SUPPLEMENTARY MATERIALS

Table S1. Comparison of estimated combination treatment effects with SGLT2i, GLP-1RA, and non-steroidal MRA based on SGLT2i treatment effects from the pooled CANVAS Program and CREDENCE trial compared with large-scale collaborative SGLT2i meta-analyses.

Table S2. Baseline characteristics of the pooled placebo group of the CANVAS Program and CREDENCE trial with at least moderately increased albuminuria (UACR ≥30mg/g).

Table S3. Absolute risk reductions and numbers needed to treat at 1 and 3 years with combination SGLT2i, GLP-1 RA and non-steroidal MRA in patients with type 2 diabetes and albuminuria (UACR ≥30mg/g) in the CANVAS Program and CREDENCE trial.

Table S4. Estimated gains in event-free and overall survival for a 50-year-old treated with combination SGLT2i, GLP-1 RA and non-steroidal MRA with estimates based on SGLT2i treatment effects from the pooled CANVAS Program and CREDENCE trial compared with large-scale collaborative SGLT2i meta-analyses.

Figure S1. Treatment benefits of combination SGLT2i, GLP-1 RA and non-steroidal MRA on cardiovascular outcomes in patients with type 2 diabetes and albuminuria UACR ≥30 mg/g, assuming 50% additive effects with each additional therapy.

Figure S2. Treatment benefits of combination SGLT2i, GLP-1 RA and non-steroidal MRA on CKD progression and all-cause mortality in patients with type 2 diabetes and albuminuria UACR ≥30 mg/g, assuming 50% additive effects with each additional therapy.

Figure S3. Treatment benefits of combination SGLT2i, GLP-1 RA and non-steroidal MRA on cardiovascular outcomes in patients with type 2 diabetes and albuminuria UACR ≥30 mg/g, assuming an annual 2% decrease in efficacy over time.

Figure S4. Treatment benefits of combination SGLT2i, GLP-1 RA and non-steroidal MRA on CKD progression and all-cause mortality in patients with type 2 diabetes and albuminuria UACR ≥30 mg/g, assuming an annual 2% decrease in efficacy over time.

Table S1. Comparison of estimated combination treatment effects with SGLT2i, GLP-1RA, and non-steroidal MRA based on SGLT2i treatment effects from the pooled CANVAS Program and CREDENCE trial compared with large-scale collaborative SGLT2i meta-analyses.[4, 6]

Outcome	Pooled CANVAS Program and CREDENCE trial	SGLT2i meta-analyses
MACE	HR 0.65 (95% CI 0.55-0.76)	HR 0.69 (95% CI 0.60-0.79)
Hospitalization for heart failure	HR 0.45 (95% CI 0.34-0.58)	HR 0.47 (95% CI 0.39-0.58)
CKD progression	HR 0.42 (95% CI 0.31-0.56)	HR 0.41 (95% CI 0.32-0.52)
Cardiovascular death	HR 0.64 (95% CI 0.51-0.80)	HR 0.66 (95% CI 0.55-0.79)
All-cause mortality	HR 0.67 (95% CI 0.55-0.80)	HR 0.69 (95% CI 0.60-0.80)

SGLT2i: sodium glucose cotransporter 2 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; MRA: mineralocorticoid receptor antagonists; MACE: major adverse cardiovascular events; CKD: chronic kidney disease.

Table S2. Baseline characteristics of the pooled placebo group of the CANVAS Program and CREDENCE trial with at least moderately increased albuminuria (UACR ≥30mg/g).

	Total (n=3,482)
Age, years (SD)	64.0 (8.9)
Female sex	1,136 (32.6%)
Race	
White	2,426 (69.7%)
Asian	633 (18.2%)
Black	162 (4.7%)
Other	261 (7.5%)
Current smoker	518 (14.9%)
Diabetes duration, years (SD)	15.6 (8.4)
History of cardiovascular disease (%)	1,963 (56.4%)
History of heart failure (%)	528 (15.2%)
HbA1c, % (SD)	8.3 (1.2)
Systolic blood pressure, mmHg (SD)	140.4 (16.0)
Body mass index, kg/m^2 (SD)	31.7 (6.2)
eGFR, mL/min/1.73m^2 (SD)	61.9 (21.3)
≥60	1,764 (50.7%)
45 to <60	886 (25.4%)
<45	832 (23.9%)
UACR, mg/g (IQR)	566.0 (163.0-1388.0)
30-<300	1,188 (34.1%)
≥300	2,294 (65.9%)
Antiplatelets	2,253 (64.7%)
Insulin	2,201 (63.2%)
Statins	2,490 (71.5%)
ACE inhibitor or ARB	3,226 (92.7%)

HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; IQR: interquartile range.

Table S3. Absolute risk reductions and numbers needed to treat at 1 and 3 years with combination SGLT2i, GLP-1 RA and non-steroidal MRA in patients with type 2 diabetes and albuminuria (UACR ≥30mg/g) in the CANVAS Program and CREDENCE trial.

Outcome	Event-rate per 1000 patient-years*	ARR (95% CI)	NNT (95% CI)
1 year			
MACE	47.1	1.6% (1.1-2.0)	63 (49-92)
Hospitalized heart failure	21.5	1.2% (0.9-1.4)	86 (71-113)
CKD progression**	26.7	1.5% (1.1-1.7)	66 (58-91)
Cardiovascular death	23.6	0.8% (0.5-1.1)	120 (88-216)
All-cause mortality	33.6	1.1% (0.7-1.5)	93 (68-153)
3 years			
MACE	47.1	4.4% (3.0-5.7)	23 (18-33)
Hospitalized heart failure	21.5	3.4% (2.6-4.1)	30 (25-39)
CKD progression**	26.7	4.4% (3.2-5.0)	23 (20-32)
Cardiovascular death	23.6	2.4% (1.3-3.3)	42 (30-75)
All-cause mortality	33.6	3.1% (1.8-4.2)	33 (24-54)

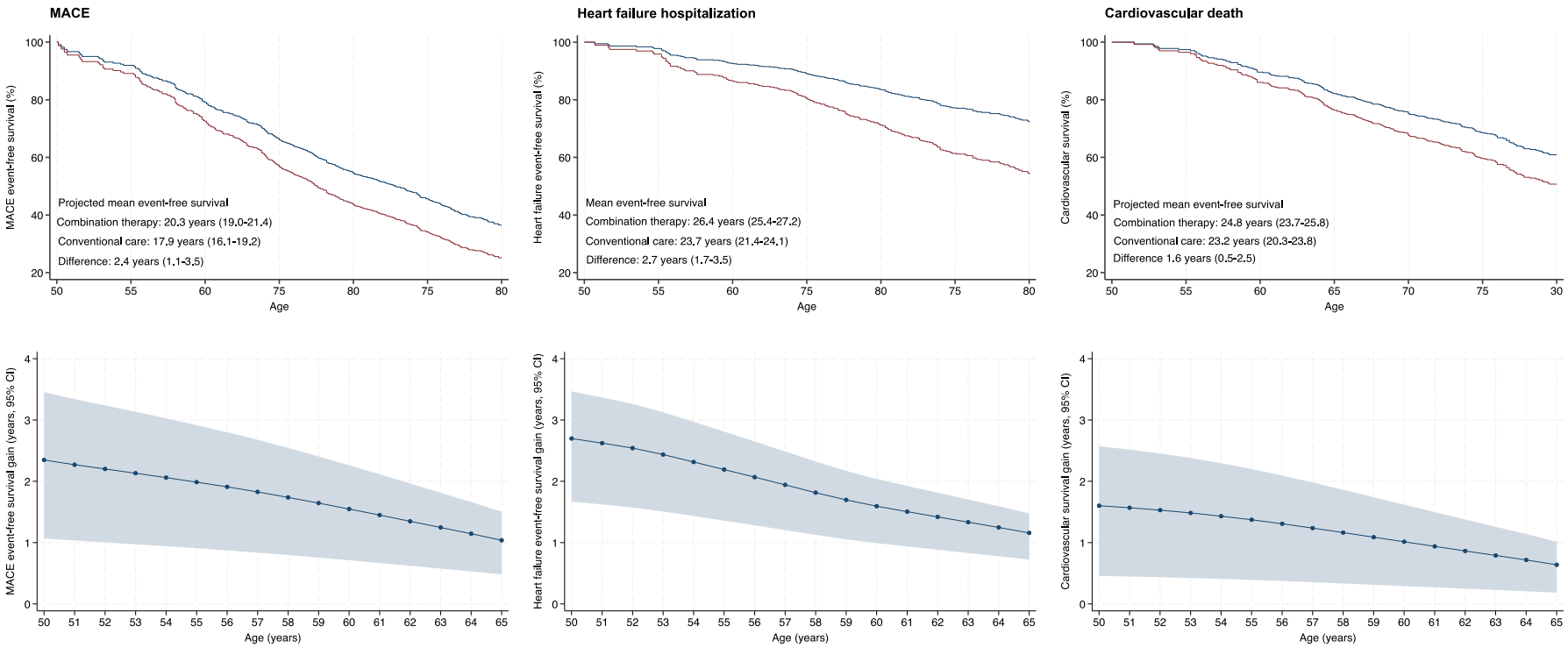
*Event rates in placebo-treated participated in the pooled CANVAS and CREDENCE trials
** Doubling of serum creatinine, kidney failure or death due to kidney failure
SGLT2i: sodium glucose cotransporter 2 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; MRA: mineralocorticoid receptor antagonists; UACR: urine albumin:creatinine ratio; MACE: major adverse cardiovascular events; CKD: chronic kidney disease; ARR: absolute risk reduction; NNT: numbers needed to treat; CI: confidence interval.

Table S4. Estimated gains in event-free and overall survival for a 50-year-old treated with combination SGLT2i, GLP-1 RA and non-steroidal MRA with estimates based on SGLT2i treatment effects from the pooled CANVAS Program and CREDENCE trial compared with large-scale collaborative SGLT2i meta-analyses.[4, 6]

Outcome	Pooled CANVAS Program and CREDENCE trial	SGLT2i meta-analyses
MACE	3.2 years (95% CI 2.1-4.3)	2.8 years (95% CI 1.9-3.7)
Hospitalization for heart failure	3.2 years (95% CI 2.4-4.0)	3.1 years (95% CI 2.4-3.6)
CKD progression	5.5 years (95% CI 4.0-6.7)	5.6 years (95% CI 4.4-6.6)
Cardiovascular death	2.2 years (95% CI 1.2-3.0)	2.0 years (95% CI 1.2-2.7)
All-cause mortality	2.4 years (95% CI 1.4-3.4)	2.3 years (95% CI 1.4-3.0)

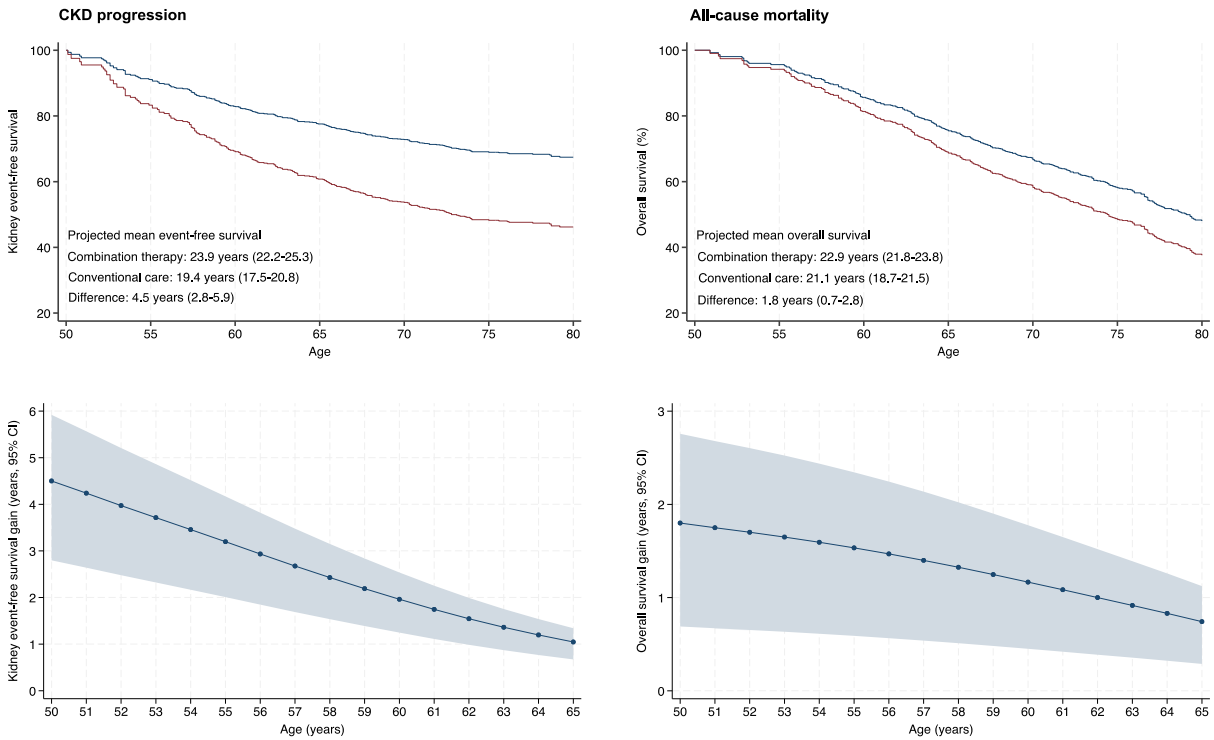
SGLT2i: sodium glucose cotransporter 2 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; MRA: mineralocorticoid receptor antagonists; MACE: major adverse cardiovascular events; CKD: chronic kidney disease.

Figure S1. Treatment benefits of combination SGLT2i, GLP-1 RA and non-steroidal MRA on cardiovascular outcomes in patients with type 2 diabetes and albuminuria UACR ≥30 mg/g, assuming 50% additive effects with each additional therapy. Displayed is the event free survival among people aged 50 years at baseline for each outcome, as well as gains in event-free survival for every age between 50 years and 65 years for each outcome.



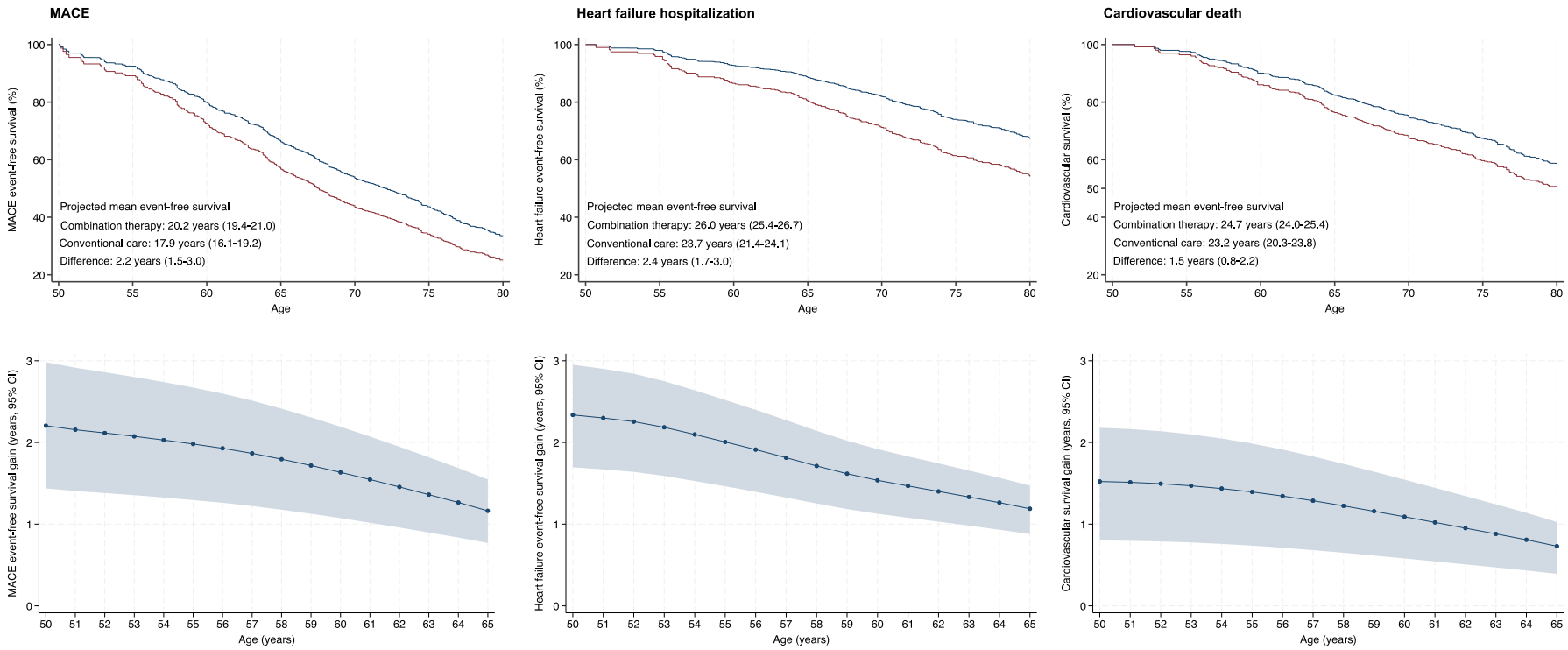
SGLT2i: sodium glucose cotransporter 2 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; MRA: mineralocorticoid receptor antagonists; MACE: major adverse cardiovascular events; UACR: urinary albumin:creatinine ratio.

Figure S2. Treatment benefits of combination SGLT2i, GLP-1 RA and non-steroidal MRA on CKD progression and all-cause mortality in patients with type 2 diabetes and albuminuria UACR ≥30 mg/g, assuming 50% additive effects with each additional therapy. Displayed is the event free survival among people aged 50 years at baseline for each outcome, as well as gains in event-free survival for every age between 50 years and 65 years for each outcome.



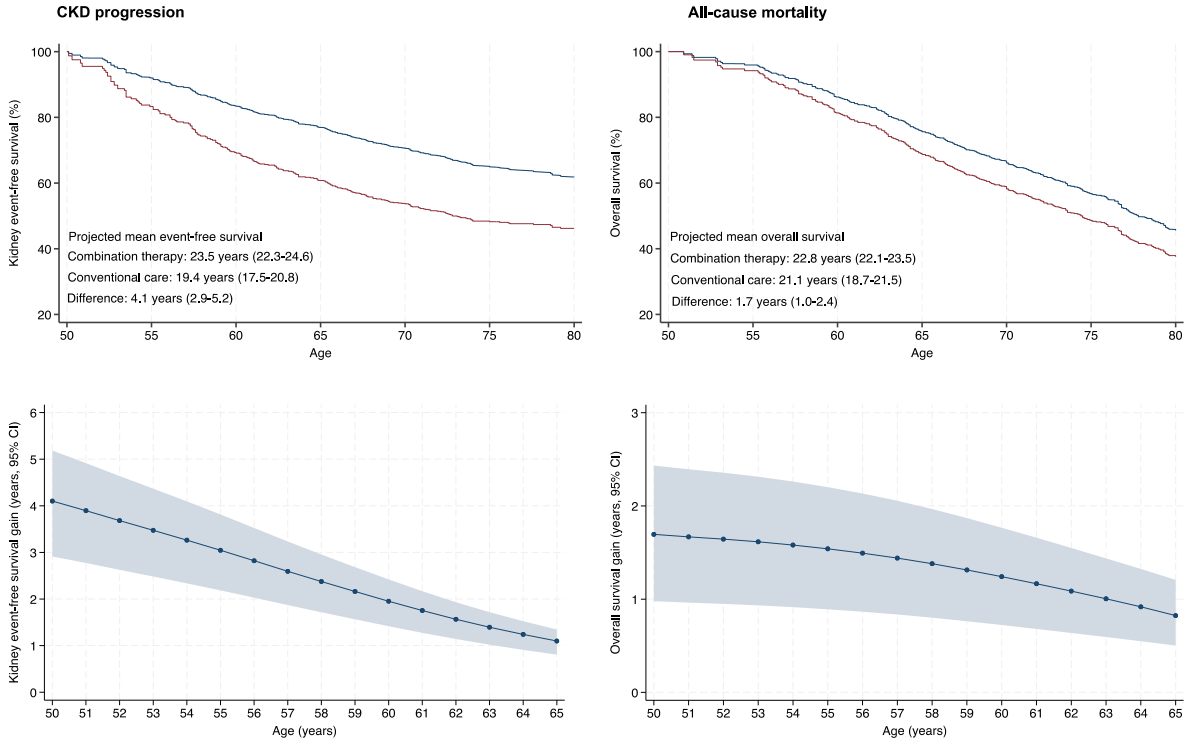
SGLT2i: sodium glucose cotransporter 2 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; MRA: mineralocorticoid receptor antagonists; CKD: chronic kidney disease; UACR: urinary albumin:creatinine ratio.

Figure S3. Treatment benefits of combination SGLT2i, GLP-1 RA and non-steroidal MRA on cardiovascular outcomes in patients with type 2 diabetes and albuminuria UACR ≥30 mg/g, assuming an annual 2% decrease in efficacy over time. Displayed is the event free survival among people aged 50 years at baseline for each outcome, as well as gains in event-free survival for every age between 50 years and 65 years for each outcome.



SGLT2i: sodium glucose cotransporter 2 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; MRA: mineralocorticoid receptor antagonists; MACE: major adverse cardiovascular events; UACR: urinary albumin:creatinine ratio.

Figure S4. Treatment benefits of combination SGLT2i, GLP-1 RA and non-steroidal MRA on CKD progression and all-cause mortality in patients with type 2 diabetes and albuminuria UACR ≥30 mg/g, assuming an annual 2% decrease in efficacy over time. Displayed is the event free survival among people aged 50 years at baseline for each outcome, as well as gains in event-free survival for every age between 50 years and 65 years for each outcome.



SGLT2i: sodium glucose cotransporter 2 inhibitors; GLP-1 RA: glucagon-like peptide-1 receptor agonists; MRA: mineralocorticoid receptor antagonists; CKD: chronic kidney disease; UACR: urinary albumin:creatinine ratio.