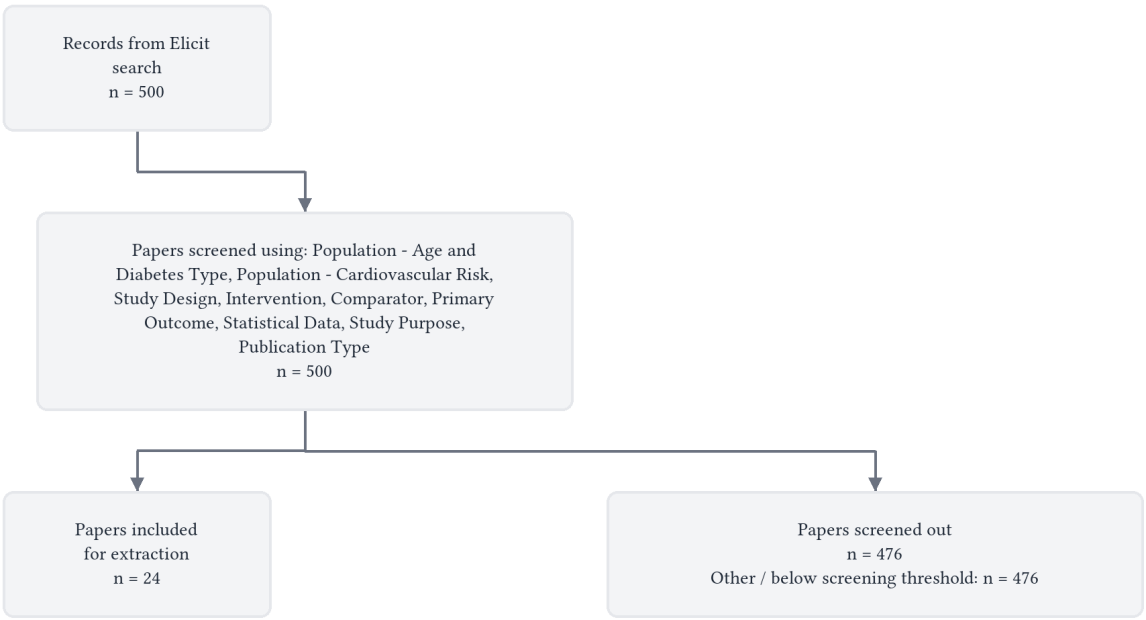
In adults with type 2 diabetes and established atherosclerotic cardiovascular disease, what is the pooled hazard ratio for the 3-point major adverse cardiovascular event (MACE) composite outcome for SGLT2 inhibitors versus placebo based strictly on dedicated cardiovascular outcome trials?

Based on pooled data from dedicated cardiovascular outcome trials, SGLT2 inhibitors reduce 3-point MACE by approximately 10% versus placebo in adults with type 2 diabetes (pooled HR ~0.90, 95% CI 0.86–0.94), with the benefit most pronounced in those with established atherosclerotic cardiovascular disease.

Abstract

Four dedicated cardiovascular outcome trials — EMPA-REG OUTCOME (empagliflozin), the CANVAS Program (canagliflozin), DECLARE-TIMI 58 (dapagliflozin), and VERTIS CV (ertugliflozin) — each met prespecified noninferiority criteria for 3-point MACE versus placebo. Individual trial hazard ratios ranged from 0.86 (95% CI 0.74–0.99) for empagliflozin [1] and 0.86 (95% CI 0.75–0.97) for canagliflozin [2] to 0.93 (95% CI 0.84–1.03) for dapagliflozin [3] and 0.97 (95.6% CI 0.85–1.11) for ertugliflozin [4], with only the first two reaching statistical significance for superiority. The largest contemporary collaborative meta-analysis, pooling 12 placebo-controlled trials encompassing 72,970 participants with diabetes, estimated a pooled MACE hazard ratio of 0.90 (95% CI 0.86–0.94) [5], consistent with other meta-analyses reporting pooled estimates between 0.87 and 0.92 [6, 7]. Heterogeneity across individual CVOTs is largely attributable to differences in the proportion of patients with established atherosclerotic cardiovascular disease: trials enrolling exclusively such patients showed larger MACE reductions, while DECLARE-TIMI 58, in which only 41% had established ASCVD [8], showed an attenuated overall signal that became significant (HR 0.84; 95% CI 0.72–0.99) when restricted to patients with prior myocardial infarction [9]. Taken together, the evidence supports an approximate 8–14% relative reduction in 3-point MACE with SGLT2 inhibitors as a class, with the benefit most clearly demonstrated in patients with established atherosclerotic cardiovascular disease.

Flow Diagram



Paper search

We performed a semantic search across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We ran this query: "In adults with type 2 diabetes and established atherosclerotic cardiovascular disease, what is the pooled hazard ratio for the 3-point major adverse cardiovascular event (MACE) composite outcome for SGLT2 inhibitors versus placebo based strictly on dedicated cardiovascular outcome trials?"

The search returned 500 total results from Elicit.

We retrieved 500 papers most relevant to the query for screening.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population - Age and Diabetes Type**: Does the study include adults (≥18 years) with type 2 diabetes mellitus?
- **Population - Cardiovascular Risk**: Does the study population have established atherosclerotic cardiovascular disease?
- **Study Design**: Is this study a randomized controlled trial?
- **Intervention**: Does the intervention arm receive SGLT2 inhibitor therapy?
- **Comparator**: Does the control arm receive placebo (rather than an active comparator)?

- **Primary Outcome**: Does the study report 3-point MACE composite outcome (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)?
- **Statistical Data**: Does the study provide hazard ratio data or sufficient data to calculate hazard ratios for the cardiovascular outcomes?
- **Study Purpose**: Is the study primarily designed to assess cardiovascular outcomes (rather than focusing solely on glycemic efficacy)?
- **Publication Type**: Is this a primary study publication (not a post-hoc analysis, subgroup analysis, or secondary publication without new outcome data)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

At abstract screening, the number of papers excluded for each primary reason was:

- **Other / below screening threshold**: n = 476

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Population Eligibility**:

  Verify the study population meets the research question criteria by extracting:

- Percentage/number of participants with type 2 diabetes
- Percentage/number with established atherosclerotic cardiovascular disease (not just high CV risk)
- Mean age and age range
- Any exclusions that would affect eligibility for this research question

- **Study Design**:

  Extract study design details to confirm this is a dedicated cardiovascular outcome trial:

- Study type (RCT, observational, etc.)
- Whether this was designed as a cardiovascular outcome trial (CVOT) vs. glycemic efficacy trial
- Primary endpoint(s) as stated by authors
- Randomization method and blinding status

- **SGLT2 Inhibitor Details**:

  Extract complete details about the SGLT2 inhibitor intervention:

- Specific SGLT2 inhibitor name(s)
- Dose(s) administered
- Frequency of administration
- Treatment duration/follow-up period
- Any dose adjustments or pooling of doses in analysis

- **MACE Definition**:

  Extract the exact definition of the MACE composite outcome used in this study:

- Specific components included (e.g., CV death, nonfatal MI, nonfatal stroke)
- Whether it's described as 3-point MACE, 4-point MACE, or other

- Any variations from standard 3-point MACE definition
- Adjudication process for MACE events

- **3-Point MACE Results**:

  Extract the primary MACE results for SGLT2 inhibitor vs. placebo:

- Number of MACE events in SGLT2i group
- Number of MACE events in placebo group
- Hazard ratio (HR) with 95% confidence interval
- P-value for statistical significance
- Time-to-event analysis method used

- **Sample Size**:

  Extract sample size data needed for meta-analysis weighting:

- Total number randomized
- Number randomized to SGLT2i group
- Number randomized to placebo group
- Number completing study/included in primary analysis
- Any significant dropouts or exclusions from primary analysis

- **Baseline Characteristics**:

  Extract key baseline characteristics that may affect pooling:

- Mean HbA1c at baseline
- Mean duration of diabetes
- Types of established ASCVD (prior MI, stroke, peripheral artery disease, etc.)
- Concomitant cardiac medications (% on statins, ACE inhibitors, etc.)
- Major comorbidities

- **Study Quality**:

  Extract methodological quality factors critical for meta-analysis:

- Risk of bias assessment elements (randomization adequacy, allocation concealment, blinding)
- Funding source and potential conflicts of interest
- Protocol registration and adherence
- Statistical analysis plan pre-specification
- Any significant protocol deviations

Results

Characteristics of Included Studies

The 24 sources identified for this review comprise a heterogeneous collection of primary cardiovascular outcome trial (CVOT) reports, subgroup and secondary analyses derived from those trials, systematic reviews and meta-analyses, pooled phase 2b/3 safety analyses, editorials, and one small single-center randomized controlled trial. The table below summarizes key characteristics of each source.

Study	Full Text Retrieved?	Study Type	SGLT2 Inhibitor	Trial / Data Source	Population (N)	ASCVD Prevalence	MACE Definition	Follow-up
S. Wiviott et al., 2019	No	Primary CVOT (RCT) [3]	Dapagliflozin [3]	DECLARE-TIMI 58	17,160 [3]	Not specified; includes patients with or at risk for ASCVD [3]	3-point MACE: CV death, MI, ischemic stroke [3]	Median 4.2 years [3]
C. Cannon et al., 2020	Yes	Primary CVOT (RCT) [4]	Ertugliflozin (5 mg, 15 mg) [4]	VERTIS CV	8,246 [4]	100% established ASCVD (CAD 75.9%, cerebrovascular 22.9%, PAD 18.7%) [4]	3-point MACE: CV death, nonfatal MI, nonfatal stroke [4]	Mean 3.5 years [4]
L. Moist, 2019	No	Commentary on RCT [8]	Dapagliflozin 10 mg/d [8]	DECLARE-TIMI 58	17,190 [8]	41% [8]	CV death, MI, or ischemic stroke [8]	Median 4.2 years [8]
R. Furtado et al., 2019	No	Subgroup analysis of RCT [9]	Dapagliflozin [9]	DECLARE-TIMI 58	17,160 (3,584 with prior MI) [9]	6,974 with established ASCVD [9]	3-point MACE: CV death, MI, ischemic stroke [9]	Not mentioned [9]
D. Fitchett et al., 2018	Yes	Subgroup analysis of CVOT (RCT) [1]	Empagliflozin 10 mg, 25 mg [1]	EMPA-REG OUTCOME	7,020 [1]	100% [1]	3-point MACE: CV death, nonfatal MI, nonfatal stroke [1]	Until ≥691 primary events [1]
K. Kaku et al., 2017	Yes	Subgroup analysis of CVOT (RCT) [10]	Empagliflozin 10 mg, 25 mg [10]	EMPA-REG OUTCOME	7,020 (1,517 Asian) [10]	99.2% [10]	3-point MACE: CV death, nonfatal MI, nonfatal stroke [10]	Until ≥691 primary events [10]

Study	Full Text Retrieved?	Study Type	SGLT2 Inhibitor	Trial / Data Source	Population (N)	ASCVD Prevalence	MACE Definition	Follow-up
K. Oyama et al., 2020	No	Risk stratification analysis of RCT [11]	Dapagliflozin [11]	DECLARE-TIMI 58	17,159 [11]	Not specified [11]	3-point MACE: CVD, MI, ischemic stroke [11]	Not mentioned [11]
R. Guthrie, 2018	Yes	Narrative review of RCT [12]	Canagliflozin 100 mg, 300 mg [12]	CANVAS / CANVAS-R	Not specified [12]	Preexisting CVD or elevated risk [12]	3-point MACE: CV death, nonfatal MI, nonfatal stroke [12]	Not mentioned [12]
S. Wiviott et al., 2018	No	Trial design paper [13]	Dapagliflozin 10 mg [13]	DECLARE-TIMI 58	17,160 [13]	6,971 with established ASCVD [13]	3-point MACE: CV death, MI, ischemic stroke [13]	Event-driven [13]
M. Fisher, 2020	Yes	Narrative review of CVOT [14]	Empagliflozin 10 mg, 25 mg [14]	EMPA-REG OUTCOME	7,020 [14]	100% [14]	CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina [14]	Not mentioned [14]
A. Cahn et al., 2021	Yes	Secondary analysis of RCT [15]	Dapagliflozin [15]	DECLARE-TIMI 58	17,160 [15]	40.6% [15]	Not explicitly defined [15]	Median 4.2 years [15]

Study	Full Text Retrieved?	Study Type	SGLT2 Inhibitor	Trial / Data Source	Population (N)	ASCVD Prevalence	MACE Definition	Follow-up
J. Brophy, 2017	No	Systematic review and meta-analysis [16]	Canagliflozin, dapagliflozin, empagliflozin [16]	37 RCTs	28,859 [16]	99% in 3 RCTs (n=8,904) [16]	3-point MACE: CV death, nonfatal MI, nonfatal stroke [16]	24–260 weeks [16]
E. M. Apperloo et al., 2024	Yes	Collaborative meta-analysis [5]	Multiple SGLT2 inhibitors [5]	12 RCTs (SMART-C)	72,970 with diabetes [5]	Not explicitly mentioned [5]	3-point MACE: nonfatal MI, nonfatal stroke, CV death [5]	Not mentioned [5]
B. M. Everett & W. Hiatt, 2016	No	Editorial / commentary [17]	Empagliflozin 10 mg, 25 mg [17]	EMPA-REG OUTCOME	7,020 [17]	Not mentioned [17]	3-point MACE: CV death, MI, stroke [17]	Not mentioned [17]
J. List et al., 2014	No	Pooled phase 2b/3 analysis [18]	Dapagliflozin [18]	21 double-blind studies	9,339 [18]	3,214 with CV disease history [18]	3-point MACE (plus UA as primary endpoint) [18]	Up to 4 years [18]
J. Ingelfinger & C. Rosen, 2015	No	Editorial [19]	Empagliflozin (implied) [19]	EMPA-REG OUTCOME	Not mentioned [19]	Not mentioned [19]	Nonfatal stroke, nonfatal MI, CV death [19]	Not mentioned [19]
A. Zhang et al., 2021	Yes	Systematic review and meta-analysis [6]	Empagliflozin, canagliflozin, dapagliflozin, ertugliflozin [6]	8 RCTs	55,763 [6]	Not explicitly stated [6]	3-point MACE: CV death, MI, ischemic stroke [6]	Varies by trial [6]

Study	Full Text Retrieved?	Study Type	SGLT2 Inhibitor	Trial / Data Source	Population (N)	ASCVD Prevalence	MACE Definition	Follow-up
M. E. Alexandrou et al., 2023	No	Systematic review and meta-analysis [7]	Canagliflozin, dapagliflozin, empagliflozin, sotagliflozin [7]	11 RCTs in CKD	83,203 [7]	Not mentioned [7]	Not explicitly defined [7]	Not mentioned [7]
T. Young et al., 2020	No	Subgroup analysis of CVOT [2]	Canagliflozin [2]	CANVAS Program	10,142 [2]	Not specified [2]	3-point MACE: CV death, nonfatal MI, nonfatal stroke [2]	Mean 3.6 years [2]
A. Odutayo et al., 2021	No	Bayesian meta-analysis [20]	Empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, sotagliflozin [20]	53 RCTs	Not mentioned [20]	Not mentioned [20]	Not explicitly defined [20]	Not mentioned [20]
M. Alexandrou et al., 2023	No	Systematic review and meta-analysis [21]	Canagliflozin, dapagliflozin, empagliflozin, sotagliflozin [21]	11 RCTs in CKD	83,203 [21]	Not mentioned [21]	Not explicitly defined [21]	Not mentioned [21]
S. Wiviott et al., 2019a	No	Summary / reply [22]	Dapagliflozin [22]	DECLARE-TIMI 58	Not mentioned [22]	Not mentioned [22]	Not explicitly defined [22]	Not mentioned [22]
D. Semirani-Nezhad et al., 2025	Yes	Systematic review and meta-analysis [23]	SGLT2 inhibitors (not specified) [23]	7 RCTs + 3 PSM studies	15,133 [23]	Acute MI population [23]	Not explicitly defined [23]	Not mentioned [23]

Study	Full Text Retrieved?	Study Type	SGLT2 Inhibitor	Trial / Data Source	Population (N)	ASCVD Prevalence	MACE Definition	Follow-up
H. Shabbir et al., 2025	Yes	Single-center RCT [24]	Empagliflozin, dapagliflozin, canagliflozin [24]	Single-center trial	195 [24]	Established CVD or high risk [24]	3-point MACE: CV death, nonfatal MI, nonfatal stroke [24]	12 months [24]

Several observations emerge from this table. First, the sources cluster around four landmark dedicated CVOTs: EMPA-REG OUTCOME (empagliflozin), the CANVAS Program (canagliflozin), DECLARE-TIMI 58 (dapagliflozin), and VERTIS CV (ertugliflozin). Multiple sources report on or re-analyze data from the same parent trial — for instance, six sources draw on DECLARE-TIMI 58 data and four on EMPA-REG OUTCOME. Second, the proportion of patients with established ASCVD varies substantially: EMPA-REG OUTCOME and VERTIS CV enrolled exclusively patients with established ASCVD [1, 4], whereas DECLARE-TIMI 58 enrolled a broader population with only approximately 41% having established ASCVD [8, 15]. Third, M. E. Alexandrou et al. (2023) and M. Alexandrou et al. (2023) appear to represent the same meta-analysis (both reporting 83,203 CKD participants with identical hazard ratios) [7, 21], likely published as a journal article and conference abstract, respectively. Finally, one source (Shabbir et al., 2025) is a small single-center trial of 195 patients conducted over only 12 months [24, 24], which is methodologically distinct from the large multinational CVOTs.

Effects

3-Point MACE Outcomes From Dedicated CVOTs

The central question of this review concerns the pooled hazard ratio for 3-point MACE with SGLT2 inhibitors versus placebo. Four large dedicated CVOTs provide the primary evidence, each testing a different SGLT2 inhibitor.

Trial	SGLT2 Inhibitor	Total N	ASCVD Prevalence	MACE Rate (SGLT2i)	MACE Rate (Placebo)	HR (95% CI)	P-value	Noninferiority Met?
EMPA-REG OUTCOME	Empagliflozin [1]	7,020 [1]	100% [1]	490 events [1]	282 events [1]	0.86 (0.74–0.99) [1]	0.038 [17]	Yes
CANVAS Program	Canagliflozin [2]	10,142 [2]	Preexisting CVD or elevated risk [12]	Not specified [2]	Not specified [2]	0.86 (0.75–0.97) [2]	Not mentioned [2]	Yes

Trial	SGLT2 Inhibitor	Total N	ASCVD Prevalence	MACE Rate (SGLT2i)	MACE Rate (Placebo)	HR (95% CI)	P-value	Noninferiority Met?
DECLARE-TIMI 58	Dapagliflozin [3]	17,160 [3]	~41% [8]	8.8% [3]	9.4% [3]	0.93 (0.84–1.03) [3]	0.17 [3]	Yes (noninferiority P<0.001)
VERTIS CV	Ertugliflozin [4]	8,246 [4]	100% [4]	653/5,493 (11.9%) [4]	327/2,745 (11.9%) [4]	0.97 (0.85–1.11) [4]	<0.001 (noninferiority) [4]	Yes

All four CVOTs met prespecified noninferiority criteria for MACE (upper boundary of 95% CI < 1.3) [3, 4]. However, only EMPA-REG OUTCOME demonstrated statistically significant superiority for 3-point MACE, with a 14% relative risk reduction (HR 0.86; 95% CI 0.74–0.99; P=0.038) [1, 17]. The CANVAS Program showed a numerically similar point estimate (HR 0.86; 95% CI 0.75–0.97) [2], with the confidence interval excluding 1.0. DECLARE-TIMI 58 showed a non-significant 7% relative risk reduction (HR 0.93; 95% CI 0.84–1.03; P=0.17) [3], and VERTIS CV showed essentially no effect on MACE (HR 0.97; 95.6% CI 0.85–1.11) [4].

Evidence From Meta-Analyses

Several meta-analyses pooled data across these and additional trials. The SMART-C collaborative meta-analysis of 12 placebo-controlled trials (72,970 participants with diabetes) reported a pooled hazard ratio for MACE of 0.90 (95% CI 0.86–0.94) in participants not receiving GLP-1 receptor agonists [5]. Zhang et al. (2021), pooling eight RCTs with 55,763 patients, reported a risk ratio for MACE of 0.92 (95% CI 0.86–0.98; P<0.007) [6]. Alexandrou et al. (2023), focusing on 11 studies in patients with chronic kidney disease (83,203 participants), reported a MACE hazard ratio of 0.87 (95% CI 0.81–0.93) [7, 21]. Semirani-Nezhad et al. (2025), in a meta-analysis restricted to early SGLT2 inhibitor initiation after acute MI, found a relative risk for MACE of 0.77 (95% CI 0.60–0.98) [23], though Bayesian analysis indicated uncertainty in some of these estimates [23].

The Bayesian meta-analysis by Odutayo et al. (2021), encompassing 53 RCTs, did not report a pooled MACE composite but provided agent-specific rate ratios for individual MACE components. Empagliflozin, canagliflozin, and dapagliflozin each showed a greater than 89% probability of reducing all-cause mortality (rate ratios 0.79, 0.86, and 0.86, respectively) [20], with weaker evidence for ertugliflozin and sotagliflozin [20]. The earlier meta-analysis by Brophy (2017), limited to pre-DECLARE and pre-VERTIS data, found that only empagliflozin significantly reduced MACE (RRR 18%; 95% CI 7–28; NNT 79), while canagliflozin and dapagliflozin showed non-significant effects [16].

Meta-Analysis	No. of Trials	Total N	Pooled MACE Estimate (95% CI)	Metric
E. M. Apperloo et al., 2024 (SMART-C) [5]	12 RCTs	72,970 [5]	0.90 (0.86–0.94) [5]	HR
A. Zhang et al., 2021 [6]	8 RCTs	55,763 [6]	0.92 (0.86–0.98) [6]	RR

Meta-Analysis	No. of Trials	Total N	Pooled MACE Estimate (95% CI)	Metric
M. E. Alexandrou et al., 2023 (CKD population) [7]	11 RCTs	83,203 [7]	0.87 (0.81–0.93) [7]	HR
D. Semirani-Nezhad et al., 2025 (acute MI) [23]	7 RCTs + 3 PSM	15,133 [23]	0.77 (0.60–0.98) [23]	RR
J. Brophy, 2017 (empagliflozin only) [16]	12 RCTs	14,584 [16]	RRR 18% (7–28) [16]	RRR

Across these meta-analyses, the pooled MACE estimates consistently favor SGLT2 inhibitors, with hazard or risk ratios ranging from 0.77 to 0.92. The largest and most contemporary collaborative meta-analysis (SMART-C, 2024) provides the most robust pooled estimate at HR 0.90 (95% CI 0.86–0.94) [5], a result that reaches statistical significance due to the large aggregate sample size.

Subgroup and Secondary Analyses

Several subgroup analyses provide additional context for interpreting MACE outcomes. In DECLARE-TIMI 58, dapagliflozin reduced MACE by 16% (HR 0.84; 95% CI 0.72–0.99; P=0.039) among patients with prior myocardial infarction, whereas no effect was observed in patients without prior MI (HR 1.00; 95% CI 0.88–1.13; P=0.97) [9]. A trend toward greater benefit was observed within 2 years after the last acute event (P for interaction trend=0.007) [9]. In EMPA-REG OUTCOME, the reduction in 3-point MACE was consistent across subgroups stratified by prior MI and stroke status and by the TIMI Risk Score for Secondary Prevention [1]. Among Asian patients in EMPA-REG OUTCOME, the hazard ratio for 3-point MACE was 0.68 (95% CI 0.48–0.95), numerically more favorable than in the overall population, though the interaction by race was not significant (P=0.0872) [10]. In the CANVAS Program, the proportional risk reduction for MACE with canagliflozin was consistent regardless of diabetes duration, number of glucose-lowering therapies, or baseline HbA1c [2]. DECLARE-TIMI 58 risk stratification using the TIMI Risk Score showed consistent relative risk reductions for cardiovascular death/hospitalization for heart failure across risk categories, though MACE-specific interaction data were not provided [11].

The Shabbir et al. (2025) single-center RCT reported markedly larger effects than the major CVOTs: a 52.7% relative risk reduction in MACE (12.2% vs. 25.8%; P=0.01) and a 67% reduction in heart failure hospitalizations (5.1% vs. 15.5%; P=0.005) [24]. These results should be interpreted with caution given the small sample size (n=195) [24], short follow-up (12 months) [24], absence of reported blinding [24], and single-center design [24].

Adverse Events

Across the CVOTs, SGLT2 inhibitors were generally well tolerated. In DECLARE-TIMI 58, diabetic ketoacidosis was more common with dapagliflozin than placebo (0.3% vs. 0.1%, P=0.02), as were serious or treatment-discontinuing genital infections (0.9% vs. 0.1%, P<0.001) [3]. In VERTIS CV, amputations occurred in 2.0% (5 mg dose) and 2.1% (15 mg dose) of ertugliflozin-treated patients versus 1.6% with placebo [4]. The SMART-C meta-analysis reported that fewer serious adverse events occurred with SGLT2 inhibitors compared with placebo overall (RR 0.87–0.91), irrespective of concomitant GLP-1 receptor agonist use [5].

Synthesis

The four dedicated CVOTs present an apparent heterogeneity in MACE outcomes: EMPA-REG OUTCOME and the CANVAS Program showed statistically significant or borderline significant MACE reductions (HR 0.86 in both cases) [1, 2], while DECLARE-TIMI 58 and VERTIS CV did not demonstrate superiority (HR 0.93 and 0.97, respectively) [3, 4]. Several factors explain this divergence.

Population composition is the most important driver of heterogeneity. EMPA-REG OUTCOME enrolled exclusively patients with established ASCVD (100%) [1], and the CANVAS Program enrolled patients with preexisting CVD or elevated cardiovascular risk [12]. By contrast, DECLARE-TIMI 58 included a substantially broader population in which only 41% had established ASCVD, with the remaining 59% enrolled on the basis of multiple risk factors alone [8, 15]. The subgroup analysis by Furtado et al. (2019) directly supports this explanation: among DECLARE patients with prior MI — the highest-risk subgroup — dapagliflozin significantly reduced MACE (HR 0.84; 95% CI 0.72–0.99), whereas no effect was observed in patients without prior MI (HR 1.00) [9]. This pattern suggests that the dilution of the treatment effect in DECLARE-TIMI 58 reflects the inclusion of a large primary prevention cohort rather than a true lack of efficacy of dapagliflozin in established ASCVD. The Cahn et al. (2021) analysis further confirms that in the primary prevention (MRF) cohort, dapagliflozin's benefits were predominantly on heart failure hospitalization and renal outcomes rather than on atherothrombotic MACE [15].

Methodological differences in trial design also contribute. VERTIS CV, despite enrolling 100% ASCVD patients [4], showed the weakest MACE signal (HR 0.97) [4]. This trial had a higher dropout rate (23.5% in the ertugliflozin group and 27.9% in the placebo group) [4], and the 2:1 randomization ratio (ertugliflozin:placebo) [4] resulted in fewer placebo-group events for comparison. The mean HbA1c at baseline was 8.2% [4] and mean diabetes duration was 13.0 years [4], comparable to other trials, suggesting that glycemic characteristics do not explain the attenuated signal.

Consistency across the class is supported by meta-analytic evidence. When individual trial-level heterogeneity is resolved through pooling, a consistent moderate MACE reduction emerges. The SMART-C meta-analysis (HR 0.90; 95% CI 0.86–0.94) [5] and the Zhang et al. meta-analysis (RR 0.92; 95% CI 0.86–0.98) [6] both demonstrate a statistically significant approximately 8–10% relative risk reduction in MACE across the SGLT2 inhibitor class. Notably, Odutayo et al. (2021) found no association between treatment effects and control group event rates, suggesting that the relative MACE benefit does not vary meaningfully by baseline cardiovascular risk level [20]. This finding, however, is in tension with the subgroup data from DECLARE showing differential absolute (if not relative) benefits by prior MI status [9].

Agent-level differences remain possible but are not well established. The Brophy (2017) network meta-analysis, conducted before DECLARE and VERTIS data were available, found that only empagliflozin significantly reduced MACE, while canagliflozin and dapagliflozin did not differ from control [16]. However, the commentary noted that the empagliflozin mortality benefit was almost entirely driven by the single EMPA-REG OUTCOME trial in patients with established coronary artery disease, cautioning against extrapolation to primary prevention [16]. The Alexandrou et al. (2023) meta-analysis in CKD patients found consistent treatment effects across agents (canagliflozin HR 0.84, dapagliflozin HR 0.89, empagliflozin HR 0.82, sotagliflozin HR 0.90; P for subgroup differences=0.85) [7], arguing against meaningful between-agent differences. Odutayo et al. (2021) similarly reported overlapping credibility intervals for all-cause and cardiovascular mortality across empagliflozin, canagliflozin, and dapagliflozin, with a probability of a true rate ratio below 1.00 exceeding 90% for all three agents [20].

Study quality considerations. All four landmark CVOTs were industry-funded [1, 3, 4, 10], double-blinded (where reported) [4, 13], and registered on ClinicalTrials.gov [3, 9]. The DECLARE-TIMI 58 trial achieved 99% follow-up [8], and outcome events were adjudicated by independent committees in VERTIS CV [4] and EMPA-REG OUTCOME [10].

The meta-analyses employed standard quality assessment tools including Cochrane Risk of Bias [6, 23] and GRADE [6, 12], and several were prospectively registered (PROSPERO) [7, 16, 21]. The Shabbir et al. (2025) trial, while reporting dramatically larger effect sizes, did not report blinding or allocation concealment [24], was unfunded [24], and enrolled only 195 patients [24] — these limitations substantially reduce its weight relative to the major CVOTs.

In summary, the available evidence from dedicated CVOTs consistently demonstrates that SGLT2 inhibitors are non-inferior to placebo for 3-point MACE. When data are pooled across trials, a statistically significant class-level MACE reduction of approximately 8–14% emerges, with the largest collaborative meta-analysis estimating a pooled HR of 0.90 (95% CI 0.86–0.94) [5]. The magnitude of MACE benefit appears greatest in populations with established ASCVD — particularly those with recent or prior myocardial infarction [9] — and is attenuated when primary prevention populations are included. Individual trial-level differences in MACE outcomes are most parsimoniously explained by variation in the proportion of patients with established ASCVD rather than by true pharmacological differences among agents.

References

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