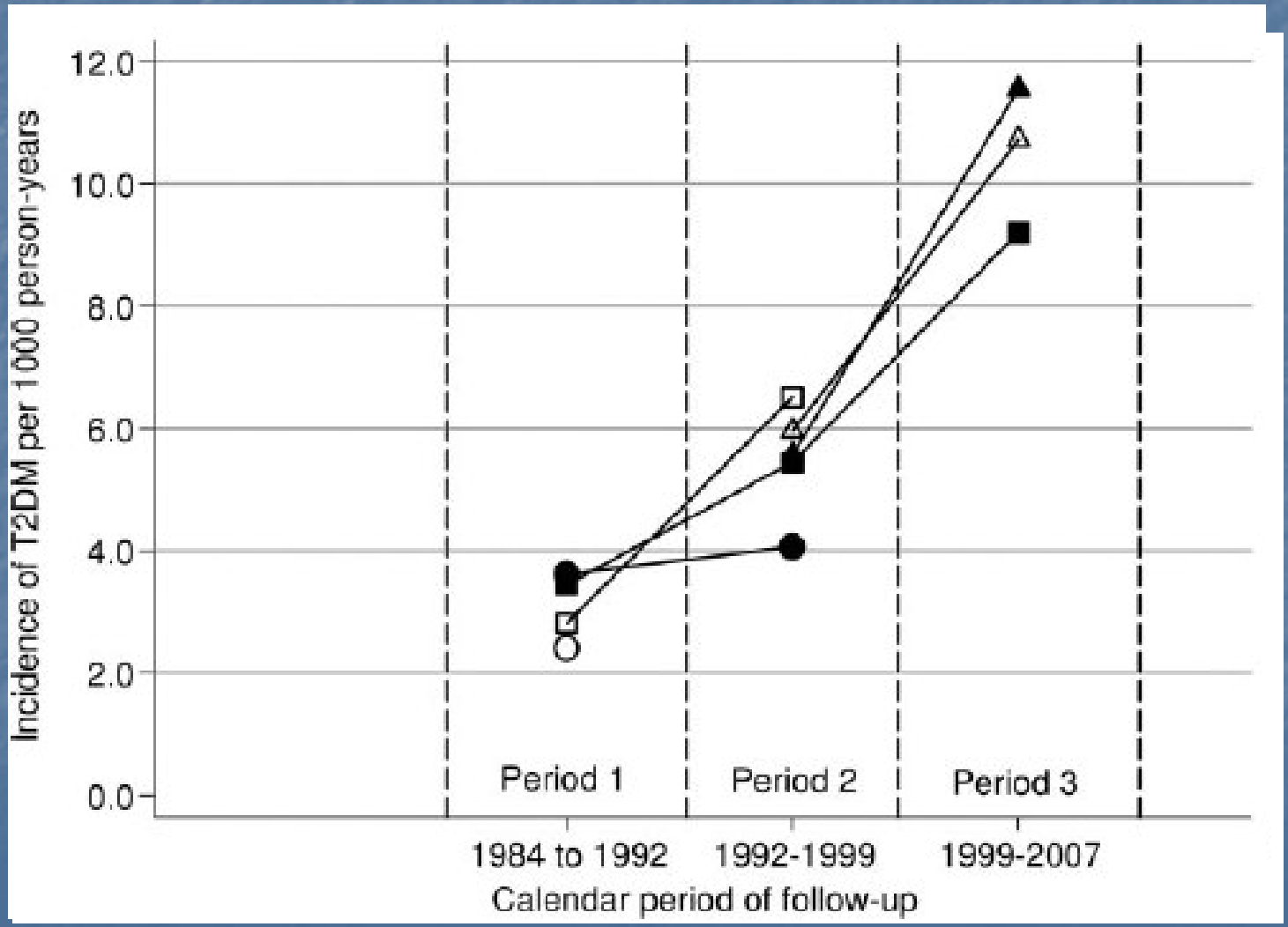


Case VI [redacted] After



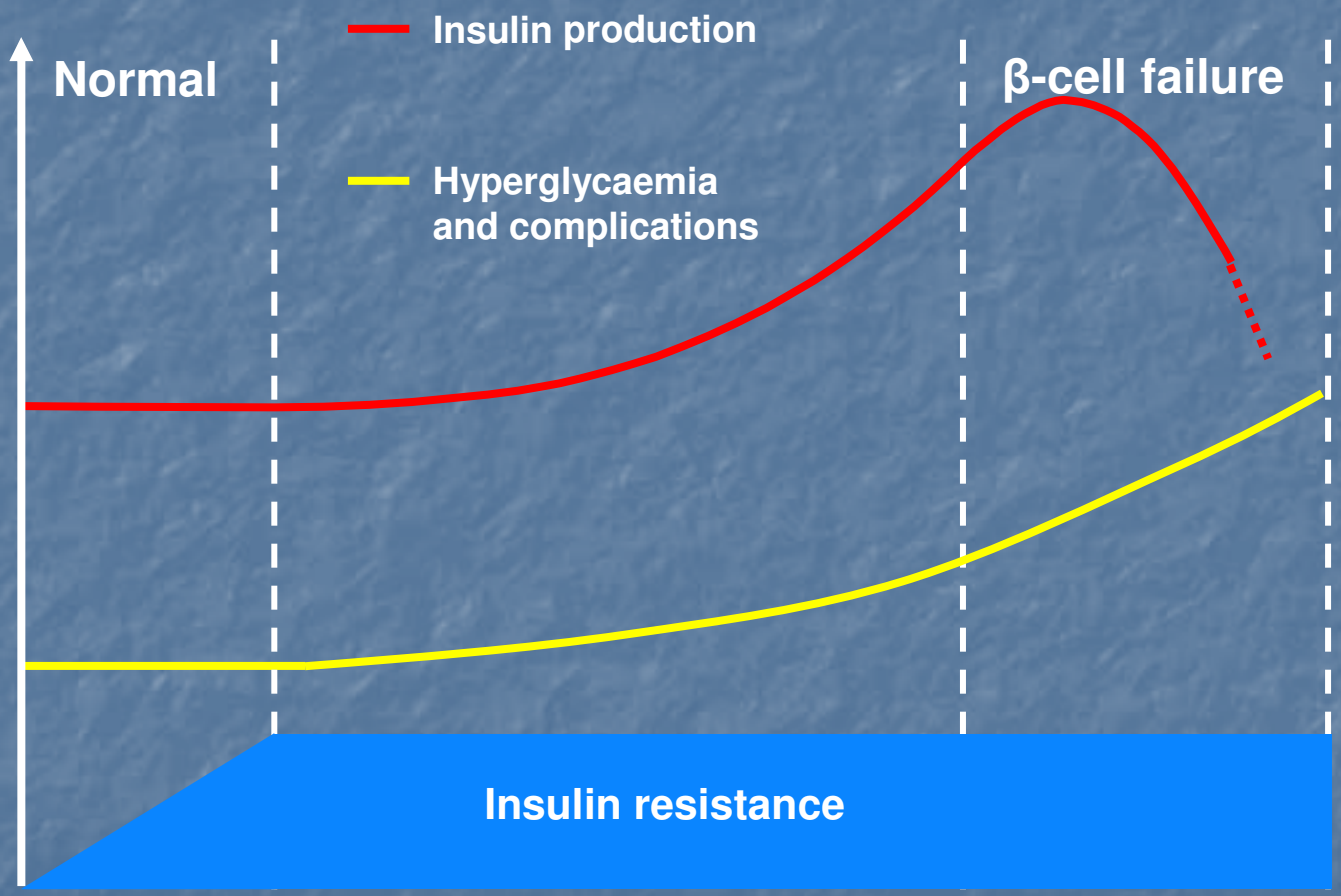


But is it *Really* Obesity?



Hardoon SL et al Diabetes Care 2010;33(7):1494-1496

Blood Glucose and Insulin Resistance



92% of people with Type 2 diabetes are insulin resistant

Epidemiology

- The 2008/9 National Diabetes Audit found the prevalence of diabetes to be 4.13% in England and Wales
- 90% of whom have type 2 diabetes
- Lifetime risk of developing diabetes is about 10%

The NHS Information Centre, National Diabetes Audit Executive Summary 2010

Some Statistics

- The incidence of diabetes has risen from 1.8 to 3.3 per 1000 person years between 1994 and 2003
- The prevalence is now 2.7 per 1000 person years
- Estimated at 4.67% of the population has either diagnosed or undiagnosed diabetes

Yorkshire and Humber Public Health Observatory March 2006

Some More Statistics

- Type 2 diabetes accounts for 92% of all cases in the UK
- The incidence of type 2 diabetes doubled between 1994 and 2000
- Diabetes reduces life expectancy by 15 years for type 1 and 5 or 7 years in type 2 (M/F)

Yorkshire and Humber Public Health Observatory March 2006

Some More Statistics

- Diabetes accounts for 5% of all NHS expenditure – in 2002 £1.3bn
- It accounts for 12% of all hospital costs
- Drugs used in the treatment of diabetes account for the second biggest cost

Yorkshire and Humber Public Health Observatory March 2006

Familial Risks – Type 1

- If neither parent – 1 in 250
- If mother has it – 1 in 50 – 100
- If father has it – 1 in 20
- If 1 sibling has it – 1 in 15 – 30
- If 1 sibling and 1 parent has it – 1 in 10

Familial Risks – Type 2

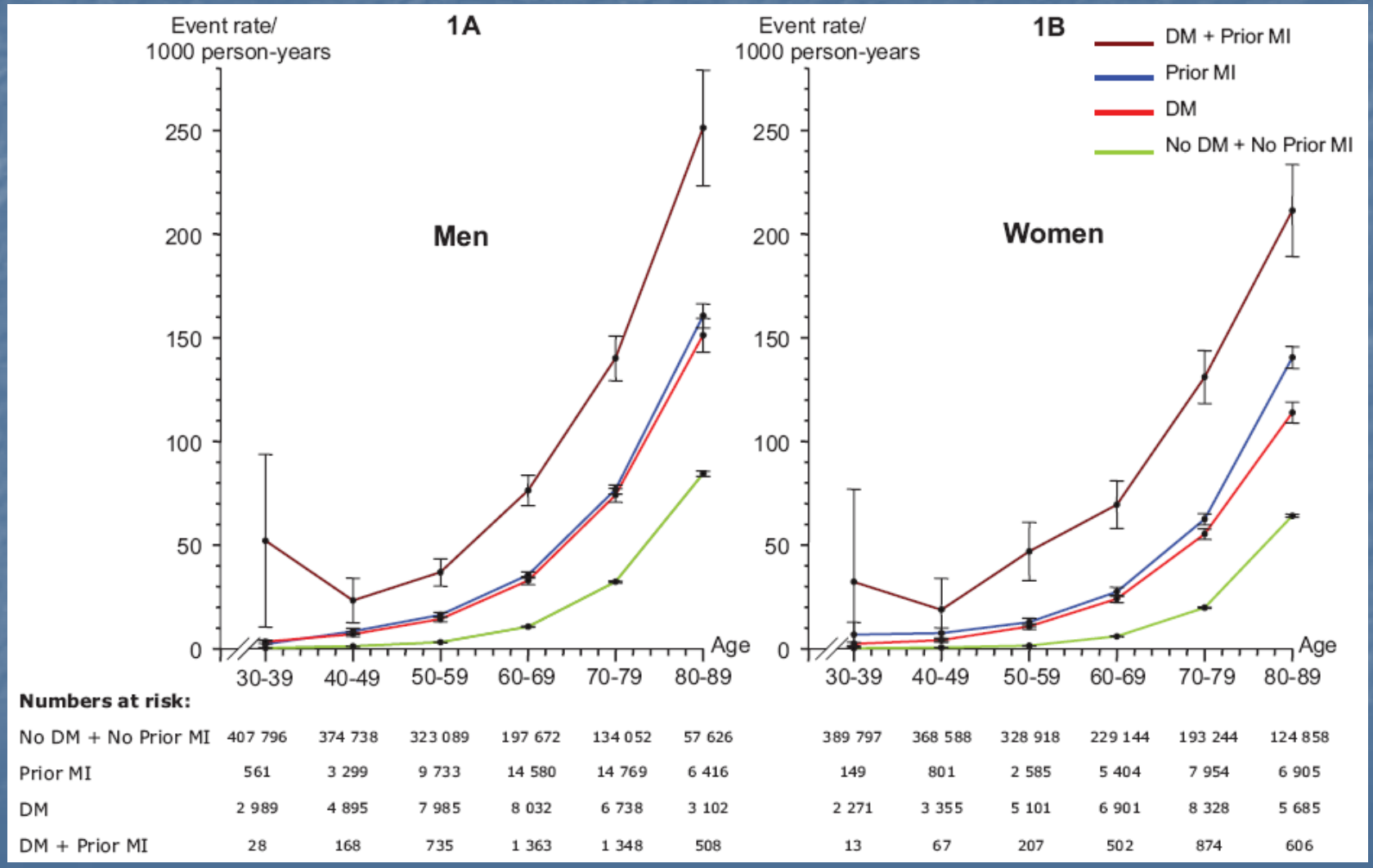
- If neither parent has type 2 diabetes = 10%
- If 1 parent has it = 30%
- If 1 sibling has it = 40%
- If both parents have it = 70%
- If an identical twin has it = 80-100%

Why is it Important?

- Poorly controlled diabetes leads to accelerated cardiovascular morbidity and mortality
- A combination of microvascular and macrovascular disease

Thom T et al Circulation 2006;113(6):e85-151

Data From 3.3M Danes

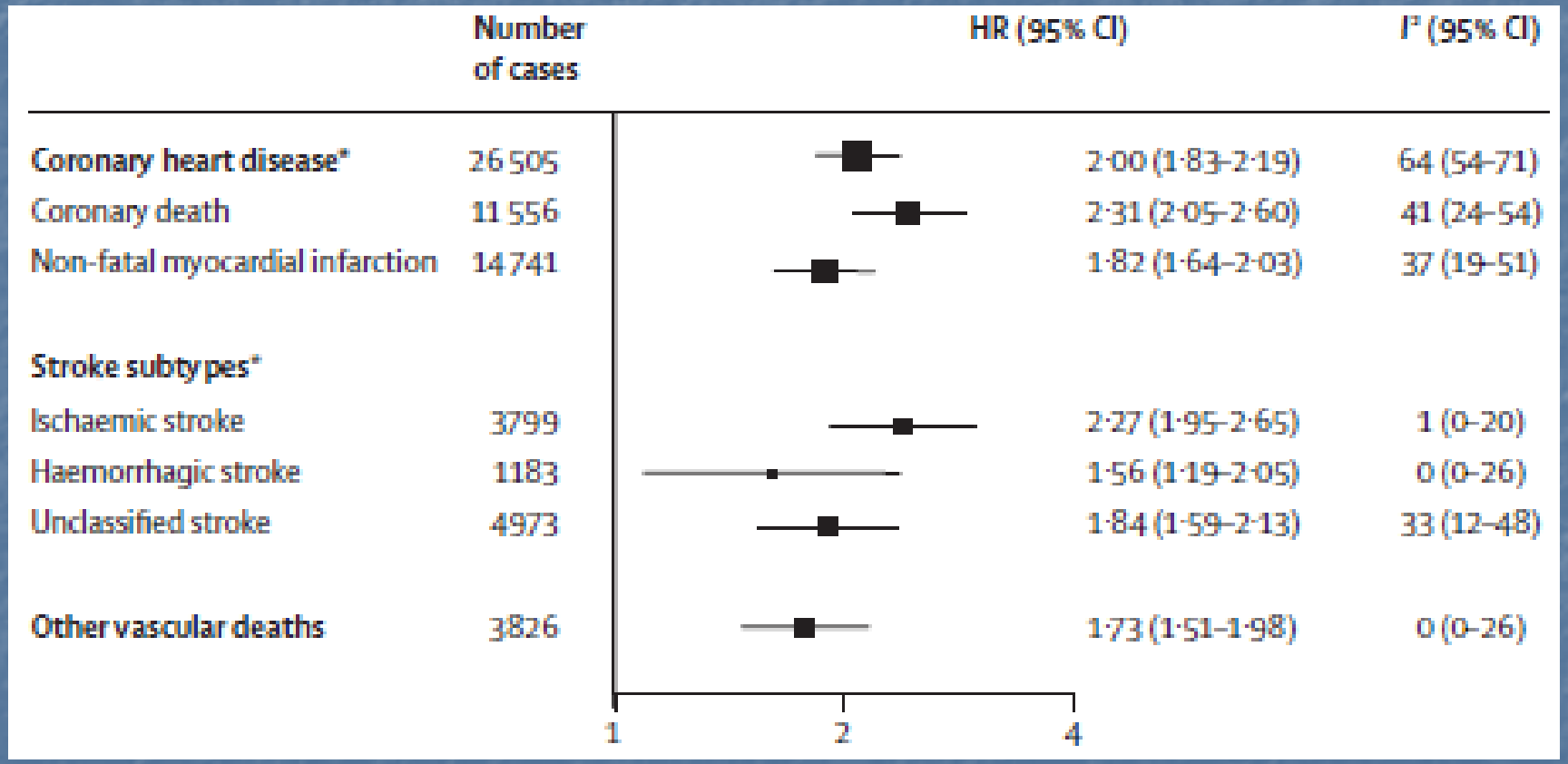


Numbers at risk:

No DM + No Prior MI	407 796	374 738	323 089	197 672	134 052	57 626	389 797	368 588	328 918	229 144	193 244	124 858
Prior MI	561	3 299	9 733	14 580	14 769	6 416	149	801	2 585	5 404	7 954	6 905
DM	2 989	4 895	7 985	8 032	6 738	3 102	2 271	3 355	5 101	6 901	8 328	5 685
DM + Prior MI	28	168	735	1 363	1 348	508	13	67	207	502	874	606

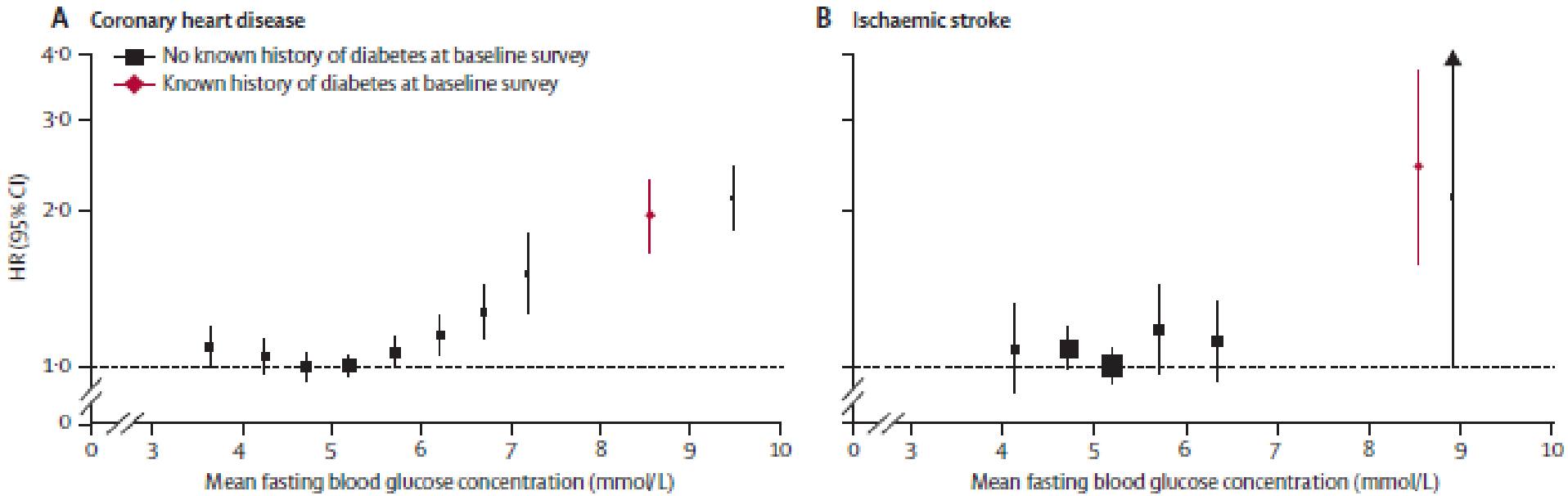
Schramm TK et al Circulation 2008;117:1945-1954

Data from 700,000 People



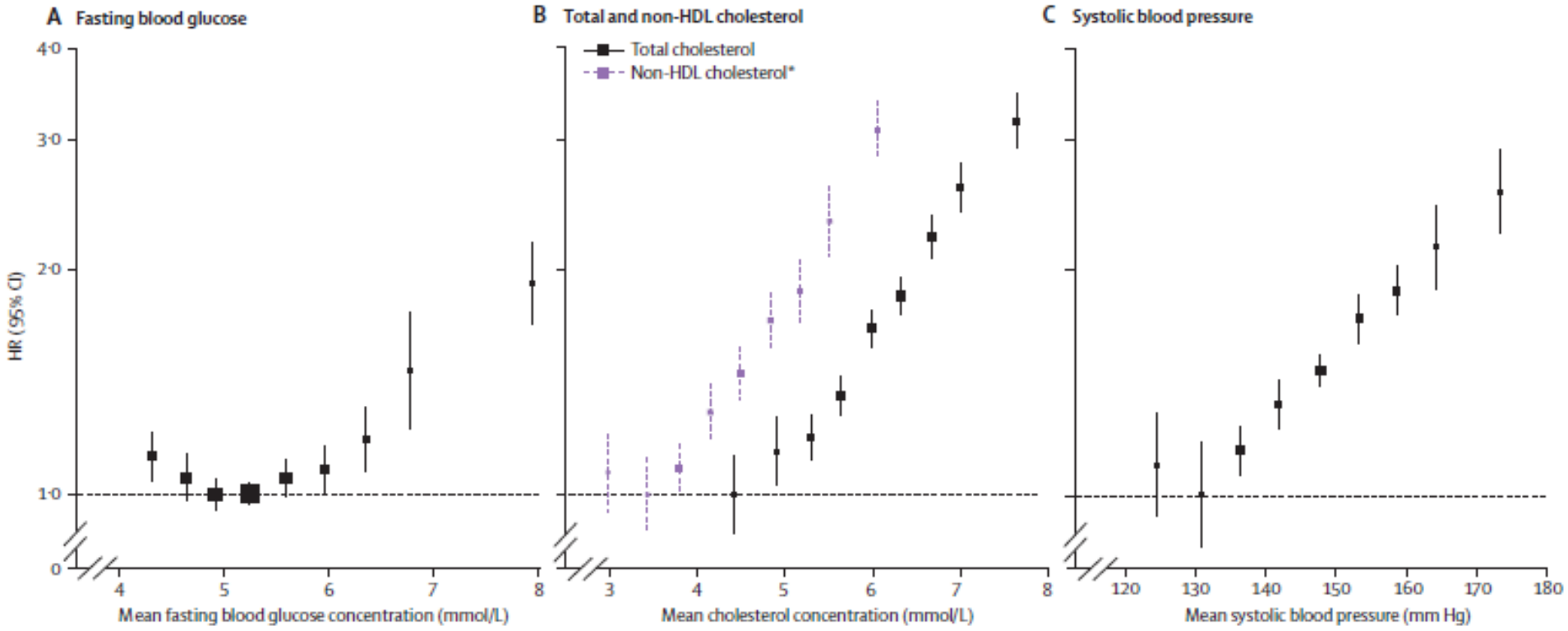
Emerging Risk Factors Collaboration Lancet 2010;375(9733):2215-2222

Data from 700,000 People



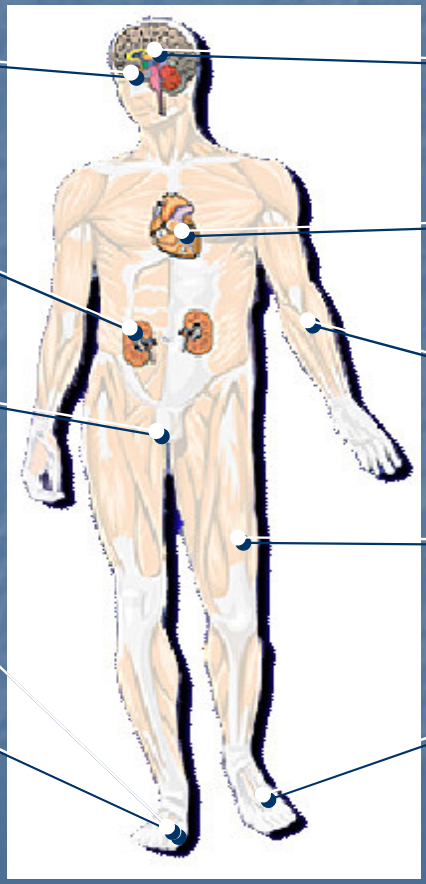
Emerging Risk Factors Collaboration Lancet 2010;375(9733):2215-2222

Risk of Developing CHD



Emerging Risk Factors Collaboration Lancet 2010;375(9733):2215-2222

Vascular Complications Of Type 2 Diabetes At The Time Of Diagnosis



Retinopathy[1]	39%	7%	Cerebrovascular disease[3]
Nephropathy[2]	18%	18%	Abnormal ECG[1]
Erectile dysfunction[1]	20%	35%	Hypertension[1]
Ischaemic skin changes (foot)[1]	6%	4.5%	Intermittent claudication[3]
Abnormal vibration threshold (foot)[1]	7%	13%	Absent foot pulses[1]

1. UKPDS 33 Lancet 1998352(9193):837-853. 2. The Hypertension in Diabetes Study Group. *J Hypertension* 1993; **11**: 30–17. 3. Wingard DL *et al. Diabetes Care* 1993; **16**: 1022–5.

Non-Insulin Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
- Thiazolidindiones
- GLP – 1 analogues
- DPP IV inhibitors
- (SGLT 2 inhibitors)

α Glucosidase Inhibitors

- There is only 1 – acarbose
- Intestinal disaccharidase inhibitor
- Taken one with each meal
- If they don't eat, no need to take the tablet

Metaglinides

- There are 2 – repaglinide and nateglinide
- Work by binding to the sulphonylurea receptor and 'squeezing' the β cell to release insulin
- They stimulate first-phase insulin release in a glucose-sensitive manner

Metformin

Derived from the plant known as Goat's Rue, French Lilac, Italian Fitch or Professor-weed (*Galega officinalis*)

Metformin

- First choice oral hypoglycaemic agent for people with type 2 diabetes, regardless of BMI
- Works by decreasing hepatic gluconeogenesis, decreasing gut glucose uptake and increasing peripheral insulin sensitivity
- Metformin does not (or very rarely) give people hypos, because it works predominantly by preventing blood glucose levels rising rather than by lowering glucose levels

Sulphonylureas

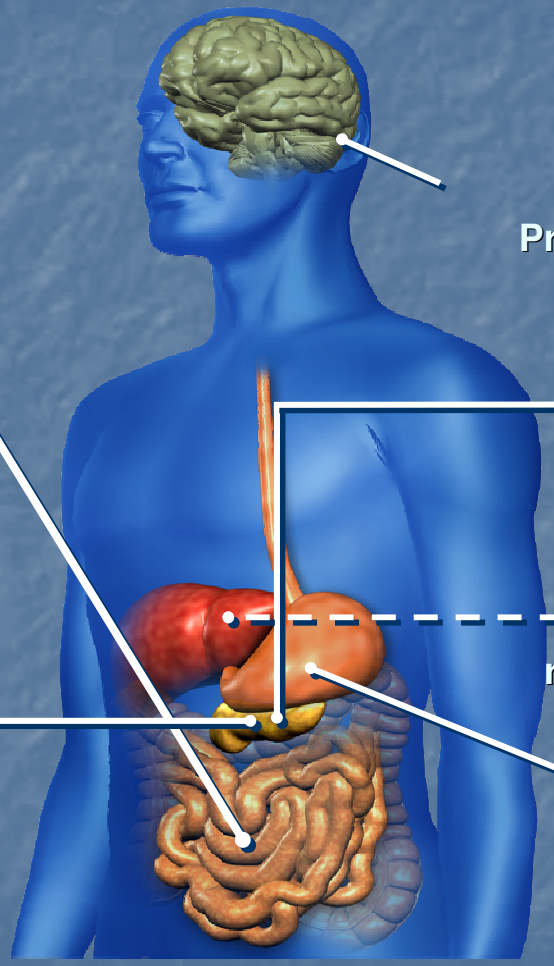
- Have been around since the 1950's
- Act by binding to the SU receptor causing an influx of Ca^{2+} and an exocytosis of insulin containing vesicles
- Use limited to individuals with a BMI < 25 or in whom metformin is contraindicated

Thiazolidinediones

- Work by increasing peripheral insulin sensitivity at a nuclear level on peroxisome proliferator-activated receptor γ (PPAR γ)

11th September 2010

GLP-1 and DPP-IV



GLP-1 secreted upon the ingestion of food

5.Brain:
Promotes satiety and reduces appetite

2.α-cell:
Suppresses postprandial glucagon secretion

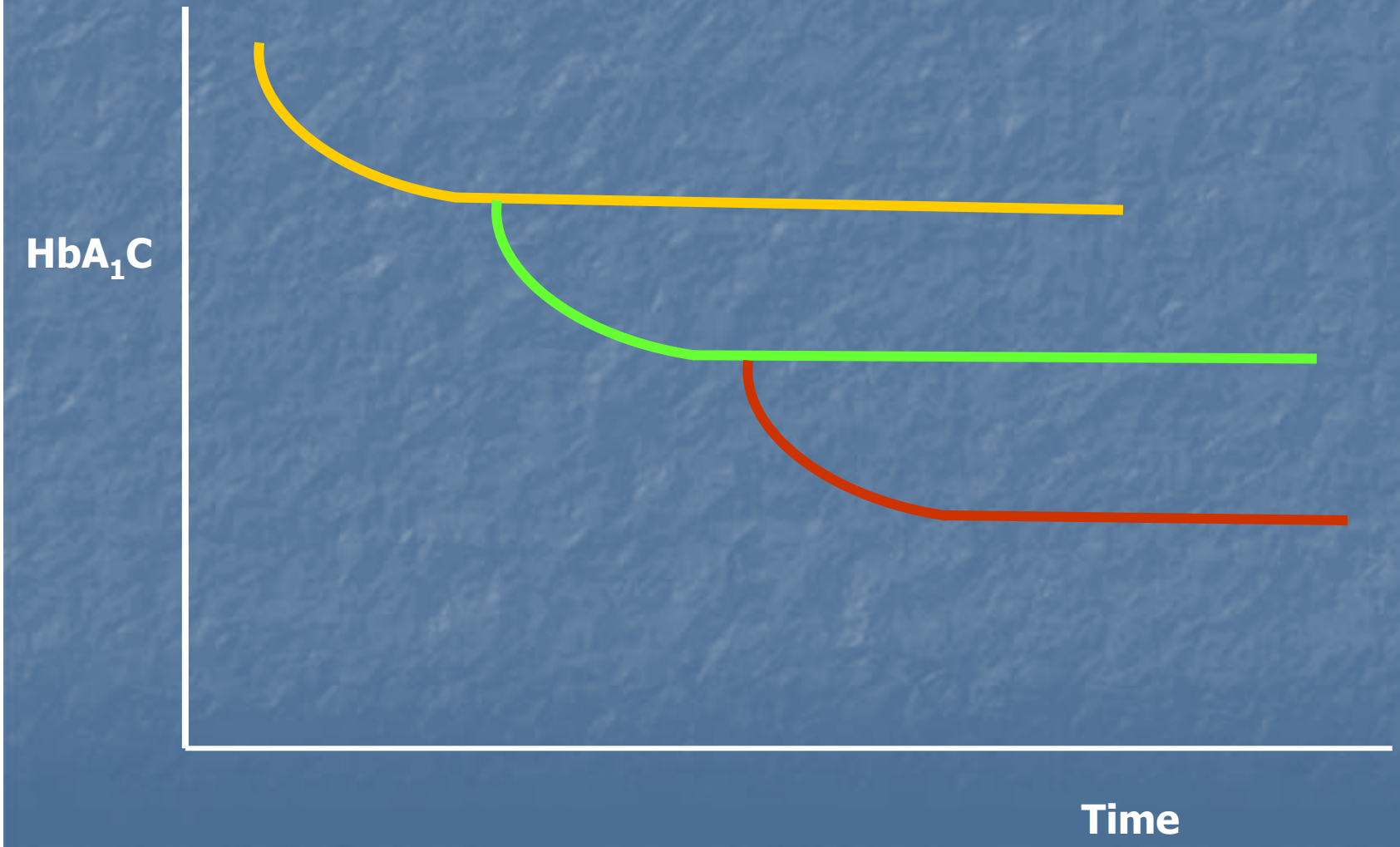
3.Liver:
reduces hepatic glucose output

1.β-cell:
Enhances glucose-dependent insulin secretion in the pancreas

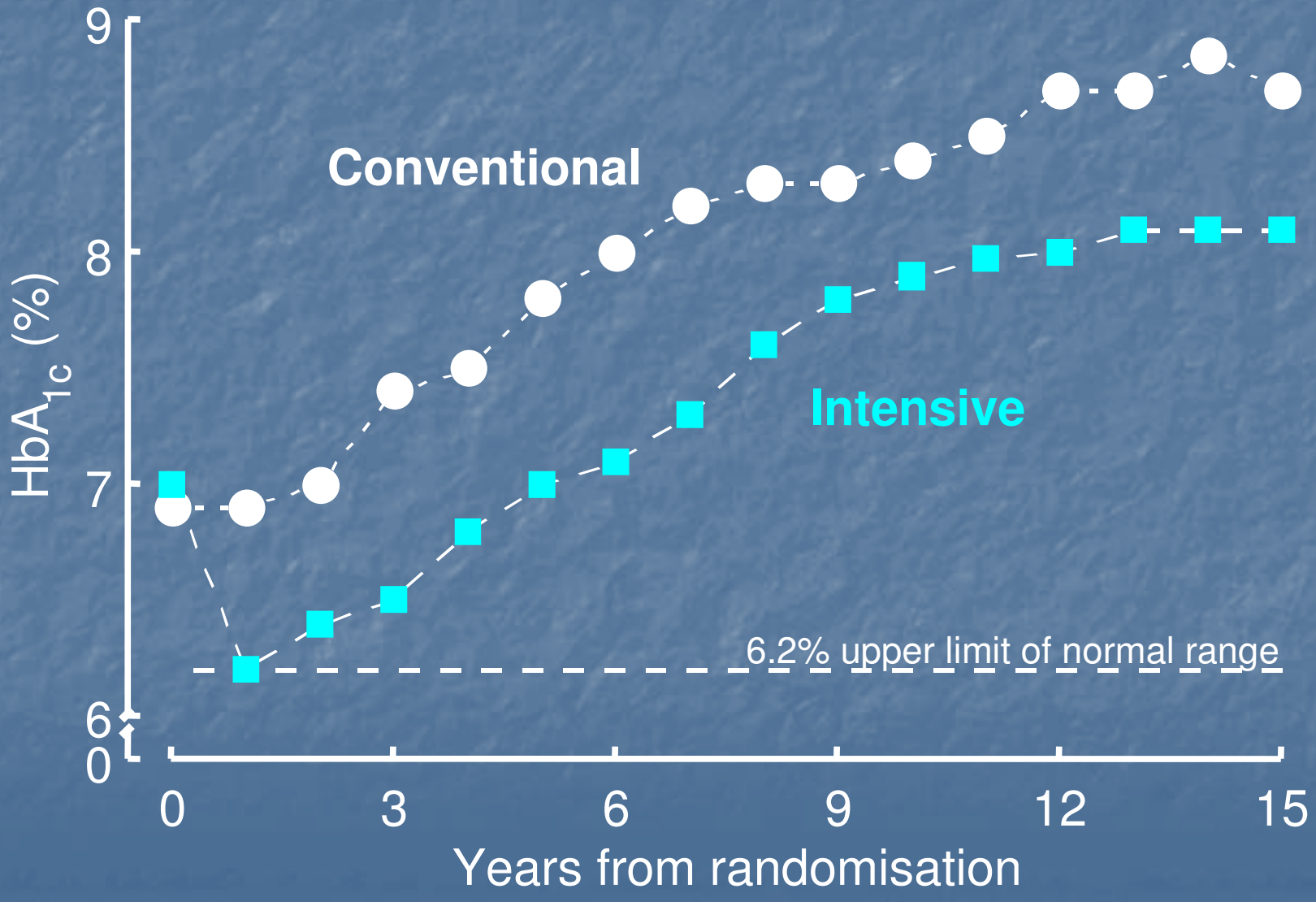
4.Stomach:
slows the rate of gastric emptying

Nauck MA et al. *Diabetologia* 1993;36:741–744; Larsson H et al. *Acta Physiol Scand* 1997;160:413–422; Nauck MA et al. *Diabetologia* 1996;39:1546–1553; Flint A et al. *J Clin Invest* 1998;101:515–520; Zander et al. *Lancet* 2002;359:824–830.

Their Effects Are Additive



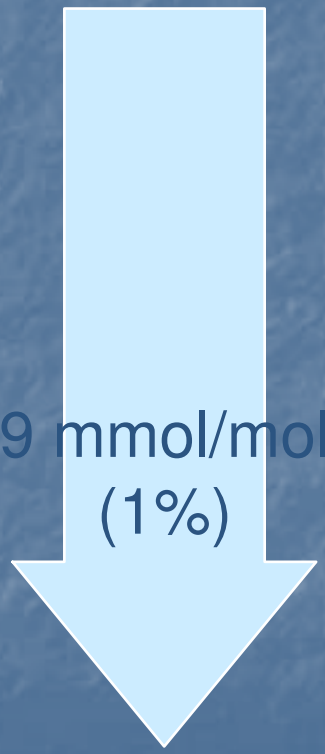
UKPDS HbA_{1c} Median Values



The Goalposts Are Changing

- HbA_1C targets are coming down
- The tighter the control, the likelihood of developing complications reduces

Lessons from UKPDS: Better Control Means Fewer Complications



	REDUCED RISK*
Deaths from diabetes	–21%
Heart attacks	–14%
Microvascular complications	–37%
Peripheral vascular disorders	–43%

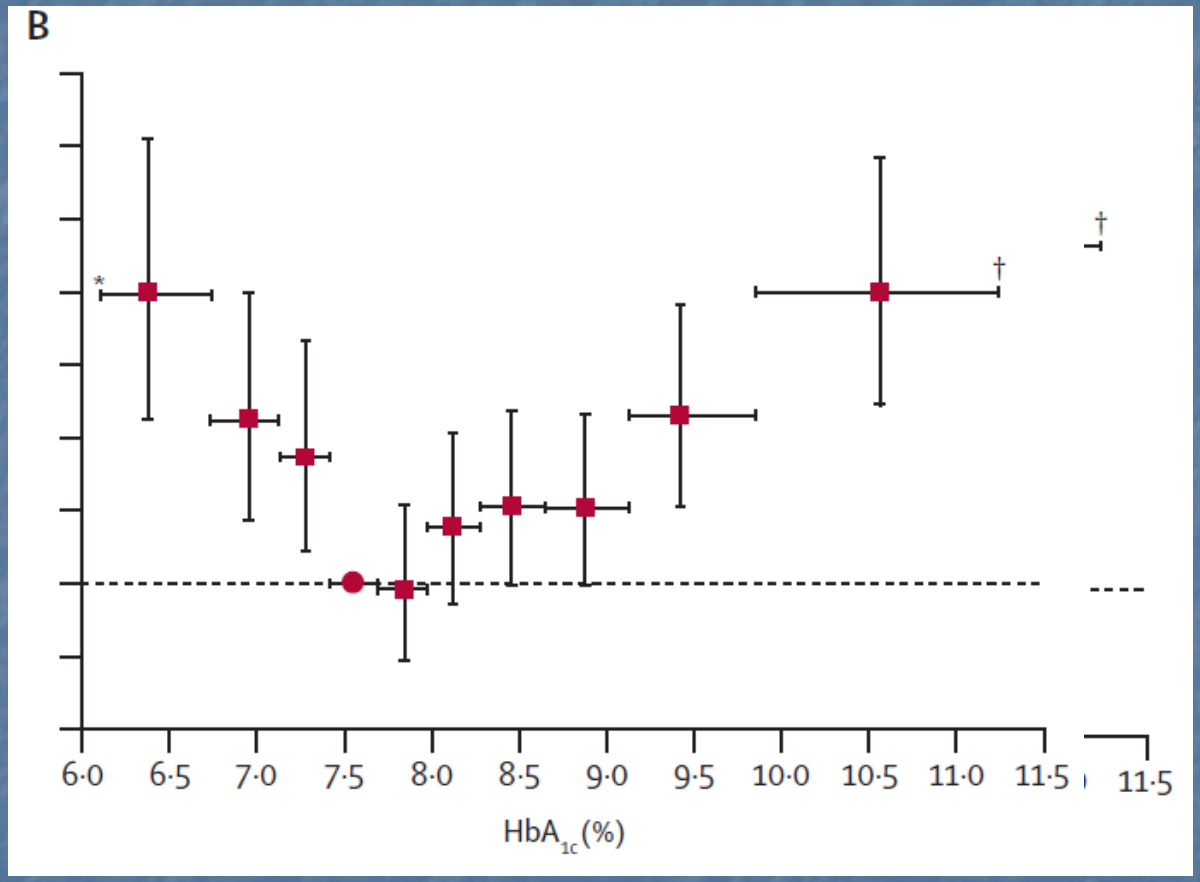
UKPDS 35. BMJ 2000;321:405–12

*p<0.0001

Tighter Control

- This means that oral agents alone may not be sufficient and that insulin needs to be added

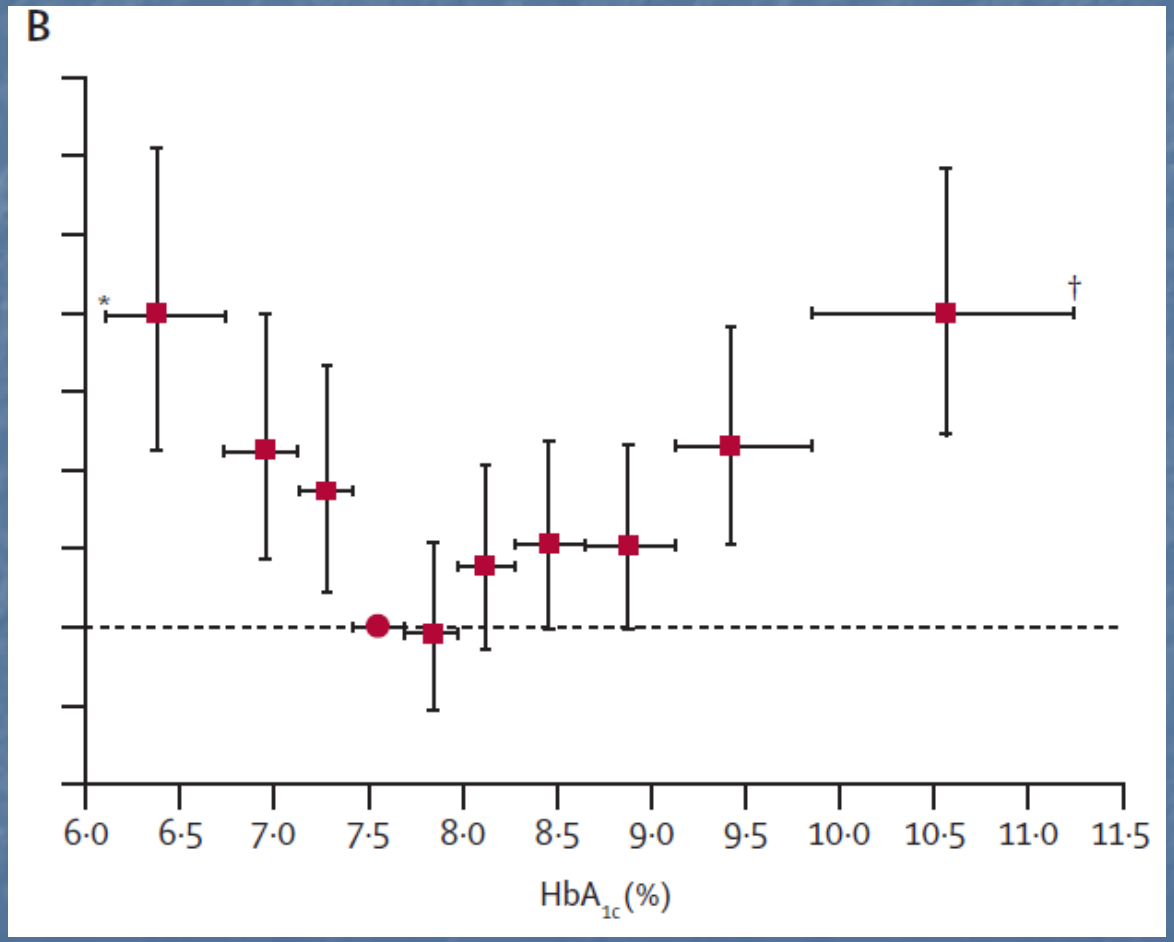
But Too Tight is Bad – Tablets



Hazard ratio for all cause mortality by HbA1c deciles in people on oral medication

Currie CJ et al Lancet 2010;375(9713):481-489

But Too Tight is Bad – Insulin



Hazard ratio for all cause mortality by HbA1c deciles in people on insulin

Currie CJ et al Lancet 2010;375(9713):481-489

The Planet is Changing

How do old and new relate?
A guide to the new values expressed as mmol/mol is:

DCCT – HbA_{1c} (%)	IFCC – HbA_{1c} (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75

IFCC (mmol/mol) = (current value (%) * 10.93) - 23.50 (reported to a whole number)

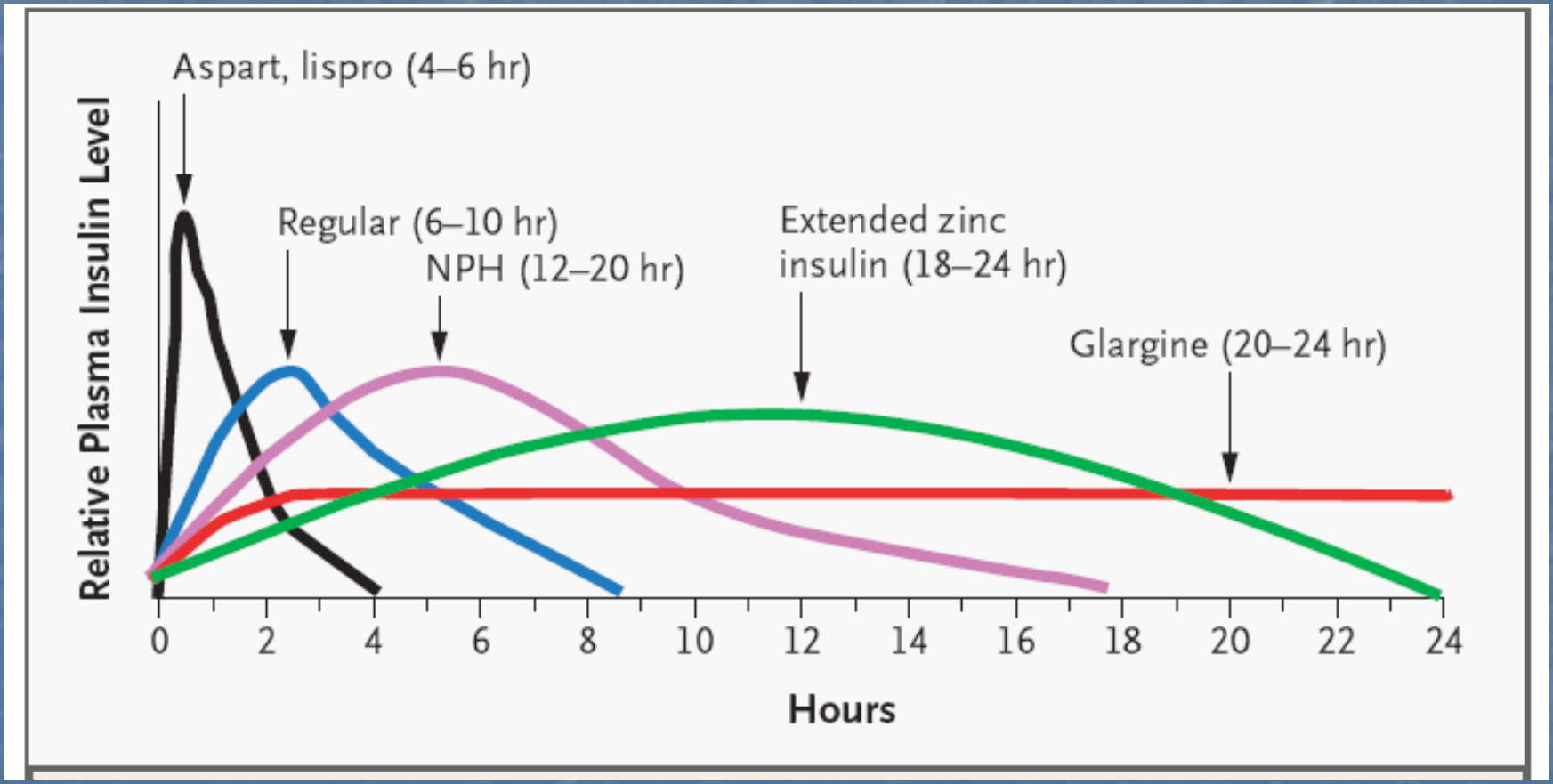
Insulin

- Should be started when the HbA_1C is ≥ 7.5% (59 mmol/mol) on maximal oral hypoglycaemics
- Or when there are severe symptoms of hyperglycaemia

Insulins

- Soluble (short acting)
- NPH (intermediate)
- Once daily
- Mixtures
- Insulin analogues – ultra short, long and mixtures

Insulin Durations



Hirsch NEJM 2005;352 (2):174-183

Remember

- Being on insulin is not ‘failure’
- It is another weapon in our armamentarium in preventing the potential ravages of diabetes

Things That Make the Most Difference

Smoking	OR 2.87
Raised ApoB/ApoA1 ratio	OR 3.25
History of hypertension	OR 1.91
Diabetes	OR 2.37
Abdominal obesity	OR 1.12
Psychosocial factors	OR 2.67
Daily fruit and veg intake	OR 0.7
Regular alcohol consumption	OR 0.9
Regular physical activity	OR 0.86

Yusuf et al Lancet 2004 364:937-952

In Summary

- There are a lot of medications to try first
- Weight loss is a cornerstone to delaying insulin
- To ensure the best outcomes for your patients with diabetes
  - Be Aggressive!
  - Treat Early!

Thank you for your attention