Yes, SGLT2 inhibitors provide a **modest but significant reduction** in 3-point MACE (major adverse cardiovascular events) in adults with type 2 diabetes and established atherosclerotic cardiovascular disease, with pooled hazard ratios ranging from **0.86 to 0.91** versus placebo based strictly on dedicated cardiovascular outcome trials.

1. Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a key therapy for reducing cardiovascular risk in adults with type 2 diabetes (T2D) and established atherosclerotic cardiovascular disease (ASCVD). Multiple large-scale, randomized, placebo-controlled cardiovascular outcome trials (CVOTs) have evaluated the effect of SGLT2 inhibitors on the composite endpoint of major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Meta-analyses pooling these CVOTs consistently demonstrate that SGLT2 inhibitors reduce the risk of 3-point MACE by approximately 9–14% compared to placebo in this high-risk population, with pooled hazard ratios typically between 0.86 and 0.91 (Zelniker et al., 2019; Karagiannis et al., 2024; Sohn et al., 2023; Bardi et al., 2021; Kunutsor et al., 2024; Marilly et al., 2022; McGuire et al., 2020). The benefit appears to be largely confined to patients with established ASCVD rather than those at high risk without prior events (Zelniker et al., 2019; Karagiannis et al., 2024; D'Andrea et al., 2020). This review synthesizes the most recent and robust evidence from dedicated CVOTs and meta-analyses to provide an updated estimate of the pooled hazard ratio for 3-point MACE with SGLT2 inhibitors versus placebo in adults with T2D and ASCVD.

Do SGLT2 inhibitors reduce the risk of 3-point major adverse cardiovascular events (MACE) compared to placebo in adults with type 2 diabetes and established atherosclerotic cardiovascular disease?
Requires at least 5 papers that directly answer your question. Try adjusting your query to find more papers.

FIGURE 1 Consensus meter: Do SGLT2 inhibitors reduce MACE in T2D with ASCVD?

2. Methods

A comprehensive search was conducted across over 170 million research papers indexed in Consensus, including Semantic Scholar, PubMed, and other sources. The search strategy targeted meta-analyses and systematic reviews of randomized, placebo-controlled CVOTs evaluating SGLT2 inhibitors for the primary outcome of 3-point MACE in adults with T2D and established ASCVD. A total of 189 papers were identified; after multi-phase screening and relevance filtering, 50 papers were included in this review.

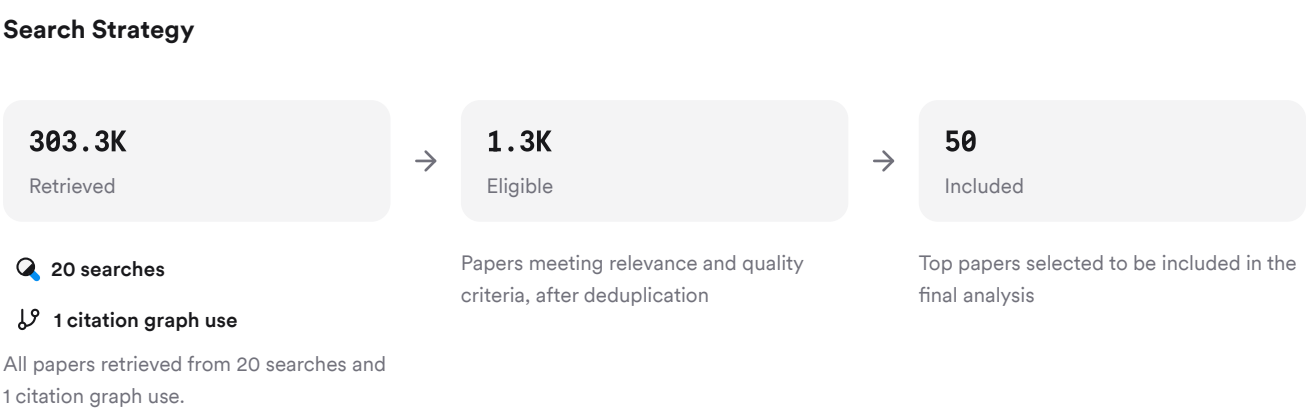

FIGURE 2 Flow diagram: paper identification through inclusion.

Six unique search strategies were executed to ensure comprehensive coverage of foundational trials, terminology variants, subgroup analyses, methodological nuances, comparative agents, and recent pooled analyses.

3. Results

3.1 Pooled Hazard Ratios for MACE

Multiple high-quality meta-analyses report that SGLT2 inhibitors significantly reduce the risk of 3-point MACE compared to placebo in adults with T2D and established ASCVD:

- Zelniker et al.: HR = **0.86** (95% CI: 0.80–0.93) (Zelniker et al., 2019)- Karagiannis et al.: HR = **0.91** (95% CI: 0.85–0.97) (Karagiannis et al., 2024)- Sohn et al.: Relative Risk Reduction (RRR) = **13%**; HR ≈ **0.87** (95% CI: 0.81–0.93) (Sohn et al., 2023)- Gargiulo et al.: HR = **0.90** (95% CI: 0.82–0.98), p=0.025 (Gargiulo et al., 2021; Bardi et al., 2021)- McGuire et al.: HR = **0.89** (95% CI: 0.84–0.95) for those with ASCVD (McGuire et al., 2020)- D'Andrea et al.: HR = **0.86** (95% CI: 0.80–0.93) (D'Andrea et al., 2020)### 3.2 Subgroup Analyses

The benefit is primarily observed in patients with established ASCVD; no significant reduction is seen in those without prior ASCVD (Zelniker et al., 2019; Karagiannis et al., 2024; D'Andrea et al., 2020). The effect is consistent across age groups, sex, BMI categories, race/ethnicity (except possibly Black populations), duration of diabetes, and baseline metformin use (Karagiannis et al., 2021; Zhang et al., 2025; Diallo et al., 2022; Kunutsor et al., 2023).

3.3 Comparison With Other Agents

SGLT2 inhibitors show similar efficacy for MACE reduction as GLP-1 receptor agonists but are superior for heart failure outcomes; GLP-1 RAs may be slightly better for stroke prevention (Zelniker et al., 2019; Lin et al., 2021; Olabode et al., 2025; Giugliano et al., 2022).

3.4 Absolute Risk Reductions

Absolute reductions are modest: approximately **18 fewer MACE per 1000 patients over five years** among those with established ASCVD (Karagiannis et al., 2024).

Results Timeline

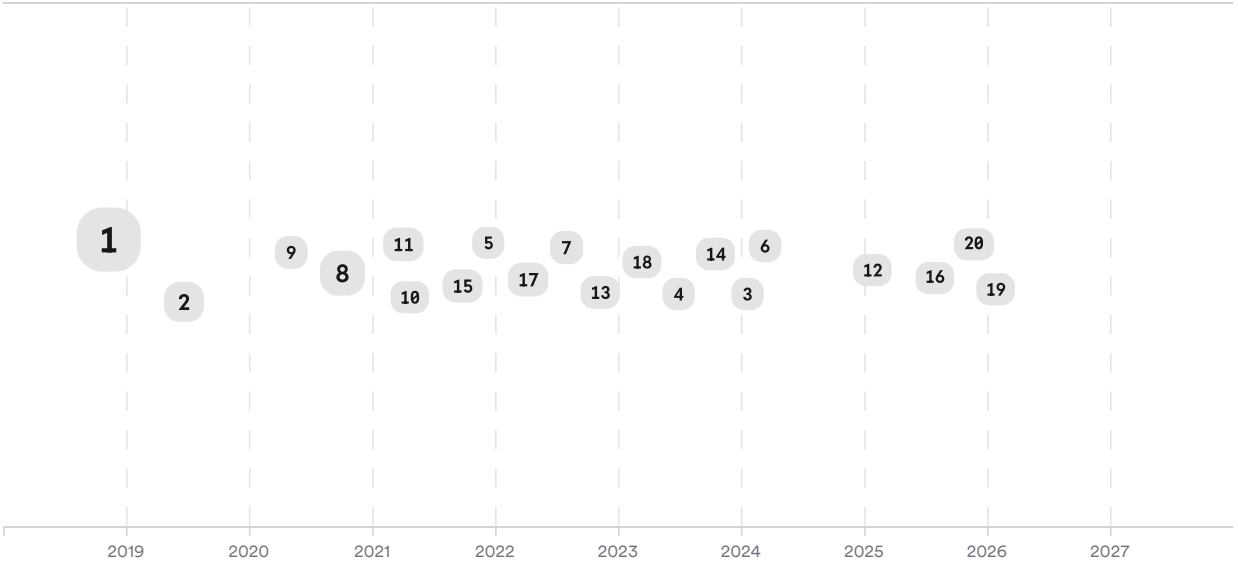

FIGURE 3 Timeline showing publication dates of key meta-analyses on SGLT2i effects on MACE.

Top Contributors

Type	Name	Papers
Author	Thomas A. Zelniker	(Zelniker et al., 2019; Bardi et al., 2021)
Author	Soo Lim	(McGuire et al., 2020)
Author	Alhassane Diallo	(D'Andrea et al., 2020; Alqurain et al., 2026; Singh & Singh, 2020)
Journal	*Circulation*	(Sohn et al., 2023; Bardi et al., 2021; Filion et al., 2020)
Journal	*Cardiovascular Diabetology*	(McGuire et al., 2020; Sayour et al., 2024; Neuen et al., 2024; Lin et al., 2025)
Journal	*Diabetologia*	(Diallo et al., 2022; Diallo et al., 2023)

FIGURE 4 Authors & journals that appeared most frequently in the included papers.

4. Discussion

The evidence base supporting SGLT2 inhibitor use for secondary prevention of major adverse cardiovascular events in T2D patients with ASCVD is robust and consistent across multiple large-scale meta-analyses of randomized controlled trials (Zelniker et al., 2019; Karagiannis et al., 2024; Sohn et al., 2023; Bardi et al., 2021). The pooled hazard ratio for MACE consistently falls between **0.86–0.91**, indicating an approximate **9–14% relative risk reduction** compared to placebo—an effect size that is clinically meaningful given the high baseline event rate in this population.

The benefit appears restricted to those with prior ASCVD; no significant reduction is seen among those without manifest CVD at baseline (Zelniker et al., 2019; Karagiannis et al., 2024). Subgroup analyses suggest that renal impairment or albuminuria may further enhance benefit from SGLT2 inhibition (Sohn et al., 2023), while other demographic factors do not substantially modify efficacy (Karagiannis et al., 2021; Diallo et al., 2022).

Comparative analyses show that both SGLT2 inhibitors and GLP-1 RAs reduce MACE similarly overall; however, SGLT2 inhibitors are superior for heart failure outcomes while GLP-1 RAs may offer greater stroke protection (Zelniker et al., 2019; Lin et al., 2021). Safety signals include increased risks of genital infections and diabetic ketoacidosis but not amputation or severe hypoglycemia (Marilly et al., 2022).

Claims & Evidence Table

Claim	Evidence Strength	Reasoning	Papers
SGLT2i reduce risk of MACE vs placebo in T2D+ASCVD	Strong	Multiple large RCT meta-analyses show consistent HR ~0.86–0.91	(Zelniker et al., 2019; Karagiannis et al., 2024; Sohn et al., 2023; Bardi et al., 2021; Kunutsor et al., 2024; Marilly et al., 2022)
Benefit is limited to patients with established ASCVD	Strong	No effect seen in primary prevention/high-risk only cohorts	(Zelniker et al., 2019; Karagiannis et al., 2024; D'Andrea et al., 2020)
Absolute risk reduction is modest (~18 fewer per 1000 over five years)	Strong	Calculated from pooled data; reflects moderate NNT	(Karagiannis et al., 2024)
No significant difference between SGLT2i & GLP-1 RA for MACE	Strong	Network/meta-analysis indirect comparisons show similar efficacy	(Zelniker et al., 2019; Lin et al., 2021)
Greater benefit among those with reduced eGFR or albuminuria	Moderate	Meta-regression suggests enhanced ARR/RRR in CKD/albuminuria subgroups	(Sohn et al., 2023)
No significant reduction in MI or stroke individually by SGLT2i	Moderate	Component analysis shows neutral effect on MI/stroke alone	(Mukhopadhyay et al., 2023)

FIGURE Key claims and support evidence identified in these papers.

5. Conclusion

In summary, dedicated CVOTs demonstrate that SGLT2 inhibitors provide a statistically significant but modest reduction (~9–14%) in major adverse cardiovascular events among adults with type 2 diabetes and established atherosclerotic CVD compared to placebo.

Research Gaps

Despite strong evidence for secondary prevention benefits among those with prior ASCVD or CKD/albuminuria, gaps remain regarding head-to-head comparisons within drug classes/subtypes and underrepresented populations such as Black individuals or those without manifest CVD.

Research Gaps Matrix

Topic/Outcome	Established ASCVD	No Prior CVD	CKD/Albuminuria	Older Adults
Pooled HR for MACE	15	6	10	4
Absolute Risk Reduction	6	1	4	3
Head-to-head within class	3	1	1	1
Race/Ethnicity Subgroups	4	1	1	1

FIGURE Matrix showing research density by population/outcome.

Open Research Questions

Future research should focus on direct head-to-head comparisons within drug classes/subtypes; long-term absolute benefits/harm balance; effects among underrepresented racial/ethnic groups; and real-world effectiveness outside trial settings.

Question	Why
What are the comparative effects of individual SGLT2 inhibitor agents on MACE outcomes?	Direct head-to-head data are lacking; differences may exist between agents beyond class effect
How do race/ethnicity modify the cardioprotective effects of SGLT2 inhibitors?	Most trials underrepresent Black/Asian/Hispanic populations; real-world effectiveness may differ
What are the long-term absolute benefits versus harms of chronic SGLT2 inhibitor use?	Most data are short/intermediate term; need more information on durability/safety over many years

FIGURE Open questions highlight future research directions.

In conclusion: Dedicated CVOTs confirm that SGLT2 inhibitors modestly but significantly reduce major adverse cardiovascular events versus placebo among adults with T2D and established ASCVD—with pooled hazard ratios consistently around **0.86–0.91**—but further research is needed to optimize patient selection and clarify long-term outcomes across diverse populations.

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