Cardiovascular, kidney and safety outcomes with GLP-1 receptor agonists alone and in combination with SGLT2 inhibitors in type 2 diabetes: A systematic review and meta –analysis

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overview

- Introduction
- method
- Results
- Discussion
- Strength & Limitations
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Introduction

- Type 2 diabetes increases CV and kidney diseases risk
- GLP-1RAs and SGLT2is improve outcomes
- Guidelines recommend both drug classes
- Mechanisms are distinct and complementary

Introduction

- Small trials: combo improves glycemia, BP, weight, albuminuria
- Combination therapy may enhance treatment effects
- SGLT2i benefits independent of GLP-1RA
- GLP-1RA independence from SGLT2i unclear
- Prior data limited by small subgroups

Study Objective

- Assess GLP-1RA effects in T2DM patients
- Compare outcomes with vs. without SGLT2i
- Focus on cardiovascular and kidney outcomes
- Provide evidence for combination therapy rationale

Methods

- Systematic review and meta-analysis design
- PRISMA guidelines and PROSPERO registered
- Searched MEDLINE and Embase (to July 2024)
- Included RCTs of GLP-1RAs in T2DM
- Trials must report outcomes by SGLT2i use

Methods

- Two authors screened and review articles
- Two authors extracted data using a standardized form
- Risk of bias assessed (Cochrane RoB2 tool)
- Two-stage inverse-variance meta-analysis used
- All analyses performed using R software

Outcomes Assessed

- Major adverse cardiovascular events (MACE)
- Hospitalization for heart failure
- Cardiovascular death
- All-cause death
- ≥50% eGFR decline, kidney failure, related death
- Total eGFR slope (CKD progression)
- Serious adverse events (SAEs)
- Severe hypoglycemia

Table 1. Characteristics of included trials.

	FLOW	AMPLITUDE-O	Harmony Outcomes
Number of participants	3533	4076	9463
Drug	Semaglutide	Efpeglenatide	Albiglutide
Primary outcome	≥50% reduction in eGFR, kidney failure, or death due to cardiovascular or kidney failure related death	Nonfatal myocardial infarction, nonfatal stroke, cardiovascular death	Nonfatal myocardial infarction, nonfatal stroke, cardiovascular death
Median follow up (years)	3.4	1.8	1.6
Age (mean [SD], years)	66.6 (9)	64.5 (8.2)	64 (7)
Women (no. [%])	1069 (30.3)	1344 (33.0)	2894 (31)
HbA1c (mean [SD], %)	7.8 (1.3)	8.91 (1.5)	8.7 (1.5)
Established cardiovascular disease (no. [%])	808 (22.9)	3650 (89.6)	9463 (100)
History of heart failure (no. [%])	678 (19.2)	737 (18.1)	1922 (20)
SGLT2i use at baseline (no. [%])	550 (15.6)	618 (15.2)	575 (6.1)
Randomization stratified by SGLT2i	Yes	Yes	No

SD: standard deviation; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate.

Table 2. Baseline characteristics of participants in the included trials according to SGLT2 inhibitor use at baseline.

	FLOW		AMPLITUDE-O		Harmony Outcomes		Pooled	
N (%) unless stated	**SGLT2i**	**No SGLT2i**	**SGLT2i**	**No SGLT2i**	**SGLT2i**	**No SGLT2i**	**SGLT2i**	**No SGLT2i**
Number of participants	550	2983	618	3458	575	8887	1743	15328
Age (mean {SD}, years)	64.8 (9.1)	67 (8.9)	64 (8.1)	64.6 (8.3)	62.9 (8.2)	64.2 (8.7)	64.1 (8.5)	65.6 (8.7)
Women	124 (22.5)	945 (31.7)	174 (28.2)	1170 (33.8)	140 (24.3)	2754 (31)	438 (25.1)	4869 (31.8)
White	320 (58.2)	2003 (67.1)	524 (84.7)	3010 (87)	491 (85.4)	6091 (68.5)	1335 (76.6)	11104 (72.4)
HbA1c (mean [SD], %))	7.8 (1.2)	7.8 (1.3)	8.6 (1.2)	9 (1.5)	8.5 (1.2)	8.8 (1.5)	8.2 (1.3)	8.3 (1.6)
BMI (mean [SD], kg/m2)	31.7 (6.2)	32 (6.4)	32.8 (6.2)	32.7 (6.1)	33.6 (5.8)	32.2 (5.9)	32.5 (6.1)	32.2 (6)
Systolic BP (mean [SD], mmHg)	134.9 (15.6)	139.3 (15.7)	131.8 (15.1)	135.4 (15.5)	132.2 (16.3)	134.9 (16.6)	133.5 (15.7)	137.3 (16.3)
Diastolic BP (mean [SD], mmHg)	75.3 (9.6)	76.7 (10.1)	75.6 (9.9)	76.9 (9.7)	75.3 (9.5)	76.9 (10.1)	75.3 (9.7)	76.8 (10)
History of heart failure	82 (14.9)	596 (20)	85 (13.8)	652 (18.9)	87 (15.1)	1835 (20.6)	254 (14.6)	3083 (20.1)
eGFR (mean [SD], ml/min/1.73m2)	51.1 (15.3)	46.3 (15)	73.6 (21)	72.2 (22.6)	80.1 (23.8)	79 (25.6)	59.3 (25.6)	54.4 (31.2)

N (%) unless otherwise stated. SGLT2i: sodium-glucose cotransporter-2 inhibitor; SD: standard deviation; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate.

Results Overview

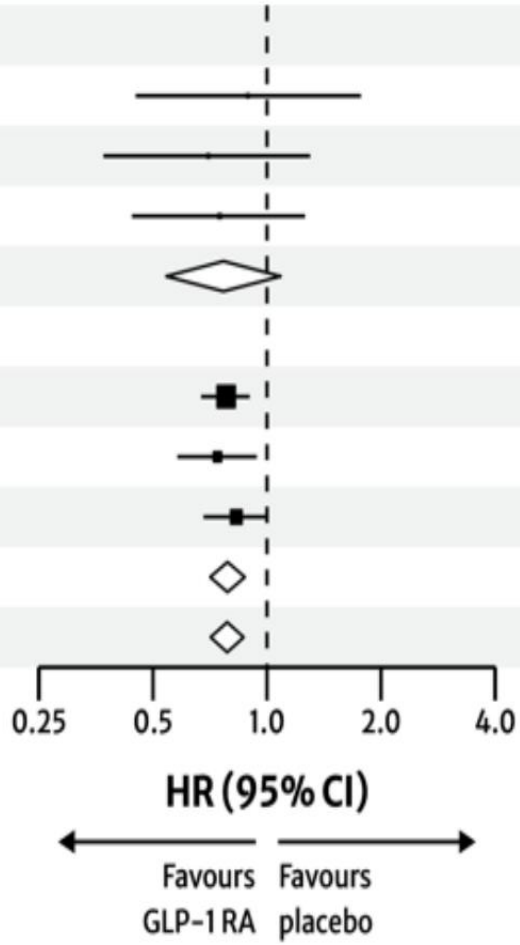
- 3 RCTs included: FLOW, AMPLITUDE-O, Harmony
- Total participants: 17,072 (10.2% on SGLT2i)
- SGLT2i users were younger, healthier overall
- Risk of bias: low in all trials
- use of SGT2 inhibitors at baseline was ≤1% in other trials

Cardiovascular Outcomes

- MACE reduced by 21% with GLP-1RAs
- Consistent MACE effect with/without SGLT2i (HR ~0.79)
- Hospitalization for heart failure also reduced
- consistently reduced the risk of HHF (HR ~0.72)

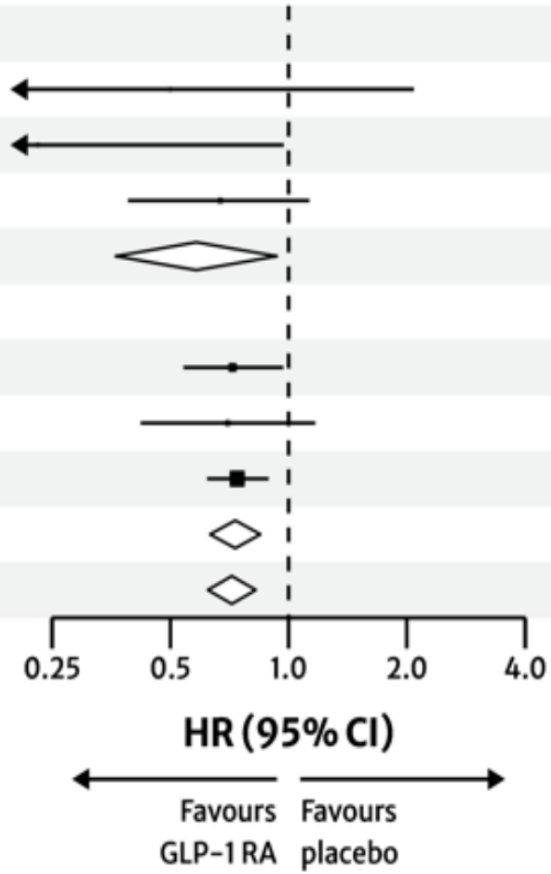
major adverse cardiovascular events

	Events/patients (%)		
	GLP-1 RA	Placebo	HR (95% CI)
Baseline use of SGLT2 inhibitor			
HARMONY	17/310 (5.5)	16/265 (6.0)	0.89 (0.45 to 1.77)
AMPLITUDE-O	25/412 (6.1)	17/206 (8.3)	0.70 (0.37 to 1.30)
FLOW	25/277 (9.0)	32/273 (11.7)	0.75 (0.44 to 1.26)
Subtotal (I-squared = 0.0%, p = 0.87)	67/999 (6.7)	65/744 (8.7)	0.77 (0.54 to 1.09)
No baseline use of SGLT2 inhibitor			
HARMONY	318/4420 (7.2)	407/4467 (9.1)	0.78 (0.67 to 0.90)
AMPLITUDE-O	164/2305 (7.1)	108/1153 (9.4)	0.74 (0.58 to 0.94)
FLOW	187/1490 (12.6)	222/1493 (14.9)	0.83 (0.68 to 1.00)
Subtotal (I-squared = 0.0%, p = 0.76)	669/8215 (8.1)	737/7113 (10.4)	0.79 (0.71 to 0.87)
Total	736/9214 (8.0)	802/7857 (10.2)	0.79 (0.71 to 0.87)
Heterogeneity by use of SGLT2 inhibitor: p = 0.78			



hospitalization for heart failure

	Events/patients (%)		
	GLP-1 RA	Placebo	HR (95% CI)
Baseline use of SGLT2 inhibitor			
HARMONY	3/310 (1.0)	5/265 (1.9)	0.50 (0.12 to 2.08)
AMPLITUDE-O	3/412 (0.7)	6/206 (2.9)	0.23 (0.05 to 0.97)
FLOW	24/277 (8.7)	34/273 (12.5)	0.67 (0.39 to 1.13)
Subtotal (I-squared = 0.0%, p = 0.40)	30/999 (3.0)	45/744 (6.0)	0.58 (0.36 to 0.93)
No baseline use of SGLT2 inhibitor			
HARMONY	76/4420 (1.7)	106/4467 (2.4)	0.72 (0.54 to 0.97)
AMPLITUDE-O	37/2305 (1.6)	25/1153 (2.2)	0.70 (0.42 to 1.17)
FLOW	198/1490 (13.3)	258/1493 (17.3)	0.74 (0.62 to 0.89)
Subtotal (I-squared = 0.0%, p = 0.97)	311/8215 (3.8)	389/7113 (5.5)	0.73 (0.63 to 0.85)
Total	341/9214 (3.7)	434/7857 (5.5)	0.72 (0.62 to 0.83)
Heterogeneity by use of SGLT2 inhibitor: p = 0.26			

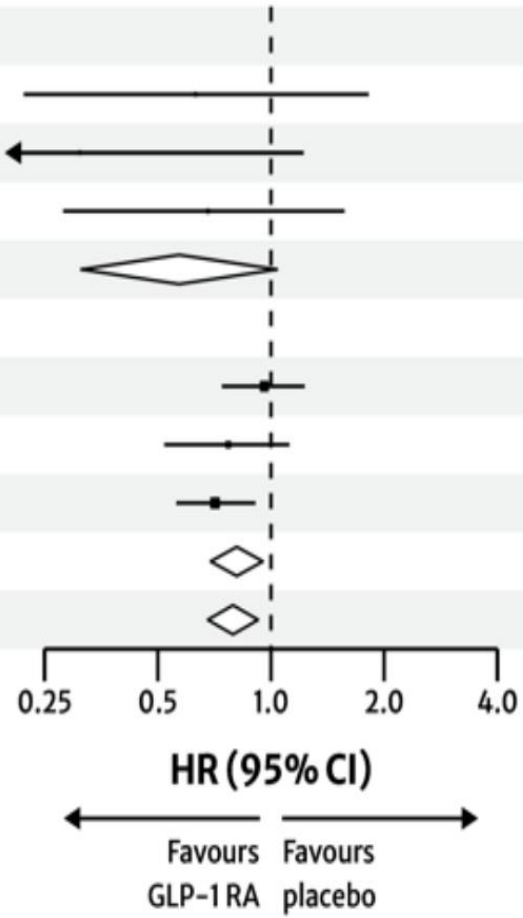


Mortality Outcomes

- Cardiovascular death reduced in both subgroups
- (HR ~0.79)
- All-cause death also consistently reduced
- (HR ~0.85)

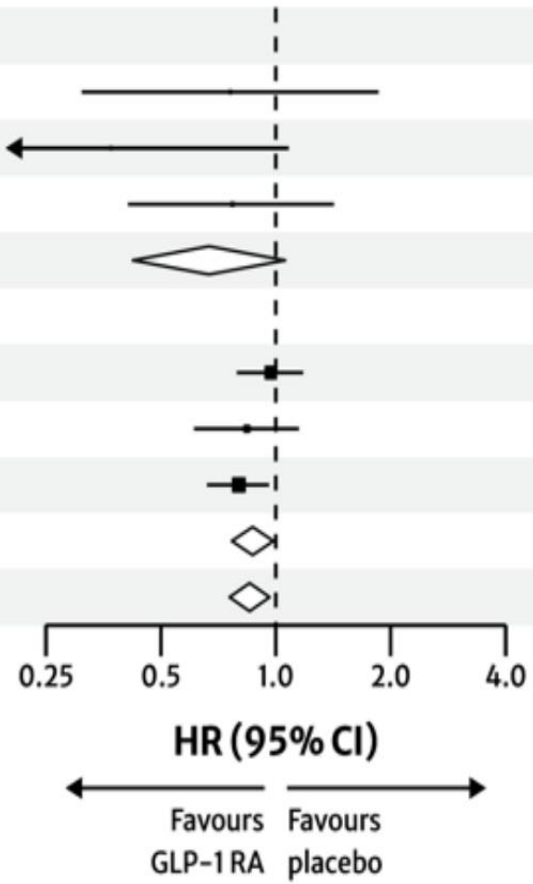
cardiovascular death

	Events/patients (%)		
	GLP-1 RA	Placebo	HR (95% CI)
Baseline use of SGLT2 inhibitor			
HARMONY	6/310 (1.9)	8/265 (3.0)	0.63 (0.22 to 1.82)
AMPLITUDE-O	5/412 (1.2)	6/206 (2.9)	0.31 (0.08 to 1.22)
FLOW	9/277 (3.2)	13/273 (4.8)	0.68 (0.28 to 1.57)
Subtotal (I-squared = 0.0%, p = 0.62)	20/999 (2.0)	27/744 (3.6)	0.57 (0.31 to 1.04)
No baseline use of SGLT2 inhibitor			
HARMONY	116/4420 (2.6)	122/4467 (2.7)	0.96 (0.74 to 1.23)
AMPLITUDE-O	70/2305 (3.0)	44/1153 (3.8)	0.77 (0.52 to 1.12)
FLOW	114/1490 (7.7)	156/1493 (10.4)	0.71 (0.56 to 0.91)
Subtotal (I-squared = 31.4%, p = 0.23)	300/8215 (3.7)	322/7113 (4.5)	0.81 (0.69 to 0.95)
Total	320/9214 (3.5)	349/7857 (4.4)	0.79 (0.68 to 0.92)
Heterogeneity by use of SGLT2 inhibitor: p = 0.31			



all-cause death

	Events/patients (%)		
	GLP-1 RA	Placebo	HR (95% CI)
Baseline use of SGLT2 inhibitor			
HARMONY	9/310 (2.9)	10/265 (3.8)	0.76 (0.31 to 1.86)
AMPLITUDE-O	7/412 (1.7)	8/206 (3.9)	0.37 (0.13 to 1.08)
FLOW	18/277 (6.5)	23/273 (8.4)	0.77 (0.41 to 1.42)
Subtotal (I-squared = 0.0%, p = 0.48)	34/999 (3.4)	41/744 (5.5)	0.67 (0.42 to 1.06)
No baseline use of SGLT2 inhibitor			
HARMONY	187/4420 (4.2)	195/4467 (4.4)	0.97 (0.79 to 1.18)
AMPLITUDE-O	104/2305 (4.5)	61/1153 (5.3)	0.84 (0.61 to 1.15)
FLOW	209/1490 (14.0)	256/1493 (17.1)	0.80 (0.66 to 0.96)
Subtotal (I-squared = 0.0%, p = 0.38)	500/8215 (6.1)	512/7113 (7.2)	0.87 (0.77 to 0.99)
Total	534/9214 (5.8)	553/7857 (7.0)	0.85 (0.76 to 0.96)
Heterogeneity by use of SGLT2 inhibitor: p = 0.31			

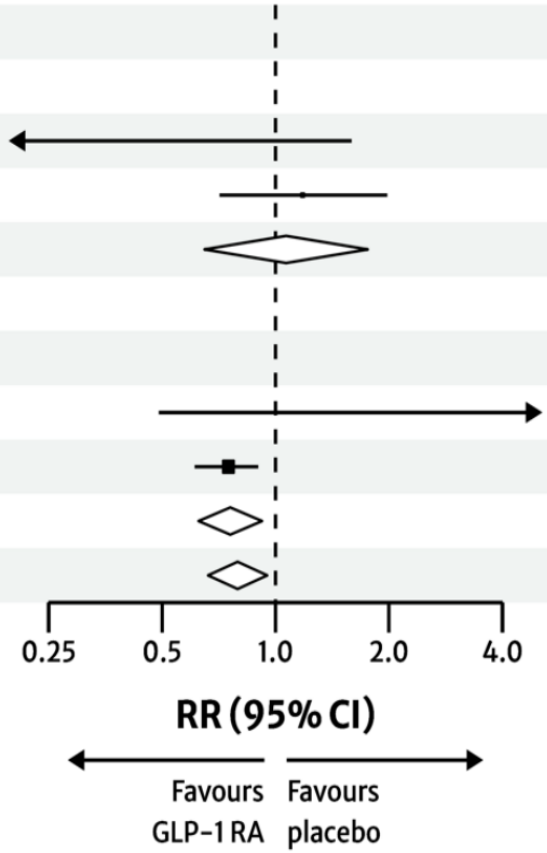


Kidney Outcomes

- GLP-1RAs lowered composite kidney risk (RR 0.79)
- eGFR slope improved in both subgroups

50% decline in eGFR, kidney failure or kidney failure-related death

	Events/patients (%)		
	GLP-1 RA	Placebo	RR (95% CI)
Baseline use of SGLT2 inhibitor			
HARMONY	..	..	..
AMPLITUDE-O	1/412 (0.2)	3/206 (1.5)	0.17 (0.02 to 1.59)
FLOW	32/277 (11.6)	27/273 (9.9)	1.18 (0.71 to 1.98)
Subtotal (I-squared = 65%, p = 0.09)	33/689 (4.8)	30/479 (6.3)	1.07 (0.65 to 1.76)
No baseline use of SGLT2 inhibitor			
HARMONY	..	..	..
AMPLITUDE-O	8/2305 (0.3)	0/1153 (0.0)	8.51 (0.49 to 147.26
FLOW	186/1490 (12.5)	233/1493 (15.6)	0.75 (0.61 to 0.90)
Subtotal (I-squared = 63.9%, p = 0.10)	194/3795 (5.1)	233/2646 (8.8)	0.76 (0.62 to 0.92)
Total	227/4484 (5.1)	263/3125 (8.4)	0.79 (0.66 to 0.95)
Heterogeneity by use of SGLT2 inhibitor: p = 0.53			

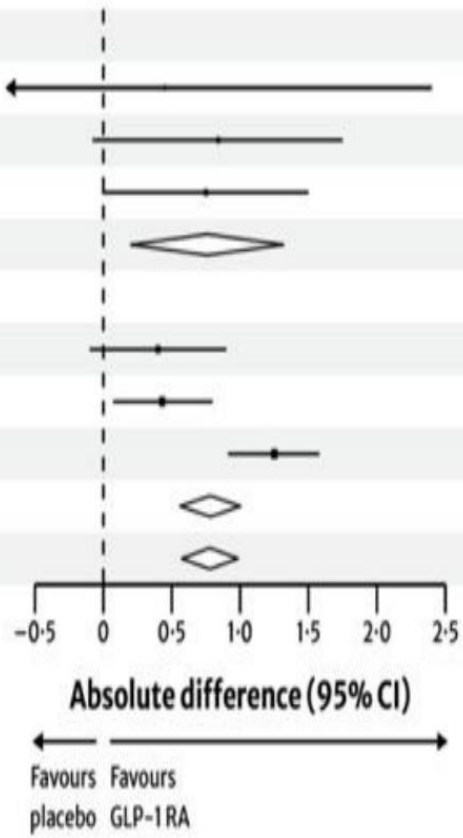


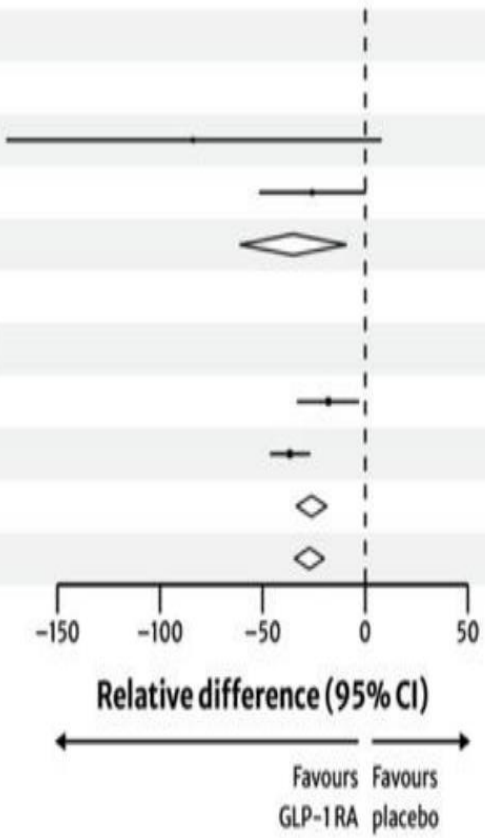
total eGFR slope

	Estimated GFR slope (ml per minute per 1·73 m2 per year)		Absolute difference (95% CI)	Relative difference (95% CI)
	GLP-1 RA	Placebo		
Baseline use of SGLT2 inhibitor				
HARMONY	..	..	0.45 (−1.50 to 2.40)	..
AMPLITUDE-O	−0.20 (0.40)	−1.00 (0.50)	0.84 (−0.08 to 1.75)	−84% (−175 to 8)
FLOW	−2.20 (0.30)	−2.90 (0.30)	0.75 (−0.01 to 1.50)	−26% (−52 to 0)
Subtotal (I-squared = 0.0%, p = 0.94)*	−1.38 (0.30)	−2.16 (0.30)	0.76 (0.20 to 1.32)	−35% (−61 to −9)
No baseline use of SGLT2 inhibitor				
HARMONY	..	..	0.40 (−0.10 to 0.90)	..
AMPLITUDE-O	−2.00 (0.30)	−2.40 (0.30)	0.43 (0.07 to 0.80)	−18% (−33 to −3)
FLOW	−2.20 (0.10)	−3.40 (0.10)	1.25 (0.91 to 1.58)	−37% (−46 to −27)
Subtotal (I-squared = 85.0%, p = 0.001)*	−2.12 (0.13)	−2.99 (0.13)	0.78 (0.56 to 1.00)	−26% (−34 to −19)
Total	−2.00 (0.12)	−2.86 (0.12)	0.78 (0.57 to 0.98)	−27% (−34 to −20)

Heterogeneity by use of SGLT2 inhibitor

Absolute difference: p = 0.94; Relative difference: p = 0.99



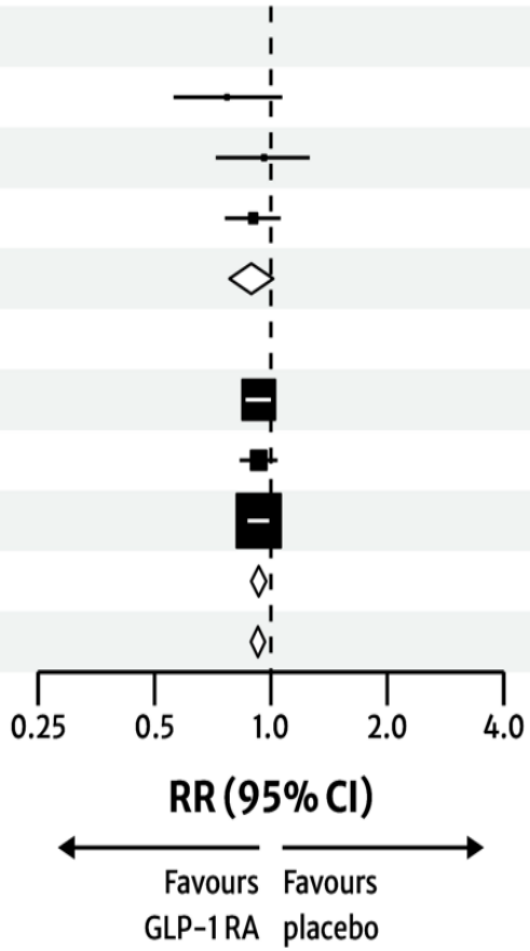


Safety Outcomes

- Serious adverse events reduced with GLP-1RAs
- Effect consistent regardless of SGLT2i use at baseline
- The effect on severe hypoglycemia also similar regardless of baseline SGLT2 inhibitor use

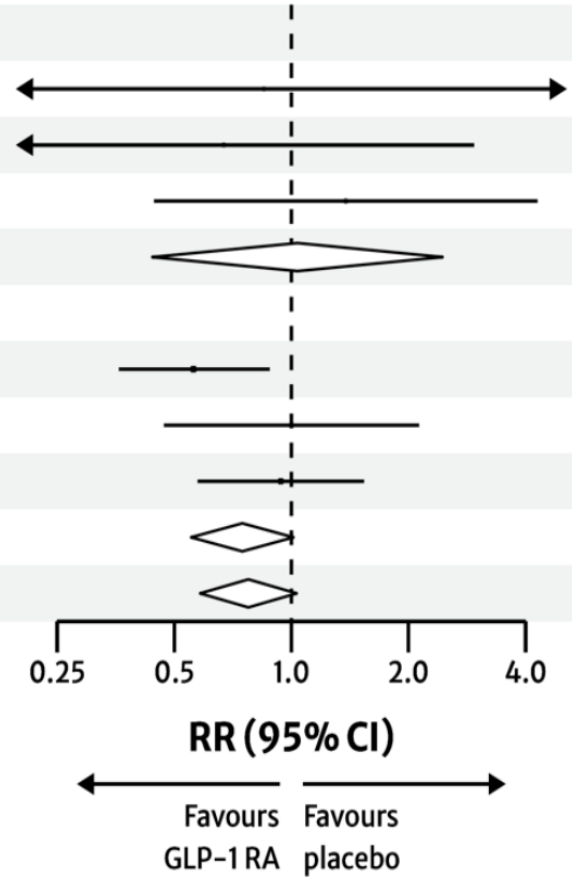
serious adverse events

	Events/patients (%)		
	GLP-1 RA	Placebo	RR (95% CI)
Baseline use of SGLT2 inhibitor			
HARMONY	56/310 (18.1)	62/265 (23.4)	0.77 (0.56 to 1.07)
AMPLITUDE-O	107/412 (26.0)	56/206 (27.2)	0.96 (0.72 to 1.26)
FLOW	134/277 (48.4)	147/273 (53.8)	0.90 (0.76 to 1.06)
Subtotal (I-squared = 0.0%, p = 0.59)	297/999 (29.7)	265/744 (35.6)	0.89 (0.78 to 1.01)
No baseline use of SGLT2 inhibitor			
HARMONY	964/4406 (21.9)	1052/4450 (23.6)	0.93 (0.86 to 1.00)
AMPLITUDE-O	606/2305 (26.3)	326/1153 (28.3)	0.93 (0.83 to 1.04)
FLOW	743/1490 (49.9)	803/1493 (53.8)	0.93 (0.87 to 0.99)
Subtotal (I-squared = 0.0%, p = 1.00)	2313/8201 (28.2)	2181/7096 (30.7)	0.93 (0.89 to 0.97)
Total	2610/9200 (28.4)	2446/7840 (31.2)	0.93 (0.89 to 0.97)
Heterogeneity by use of SGLT2 inhibitor: p = 0.29			



severe hypoglycemia

	Events/patients (%)		
	GLP-1 RA	Placebo	RR (95% CI)
Baseline use of SGLT2 inhibitor			
HARMONY	1/310 (0.3)	1/265 (0.4)	0.85 (0.05 to 13.6)
AMPLITUDE-O	4/412 (1.0)	3/206 (1.5)	0.67 (0.15 to 2.95)
FLOW	7/277 (2.5)	5/273 (1.8)	1.38 (0.44 to 4.29)
Subtotal (I-squared = 0.0%, p = 0.74)	12/999 (1.2)	9/744 (1.2)	1.04 (0.44 to 2.45)
No baseline use of SGLT2 inhibitor			
HARMONY	30/4406 (0.7)	54/4450 (1.2)	0.56 (0.36 to 0.88)
AMPLITUDE-O	20/2305 (0.9)	10/1153 (0.9)	1.00 (0.47 to 2.13)
FLOW	30/1490 (2.0)	32/1493 (2.1)	0.94 (0.57 to 1.54)
Subtotal (I-squared = 33.3%, p = 0.22)	80/8201 (1.0)	96/7096 (1.4)	0.75 (0.55 to 1.01)
Total	92/9200 (1.0)	105/7840 (1.3)	0.78 (0.58 to 1.03)
Heterogeneity by use of SGLT2 inhibitor: p = 0.50			



Discussion

Key Findings

- GLP-1RAs improve CV, kidney, mortality outcomes
- Effects consistent regardless of SGLT2i use
- Largest dataset on this comparison to date
- Supports independent and additive drug effects

Discussion

- Guidelines vary on combined drug use
- European Society of Cardiology guidelines

Evidence gap

- American Diabetes Association Standards of Care

Recommends

Discussion

- meta-analysis of 12 completed SGLT2 inhibitor outcome trials, the cardiovascular and kidney benefits of SGLT2 inhibitors were consistent regardless of background use of GLP-1 receptor agonists.
- Combination GLP-1RA and SGLT2i independent and additive effects on clinical outcomes

Heart Failure Insights

- GLP-1RAs reduce heart failure hospitalization
- SGLT2i strongly guideline recommended
- STEP-HFpEF, SELECT and FLOW trials, semaglutide

Kidney Outcomes Discussion

- eGFR slope validated as CKD progression
- Semaglutide shows strong renal protective effect
- REWIND trial, dulaglutide benefits on kidney outcomes
- GLP-1RAs should complement SGLT2i in CKD

Mechanisms of Action

- GLP-1RAs: anti-atherosclerotic, anti-inflammatory effects
- SGLT2i: reduce hyperfiltration, improve metabolism
- Distinct pathways suggest additive therapeutic potential
- Benefit on glycemia and body weight greater in GLP-1RA

Strengths and Limitations

- Largest analysis of GLP-1RA + SGLT2i to date
- Unpublished data increased statistical power
- FLOW only dedicated kidney outcome trial included
- Few kidney/HF events in SGLT2i subgroup
- Could not assess GLP-1RAs like dulaglutide

Conclusion

- ✓ GLP-1RAs improve CV and kidney outcomes
- ✓ Effects consistent regardless of SGLT2i use
- ✓ Findings support independent therapeutic roles
- ✓ Combination therapy likely offers added benefit
- ✓ Should be considered in T2DM management

References

- ✓ 1)://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.124.071689
- ✓ 2)Harrison's Principles of Internal Medicine, 21e
- ✓ 3)chatgpt4.5

Thank you for your attention