

New Treatments for Diabetes: Is gliclazide a gonner?

Tahseen A Chowdhury
Consultant Diabetologist
Royal London Hospital

What I will cover

- ◆ Reminder about why diabetes is the most important long-term condition
- ◆ Recent controversies
 - is tight glycaemic control important?
 - do glitazones and insulin increase cardiovascular risk?
 - do sulphonylureas increase cardiovascular risk?
- ◆ Update on NICE guidelines¹:
 - type 2 diabetes: newer agents for blood glucose control
 - case studies.

Why is diabetes important?

Retinopathy

Commonest cause of blindness in people of working age

Stroke

3x increased risk

Heart disease

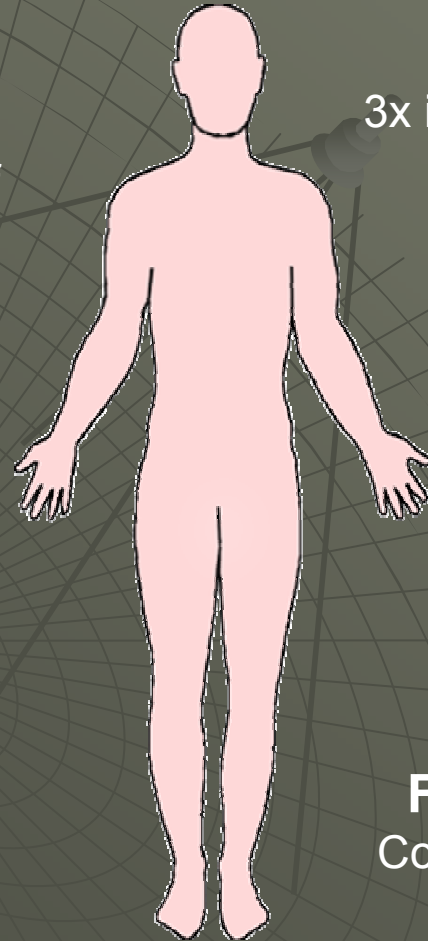
75% of patients with diabetes die of CVD

Nephropathy

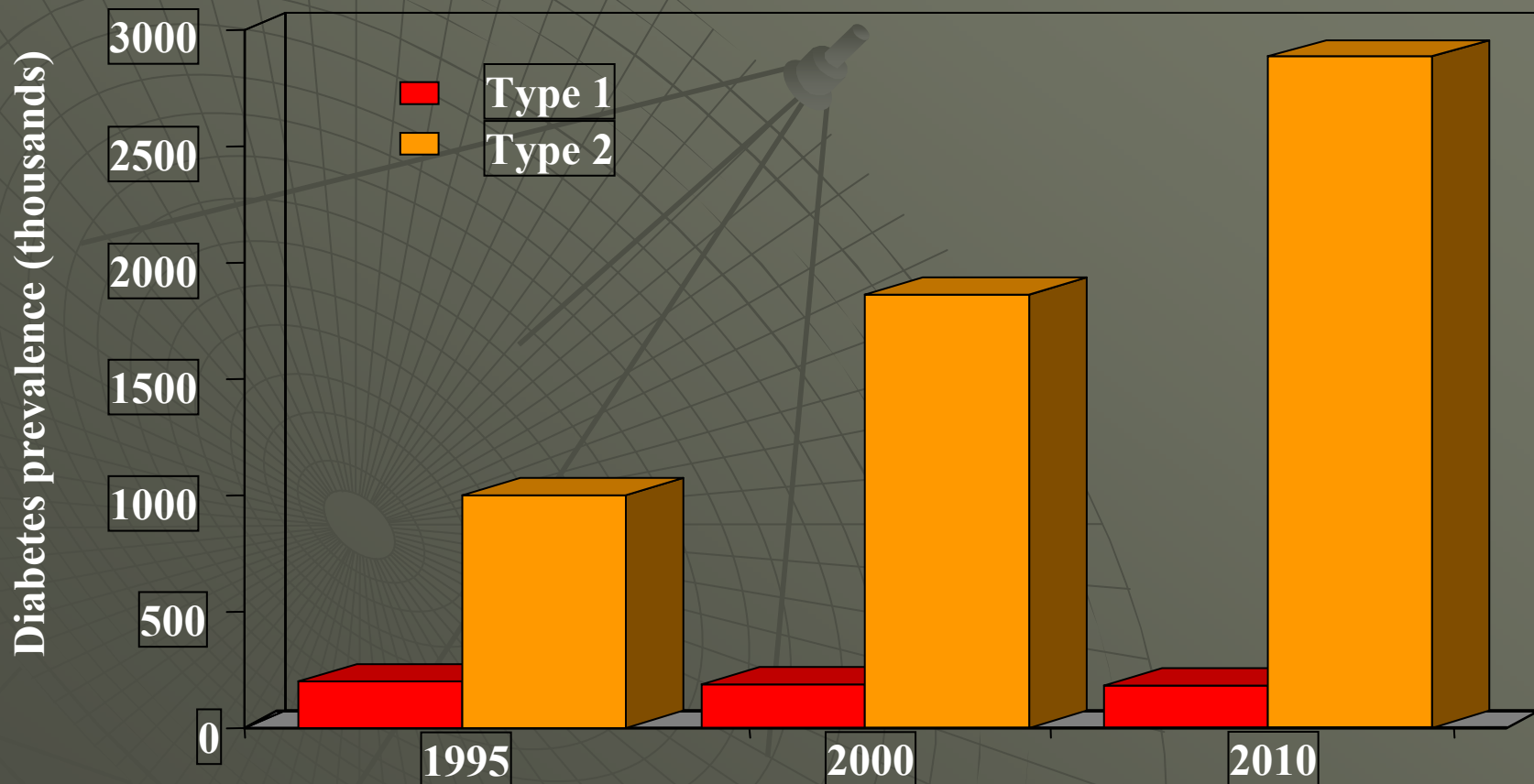
Commonest cause of ESRF

Foot problems

Commonest cause of amputation

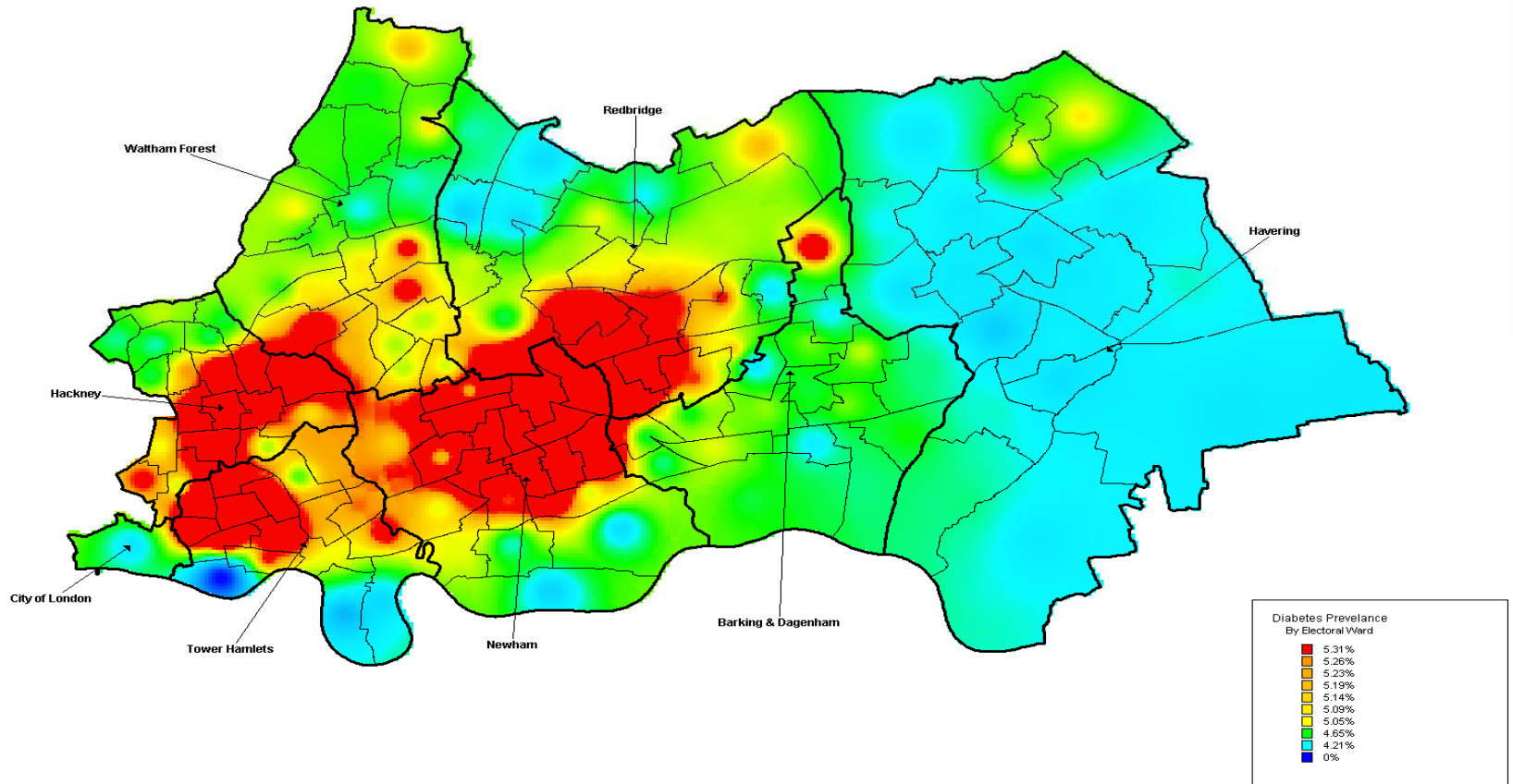


Prevalence of diabetes in the UK 1995–2010



Diabetes in North East London

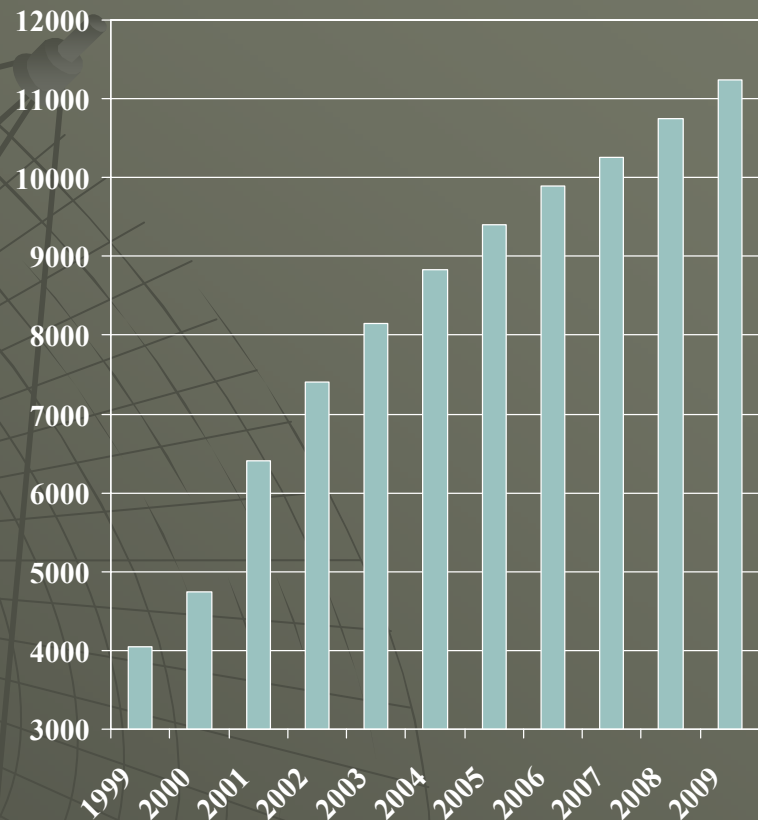
NORTH EAST LONDON ESTIMATE DIABETES PREVELANCE TYPE 1 & TYPE 2



Diabetes in Tower Hamlets

- ◆ Current prevalence – 4.4% (3.6% in London, 3.7% in England)
- ◆ ~2000 undiagnosed
- ◆ Predicted to rise by 1% in next 10 years
- ◆ 42% of Bangladeshis >65yrs have T2D (18% of Whites)
- ◆ 70% have another LTC (16% CHD, 14% depression, 53% HT)
- ◆ ~20% of in-patients have diabetes

- ◆ Direct costs ~£14.3million
- ◆ Indirect costs ~£46million



What we already know

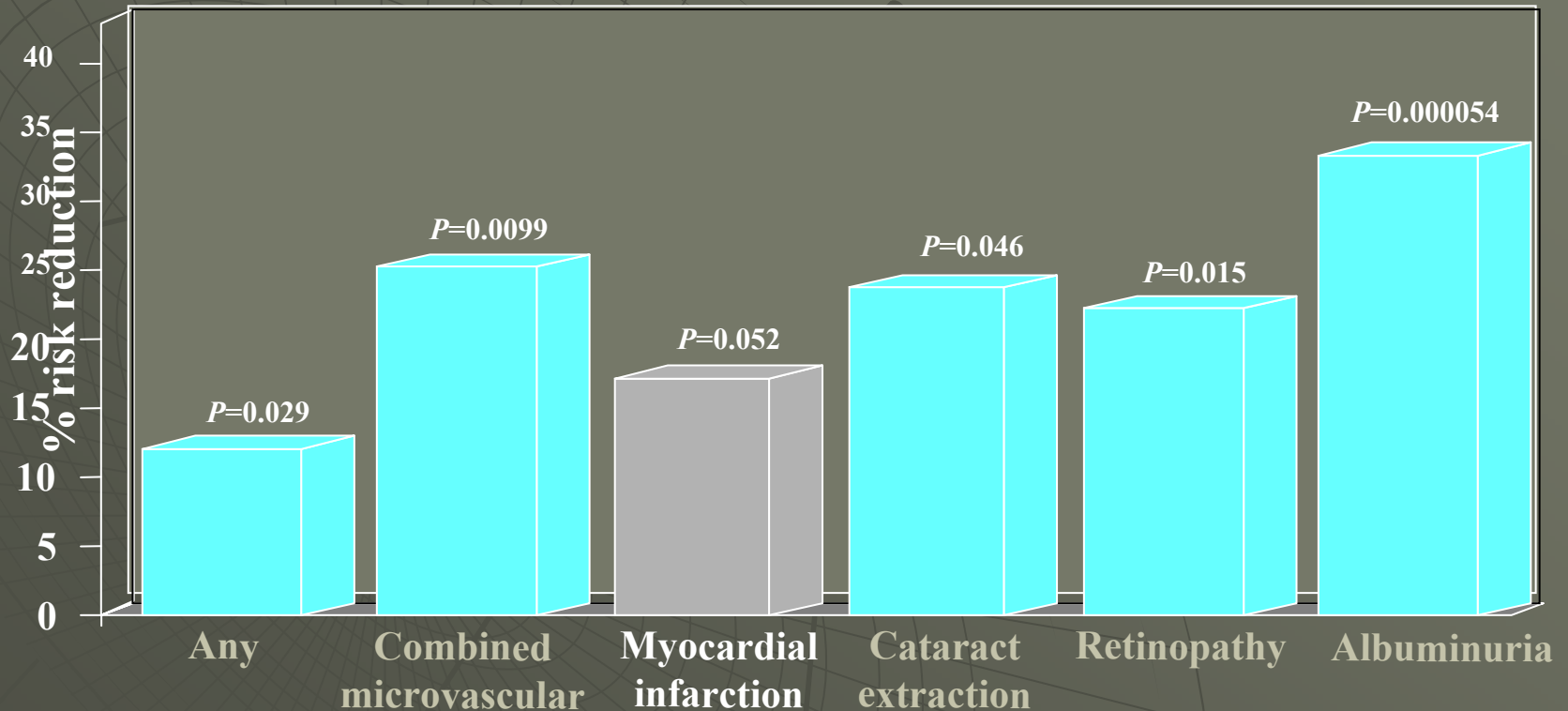
- ◆ Treat diabetes as a cardiovascular disease:
 - risk of CVD in a person with diabetes is similar to a person without diabetes with known CVD
- ◆ Certain groups are at high risk:
 - South Asian/Afro-Caribbean
 - previous gestational DM, obese, family history, known impaired fasting glucose/impaired glucose tolerance
- ◆ Presence of microvascular complications increases risk of CVD
- ◆ Diabetes costs ~9% of NHS budget; major cost is treatment of complications.

NICE¹: therapy to prevent complications

- ◆ Smoking cessation
- ◆ Blood pressure:
 - aim for 140/80 mmHg (130/80 mmHg if CVD or renal disease)
 - first line: ACEI, calcium channel blockers (often >2)
- ◆ Cholesterol:
 - all patients with diabetes >40 years, or with diabetes <40 years + 1 risk factor: statin
 - aim for total cholesterol <4.0 mmol/l
- ◆ Aspirin:
 - all patients with diabetes >50 years if BP <145/90 mmHg
 - BUT – recent evidence suggests no benefit in primary prevention
- ◆ Screening:
 - eyes: yearly digital retinal photograph
 - feet: yearly check
 - kidneys: yearly albumin/creatinine ratio and eGFR measurements.

Glycaemic control—is it important?

UKPDS results of tight glycaemic control



UKPDS follow-up study

- ◆ UKPDS 80
 - 3277 patients at 10-year follow-up
 - overall:
 - ◆ risk reduction for myocardial infarction (15%, $p=0.01$)
 - ◆ death from any cause (13%, $p=0.007$)
 - metformin group:
 - ◆ risk reduction for myocardial infarction (33%, $p=0.005$)
 - ◆ death from any cause (27%, $p=0.002$).

VADT: negative trial

- ◆ VADT¹
 - 1791 patients, 5.6-year follow-up
 - HbA_{1c}: 8.4% vs 6.9%
 - overall:
 - ◆ no significant difference in macrovascular or microvascular complications

Glycaemic targets

- ◆ Is lower better?
 - perhaps not:
 - ◆ ACCORD¹
 - ◆ tight control group: HbA_{1c} <6.0% vs less tight control group: HbA_{1c} 7.0%–7.9%
 - ◆ tight control group: 257 deaths vs less tight control group: 203 deaths (relative risk increased by 22%)
 - ◆ deaths appeared to be more CVD events
 - ◆ ?induced by hypoglycaemia (dead-in-bed syndrome).

Meta-analysis

- ◆ Lancet 2009; 373
 - 5 prospective randomised studies
 - ◆ 33040 patients, 7834 events (163000 person years f.u.)
 - ◆ Intensive – HbA1c 6.6-7.0%
 - ◆ Conventional – HbA1c 7.3-8.4%
 - ◆ 17% RR in non-fatal MI
 - ◆ 15% RR in CHD
 - ◆ No effect on all cause mortality

What is the bottom line?

- ◆ Glycaemic control early in type 2 diabetes is probably important (aim for HbA_{1c} <7.0% early)
- ◆ Later (5–10 years), it is less important and more risky (aim for HbA_{1c} <7.5% later)
- ◆ NICE suggests individualised targets¹:
 - target for an 80-year-old lady with type 2 diabetes and dementia might be very different to that of a 40-year-old man with type 2 diabetes and a family history of CHD
 - 'target level for an individual may be above the general target of 6.5% and should be negotiated with the patient'.

Therapy for hyperglycaemia

1. Metformin
2. Sulphonylurea
3. Pioglitazone
4. Insulin
5. DPP-4 inhibitor
6. GLP-1 analogue

Reminder about metformin

- ◆ Mortality benefit in obese type 2 diabetes
- ◆ Start slow and titrate—after meals
- ◆ If not tolerated, metformin MR is an option
- ◆ Stop at eGFR of 30 ml/min/1.73 m² (consider reducing at 40 ml/min/1.73 m²)
- ◆ Beneficial in heart failure
- ◆ Continue when commencing insulin
- ◆ Continue in women who get pregnant
- ◆ Can be used in gestational diabetes mellitus.

Glitazones

- ◆ Advantages:
 - oral
 - once daily
 - generally well tolerated
 - HbA_{1c} reduction 1%–1.5% (takes 2-3 months)
 - infrequent hypoglycaemia
- ◆ Disadvantages:
 - heart failure/oedema
 - LFT monitoring (but may be of benefit in NASH)
 - risk of fractures in post-menopausal women
 - body weight gain.

Do glitazones cause CVD?

- ◆ Probably not:
 - meta-analysis of small RCTs was not powered for CVD; showed a 43% increased risk of myocardial infarction with rosiglitazone vs placebo¹
 - analysis of the RECORD study showed no increased CVD, **but no evidence of reduction in CVD**
- ◆ PRO-active:
 - 5238 patients with type 2 diabetes and macrovascular disease
 - 3-year follow-up
 - 16% risk reduction in all-cause mortality, nonfatal myocardial infarction, or stroke.

When should you use pioglitazone?

- ◆ NICE¹ suggests:
 - 2nd line with metformin if concern over hypoglycaemia with sulphonylurea, or sulphonylurea is not tolerated
 - 2nd line with sulphonylurea if metformin not tolerated
 - 3rd line with metformin and sulphonylurea
- ◆ Continue if HbA_{1c} reduces by 0.7% in six months
- ◆ Use with insulin if high dose insulin therapy is needed, or previously had good response to a glitazone
- ◆ Pioglitazone may be preferable to DPP-4:
 - for people who are likely to be insensitive to insulin (e.g. patients with higher BMI, features of metabolic syndrome)
 - DPP-4 contra-indicated
 - poor response or intolerant to DPP-4.

Do sulphonylureas cause CVD?

- ◆ New concerns:
 - GP database: 91,355 patients with diabetes
 - Compared to metformin, sulphonylurea prescription led to 24-61% increase risk in all cause mortality
 - (Pioglitazone led to lower risk of death compared to metformin)
- ◆ Previous studies:
 - UDGP (1980s) – increased deaths in SU treated
 - UKPDS (1998) – unexplained slight increased risk of death in MF + SU treated

Insulin

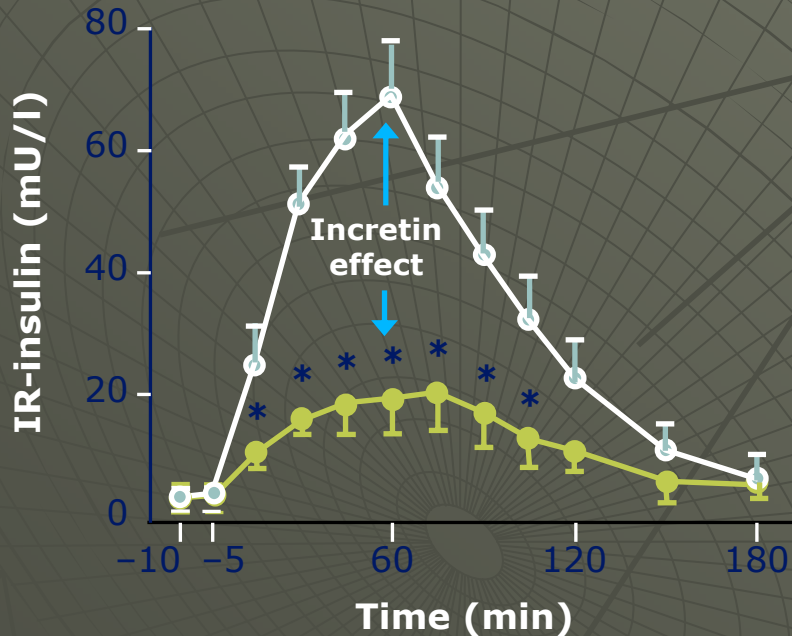
- ◆ Advantages:
 - good glycaemic control
 - generally well tolerated
 - HbA_{1c} reduction 1%–3%
- ◆ Disadvantages:
 - injection (needs considerable nursing input)
 - blood glucose monitoring
 - hypoglycaemia
 - body weight gain.

Insulin

- ◆ Any benefit of analogue over intermediate?
 - no convincing evidence
 - NICE¹ suggests NPH first line
 - analogues for patients who:
 - ◆ require assistance to give injections
 - ◆ have recurrent hypoglycaemia
 - ◆ would need twice-daily NPH insulin
 - ◆ cannot use device for NPH insulin (?availability)
- ◆ Twice-daily premix if $HbA_{1c} > 9.0\%$
- ◆ Better results when started early ($HbA_{1c} \sim 7.5\%$)
- ◆ Continue metformin—less body weight gain and less insulin requirement
- ◆ Consider with a glitazone if high dose insulin required.

What is GLP-1?

The incretin effect



Key observations

- A hormone produced from the L-cells of the small intestine
- Produced when you eat
- Stimulates insulin release from the pancreas
- Helps increase size and number of beta cells
- Reduces appetite
- Is reduced in diabetes.

Gila Monster (*Heloderma suspectum*)



Exendin-4 (Exenatide)



- ◆ GLP-1 analogue
- ◆ Twice-daily injection.

Does it work?

- ◆ 30-week trials:
 - In addition to tablets:
 - ◆ HbA_{1c} reduction of ~1%
 - ◆ 2.5 kg body weight loss
- ◆ Around 1000 people treated for 4 years:
 - sustained reduction in HbA_{1c} of 1.1%
 - continued body weight loss of ~4.5 kg.

Exenatide vs insulin glargine

- ◆ Patients with poor diabetes control on gliclazide and metformin
- ◆ Treated with either:
 - exenatide
 - titrated insulin glargine (Lantus)
- ◆ ~1% reduction in HbA_{1c} in both groups:
 - glargine—body weight gain 1.8 kg
 - exenatide—body weight loss 2.3 kg.

Side effects

- ◆ Nausea—40%
- ◆ ?Pancreatitis

Liraglutide

- ◆ Once daily
- ◆ One study suggests greater efficacy than exenatide

Where do GLP-1 analogues fit in?

- ◆ NICE¹ - consider adding to metformin and sulphonylurea if:
 - BMI >35
 - BMI <35 in whom insulin would have occupational implications, or weight loss may aid co-morbidities (e.g. sleep apnoea)
- ◆ Continue if HbA_{1c} reduces by 1%.

BMI=body mass index; HbA_{1c}=glycated haemoglobin A_{1c}

1. National Institute for Health and Clinical Excellence. *Type 2 diabetes newer agents*. Clinical guideline. London: NICE, May 2009

Gliptins

- ◆ DPP-4 inhibitors:

- DPP-4 is the enzyme that breaks down GLP-1
- DPP-4 inhibition leads to increased levels of GLP-1

- Sitagliptin
- Vildagliptin
- Saxagliptin

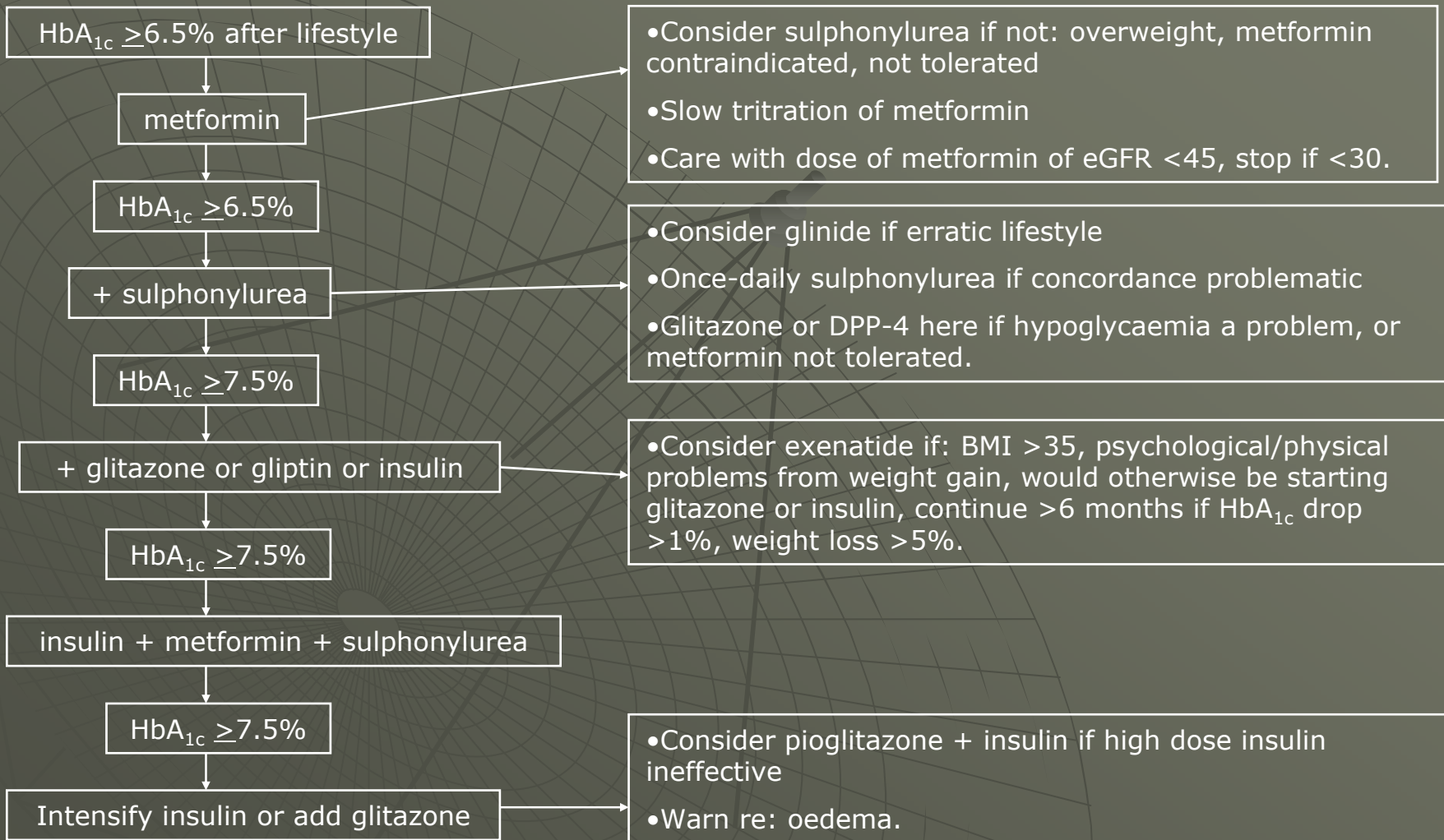
Do they work?

- ◆ Regulatory studies—52-week administration appears to result in 0.8% reduction in HbA_{1c}
- ◆ No weight change
- ◆ Beta-cell function improves
- ◆ Very well tolerated—no major side effects.

Where do gliptins fit in?

- ◆ NICE:
 - 2nd line with metformin if concern over hypoglycaemia with sulphonylurea, or sulphonylurea is not tolerated
 - 2nd line with sulphonylurea if metformin is not tolerated
 - 3rd line with metformin and sulphonylurea
- ◆ ? Third line instead of pioglitazone in patients who are obese
- ◆ Larger studies required for these drugs to be widely used.

NICE 2009¹—glucose lowering



HbA_{1c}=glycated haemoglobin A_{1c}; eGFR-estimated glomerular filtration rate; DPP-4=dipeptidyl peptidase-4; 1. National Institute for Health and Clinical Excellence. *Type 2 diabetes newer agents*. Clinical guideline. London: NICE, May 2009.

Case studies

- ◆ A 56-year-old South Asian man with type 2 diabetes but no complications has an HbA_{1c} of 8.5% on maximal dose of metformin and sulphonylurea
- ◆ BMI is 26.6kg/m²; waist circumference is 104 cm
- ◆ Other risk factors are well controlled
- ◆ Diet is reasonable

- ◆ What would you suggest as the next therapeutic option?
 - Insulin
 - Pioglitazone
 - Gliptin
 - Exenatide

Case studies

- ◆ A 58 year old Afro-Caribbean man attends annual review. He takes metformin 1 g bd and rosiglitazone 4mg bd, simvastatin 20mg od, lisinopril 10mg od
- ◆ He has the following clinical findings:

• BP	140/75 mmHg
• BMI	26 kg/m ²
• total cholesterol	4.3 mmol/l
• HbA _{1c} (4.8%-6.4%)	8.7%
• creatinine	145 (eGFR 56 ml/min/1.73m ²)
• albumin/creatinine ratio (<3.0)	25.1
• smoker	5 cigarettes/day
- ◆ How would you manage this man?

Case studies

- ◆ A 47-year-old White Caucasian lady attends your surgery with symptoms of painful peripheral neuropathy. She is on Novomix 30 insulin 78 μ am and 68 μ pm, with metformin 1g bd, simvastatin 40mg od, ramipril 10mg od
- ◆ She has the following clinical findings:
 - BP 130/75 mmHg
 - BMI 26 kg/m²
 - total cholesterol 4.0 mmol/l
 - HbA_{1c} (4.8%-6.4%) 9.6%
 - creatinine 74 (eGFR 86 ml/min/1.73m²)
 - albumin/creatinine ratio (<3.0) 3.4
 - smoker 5 cigarettes/day
- ◆ How would you manage this lady?

Take home messages

- ◆ Diabetes is getting commoner
 - the most important long-term condition!
- ◆ Cardiovascular risk reduction is mandatory
 - BP <140/80 mmHg, total cholesterol <4.0 mmol/l, aspirin, smoking cessation
 - HbA_{1c} <6.5% (individualised)
- ◆ Metformin should be given to all patients with type 2 diabetes unless it is not tolerated or contraindicated
- ◆ Tight glycaemic control is probably important early in the condition
- ◆ A number of new treatments for glycaemia offer different therapeutic options in type 2 diabetes.