Diabetes Update 2015

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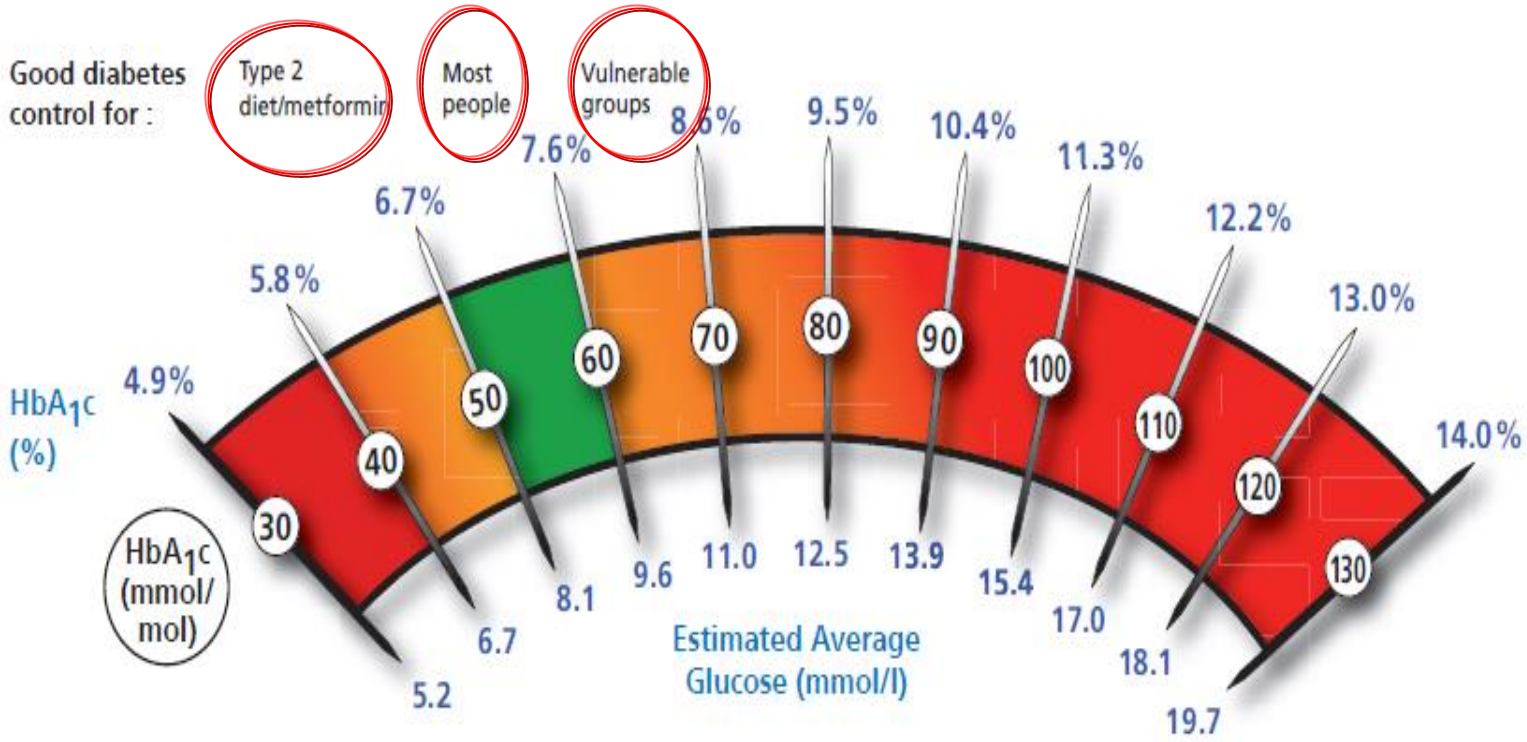
Barnsley Diabetes CCG profile 2013

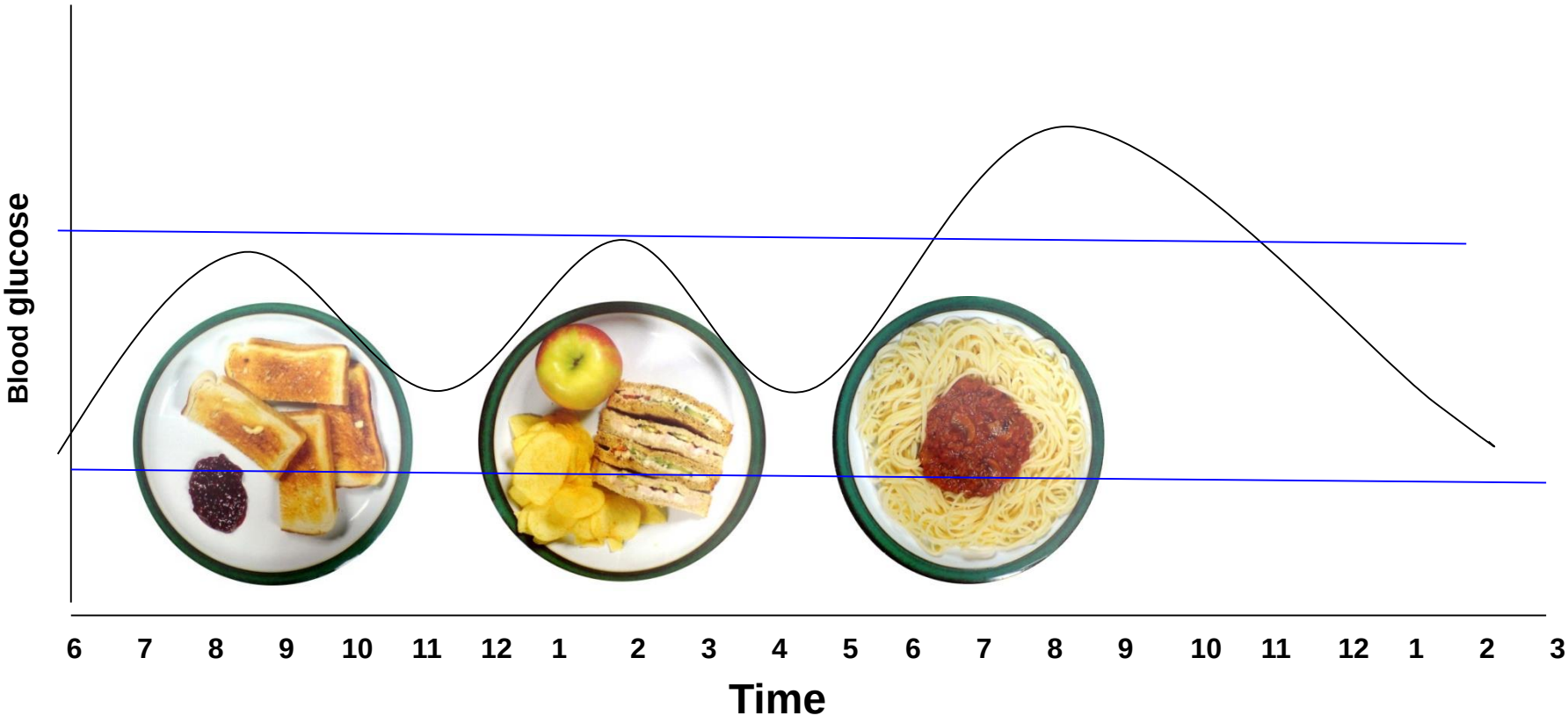
- The prevalence of diagnosed diabetes among people aged 17 years and older in NHS Barnsley CCG is 6.8% compared to 5.9% in similar CCGs.
- In 2012/13, 63.6% of adults with diabetes in NHS Barnsley CCG, had a HbA1c measurement of 59mmol/mol or less. This is higher than in other similar CCGs and higher than England. At practice level, it ranges from 48% to 80%.
- People with diabetes in NHS Barnsley CCG were 46.4% more likely to have a myocardial infarction, 33.8% more likely to have a stroke, 75.3% more likely to have a hospital admission related to heart failure and 38.3% more likely to die than the general population in the same area
- Spending on prescriptions for items to treat diabetes in 2012/13 cost £290.24 per adult with diabetes in NHS Barnsley CCG compared to £281.52 across England.

HbA_1c as a measure of Diabetes Control



What are the options for the person with Type 2 diabetes where Metformin is failing?

Always consider dietary intervention before adding more medication



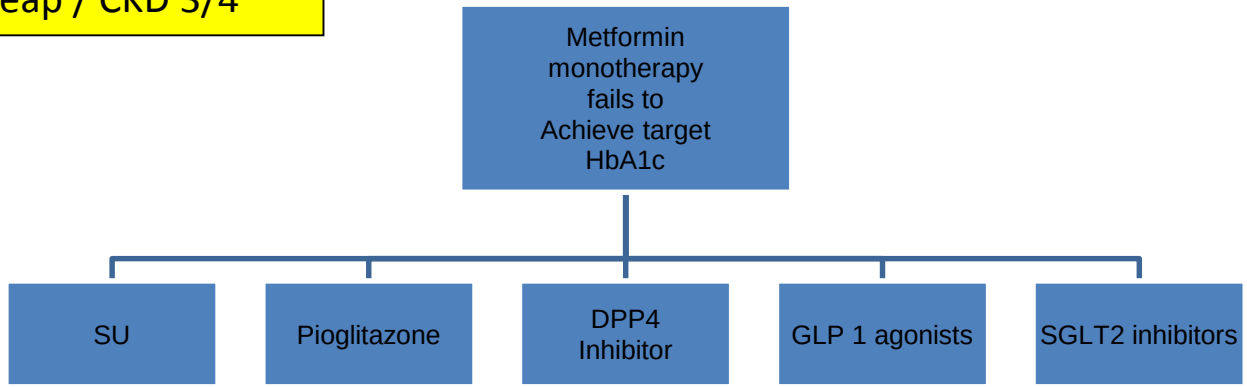
The importance of Carbohydrate awareness

50g at breakfast and lunch but 90g at evening meal

What to add when metformin monotherapy fails

Sulphonylureas

Risk of hypos / need for BG testing / wt gain / strong evidence / cheap / CKD 3/4



DVLA current medical guidelines:
Diabetes managed by tablets which carry a risk of inducing hypoglycaemia (includes sulphonylureas and glinides)

‘It may be appropriate to monitor blood glucose regularly and at times relevant to driving to enable the detection of hypoglycaemia’

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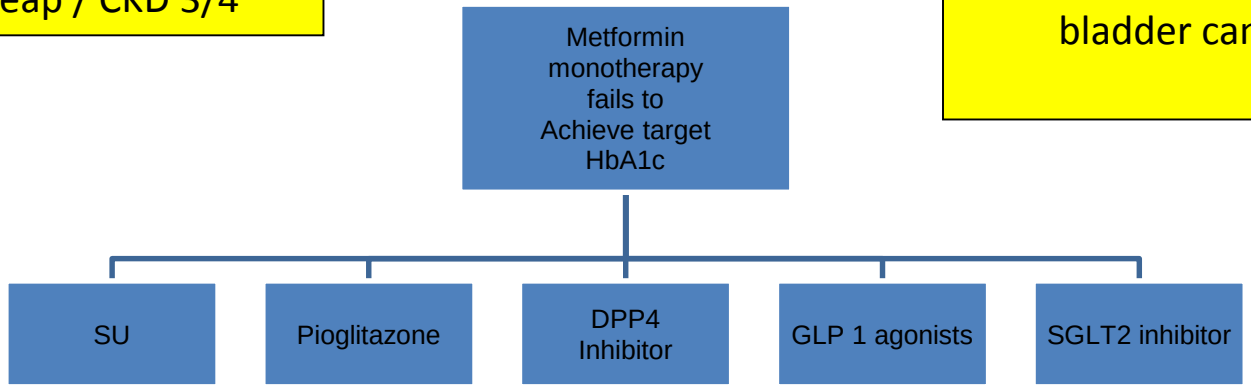
Pioglitazone

Low risk hypos / decreased vascular risk / CKD ¾ / Wt gain / CCF / fractures / bladder cancer



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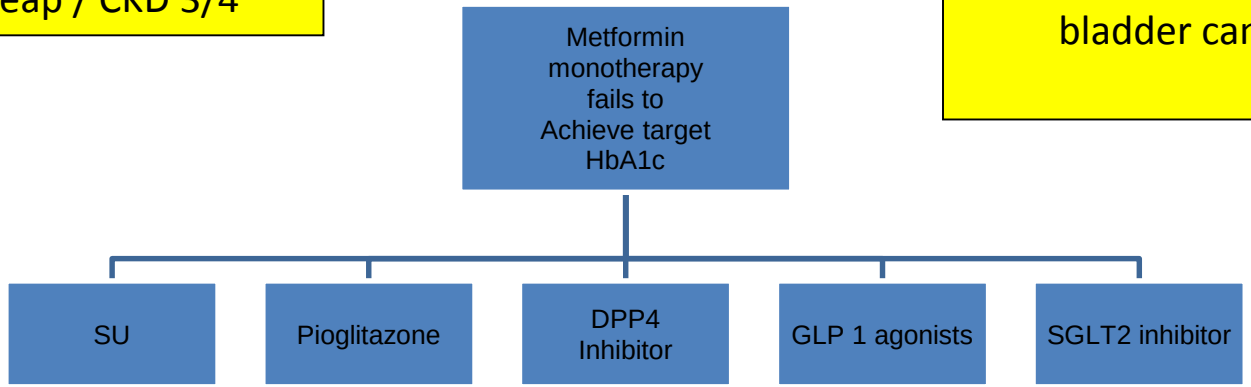


Gliptins

No long term data / Low risk hypos / wt neutral / ? pancreatitis / license in renal impairment varies

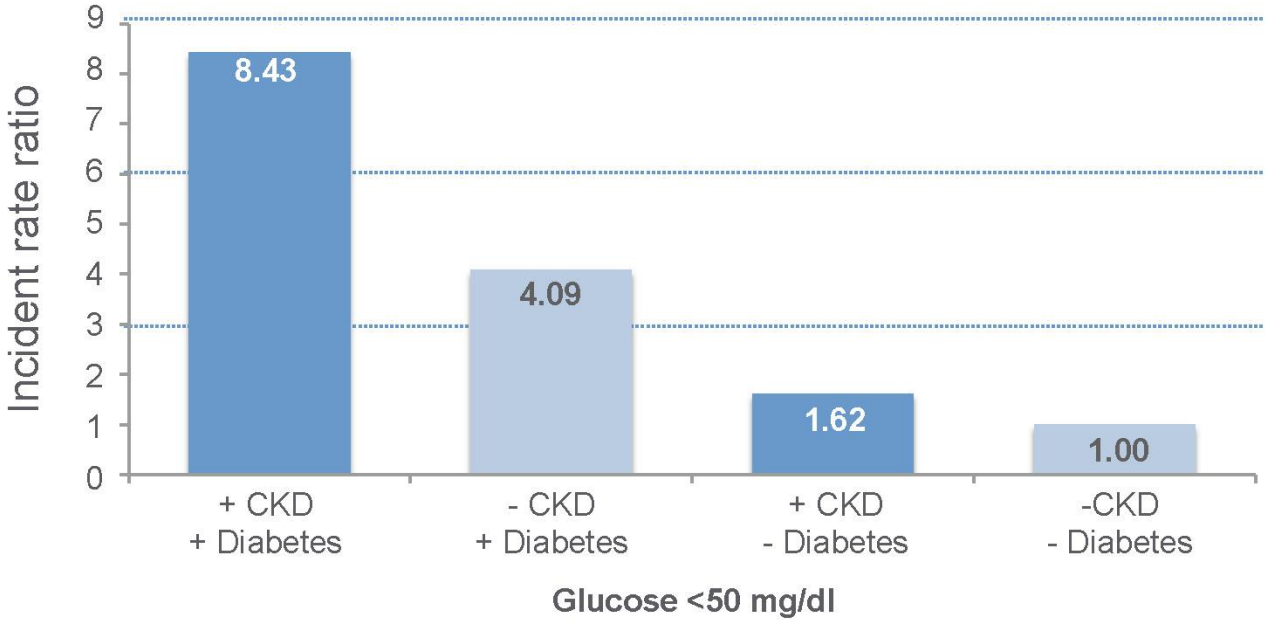
DPP-4 Inhibitors

- Dipeptidyl-peptidase 4 (DPP-4) is an enzyme present in vascular endothelial lining which inactivates the incretin hormones GIP and GLP-1
- DPP-4 Inhibitors work by acting as competitive antagonists of the DPP-4 enzyme - enhance the effects of both GIP and GLP-1
- Glucose dependent reduction in fasting and postprandial glucose levels in addition to decreasing glucagon secretion. Low risk hypoglycaemia.
- Body weight unchanged
- Possible risk of pancreatitis

Renal impairment and hypoglycaemia risk

- Renal impairment increases hypoglycaemia risk in patients with diabetes[1,2]
- In elderly subjects (>70 years) hypoglycaemia occurs more frequently in subjects with CKD stages 3–5[1]

Risk for severe hypoglycaemia in elderly adults classified by CKD and diabetes status[2]



- Reference group was adults without CKD or diabetes (for whom the incident ratio =1)
- Groups adjusted for race, gender, age, cancer, diabetes and CV disease (all rate ratios p<0.0001)

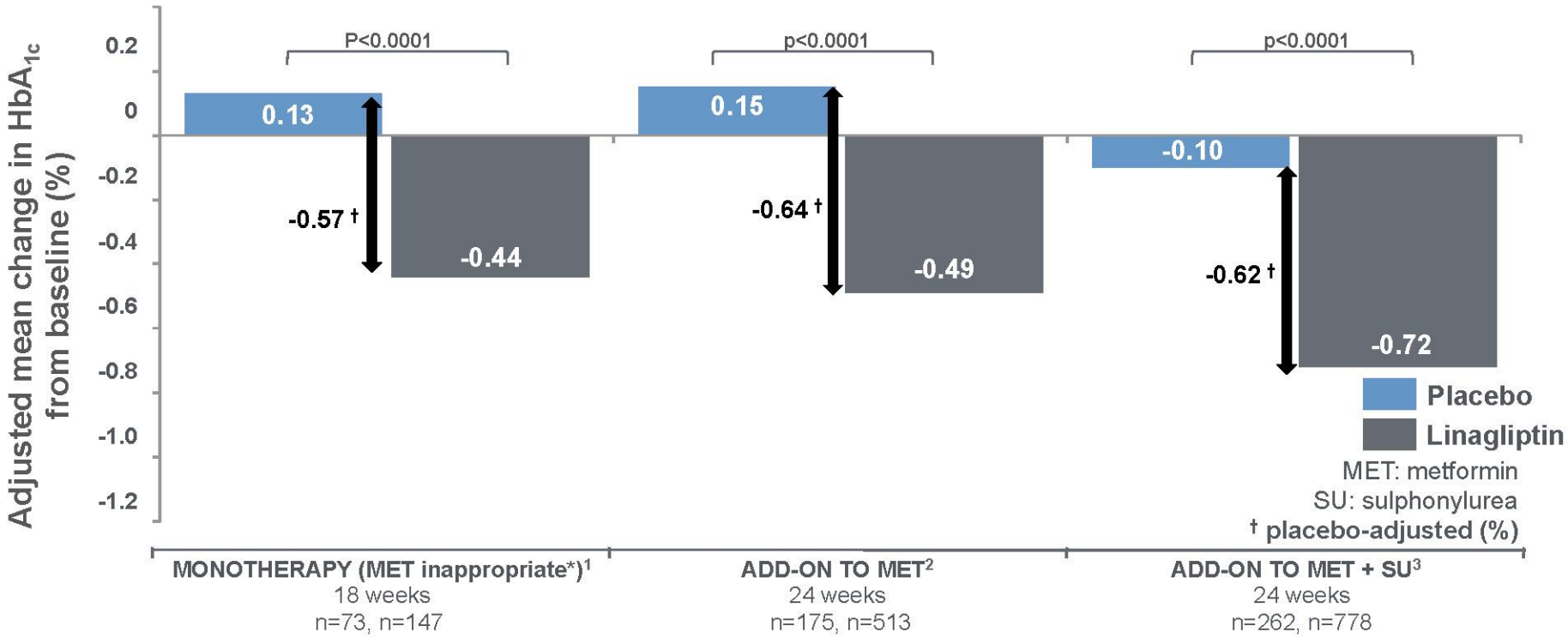
1. Haneda M and Morikawa A. *Nephrol Dial Transplant* 2009;24:338-341.
2. Moen M, et al. *Clin J Am Soc Nephrol* 2009;4:1121-1127.

Gliptins

- Sitagliptin - on Sheffield CCG formulary (Barnsley)
- Vildagliptin
- Saxagliptin
- Linagliptin ▼ – on Sheffield CCG formulary(Barnsley)
- Alogliptin ▼ - on Sheffield CCG formulary (Barnsley)

Linagliptin data summary: HbA1c reduction vs. placebo

- Linagliptin demonstrated significant reductions in HbA1c levels vs. placebo across the major phase III studies[1-3]

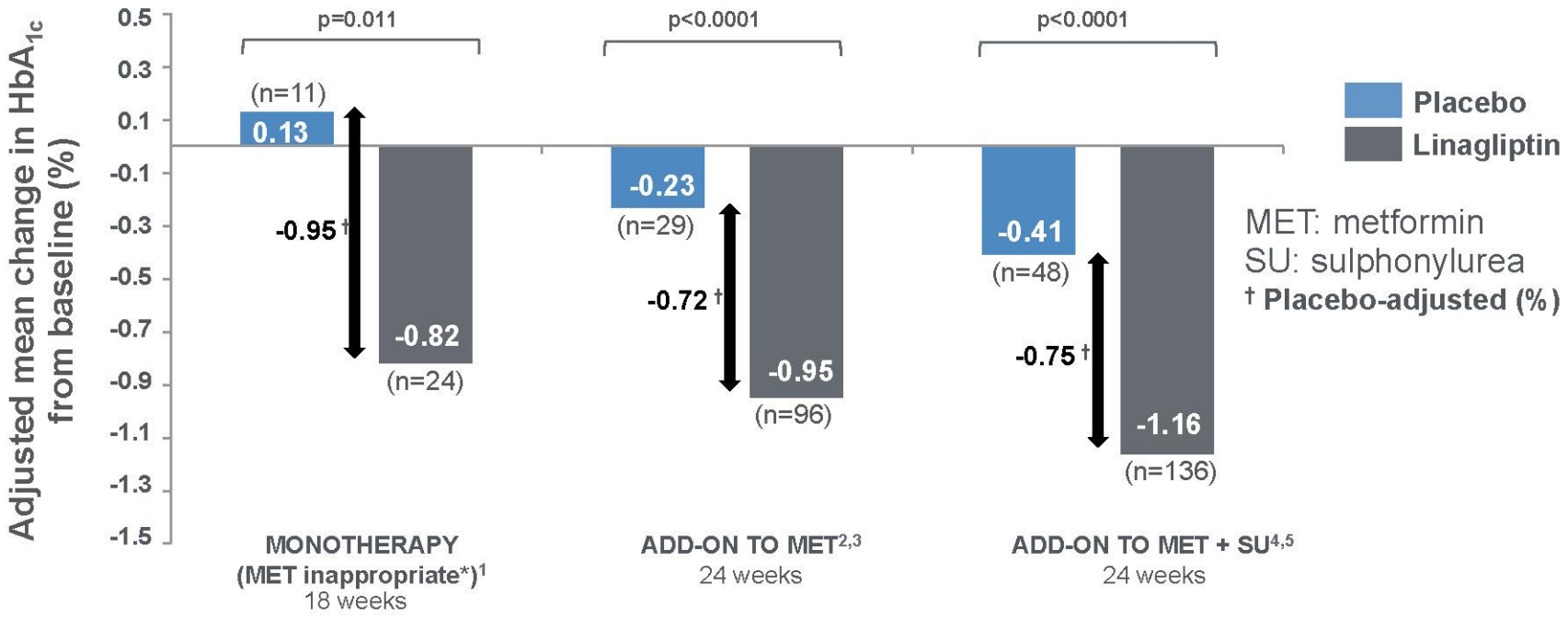


*Metformin inappropriate due to intolerance, or contraindicated due to renal impairment.

1.Barnett A, et al. *EASD* 2010;Poster #823.
2.Taskinen MR, et al. *Diabetes Obes Metab* 2011;13:65-74
3. Owens D, et al. *Diabetic Med* 2011(submitted).

Linagliptin data summary: Reduction from baseline HbA1c ≥9%

- Significant HbA1c reductions in a subgroup of poorly-controlled patients vs. placebo (baseline HbA1c ≥ 9%)[1-5]



Pre-specified HbA1c subgroup analyses from three multicentre, randomised, parallel-group 18-week[1] or 24-week phase III studies[2–4]
*Ineligible: metformin inappropriate due to intolerance, or contraindicated due to renal impairment.

1. Barnett AH et al. Poster No. 823-P. *EASD* 46th Annual Meeting, 2010. 2. Taskinen M-R et al. *Diabetes Obes Metab* 2011;13:65–74. 3. Boehringer Ingelheim, data on file LIN11-05. 4. Owens D, et al. *Diabetic Med* 2011 (submitted) . 5. Owens DR et al. Poster No. 548-P. *ADA* Scientific Sessions, 2010.

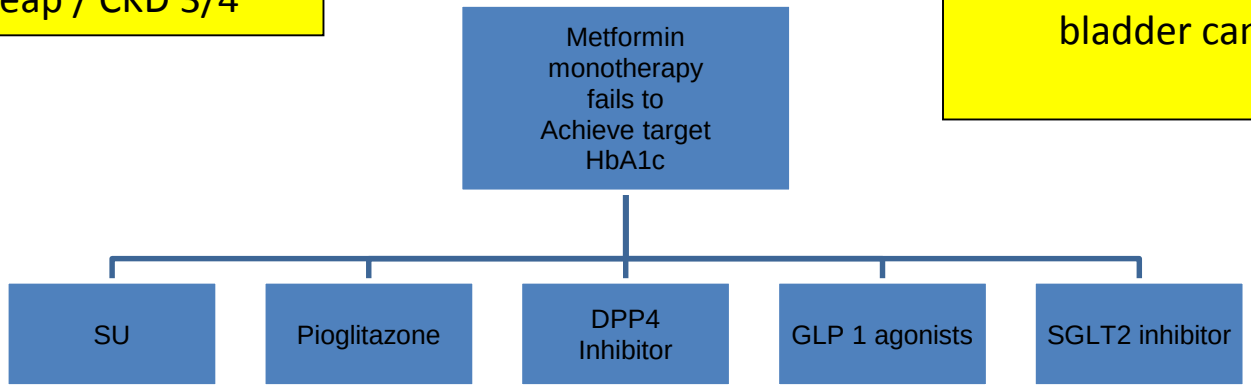
What to add when metformin monotherapy fails

Sulphonylureas

Risk of hypos / need for BG testing / wt gain / strong evidence / cheap / CKD 3/4

Pioglitazone

Low risk hypos / decreased vascular risk / CKD ¾ / Wt gain / CCF / fractures / bladder cancer



Gliptins

No long term data / Low risk hypos / wt neutral / ? pancreatitis / license in renal impairment varies

GLP1 agonists

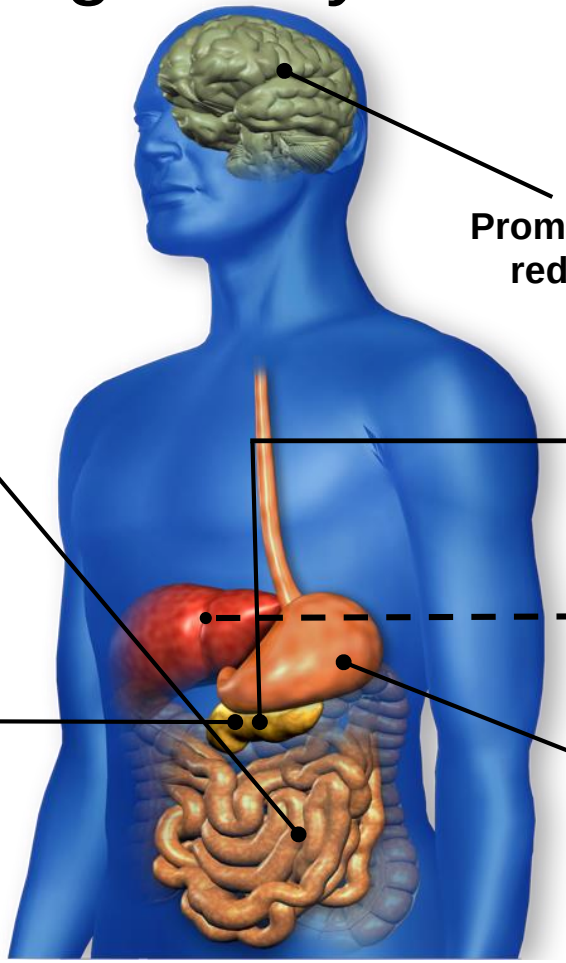
Low risk hypos / wt loss / no long term data / ?pancreatitis / license in renal impairment varies

GLP1 agonists

- Exenatide BD - on Sheffield CCG formulary
- Liraglutide od - on Sheffield CCG formulary
- Lixizenatide od - on Sheffield CCG formulary
- Bydureon weekly - on Sheffield CCG formulary
- Duraglutide weekly

- (Barnsley exenetide weekly/ liraglutide /lixisenetide
- Exenetibe bd may come back on soon?)

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

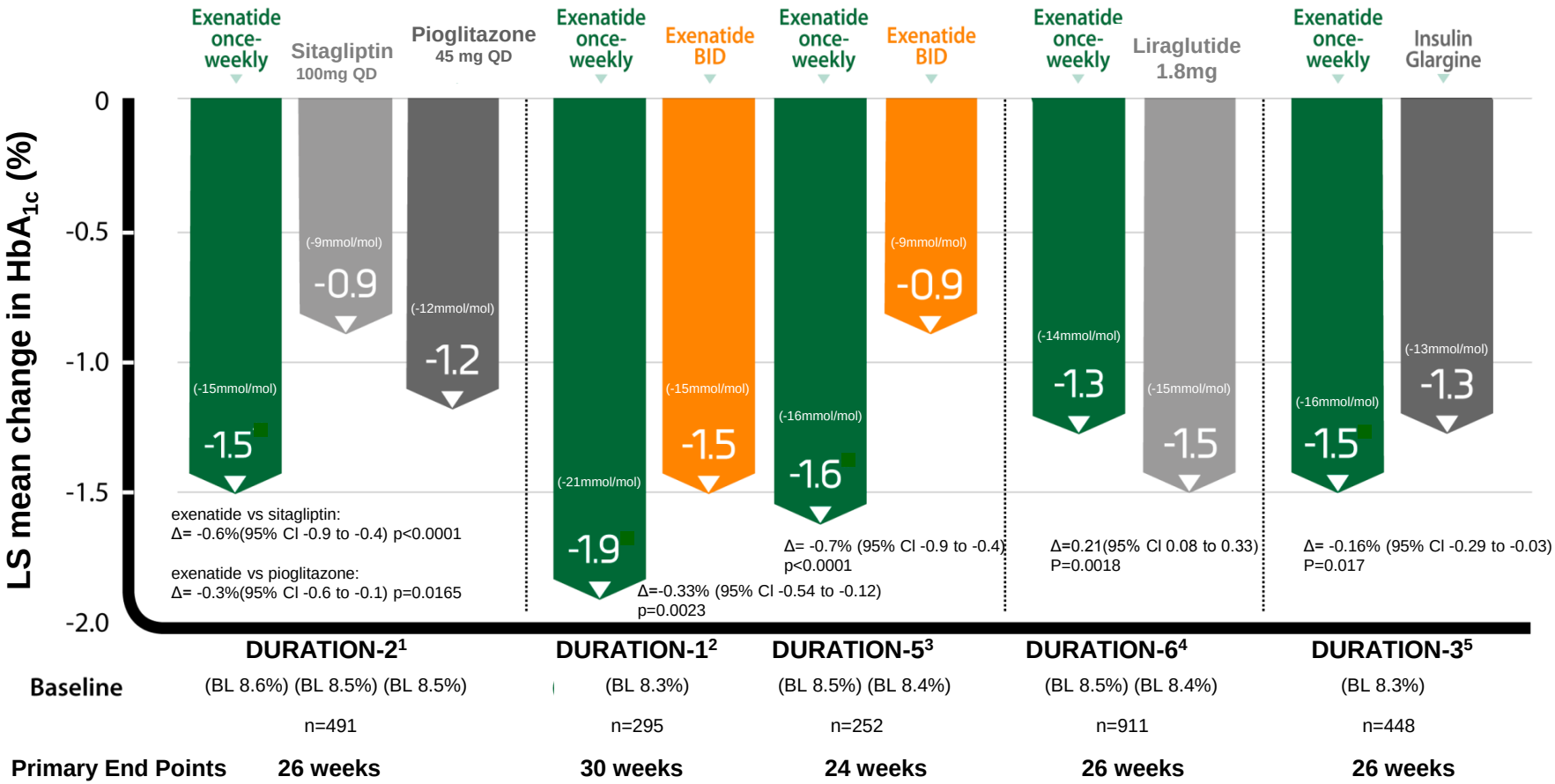
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Adapted from Drucker DJ. *Diabetes.* 1998;47:159-169.

In the DURATION clinical trial programme, adding exenatide QW provided significant HbA_{1c} reductions from baseline of between -1.3% and -1.9%[1-5]



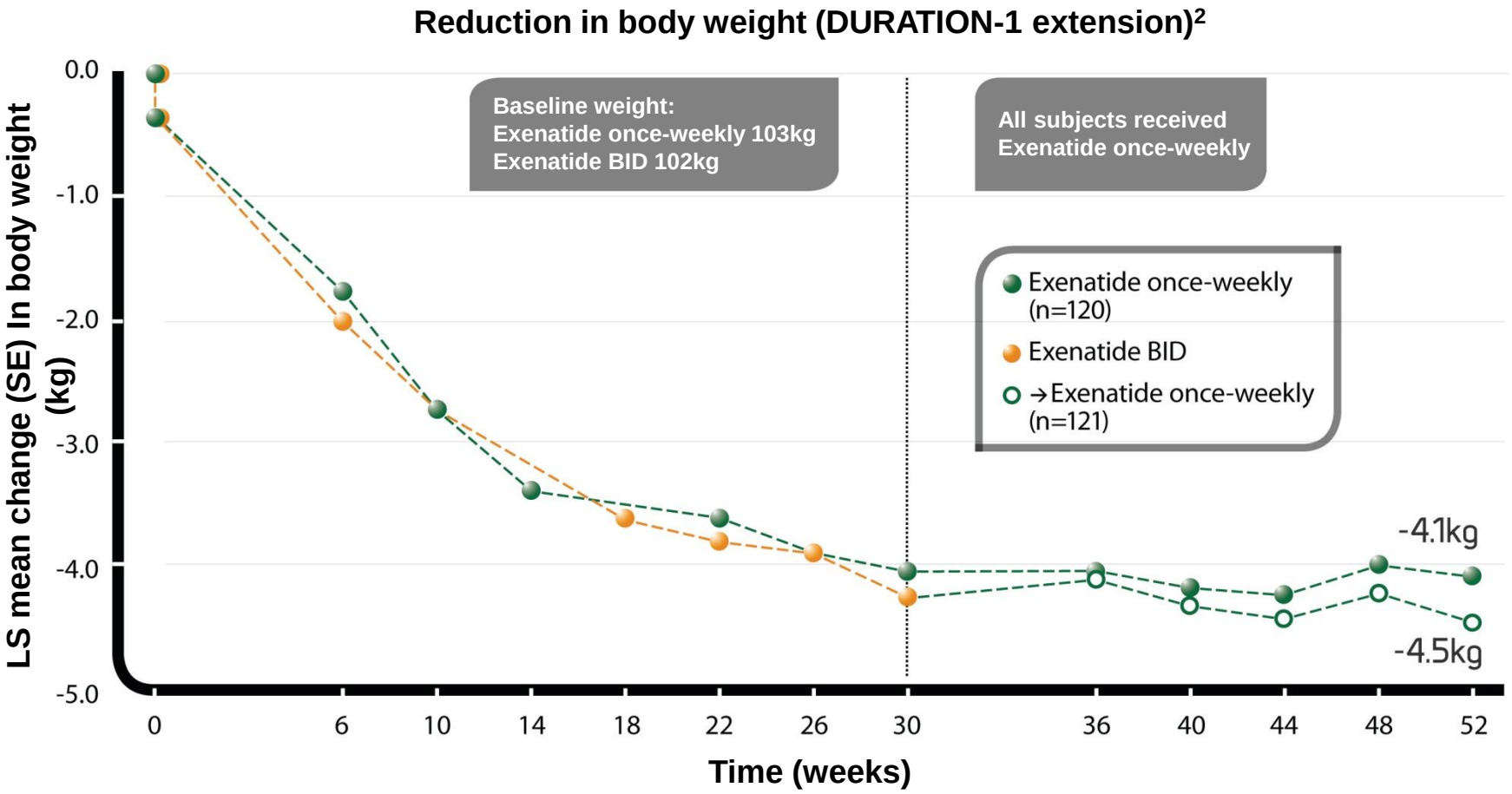
	DURATION-2[1]	DURATION-1[2]	DURATION-5[3]	DURATION-6[4]	DURATION-3[5]
Baseline	(BL 8.6%) (BL 8.5%) (BL 8.5%)	(BL 8.3%)	(BL 8.5%) (BL 8.4%)	(BL 8.5%) (BL 8.4%)	(BL 8.3%)
	n=491	n=295	n=252	n=911	n=448
Primary End Points	**26 weeks**	**30 weeks**	**24 weeks**	**26 weeks**	**26 weeks**

Baseline
8.6% =70mmol/mol
8.5% = 69mmol/mol
8.4% = 68mmol/mol
8.3% = 67mmol/mol

Abbreviations: BL, baseline; QD, once daily; BID, twice daily.
Clinical trials are conducted under varying conditions and results from individual trials cannot be directly compared.
Results of DURATION-4 excluded as study is not within licensed indications. Liraglutide 1.8mg is not recommended by NICE

1. Bergenstal RM *et al* Lancet 2010; 376: 431–439. 2. Drucker DJ *et al* Lancet 2008; 372: 1240–1250. 3. Blevins T *et al* J Clin Endocrinol Metab 2011; 96: 1301–1310.
4. Buse JB *et al.* Lancet 2013; 381: 117–124. 5. Diamant M *et al.* Lancet 2010; 375: 2234–2243.

The secondary benefit of weight loss seen with exenatide QW at 30 weeks was sustained at 52 weeks[1,2]



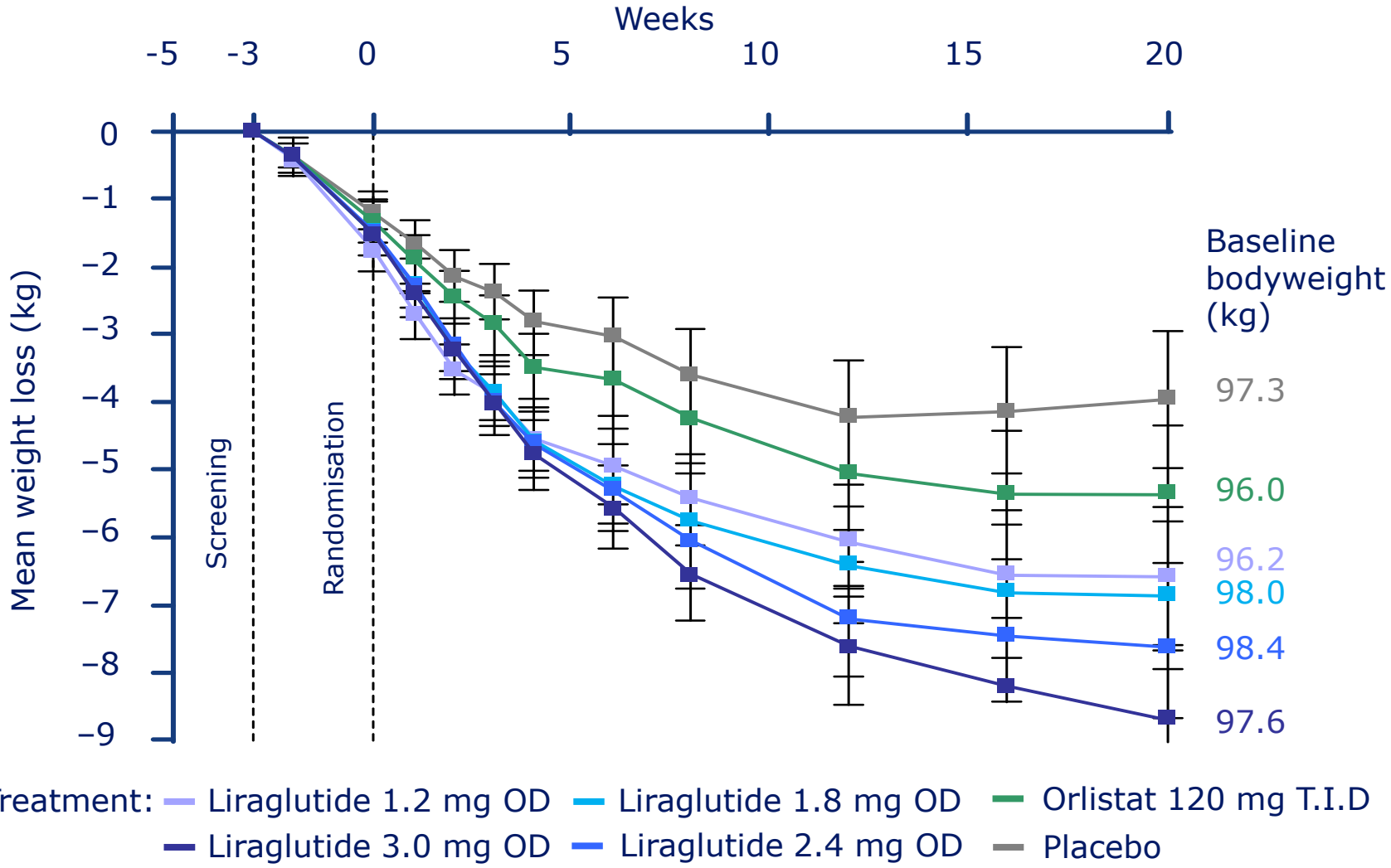
Analysis of evaluable patients (exenatide QW evaluable n=120, intent-to-treat n=148; exenatide BID to exenatide QW evaluable n=121, intent-to-treat n=147). The 52 week evaluable population consisted of ITT patients who completed the study visit to at least week 48 in compliance with the protocol.

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.[1] Exenatide QW and exenatide BID are not indicated for weight loss

References : 1. BYDUREON Summary of Product Characteristics. 2. Buse JB, et al. *Diabetes Care.* 2010;33:1255-1261.

BID=twice daily

Body weight reduction from baseline over 20 weeks in obese people without diabetes



Astrup et al. Lancet 2009; DOI:10.1016/S0140-6736(09)61375-1.

Liraglutide is not indicated for weight loss and not for use in people without diabetes

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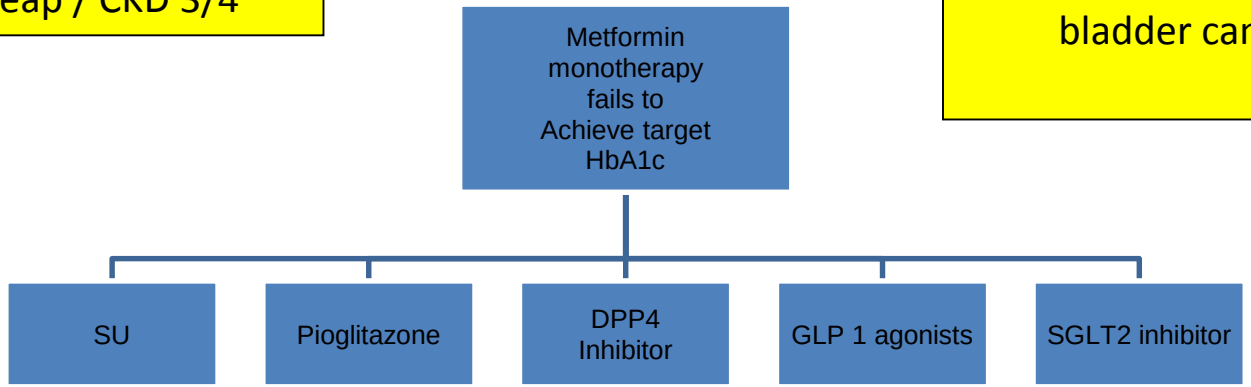


Gliptins

No long term data / Low risk hypos / wt neutral / ? pancreatitis / license in renal impairment varies

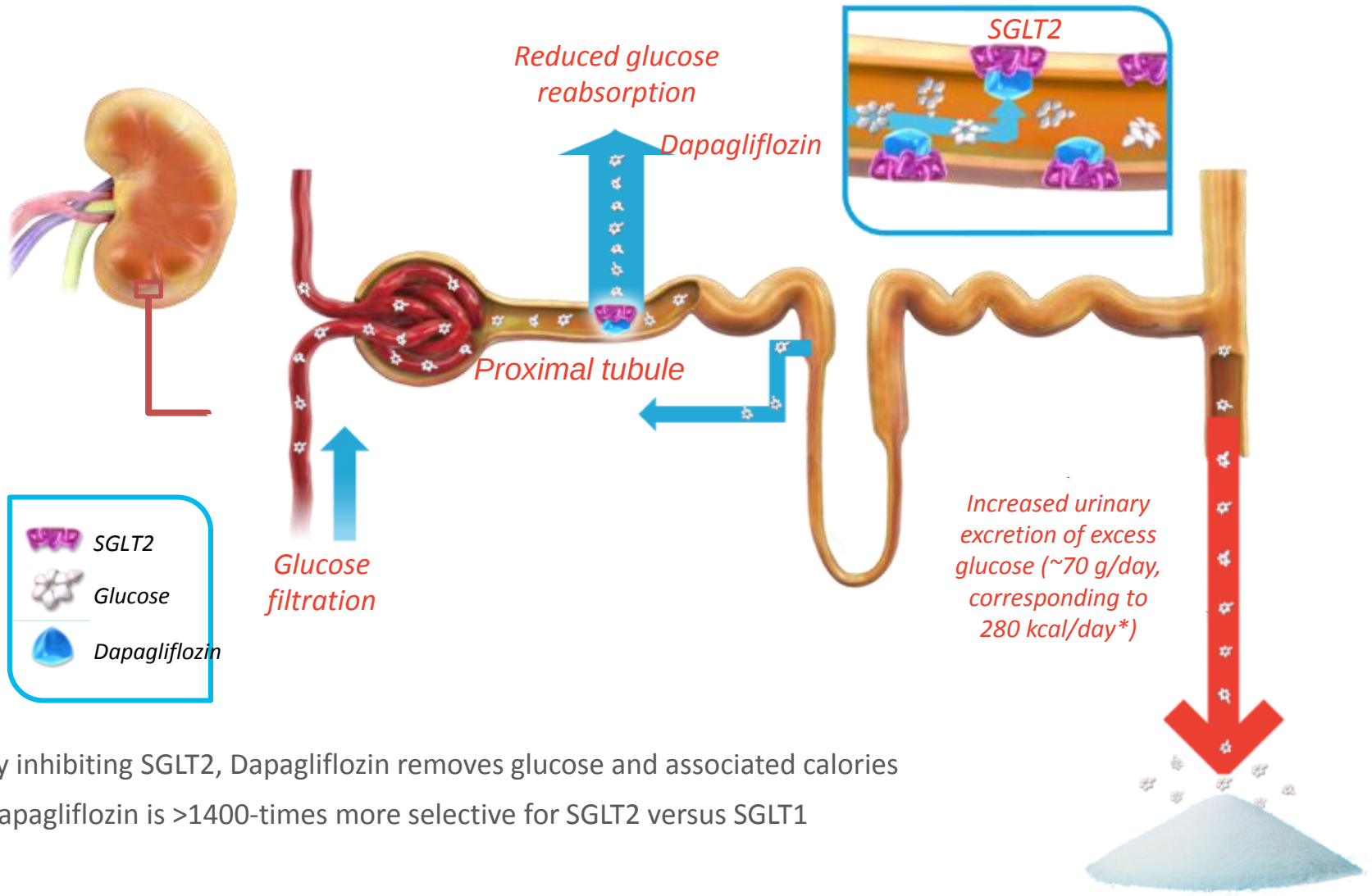
SGLT2 inhibitors

Low risk hypos /Secondary benefit of wt loss / genital infections /not if eGFR<60

GLP1 agonists

Low risk hypos / wt loss / no long term data / ?pancreatitis / license in renal impairment varies

Dapagliflozin inhibits SGLT2 and removes excess glucose in the urine independently of insulin

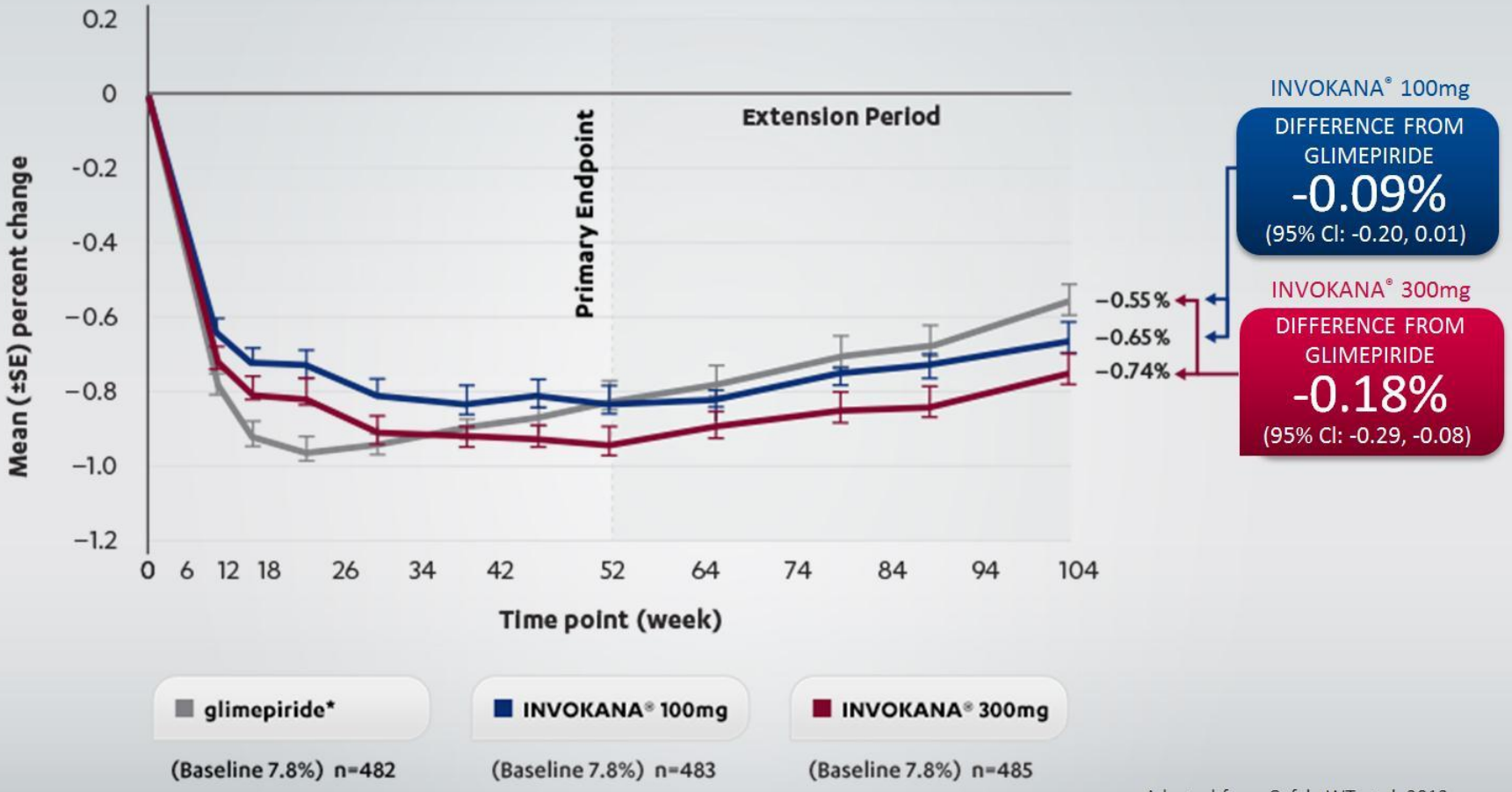


- By inhibiting SGLT2, Dapagliflozin removes glucose and associated calories
- Dapagliflozin is >1400-times more selective for SGLT2 versus SGLT1

*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.

FORXIGA®. Summary of product characteristics, 2014.

LS MEAN CHANGE IN HbA1c FROM BASELINE AFTER 104 WEEKS FOLLOW-UP (LOCF)[2]



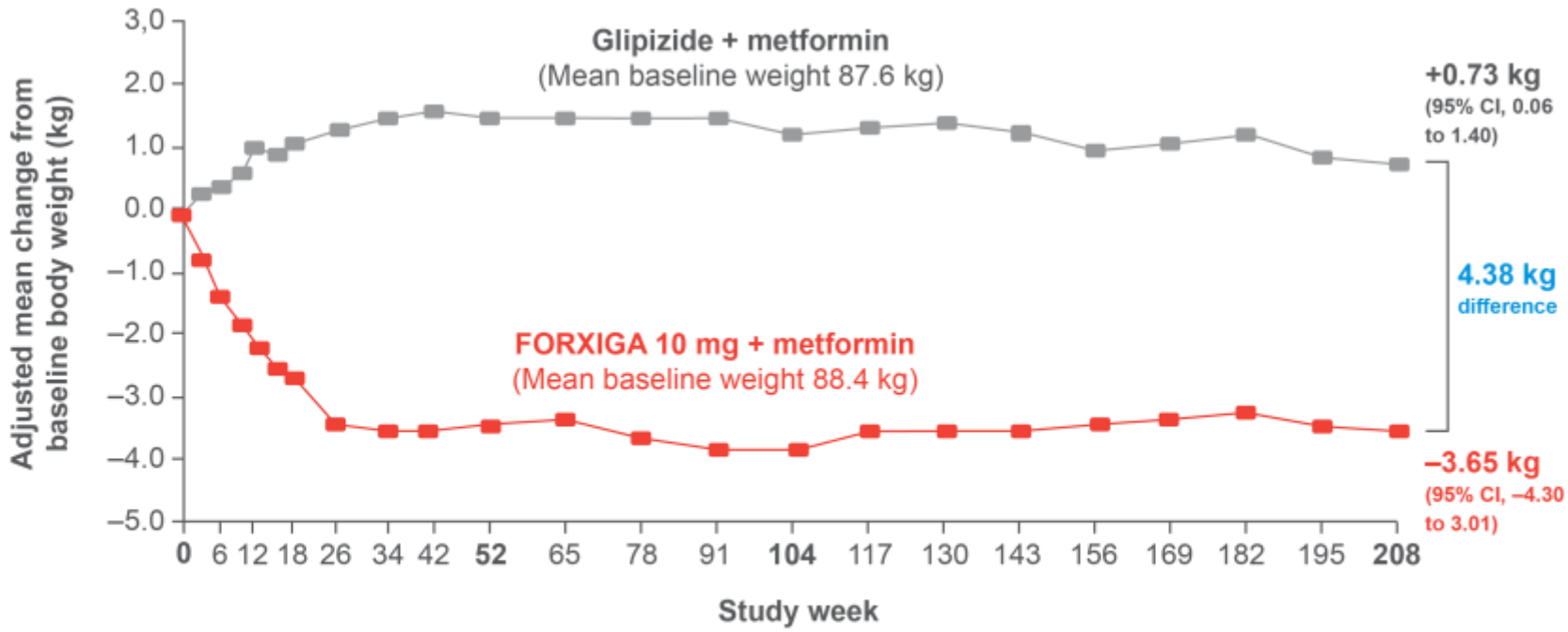
Adapted from Cefalu WT et al. 2013.

*glimepiride titrated up to a maximum of 8mg once-daily.[1] The maximum licensed dose of glimepiride is 6mg.[3]
LS: Least-squares. CI: Confidence interval. SE: Standard error. LOCF: Last observation carried forward. For INVOKANA® 100mg, the upper limit of the 95% CI was less than the pre-specified non-inferiority margin of 0.3% compared with glimepiride.[1]

Reference:
1. Cefalu WT et al. The Lancet 2013; 382 (9896): 941-950.
2. Cefalu WT et al. Poster presented at the 73rd Scientific Sessions of the American Diabetes Association (ADA), 2013; Jun. 21-25; chicago, Illinois, (65-LB).
3. AMARYL Summary of Product Characteristics. Date: March 2011.

Dapagliflozin as add-on to metformin versus SU: Additional benefit of weight loss sustained over 4 years[1]

At 52 weeks, dapagliflozin was associated with weight loss of –3.2 kg versus weight gain of +1.4 kg with glipizide ($p<0.0001$)[2]



Sample size (including data after rescue)				
FORXIGA + metformin	400	323	234	159
Glipizide + metformin	401	315	211	140

FORXIGA is not indicated for the management of obesity.[3] Weight change was a secondary endpoint in clinical trials.[3,4]
Data are adjusted mean change from baseline derived from a longitudinal repeated measures mixed model.
A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study with a double-blind extension to evaluate the efficacy and safety of FORXIGA 10 mg + metformin (1500–2000 mg/day) versus glipizide + metformin (1500–2000 mg/day) in patients with inadequate glycaemic control (HbA_{1c} >6.5% and ≤10%) on metformin alone.

1. Del Prato S, *et al*. Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA. 21–25 June 2013. Abstract 62-LB; 2. Nauck MA, *et al. Diabetes Care* 2011;34:
3. Bailey CJ, et al. Lancet 2010;**375**:2223–33; 4. FORXIGA®. Summary of product characteristics, 2014.

SGLT2 inhibitors

- Are ineffective if there is significant renal impairment (check the licence)
- are not recommended in:
  - Patients aged ≥75 years
  - Patients treated concomitantly with pioglitazone
  - Patients receiving loop diuretics
- A lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination

Summary

- There are an increasing number of potential interventions for people with Type 2 diabetes
- Ask yourself: what is the aim of treatment?
  - Complication prevention (tight control + surveillance / risk stratification))
  - Symptom control and complication surveillance
  - Avoidance of hypoglycaemia

- Be clear about what you want the new therapy to achieve
- Give it 3-6 months but if not working STOP IT!

What to do when insulin fails

Review what has been achieved since being started: has wt gone up? Are they having hypos? Has HbA1c improved?

Options

- Dietary advice
- Change of regimen
- Add a GLP1 agonist
- Add an SGLT2 inhibitor
- Very low calorie diet / stop insulin / start GLP1

Consider referral to the Diabetes Team