Are we treating a patient with obesity complicated by diabetes or a patient with diabetes complicated by obesity?

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Disclaimer

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Overall Context

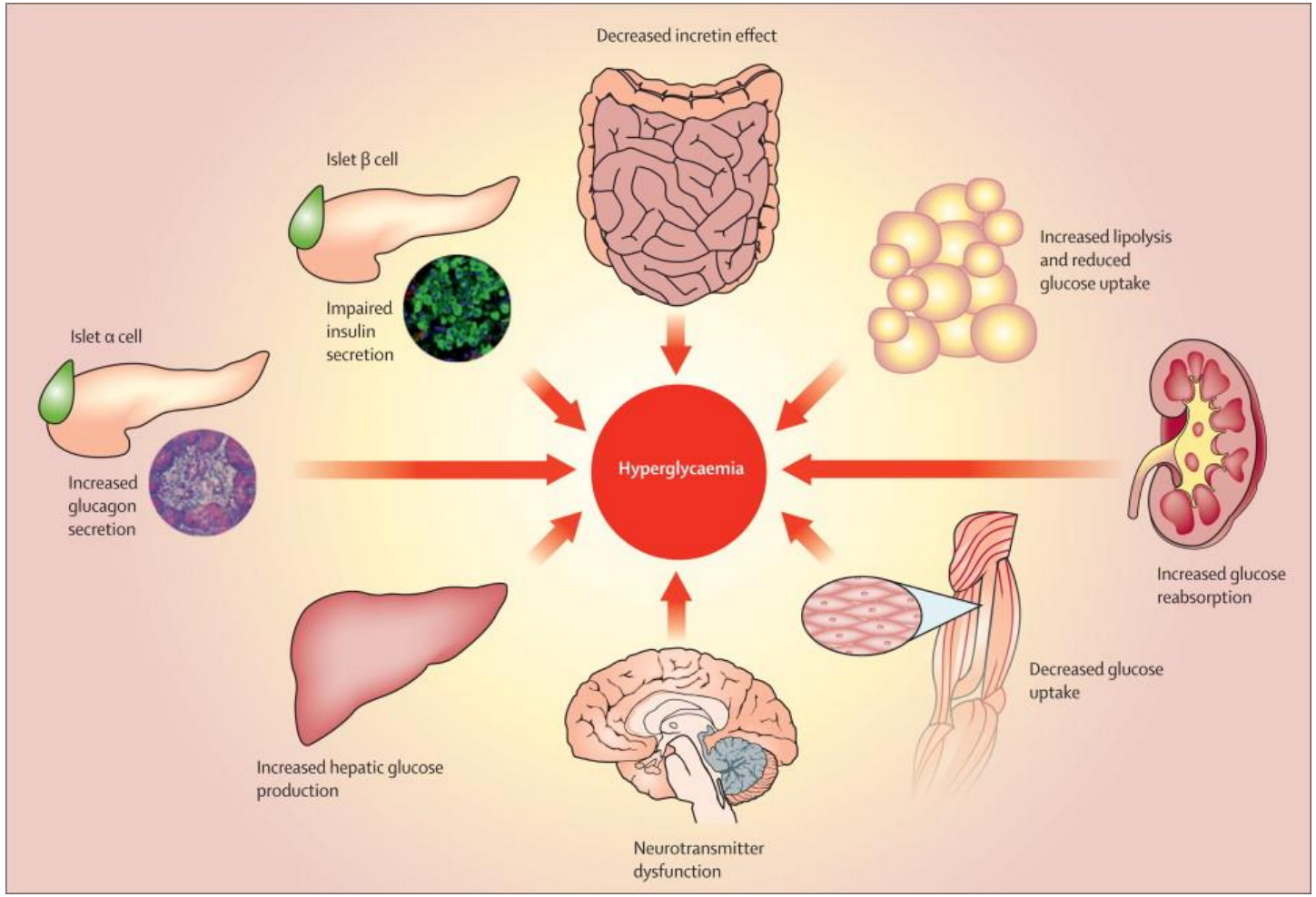
- A 40 year old woman with a BMI of 40 kg/m2 and Type 2 diabetes for 5 years on metformin monotherapy. HbA1c 7.4%.
- A 40 year old woman with a BMI of 31 kg/m2 and Type 2 diabetes for 7 years on metformin and insulin therapy (failed previous oral therapy). HbA1c 8.5%
- Are these two patients the same?
- Do they have the same “obesity”?
- Do they have the same Type 2 diabetes?
- Is the treatment for diabetes the same?
- Should treatment focus on glycaemic control or “obesity control”?

Overview

- Type 2 diabetes pathogenesis (insulin resistance and β-cell failure)
- The relationship between the pathogenesis and pharmacotherapy of Type 2 diabetes
- Not all the fat is the same (visceral vs. subcutaneous; brown vs. white)
- Impact of diabetes treatment on weight
- Weight control vs. glycaemic control in relation to diabetes-related outcomes

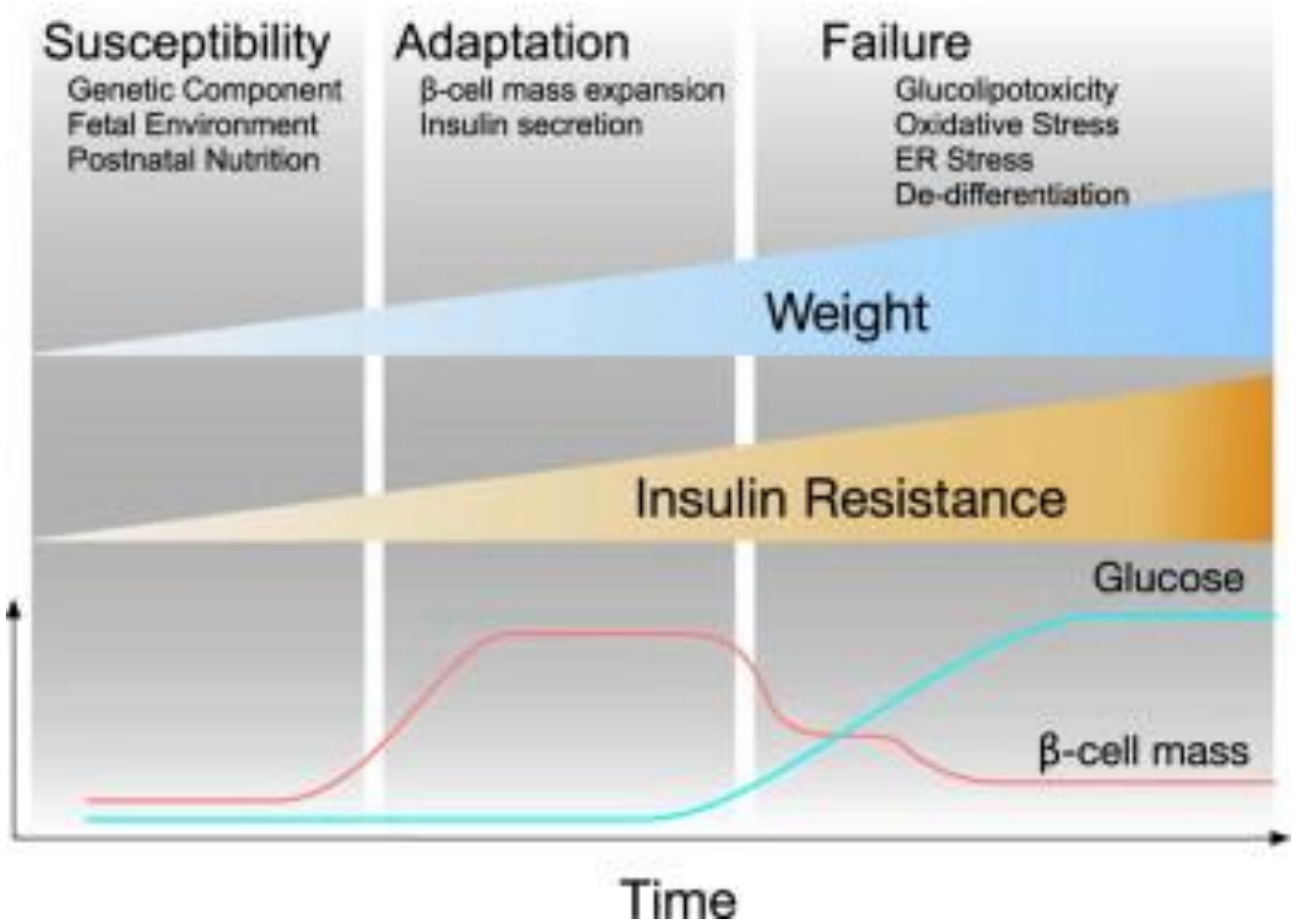
Pathogenesis of Type 2 Diabetes

Pathogenesis of Type 2 Diabetes



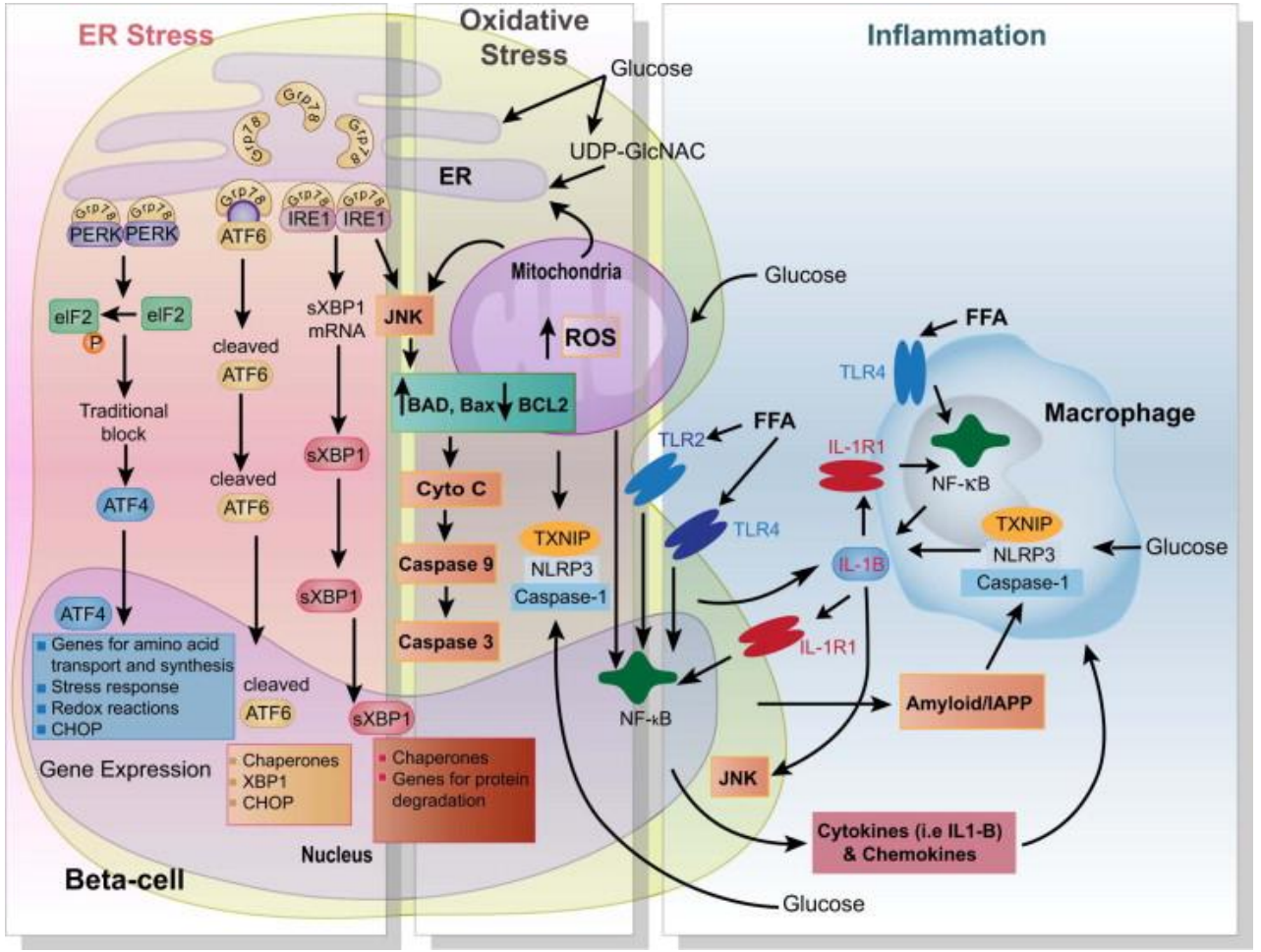
Tahrani et al. The Lancet Volume 378, Issue 9786, 2011, 182–197

Natural history of β-cell adaptation and failure in type 2 diabetes



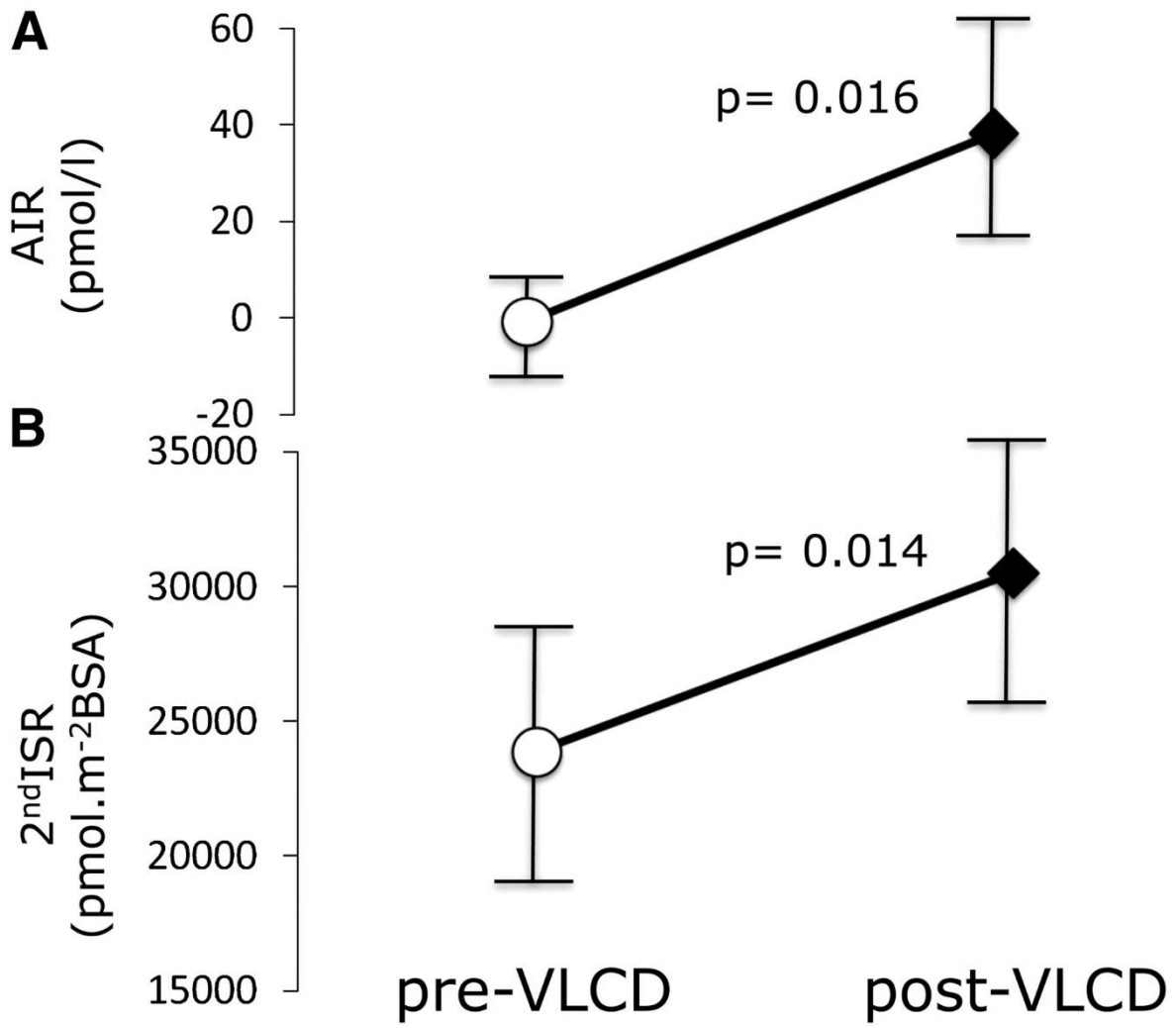
Alejandro et al. Molecular Aspects of Medicine, Volume 42, 2015, 19–41

Mechanisms of β-cell Failure in T2D



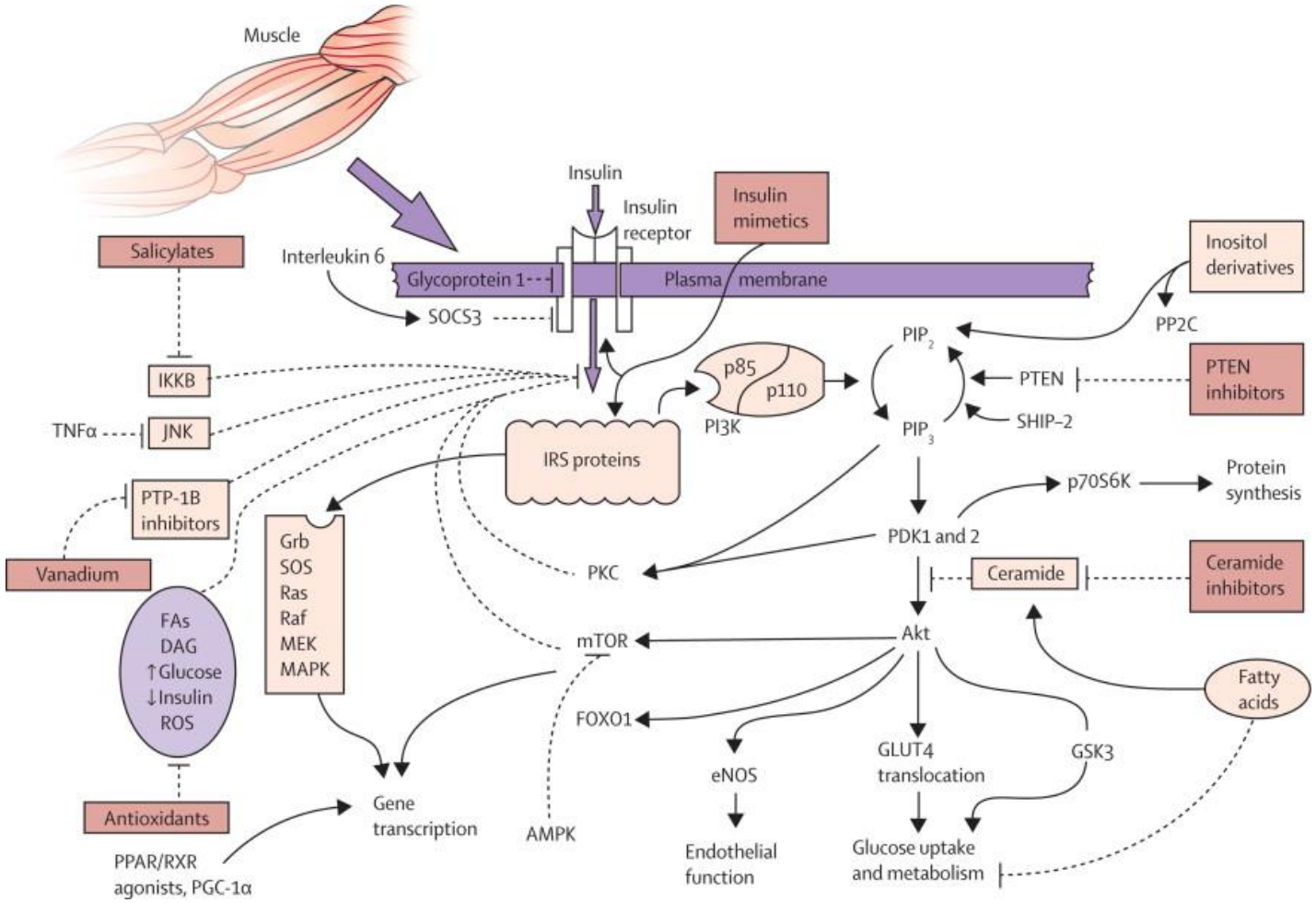
Alejandro et al. Molecular Aspects of Medicine, Volume 42, 2015, 19–41

Mean (±SEM) AIR (A) and 2ndISR (B) in response to a VLCD. n = 14 in each panel.



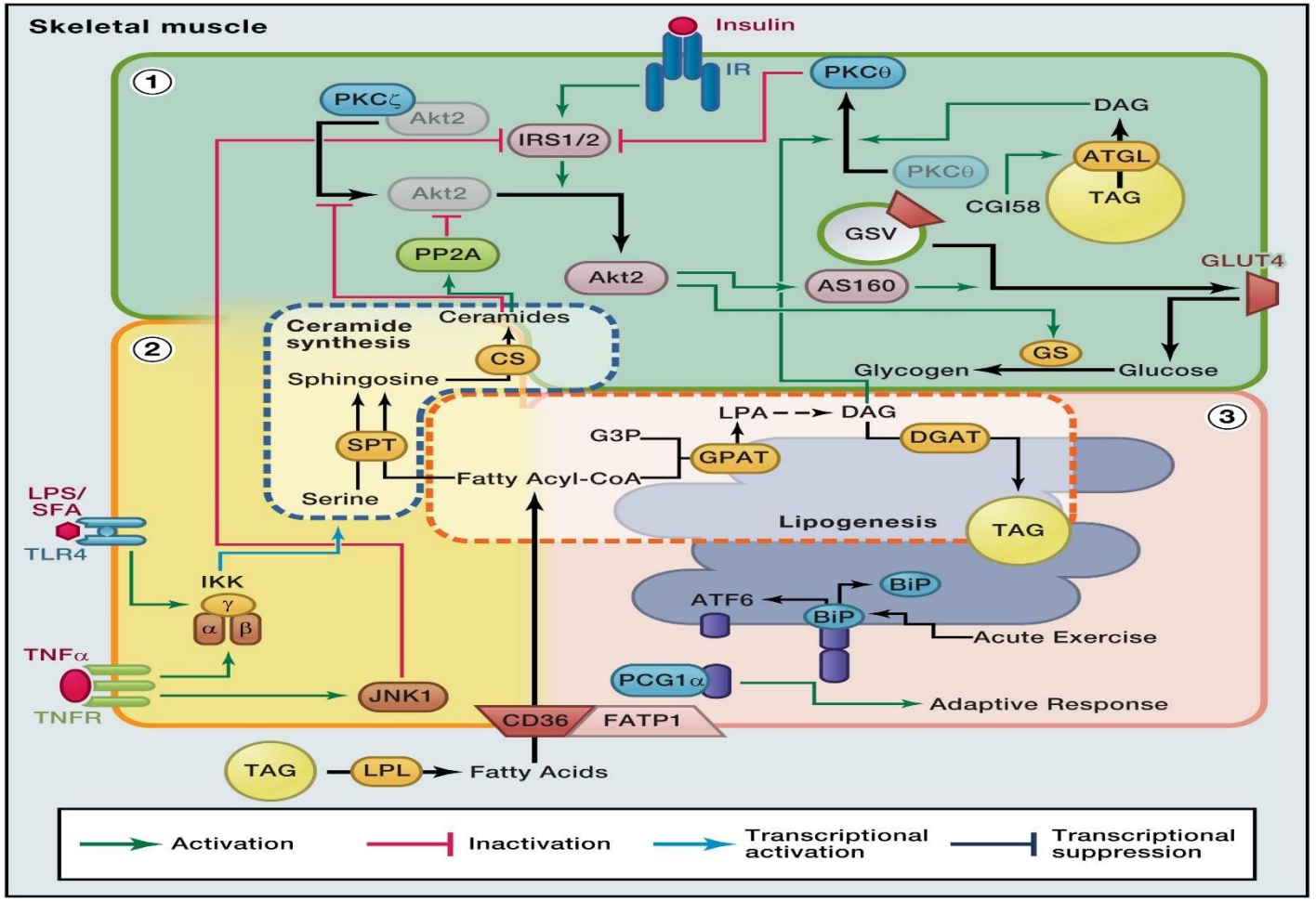
Ilaria Malandrucco et al. Am J Clin Nutr 2012;95:609-613

Insulin Signalling



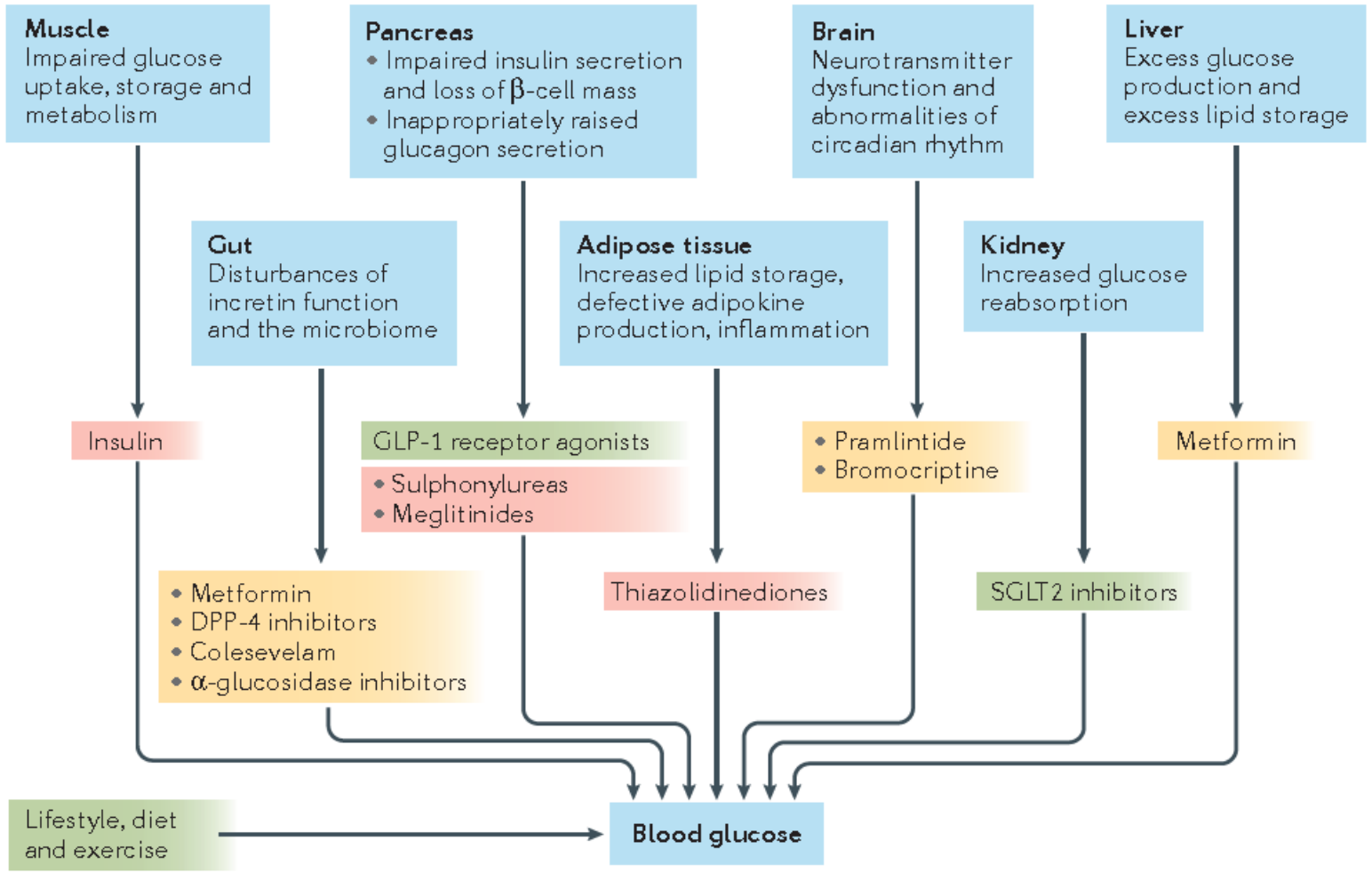
Tahrani et al. The Lancet Volume 378, Issue 9786, 2011, 182–197
Altaf & Tahrani Diabetes, obesity & metabolism, 17 (4). pp. 319-34

Mechanisms of Insulin Resistance in T2D



Samuel et al. Cell 2012 148, 852-871

T2D Pharmacology



Tahrani et al. Nature Reviews in Endocrinology 2016 In Press

Very-Low-Calorie Diet and 6 Months of Weight Stability in Type 2 Diabetes: Pathophysiologic Changes in Responders and Nonresponders

Sarah Steven, Kieren G. Hollingsworth, Ahmad Al-Mrabeh, Leah Avery, Benjamin Aribisala, Muriel Caslake, Roy Taylor

Diabetes Care 2016 Mar; dc151942. http://dx.doi.org/10.2337/dc15-1942

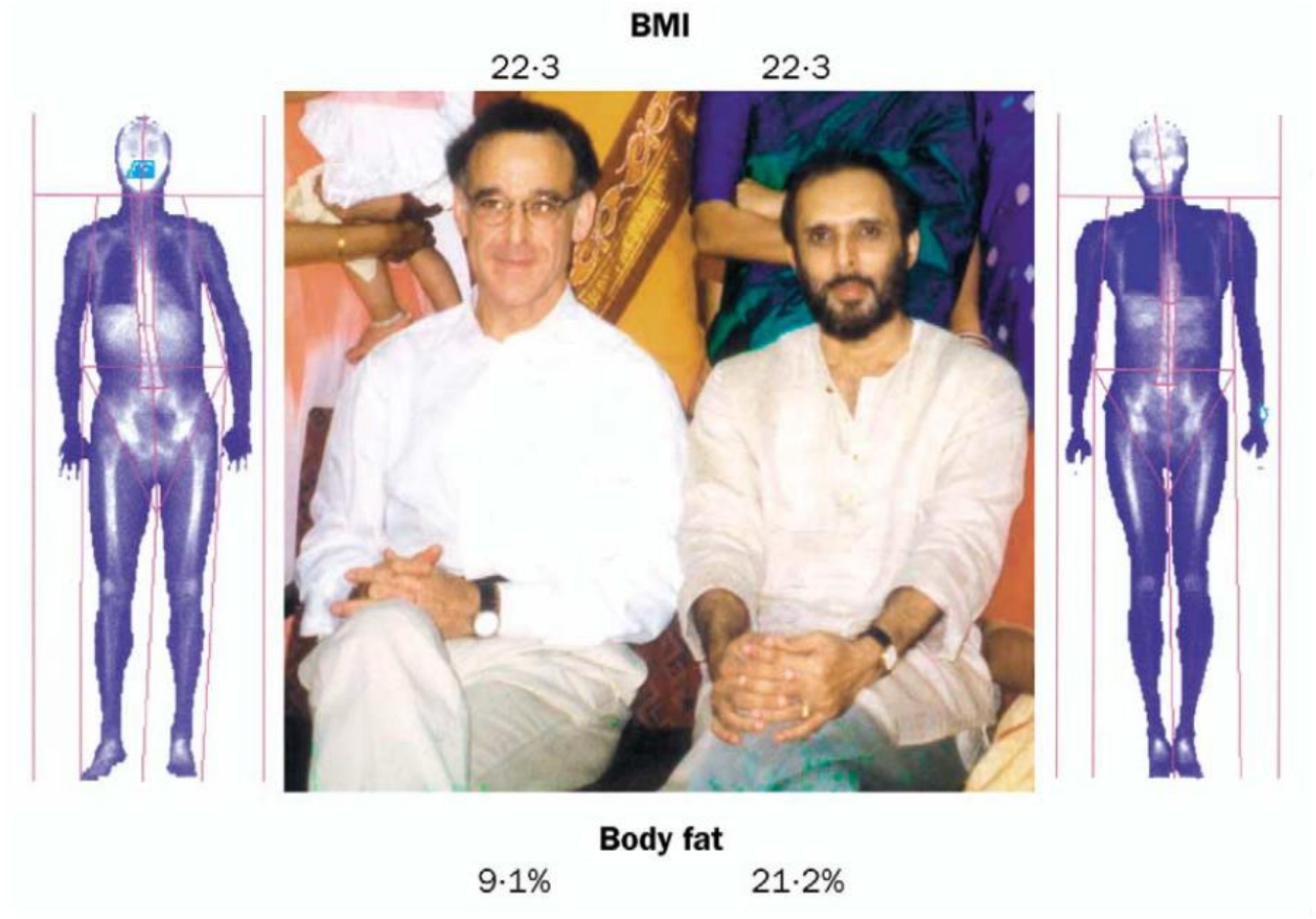
- A 40 year old woman
- BMI of 40 kg/m2
- Type 2 diabetes for 5 years
- metformin monotherapy.
- HbA1c 6.8%.

- A 40 year old woman
- BMI of 31 kg/m2
- Type 2 diabetes for 10 years
- metformin and insulin therapy.
- HbA1c 8.5%.

Does β-cell failure and insulin resistance contribute similarly to the pathogenesis of Type 2 Diabetes in these two patients?

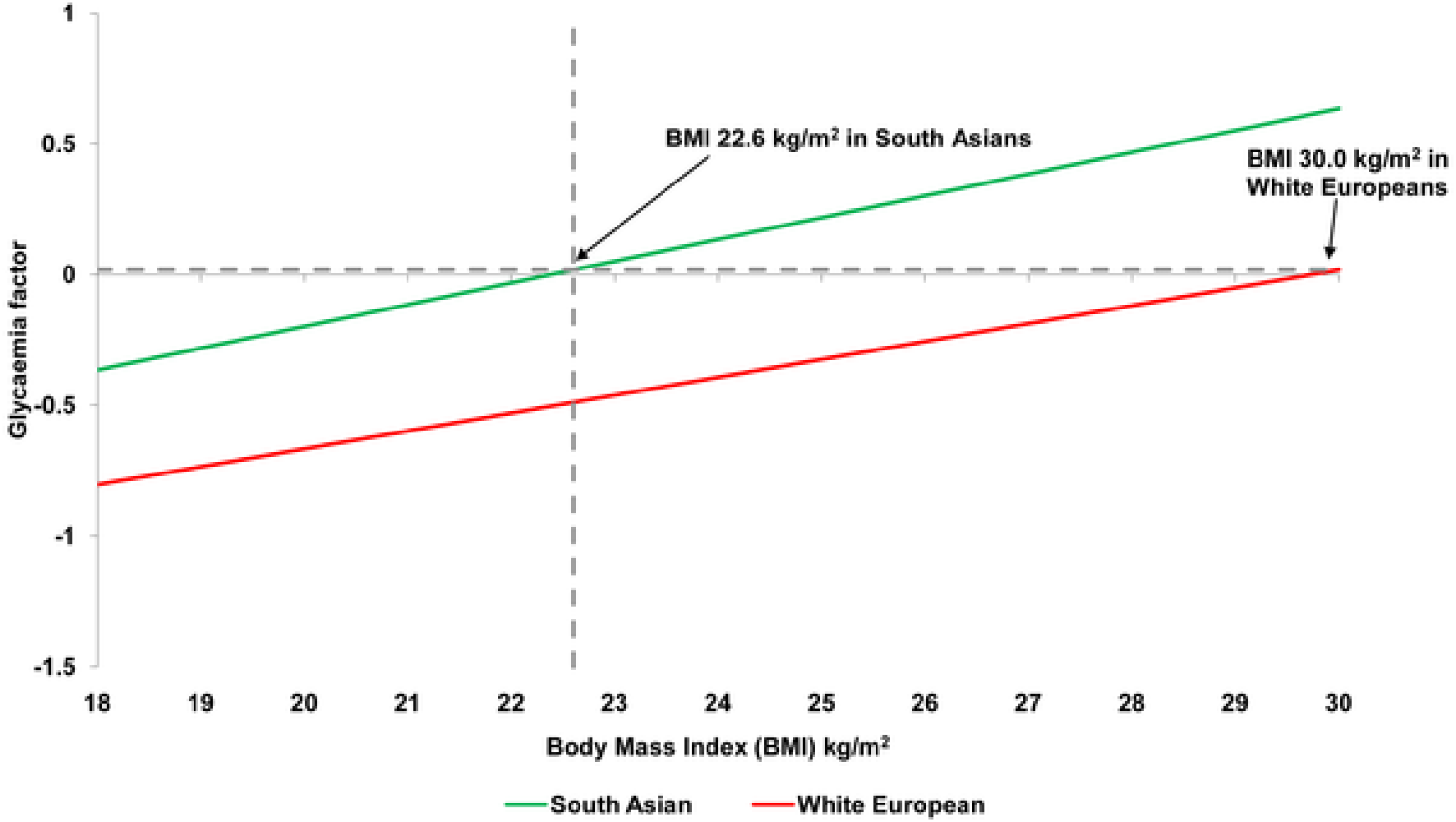
Not All Fat Is The Same…

Ethnicity



Yajnik et al. Lancet 2004

Figure 1. Relationship between glycaemia factor and BMI among White European and South Asian males.



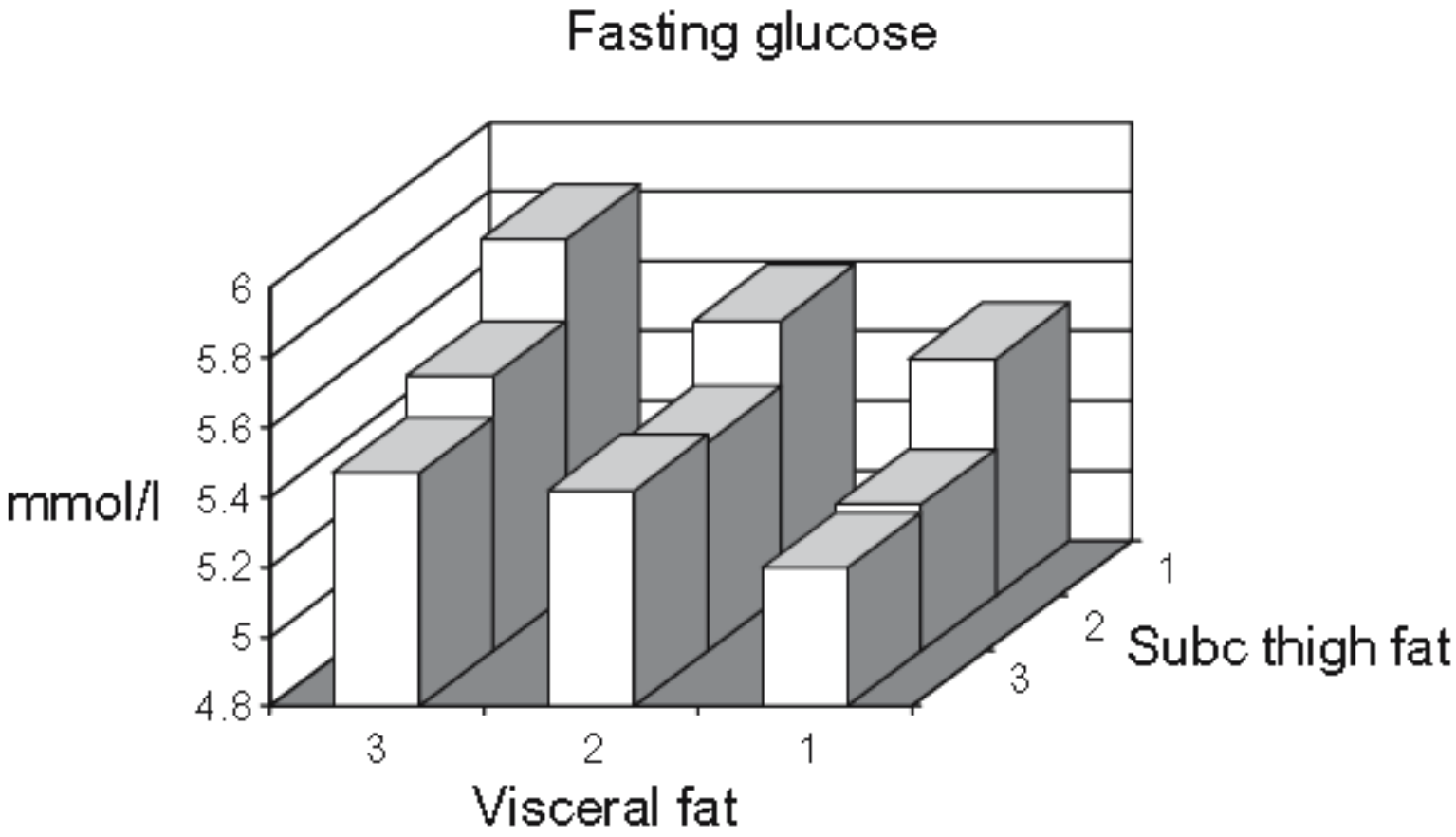
Gray LJ, Yates T, Davies MJ, Brady E, Webb DR, et al. (2011) Defining Obesity Cut-Off Points for Migrant South Asians. PLoS ONE 6(10): e26464.

Visceral vs. Subcutaneous Fat & Future IR

	Log_e (10-year HOMA-IR)		
Independent variables from baseline in the model	β	β′	*P*
Model 1			
Intra-abdominal fat area	0.00272	0.237	0.002
Abdomen subcutaneous fat area	0.00052	0.076	0.256
HOMA-IR	0.12450	0.378	<0.001
Fasting plasma insulin	—	—	—
Incremental insulin response	0.00017	0.014	0.799
2-h plasma glucose	−0.03071	−0.095	0.072
Age	−0.00261	−0.061	0.281
Female sex	−0.08949	−0.089	0.158

Hayashi et al. Diabetes 2008 May; 57(5): 1269-1275

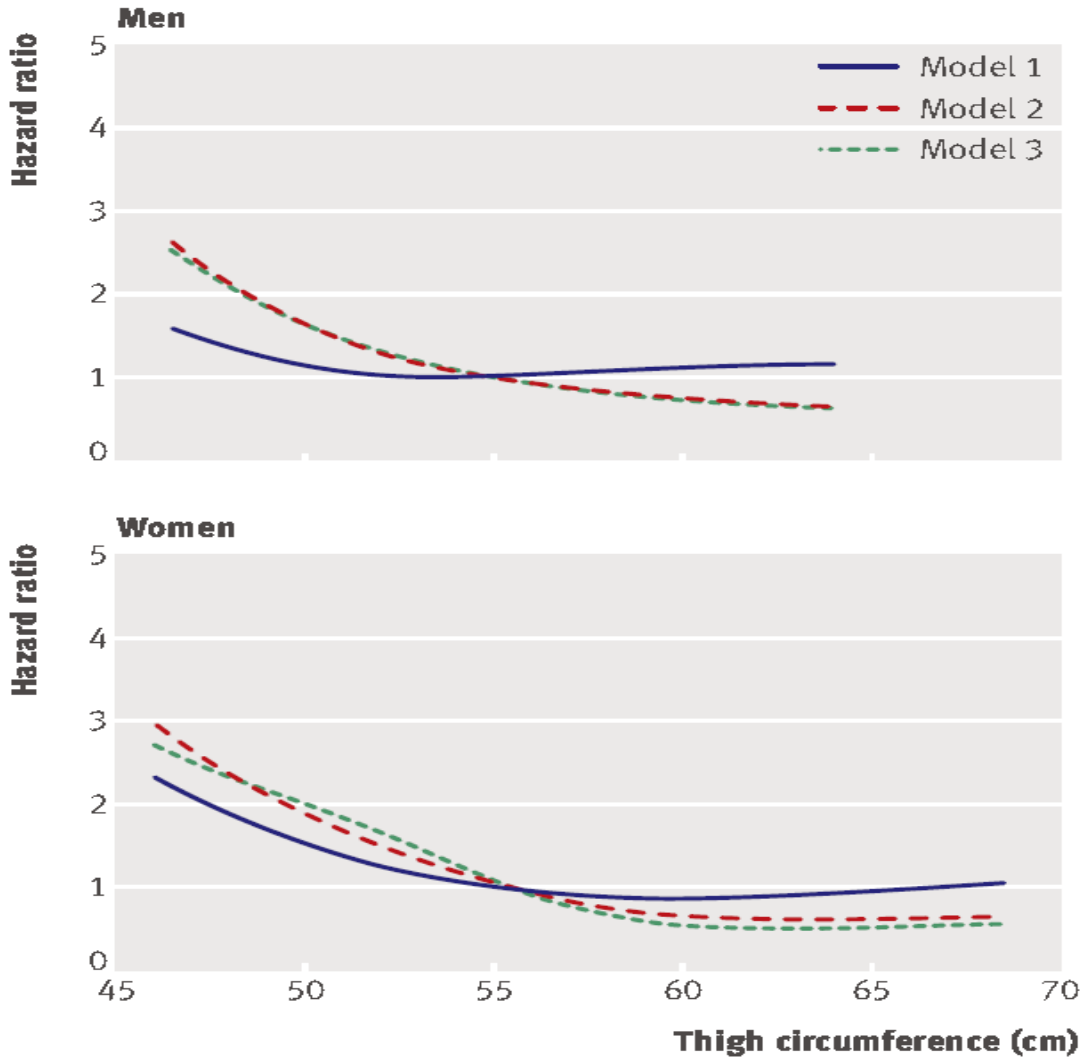
Visceral vs. Thighs Fat



Snijder et al. Diabetologia February 2005, Volume 48, Issue 2, pp 301-308

Visceral vs. Thigh Fat & CVD Mortality

Model 1 adjusted for smoking status,
education, physical activity, and menopause in women;
model2 additionally adjusted for baseline BMI and waist circumference;
model 3 additionally adjusted for body fat %
and body height



Heitmann et al. BMJ. 2009 Sep 3;339:b3292

Changes in Visceral Fat Predicts Incident T2D

Table 3—*Odds of incident diabetes at 10-year follow-up*

Model	Variable	OR (95% CI)*
Minimally adjusted model (model 1)	Baseline IAF	1.52 (1.02–2.28)
	Change in IAF	1.52 (1.17–1.98)
Adjusted for above and thoracic SCF, thigh SCF, abdominal SCF, and generation** (model 2)	Baseline IAF	1.53 (1.00–2.34)
	Change in IAF	1.53 (1.17–2.01)
Adjusted for above and change in weight, alcohol consumption, smoking status, and activity level (model 3)	Baseline IAF	1.64 (1.06–2.53)
	Change in IAF	1.65 (1.21–2.25)
	Change in weight	0.95 (0.66–1.35)

All models adjusted for age, sex, family history, BMI, and baseline IAF. *ORs for continuous variables reflect a 1-SD magnitude increase ± SD for means or proportions shown. **Second-generation Japanese American (Nisei) compared with third-generation Japanese American (Sansei).

Wander et al. DIABETES CARE, VOLUME 36, FEBRUARY 2013

- A 40 year old WE woman
- BMI of 35 kg/m2
- Type 2 diabetes for 5 years
- metformin monotherapy.
- HbA1c 7.3%.
- No CVD

- A 40 year old SA woman
- BMI of 31 kg/m2
- Type 2 diabetes for 7 years
- metformin and insulin therapy.
- HbA1c 8.5%.
- History of Angina

Which patient is more “obese”?

Could differences in fat distribution explain differences in clinical picture?

Glucose Lowering Treatments And Weight…

Weight gain

Drug class	Mode of action on body weight	Impact on body weight
Drugs associated with weight gain		
Insulins	Insulin promotes fat storage, inhibits lipolysis, leading to	
Prandial	increased body fat mass	+6.4 kg (6)
Biphasic	Central effect of insulin on appetite regulation, which	+5.7 kg (6)
Basal (detemir)	may be impaired in type 2 diabetes	+3.6 kg (6); −0.2 BMI units less than glargine (9)
Glargine	Decreased glucosuria resulting in more glucose calories	+2.1 kg (7)
NPH	reabsorbed	+7 kg (12); +0.2 BMI units more than detemir (9)
Sulfonylureas	Overcorrection or prevention of hypoglycemia with food	
First generation (chlorpropamide 500 mg QD)		+5.5 kg (15)
Second-generation (glyburide 5 to 10 mg BID)		+2.6 kg (15)
Third-generation (glimeperide 4 to 8 mg QD)		+1.1-2.1 kg (15)
(gliclazide MR 30 to 60 mg QD)		+1.8 kg (15)
Meglitinides	Overcorrection or prevention of hypoglycemia with food	+0.3 kg (15)
Repaglinide (0.5 to 4 mg TID)		
Nateglinide (60 to 180 mg TID)		
Thiazolidinediones (TZDs)	Increase total body fat, with redistribution from visceral	
Rosiglitazone (4 to 8 mg QD)	to subcutaneous	+4.8 kg (13)
Pioglitazone (15 to 30 mg QD)	Increased fluid retention	+2.6 kg (15)

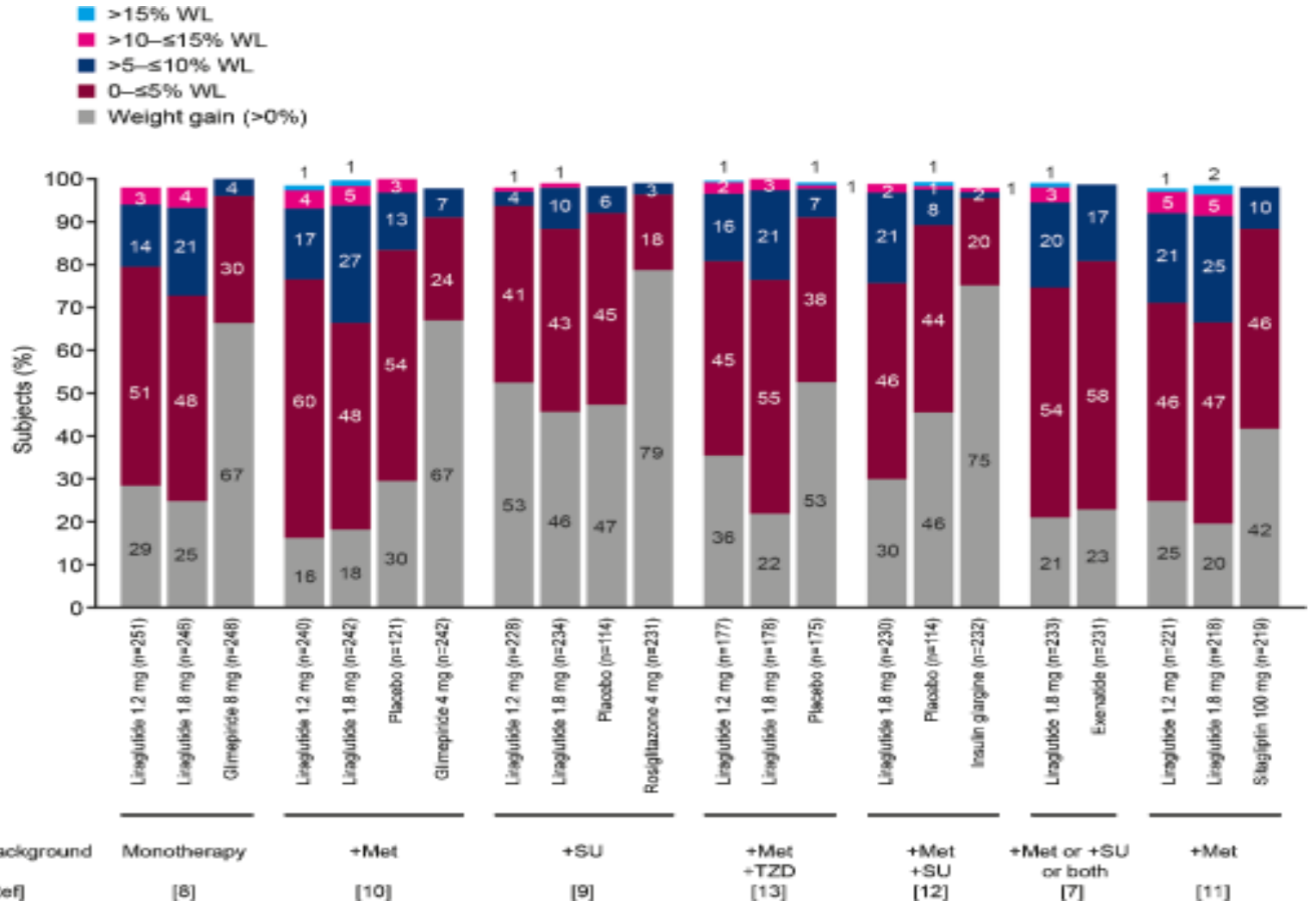
Lau et al. Can J Diabetes 39 (2015) S148–S154

Weight Neutral/Weight Loss

Alpha-glucosidase inhibitors	Decreased carbohydrate digestion and absorption with	−0.4–1.8 kg (35, 39
Acarbose (50 to 100 mg TID)	less caloric intake	
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Decreased food intake and fat absorption	−0.4 kg (39)
Sitagliptin (25 to 100 mg QD)		+0.55 kg (15)
Saxagliptin (2.5 to 5 mg QD)		
Linagliptin (5 mg QD)		
Alogliptin (10 mg QD)		
Drugs associated with weight loss		
Lipase inhibitor	Decreased fat digestion and absorption, with 30% less fa	−1.9 kg (1.9%) (22)
Orlistat (120 mg TID)	calorie intake	
Biguanides	Inhibits hepatic glucose production, but also has effect	−1.1 kg (15)
Metformin	on muscle insulin sensitivity	
	Nausea	
GLP-1 receptor agonists	Reduced gastric emptying	−2.8 kg (15, 24)
Exenatide (10 μg sc BID)	Central inhibitory effect on appetite and food intake	−2.8 kg (14)
Liraglutide (0.6 to 1.8 mg sc QD)		−3.2 kg (14)
Sodium-glucose cotransporter-2 inhibitors	Decreased glucose calories through increased glucosuria	(25,26,40)
Canagliflozin (100 to 300 mg QD)		−2.3–3.3 kg (27)
Dapagliflozin (5 to 10 mg QD)		−1.8–2.4 kg
Empagliflozin (25 to 50 mg QD)		−2.3–2.5 kg

Lau et al. Can J Diabetes 39 (2015) S148–S154

Variation in Weight Loss with GLP-1 RA



Niswender at al. Diabetes, Obesity and Metabolism Volume 15, Issue 1, pages 42-54, 9 SEP 2012

Does it matter if patients with T2D gained weight?

- For a 1 unit increase in BMI during follow-up, the RR of CHD was 1.13 (1.04-1.23; p = 0.005) after 5.6 years (adjusted for age, sex, diabetes duration, hypoglycaemic treatment and smoking, HbA1c, blood pressure, antihypertensive drugs, lipid-reducing drugs and microalbuminuria).
- Weight gain… leads to the frustration and may contribute to early discontinuation or decreased adherence.
- Weight gain might have contributed to the lack of beneficial impact of intensive glycaemic control on macrovascular disease (ADVANCE, ACCORD)

Eeg-Olofsson K et al. Diabetologia. 2009 Jan;52(1):65-73
Pi-Sunyer. Postgrad Med. 2009 Sep; 121(5): 94–107

- A 40 year old woman
- BMI of 40 kg/m2
- Type 2 diabetes for 10 years
- metformin monotherapy.
- HbA1c 7.3%.

- A 40 year old woman
- BMI of 31 kg/m2
- Type 2 diabetes for 10 years
- metformin and basal-bolus insulin therapy Previously failed SUs, TZDs, DPP-4 inhibitors).
- HbA1c 8.5%.

Is the obesity in these patients drug-induced?
Is there a different “weight friendly” approach?

In Patients With T2D: Glycaemic Control, Obesity Control, Or both?

Why Do We Treat Patients With T2D?

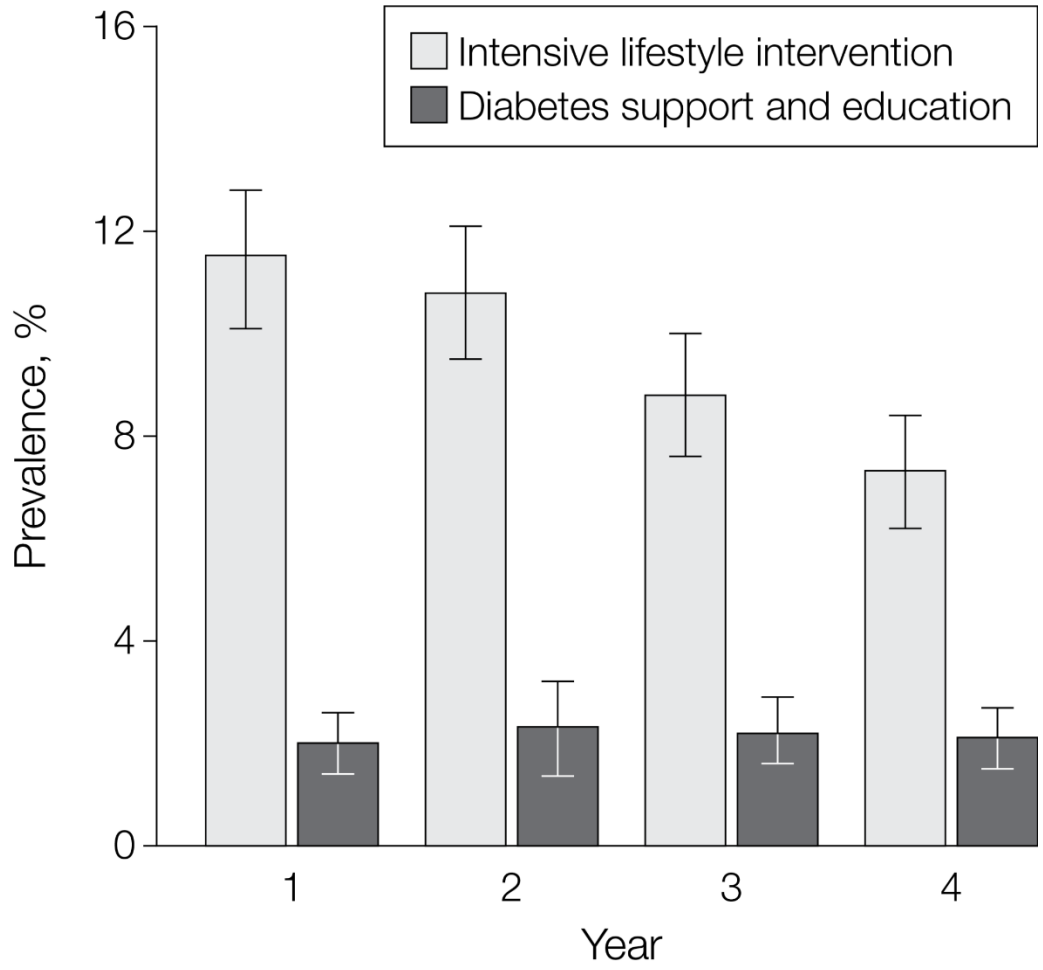
- Reduce Cardiovascular disease
- Reduce microvascular complications (end-stage renal disease, albuminuria, sight-threatening retinopathy, neuropathy, foot disease..etc.)
- Improve quality of life
- Reduce mortality

How do we achieve these aims?

- Lowering HbA1c
- Lowering BP
- Lowering LDL
- Use of ACEi, AR blockers, statins, anti-platelets… etc.

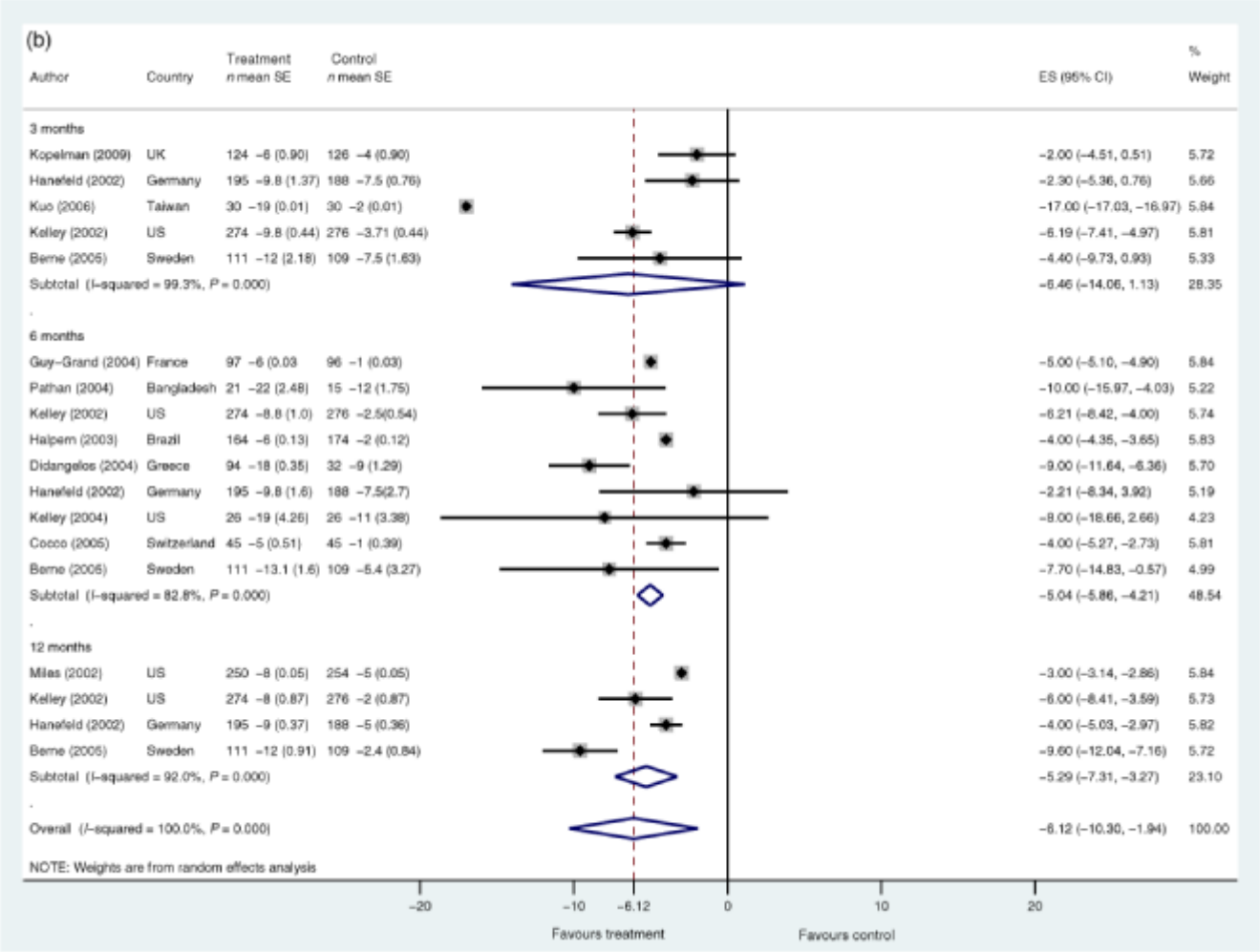
- What about controlling weight?

Intensive Lifestyle Intervention and Diabetes Remission



Gregg et al. JAMA. 2012 Dec 19;308(23):2489-96

Effect of orlistat on glycaemic control in overweight and obese patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials



Obesity Reviews
Volume 16, Issue 12, pages 1071-1080, 8 SEP 2015 DOI: 10.1111/obr.12318
http://onlinelibrary.wiley.com/doi/10.1111/obr.12318/full#obr12318-fig-0002

Bariatric surgery in T2D

	RYGB[19-21,24-27]	LAGB[18,24-28]	VSG[19,25,26,29]	BPD±DS[24-27]
Total bodyweight loss (%)	25–30%	15–25%	25–30%	30–40%
Absolute HbA_{1c} reduction (%)	2·1–2·9%	1·8%	2·9%	3·8%
Baseline HbA_{1c} (%)	8·6–9·3%	7·8%	9·5%	8·9%
30 day mortality (%)	<0·5%	<0·1%	<0·4%	<1·0%
Main surgical complications	Anastomotic leak, bleeding, stricture ulceration, internal herniation	Band slippage, erosion into the stomach, gastric pouch dilatation, band leak	Staple line leak, bleeding	Anastomotic leak, bleeding, stricture ulceration, internal herniation
Nutritional deficiencies	Trace metals, iron, folate, vitamin D, B12	Iron, folate, vitamin D, B12	Trace metals, iron, folate, vitamin D, B12	Protein, trace metals, iron, folate, vitamin A, D, E, K, B12
Risk	Moderate	Low	Moderate	High

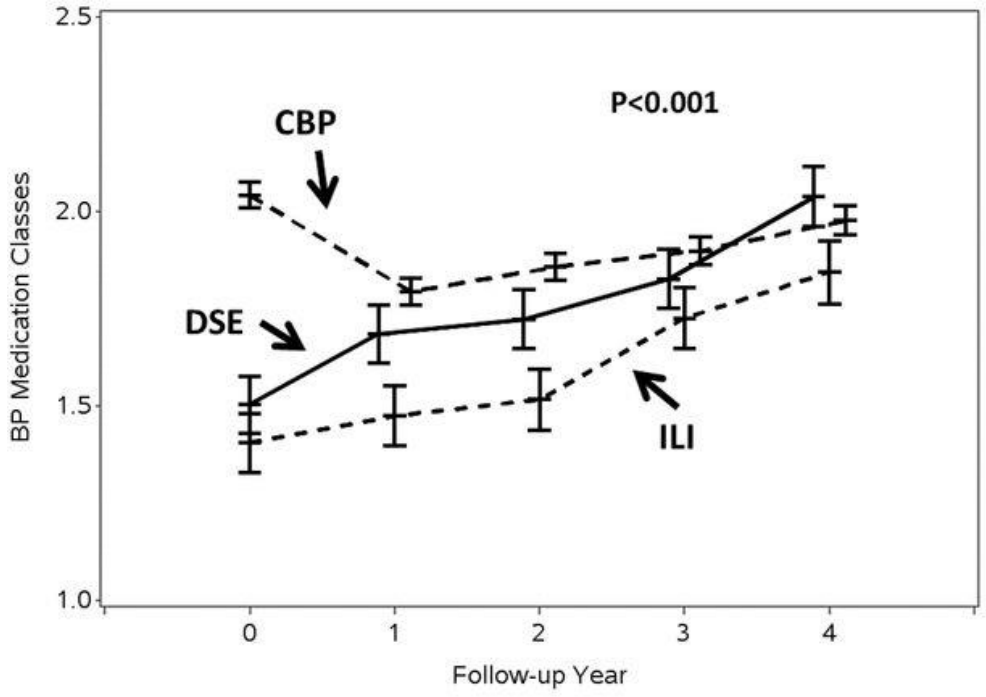
Data obtained from meta-analyses and systematic reviews. HbA_{1c} reductions refer only to patients with obesity and type 2 diabetes treated in randomised controlled clinical trials. Risk level is a gross categorical classification based on the references included in the table.

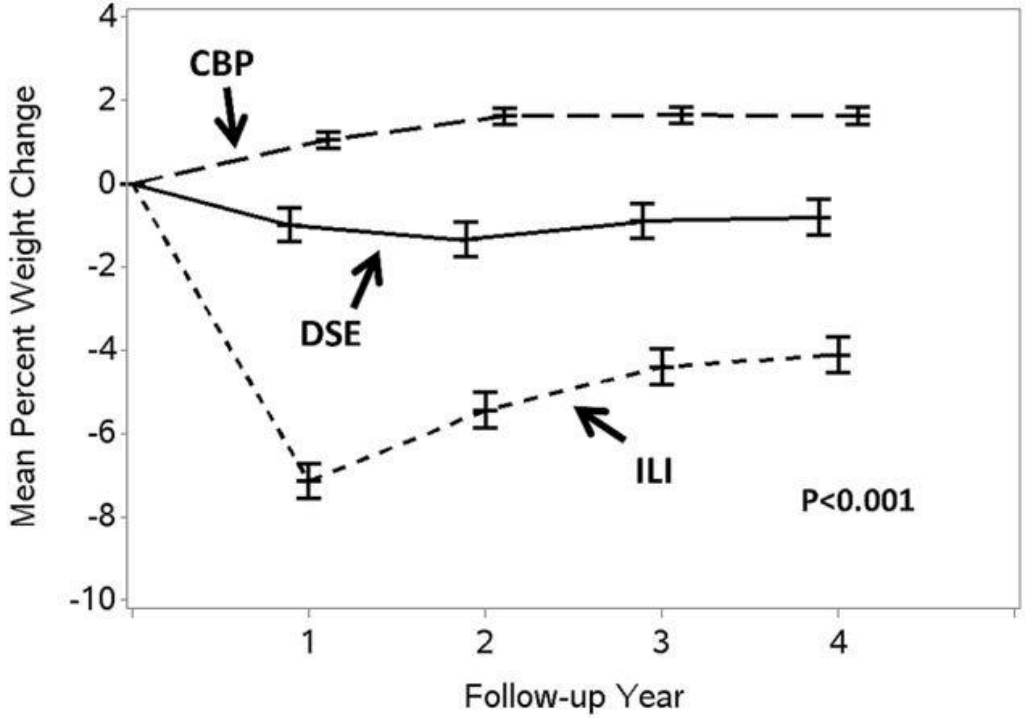
Table 1: **Clinical efficacy and complications after Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), vertical sleeve gastrectomy (VSG), and biliopancreatic diversion with or without duodenal switch (BPD±DS) in patients with obesity, type 2 diabetes, or both**

BPD±DS=Biliopancreatic diversion with duodenal switch

Miras et al. The Lancet Diabetes & Endocrinology 2014;2(2):141–151

Intensive Lifestyle Intervention and BP control in T2D

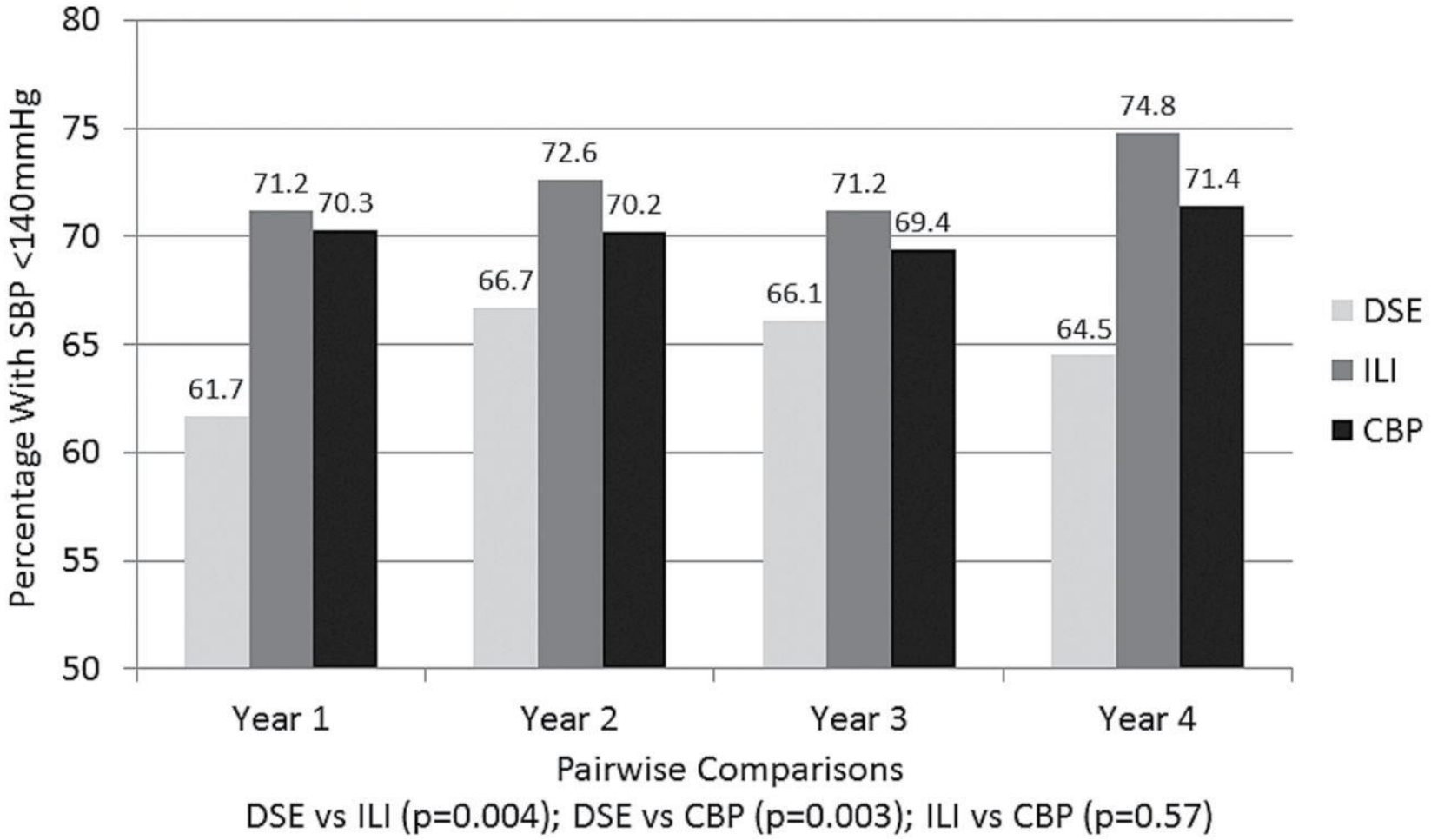




Mark A. Espeland et al. Am J Hypertens 2015;28:995-1009

American Journal of Hypertension

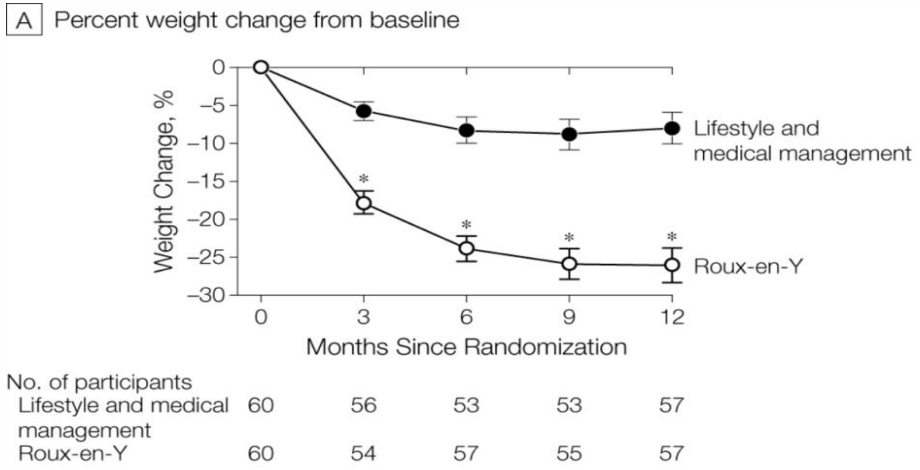
Percentage of participants with SBP <140mm Hg over time by intervention group.

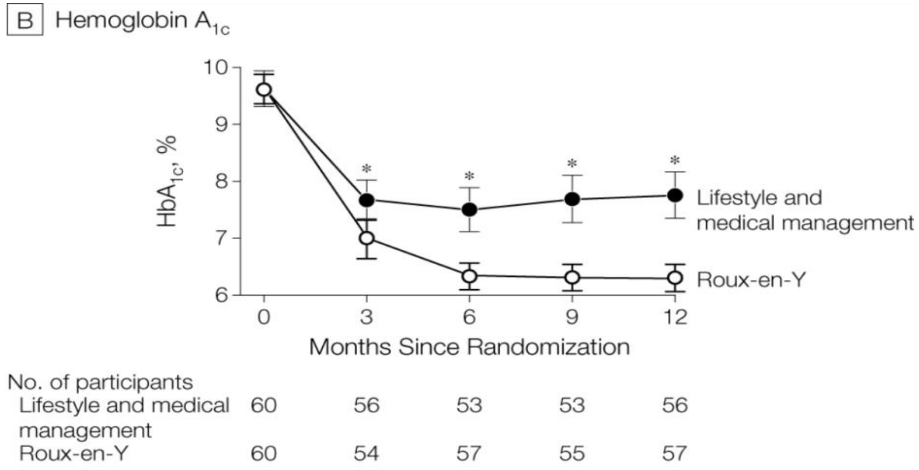


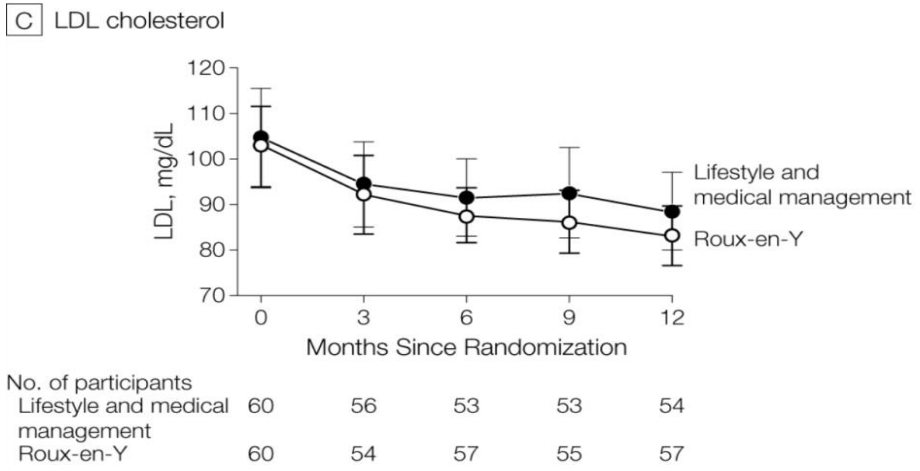
Mark A. Espeland et al. Am J Hypertens 2015;28:995-1009

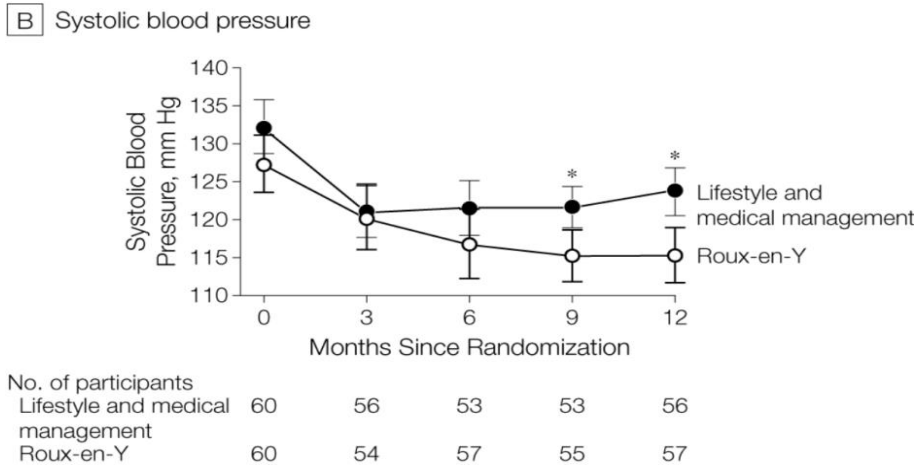
American Journal of Hypertension

Bariatric Surgery and BP in T2D







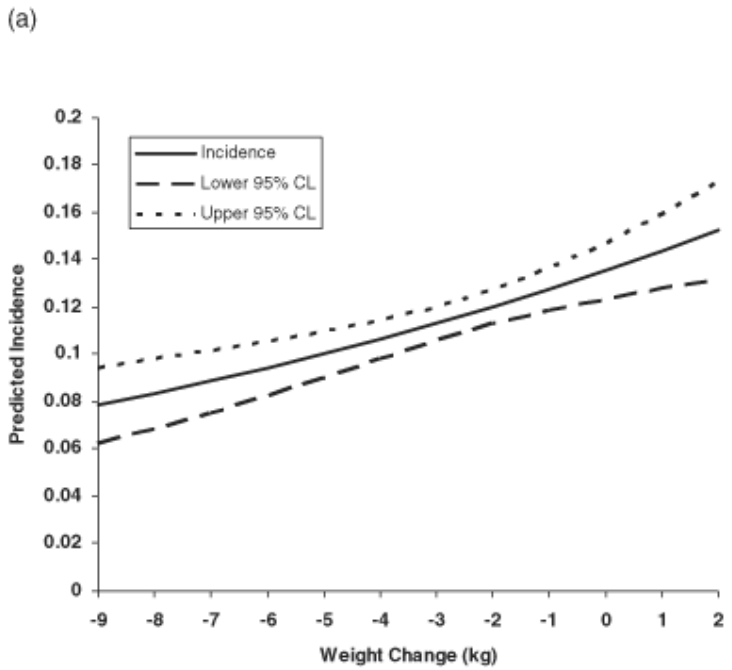


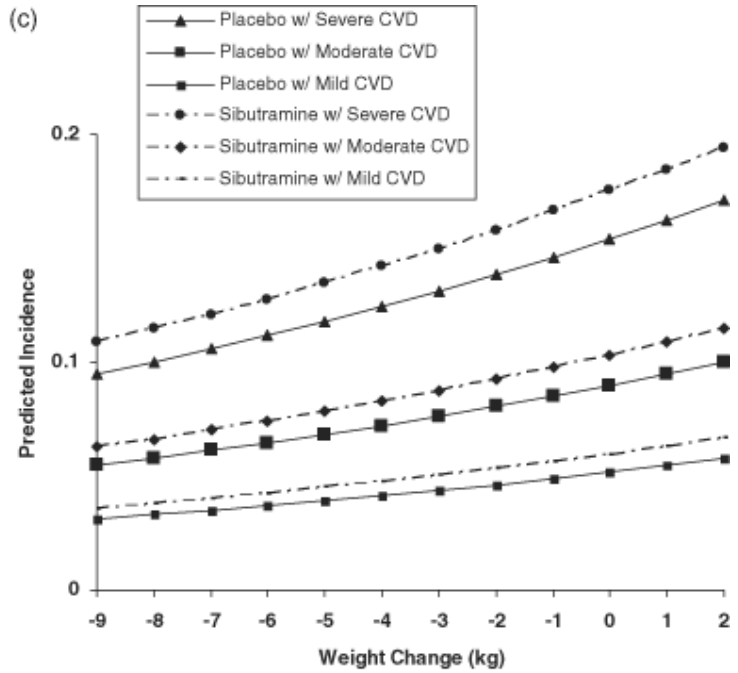
BS=Bariatric surgery, BP=Blood pressure

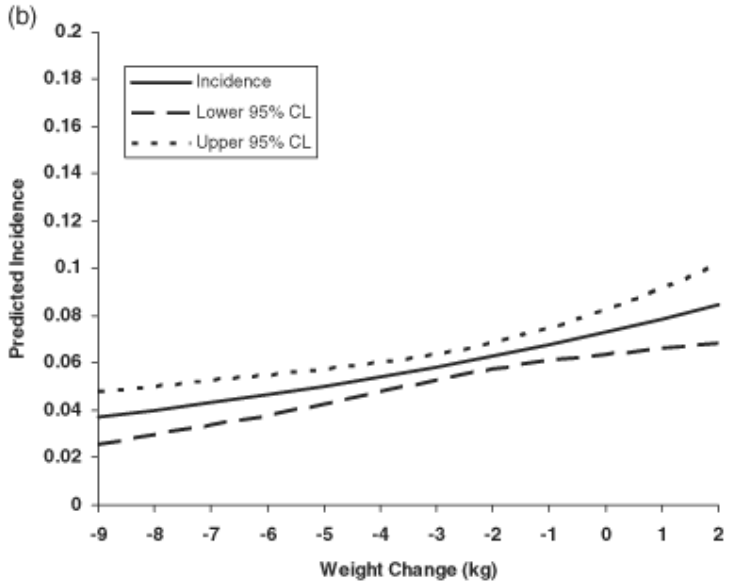
Ikramuddin et al. JAMA. 2013;309(21):2240–2249

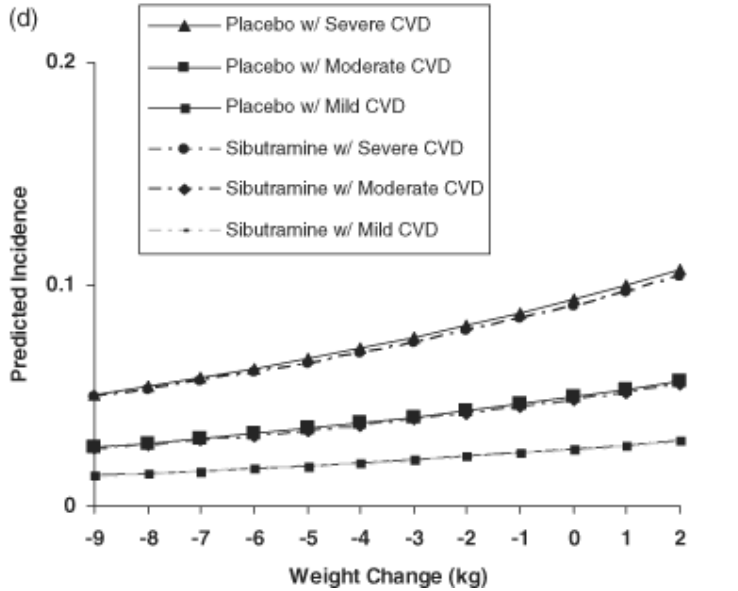
Weight Loss and CVD In T2D

- Conflicting
- LOOKAhead: Intensive lifestyle intervention did not reduce CVD but number of events was less than expected in the control group
- In PROACTIVE: pioglitazone reduced all-cause mortality, non-fatal myocardial infarction and stroke despite weight gain. Weight loss was associated with worse outcomes in the pioglitazone group but not the placebo arm.
- In SCOUT: Sibutramine was associated with increased CVD, however…..



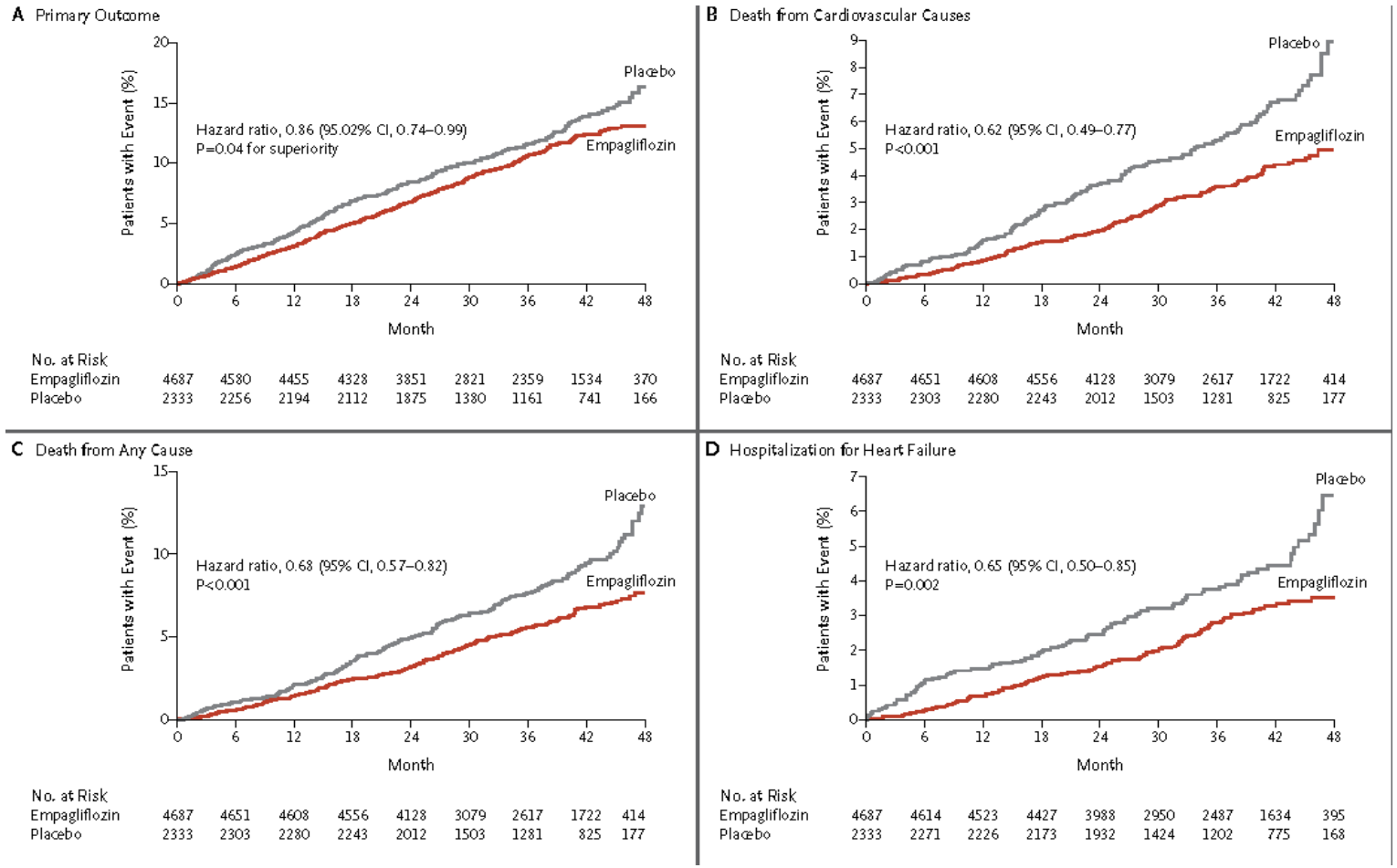






Caterson et al. Diabetes Obes Metab. 2012 Jun;14(6):523-30

Weight Loss Pharmacotherapy and CVD



Ziinman e tal. N Engl J Med 2015; 373:2117-2128

company announcement

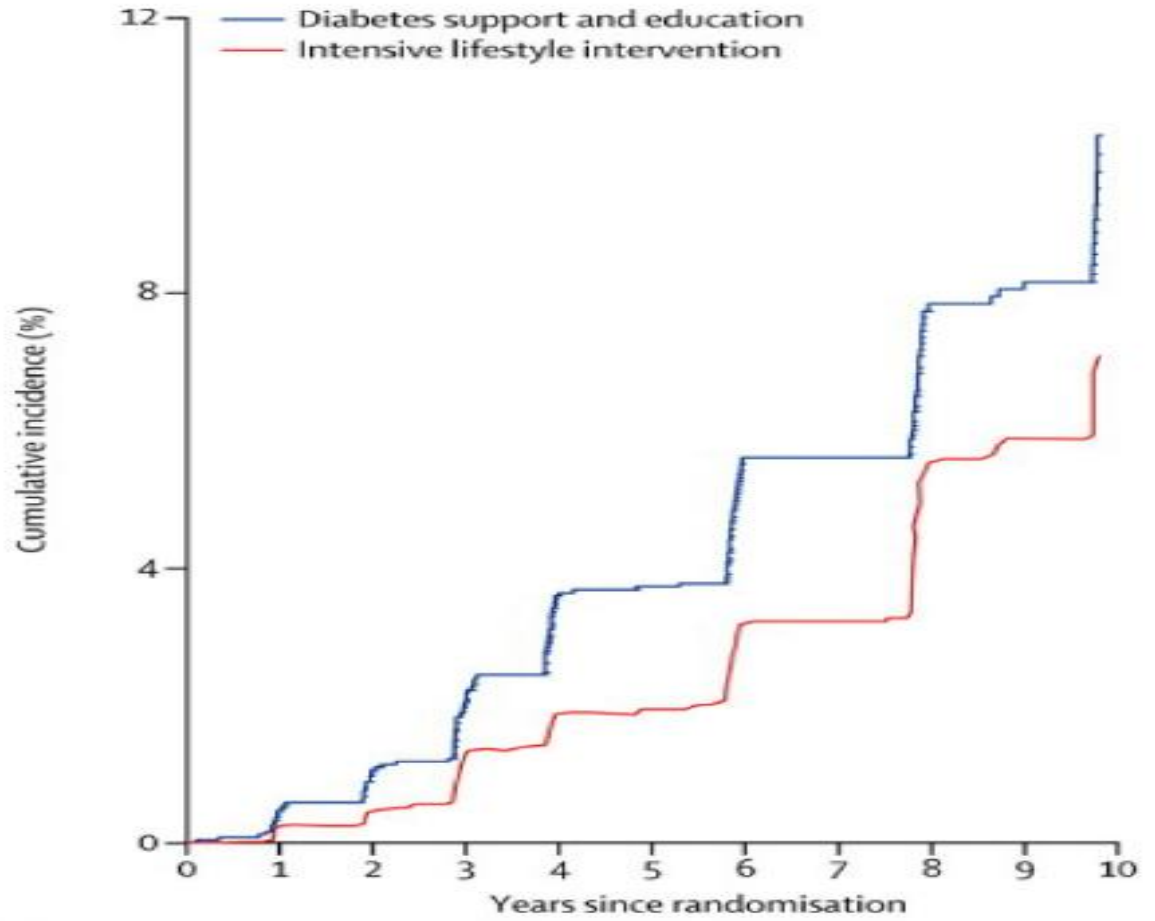
Victoza® significantly reduces the risk of major adverse cardiovascular events in the LEADER trial

Bagsværd, Denmark, 4 March 2016 - Novo Nordisk today announced the top-line results from the LEADER trial, which investigated the cardiovascular safety of Victoza® (liraglutide) over a period of up to 5 years in more than 9,000 adults with type 2 diabetes at high risk of major adverse cardiovascular events. The trial compared the addition of

http://www.novonordisk.com/media/news-details.1991879.html

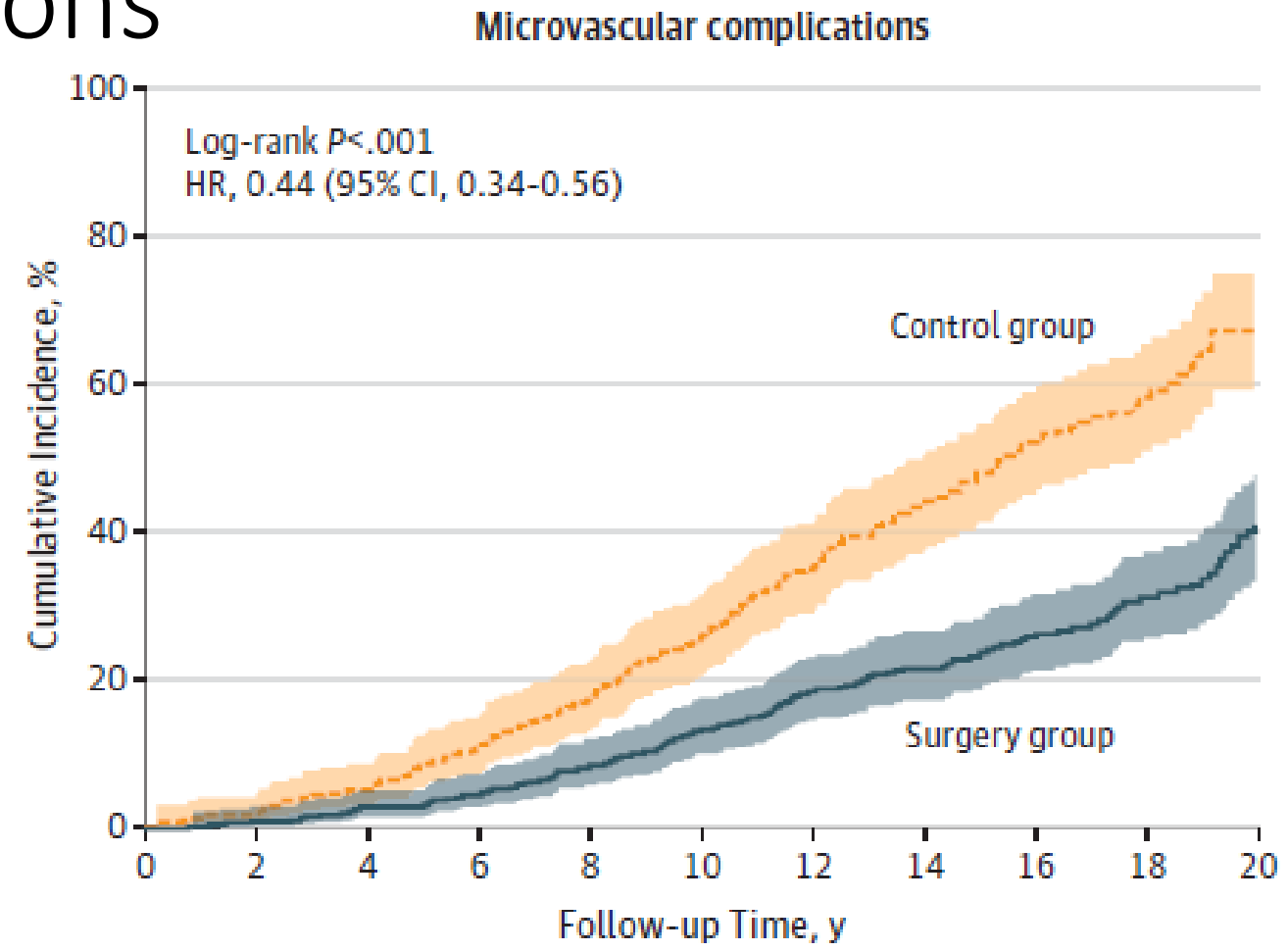
Intensive Lifestyle Intervention And Diabetic Nephropathy

Very high risk is defined if a) eGFR <30 ml/min/1.73m2 regardless of ACR; b) eGFR <45 ml/min/1.73m2 and ACR ≥30 mg albumin/g creatinine; or c) eGFR <60 ml/min/1.73m2 and ACR >300 mg/g



Knowler et al. Lancet Diabetes Endocrinol. 2014 Oct; 2(10): 801–809.

Bariatric Surgery and Microvascular Complications



Sjöström et al. JAMA. 2014;311(22):2297–2304

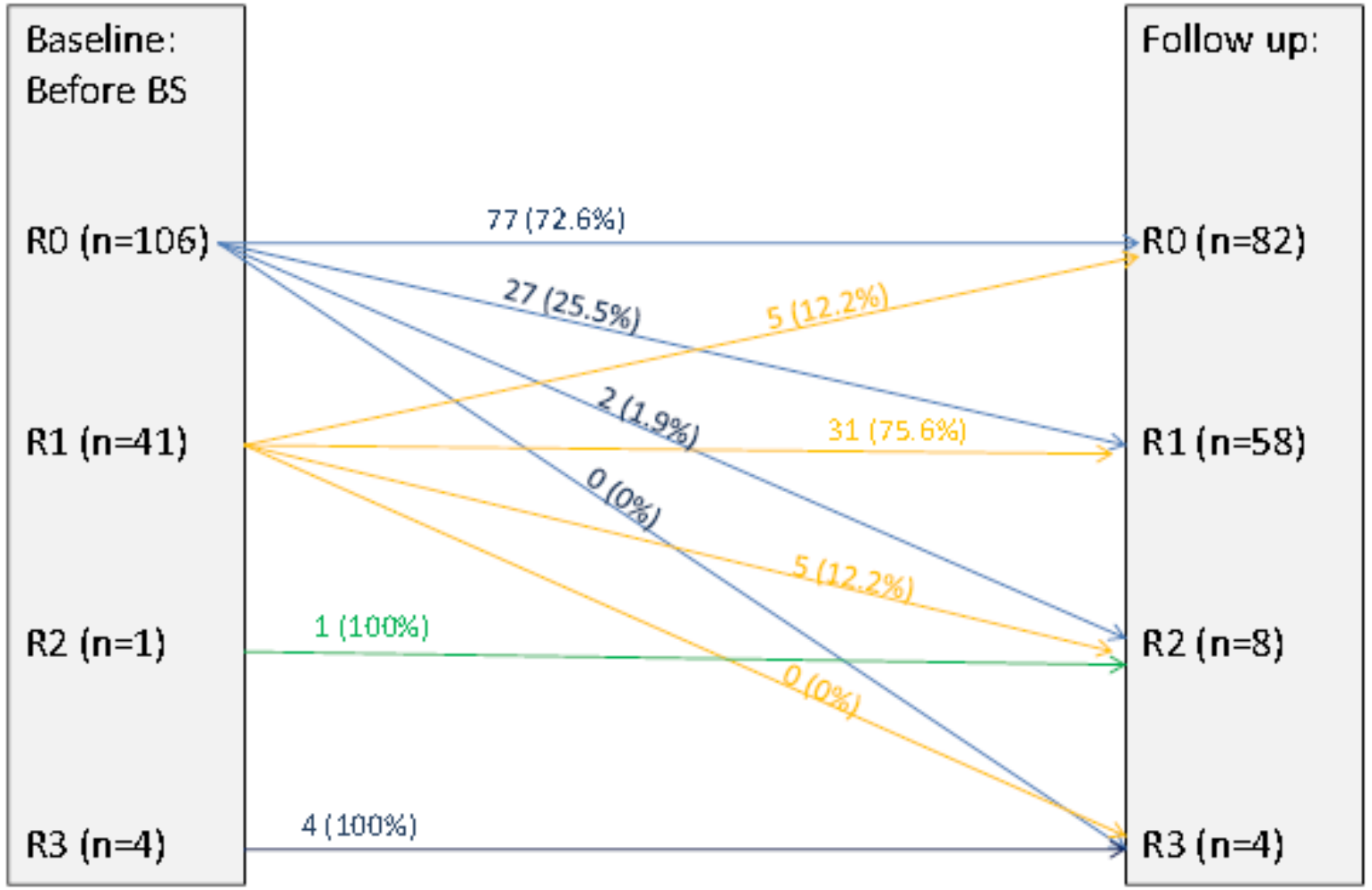
Bariatric Surgery and Renal Function

Patient population	Bariatric surgery (n = 163)	Routine care (n = 225)	*P* value
Total study population			
Baseline eGFR mL/min/1.73 m^2	86.5 + 20.8	86.1 + 26.5	.89
Study-end eGFR mL/min/1.73 m^2	88.8 + 18.9	81.0 + 27.5	.001
eGFR change (study end minus baseline values) mL/min/1.73 m^2	2.3 + 15.3	−5.1 + 11.0	<.001*
Patients with baseline eGFR ≤ 60 mL/min/1.73 m^2	Bariatric surgery (n = 15)	Routine care (n = 41)	*P* value
Baseline eGFR mL/min/1.73 m^2	47.9 + 9.1	46.9 + 11.2	.72
Study-end eGFR mL/min/1.73 m^2	60.7 + 14.0	41.5 + 14.3	<.001
eGFR change (study end minus baseline values) mL/min/1.73 m^2	12.8 + 13.2	−5.2 + 10.3	<.001*

Variable	B	*P* value
Baseline eGFR	0.822	<.001
Baseline BMI	−0.067	.36
Baseline HbA1C	−0.385	.33
Gender	0.603	.65
Baseline age	−0.211	.002
Follow-up duration	−1.813	<.001
Bariatric surgery versus routine care	7.787	<.001

Mirjakar & Tahrani et al. Surgery for Obesity and Related Diseases 2016; In Press

Bariatric Surgery and DR



Amin & Tahrani et al. Surgery for Obesity and Related Diseases 2015.

The progression to STDR was lower numerically (but not significant statistically) in the bariatric surgery group compared with the routine care group (5.7% [8/141] versus 12.1% [12/99], respectively, $P = .075$).

Progression to maculopathy was significantly less in the bariatric surgery group compared with the routine care group (5.6% [8/143] versus 15.4% [16/104], respectively, $P = .01$).

Amin & Tahrani et al. Surgery for Obesity and Related Diseases 2015.

- In Patients With T2D: Glycaemic Control, Obesity Control, Or both?

- The answer is both…but:
- 1. Life Style interventions is essential part of the management of all patients with T2D
- 2. Use strategies to improve glycaemic measures that result in weight loss (or at least weight neutrality)
- 3. Bariatric surgery is an important tool in the right patient.

- A 40 year old woman
- BMI of 40 kg/m2
- Type 2 diabetes for 5 years
- metformin monotherapy.
- HbA1c 7.3%.
- No Diabetes Complications

- A 40 year old woman
- BMI of 31 kg/m2
- Type 2 diabetes for 10 years
- metformin and basal-bolus insulin therapy
- HbA1c 8.5%.
- Laser treatment for DR

In your opinions, what is the preferable treatment options for each of these patients?

Would you recommend the second patient to have bariatric surgery?

Summary and Conclusions-1

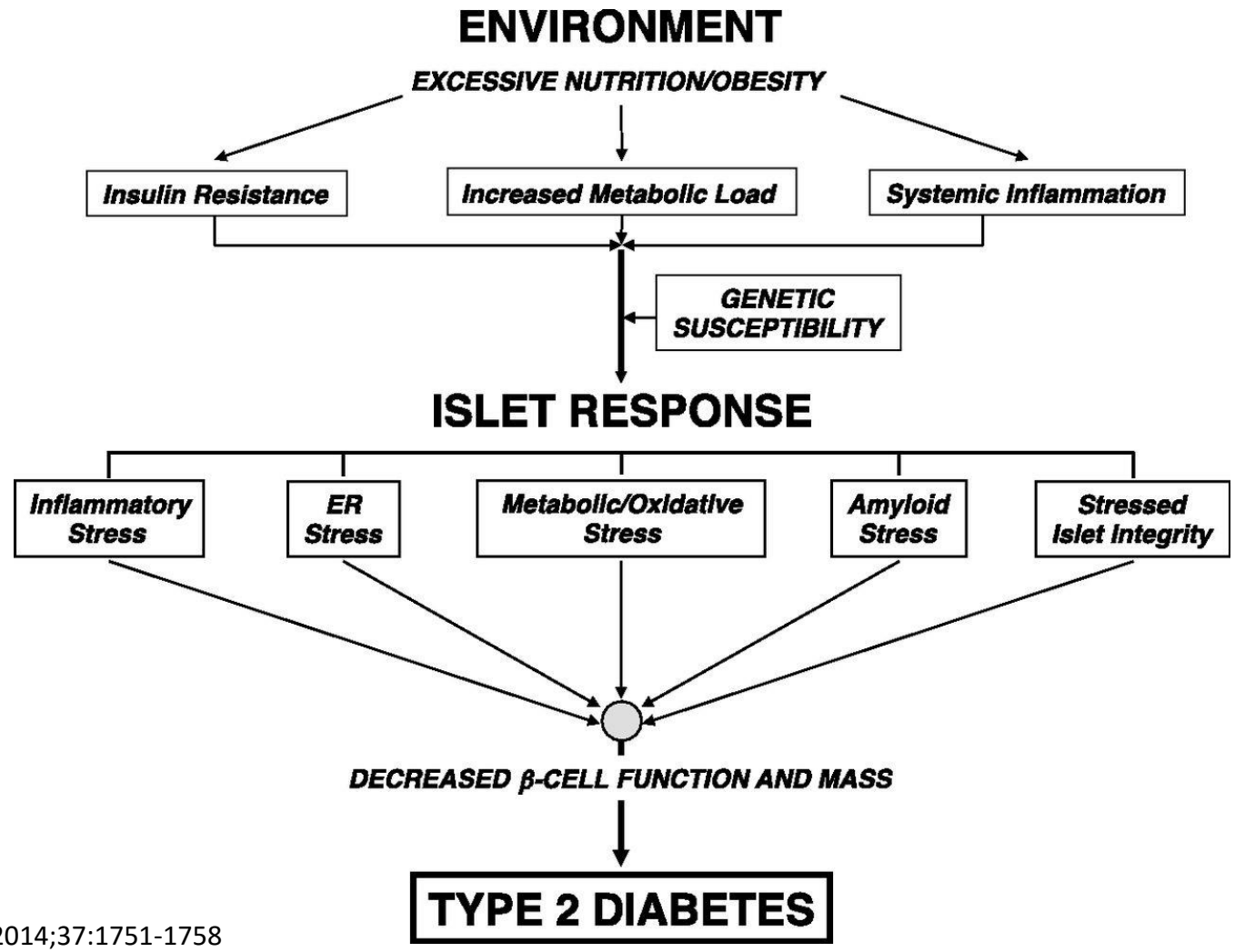
- Type 2 Diabetes is a heterogeneous disease in which variable degree of imbalance between insulin sensitivity and Beta cell function result in hyperglycaemia and vascular disease
- Obesity is a major contributor to the development of insulin resistance and beta cell failure
- The impact of obesity on glucose metabolism vary considerably amongst patients based on background susceptibility
- Better understanding of the pathogenesis of Type 2 Diabetes in individual patients all better treatment individualising

Summary and Conclusions-2

- Improvements in glycaemic and metabolic control are essential to reduce the burden of Type 2 Diabetes but the impact on the patient adiposity should be taken into account.
- Obesity treatment is essential component of managing patients with Type 2 diabetes and in some individuals might lead to diabetes remission
- Bariatric surgery is an important tool in the treatment of Type 2 Diabetes
- Not all patients with Type 2 Diabetes are the same…. Choose the best treatment modality for the right patient

Thank You

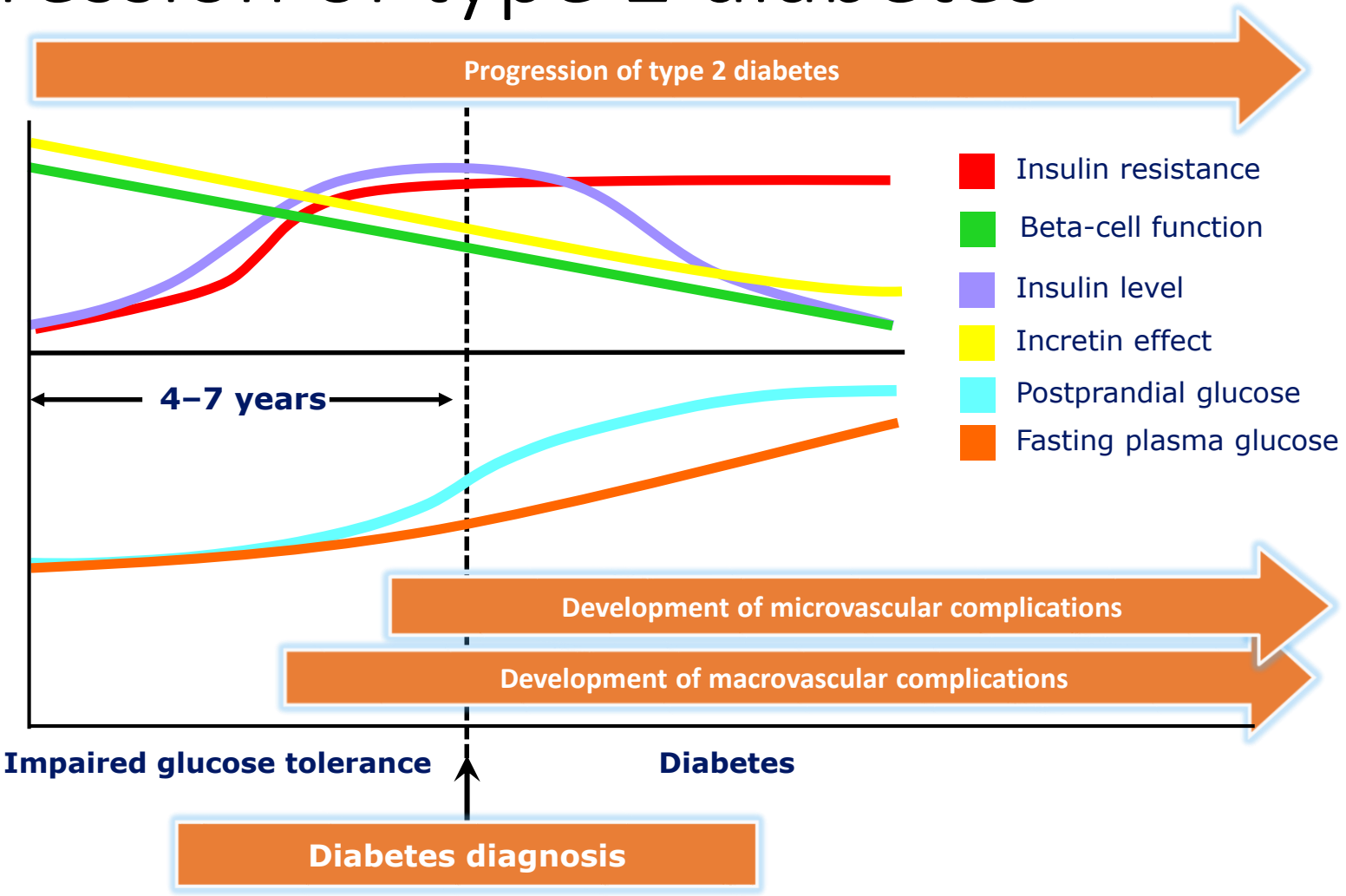
Mechanisms of β-cell Failure in T2D



Philippe A. Halban et al. Dia Care 2014;37:1751-1758

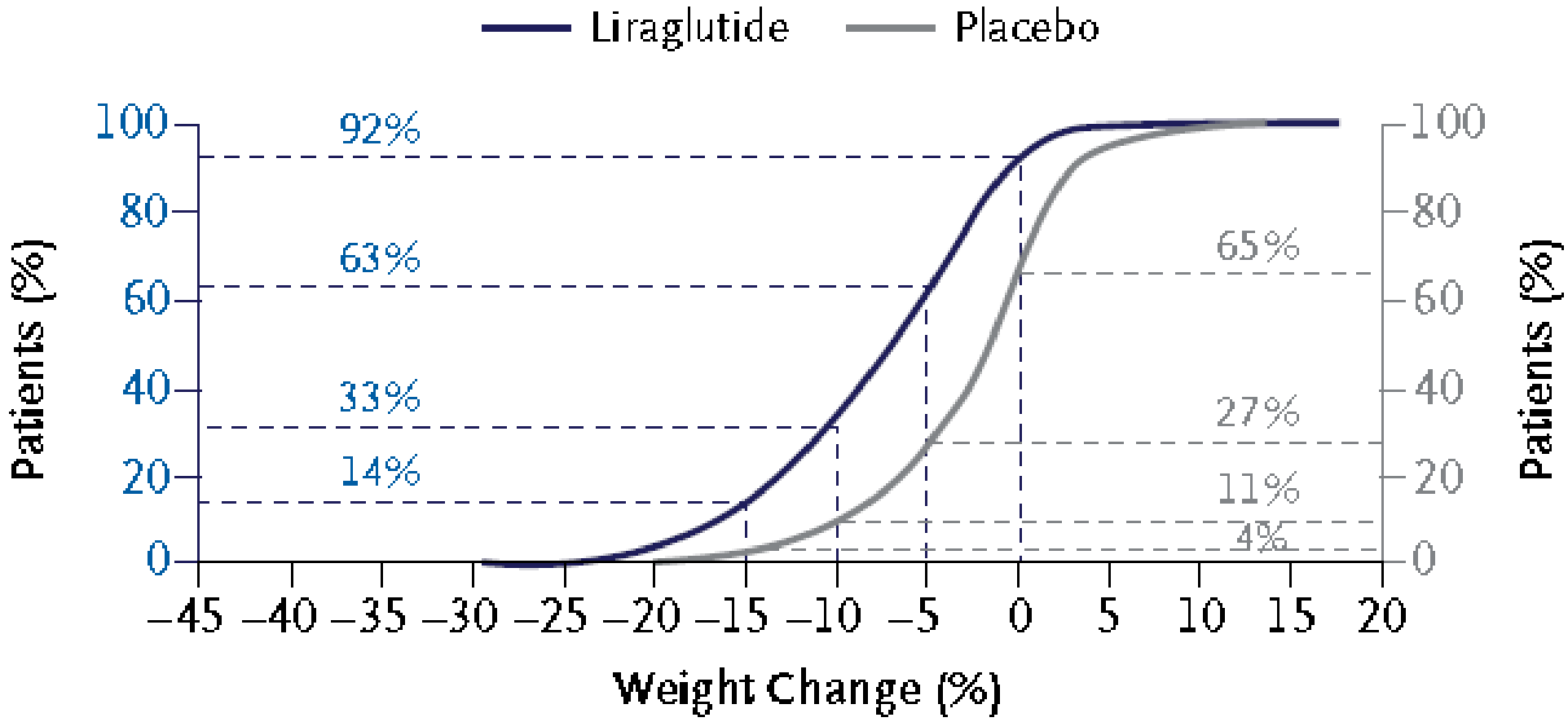
American Diabetes Association.

Progression of type 2 diabetes

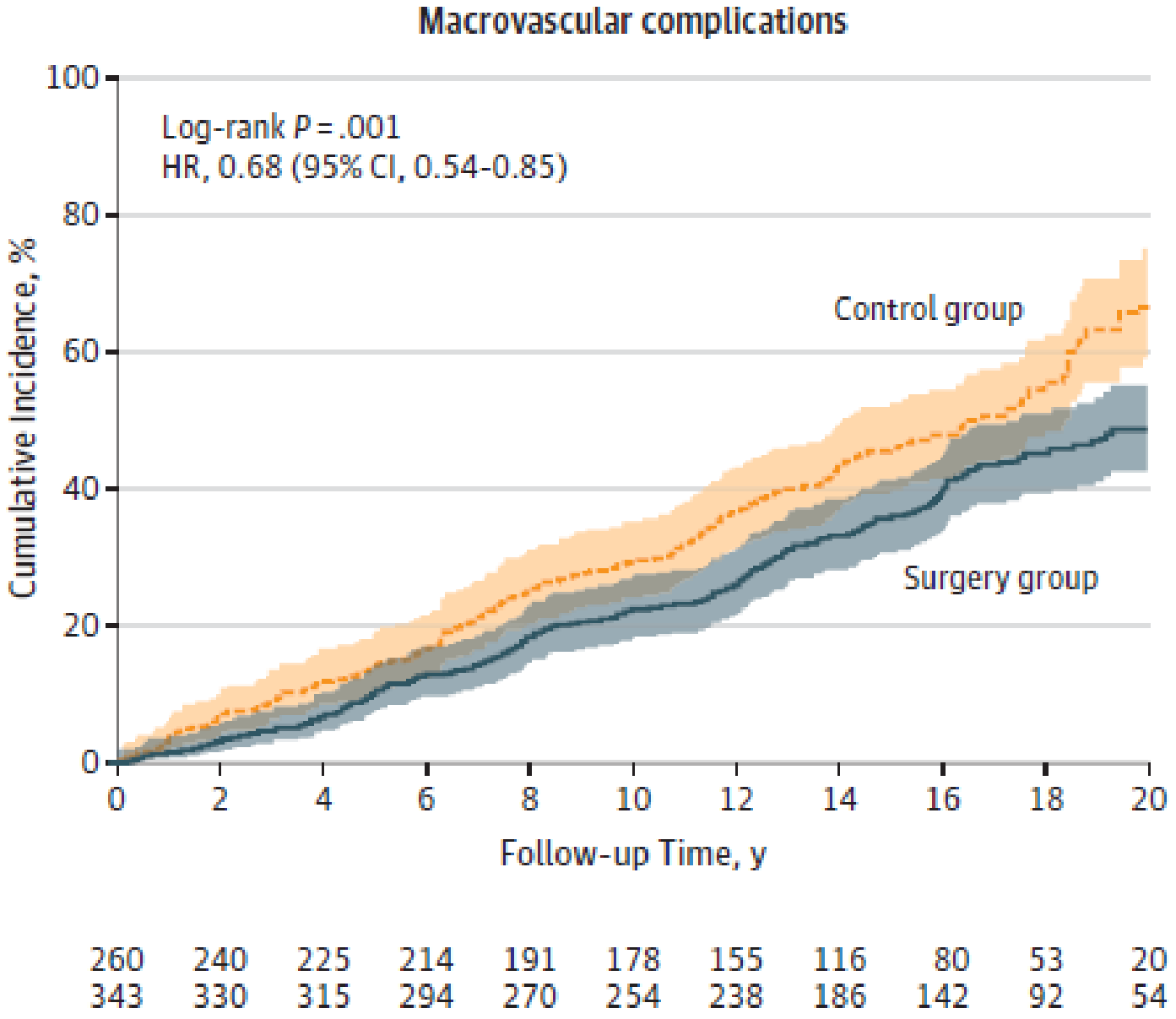


Adapted from Kendall *et al*. *Am J Med* 2009:122(Suppl. 6):S37–50

Variation in Weight Loss with GLP-1 RA



Pi-Sunyer et al. N Engl J Med 2015; 373:11-22



Sjöström et al. JAMA. 2014;311(22):2297–2304

Visceral vs. Subcutaneous vs. Thigh

TABLE 2 Hazard ratios and 95% confidence intervals of mortality according to abdominal visceral and subcutaneous fat and thigh intermuscular and subcutaneous fat[a]

	Men						Women					
	Model 1[b]		Model 2[c]		Model 3[d]		Model 1[b]		Model 2[c]		Model 3[d]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Abdomen												
Visceral fat	1.00	0.94-1.07	0.97	0.88-1.06	0.96	0.87-1.05	1.03	0.96-1.10	1.16	1.05-1.28	1.13	1.03-1.25
Subcutaneous fat	1.04	0.97-1.11	1.04	0.92-1.17	1.03	0.92-1.16	0.82	0.76-0.89	0.68	0.59-0.77	0.70	0.61-0.80
Thigh												
Intermuscular fat	1.12	1.05-1.20	1.15	1.07-1.24	1.17	1.08-1.26	0.98	0.91-1.05	1.01	0.94-1.09	1.01	0.94-1.09
Subcutaneous fat	1.05	0.99-1.12	1.05	0.97-1.15	1.08	0.99-1.18	0.89	0.83-0.96	0.89	0.80-0.99	0.91	0.82-1.01

[a]HR per SD increment in each fat depot.
[b]Model 1 Adjusted for age, education, smoking status, physical activity, and alcohol consumption.
[c]Model 2 Adjusted for age, education, smoking status, physical activity, alcohol consumption, and BMI.
[d]Model 3 Adjusted for age, education, smoking status, physical activity, alcohol consumption, BMI, type 2 diabetes, and coronary heart disease.

Kostert et al. Obesity (Silver Spring). 2015 Apr;23(4):893-7

- The odds of SBP control associated with a 5% loss in BMI were increased by a factor of
- 1.08 [1.02–1.13] among CPB participants,
- 1.23 [1.07–1.42] among DSE participants, and
- 1.19 [1.04–1.34] among ILI participants.

Weight Loss Pharmacotherapy and BP

Blood pressure, mean (SD), mm Hg[b]								
Systolic	-2.8 (13.5)	-3.5 (12.7)	-0.4 (13.4)	Treatment difference	-2.59 (-4.56 to -0.62)	.01	-2.68 (-4.98 to -0.38)	.02
Diastolic	-0.9 (8.7)	-1.1 (9.4)	-0.5 (9.1)	Treatment difference	-0.36 (-1.69 to 0.96)	.59	-0.19 (-1.74 to 1.36)	.81

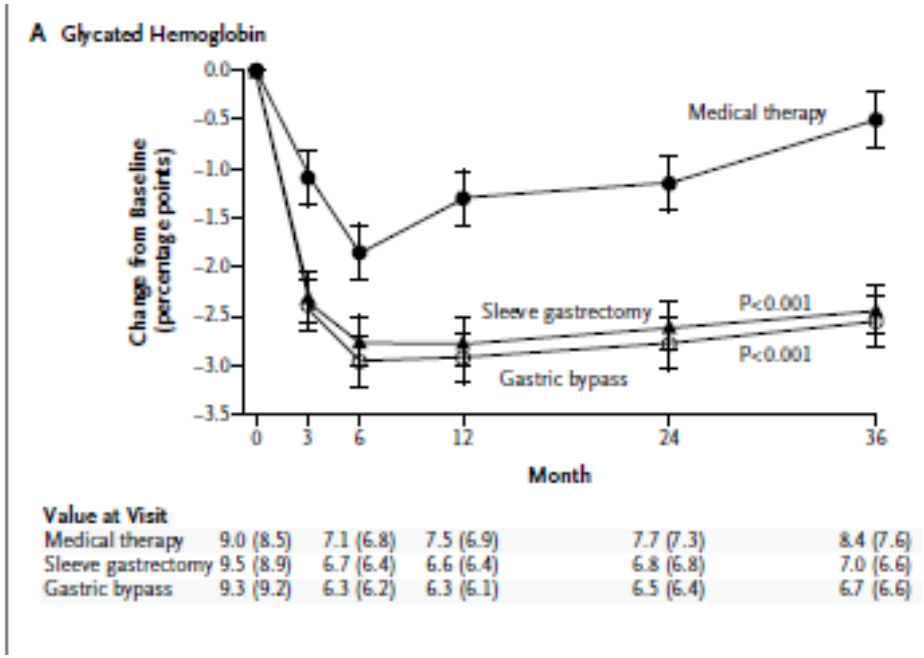
Davies et al. JAMA. 2015;314(7):687-699

	Men			Women		
	β*	95% CI	P	β*	95% CI	P
Model 1: fasting glucose						
Trunk fat mass	0.44	0.25–0.64	0.00	0.49	0.35–0.63	0.00
Trunk lean mass	0.26	0.05–0.46	0.02	0.27	0.09–0.45	0.00
Leg fat mass	−0.24	−0.43 to −0.05	0.01	−0.24	−0.37 to −0.10	0.00
Leg lean mass	−0.27	−0.48 to −0.06	0.01	−0.15	−0.34 to 0.03	0.11
Model 2: postload glucose						
Trunk fat mass	0.41	0.22–0.60	0.00	0.47	0.33–0.61	0.00
Trunk lean mass	−0.02	−0.22 to 0.19	0.89	0.08	−0.10 to 0.25	0.38
Leg fat mass	−0.12	−0.31 to 0.07	0.23	−0.27	−0.40 to −0.13	0.00
Leg lean mass	−0.12	−0.33 to 0.10	0.28	−0.04	−0.22 to 0.14	0.69
Model 3: ln-HOMA-IR						
Trunk fat mass	0.59	0.41–0.76	0.00	0.65	0.52–0.77	0.00
Trunk lean mass	0.16	−0.03 to 0.36	0.10	0.19	0.03–0.34	0.02
Leg fat mass	−0.18	−0.35 to 0.00	0.05	−0.19	−0.30 to −0.06	0.00
Leg lean mass	−0.18	−0.38 to 0.01	0.07	0.00	−0.16 to 0.16	0.98

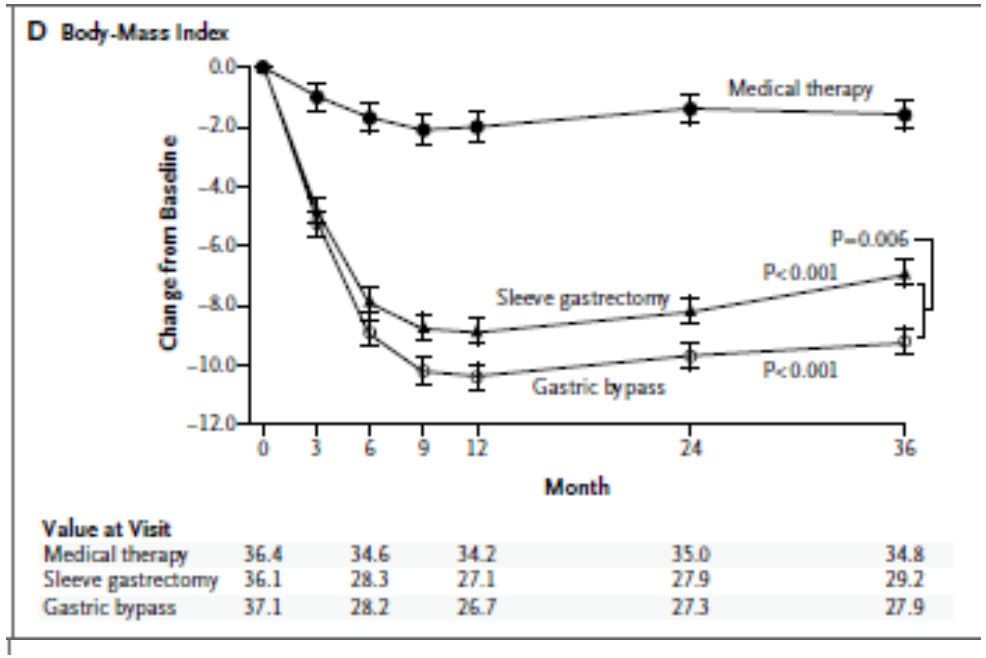
*β, standardized β.

Snijder et al. Diabetes Care, Volume 27, Number 2, February 2004

3 year follow-up outcomes



Value at Visit					
Medical therapy	9.0 (8.5)	7.1 (6.8)	7.5 (6.9)	7.7 (7.3)	8.4 (7.6)
Sleeve gastrectomy	9.5 (8.9)	6.7 (6.4)	6.6 (6.4)	6.8 (6.8)	7.0 (6.6)
Gastric bypass	9.3 (9.2)	6.3 (6.2)	6.3 (6.1)	6.5 (6.4)	6.7 (6.6)



Value at Visit					
Medical therapy	36.4	34.6	34.2	35.0	34.8
Sleeve gastrectomy	36.1	28.3	27.1	27.9	29.2
Gastric bypass	37.1	28.2	26.7	27.3	27.9

Schauer et al. N Engl J Med 2014; 370:2002–2013

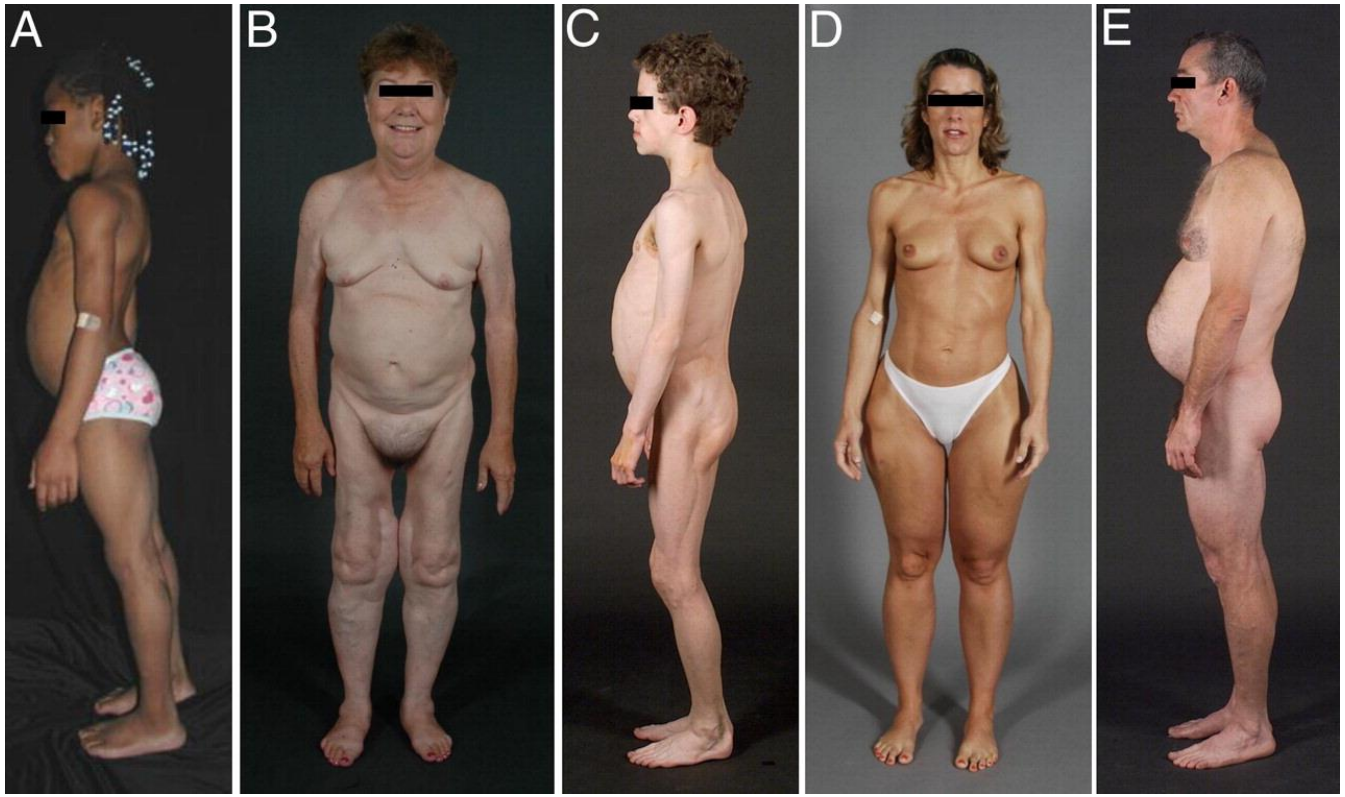
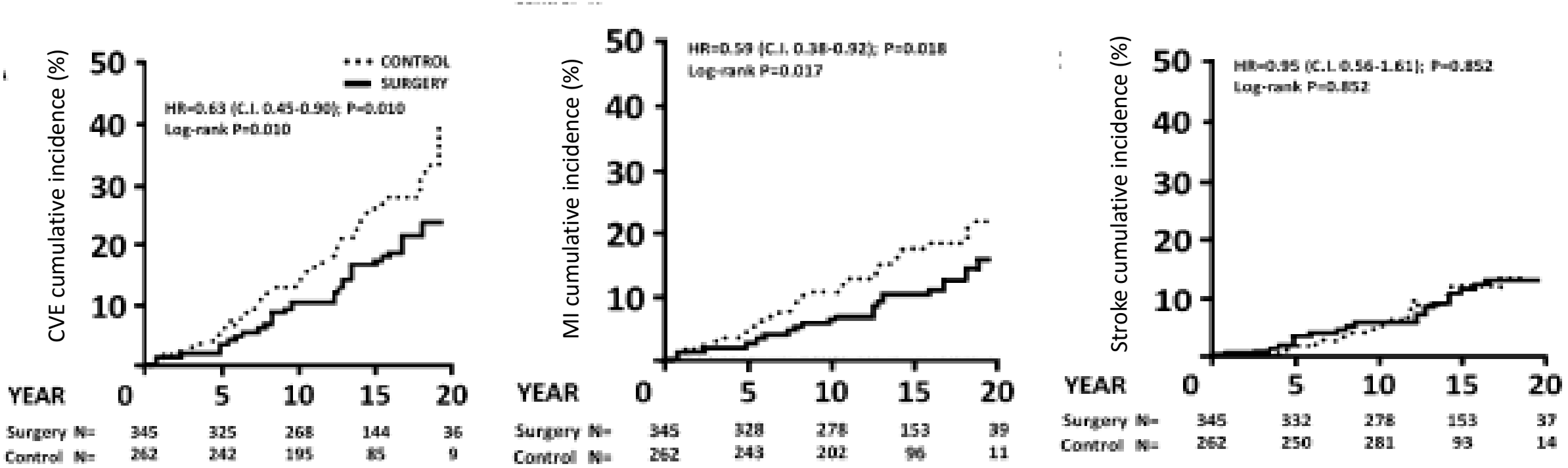


Fig. 1

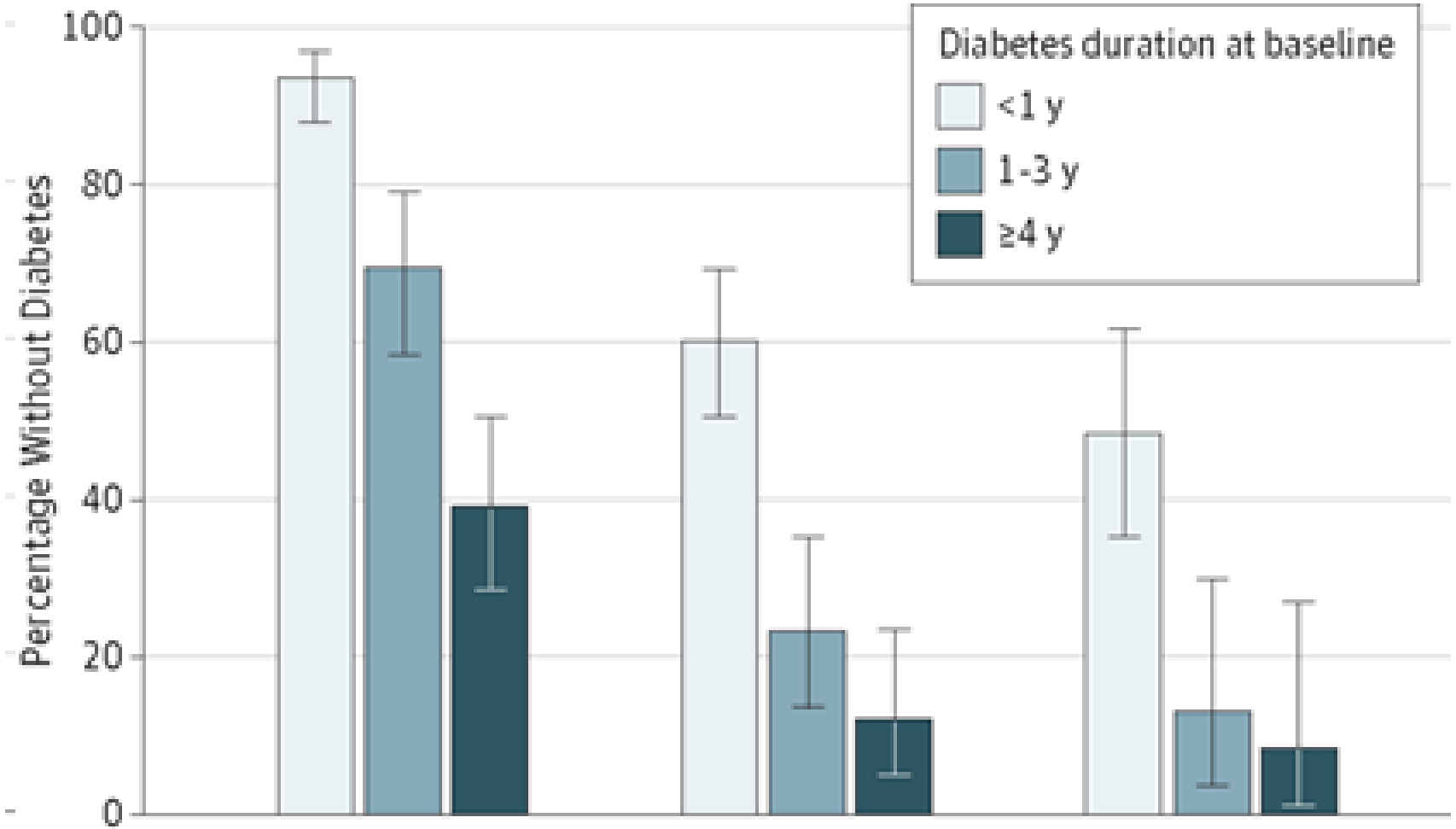
Published in: Abhimanyu Garg; *The Journal of Clinical Endocrinology & Metabolism* **2011,** 96, 3313-3325.
DOI: 10.1210/jc.2011-1159

Bariatric Surgery and CVD in T2D



CVE=Cardiovascular event, MI=myocardial infarction

Romeo et al. Diabetes Care 2012; 35 (12):12 2613–2617



Total participants			
<1 y	139	113	60
1-3 y	82	65	31
≥4 y	82	58	24

Sjöström et al. JAMA. 2014;311(22):2297–2304

Weight Loss Pharmacotherapy and Glycaemic Control

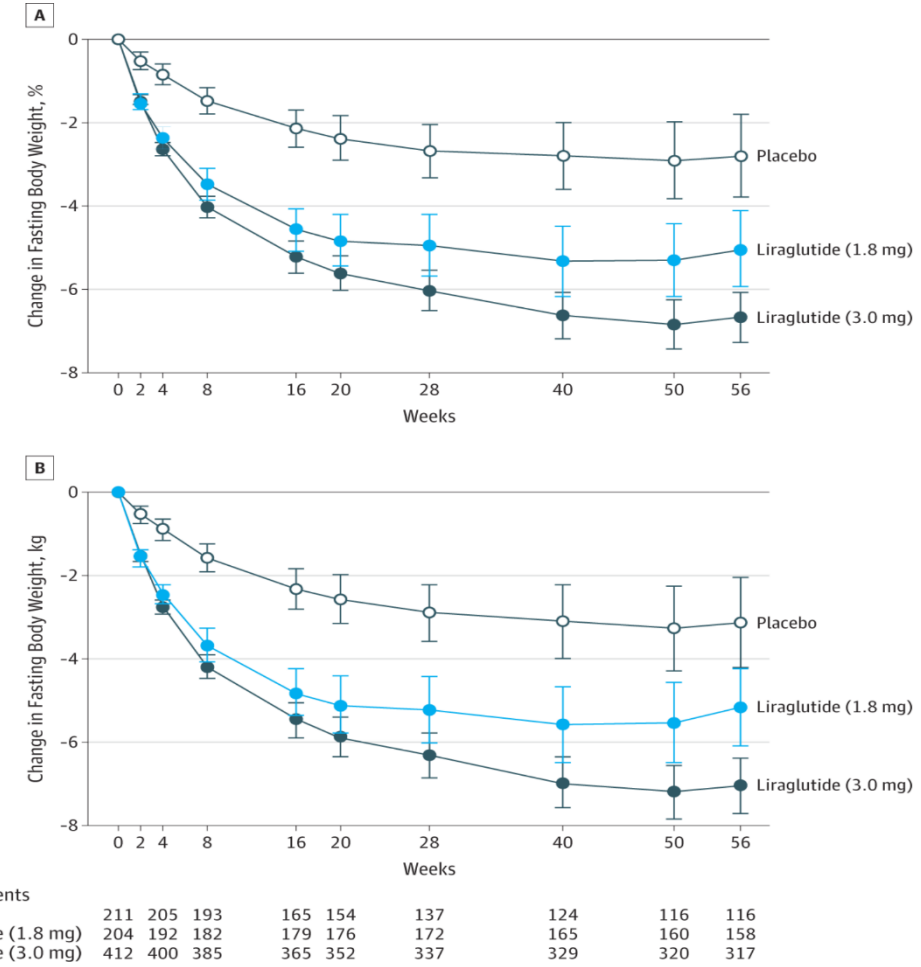


Table 3. Summary of Secondary Efficacy End Points At Week 56[a]

	Change From Baseline to Week 56 or Percentage At Week 56			Estimate (95% CI)				
	Liraglutide				Liraglutide			
End Point	3.0 mg (n = 411)	1.8 mg (n = 204)	Placebo (n = 211)	Estimate Type	3.0 mg vs Placebo	*P* Value	1.8 mg vs Placebo	*P* Value
Waist circumference, mean (SD), cm[b]	-6.1 (6.5)	-4.8 (5.6)	-2.7 (5.4)	Treatment difference	-3.22 (-4.20 to -2.23)	<.001	-2.06 (-3.20 to -0.92)	<.001
Body mass index, mean (SD)[b,c]	-2.2 (2.1)	-1.7 (2.1)	-0.8 (1.7)	Treatment difference	-1.50 (-1.83 to -1.18)	<.001	-0.95 (-1.33 to -0.57)	<.001
HbA_{1c}, mean (SD), % change[b]	-1.3 (0.9)	-1.1 (1.0)	-0.3 (0.9)	Treatment difference	-0.93 (-1.08 to -0.78)	<.001	-0.74 (-0.91 to -0.57)	<.001
No. of individuals achieving HbA_{1c} target, No. %[d]								
<7.0 %	278 (69.2)	130 (66.7)	56 (27.2)	Odds ratio	8.79 (5.74 to 13.44)	<.001	7.71 (4.76 to 12.51)	<.001
≤6.5 %	227 (56.5)	89 (45.6)	31 (15.0)	Odds ratio	9.61 (6.05 to 15.26)	<.001	5.98 (3.59 to 9.97)	<.001
Fasting plasma glucose, mean (SD), mg/dL[b]	-34.3 (38.5)	-26.8 (50.3)	-0.2 (37.0)	Treatment difference	-31.89 (-38.02 to-25.59)	<.001	-23.06 (-30.27 to -15.86)	<.001
PPG increment, mean (SD), mg/dL[b]	-16.2 (37.8)	-12.6 (37.8)	-5.4 (36.0)	Treatment difference	-9.91 (-15.14 to -4.68)	<.001	-7.93 (-13.87 to -1.98)	.009

Davies et al. JAMA. 2015;314(7):687-699

T2D treatment and CVD

- Drugs that improve HbA1c and increased weight (such as insulin, Sulphonylureas & rosiglitazone) are at best neutral in terms of CVD and at worst increase the risk of CVD
- Drugs cause weight loss and improve hbA1c such as (Empagiflozin and Liraglutide) result in reductions in CVD
- Weight neutral drugs can reduce CVD (such as Acarbose, Bromocriptin, and colesevelam) or is CVD neutral (such as DPP-4 inhibitors except saxagliptin)

Tahrani et al. Nature Reviews Endocrinology. In Press