Obesity and T2DM trials

Dr Alexander Miras

Senior Clinical Lecturer
Endocrinology

Imperial College London

LOOK AHEAD trial - weight loss for diabetes

Variable	Control Group (N=2575)	Intervention Group (N=2570)
Age — yr	58.9±6.9	58.6±6.8
Female sex — no. (%)	1537 (59.7)	1526 (59.4)
Race or ethnic group — no. (%)†		
Black	404 (15.7)	400 (15.6)
Native American	128 (5.0)	130 (5.1)
Asian or Pacific Islander	21 (0.8)	29 (1.1)
White	1631 (63.3)	1621 (63.1)
Hispanic	340 (13.2)	340 (13.2)
Other	51 (2.0)	50 (1.9)
History of cardiovascular disease — no. (%)‡	348 (13.5)	366 (14.2)
Use of insulin — no. (%)§	410 (16.5)	382 (15.4)
Current smoking — no. (%)	110 (4.3)	117 (4.6)
Median duration of diabetes (interquartile range) — yr	5.0 (2.0–10)	5.0 (2.0–10)
Weight — kg	101±19	101±20
Body-mass index¶	36.0±5.8	35.9±6.0
Waist circumference — cm	114±14	114±14
Glycated hemoglobin — %	7.3±1.2	7.2±1.1
Blood pressure — mm Hg		
Systolic	129±17	128±17
Diastolic	70.4±9.6	69.9±9.5
Cholesterol — mg/dl		
High-density lipoprotein	43.5±12	43.4±12
Low-density lipoprotein	112±32	112±32
Median triglycerides (interquartile range) — mg/dl	152 (107–218)	155 (110–221)

"with and without cardiovascular disease"

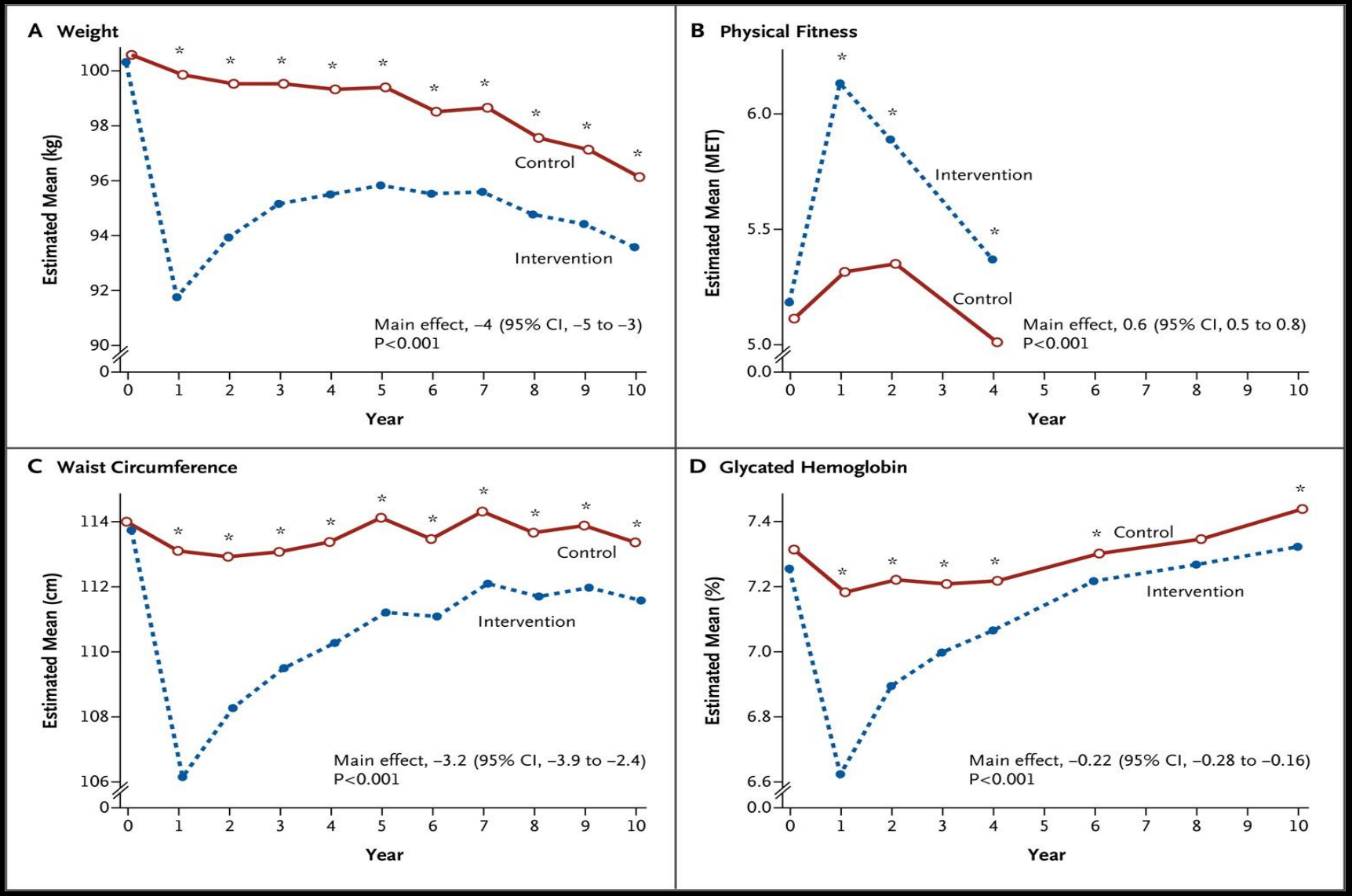
Look AHEAD NEJM 2013

LOOK AHEAD trial - weight loss for diabetes

- aimed 7% weight loss
- 1200 to 1800 kcal per day
- <30% from fat and
- >15% from protein
- group and individual counselling sessions weekly, then less
- meal-replacement products
- 175 minutes of moderate-intensity physical activity per week
- “toolbox”

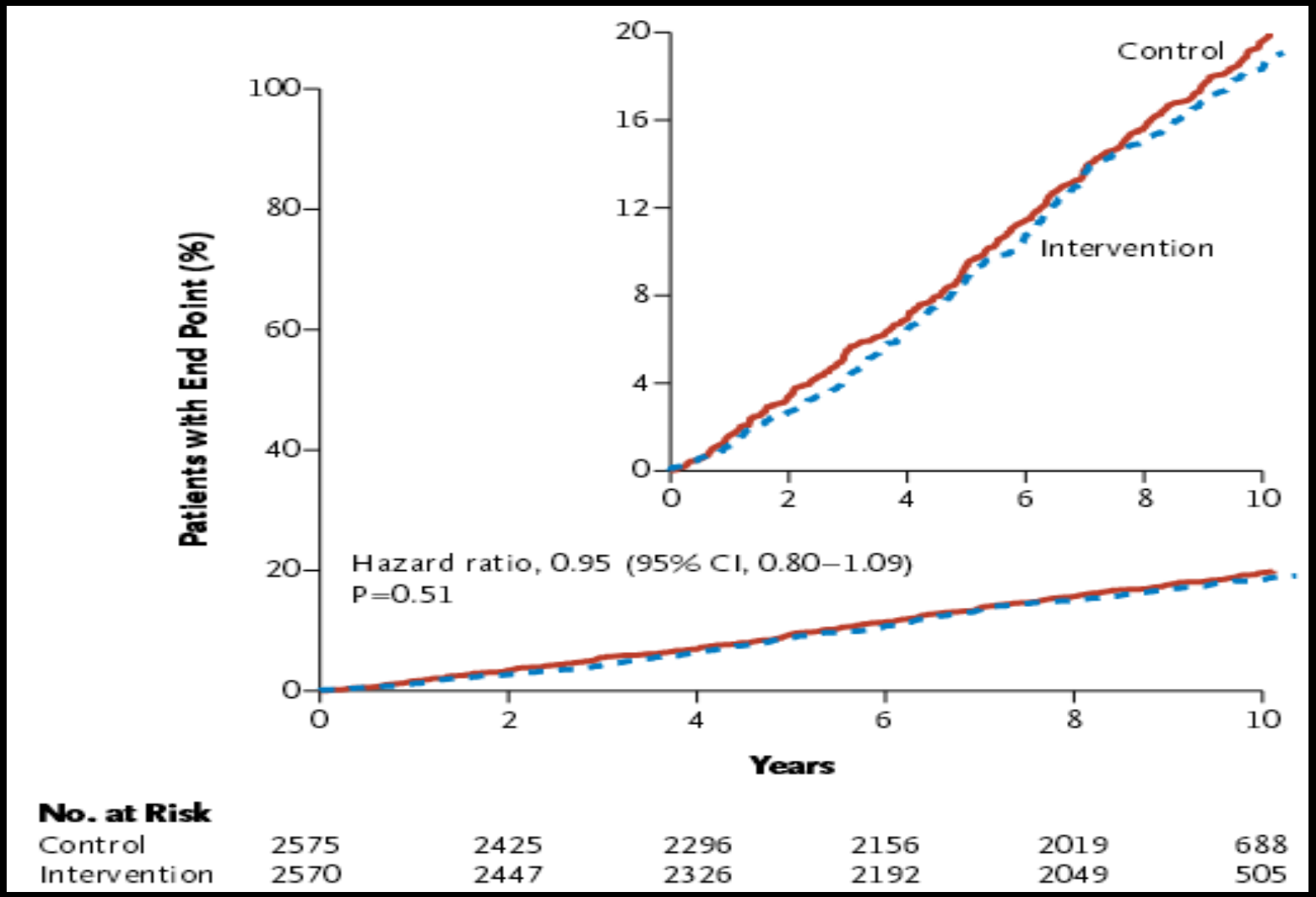
Look AHEAD NEJM 2013

Lifestyle intervention in obese T2DM patients



Look AHEAD NEJM 2013

No effect of lifestyle intervention on CV mortality



No. at Risk						
Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Look AHEAD NEJM 2013

PREDIMED - CV outcomes

- N=7447
- BMI < 40
- High CV risk (50% had T2DM)

Randomised to:

- control group - low fat diet
- MedDiet + virgin olive oil
- MedDiet + nuts

No weight loss

PREDIMED

Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Female sex — no. (%)†	1493 (58.7)	1326 (54.0)	1463 (59.7)
Age — yr†	67.0±6.2	66.7±6.1	67.3±6.3
Race or ethnic group — no. (%)			
White, from Europe	2470 (97.1)	2390 (97.4)	2375 (96.9)
Hispanic, from Central or South America	35 (1.4)	29 (1.2)	38 (1.6)
Other	38 (1.5)	35 (1.4)	37 (1.5)
Smoking status — no. (%)			
Never smoked	1572 (61.8)	1465 (59.7)	1527 (62.3)
Former smoker	618 (24.3)	634 (25.8)	584 (23.8)
Current smoker	353 (13.9)	355 (14.5)	339 (13.8)
Body-mass index†‡			
Mean	29.9±3.7	29.7±3.8	30.2±4.0
<25 — no. (%)	195 (7.7)	204 (8.3)	164 (6.7)
25–30 — no. (%)	1153 (45.3)	1163 (47.4)	1085 (44.3)
>30 — no. (%)	1195 (47.0)	1087 (44.3)	1201 (49.0)
Waist circumference — cm	100±10	100±11	101±11
Waist-to-height ratio†§	0.63±0.06	0.63±0.06	0.63±0.07
Hypertension — no. (%)¶	2088 (82.1)	2024 (82.5)	2050 (83.7)
Type 2 diabetes — no. (%)†‖	1282 (50.4)	1143 (46.6)	1189 (48.5)
Dyslipidemia — no. (%)**	1821 (71.6)	1799 (73.3)	1763 (72.0)

Estruch R et al, NEJM 2013

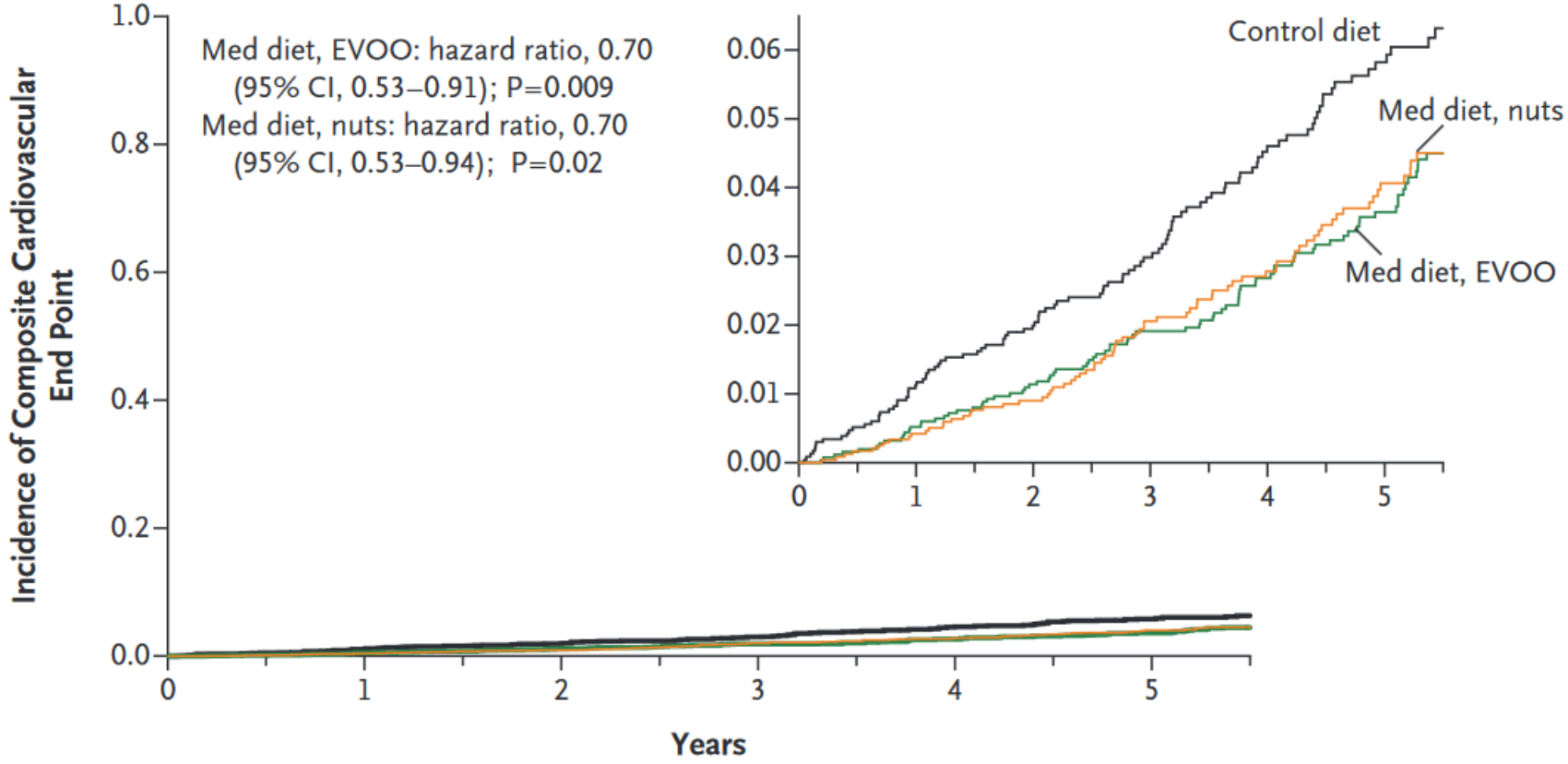
PREDIMED Interventions

MedDiet

- abundant use of free olive oil or
- free mixed nuts (30 g/day)
- fruit, vegetables, legumes and fish
- reduction in total meat consumption
- high (≥2) MUFA/SFA ratio
- homemade sauce with tomato
- avoidance of butter, cream, fast food, sweets, pastries, and sugar-sweetened beverages
- moderate consumption of red wine

30% reduction in cardiovascular morbidity (not mortality)

Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

Estruch R et al, NEJM 2013

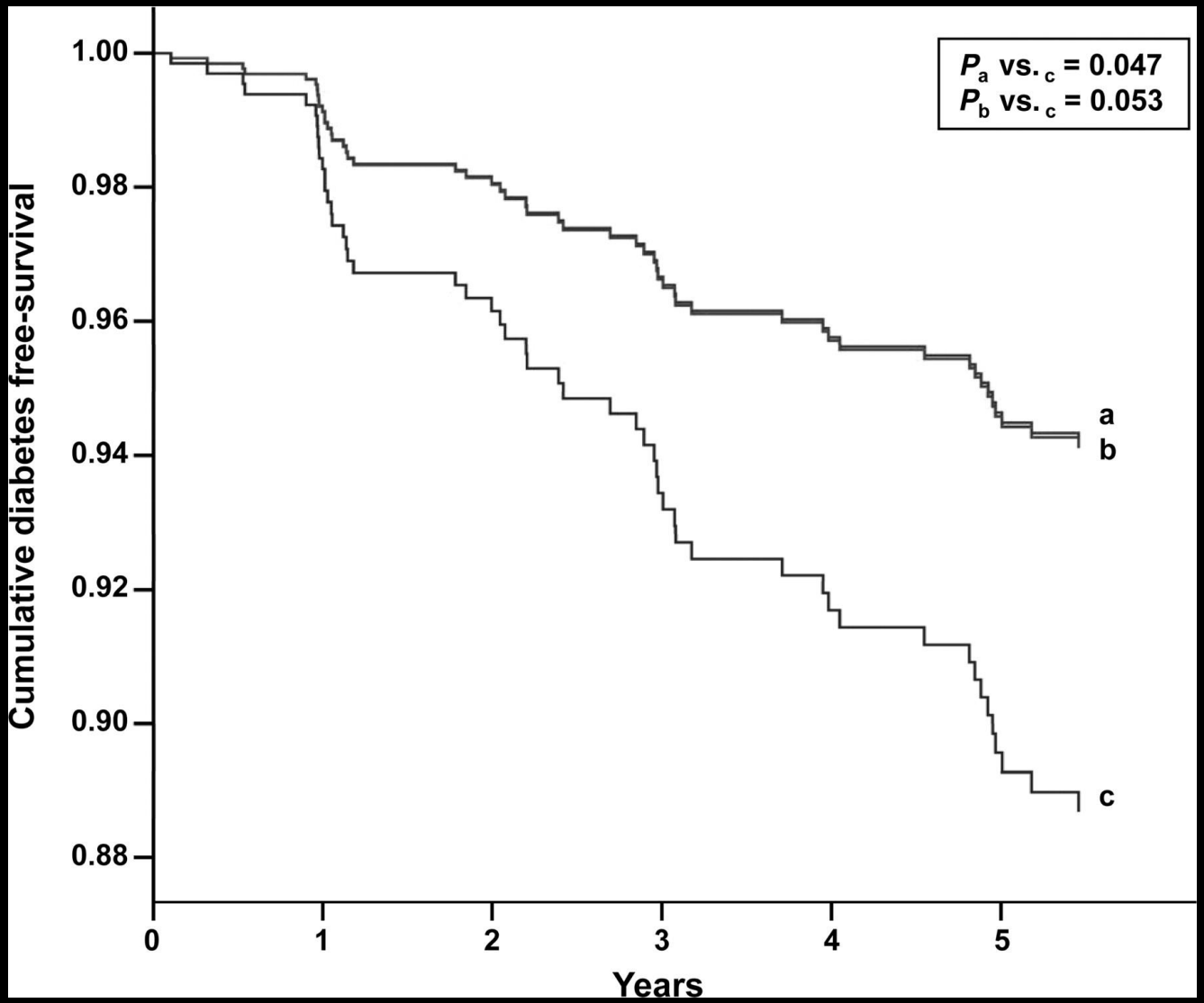
PREDIMED (diabetes)

- N=418
- BMI <40
- High CV risk

Randomised to:

- control group - low fat diet
- MedDiet + extra virgin olive oil
- MedDiet + nuts

50% reduction in diabetes incidence in PREDIMED



Jordi Salas-Salvadó et al. Dia Care 2011;34:14-19

GLP-1 receptor agonists for weight loss (no diabetes)

- 500 kcal deficit
- 30% fat
- 20% protein
- 50% carbohydrate
- physical activity 150 minutes per week
  - pedometers
  - 3-day food diary was dispensed

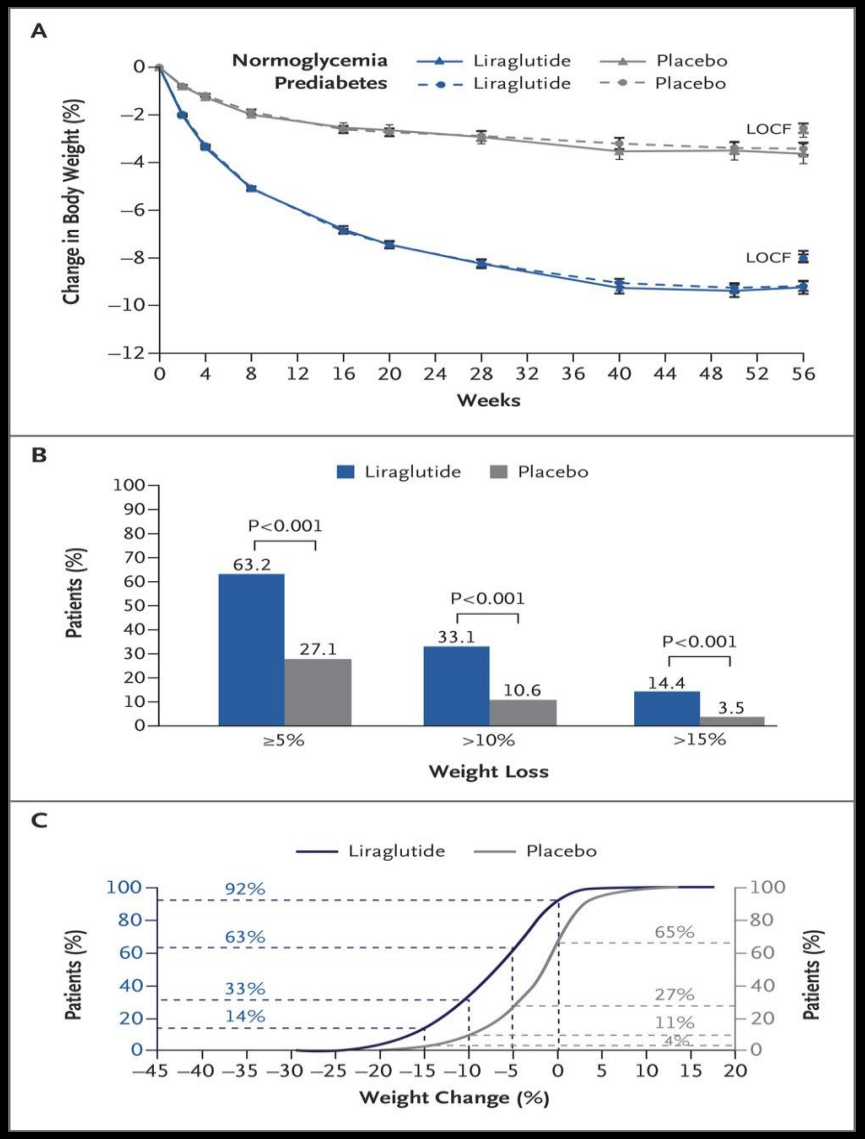
Pi-Sunyer X et al. N Engl J Med 2015;373:11-22

GLP-1 receptor agonists and body weight

Characteristic	Liraglutide (N=2487)	Placebo (N=1244)
Sex — no. (%)		
Female	1957 (78.7)	971 (78.1)
Male	530 (21.3)	273 (21.9)
Age — yr	45.2±12.1	45.0±12.0
Race or ethnic group — no. (%)†		
White	2107 (84.7)	1061 (85.3)
Black	242 (9.7)	114 (9.2)
Asian	90 (3.6)	46 (3.7)
American Indian or Alaska Native	5 (0.2)	4 (0.3)
Native Hawaiian or other Pacific Islander	2 (<0.1)	2 (0.2)
Other	41 (1.6)	17 (1.4)
Hispanic or Latino ethnic group†	259 (10.4)	134 (10.8)
Weight — kg	106.2±21.2	106.2±21.7
Body-mass index‡	38.3±6.4	38.3±6.3
Body-mass index categories — no. (%)‡		
27–29.9: overweight	66 (2.7)	44 (3.5)
30–34.9: obese class I	806 (32.4)	388 (31.2)
35–39.9: obese class II	787 (31.6)	398 (32.0)
≥40: obese class III	828 (33.3)	414 (33.3)
Waist circumference — cm	115.0±14.4	114.5±14.3
Glycated hemoglobin — %	5.6±0.4	5.6±0.4

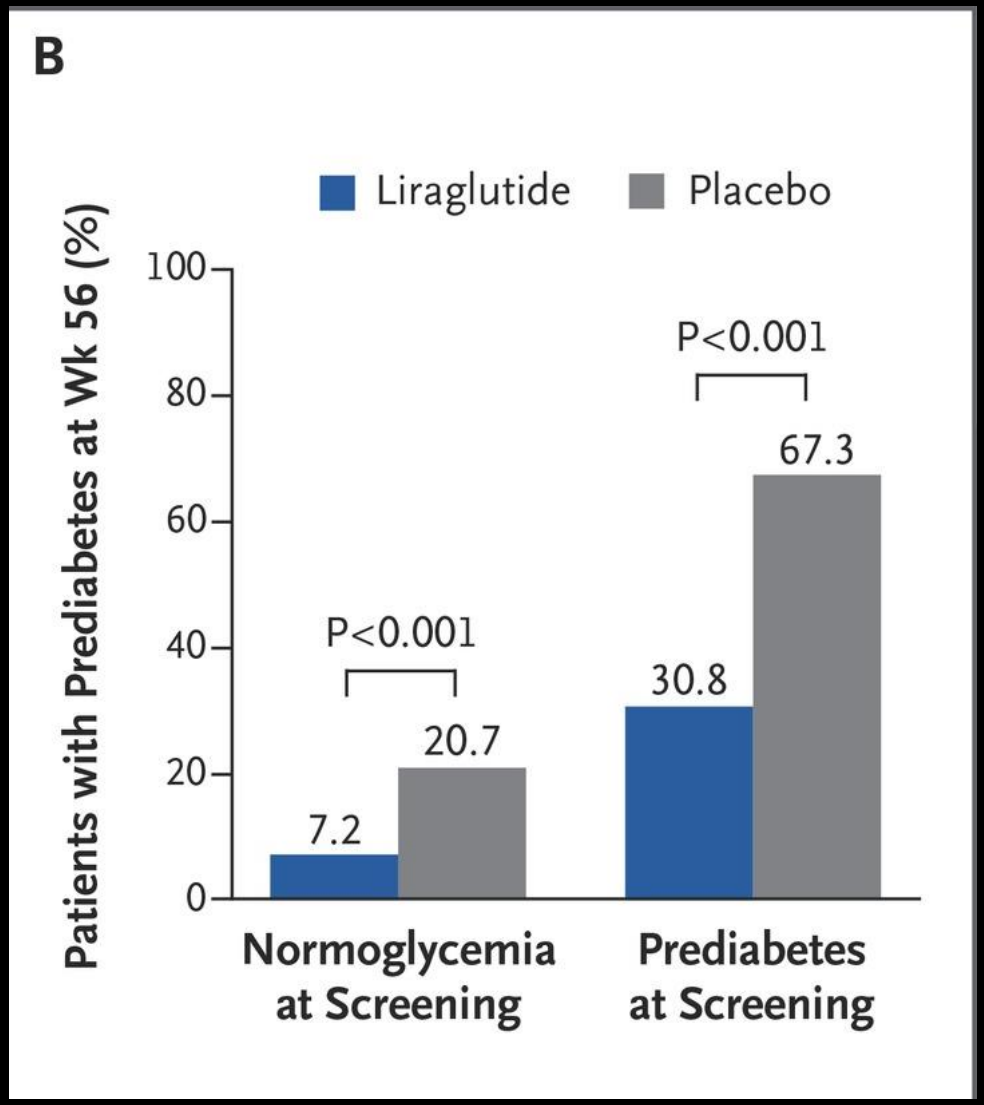
Pi-Sunyer X et al. N Engl J Med 2015;373:11-22

GLP-1 receptor agonists and body weight



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

Liraglutide and glycaemia



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

GLP-1 receptor agonists and CV risk factors

End Point	Liraglutide (N=2437)	Placebo (N=1225)	Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)†	P Value
Coprimary end points				
Change in body weight				
% of body weight	−8.0±6.7	−2.6±5.7	−5.4 (−5.8 to −5.0)	<0.001
Kilograms of body weight	−8.4±7.3	−2.8±6.5	−5.6 (−6.0 to −5.1)	<0.001
Loss of ≥5% body weight (%)‡	63.2	27.1	4.8 (4.1 to 5.6)	<0.001
Loss of >10% body weight (%)‡	33.1	10.6	4.3 (3.5 to 5.3)	<0.001
Body weight-related end points				
Body-mass index	−3.0±2.6	−1.0±2.3	−2.0 (−2.2 to −1.9)	<0.001
Waist circumference (cm)	−8.2±7.3	−3.9±6.6	−4.2 (−4.7 to −3.7)	<0.001
Glycemic control variables				
Glycated hemoglobin (%)	−0.30±0.28	−0.06±0.30	−0.23 (−0.25 to −0.21)	<0.001
Fasting glucose (mg/dl)	−7.1±10.8	0.1±10.4	−6.9 (−7.5 to −6.3)	<0.001
Fasting insulin (%)	−12.6	−4.4	−8 (−12 to −5)	<0.001
Fasting C-peptide (%)	−8.9	−7.9	−1 (−3 to 2)	0.51
Vital signs				
Systolic blood pressure (mm Hg)	−4.2±12.2	−1.5±12.4	−2.8 (−3.56 to −2.09)	<0.001
Diastolic blood pressure (mm Hg)	−2.6±8.7	−1.9±8.7	−0.9 (−1.41 to −0.37)	<0.001
Pulse (beats/min)	2.5±9.8	0.1±9.5	2.4 (1.9 to 3.0)	<0.001
Fasting lipid profile				
Cholesterol (%)				
Total	−3.1	−1.0	−2.3 (−3.3 to −1.3)	<0.001
LDL	−3.0	−1.0	−2.4 (−4.0 to −0.9)	0.002
HDL	2.3	0.7	1.9 (0.7 to 3.0)	0.001
VLDL	−13.1	−5.5	−9.1 (−11.4 to −6.8)	<0.001
Non-HDL	−5.1	−1.8	−3.9 (−5.2 to −2.5)	<0.001
Triglycerides	−13.3	−5.5	−9.3 (−11.5 to −7.0)	<0.001

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

SCALE Diabetes - aim for weight loss

	3.0 mg	1.8 mg	Placebo
Demographic Characteristics[a]			
Patients, No.	423	211	212
Age, mean (SD), y	55.0 (10.8)	54.9 (10.7)	54.7 (9.8)
Women	203 (48.0)	103 (48.8)	115 (54.2)
Race/ethnicity[b]			
Asian	11 (2.6)	4 (1.9)	4 (1.9)
Black or African American	44 (10.4)	27 (12.8)	27 (12.7)
White	353 (83.5)	177 (83.9)	175 (82.5)
Other	13 (3.1)	3 (1.4)	5 (2.4)
Ethnic origin			
Hispanic or Latino	46 (10.9)	17 (8.1)	24 (11.3)
Non-Hispanic	375 (88.7)	194 (91.9)	187 (88.2)
Body weight, mean (SD), kg	105.7 (21.9)	105.8 (21.0)	106.5 (21.3)
Body mass index, mean (SD)[c]	37.1 (6.5)	37.0 (6.9)	37.4 (7.1)
Body mass index group[c]			
25.0-29.9 (preobese)	52 (12.3)	34 (16.1)	30 (14.2)
30.0-34.9 (obese class I)	139 (32.9)	62 (29.4)	59 (27.8)
35.0-39.9 (obese class II)	108 (25.5)	50 (23.7)	60 (28.3)
>40.0 (obese class III)	124 (29.3)	65 (30.8)	63 (29.7)
Waist circumference, mean (SD), cm	118.0 (14.4)	117.5 (14.7)	117.3 (14.0)
Duration of diabetes, mean (SD), y **HbA1c 8%**	7.5 (5.65)	7.4 (5.16)	6.7 (5.07)

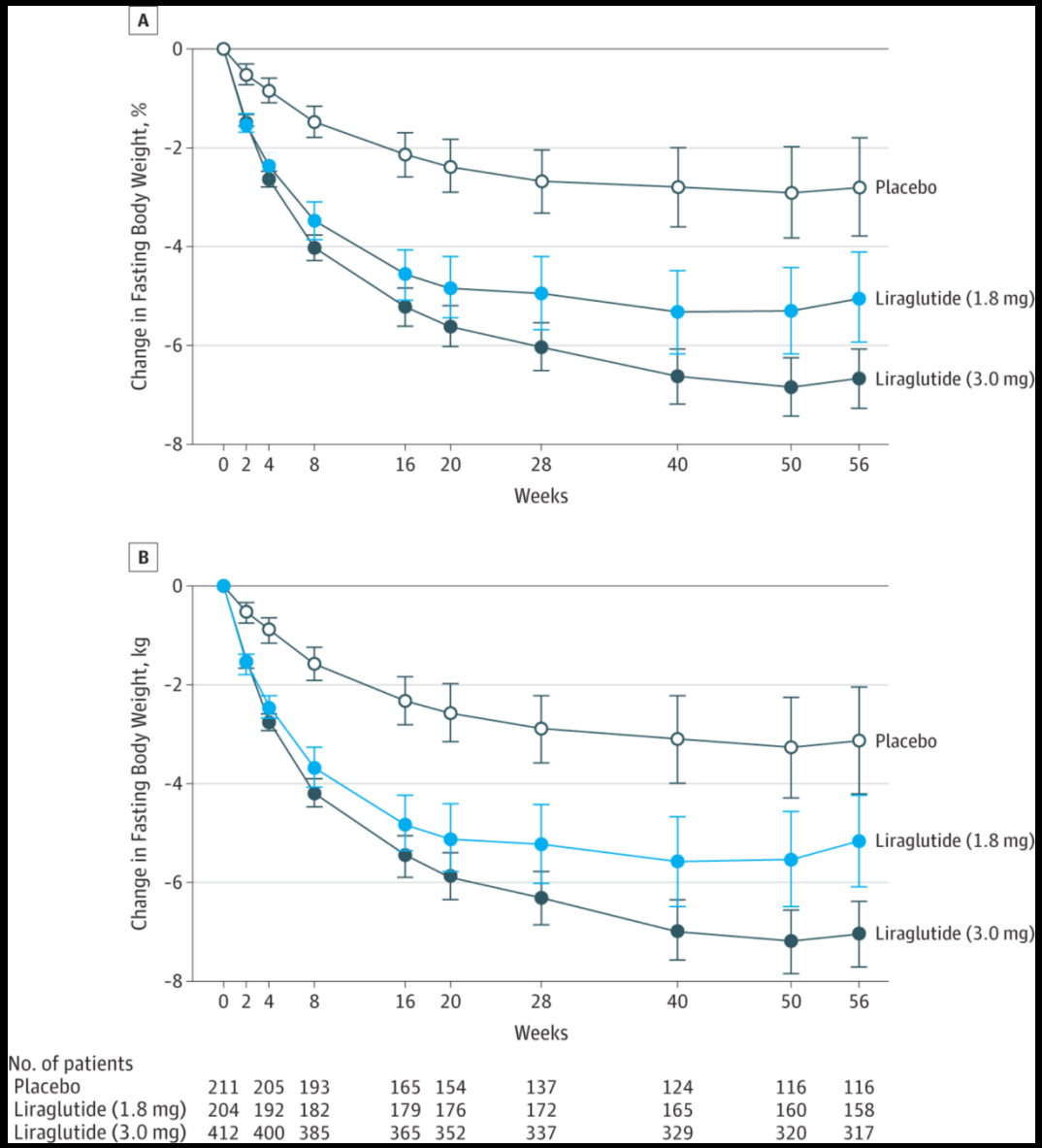
Davies et al, JAMA. 2015;314(7):687-699

SCALE Diabetes - lifestyle

- <30% from fat
- 20% from protein
- 50% of energy from carbohydrates
- 500-kcal/d deficit
- ≥150 min/wk of brisk walking

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

SCALE Diabetes results



No. of patients									
Placebo	211	205	193	165	154	137	124	116	116
Liraglutide (1.8 mg)	204	192	182	179	176	172	165	160	158
Liraglutide (3.0 mg)	412	400	385	365	352	337	329	320	317

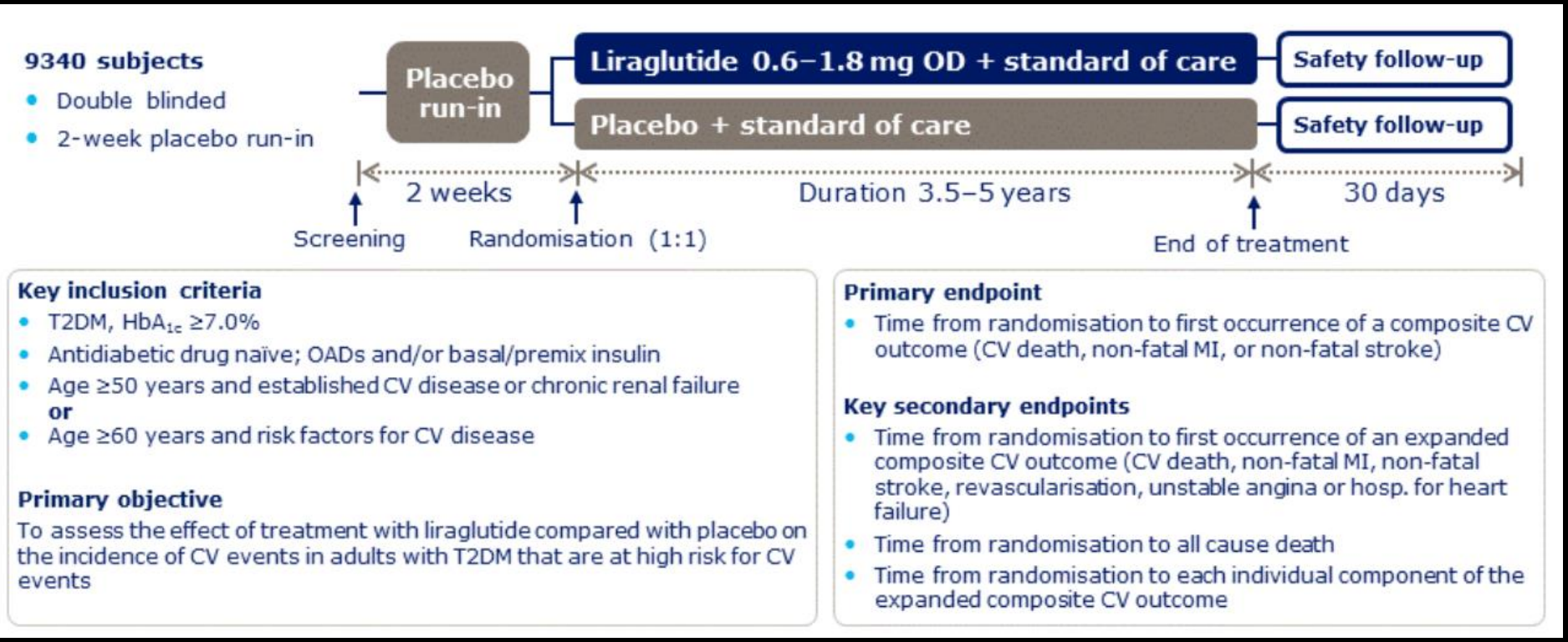
JAMA. 2015;314(7):687-699

SCALE Diabetes results

End Point	Baseline Value, Full Analysis Set, Mean (SD), kg	Mean and Categorical Weight Loss at Week 56		
		Liraglutide		
		3.0 mg (n = 412)	1.8 mg (n = 204)	Placebo (n = 211)
Change from baseline, fasting body weight, %	106.0 (21.5)	-6.0	-4.7	-2.0
Observed means, %[b]	106.0 (21.5)	-5.9	-4.6	-2.0
Weight loss ≥5%, %	NA	54.3[c]	40.4[c]	21.4[c]
Observed proportions, No. (%)[b]	NA	205 (49.9)	72 (35.6)	29 (13.8)
Weight loss, >10%, %	NA	25.2[c]	15.9[c]	6.7[c]
Observed proportions, No. (%)[b]	NA	96 (23.4)	29 (14.4)	9 (4.3)

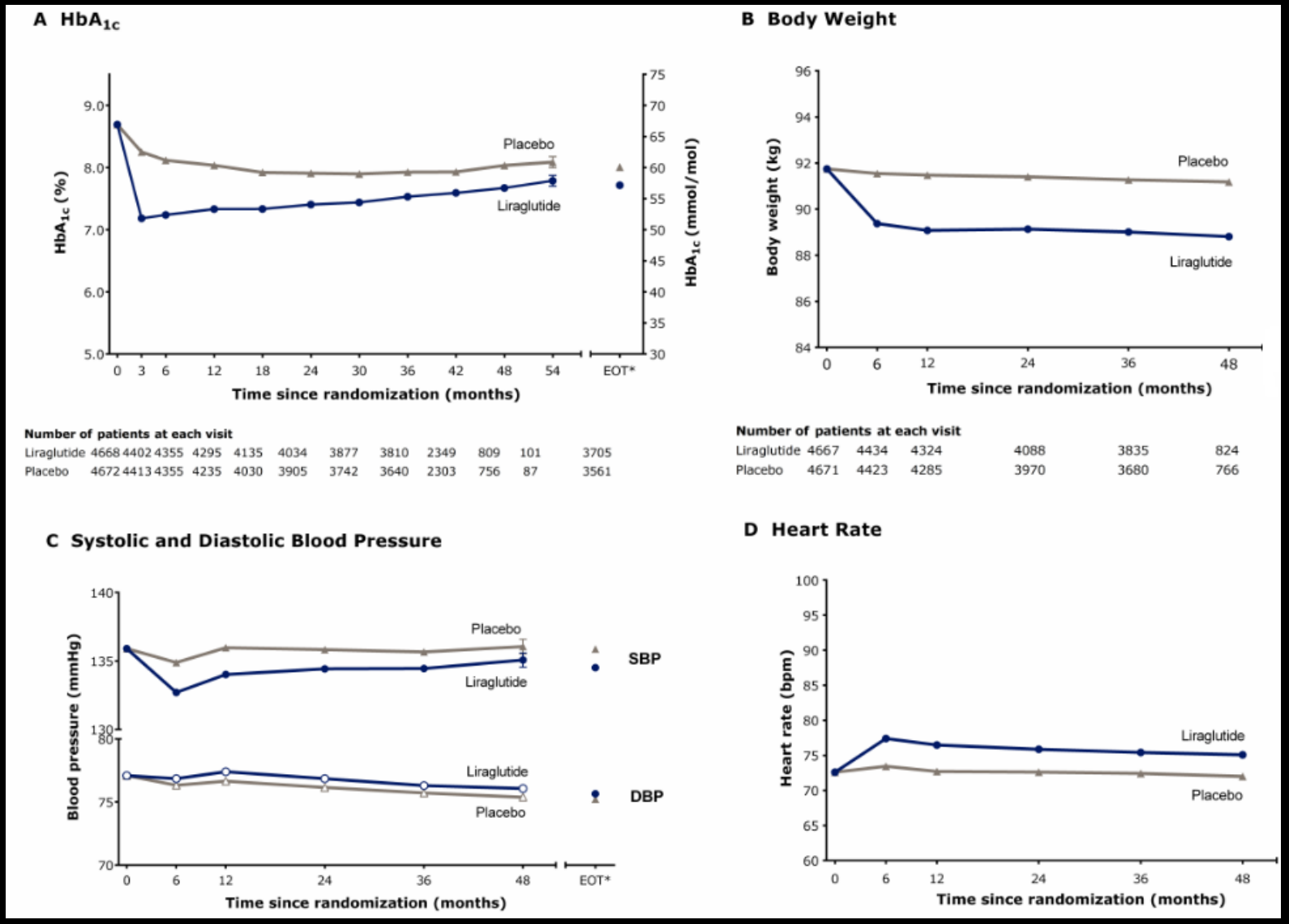
JAMA. 2015;314(7):687-699

Liraglutide for CV events in diabetes



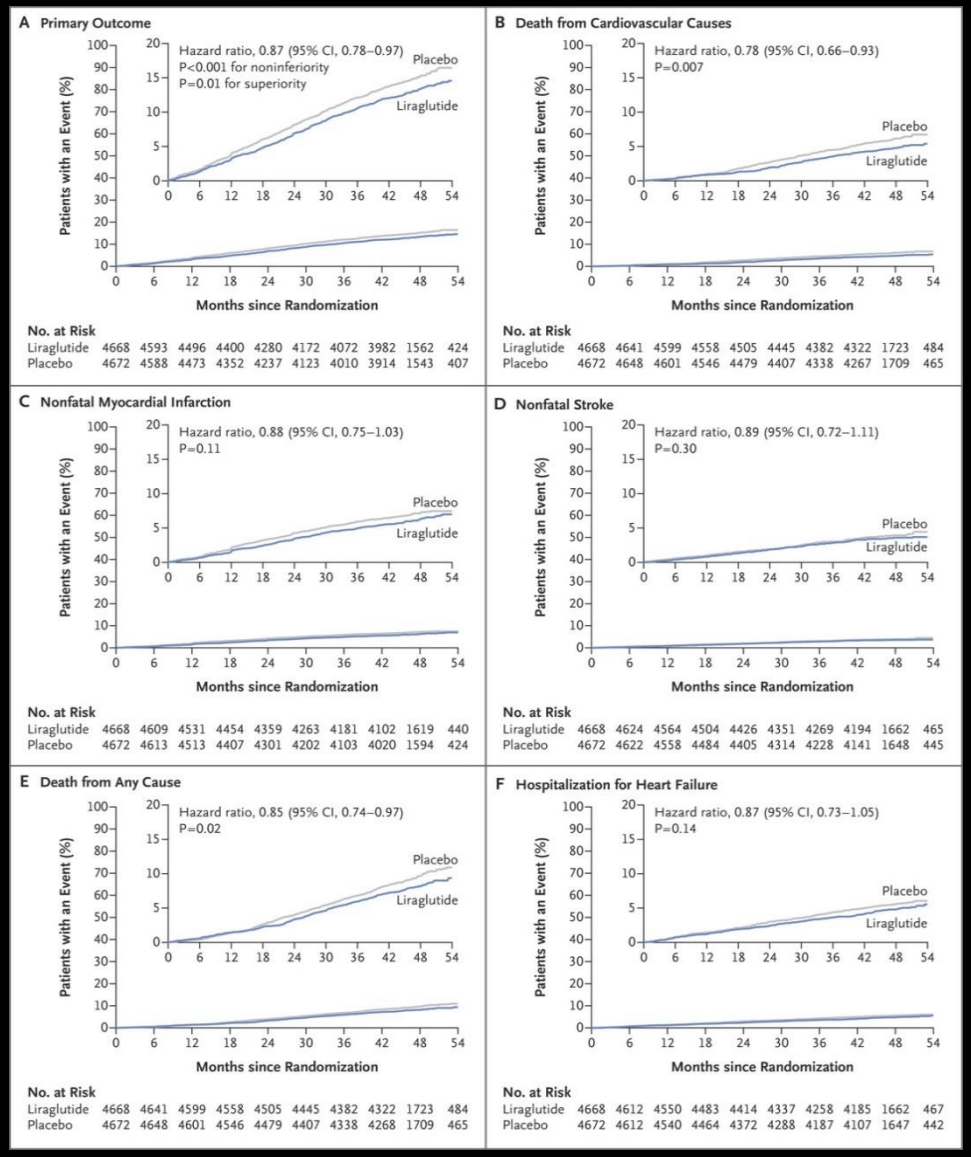
Marso SP et al. N Engl J Med 2016

Liraglutide for CV events in diabetes



Marso SP et al. N Engl J Med 2016

Primary and Exploratory Outcomes



Marso SP et al. N Engl J Med 2016.

Selected Adverse Events Reported during the Trial

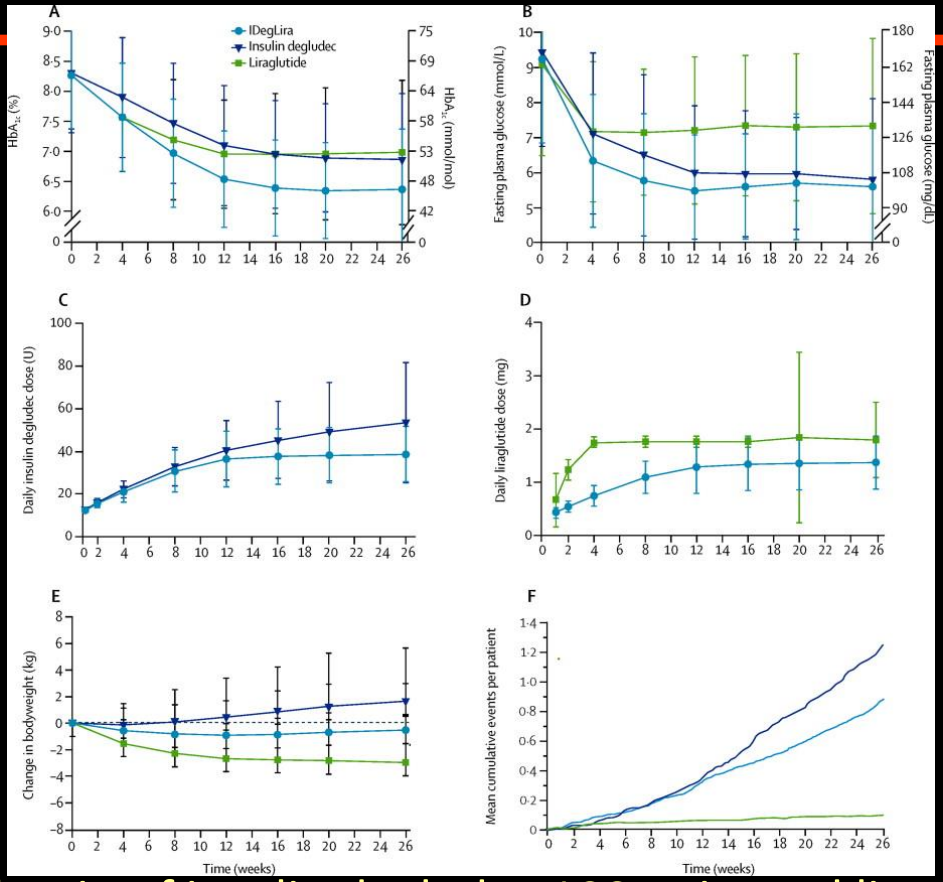
Table 2. Selected Adverse Events Reported during the Trial.*

Event	Liraglutide (N=4668)	Placebo (N=4672)	P Value
	no. of patients (%)		
Adverse event			
Any adverse event	2909 (62.3)	2839 (60.8)	0.12
Serious adverse event	2320 (49.7)	2354 (50.4)	0.51
Confirmed hypoglycemia†	2039 (43.7)	2130 (45.6)	0.06
Severe adverse event	1502 (32.2)	1533 (32.8)	0.51
Severe hypoglycemia†	114 (2.4)	153 (3.3)	0.02
Acute gallstone disease	145 (3.1)	90 (1.9)	<0.001
Cholelithiasis	68 (1.5)	50 (1.1)	0.09
Acute cholecystitis	36 (0.8)	21 (0.4)	0.046
Hypothyroidism	44 (0.9)	33 (0.7)	0.21
Hyperthyroidism	13 (0.3)	8 (0.2)	0.27
Diabetic foot ulcer	181 (3.9)	198 (4.2)	0.38
Allergic reaction	59 (1.3)	44 (0.9)	0.14
Injection-site reaction	32 (0.7)	12 (0.3)	0.002
Adverse event leading to permanent discontinuation of trial regimen			
Any adverse event	444 (9.5)	339 (7.3)	<0.001
Serious adverse event	192 (4.1)	245 (5.2)	0.01
Severe adverse event	164 (3.5)	188 (4.0)	0.20
Nausea	77 (1.6)	18 (0.4)	<0.001
Vomiting	31 (0.7)	2 (<0.1)	<0.001
Diarrhea	27 (0.6)	5 (0.1)	<0.001
Increased lipase level‡	15 (0.3)	11 (0.2)	0.43
Abdominal pain	11 (0.2)	3 (0.1)	0.03
Decreased appetite	11 (0.2)	2 (<0.1)	0.01
Abdominal discomfort	10 (0.2)	0	0.002
Pancreatitis or neoplasm§			
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Medullary thyroid carcinoma	0	1 (<0.1)	0.32

* Serious adverse events and nonserious medical events of special interest were identified by search in the *Medical Dictionary for Regulatory Activities*, version 18.0. Permanent discontinuation of the treatment regimen was indicated by the investigator in the adverse-event form. P values were calculated by means of Pearson's chi-square test.
† Confirmed hypoglycemia was defined a plasma glucose level of less than 56 mg per deciliter (3.1 mmol per liter). Severe hypoglycemia was defined as hypoglycemia for which the patient required assistance from a third party.
‡ Increased lipase levels were those that were reported by the investigator as adverse events.
§ Events of pancreatitis and neoplasms were adjudicated by the event-adjudication committee. This committee interpreted neoplastic growth as clonal disorders that grow in an autonomous manner. The abnormality of clonal disorder may not always have been identified nor could autonomous growth always be determined, but both were considered to be fundamental aspects of neoplastic growth.

Marso SP et al. N Engl J Med 2016

GLP-1 and insulin



- pen contains a fixed ratio of insulin degludec 100 units and liraglutide 1.8mg per mL
- doses can be adjusted by 1 unit of insulin degludec and 0.036 mg of liraglutide
- maximum dose at one time of 50 units of insulin degludec and 1.8 mg of liraglutide

The Lancet Diabetes & Endocrinology, Volume 2, Issue 11, 2014, 885–893

DPP4i CV data

	SAVOR-TIMI	EXAMINE	TECOS
Title	The Saxaglitpin Assessment of vascular Outcomes Recorded in Patients with DM	EXamination of cardiovascular outcomes with aloglitpiN versus standard of carE in patients with T2DM and acute coronary syndrome	Trial Evaluationg Cardiovascular Outcomes With Sitaglitpin
Population	age>40, CV disease OR multiple CV risk factors (1/4 of pts)	age >18 Acute Coronary Sy within 15-90 days	age>50 Established CV disease
Sample size	16,492	5,380	14,700
HbA1c range	6.5-12%	6.5-11%	6.5-8%
1o endpoint	Composite of CV death, non fatal MI, nonfatal stroke	Composite of CV death, non fatal MI, nonfatal stroke	Composite of CV death, non fatal MI, nonfatal stroke, or unstable angina requiring hospitalisation
Duration of FU	2.1 yrs	1.5yrs	4yrs

White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35

Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and car- diovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26

Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J. 2013;166(6):983–9

DPP4i CV data

	SAVOR-TIMI	EXAMINE	TECOS
Title	The Saxaglitpin Assessment of vascular Outcomes Recorded in Patients with DM	EXamination of cardiovascular outcomes with aloglitpiN versus standard of carE in patients with T2DM and acute coronary syndrome	Trial Evaluationg Cardiovascular Outcomes With Sitaglitpin
Population	**No increase or decrease in the rate of ischaemic events, though the rate of hospitalization for heart failure was increased**	age >18 Acute Coronary Sy within 15-90 days	age>50 Established CV disease
Sample size		5,380	14,700
HbA1c range		6.5-11%	6.5-8%
1o endpoint	Composite of CV death, non fatal MI, nonfatal stroke	Composite of CV death, non fatal MI, nonfatal stroke	Composite of CV death, non fatal MI, nonfatal stroke, or unstable angina requiring hospitalisation
Duration of FU	2.1 yrs	1.5yrs	4yrs

White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35

Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and car- diovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26

Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiov

DPP4i CV data

	SAVOR-TIMI	EXAMINE	TECOS
Title	The Saxaglitpin Assessment of vascular Outcomes Recorded in Patients with DM	EXamination of cardiovascular outcomes with aloglitpiN versus standard of carE in patients with T2DM and acute	Trial Evaluationg Cardiovascular Outcomes With Sitaglitpin
Population	age>40, CV disease OR multiple CV risk factors (1/4 of pts)		ge>50 Established CV disease
Sample size	16,492		4,700
HbA1c range	6.5-12%		5-8%
1o endpoint	Composite of CV death, non fatal MI, nonfatal stroke	death, non fatal MI, nonfatal stroke	Composite of CV death, non fatal MI, nonfatal stroke, or unstable angina requiring hospitalisation
Duration of FU	2.1 yrs	1.5yrs	4yrs

No increase CV risk in Type 2 diabetes patients at high-risk for major adverse cardiac events (MACE) due to a recent acute coronary syndrome

White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35

Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and car- diovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26

Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiov

Lorcaserin

Parameter	BLOOM-DM[17]			BLOSSOM[16]			BLOOM[15] (original study)		BLOOM[15] (extension)		
	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg	Placebo	20 mg	Placebo (2 years)	20 mg then placebo (1 year each)	20 mg (2 years)
Enrolled (*n*)	252	95	256	1,601	801	1,602	1,499	1,538	697	283	573
Completed the study *n* (%)	157 (62)	75 (79)	169 (66)	834 (52)	473 (59)	917 (57)	716 (45)	883 (55)	550 (79)	195 (69)	383 (67)
Weight change											
%	–1.6	–5*	–4.7*	–2.9	–4.7*	–5.8*	–2.2	–5.8*	–2.4	–3.3	–5.6*
Kg	–1.5	–5*	–4.5*	–2.8	–4.7*	–5.8*	–2.2	–5.8*	–2.4	–3.3	–5.6*
Placebo-corrected (%)	—	–3.4*	–3.1*	—	–1.8*	–2.9*	—	–3.6*	—	–0.9	–3.2*

- 5-HT_{2C} receptor agonist
- 0.5% absolute decrease in HbA1c
- Improvements in lipids and blood pressure
- No increase in the rate of cardiac valvular disease
- Side effects: headache, dizziness, dry mouth and nausea
- EMEA - marketing application withdrawn May 2013

Rueda Clausen, Nature Reviews Endo, 2013

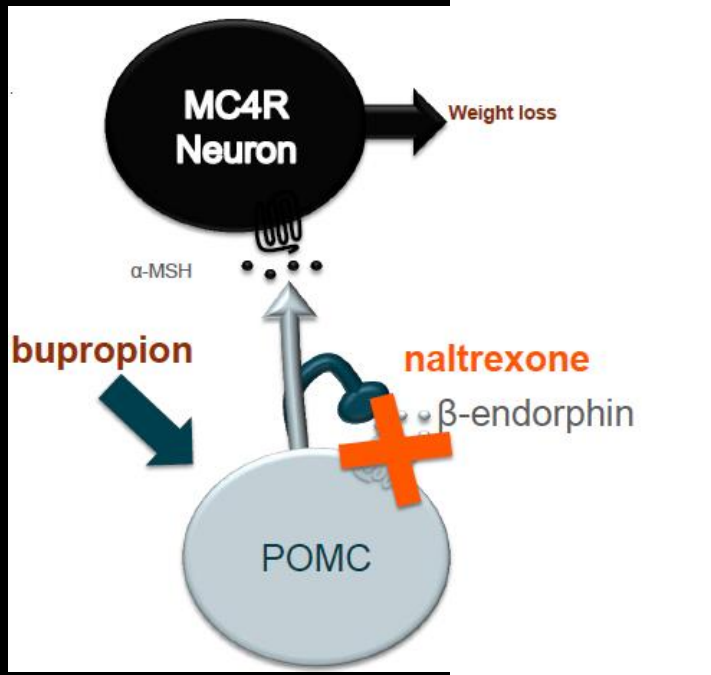
Phentermine + Topiramate

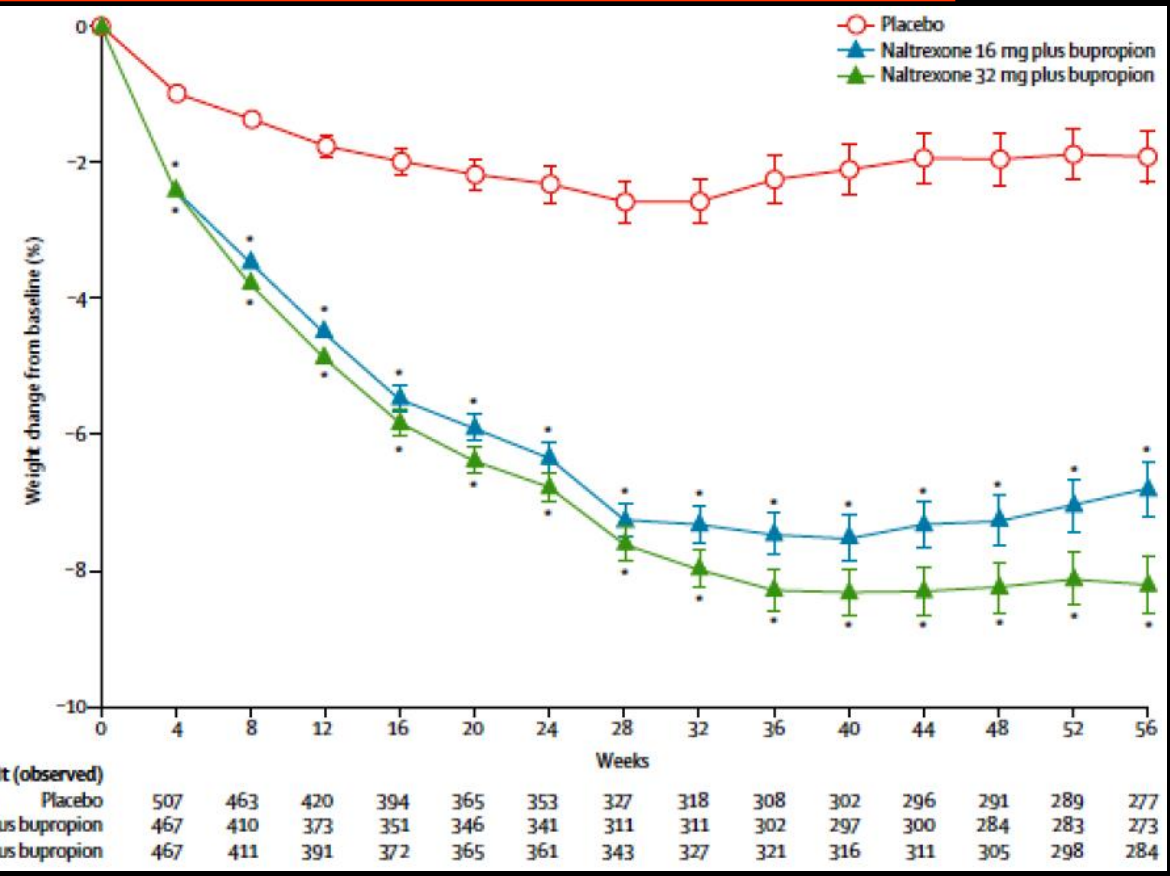
Parameter	EQUATE[29]			EQUIP[30]			CONQUER[31]			SEQUEL[32]		
	Placebo	P-T 7.5-46 mg	P-T 15-92 mg	Placebo	P-T 3.75-23 mg	P-T 15-92 mg	Placebo	P-T 7.5-46 mg	P-T 15-92 mg	Placebo	P-T 7.5-46 mg	P-T 15-92 mg
Enrolled *n*	103	103	103	514	241	512	994	498	995	227	153	295
Completed study *n*, (%)	69 (63)	73 (69)	68 (63)	241 (47)	138 (57)*	301 (59)*	616 (62)	374 (75)*	733 (74)*	165 (73)	99 (65)	195 (66)
Weight loss												
%	−1.5	−8.2*	−9.0*	−1.6	−5.1*	−10.9*	−1.2	−7.8*	−9.8*	−1.8	−9.3*	−10.5*
Kg	−1.5	−8.4*	−8.9*	−1.8	−6*	−12.6*	−1.4	−8.1*	−10.2*	−2.1	−9.6*	−10.9*
Placebo-corrected (%)	—	−6.8*	−7.5*	—	−3.5*	−9.3*	—	−6.6*	−8.6*	—	−7.5*	−8.7*
>5%	16	62*	66*	17	45*	67*	21	62*	70*	30	75*	79*
>10%	7	39*	41*	3	19*	47*	7	37*	48*	12	50*	54*

- Neuropsychiatric side effects
- EMEA - rejected October 2012 (CV risk profile, neuropsychiatric, teratogenicity)

Rueda Clausen, Nature Reviews Endo, 2013

Naltrexone + Bupropion

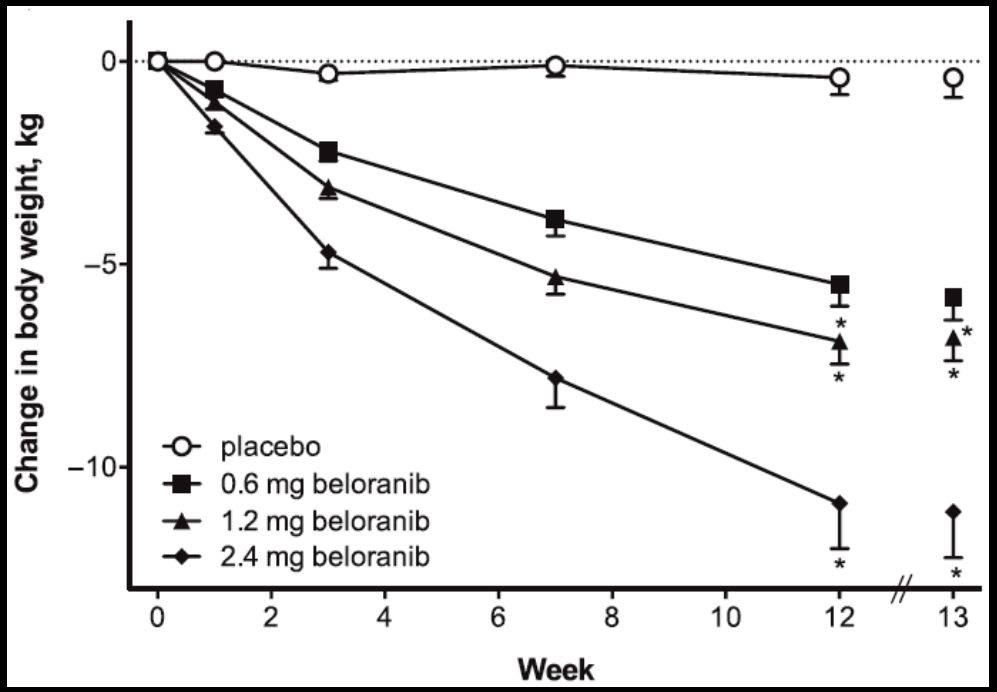


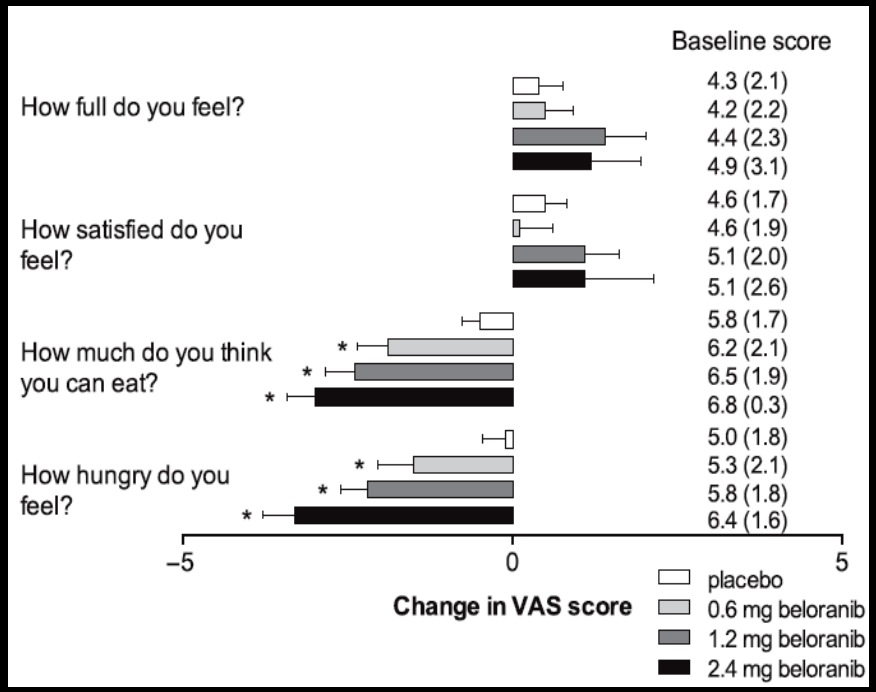


- Adverse effects include nausea, dry mouth, constipation
- Transient rise in BP (~1.5mmHg)
- Neuropsychiatric side effects (anxiety, insomnia)
- Now approved in USA & EU but requires a new CV outcomes trial

Greenway et al Lancet 2010

Belonarib





- Inhibitor of methionine aminopeptidase 2 (MetAP2)
- Stimulates fat oxidation, lipolysis, reduces appetite
- No lifestyle advice
- Main adverse effect increase in sleep latency, insomnia
- Favourable changes in CV risk factors
- Prader-Willi Syndrome & hypothalamic obesity

DOM 2015

EMPAREG - Design

- Randomized, double-blind, placebo-controlled trial
- once-daily empagliflozin versus placebo
- cardiovascular events in adults with type 2 diabetes
- at high cardiovascular risk

- Patients were treated at 590 sites in 42 countries

- Trial continued until an adjudicated primary outcome event had occurred in at least 691 patients

Participants

- BMI < 45
- eGFR >30
- established cardiovascular disease
- no glucose-lowering agents for at least 12 weeks and HbA1c 7-9% or
- stable glucose-lowering and HbA1c 7-10%

Intervention

- 2-week, open-label, placebo run-in period in which background glucose- lowering therapy was unchanged
- Randomisation 1:1:1 ratio stratified according to:
  - HbA1c
  - BMI
  - eGFR
  - geographic region
- Background glucose-lowering therapy unchanged for 12 weeks
- After week 12 investigators encouraged to adjust therapies at their discretion

Outcomes

- Primary outcome: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

- Secondary outcome: composite of the primary outcome plus hospitalization for unstable angina.

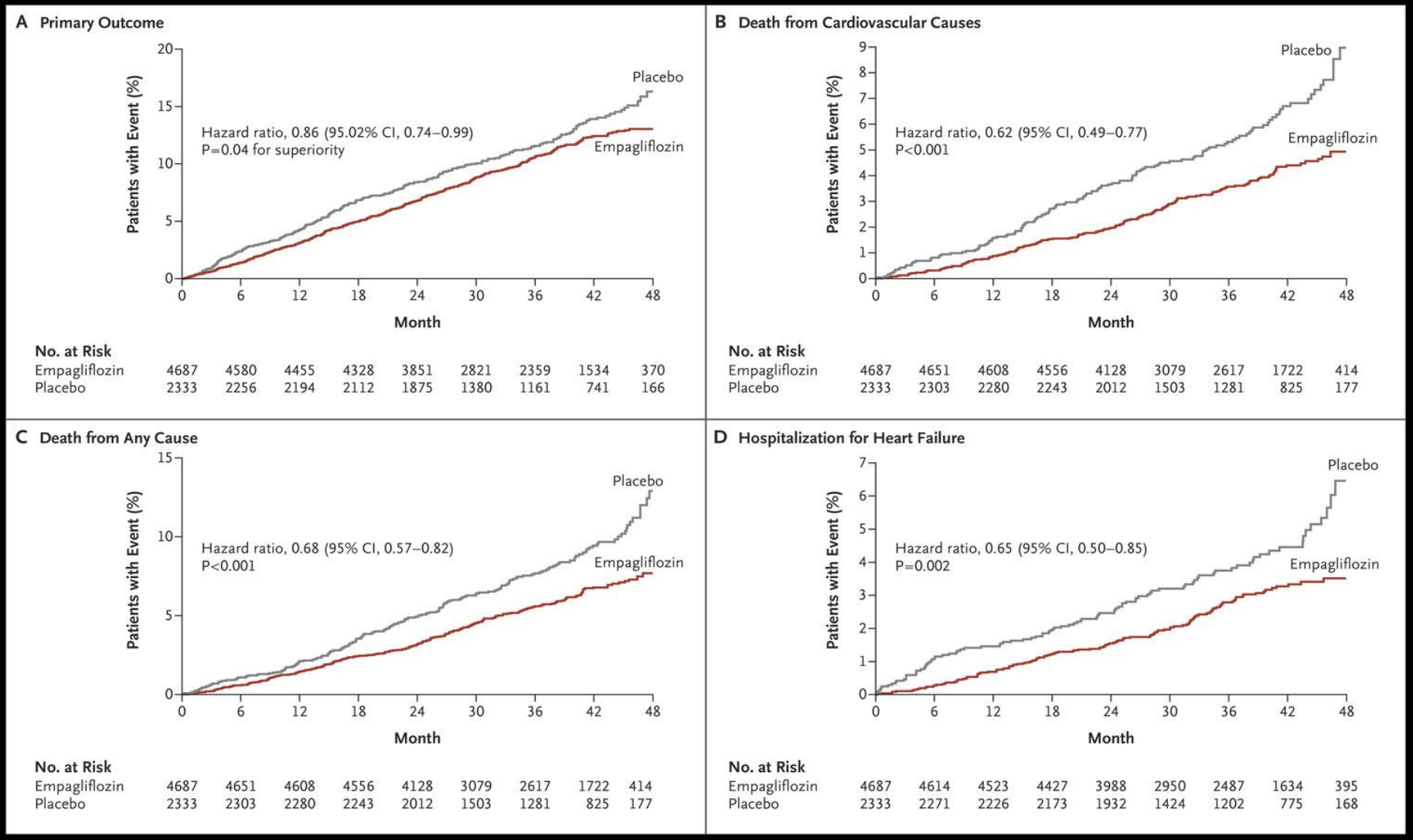
- Adverse events of special interest:
  - confirmed hypoglycaemia
  - urinary tract infection
  - genital infection
  - Volume depletion
  - acute renal failure
  - bone fracture
  - Diabetic ketoacidosis
  - thromboembolic events

Baseline characteristics

- 7028 patients
- 97.0% of patients completed the study
- 25.4% of patients prematurely discontinued a study drug
- Final vital status was available for 99.2%

- Demographic and clinical characteristics were well balanced
- > 99% of patients had established cardiovascular disease
- patients were well treated
- median duration of treatment 2.6 years
- median observation time 3.1 years

Cardiovascular Outcomes and Death from Any Cause



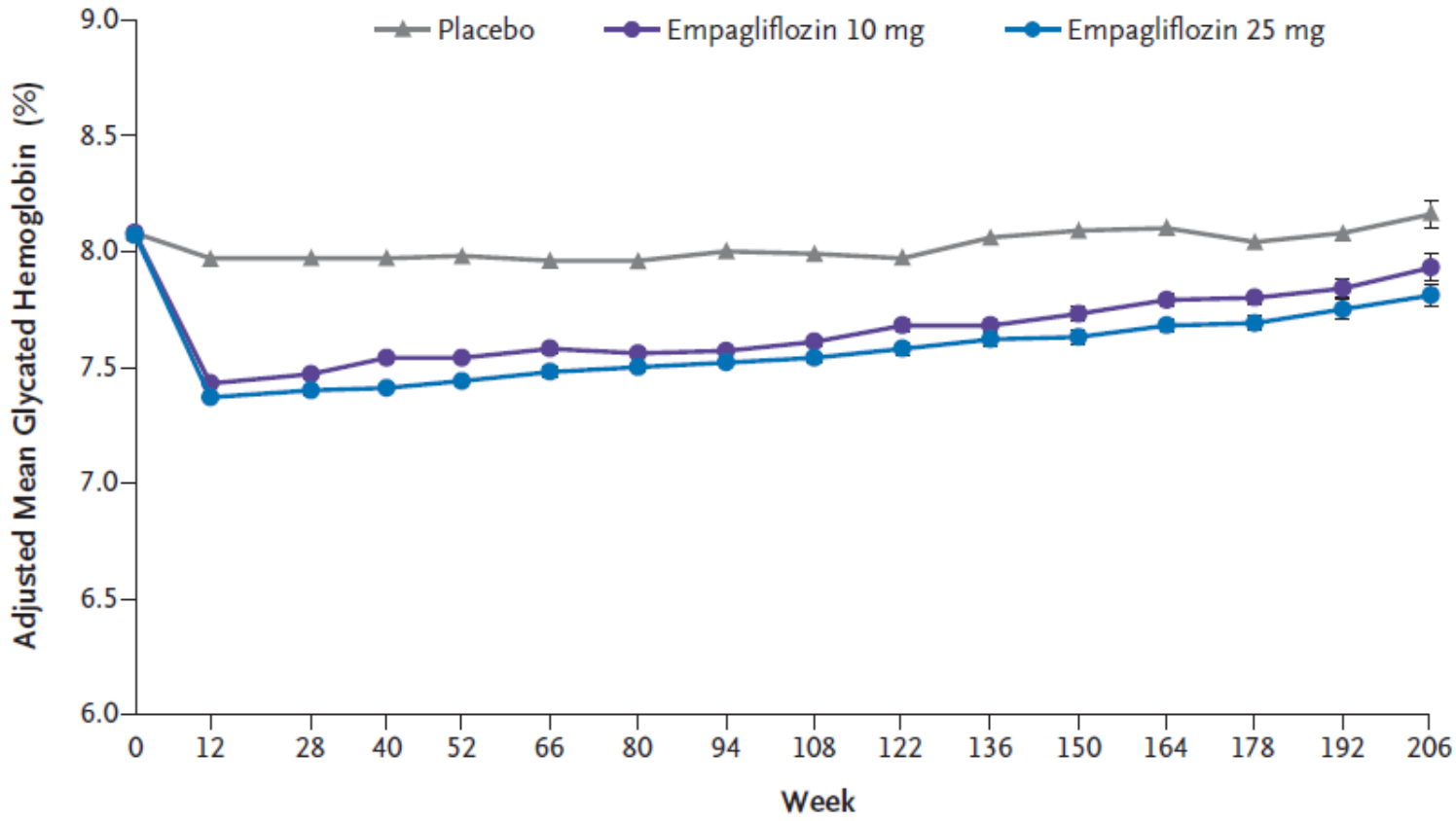
Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

Secondary outcomes

Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

HbA1c

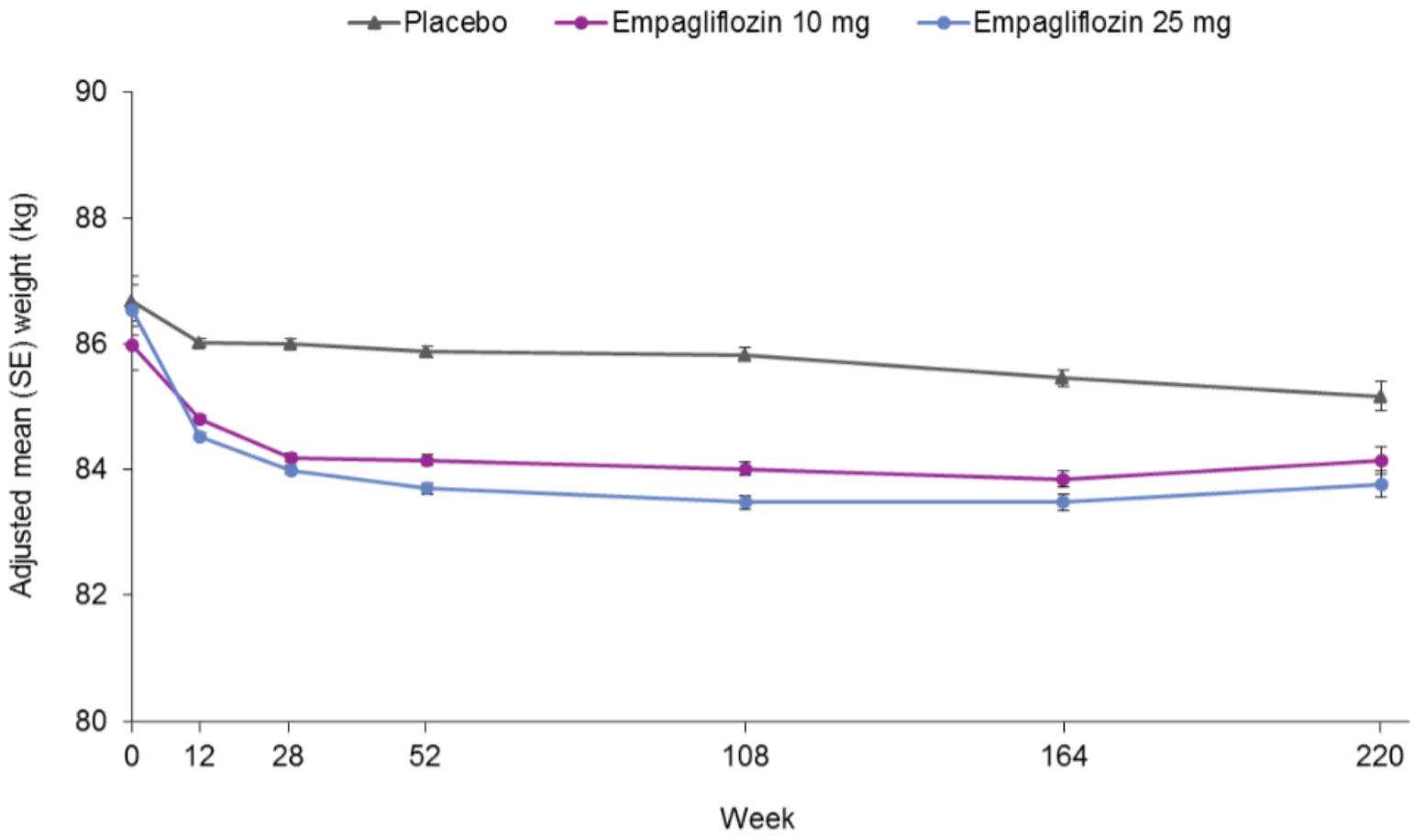


No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

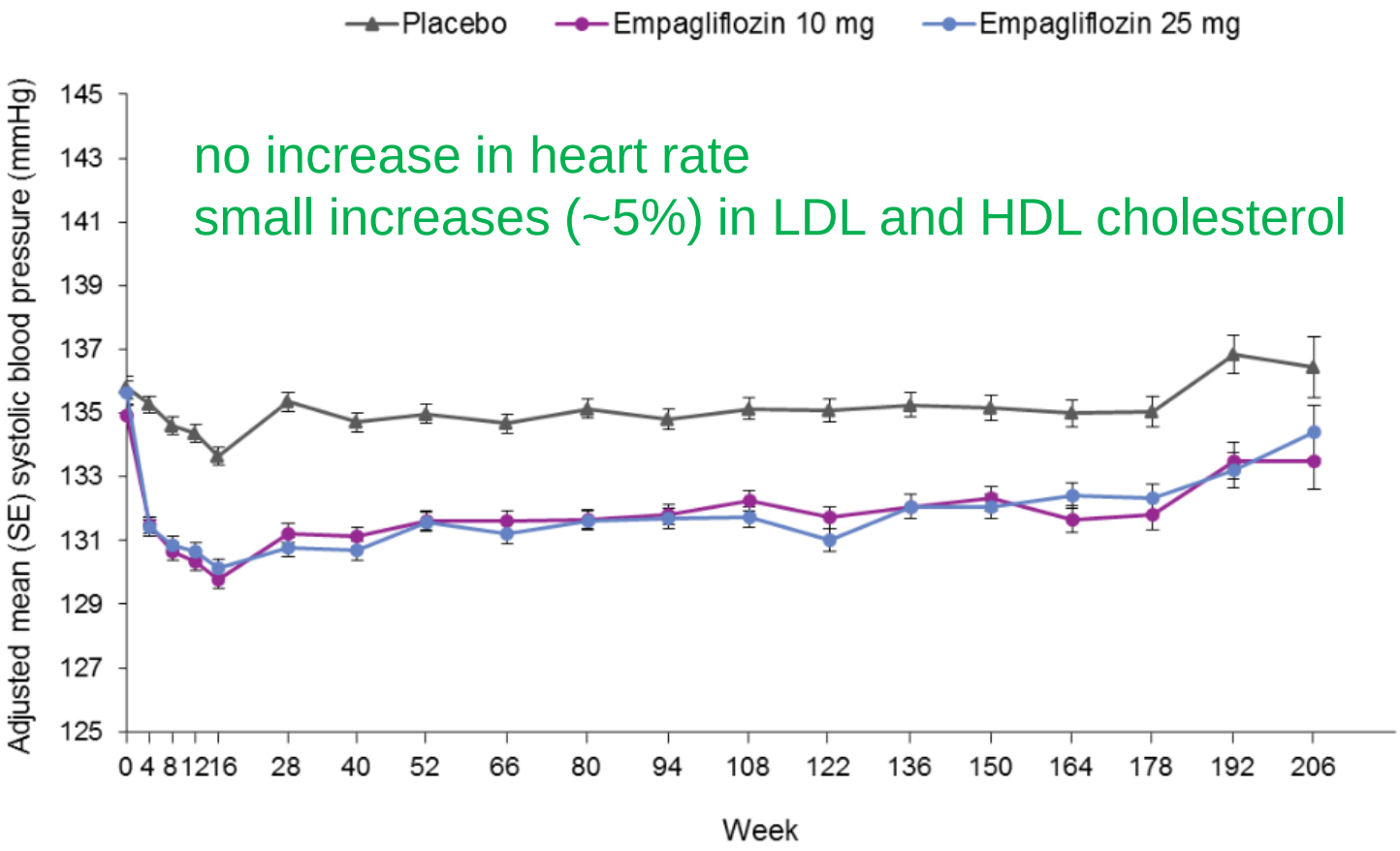
Weight



Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

Systolic BP



Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

Mechanisms

Multifactorial

- arterial stiffness
- cardiac function and oxygen demand
- cardio-renal effects
- reduction in albuminuria
- reduction in uric acid
- weight
- visceral adiposity
- blood pressure

- Main effect was on death. Why?

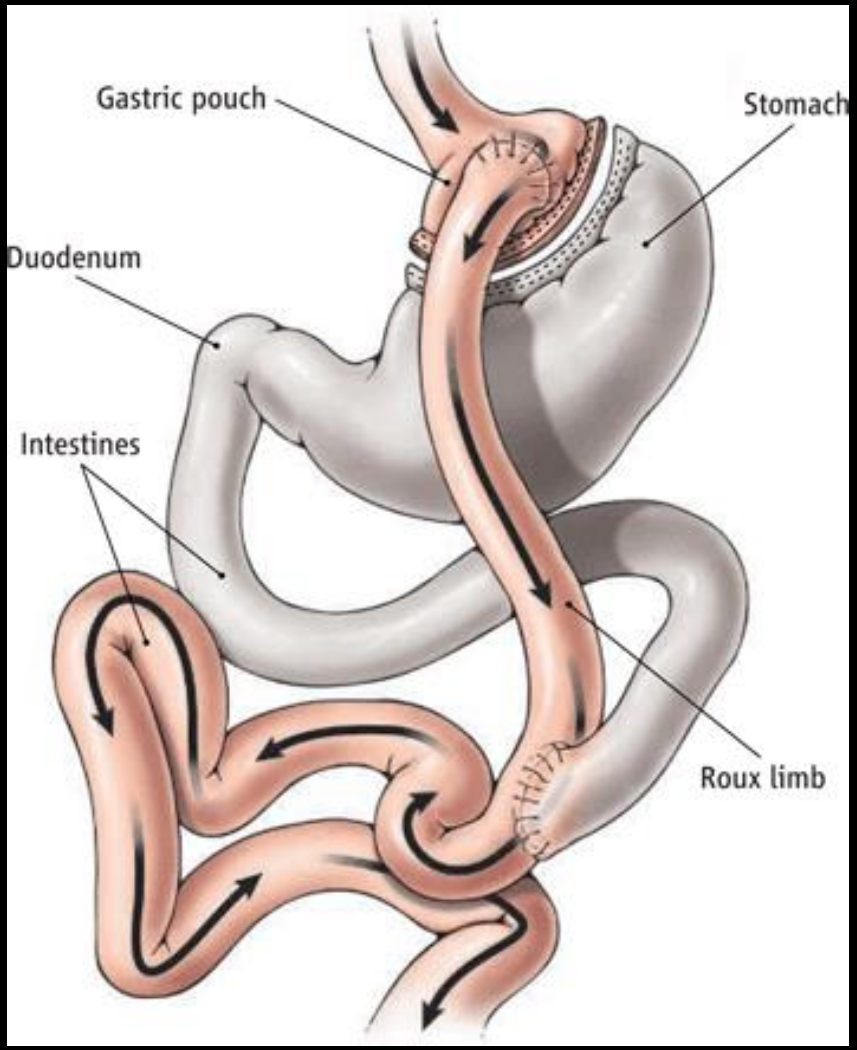
- ? Type 1 DM

Discussion

- Hurray!
- ? class effect
- No differences in MI or strokes
- Difference between doses tiny
- NNT: 39 patients during 3-year period to prevent 1 death

(too good to be true?)

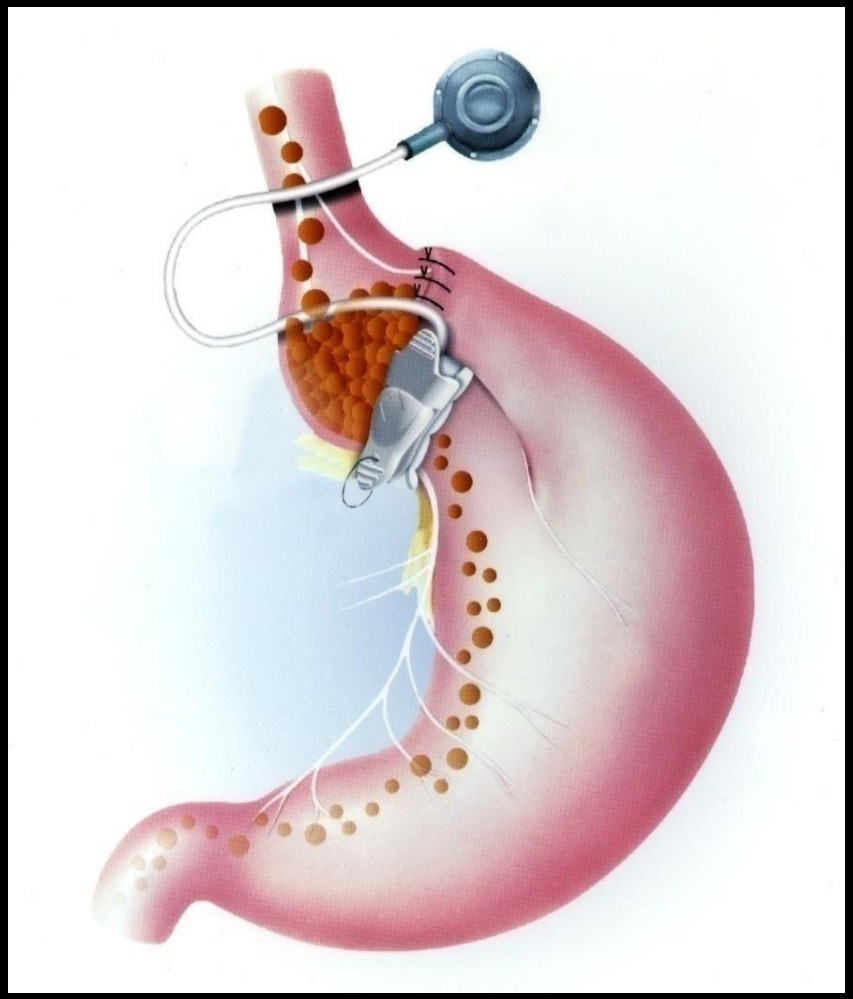
Gastric bypass - It's five operations in one!



- **Laparoscopic**
  - 1-2 hour procedure
  - 2-3 days in-patient
  - 25-30% weight loss
  - 1:300 Risk of Death

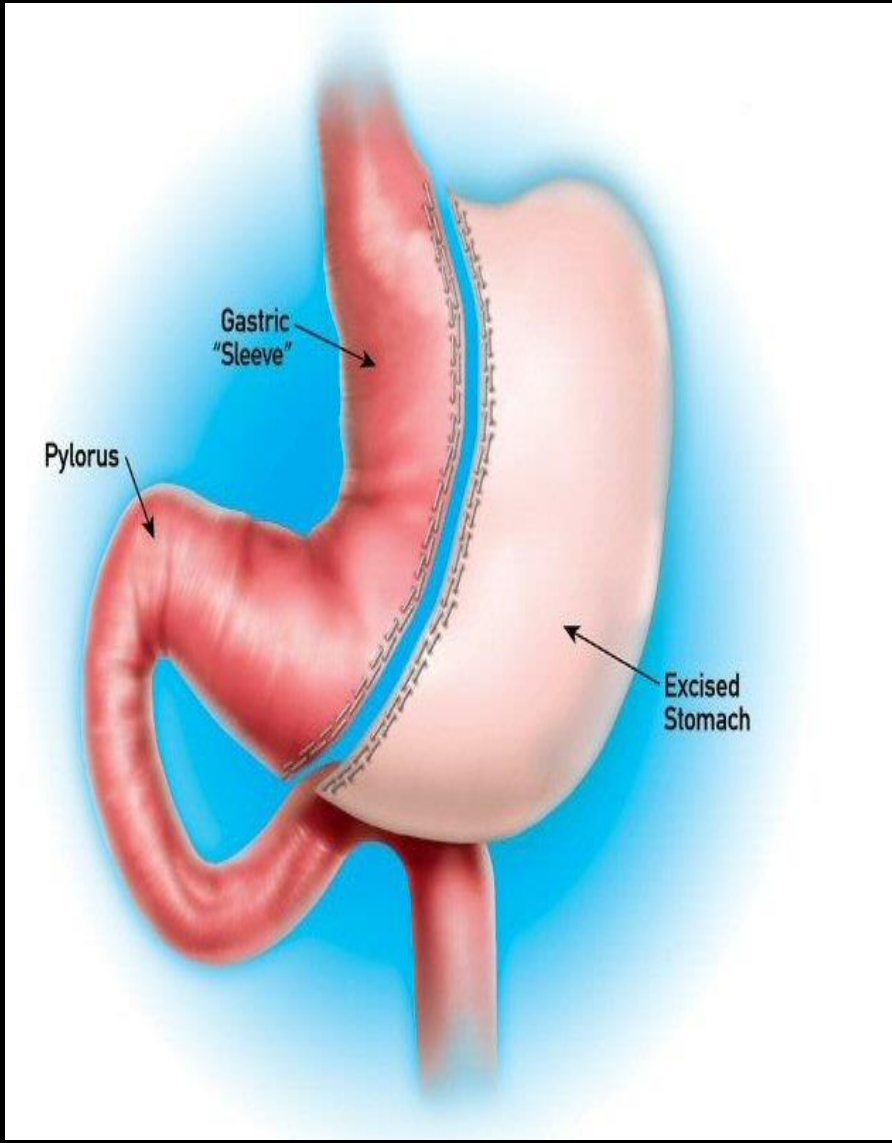
    Similar to a cholecystectomy

Adjustable Silastic Gastric Banding



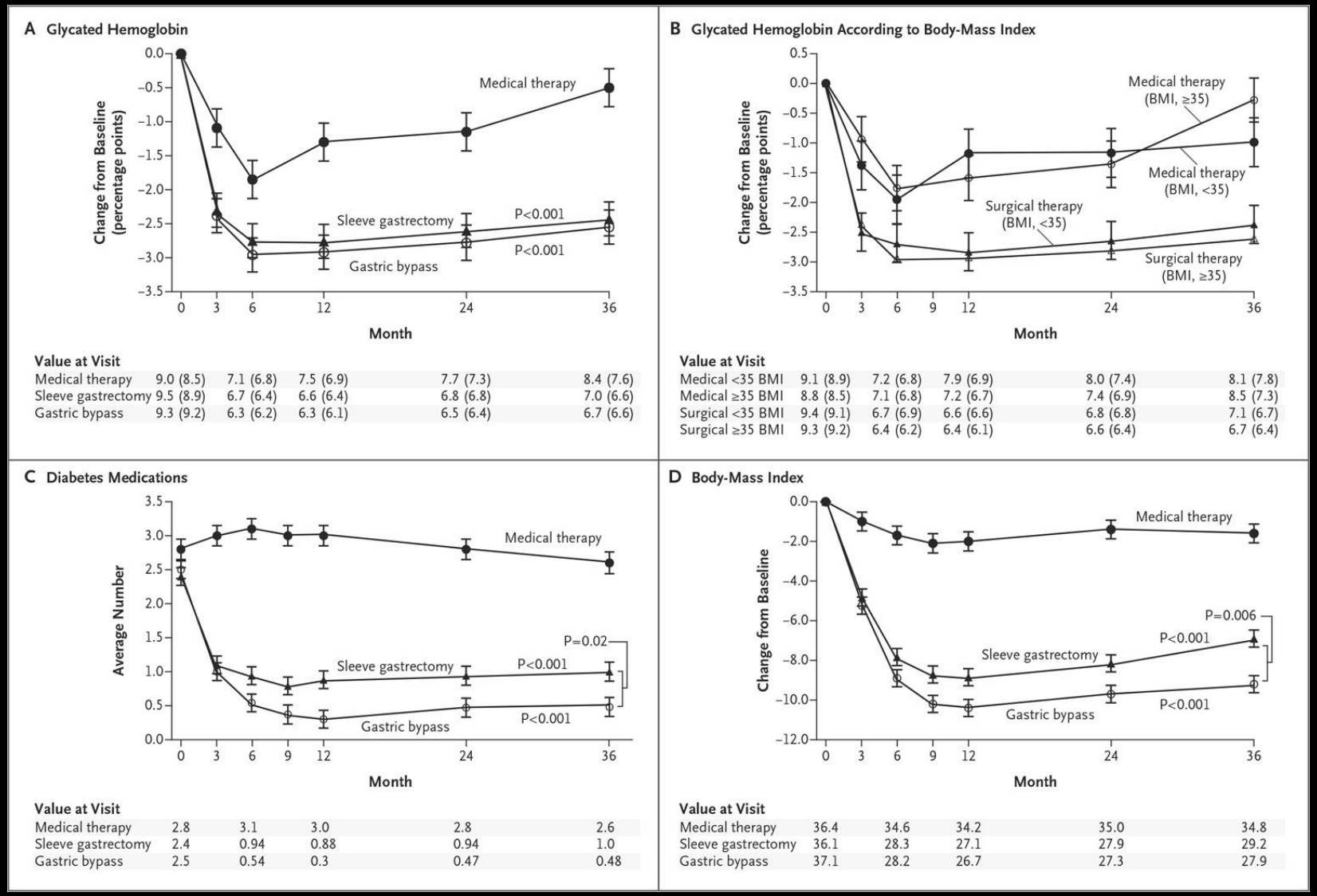
- Adjustable Lap Band
  - <1 hr procedure
  - 1 day in-patient
  - 20% weight loss
  - 1:1000 Risk of Death
  - High risk of re-operation
  - Self-sabotage easier
  - Reversible

Vertical sleeve gastrectomy



- **Laparoscopic**
  - 1-2 hour procedure
  - 2-3 days in-patient
  - 25% weight loss
  - 1:300 Risk of Death
  - ? 1st choice for very obese

3 year effects of metabolic surgery



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 <35 BMI	9.1 (8.9)	7.2 (6.8)	7.9 (6.9)	8.0 (7.4)	8.1 (7.8)
Medical ≥35 BMI	8.8 (8.5)	7.1 (6.8)	7.2 (6.7)	7.4 (6.9)	8.5 (7.3)
Surgical <35 BMI	9.4 (9.1)	6.7 (6.9)	6.6 (6.6)	6.8 (6.8)	7.1 (6.7)
Surgical ≥35 BMI	9.3 (9.2)	6.4 (6.2)	6.4 (6.1)	6.6 (6.4)	6.7 (6.4)

Value at Visit

Medical therapy	2.8	3.1	3.0	2.8	2.6
Sleeve gastrectomy	2.4	0.94	0.88	0.94	1.0
Gastric bypass	2.5	0.54	0.3	0.47	0.48

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

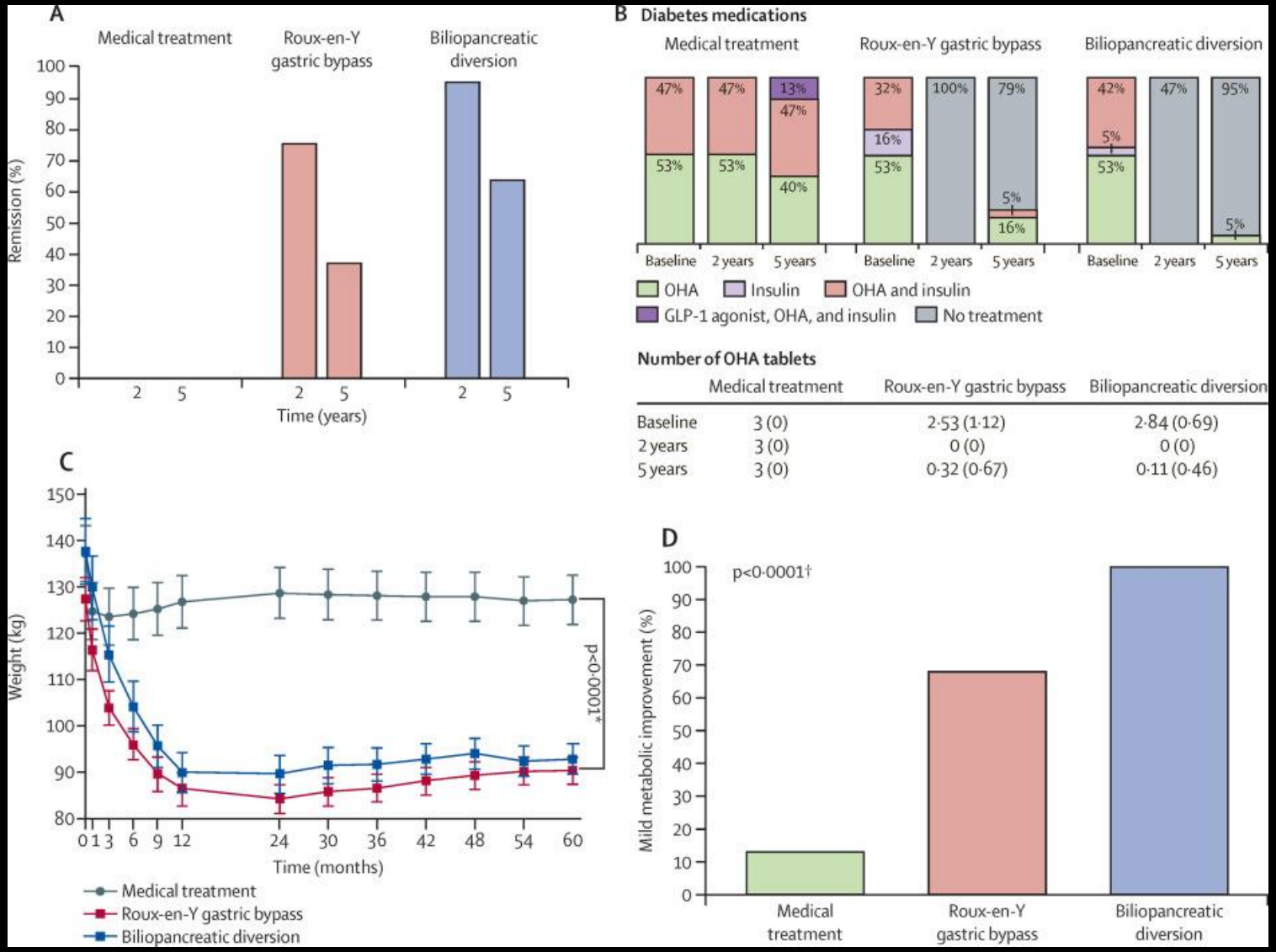
Schauer PR et al. N Engl J Med 2014;370:2002-2013

3 year metabolic effects of surgery

End Point	Medical Therapy (N=40)	Gastric Bypass (N=48)	Sleeve Gastrectomy (N=49)	P Value		
				Gastric Bypass vs. Medical Therapy	Sleeve Gastrectomy vs. Medical Therapy	Gastric Bypass vs. Sleeve Gastrectomy
Other risk factors						
% Change from baseline in low-density lipoprotein cholesterol	2.5±29.9	16.9±54.5	14.5±52.2	0.14	0.20	0.82
% Change from baseline in high-density lipoprotein cholesterol	4.6±20.7	34.7±27.3	35.0±31.0	<0.001	<0.001	0.96
Median % change from baseline in triglycerides (IQR)	−21.5 (−45.4 to 16.4)	−45.9 (−61.0 to −7.5)	−31.5 (−52.1 to −6.9)	0.01	0.01	0.18
Change from baseline in blood pressure — mm Hg						
Systolic	0.63±22.63	1.29±20.38	−4.43±20.69	0.88	0.27	0.17
Diastolic	−6.48±12.33	−4.25±10.57	−6.27±13.30	0.36	0.94	0.41

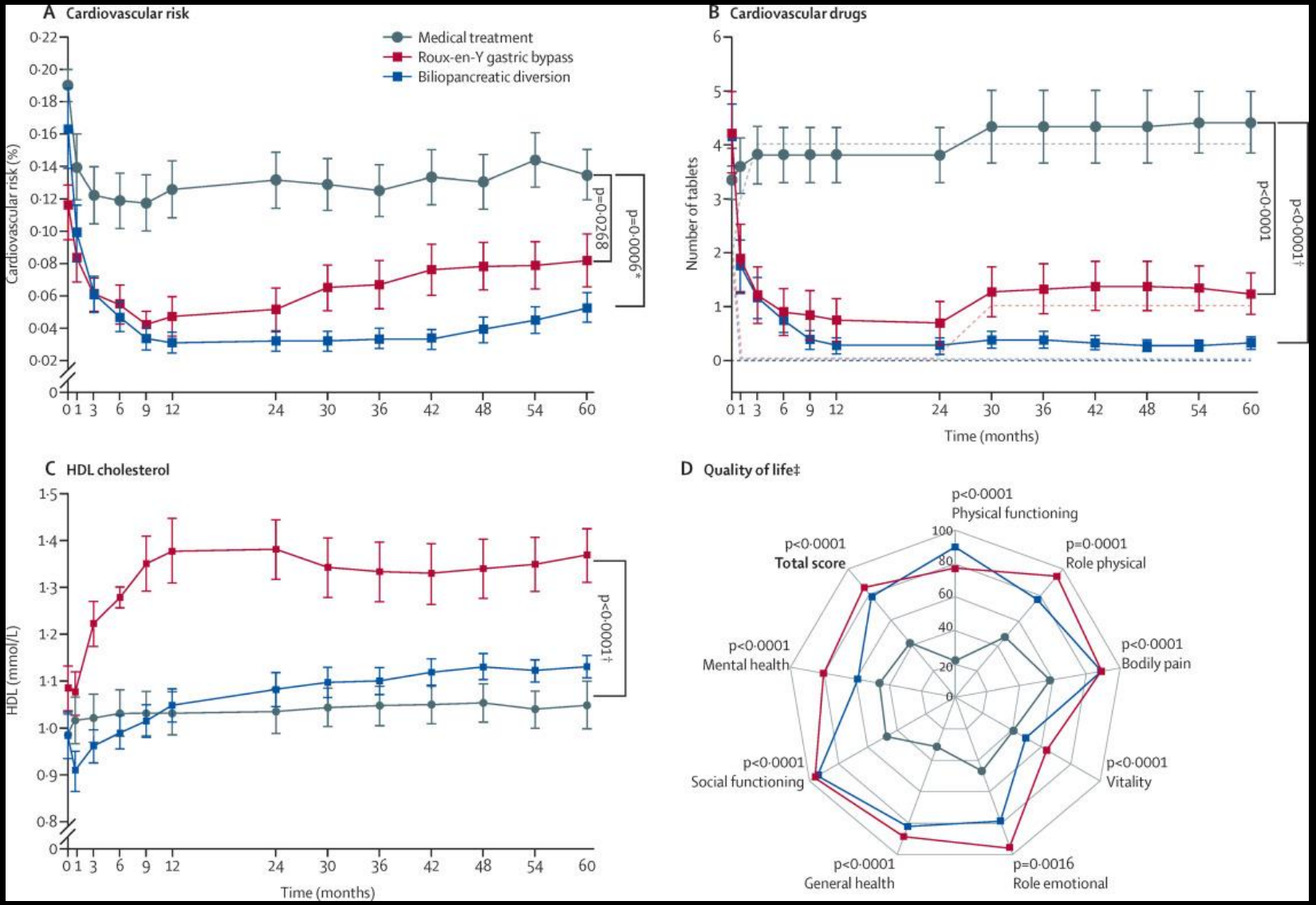
Schauer PR et al. N Engl J Med 2014;370:2002-2013

5 year effects of metabolic surgery



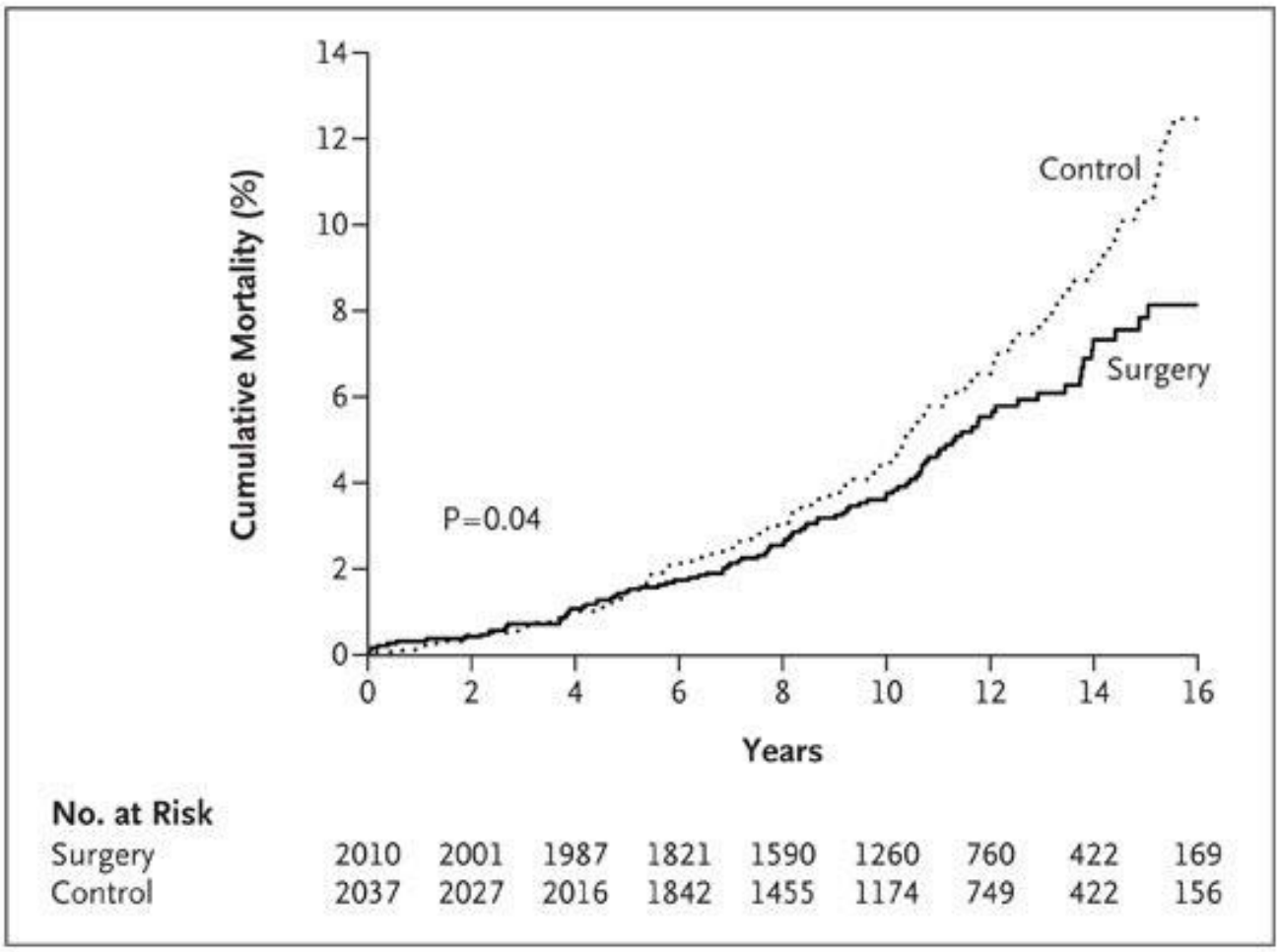
Geltrude Mingrone et al Lancet 2015

5 year metabolic effects of surgery



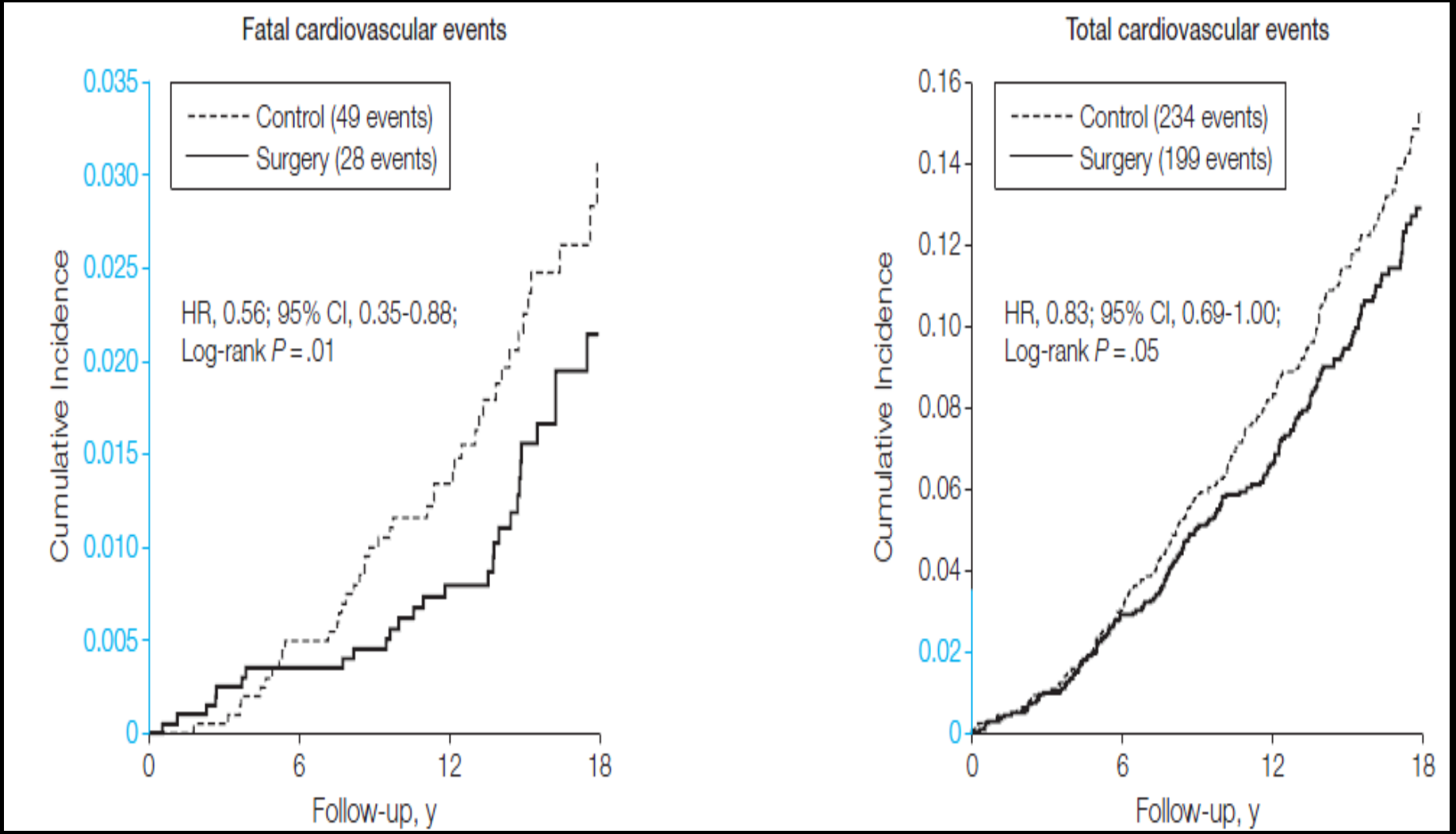
Geltrude Mingrone et al Lancet 2015

SOS - Mortality benefit



Sjostrom NEJM 2007

Bariatric surgery and CV mortality



Sjostrom et al, JAMA 2012, 307 (1) 56-65

Case 1

- 50 year old man
- BMI 40
- T2DM for 4 years on Metformin
- HbA1c 8%, BP 154/97, Cholesterol 6.3

Case 2

- 50 year Asian old man
- BMI 29.8
- T2DM for 8 years on Metformin+Dapa+Lira+Glic
- HbA1c 8%, BP 154/97, Cholesterol 6.3

Case 3

- 50 year old man
- BMI 60
- No T2DM
- BP 120/75, Cholesterol 3.1
- No other comorbidities

Case 4

- 50 year old man
- BMI 40
- Pre-diabetes
- BP 120/75, Cholesterol 3.1

Case 5

- 50 year old man
- BMI 40
- T2DM on basal bolus, HbA1c 11%
- Unstable retinopathy

Acknowledgements

Imperial College London
Steve Bloom
Tricia Tan
Harvinder Chahal
Samantha Scholtz
Christina Prechtl
Ahmed Ahmed
Sanjay Purkayastha
Krishna Moorthy

University College Dublin
Carel W le Roux
Sabrina Jackson

Florida State University
Alan C Spector

King's College London
Francesco Rubino
Ameet Patel
Royce Vincent

King Saud University,
Ghalia Abdeen

University of Wurzburg
Florian Seyfried

University of Zurich
Marco Bueter

a.miras@nhs.net

Definition of cardiovascular disease

- MI >2 months prior to informed consent
- Multi vessel coronary artery disease
- Evidence of single vessel coronary artery disease
- Unstable angina >2 months prior to consent
- History of stroke >2 months prior to consent
- Occlusive peripheral artery disease