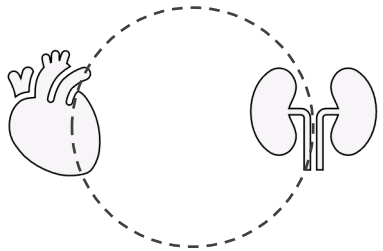
Efficacy and safety of SGLT2 inhibitors with and without GLP-1 receptor agonists

A SMART-C Collaborative Meta-Analysis



Dr Brendon Neuen MBBS(Hons) MSc(Oxon) PhD FRACP FASN

The George Institute for Global Health, Sydney, Australia

Royal North Shore Hospital, Sydney, Australia

𝕏 @brendonneuen

The George Institute for Global Health

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Disclosures

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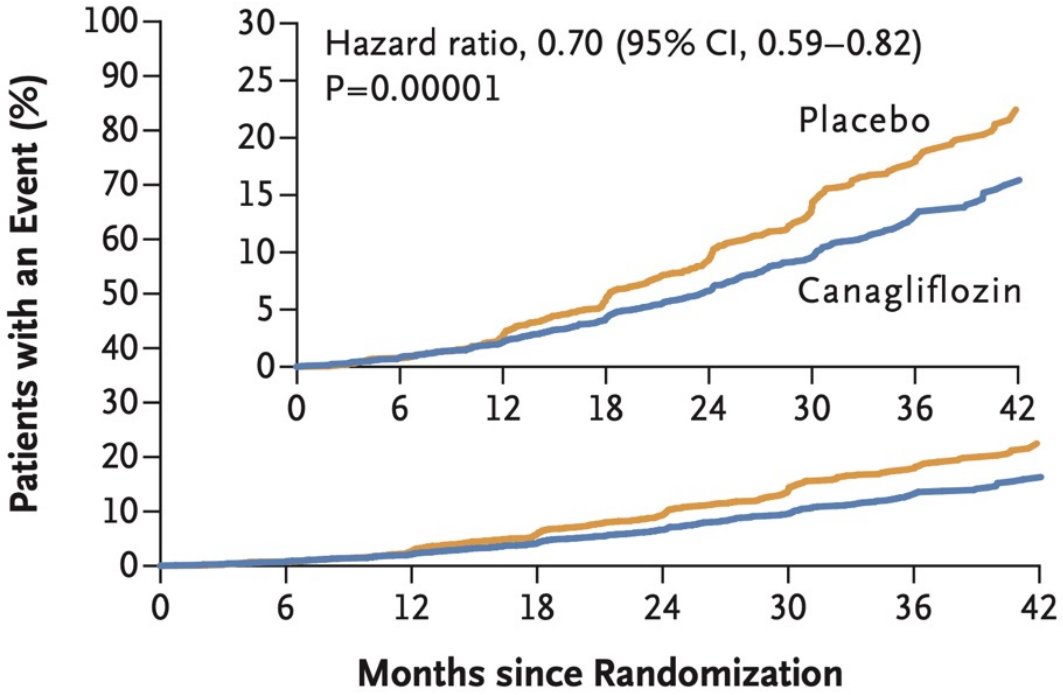
In type 2 diabetes, SGLT2i and GLP-1RA both improve kidney and cardiovascular outcomes

CREDENCE



Perkovic V et al. NEJM 2019

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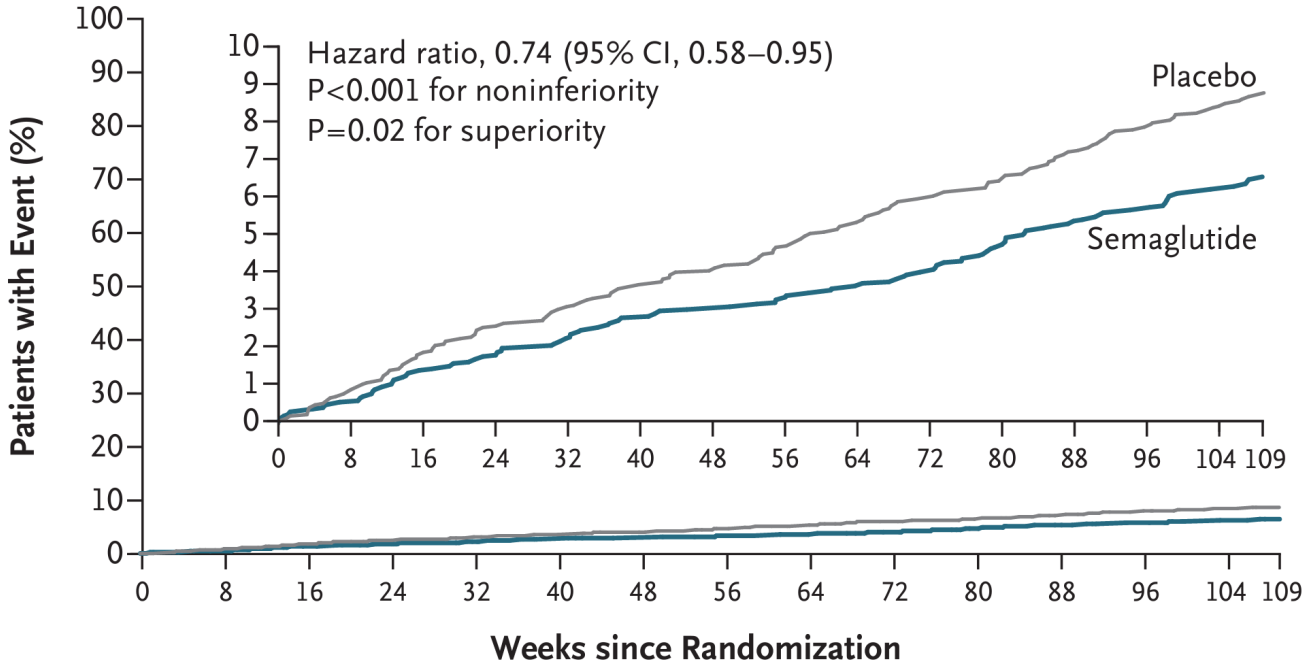


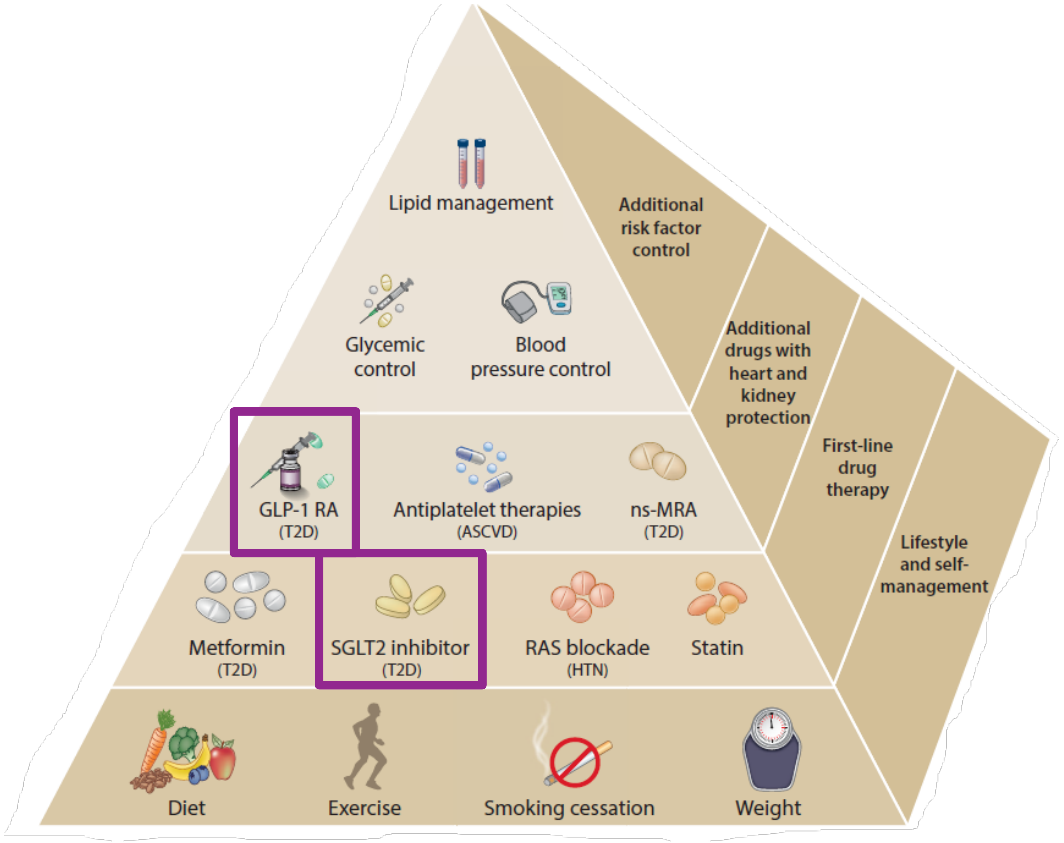
Marso S et al. NEJM 2016

Guidelines recognise the potential of combination SGLT2i and GLP-1RA

American Diabetes Association. Diabetes Care

10.41c In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, combined therapy with an SGLT2 inhibitor with demonstrated cardiovascular benefit and a GLP-1 receptor agonist with demonstrated cardiovascular benefit may be considered for additive reduction of the risk of adverse cardiovascular and kidney events. **A**

Cardiovascular disease risk management: Standards of Care in Diabetes – 2024. American Diabetes Association. Diabetes Care 2024



KDIGO 2022 Clinical Practice Guideline on Diabetes Management in CKD. Kidney Int 2022

Rationale and aim

- Evidence for combined use of SGLT2i and GLP-1RA mainly from small trials assessing effects on cardiometabolic risk factors

- Background use of GLP-1RA too infrequent in any single outcome trial to understand the effects of SGLT2i on clinical outcomes with and without GLP-1RA

AIM

- Conduct a collaborative meta-analysis to evaluate the effects of SGLT2i on cardiovascular, kidney and safety outcomes in patients with diabetes by baseline GLP-1RA use

Methods

- SGLT2i Meta-Analysis Cardio-Renal Trialists Consortium (SMART-C) collaborative meta-analysis
  - Eligibility: Randomised, double-blind, placebo-controlled trial assessing effects on a primary clinical outcome
  - Led by academic steering committee with representatives from each trial
- Analysis restricted to participants with diabetes
- Outcomes: MACE, HHF or CV death, CKD progression, eGFR slope, safety outcomes

Statistical analysis

- Two-stage meta-analysis using a harmonised analytical approach and endpoint definitions
- Treatment effects by baseline GLP-1RA obtained from Cox regression models
- Two slope linear mixed effects model with unstructured covariance matrix used to calculate chronic and total eGFR slope
- Inverse variance weighted meta-analysis

Baseline characteristics: T2D at high CV risk trials

	GLP-1RA yes		GLP-1RA no	
	SGLT2i	Placebo	SGLT2i	Placebo
Participants, n	937	693	23626	17312
Age, years (SD)	63.0 (7.1)	62.8 (6.8)	63.7 (7.8)	63.8 (7.6)
Female, n (%)	269 (28.7)	207 (29.9)	7922 (33.5)	6138 (35.5)
History of CV disease, n (%)	602 (64.3)	410 (59.2)	16784 (71.0)	11044 (63.8)
History of heart failure, n (%)	85 (9.1)	58 (8.4)	3318 (14.0)	2388 (13.8)
Systolic BP, mmHg (SD)	132.8 (15.5)	133.8 (15.2)	135.0 (15.5)	135.1 (15.6)
BMI, kg/m2 (SD)	34.9 (5.8)	35.0 (6.8)	31.5 (5.7)	31.5 (5.8)
HbA1c, % (SD)	8.2 (1.0)	8.1 (1.0)	8.2 (1.0)	8.2 (1.1)
eGFR, mL/min/1.73m^2 (SD)	79.3 (20.5)	77.5 (19.8)	79.3 (19.8)	78.9 (19.4)
uACR ≥30 mg/g, n (%)	312 (33.7)	228 (33.3)	8034 (34.2)	5680 (33.1)
RAS blockade use, n (%)	807 (86.1)	583 (84.1)	19063 (80.7)	13977 (80.7)
Insulin use, n (%)	477 (50.9)	349 (50.4)	10788 (45.7)	7781 (45.0)

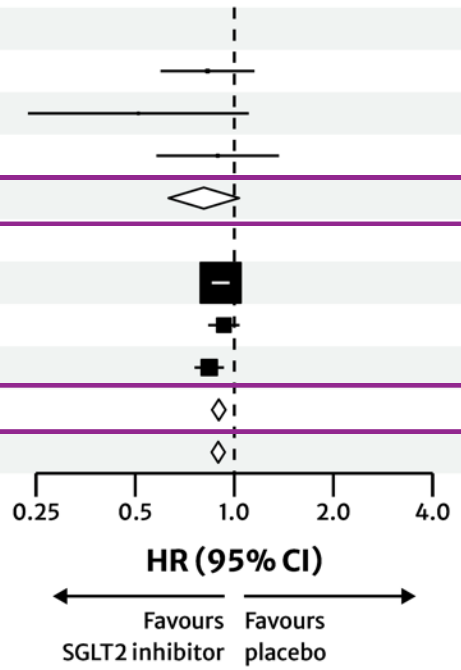
Baseline characteristics: CKD trials

	GLP-1RA yes		GLP-1RA no	
	SGLT2i	Placebo	SGLT2i	Placebo
CKD trials				
Participants, n	635	640	9839	9817
Age, years (SD)	66.0 (8.8)	65.5 (9.1)	66.0 (9.4)	66.3 (9.3)
Female, n (%)	217 (34.2)	234 (36.6)	3885 (39.5)	3873 (39.5)
History of CV disease, n (%)	296 (46.6)	273 (42.7)	4560 (46.3)	4621 (47.1)
History of heart failure, n (%)	116 (18.3)	112 (17.5)	2248 (22.8)	2252 (22.9)
BMI, kg/m2 (SD)	35.4 (6.8)	35.7 (7.6)	31.2 (6.4)	31.2 (6.3)
eGFR, mL/min/1.73m^2 (SD)	44.4 (13.5)	43.0 (13.7)	43.8 (14.4)	43.6 (14.4)
uACR ≥30 mg/g, n (%)	477 (75.1)	463 (72.3)	7804 (79.3)	7799 (79.4)
RAS blockade use, n (%)	568 (89.4)	583 (91.1)	9057 (92.1)	8960 (91.3)
Insulin use, n (%)	454 (71.5)	496 (77.5)	6024 (61.2)	5893 (60.0)

Consistent benefit on MACE by baseline GLP-1RA use

(MI, stroke, CV death)

	Events/patients (%)		Event rate per 100 patient years		
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	HR (95% CI)
Baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	85/937 (9·1)	66/693 (9·5)	2·7	4·3	0·83 (0·60 to 1·15)
Stable heart failure trials	12/88 (13·6)	17/72 (23·6)	7·3	19·0	0·51 (0·24 to 1·11)
Chronic kidney disease trials	42/635 (6·6)	46/640 (7·2)	3·6	4·1	0·89 (0·58 to 1·37)
Subtotal (I-squared = 0·0%, p = 0·86)	139/1660 (8·4)	129/1405 (9·2)	3·3	5·0	0·81 (0·63 to 1·03)
No baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	2408/23620 (10·2)	1789/17310 (10·3)	3·0	4·6	0·91 (0·85 to 0·97)
Stable heart failure trials	614/4781 (12·8)	661/4798 (13·8)	7·6	8·1	0·93 (0·83 to 1·04)
Chronic kidney disease trials	665/9839 (6·8)	782/9817 (8·0)	3·8	4·6	0·84 (0·76 to 0·93)
Subtotal (I-squared = 0·0%, p = 0·80)	3687/38240 (9·6)	3232/31925 (10·1)	3·8	5·1	0·90 (0·86 to 0·94)
Total	3826/39900 (9·6)	3361/33330 (10·1)	3·8	5·1	0·89 (0·85 to 0·94)
Heterogeneity by use of GLP-1 RA: p = 0·31					



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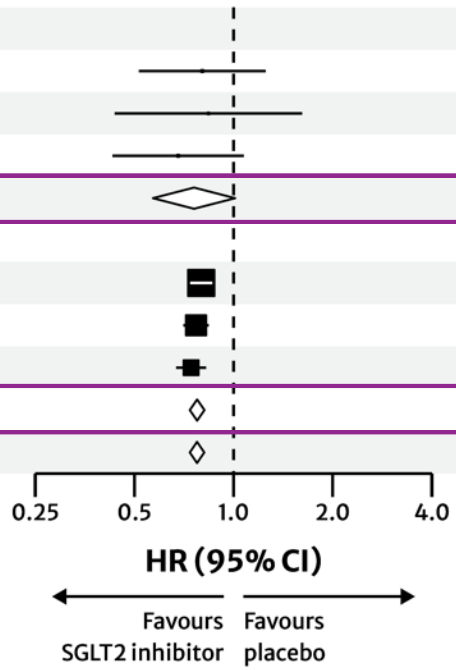
Consistent benefit on heart failure hospitalisation or CV death by baseline GLP-1RA use

	Events/patients (%)		Event rate per 100 patient years		
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	HR (95% CI)
Baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	52/937 (5·5)	42/693 (6·1)	1·7	2·5	0·80 (0·52 to 1·25)
Stable heart failure trials	23/88 (26·1)	18/72 (25·0)	17·6	20·9	0·84 (0·44 to 1·62)
Chronic kidney disease trials	32/635 (5·0)	44/640 (6·9)	2·7	3·9	0·68 (0·43 to 1·07)
Subtotal (I-squared = 6%, p = 0·39)	107/1660 (6·4)	104/1405 (7·4)	2·9	4·1	0·76 (0·57 to 1·01)
No baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	1453/23626 (6·2)	1201/17312 (6·9)	1·7	3·1	0·80 (0·74 to 0·86)
Stable heart failure trials	877/4781 (18·3)	1104/4798 (23·0)	11·4	14·9	0·77 (0·70 to 0·84)
Chronic kidney disease trials	611/9839 (6·2)	803/9817 (8·2)	3·6	4·7	0·74 (0·67 to 0·83)
Subtotal (I-squared = 4·2%, p = 0·40)	2941/38246 (7·7)	3108/31927 (9·7)	3·4	5·4	0·78 (0·74 to 0·82)
Total	3048/39906 (7·6)	3212/33332 (9·6)	3·4	5·3	0·77 (0·74 to 0·81)
Heterogeneity by use of GLP-1 RA: p = 0·90					



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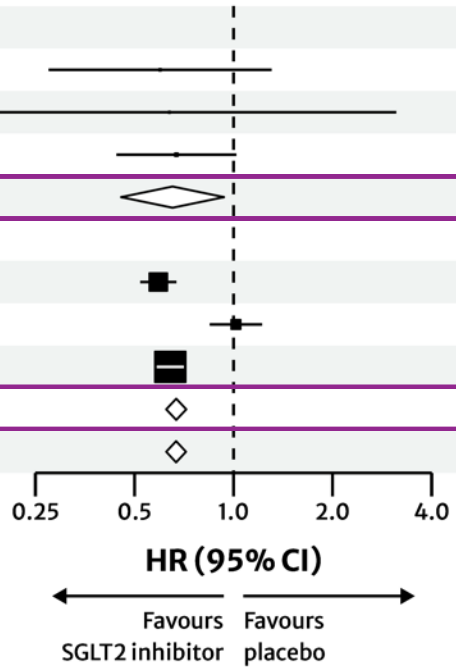
Consistent benefit on CKD progression by baseline GLP-1RA use

(40% decline in eGFR, kidney failure or death due or kidney failure)

	Events/patients (%)		Event rate per 100 patient years		
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	HR (95% CI)
Baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	14/936 (1·5)	17/693 (2·5)	0·4	1·0	0·60 (0·27 to 1·31)
Stable heart failure trials	3/47 (6·4)	3/33 (9·1)	2·2	4·7	0·64 (0·13 to 3·12)
Chronic kidney disease trials	40/635 (6·3)	53/640 (8·3)	3·2	4·5	0·67 (0·44 to 1·02)
Subtotal (I-squared = 0·0%, p = 0·64)	57/1618 (3·5)	73/1366 (5·3)	1·6	2·9	0·65 (0·46 to 0·94)
No baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	469/23585 (2·0)	526/17302 (3·0)	0·6	1·3	0·59 (0·52 to 0·67)
Stable heart failure trials	235/4781 (4·9)	231/4798 (4·8)	2·9	3·1	1·02 (0·85 to 1·22)
Chronic kidney disease trials	688/9839 (7·0)	1015/9817 (10·3)	3·7	5·6	0·64 (0·58 to 0·71)
Subtotal (I-squared = 70·4%, p<0.001)	1392/38205 (3·6)	1772/31917 (5·6)	1·7	2·9	0·67 (0·62 to 0·72)
Total	1449/39823 (3·6)	1845/33283 (5·5)	1·7	2·9	0·67 (0·62 to 0·72)
Heterogeneity by use of GLP-1 RA: p = 0·81					



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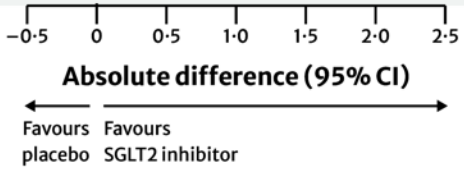
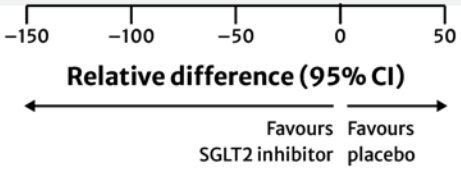
Consistent benefit on chronic eGFR slope by baseline GLP-1RA use

	Estimated GFR slope (ml per minute per 1·73 m2 per year)		Absolute difference (95% CI)	Relative difference (95% CI)
	SGLT2 inhibitor	Placebo		
Baseline use of GLP-1 RA				
High atherosclerotic cardiovascular risk trials	−0·84 (0·21)	−2·00 (0·21)	1·16 (0·76 to 1·57)	−58% (−78 to −38)
Stable heart failure trials	0·18 (1·24)	−5·40 (1·24)	5·65 (3·22 to 8·09)	−105% (−150 to −60)
Chronic kidney disease trials	−1·00 (0·33)	−2·40 (0·33)	1·40 (0·76 to 2·04)	−58% (−85 to −32)
Subtotal (I-squared = 60·0%, p = 0·002)*	−0·87 (0·17)	−2·18 (0·17)	1·32 (0·98 to 1·66)	−60% (−76 to −45)
No baseline use of GLP-1 RA				
High atherosclerotic cardiovascular risk trials	−0·88 (0·04)	−1·89 (0·04)	1·01 (0·93 to 1·09)	−54% (−58 to −49)
Stable heart failure trials	−0·89 (0·16)	−2·85 (0·16)	1·92 (1·61 to 2·23)	−68% (−78 to −57)
Chronic kidney disease trials	−1·19 (0·10)	−3·33 (0·10)	2·14 (1·96 to 2·33)	−64% (−70 to −59)
Subtotal (I-squared = 93·5%, p < 0·001)*	−0·93 (0·04)	−2·14 (0·04)	1·21 (1·14 to 1·28)	−57% (−60 to −53)
Total	−0·92 (0·03)	−2·14 (0·03)	1·22 (1·15 to 1·28)	−57% (−60 to −54)

Heterogeneity by use of GLP-1 RA
Absolute difference: p = 0·55; Relative difference: p = 0·43





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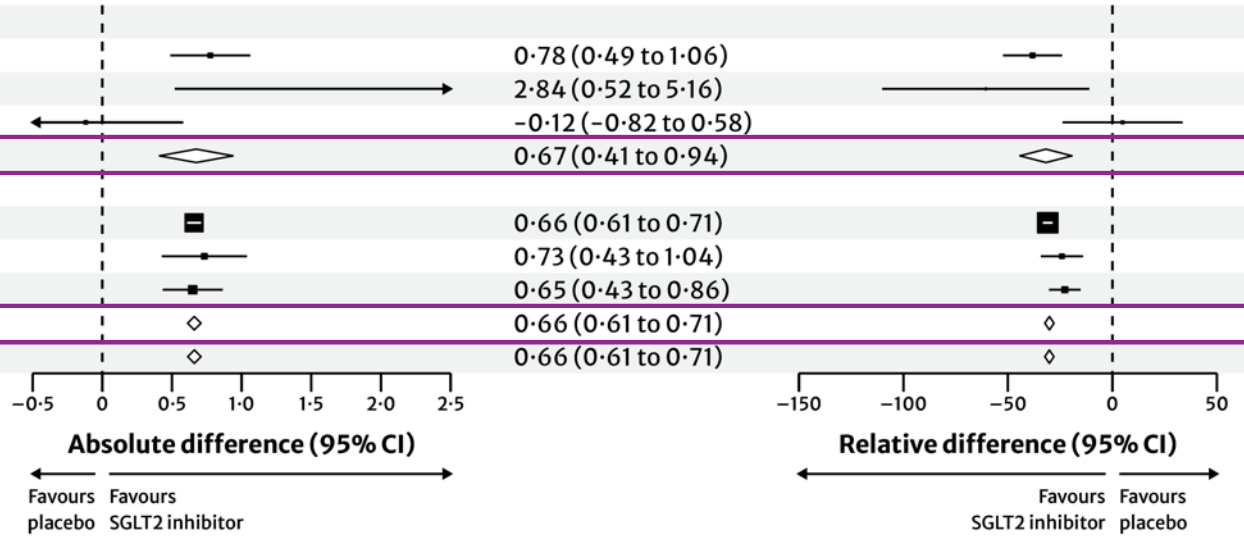
Consistent benefit on total eGFR slope by baseline GLP-1RA use

	Estimated GFR slope (ml per minute per 1·73 m2 per year)		Absolute difference (95% CI)	Relative difference (95% CI)
	SGLT2 inhibitor	Placebo		
Baseline use of GLP-1 RA				
High atherosclerotic cardiovascular risk trials	−1·26 (0·15)	−2·03 (0·15)	0·78 (0·49 to 1·06)	-38% (-52 to -24)
Stable heart failure trials	−1·85 (1·18)	−4·68 (1·18)	2·84 (0·52 to 5·16)	-61% (-110 to -11)
Chronic kidney disease trials	−2·54 (0·36)	−2·43 (0·36)	-0·12 (-0·82 to 0·58)	5% (-24 to 34)
Subtotal (I-squared = 58·0%, p = 0·01)*	−1·45 (0·13)	−2·12 (0·13)	0·67 (0·41 to 0·94)	-32% (-44 to -19)
No baseline use of GLP-1 RA				
High atherosclerotic cardiovascular risk trials	−1·47 (0·03)	−2·13 (0·03)	0·66 (0·61 to 0·71)	-31% (-33 to -29)
Stable heart failure trials	−2·3 (0·16)	−3·03 (0·16)	0·73 (0·43 to 1·04)	-24% (-34 to -14)
Chronic kidney disease trials	−2·2 (0·11)	−2·85 (0·11)	0·65 (0·43 to 0·86)	-23% (-30 to -15)
Subtotal (I-squared = 75·1%, p = 0·89)*	−1·53 (0·02)	−2·19 (0·02)	0·66 (0·61 to 0·71)	-30% (-32 to -28)
Total	−1·53 (0·02)	−2·19 (0·02)	0·66 (0·61 to 0·71)	-30% (-32 to -28)

Heterogeneity by use of GLP-1 RA
Absolute difference: p = 0·92; Relative difference: p = 0·82



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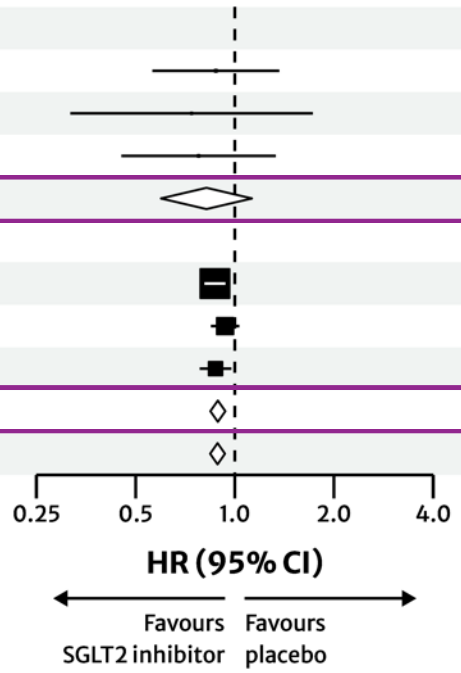
Consistent benefit on all-cause mortality by baseline GLP-1RA use

	Events/patients (%)		Event rate per 100 patient years		HR (95% CI)
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	
Baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	47/937 (5·0)	35/693 (5·1)	1·4	2·1	0·88 (0·56 to 1·37)
Stable heart failure trials	11/75 (14·7)	12/66 (18·2)	5·9	11·1	0·74 (0·32 to 1·73)
Chronic kidney disease trials	25/635 (3·9)	30/640 (4·7)	2·2	2·7	0·78 (0·45 to 1·33)
Subtotal (I-squared = 0·0%, p = 0·85)	83/1647 (5·0)	77/1399 (5·5)	2·0	2·8	0·82 (0·60 to 1·13)
No baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	1624/23626 (6·9)	1264/17312 (7·3)	1·9	3·0	0·87 (0·81 to 0·94)
Stable heart failure trials	746/4781 (15·6)	801/4798 (16·7)	8·7	9·4	0·93 (0·85 to 1·03)
Chronic kidney disease trials	574/9839 (5·8)	653/9817 (6·7)	3·3	3·6	0·87 (0·78 to 0·98)
Subtotal (I-squared = 32·8%, p = 0·13)	2944/38246 (7·7)	2718/31927 (8·5)	3·1	4·2	0·89 (0·84 to 0·94)
Total	3027/39893 (7·6)	2795/33326 (8·4)	3·0	4·1	0·89 (0·84 to 0·93)
Heterogeneity by use of GLP-1 RA: p = 0·63					



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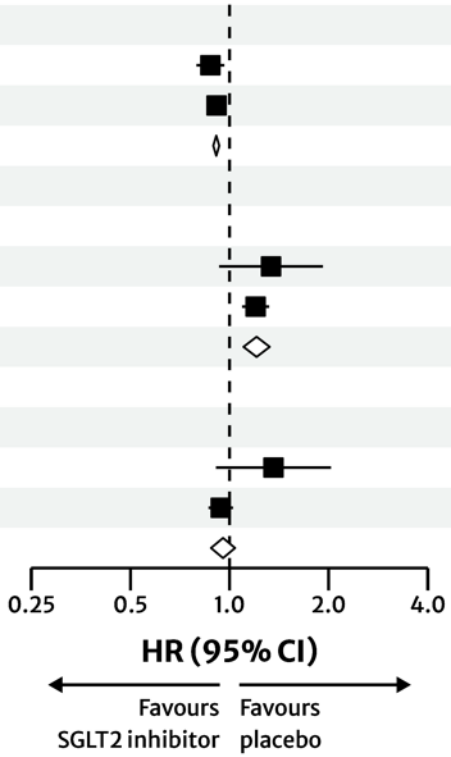
Consistent effects on safety outcomes regardless of GLP-1RA

	Events/patients (%)		
	SGLT2 inhibitor	Placebo	HR (95% CI)
Serious adverse events			
Baseline use of GLP1–RA	620/1658 (37·4)	557/1404 (39·7)	0·87 (0·79 to 0·96)
No baseline use of GLP1–RA	13219/38221 (34·6)	11709/31900 (36·7)	0·91 (0·89 to 0·93)
Total	13839/39879 (34·7)	12266/33304 (36·8)	0·91 (0·89 to 0·93)
Heterogeneity by use of GLP–1 RA: p = 0·41			
Volume depletion			
Baseline use of GLP1–RA	78/1227 (6·4)	52/1186 (4·4)	1·34 (0·93 to 1·92)
No baseline use of GLP1–RA	1054/27891 (3·8)	784/24194 (3·2)	1·20 (1·09 to 1·32)
Total	1132/29118 (3·9)	836/25380 (3·3)	1·21 (1·10 to 1·32)
Heterogeneity by use of GLP–1 RA: p = 0·55			
Hypoglycaemia			
Baseline use of GLP1–RA	62/1125 (5·5)	42/1088 (3·9)	1·36 (0·91 to 2·03)
No baseline use of GLP1–RA	1192/28804 (4·1)	1033/25114 (4·1)	0·94 (0·86 to 1·02)
Total	1254/29929 (4·2)	1075/26202 (4·1)	0·96 (0·88 to 1·04)
Heterogeneity by use of GLP–1 RA: p = 0·13			



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Discussion

- Largest and most comprehensive assessment of the effects of SGLT2i on clinical outcomes by baseline GLP-1RA use
- Important clinical implications given the rapidly expanding indications for GLP1-RA use
- Clear benefits on composite kidney endpoint and eGFR slope in patients receiving and not receiving GLP-1RA
  - Strongest evidence yet for combination SGLT2i and GLP-1RA to reduce kidney failure due to diabetes

Limitations

- Relatively small proportion of patients receiving GLP-1RA
  - Fewer composite kidney endpoints in this subgroup
- All GLP-1RAs considered together
  - There may be important differences within the class
- Does not address the question of combined initiation of SGLT2i and GLP-1RA
  - Requires a dedicated clinical trial

Conclusion

- **Pooled data from the totality of the worldwide placebo-controlled SGLT2i trials indicates the effects of SGLT2i on cardiovascular and kidney outcomes are similar regardless of background use of GLP-1RA**

- **These findings suggest independent effects of these evidence-based therapies and support clinical practice guidelines recommending the use of both these agents to optimise cardiovascular and kidney outcomes**

Acknowledgements

SMART-C

SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists Consortium

Find out more:

www.SMART-C.net

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Ellen Apperloo MD,* Brendon L Neuen PhD,* Robert A Fletcher MSc, Niels Jongs PhD, Stefan D Anker MD, Deepak L Bhatt MD, Javed Butler MD, David ZI Cherney PhD, William G Herrington MD, Silvio E Inzucchi MD, Meg J Jardine PhD, Chih-Chin Liu PhD, Kenneth W Mahaffey MD, Darren K McGuire MD, John JV McMurray MD, Bruce Neal PhD, Milton Packer MD, Prof Vlado Perkovic PhD, Marc S Sabatine MD, Scott D Solomon MD, Natalie Staplin PhD, Michael Szarek PhD, Muthiah Vaduganathan MD, Christoph Wanner MD, David C Wheeler MD, Stephen D Wiviott MD, Faiez Zannad MD, Hiddo J.L. Heerspink PhD
*Contributed equally

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