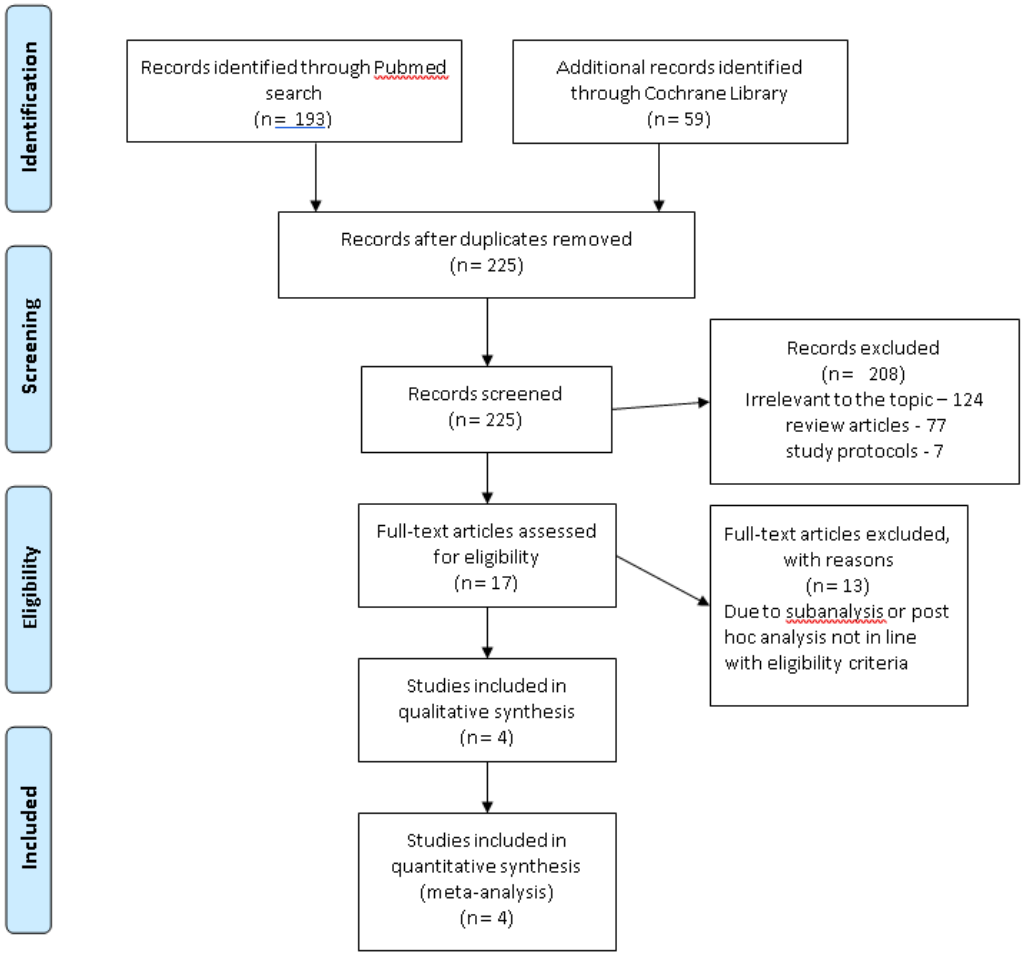
Supplementary Material

Search Strategy

("diabetes mellitus, type 2"[MeSH] OR diabetes mellitus type 2[tiab] OR type 2 diabetes mellitus[tiab] AND (canagliflozin[tiab] OR empagliflozin[tiab] OR dapagliflozin[tiab]) AND (rand*[tw] OR trial [tiab]) AND ("myocardial infarction"[MeSH] OR myocardial infarction[tiab] OR "stroke"[MeSH] OR stroke[tiab] OR MACE[tiab] OR major adverse cardiovascular event[tiab] OR major adverse cardiac event[tiab] OR "death"[MeSH] OR death[tiab] OR mortality [tiab] OR "heart failure"[MeSH] OR heart failure[tiab]). The search strategy for Cochrane library (type 2 diabetes mellitus OR diabetes mellitus type 2 OR type 2 diabetes):ti,ab,kw AND (empagliflozin OR dapagliflozin OR canagliflozin):ti,ab,kw AND (myocardial infarction OR stroke OR heart failure OR death OR mortality OR MACE OR major adverse cardiac events OR major adverse cardiovascular events):ti,ab,kw AND ("randomized controlled trial" OR randomized clinical trial OR RCT OR trial):pt".

Supplementary Figure 1: Prisma Flow Diagram of the Meta -Analysis

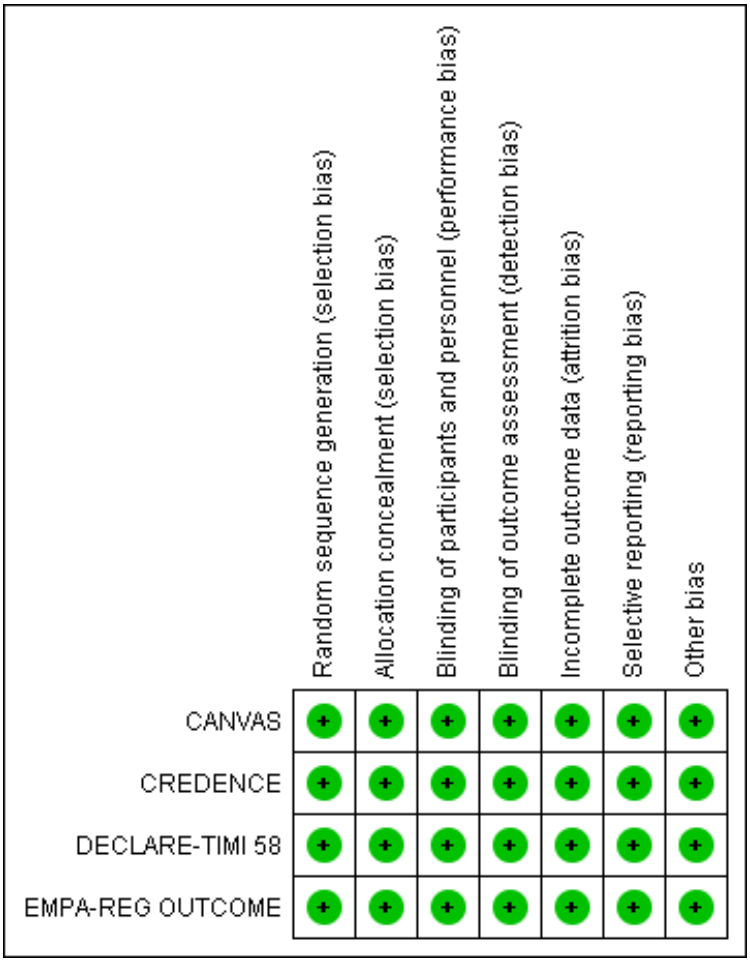


Supplementary Table 1. Studies included in the meta-analysis

Study (n)	Study drug & Level of evidence ǂ	Study population	Median follow-up time (years)	Cardiovascular composite outcome	Renal composite outcome
EMPA-REG OUTCOME (n=7020)	Empa-gliflozin 1	-≥18 years of age with type 2 DM -BMI ≤45 -eGFR ≥30 ml/min./1.73 m2 (mean study eGFR = 74 ml/min./1.73 m2) All the patients had established cardiovascular disease (hx of MI, UA, CVA, documented CAD, PAD)	3.1	Death from cardiovascular causes, nonfatal MI, nonfatal stroke	Doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease
CANVAS (n=10,142)	Cana-gliflozin 1	-≥30 years of age with type 2 DM -eGFR ≥30 ml/min./1.73 m2 (mean study eGFR = 76 ml/min./1.73 m2) -with history of symptomatic atherosclerotic cardiovascular disease Or -≥50 years of age with 2 or more of the following risk factors: diabetes>10 years, systolic blood pressure >140mmHg while receiving antihypertensive agents, smoking, micro or macroalbuminuria, HDL <1mmol/L, 65% had established cardiovascular disease	2.4	Death from cardiovascular causes, nonfatal MI, nonfatal stroke	40% decrease in eGFR, renal death or renal replacement therapy requirement
DECLARE-TIMI 58 (n=17,160)	Dapa-gliflozin 1	-≥40 years of age with type 2 DM -eGFR ≥60 ml/min./1.73 m2 (mean study eGFR = 85 ml/min./1.73 m2) -established cardiovascular disease (evidence of CAD, CVA, PAD) Or -men ≥55 or women ≥60 with one or more of the following: (Hypertension, dyslipidemia, tobacco use) 40% had established cardiovascular disease	4.2	Death from cardiovascular causes, nonfatal MI, nonfatal stroke	40% decrease in eGFR, ESRD, or renal death
CREDENCE 2019 (n=4,401)	Cana-gliflozin 1	-≥30 years of age with type 2 DM -CKD eGFR 30 to 90 ml/min./1.73 m2 (mean study eGFR = 56 ml/min./1.73 m2) -albuminuria (urinary albumin-to-creatinine ratio, ≥300 to 5000 mg/g) -on maximum tolerated dose of ACEi/ARB at least 4 weeks prior 50% had established cardiovascular disease (no definitions)	2.6	Death from cardiovascular causes, nonfatal MI, nonfatal stroke	End stage kidney disease, doubling of serum creatinine, renal death

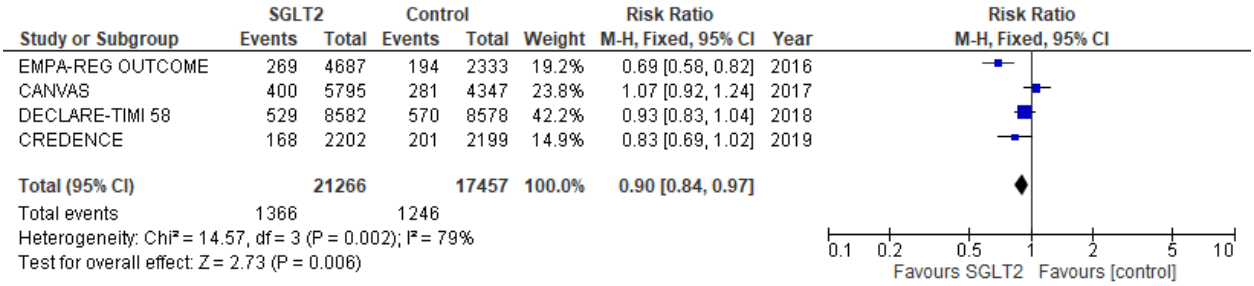
**MI – myocardial infarction, eGFR – estimated glomerular filtration rate, ESRD – end stage renal disease, ACEi – angiotensin coverting enzyme inhibitor, ARB – angiotensin receptor blocker, CKD – chronic kidney disease, DM – diabetes mellitus, BMI – body mass index, CAD – coronary artery disease, UA – unstable angina, CVA – cerebrovascular accident, PAD – peripheral arterial disease, ǂLevel of evidence: 1-systematic review and meta-analysis or properly powered and conducted randomized clinical trial, 2 - Well-designed controlled trial without randomization; prospective comparative cohort trial, 3 - Case-control studies; retrospective cohort study, 4 - Case series with or without intervention; cross-sectional study, 5 - Opinion of respected authorities; case reports

Supplementary Figure 2. Risk of bias summary



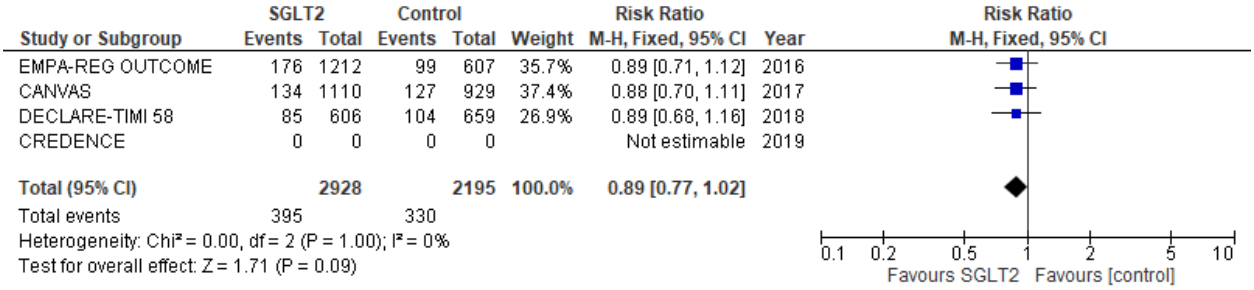
*green circles- low risk of bias, yellow circles – uncertain or moderate risk of bias, red – high risk of bias

Supplementary Figure 3. Forest plot for all-cause mortality in patients with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors

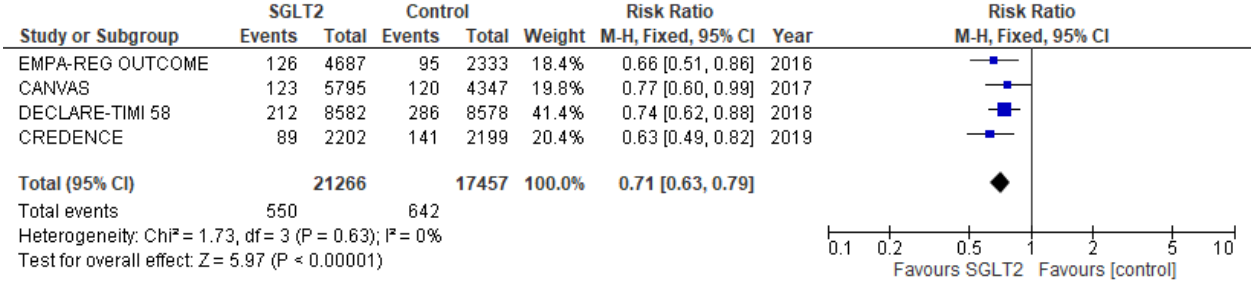


Supplementary Figure 4. Forest plot for death from cardiovascular causes alone in patients with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors

Supplementary Figure 5. Forest plot for death from cardiovascular causes alone in patients with eGFR <60 ml/min/1.73m2 with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors



Supplementary Figure 6. Forest plot for heart failure hospitalization in patients with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors



Supplementary Figure 7. Forest plot for progression of albuminuria in patients with type 2 diabetes with either established cardiovascular disease or cardiovascular risk factors