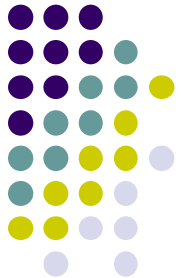


Aspects of Diabetes including Obesity

Dr Bob Wilkinson

HbA1c

%	mol/mol
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75
10.0	86
11.0	97
12.0	108

Was planned to change in June 2011 but only implemented in January 2012

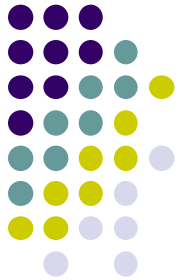
Structure of Lecture

- An Approach to Type 2 DM in the obese patient

- Food Plan – Main Stay of treatment
  - Role of Dietitian
  - Reduce CHO, but also reduce calories

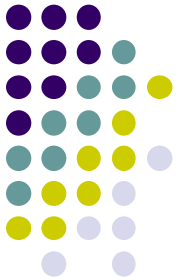
- Medications that do not put on weight
  - Metformin
  - SGLT2 inhibitors
  - Gliptins
  - GLP-1

Patient Blood Glucose Monitoring



HbA1c		Average b. glucose
108	12	19.5
97	11	17.5
86	10	15.5
75	9	13.5
64	8	11.5
53	7	9.5

Diabetes



- Type1

  insulin deficiency. Ketone prone

  Treat with insulin

- Type2

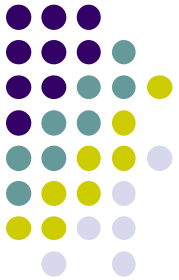
  insulin resistance. Not ketone prone

  Treat with metformin, GLP-1 mimetics

- Type1.5

  type 1 with obesity. Deficiency of insulin plus insulin resistance

Type 2 Diabetes



My clinic population

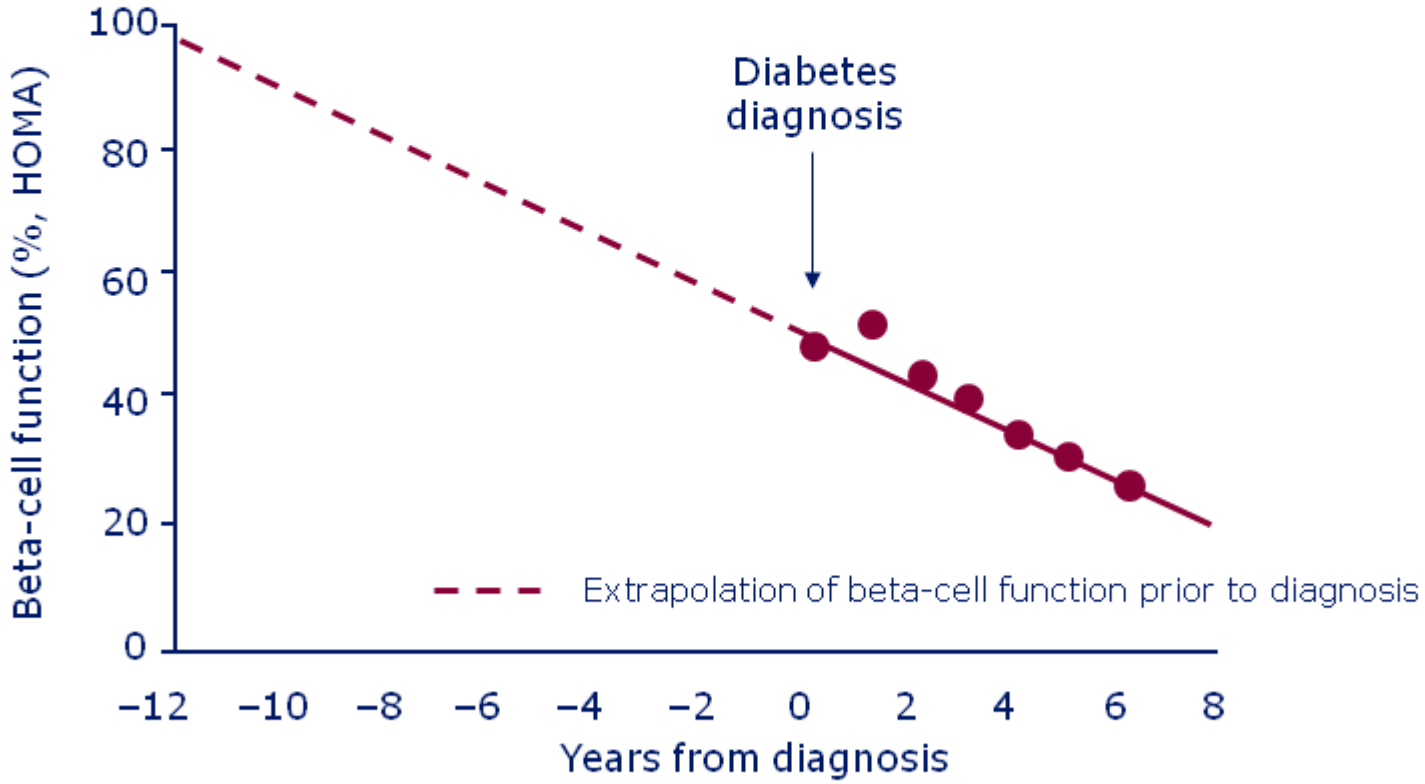
- either Good HbA1c and Weight gain
- or Less Good HbA1c and less weight gain

Sulphonylureas, glitazones and insulin put on weight

Date of preparation : September 2010

Challenges of T2D: beta-cell function

Progressive decline of beta-cell function



Lebovitz. *Diabet Rev* 1999;7:139–53 (data are from the UKPDS population)

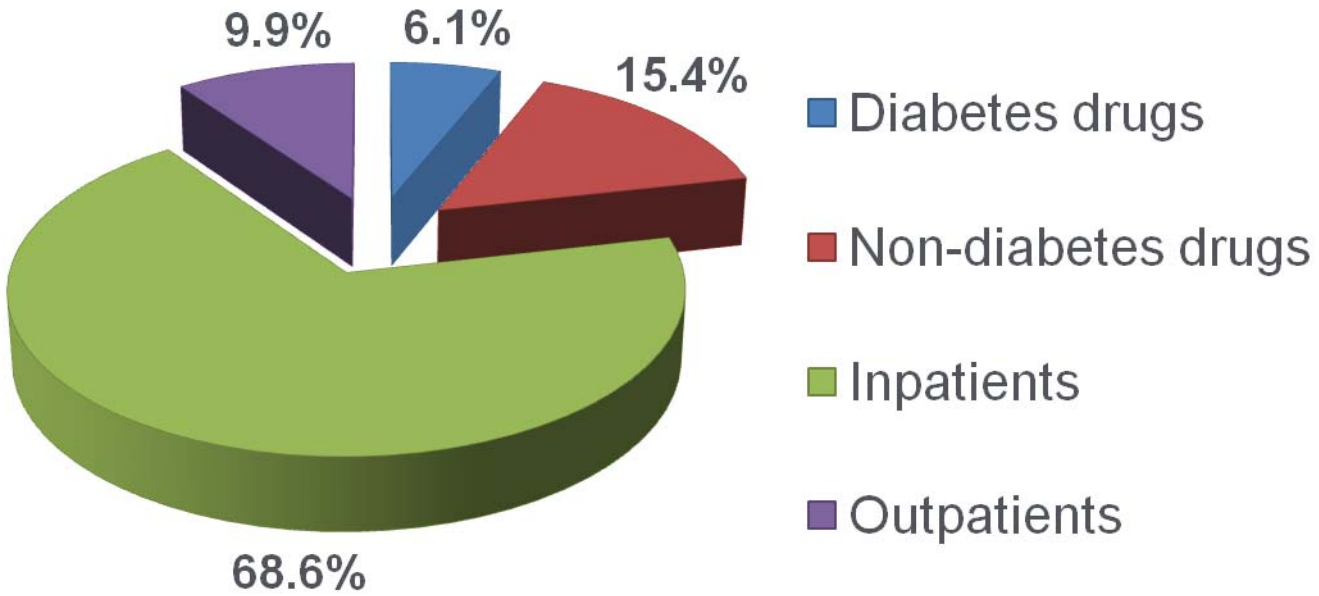
Diabetes in the UK

- Approximately 2.61 million adults suffer from type 2 diabetes in the UK (2011)[1]
- It is estimated that there are around 850,000 people in the UK who have type 2 diabetes but have not been diagnosed[1]
- By 2025, it is estimated that 5 million people will have diabetes in the UK

1. Diabetes in the UK 2011/2012: key statistics in diabetes

COST Of T2D CARE

- Of total the £11.718 billion spent on T2D in 2011 in the UK, only 6.1% was spent on T2D drugs in comparison to 68.6% spent on inpatient care
- This highlights the need for effective management of T2D



Adapted from: http://www.diabetes.co.uk/cost-of-diabetes.html (accessed September 2012).

The challenge of modern diabetes management[1]

The challenge of glucose control

- The NICE recommended HbA_{1c} **≤7.5% (59mmol/mol)** target **was not achieved** by **33.5%** of the measurements from people in England with type 2 diabetes

The challenge of obesity

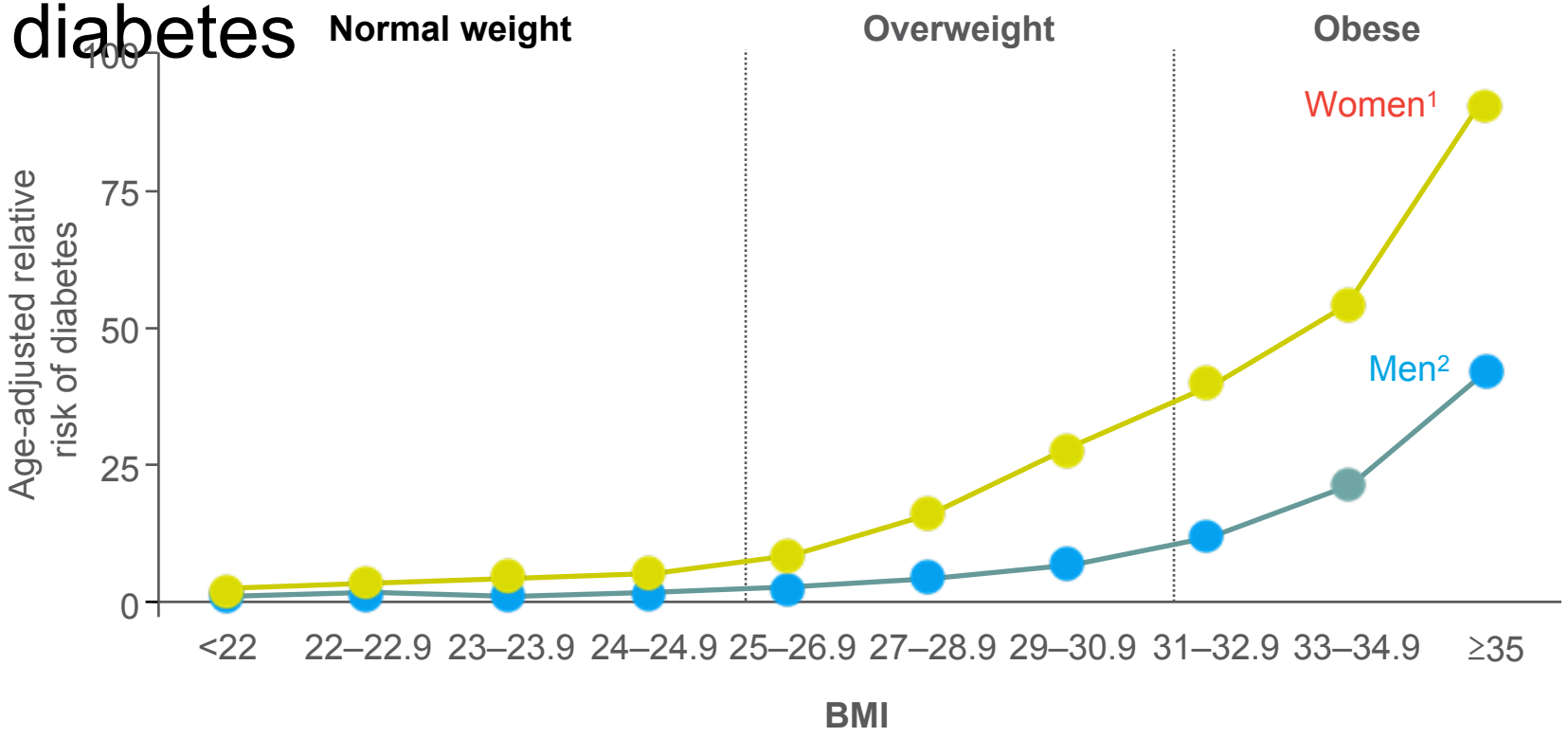
Body Mass Index (BMI) in people with type 2 diabetes:

	Normal or underweight	Overweight	Obese
Aged 16-54 yrs	**10.0**	**26.9**	**63.0**
Aged 55yrs or over	**16.3**	**36.0**	**47.6**

Reference: 1. NHS Diabetes Audit.
http://www.ic.nhs.uk/webfiles/Services/NCASP/Diabetes/200910 annual report documents/
National_Diabetes_Audit_Executive_Summary_2009_2010.pdf
Copyright 2011, Re-used with permission of The Health and Social Information Centre. All rights reserved.

Diabetes and obesity are related

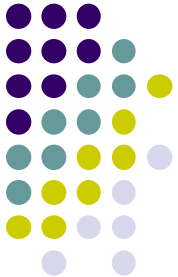
Relationship between BMI and risk of type 2 diabetes



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.

Obese Type 2 Diabetic

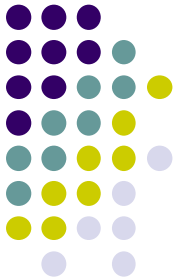


- Loose weight
  - decrease insulin requirement
  - decrease insulin resistance
- Exercise
  - increases insulin sensitivity
- Dietitian
  - less calories, less CHO

* Food Plan
  - for 3 months unless glucose very high
  - reinforced by dietitian
- Metformin
  - gradually build up dose
  - decreases insulin resistance
- Reinforce food plan

- If you add sulphonylurea or insulin or TZD the weight will go up as appetite will be stimulated

Myths about Obesity/Dieting



- I do not eat very much!
  - eat more than need.
  - underestimate what do eat.
  - total calories in that counts

. I eat healthily!
  - maybe but TOO Much. Portion size. Smaller plate

. I can not exercise because of back/heart
  - exercise does not burn many calories
  - can exercise in chair

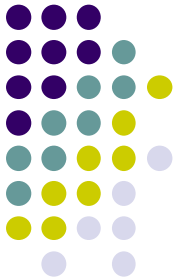
. I have a slow metabolism
  - Rubbish obese have higher BMR than normal weight

. Its my glands
  - Rubbish if thyroid is ok
  - v.v.v.rare metabolic problems associated with obesity
  - only gland that's wrong is …….

Calorie Intake – rule of thumb

BMI	Calorie Intake
25	2500
30	3000
35	3500
40	4000
50	5000

OBESE



- Need to eat less permanently

  -not diet – short term.

  - alter eating habits permanently – food plan/life style

  - difficult – food is pleasurable + social

. Respond to Satiety signals

  -eating is a habit. Stop eating when full. LEAVE FOOD ON PLATE.

. Never tell obese T2D to snack between meals/ have a supper unless they have gone hypo.

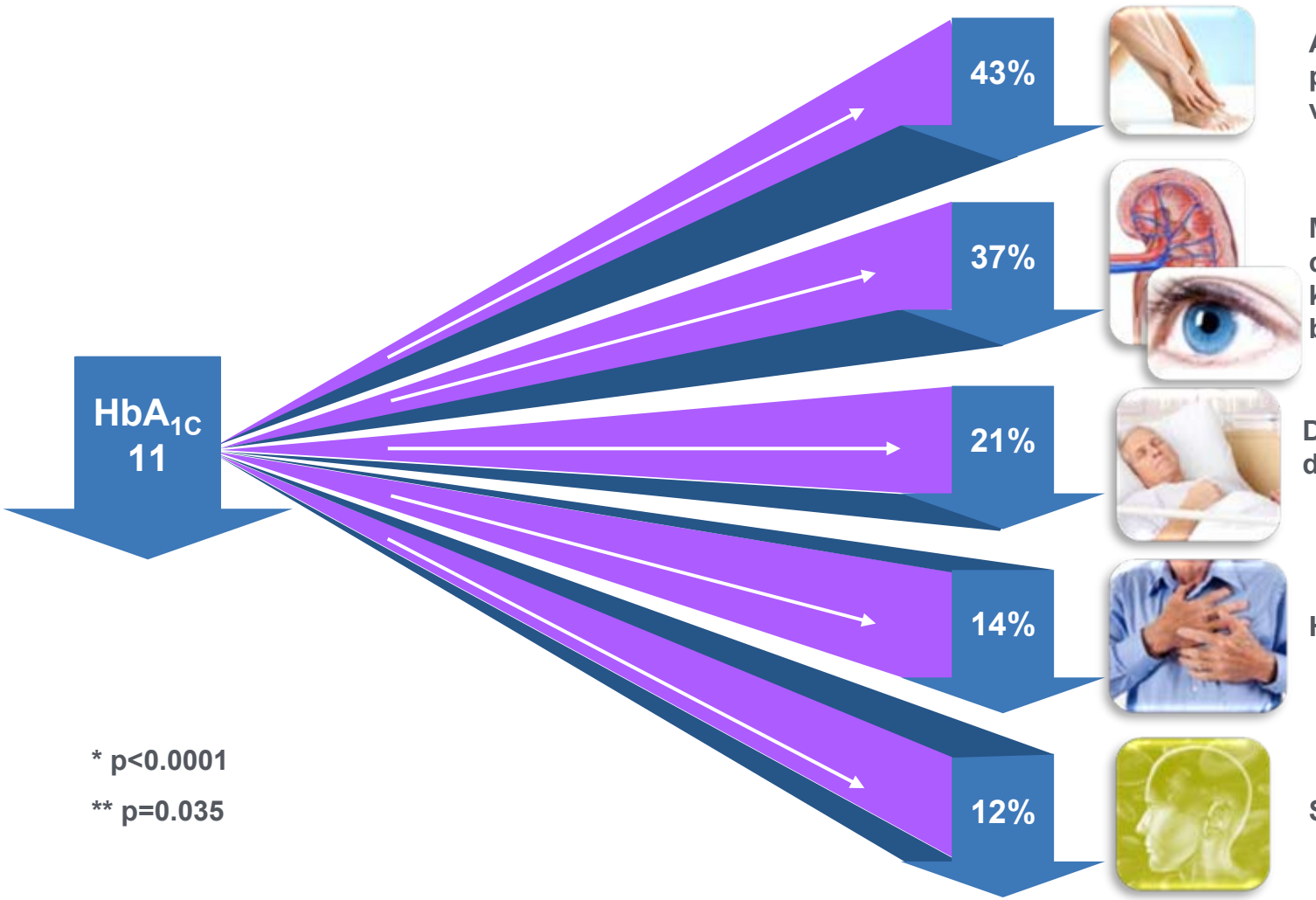
. Anticipate exercise and take less medication before it rather than snack to cover it.

. EAT + DRINK LESS

George

Age	Treatment	wt	HbA1c
44	diet + tablets	109	81
46	MI		
54	Mixtard 20u bd	109	81
63	Mixtard 30 ubd	108	69
65	Mixtard 60u bd	109	75
	Rosiglit/metformin		

UKPDS: A 1% decrease in HbA_{1c} is associated with a reduction in complications

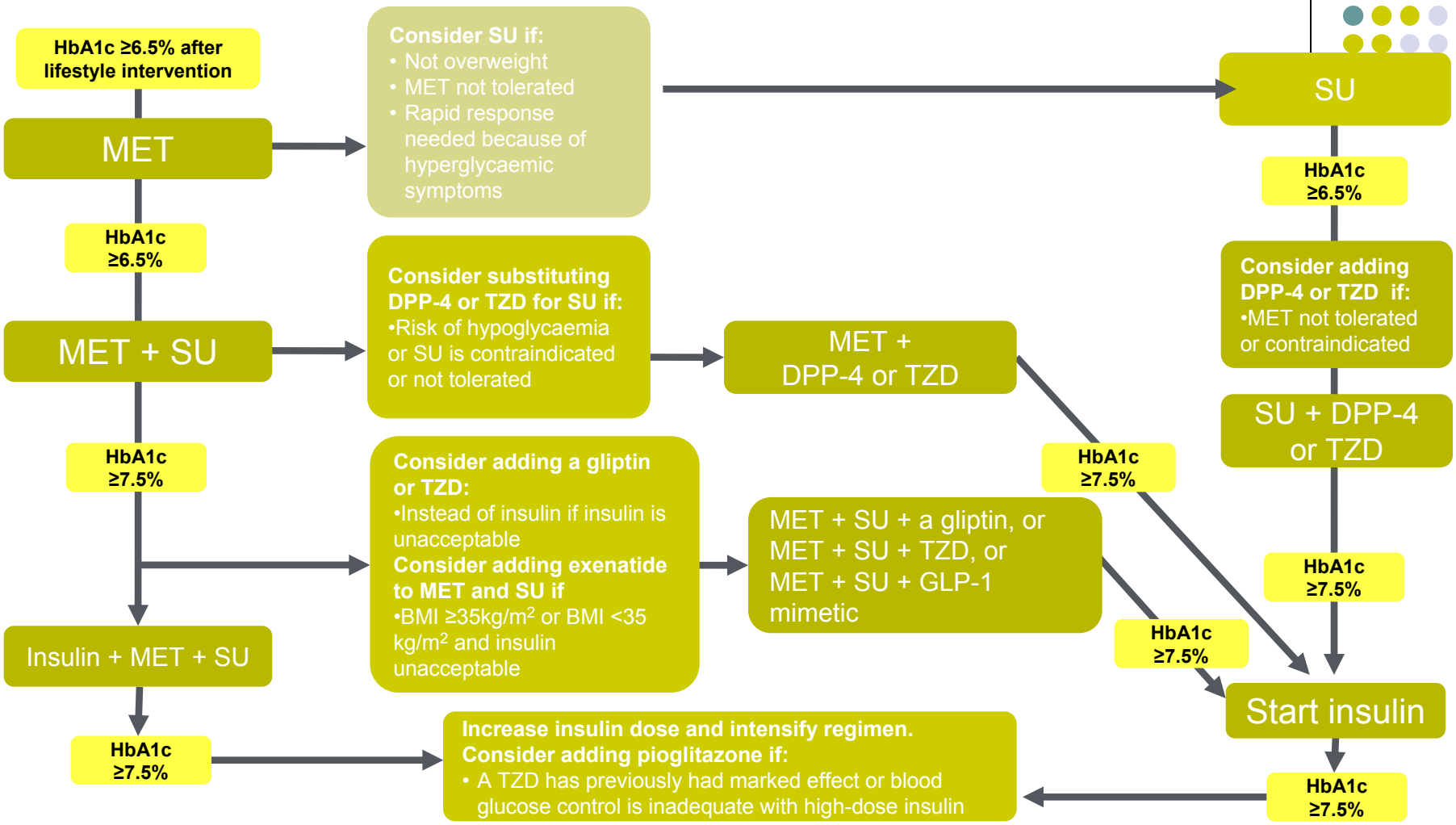


* p<0.0001

** p=0.035

Stratton IM, et al. *BMJ* 2000; 321: 405–12.

National Institute for Health and Clinical Excellence (NICE): T2D treatment algorithm[1]



MET = metformin, SU = sulphonylureas, TZD = thiazolidinedione, DPP-4= dipeptidyl peptidase-4 inhibitor

1. Adapted from: National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes - newer agents (a partial update of CG66): quick reference guide.

Scottish Intercollegiate Guidelines Network (SIGN): T2D treatment algorithm[1]

1st LINE OPTIONS in addition to lifestyle measures; START ONE OF

Metformin (MET)

Sulphonylurea* (SU)

- If intolerant to metformin
- If weight loss/osmotic symptoms

	Usual approach
	Alternative approach
*	**Continue medication if EITHER individualised target achieved OR HbA1c falls >0.5% (5.5 mmol/mol) in 3-6 months**

Review and if not reaching target move to 2nd line

2nd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF

SU*

Thiazolidinedione*
- If hypos a concern (e.g. driving, occupational hazards, at risk of falls) and if no congestive heart failure

DPP-4 inhibitor*
- If hypos a concern (e.g. driving, occupational hazards, at risk of falls, or if weight gain a concern

Review and if not reaching target move to 3rd line

3rd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD OR SUBSTITUTE WITH ONE OF

ORAL (continue MET/SU if tolerated)

Thiazolidinedione*
If no congestive heart failure

DPP-4 inhibitor*
If weight gain a concern

INJECTABLE (if willing to self inject; continue MET/SU if tolerated)

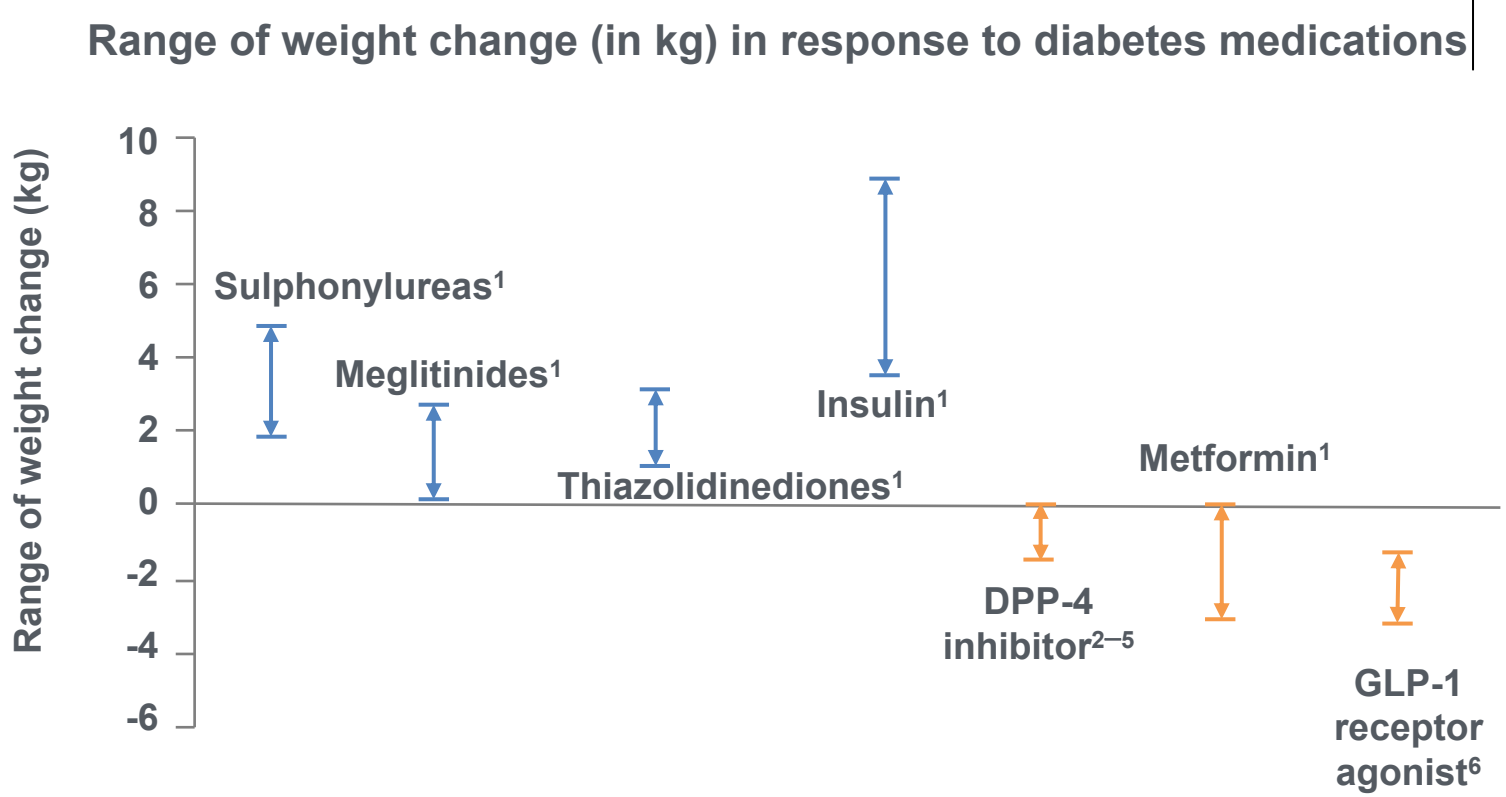
Insulin* (inject before bed)
- If osmotic symptoms/rising HbA1c; NPH insulin initially
- If hypos a concern, use basal analogue
- Add prandial insulin with time if required

GLP-1 agonists*
- If BMI > 30 kg/m^2
- If a desire to lose weight
- Usually <10 years from diagnosis

DPP-4= dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide 1

1. Adapted from: Scottish Intercollegiate Guidelines Network. Management of diabetes: a national clinical guideline. March 2010. Prescribers should refer to the British National Formulary (www.bnf.org) and the Scottish Medicines Consortium (www.scottishmedicines.org.uk) for updated guidance on licensed indications, full contraindications and monitoring requirements.

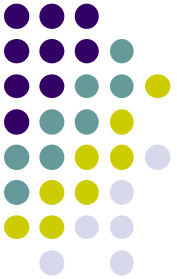
Glucose-lowering medications and weight profile



Weight change (Kg): -1.39 (linagliptin vs glimepiride) [2], -0.6 (sitagliptin vs glipizide)[3], -1.5 (sitagliptin vs glipizide)[3], -0.3 (vildagliptin vs rosiglitazone)[4], -0.2 (vildagliptin vs glimepiride), +0.1 (vildagliptin vs gliclazide)[4], -1.1 (saxagliptin vs glipizide)[5], -1.0 to -2.8 (liraglutide in combination with metformin, metformin + glimepiride and metformin + rosiglitazone)[6]

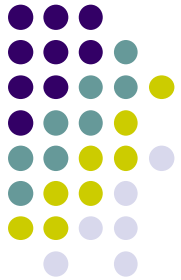
Reproduced from 1. Mitri J, Hamdy O. *Expert Opin Drug Saf* 2009; 8:573–8; 2. Boehringer Ingelheim and Eli Lilly and Company Limited. Trajenta (linagliptin) Summary of Product Characteristics. http://www.medicines.org.uk/EMC/medicine/25000/SPC/ Aug 2011 (accessed September 2012); 3. MSD Januvia (sitagliptin) Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/19609/SPC/ Mar 2012 (accessed September 2012); 4. Novartis Galvus (vildagliptin) Summary of Product Characteristics http://www.medicines.org.uk/EMC/medicine/20734/SPC/Galvus+50+mg+Tablets/ Jul 2012 (accessed September 2012); 5. AstraZeneca Onglyza (saxagliptin) Summary of Product Characteristics. http://www.medicines.org.uk/emc/medicine/22315/SPC/ Jan 2012 (accessed September 2012); 6. Novo Nordisk Limited. Victoza (liraglutide) Summary of Product Characteristics. http://www.medicines.org.uk/EMC/medicine/21986/SPC/Victoza+6+mg+ml+solution+for+injection+in+pre-filled+pen/ July 2012 (accessed September 2012).

Case Study



- Keep on with Food Plan alone for 3 months (but see them regularly)
- Then add METFORMIN gradually 500mg with main meal for two weeks then 500mg BD etc
- Never liquid metformin use sachets
- Try Metformin SR if bowel intolerant
- If not to target send to NASTY dietitian

Diabetes is Different



- It is not like hypertension, lipid problems or even IHD – take the medication
- Diabetes take the medication

PLUS

Monitor BM

24/7 stick to the food plan

Balance food, activity + medication

No Holidays from it

WILL ONLY WORK IF PATIENT WILLING TO INPUT

Waste of time & money – if patient is not willing to help themselves

The role of the kidney in type 2 diabetes and SGLT2 inhibition

Normal glucose homeostasis

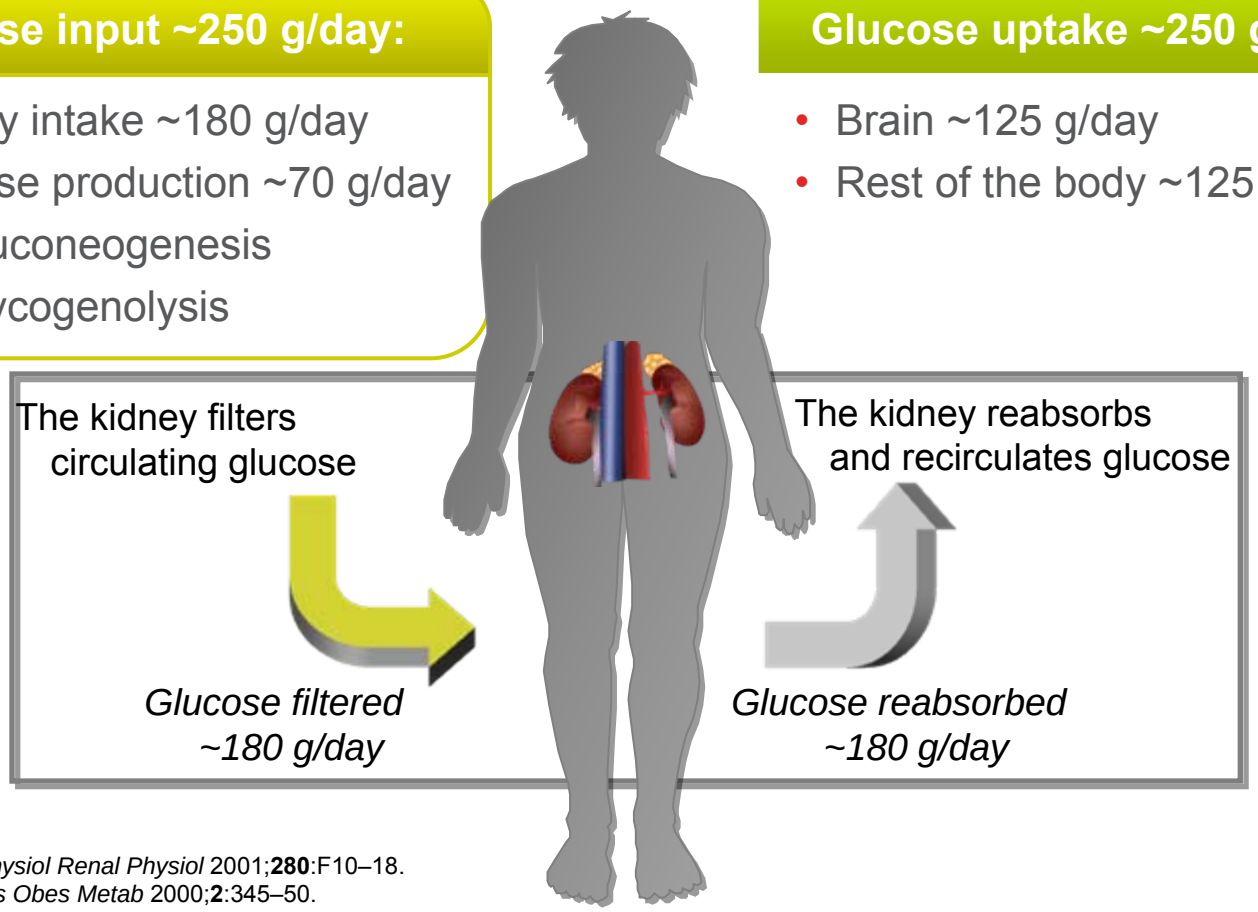
Net balance ~0 g/day

Glucose input ~250 g/day:

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

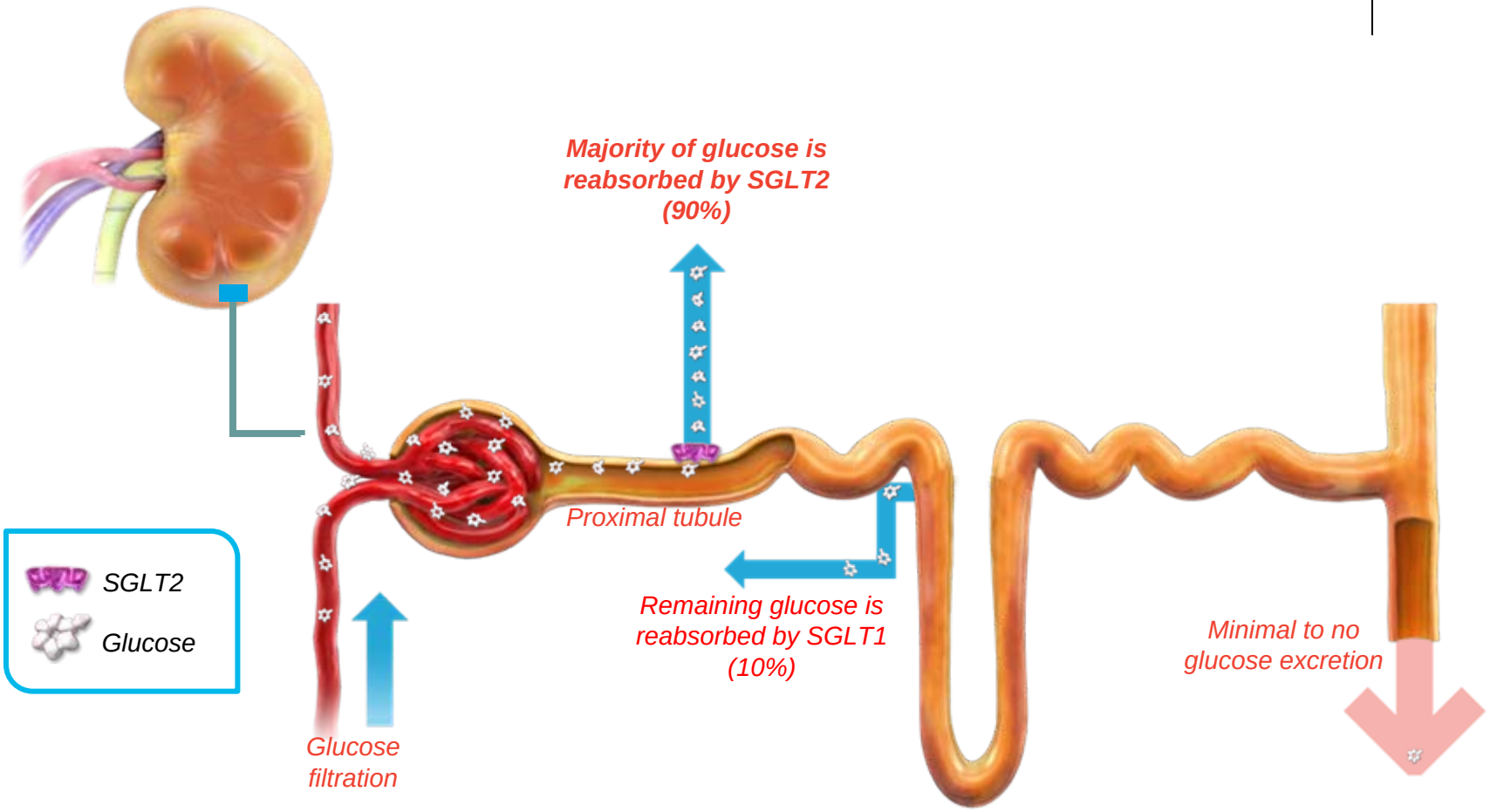
Glucose uptake ~250 g/day:

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



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

Normal renal glucose handling[1–3]



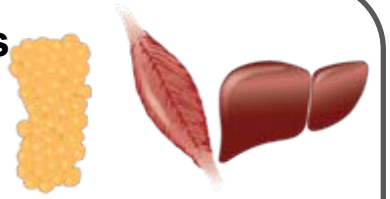
SGLT, sodium-glucose co-transporter.

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21.

Existing and novel mechanisms to reduce hyperglycaemia in type 2 diabetes[1–4]

Insulin-dependent mechanisms

1 Insulin sensitisers
- Thiazolidinediones
- Metformin



Adipose tissue, muscle and liver

2 Insulin releasers
- Sulphonylureas
- GLP-1 agonists*
- DPP-4 inhibitors*
- Meglitinides

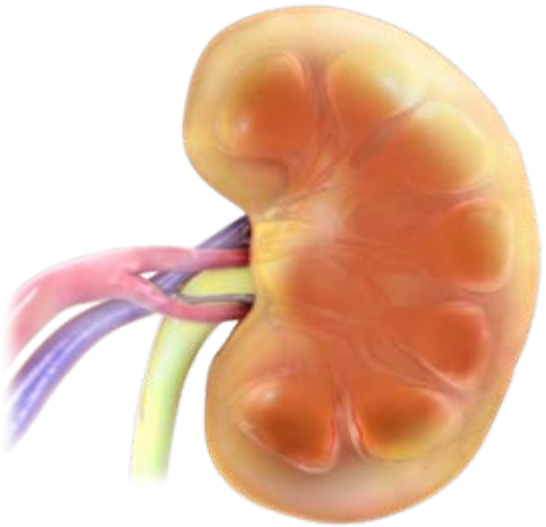
Pancreas

3 Insulin replacement
- Insulin

Glucose utilisation

Insulin-independent mechanism

SGLT2 inhibition

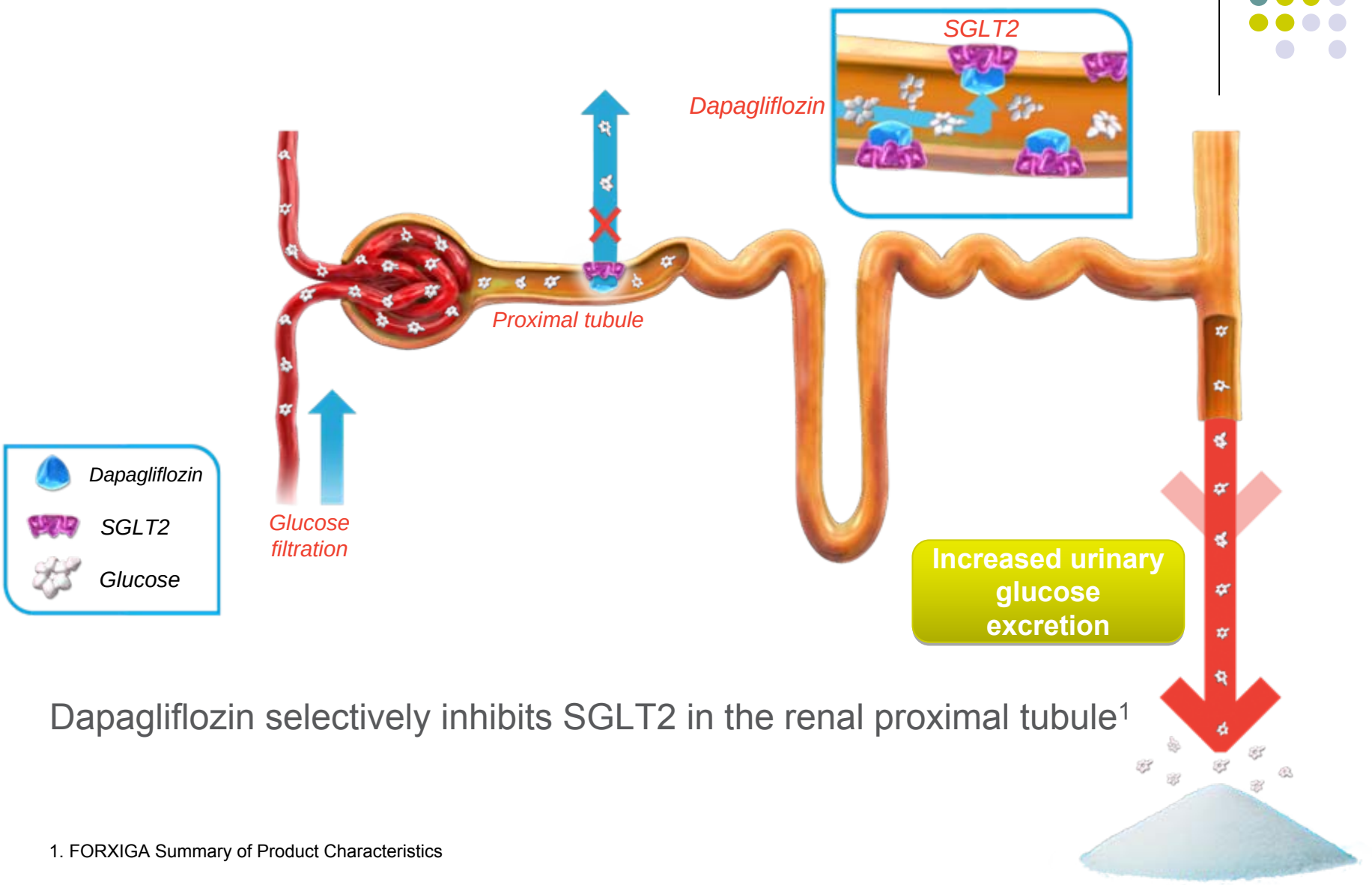


Glucose excretion/caloric loss

*In addition to increasing insulin secretion, which is the major mechanism of action, GLP-1 agonists and DPP4 inhibitors also act to decrease glucagon secretion.
DDP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

1. Washburn WN. *J Med Chem* 2009;**52**:1785–94; 2. Bailey CJ. *Curr Diab Rep* 2009;**9**:360–7; 3. Srinivasan BT, *et al. Postgrad Med J* 2008;**84**:524–31;
4. Rajesh R, *et al. Int J Pharma Sci Res* 2010;**1**:139–47.

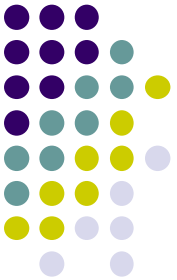
Dapagliflozin: A novel insulin-independent approach to remove excess glucose



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

1. FORXIGA Summary of Product Characteristics

The benefits of dapagliflozin's novel mechanism of action



- Dapagliflozin offers an insulin-independent mechanism that can be used as add-on therapy[1,4]
- Dapagliflozin inhibition of SGLT2 results in daily urinary glucose excretion of approximately 70g,[2] providing:
  - Significant and sustained HbA_{1c} reductions versus placebo when added to metformin[1,3]
  - Secondary benefit of weight loss[1]

1. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33;
2. List JF, *et al. Diabetes Care* 2009;**32**:650–7;
3. Bailey CJ, *et al.* Poster 988-P. Poster presented at 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June, 2011
4. FORXIGA Summary of Product Characteristics

Dapagliflozin is indicated in adults aged 18 and over with type 2 diabetes to improve control as: glycaemic

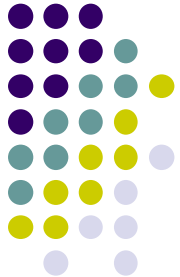
- **Add-on combination therapy[1]**
  - In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
- **Monotherapy[1]**
  - When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance

1. FORXIGA Summary of Product Characteristics

The use of dapagliflozin with pioglitazone is not recommended.
Dapagliflozin has not been studied in combination with GLP-1 analogues.

NICE TA288: Dapagliflozin in combination therapy for treating type 2 diabetes

On 26th June 2013, NICE issued its technology appraisal guidance 288 on the use of dapagliflozin as follows[1]:



- 1.1 Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidylpeptidase-4 (DPP-4) inhibitors in type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87).

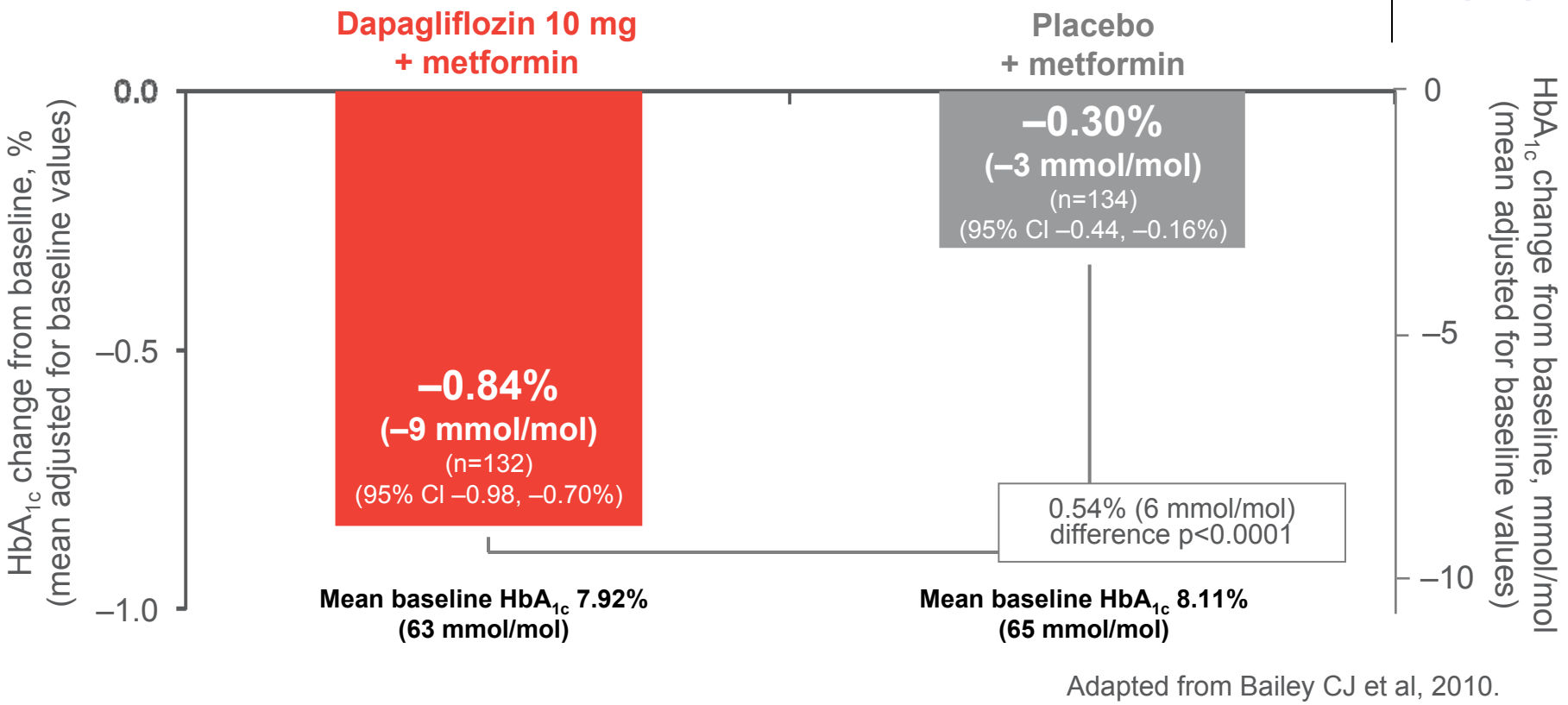
- 1.2 Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

- 1.3 Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes, except as part of a clinical trial.

- 1.4 People currently receiving dapagliflozin in a dual or triple therapy regimen that is not recommended for them in 1.1 or 1.3 should be able to continue treatment until they and their clinician consider it appropriate to stop.

The full NICE technology appraisal guidance 288 can be accessed at: www.nice.org.uk

Significant decrease in HbA1c



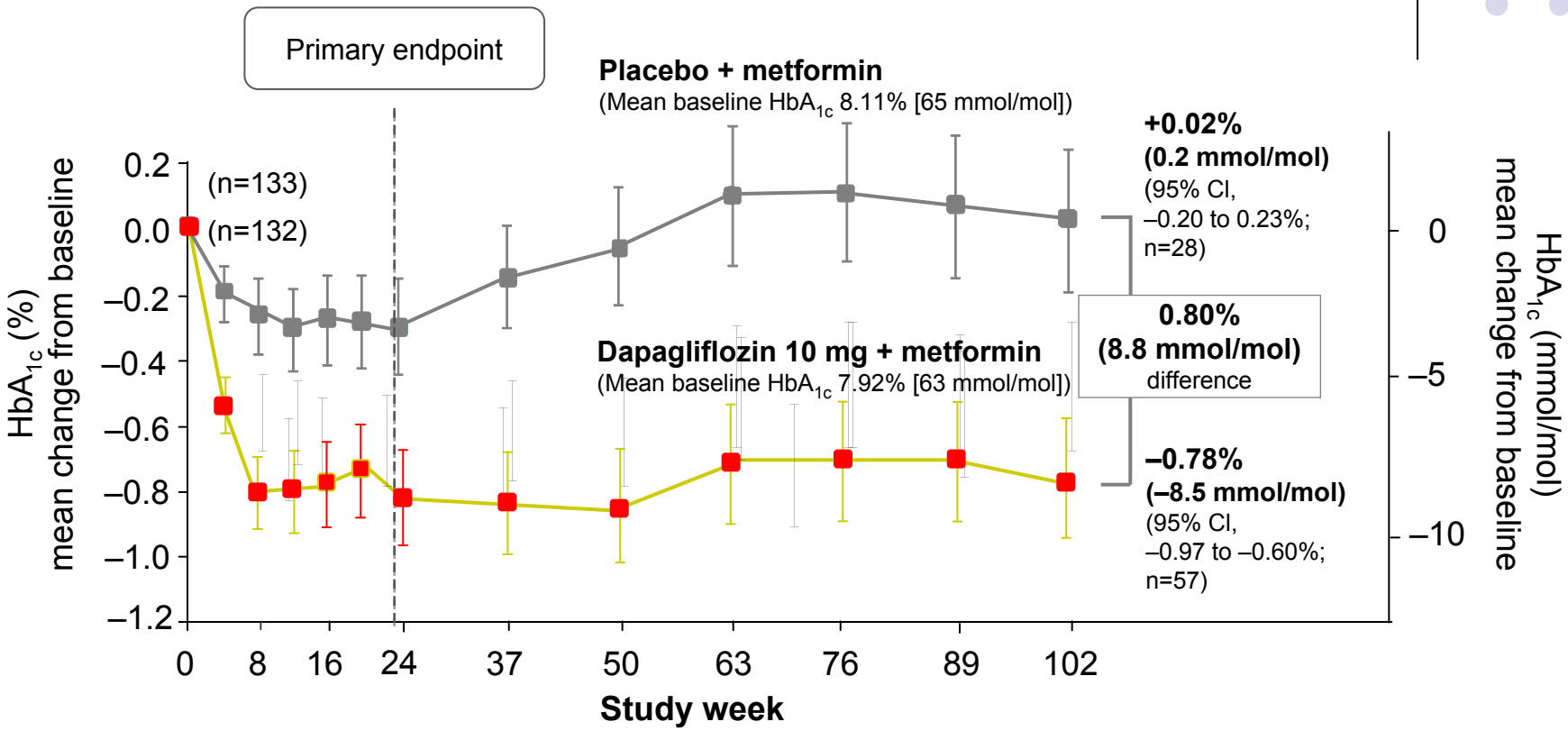
Adapted from Bailey CJ et al, 2010.

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

Bailey CJ *et al. Lancet* 2010; **375**(9733):2223–2233.

.

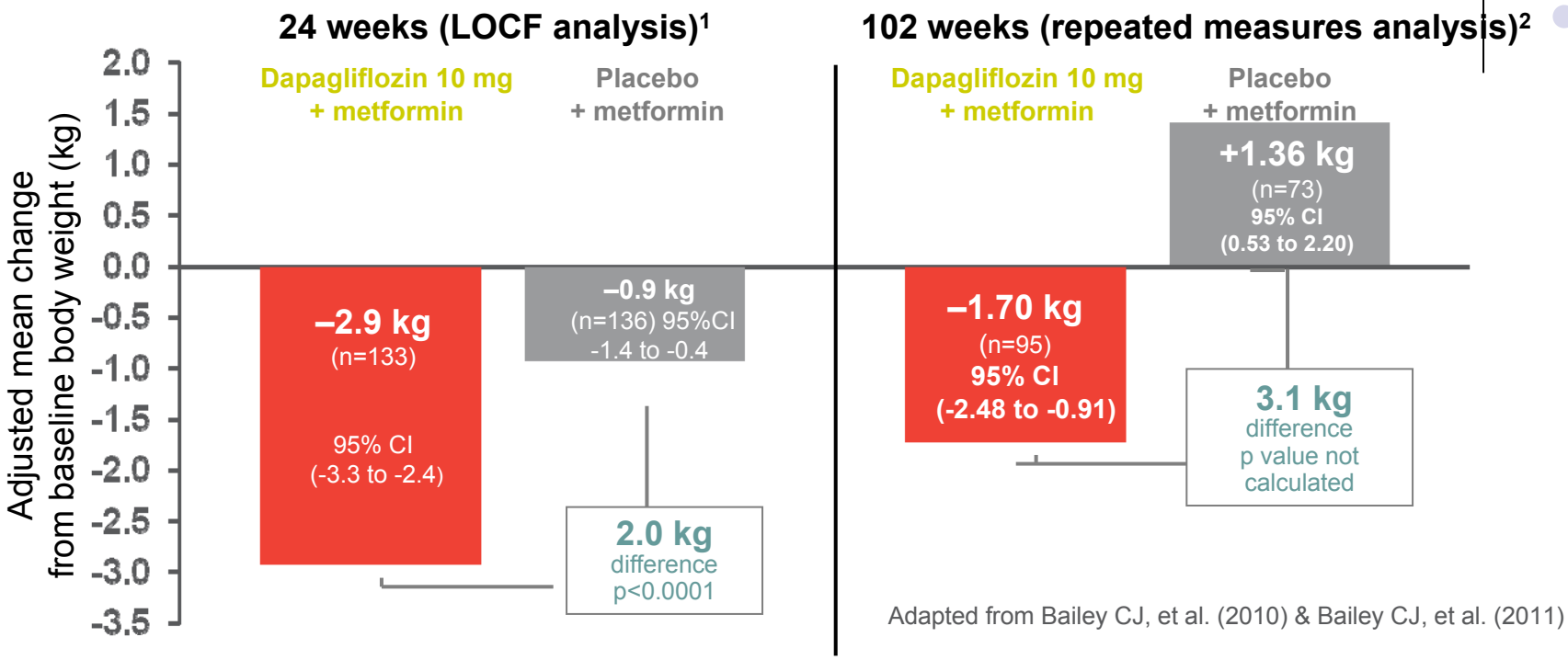
Dapagliflozin: Reductions in HbA_{1c} were sustained over 102 weeks



Data are mean change from baseline after adjustment for baseline value. Data after rescue are excluded. Analyses were obtained by longitudinal repeated measures analyses. CI, confidence interval.

Adapted from 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.

Dapagliflozin: secondary benefit of weight loss over 102 weeks

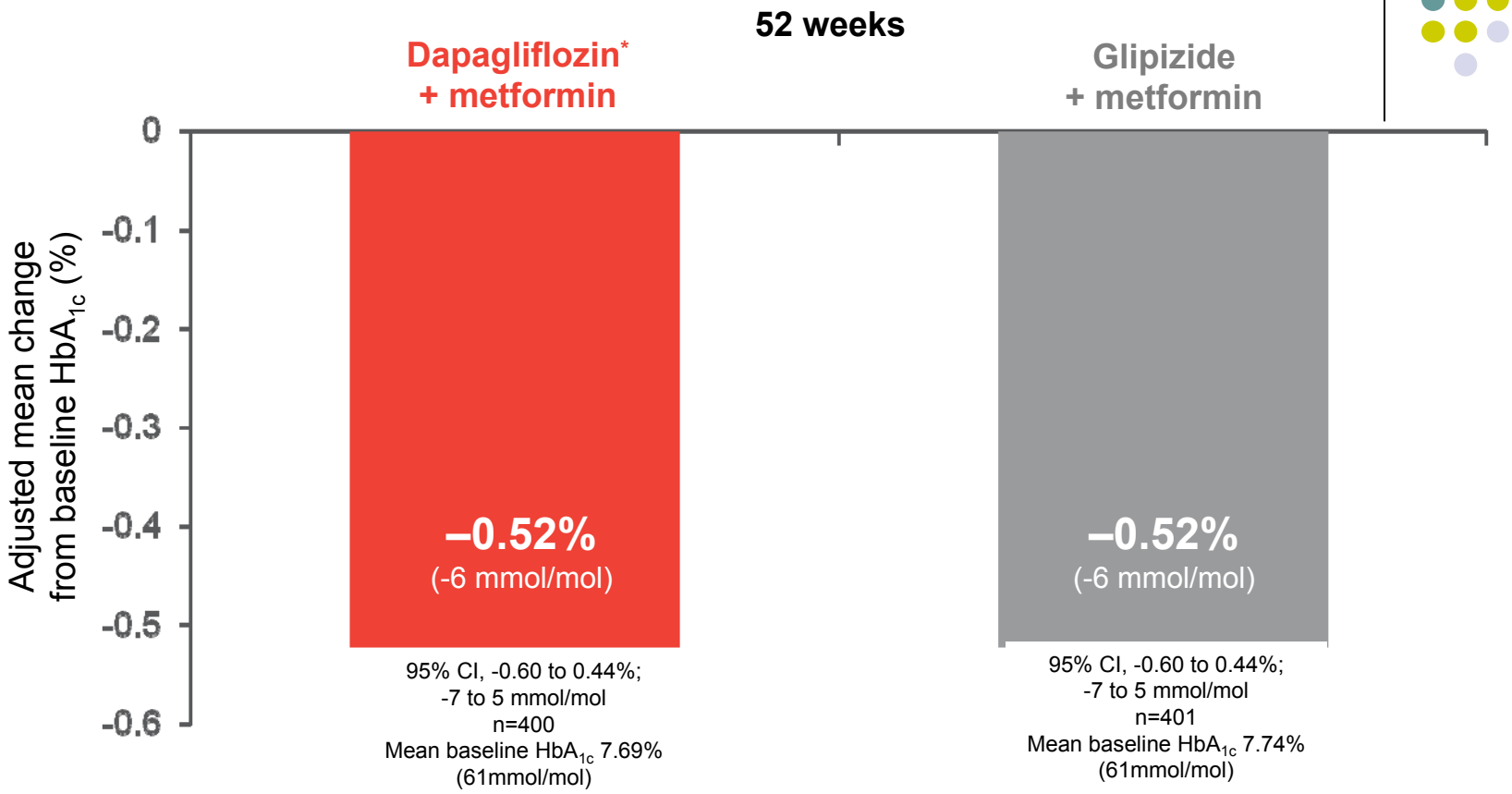


- **Weight loss at 24 weeks, with decreased waist circumference is consistent with a reduction of body-fat mass** [1]
- **In a separate study, weight loss was mainly attributable to reduction in body fat mass rather than loss of fluid or lean tissue** [3 #]

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: Comparable HbA_{1c} reduction to a sulphonylurea at the 52-week primary endpoint in a non-inferiority study



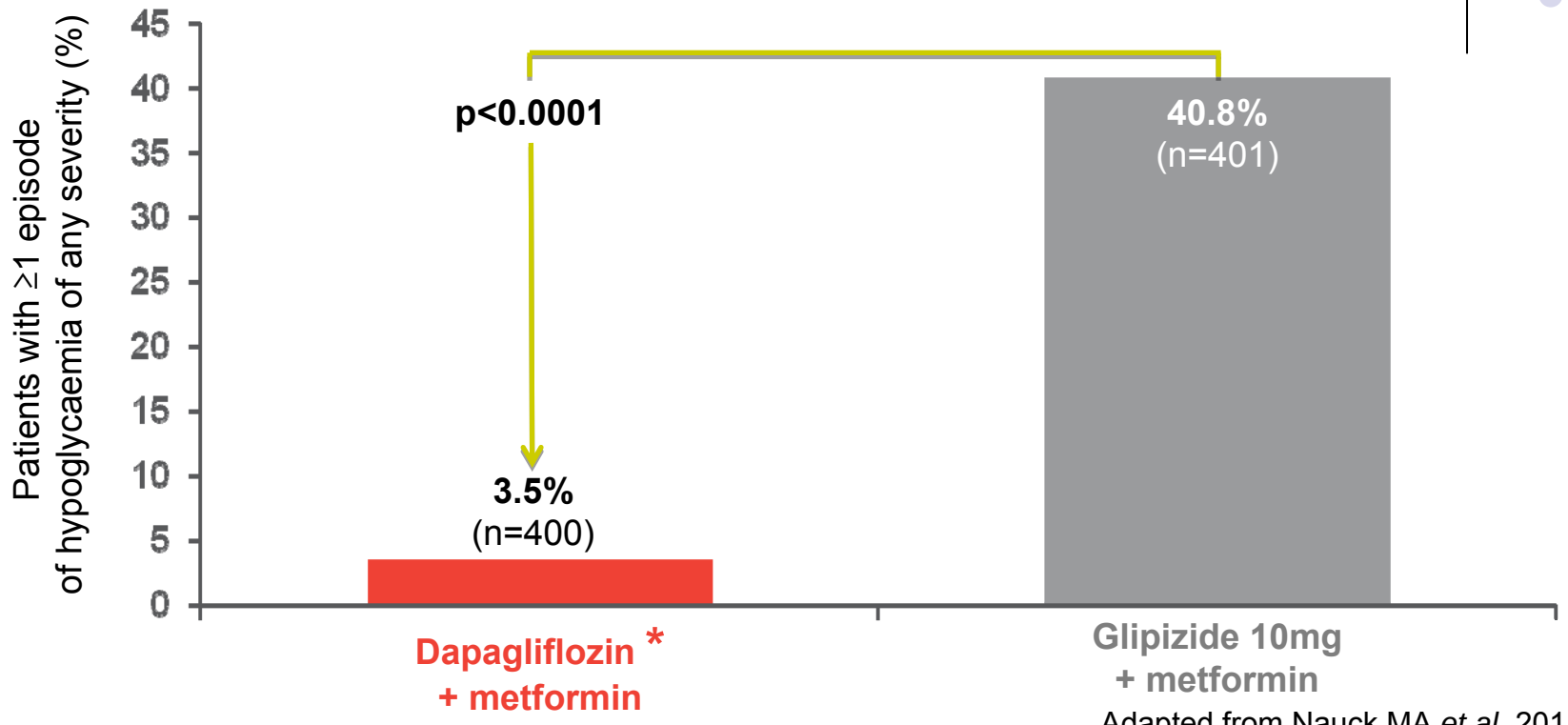
Adapted from Nauck MA *et al,* 2011.

Data are adjusted mean change from baseline and 95% confidence interval (CI) derived from analysis of covariance using the full analysis set and last observation carried forward (LOCF) values. Statistical non-inferiority of dapagliflozin versus glipizide was established if the upper limit of the 95% confidence interval for the treatment difference in mean HbA1c change from baseline to week 52 was <0.35%. Treatment difference between arms at week 52: 0.00% (95% CI: -0.11, 0.11)
*Dapagliflozin dose was up-titrated to a maximum of 10mg (achieved in 87% of patients) over an 18-week period based on glycaemic response and tolerability.

Nauck MA *et al. Diabetes Care* 2011;**34**:2015–2022.

Lower incidence of hypoglycaemia with dapagliflozin compared with a sulphonylurea

Number of patients who experienced ≥1 hypoglycaemic episode over 52 weeks[1]



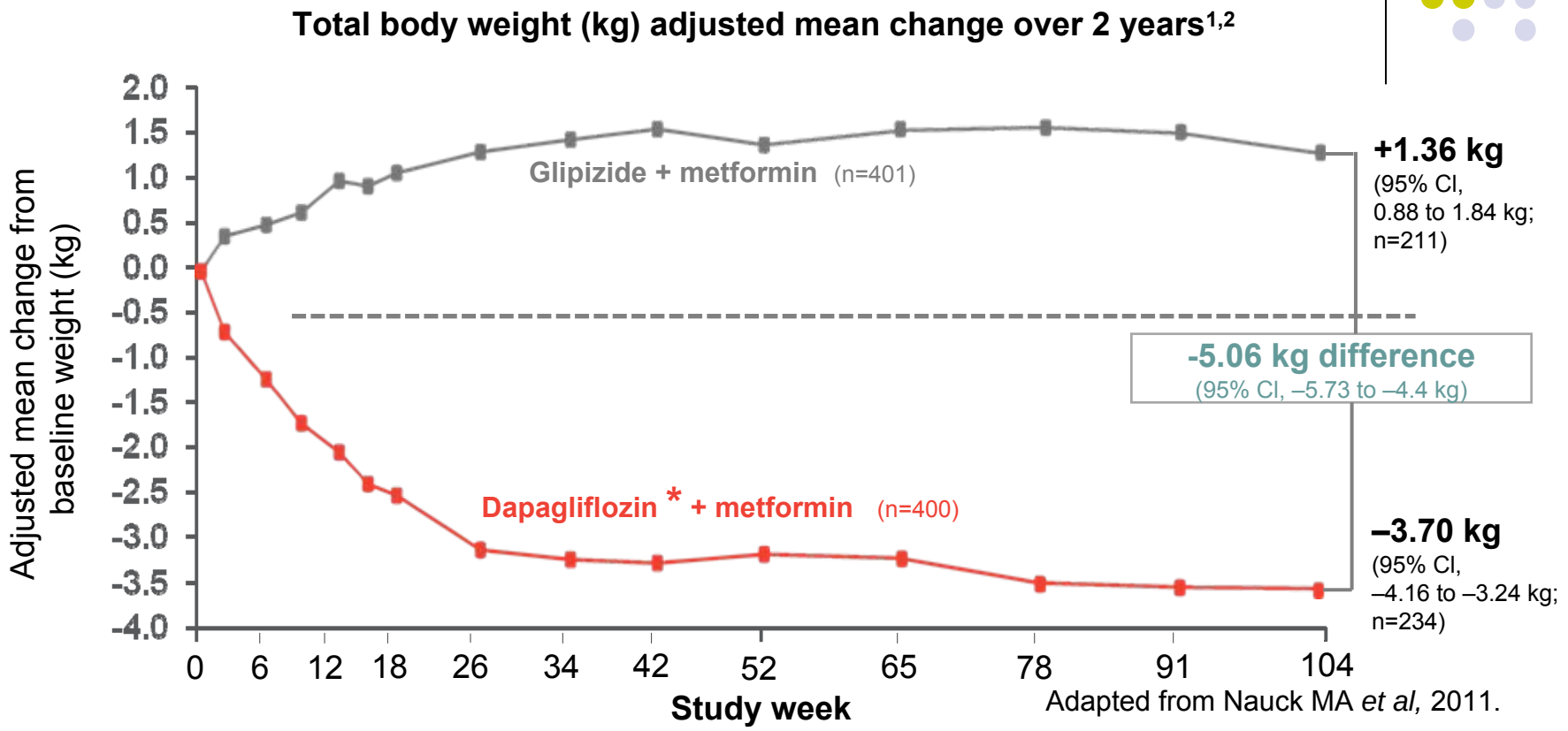
Adapted from Nauck MA *et al,* 2011.

Dapagliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin[2]

*Dapagliflozin was up-titrated to a maximum of 10mg (achieved by 87% of patients) over an 18-week period based on glycaemic response and tolerability. **Major hypoglycaemia was defined as a symptomatic episode requiring external assistance due to severely impaired consciousness or behaviour, with capillary or plasma glucose levels of 54 mg/dL (3.0 mmol/L) and recovery after glucose or glucagon administration. There were no major hypoglycaemic events in the dapagliflozin plus metformin arm and 3 episodes in the glipizide plus metformin arm. Minor hypoglycaemia was defined as a symptomatic episode with capillary or plasma glucose levels of 63 mg/dL (3.5 mmol/L), irrespective of the need for external assistance, or an asymptomatic episode with capillary or plasma glucose levels of 63 mg/dL (3.5 mmol/L) that did not qualify as a major episode. Other hypoglycaemia was defined as an episode with symptoms suggestive of hypoglycaemia but without measurement confirmation.

1. Nauck MA *et al. Diabetes Care* 2011;**34**:2015–2022.
2. FORXIGA™. Summary of product characteristics.

Dapagliflozin: Secondary benefit of weight loss compared with a sulphonylurea



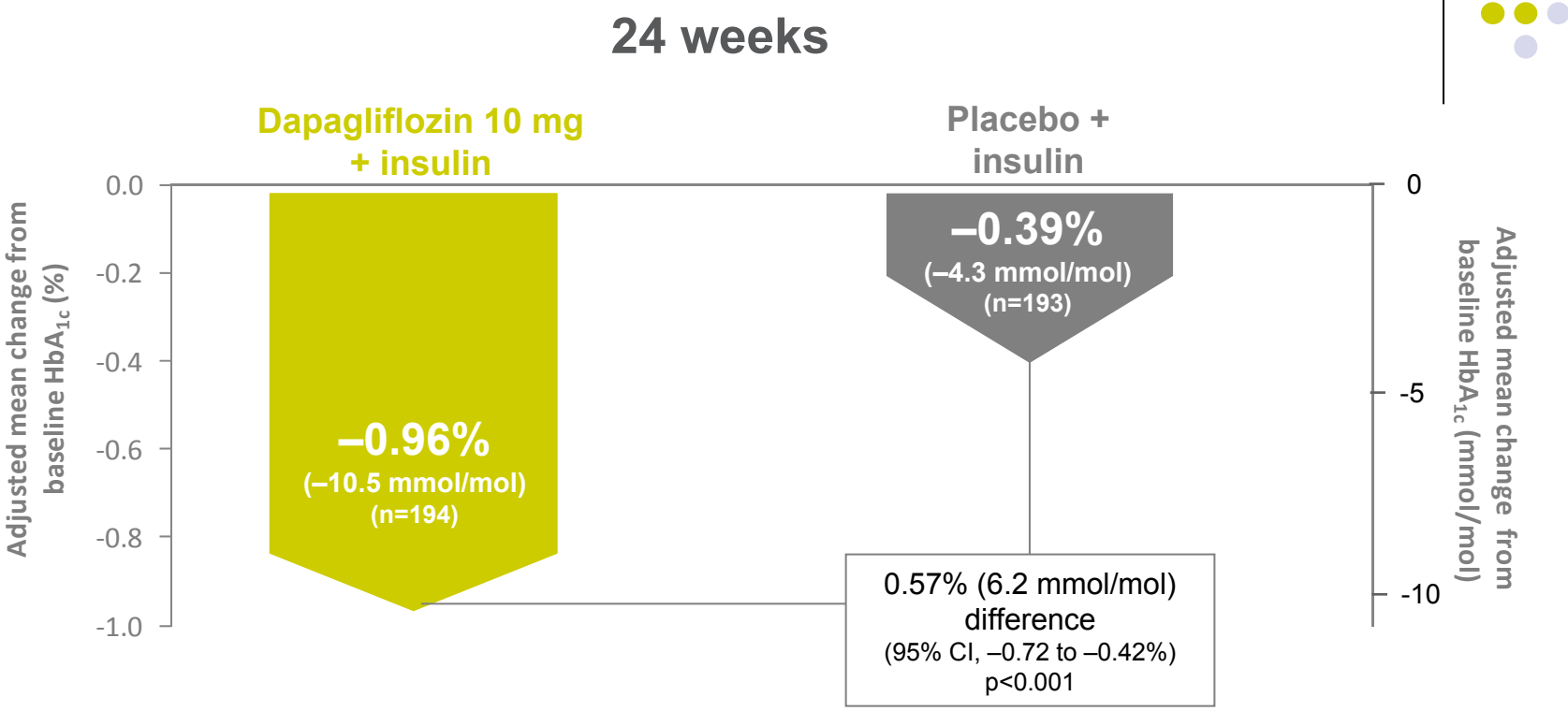
*Dapagliflozin dose was up-titrated to a maximum of 10mg (achieved in 87% of patients) over an 18-week period based on glycaemic response and tolerability

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).

1, Nauck MA *et al. Diabetes Care* 2011;**34**:2015–2022.

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

Reductions in HbA_{1c} with insulin + dapagliflozin compared with insulin + placebo at 24 weeks



Adapted from Wilding J, *et al*. 2012

Last observation carried forward (LOCF). Data are adjusted mean change from baseline. Mean HbA_{1c} at baseline were 8.47% (69 mmol/mol) for insulin + placebo and 8.57% (70 mmol/mol) for insulin + dapagliflozin 10mg.
Consider a reduction in insulin dose on commencement of dapagliflozin to reduce the risk of hypoglycaemia[2]

1. Wilding J, *et al. Ann Intern Med* 2012;**156**:405–415.
2. FORXIGA™. Summary of product characteristics.

Pooled safety and tolerability data

Safety and tolerability data from a comprehensive clinical programme

- The overall incidence of adverse events in subjects treated with dapagliflozin 10mg was similar to placebo at 24 weeks[1]

Adverse reactions in placebo-controlled studies of dapagliflozin

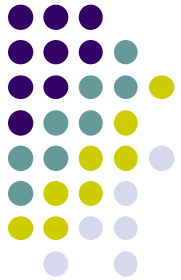
Pre-specified pooled analysis of 12 placebo controlled studies with 1193 patients on dapagliflozin 10mg and 1393 patients on placebo

System organ class	Very common (≥10%)	Common (≥1% to <10%)	Uncommon (≥0.1% to <1%)
Infections and infestations		Vulvovaginitis, balanitis and related genital infections UTIs	Vulvovaginal pruritus
Metabolism and nutrition disorders	Hypoglycaemia (when used with a SU or insulin)		Volume depletion Thirst
Gastrointestinal disorders			Constipation
Skin and subcutaneous tissue disorders			Hyperhidrosis
Musculoskeletal and connective tissue disorders		Back pain	
Renal and urinary disorders		Dysuria Polyuria	Nocturia
Investigations		Dyslipidaemia Haematocrit increased	Blood creatinine increased Blood urea increased

SU, sulphonylurea; UTI, urinary tract infection.

1. FORXIGA Summary of product characteristics.

Genital infections and urinary tract infections*



•Most genital infections† and UTIs were mild to moderate, responded to initial course of standard therapy, and rarely led to discontinuation of dapagliflozin

•Events of genital infection (vulvovaginitis, balanitis and related genital infections) and UTIs with dapagliflozin 10 mg versus placebo:

•Pyelonephritis was uncommon and occurred at a similar frequency to control

Frequency at 24 weeks	Genital infections	UTIs
Dapagliflozin 10mg	4.8%	4.3%
Placebo	0.9%	3.7%

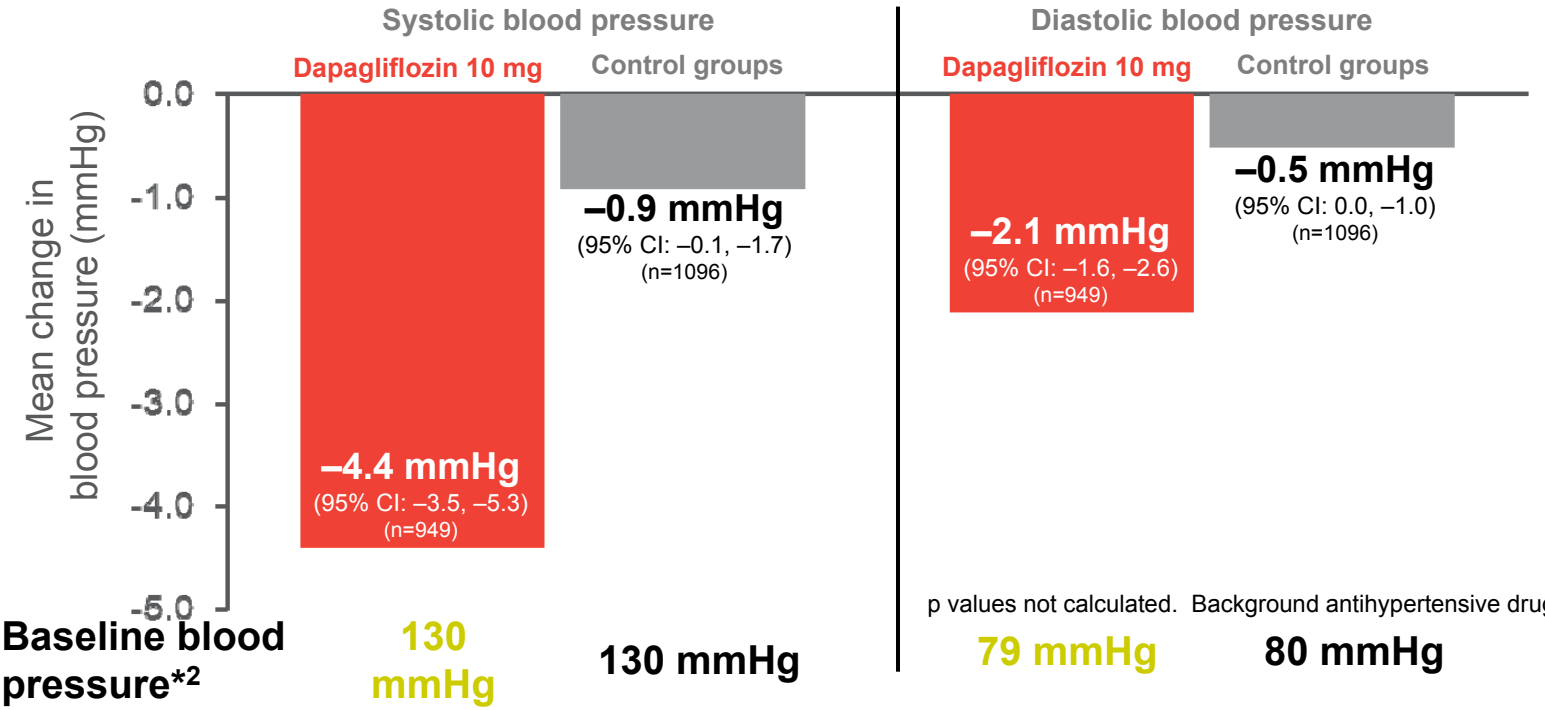
*In a prespecified pooled analysis of 12 placebo-controlled studies;
†Genital infection includes the preferred terms, listed in order of frequency reported: Vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, and vulval abscess.

FORXIGA Summary of product characteristics.

Cardiovascular considerations

A modest decrease in blood pressure was observed with dapagliflozin during clinical trials[1,2]

Reduction in blood pressure at 24 weeks in a placebo-controlled pooled analysis



- Caution should be exercised in patients for whom a drop in blood pressure induced by dapagliflozin could pose a risk, such as:
  - Patients with known cardiovascular disease
  - Patients on anti-hypertensive therapy with a history of hypotension
  - Elderly patients[3]
- Dapagliflozin is not recommended in patients receiving loop diuretics as it may add to the diuretic effect and may increase the risk of dehydration and hypotension[3]

*Baseline BP values are for the total population in the pooled analysis (dapagliflozin 10 mg n=1193, placebo n=1393)

1. Ptaszynska A *et al.* Poster presented at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, PA ,June 8–12, 2012.
2. Sjöström C *et al*. Oral presentation at the European Society of Cardiology, Munich, Germany, August 25–29, 2012.
3. FORXIGA™. Summary of product characteristics.

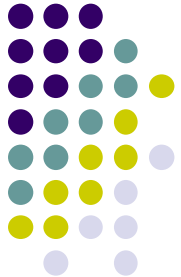
Dosing and administration

Dapagliflozin dosing

- Dapagliflozin 10mg daily can be used in patients with mild or moderate hepatic impairment
- In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg
- Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension
- •Consider a lower dose of insulin or insulin secretagogue in combination with dapagliflozin to reduce the risk of hypoglycaemia
- Dapagliflozin has a low potential for other interactions with commonly used agents in patients with type 2 diabetes

FORXIGA Summary of product characteristics

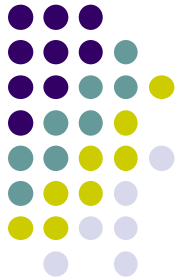
Considerations for dapagliflozin dosage and administration



- Dapagliflozin should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Dapagliflozin is not recommended for patients concomitantly treated with pioglitazone
- Monitoring of renal function is recommended prior to the initiation of dapagliflozin and at least annually thereafter prior to the initiation of concomitant medicines that may reduce renal function and periodically thereafter, and at least 2 to 4 times per year for patients approaching moderate renal impairment. No dosage adjustment is indicated in patients with mild renal impairment (eGFR ≥ 60 ml/min/1.73m2)
- Dapagliflozin is not recommended in moderate to severe renal impairment.
- In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic: experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended in this patient group.
- Dapagliflozin is not recommended in patients who are volume depleted, e.g. due to acute illness such as gastrointestinal illness. (eGFR < 60 ml/min/ 1.73/m^2)
- Dapagliflozin 10 mg daily can be used in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.
- Haematocrit increase was observed with dapagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted.

FORXIGA. Summary of product characteristics..

Scottish Medicines Consortium Advice: Dapagliflozin



Dapagliflozin (Forxiga®) is accepted for restricted use within NHS Scotland.

Indication under review: For use in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

- Add-on combination therapy
- In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control

SMC restriction: Dapagliflozin is restricted to use as dual therapy in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control and a sulphonylurea is inappropriate.

Scottish Medicines Consortium. Dapagliflozin 5mg and 10mg film-coated tablets. SMC No. (799/12). Issued 7 December 2012. Available at: http://www.scottishmedicines.org.uk/files/advice/dapagliflozan_Forxiga_FINAL_September_2012_amended_041012_for_website.pdf Last acccessed February 2013.

Summary

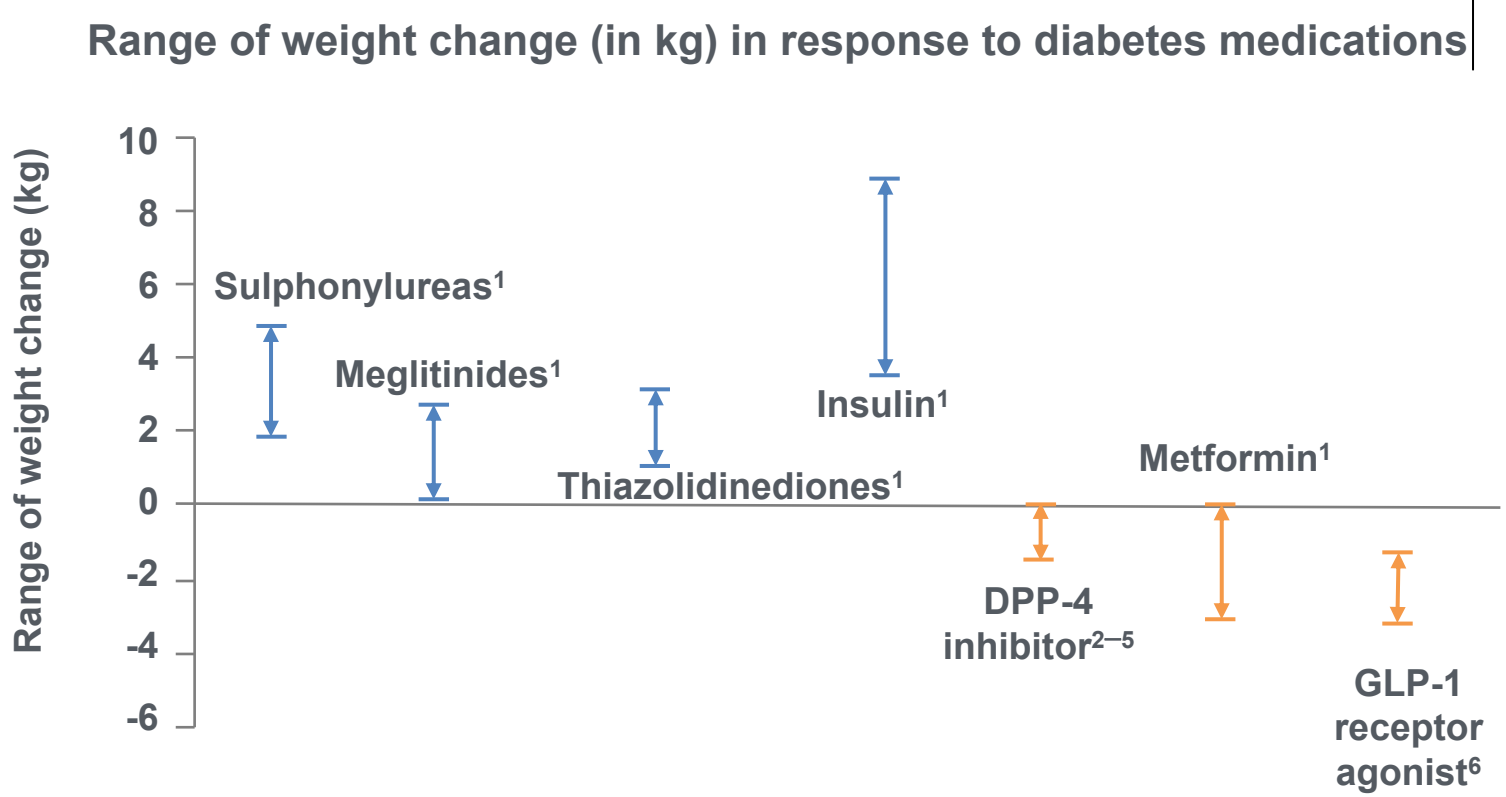
In patients with type 2 diabetes uncontrolled on metformin FORXIGA® (dapagliflozin) offers;

- Significant and sustained HbA_{1c} reduction at 2 years compared with placebo[1-3]
- Secondary benefit of weight loss[1-3]
- Low incidence of hypoglycaemia when added to metformin[1]
- Oral, once daily dosing[3]

.

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, 24–28 June, 2011;
3.FORXIGA. Summary of product characteristics;

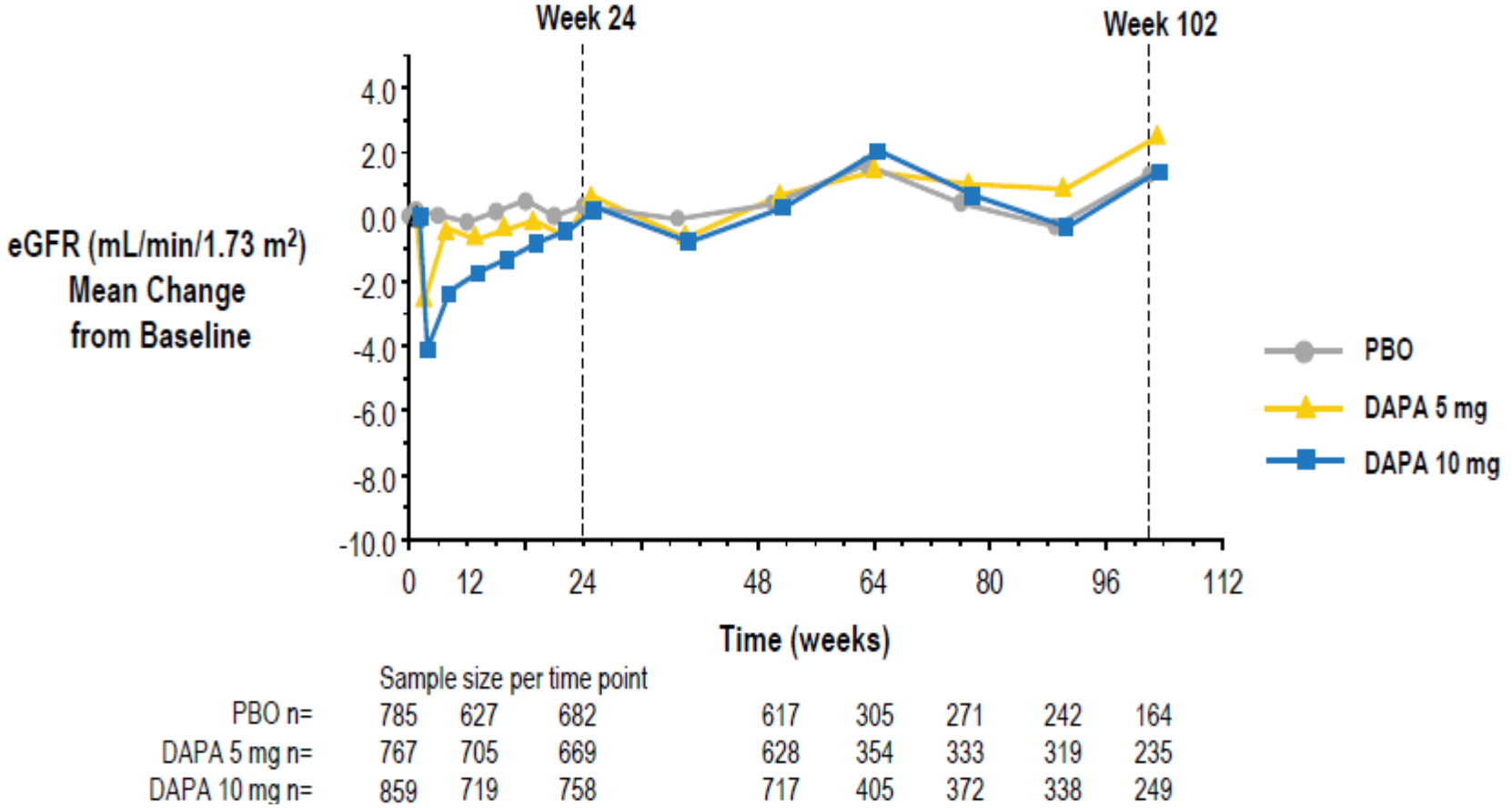
Glucose-lowering medications and weight profile



Weight change (Kg): -1.39 (linagliptin vs glimepiride) [2], -0.6 (sitagliptin vs glipizide)[3], -1.5 (sitagliptin vs glipizide)[3], -0.3 (vildagliptin vs rosiglitazone)[4], -0.2 (vildagliptin vs glimepiride), +0.1 (vildagliptin vs gliclazide)[4], -1.1 (saxagliptin vs glipizide)[5], -1.0 to -2.8 (liraglutide in combination with metformin, metformin + glimepiride and metformin + rosiglitazone)[6]

Reproduced from 1. Mitri J, Hamdy O. *Expert Opin Drug Saf* 2009; 8:573–8; 2. Boehringer Ingelheim and Eli Lilly and Company Limited. Trajenta (linagliptin) Summary of Product Characteristics. http://www.medicines.org.uk/EMC/medicine/25000/SPC/ Aug 2011 (accessed September 2012); 3. MSD Januvia (sitagliptin) Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/19609/SPC/ Mar 2012 (accessed September 2012); 4. Novartis Galvus (vildagliptin) Summary of Product Characteristics http://www.medicines.org.uk/EMC/medicine/20734/SPC/Galvus+50+mg+Tablets/ Jul 2012 (accessed September 2012); 5. AstraZeneca Onglyza (saxagliptin) Summary of Product Characteristics. http://www.medicines.org.uk/emc/medicine/22315/SPC/ Jan 2012 (accessed September 2012); 6. Novo Nordisk Limited. Victoza (liraglutide) Summary of Product Characteristics. http://www.medicines.org.uk/EMC/medicine/21986/SPC/Victoza+6+mg+ml+solution+for+injection+in+pre-filled+pen/ July 2012 (accessed September 2012).

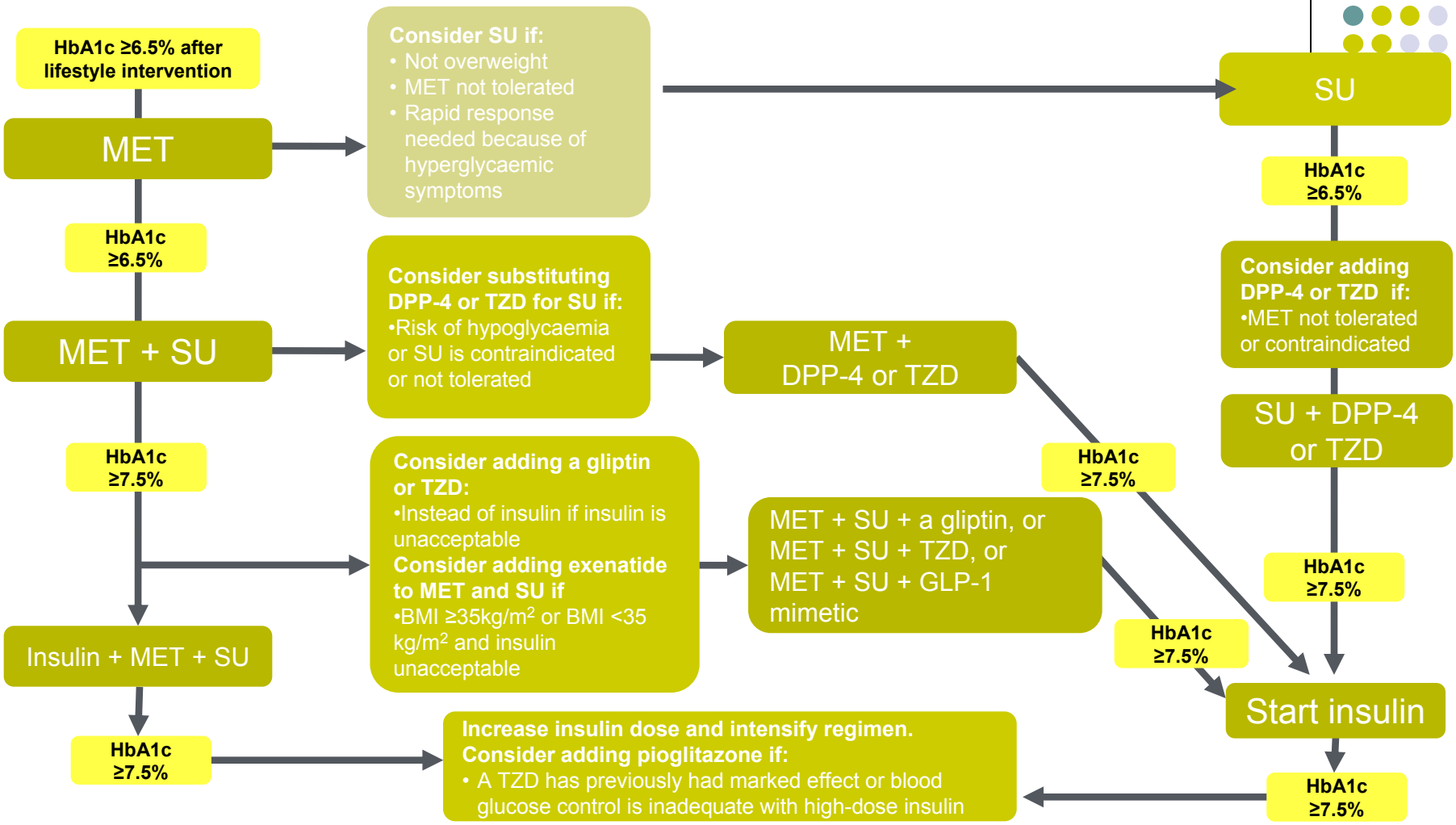
Long-term data, up to 102 weeks shows that FORXIGA does not significantly change eGFR from baseline



- With DAPA, mean eGFR decreased at Week 1 then returned to or above baseline by Week 24 and was maintained to Week 102

Adapted from Ptaszynska A et al. Effect of Dapagliflozin on Renal Function. Poster number 1098-P. Presented at American Diabetes Association 72ndScientific Sessions, June 8-12, 2012, Philadelphia, PA, USA

National Institute for Health and Clinical Excellence (NICE): T2D treatment algorithm[1]



MET = metformin, SU = sulphonylureas, TZD = thiazolidinedione, DPP-4= dipeptidyl peptidase-4 inhibitor

1. Adapted from: National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes - newer agents (a partial update of CG66): quick reference guide.

Management of hyperglycaemia in type 2 diabetes: a patient-centred approach.

Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Key points

• Glycaemic targets and glucose-lowering therapies must be individualised.

• Diet, exercise and education remain the foundation of any type 2 diabetes treatment programme.

• Unless there are prevalent contraindications, metformin is the optimal first line drug.

• After metformin, there are limited data to guide us. Combination therapy with an additional 1–2 oral or injectable agents is reasonable, aiming to minimise side effects where possible.

• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.

• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs and values.

• Comprehensive cardiovascular risk reduction must be a major focus of therapy.

Inzucchi SE, et al. Diabetes Care 2012; 35:1364–79.

Scottish Intercollegiate Guidelines Network (SIGN): T2D treatment algorithm[1]

1st LINE OPTIONS in addition to lifestyle measures; START ONE OF

Metformin (MET)

Sulphonylurea* (SU)

- If intolerant to metformin
- If weight loss/osmotic symptoms

Review and if not reaching target move to 2nd line

	Usual approach
	Alternative approach
*	**Continue medication if EITHER individualised target achieved OR HbA1c falls >0.5% (5.5 mmol/mol) in 3-6 months**

2nd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF

SU*

Thiazolidinedione*
- If hypos a concern (e.g. driving, occupational hazards, at risk of falls) and if no congestive heart failure

DPP-4 inhibitor*
- If hypos a concern (e.g. driving, occupational hazards, at risk of falls, or if weight gain a concern

Review and if not reaching target move to 3rd line

3rd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD OR SUBSTITUTE WITH ONE OF

ORAL (continue MET/SU if tolerated)

Thiazolidinedione*
If no congestive heart failure

DPP-4 inhibitor*
If weight gain a concern

INJECTABLE (if willing to self inject; continue MET/SU if tolerated)

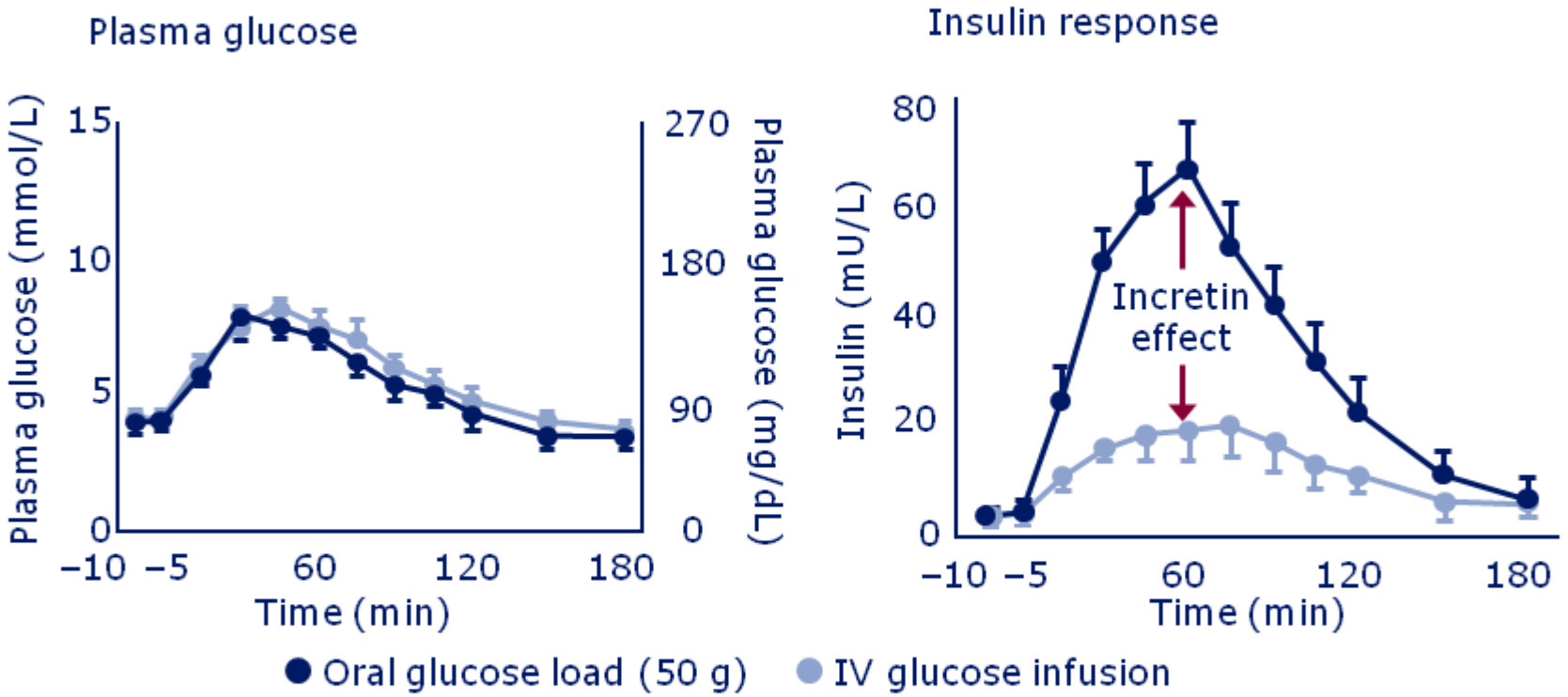
Insulin* (inject before bed)
- If osmotic symptoms/rising HbA1c; NPH insulin initially
- If hypos a concern, use basal analogue
- Add prandial insulin with time if required

GLP-1 agonists*
- If BMI > 30 kg/m^2
- If a desire to lose weight
- Usually <10 years from diagnosis

DPP-4= dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide 1

1. Adapted from: Scottish Intercollegiate Guidelines Network. Management of diabetes: a national clinical guideline. March 2010. Prescribers should refer to the British National Formulary (www.bnf.org) and the Scottish Medicines Consortium (www.scottishmedicines.org.uk) for updated guidance on licensed indications, full contraindications and monitoring requirements.

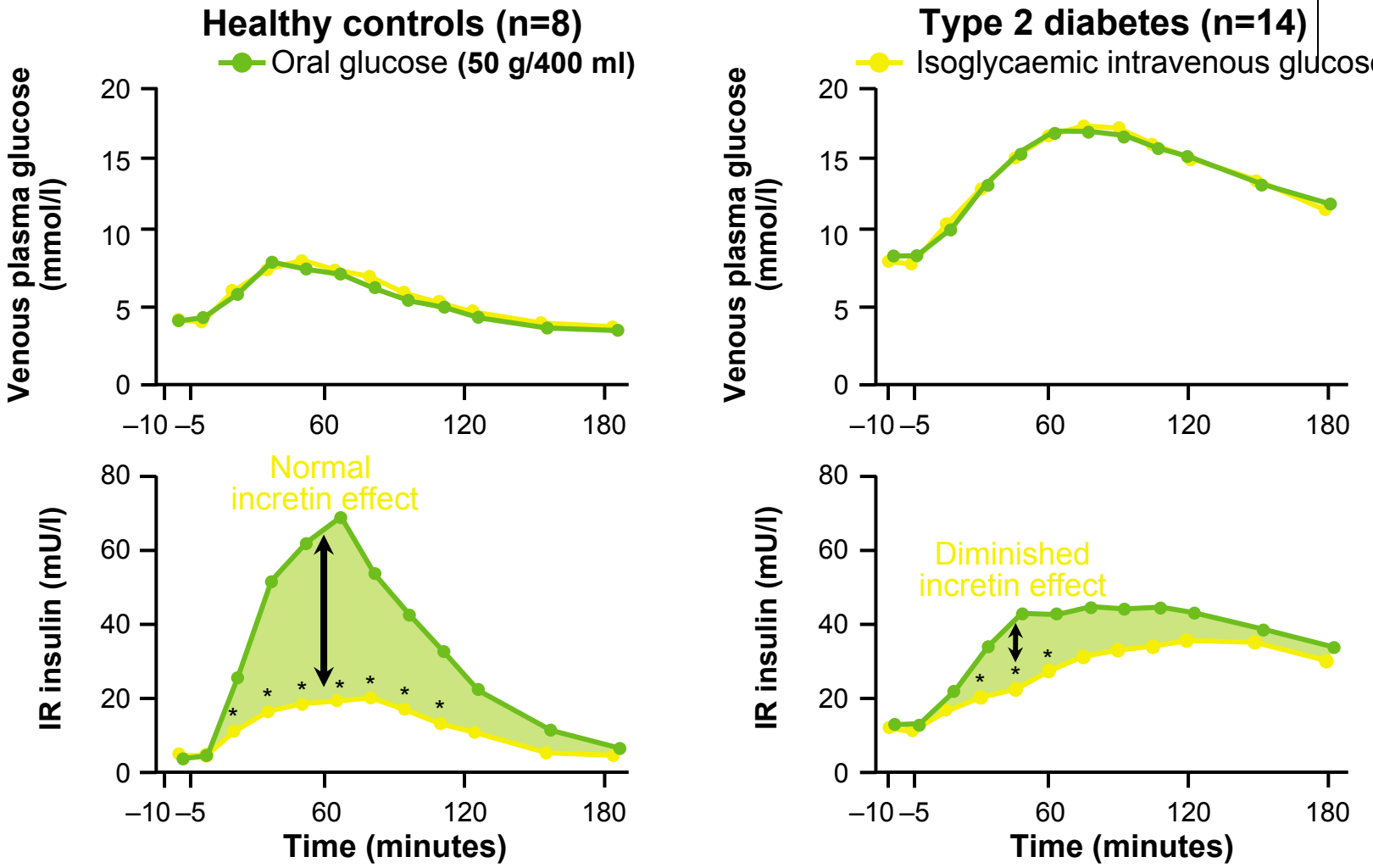
Incretin hormones play an important role in a healthy insulin response



- Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration

Nauck *et al. Diabetologia* 1986;29:46–52, healthy volunteers (n=8)
Wick & Newlin. *J Am Acad Nurse Pract* 2009;21:623–30

Incretin effect after oral glucose was diminished in type 2 diabetes[6]

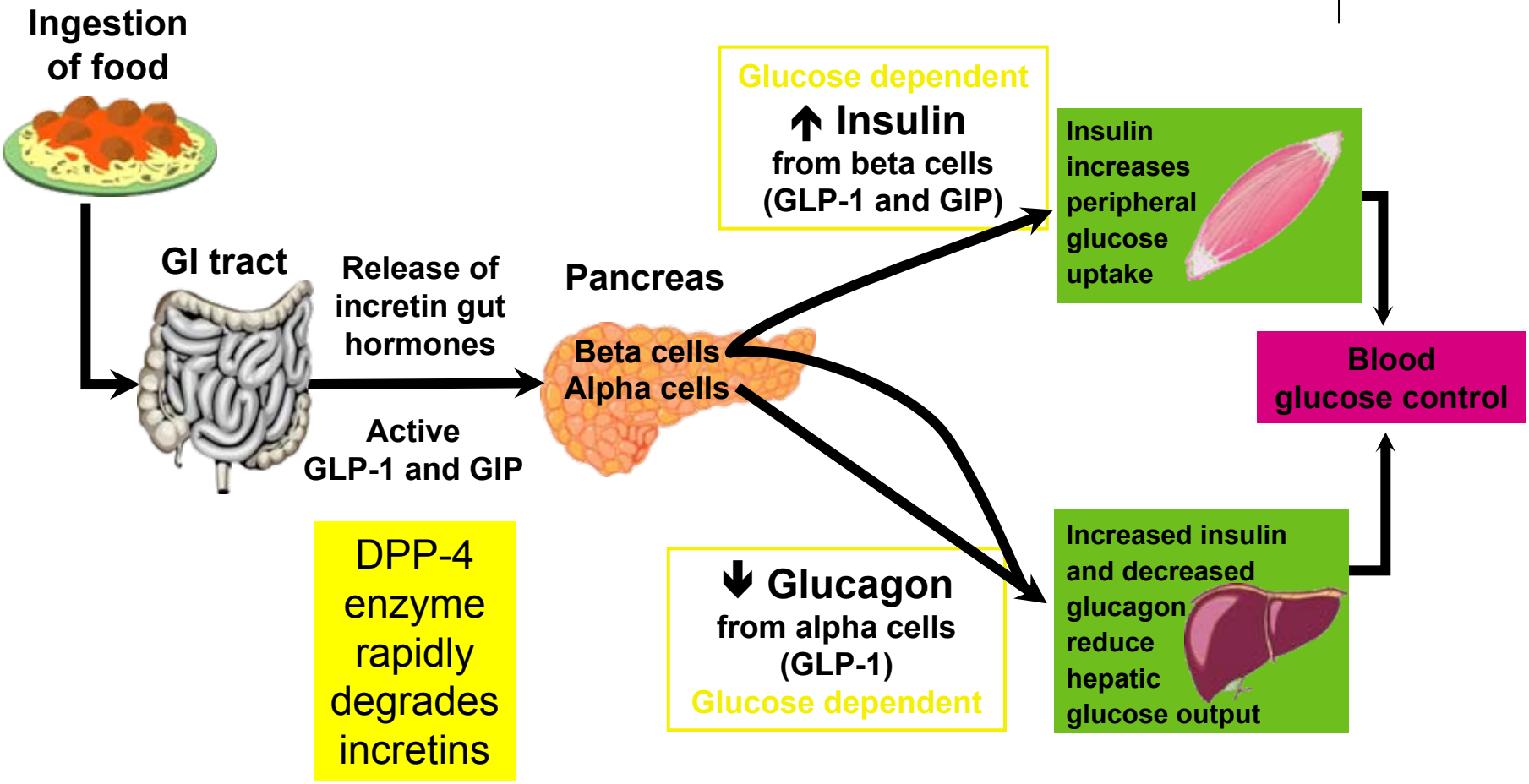


*p≤0.05 vs. respective value after oral load

IR=immunoreactive

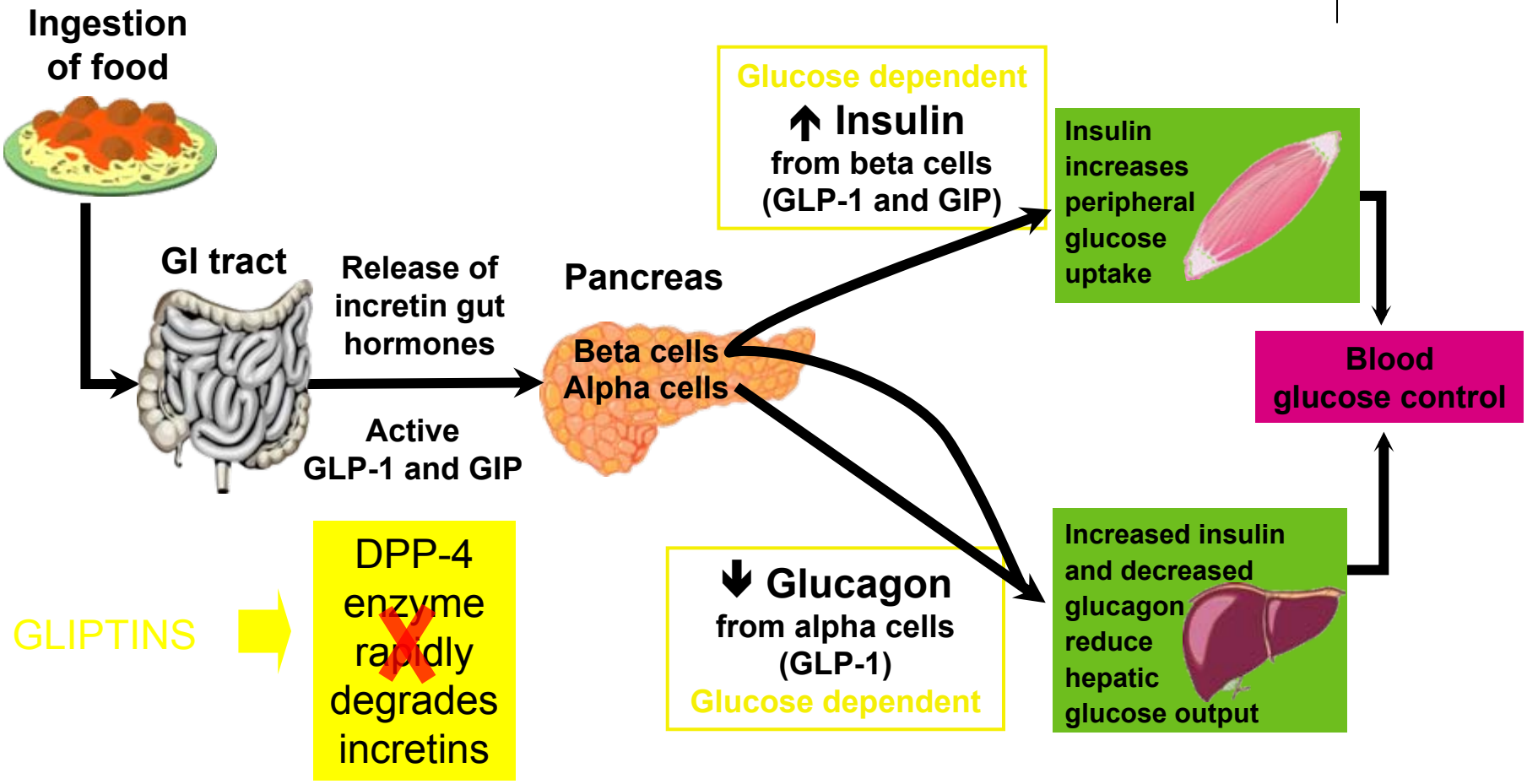
6. Adapted from Nauck M et al *Diabetologia* 1986;29:46–52.

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.

Mode of action of gliptins[8]



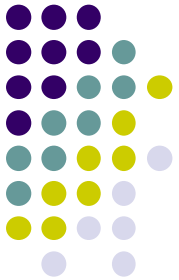
DPP-4= dipeptidyl peptidase 4 inhibitor

Adapted from 8. Miller S, St Onge EL. *Ann Pharmacother* 2006;40:1336-1343.

GLIPTINS

- DPP-4 inhibitors - WEIGHT NEUTRAL
- Will reduce HbAc by 7-9 mmol/mol
- Few side effects
- I believe should be added to type 2 regimen before sulphonylureas

DPP-4 inhibitors excretion



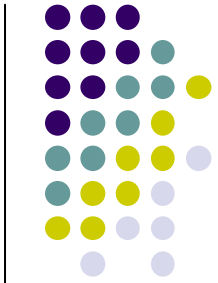
	Renal excretion
Linagliptin	5%
Sitagliptin	87%
Saxagliptin	75%
Vildagliptin	85%

All need dose reduction as eGFR falls except Linagliptin

George

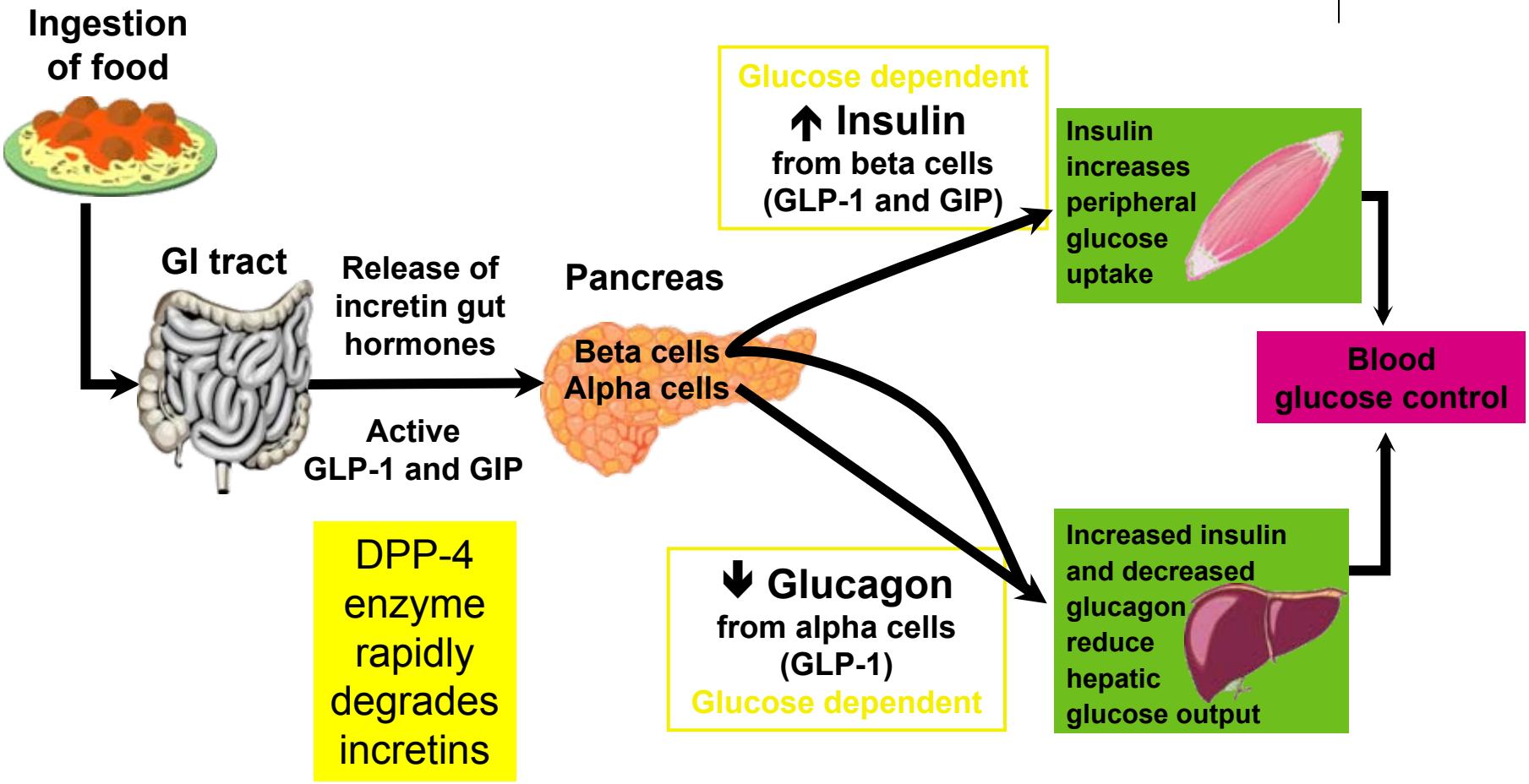
Age	Treatment	wt	HbA1c
44	diet + tablets	109	81
46	MI		
54	Mixtard 20u bd	109	81
63	Mixtard 30 ubd	108	69
65	Mixtard 60u bd	109	75
	Rosiglit/metformin		

OBESE DIABETIC



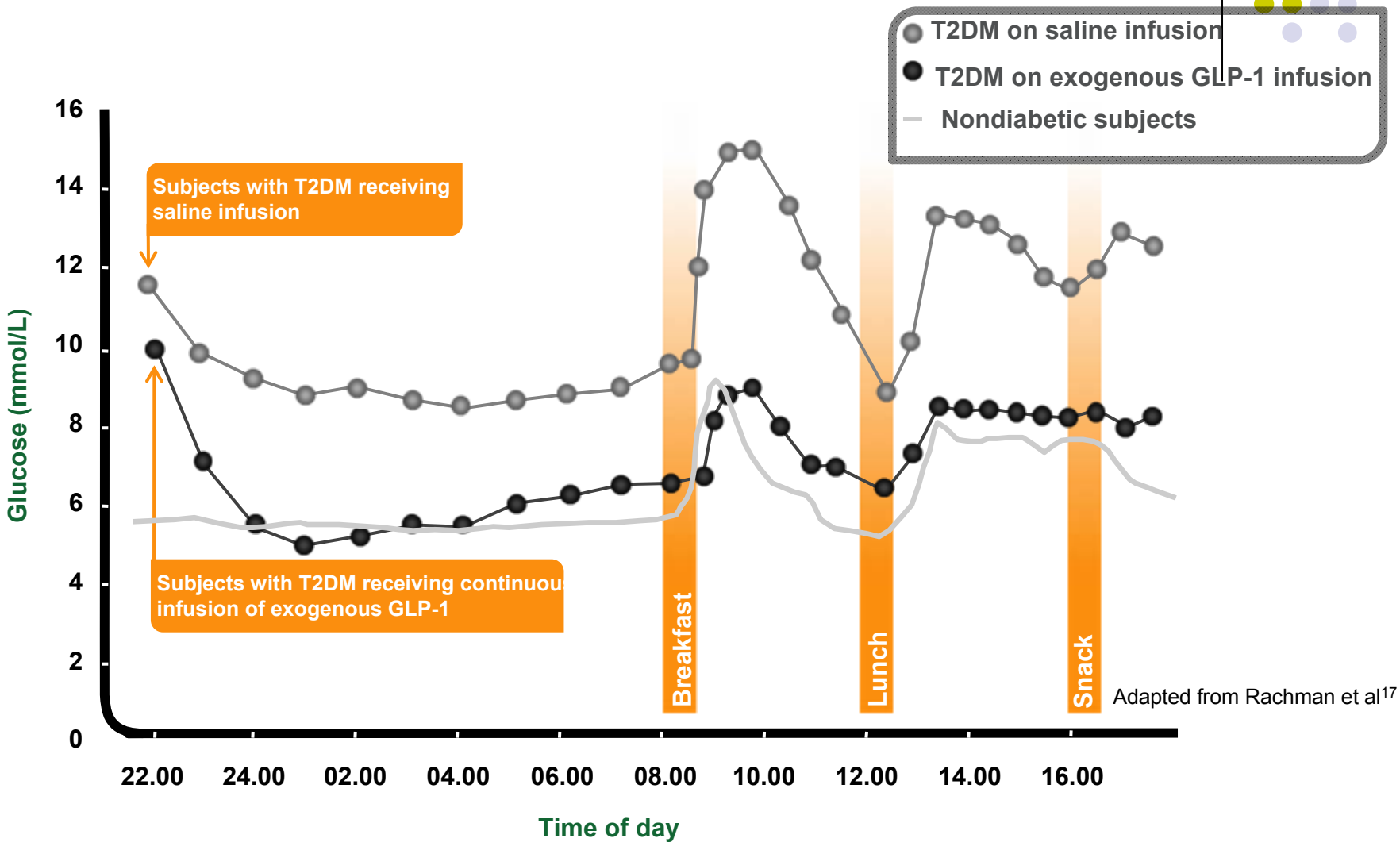
- Comply with calorie/CHO restriction
- Metformin
- SGLT2 – Dapagliflozin
- Gliptin
- STOP gliptin and use GLP-1 agonist

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.

Continuously infused GLP-1 nearly normalised blood glucose in patients with type 2 diabetes[17]



Adapted from Rachman et al[17]

Healthy subjects, n=6; Patients with T2D, n=7; Mean data are shown.

Reference: 17. Rachman J. *Diabetologia. 1997;40:205-211*

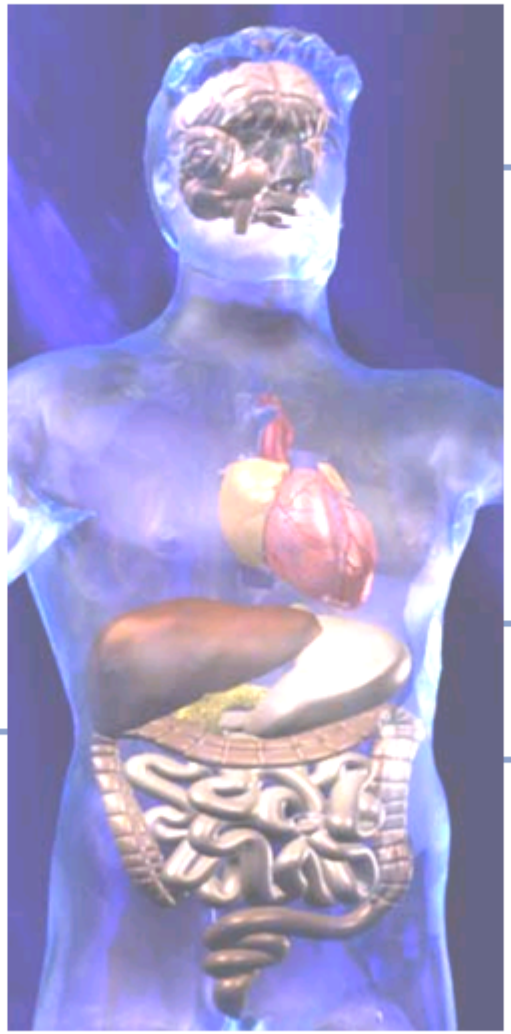
GLP-1=glucagon-like peptide-1; T2D=type 2 diabetes.

Native GLP-1 has multiple direct effects on human physiology

Pancreas

- ↑ Insulin secretion (glucose-dependent)
- ↑ Insulin synthesis
- ↑ Beta-cell mass*
- ↓ Glucagon secretion

*Animal data



Brain

- ↓ Energy intake

Liver

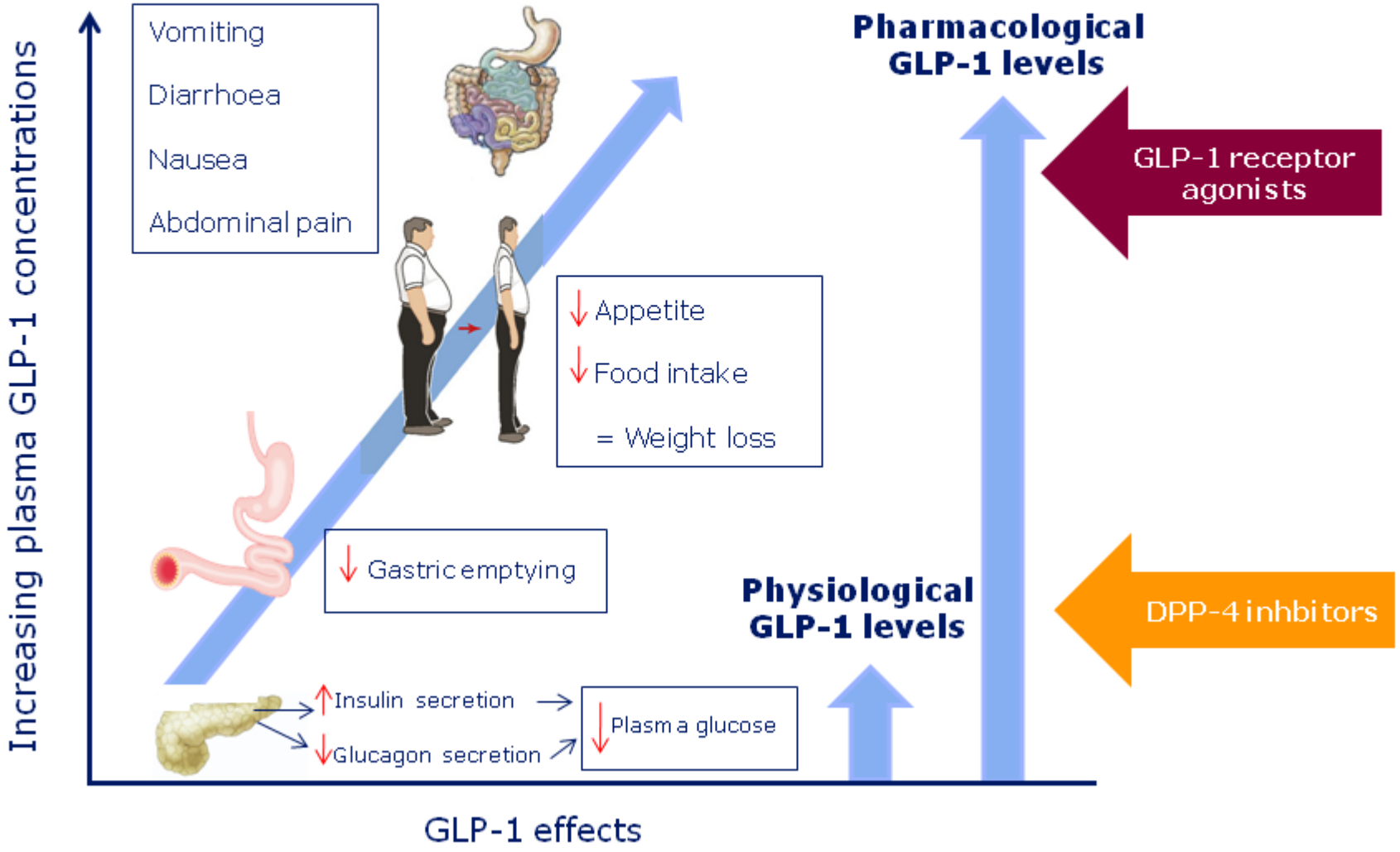
- ↓ Hepatic glucose output

GI tract

- ↓ Motility

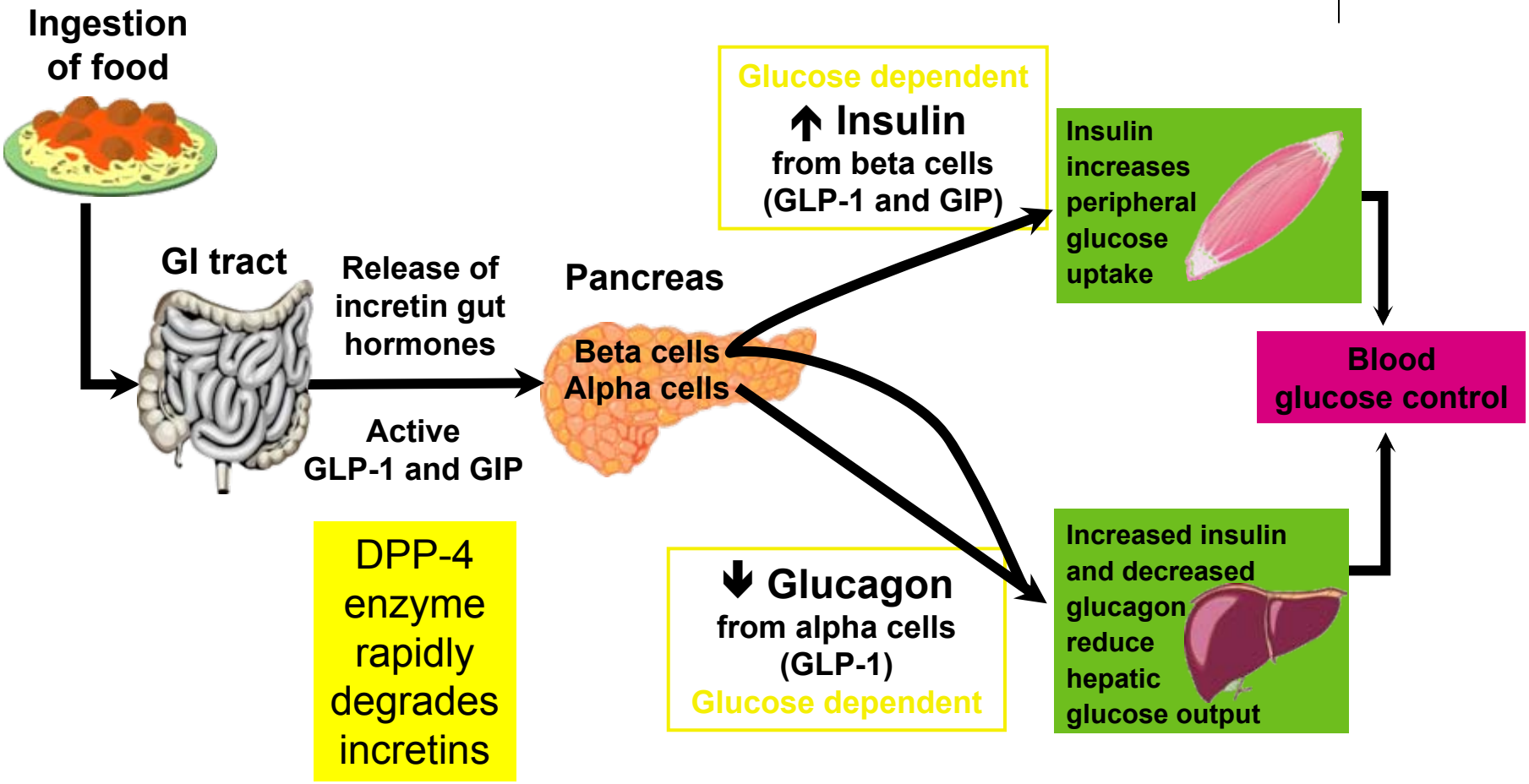
Baggio *et al. Gastroenterol* 2007; 132: 2131–57;
Bulotta *et al. J Mol Endocrinol* 2002;29:347–60;
Drucker *et al. Proc Natl Acad Sci USA* 1987;84:3434–8;
Farilla *et al. Endocrinology* 2002;143:4397–408;
Gutzwiller *et al. Gut* 1999;44:81–6;
Kieffer *et al. Endocr Rev* 1999;20:876–913;
Wettergren *et al. Dig Dis Sci* 1993;38:665–73;
Nauck *et al. Diabetologia* 1993;36:741–4;
Zander *et al. Lancet* 2002;359:824–30.

GLP-1 dose–response relationships



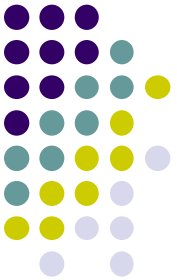
1. Holst. *Trends Mol Med* 2008;14:161–8

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.

GLP-1 Receptor Agonists



* BYETTA

  sc twice a day before meals

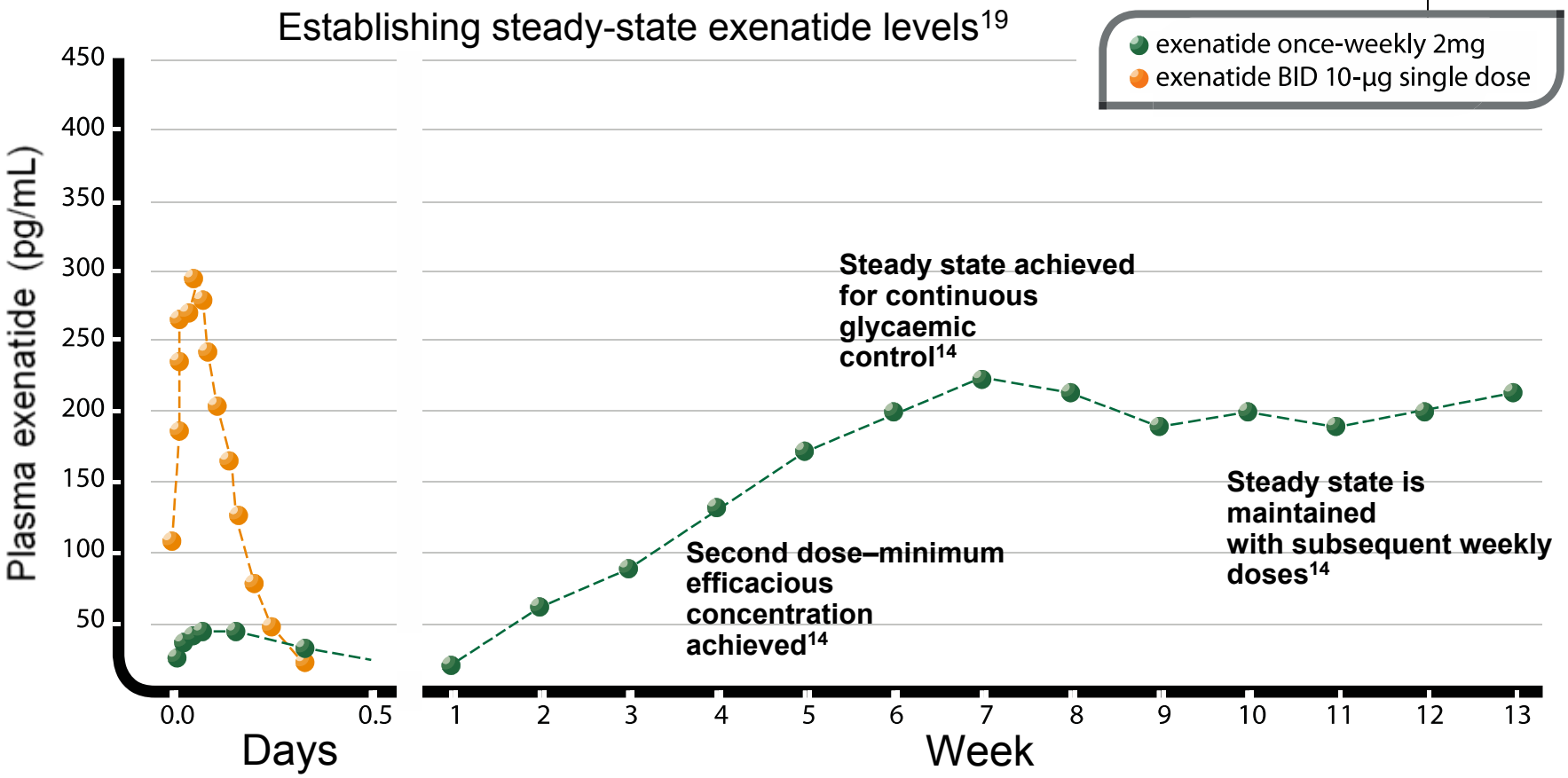
- LIRAGLUTIDE

  sc once a day

- BYDUREON

  sc once a week

Microsphere technology provides steady-state exenatide concentrations ensuring minimal peak-to-trough fluctuations[19]

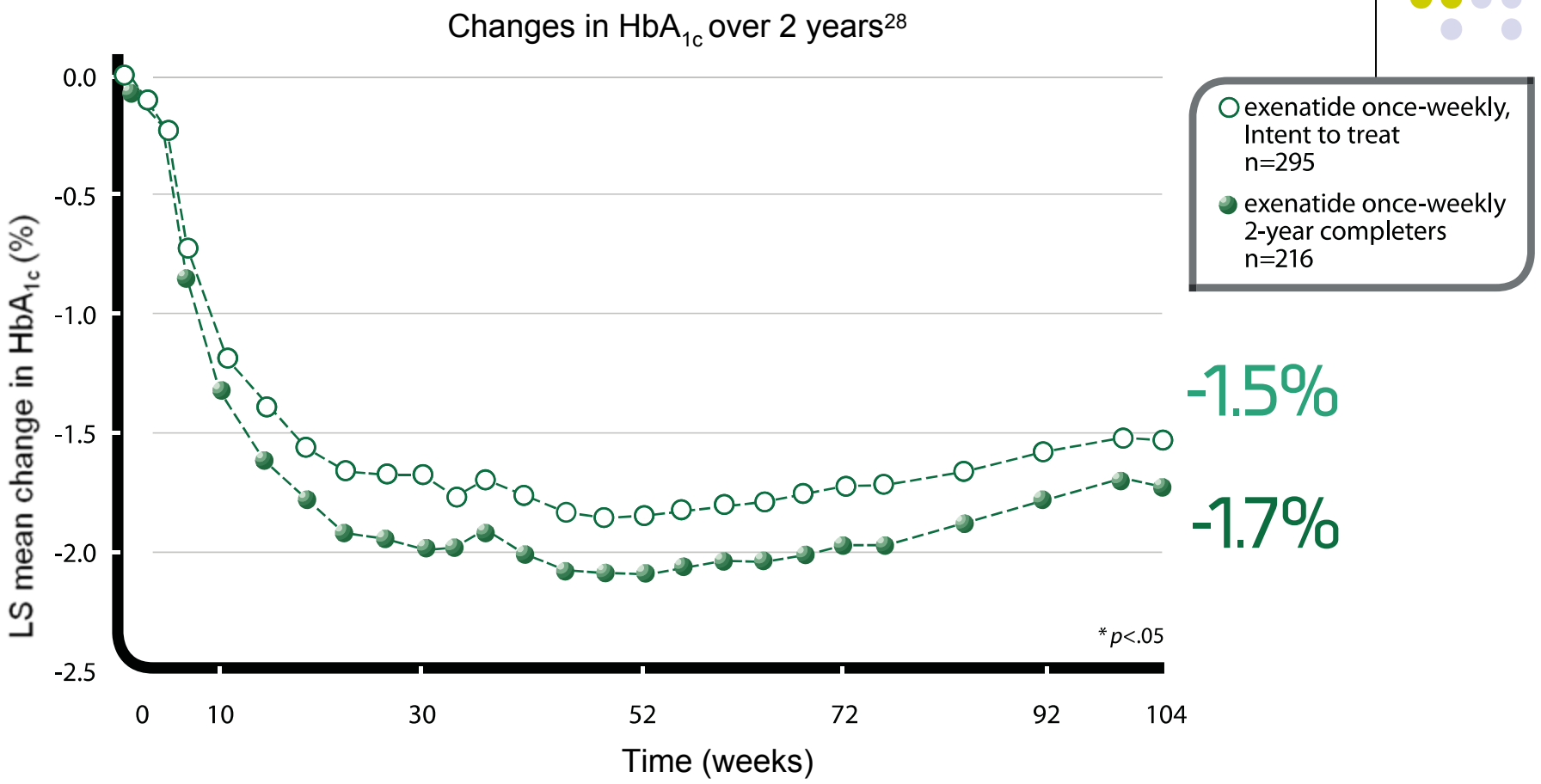


Adapted from Fineman et al.[19]

References: 14. BYDUREON Summary of Product Characteristics ;**19.** Fineman M, et al. *Clin Pharmacokinet*. 2011;50(1):65-74; .

BID=twice daily

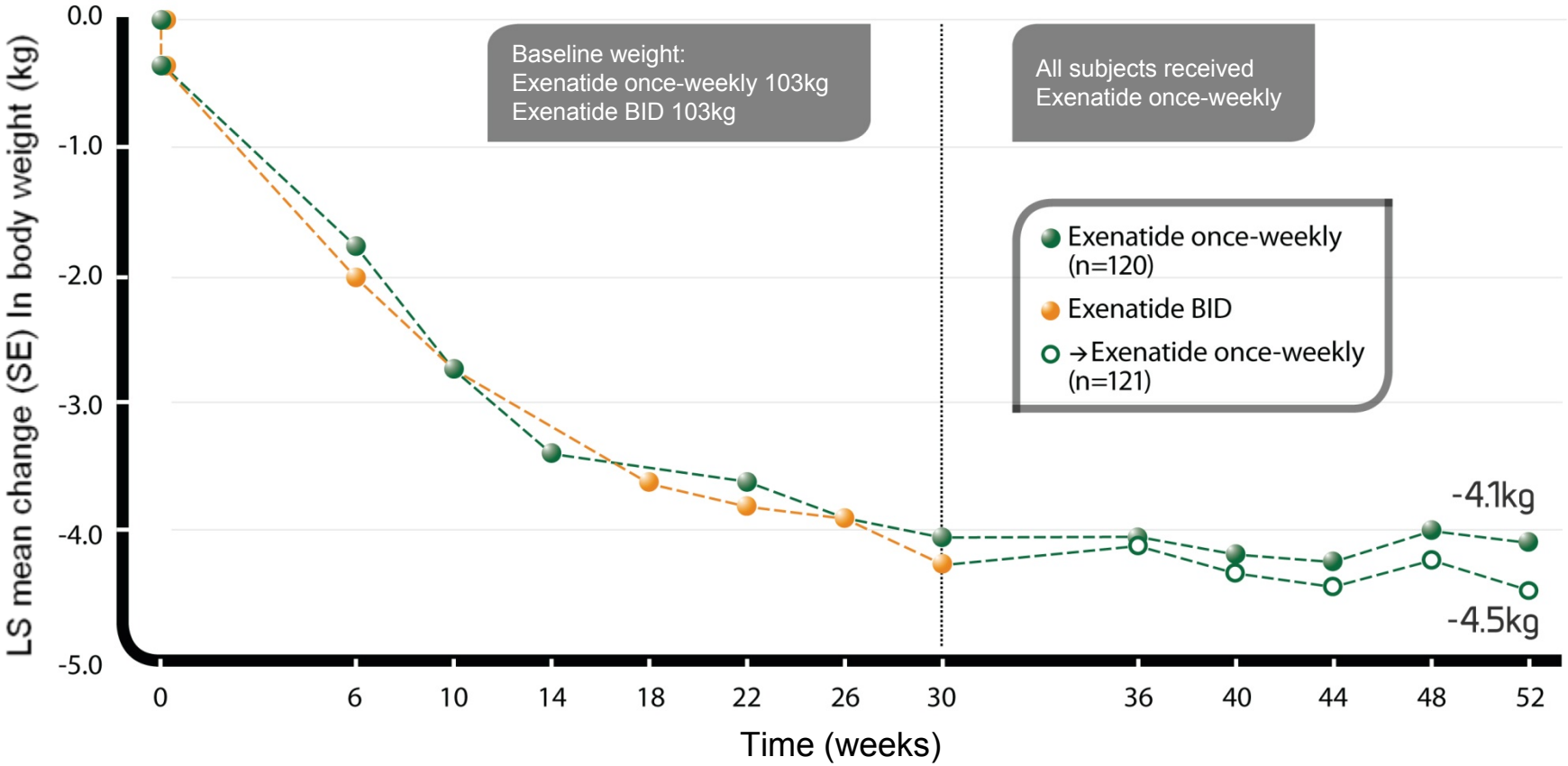
DURATION-1: Sustained changes in HbA_{1c}



Reference: 28. Taylor K, et al. *BMC Endocr Disord.* 2011;11(1):9 [Epub].

Exenatide once-weekly vs exenatide BID: Body weight over 52 weeks*[14,26]

Reduction in body weight (DURATION-1 extension)[26]



Analysis of evaluable patients (exenatide once-weekly evaluable n=120, intent-to-treat n=148; exenatide bid exenatide once-weekly evaluable n=121, intent-to-treat n=147).

*** Rapid weight loss at a rate of >1.5 kg per week has been reported in patients treated with exenatide. Weight loss of this rate may have harmful consequences.[14]**

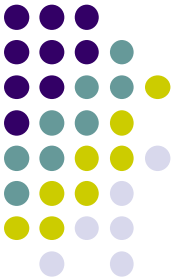
References : 14. BYDUREON Summary of Product Characteristics. **26.** Buse JB, et al. *Diabetes Care.* 2010;33:1255-1261.

BID=twice daily

BYDUREON

- Can be given weekly at drop in clinic by DNS or by practice nurse or district nurse
- Can encourage patient in early weeks when having minor side effects
- Can encourage patient to comply with food plan
- In some patients aids compliance

The Obese Type 2 Diabetic



- Still not controlled
- Add sulphonylurea/prandial regulator
- Especially if fasting glucose raised add basal insulin
- May even need Mixed insulin BD

- IF PATIENT DOES NOT CALORIE RESTRICT CAN OVERCOME TABLETS GLP-1 AND 300-400 units of INSULIN !!

TOM

- Age 55 DM 8 years ago

- Please see as despite
  metformin & glargine 52 units morning
  Fasting BM up to 13.4, HbA1c 65 and gaining
  weight 124.1 (BMI 42.4)

TOM

- FOOD PLAN never seen dietitian
- Never really taken on board advice re life style exercise, stopping smoking and food
- HE WAS KEEN TO TRY

- Dietetic advice
- Stop insulin
- Walking

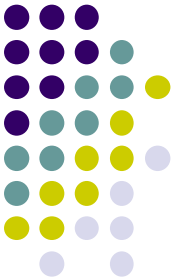
TOM

Date	Weight	BMI	HbA1c
08/2010	124.1	40.7	65
09/2010	118.9	38.8	
11/2010	98.7	33.8	55
	Exenatide added		
01/2011	95.8	32.8	
03/2011	90.2	30.8	50
06/2011	80.2	27.4	40
	Exenatide stopped		
09/2011	80.2	27.4	40

GEORGE

Age	Treatment	Wt	HbA1c
65	exenatide wean insulin metforminsr stop rosigl	108	79
65	exenatide/ins/met	104	85
66	exen/met/gliclazidemr	95	91
67	as above	93	58
68	as above	89	50
69	exen/met/less glic	86	48

OBESE TYPE 2 DIABETIC



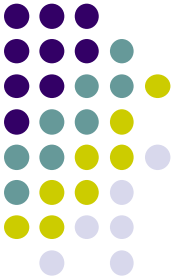
- DIETITIAN – more pragmatic.
  must restrict CALORIES as well as CHO
- Metformin
- SGLT2
- Then Gliptins
- Then add GLP-1 (stop gliptin)

- Only then if have to add sulphonylureas/insulin

GEORGE

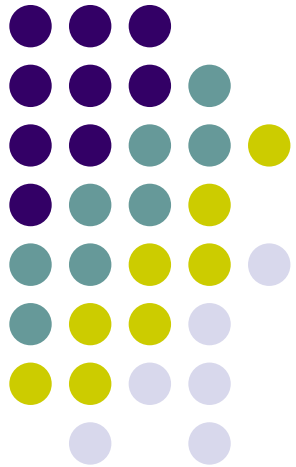
- BMI start 35 BMI now 27.5
- HbA1c start 81 HbA1c now 48
- Lost 109 to 86 = 23kg or 50.6lb
- Takes time CANNOT do it all at once!
- Diabetic patient is yours for life!

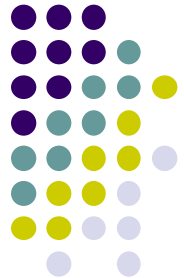
OBESE TYPE 2 DIABETIC



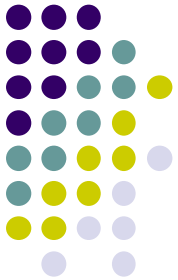
- Losing Weight and Normalising HbA1c
  Takes Time

THANK YOU



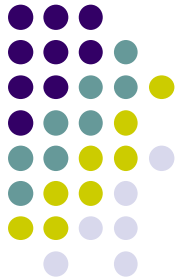


WHEN TO START INSULIN



- When obese Type 2 Diabetic is very symptomatic despite adherence to food plan, metformin sulphonylureas and other medications
- When thin Type 2 Diabetic is very symptomatic despite adherence to food plan and maximum dose of sulphonylureas
- To cover acute stress illness/ steroids in Type 2 diabetes.

How to Start Insulin



- Use a basal insulin (medium long acting) once a day Insulatard (cheap not smooth)

  Lantus(glargine) long acting smooth but not cheap
  Levemir(determir) medium long acting smooth not cheap
- Give at breakfast initially once a day continue other diabetic drugs but look out for hypos

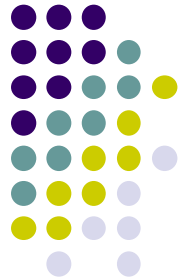
- Start with 10 units and increase by 4 units every 4 days until fasting glucose around 6

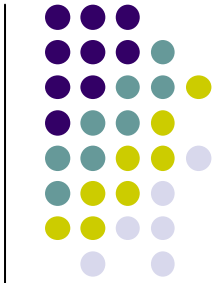
Insulin

- Sometimes the basal insulin is given at bedtime once a day
- If hypos in day may need to reduce daytime diabetic tablets
- When the basal dose is 26-30 units may need to split it to twice a day 12 hours apart
- May need 60-80 units twice a day if insulin resistant or dietary non compliance – if in doubt refer.

Hypoglycaemia

- Biggest worry is nocturnal hypoglycaemia especially if live alone
- Set alarm and test during night
- If hypo in day or night take 4-6 glucose tablets then digestive biscuits/sandwich. Do not miss meals. Omit next two doses of sulphonylureas but continue to give insulin and monitor BMs
- Glucose will run high for 24-48 hours do not chase it it will settle
- A hypo is a teaching point – discuss why it occurred





THANK YOU