Type 1 and Type 2 Diabetes

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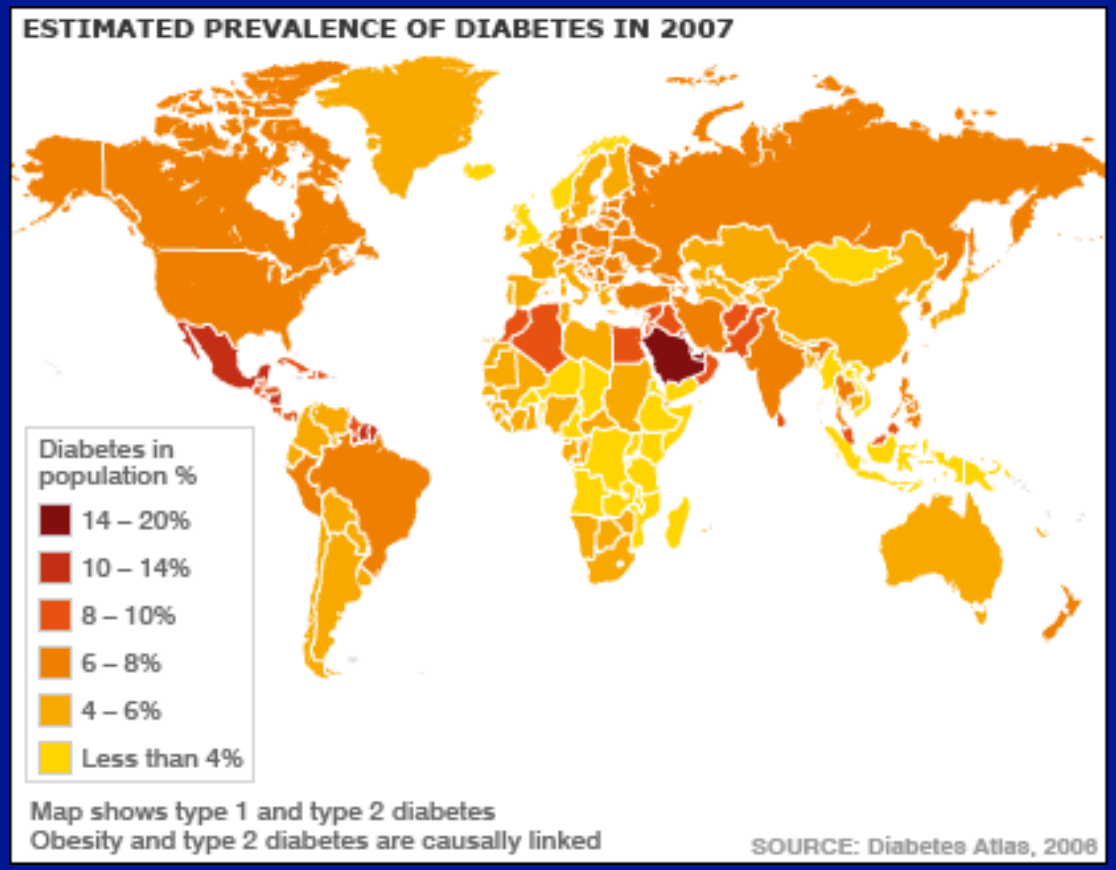
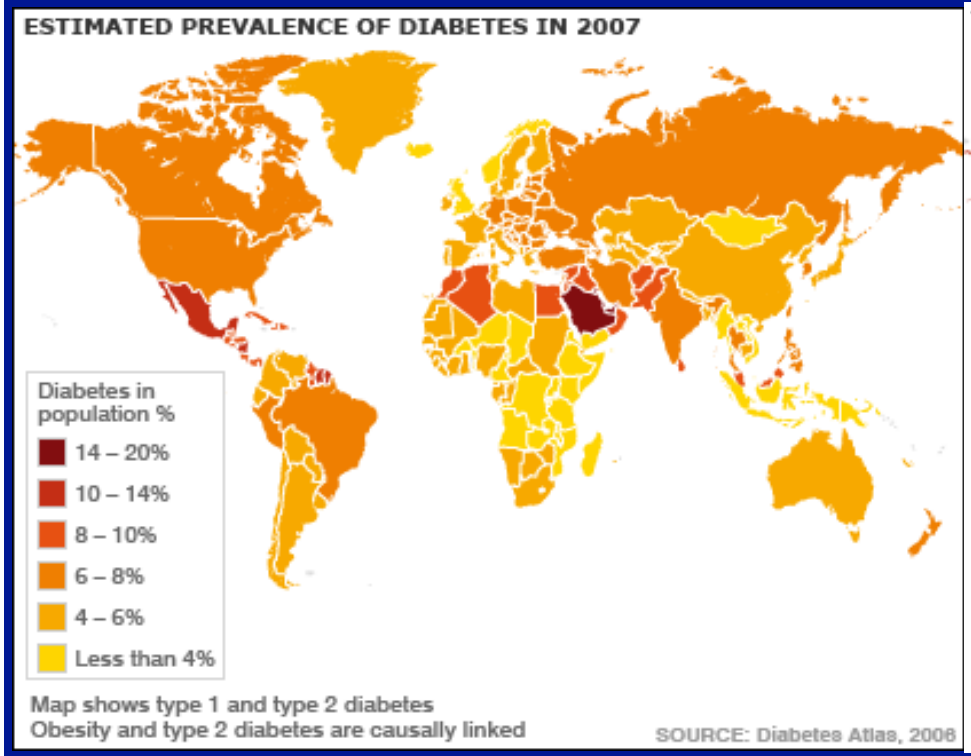
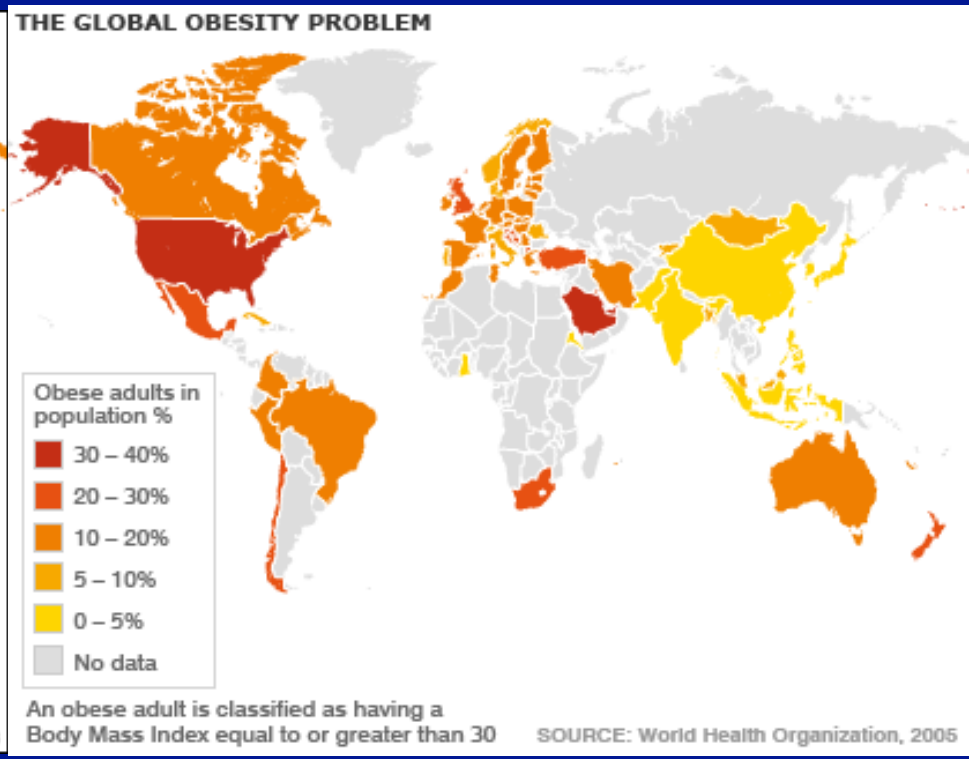
Worldwide, there are >170 million with diabetes mellitus
2.7 million in UK (nearly 1 in 20)



- This prevalence will double before 2030
- Worldwide 3.2 million deaths annually attributable to diabetes
- Commonest cause of end stage renal failure, blindness and non-traumatic amputations

Worldwide, there are >170 million with diabetes mellitus





- The increase in diabetes is linked strongly to the increasing prevalence of obesity
- 25% of UK obese, 32-42% overweight

Aims

- Acquire a basic understanding of:
  - clinical aspects of diabetes mellitus
  - its pathophysiology
  - Its subtypes
  - diabetes treatments
  - diabetes complications

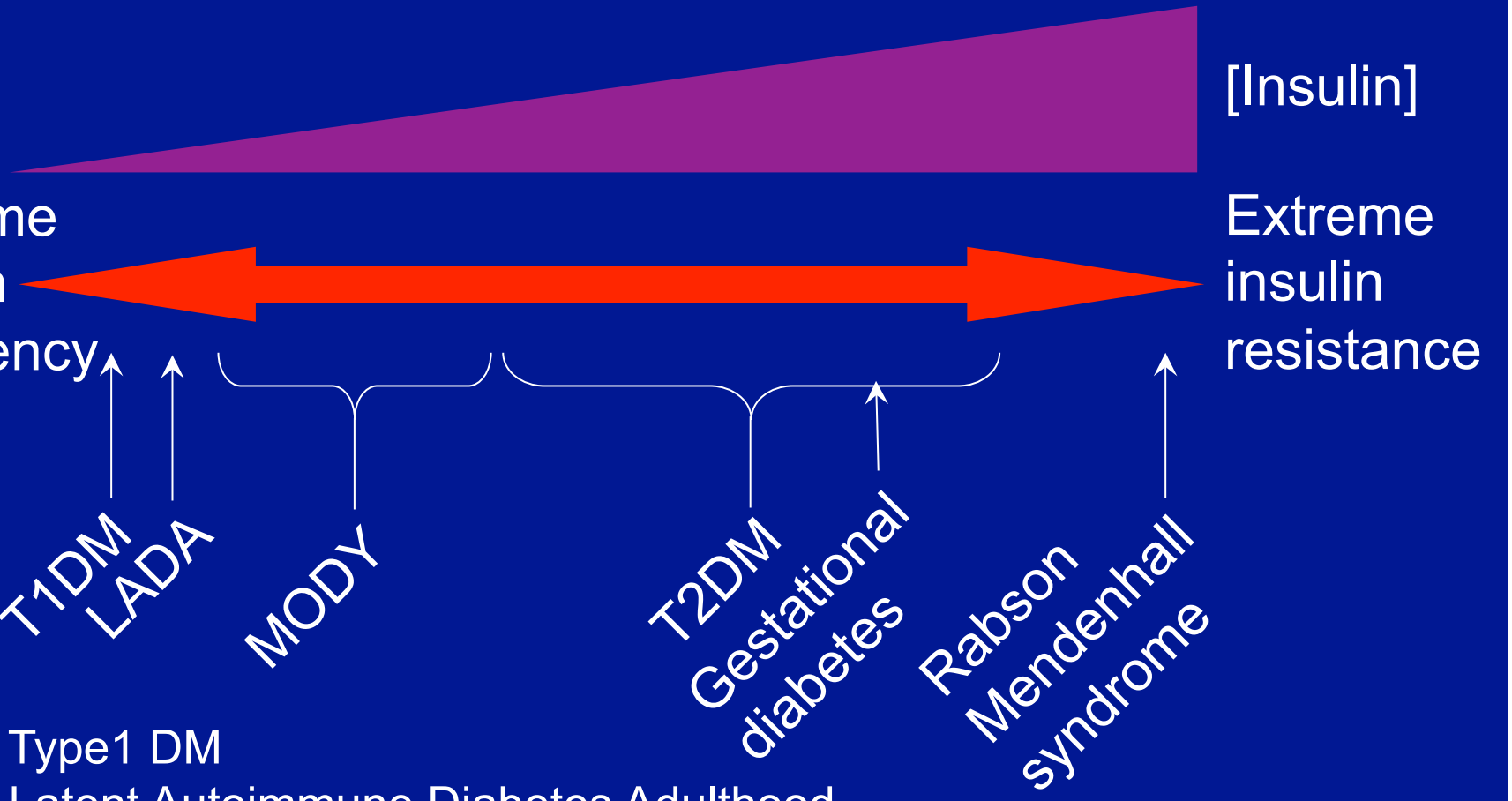
Learning objectives

1. List the signs and symptoms of DM
2. Distinguish between T1DM and T2DM
3. Understand their pathophysiology
4. Know the treatment options appropriate to each type
5. Classify types of complications
6. Have a theoretical knowledge of managing diabetic emergencies

Compare and Contrast

	Type 1	Type 2
Age onset	Young	Mature
Insulin levels	Low (zero)	High
Aetiology	Insulin deficiency	Insulin resistance
Pathogenesis	Autoimmune	Obesity
Body Habitus	Thin	Normal/↑BMI
Hyperglycaemic crisis	DKA	HHS
Treatment	Mandatory insulin	Diet/OHAs/insulin
GAD Abs	+ve	-ve
C peptide	Low	High

In Reality



- T1DM Type1 DM
- LADA Latent Autoimmune Diabetes Adulthood
- MODY Maturity Onset Diabetes of Youth
- T2DM Type 2 DM
- Rabson-Mendenhall syndrome = severe genetic insulin receptor defect
- Others eg mitochondrial, secondary

Symptoms and Signs

- Polyuria, polydipsia, dehydration
- Blurring of vision
- Weight loss & cachexia
- Infections
- Ketotic foetor
- Glycosuria
- Delirium and coma

Pathophysiology of T2DM

- INSULIN RESISTANCE
  - Related to adipose tissue “dysfunction”
  - Visceral > Subcutaneous obesity
- plus β CELL FAILURE
- Associated with
  - Hypertension, dyslipidaemia, PCOS
- Stronger genetic component than T1DM
- Ethnically linked
  - S Asian Indians
  - Pima Indians in Arizona

Metabolic syndrome (WHO)

- One of:
  - T2DM / Imp gluc tolerance / Imp fasting gluc / Insulin resistance
- Plus two of:
  - BP ≥140/90
  - Trigs ≥1.695 and HDL ≤ 0.9(M) ≤1.0 (F)
  - Central obesity: waist:hip >0.90 (M) >0.85 (F) or BMI >30
  - Microalbuminuria: Alb:Creat ratio ≥30 mg/g

Pathophysiology of T1DM

- Autoimmune destruction of islets
- Combination of
  - genetic predisposition (HLA DR3 & 4)
  - viral infection (Coxsackie)
  - ➢ T-cell mediated ß cell destruction.
- 30-50% concordance in identical twins
- Geographic factors
  - Most common in European population
  - ?link to Vit D deficiency

Diagnosis of Diabetes

If symptoms, DM=

- Fasting plasma glucose ≥7.0 mmol/L
- Random PG or 2 hour OGTT ≥11.1

If no symptoms, DM=

- Two of above criteria

Impaired Gluc Tolerance=

- Fasting PG <7.0, 2 hr OGTT ≥7.8 but <11.1

Impaired Fasting Gluc=

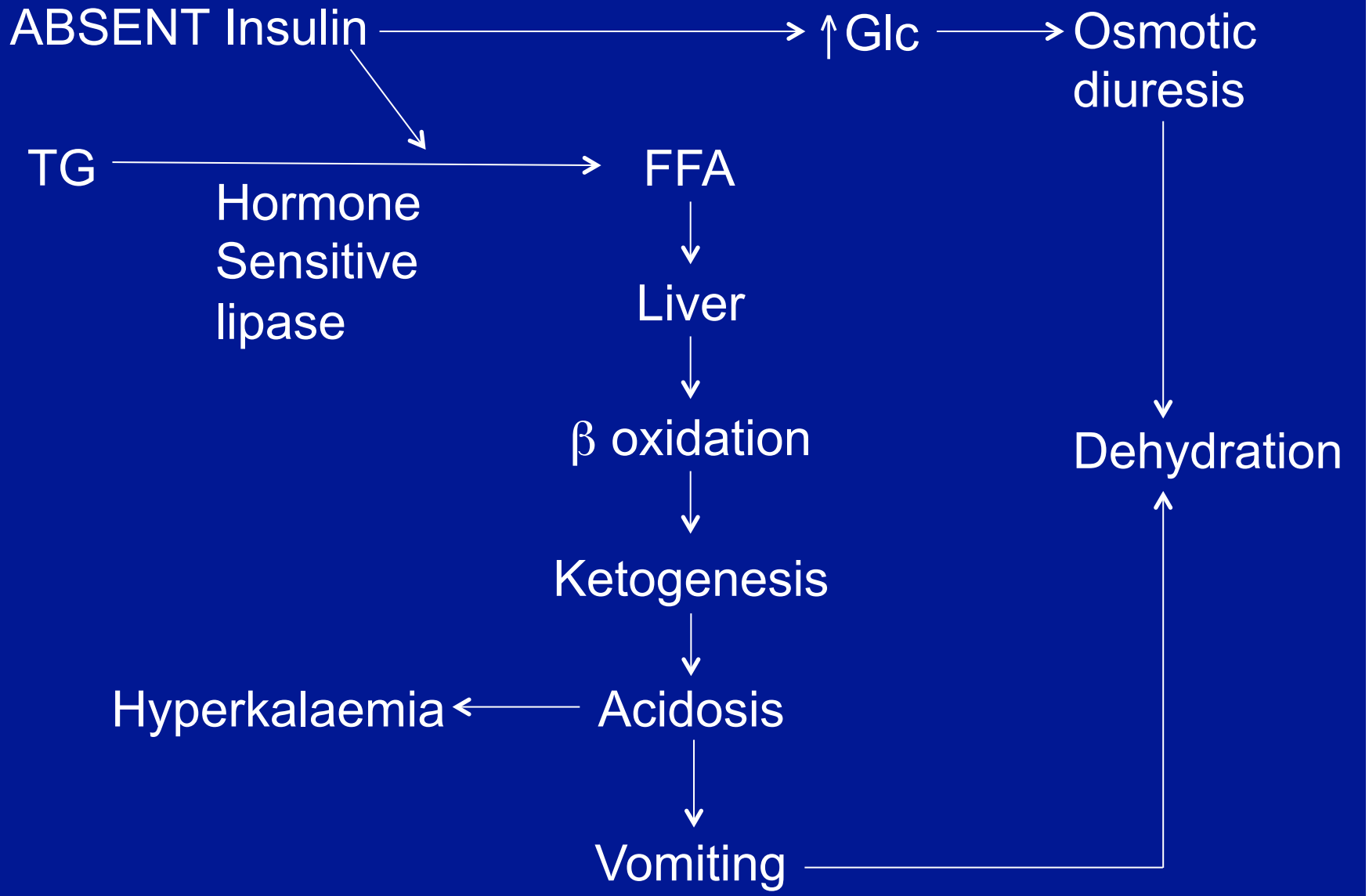
- Fasting PG ≥6.1 but <7.0

A new definition of diabetes

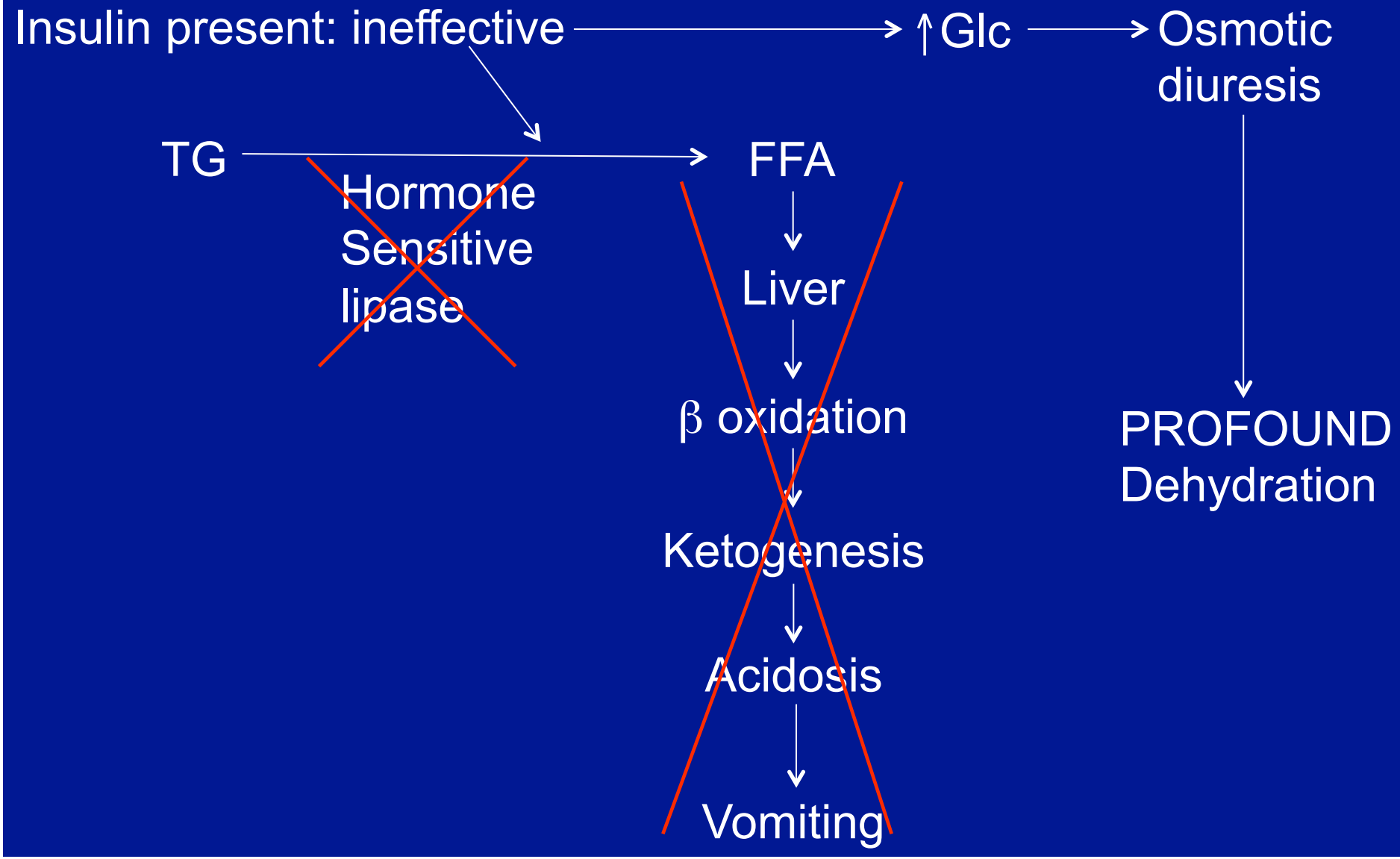
- HbA1c >48 mmol/mol (≥6.5%)
- But
  - Cannot be used as sole test for diagnosis
  - Hb variants, RBC destruction may interfere with testing
  - Cannot be used in children
  - Short duration of hyperglycaemia may cause false negative

Complications

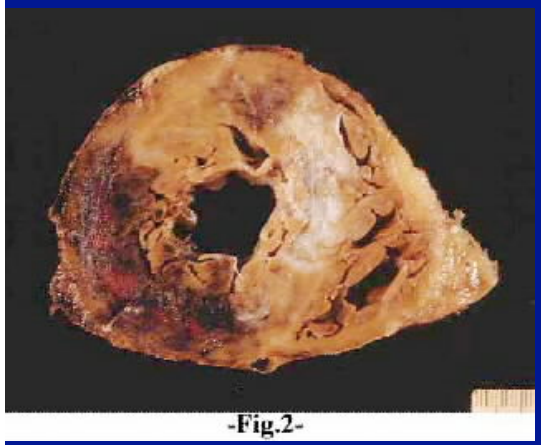
Diabetic Ketoacidosis

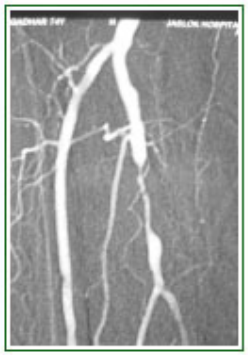


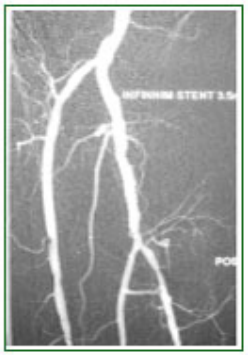
Hyperglycaemic Hyperosmolar State (HHS or "HONK")



Complications





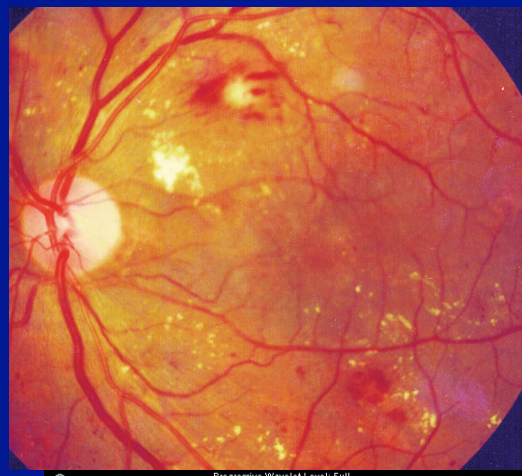


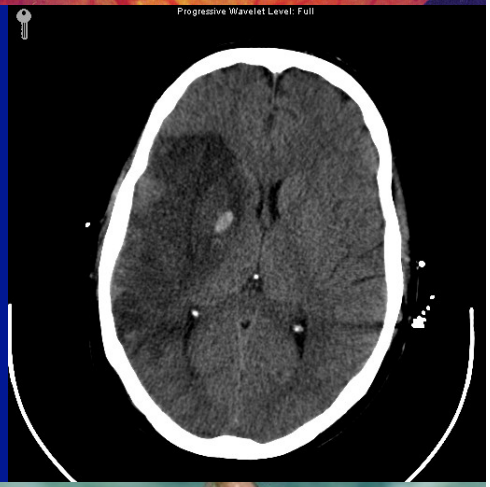
Microvascular

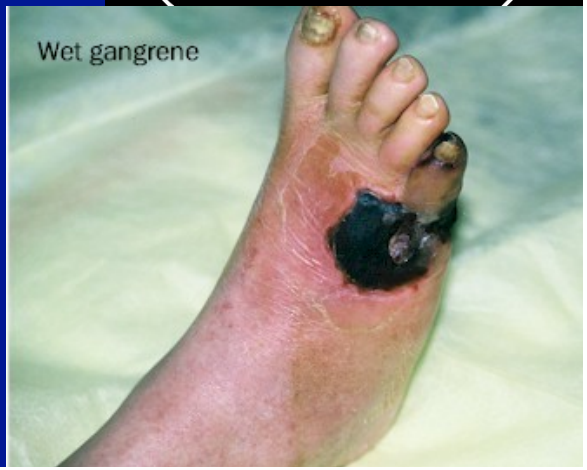
- Glycosylation of basement membrane proteins -> “leaky” capillaries
- Retinopathy
- Nephropathy
- Neuropathy

Macrovascular

- Dyslipidaemia, hypertension
- IHD
- CVA
- Peripheral vascular disease







Treatment

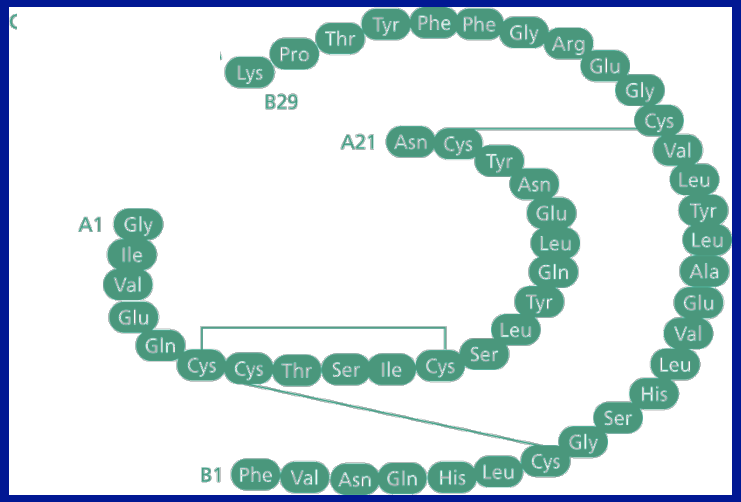
T2DM treatment

- Mediterranean diet
  - Olive oil, fruit & veg, fish, white meats
- Exercise
  - 3x 60 mins per week
  - Moderate physical activity
- Loss of weight for obese
  - Bariatric surgery as new treatment

T2DM Drugs

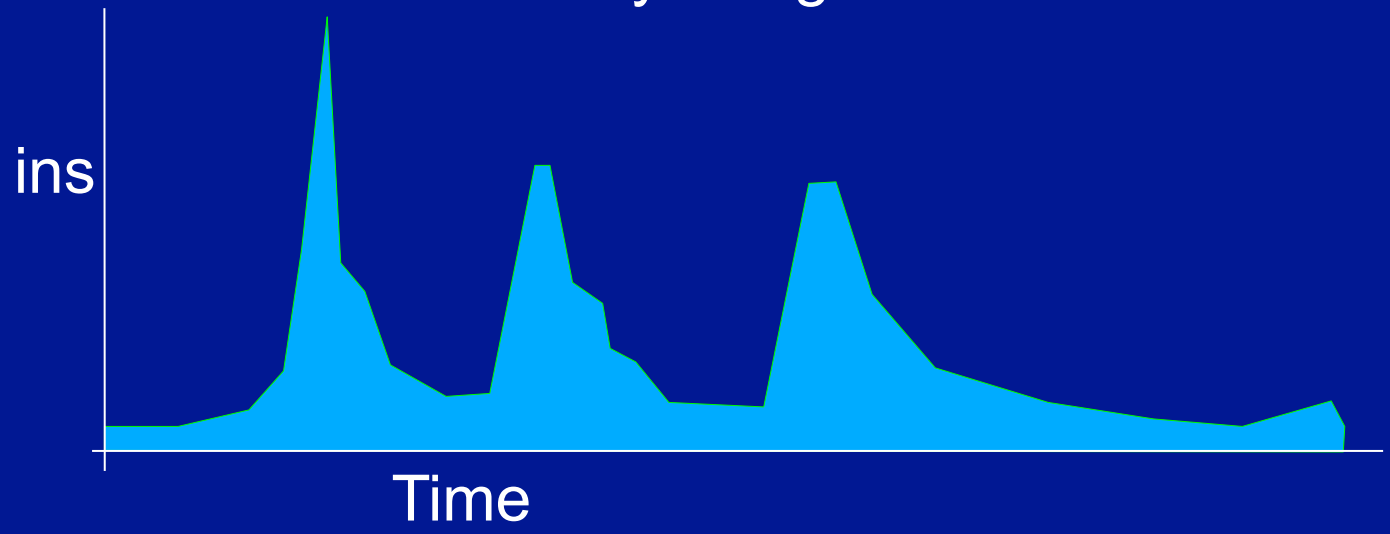
Example	Class	Mode of Action	Notes
Metformin	Biguanide	Insulin sensitizer	CKD, lactate
Gliclazide	Sulphonylurea	Secretagogue	Wt gain, hypo
Repaglinide	Meglitinide	Secretagogue	Not v useful
Acarbose	Glucosidase inhibitor	Retards CHO abs	Flatus+++
Pioglitazone	TZD	Insulin sensitizer	Arm #/CCF
Exenatide	GLP1-analogue	Secretagogue	Injections
Sitagliptin	DPP-IV inh	Secretagogue	New
Dapagliflozin	SGLT2 inh	Increases glucosuria	UTIs

Insulin Synthesis and Secretion

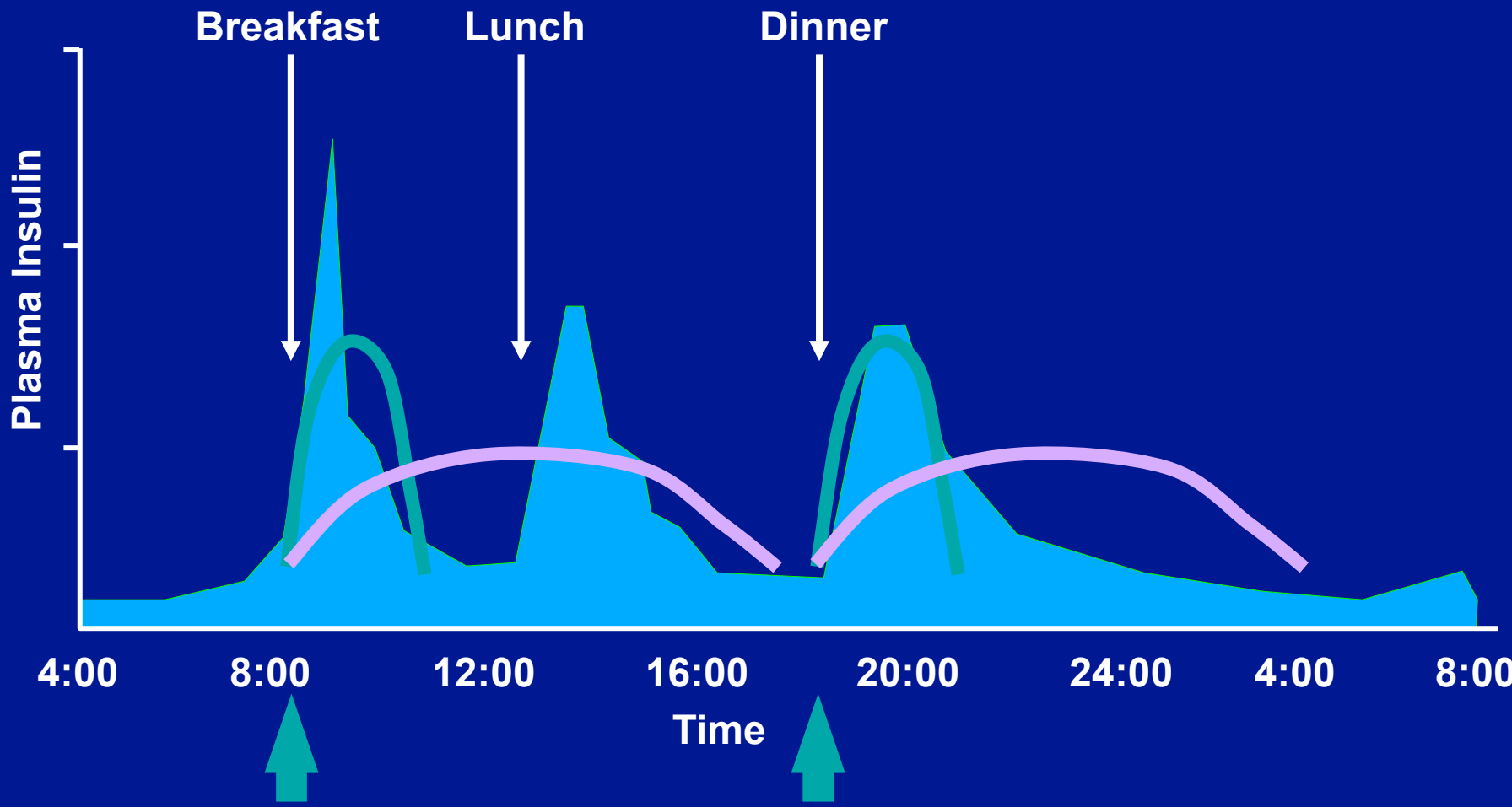


- 50 AA peptide, 3 intramolecular disulphide bridges, 5808 kDa
- Synthesised as preproinsulin
- ER peptidases cleave C-peptide
- Half life of insulin in the circulation = 6 minutes

Physiological Insulin Profile:



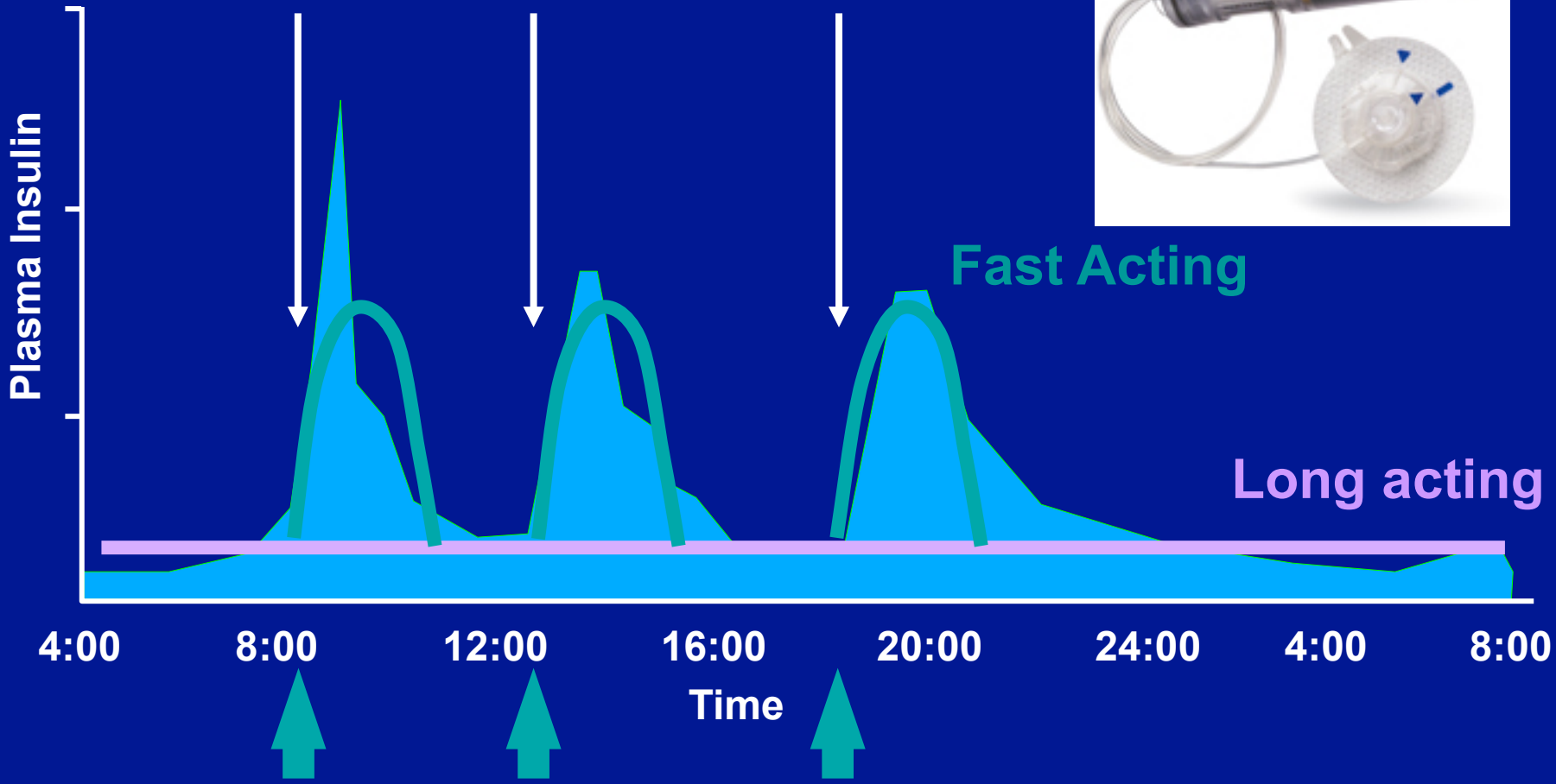
BD Mixed insulin



Advantage: fewer injections/day
simpler

Disadvantage: less flexibility

"Basal Bolus"

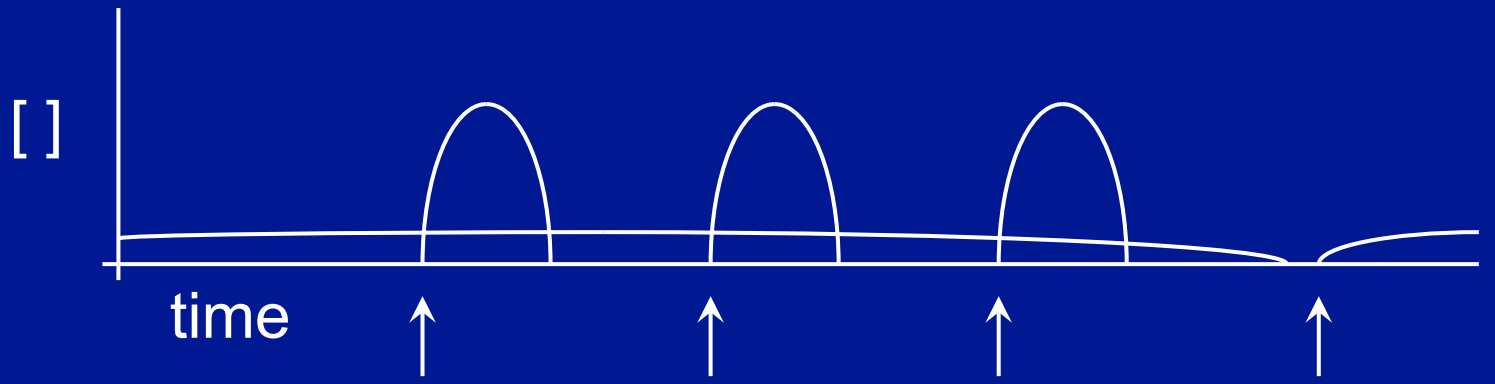


Advantage: Flexibilty

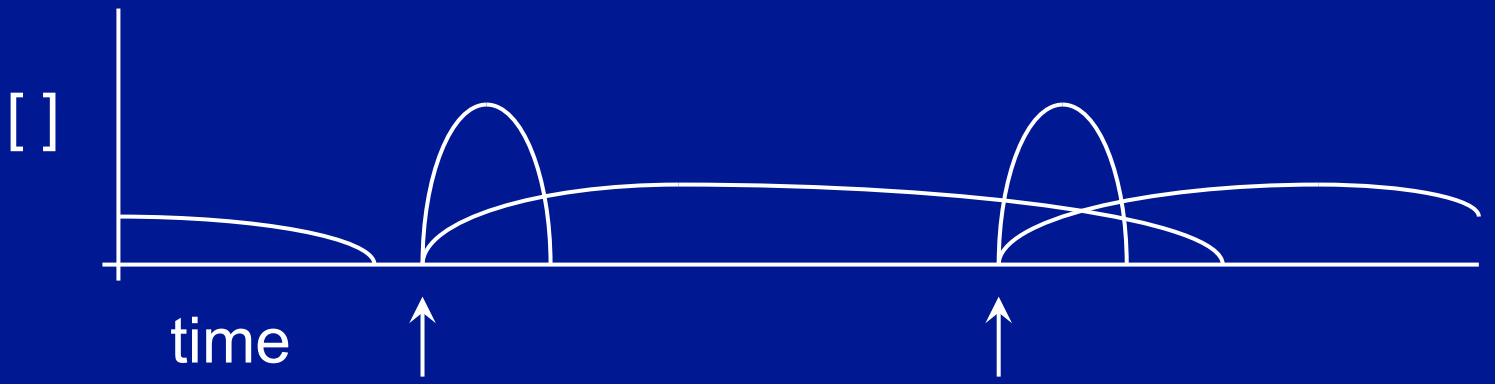
Disadvantage: 4 injections/day or needs pump

Insulin Regimens

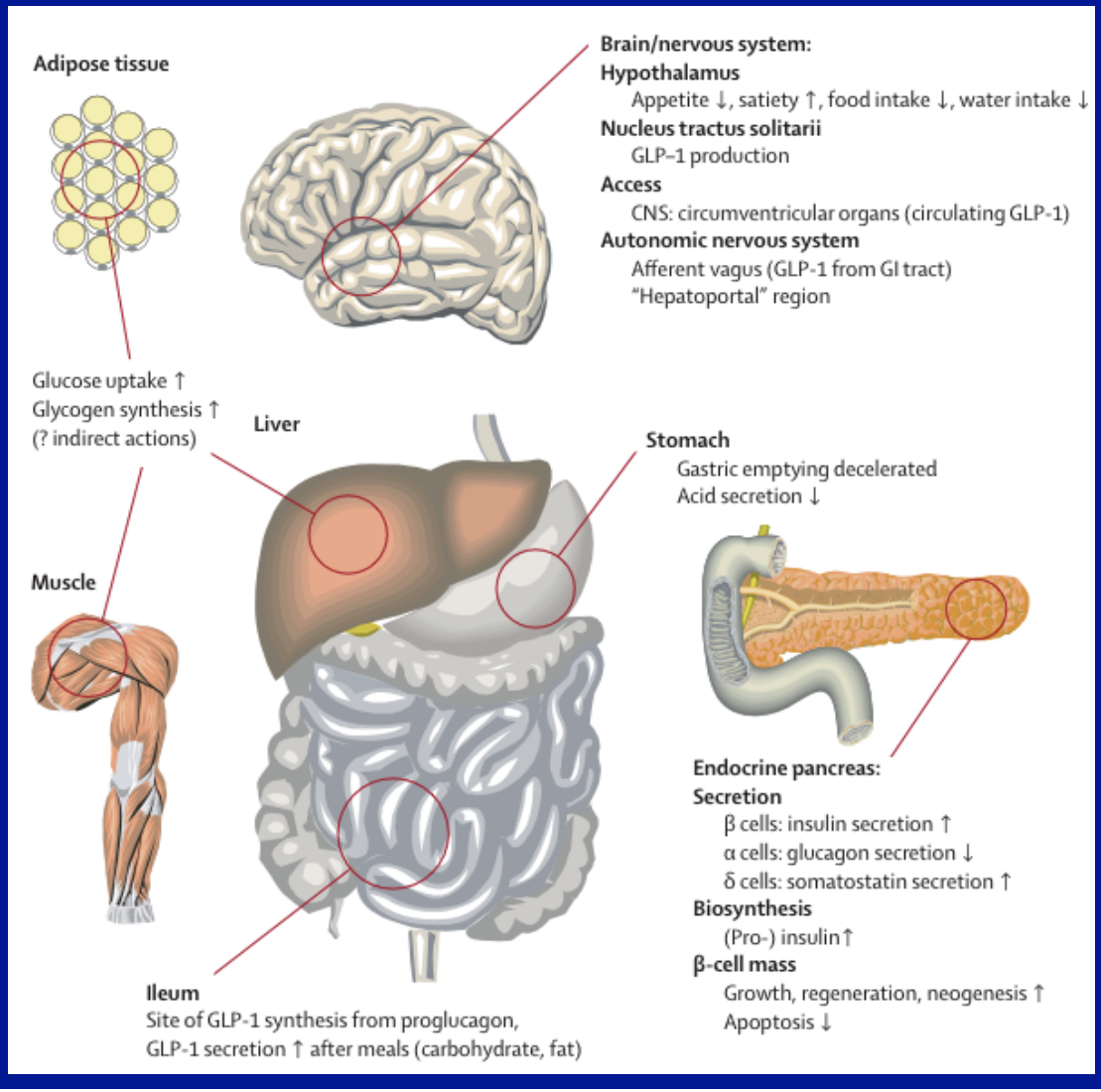
Basal/Bolus eg Insulatard/Actrapid



Twice Daily Mixed/Biphasic eg Mixtard 30



Glucagon-like peptide 1 (GLP-1)



- Stimulates Insulin secretion
- Inhibits Glucagon secretion
- Inhibits Gastric emptying
- Inhibits Appetite
- Stimulates Nausea

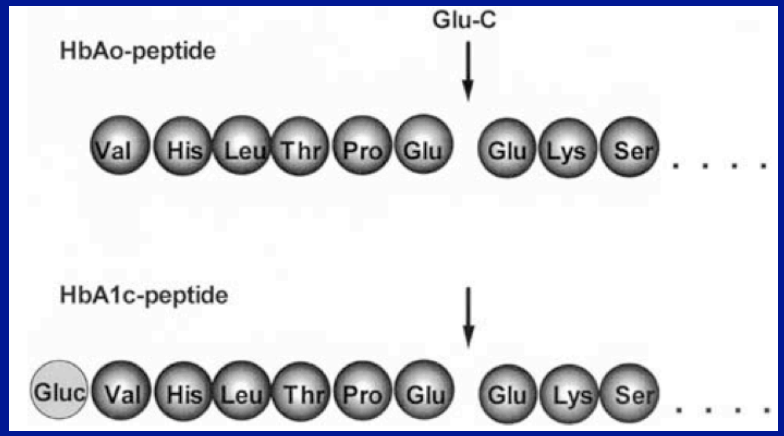
Why we treat diabetes

Aims of treatment

- Relieve symptoms of hyperglycaemia
  - Fatigue
  - Polyuria, polydipsia
  - Weight loss
- Prevent complications
  - Microvascular: retinal, renal, neural
  - Macrovascular: MI, stroke, peripheral vessels

What is HbA1c?

- Non-enzymatic glycosylated product of Hb (N-terminus of ß-chain HbA0)
- Mostly measures average glycaemia over 2-4 weeks
- HPLC, immunoassay, boronate affinity chromatography



- Rapidly available
- Point of care testing in 5 minutes

HbA1c FOR THE DIAGNOSIS OF DIABETES

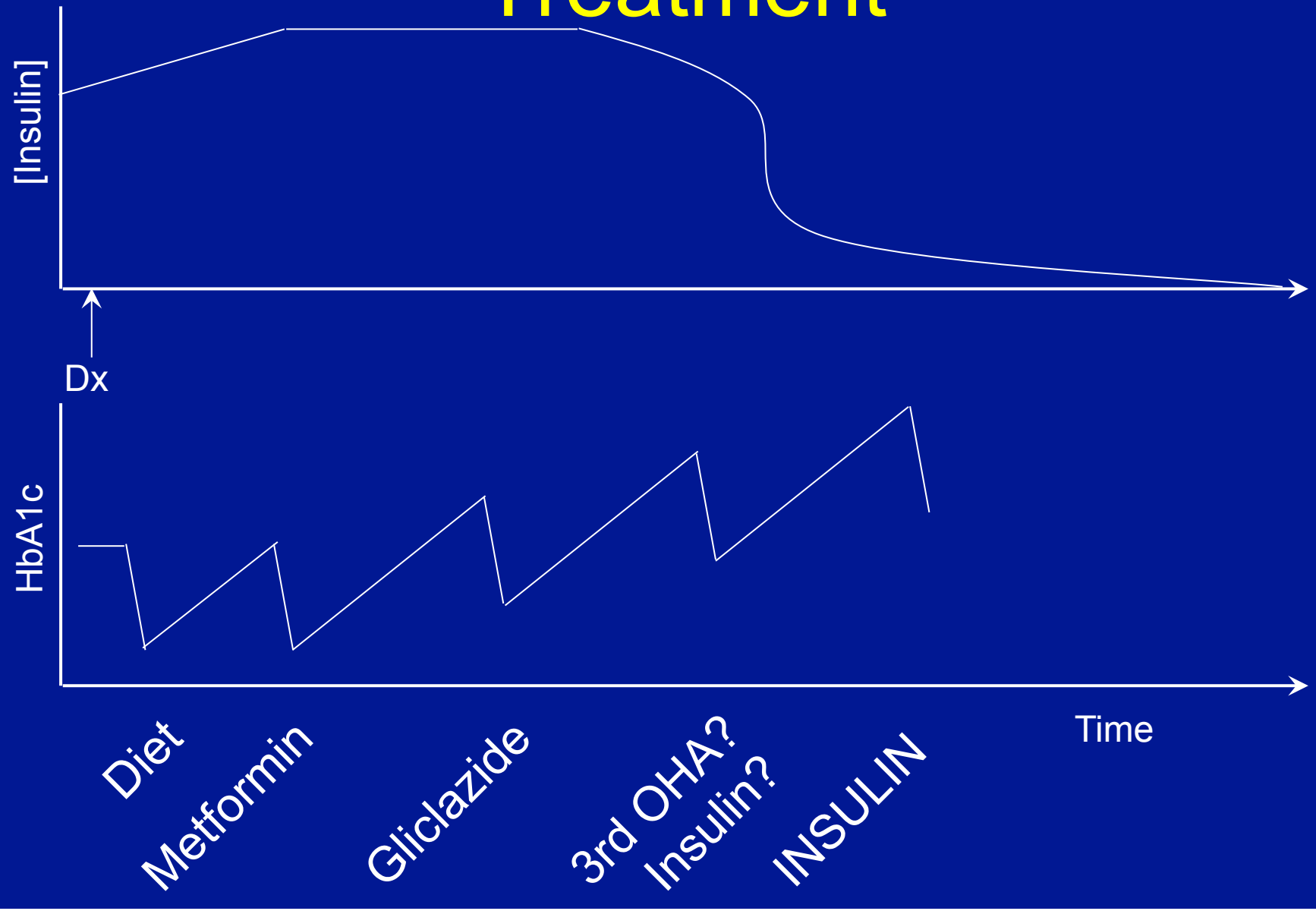
- Recommendations from the WHO 2011:
  - An HbA1c of 6.5% is recommended as the cut off point for diagnosing diabetes.
  - A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

HbA1c – Change in Units

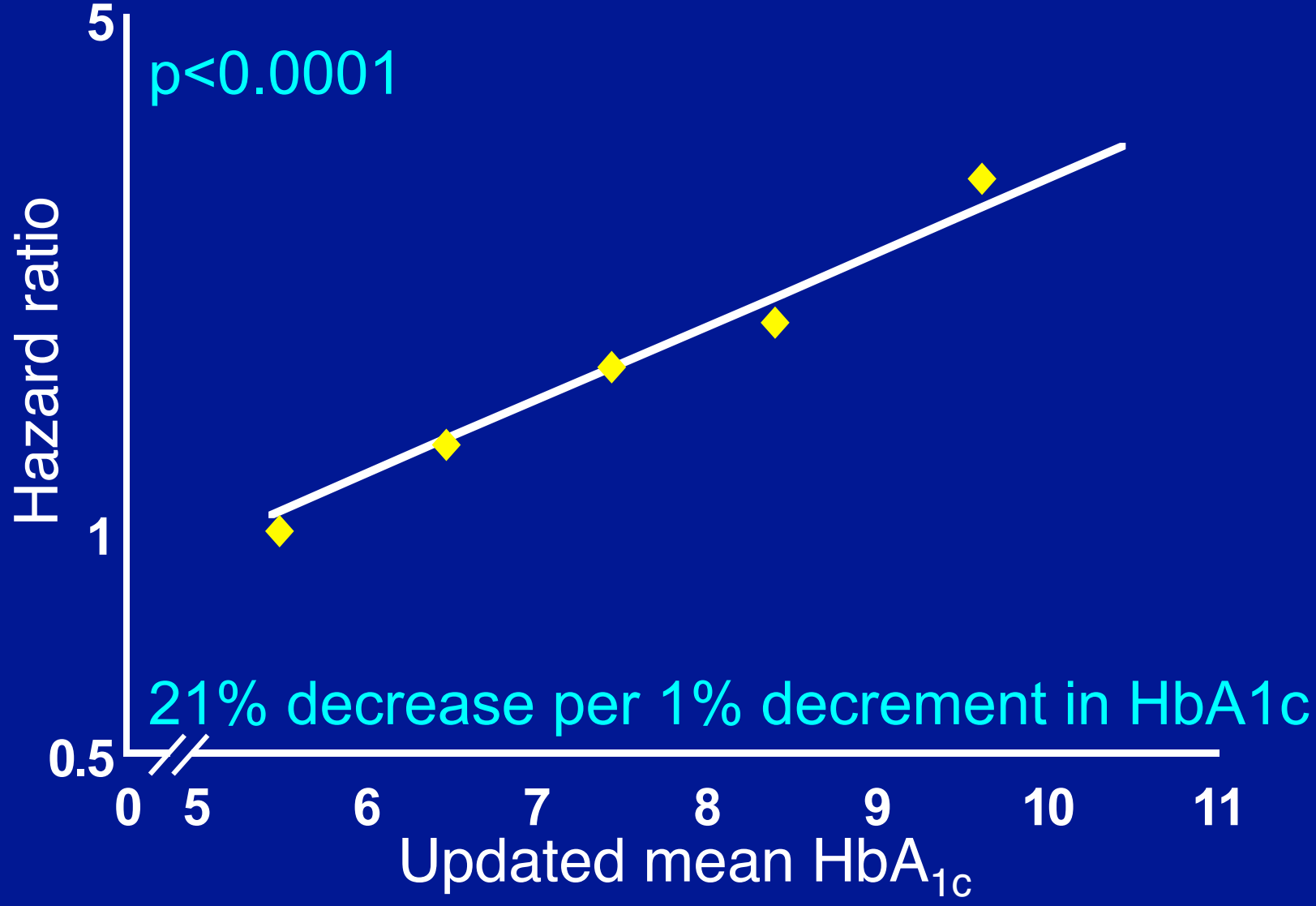
- Until 2009, it was traditional to express HbA1c as %
- HbA1c is now expressed as mmol/mol

DCCT- HbA1c %	IFCC-HbA1c mmol/mol
6.0	42
6.5	48
7.0	53
7.5	58
8.0	64
9.0	75
10.0	86

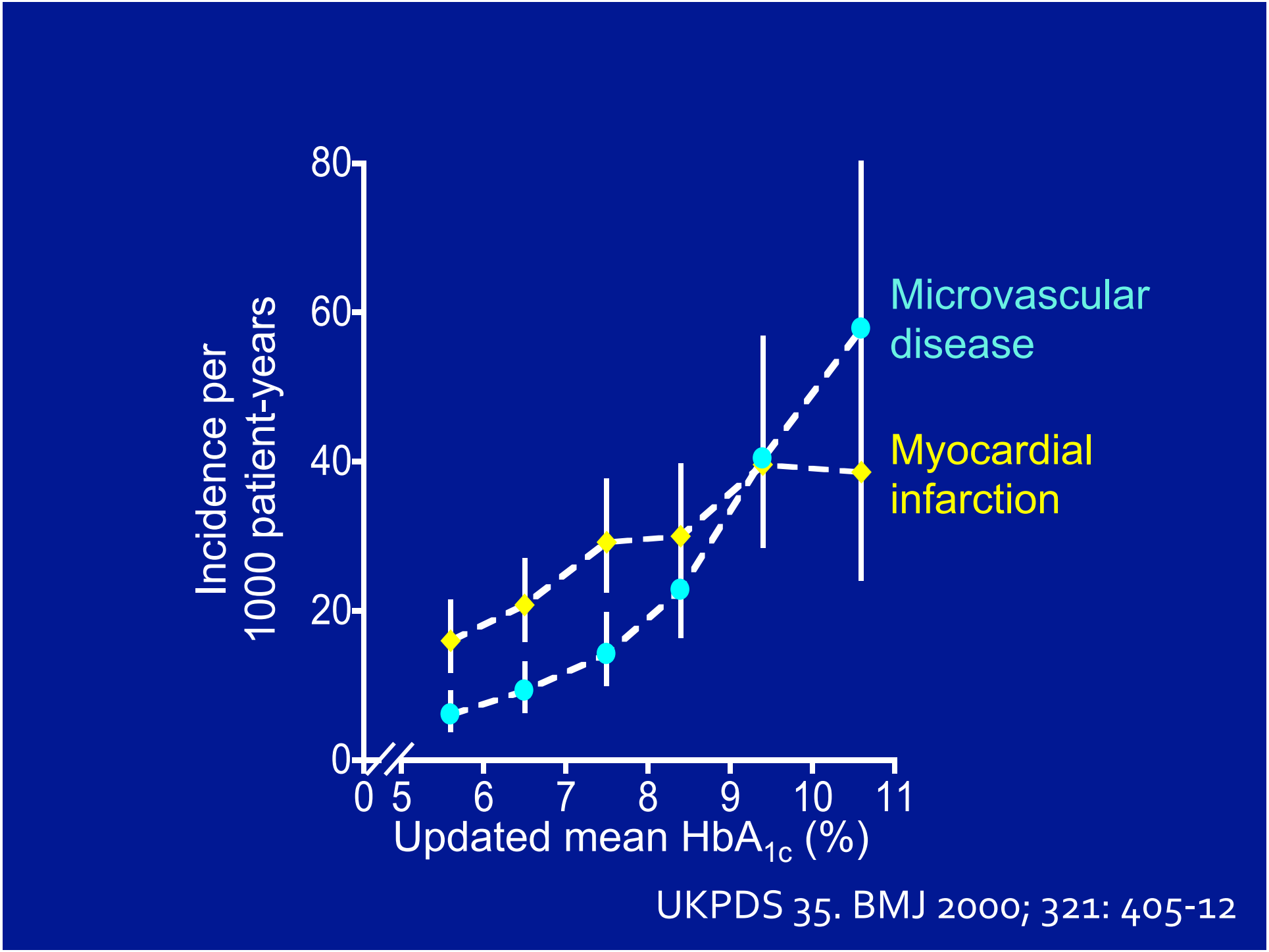
T2DM Pathophysiology and Treatment



Any Diabetes Related Endpoint



UKPDS 35. BMJ 2000; 321: 405-12



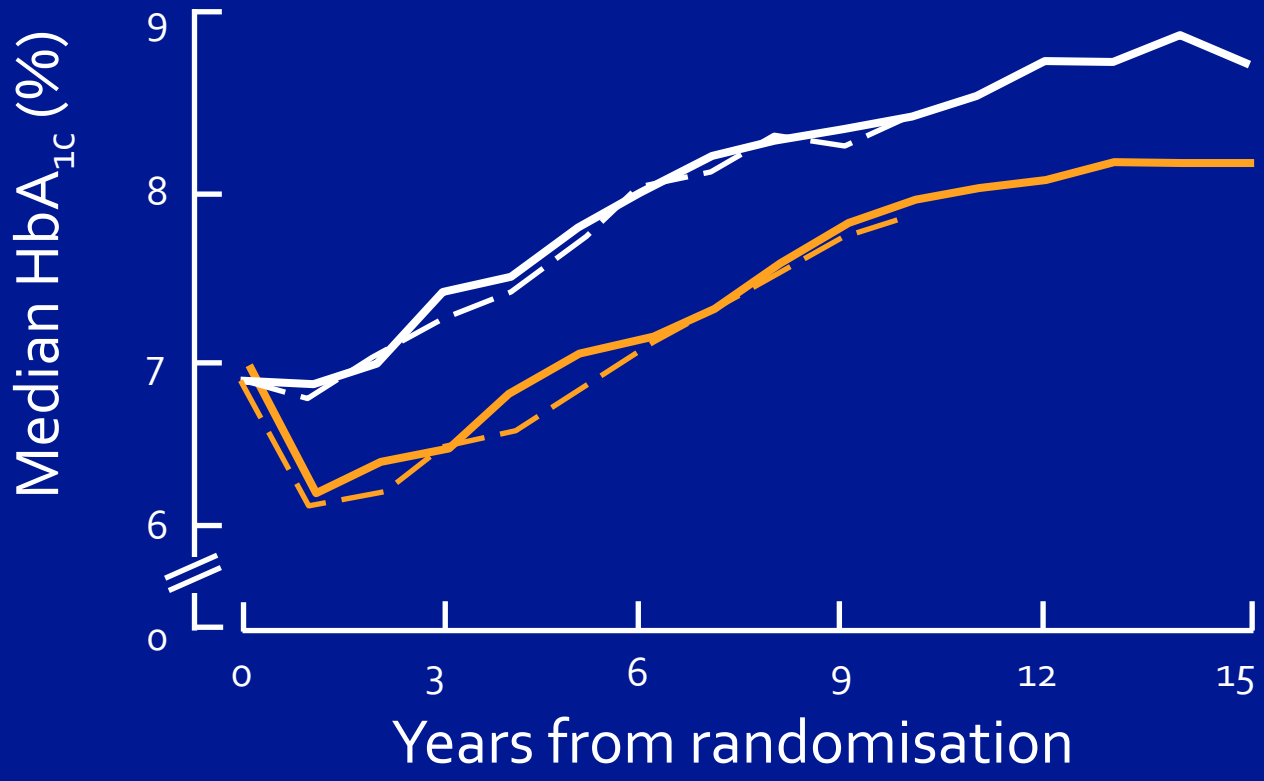
UKPDS 35. BMJ 2000; 321: 405-12

UKPDS 33: intensive therapy reduced HbA1c

Intensive policy, median HbA_{1c} 7.0%

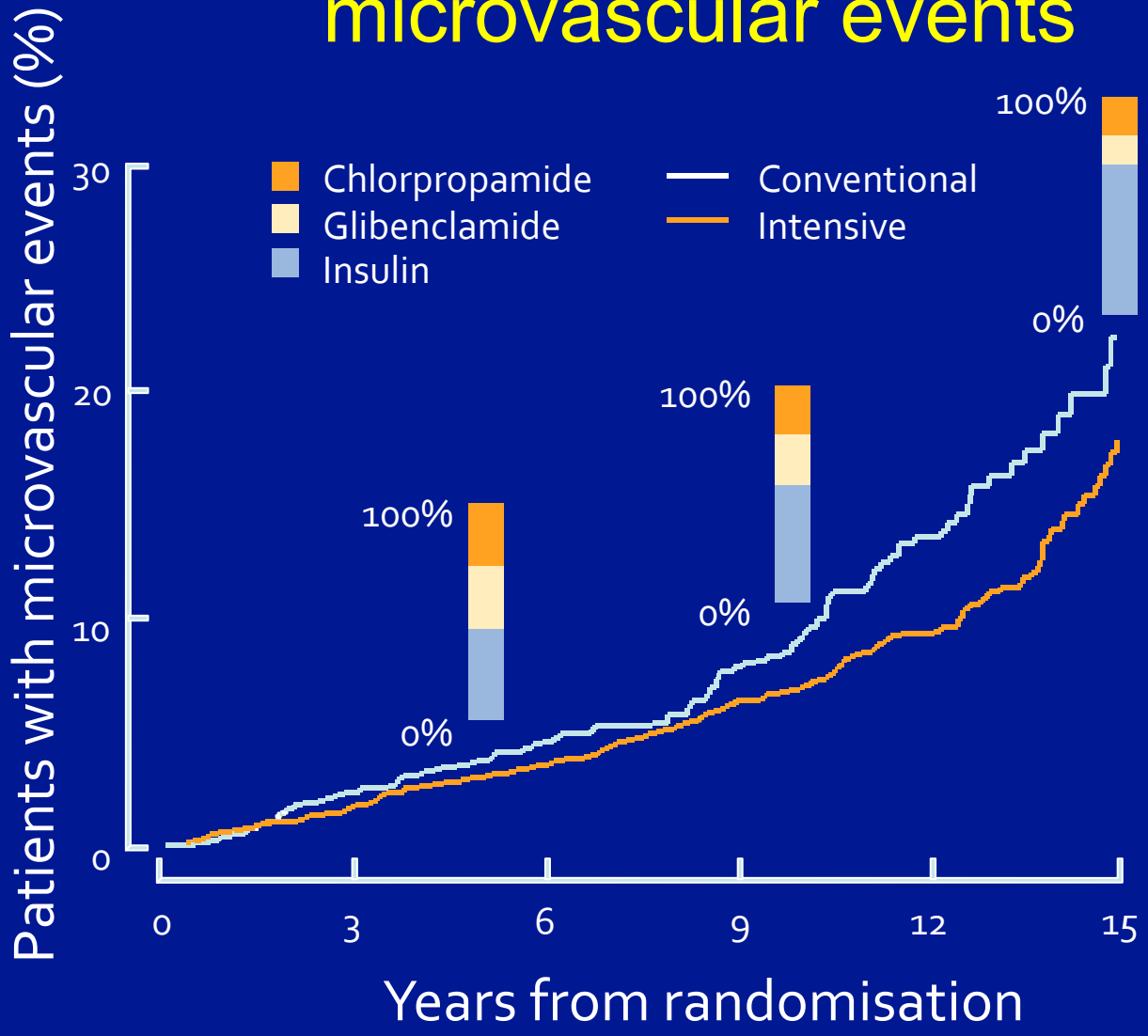
Conventional policy, median HbA_{1c} 7.9%

Dashed lines indicate patients followed for 10 years
Solid lines indicate all patients assigned to regimen



Lancet 1998;352:837–53

UKPDS 33: intensive therapy reduced microvascular events



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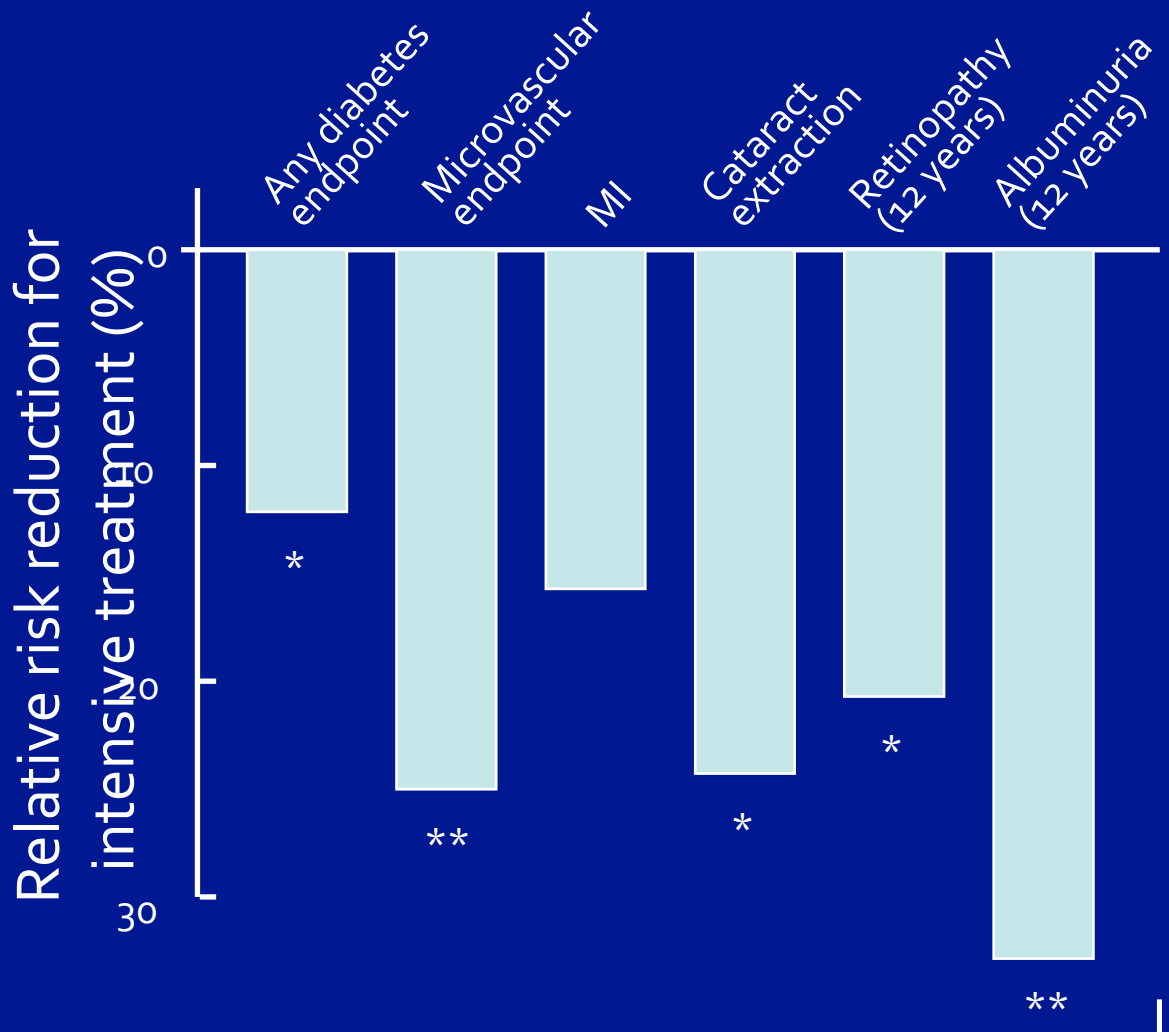
UKPDS 33: relative risk reduction with intensive treatment



Intensive treatment reduced HbA_{1c} by 0.9% for a median of 10 years in 3,867 patients with type 2 diabetes

* $p < 0.05$ ** $p < 0.01$

Lancet 1998;352:837–53

Summary

- T1DM is
  - due to autoimmune islet destruction causing insulin deficiency
  - treated with insulin replacement therapy
- T2DM is
  - due to insulin resistance plus ß cell failure
  - treated with diet, OHAs and eventually insulin
- Complications of both types
  - broadly similar
  - can be classified as macro- and micro- vascular
- Treatment is aimed to
  - Relieve symptoms
  - Prevent complications