GLP-1 AXIS MEDICATIONS

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We will talk about

- Some physiology... Of GLP-1 axis
- Drugs in the classes of GLP analogues and DPP4 inhibitors
- Will look into the similarities and differences between the medications and classes
- Indications and side effects

Possible Second Line Treatments

- ✤ Sulfonylureas (Not Glibenclamide)
- ✤ PPG's (Postprandial Glucose Regulators)
- ✤ TZDs
- ✤ DPP- 4 Inhibitors
- ✤ GLP-1 Analogues
- ✤ α glucosidaze inhibitors
- ✤ Insulin

Treating Hyperglycaemia ± NICE

- First Line Treatment: Diet and Exercise
- First Line Medication: Metformin

GLP-1

- Gut derived incretin hormone
- Augments glucose dependent insulin secretion
- Supports the synthesis of proinsulin

  In vitro/ rodents
- Reduces the rate of β cell apoptosis in a toxic environment
- Promotes β cell differentiation from the precursor cells

GLP-1

- Secretion is mainly postprandial
- There is, however, basal secretion...
- Basal secretion has some influence on fasting glucose levels

Diabetes Care 24:1416–1421, 2001

- 40 patients: 5 groups of 8 for 1 week
- Placebo + GLP-1 4ng/kg 16h + GLP-1 8ng/kg 16h + GLP-1 4ng/kg 24h + GLP-1 8ng/kg 24h
- Patients were "Sulfonylurea failures"

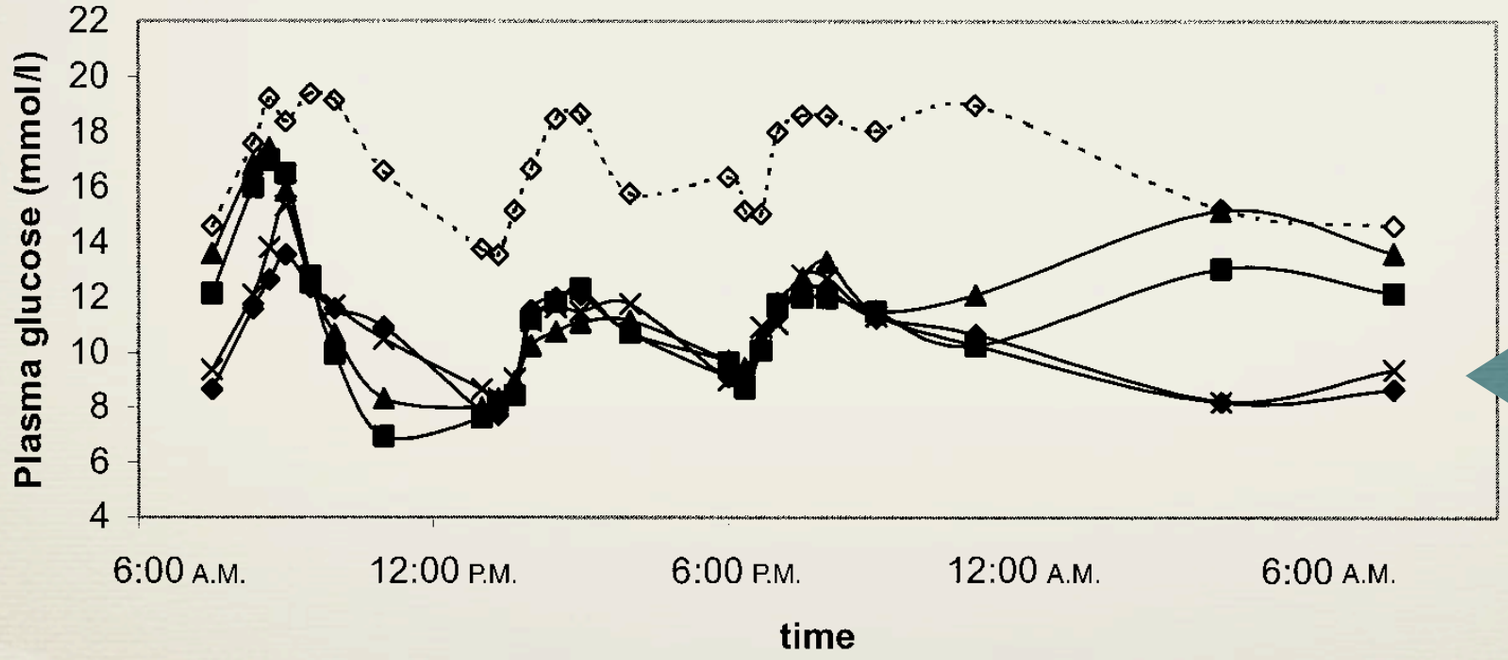


Figure 1—*24-h plasma glucose profiles for the five groups on day 7. - -◇- -, placebo group; —■—, GLP-1 4 ng · kg^{-1} · min^{-1} 16-h group; —▲—, GLP-1 8 ng · kg^{-1} · min^{-1} 16-h group; —◆—, GLP-1 4 ng · kg^{-1} · min^{-1} 24-h group; —×—, GLP-1 8 ng · kg^{-1} · min^{-1} 24-h group.*

Diabetes Care 24:1416–1421, 2001

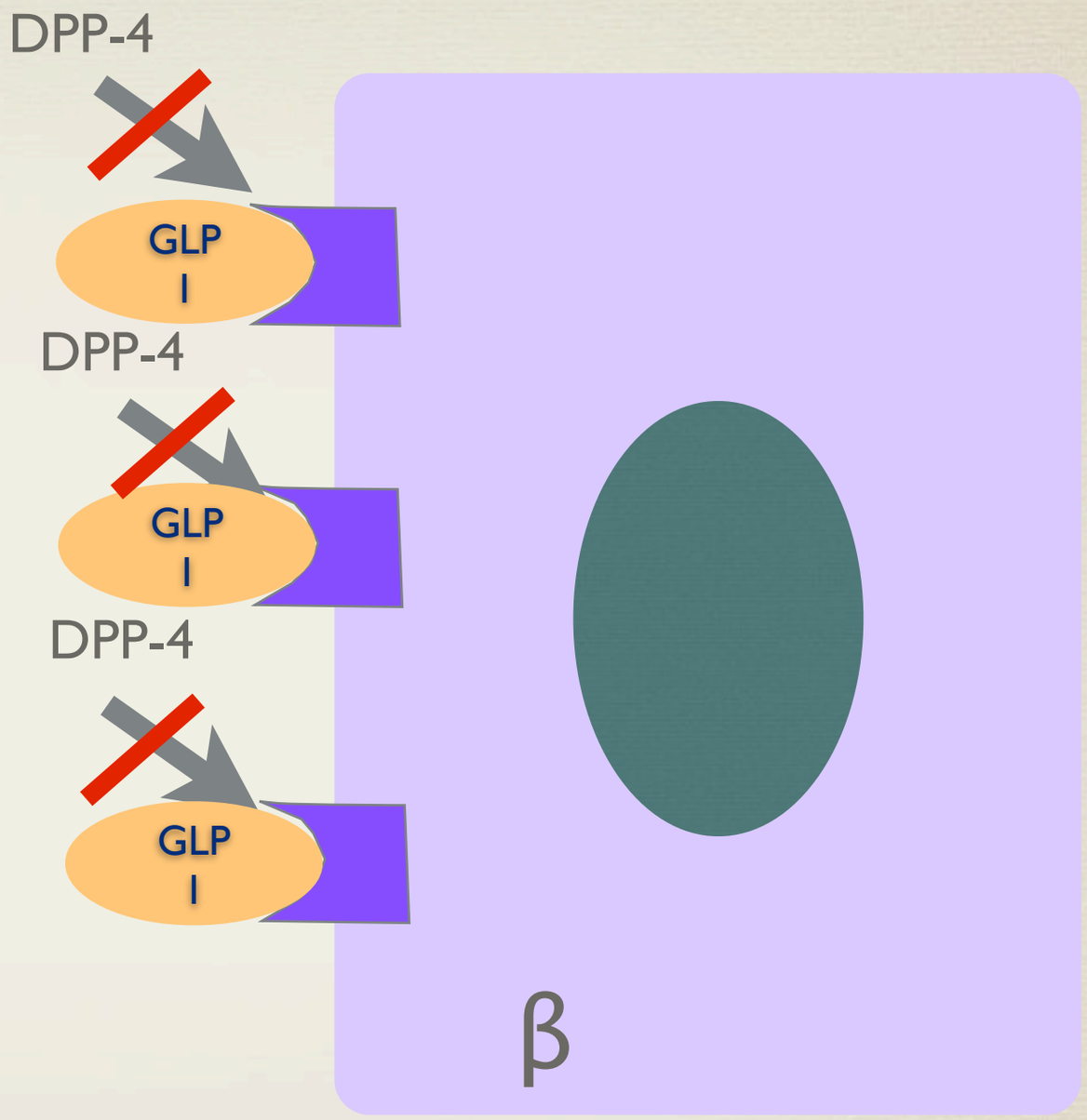
Prolonging t1/2 of GLP-1: Option 1- DPP-4

Sitaliptin

Vildagliptin

Saxagliptin

Linagliptin



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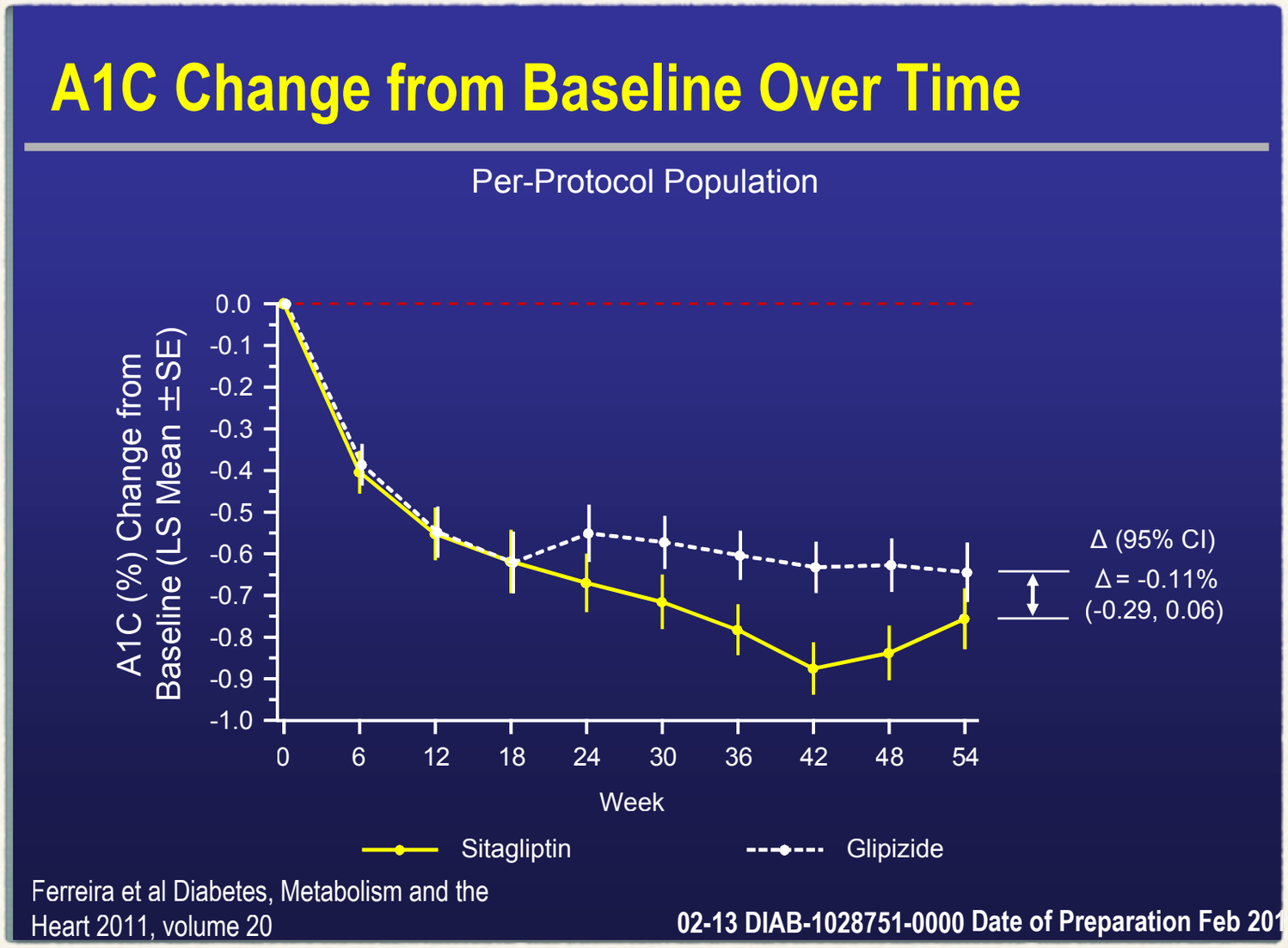
Indications: Sitagliptin

- Monotherapy if Metformin is not tolerated and SU unsuitable
- Dual therapy with SU or Metformin or TZD
- Triple therapy with combination of Metformin + SU or Metformin + TZD
- Dose 100mg OD
- License for use with insulin
- Renal failure: dose adjustment needed

Sitagliptin vs Glipizide



Vildagliptin

- As monotherapy
- In combination with Metformin 50 mg BD
- In combination with TZD 50 mg BD
- In combination with SU 50 mg OD
- Monitor LFT's; reduce if GFR< 50mL/minute/1.73m^2

Saxagliptin

- 2.5 or 5 mg OD
- In addition to Metformin
- In addition to SU
- In addition to TZD
- In addition to Insulin
- Can be used in CRF; dose adjustment needed

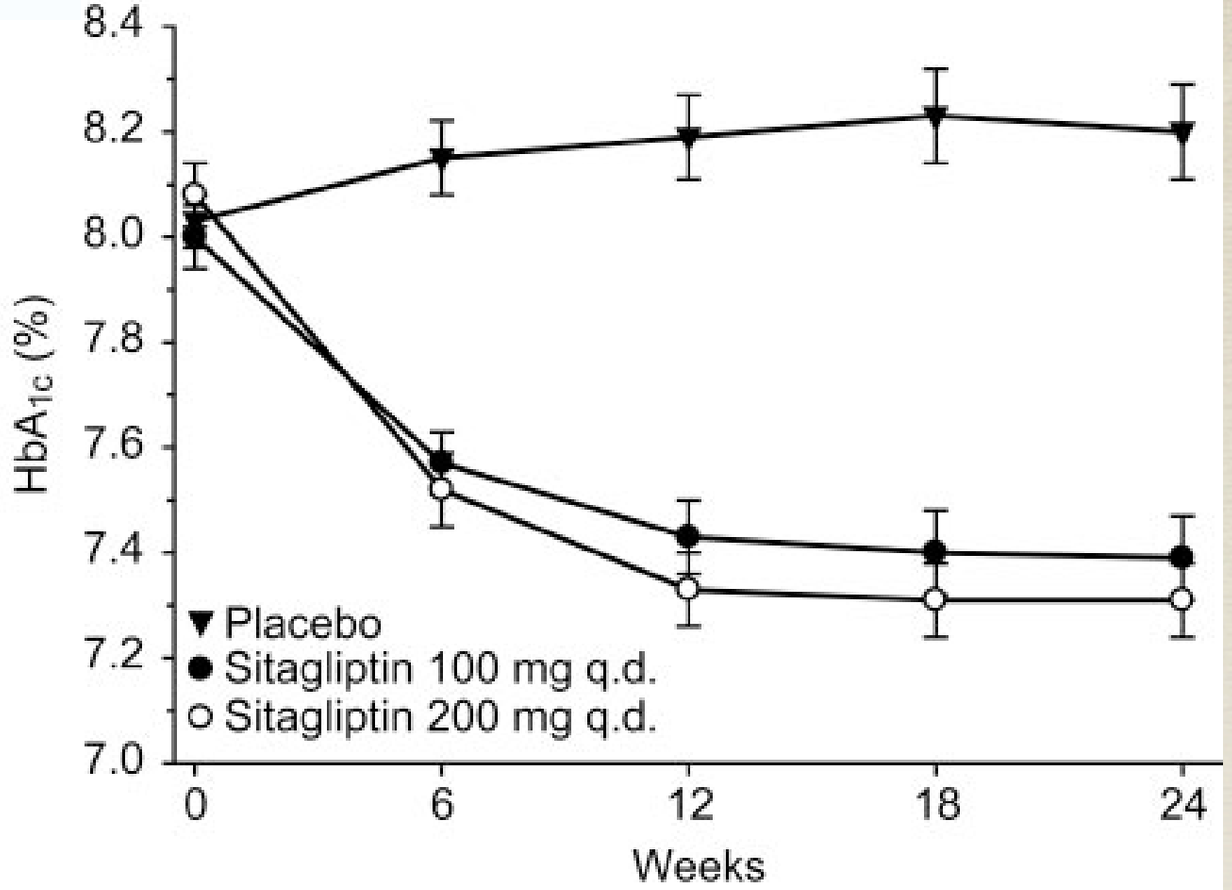
Linagliptin

- 5mg OD
- As monotherapy
- As an addition to Metformin
- As an addition to Metformin and SU
- Renal failure: no dose adjustment needed

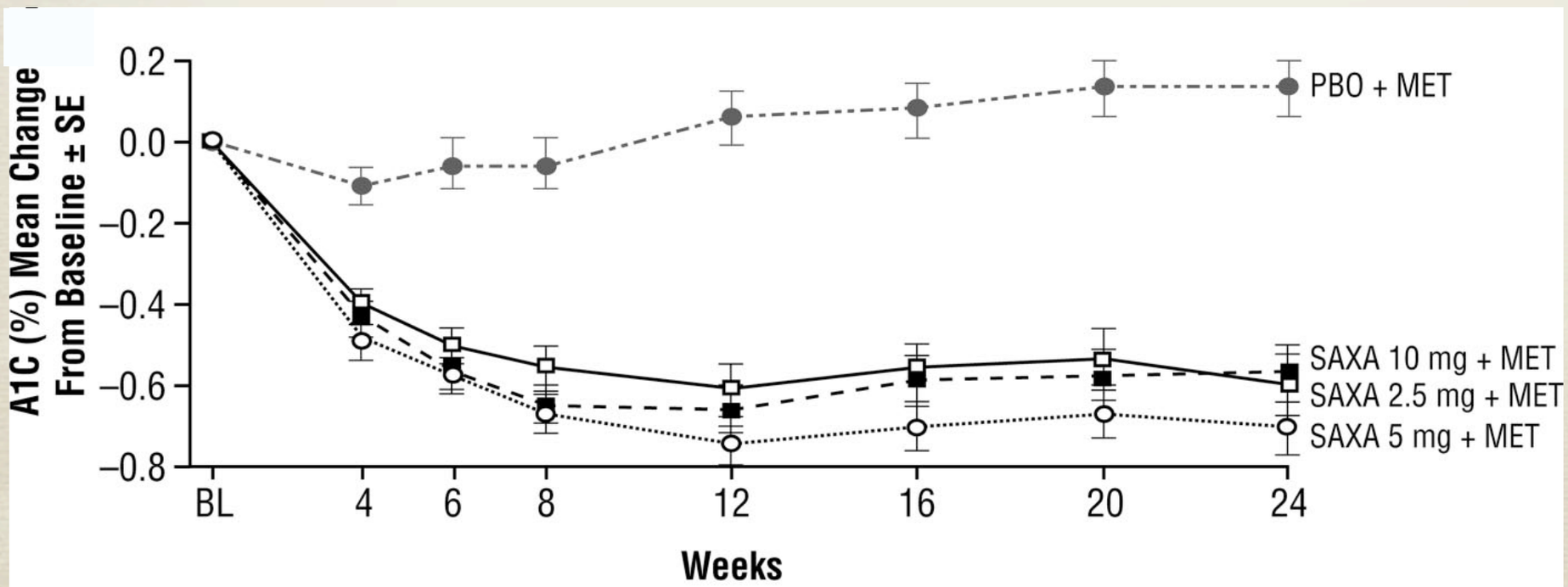
DPP-4 inhibitors side effects

- Hypos are rare
- Increased risk of nasopharyngitis
- Increase the RR of UTI 1.5x
- 50,000 UTIs on 1,000, 000 patients treated
- Avoid in patients with recurrent UTI's?

Sitagliptin:100 vs 200 mg



Saxagliptin: 2.5 vs 5 vs 10



DPP-4 inhibitors in Renal Failure

Stage	Estimated GFR	Sitagliptin	Saxagliptin	Vildagliptin
I	> 90 ml/mi/ 1.73m^2	100 mg OD	5 mg OD	50 mg BD
II	60-89 ml/mi/ 1.73m^2	100 mg OD	5mg OD	50 mg BD
III	30-59 ml/mi/ 1.73m^2	50mg OD	2.5mg OD	50 mg OD*
IV	15- 29 ml/mi/ 1.73m^2	25mg OD	2.5mg OD	50 mg OD
V	< 15 ml/mi/ 1.73m^2	25mg OD	not recommended	50 mg OD use with caution!

50 mg BD if Cr Cl>50

GLP-1 ANALOGUES

Exenatide

- Exendin 4 analogue
- 53% sequence identity to native GLP-1
- t 1/2 : 2.4h
- Injection: 5-10 ug BD
- Licensed with SU/ Metformin or in combination
- HbA1c reduction ~ 1% & FPG reduction of 1.5 mmol/l

Exenatide

- Induces ~2kg weight loss
- Greatest weight loss when added to Metformin: 2.8kg*
- Reduction in postprandial hyperglycaemia
- Rare hypos
- Antibodies 61%; patients with higher titers: lesser reductions in HbA1c**

*Diabetes Care 2005;28:1092–

**Diabetes Care 2011, 34: S279-84

Liraglutide

- 97% sequence identity to native GLP-1
- t1/2: 13h
- Dose: 0.6mg week 1/ after that 1.2mg
- 1.8mg....
- Antibodies 8.6%- these have not affected the efficacy*

*DIABETES CARE 2011, 34: S279-84

BYDUREON

- Exenatide- incorporated in Medisorb Microspheres
- Dose: 2 mg once weekly
- Expected weight loss <4kg
- License same as Exenatide

GLP-1 Agonists Side Effects

- Nausea, vomiting
- GI side effects
- Injection site reactions
- Hypos are rare
- ?? Pancreatitis

Pancreatitis

Database Study: n= 786,656 Diabetic 38,615

	Control	DM Control	Sitagliptin	Exenatide
n	748,041	16,244	15,826	6,545
Pancreatitis/1000 patient years	1.9	5.6	5.6	5.7

Diabetes Care 33:2349–54, 2010

Pancreatitis

- HR Diabetic Group 2.1 (95% CI 1.7-2.5)
- No difference among the DM treatment groups

Diabetes Care 33:2349–54, 2010

BYDURON vs Liraglutide: DURATION-6

- 26 weeks: BYDUREON n= 461; Liraglutide n= 450
- BMI 32.3; HbA1c 8.5± 1%
- Patients were on Metformin, Sulfonilurea ± Pioglitazone
- Non inferiority study
- Condition of non inferiority was difference in HbA1c of <0.25% between Liraglutide and EQW

Diabetologia 2011;54: s75

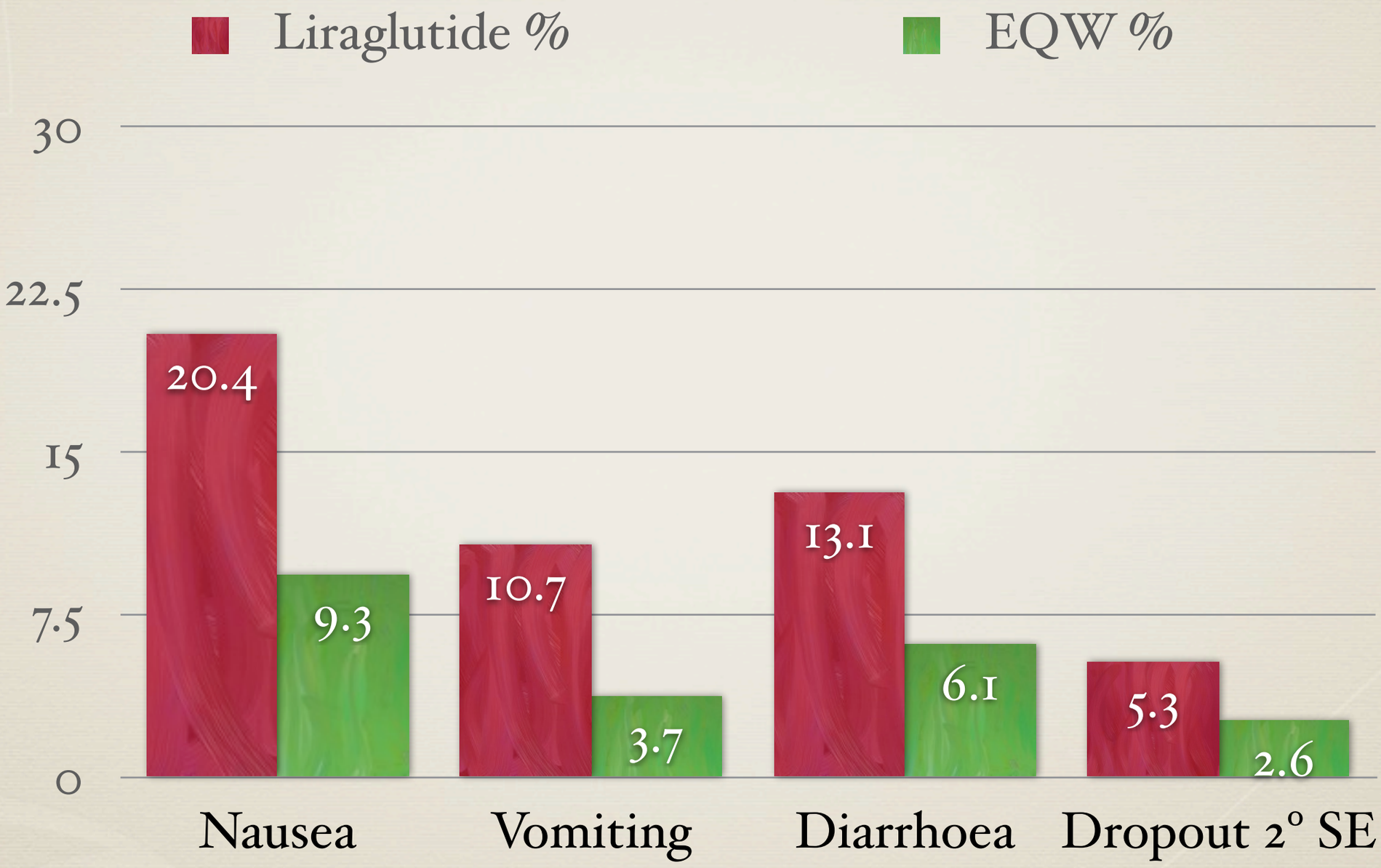
DURATION-6: Results

	BYDUREON	Liraglutide	p
%HbA1c < 7%	53.8	60.2	<0.01
↓ %HbA1c	1.28	1.46	
Weight	2.68	3.58	

There was no major hypoglycaemia
Minor hypoglycaemia ~ 9-10% p=NS

Diabetologia 2011;54: s75

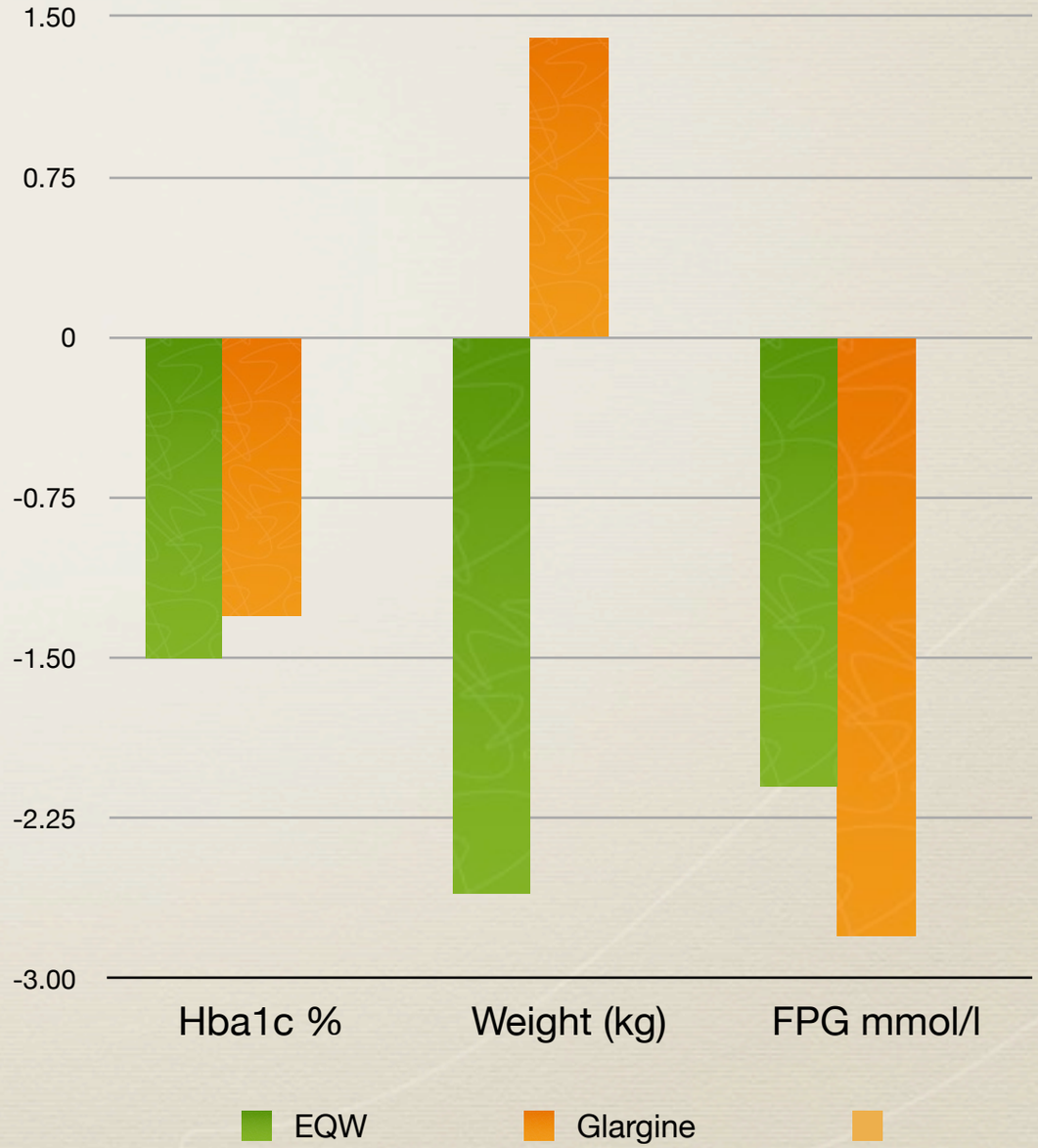
DURATION-6: Side Effects



Diabetologia 2011;54: s75

DURATION3: EQW vs Insulin Glargine

- 26 weeks
- EQW: 233 patients;
  Glargine: 223 patients
- Patients were on
  Metformin ± SU
- Starting HbA1c
  8.3±0.7%



Lancet 2010; 375: 2234

DURATION3: EQW vs Insulin Glargine

- 79% of patients taking EQW had reduction in HbA1c and lost weight
- 63% of patients in the Glargine group had a reduction in HbA1c paired with weight gain
- Minor hypoglycaemia occurred more frequently in the Glargine group

Lancet 2010; 375: 2234

DURATION-4: Monotherapy

- In medication naive patients sub-optimally controlled on diet and exercise
- EQW 2mg weekly; n= 248
- Metformin 2000mg daily; n=246
- Sitagliptin 100mg OD; n= 163
- Pioglitazone 45mg OD; n= 163

Diabetes Care 35:252–258, 2012

GLP-1 Analogues: Comparison

	Exenetide	Liraglutide	Bydureon
Metformin and/or SU	✓	✓	✓
TZD	-	✓	-
Insulin	Long acting	Levemir only	-
Frequency of Use	BD	OD	Weekly
Renal Failure	✓	-	-
Head to Head Studies	✓	✓	✓
% HbA1c Reduction	0.9-1	-1.1 to -1.6	up to -1.9
Weight Loss (kg)	up to -2.8	up to -3.2	up to -3.7

GLP-1 analogues and DPP-4 inhibitors: similarities

Action	GLP 1 analogues	DPP4 inhibitors
Glucose dependent insulin secretion	yes	yes
Glucose dependent glucagonostatic effect	yes	yes
FPG reduction	1.4- 3.4 mmol/l	1.0- 1.4 mmol/l
Postprandial glucose reduction	yes	yes (weaker)
A1c reduction	0.8- 1.8%	0.5-1.1%
Effect on proinsulin synthesis	yes	yes (? weaker)
Improved in vivo β cell function- humans	??	??
Beneficial CVD effects	not proven	possible

GLP-1 analogues and DPP-4 inhibitors: Differences

Action	GLP 1 analogues	DPP4 inhibitors
Route of use	Injection (SC)	Oral
Receptor stimulation	Direct	Indirect
GLP-1 levels attained	6-10 x > normal	2-3 x > normal
Other mediators	No	Yes (GIP etc)
Effects on Gastric Emptying	Yes	Hardly
Appetite Reduction	Yes	Less than GPL-1
Body Weight	Reduction	Neutral
Side Effects	Nausea, Vomiting, ~~? Pancreatitis~~	Nasopharyngitis, UTI's, Deranged LFTs (Vilda), Skin Reactions (Sita)

In Conclusion

- GLP-1 analogues and DPP-4 inhibitors are new classes of drugs for treatment of T2DM
- These medications will improve glycaemic control and HbA1c by 0.7- 1.2%
- Indications and tolerability vary among the drugs in the same class
- Long term use...