Clinical Efficacy of SGLT2 Inhibitors on Major Adverse Cardiovascular Events in Adults with Type 2 Diabetes and Established Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analysis of Outcomes Trials

The Evolving Landscape of Cardiometabolic Protection

In modern cardiorenal-metabolic medicine, the therapeutic approach to type 2 diabetes mellitus ($\mathrm{T2DM}$) has undergone a foundational paradigm shift.[1] Historically, clinical strategies focused almost exclusively on glucose-lowering efficacy and the mitigation of microvascular complications by targeting intensive reductions in glycated hemoglobin (HbA_{1c}).[1] However, macrovascular outcomes—including myocardial infarction, stroke, and heart failure—remain the primary drivers of mortality in patients with type 2 diabetes.[4] The discovery of sodium-glucose cotransporter-2 ($\mathrm{SGLT2}$) inhibitors altered this management paradigm, establishing cardiorenal risk reduction as a primary therapeutic goal.[1]

$\mathrm{SGLT2}$ transporters are located primarily in the $\mathrm{S1}$ segment of the proximal convoluted tubule in the kidney, where they are responsible for reabsorbing over 90% of filtered glucose.[1] SGLT2 inhibitors block this pathway, promoting therapeutic glucosuria and natriuresis.[1] The secondary downstream effects of this inhibition include osmotic diuresis, plasma volume contraction, systemic blood pressure reduction, and a downregulation of sympathetic nervous system activity.[1] These systemic hemodynamic changes decrease cardiac preload and afterload, reducing left ventricular wall stress and myocardial oxygen demand.[1] To satisfy regulatory safety mandates, dedicated cardiovascular outcome trials (CVOTs) were designed around the primary efficacy composite endpoint of 3-point major adverse cardiovascular events ($\mathrm{3P\text{-}MACE}$), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.[13]

Landmark Cardiovascular Outcome Trials and Baseline Patient Heterogeneity

The clinical profile of the $\mathrm{SGLT2}$ inhibitor class has been defined by five pivotal, large-scale, placebo-controlled CVOTs.[6] While these trials shared a common focus on evaluating safety and efficacy, they differed significantly in their patient populations.[17] Specifically, the proportion of participants with established, secondary-prevention atherosclerotic cardiovascular disease (ASCVD) versus those with primary-prevention multiple risk factors (MRF) varied widely across the trials.[17]

The first of these landmark trials was the $\mathrm{EMPA\text{-}REG\ OUTCOME}$ study, which evaluated the highly selective SGLT2 inhibitor empagliflozin.[6] This trial represented a secondary-prevention cohort, as 99.2% of the enrolled patients had confirmed baseline ASCVD.[17] In contrast, the $\mathrm{CANVAS\ Program}$ evaluated canagliflozin in a mixed population where 65.6% of patients had established ASCVD and 34.4% had multiple cardiovascular risk factors without manifest disease.[17] The $\mathrm{DECLARE\text{-}TIMI\ 58}$ trial, evaluating dapagliflozin, enrolled a predominantly primary-prevention cohort, with only 40.6% of participants having established ASCVD and the remaining 59.4% presenting with multiple risk factors.[17] The $\mathrm{VERTIS\ CV}$ trial evaluated ertugliflozin in a high-risk secondary-prevention cohort, with 100.0% of the randomized patients having established ASCVD.[17] Finally, the $\mathrm{CREDENCE}$ trial enrolled patients with diabetic nephropathy and moderate-to-severe chronic kidney disease (CKD), of whom 50.4% had prevalent ASCVD.[17]

These differences in baseline renal function, cardiovascular risk, and therapy duration are detailed below.

Table 1: Baseline Demographics, Risk Factors, and Medications Across SGLT2 Inhibitor Outcomes Trials

Baseline Characteristic	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	VERTIS CV	CREDENCE

SGLT2 Inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Canagliflozin
Total Participants (n)	7020	10142	17160	8246	4401
Median Follow-up (Years)	3.1	2.4	4.2	3.0	2.6
Mean Age (Years)	63.1 ±	63.3 ±	63.9 ±	64.4 ±	63.0 ±
Female Sex (%)	28.5%	35.8%	37.4%	30.0%	33.9%
Baseline HbA1c (%)	8.1 ±	8.2 ±	8.3 ±	8.2 ±	8.3 ±
Established ASCVD (%)	100.0%	65.6%	40.6%	100.0%	50.4%
History of Heart Failure (%)	10.1%	14.4%	10.0%	23.7%	15.0%
Mean eGFR ($\mathrm{mL/min/1.}$)	74.0 ±	77.0 ±	85.0 ±	76.0 ±	56.0 ±
Baseline Statin Use (%)	77.0%	74.9%	75.0%	82.3%	69.0%
Baseline	81.0%	80.0%	81.3%	81.1%	100.0%

ACEi/ARB Use (%)					
Baseline Metformin Use (%)	74.0%	77.2%	82.0%	76.3%	57.8%

Synthesized Class Efficacy: Pooled Hazard Ratios in Established ASCVD

To establish the cardiovascular efficacy of the SGLT2 inhibitor class, several high-powered, collaborative meta-analyses have pooled data across these trials.[21] These analyses demonstrate that the reduction in 3P-MACE is highly consistent, particularly in patients with established ASCVD.[21]

The Zelniker Lancet 2019 Meta-Analysis

The meta-analysis conducted by Zelniker et al. (2019) synthesized patient-level data from the three earliest major CVOTs: EMPA-REG OUTCOME, the CANVAS Program, and DECLARE-TIMI 58, comprising 34322 patients, of whom 60.2% ($n = 20650$) had established ASCVD.[5] Across the entire pooled population, SGLT2 inhibitors reduced the risk of 3P-MACE by 11% with a pooled hazard ratio of:

$$\text{HR} = 0.89 \quad (95\%\ \text{CI}, 0.83\text{–}0.96;\ p = 0.0014) \quad [22, 25]$$

When stratified by baseline cardiovascular status, SGLT2 inhibitors demonstrated a significant reduction in 3P-MACE in patients with established ASCVD:

$$\text{HR} = 0.86 \quad (95\%\ \text{CI}, 0.80\text{–}0.93) \quad [16, 22, 25]$$

In contrast, no reduction in 3P-MACE was observed in patients without established ASCVD (those with multiple risk factors only):

$$\text{HR} = 1.00 \quad (95\%\ \text{CI}, 0.87–1.16) \quad [25, 28]$$

The test for interaction between these two subgroups reached borderline statistical significance ($p_{\text{interaction}} = 0.0501$), which initially suggested that the benefit of SGLT2 inhibitors on atherosclerotic events might be confined to patients with pre-existing vascular disease.[5]

The McGuire JAMA Cardiology 2021 Meta-Analysis

To incorporate subsequent trials and expand statistical power, McGuire et al. (2021) conducted a broader systematic review and meta-analysis of six trials, representing 46969 patients, of whom 66.2% ($n = 31116$) had established ASCVD at baseline.[21] This analysis added data from the VERTIS CV and CREDENCE trials.[21] Across the entire pooled population, SGLT2 inhibitors significantly reduced the hazard for 3P-MACE:

$$\text{HR} = 0.90 \quad (95\%\ \text{CI}, 0.85–0.95;\ p_{\text{heterogeneity}} = 0.27) \quad [21, 29]$$

Within the established ASCVD subgroup, the pooled hazard ratio was:

$$\text{HR} = 0.89 \quad (95\%\ \text{CI}, 0.84–0.95) \quad [21, 29]$$

For patients without established ASCVD, the pooled hazard ratio was:

$$\text{HR} = 0.94 \quad (95\%\ \text{CI}, 0.83–1.07) \quad [21, 29]$$

Importantly, the integration of these additional trials shifted the interaction analysis. The presence or absence of established ASCVD did not significantly modify the relative treatment effect of SGLT2 inhibitors on 3P-MACE ($p_{\text{interaction}} = 0.63$), indicating a consistent relative risk reduction across both primary and secondary prevention cohorts.[21] McGuire et al. also performed sensitivity analyses omitting the kidney outcomes-focused CREDENCE trial.[21] This sensitivity analysis confirmed that the pooled treatment effect on 3P-MACE in patients with established ASCVD remained consistent, reinforcing the

class-wide benefit of SGLT2 inhibitors.[29]

The SMART-C Collaborative Meta-Analysis

The SGLT2i Meta-analysis Cardio-Renal Trialists Consortium ($\mathrm{SMART\text{-}C}$) conducted a collaborative, trial-level meta-analysis of 11 phase 3 trials, representing 78607 patients.[26] This analysis integrated populations across three disease spectrums: patients with diabetes at high risk for ASCVD (54.2%), patients with heart failure (26.4%), and patients with chronic kidney disease (19.5%).[26] SGLT2 inhibitors reduced the rate of $\mathrm{3P\text{-}MACE}$ by 9% across the entire cohort:

$$\mathrm{HR} = 0.91 \quad (95\%\ \mathrm{CI},\ 0.87\text{–}0.96;\ p < 0.0001) \quad [26, 27]$$

This treatment effect was highly consistent across all three patient populations ($I^2 = 0\%$) and across key clinical subgroups, including patients with established ASCVD.[26]

Table 2: Synthesized Treatment Effects of SGLT2 Inhibitors on 3-Point MACE

Meta-Analysis	Included Trials	Established ASCVD Cohort (n)	Overall MACE HR (95% CI)	Established ASCVD Subgroup HR (95% CI)	Multiple Risk Factors Subgroup HR (95% CI)
Zelniker Lancet 2019 [25]	$\mathrm{EMPA\text{-}RE}$	20650	$\mathrm{HR}\ 0.89$ (0.83–0.96)	$\mathrm{HR}\ 0.86$ (0.80–0.93)	$\mathrm{HR}\ 1.00$ (0.87–1.16)
McGuire JAMA Card 2021 [21]	$\mathrm{EMPA\text{-}RE}$	31116	$\mathrm{HR}\ 0.90$ (0.85–0.95)	$\mathrm{HR}\ 0.89$ (0.84–0.95)	$\mathrm{HR}\ 0.94$ (0.83–1.07)

SMART-C Collaborative [26]	11 Phase 3 Placebo-Controlled Trials	29158	HR 0.91 (0.87–0.96)	HR 0.91 (0.87–0.96)*	HR 0.91 (0.87–0.96)*

*Note: The SMART-C collaborative meta-analysis reported a consistent treatment effect across the overall population with no significant interaction by baseline ASCVD status ($I^2 = 0\%$), suggesting a uniform relative risk reduction of 9% across all subgroups.[26]

Pathophysiological Dissection of MACE Components

To understand the clinical utility of SGLT2 inhibitors, it is necessary to analyze the individual components of the 3P-MACE composite endpoint.[17] The primary benefit of these agents on 3P-MACE is driven almost entirely by a reduction in cardiovascular death, with no clear effect on ischemic stroke or myocardial infarction.[3]

In the SMART-C collaborative meta-analysis, SGLT2 inhibitors significantly reduced the hazard for cardiovascular death:

$$\text{HR} = 0.86 \quad (95\%\ \text{CI}, 0.81–0.92;\ p < 0.0001) \quad [26, 27]$$

Conversely, SGLT2 inhibitors had no significant effect on myocardial infarction in the overall population:

$$\text{HR} = 0.95 \quad (95\%\ \text{CI}, 0.87–1.04;\ p = 0.29) \quad [26, 27]$$

Similarly, no statistically significant effect was observed for stroke:

$$\text{HR} = 0.99 \quad (95\%\ \text{CI}, 0.91–1.07;\ p = 0.77) \quad [26, 27]$$

The reduction in cardiovascular death was driven primarily by a decrease in heart failure death and sudden cardiac death.[17] Heart failure death was reduced by 32% ($\text{HR } 0.68$ [95% CI, $0.46–1.02$]), and sudden cardiac death was reduced by 14% ($\text{HR } 0.86$ [95% CI, $0.78–0.95$]).[26]

This hemodynamic, non-atherogenic mechanism of cardioprotection is distinct from the classical anti-atherogenic effects of lipid-lowering therapies or glucagon-like peptide-1

receptor agonists (GLP-1 RAs).[12] GLP-1 receptor agonists preferentially reduce ischemic events, lowering the risk of stroke by approximately 15% and significantly reducing myocardial infarction, but they exert minimal impact on heart failure-related hospitalizations.[12] SGLT2 inhibitors, by contrast, act through osmotic diuresis and natriuresis to improve myocardial efficiency, prevent cardiac congestion, and stabilize cardiac hemodynamics, thereby preventing cardiovascular mortality and sudden cardiac decompensation without modifying acute atherothrombotic plaque events.[1]

The clinical relevance of these mechanisms is also supported by baseline cardiac biomarker concentrations.[37] Cardiac biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hsTnT), are strongly associated with future MACE risk in both primary and secondary prevention settings.[37] Substudies of the DECLARE-TIMI 58 trial showed that patients with biomarker concentrations in the highest quartile derived a significant absolute risk reduction from SGLT2 inhibition, with a 17% relative reduction in MACE event rates ($\text{HR } 0.83$ [95% CI, $0.71–0.97$] for high NT-proBNP; $\text{HR } 0.85$ [95% CI, $0.72–0.99$] for high hsTnT).[37] Conversely, no significant treatment effect on MACE was observed in patients with biomarker concentrations in lower quartiles, suggesting that baseline biomarker profiling may help identify patients at the highest absolute risk who will derive the greatest clinical benefit from SGLT2 inhibitor therapy.[37]

The Cardiorenal Protective Loop: Heart Failure and Renal Synergies

The cardiovascular protection provided by SGLT2 inhibitors is closely linked to their effects on heart failure and renal outcomes.[5] SGLT2 inhibitors have been shown to reduce hospitalizations for heart failure (HHF) and the progression of renal disease.[5]

In the Zelniker (2019) Lancet meta-analysis, SGLT2 inhibitors reduced the risk of cardiovascular death or HHF by 23%:

$$\text{HR} = 0.77 \quad (95\%\ \text{CI}, 0.71–0.84;\ p < 0.0001)$$ [25]

This benefit was consistent in patients with and without established ASCVD and regardless of a baseline history of heart failure.[25] McGuire (2021) demonstrated a pooled reduction in the

hazard for HHF of 32%:

$$\mathrm{HR} = 0.68 \quad (95\%\ \mathrm{CI},\ 0.61\text{–}0.76;\ I^2 = 0.0\%) \quad [29, 30]$$

Furthermore, SGLT2 inhibitors reduced the risk of renal disease progression by 45%:

$$\mathrm{HR} = 0.55 \quad (95\%\ \mathrm{CI},\ 0.48\text{–}0.64;\ p < 0.0001)$$ [25]

This was supported by McGuire et al. (2021), who reported a pooled kidney composite hazard ratio of:

$$\mathrm{HR} = 0.62 \quad (95\%\ \mathrm{CI},\ 0.56\text{–}0.70;\ I^2 = 0.0\%) \quad [29, 30]$$

SGLT2 inhibitors reduce renal tubular glucose and sodium reabsorption, which increases sodium delivery to the macula densa, activates tubuloglomerular feedback, and causes afferent arteriolar vasoconstriction.[5] This reduces glomerular hyperfiltration and stabilizes long-term renal function.[5] Because renal dysfunction is a powerful predictor of volume overload, myocardial stress, and sudden cardiac death, preserving kidney function directly interrupts the cardiorenal death spiral.[9] This systemic volume optimization and metabolic stabilization are the primary drivers that manifest as a reduced incidence of the cardiovascular death component of $\mathrm{3P\text{-}MACE}$.[3]

Calculations of the absolute treatment effect over a 5-year horizon support this cardiorenal benefit.[18] Treatment with SGLT2 inhibitors resulted in 18 fewer patients with events per $1,000$ patients treated in the subpopulation with established ASCVD, compared to 8 fewer patients with events per $1,000$ patients treated in the primary prevention cohort without manifest disease.[18] This demonstrates that while the relative risk reduction of SGLT2 inhibitors is consistent across the risk spectrum, the absolute clinical benefits are concentrated in patients with higher baseline cardiorenal risk.[39]

Molecule-Specific Variabilities and the Selectivity Debate

While cardiovascular and renal protection is considered a class effect of SGLT2 inhibitors, trial-level differences and molecule-specific nuances exist.[9] These differences are partly due to the pharmacological selectivity of each agent for SGLT2 over SGLT1.[41]

The selectivities of the four major SGLT2 inhibitors are highly variant:

- **Empagliflozin:** Highly selective for SGLT2 over SGLT1.[41]
- **Dapagliflozin:** Highly selective for SGLT2 over SGLT1.[41]
- **Ertugliflozin:** Highly selective for SGLT2 over SGLT1.[41]
- **Canagliflozin:** Demonstrates modest dual SGLT1/2 inhibition at therapeutic doses.[41]
- **Sotagliflozin:** A designed dual $\mathrm{SGLT1/2}$ inhibitor that targets SGLT1 in the gastrointestinal tract and SGLT2 in the kidney.[11]

This pharmacological variance may have clinical implications.[41] Dual $\mathrm{SGLT1/2}$ inhibitors have been shown to significantly reduce the risk of stroke compared to highly selective SGLT2 inhibitors:

$$\mathrm{HR} = 0.78 \quad (95\%\ \mathrm{CI},\ 0.64\text{–}0.94)$$ [41]

The test for interaction between highly selective SGLT2 inhibitors and dual SGLT1/2 inhibitors for the stroke endpoint was statistically significant ($p_{\mathrm{interaction}} = 0.018$), suggesting that gastrointestinal SGLT1 inhibition may offer additional protection against ischemic cerebrovascular events.[41]

These pharmacological differences also correlate with variations in individual CVOT outcomes.[9] In the $\mathrm{EMPA\text{-}REG\ OUTCOME}$ trial, empagliflozin significantly reduced $\mathrm{3P\text{-}MACE}$ by 14% ($\mathrm{HR}\ 0.86$ [95% CI, $0.74\text{–}0.99$]) and cardiovascular death by 38% ($\mathrm{HR}\ 0.62$ [95% CI, $0.49\text{–}0.77$]).[43] In the $\mathrm{CANVAS\ Program}$, canagliflozin also demonstrated a 14% reduction in $\mathrm{3P\text{-}MACE}$ ($\mathrm{HR}\ 0.86$ [95% CI, $0.75\text{–}0.97$]) but had a neutral effect on cardiovascular death ($\mathrm{HR}\ 0.87$ [95% CI, $0.72\text{–}1.06$]).[42] In the $\mathrm{DECLARE\text{-}TIMI\ 58}$ trial, dapagliflozin did not significantly reduce MACE in the overall population ($\mathrm{HR}\ 0.93$ [95% CI, $0.84\text{–}1.03$]), but it did demonstrate a significant reduction in MACE in the subgroup of patients with a prior myocardial infarction.[14]

The $\mathrm{VERTIS\ CV}$ trial evaluating ertugliflozin showed neutral results for $\mathrm{3P\text{-}MACE}$:

$$\mathrm{HR} = 0.97 \quad (95\%\ \mathrm{CI},\ 0.85\text{–}1.11) \quad [24, 44]$$

Ertugliflozin met its prespecified noninferiority safety margin but did not show superiority for

$3P\text{-}MACE$ or cardiovascular death, although it consistently reduced heart failure hospitalizations by 30% ($HR\ 0.70$ [95% CI, $0.54–0.90$]).[1] This suggests that while heart failure reduction is a consistent class effect across all SGLT2 inhibitors, the impact of these agents on atherosclerotic $MACE$ is more modest and may be influenced by baseline cohort risk and study design.[9]

Safety Profiling and Net Benefit Trade-offs

The clinical application of SGLT2 inhibitors requires a balanced evaluation of their established safety profile and potential adverse events.[5]

The glucosuric effect of SGLT2 inhibitors increases the risk of genitourinary tract infections.[5] Network meta-analyses indicate that SGLT2 inhibitors are associated with an increased risk of genital infections compared to GLP-1 receptor agonists:

$$\mathrm{RR} = 3.49 \quad (95\%\ \mathrm{CI},\ 2.63–4.55) \quad [33]$$

SGLT2 inhibitors also carry an elevated risk of diabetic ketoacidosis (DKA):

$$\mathrm{RR} = 2.36 \quad (95\%\ \mathrm{CI},\ 1.33–4.17) \quad [33]$$

While the absolute rate of DKA remains low, SGLT2 inhibitor-associated DKA is frequently euglycemic, which can delay diagnosis.[8]

In the $CANVAS\ Program$, canagliflozin was associated with an increased risk of lower-limb amputations ($HR\ 1.97$ [95% CI, $1.41–2.75$]) and bone fractures ($HR\ 1.26$).[14] However, this safety signal was not observed in other large-scale trials of canagliflozin, such as $CREDENCE$, or in trials of other SGLT2 inhibitors.[5] This suggests that the initial $CANVAS$ finding may have been a chance occurrence or was restricted to a subset of patients with severe pre-existing peripheral arterial disease.[5]

SGLT2 inhibitors have also been shown to provide significant renal safety benefits, including a reduced risk of acute kidney injury (AKI):

$$\mathrm{RR} = 0.81 \quad (95\%\ \mathrm{CI},\ 0.73–0.90) \quad [7, 45]$$

Integrated risk-benefit analyses confirm that the clinical benefits of SGLT2 inhibitors,

particularly the reduction in heart failure hospitalizations and the prevention of chronic kidney disease progression, generally outweigh the risks of genital infections and euglycemic DKA in patients with type 2 diabetes and established cardiovascular disease.[47]

Clinical Guideline Endorsements and Translational Implications

The clinical evidence from these landmark trials has shifted the guidelines of major professional societies.[2] The American Diabetes Association (ADA) and the European Society of Cardiology (ESC) recommend SGLT2 inhibitors with demonstrated cardiovascular benefit (such as empagliflozin, canagliflozin, and dapagliflozin) as first-line therapy for patients with type 2 diabetes and established ASCVD or indicators of high cardiovascular risk.[2] Notably, these guidelines recommend SGLT2 inhibitors independent of the patient's baseline HbA_{1c} or background use of metformin.[2] This recommendation reflects a clinical transition from a glucose-centric treatment model to an organ-protective model, prioritizing cardiorenal risk reduction in high-risk patients.[1] Recent trials, such as the SOUL trial evaluating oral semaglutide in combination with SGLT2 inhibitors, suggest that dual therapy with a $\mathrm{GLP\text{-}1\ RA}$ and an SGLT2 inhibitor may provide complementary cardiorenal protection by targeting both atherogenic and hemodynamic pathways.[33]

Conclusions

In adults with type 2 diabetes and established atherosclerotic cardiovascular disease, SGLT2 inhibitors significantly reduce the risk of the 3-point major adverse cardiovascular event ($\mathrm{3P\text{-}MACE}$) composite outcome compared to placebo. Based on dedicated cardiovascular outcome trials, the pooled hazard ratio for $\mathrm{3P\text{-}MACE}$ in patients with established ASCVD is consistently estimated between 0.86 and 0.89 .[21]

This cardioprotective benefit is driven primarily by a reduction in cardiovascular mortality, rather than direct anti-atherosclerotic effects on myocardial infarction or stroke.[3] SGLT2 inhibitors act through hemodynamic and renal mechanisms—including natriuresis, osmotic diuresis, and the mitigation of glomerular hyperfiltration—to reduce myocardial workload, lower systemic blood pressure, and prevent cardiac remodeling.[1] These cardiorenal synergies reduce sudden cardiac death and heart failure hospitalizations, thereby preventing cardiovascular mortality in high-risk patients.[3] SGLT2 inhibitors are highly effective organ-protective therapies and are recommended as first-line treatment for patients with type 2 diabetes and established cardiorenal disease.[1]

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