Medical Management of Obese Renal Failure Patients awaiting Transplantation

John New

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Diabetes & Obesity
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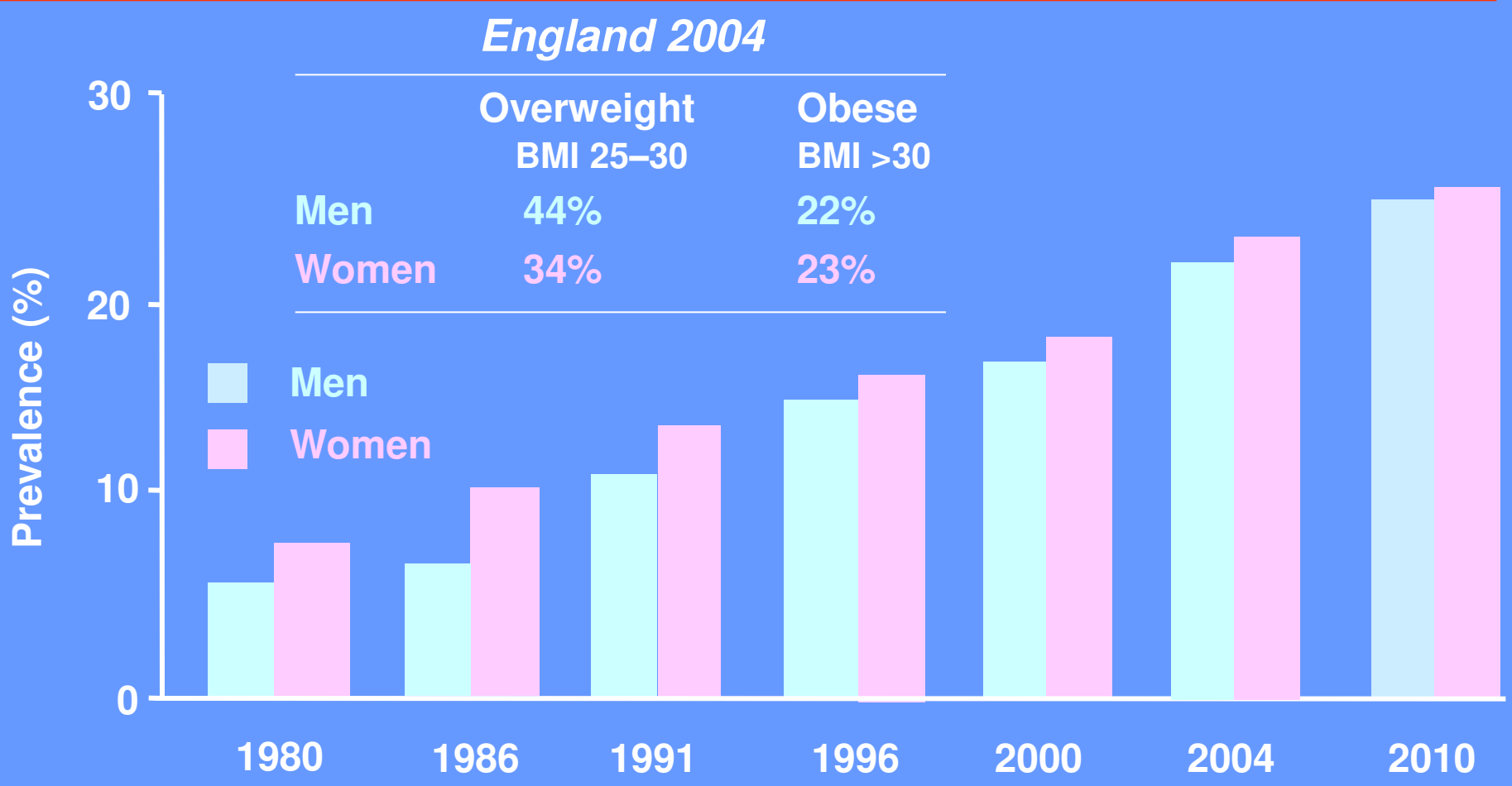
Hope you enjoyed lunch

Prevalence of adult obesity (BMI >30) in England



% overweight has stayed approx constant since 1993 (M~44%, F~33%)

Obesity causes ~30,000 premature deaths annually; 18 million lost working days in 1998

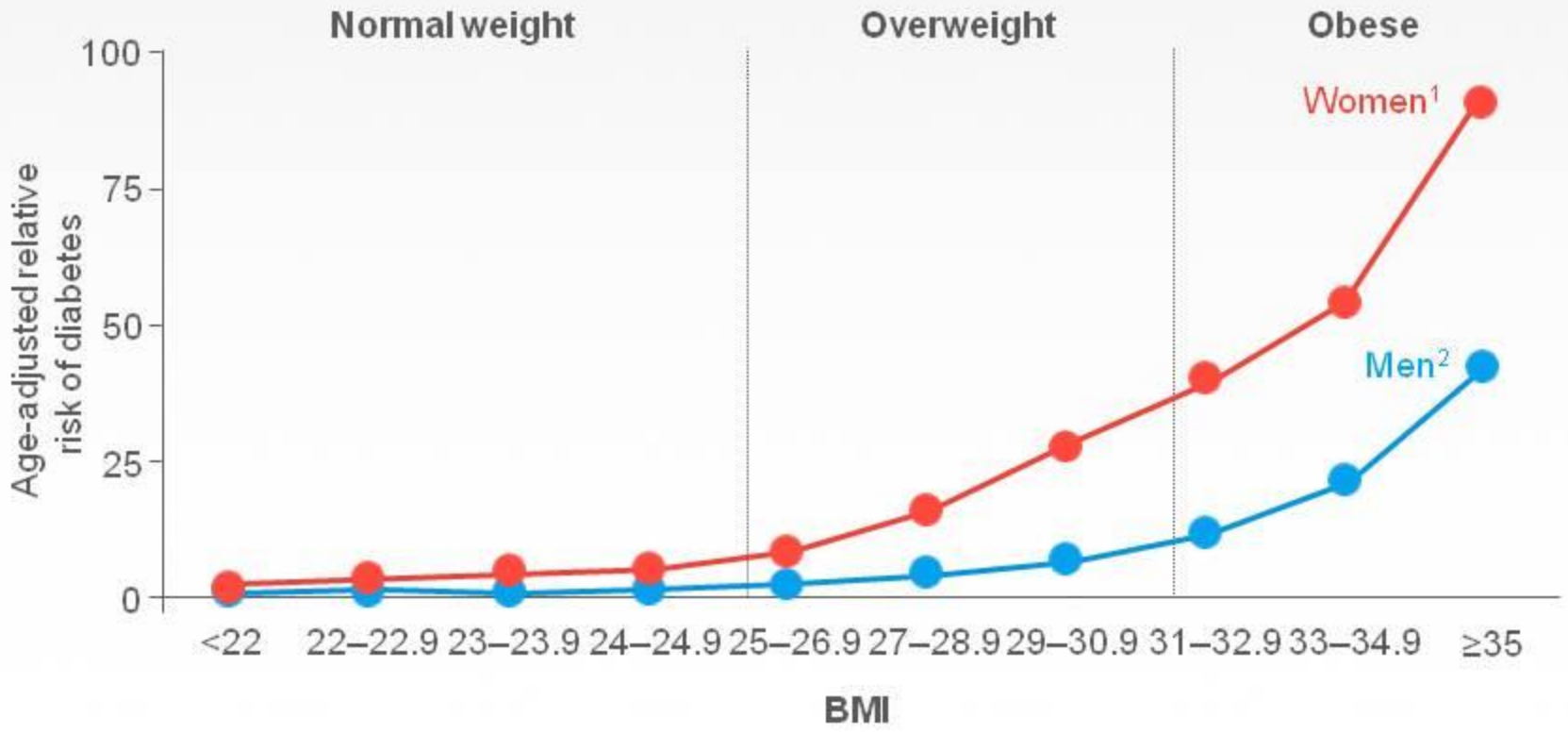
Cost to the nation (including the NHS) > £2.5 billion

Kopelman PG. *Nature* 2000; **404**: 635–643; Health Survey for England, 2004; National Audit Office, February 2001; Select Committee on Public Accounts (9th Report), January 2002.

Date of preparation: August 2006

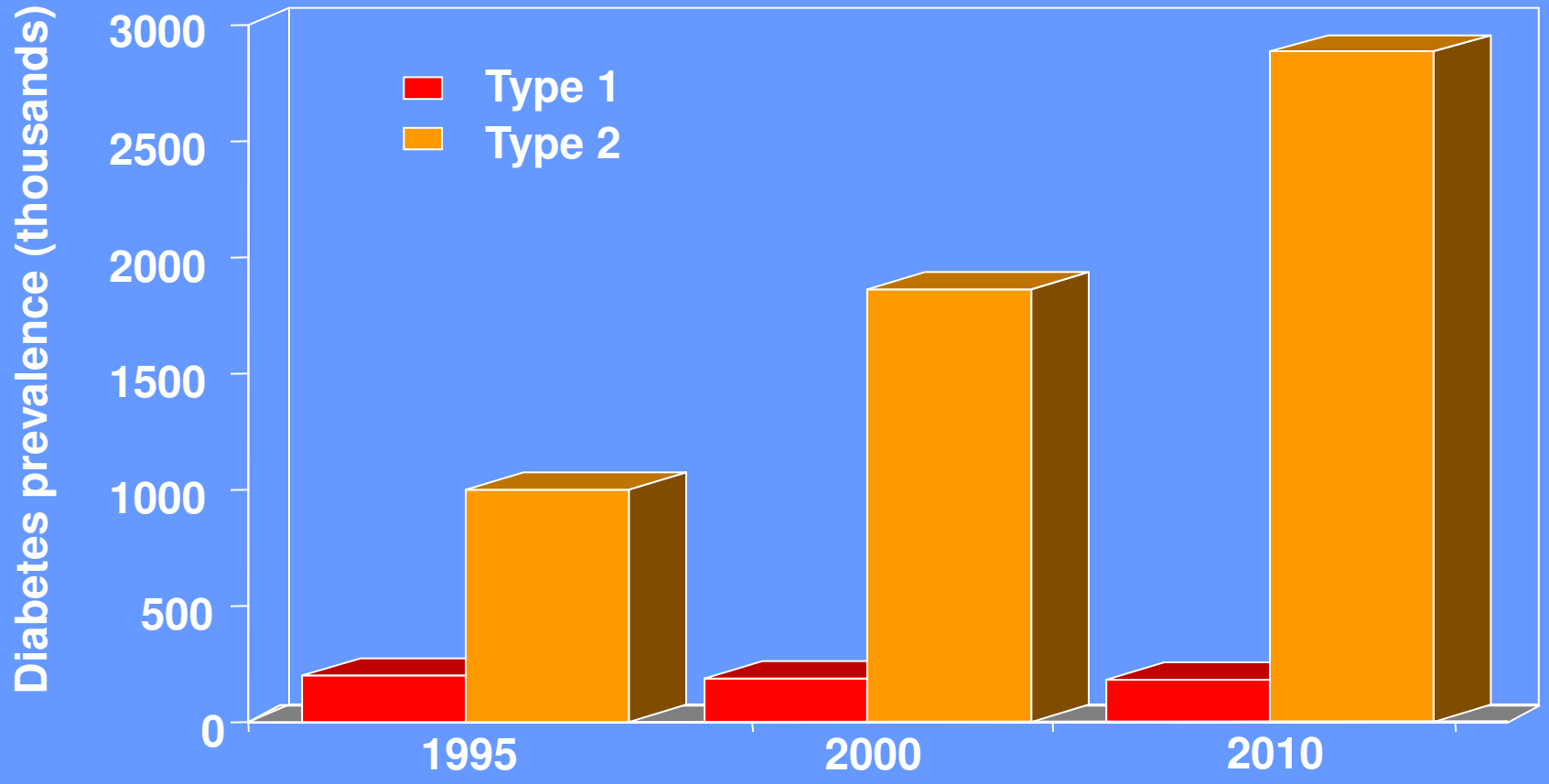
Diabetes and obesity are closely interlinked

Relationship between BMI and risk of type 2 diabetes



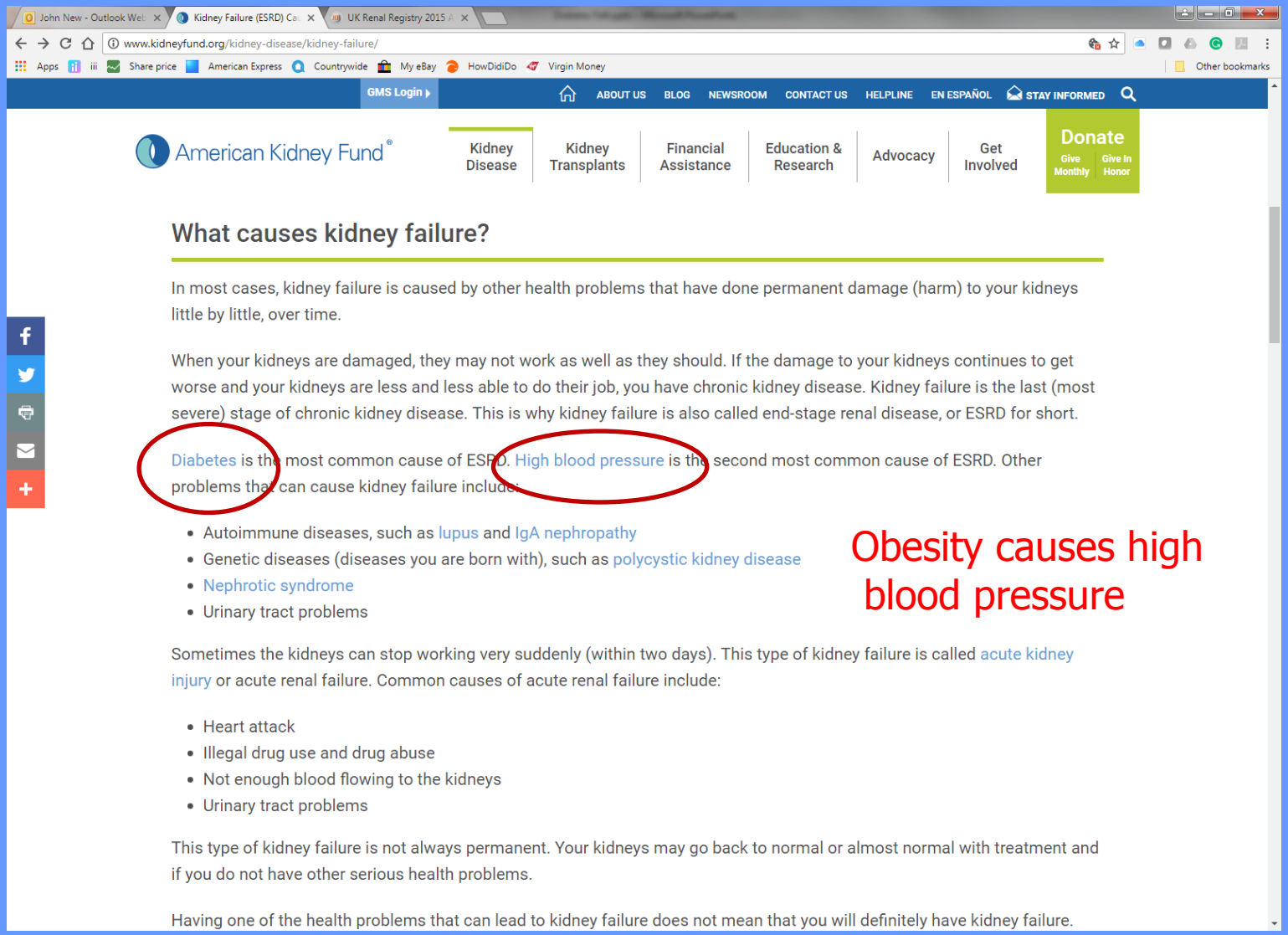
BMI, body mass index.
1. Colditz GA, *et al. Ann Intern Med* 1995;**122**:481–6; 2. Chan J, *et al. Diabetes Care* 1994;**17**:961–9.

Prevalence DM in UK



Amos AF *et al. Diabet Med* 1997;**14**(Suppl 5);S1–S85

Diabetes, Obesity & Renal Failure



Management of Obesity

- Difficult

COMPLETELY UPDATED!
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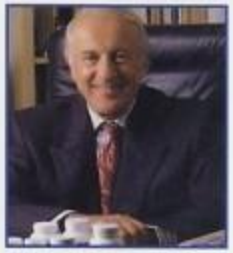
DR. ATKINS' NEW DIET REVOLUTION



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—Joan Lunden, best-selling author of Intimate Lunch and ABC weekend columnist

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Dr. Jennie Brand-Miller
Kaye Foster-Powell
nna McMillan-Price

AUTHORITIES ON THE GLYCEMIC INDEX

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BY DAVID ZINCZENKO
Editor-in-Chief of Men's Health
WITH MATT GOULDING

Management of Obesity

- Difficult
  - Exercise
  - Energy restriction
  - Pharmacological
  - Bariatric Surgery

1 Kg fat

=

X 13 = 9000 Cals

=

X 50

=

70 kg = 130 km

100 kg = 90 km

Difficulties with weight loss in people awaiting transplant

- Fluid retention masks weight loss
  - Need careful assessment of dry weight
  - Fluid retention, SOB, poor motivation
- Low calorie diets difficult to maintain protein and nutritional intake
- Medications – steroids,
- People on insulin tendency to hypos
  - Reduce fast acting, maintain on slow acting

Advantages of weight loss in people awaiting transplant

- Very Motivated
- Longer term maintenance of weight not as important

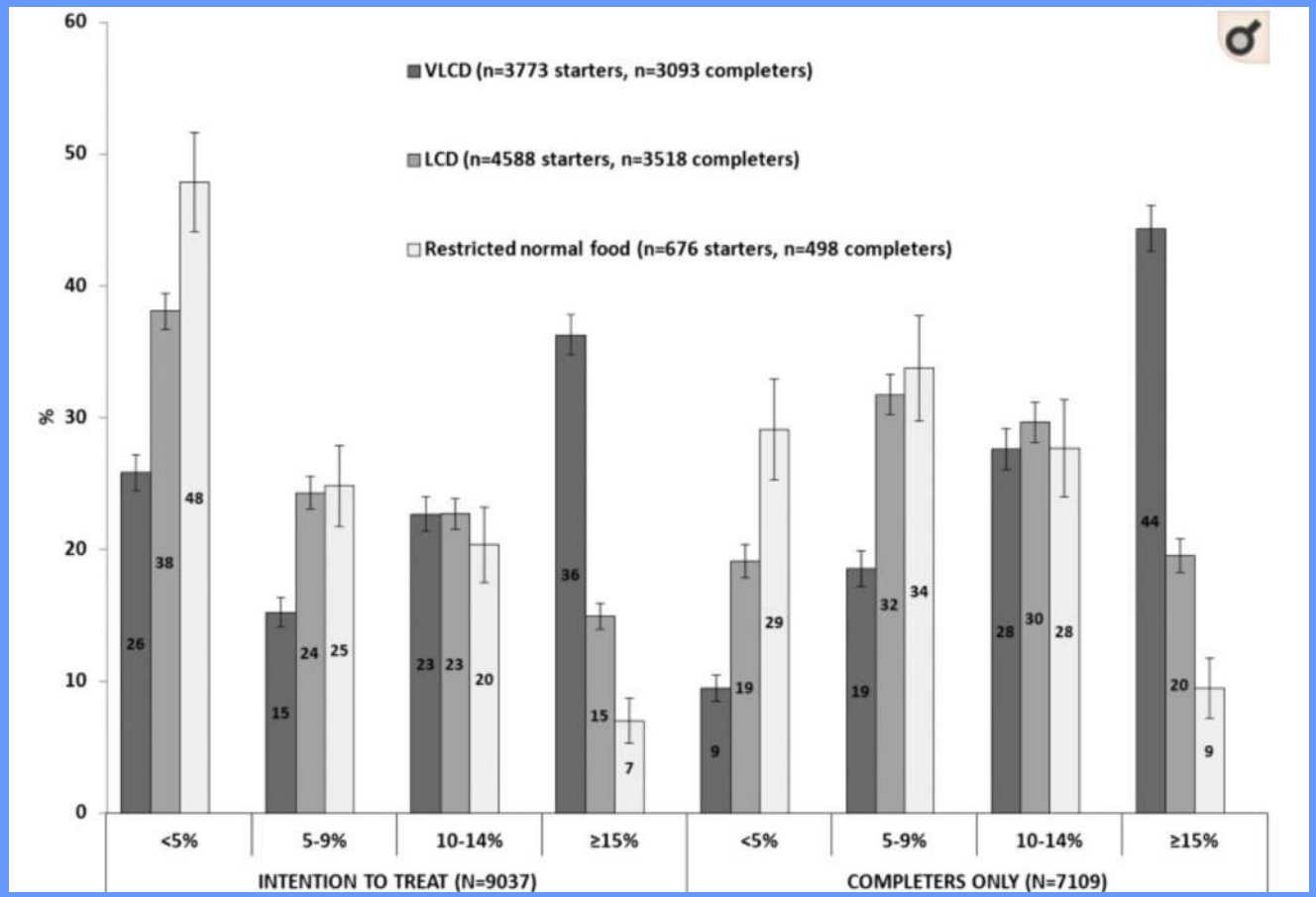
Diet, Orlistat, GLP1 & SGLT2

- Orlistat
  - Licensed for obesity
- GLP1
  - Liraglutide - licensed for obesity
  - diabetes and non diabetes
- SGLT2 inhibitors
  - Not licensed for obesity
  - Only suitable for people with diabetes
- If no weight loss 4 weeks unlikely to succeed

Low Calorie Diets

- Traditional diet
  500 Cal per day restriction
- LCD 1500-1800-kcal/day restricted normal-food diet
- VLCD 500 – 800 Cal per day allowance

Low Calorie Diets

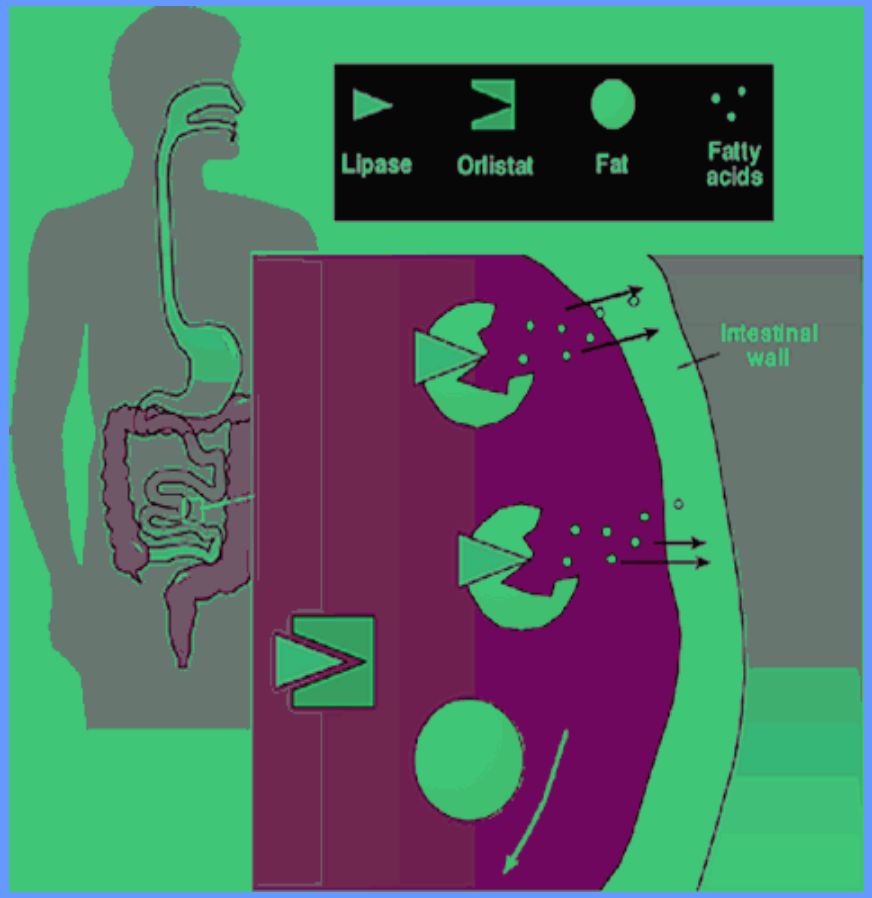


Categories of percentage weight loss at 1 y in a commercial weight-loss program including a VLCD, an LCD, or a restricted normal-food diet.

Very Low Calorie Diets

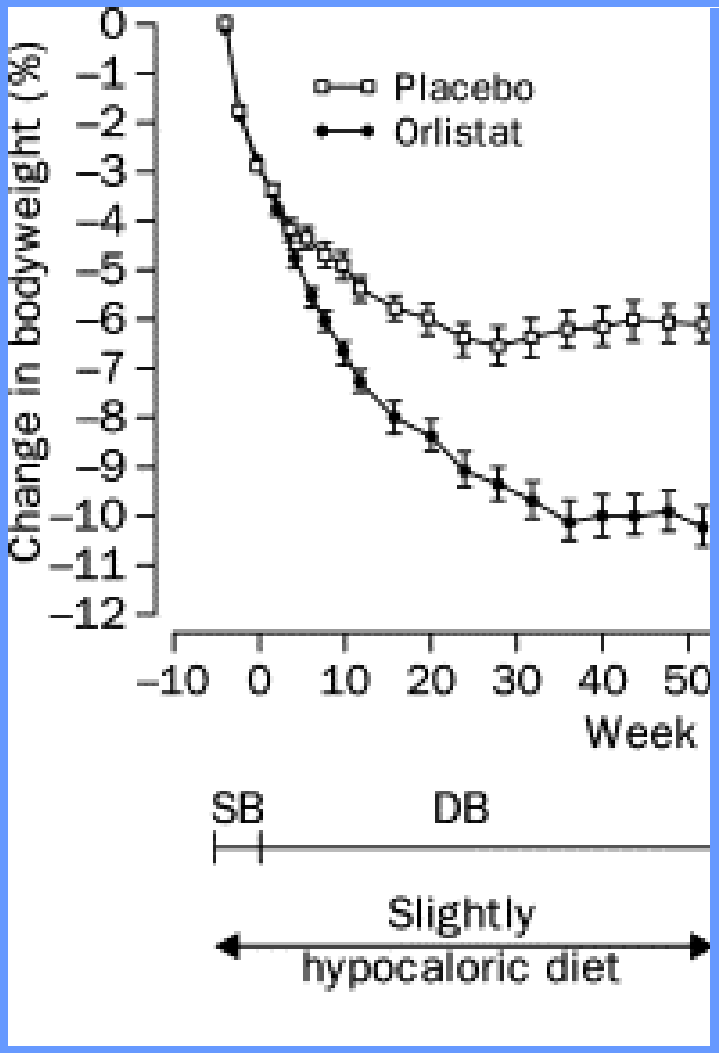
- Short term weight loss is excellent
  - Longer term weight loss poor
- Ideal for motivated person
  - Transplant or joint replacement
- Used in conjunction with medications improve compliance
- Should be followed up with nutritional and psychological support

Orlistat



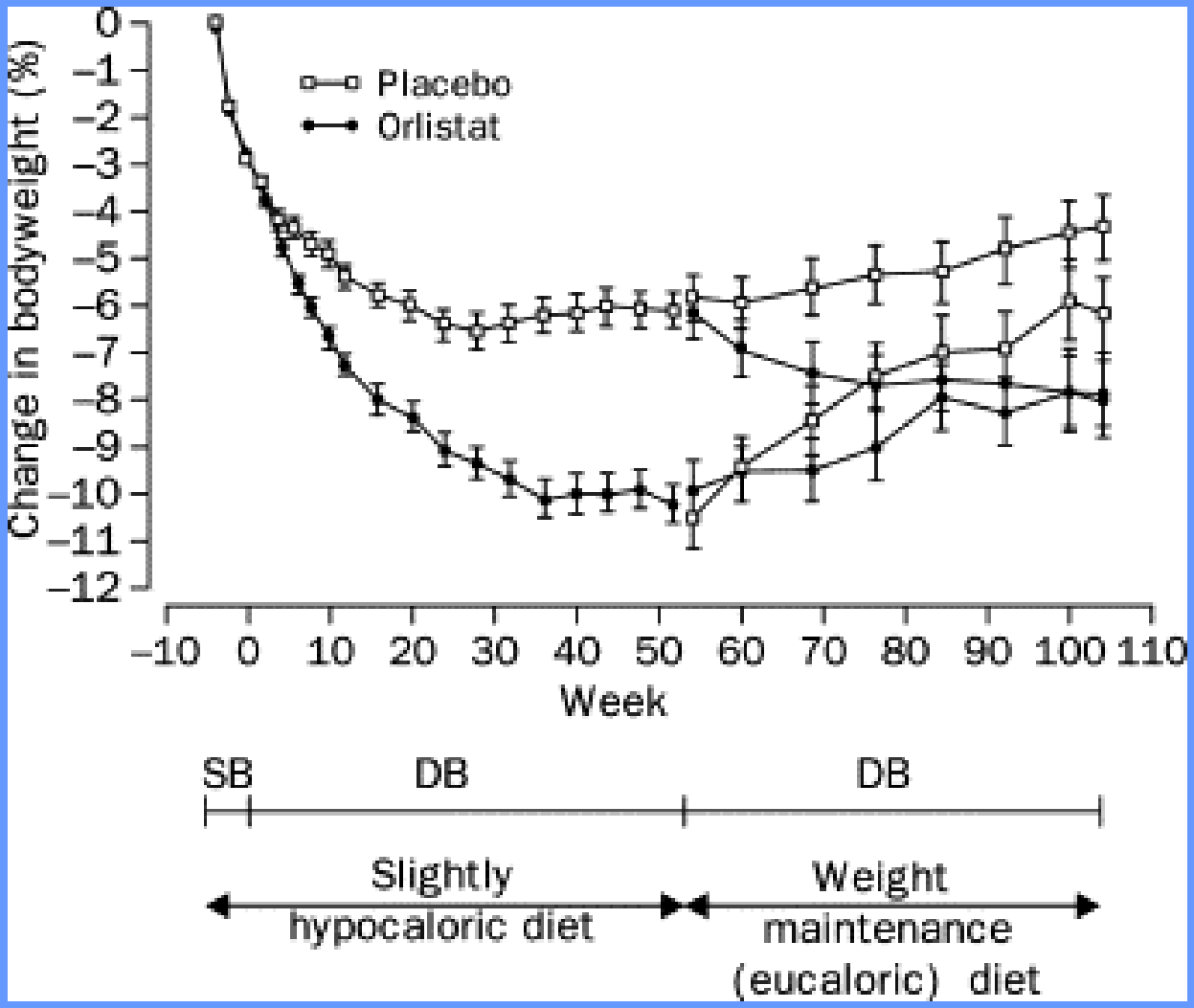
- Inhibition of lipases blocks systemic absorption of fat
- Take with each meal
- Unabsorbed fat is excreted into faeces (up to one-third of ingested fat)
- Deterrent to eating fat
- Faecal urgency & leaking

Orlistat & Weight loss



Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. Lars Sjöström Lancet

Orlistat & Weight loss



Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. Lars Sjöström Lancet

What is GLP1?

- GLP 1 is an incretin hormone
  - Secreted by L cells in gut
  - Half life of 2 minutes (degraded by DPP4)
- Postprandial
  - Slows gastric emptying
  - Reduces apetite and food intake
  - Stimulates glucose dependent insulin secreation
  - Suppresses glucagon secretion decreased hepatic glucose production

Exenatide

- Exenatide is a synthetic version of exendin-4
  - Isolated from the Gila monster lizard saliva
  - Shares over 50% similarity with human GLP-1
- Exenatide and GLP-1 bind to the GLP-1 receptor with equal affinity
  - Effects of exenatide when bound to the GLP-1 receptor are equivalent to native GLP-1
- Unlike native GLP-1, exenatide is not inactivated by the DPP4 enzyme, which means it remains active for longer
- Renal excreation – Avoid in Renal disease

Liraglutide

- Once daily injection
- Licensed for treatment
  - T2DM
  - Obesity
  - eGFR >30
    - but not renally metabolised
    - Trials in dialysis patient's appear safe
- Nausea, gall stones, pancreatitis

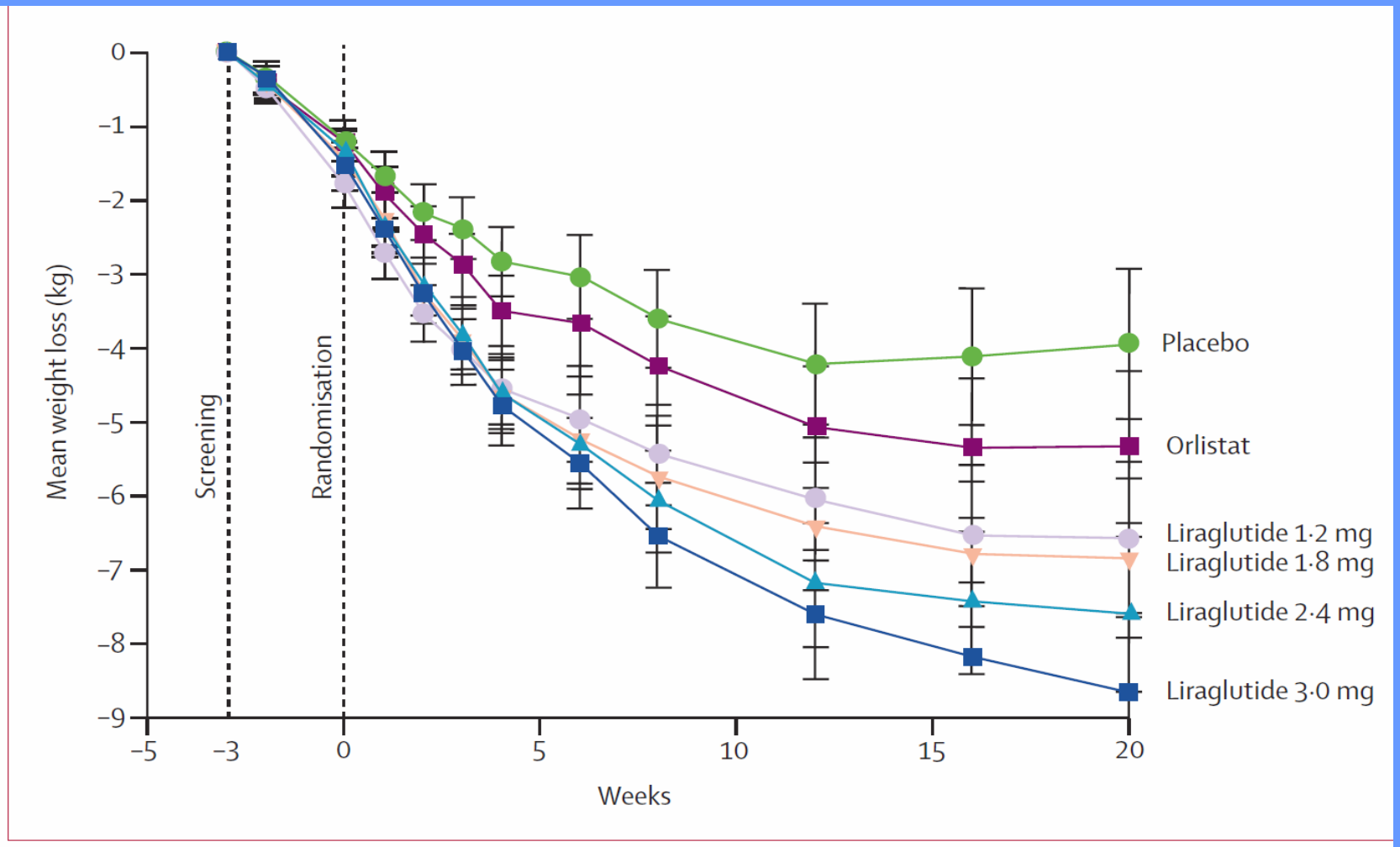


Figure 2: **Change in bodyweight**

	Placebo	Liraglutide				Orlistat
		1·2 mg	1·8 mg	2·4 mg	3·0 mg	
Weight (kg)	−4·1 (3·9)	−6·7 (4·0)	−7·1 (5·8)	−7·9 (5·0)	−9·1 (5·2)	−5·5 (4·3)
SBP (mm Hg)	−7·8 (15·0)	−12·8 (14·4)	−10·7 (13·6)	−14·7 (12·0)	−13·3 (13·2)	−9·3 (11·7)
DBP (mm Hg)	−4·8 (9·0)	−4·9 (8·8)	−4·9 (9·0)	−5·1 (8·0)	−7·1 (9·8)	−4·5 (8·0)

Arne Astrup, Lancet 2009: 374, 1606–16

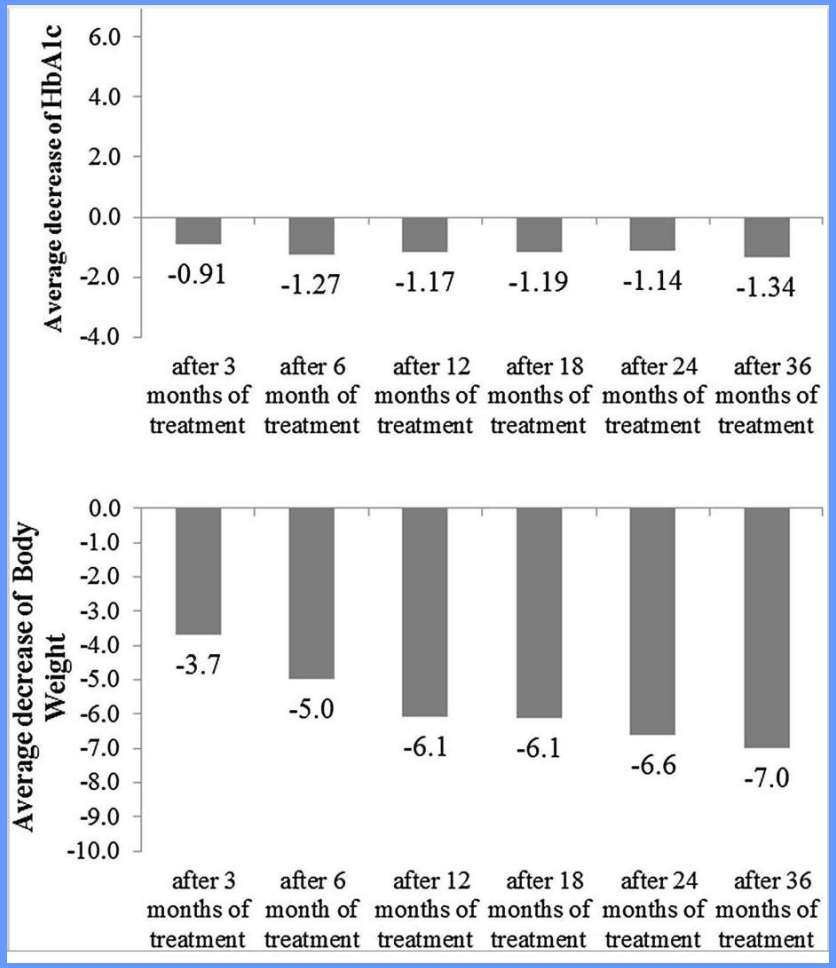
Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study

- 20-week trial, with open-label orlistat
- 564 individuals

  18–65 yrs, BMI 30–40
  - 4 liraglutide: 1.2, 1.8, 2.4 or 3.0 mg OD
  - placebo
  - orlistat 120mg TDS
- 500 kcal per day energy-deficit diet & increased physical activity

Arne Astrup, Lancet 2009: 374, 1606–16

Longer term effects of liraglutide



Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide
International Journal of Obesity 2012, 843–854

Changes in bodyweight and cardiometabolic risk factors between baseline and week 160

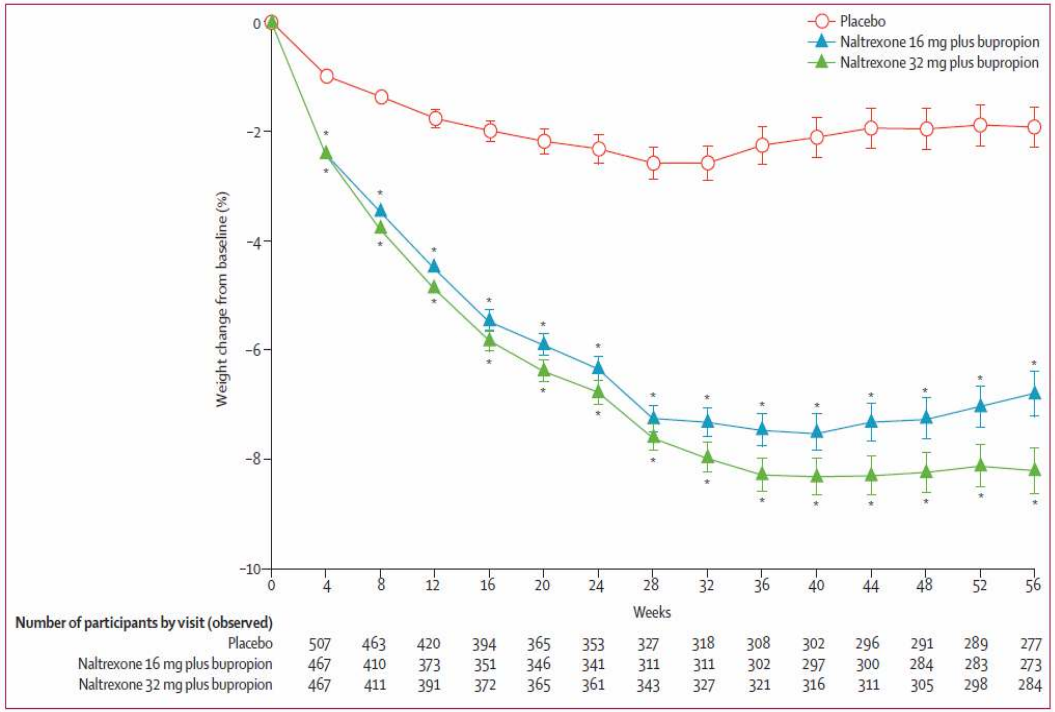
	Liraglutide 3·0 mg (n=1472)	Placebo (n=738)	Estimated treatment difference, liraglutide vs placebo (95% CI)*	p value
Change in bodyweight				
Percentage of bodyweight	-6·1% (7·3)	-1·9% (6·3)	-4·3 (-4·9 to -3·7)	<0·0001
Kg of bodyweight	-6·5 (8·1)	-2·0 (7·3)	-4·6 (-5·3 to -3·9)	<0·0001
Loss of ≥5% bodyweight (%)†	49·6%	23·7%	3·2 (2·6 to 3·9)	<0·0001
Loss of >10% bodyweight (%)†	24·8%	9·9%	3·1 (2·3 to 4·1)	<0·0001
Loss of >15% bodyweight (%)†	11·0%	3·1%	4·0 (2·6 to 6·3)	<0·0001
Bodyweight-related endpoints				
BMI (kg/m²)	-2·4 (2·9)	-0·7 (2·6)	-1·7 (-1·9 to -1·4)	<0·0001
Waist circumference (cm)	-6·9 (8·3)	-3·4 (7·5)	-3·5 (-4·2 to -2·8)	<0·0001
Women (n=1110 vs 565)	-7·2 (8·3)	-3·1 (7·3)	-4·0 (-4·8 to -3·2)	<0·0001
Men (n=362 vs 173)	-5·9 (8·1)	-4·3 (8·0)	-1·9 (-3·4 to -0·5)	0·0080

3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial
The Lancet Volume 389, Issue 10077, Pages 1399-1409 (April 2017)

Mysimba

- centrally acting anti-obesity drug
  - naltrexone
  - bupropion
- Used to help stop smoking and opiate addiction
- Reduces the pleasure from eating

Naltrexone plus burprion



Number of participants by visit (observed)														
Placebo	507	463	420	394	365	353	327	318	308	302	296	291	289	277
Naltrexone 16 mg plus bupropion	467	410	373	351	346	341	311	311	302	297	300	284	283	273
Naltrexone 32 mg plus bupropion	467	411	391	372	365	361	343	327	321	316	311	305	298	284

Figure 2: Change in bodyweight
Observed least squares mean (SE) percentage change from baseline in bodyweight and number of participants at each visit during 56 weeks. *p<0·0001 compared with placebo.

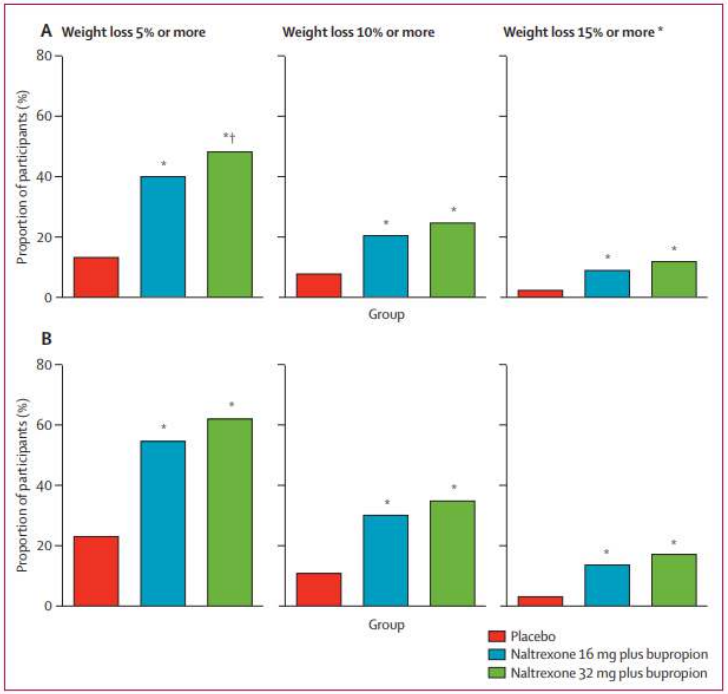


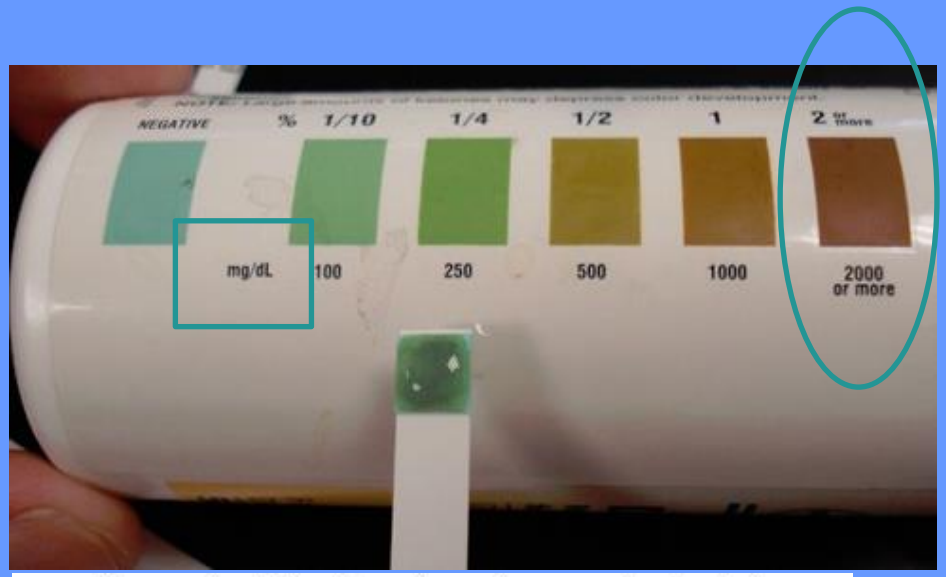
***Figure 3:* Proportion of participants who lost at least 5%, 10%, and 15% of baseline weight at week 56**
(A) Primary analysis population. (B) Participants who completed 56 weeks of treatment. *p<0·0001 compared with placebo. †p=0·0099 for naltrexone 32 mg plus bupropion compared with naltrexone 16 mg plus bupropion (exploratory analysis performed for primary analysis population only).

Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I)
Lancet 2010 p595-605

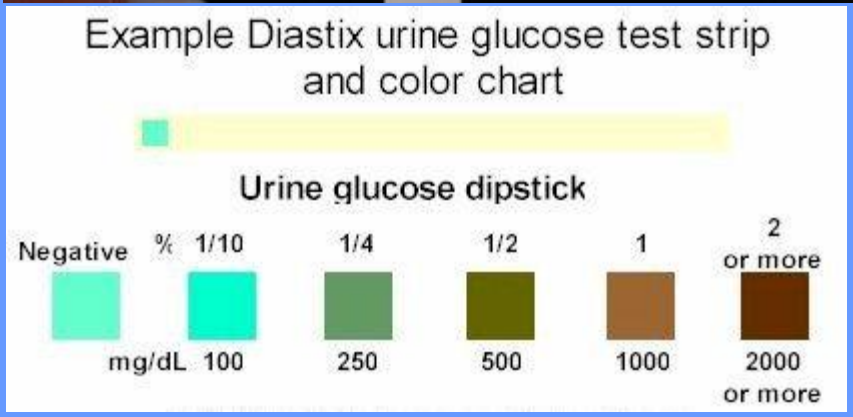
Mysimba: Nice recommendation

- Naltrexone–bupropion is not recommended for managing overweight and obesity in adults alongside a reduced-calorie diet & increased physical activity.
- Clinical trial evidence shows that naltrexone–bupropion with lifestyle measures is more effective than lifestyle measures alone, but its long-term effectiveness is unknown.

Treatment of T2DM and weight



Example Diastix urine glucose test strip and color chart



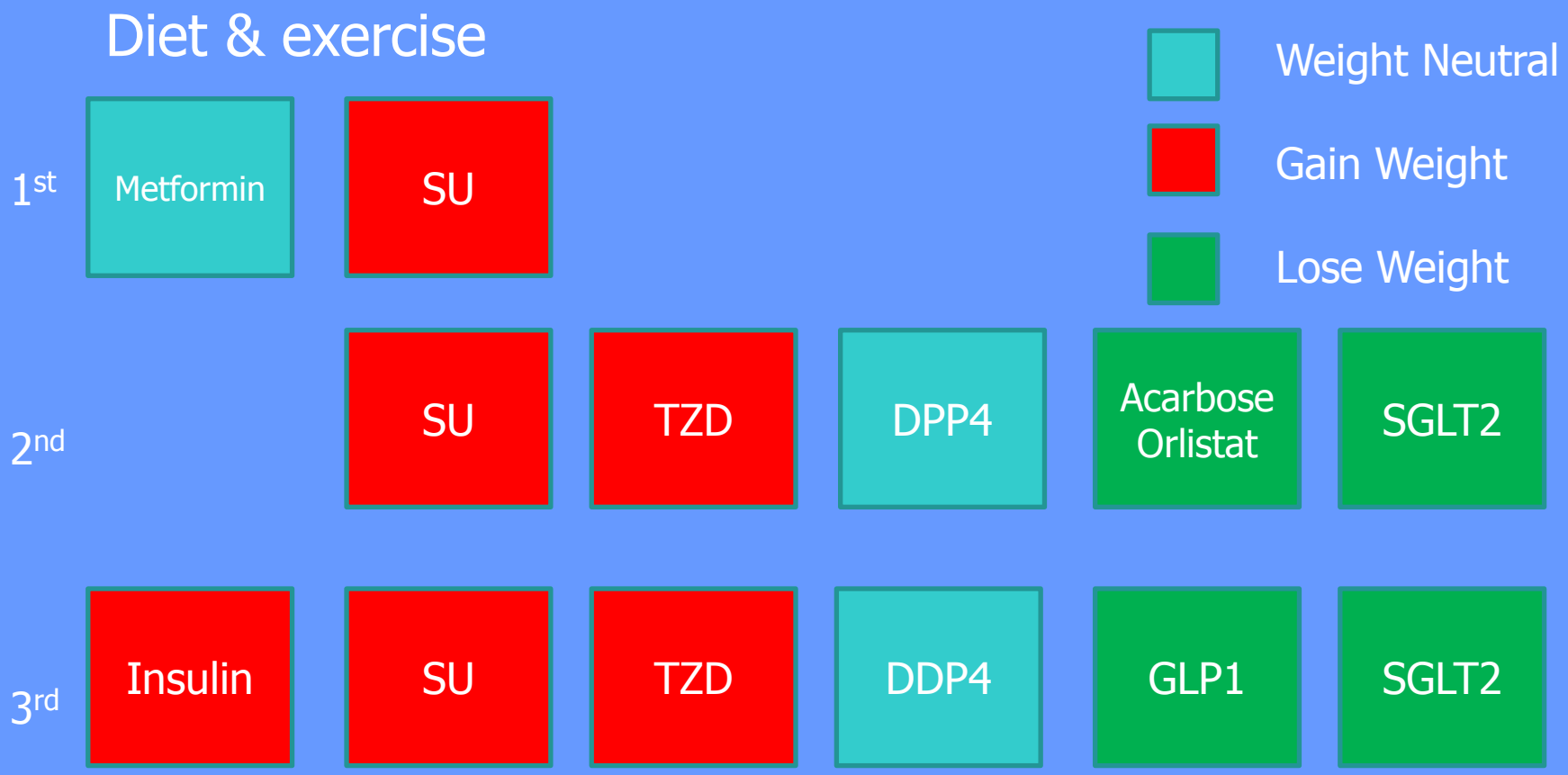
Glycosuria if > 10 mmol/L

May lose 50gm glucose

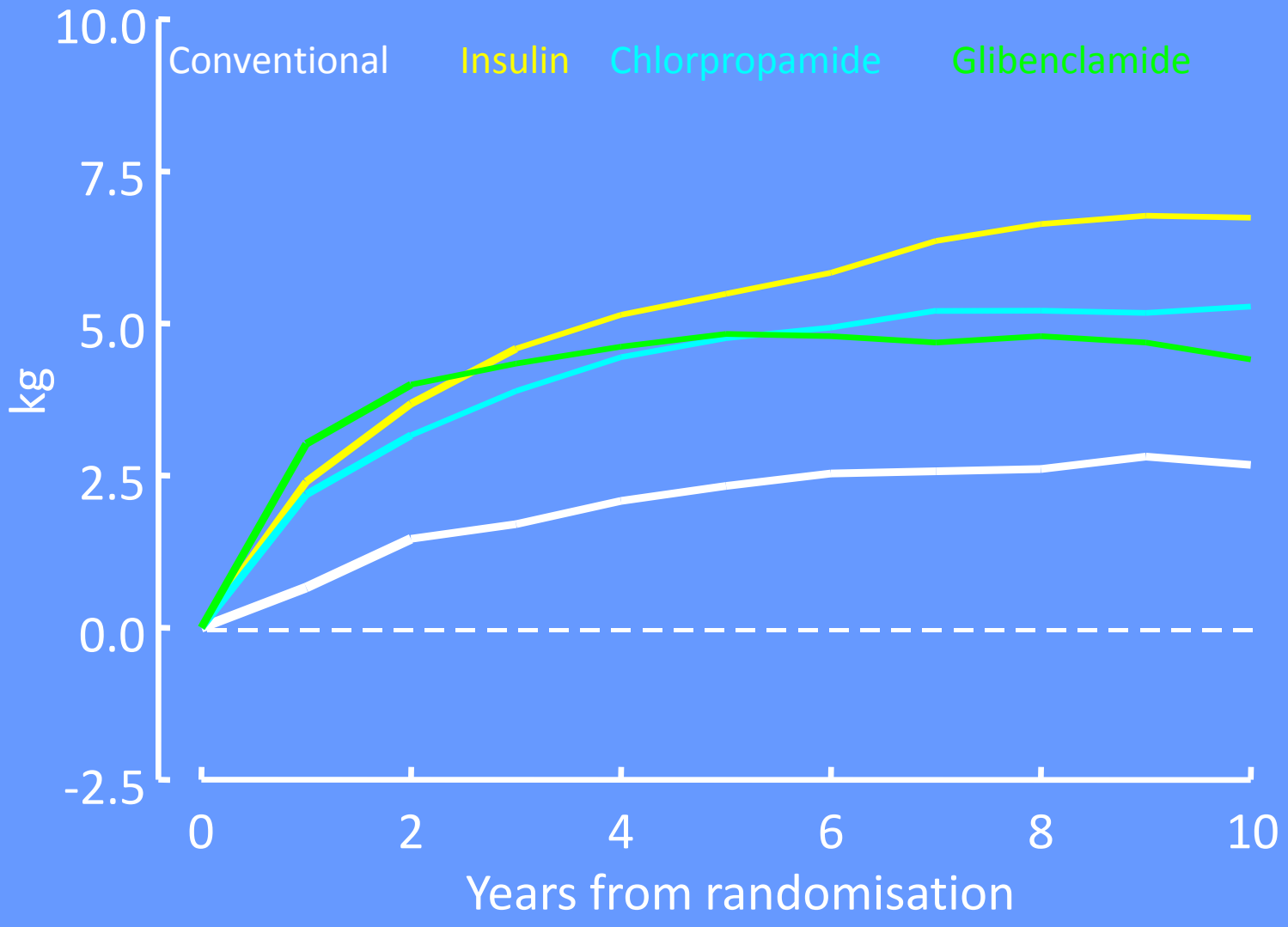
- 200 calories
- More than a can of pop

20 grams glucose per litre

Treatment of Type 2 Diabetes



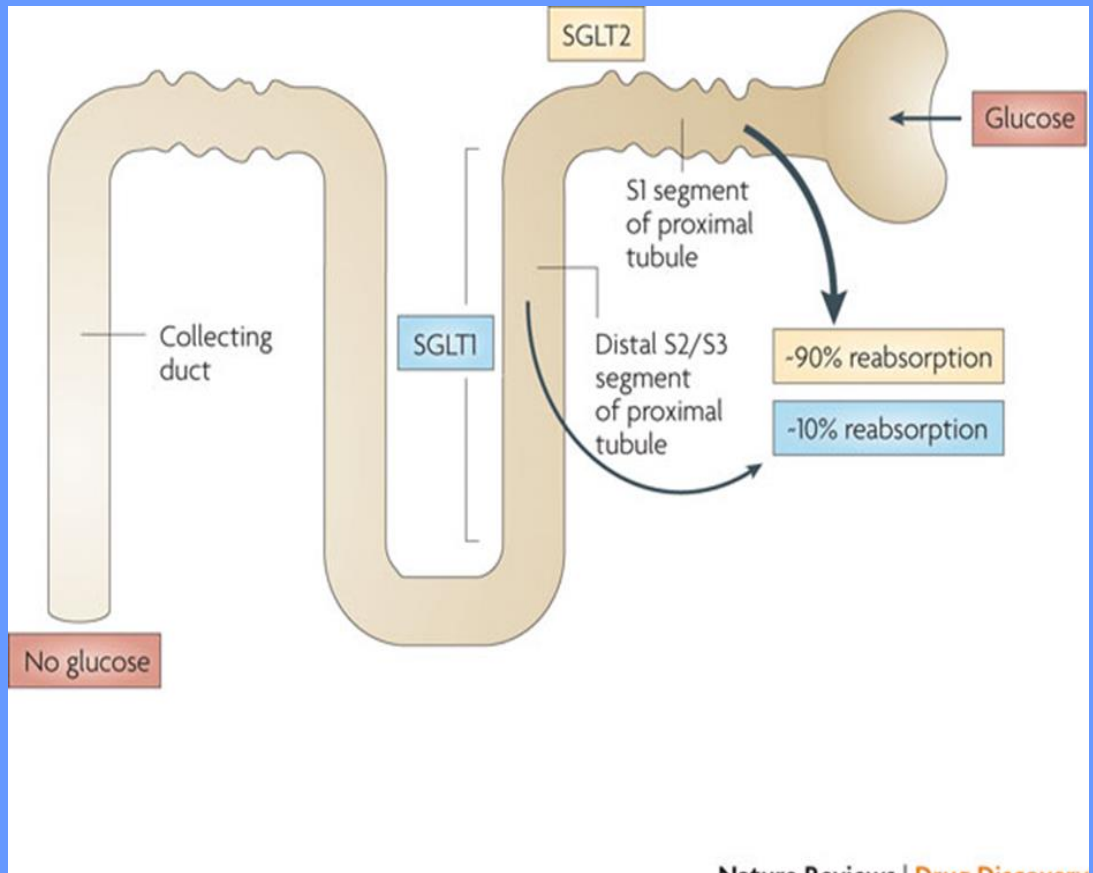
UKPDS: change in weight



UKPDS Study Group. Lancet 1998:352:854–865

Sodium Glucose Transporter 2 Inhibitors- SGLT2

- Kidney filters about 180g glucose per day
- With normal glucose levels
  - 90% reabsorbed by SGLT2
  - 10% reabsorbed by SGLT1



SGLT 2 Inhibitors

Pros

- Action independent of insulin
  - No hypoglycaemia
- Result in Glycosuria
  - Typically 70g Glucose per day (250 cals)

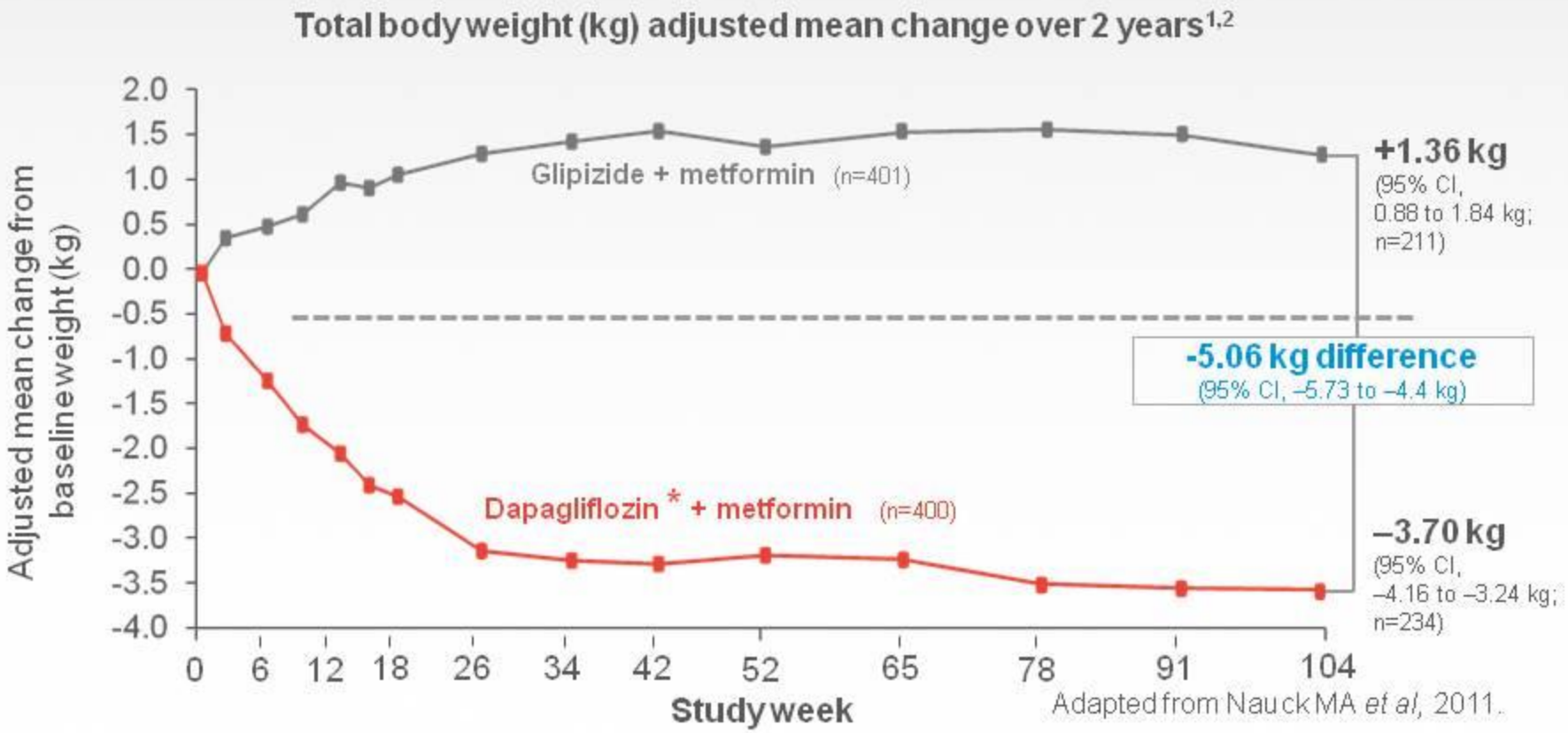
Cons

- Increased risk UTI & Thrush
- Increased urine output
- Risk ketoacidosis

- May prevent renal impairment

- If less renal function, less glucose lost in urine

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.

Medical Tx: long term outcomes

- Disappointing
  - Maintaining weight loss difficult
- Long term treatment helps
  - Expensive
  - Motivation
- Psychological treatment / CBT
  - Improves weight loss
  - Very little access

Summary

- Weight loss is hard
- For people with diabetes comsider medications
- Medical therapies are
  - OK for 10-15% weight loss in short term
  - Less reliable longer term
  - Expensive
- Bariatric surgery very effective

Thank You

Any Questions?