Cardiometabolic syndrome

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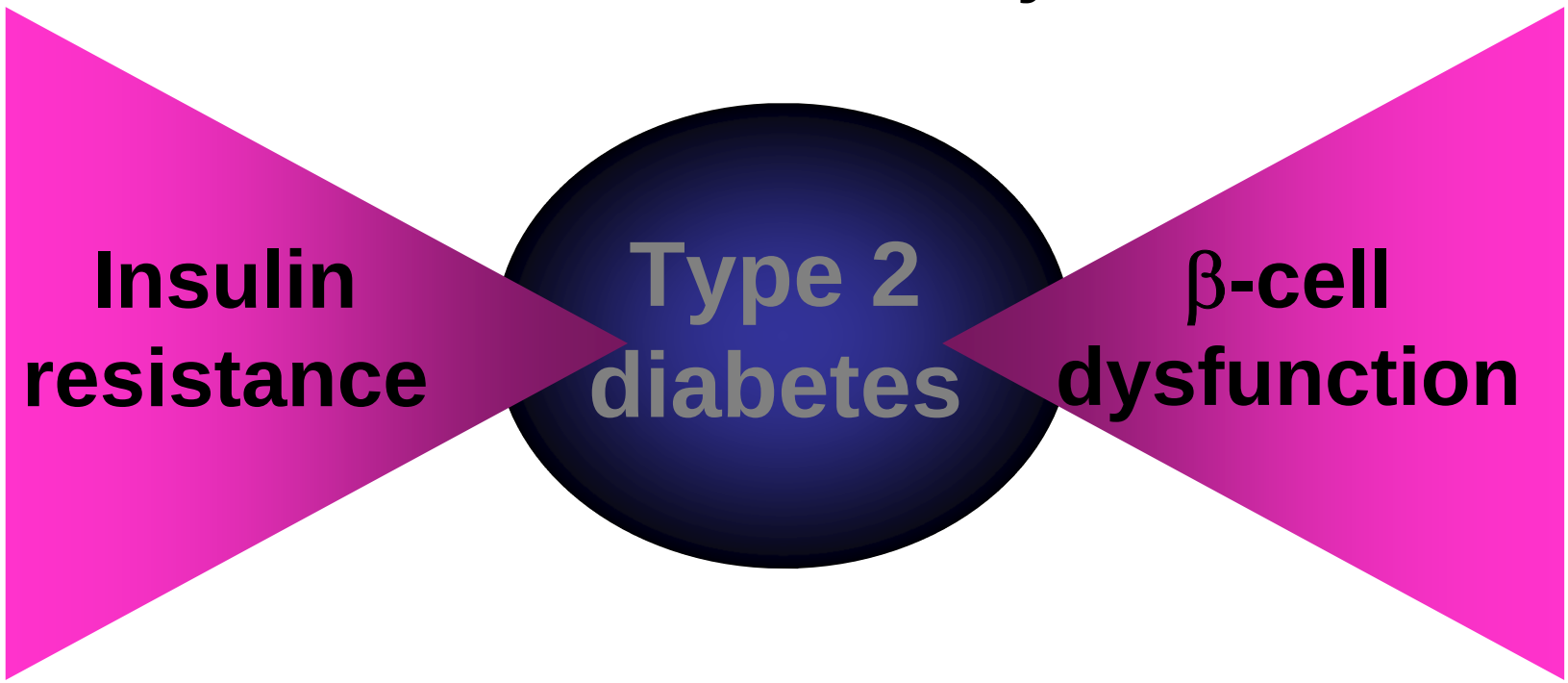
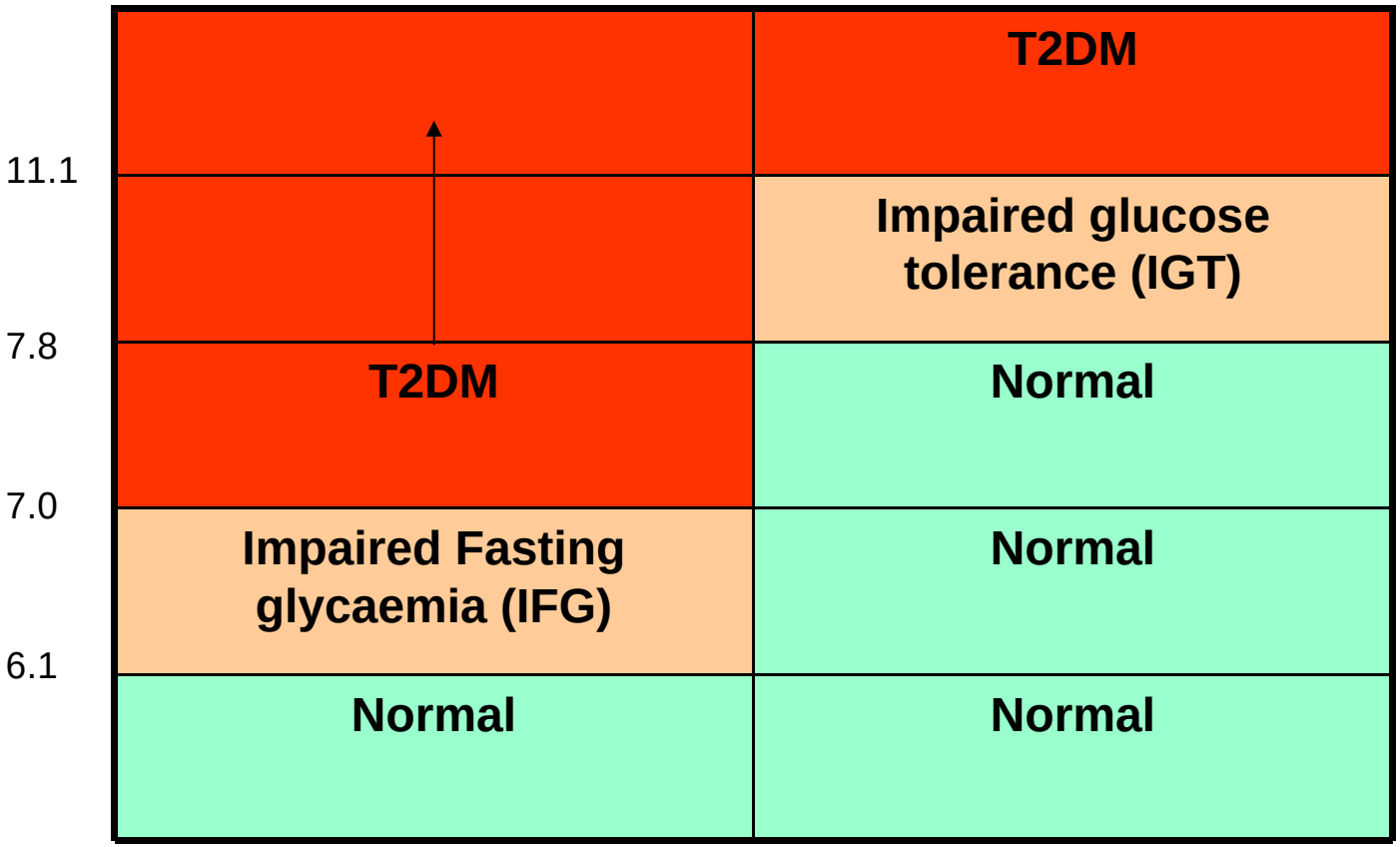
What is Type 2 diabetes?

A progressive metabolic disorder characterised by:



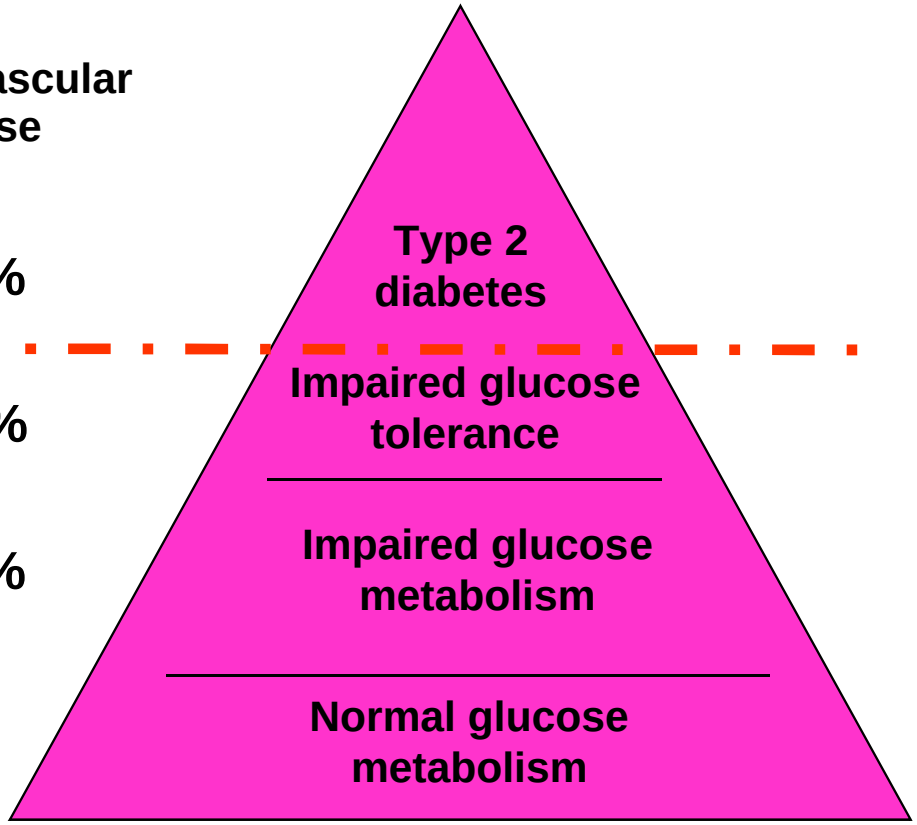
Adapted from: Beck-Nielson H *et al*. *J Clin Invest* 1994;**94**:1714–1721 and Saltiel AR, Olefsky JM. *Diabetes* 1996;**45**:1661–1669

Type 2 diabetes Diagnostic criteria



Insulin resistance and insulin hypersecretion precede Type 2 diabetes

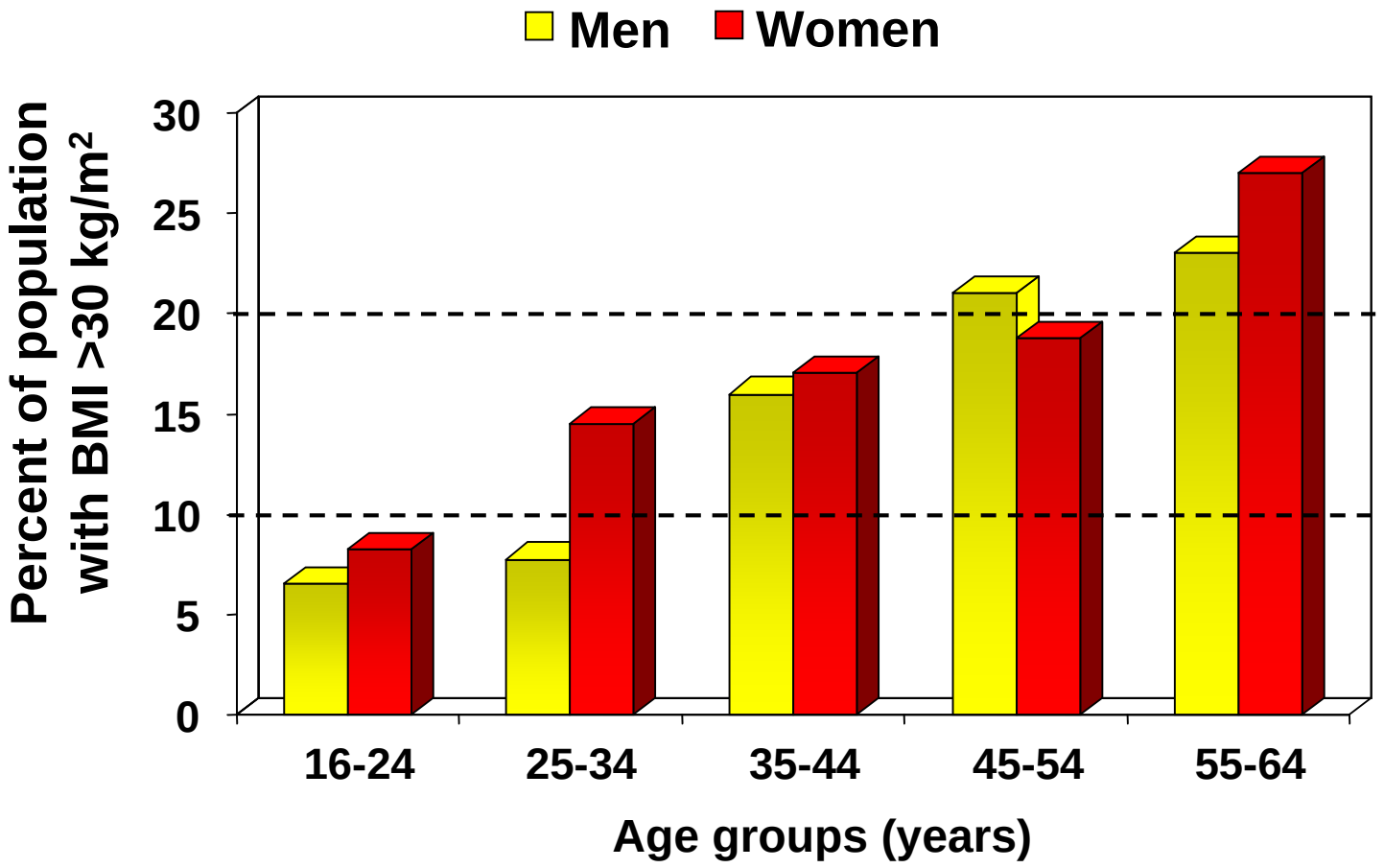
Insulin sensitivity	Insulin secretion	Macrovascular disease
30%	50%	50%
50%	70–100%	40%
70%	150%	10%
100%	100%	



Adapted from: Beck-Nielsen H, Groop LC. *J Clin Invest* 1994;**94**:1714–1721

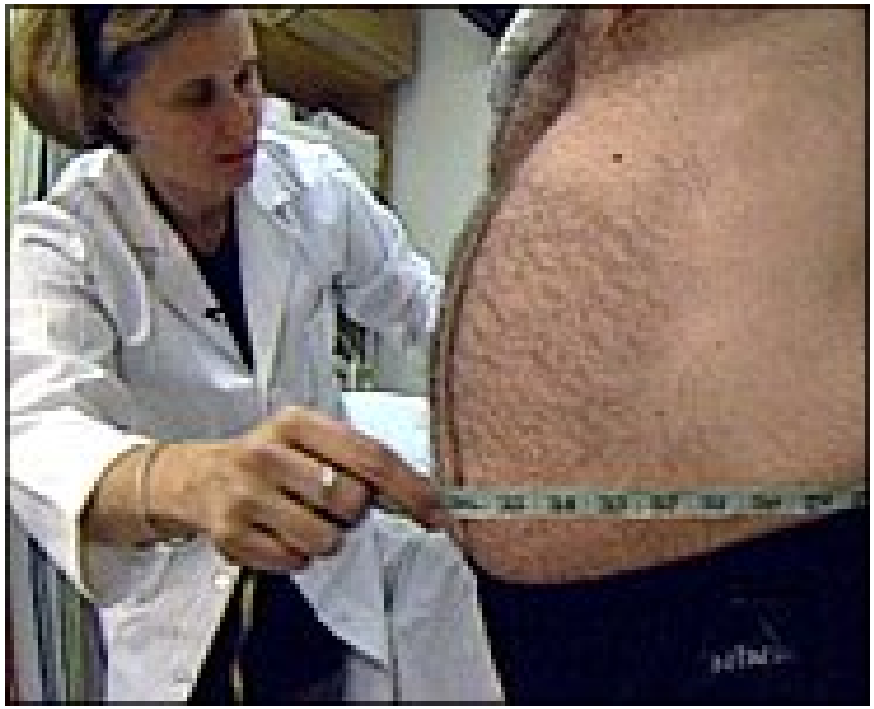
Why does Type 2 diabetes if not effectively managed, lead to such macrovsacular disease?

Obesity and Increasing Age in UK



Department of Health. Health Survey for England. Adult Data 1993-1998.

Waist circumference



Type 2 Diabetes and visceral fat or …

The perils of the pot belly!

… but what's the connection with cardiovascular risk?

Visceral Fat – metabolically active!!

FFA's
TNF *a*
IL - 6
PAI – 1
Leptin
RAS
Adiponectin

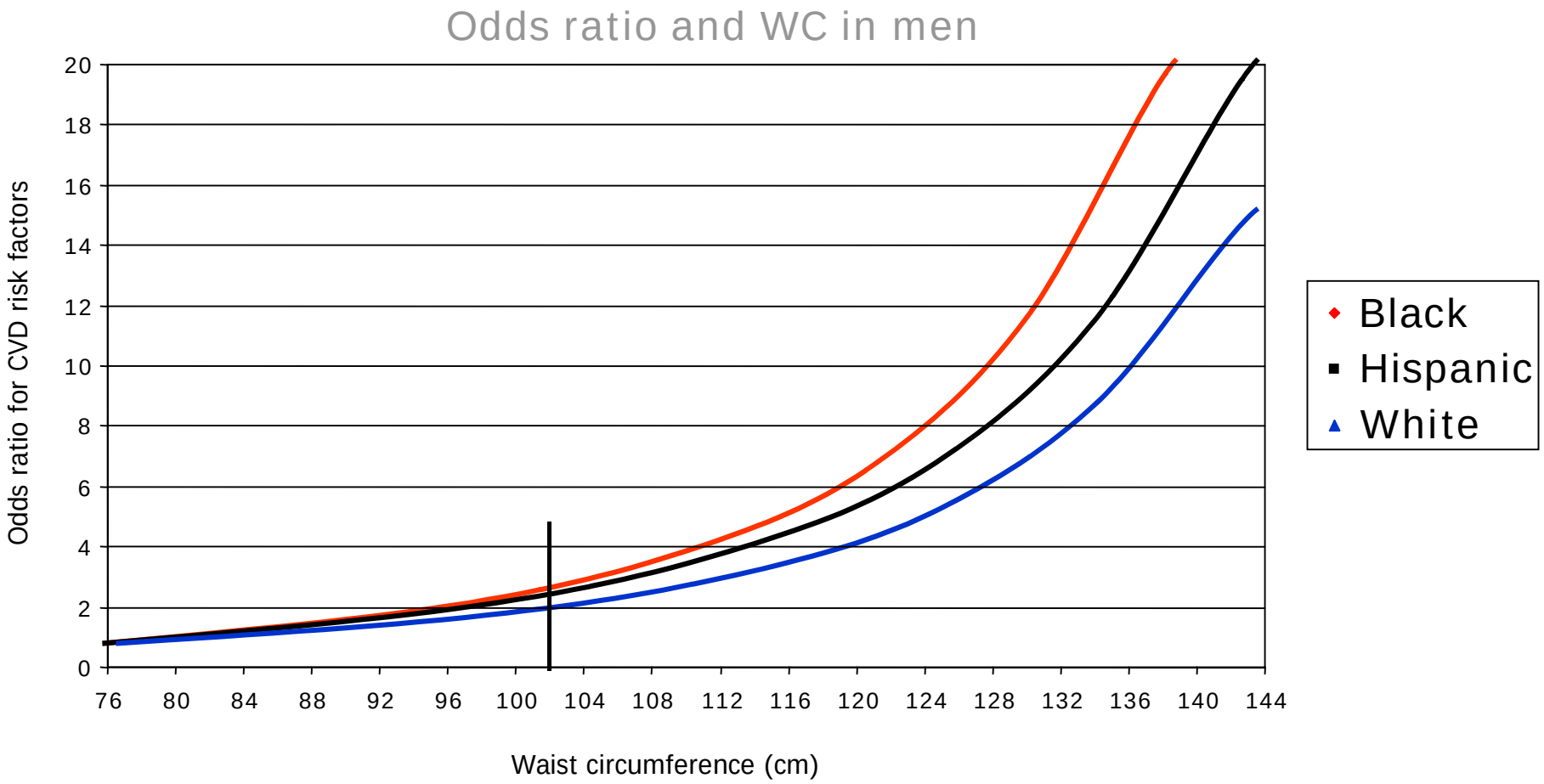
Dyslipidaemia
Insulin signalling
Endothelial dysfunction
Pro-inflammatory (CRP's)
Pro-thrombosis
SNS (>BP)
Angiotensin II (>BP)
Insulin sensitising
Anti-inflammatory
Anti-atheromatic

Type 2 Diabetes and visceral fat

Visceral fat becomes metabolically active in obesity, leading to increased FFA's and increased production of a range of inflammatory agents, adipokines and cytokines.

Leading to insulin resistance, hyperglycaemia, increased cardiovascular risk and leading to the term 'cardiometabolic state'

Race-ethnicity specific waist circumference cut offs for identifying CVD risk factors



Am J Clin Nutrition 2005; 81: 409-15

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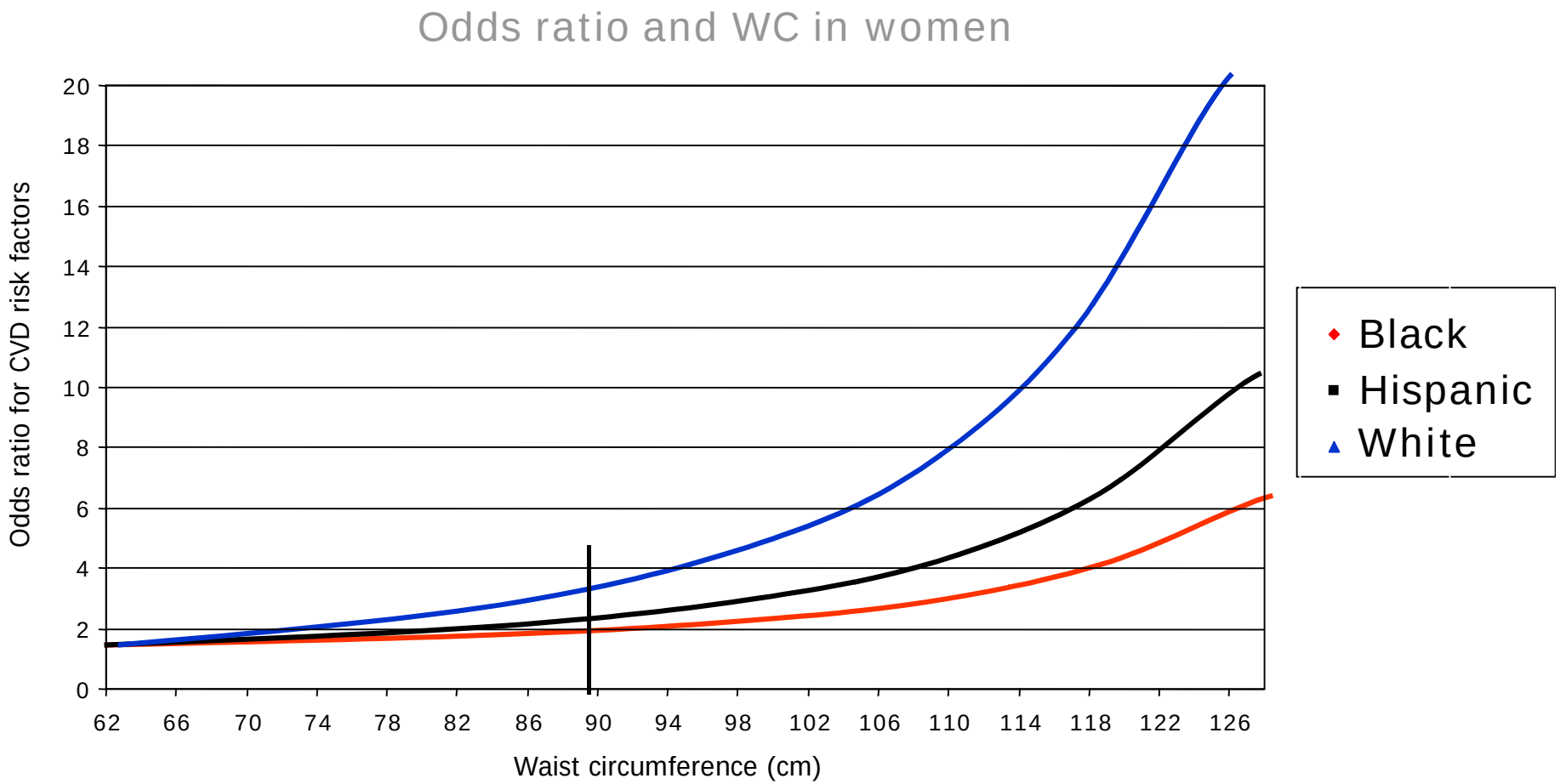
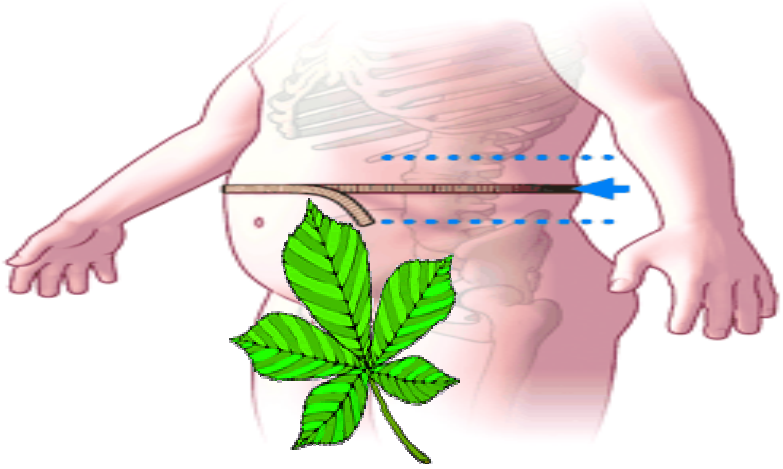


Am J Clin Nutrition 2005; 81: 409-15

Waist Circumference



Interheart Study: Waist circumference a much better predictor of CV risk than BMI.

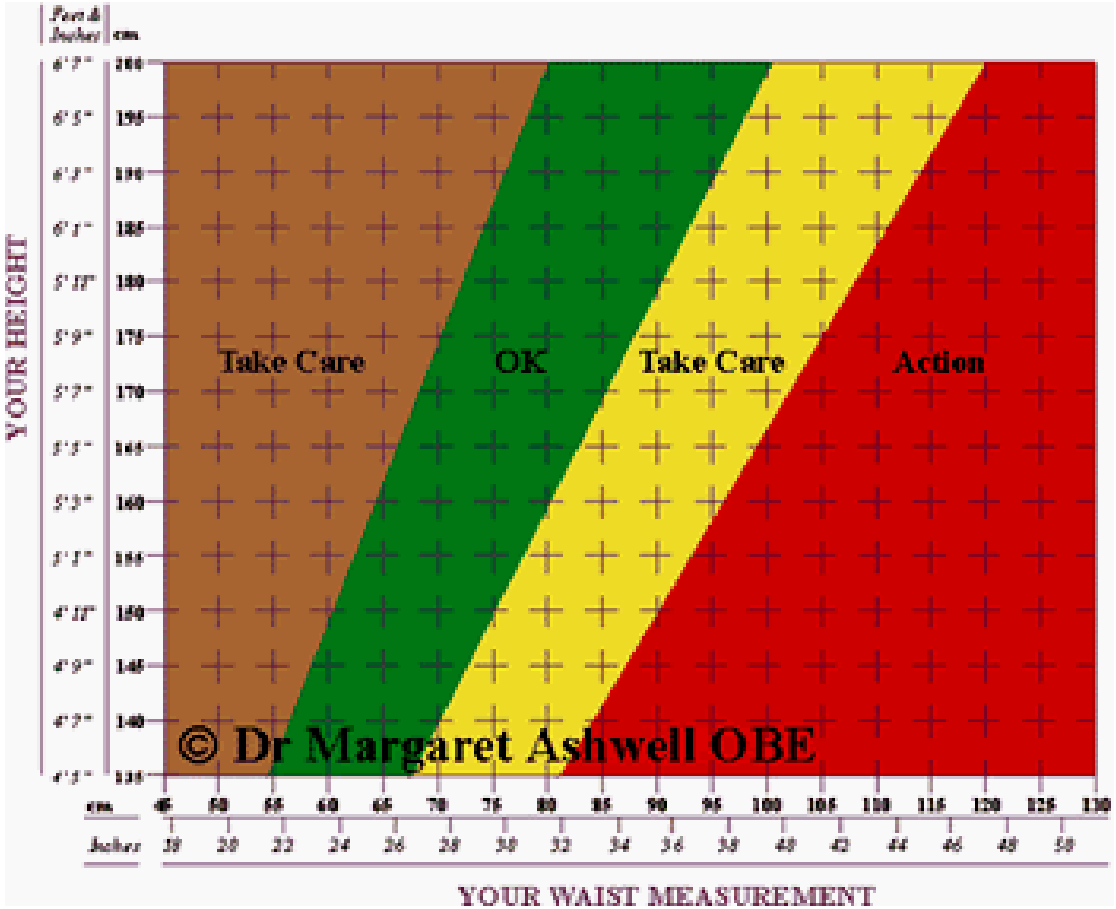
Yusuf S et al (2004) Lancet 364:912-914

Waist circumference ‘targets’

	Increased risk	Substantially increased risk
Men	>= 94 cm	>= 102 cm
Asian men *		>= 90 cm
Women	>= 80 cm	>= 88 cm
Asian women *		>= 80 cm

** Cut off values of risk for individuals of Asian origin have been set at a lower waist measurement (WHO available at www.diabetes.com.au/pdf)*

Waist measurement risk



What's in a name?

Reaven's syndrome; Syndrome X; Cardiometabolic syndrome; Insulin Resistance Syndrome.

Metabolic syndrome (IDF definition)

Central obesity plus and 2 of the following:	
Trigs	≥ 1.7 mmols/L
HDL	< 1.03 males < 1.29 females Or on lipid lowering agents
BP	≥ 130 / 85 Or present / previous treatment of hypertension
FPG	>5.6 mmols/l Or previously treated T2DM FPG > 5.6 mmols/L OGTT strongly recommended

San Antonio Heart Study

(Metabolic Syndrome as Predictor of Type 2 Diabetes)

- 2,569 patient epidemiological study looking at DM diagnostic criteria on prediction of DM and prediction of CV risk.
- Participants who did not have T2DM at entry to study but went on to develop T2DM by end of 8 years follow up had:
- Substantially higher total cholesterol LDL and trigs and lower HDL
- Increased BMI
- Hypertension …
- Than those who did not go on to develop T2DM.
- This led to the 'ticking click' hypothesis for CHD

Vasudevan A R, & Ballentyne C (2005) Clinical Cornerstone 7 [2/3] 7-16

Botnia Study

(Metabolic consequences of a family history of NIDDM)

- 3,606 first degree relatives of T2DM patients in Western Finland
- Follow-up period 7 years
- Cardiovascular mortality was 12% in individuals with metabolic syndrome (MetS) (defined by WHO criteria) compared with 2.2 % in individuals without.
- In all subjects, a history of CHD, MI, and stroke was more common in those with the Met S than it was in those without ($P < 0.001$).
- In IFG / IGT , the prevalence of CHD was increased even further in patients with the Met S (35% vs. 8%, $P < 0.001$).
- A history of MI was increased in T2DM with Met S compared with those without (11.2 vs. 4.7%; $P = 0.007$).
- Similarly, a history of stroke was more common in IFG/IGT subjects clear Met S than it was in those without (3.6 vs. 0.9%; $P = 0.05$).

Groop et al., Diabetes (1996) vol., 11, 1585 - 93

Type 2 Diabetes Prevention

- Note – the 2 big diabetes prevention programmes (DPP and DPS) reduced the progression from IGT to T2DM by 58% in the lifestyle arm, 33% in the Metformin arm.
- This by 5% body weight loss over 4-5 year course of study and engagement in 150 mins exercise per week (*multiples of 10 mins upwards*).
- 53% of subjects reached a definition of the Metabolic syndrome at baseline:

- This was reduced at 4 years by 41% *($p<0.001$)* in lifestyle and 17% *($p=0.03$)* in Metformin arm

T2DM: The risks

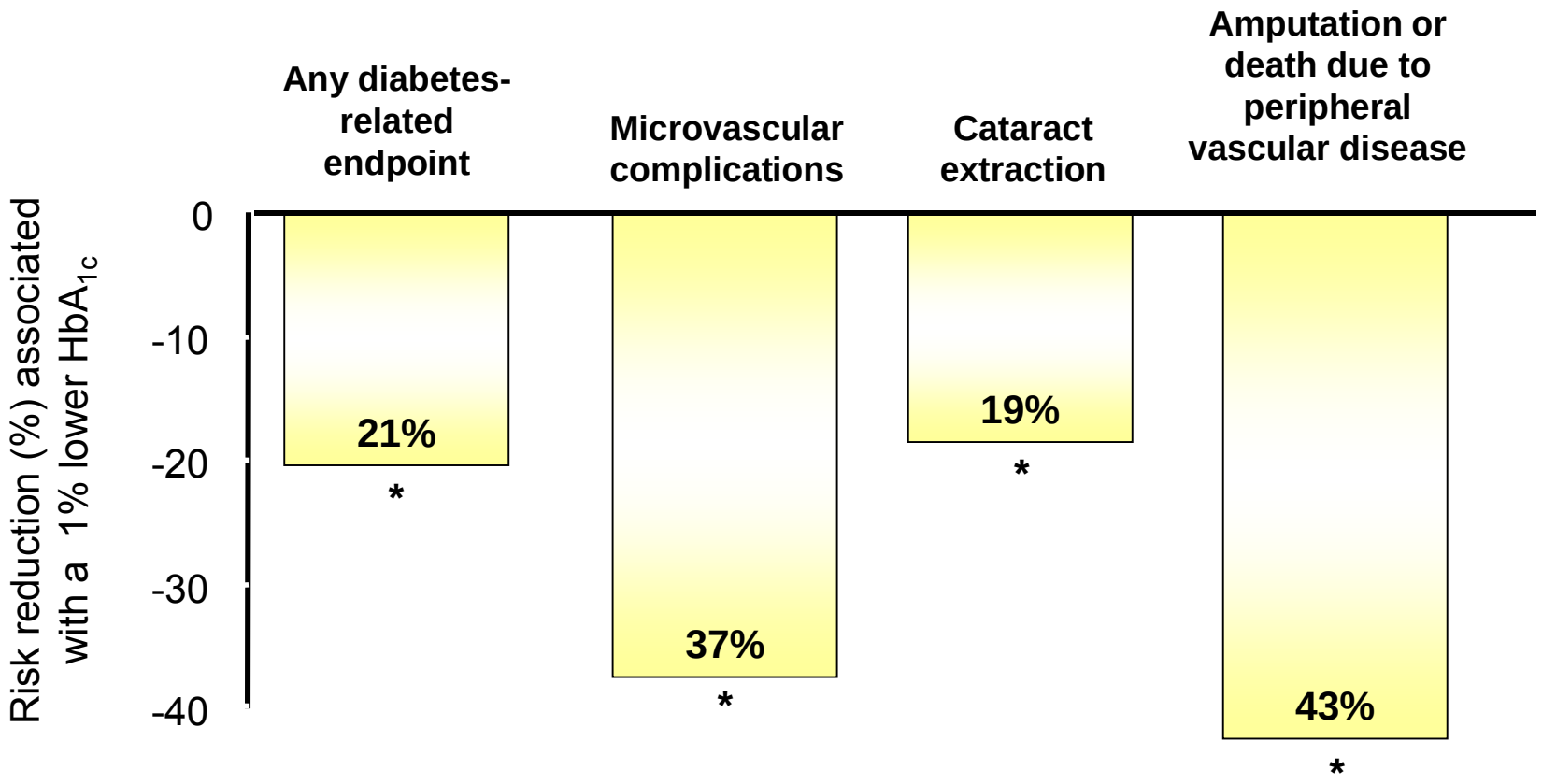
Type 2 Diabetes: The Risks

- 2-4 fold risk of CVD
- Risk of MI equivalent to that on so… DM who has already suffered an M…
- 2-5 fold risk of stroke
- Even higher CV risk… …an patients
- The leading ca… …umatic limb amputation
- Leading c… …end-stage renal failure
- High… …pression over general population
- … expectancy of 8-12 years – what does … for those diagnosed increasingly younger?

Unless aggressive clinical risk management and educational strategies in place

Type 2 Diabetes – reducing the risks

Risk reduction for each 1% reduction in HbA_{1c} in T2DM



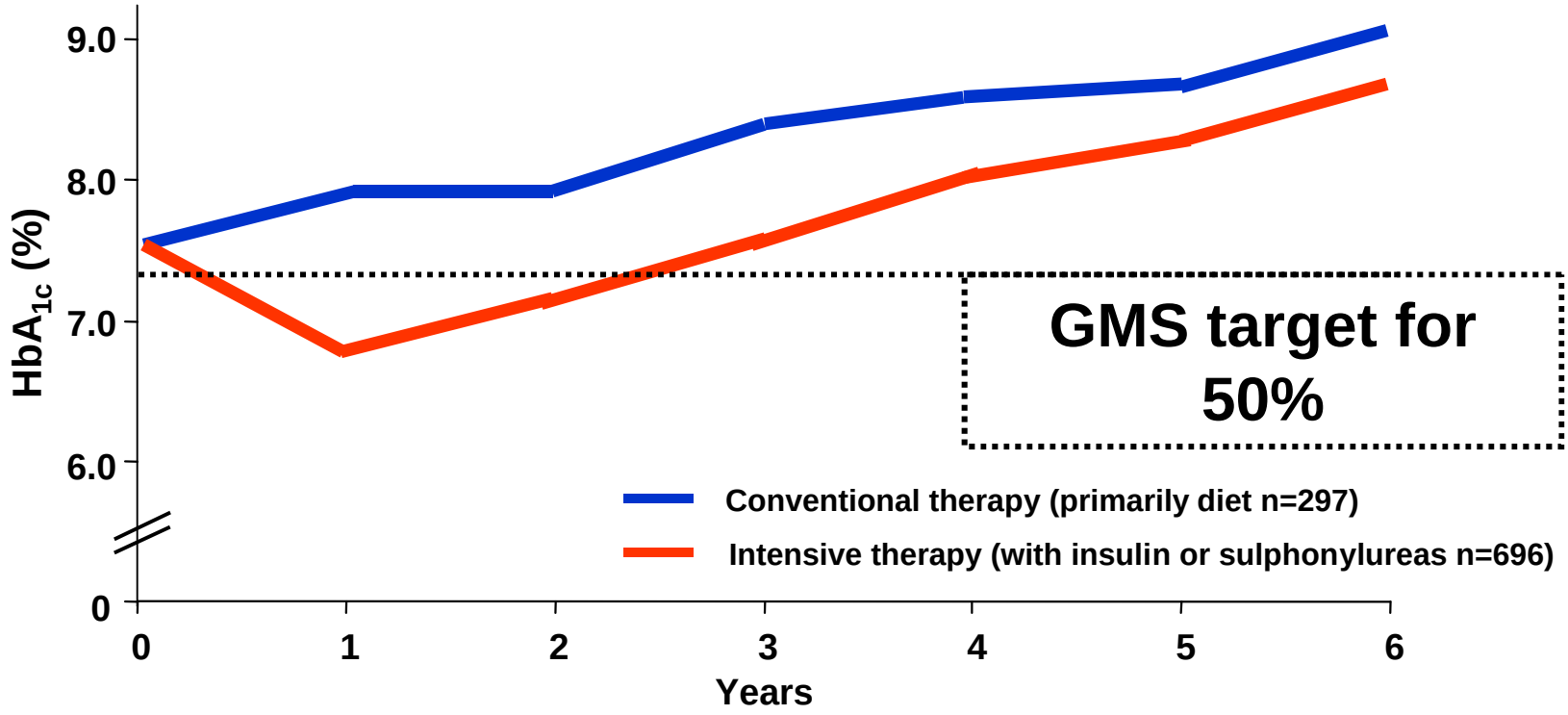
Epidemiological extrapolation showing benefit of a 1% reduction in mean HbA_{1c} at 12 years

*p < 0.0001

Stratton IM *et al*. *BMJ* 2000; **321**: 405–412.

The need for regular surveillance and regular treatment increase

Deterioration of glycaemic control in the UKPDS



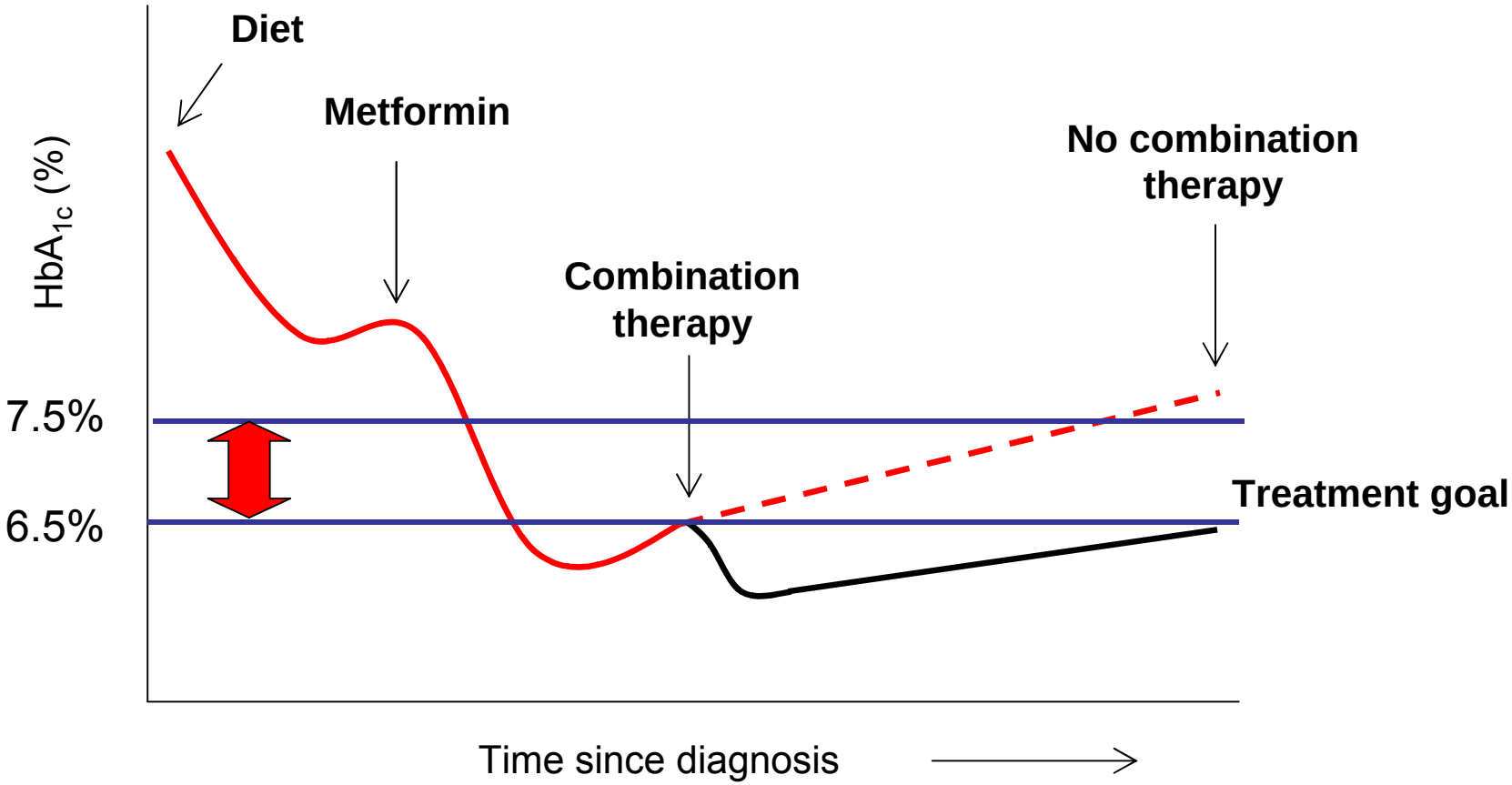
*UKPDS. Diabetes 1995; **44**: 1249–58.*

What the evidence shows …….

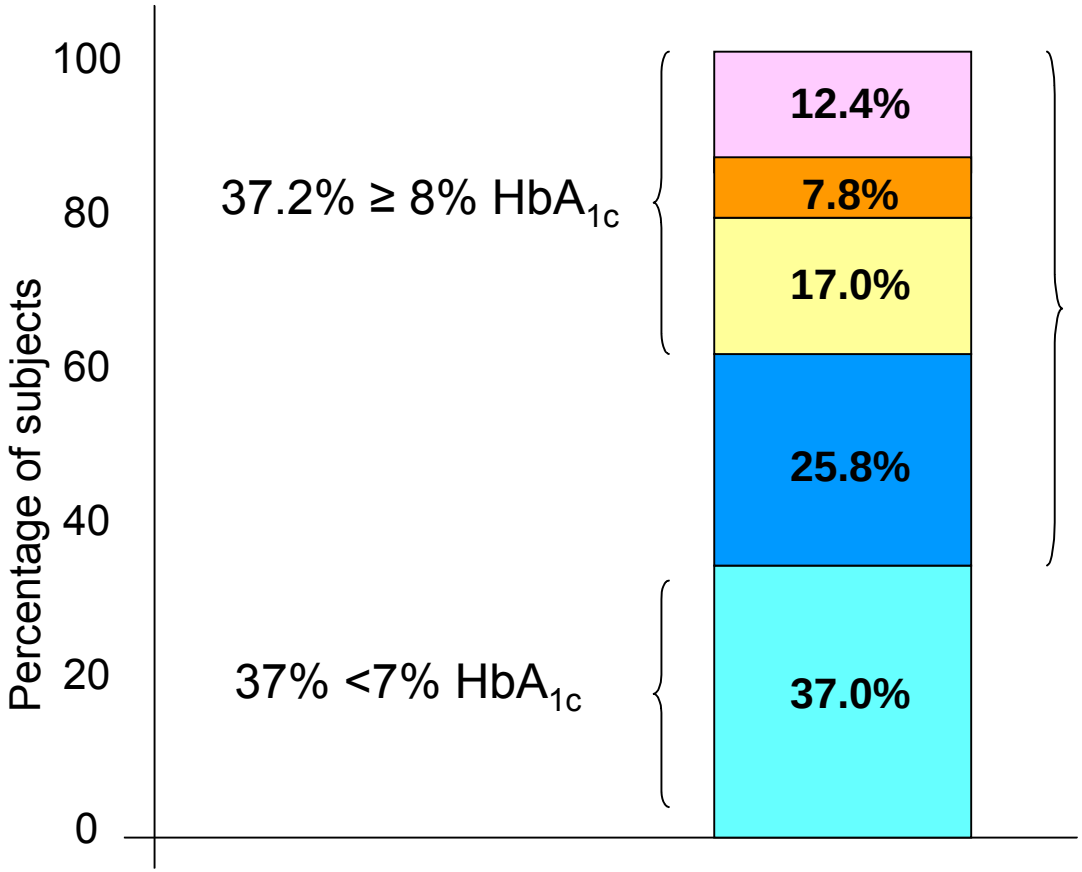
Hyperglycaemia + time = complications

Bailey CJ. *Diab Vas Dis Res* 2006; **3**: 145–146.

Early intervention: Avoiding glycaemic burden and microvascular complications



63% of patients are not at ADA goal of $HbA_{1c} \leq 7.0\%$



Only **7%** of adults with diabetes in NHANES 1999 - 2000 achieved:

HbA1c <7%

BP < 130/80 mm/Hg

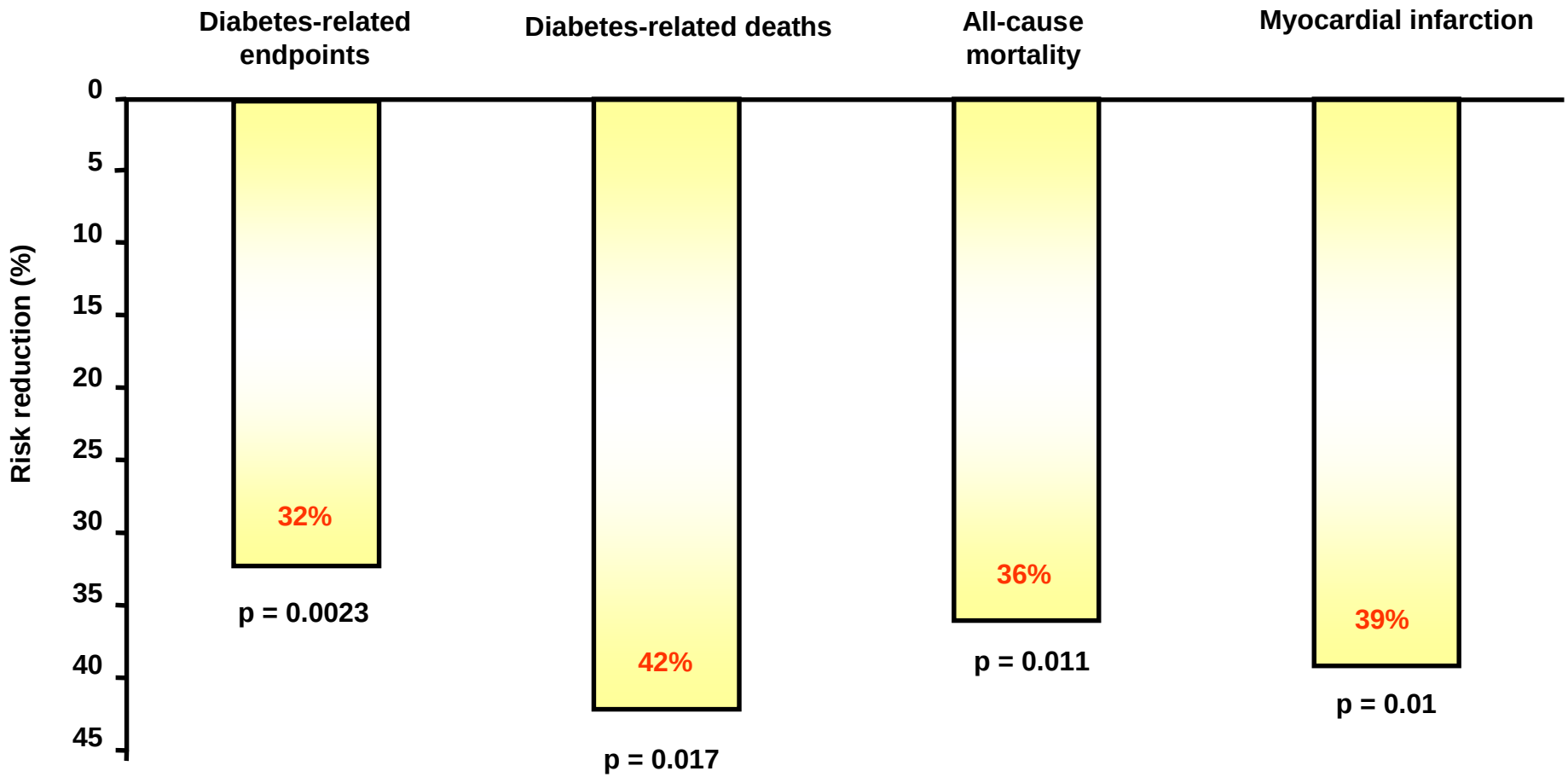
Chol < 5 mmol/l

Saydah SH et al. JAMA, 2004; 291:335-42

An important diabetes drug …

- No weight gain
- No hypoglycaemia
- Significant reduction in HbA_{1c}
- Cardiovascular protection in overweight patients over and above glucose lowering effect
- Cheap
- Around for 50 years
- Documented use in 1652 (Culpepper)

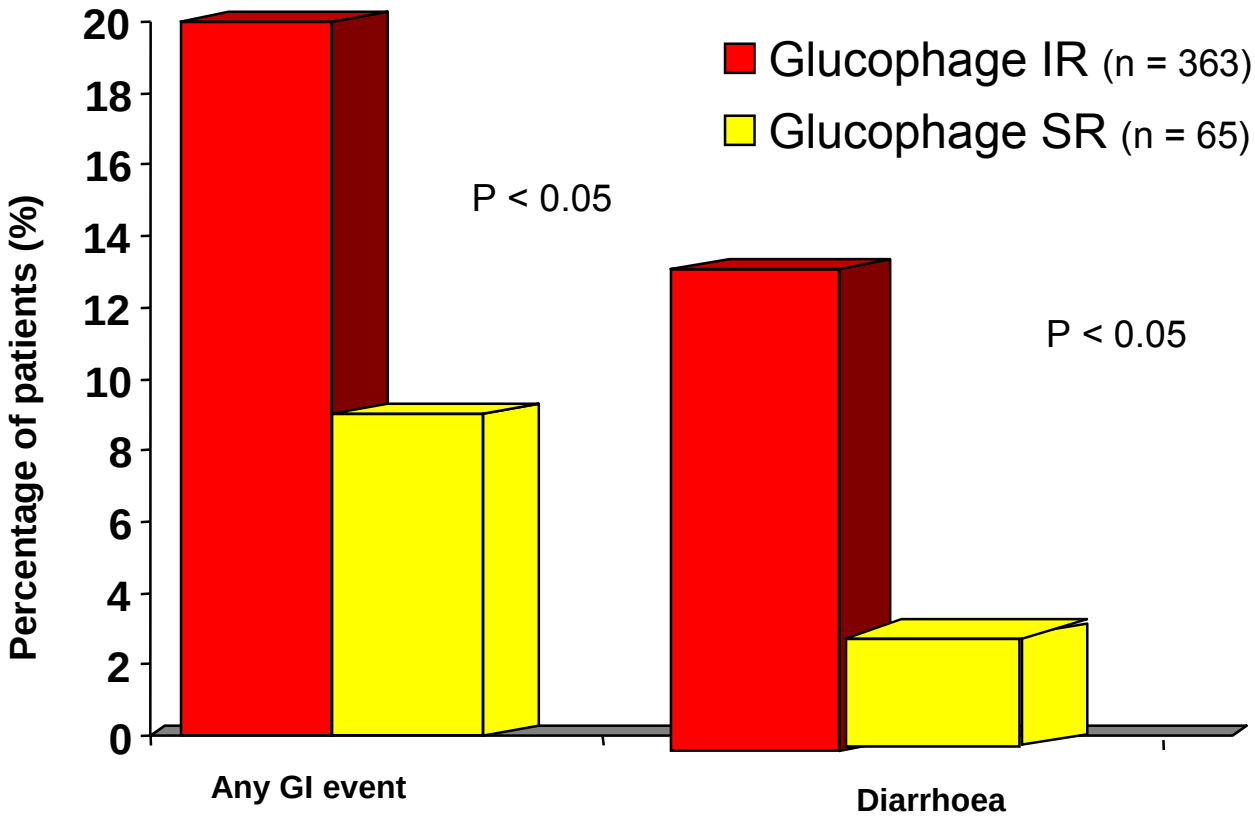
The reduction in risk with metformin in overweight T2DM patients



p values in comparison to conventional treatment group

United Kingdom Prospective Diabetes Study (UKPDS) Group. Lancet 1998; ***352****: 854–865.*

Glucophage SR – superior GI tolerability to Glucophage IR[5]

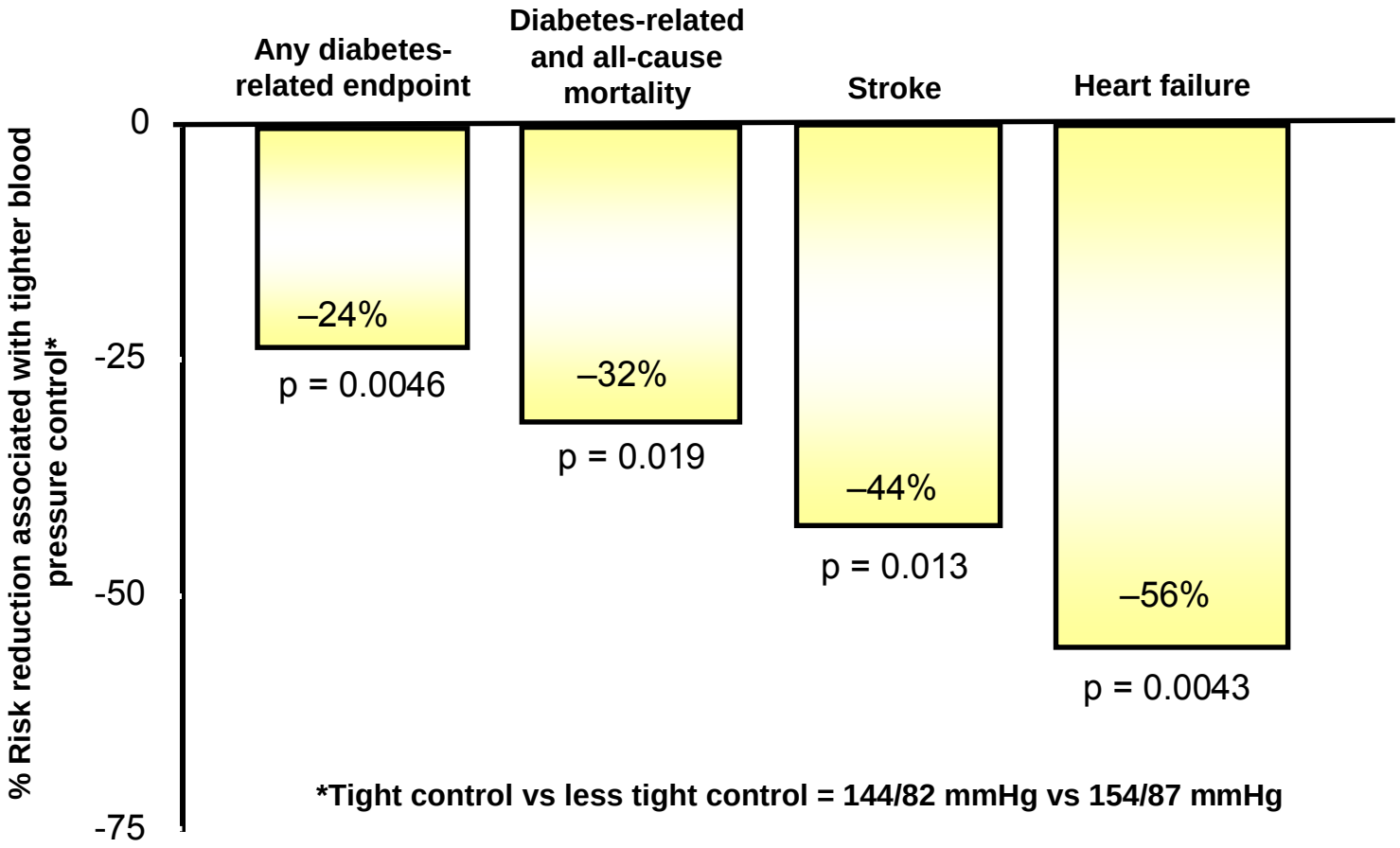


Side effects during first year of treatment

With Glucophage SR there are fewer than half the gastrointestinal side effects during the first year of treatment compared with Glucophage IR[5]

Adapted from Blonde L *et al*. *Curr Med Res Opin*, 2004; 20 (4): 565-572.

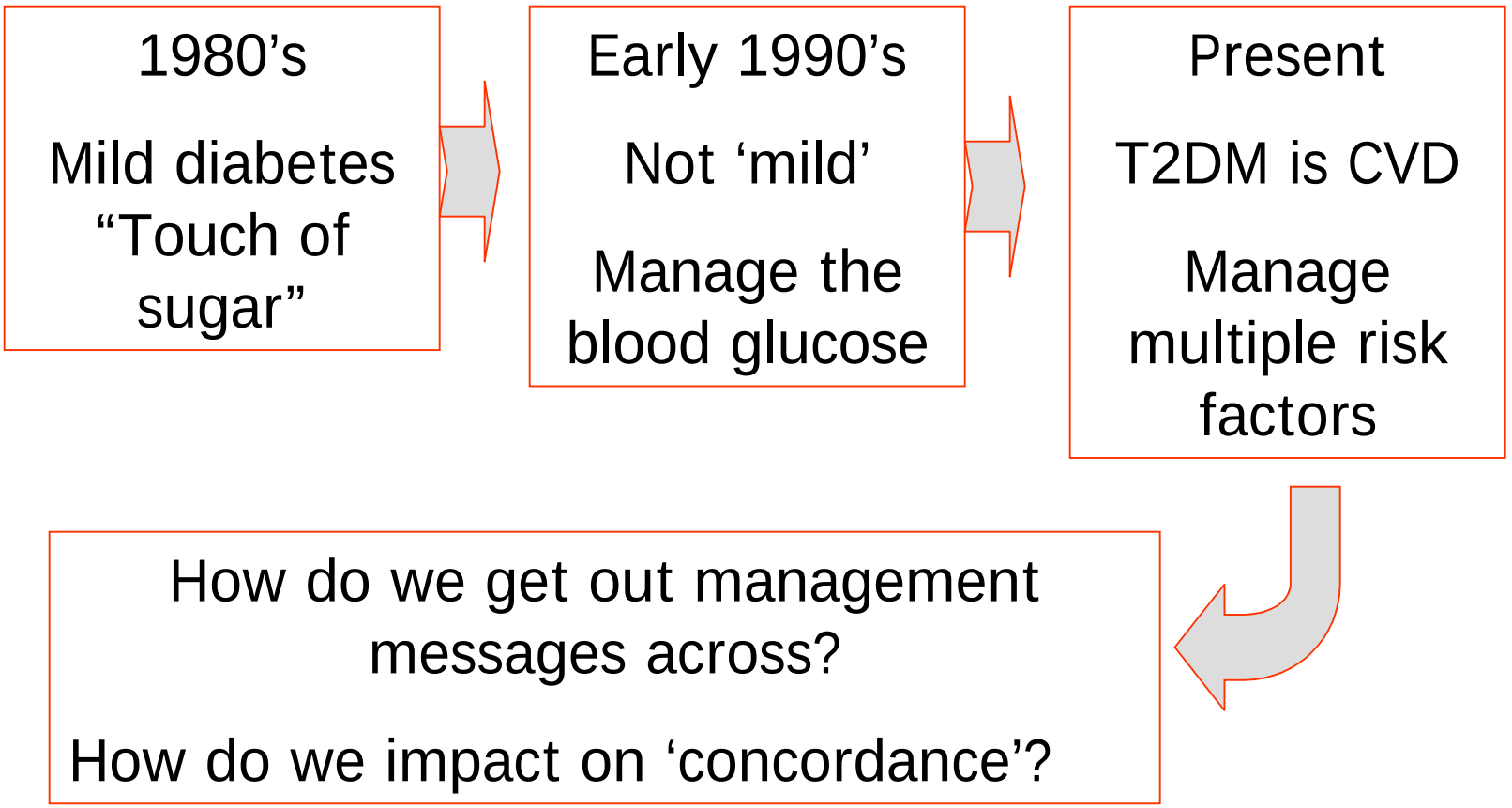
UKPDS: Tight blood pressure control reduces cardiovascular risk in T2DM



UK Prospective Diabetes Study Group. *BMJ* 1998; **317**: 703–713.

Multiple risk-factor management for Type 2 Diabetes

Change in T2DM management strategies



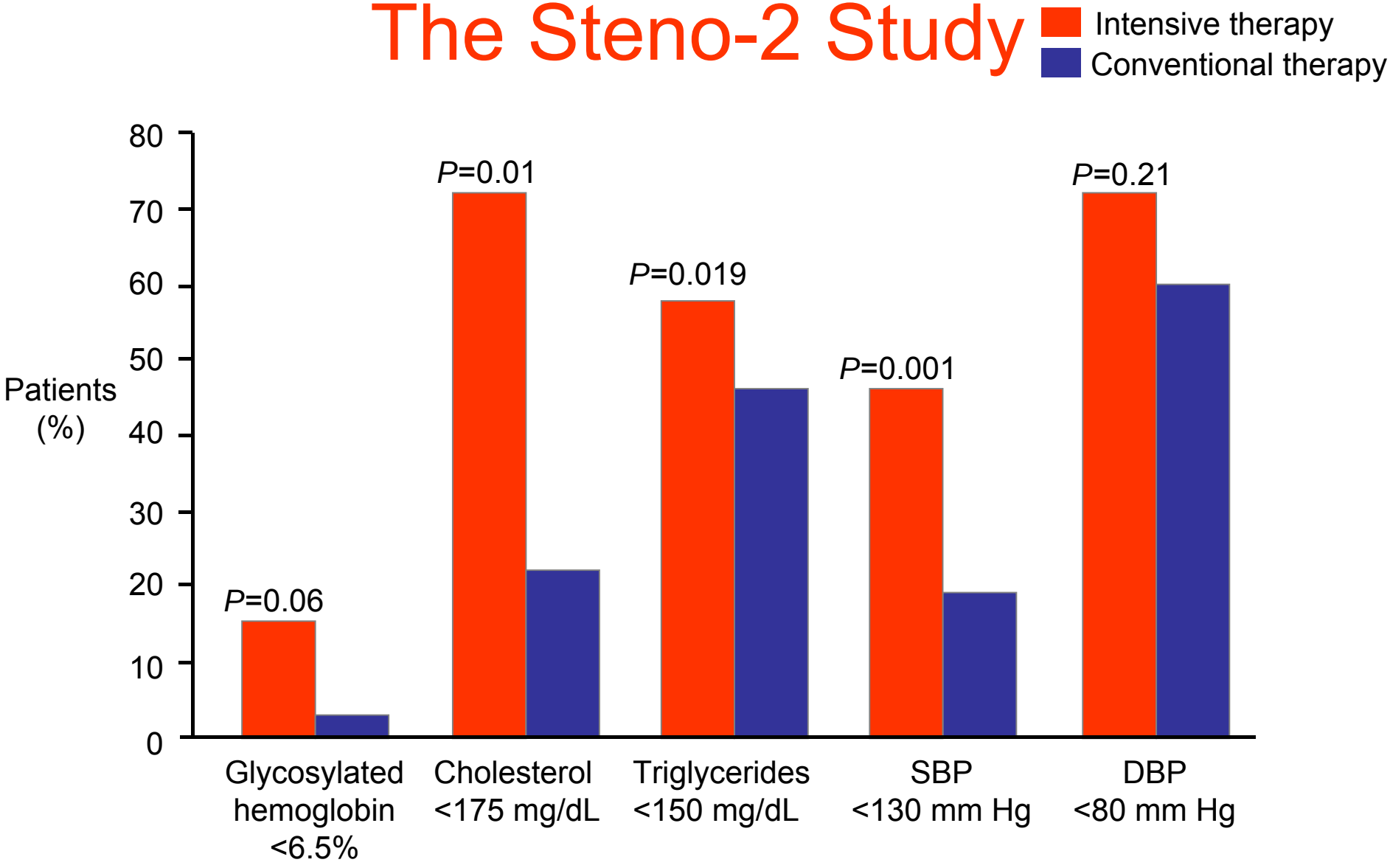
NNT to prevent one event

Risk level: 5-year CV risk (fatal and non-fatal)	**Benefits: NNT for 5 years to prevent one event** (CVD events prevented per 100 people treated for 5 years)		
	1 intervention (25% risk reduction)	**2 interventions (45% risk reduction)**	**3 interventions (55% risk reduction)**
30%	13 (7.5 per 100)	7 (14 per 100)	6 (16 per 100)
20%	20 (5 per 100)	11 (9 per 100)	9 (11 per 100)
15%	27 (4 per 100)	15 (7 per 100)	12 (8 per 100)
10%	40 (2.5 per 100)	22 (4.5 per 100)	18 (5.5 per 100)
5%	80 (1.25 per 100)	44 (2.25 per 100)	36 (3 per 100)

Based on the conservative estimate that each intervention: aspirin, blood pressure treatment (lowering systolic blood pressure by 10 mm Hg) or lipid modification (lowering LDL-C by 20%) reduces CV risk by about 25% over 5 years.

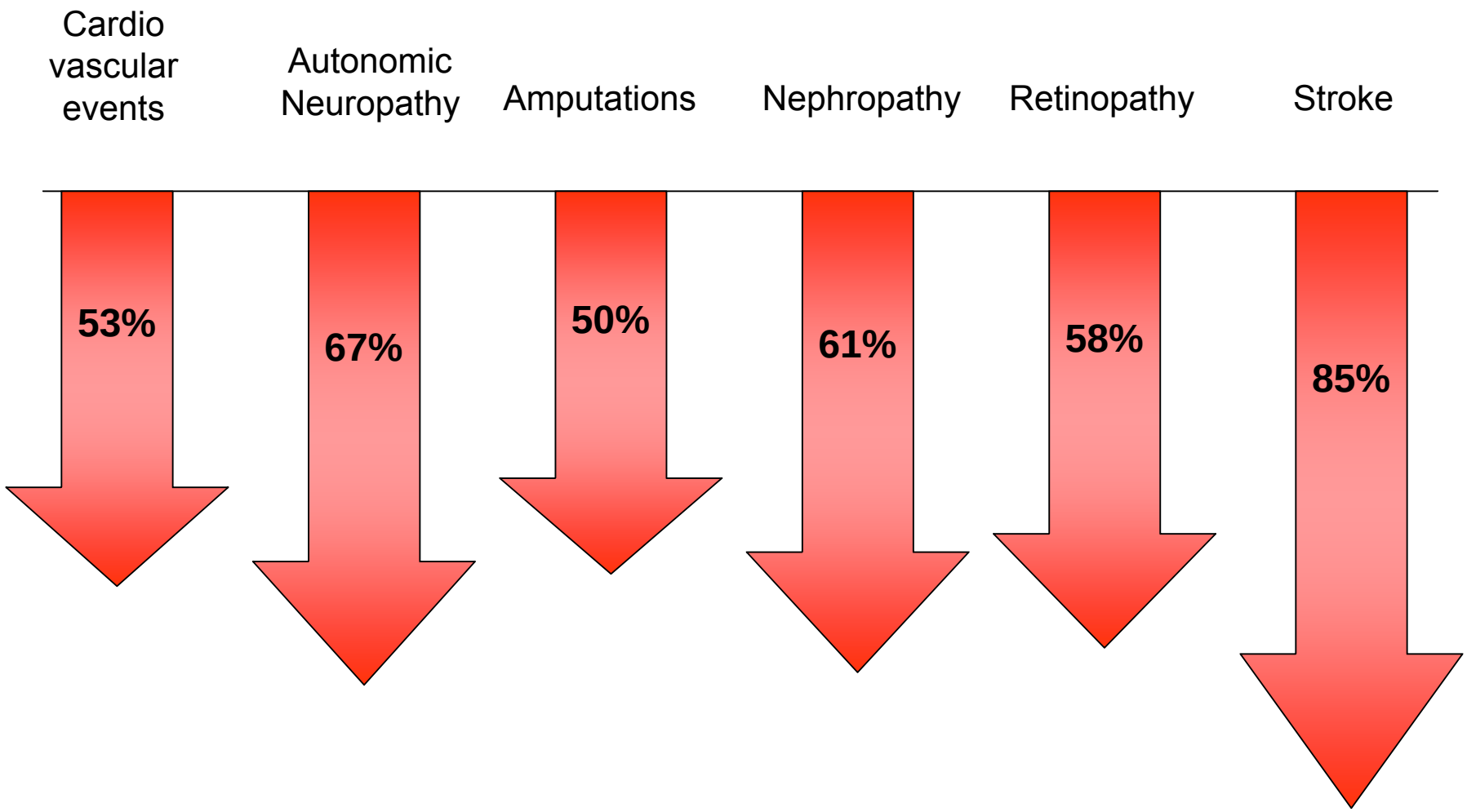
Assessment and management of cardiovascular risk . New Zealand Guidelines Group(2003) www.nzgg.org.nz

Multiple Risk Factor Intervention: The Steno-2 Study



Gaede P et al. *N Engl J Med*. 2003;348:383-393.

Multiple Risk Factor Intervention: Risk reduction in the Steno-2 Study



Case studies

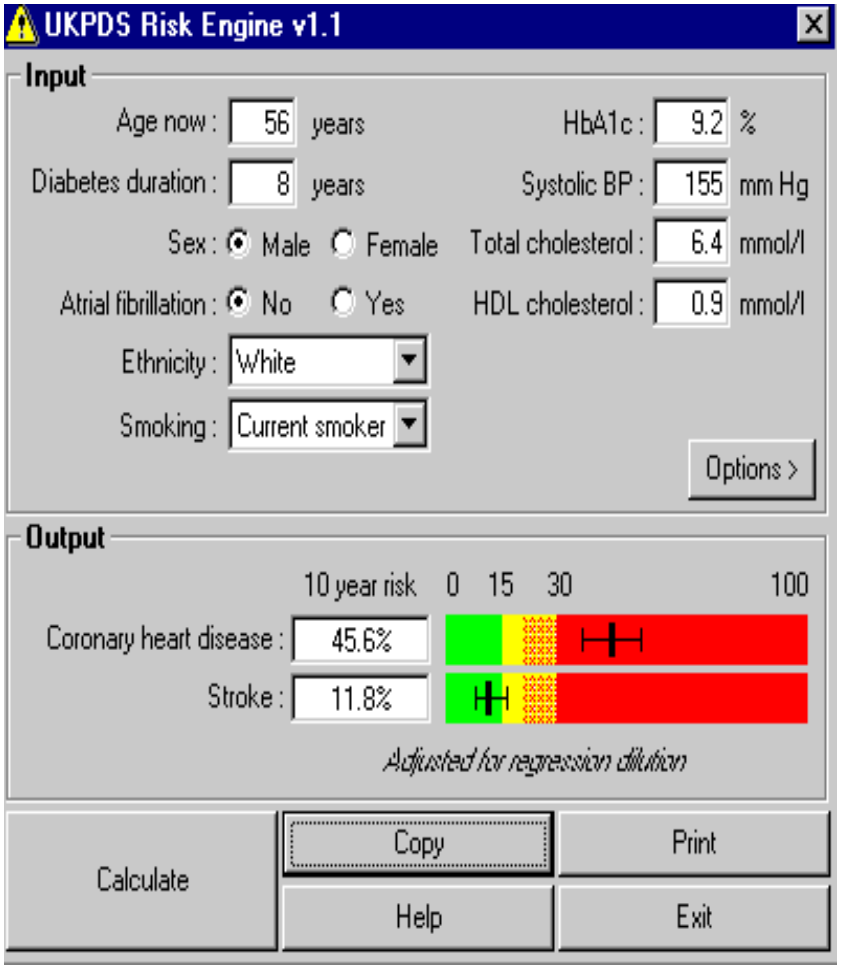
Case study - Joan

- Joan (64). Diagnosed with T2DM 5 years ago.
- Ex-smoker – gave up 6 years ago
- BMI 34.2 kg/m^2.
- Blood pressure 155/88.
- Cholesterol is raised at 6.4 mmols/L, HDL 0.9 mmols/L.
- Home blood sugars generally 12–16 mmols. HbA_{1c} 9.2%. On Metformin 6 tabs day Glic 4 tabs day
- States she generally feels very well.
- **Action?**

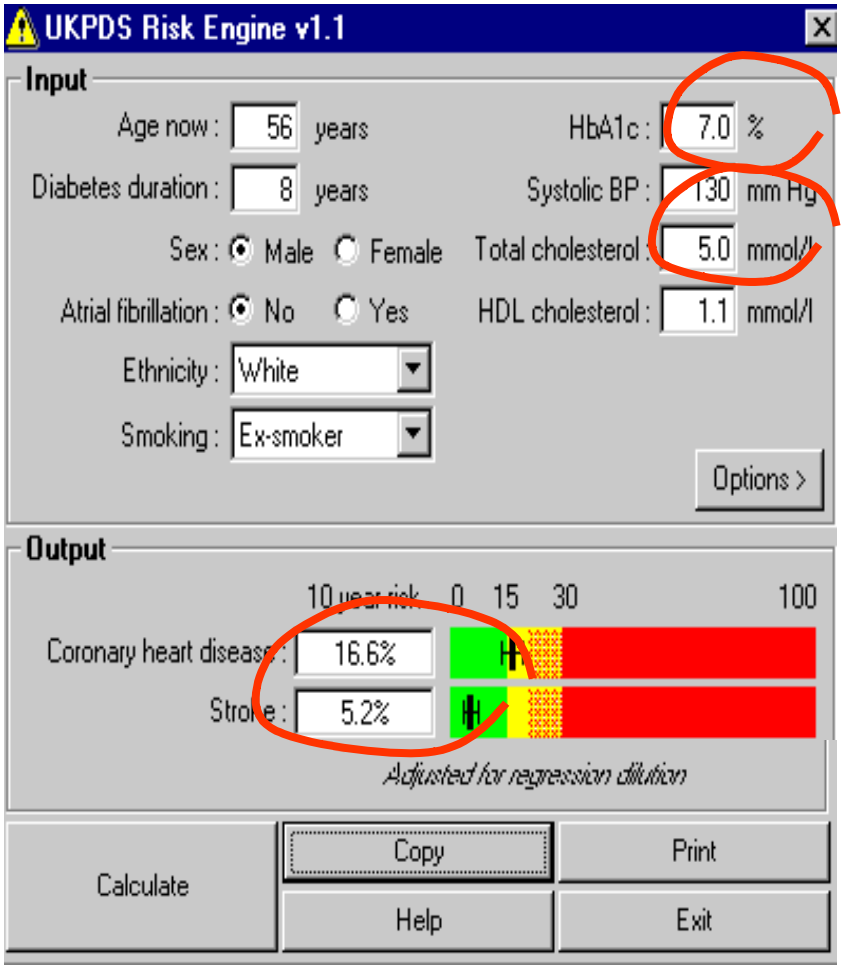
Case study - Sid

- Sid - 56 yrs. T2DM.
- HbA_{1c} never below 7.3% since diagnosis 8yrs ago. Latest value 9.2%.
- BMI 34.6 kg/m^2, BP 155/82, Cholesterol 6.4, HDL 0.9
- Urine microalbuminuria +ve. Background retinopathy *(left)* Pre-prolifeative *(right)*
- Current smoker.
- Dislikes taking his tablets. Complains of 'tummy ache'
- Drug history: Metformin 500mg tds, Rosiglitazone 4mg od, Gliclazide 160mg bd, Aspirin 75mg od, Atorvastatin 40mg nocte
- **What is his 10 year cardiovascular risk?**
- **How (*on earth*) are you going to engage him with his health and future risks?**

10 year Coronary Heart Disease Risk



Before



After

Cardiometabolic Disease Key Points

- It is now recognised that adipose tissue synthesises and releases many factors which influence the body's metabolic actions.
- Increased visceral fat has an important role to play in metabolic and vascular risk.
- Body mass index is often used as a marker of obesity but gives a limited indication of body composition and so cardiometabolic risk.
- Measuring waist circumference is a more discriminative predictor.
- Rising visceral fat mass predicts worsening insulin resistance - changes in subcutaneous fat are not correlated.

Cardiometabolic Disease Key Points

- Early, aggressive multi-risk management is required from diagnosis of T2DM but probably before.
- Given it's cardio-protective benefits of Metformin in overweight patients and lack of weight gain, is is a key drug in our armoury.
- Revisiting patients previously unable to tolerate the immediate release form will help cardiovascular risk reduction.
- Increasingly the challenge is in persuading the patient to 'buy-into' an ever more aggressive treatment regime …
- Particularly when they are unlikely to have expected (*or wanted*) their diabetes diagnosis and perhaps have never experienced any of the physical symptoms of diabetes or the cardio-metabolic syndrome.

Central obesity can be dangerous