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LEEDS TEACHING HOSPITALS

DIABETES UPDATE 2013

AIMS OF THE SEMINAR

- Diagnosis
- Investigation
- Management
- New treatments
- When to refer
- How to liaise with a specialist

WHAT IS DIABETES?

- A syndrome of raised blood glucose, hyperglycaemia, due to various causes.
- It has acute and chronic complications.
- Patients often have high BP and high lipid levels.

DIAGNOSIS OF DIABETES

- Typical symptoms and high RANDOM blood glucose
- Fasting blood glucose >7mmol/l
- 75g OGTT
- HbA1c; 48 mmol/mol (6.5%)

Investigations

- HbA1c
- Renal function
- Liver function
- Lipids
- Thyroid function

MANAGEMENT

DEPENDS ON THE TYPE OF DIABETES

WHICH TYPES OF DIABETES CAN YOU NAME?

TYPES OF DIABETTES

- Type 1: insulin dependent
- LADA latent autoimmune diabetes in adults
- Type 2
- Pancreatic disorders
- Drug induced
- Endocrine disorders
- Ethnic variants of diabetes
- Genetic syndromes

TYPE 1 DIABETES

- Autoimmune destruction of the insulin producing islet beta cells
- Insulin deficient: insulin dependent
- Usually young, but can be ANY age
- Autoantibody tests: ICA, IA2, GAD
- Often other endocrine disorders in patient or family

LADA
latent autoimmune diabetes in adults

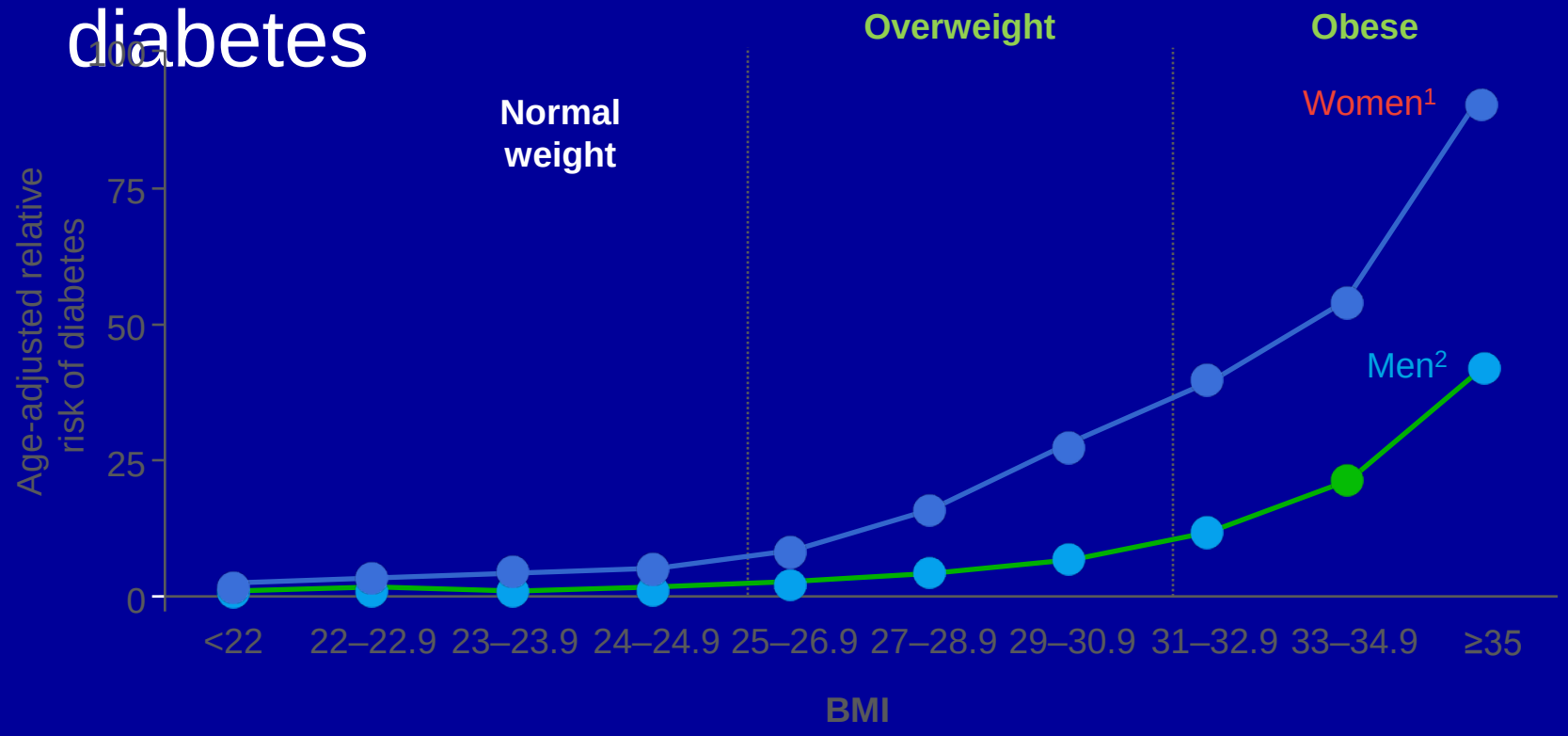
- Older patients, often female
- Medical or family history of related conditions: type 1 diabetes, thyroid, PA, Addison's, coeliac, vitiligo
- Presents as type 2 diabetes
- Progressive deterioration in control, increasing therapy
- Autoantibodies: GAD, ICA, tTG, TPO

TYPE 2 DIABETES

- Insulin resistant/deficient
- Not absolutely insulin dependent
- Strong family history
- Often obese or overweight
- Usually hypertensive and hyperlipidaemic

Diabetes and obesity are closely interlinked

Relationship between BMI and risk of type 2 diabetes



BMI, body mass index.

1. Colditz GA, *et al. Ann Intern Med* 1995;**122**:481–6; 2. Chan J, *et al. Diabetes Care* 1994;**17**:961–9.

DIABETES SECONDARY TO PANCREATIC DISORDERS

- Chronic or acute pancreatitis
- Calcific, tropical pancreatitis
- Pancreatectomy
- Pancreatic cancer
- Cystic fibrosis
- Haemochromatosis

DRUG INDUCED DIABETES

- Diuretics
- Steroids
- Antipsychotics e.g. Olanzapine
- Psychiatric drugs: weight gain

ENDOCRINE DISORDERS

- Acromegaly
- Cushing’s syndrome
- Phaeochromocytoma

ETHNIC VARIANTS OF DIABETES

- J type diabetes: ‘Jamaican’ diabetes, Afro-Caribbeans
- Flatbush diabetes: US Affo-Americans
- MRDM: malnutrition- related diabetes, tropical diabetes
- Chronic calcific pancreatitis: secondary diabetes
- Z type diabetes

GENETIC SYNDROMES

- Friedreich’s ataxia
- Dystrophia myotonica

GESTATIONAL DIABETES

- Diabetes appears during pregnancy
- Diabetes resolves after pregnancy
- At risk of diabetes in later pregnancy
- At risk of diabetes in future
- Pregnancy in the known diabetic case
- Diabetes arising or diagnosed in pregnancy

MODY
‘Maturity onset diabetes in the young: Mason diabetes, Tattersall & Fajans

- Autosomal dominant pattern
- 1-2% of diabetic cases
- Onset under 25
- Insulin not required initially
- Glucokinase, HNF 1A, HNF 4A

INSULIN THERAPY

- Twice daily mix: Novomix 30, Humalog Mix 25
- Basal bolus: Lantus or Levemir, Novorapid or Humalog
- Pump therapy
- Insulin side effects: weight gain, hypoglycaemia

INSULIN PEN

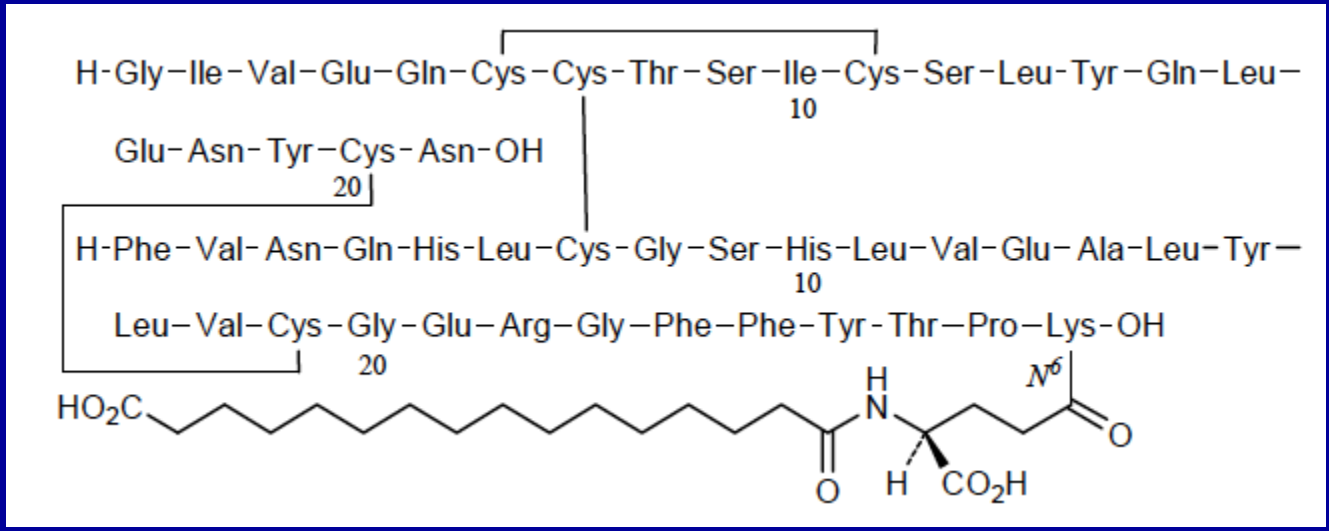
TRESIBA:DEGLUDEC INSULIN

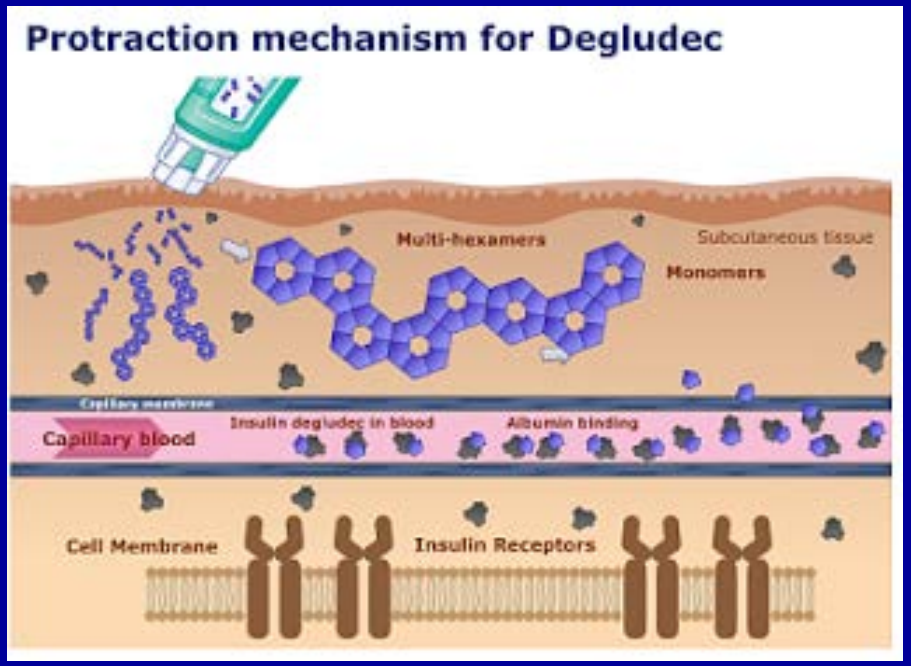
- Insulin degludec is a modified insulin that has one single amino acid deleted in comparison to human insulin, and is conjugated to hexadecanedioic acid via gamma-L-glutamyl spacer at the amino acid lysine at position B29

TRESIBA:DEGLUDEC INSULIN

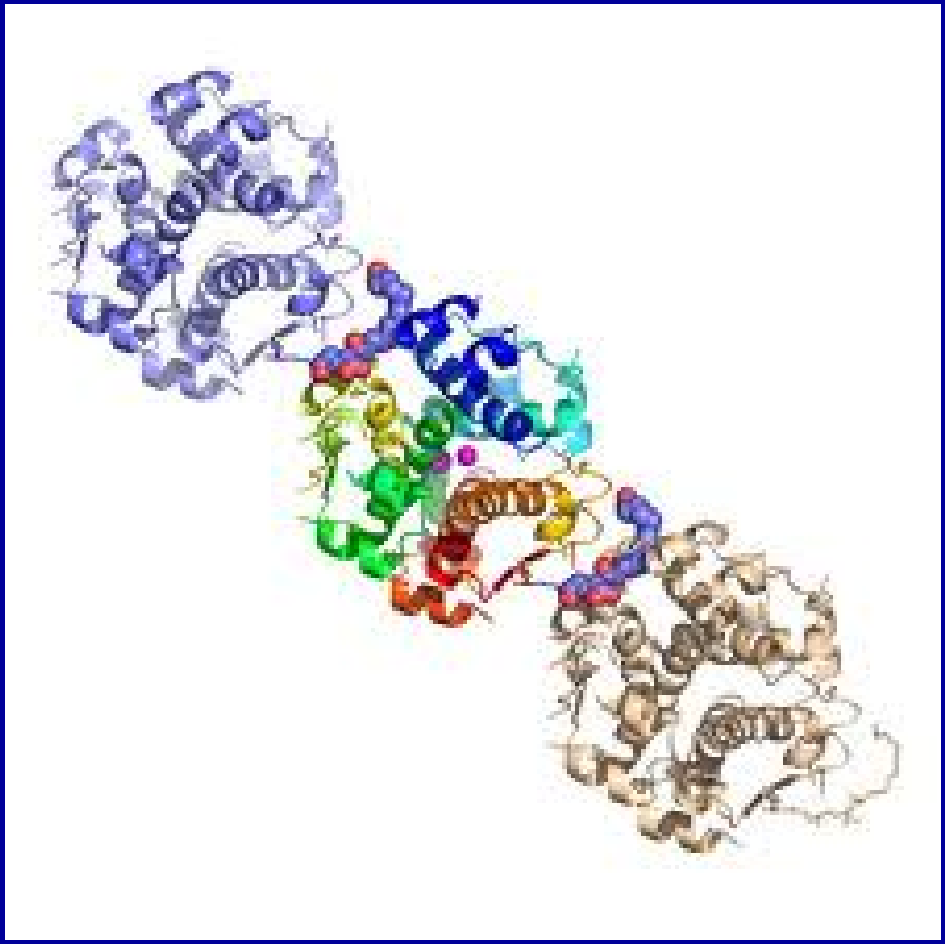
- Ultra-long lasting insulin: 40 hours
- Injected thrice weekly or daily
- Flat profile
- Daily time of injection not critical
- Allows for missed injection
- Nocturnal hypos 27% lower: (3.91 vs. Lantus 5.22%,p=0.024), HbA1c similar

TRESIBA:DEGLUDEC INSULIN

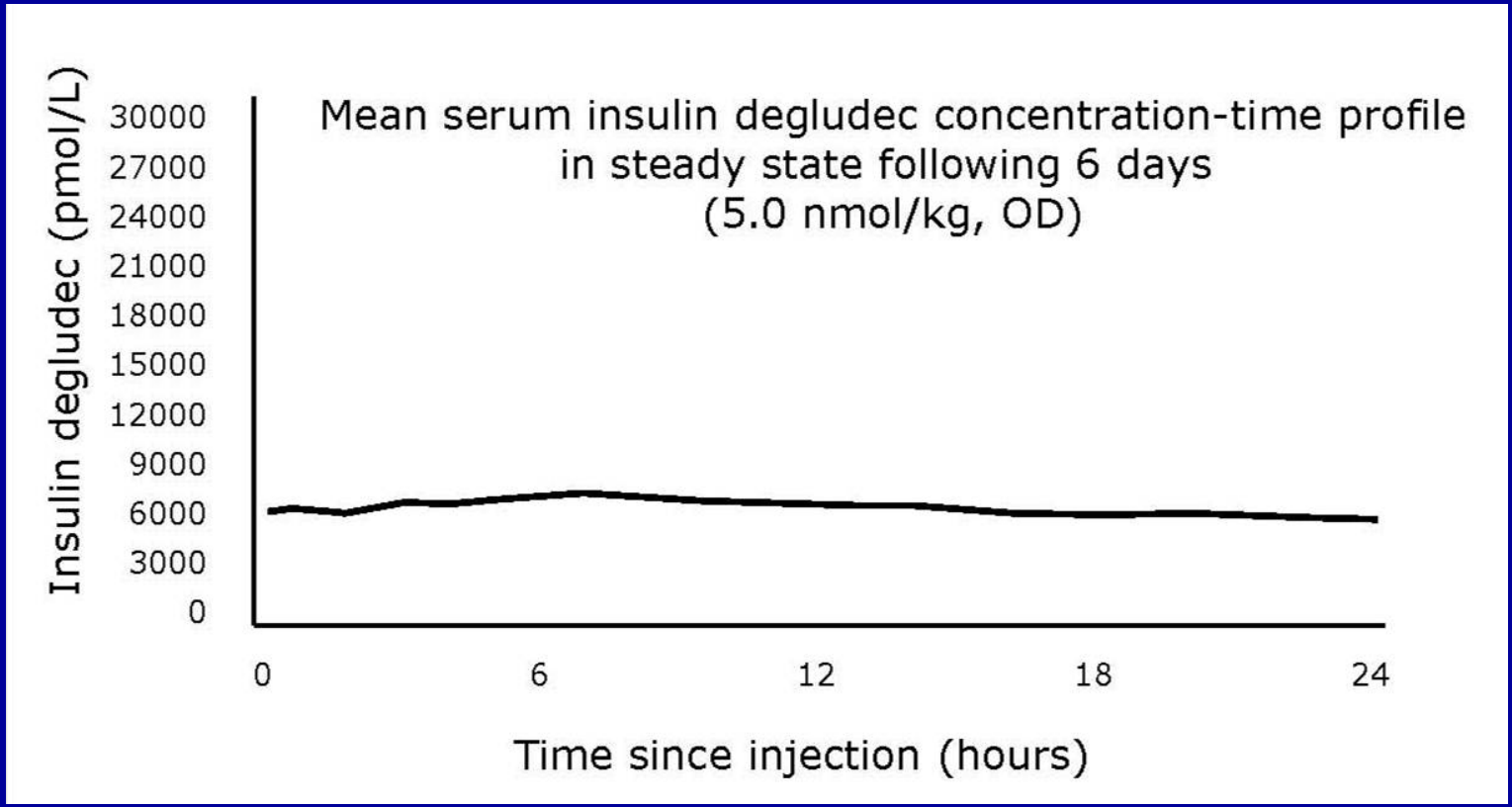



Protraction mechanism for Degludec
Multi-hexamers
Subcutaneous tissue
Monomers
Capillary membrane
Capillary blood
Insulin degludec in blood
Albumin binding
Cell Membrane
Insulin Receptors

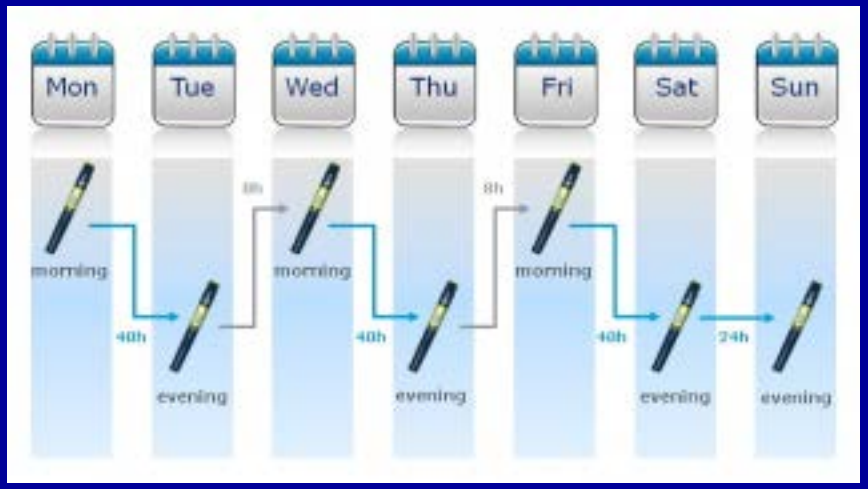
TRESIBA:DEGLUDEC INSULIN



DEGLUDEC: STEADY STATE



TRESIBA:DEGLUDEC INSULIN: ALTERING THE TIME OF INJECTION: FORCED FLEXIBLE DOSING REGIMEN STEADY STATE MAINTAINED



INSULIN PUMP THERAPY

LIFESTYLE THERAPY

- Diet
- Physical activity
- Bariatric surgery

LIFESTYLE THERAPY

TABLET THERAPY

- Metformin, immediate or slow release
- Sulphonylureas e.g. gliclazide, glimepiride
- DPP-4 inhibitors,e.g.sitagliptin
- Glycosuric drugs e.g.Forxiga:dapagliflozin

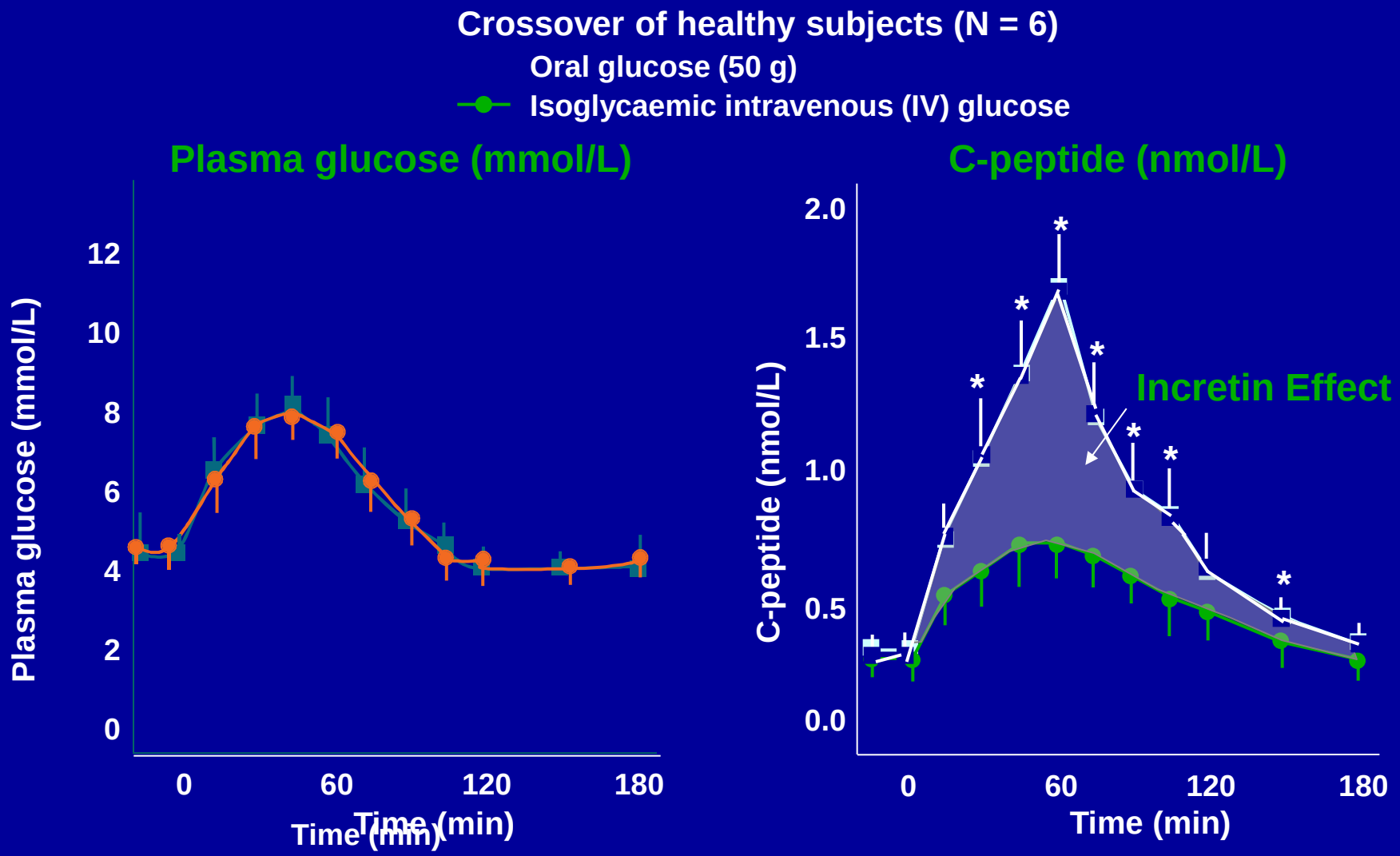
THE INCRETIN EFFECT

FOOD STIMULATES GUT HORMONES AND ENHANCES THE RELEASE FO INSULIN

INCRETIN PATHWAY

- IV glucose stimulates insulin release.
- Food stimulates the release of insulin *and* gut hormones e.g. GLP-1
- GLP-1 boosts insulin, reduces glucagon, slows gastric emptying and reduces appetite
- The increase in insulin release caused by food v. IV glucose = '**incretin effect**'

The incretin effect : β-cell response to oral vs IV glucose

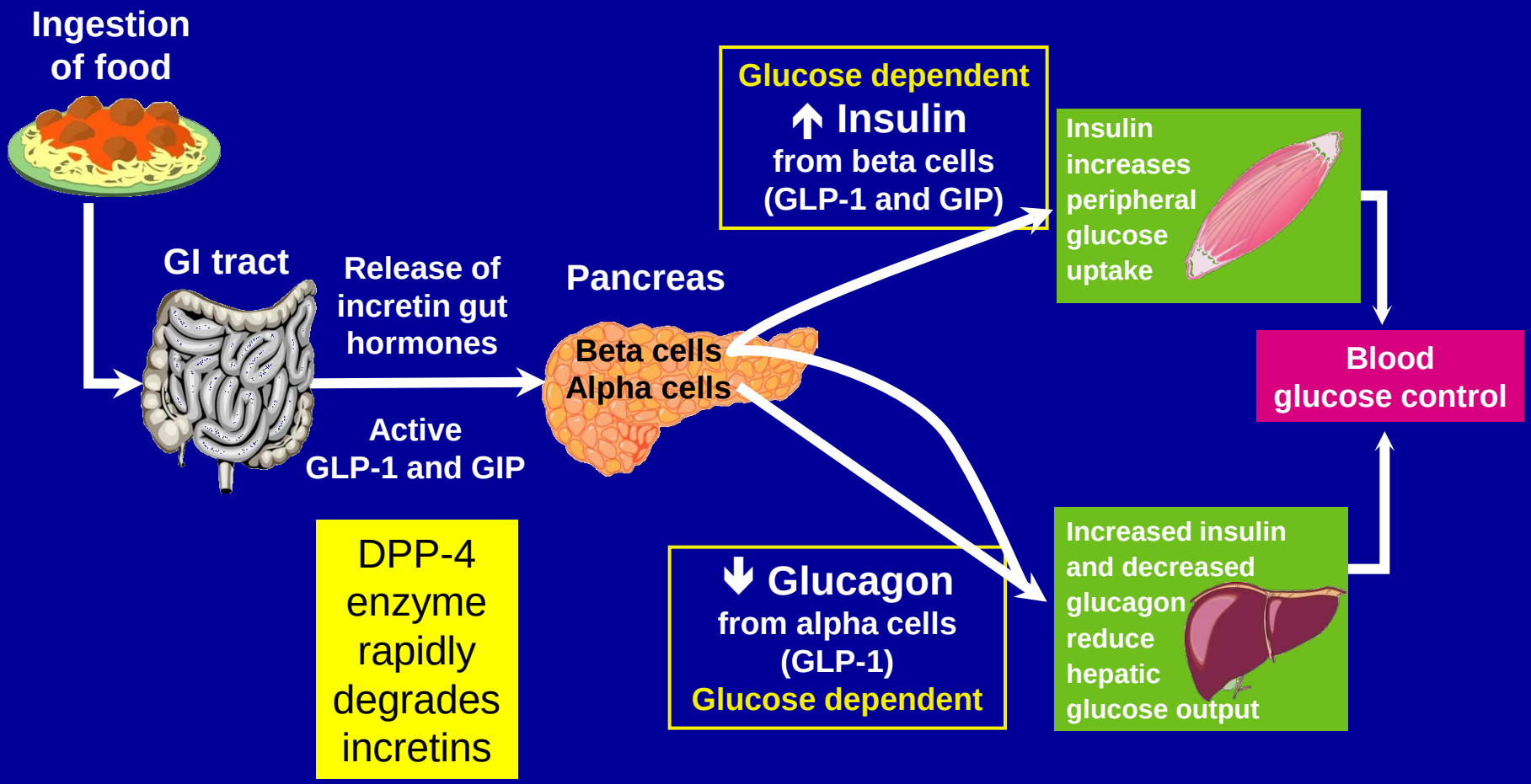


Incretin hormones ; GLP-1 , GIP

GLP-1	GIP
30 amino acid peptide[1]	42 amino acid peptide[2]
Synthesised and released by L cells of ileum and colon[2]	Synthesised and released from K cells of jejunum and duodenum[2]
Sites of action[1]: Pancreatic β-cells and α-cells GI tract CNS Lungs Heart	Sites of action[2]: Pancreatic β-cells Adiopocytes

[1]Wei Y, et al. *FEBS Lett* 1995;358:219–224; [2]Drucker DJ. *Diabetes Care* 2003;26:2929–2940.

Incretins and glycaemic control[7,8]



Adapted from 7. Drucker DJ. *Cell Metab*. 2006;3:153–165. 8. Miller S, St Onge EL. *Ann Pharmacother* 2006;40:1336-1343.

INCRETIN THERAPY

- Lowers glucose levels
- Weight loss
- Incretin mimetics: Byetta, Victoza, Bydureon
- DPP4 inhibitors e.g. Januvia/sitagliptin

INCRETIN THERAPY
VICTOZA PEN

FORXIGA®▼ (dapagliflozin)
The first SGLT2 inhibitor for the treatment of type 2 diabetes

Normal glucose homeostasis

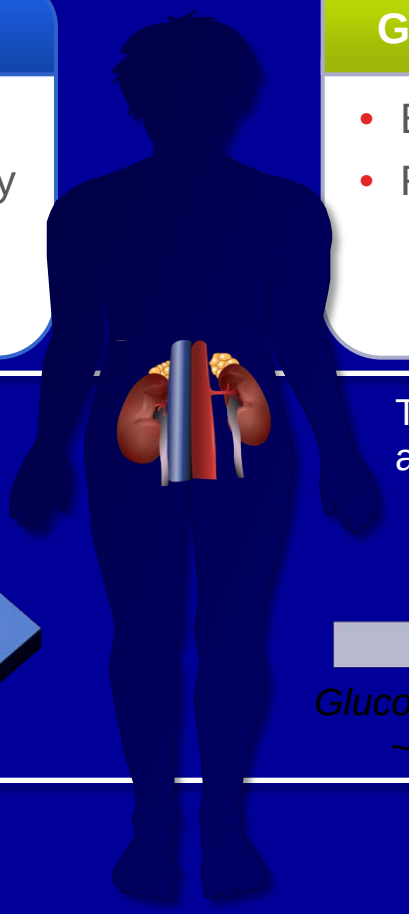
Net balance ~0 g/day

Glucose input ~250 g/day:

- Dietary intake ~180 g/day
- Glucose production ~70 g/day
  - Gluconeogenesis
  - Glycogenolysis

Glucose uptake ~250 g/day:

- Brain ~125 g/day
- Rest of the body ~125 g/day



The kidney filters circulating glucose

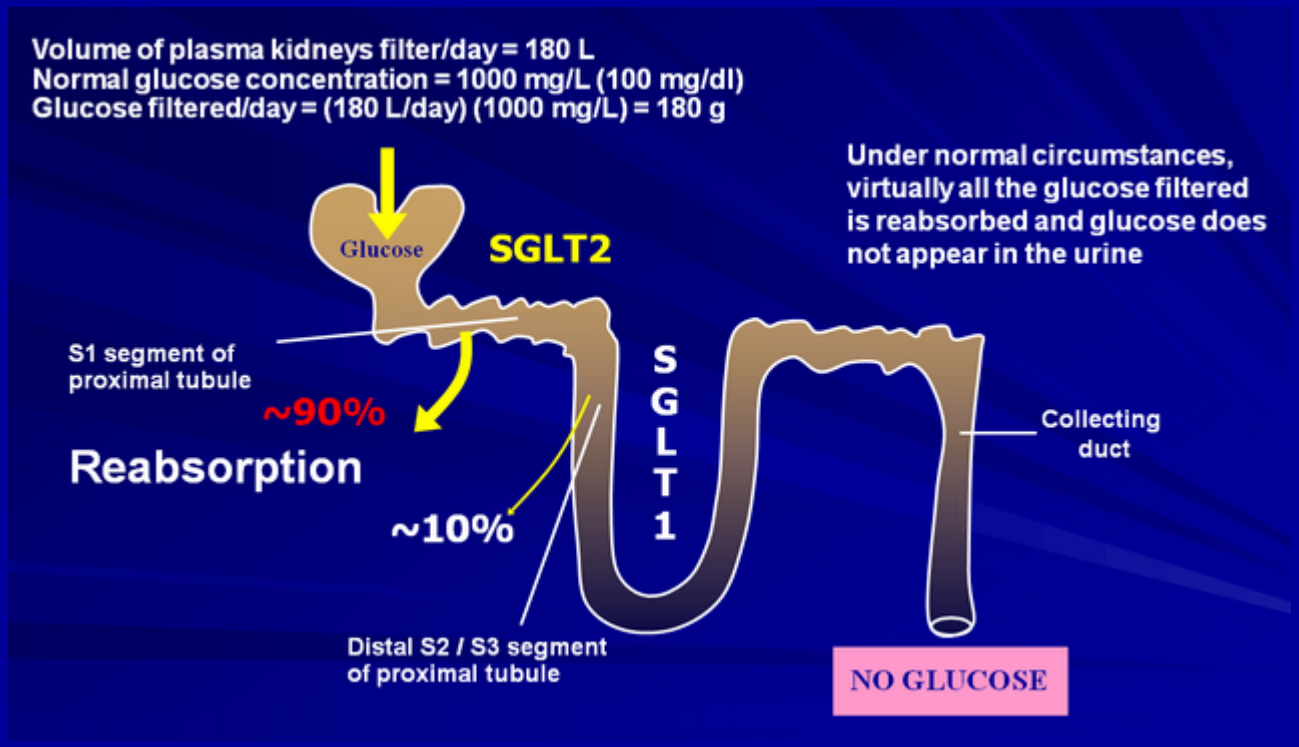
Glucose filtered ~180 g/day

The kidney reabsorbs and recirculates glucose

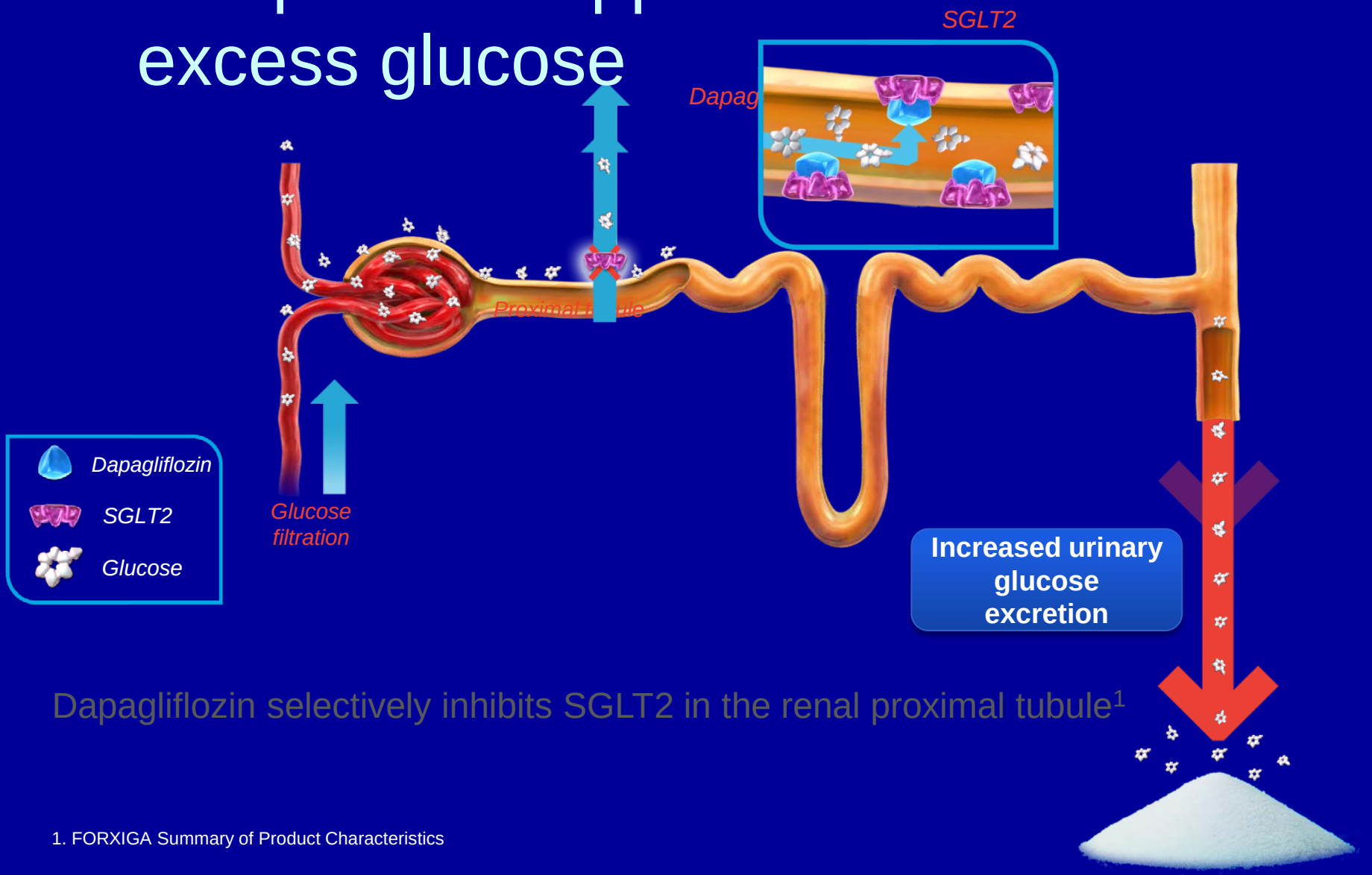
Glucose reabsorbed ~180 g/day

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18.
2. Gerich, JE. *Diabetes Obes Metab* 2000;**2**:345–50.

SGLT sodium-glucose cotransporter blockade



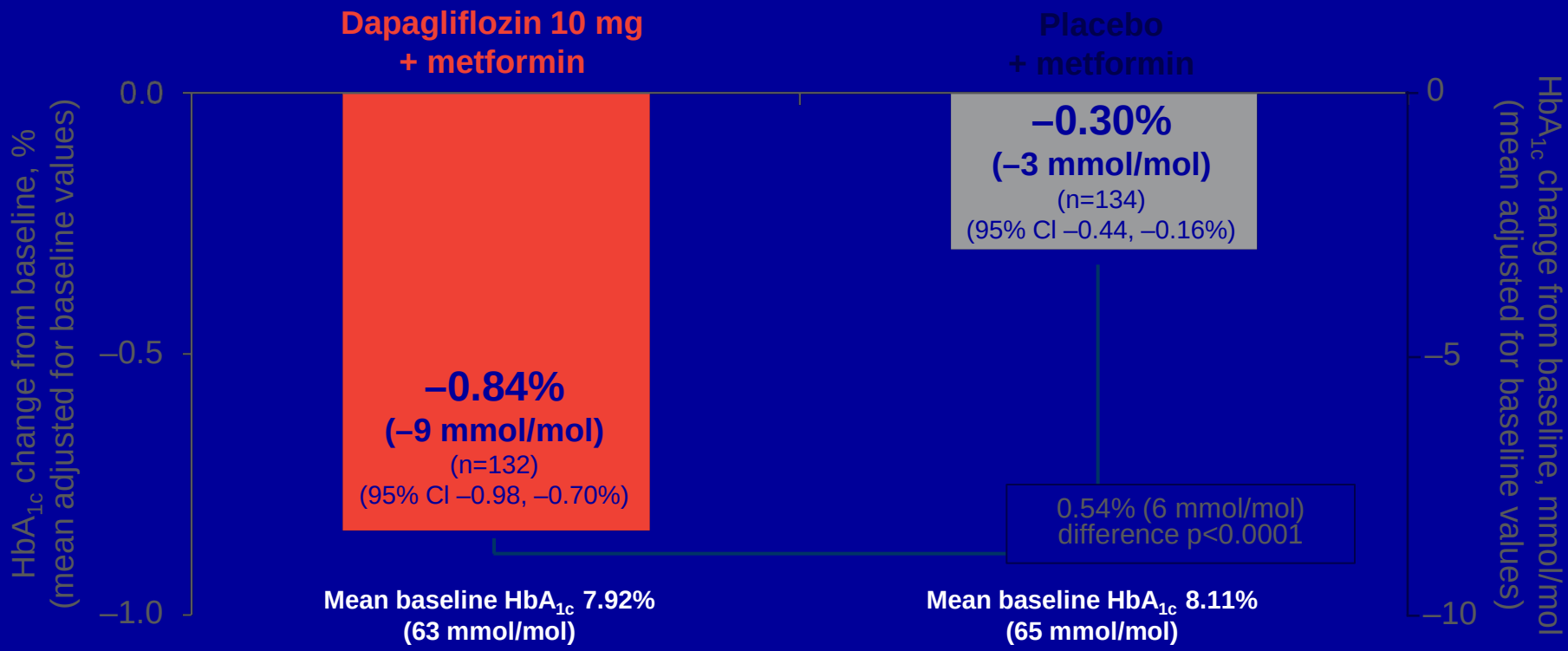
Dapagliflozin: A novel insulin-independent approach to remove excess glucose



Dapagliflozin selectively inhibits SGLT2 in the renal proximal tubule[1]

1. FORXIGA Summary of Product Characteristics

Dapagliflozin: Significant reductions in HbA_{1c} compared with placebo at the 24-week primary endpoint

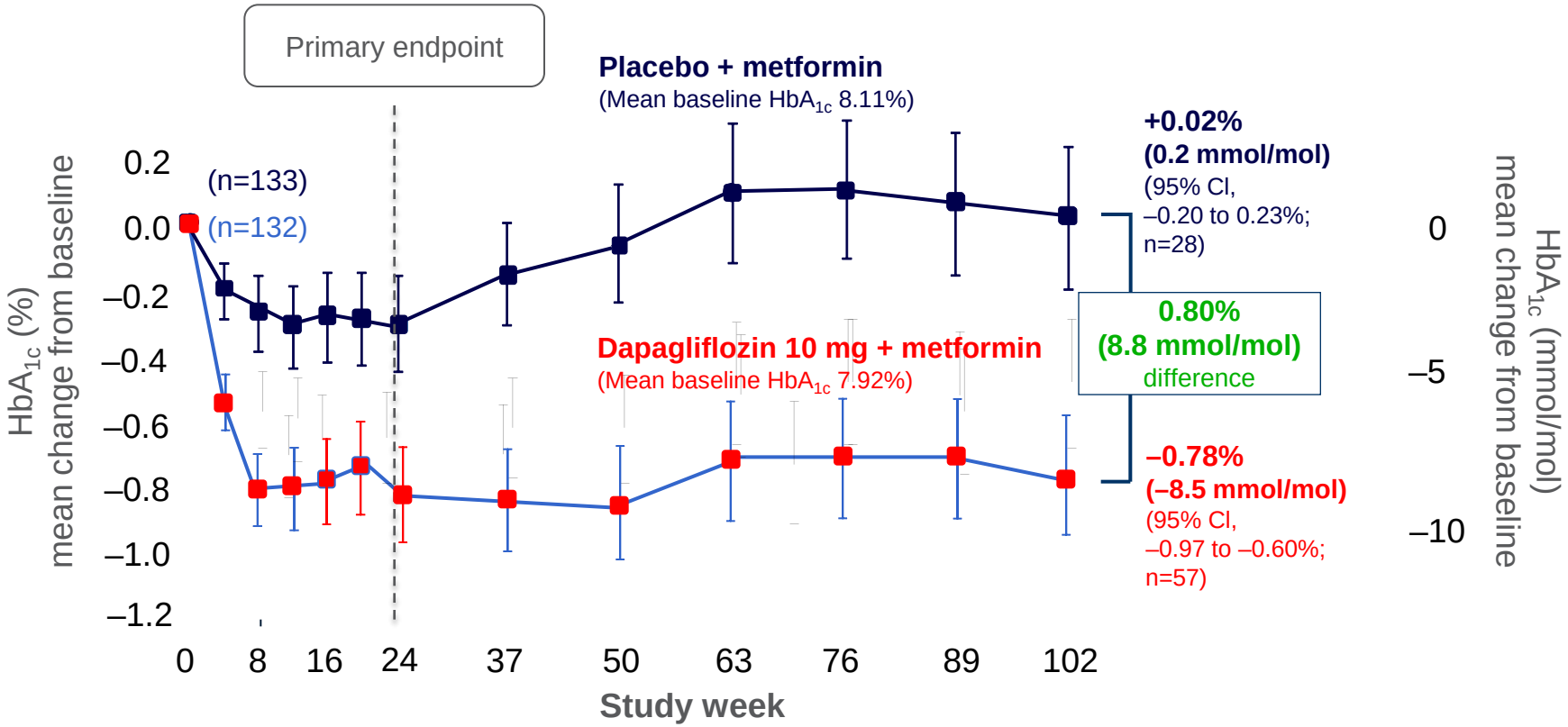


Adapted from Bailey CJ, *et al*. 2010.

Changes reported for Week 24 are adjusted for baseline values and are based on last observation carried forward (LOCF).

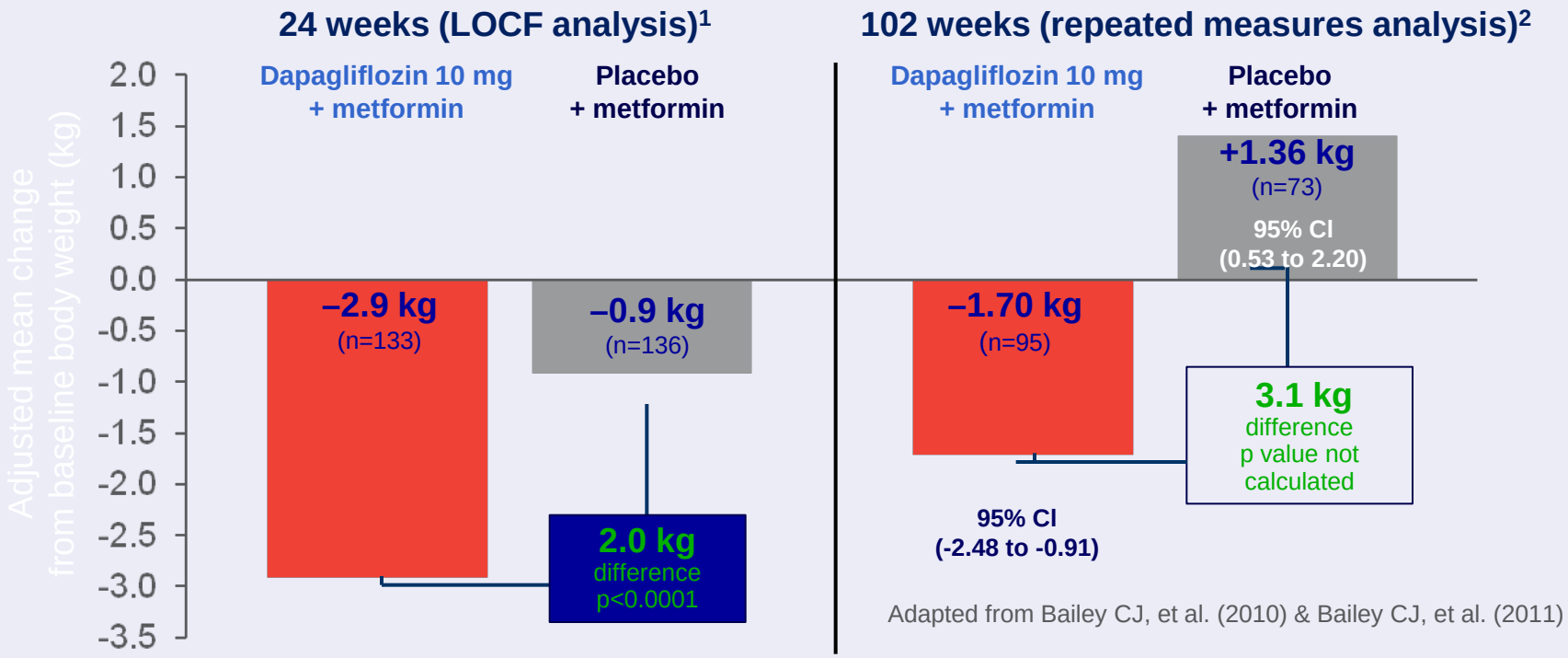
A Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24- week clinical study to evaluate the efficacy and safety of dapagliflozin 10 mg + metformin (≥1500 mg/day) versus placebo + metformin (≥1500 mg/day) in adult patients with Type 2 diabetes who had inadequate glycaemic control (HbA_{1c} ≥7% and ≤10%) on metformin alone. Primary endpoint: HbA_{1c} reduction at 24 weeks.
Bailey C, *et al. Lancet* 2010;**375**:2223–33.

Dapagliflozin: Reductions in HbA_{1c} were sustained over 102 weeks



CI, confidence interval.

Dapagliflozin: secondary benefit of weight loss over 102 weeks



Adapted from Bailey CJ, et al. (2010) & Bailey CJ, et al. (2011)

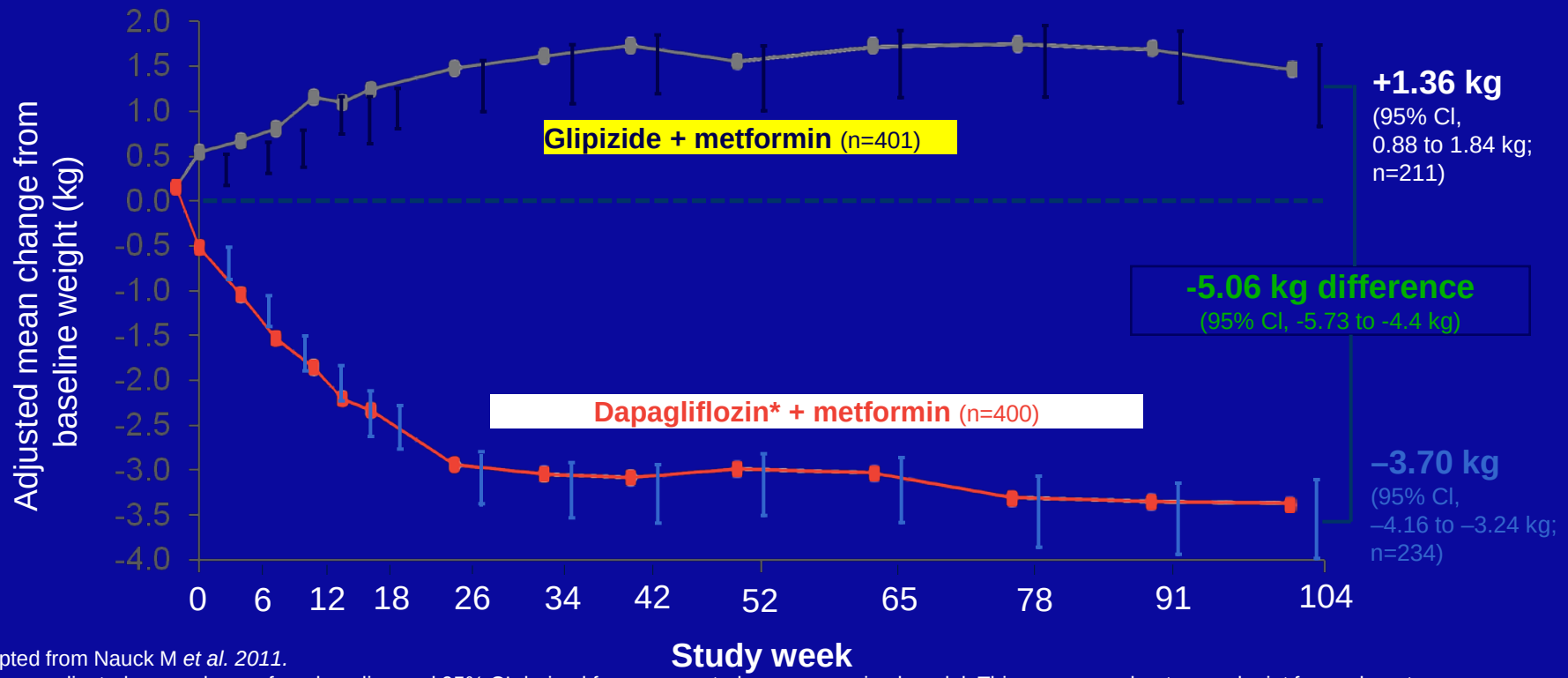
- **Weight loss at 24 weeks, with decreased waist circumference is consistent with a reduction of body-fat mass** [1]
- **In a separate study, weight loss was mainly attributable to reduction in body fat mass rather than loss of fluid or lean tissue** [3,#]

Data are mean change from baseline after adjustment for baseline value (mean baseline weight: dapagliflozin 86.3 kg, placebo 87.7 kg).
24-week data are based on LOCF analysis excluding data after rescue; 102-week data are based on longitudinal repeated measures analysis and include data after rescue.
As measured by dual energy absorptiometry at 24 weeks

1. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 2. Bailey CJ, *et al.* Poster 988-P. Poster presented at 71st Scientific Sessions of the American Diabetes Association, San Diego, California, June 24–28, 2011; 3. Bolinder J, *et al. J Clin Endocrinol Metab* 2012;**97**:1020–31.

Dapagliflozin: secondary benefit of weight loss versus a sulphonylurea

Total body weight (kg) adjusted mean change over 2 years[1,2]



Adapted from Nauck M *et al. 2011.*

Data are adjusted mean change from baseline and 95% CI derived from a repeated measures mixed model. This was an exploratory endpoint from a long-term follow-up study. Weight loss in the initial 52 week study was a key secondary endpoint and was measured using LOCF analysis. Results at 52 weeks were –3.22 kg in the dapagliflozin arm (baseline weight 88.4 kg) and +1.44 kg in the SU arm (baseline weight 87.6 kg) p<0.0001.

1. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22;
2. Nauck M, *et al.* Poster 40-LB. Poster presented 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June, 2011.

A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week clinical study, plus a 52-week extension period, glipizide-controlled non-inferiority study to evaluate the efficacy and safety of dapagliflozin 10 mg + metformin (≥1500 mg/day) versus glipizide + metformin (≥1500 mg/day) in patients with inadequate glycaemic control (HbA_{1c} >6.5% and ≤10%) on oral antidiabetic medication including metformin. Primary endpoint:HbA_{1c} change at 52 weeks. *Dapagliflozin dose was up-titrated to a maximum of 10 mg (achieved by 87% of patients) over an 18-week period based on glycaemic response and tolerability.

Nauck M, *et al*. Presented at: American Diabetes Association (ADA); June 24-28, 2011; San Diego, CA.

AIMS OF THERAPY

- Control symptoms
- Avoid hyperglycaemia and hypoglycaemia
- Current targets: type 2 diabetes HbA1c <53. BP <130/80
- Optimize weight
- Prevent complications

LIFESTYLE THERAPY

TREATMENT ADHERENCE

NONE OF THE TREATMENT ANY OF THE TIME

SOME OF THE TREATMENT SOME OF THE TIME

ALL OF THE TREATMENT ALL OF THE TIME

ERRATIC GLUCOSE CONTROL ON INSULIN

- Treatment adherence?
- Insulin regimen?
- Insulin dose?
- Erratic glucose levels usually reflect erratic insulin adherence

CATEGORIES OF ILLNESS

- Curable
- Treatable, but incurable
- Untreatable and incurable

TRANSFER OF CATEGORY

A diabetic patient can **transfer** him/herself from treatable to **untreatable** with adherence issues, eating disorders or alcohol or drug abuse

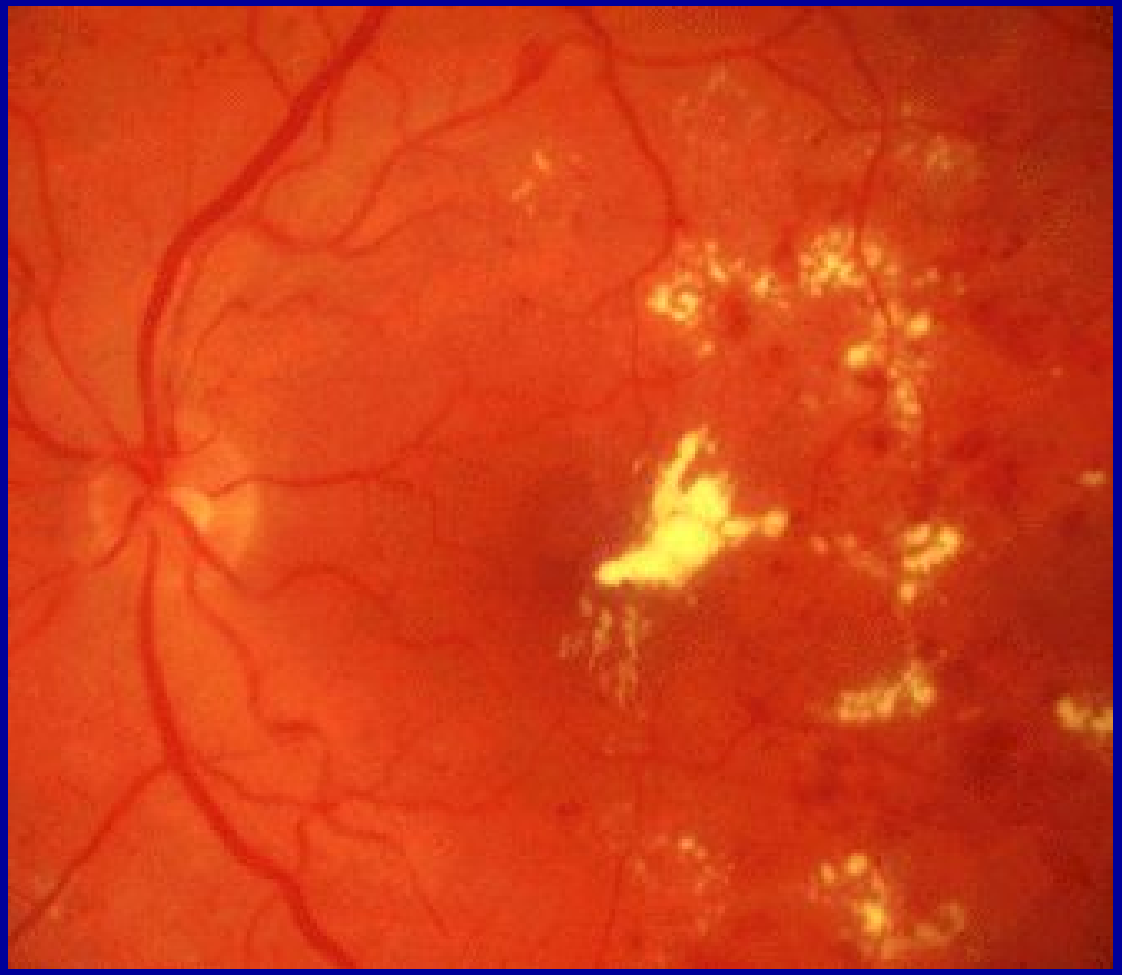
SCREENING FOR COMPLICATIONS

- Retinal imaging annually
- First pass urine albumin/creatinine ratio annually
- Foot examination for pulses, neuropathy annually

DIABAETIC COMPLICATIONS

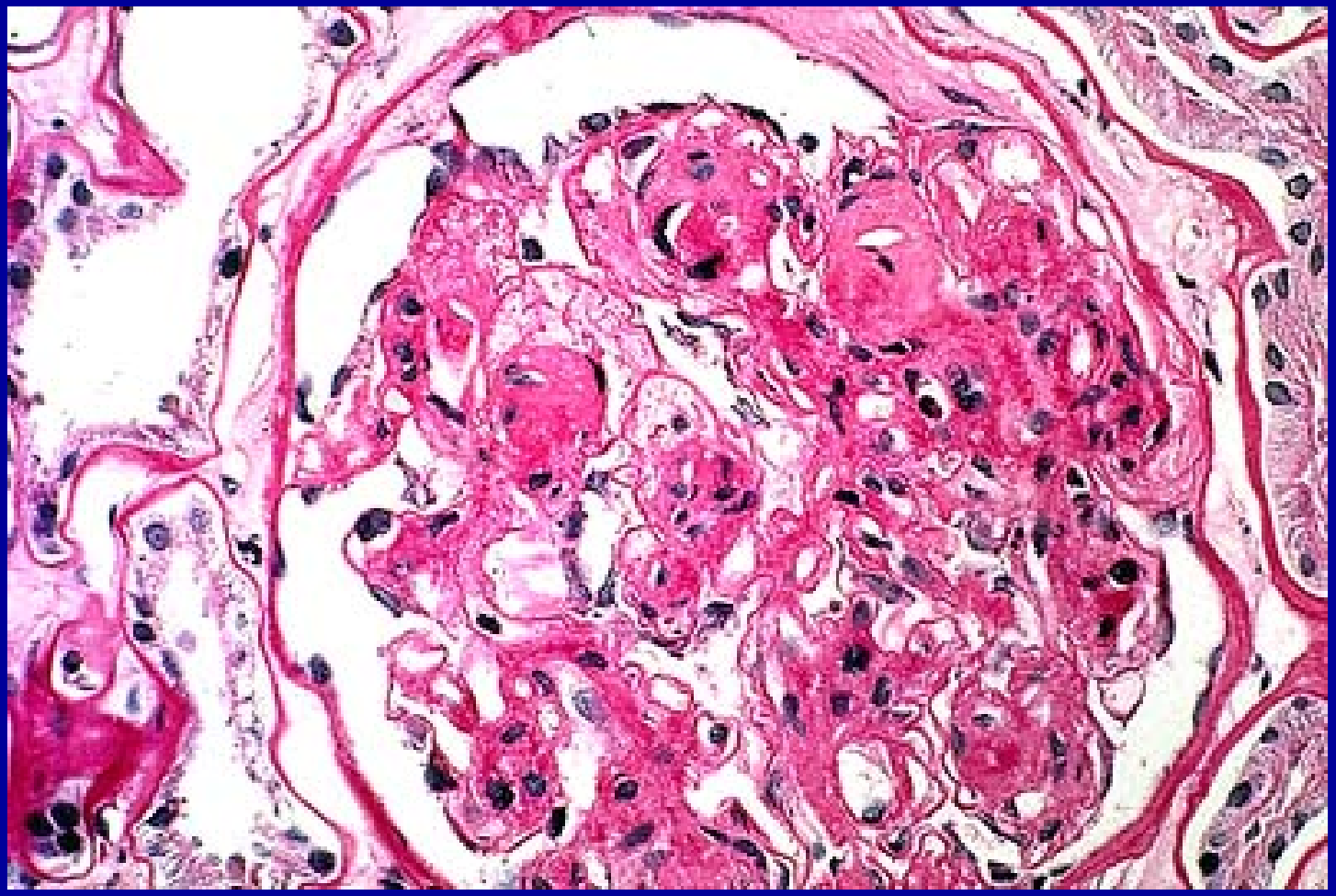
- Retinopathy and blindness
- Renal impairment and failure
- Stroke
- Ischaemic heart disease
- Peripheral vascular disease
- Foot ulceration, infection, amputation
- Neuropathy
- Sexual disorders

MACULOPATHY

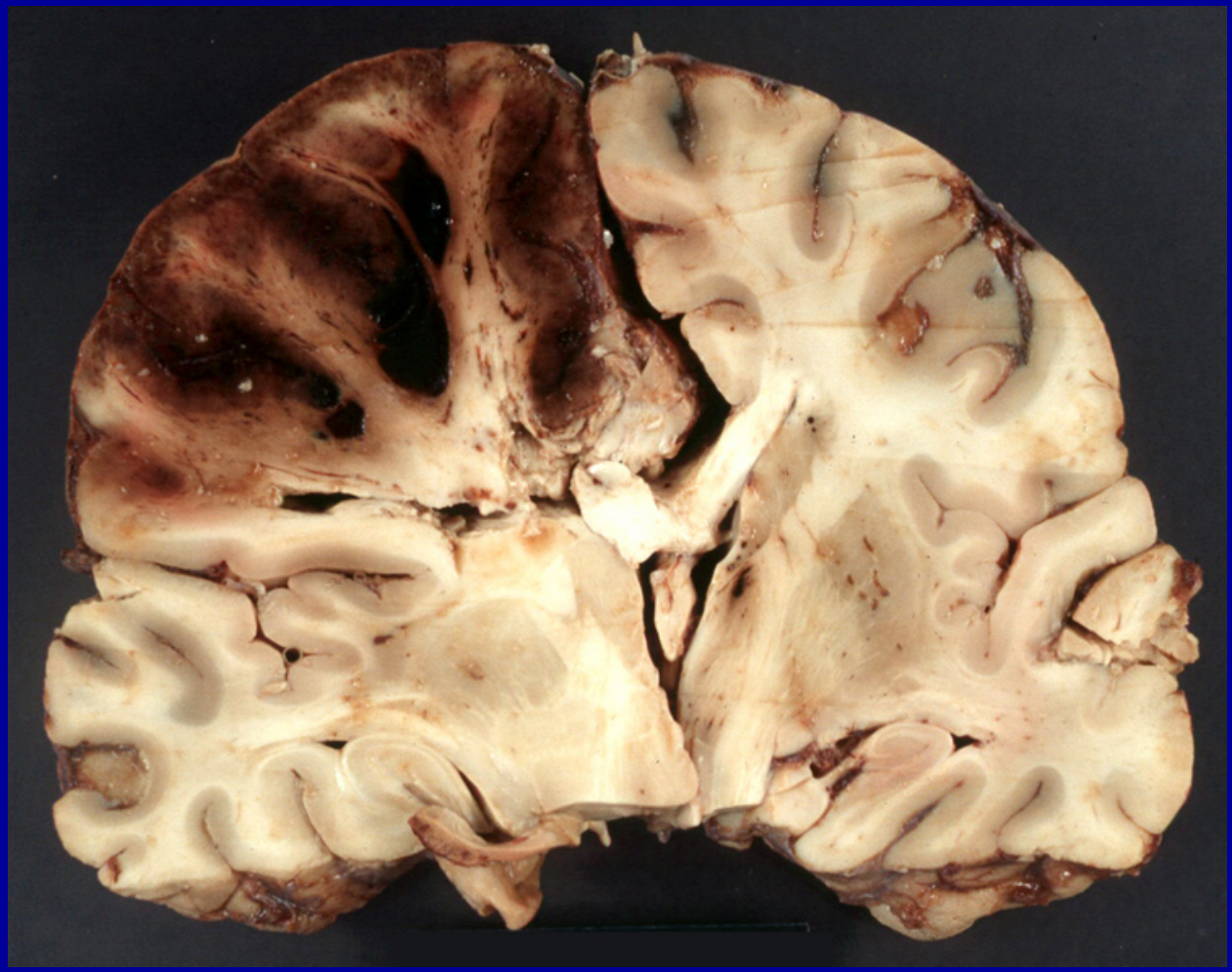


RETINAL HEAMORRHAGE

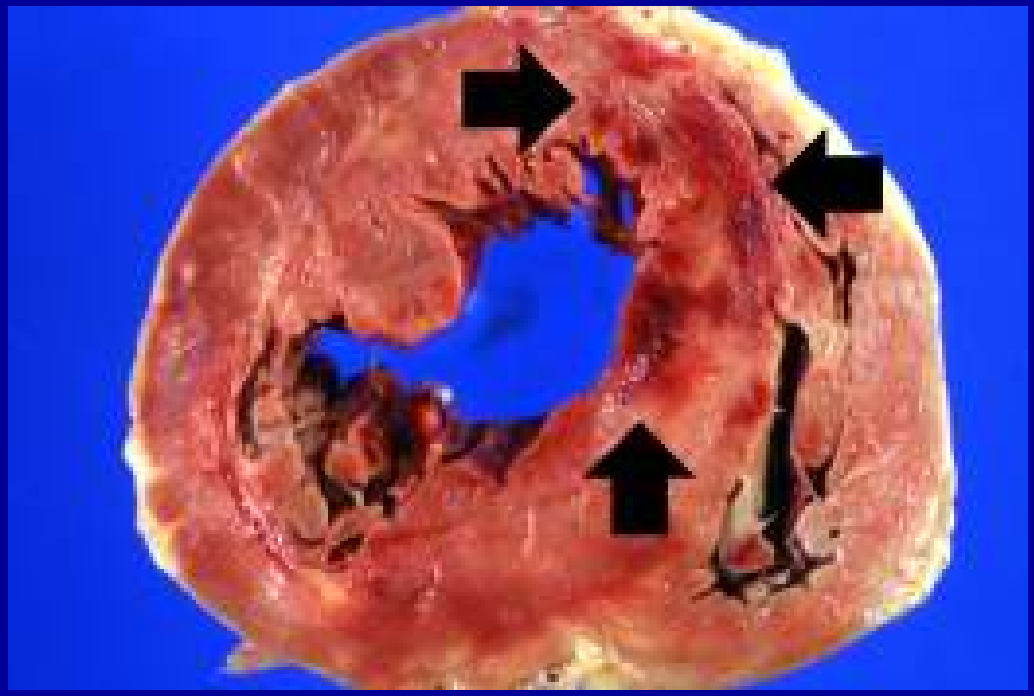
DIABETIC NEPHROPATHY HISTOLOGY



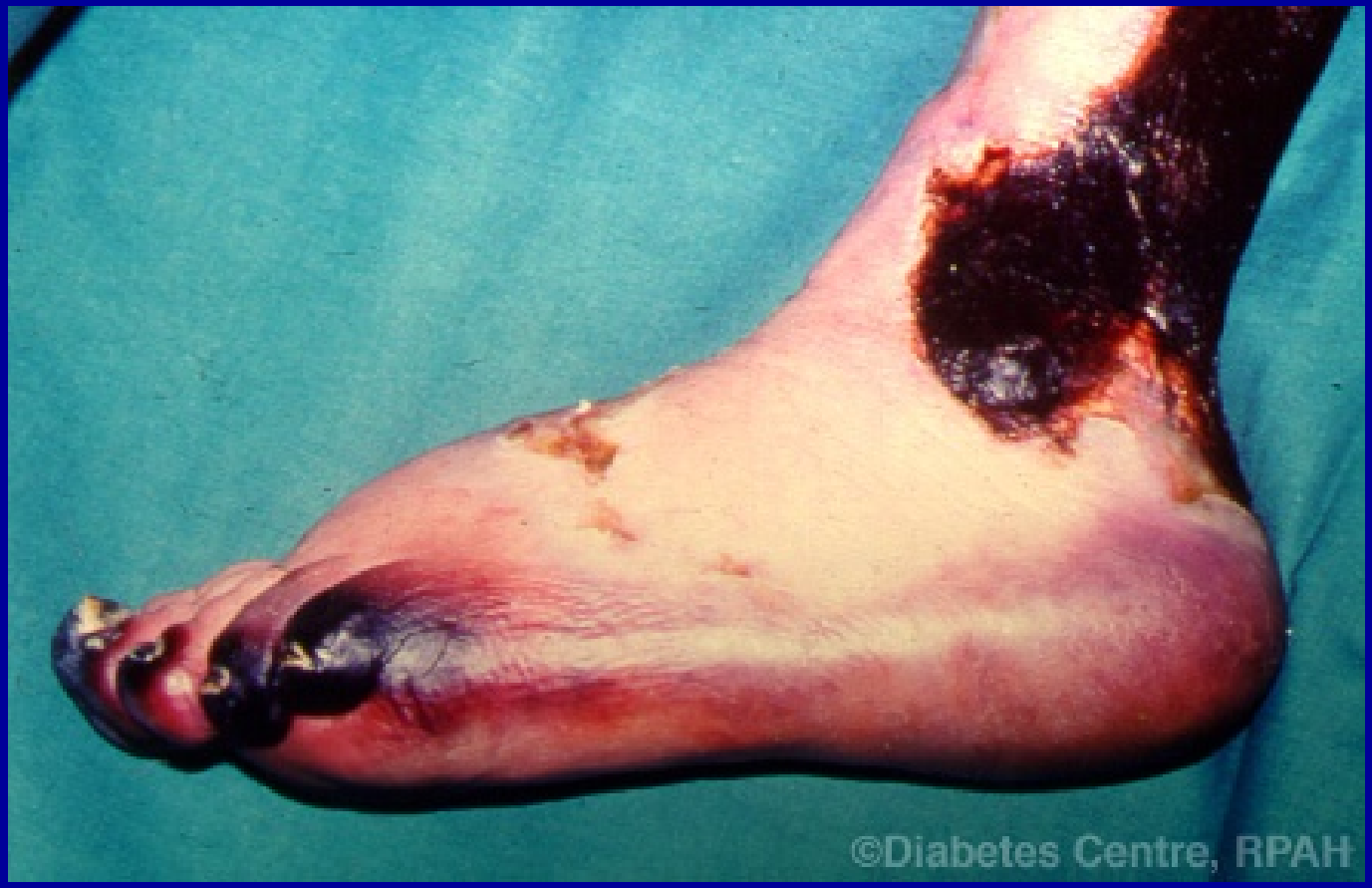
CEREBRAL THROMBOSIS



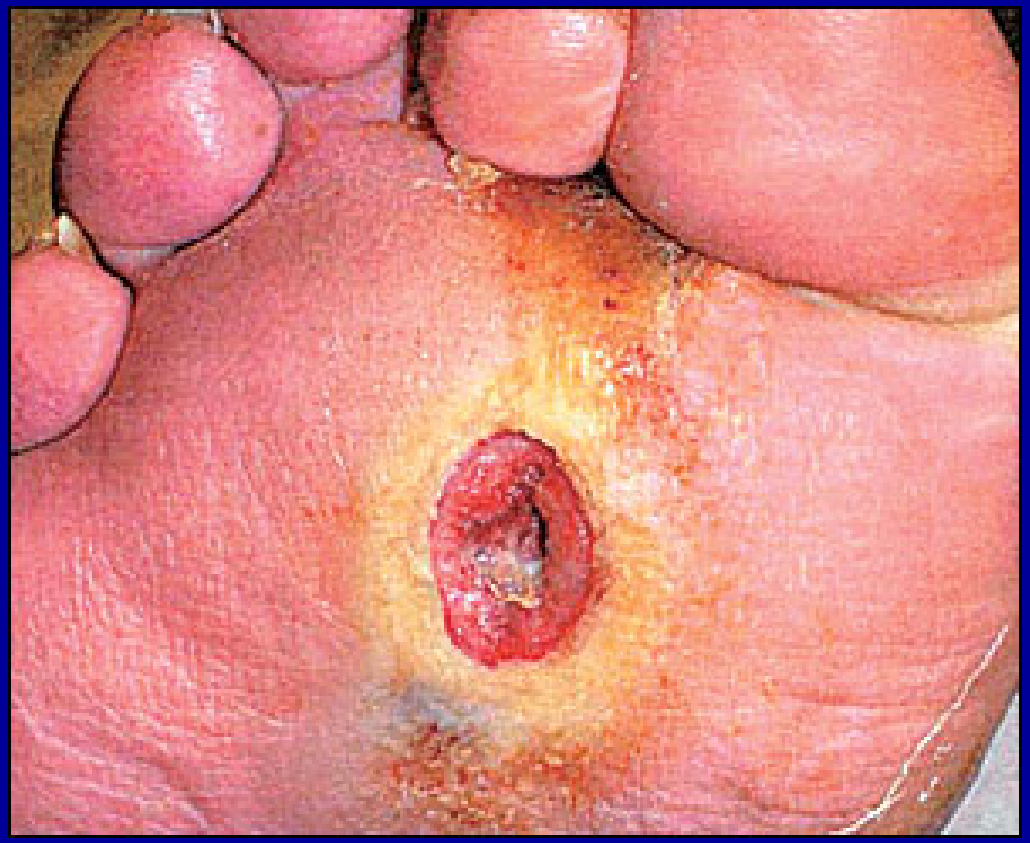
MYOCARDIAL INFARCTION



WET GANGRENE



DIABETIC NEUROPATHY



WHEN TO REFER

When the aims of treatment have not been reached

Diabetic complications

Is this urgent?, uncontrolled diabetes, foot infection: IMMEDIATE REFERRAL

HOW TO REFER

- Referral letter
- Phone if acute problem: ‘HOT FOOT PHONE’

THANK YOU FOR YOUR ATTENTION

ANY QUESTIONS OR COMMENTS?