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CAT Final Version

Clinical & PICO Question:
A 58-year-old woman with type 2 diabetes presents for her annual check-up, reporting increased chest pain during physical activity. Despite being on metformin, her HbA1c is 8.2%, and her family history includes cardiovascular disease. To manage her worsening condition, we are discussing intensifying her diabetes management with either like SGLT-2 inhibitors versus GLP-1 receptor agonists.

PICO Search Elements:
In adults with type 2 diabetes, how does the use of SGLT-2 inhibitors compared to GLP-1 receptor agonists in reduction of mortality and cardiovascular outcomes?

P (Population): Adults with type 2 diabetes
I (Intervention): SGLT-2 inhibitors
C (Comparison): GLP-1 receptor agonists
O (Outcome): Reduction of mortality and cardiovascular outcomes such MI, Stroke, heart failure.

Search Strategy:
Pubmed:
SGLT-2 inhibitors AND GLP-1 receptor agonists: 1297
Systematic review: 120
Random control Trial: RCT: 67
Clinical Trial: 73

Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists: (<10 years) 1131 results.
Meta-analysis and Systematic review: 159
Random control Trial: RCT:63
Clinical Trial: 68

Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists AND cardiovascular outcomes: (<10 years) 501 results.
Meta-analysis and Systematic review: 86
Random control Trial: RCT: 18
Clinical Trial: 19

Cochrane:
Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists: 1 Sys review, 17 RCTs
Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists AND cardiovascular outcomes: 1 Sys review, 12 RCTs
Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists AND Reduction of mortality: 0 Sys review, 3 RCTs

Google scholars
Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists AND cardiovascular outcomes: 11,200 results
Reviewed articles: 4380

Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists AND Reduction of mortality: 9590 results
Reviewed article: 3970

Science direct:
Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists AND cardiovascular: 1481 results.
Review article :570
Diabetes and Metabolic Syndrome: clinical research and review: 21
Type 2 diabetes AND SGLT-2 inhibitors AND GLP-1 receptor agonists AND Reduction of mortality: < 10 years: 948
Reviewed article: 446
Diabetes and Metabolic Syndrome: clinical research and review: 16

When selecting articles for my CAT question, I prioritized those with the highest level of evidence, including systematic reviews and meta-analyses. I began by evaluating the relevance of each article through its title to ensure alignment with my PICO question. Subsequently, I thoroughly reviewed and analyzed the objectives, discussions, and conclusions to confirm that the research addressed my specific inquiry. I ensured that the articles examined both SGLT-2 inhibitors and GLP-1 receptor agonists in comparative studies. Additionally, I focused on selecting studies published in the U.S. and those released within the last ten years to guarantee their relevance to my target population.

Articles Chosen

Article 1
Kutz A, Kim DH, Wexler DJ, Liu J, Schneeweiss S, Glynn RJ, Patorno E. Comparative Cardiovascular Effectiveness and Safety of SGLT-2 Inhibitors, GLP-1 Receptor Agonists, and DPP-4 Inhibitors According to Frailty in Type 2 Diabetes. Diabetes Care. 2023 Nov 1;46(11):2004-2014. doi: 10.2337/dc23-0671. PMID: 37677118; PMCID: PMC10620535.

Abstract
Objective: To evaluate the comparative cardiovascular effectiveness and safety of sodium-glucose cotransporter 2 inhibitors (SGLT-2is), glucagon-like peptide 1 receptor agonists (GLP-1RAs), and dipeptidyl peptidase 4 inhibitors (DPP-4is) in older adults with type 2 diabetes (T2D) across different frailty strata.
Research design and methods: We performed three 1:1 propensity score-matched cohort studies, each stratified by three frailty strata, using data from Medicare beneficiaries (2013-2019) with T2D who initiated SGLT-2is, GLP-1RAs, or DPP-4is. In time-to-event analyses, we assessed the primary cardiovascular effectiveness composite outcome of acute myocardial infarction, ischemic stroke, hospitalization for heart failure, and all-cause mortality. The primary safety outcome was a composite of severe adverse events that have been linked to SGLT-2i or GLP-1RA use.
Results: Compared with DPP-4is, the overall hazard ratio (HR) for the primary effectiveness outcome associated with SGLT-2is (n = 120,202 matched pairs) was 0.72 (95% CI 0.69-0.75), corresponding to an incidence rate difference (IRD) of -13.35 (95% CI -15.06 to -11.64). IRD ranged from -6.74 (95% CI -8.61 to -4.87) in nonfrail to -27.24 (95% CI -41.64 to -12.84) in frail people (P for interaction < 0.01). Consistent benefits were observed for GLP-1RAs compared with DPP-4is (n = 113,864), with an overall HR of 0.74 (95% CI 0.71-0.77) and an IRD of -15.49 (95% CI -17.46 to -

13.52). IRD in the lowest frailty stratum was -7.02 (95% CI -9.23 to -4.81) and -25.88 (95% CI -38.30 to -13.46) in the highest (P for interaction < 0.01). Results for SGLT-2is versus GLP-1RAs (n = 89,865) were comparable. Severe adverse events were not more frequent with SGLT-2is or GLP-1RAs than DPP-4is.
Conclusions: SGLT-2is and GLP-1RAs safely improved cardiovascular outcomes and all-cause mortality, with the largest absolute benefits among frail people.

Article 2
Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, Tunnicliffe D, Ruospo M, Natale P, Saglimbene V, Nicolucci A, Johnson DW, Tonelli M, Rossi MC, Badve SV, Cho Y, Nadeau-Fredette AC, Burke M, Faruque LI, Lloyd A, Ahmad N, Liu Y, Tiv S, Millard T, Gagliardi L, Kolanu N, Barmanray RD, McMorrow R, Raygoza Cortez AK, White H, Chen X, Zhou X, Liu J, Rodríguez AF, González-Colmenero AD, Wang Y, Li L, Sutanto S, Solis RC, Díaz González-Colmenero F, Rodriguez-Gutierrez R, Walsh M, Guyatt G, Strippoli GFM. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2021 Jan 13;372:m4573. doi: 10.1136/bmj.m4573. Erratum in: BMJ. 2022 Jan 18;376:o109. doi: 10.1136/bmj.o109. PMID: 33441402; PMCID: PMC7804890.

Abstract
Objective: To evaluate sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes at varying cardiovascular and renal risk.
Design: Network meta-analysis.
Data sources: Medline, Embase, and Cochrane CENTRAL up to 11 August 2020.
Eligibility criteria for selecting studies: Randomised controlled trials comparing SGLT-2 inhibitors or GLP-1 receptor agonists with placebo, standard care, or other glucose lowering treatment in adults with type 2 diabetes with follow up of 24 weeks or longer. Studies were screened independently by two reviewers for eligibility, extracted data, and assessed risk of bias.
Main outcome measures: Frequentist random effects network meta-analysis was carried out and GRADE (grading of recommendations assessment, development, and evaluation) used to assess evidence certainty. Results included estimated absolute effects of treatment per 1000 patients treated for five years for patients at very low risk (no cardiovascular risk factors), low risk (three or more cardiovascular risk factors), moderate risk (cardiovascular disease), high risk (chronic kidney disease), and very high risk (cardiovascular disease and kidney disease). A guideline panel provided oversight of the systematic review.
Results: 764 trials including 421 346 patients proved eligible. All results refer to the addition of SGLT-2 inhibitors and GLP-1 receptor agonists to existing diabetes treatment. Both classes of drugs lowered all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure (high certainty evidence). Notable differences were found between the two agents: SGLT-2 inhibitors reduced admission to hospital for heart failure more than GLP-1 receptor agonists, and GLP-1 receptor agonists reduced non-fatal stroke more than SGLT-2 inhibitors (which appeared to have no effect). SGLT-2 inhibitors caused genital infection (high certainty), whereas GLP-1 receptor agonists might cause severe gastrointestinal events (low certainty). Low certainty evidence suggested that SGLT-2 inhibitors and GLP-1 receptor agonists might lower body weight. Little or no evidence was found for the effect of SGLT-2 inhibitors or GLP-1 receptor agonists on limb amputation, blindness, eye disease, neuropathic pain, or health related quality of life. The absolute

benefits of these drugs vary substantially across patients from low to very high risk of cardiovascular and renal outcomes (eg, SGLT-2 inhibitors resulted in 3 to 40 fewer deaths in 1000 patients over five years; see interactive decision support tool (https://magicevidence.org/match-it/200820dist/#!/) for all outcomes.
Conclusions: In patients with type 2 diabetes, SGLT-2 inhibitors and GLP-1 receptor agonists reduced cardiovascular and renal outcomes, with some differences in benefits and harms. Absolute benefits are determined by individual risk profiles of patients, with clear implications for clinical practice, as reflected in the BMJ Rapid Recommendations directly informed by this systematic review.

Article 3

Edwards K, Li X, Lingvay I. Clinical and Safety Outcomes With GLP-1 Receptor Agonists and SGLT2 Inhibitors in Type 1 Diabetes: A Real-World Study. J Clin Endocrinol Metab. 2023 Mar 10;108(4):920-930. doi: 10.1210/clinem/dgac618. PMID: 36268825.

Abstract

Context: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) are used off-label in the management of type 1 diabetes mellitus (T1DM) in real-world practice as adjuvant therapies to insulin. There are few real-world data regarding efficacy and safety of this practice.
Objective: This work aimed to determine the efficacy and safety of GLP-1RAs and sodium-glucose SGLT2is in the management of T1DM in real-world practice.
Methods: A retrospective chart review was performed of all instances of GLP-1RA and/or SGLT2i use greater than 90 days in adult patients with T1DM at a single academic center. We report the clinical and safety outcomes over the duration of use.
Results: We identified 104 patients with T1DM who ever used a GLP-1RA (76 patients) or SGLT2i (39 patients) for more than 90 days. After 1 year of therapy, GLP-1RA users had statistically significant reductions in weight (90.5 kg to 85.4 kg; $P < .001$), glycated hemoglobin A1c (HbA1c) (7.7% to 7.3%; $P = .007$), and total daily dose of insulin (61.8 units to 41.9 units; $P < .001$). SGLT2i users had statistically significant reductions in HbA1c (7.9% to 7.3%; $P < .001$) and basal insulin (31.3 units to 25.6 units; $P = .003$). GLP-1RA users compared to SGLT2i users had greater reduction in weight ($P = .027$) while HbA1c reduction was comparable between the groups. Over a mean total duration of use of 29.5 months/patient for both groups, more SGLT2i users experienced diabetic ketoacidosis (DKA) (12.8% vs 3.9%). Therapy was discontinued because of adverse events 26.9% of the time for GLP-1RA users vs 27.7% for SGLT2i users.
Conclusion: GLP-1RA and SGLT2i use in T1DM is associated with clinically relevant benefits. DKA remains a clinical concern with SGLT2i use, requiring careful patient selection and monitoring, with the risk to benefit ratio of treatment evaluated at an individual level.
Keywords: GLP-1RA; SGLT2i; real-world outcomes; safety; t1DM.

Article 4

Xie Y, Bowe B, Xian H, Loux T, McGill JB, Al-Aly Z. Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events: emulation of a randomised target trial using electronic health records. Lancet Diabetes Endocrinol. 2023 Sep;11(9):644-656. doi: 10.1016/S2213-8587(23)00171-7. Epub 2023 Jul 24. PMID: 37499675.

Abstract

Background: Randomised clinical trials showed that compared with placebo, SGLT2 inhibitors and GLP-1 receptor agonists reduced risk of adverse cardiovascular events. The evidence base for the older antihyperglycaemic drug classes (DPP-4 inhibitors and sulfonylureas) is generally less well developed. Because most randomised trials evaluated one antihyperglycaemic medication versus placebo, a head-to-head comparative effectiveness analysis of the newer drug classes (SGLT2 inhibitors vs GLP-1 receptor agonists) or newer (SGLT2 inhibitors or GLP-1 receptor agonists) versus older (DPP-4 inhibitors or sulfonylureas) drug classes on risk of major adverse cardiovascular events (MACE) is not available. In this study, we aimed to evaluate the comparative effectiveness of incident use of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, or sulfonylureas on risk of MACE.
Methods: We first specified the protocol of a four-arm randomised pragmatic clinical trial and then emulated it using the health-care databases of the US Department of Veterans Affairs. We built a cohort of metformin users with incident use of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, or sulfonylureas between Oct 1, 2016 and Sept 30, 2021, and followed up until Dec 31, 2022. We used the overlap weighting approach to balance the treatment groups using a battery of predefined variables and a set of algorithmically selected variables from high-dimensional data domains. Both intention-to-treat and per-protocol analyses (the latter estimated the effect of maintained use of the antihyperglycaemic throughout follow-up) were conducted to estimate risk of MACE-defined as a composite endpoint of stroke, myocardial infarction, and all-cause mortality.
Findings: The final cohort consisted of 283 998 new users of SGLT2 inhibitors (n=46 516), GLP-1 receptor agonists (n=26 038), DPP-4 inhibitors (n=55 310), or sulfonylureas (n=156 134). In intention-to-treat analyses, compared with sulfonylureas, SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors were associated with lower risk of MACE (hazard ratio [HR] 0·77 [95% CI 0·74-0.80], 0·78 [0·74-0·81), and 0·90 [0·86-0.93], respectively). Both SGLT2 inhibitors and GLP-1 receptor agonists were associated with a lower risk of MACE when compared with DPP-4 inhibitors (HR 0·86 [0·82-0·89] and 0·86 [0·82-0·90], respectively). The risk of MACE between SGLT2 inhibitors and GLP-1 receptor agonists yielded an HR of 0·99 (0·94-1·04). In per-protocol analyses, compared with sulfonylureas, SGLT2 inhibitors, GLP1 receptor agonists, and DPP-4 inhibitors were associated with reduced risk of MACE (HR 0·77 [95% CI 0·73-0·82], 0·77 [0·72-0·82], and 0·88 [0·83-0·93], respectively). Both SGLT2 inhibitors and GLP-1 receptor agonists were associated with a lower risk of MACE when compared with DPP-4 inhibitors (HR 0·88 [0·83-0·93] and 0·88 [0·82-0·93], respectively). The risk of MACE between SGLT2 inhibitors and GLP-1 receptor agonists yielded an HR of 1·01 (0·94-1·07).
Interpretation: Both SGLT2 inhibitors and GLP-1 receptor agonists were associated with reduced risk of MACE compared with DPP-4 inhibitors or sulfonylureas. DPP-4 inhibitors were associated with reduced risk of MACE compared with sulfonylureas. There was no statistically significant difference in risk of MACE between SGLT2 inhibitors and GLP-1 receptor agonists. The results provide evidence of the real-world comparative effectiveness of the four most commonly used second-line antihyperglycaemics and could guide choice of antihyperglycaemic therapy.
Funding: US Department of Veterans Affairs and the American Society of Nephrology.

Article 5

Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus.

Circulation. 2019 Apr 23;139(17):2022-2031. doi: 10.1161/CIRCULATIONAHA.118.038868. PMID: 30786725.

Abstract

Background: Glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as 2 new classes of antihyperglycemic agents that also reduce cardiovascular risk. The relative benefits in patients with and without established atherosclerotic cardiovascular disease for different outcomes with these classes of drugs remain undefined.

Methods: We performed a systematic review and trial-level meta-analysis of GLP1-RA and SGLT2i cardiovascular outcomes trials using the PubMed and EMBASE databases (Excerpta Medica Database). The primary outcomes were the composite of myocardial infarction, stroke, and cardiovascular death (MACE); hospitalization for heart failure; and progression of kidney disease.

Results: In total, data from 8 trials and 77 242 patients, 42 920 (55.6%) in GLP1-RA trials, and 34 322 (44.4%) in SGLT2i trials, were included. Both drug classes reduced MACE in a similar magnitude with GLP1-RA reducing the risk by 12% (hazard ratio [HR], 0.88; 95% CI, 0.84-0.94; P<0.001) and SGLT2i by 11% (HR, 0.89; 95% CI, 0.83-0.96; P=0.001). For both drug classes, this treatment effect was restricted to a 14% reduction in those with established atherosclerotic cardiovascular disease (HR, 0.86; 95% CI, 0.80-0.93; P=0.002), whereas no effect was seen in patients without established atherosclerotic cardiovascular disease (HR, 1.01; 95% CI, 0.87-1.19; P=0.81; P interaction, 0.028). SGLT2i reduced hospitalization for heart failure by 31% (HR, 0.69; 95% CI, 0.61-0.79; P<0.001), whereas GLP1-RA did not have a significant effect (HR, 0.93; 95% CI, 0.83-1.04; P=0.20). Both GLP1-RA (HR, 0.82; 95% CI, 0.75-0.89; P<0.001) and SGLT2i (HR, 0.62; 95% CI, 0.58-0.67; P<0.001) reduced the risk of progression of kidney disease including macroalbuminuria, but only SGLT2i reduced the risk of worsening estimated glomerular filtration rate, end-stage kidney disease, or renal death (HR, 0.55; 95% CI, 0.48-0.64; P<0.001).

Conclusions: In trials reported to date, GLP1-RA and SGLT2i reduce atherosclerotic MACE to a similar degree in patients with established atherosclerotic cardiovascular disease, whereas SGLT2i have a more marked effect on preventing hospitalization for heart failure and progression of kidney disease. Their distinct clinical benefit profiles should be considered in the decision-making process when treating patients with type 2 diabetes mellitus.

Keywords: diabetes mellitus, type 2; glucagon-like peptide 1 receptor agonists; meta-analysis; sodium-glucose co; transporter-2 inhibitors.

Article 6

Sajja AP, Dey AK, Guha A, Elnabawi Y, Joshi AA, Kalra A. SGLT-2 Inhibitors and GLP-1 Agonists: First-Line Therapy for Diabetes With Established Cardiovascular Disease. J Cardiovasc Pharmacol Ther. 2019 Sep;24(5):422-427. doi: 10.1177/1074248419838511. Epub 2019 May 7. PMID: 31064213.

Abstract

There is a growing body of evidence that diabetes represents a significant and largely modifiable risk factor for cardiovascular disease (CVD). It is known to markedly increase the risk of CVD-with CVD accounting for 2 of every 3 deaths in patients with diabetes. It is suggested that once patients with diabetes develop clinical coronary disease, they have a grim prognosis. In 2008, the Food and Drug Association mandated the evidence of CV safety in any new diabetic therapy, leading to a multitude of large CV outcome trials to assess CV risk from these medications. However, several of these outcome trials with novel antidiabetic therapies have demonstrated not only safety but a clear and definite CV advantage in patients with type 2 diabetes. In this review, we discuss 2 relatively newer classes of diabetic drugs, sodium glucose cotransport 2 inhibitors and glucagon-

like peptide 1 agonists, evaluate their efficacy in improving CV outcomes, and discuss the future of CV prevention with these agents.

Keywords: GLP-1 agonists; SGLT-2 inhibitors; diabetes.

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
Kutz et al., 2023	Cohort study	89,865 pairs for SGLT-2 inhibitors vs. GLP-1 receptor agonists. Medicare beneficiaries with type 2 diabetes from 2013-2019, stratified by frailty levels	Primary cardiovascular effectiveness composite: acute myocardial infarction, ischemic stroke, heart failure hospitalization, and all-cause mortality Safety outcome: Severe adverse events linked to SGLT-2i or GLP-1RA use	SGLT-2 inhibitors and GLP-1 receptor agonists significantly improved cardiovascular outcomes compared to DPP-4 inhibitors, with hazard ratios of 0.72 and 0.74, respectively. The absolute benefit was greatest in frail individuals, with incidence rate differences (IRD) of -27.24 (SGLT-2is) and -25.88 (GLP-1RAs) in the highest frailty group. No increase in severe adverse events was noted with SGLT-2 inhibitors or GLP-1 receptor agonists compared to DPP-4 inhibitors.	Use of observational data from Medicare beneficiaries may limit generalizability to younger populations or those outside the U.S. The cohort did not account for variations in adherence, drug discontinuation, or individual patient preferences, which could influence outcomes.
Palmer SC,	Systematic review and	764 randomized	All-cause mortality,	*Both SGLT-2 inhibitors and	* The analysis pooled data

Tendal B, Mustafa RA, Vandvik PO, et al. (2021)	network meta-analysis of randomized controlled trials	controlled trials 421,346 adult patients with type 2 diabetes Studies included had at least 24 weeks of follow-up and involved comparisons of SGLT-2 inhibitors or GLP-1 receptor agonists with placebo, standard care, or other glucose-lowering treatments	cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, heart failure hospitalization, kidney failure, genital infections, and gastrointestinal adverse events. Assessed outcomes in patients at varying cardiovascular and renal risk profiles (from very low to very high risk)	GLP-1 receptor agonists significantly reduced all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure. *SGLT-2 inhibitors showed a greater reduction in hospitalization for heart failure, while GLP-1 receptor agonists had a greater effect in reducing non-fatal strokes. *SGLT-2 inhibitors were associated with genital infections (high certainty), and GLP-1 receptor agonists with gastrointestinal adverse events (low certainty). *The absolute benefits varied significantly depending on patients' cardiovascular and renal risk profiles (e.g., SGLT-2 inhibitors prevented 3 to 40 deaths per	from diverse studies with varying designs, which may introduce heterogeneity. * The effect of SGLT-2 inhibitors or GLP-1 receptor agonists on certain outcomes like limb amputation, blindness, and quality of life was uncertain due to low-quality or insufficient data. * The study relied on existing RCTs and may not capture long-term effects beyond the duration of included trials.

				1000 patients over five years).	
Edwards K, Li X, Lingvay I. (2023)	Retrospective cohort study	*104 adult patients with type 1 diabetes mellitus (T1DM) at a single academic center *76 patients used GLP-1 receptor agonists (GLP-1RAs), 39 patients used SGLT2 inhibitors (SGLT2is) for more than 90 days * Mean duration of use: 29.5 months per patient.	* Efficacy outcomes: Weight reduction, glycated hemoglobin (HbA1c), total daily insulin dose * Safety outcomes: Diabetic ketoacidosis (DKA), therapy discontinuation due to adverse events	**GLP-1RA users:** Significant reductions in weight (from 90.5 kg to 85.4 kg; P < .001) HbA1c decreased (from 7.7% to 7.3%; P = .007) Total daily insulin dose reduced (from 61.8 units to 41.9 units; P < .001) SGLT2i users: Significant reduction in HbA1c (from 7.9% to 7.3%; P < .001) Basal insulin reduced (from 31.3 units to 25.6 units; P = .003) Comparison: **GLP-1RA users** had greater weight reduction compared to SGLT2i users (P = .027), while HbA1c reduction was similar between the groups. Safety: DKA occurred more frequently in SGLT2i users (12.8%)	*Small sample size from a single academic center limits generalizability. * Retrospective nature of the study introduces potential selection bias. * Lack of a control group (insulin-only therapy) makes it difficult to attribute all changes solely to GLP-1RA or SGLT2i use. * The study did not explore long-term complications beyond the mean follow-up duration of 29.5 months.

				compared to GLP-1RA users (3.9%). Therapy was discontinued due to adverse events in 26.9% of GLP-1RA users and 27.7% of SGLT2i users.	
Xie Y, Bowe B, et al (2023)	Cohort study (emulation of a randomized trial using electronic health records	*283,998 metformin users with new onset use of SGLT2 inhibitors (n=46,516), GLP-1 receptor agonists (n=26,038), DPP-4 inhibitors (n=55,310), or sulfonylureas (n=156,134) * Study based on U.S. Department of Veterans Affairs healthcare databases * Incident use between October 1, 2016, and September 30, 2021, followed up until December 31, 2022	* Primary outcome: Major adverse cardiovascular events (MACE), defined as a composite of stroke, myocardial infarction, and all-cause mortality * Intention-to-treat and per-protocol analyses were performed	* SGLT2 inhibitors and GLP-1 receptor agonists were associated with a lower risk of MACE compared to DPP-4 inhibitors: HR 0.86 (95% CI 0.82-0.89) and HR 0.86 (95% CI 0.82-0.90), respectively *No statistically significant difference in MACE risk was found between SGLT2 inhibitors and GLP-1 receptor agonists: • HR 0.99 (95% CI 0.94-1.04) □ Per-protocol analyses showed similar findings to the intention-to-treat analysis, reinforcing the	*Observational design, despite emulating a randomized trial, may be prone to residual confounding and selection bias. *The study population was primarily male and from the U.S. Department of Veterans Affairs system, limiting generalizability to broader populations. * While the study emulated a randomized trial, it cannot replace the internal validity of an actual randomized controlled trial.

				robustness of the results	
Zelniker TA, Wiviott SD, Raz I, et al. (2019)	Meta-analysis of trial-level data	* **77,242 patients** from 8 cardiovascular outcomes trials. *Of these, **42,920 patients (55.6%)** participated in trials of glucagon-like peptide 1 receptor agonists (GLP1-RA), and **34,322 patients (44.4%)** were in sodium-glucose cotransporter-2 inhibitor (SGLT2i) trials. * The focus was on patients with **type 2 diabetes mellitus**, with a subgroup analysis for those with **established atherosclerotic cardiovascular disease (ASCVD)** versus those without it.	The primary outcomes were: **Major Adverse Cardiovascular Events (MACE)** (composite of myocardial infarction, stroke, cardiovascular death). **Hospitalization for heart failure**. **Progression of kidney disease**.	Both GLP1-RA and SGLT2i reduced the risk of MACE by 12% and 11%, respectively. GLP1-RA: HR 0.88 (95% CI 0.84-0.94; P<0.001). SGLT2i: HR 0.89 (95% CI 0.83-0.96; P=0.001). This benefit was only significant in patients with established ASCVD, where both drug classes reduced the risk of MACE by 14% (HR 0.86). SGLT2i significantly reduced hospitalization for heart failure by 31% (HR 0.69), while GLP1-RA had no significant effect (HR 0.93). Both drug classes reduced the risk of kidney disease progression, but SGLT2i had a more marked effect, particularly on	The study pooled data from multiple trials, introducing heterogeneity in patient populations, treatment protocols, and follow-up times. Lack of individual patient-level data limits deeper subgroup analysis. There could be confounding factors related to differences in baseline characteristics not fully accounted for in trial-level data.

				worsening kidney function and renal death (HR 0.55).	
Sajja AP, Dey AK, Guha A, Elnabawi Y, Joshi AA, Kalra A. (2019)	Narrative review of clinical trials	This review discusses findings from various cardiovascular outcome trials SGLT-2i and GLP-1 RA in patients with type 2 diabetes mellitus and established cardiovascular disease (CVD). Specific trials are not quantitatively analyzed, as the article summarizes the efficacy of these drug classes based on prior studies.	The primary focus of the article is on the cardiovascular safety and efficacy of SGLT-2 inhibitors and GLP-1 agonists in reducing adverse cardiovascular outcomes in patients with type 2 diabetes. Cardiovascular mortality, hospitalization for heart failure, myocardial infarction, stroke, and progression of kidney disease are highlighted.	Both SGLT-2 inhibitors and GLP-1 agonists have demonstrated significant cardiovascular benefits beyond glycemic control in patients with type 2 diabetes. SGLT-2 inhibitors have been shown to reduce the risk of hospitalization for heart failure and kidney disease progression, in addition to lowering cardiovascular death rates. GLP-1 agonists primarily reduce the risk of major adverse cardiovascular events (MACE), particularly in patients with established CVD, but do not significantly reduce heart failure hospitalizations.	The article is a narrative review, which lacks a systematic methodology for selecting studies and may introduce selection bias. There is no direct comparison of the efficacy of SGLT-2 inhibitors and GLP-1 agonists through meta-analysis or pooled data. The findings rely on a qualitative synthesis of results from multiple trials, which may not offer precise risk estimates.

				These findings support the use of these two drug classes as first-line therapies in type 2 diabetes patients with established cardiovascular disease, based on their cardioprotectiv e profiles.	

Conclusion(s):

Conclusions of each article

Article1: Kutz et al., 2023. The study evaluated the cardiovascular effectiveness and safety of SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors in older adults with type 2 diabetes, stratified by frailty. Both SGLT-2 inhibitors and GLP-1 receptor agonists were associated with improved cardiovascular outcomes and reduced all-cause mortality compared to DPP-4 inhibitors, with the largest benefits seen in frail patients. No significant increase in severe adverse events was observed.

Article 2: Palmer et al, 2021 : This systematic review and network meta-analysis evaluated the cardiovascular and renal benefits of SGLT-2 inhibitors and GLP-1 receptor agonists in adults with type 2 diabetes. Both drug classes reduced all-cause mortality and major cardiovascular and renal outcomes, though SGLT-2 inhibitors were more effective at preventing heart failure hospitalizations, while GLP-1 receptor agonists reduced non-fatal strokes.

Article 3: Edwards K, Li X, Lingvay I. (2023): Over an average treatment duration of nearly 30 months, both drug classes showed significant reductions in HbA1c and insulin requirements. GLP-1RAs were associated with greater weight reduction, while SGLT2is were linked to a higher incidence of diabetic ketoacidosis (DKA). Despite their benefits, therapy discontinuation rates due to adverse events were similar between the groups, highlighting the need for individualized patient management and risk assessment.

Article 4: Xie Y, Bowe B, et al (2023): This cohort study emulated a four-arm randomized clinical trial to compare the cardiovascular outcomes of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas in metformin users with type 2 diabetes. The findings suggest that SGLT2 inhibitors and GLP-1 receptor agonists significantly reduce the risk of major adverse cardiovascular events (MACE) compared to sulfonylureas and DPP-4 inhibitors, with no significant difference between the two newer drug classes.

Article 5: Zelniker TA, Wiviott SD, Raz I, et al. (2019): This meta-analysis compared the cardiovascular and renal benefits of GLP1-RA and SGLT2i in patients with type 2 diabetes. Both drug classes reduced MACE in patients with ASCVD, but SGLT2i provided additional benefits in reducing hospitalization for heart failure and progression of kidney disease. These results suggest that while both drug classes offer significant cardiovascular protection, SGLT2i may be the preferred choice for patients at risk of heart failure and renal decline.

Article 6: Sajja AP, Dey AK, Guha A, Elnabawi Y, Joshi AA, Kalra A. (2019) This narrative review discusses the cardiovascular benefits of SGLT-2 inhibitors and GLP-1 agonists in patients with type 2 diabetes and established cardiovascular disease. SGLT-2 inhibitors significantly reduce heart failure hospitalizations and kidney disease progression, while GLP-1 agonists are effective in reducing major adverse cardiovascular events. Both drug classes are recommended as first-line therapies for managing diabetes with cardiovascular risk, as they provide not only glycemic control but also cardioprotective effects.

Overarching conclusion.
Both SGLT-2 inhibitors and GLP-1 receptor agonists show substantial cardiovascular and renal benefits in patients with type 2 diabetes, particularly those with established cardiovascular disease (CVD). Meta-analyses reveal that SGLT-2 inhibitors reduce the risk of heart failure hospitalizations by 31% (HR, 0.69; 95% CI, 0.61-0.79; P<0.001) and lower the risk of kidney disease progression by 38% (HR, 0.62; 95% CI, 0.58-0.67; P<0.001). Meanwhile, GLP-1 receptor agonists reduce the risk of non-fatal strokes by 12% (HR, 0.88; 95% CI, 0.84-0.94; P<0.001) and achieve greater weight reduction in patients. Both classes significantly lower all-cause mortality, with SGLT-2 inhibitors and GLP-1 receptor agonists reducing MACE by 11% and 12%, respectively. These findings support their use as first-line therapies in diabetes management, tailored to each patient's cardiovascular and renal risk profile.

Clinical Bottom Line:

- **Weight of the evidence**

  Kutz et al., 2023: The large sample size, real-world setting, and use of a matched cohort design provide strong evidence. However, as an observational study, it is subject to confounding and bias, limiting it slightly compared to randomized controlled trials. The cohort did not account for variations in adherence, drug discontinuation, or individual patient preferences, which could influence outcomes.

  Palmer et al, 2021 : Weight of the evidence is High; This is a systematic review and network meta-analysis with extensive data from 764 RCTs, providing strong and reliable evidence. The large sample size and use of the GRADE framework enhance the credibility of the findings. However, some uncertainty remains for certain secondary outcomes.

  Edwards K, Li X, Lingvay I. (2023): Moderate—Although it is a real-world study, which strengthens its clinical relevance, the retrospective design and single-center setting limit the generalizability of the findings. Nonetheless, the study provides important insights into the off-label use of these drugs in T1DM and emphasizes safety concerns, particularly with SGLT2 inhibitors.

  Xie Y, Bowe B, et al (2023): The weight of evidence is High. This study utilizes a large sample size and real-world data from a comprehensive healthcare system, combined with advanced statistical techniques to emulate a randomized clinical trial. Despite its observational nature, it offers strong comparative evidence on cardiovascular outcomes among second-line antihyperglycemic agents, making it a valuable contribution to clinical decision-making in diabetes management.

  Zelniker TA, Wiviott SD, Raz I, et al. (2019): the weight of evidence is High. The large sample size, systematic review approach, and inclusion of data from robust clinical trials provide strong evidence. The large sample size from 8 trials enhances the reliability of the findings and generalizability to real-world settings. Lack of individual patient-level data limits deeper subgroup analysis.

Sajja AP, Dey AK, Guha A, Elnabawi Y, Joshi AA, Kalra A. (2019: While the article effectively summarizes key clinical trials and findings, it does not perform a systematic review or meta-analysis. The narrative format limits the ability to draw precise conclusions about the relative efficacy of SGLT-2 inhibitors versus GLP-1 agonists. However, it provides valuable insights for clinical decision-making based on current evidence.

- **Magnitude of any effects**
  Both drug classes are associated with reduced cardiovascular risks in patients with established atherosclerotic cardiovascular disease (ASCVD), but SGLT-2 inhibitors show a more pronounced effect in preventing heart failure and renal decline, while GLP-1 receptor agonists offer specific protection against stroke.
- **Clinical significance**

Both classes of medications are linked to a decrease in all-cause mortality. For example, SGLT-2 inhibitors such as **Empagliflozin (Jardiance), Dapagliflozin (Farxiga), Canagliflozin (Invokana**) have demonstrated an approximate 11% reduction in all-cause mortality, though specific statistics can vary across different studies. Similarly, GLP-1 receptor agonists such as **Semaglutide(injectable (Ozempic), Oral (Rybelsus), Dulaglutide (Trulicity), Liraglutide (Victoza),** also contribute to this reduction, highlighting the need for further research to compare the effectiveness of these two classes. The evidence indicates that SGLT-2 inhibitors are particularly effective at lowering the risk of heart failure hospitalizations by 31% (HR, 0.69; 95% CI, 0.61-0.79) and offer significant protection against the progression of kidney disease (HR, 0.62; 95% CI, 0.58-0.67). In contrast, GLP-1 receptor agonists significantly decrease the incidence of non-fatal strokes by around 12% (HR, 0.88; 95% CI, 0.84-0.94), suggesting that these medications exert different but complementary effects. **Both SGLT-2 inhibitors and GLP-1 receptor agonists have been shown to lower the incidence of major adverse cardiovascular events (MACE). Specifically, SGLT-2 inhibitors reduce MACE by 11% (HR, 0.89; 95% CI, 0.83-0.96), while GLP-1 receptor agonists demonstrate a 12% reduction (HR, 0.88; 95% CI, 0.84-0.94). These findings indicate that both drug classes effectively mitigate cardiovascular risks, although SGLT-2 inhibitors may have a more significant impact on heart failure and renal outcomes.**

Further investigations are warranted to assess the long-term effects of these relatively new medications on mortality and cardiovascular events, particularly within diverse populations. Additionally, exploring the efficacy and safety of combining SGLT-2 inhibitors and GLP-1 receptor agonists may uncover further benefits for high-risk groups. Furthermore, analyzing the cost-effectiveness of these therapies in relation to their cardiovascular advantages would provide valuable insights for clinical decision-making.