

Supplementary Material

Title

Risk–Benefit Trade-offs of GLP-1RAs and SGLT-2is in Type 2 Diabetes Mellitus (T2D): Systematic Review, Meta-Analysis, and Net Benefit Modelling

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Supplementary Text 1: Conversion formulas applied to reported summary statistics.

[Abbreviations: IQR: Interquartile Range, SD: standard deviation, HR: hazard ratio, CI: confidence interval, SE: standard error]

When trials reported outcomes in non-standard formats, we applied established methods to derive approximate mean and standard deviation (SD) values for inclusion in the meta-analyses.

Median and interquartile range (IQR):

Using Wan et al. (BMC Med Res Methodol 2014):

$$\text{Mean} \approx \text{Median}, SD \approx \frac{IQR}{1.35}$$

where $IQR = Q_3 - Q_1$.

Median and range:

Using Hozo et al. (BMC Med Res Methodol 2005):

$$\text{Mean} \approx \frac{a + 2m + b}{4}, SD \approx \frac{b - a}{4}$$

where $a = \text{minimum}$, $b = \text{maximum}$, $m = \text{median}$.

Hazard ratios (HRs) and confidence intervals (CIs):

All time-to-event outcomes were log-transformed:

where y is the observed effect size, and SE is its standard error.

These formulas were only applied where necessary; otherwise, published mean (SD) or HR (95% CI) values were used directly.

Supplementary Text 2: Mathematical specification of the trivariate random-effects model used to jointly analyse MACE, hospitalisation for heart failure (hHF), and renal composite outcomes. Trial-level log(HR) estimates were modelled with unstructured covariance across endpoints, estimated via REML in the metafor package (R, version 4.4.1).

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, HR: hazard ratio, REML = restricted maximum likelihood]

For each trial i and outcome j (MACE, hHF, renal), we modelled:

$$y_{ij} = \theta_j + u_{ij} + \varepsilon_{ij}$$

where,

- y_{ij} : is the observed log hazard ratio (log[HR]) for outcome j in trial i ,
- θ_j : is the pooled mean effect for outcome j ,

- U_{ij} : is the trial-specific random effect with covariance matrix $\Sigma_u \backslash \Sigma_u \{u\} \Sigma_u$, and
- ϵ_{ij} : is the sampling error, assumed normally distributed with known variance from trial-level SEs.

The random-effects covariance matrix $\Sigma_u \backslash \Sigma_u \{u\} \Sigma_u$ was estimated without structural constraints (unstructured), thereby allowing correlations between outcomes. Parameters were estimated using **restricted maximum likelihood (REML)** with the `rma.mv()` function in the **metafor** R package (version 4.4.1). Hartung–Knapp adjustments were applied at the endpoint level, with joint covariance informing cross-endpoint prediction intervals.

Supplementary Table 1: Detailed Baseline Characteristics of Participants in Cardiovascular Outcome Trials

Baseline characteristics of 132,038 participants across 17 cardiovascular outcome trials (CVOTs), including 10 GLP-1 receptor agonist (GLP-1RA; N=73,263) and 7 SGLT-2 inhibitor (SGLT-2i; N=58,775) trials. Data are presented as mean with standard deviation (SD) or median with interquartile range (IQR) as reported in each trial; missing data are denoted as not reported (NR).

[Abbreviations: CVOT = cardiovascular outcomes trial, SGLT-2i = sodium glucose cotransporter-2 inhibitor, GLP-1 = glucagon like peptide-1, Int/Con, intervention/control; T2DM, type 2 diabetes mellitus; HbA1c, glycated haemoglobin; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; eGFR, estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range].

Trial	Year	Drug Class	N (Int/Con) n	Age ^a	% Male	T2DM Duration, y ^{a,b}	Follow-up, y	HbA1c, % ^{a,b}	BMI, kg/m ² ^{a,b}	SBP, mmHg ^a	DBP, mmHg ^a	ASCVD, %	HF, %	eGFR, ml/min/1.73m ^{2a,b}
GLP-1RA														
LEADER	2016	GLP-1RA	4,668/4,672	64.2 (7.2)	64.5	12.8 (8.0)	3.8	8.7 (1.6)	32.5 (6.3)	135.9 (17.8)	77.2 (10.3)	82.1	17.9	80.0 (21.3)
ELIXA	2015	GLP-1RA	3,034/3,034	59.9 (9.7)	69.1	9.2 (8.2)	2.1	7.7 (1.3)	30.1 (5.6)	129.0 (17.0)	NR	100.0	22.5	76.7 (21.3)

EXSCEL	2017	GLP-1RA	7,356/ 7,396	62.0 (56.0–68.0) ^b	62.0	12.0 (7.0–17.0) ^b	3.2	8.0 (7.3–8.9) ^b	31.8 (28.2–36.2) ^b	135.0 (NR)	80.0 (10.2)	73.1	15.8	76.6 (61.3–92.0) ^b
HARMONY	2018	GLP-1RA	4,731/ 4,732	64.1 (8.7)	70.0	14.1 (8.6)	1.5	8.8 (1.5)	32.3 (5.9)	134.8 (16.6)	76.8 (10.1)	100.0	10.6	79.1 (25.6)
REWIND	2019	GLP-1RA	4,949/ 4,952	66.2 (6.5)	54.7	10.5 (7.3)	5.4	7.2 (6.6–8.1) ^b	32.3 (5.7)	137.1 (16.6)	78.4 (9.8)	31.5	8.5	75.3 (61.6–91.8) ^b
PIONEER 6	2019	GLP-1RA	1,591/ 1,592	66.0 (7.0)	68.1	14.7 (8.5)	1.3	8.2 (1.6)	32.3 (6.6)	135.0 (18.0)	76.0 (10.0)	84.9	11.8	74.0 (21.0)
SUSTAIN-6	2016	GLP-1RA	1,648/ 1,649	64.7 (7.1)	63.0	14.1 (8.2)	2.1	8.7 (1.5)	32.0 (NR)	135.8 (17.0)	76.9 (10.2)	83.0	21.9	78.0 (NR)
AMPLITUDE-O	2021	GLP-1RA	2,717/ 1,359	64.6 (8.2)	66.0	15.6 (8.8)	1.8	8.9 (1.5)	32.9 (6.2)	135.1 (15.5)	76.8 (9.7)	89.1	17.9	72.2 (21.9)
FLOW	2024	GLP-1RA	1,767/ 1,766	66.6 (9.0)	70.6	17.4 (9.3)	3.4	7.8 (1.3)	31.9 (6.1)	138.9 (16.1)	76.8 (10.0)	22.9	19.4	46.9 (15.6)
SOUL	2025	GLP-1RA	4,825/ 4,825	66.1 (7.6)	71.1	15.4 (8.8)	4.1	8.0 (1.1)	31.1 (5.8)	134.6 (16.3)	76.7 (10.1)	70.7	23.0	75.3 (22.4)
SGLT-2i														
EMPA-REG	2015	SGLT-2i	4,687/ 2,333	63.0 (8.6)	70.5	NR	3.1	8.1 (0.9)	30.6 (5.2)	134.9 (16.8)	76.6 (9.8)	98.9	10.2	74.3 (21.8)
DECLARE-TIMI 58	2019	SGLT-2i	8,582/ 8,578	63.9 (6.8)	63.1	11.0 (6.0–16.0) ^b	4.2	8.3 (1.2)	32.1 (6.0)	135.1 (15.3)	78.0 (NR)	40.5	9.9	85.4 (15.8)
CANVAS Program	2017	SGLT-2i	5,795/ 4,347	63.2 (8.3)	64.9	13.5 (7.7)	3.6	8.2 (0.9)	31.9 (5.9)	136.4 (15.8)	77.6 (9.6)	71.2	13.9	76.7 (20.3)
VERTIS CV	2020	SGLT-2i	5,499/ 2,747	64.4 (8.1)	70.3	12.9 (8.3)	3.5	8.2 (1.0)	31.9 (5.4)	133.5 (13.7)	76.8 (8.3)	100.0	23.4	76.1 (20.9)

SCORED	2021	SGLT-2i	5,292/5,292	69.0 (63–74) ^b	65.7	14.8 (NR)	1.3	8.3 (7.6–9.3) ^b	31.9 (28.1–36.2) ^b	139.0 (17.0)	78.0 (10.0)	36.5	31.0	44.4 (37.0–51.3) ^b
SOLOIST-WHF	2021	SGLT-2i	608/614	69.0 (63–76) ^b	67.4	14.7 (NR)	0.8	7.1 (6.4–8.3) ^b	30.4 (26.3–34.3) ^b	122.3 (16.7)	71.1 (10.5)	78.3	100.0	49.2 (39.5–61.2) ^b
CREDENCE	2019	SGLT-2i	2,202/2,199	62.9 (9.2)	65.4	15.5 (8.7)	2.6	8.3 (1.3)	31.4 (6.2)	139.8 (15.6)	78.2 (9.4)	50.5	14.9	56.3 (18.2)

Footnotes:

- ^a Mean (SD) unless otherwise noted.
- ^b Median (IQR).
- Int/Con = Intervention/Control; NR = Not reported; y = years; HbA1c = Glycated hemoglobin; BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; ASCVD = Atherosclerotic cardiovascular disease; HF = Heart failure; eGFR = Estimated glomerular filtration rate.

Supplementary Table 2: Sensitivity net-benefit calculations per 1,000 treated, evaluating each harm individually. Trial-level and scenario-wise net benefit estimates (per 1,000 patients treated) for GLP-1 receptor agonists (GLP-1RAs) and SGLT-2 inhibitors (SGLT-2i). Estimates combine absolute risk reductions (ARR) for efficacy outcomes with absolute excess risks (AER) for safety outcomes. Scenarios include additional harms beyond those summarised in Table 3, such as gallbladder disease, pancreatitis, amputation, diabetic ketoacidosis, and volume depletion. Negative values indicate net harm.

[Abbreviations: GLP-1RAs = glucagon like peptide-1 receptor agonists, SGLT-2i = sodium glucose cotransporter-2 inhibitor, ARR = absolute risk reduction, MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, GU = genito-urinary, DKA = diabetic ketoacidosis]

Drug class	Efficacy endpoint	ARR (/1,000)	Harm	AER (/1,000)	Net benefit (/1,000)
GLP-1RA	MACE	+9	Retinopathy	–6.5	+2.5
GLP-1RA	MACE	+9	Gallbladder disease	–4.0	+5.0

GLP-1RA	MACE	+9	Pancreatic cancer (signal)	-0.5	+8.5
SGLT-2i	hHF	+15	GU infection	-19.9	-4.9
SGLT-2i	hHF	+15	Volume depletion	-6.9	+8.1
SGLT-2i	hHF	+15	Amputation	-3.1	+11.9
SGLT-2i	hHF	+15	DKA	-1.2	+13.8
SGLT-2i	Renal	+18	Genital-mycotic infection	-19.9	-1.9
SGLT-2i	Renal	+18	Volume depletion	-6.9	+11.1
SGLT-2i	Renal	+18	Amputation	-3.1	+14.9
SGLT-2i	Renal	+18	DKA	-1.2	+16.8

Supplementary Table 3. Univariate meta-regression analyses evaluating potential effect modifiers across major outcomes (MACE, hospitalisation for heart failure [hHF], and renal composite events). Moderators tested included baseline HbA1c, systolic blood pressure, body mass index, proportion with established ASCVD, proportion with heart failure, baseline eGFR, proportion of male participants, and trial follow-up duration. None of the baseline characteristics significantly influenced treatment effects for MACE or hHF. For renal composite outcomes, the duration of T2D follow-up was identified as a significant effect modifier.

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, HF = heart failure, HbA1c = glycated haemoglobin, ASCVD = atherosclerotic cardiovascular disease, T2D = type 2 diabetes, SD = standard deviation, NS = not significant, HR = hazard ratio, eGFR = Estimated glomerular filtration rate, SBP = systolic blood pressure, BMI = body mass index].

Outcome	Moderator	k	HR change (95% CI)	p-value	Interpretation
MACE	HbA1c (per 1 SD)	16	0.97 (0.94 – 1.01)	0.21	NS
	SBP (per 1 SD)	16	0.98 (0.94 – 1.02)	0.27	NS
	BMI (per 1 SD)	16	0.98 (0.94 – 1.02)	0.34	NS
	ASCVD % (per 1 SD)	16	1.00 (0.96 – 1.04)	0.85	NS
	HF % (per 1 SD)	16	0.99 (0.95 – 1.04)	0.81	NS
	eGFR (per 1 SD)	16	0.98 (0.95 – 1.02)	0.34	NS
	Male % (per 1 SD)	16	1.00 (0.96 – 1.03)	0.79	NS

	Follow-up (per 1 SD)	16	1.03 (0.99 – 1.07)	0.21	NS
hHF	HbA1c (per 1 SD)	15	1.00 (0.93 – 1.08)	0.92	NS
	SBP (per 1 SD)	15	1.00 (0.93 – 1.08)	0.99	NS
	BMI (per 1 SD)	15	1.04 (0.97 – 1.12)	0.29	NS
	ASCVD % (per 1 SD)	15	1.02 (0.94 – 1.10)	0.65	NS
	HF % (per 1 SD)	15	0.98 (0.92 – 1.05)	0.60	NS
	eGFR (per 1 SD)	15	1.05 (0.98 – 1.12)	0.18	NS
	Male % (per 1 SD)	15	0.94 (0.88 – 1.01)	0.08	NS
	Follow-up (per 1 SD)	15	1.00 (0.92 – 1.08)	0.98	NS
Renal	HbA1c (per 1 SD)	11	0.97 (0.87 – 1.08)	0.55	NS
	SBP (per 1 SD)	11	0.98 (0.86 – 1.11)	0.74	NS
	BMI (per 1 SD)	11	1.00 (0.91 – 1.11)	0.97	NS
	ASCVD % (per 1 SD)	11	0.97 (0.89 – 1.07)	0.57	NS
	HF % (per 1 SD)	11	1.03 (0.89 – 1.18)	0.70	NS
	eGFR (per 1 SD)	11	1.01 (0.92 – 1.11)	0.81	NS
	Male % (per 1 SD)	11	1.05 (0.96 – 1.14)	0.26	NS
	Follow-up (per 1 SD)	11	1.09 (1.00 – 1.18)	0.038	Significant

Supplementary Table 4: Design-adjusted exploratory meta-regression of trial-level baseline imbalances (mean eGFR, heart failure prevalence) on class-wise contrasts.

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, HF = heart failure, eGFR = Estimated glomerular filtration rate, SE = standard error, CI = confidence interval].

Outcome domain	Moderator	Beta	SE	95% CI (Lower)	95% CI (Upper)	p-value	Interpretation
Renal composite	Mean baseline eGFR	0.0099	0.0039	0.0023	0.0175	0.0123	Significant modifier
Renal composite	% HF prevalence	– 0.0024	0.0059	–0.0139	0.0091	0.6840	No effect
MACE	Mean baseline eGFR	0.0029	0.0021	–0.0013	0.0071	0.1610	No effect
MACE	% HF prevalence	– 0.0061	0.0022	–0.0104	–0.0018	0.0053	Significant modifier

hHF	Mean baseline eGFR	0.0057	0.0040	-0.0022	0.0136	0.1600	No effect
hHF	% HF prevalence	-0.0032	0.0049	-0.0129	0.0065	0.5120	No effect

Supplementary Table 5: Estimated between-study covariance (Ψ) and correlation matrices from the trivariate random-effects model jointly analysing MACE, hospitalisation for heart failure (hHF), and renal composite outcomes (11 trials). Models were fit by REML using the mvmeta package in R. Sampling variances were assumed independent across endpoints within trials. The unstructured random-effects covariance Ψ captures cross-endpoint dependence; corresponding correlation coefficients are shown below for interpretability.

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, REML = restricted maximum likelihood].

Outcome	MACE	hHF	Renal
MACE	1.00	-0.03	-0.12
hHF	-0.03	1.00	0.99
Renal	-0.12	0.99	1.00

Supplementary Table 6: Internal calibration results from bootstrap leave-one-out validation (1,000 replicates). Values are medians and 95% quantiles for calibration intercepts and slopes, reported on the logit scale.

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure].

Endpoint	Intercept (median [95%])	Slope (median [95%])	B Success
MACE	-25.9 [-36.3, -19.5]	-11.5 [-16.8, -8.6]	1000
hHF	-40.3 [-55.7, -31.4]	-12.6 [-18.1, -9.4]	1000
Renal	-25.0 [-44.2, -18.2]	-8.8 [-13.6, -5.6]	1000

Supplementary Table 7. GRADE Summary of Findings.

[Abbreviations: GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HR = hazard ratio, RR = relative risk, ARR = absolute risk reduction, AER = absolute event rate, CI = confidence interval, GLP-1RA = glucagon like peptide-1 receptor agonists, SGLT-2i = sodium glucose cotransporter-2 inhibitor, MACE = major adverse cardiac

events, hHF = hospitalisation due to heart failure, RCT = randomised controlled trial, DKA = diabetic ketoacidosis].

Outcome	Intervention	Effect (HR/RR, 95% CI)	Absolute Effect (ARR/AER per 1,000)	Certainty (GRADE)	Notes / Reasons for Downgrade
Major Adverse Cardiovascular Events (MACE)	GLP-1RA	HR 0.86 (0.82–0.91)	ARR ≈ 9/1,000	High	Robust, consistent RCT data
	SGLT-2i	HR 0.88 (0.82–0.94)	ARR ≈ 5/1,000	High	No downgrade
Hospitalization for Heart Failure (hHF)	GLP-1RA	HR 0.88 (0.82–0.95)	ARR ≈ 3/1,000	Moderate	Downgraded: imprecision
	SGLT-2i	HR 0.69 (0.64–0.75)	ARR ≈ 15/1,000	High	Consistent effect
Renal Composite Outcomes	GLP-1RA	HR 0.79 (0.73–0.85)	ARR ≈ 7/1,000	Moderate	Downgraded: endpoint heterogeneity
	SGLT-2i	HR 0.68 (0.61–0.76)	ARR ≈ 18/1,000	High	Strong consistent evidence
Retinopathy	GLP-1RA	RR 1.18 (1.01–1.37)	AER ≈ +6.5/1,000	Moderate	Downgraded: inconsistency
Genital-mycotic infection	SGLT-2i	RR 3.34 (2.19–5.08)	AER ≈ +19.9/1,000	High	Robust across trials
Amputation	SGLT-2i	RR 1.19 (1.01–1.40)	AER ≈ +3.1/1,000	Moderate	Downgraded: imprecision

DKA	SGLT-2i	RR 2.67 (1.24–5.71)	AER ≈ +1.2/1,000	Moderate	Downgraded: wide CI
Other harms (pancreatitis, thyroid malignancy, fractures, hypoglycemia)	GLP- 1RA/SGLT-2i	RR ~1.0 (various CIs)	Neutral	Moderate	Downgraded: low event rates

Supplementary Table 8: RoB2 (domain-level) by trial and outcome.

[Abbreviations: RoB = risk of bias, GLP-1RA = glucagon like peptide-1 receptor agonists, SGLT-2i = sodium glucose cotransporter-2 inhibitor, MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure].

Trial	Drug class	Outcome	Bias arising from randomisation	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported result
ELIXA	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
ELIXA	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
ELIXA	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
LEADER	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
LEADER	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
LEADER	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
SUSTAIN-6	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
SUSTAIN-6	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
SUSTAIN-6	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
EXSCEL	GLP-1RA	MACE	Low risk	Some concerns	Some concerns	Low risk	Low risk
EXSCEL	GLP-1RA	hHF	Low risk	Some concerns	Some concerns	Low risk	Low risk
EXSCEL	GLP-1RA	Renal composite	Low risk	Some concerns	Some concerns	Low risk	Low risk
HARMONY	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
HARMONY	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
HARMONY	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
REWIND	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
REWIND	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
REWIND	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
PIONEER-6	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Some concerns
PIONEER-6	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Some concerns
PIONEER-6	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Some concerns
AMPLITUDE-O	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Low risk

AMPLITUDE-O	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
AMPLITUDE-O	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
FLOW	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
FLOW	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
FLOW	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
SOUL	GLP-1RA	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
SOUL	GLP-1RA	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
SOUL	GLP-1RA	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
EMPA-REG	SGLT-2i	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
EMPA-REG	SGLT-2i	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
EMPA-REG	SGLT-2i	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
CANVAS	SGLT-2i	MACE	Low risk	Some concerns	Low risk	Low risk	Low risk
CANVAS	SGLT-2i	hHF	Low risk	Some concerns	Low risk	Low risk	Low risk
CANVAS	SGLT-2i	Renal composite	Low risk	Some concerns	Low risk	Low risk	Low risk
DECLARE	SGLT-2i	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
DECLARE	SGLT-2i	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
DECLARE	SGLT-2i	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
CREDENCE	SGLT-2i	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
CREDENCE	SGLT-2i	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
CREDENCE	SGLT-2i	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
VERTIS	SGLT-2i	MACE	Low risk	Low risk	Low risk	Low risk	Low risk
VERTIS	SGLT-2i	hHF	Low risk	Low risk	Low risk	Low risk	Low risk
VERTIS	SGLT-2i	Renal composite	Low risk	Low risk	Low risk	Low risk	Low risk
SCORED	SGLT-2i	MACE	Low risk	Some concerns	Some concerns	Low risk	Some concerns
SCORED	SGLT-2i	hHF	Low risk	Some concerns	Some concerns	Low risk	Some concerns
SCORED	SGLT-2i	Renal composite	Low risk	Some concerns	Some concerns	Low risk	Some concerns
SOLOIST	SGLT-2i	MACE	Low risk	Some concerns	Some concerns	Low risk	Some concerns
SOLOIST	SGLT-2i	hHF	Low risk	Some concerns	Some concerns	Low risk	Some concerns
SOLOIST	SGLT-2i	Renal composite	Low risk	Some concerns	Some concerns	Low risk	Some concerns

Supplementary Table 9: GRADE evidence profiles (per endpoint & per class / class-to-class).

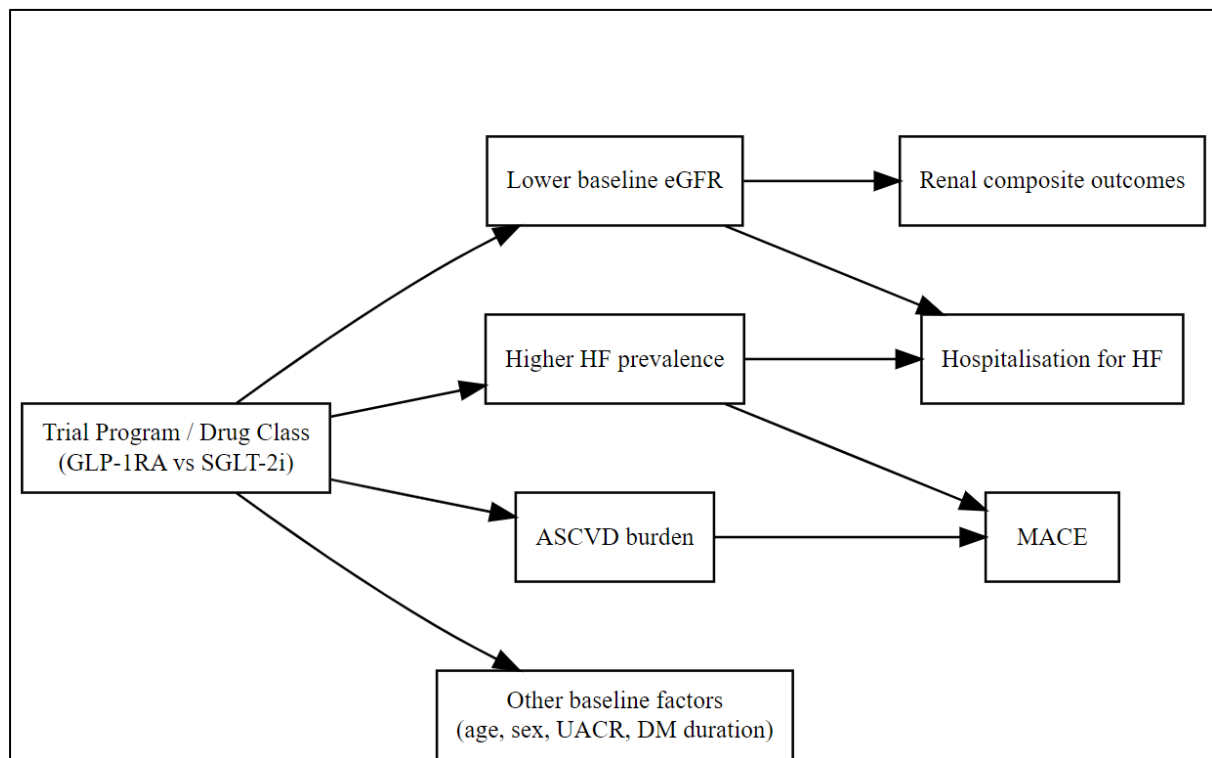
[Abbreviations: GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HR = hazard ratio, RR = relative risk, ARR = absolute risk reduction, AER = absolute event rate, CI = confidence interval, GLP-1RA = glucagon like peptide-1 receptor agonists, SGLT-2i = sodium glucose cotransporter-2 inhibitor, MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, RCT = randomised controlled trial, DKA = diabetic ketoacidosis, UTI = urinary tract infection].

Endpoint	Class / Comparison	Effect (summary)	k	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Downgrade rationale / Notes
MACE	GLP-1RA vs Placebo	HR ≈0.86 (benefit)	10	Not serious	Not serious	Not serious	Not serious	Possible	High	Small-study effect possible; pooled estimate robust.
MACE	SGLT-2i vs Placebo	HR ≈0.88 (benefit)	6	Not serious	Not serious	Not serious	Not serious	Possible	High	Similar magnitude to GLP-1RA.
hHF	SGLT-2i vs Placebo	HR ≈0.69 (benefit)	11	Not serious	Not serious	Not serious	Not serious	Unlikely	High	Consistent across programs.
hHF	GLP-1RA vs Placebo	HR ≈0.88 (modest benefit)	6	Not serious	Serious	Not serious	Serious	Unlikely	Moderate	Heterogeneity and wider CIs.
Renal composite	SGLT-2i vs Placebo	HR ≈0.68 (benefit)	11	Not serious	Serious	Not serious	Not serious	Unlikely	High	Composite heterogeneity but direction consistent.
Renal composite	GLP-1RA vs Placebo	HR ≈0.79 (benefit)	6	Not serious	Serious	Not serious	Serious	Unlikely	Moderate	Greater heterogeneity and imprecision.
Retinopathy	GLP-1RA vs Placebo	RR ≈1.18 (↑ risk)	6	Not serious	Serious	Not serious	Not serious	Unlikely	Moderate	I ² ~48%; modest magnitude.
Pancreatitis	GLP-1RA vs Placebo	RR ≈1.05 (NS)	10	Not serious	Not serious	Not serious	Serious	Unlikely	Moderate	Sparse events; wide CI.
Genital-mycotic infection	SGLT-2i vs Placebo	RR ≈3.34 (↑ risk)	7	Not serious	Not serious	Not serious	Not serious	Unlikely	High	Large, consistent effect.
DKA	SGLT-2i vs Placebo	RR ≈2.67 (↑ risk)	7	Not serious	Not serious	Not serious	Serious	Unlikely	Moderate	Sparse events; low absolute risk.
Amputation	SGLT-2i vs Placebo	RR ≈1.19 (borderline)	7	Not serious	Serious	Not serious	Serious	Unlikely	Low	Sensitive to CANVAS; null in sensitivity.
UTI	SGLT-2i vs Placebo	RR ≈1.05 (NS)	7	Not serious	Not serious	Not serious	Not serious	Unlikely	High	No consistent signal.
Fracture	SGLT-2i vs Placebo	RR ≈1.05 (NS)	7	Not serious	Not serious	Not serious	Not serious	Unlikely	High	No consistent signal.
MACE	GLP-1RA vs SGLT-2i (indirect)	Similar	16	Not serious	Not serious	Serious	Not serious	Possible	Low	Population differences (eGFR/HF prevalence).
hHF	GLP-1RA vs SGLT-2i (indirect)	Favours SGLT-2i	11	Not serious	Not serious	Serious	Not serious	Unlikely	Moderate	Superiority consistent for SGLT-2i.
Renal composite	GLP-1RA vs SGLT-2i (indirect)	Favours SGLT-2i	11	Not serious	Serious	Serious	Not serious	Unlikely	Moderate	Composite differences + indirectness.

Supplementary Figures

Supplementary Figure S1: Directed acyclic graph (DAG) illustrating potential structural confounding across CVOT programs. Trial program/drug class influences baseline characteristics (e.g., lower eGFR, higher HF prevalence, ASCVD burden), which in turn affect renal, HF, and MACE outcomes. Cross-links depict secondary influences (e.g., low eGFR contributing to HF events). This motivated design-adjusted sensitivity analyses via meta-regression.

[Abbreviations: DAG = directed acyclic graph, HF = heart failure, eGFR = Estimated glomerular filtration rate, MACE = major adverse cardiac events, ASCVD = atherosclerotic cardiovascular disease, UACR = urinary albumin creatinine ratio, GLP-1RA = glucagon like peptide-1 receptor agonists, SGLT-2i = sodium glucose cotransporter-2 inhibitor, DM = diabetes mellitus].

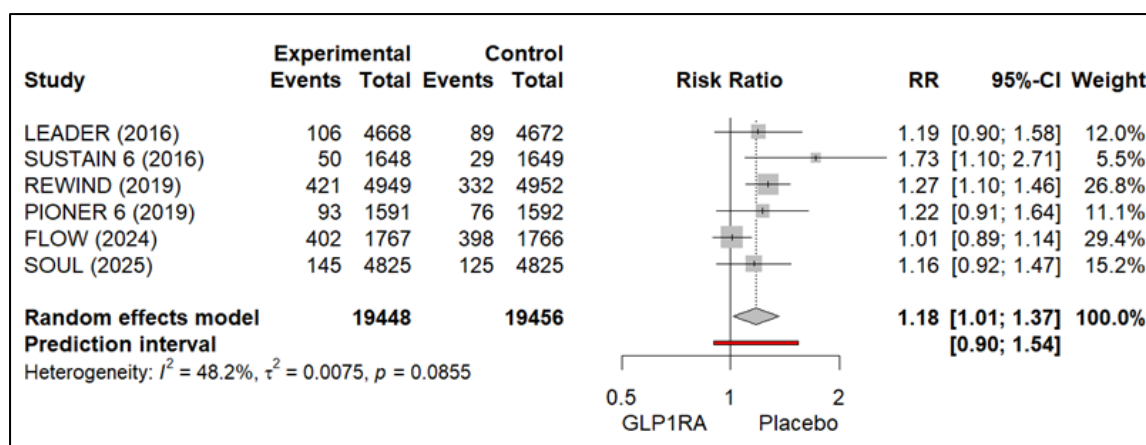


Safety (Harms):

Supplementary Figures S2-S16

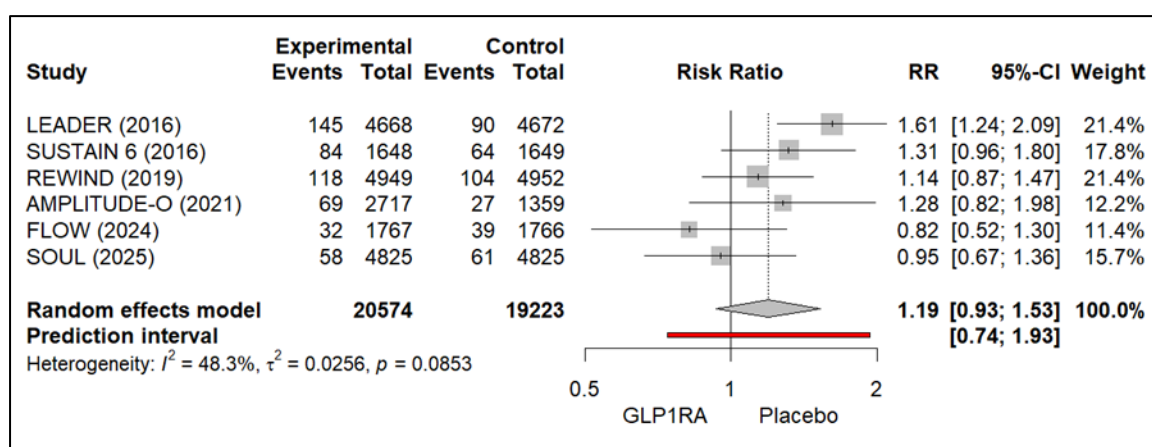
Supplementary Figure S2. Forest plot of retinopathy risk with GLP-1 receptor agonists compared with placebo in cardiovascular outcome trials.

[Abbreviations: GLP-1RA = glucagon like peptide-1 receptor agonists, RR = relative risk, CI = confidence interval]



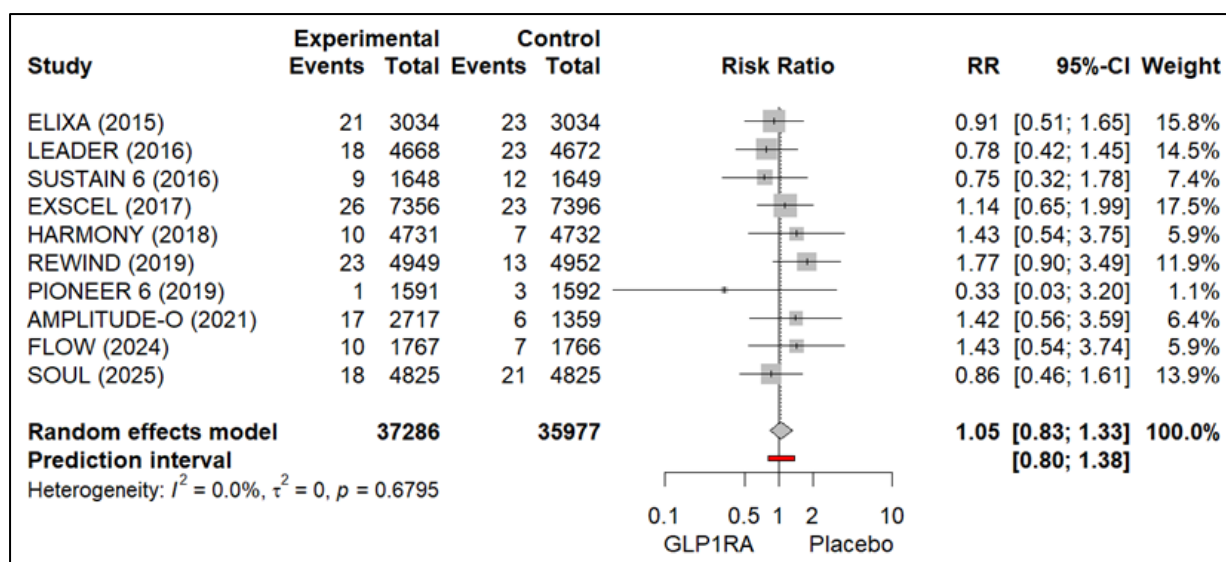
Supplementary Figure S3. Forest plot of gallbladder disease risk with GLP-1 receptor agonists compared with placebo.

[Abbreviations: GLP-1RA = glucagon like peptide-1 receptor agonists, RR = relative risk, CI = confidence interval]



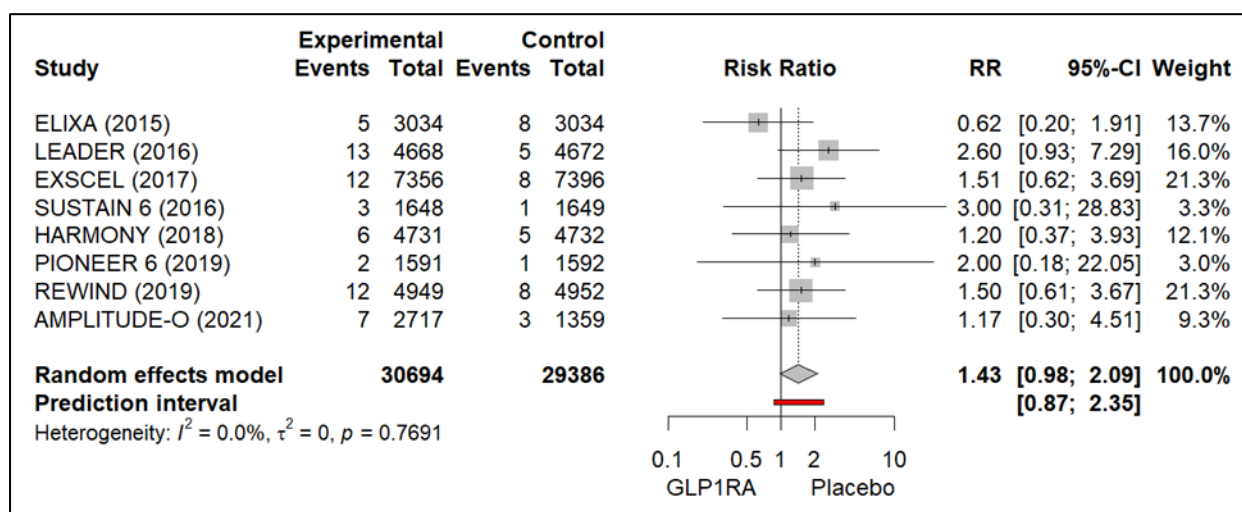
Supplementary Figure S4. Forest plot of risk of pancreatitis with GLP-1 receptor agonists versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: GLP-1RA = glucagon like peptide-1 receptor agonists, RR = relative risk, CI = confidence interval]



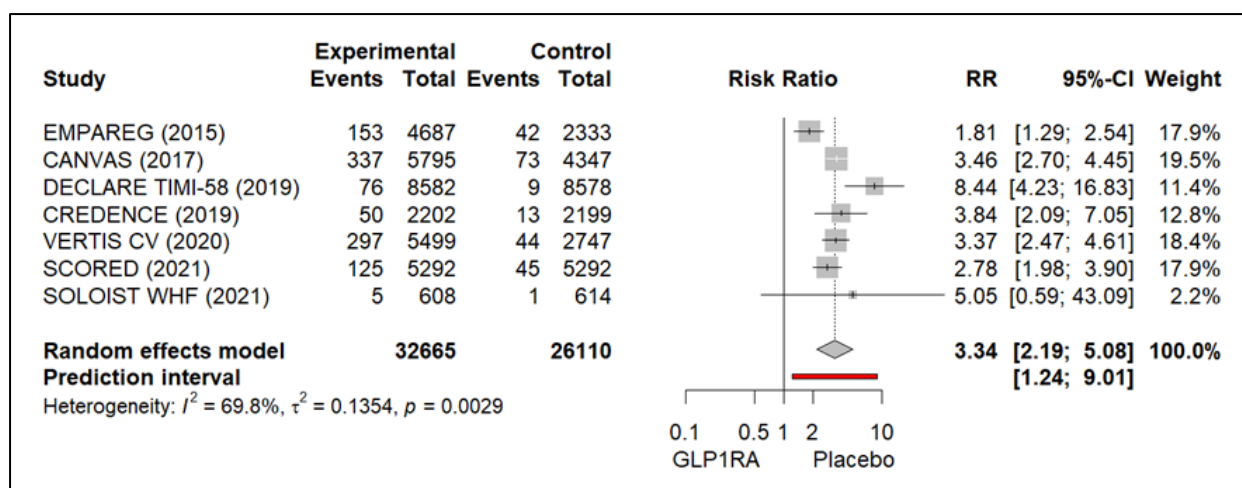
Supplementary Figure S5. Forest plot of pancreatic cancer risk with GLP-1 receptor agonists compared with placebo.

[Abbreviations: GLP-1RA = glucagon like peptide-1 receptor agonists, RR = relative risk, CI = confidence interval]



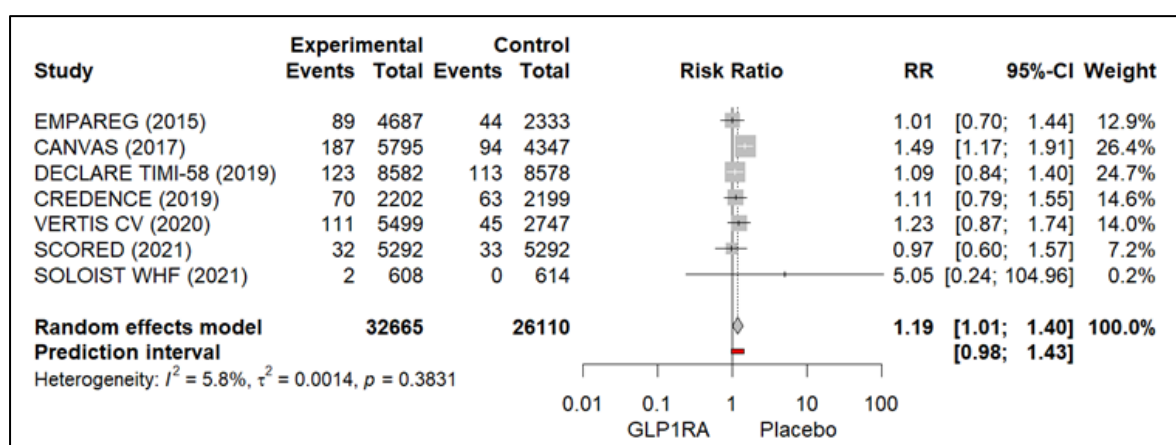
Supplementary Figure S6. Forest plot of genital-mycotic infection risk with SGLT-2 inhibitors compared with placebo.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, RR = relative risk, CI = confidence interval].



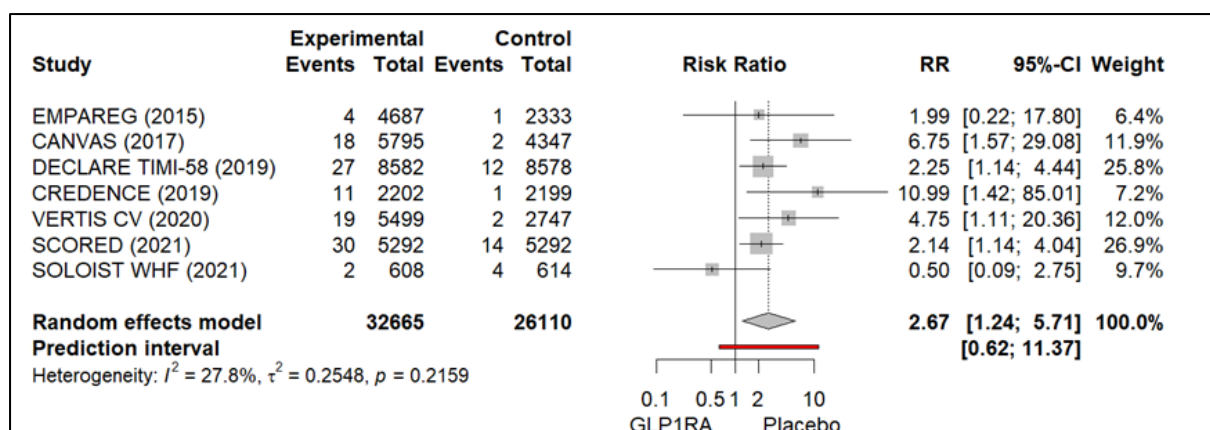
Supplementary Figure S7. Forest plot of risk of amputations with SGLT-2 inhibitors versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, RR = relative risk, CI = confidence interval].



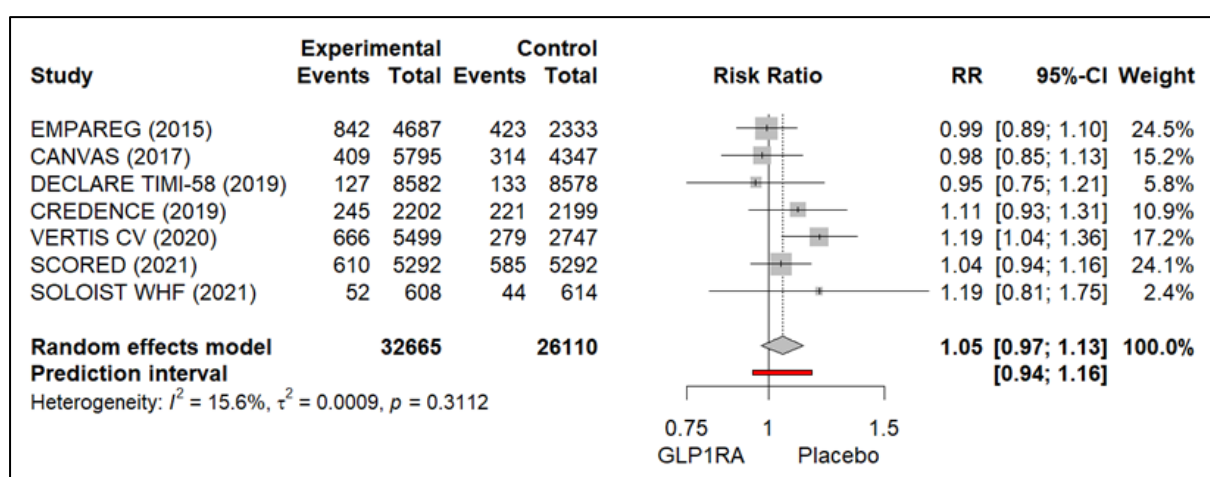
Supplementary Figure S8. Forest plot of risk of diabetic ketoacidosis (DKA) with SGLT-2 inhibitors versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, RR = relative risk, CI = confidence interval, DKA = diabetic ketoacidosis].



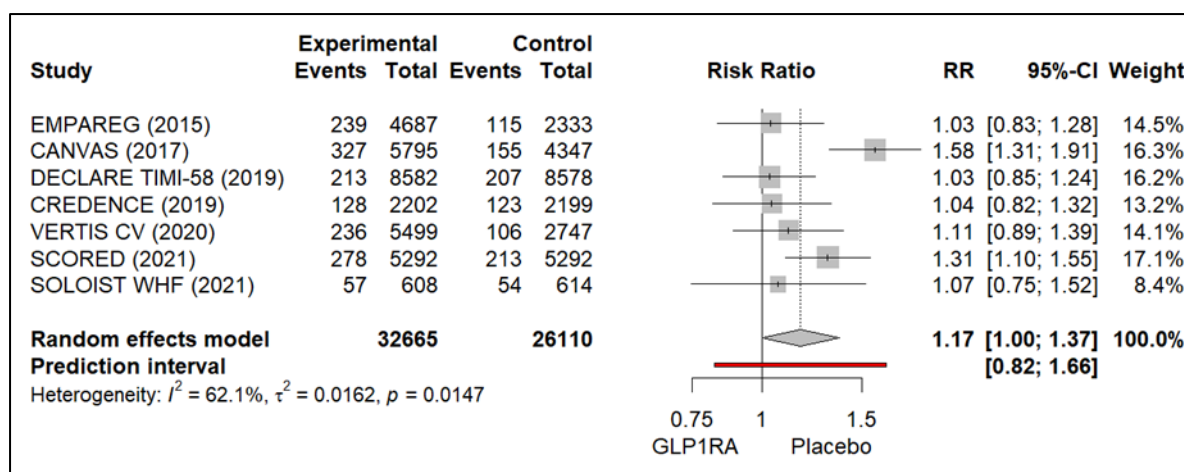
Supplementary Figure S9. Forest plot of risk of urinary tract infections (UTI) with SGLT-2 inhibitors versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, RR = relative risk, CI = confidence interval, UTI = urinary tract infection].



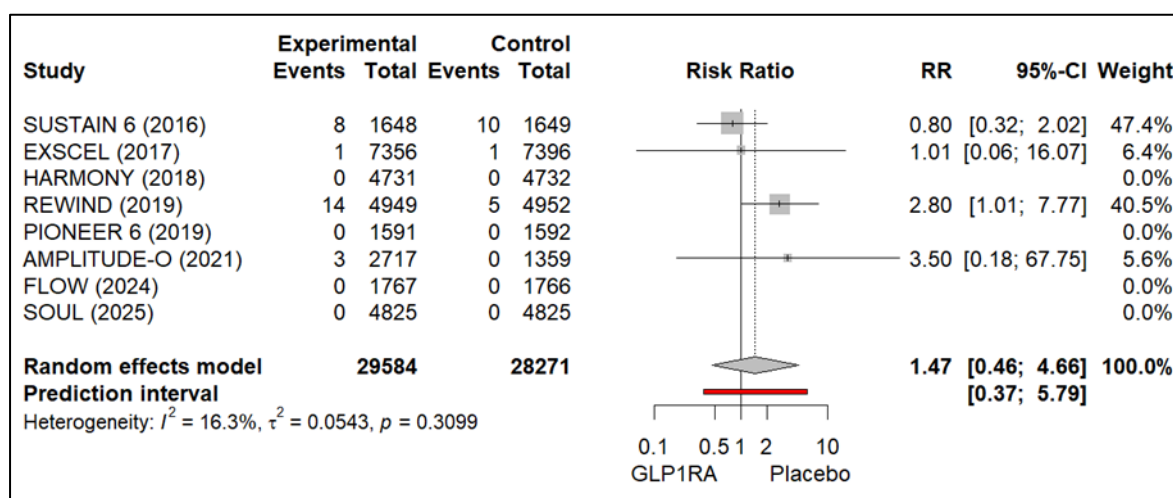
Supplementary Figure S10. Forest plot of risk of volume depletion with SGLT-2 inhibitors versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, RR = relative risk, CI = confidence interval].



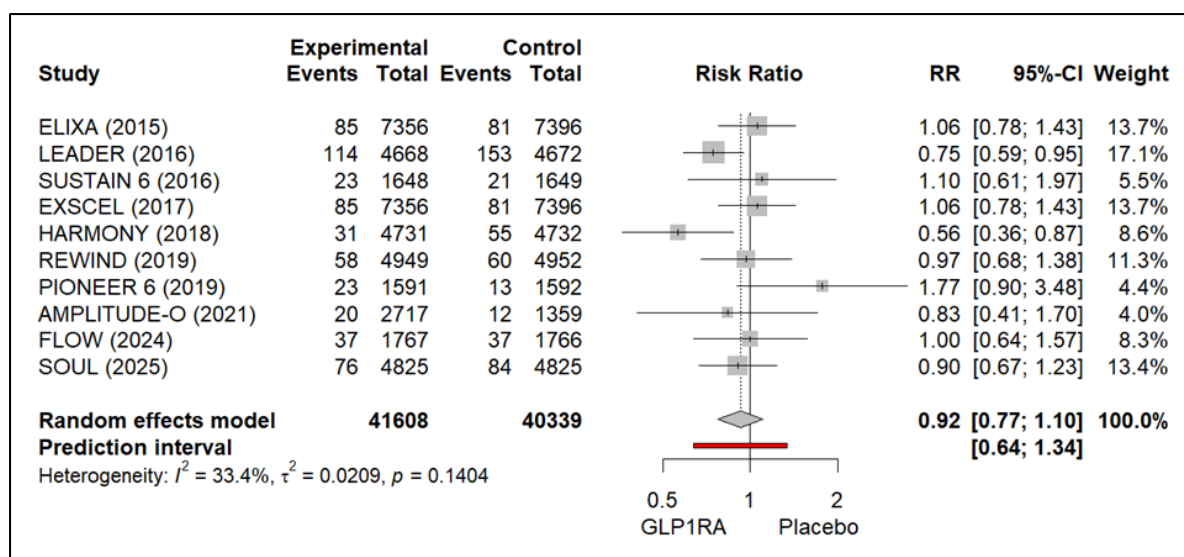
Supplementary Figure S11. Forest plot of risk of thyroid malignancy with GLP-1 receptor agonists versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: GLP-1RA = glucagon like peptide-1 receptor agonists, RR = relative risk, CI = confidence interval]



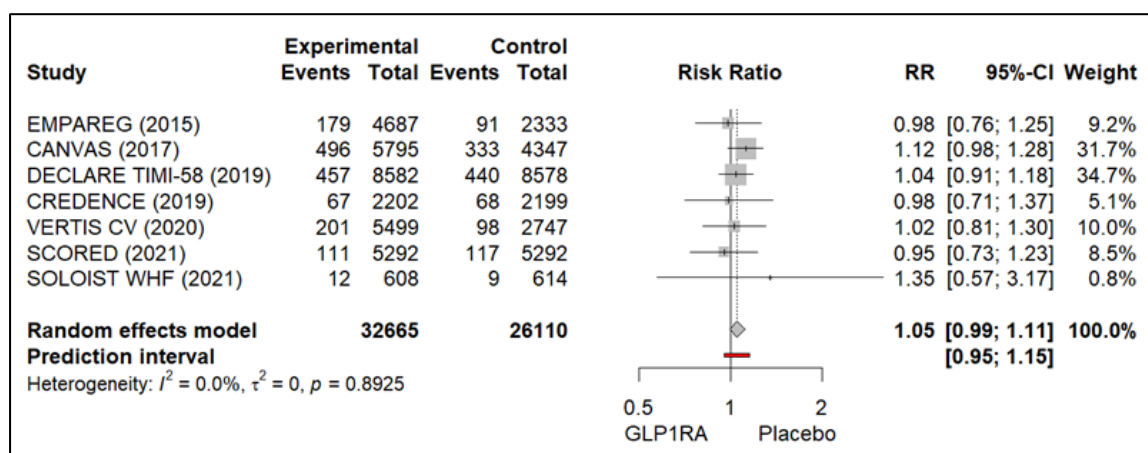
Supplementary Figure S12. Forest plot of risk of severe hypoglycaemia with GLP-1 receptor agonists versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: GLP-1RA = glucagon like peptide-1 receptor agonists, RR = relative risk, CI = confidence interval]



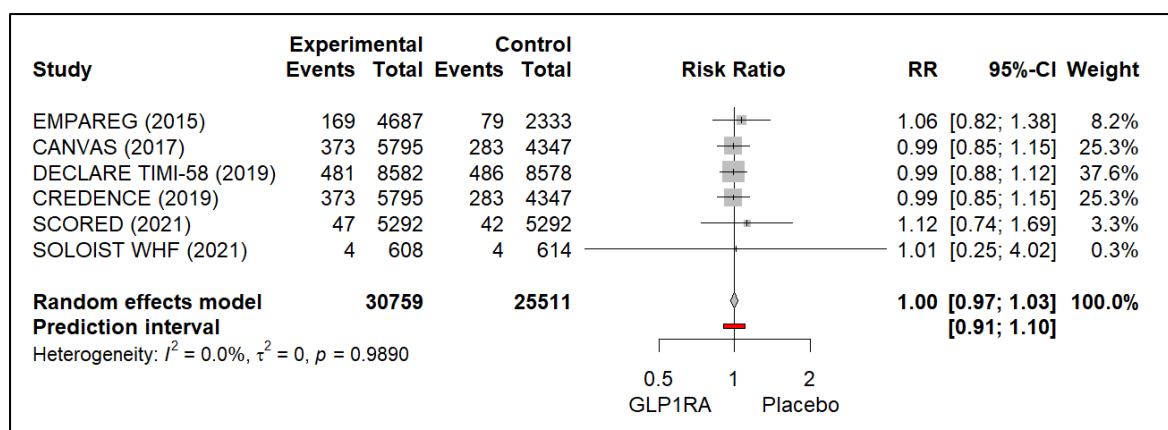
Supplementary Figure S13. Forest plot of risk of fractures with SGLT-2 inhibitors versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, RR = relative risk, CI = confidence interval].



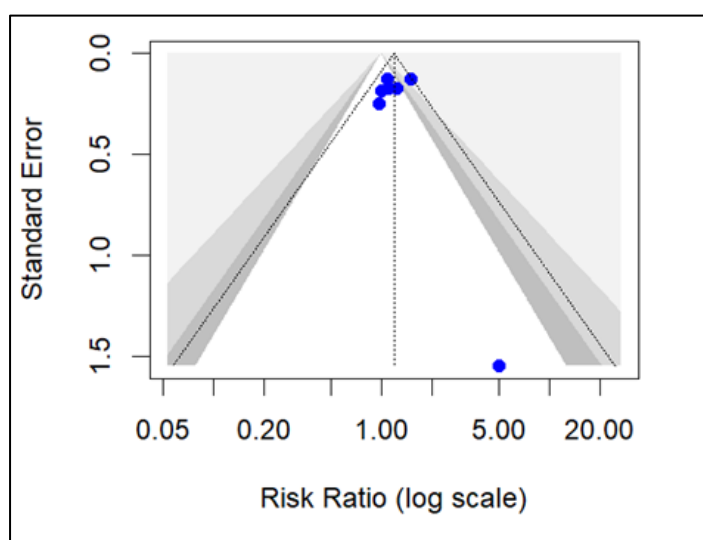
Supplementary Figure S14. Forest plot of risk of malignancies with SGLT-2 inhibitors versus placebo. Effect estimates are presented as RR with 95% CI.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, RR = relative risk, CI = confidence interval].



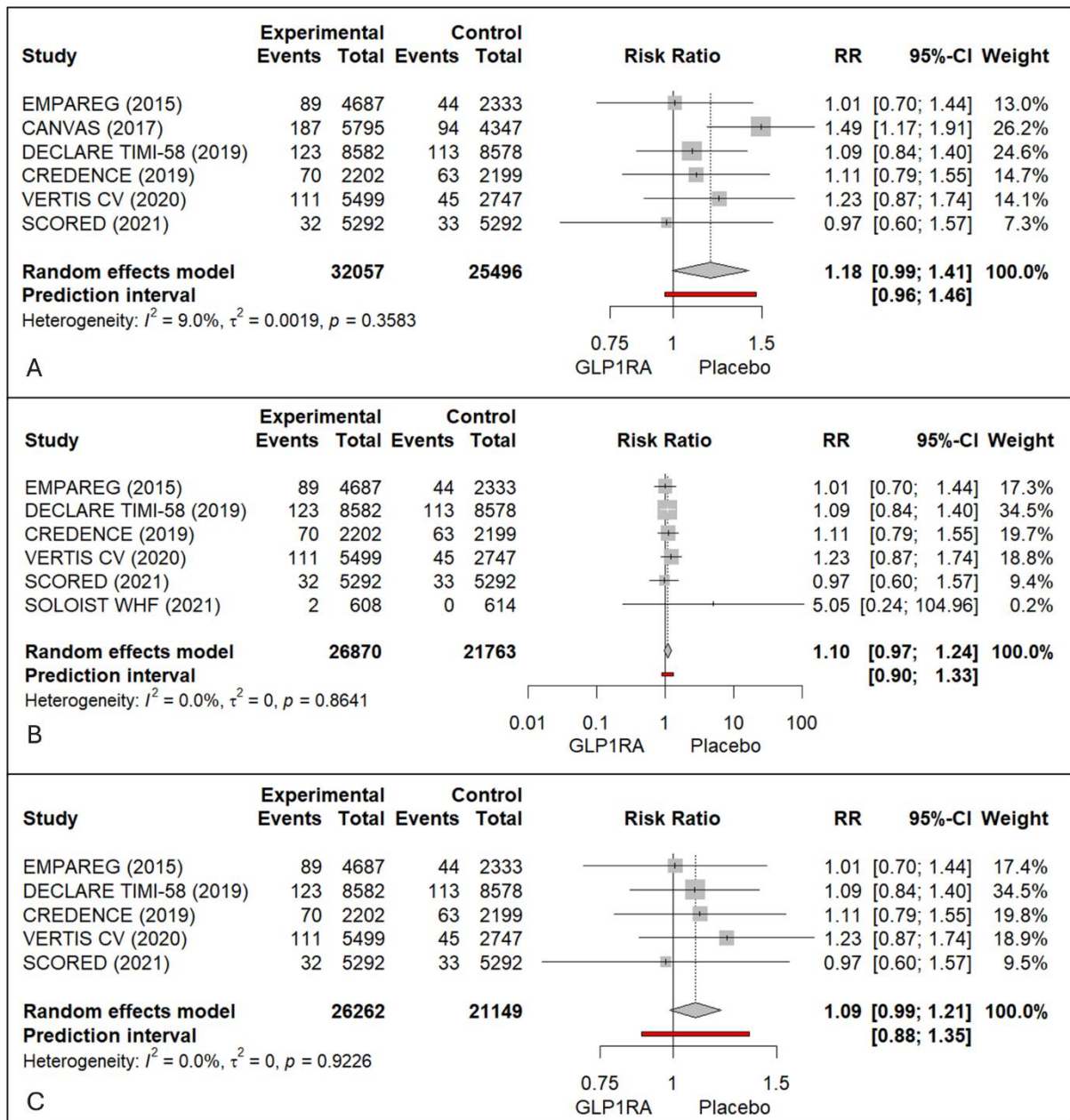
Supplementary Figure S15: Funnel plot for amputation signal with SGLT-2i.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor].



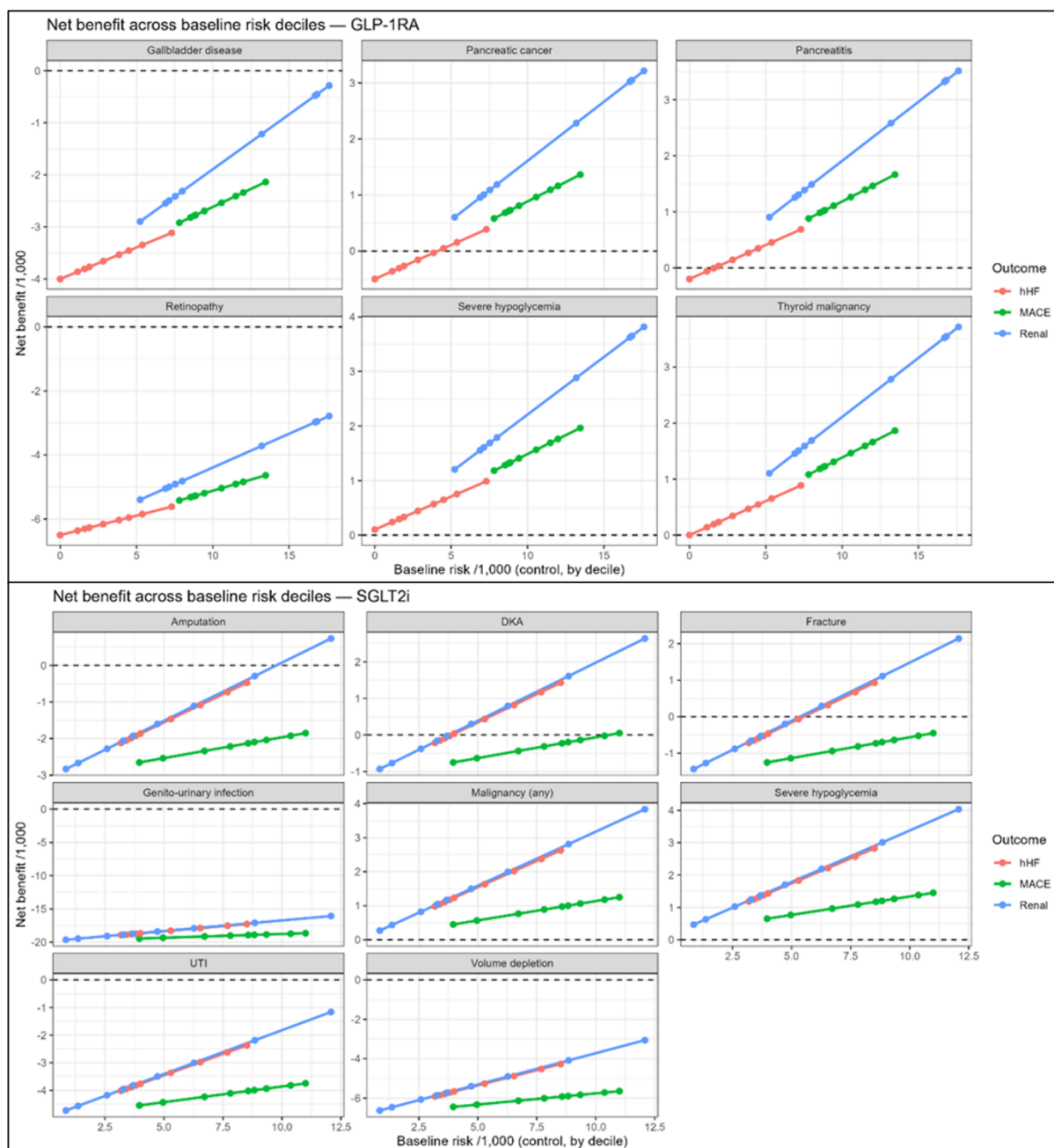
Supplementary Figure S16: Forest plots of amputation signal with SGLT-2i. [A] Excluding SOLOIST WHF, [B] Excluding CANVAS Program, and [C] Excluding both SOLOIST WHF and CANVAS Program.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, RR = relative risk, CI = confidence interval].



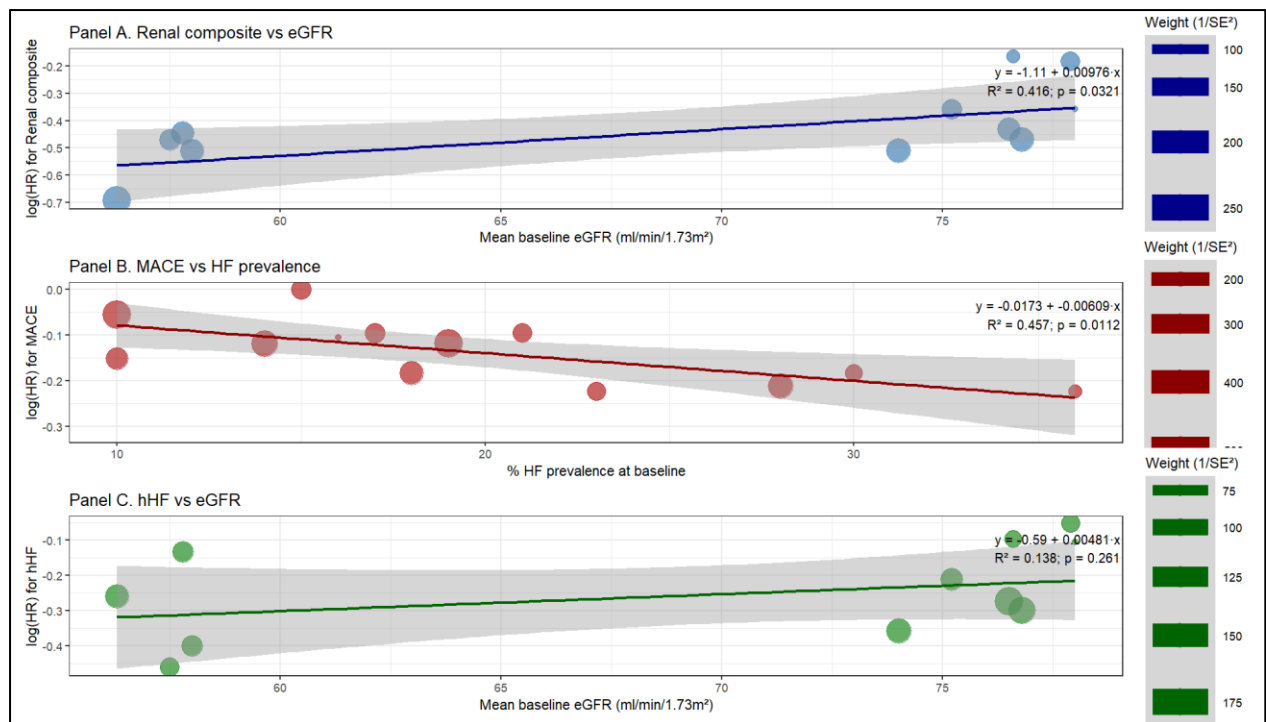
Supplementary Figure S17. Risk distribution curves by baseline deciles. [A] GLP-1RA. [B] SGLT-2i.

[Abbreviations: SGLT-2i = sodium glucose cotransporter-2 inhibitor, GLP-1RA = glucagon like peptide-1 receptor agonists].



Supplementary Figure 18: Bubble plots from exploratory meta-regression analyses. Panel A: $\log(\text{HR})$ for renal composite outcomes vs mean baseline eGFR; Panel B: $\log(\text{HR})$ for MACE vs percentage of patients with baseline heart failure (HF); Panel C: $\log(\text{HR})$ for hospitalisation for HF vs mean baseline eGFR. Bubble size is proportional to study weight (inverse variance), regression line fitted with precision weights. Shaded bands denote 95% confidence intervals.

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, eGFR = Estimated glomerular filtration rate, HR = hazard ratio].

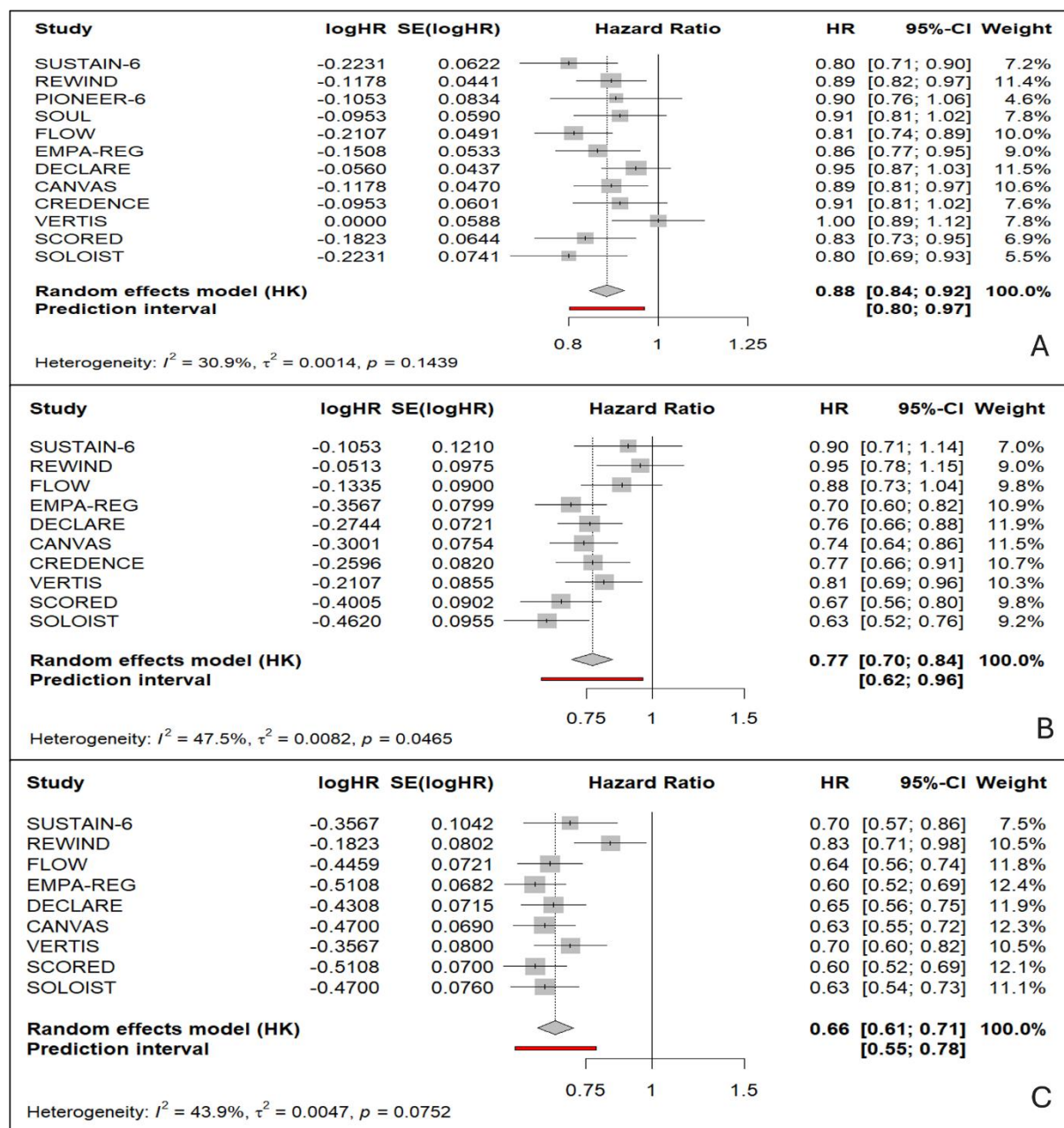


Supplementary Figure 19: Exclusion sensitivity analyses.

(A) MACE, (B) Hospitalisation for heart failure, (C) Renal composite.

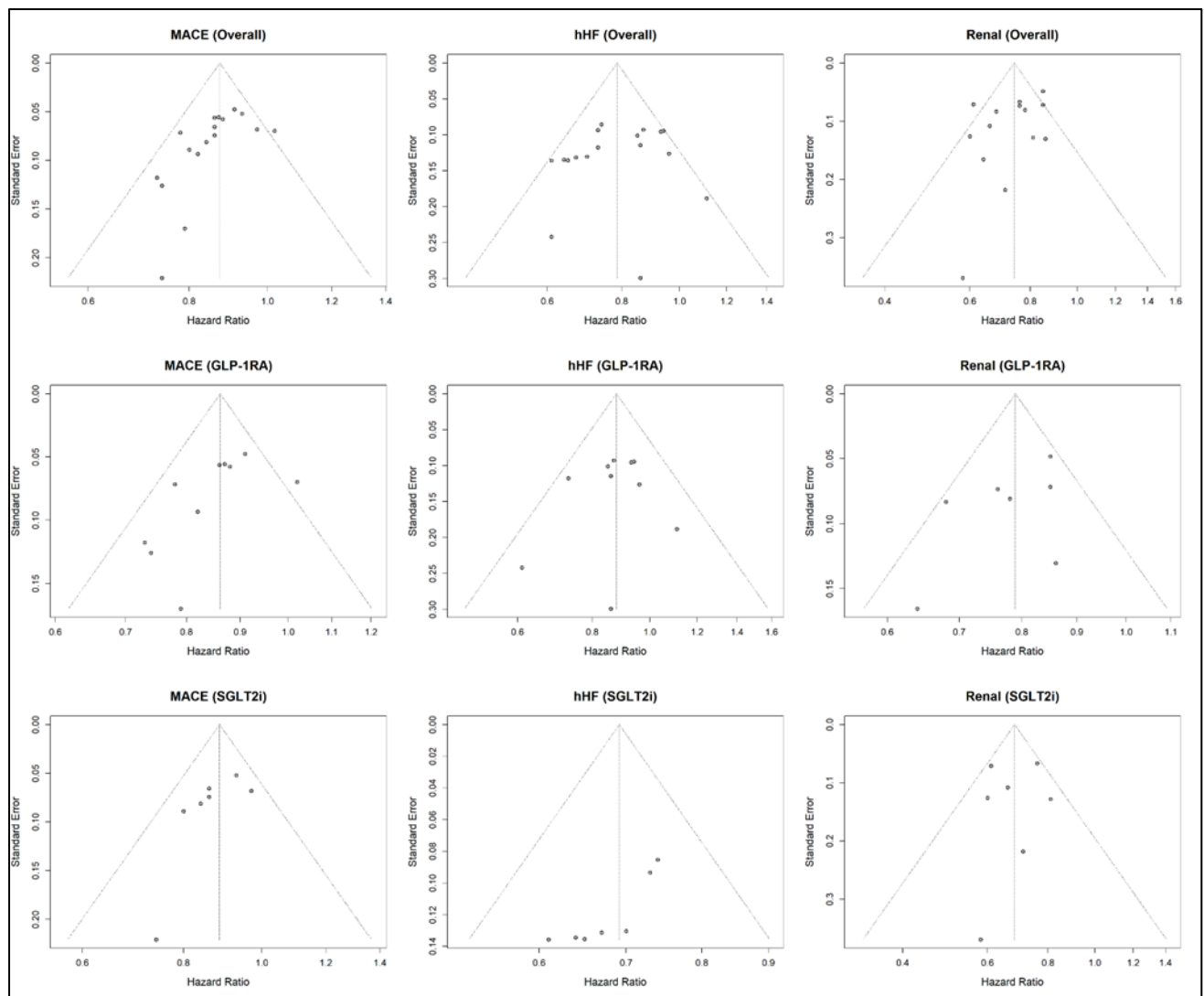
Forest plots display random-effects (Hartung–Knapp, Paule–Mandel τ^2) pooled estimates after exclusion of trials requiring baseline variable conversions. Results show near-identical effect sizes compared to primary analyses.

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, SE = standard error, HR = hazard ratio].



Supplementary Figure 20. Funnel plots (MACE, hHF, Renal).

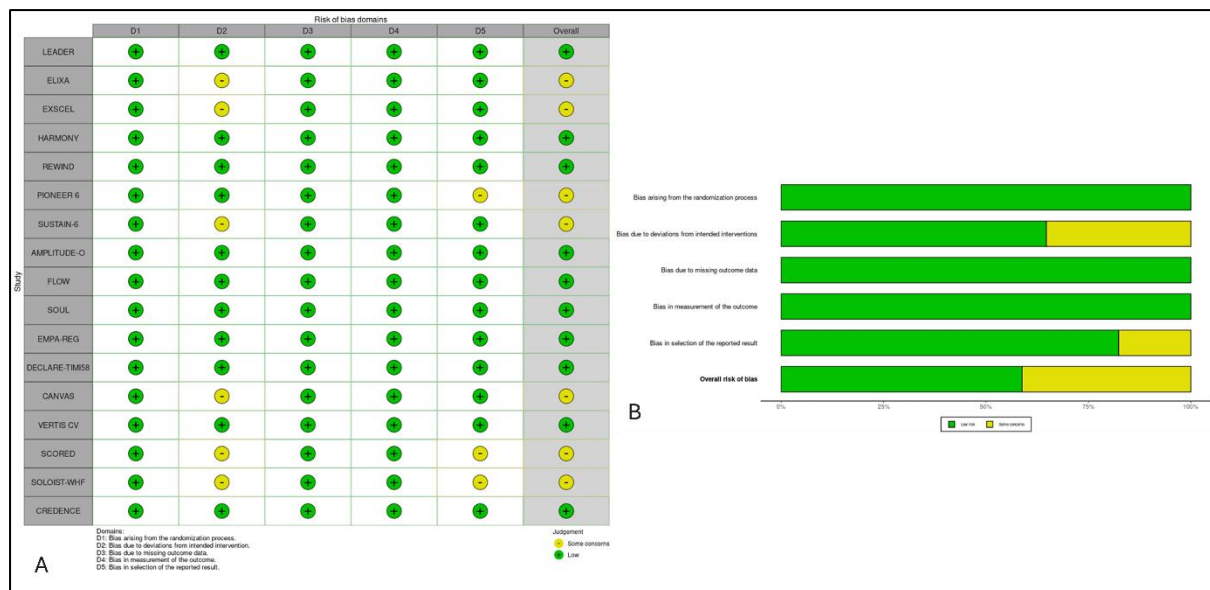
[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, GLP-1RAs = glucagon like peptide-1 receptor agonists, SGLT-2i = sodium glucose cotransporter-2 inhibitor].



- **MACE overall:** $p = 0.016$. Evidence of small-study effects/asymmetry.
- **hHF overall:** $p = 0.435$. No evidence of bias.
- **Renal overall:** $p = 0.157$. No evidence of bias.
- **GLP-1RA only (MACE):** $p = 0.09$. No evidence of bias.
- **All others:** Not enough studies ($k < 10$) for quantitative analysis. Non-significant on visual inspection.

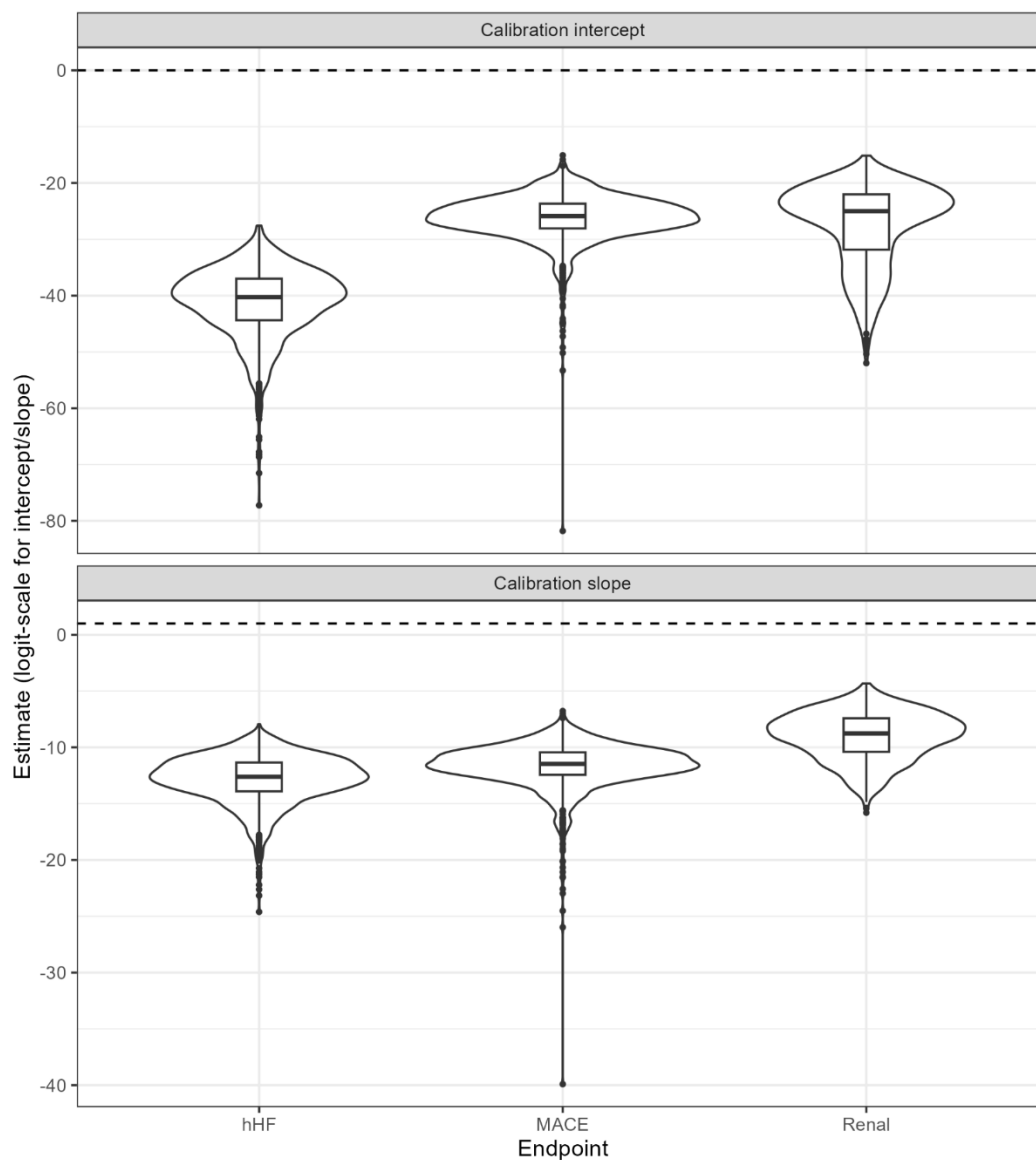
Supplementary Figure S21. ROB 2. [A] Traffic-light plot. [B] Weighted bar plot.

[Abbreviations: Rob = risk of bias].



Supplementary Figure S22: Distribution of calibration intercepts (upper panel) and calibration slopes (lower panel) from 1,000 bootstrap leave-one-out replicates for each endpoint (MACE, hHF, renal composite). Violin plots show the full distribution, with embedded boxplots showing median and IQR. Dashed lines represent perfect calibration (intercept = 0, slope = 1).

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, IQR = interquartile range].



Supplementary Figure S23: Prototype Shiny-based interactive decision-support tool. The interface allows users to specify baseline risks (MACE, HF, renal) and endpoint weights, generating policy curves of absolute risk reduction (ARR) and numbers needed to treat (NNT) for GLP-1RAs versus SGLT-2is. The shaded areas represent 95% simulation intervals. This prototype illustrates how meta-analytic findings can be translated into patient-tailored recommendations.

[Abbreviations: MACE = major adverse cardiac events, hHF = hospitalisation due to heart failure, GLP-1RAs = glucagon like peptide-1 receptor agonists, SGLT-2i = sodium glucose cotransporter-2 inhibitor, NNT = number needed to treat, ARR = absolute risk reduction].

Cardiorenal multivariate meta-analysis — patient tool

Selected horizon
Overlay (2y vs 5y)

Within-endpoint correlation (HF ↔ Renal)

Patient baseline risks (chosen horizon)

MACE risk (%)

HF risk (%)

Renal risk (%)

Endpoint weights

MACE weight

HF weight

Renal weight

Decision threshold

Minimum clinically important ARR (absolute %)

Monte Carlo draws (uncertainty)

Number of draws

Update

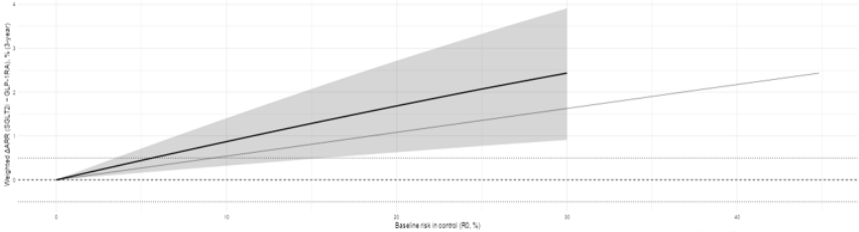
Recommendation

ARR & NNT per class/endpoint

Class	Endpoint	RR (%)	ARR (%)	NNT
GLP-1RA	MACE	10.00	1.34	74.6
GLP-1RA	HF	10.00	1.15	87.3
GLP-1RA	Renal	10.00	2.01	49.7
SGLT3	MACE	10.00	1.15	87.3
SGLT3	HF	10.00	2.99	33.5
SGLT3	Renal	10.00	3.09	32.4

Policy curves

Positive values favor SGLT3; negative values favor GLP-1RA



[Download selected-horizon plot \(PNG, 600 dpi\)](#) [Download selected-horizon plot \(PDF, vector\)](#) [Download selected-horizon data \(CSV\)](#)