How do I select between SGLT-2i and GLP-1 receptor analogues in people with established CV disease and type 2 diabetes?

Dr.Martin Whyte

Case study

50 year old Black British female

T2DM 10 years

BMI 34 kg/m^2

History of intermittent claudication

**FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA$_{1c}$ ABOVE TARGET PROCEED AS BELOW**

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD
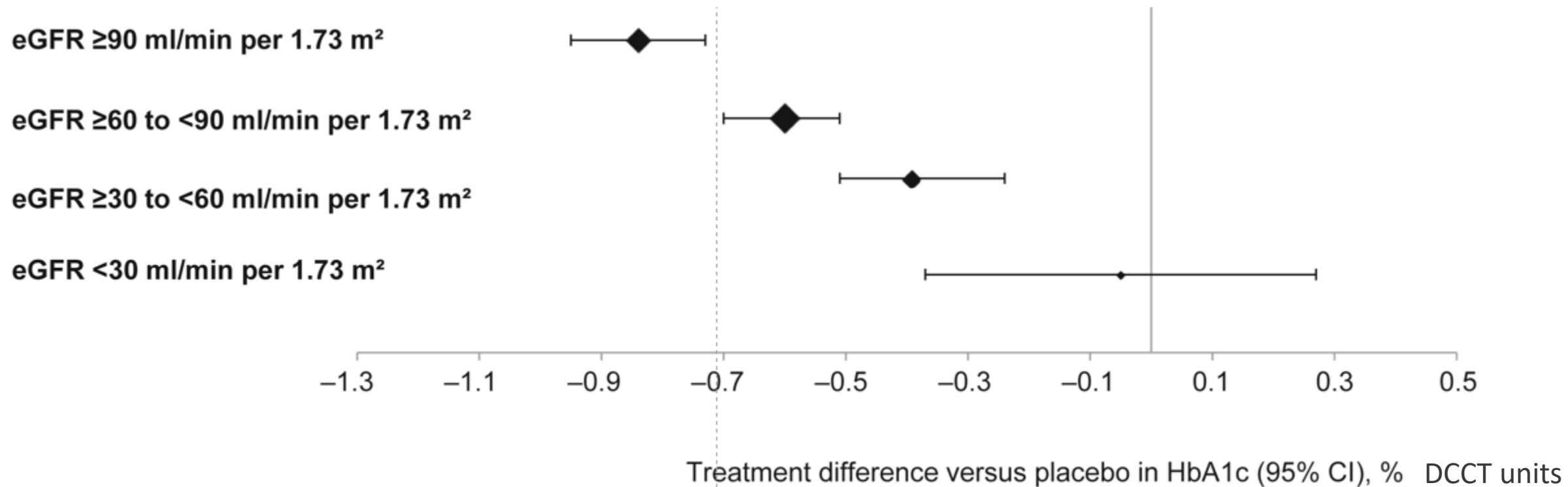
ASCVD PREDOMINATES

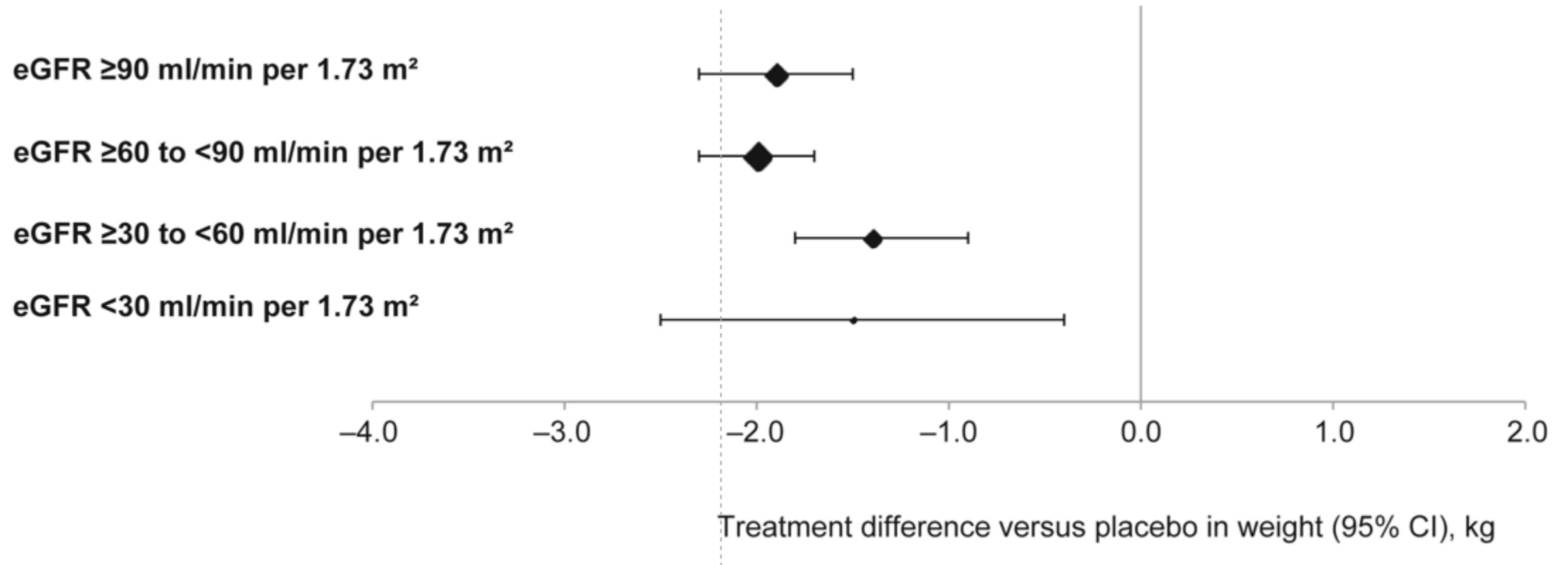**EITHER/OR**

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

Pooled analysis, change in HbA1c with empagliflozin

Pooled analysis, change in weight with empagliflozin

eGFR ≥90 ml/min per 1.73 m²

eGFR ≥60 to <90 ml/min per 1.73 m²

eGFR ≥30 to <60 ml/min per 1.73 m²

eGFR <30 ml/min per 1.73 m²

-4.0   -3.0   -2.0   -1.0   0.0   1.0   2.0

Treatment difference versus placebo in weight (95% CI), kg

CANVAS trial amputation

187 (1.8%) participants with atraumatic lower extremity amputations (minor 71%, major 29%)

6.30 vs 3.37 per 1000 participant-years with canagliflozin vs placebo (HR 1.97 [95% CI 1.41, 2.75]).

Risk similar for ischaemic and infective aetiologies, and for 100 mg and 300 mg doses.

Overall amputation risk associated with baseline history of prior amputation (major or minor) (HR 21.31 [95% CI 15.40, 29.49]) and other established risk factors.

The Impact of Liraglutide on Diabetes-Related Foot Ulceration and Associated Complications in Patients With Type 2 Diabetes at High Risk for Cardiovascular Events: Results From the LEADER Trial
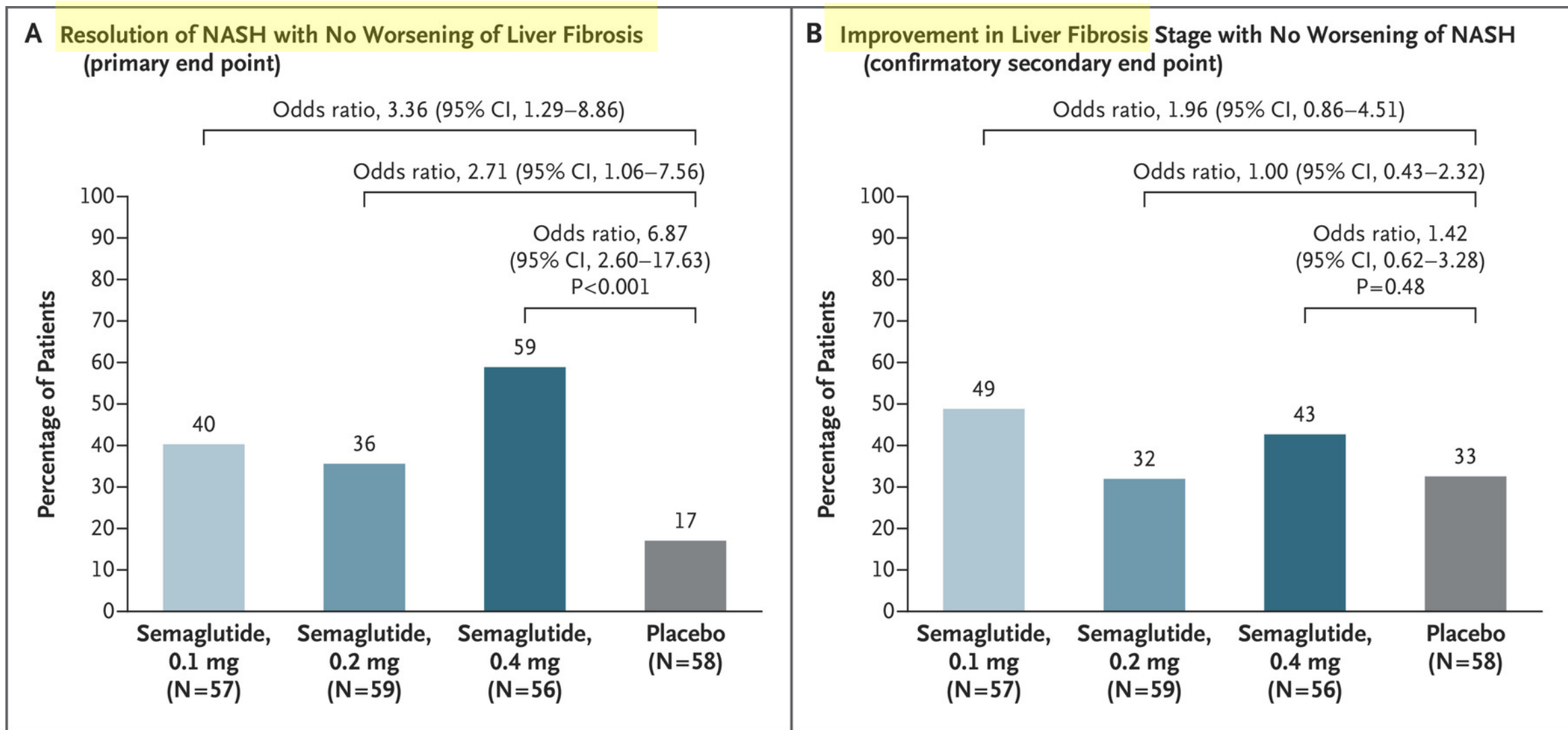
Ketan Dhatariya [1] [2], Stephen C Bain [3], John B Buse [4], Richard Simpson [5], Lise Tarnow [6], Margit Staum Kaltoft [7], Michael Stellfeld [7], Karen Tornøe [7], Richard E Pratley [8]; LEADER Publication Committee on behalf of the LEADER Trial Investigators

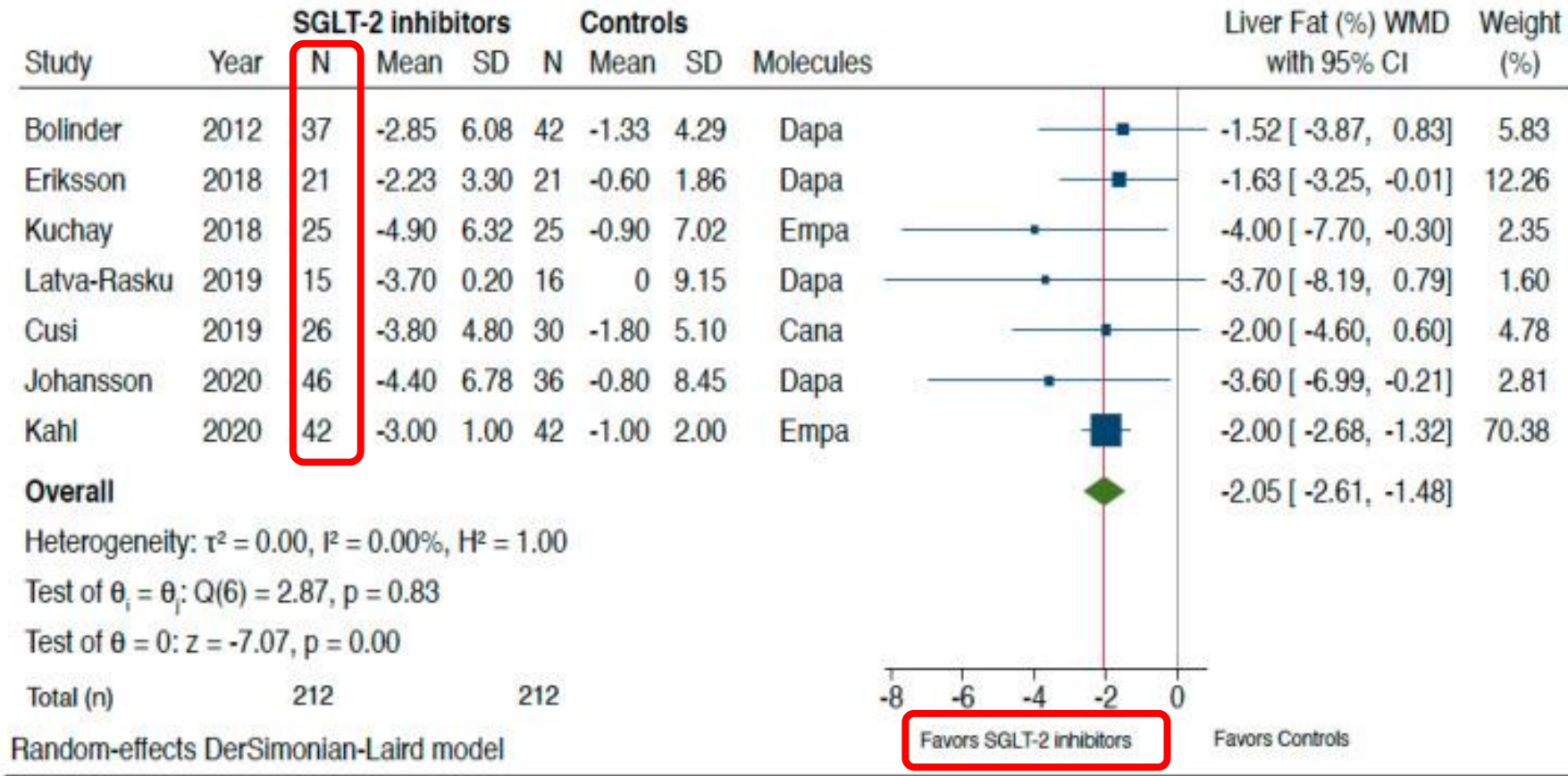What if liver stiffness 9 kPa; abdominal circumference 35 inches (90 cm)?

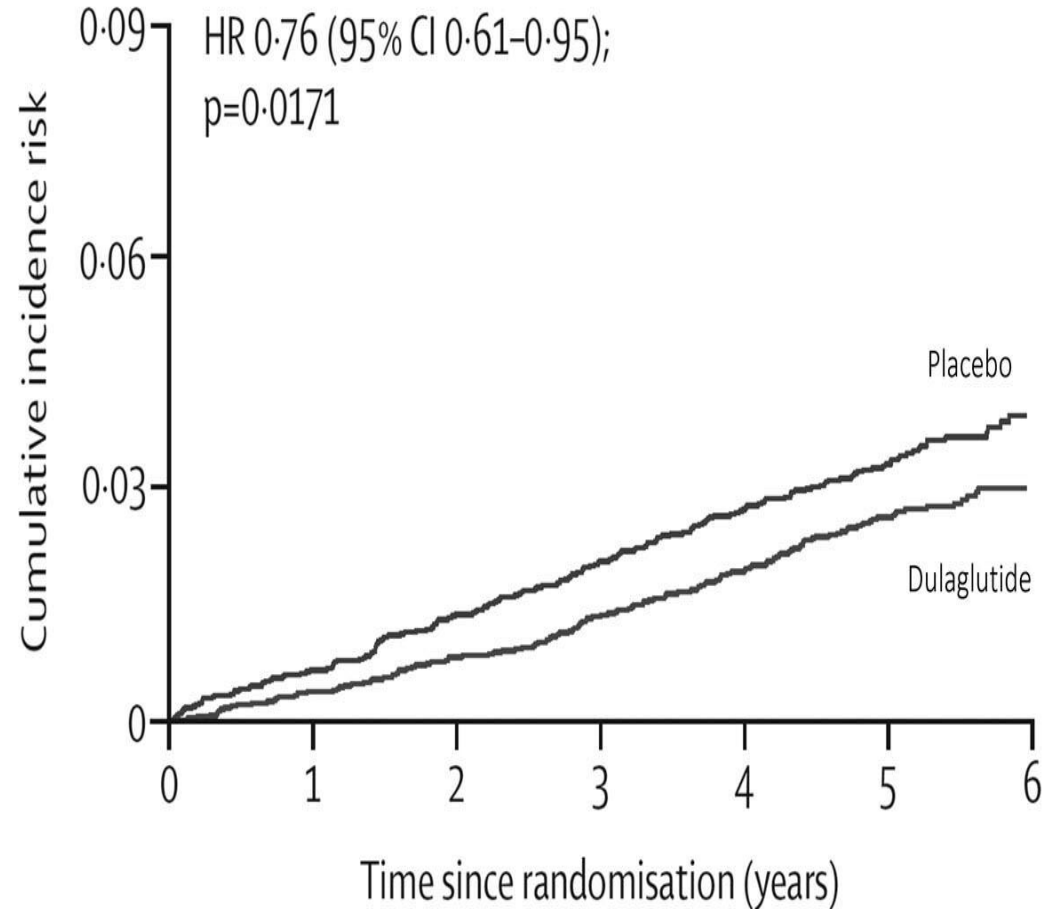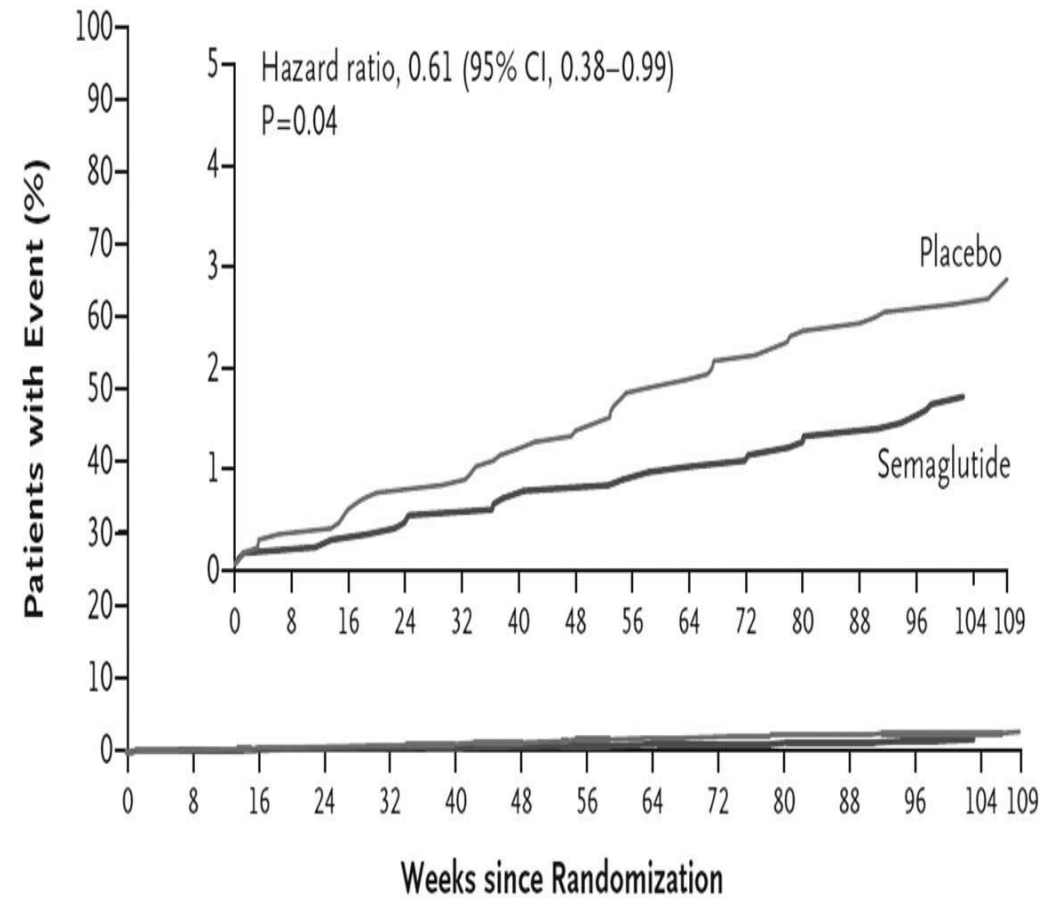# A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

Benefits of SGLT2i on liver fat by MR imaging

Study	Year	SGLT-2 inhibitors			Controls			Molecules	Liver Fat (%) WMD with 95% CI	Weight (%)
		N	Mean	SD	N	Mean	SD			
Bolinder	2012	37	-2.85	6.08	42	-1.33	4.29	Dapa	-1.52 [-3.87, 0.83]	5.83
Eriksson	2018	21	-2.23	3.30	21	-0.60	1.86	Dapa	-1.63 [-3.25, -0.01]	12.26
Kuchay	2018	25	-4.90	6.32	25	-0.90	7.02	Empa	-4.00 [-7.70, -0.30]	2.35
Latva-Rasku	2019	15	-3.70	0.20	16	0	9.15	Dapa	-3.70 [-8.19, 0.79]	1.60
Cusi	2019	26	-3.80	4.80	30	-1.80	5.10	Cana	-2.00 [-4.60, 0.60]	4.78
Johansson	2020	46	-4.40	6.78	36	-0.80	8.45	Dapa	-3.60 [-6.99, -0.21]	2.81
Kahl	2020	42	-3.00	1.00	42	-1.00	2.00	Empa	-2.00 [-2.68, -1.32]	70.38
Overall									-2.05 [-2.61, -1.48]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\theta_i = \theta_j$: Q(6) = 2.87, p = 0.83

Test of $\theta = 0$: z = -7.07, p = 0.00

Total (n)	212	212

Random-effects DerSimonian-Laird model

Favors SGLT-2 inhibitors   Favors Controls

Mantovani *et al. Metabolites* 2021 Jan; 11(1): 22

What if first degree relative with Stroke?

A REWIND

HR 0·76 (95% CI 0·61–0·95);
p=0·0171

Placebo

Dulaglutide

Cumulative incidence risk — Time since randomisation (years)

B SUSTAIN-6

Hazard ratio, 0.61 (95% CI, 0.38–0.99)
P=0.04

Placebo

Semaglutide

Patients with Event (%) — Weeks since Randomization
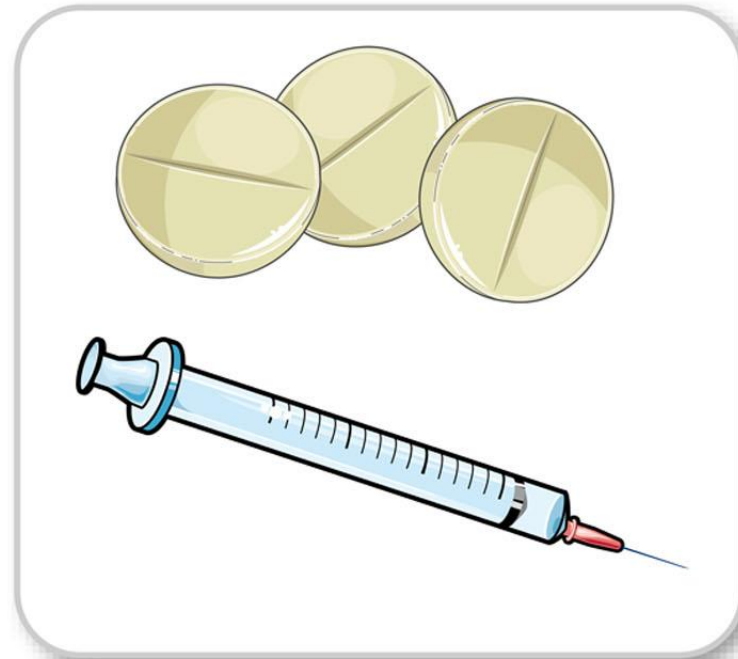
In the EMPA-REG trial, non-fatal stroke increased by 30% with empagliflozin

meta-analyses of the CVOTs in diabetes showed that SGLT2 inhibitors as a class may have a neutral effect on fatal, non-fatal, and total stroke compared to placebo.

What if ejection fraction 30%?
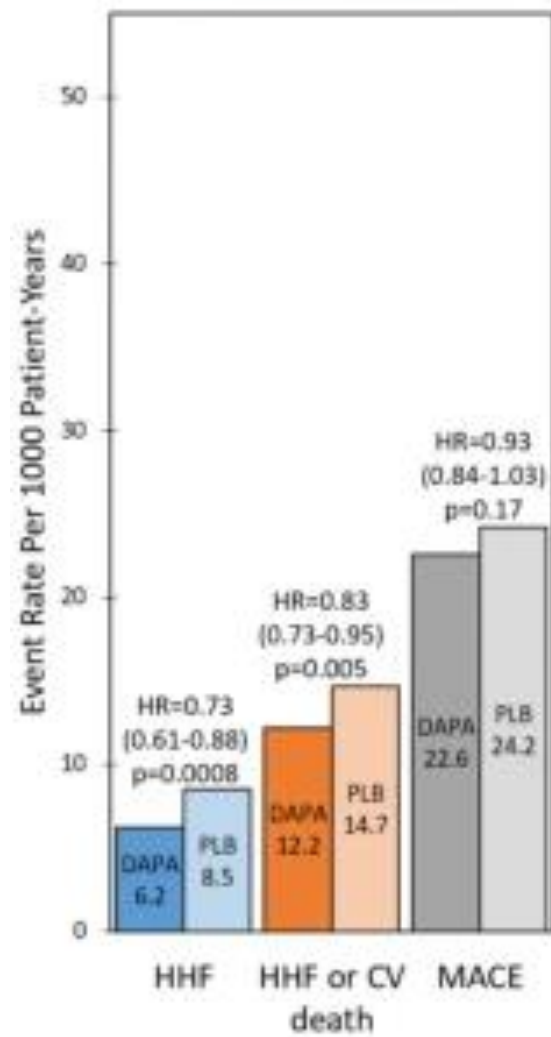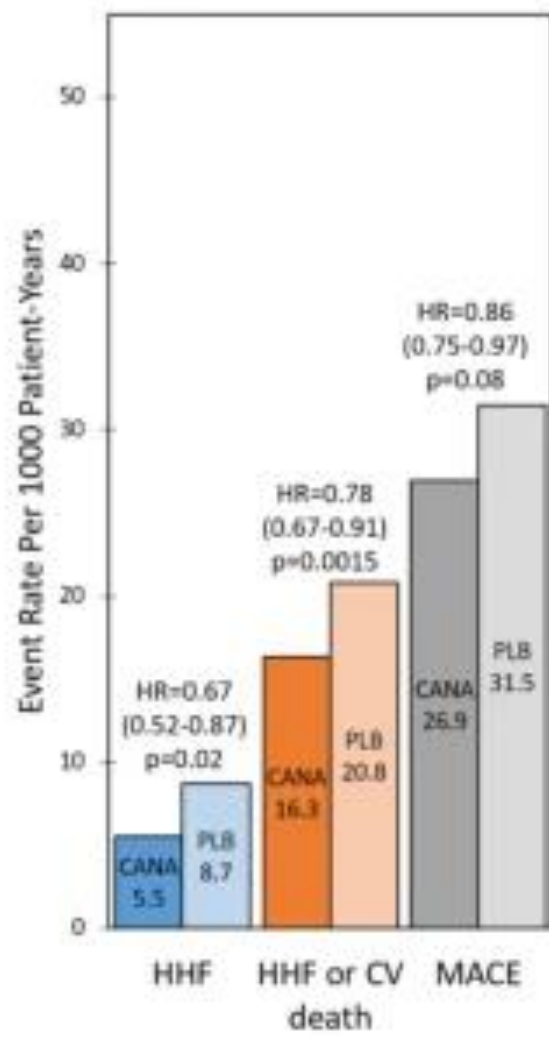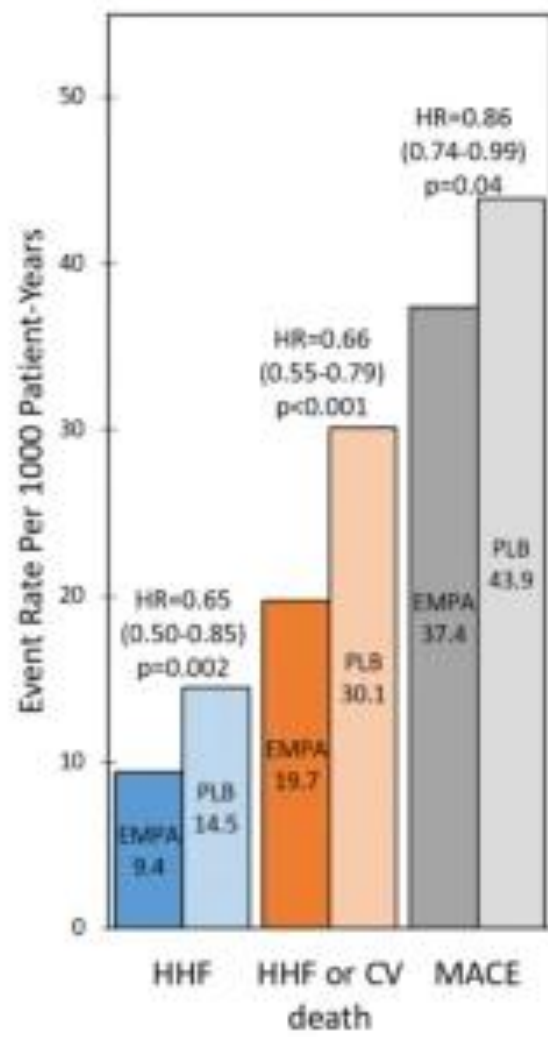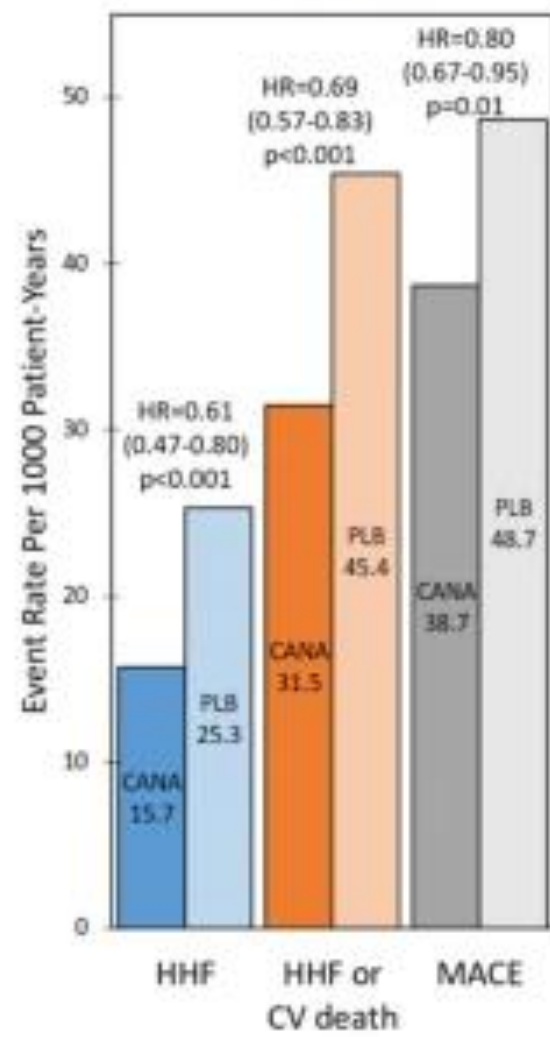
DECLARE-TIMI 58

Event Rate Per 1000 Patient-Years

HR=0.73 (0.61-0.88) p=0.0008 — HHF: DAPA 6.2, PLB 8.5
HR=0.83 (0.73-0.95) p=0.005 — HHF or CV death: DAPA 12.2, PLB 14.7
HR=0.93 (0.84-1.03) p=0.17 — MACE: DAPA 22.6, PLB 24.2

CANVAS

Event Rate Per 1000 Patient-Years

HR=0.67 (0.52-0.87) p=0.02 — HHF: CANA 5.5, PLB 8.7
HR=0.78 (0.67-0.91) p=0.0015 — HHF or CV death: CANA 16.3, PLB 20.8
HR=0.86 (0.75-0.97) p=0.08 — MACE: CANA 26.9, PLB 31.5

EMPA-REG OUTCOME

Event Rate Per 1000 Patient-Years

HR=0.65 (0.50-0.85) p=0.002 — HHF: EMPA 9.4, PLB 14.5
HR=0.66 (0.55-0.79) p<0.001 — HHF or CV death: EMPA 19.7, PLB 30.1
HR=0.86 (0.74-0.99) p=0.04 — MACE: EMPA 37.4, PLB 43.9

CREDENCE

Event Rate Per 1000 Patient-Years

HR=0.61 (0.47-0.80) p<0.001 — HHF: CANA 15.7, PLB 25.3
HR=0.69 (0.57-0.83) p<0.001 — HHF or CV death: CANA 31.5, PLB 45.4
HR=0.80 (0.67-0.95) p=0.01 — MACE: CANA 38.7, PLB 48.7

Meta-analyses of cardiorenal effects of GLP-1RA and SGLT2i in patients with or without type 2 diabetes

CVOTs	HR	(95% CI)
GLP-1RA	0.86	(0.79 - 0.94)
SGLT-2i	0.88	(0.83 - 0.92)
MACE		
GLP-1RA	0.87	(0.78 - 0.96)
SGLT-2i	0.86	(0.76 - 0.96)
CV mortality		
GLP-1RA	0.90	(0.83 - 0.98)
SGLT-2i	0.89	(0.80 - 0.97)
Myocardial infarction		
GLP-1RA	0.83	(0.76 - 0.92)
SGLT-2i	0.95	(0.85 - 1.05)
Stroke		
GLP-1RA	0.88	(0.82 - 0.94)
SGLT-2i	0.87	(0.74 - 0.98)
Total mortality		
GLP-1RA	0.90	(0.83 - 0.98)
SGLT-2i	0.68	(0.62 - 0.74)
Hospitalization for HF		

Cardiovasc Diabetology 2021; 20: 205
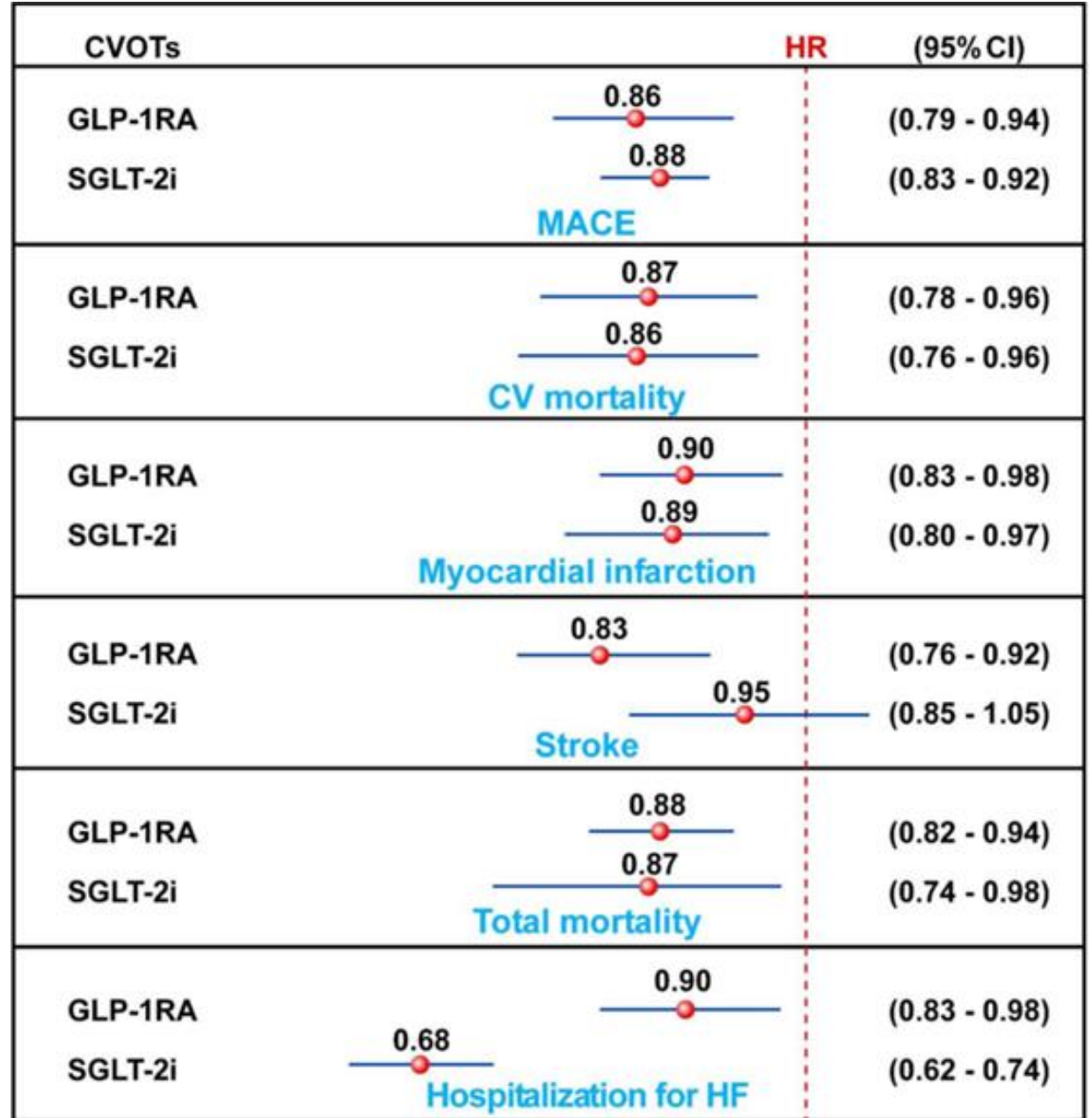
Perhaps combination therapy?

………. Note that GLP-1 and SGLT2i have opposing effects on glucagon

Summary comparison (efficacy)

SGLT2i

eGFR decline

HHF

Glycaemic reduction with lower intrinsic insulin reserve

GLP-1

MACE reduction as <u>primary</u> prevention?

Stroke reduction

Proteinuria

Glycaemic reduction at lower eGFR