REVIEW

Annals of Internal Medicine

Newer Pharmacologic Treatments in Adults With Type 2 Diabetes: A Systematic Review and Network Meta-analysis for the American College of Physicians

Tyler Drake, MD; Adrienne Landsteiner, PhD, MPH; Lisa Langsetmo, PhD, MS; Roderick MacDonald, MS; Maylen Anthony, MPH; Caleb Kalinowski, MS; Kristen Ullman, MS; Charles J. Billington, MD; Anjum Kaka, MD; Shahnaz Sultan, MD; and Timothy J. Wilt, MD, MPH

Background: Newer diabetes medications may have beneficial effects on mortality, cardiovascular outcomes, and renal outcomes.

Purpose: To evaluate the effectiveness, comparative effectiveness, and harms of sodium–glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP1) agonists, dipeptidyl peptidase-4 (DPP4) inhibitors, and long-acting insulins as monotherapy or combination therapy in adults with type 2 diabetes mellitus (T2DM).

Data Sources: MEDLINE and EMBASE for randomized controlled trials (RCTs) published from 2010 through January 2023.

Study Selection: RCTs lasting at least 52 weeks that included at least 500 adults with T2DM receiving eligible medications and reported any outcomes of interest.

Data Extraction: Data were abstracted by 1 reviewer and verified by a second. Independent, dual assessments of risk of bias and certainty of evidence (CoE) were done.

Data Synthesis: A total of 130 publications from 84 RCTs were identified. CoE was appraised using GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria for direct, indirect, and network meta-analysis (NMA); the highest CoE was reported. Compared with usual care, SGLT2 inhibitors and GLP1 agonists reduce all-cause mortality (high CoE) and major adverse cardiovascular events (MACE) (moderate to high CoE), SGLT2 inhibitors reduce progression of chronic kidney disease (CKD) and heart failure hospitalizations and GLP1 agonists reduce stroke (high CoE), and SGLT2 inhibitors reduce serious adverse events and severe hypoglycemia (high CoE). The threshold for minimally important differences, which was predefined with the American College of Physicians Clinical Guidelines Committee, was not met for these outcomes. Compared with usual care, insulin, tirzepatide, and DPP4 inhibitors do not reduce all-cause mortality (low to high CoE). Compared with insulin, SGLT2 inhibitors and GLP1 agonists reduce all-cause mortality (low to moderate CoE). Compared with DPP4 inhibitors, GLP1 agonists reduce all-cause mortality (moderate CoE). Compared with DPP4 inhibitors and sulfonylurea (SU), SGLT2 inhibitors reduce MACE (moderate to high CoE). Compared with SU and insulin, SGLT2 inhibitors and GLP1 agonists reduce severe hypoglycemia (low to high CoE).

Limitations: Infrequent direct comparisons between drugs of interest; sparse data for NMA on most outcomes; possible incoherence due to differences in baseline patient characteristics and usual care; insufficient data on predefined subgroups, including demographic subgroups, patients with prior cardiovascular disease, and treatment-naive persons.

Conclusion: In adults with T2DM, SGLT2 inhibitors and GLP1 agonists (but not DPP4 inhibitors, insulin, or tirzepatide) reduce all-cause mortality and MACE compared with usual care. SGLT2 inhibitors reduce CKD progression and heart failure hospitalization and GLP1 agonists reduce stroke compared with usual care. Serious adverse events and severe hypoglycemia are less frequent with SGLT2 inhibitors and GLP1 agonists than with insulin or SU.

Primary Funding Source: American College of Physicians. (PROSPERO: CRD42022322129)

Ann Intern Med. 2024;177:618-632. doi:10.7326/M23-1490 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 19 April 2024.

See also:

Editorial comment. 680
Related articles 633, 658

Web-Only
Supplement
Annals Video Summary

Type 2 diabetes mellitus (T2DM) has historically been treated with injectable insulin and oral agents, including metformin, sulfonylurea (SU), and thiazolidinediones, with the goal of reaching a target hemoglobin A_{1c} (HbA_{1c}) level by reducing blood glucose (1). It was believed that achieving HbA_{1c} targets would decrease risks for long-term outcomes, such as cardiovascular disease (CVD), the most common cause of death for persons with diabetes. Newer oral and injectable

medications, such as dipeptidyl peptidase-4 (DPP4) inhibitors, sodium–glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP1) agonists, and dual GLP1 and glucose-dependent insulinotropic polypeptide (GIP) agonists, are now available. In addition to improving glycemic control, these newer diabetes medications may have beneficial effects on mortality, cardiovascular outcomes, and renal outcomes. Hence, pharmacologic management decisions may now explicitly include not only glycemic control but also considerations of prevention of CVD, congestive heart failure (CHF), and chronic kidney disease (CKD) (2).

We conducted a systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) that included adults with T2DM to evaluate the effectiveness, comparative effectiveness, and harms of SGLT2 inhibitors, GLP1 agonists, DPP4 inhibitors, and long-acting insulins used either as monotherapy or in combination with other antidiabetic medications. We also conducted a contextual review to assess patient values and preferences for antidiabetic medications. This review was commissioned by the American College of Physicians (ACP) to inform its clinical guideline on treatment of T2DM by the ACP Clinical Guidelines Committee (CGC) (3). In a separate manuscript, we review the cost-effectiveness of these medications.

METHODS

Data Sources and Searches

Our protocol was registered in PROSPERO on 30 March 2022 (CRD42022322129). Key question 1 (KQ1) addressed effectiveness, comparative effectiveness, and harms of SGLT2 inhibitors, GLP1 agonists, DPP4 inhibitors, and long-acting insulins used as monotherapy or combination therapy in adults with T2DM. Key question 2 (KQ2) addressed patients' values and preferences regarding antidiabetic medications for T2DM management. For KQ1, we searched MEDLINE and EMBASE for RCTs published from 2010 to 31 January 2023 (**Appendix A** of **Supplement 1**, available at Annals.org). We supplemented this search with reference lists of systematic reviews identified through the Cochrane Library and Agency for Healthcare Research and Quality databases. We searched U.S. Food and Drug Administration (FDA) websites on 13 January 2023 to identify drug- and class-specific adverse effects that were listed as occurring in at least 5% of participants and being more common than with placebo or were listed as contraindications or warnings (**Appendixes A** and **B** of **Supplement 1**). The threshold of 5% was chosen based on reporting threshold information for adverse reactions provided in FDA documents. For KQ2, we searched MEDLINE and EMBASE (**Appendix A** of **Supplement 1**) from 2010 to 31 January 2023 to identify non–industry-sponsored systematic reviews with a U.S. perspective related to values and preferences regarding antidiabetic medications among patients with T2DM.

Study Selection

Trials were eligible if they enrolled adult participants aged 18 years or older with T2DM; evaluated SGLT2 inhibitors, GLP1 agonists, DPP4 inhibitors, or long-acting insulins; had treatment duration of at least 52 weeks; enrolled at least 500 participants; and reported any outcome of interest (**Tables 1** to **5** of **Supplement 2**, available at Annals.org). For medications approved after protocol development (for example, GLP1/GIP agonists), RCTs lasting 6 months or longer were eligible for inclusion. Thiazolidinediones and SU were originally listed as interventions in the protocol but are reported only as comparators. Titles and abstracts were screened by 2 reviewers for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text screening stage, 2 independent reviewers agreed on the final decision about inclusion or exclusion. In cases where consensus between the 2 reviewers could not be reached, a third reviewer was included.

Data Abstraction and Quality Assessment

Study, population, and intervention characteristics and outcomes were abstracted into a customized DistillerSR database by one reviewer and verified by a second reviewer. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion when consensus could not be reached. We categorized participants according to antidiabetic drug use before study enrollment (metformin, prior standard of care, or drug-naive). We abstracted baseline age, sex, ethnicity, body mass index (BMI), T2DM duration, HbA_{1c} level, CVD status, and CKD status (**Tables 1** and **2** of **Supplement 2**).

Two reviewers independently assessed risk of bias (RoB) for critical and important outcomes of included studies using the Cochrane RoB 2 tool (4). The 2 reviewers assessed each of 5 domains as having low RoB, some concerns, or high RoB, which were then summarized as an overall RoB. When consensus could not be reached, a third reviewer was included (**Appendix C** of **Supplement 1**).

Data Synthesis and Analysis

Eligible articles were summarized by drug class, critical outcomes (all-cause mortality, major adverse cardiovascular events [MACE], fatal and nonfatal myocardial infarction [MI], fatal and nonfatal stroke, and CKD), and important outcomes (hospitalization for CHF, severe hypoglycemia, weight loss of ≥10%, and serious adverse events) as determined by the ACP CGC (**Appendix D** of **Supplement 1**). MACE was defined by the trial authors and was not consistently defined across all studies. We accepted author definitions of MACE and serious adverse events. The specific adverse events classified as serious were variably and not always fully reported but typically included mortality and life-threatening events. Analysis of events was done at the participant level (that is, repeated events were ignored). We analyzed outcomes at the longest follow-up except for HbA_{1c} level and changes in body weight, for which 1-year outcomes were prioritized.

Predefined clinically important absolute effect thresholds, determined in agreement with the ACP CGC, were used to derive GRADE (Grading of Recommendations Assessment, Development and Evaluation) certainty of evidence (CoE). Because data on weight loss of at least 10% were sparse, we also assessed mean absolute weight loss as a continuous outcome.

To summarize direct comparisons between drug classes, we performed traditional pairwise meta-analyses for all intervention pathways with direct comparisons. If a trial included multiple groups assigned to the same class (including different doses of the same drug), the results were pooled based on the size of the 2 groups and the outcome data (number for event outcomes and mean and SD for continuous outcomes). The summary effect size was the risk ratio (RR) for event outcomes or mean differences (MDs) for continuous outcomes (change in HbA_{1c} level or weight) with a 95% CI. Heterogeneity within each pairwise comparison was tested using the Cochran *Q* statistic and quantified with the I^2 statistic, which was used to assess heterogeneity (for example, possible individual drug effect within class or variation by baseline characteristics or comparator). To facilitate the NMA, we combined data regardless of the number of RCTs for a given comparison (some comparisons included <4 RCTs) and calculated both fixed and random effects.

We constructed a network graph for each outcome (MACE, overall mortality, total MI, total stroke, serious adverse events, CHF hospitalization, CKD stage 3+, severe hypoglycemia, HbA_{1c} level, and change in weight) in which nodes were drugs grouped by class regardless of the dose and the method of administration. Most trials used 1 of 3 designs: comparison with placebo, an active comparator, or both. Some trials included monotherapy with a drug class of interest versus combination therapy with multiple drugs; however, these comparisons were not included in the network analysis (that is, all groups with multiclass combination therapy were dropped). Interventions that were not part of the connected graph were also dropped from the analysis. Only 1 placebo-controlled trial required all patients to be treatment-naive at entry; another 17 permitted treatment-naive participants to be included. Most trials allowed for various baseline medications (such as metformin or SU) but generally did not require their use and did not stratify participants by baseline medication. Participants were allowed add-on therapy during the trial at the discretion of the treating clinician. We therefore combined these concomitant diabetes treatment groups into the category of "usual care." The trials were analyzed together, but heterogeneity due to this factor was assessed based on pairwise meta-analyses. We used the resulting network for the NMA (Table; Appendix E of Supplement 1).

The network graphs were limited in that direct comparisons were present for a small subset of all possible class comparisons. Based on performance of these direct comparisons, feasibility of an NMA was assessed, specifically the assumption of transitivity. Where feasible, we performed an NMA using a frequentist graph-theoretical model and implemented in the R package netmeta (5, 6). Several of the networks included multigroup studies, and the necessary adjustments were made to the input pairwise comparisons before the NMA. A fixed- or random-effects model was used depending on the sparsity of the network, with a sparse network defined as one with pairwise associations present with fewer than 5 studies. The NMA included calculation of indirect and combined effects with league tables, forest plots, and assessment of model assumptions (that is, using generalized heterogeneity statistics for global incoherence and separate indirect from direct evidence [SIDE] for local incoherence).

We explored the feasibility of assessing whether treatment effects varied by baseline age, sex, ethnicity, HbA_{1c} level, CVD, CHF, obesity (BMI >30 kg/m^2), or CKD stage 3+ (Tables 1 and 4 of Supplement 2). We limited subgroup analyses to those that were prespecified by the individual study investigators and planned with stratified randomization. However, results were sparsely and variably reported, so we provide a brief narrative summary.

We used the GRADE approach to rate overall CoE for critical outcomes as high, moderate, low, or insufficient (7–9). As recommended by the ACP CGC, direct evidence was prioritized only when it provided a higher CoE than the NMA evidence. We downgraded by 1 level when no direct evidence was available. The NMA CoE was based on the component (direct or indirect) that had a larger contribution to the NMA as well as the consistency of direct and indirect estimates (10–12). The absolute risk differences were calculated using GRADEpro (McMaster University and Evidence Prime Inc.) for each of the direct comparisons using the common effect measures from the direct pairwise analysis (7). We determined whether absolute risk differences achieved thresholds indicating clinical minimally important differences (MIDs) for decision making about the effect of antidiabetic drugs on our critical outcomes. The MIDs were predetermined with the ACP CGC (Appendix F of Supplement 1).

Role of the Funding Source

This review was funded by ACP. The ACP CGC assisted in the development of KQs, study inclusion criteria, and outcome measures of interest. ACP and the CGC were not involved in data collection, analysis, or manuscript preparation, though they reviewed and provided comments on each.

RESULTS

Overview

For KQ1, we identified 13 386 citations in MEDLINE and EMBASE. After removal of duplicates, conference abstracts, dissertations, and theses, 9437 citations were dual-reviewed at the abstract and title stage (Appendix Figure 1, available at Annals.org). In total, 701 citations

Table. Summary of Findings

Comparison	Trials, *k*; Participants, *n* RR (95% CI) Absolute Risk Difference per 1000 Persons (95% CI)* Certainty of Evidence†							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD Stage 3 +**	**Serious Adverse Event**	**Severe Hypoglycemia**
Compared with placebo or usual care								
DPP4 inhibitors	$k = 10$; $n =$ 47 577 RR, 1.01 (0.94 to 1.08)‡ 1 more (4 fewer to 5 more) ⊕⊕⊕	$k = 5$; $n =$ 44 595 RR, 1.0 (0.94 to 1.06)‡ 0 fewer (6 fewer to 6 more) ⊕⊕⊕	$k = 2$; $n =$ 31 015 RR, 0.95 (0.85 to 1.06)‡ 2 fewer (6 fewer to 2 more) ⊕⊕⊕	$k = 1$; $n =$ 14 523 RR, 0.97 (0.79 to 1.19)‡ 1 fewer (5 fewer to 5 more) ⊕⊕⊕	$k = 3$; $n =$ 37 994 RR, 1.06 (0.96 to 1.17)‡ 2 more (1 fewer to 6 more) ⊕⊕⊕	$k = 2$; $n =$ 23 477 RR, 1.07 (0.95 to 1.21)‡ 3 more (2 fewer to 9 more) ⊕⊕⊕	$k = 9$; $n =$ 26 256 RR, 0.96 (0.92 to 1.01)‡ 8 fewer (15 fewer to 2 more) ⊕⊕⊕	$k = 9$; $n =$ 47 160 RR, 1.14 (1.00 to 1.30)‡ 2 more (0 fewer to 5 more) ⊕⊕⊕
GLP1 agonists	$k = 8$; $n =$ 48 481 RR, 0.88 (0.83 to 0.94)‡ 10 fewer (14 fewer to 5 fewer) ⊕⊕⊕	$k = 6$; $n =$ 46 541 RR, 0.91 (0.87 to 0.96)‡ 11 fewer (16 fewer to 5 fewer) ⊕⊕⊕	$k = 5$; $n =$ 43 244 RR, 0.96 (0.89 to 1.04)‡ 3 fewer (7 fewer to 3 more) ⊕⊕⊕	$k = 5$; $n =$ 43 244 RR, 0.86 (0.77 to 0.95)‡ 5 fewer (7 fewer to 2 fewer) ⊕⊕⊕	$k = 4$; $n =$ 33 904 RR, 0.95 (0.85 to 1.06)‡ 2 fewer (5 fewer to 2 more) ⊕⊕⊕	GLP1 agonists not in network	$k = 8$; $n =$ 36 188 RR, 0.98 (0.95 to 1.01)‡ 5 fewer (13 fewer to 3 more) ⊕⊕⊕	$k = 8$; $n =$ 42 250 RR, 1.02 (0.92 to 1.15)‡ 0 fewer (2 fewer to 3 more) ⊕⊕○§
SGLT2 inhibitors	$k = 14$; $n =$ 47 478 RR, 0.86 (0.80 to 0.93)‡ 9 fewer (13 fewer to 5 fewer) ⊕⊕⊕	$k = 3$; $n =$ 19 659 RR, 0.90 (0.83 to 0.98)‡ 12 fewer (21 fewer to 2 fewer) ⊕⊕○§	$k = 2$; $n =$ 15 266 RR, 0.97 (0.85 to 1.12)‡ 2 fewer (8 fewer to 7 more) ⊕⊕⊕	$k = 2$; $n =$ 15 266 RR, 1.12 (0.93 to 1.34)‡ 4 more (2 fewer to 10 more) ⊕⊕⊕	$k = 2$; $n =$ 11 421 RR, 0.64 (0.54 to 0.77)‡ 19 fewer (24 fewer to 12 fewer) ⊕⊕⊕	$k = 4$; $n =$ 32 713 RR, 0.66 (0.58 to 0.75)‡ 12 fewer (14 fewer to 9 fewer) ⊕⊕⊕	$k = 14$; $n =$ 46 096 RR, 0.93 (0.90 to 0.95)‡ 23 fewer (33 fewer to 16 fewer) ⊕⊕⊕	$k = 9$; $n =$ 39 902 RR, 0.85 (0.74 to 0.97)‡ 3 fewer (5 fewer to 1 fewer) ⊕⊕⊕
Tirzepatide	NMA RR, 0.98 (0.56 to 1.73) ⊕○○‖¶**	○○○††	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	$k = 3$; $n = 1069$ RR, 0.79 (0.51 to 1.22)‡ 17 fewer (39 fewer to 17 more) ⊕⊕⊕	$k = 3$; $n = 1373$ RR, 1.32 (0.78 to 2.22)‡ 15 more (10 fewer to 55 more) ⊕⊕○¶
Basal insulin	NMA RR, 1.23 (0.89 to 1.70) ⊕○○‖¶**	NMA RR, 1.10 (0.83 to 1.46) ⊕○○‖¶**	Basal insulin not in network	Basal insulin not in network	NMA RR, 1.01 (0.64 to 1.60) ⊕○○‖¶**	Basal insulin not in network	NMA RR, 1.17 (0.99 to 1.39) ⊕⊕○‖**	NMA RR, 3.81 (2.70 to 5.38) ○○○‖‡‡**
DPP4 inhibitors (head-to-head)								
DPP4 inhibitors vs. GLP1 agonists	$k = 4$; $n = 4612$ RR, 1.64 (1.05 to 2.56)‡ 7 more (1 more to 14 more) ⊕⊕○§§	$k = 1$; $n = 2515$ RR, 1.42 (0.99 to 2.04)‡ 16 more (0 fewer to 40 more) ⊕⊕⊕	NMA RR, 0.98 (0.86 to 1.13) ⊕⊕○‖**	NMA RR, 1.14 (0.90 to 1.43) ⊕⊕○‖**	$k = 1$; $n = 2515$ RR, 2.12 (1.13 to 3.98)‡ 13 more (1 more to 33 more) ⊕⊕○¶	GLP1 agonists not in network	$k = 5$; $n = 5168$ RR, 1.07 (0.89 to 1.29)‡ 6 more (10 fewer to 26 more) ⊕⊕⊕	$k = 4$; $n = 6724$ RR, 1.25 (0.91 to 1.73)‡ 7 more (2 fewer to 20 more) ⊕⊕⊕
DPP4 inhibitors vs. basal insulin	$k = 1$; $n = 2531$ RR, 0.97 (0.64 to 1.48)‡ 1 fewer (12 fewer to 16 more) ⊕⊕⊕	$k = 1$; $n = 2521$ RR, 1.06 (0.76 to 1.47)‡ 3 more (12 fewer to 24 more) ⊕⊕⊕	Basal insulin not in network	Basal insulin not in network	$k = 1$; $n = 2521$ RR, 1.15 (0.68 to 1.93)‡ 3 more (7 fewer to 19 more) ⊕⊕⊕	Basal insulin not in network	NMA RR, 0.82 (0.68 to 0.97) ⊕○○§§‖**	$k = 1$; $n = 2531$ RR, 0.56 (0.25 to 1.26)‡ 6 fewer (10 fewer to 3 more) ⊕⊕○¶

Continued on following page

Table–Continued

Comparison	Trials, *k*; Participants, *n* RR (95% CI) Absolute Risk Difference per 1000 Persons (95% CI)* Certainty of Evidence†							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD Stage 3 +**	**Serious Adverse Event**	**Severe Hypoglycemia**
DPP4 inhibitors vs. SGLT2 inhibitors	*k* = 5; *n* = 3878 RR, 1.20 (0.32 to 4.48)‡ 0 fewer (2 fewer to 8 more) ⊕○○‡‡	NMA RR, 1.13 (1.03 to 1.25) ⊕⊕○‖**	NMA RR, 0.98 (0.82 to 1.17) ⊕⊕○‖**	NMA RR, 0.87 (0.66 to 1.15) ⊕⊕○‖**	NMA RR, 1.68 (1.36 to 2.07) ⊕○○‖¶**	NMA RR, 1.62 (1.36 to 1.94) ⊕⊕○‖**	*k* = 4; *n* = 3455 RR, 0.99 (0.75 to 1.31)‡ 1 fewer (14 fewer to 17 more) ⊕⊕⊕	*k* = 4; *n* = 3105 RR, 0.78 (0.10 to 5.99)‡ 0 fewer (2 fewer to 10 more) ⊕○○‡‡
DPP4 inhibitors vs. sulfonylurea	*k* = 10; *n* = 22 352 RR, 0.90 (0.79 to 1.03)‡ 4 fewer (8 fewer to 1 more) ⊕⊕⊕	*k* = 4; *n* = 12 715 RR, 0.96 (0.85 to 1.09)‡ 3 fewer (12 fewer to 7 more) ⊕⊕⊕	*k* = 1; *n* = 6033 RR, 1.03 (0.83 to 1.28)‡ 1 more (8 fewer to 14 more) ⊕⊕⊕	*k* = 1; *n* = 6033 RR, 0.86 (0.67 to 1.12)‡ 6 fewer (13 fewer to 5 more) ⊕⊕⊕	*k* = 2; *n* = 8544 RR, 1.16 (0.91 to 1.47)‡ 5 more (3 fewer to 13 more) ⊕⊕⊕	Sulfonylurea not in network	*k* = 10; *n* = 20 439 RR, 0.95 (0.91 to 0.99)‡ 12 fewer (21 fewer to 2 fewer) ⊕⊕○¶	*k* = 8; *n* = 18 081 RR, 0.14 (0.11 to 0.19)‡ 44 fewer (46 fewer to 42 fewer) ⊕⊕⊕
DPP4 inhibitors vs. tirzepatide	NMA RR, 1.04 (0.59 to 1.83) ⊕○○‖¶**	NMA RR, 1.21 (0.76 to 1.92) ⊕○○‖¶**	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	NMA RR, 0.99 (0.80 to 1.22) ⊕⊕○‖**	NMA RR, 1.03 (0.68 to 1.57) ○○○‖‡‡**
GLP1 agonists (head-to-head)								
GLP1 agonists vs. DPP4 inhibitors	*k* = 4; *n* = 4612 RR, 0.61 (0.39 to 0.95)‡ 9 fewer (14 fewer to 1 fewer) ⊕⊕○§§	*k* = 1; *n* = 2515 RR, 0.70 (0.49 to 1.01)‡ 16 fewer (28 fewer to 1 more) ⊕⊕⊕	NMA RR, 1.02 (0.88 to 1.16) ⊕⊕○‖**	NMA RR, 0.88 (0.70 to 1.11) ⊕⊕○‖**	*k* = 1; *n* = 2515 RR, 0.47 (0.25 to 0.88)‡ 13 fewer (18 fewer to 3 fewer) ⊕⊕○¶	GLP1 agonists not in network	*k* = 5; *n* = 5168 RR, 0.94 (0.78 to 1.13)‡ 5 fewer (20 fewer to 12 more) ⊕⊕⊕	*k* = 4; *n* = 6724 RR, 0.81 (0.59 to 1.11)‡ 4 fewer (9 fewer to 2 more) ⊕⊕⊕
GLP1 agonists vs. basal insulin	*k* = 4; *n* = 4792 RR, 0.62 (0.41 to 0.93)‡ 10 fewer (16 fewer to 2 fewer) ⊕⊕○¶	*k* = 1; *n* = 2508 RR, 0.74 (0.52 to 1.07)‡ 13 fewer (25 fewer to 4 more) ⊕⊕⊕	Basal insulin not in network	Basal insulin not in network	*k* = 1; *n* = 2508 RR, 0.54 (0.28 to 1.03)‡ 10 fewer (15 fewer to 1 more) ⊕⊕○¶	GLP1 agonists and basal insulin not in network	*k* = 5; *n* = 3579 RR, 0.86 (0.72 to 1.04) 16 fewer (33 fewer to 5 more) ⊕○○§¶	*k* = 6; *n* = 6104 RR, 0.23 (0.16 to 0.33) 38 fewer (42 fewer to 33 fewer) ⊕⊕○¶‖‖
GLP1 agonists vs. SGLT2 inhibitors	NMA RR, 1.02 (0.93 to 1.12) ⊕⊕○‖**	NMA RR, 1.01 (0.92 to 1.11) ⊕⊕○‖**	NMA RR, 0.99 (0.85 to 1.16) ⊕⊕○‖**	NMA RR, 0.77 (0.62 to 0.95) ⊕⊕○‖**	NMA RR, 1.44 (1.16 to 1.78) ⊕⊕○‖**	GLP1 agonists not in network	*k* = 2; *n* = 1249 RR, 0.93 (0.60 to 1.45)‡ 4 fewer (25 fewer to 28 more) ⊕⊕○¶	*k* = 3; *n* = 2068 RR, 1.00 (0.47 to 2.14)‡ 0 fewer (7 fewer to 14 more) ⊕⊕○¶
GLP1 agonists vs. sulfonylurea	*k* = 3; *n* = 4281 RR, 0.67 (0.44 to 1.04)‡ 8 fewer (13 fewer to 10 more) ⊕⊕⊕	*k* = 1; *n* = 2498 RR, 0.81 (0.56 to 1.18)‡ 9 fewer (21 fewer to 9 more) ⊕⊕⊕	○○○††	○○○††	*k* = 1; *n* = 2498 RR, 0.47 (0.25 to 0.87)‡ 13 fewer (18 fewer to 3 fewer) ⊕⊕○¶	GLP1 agonists and sulfonylurea not in network	*k* = 2; *n* = 1765 RR, 1.08 (0.83 to 1.41)‡ 9 more (20 fewer to 48 more) ⊕⊕○¶	*k* = 3; *n* = 4281 RR, 0.49 (0.26 to 0.92)‡ 7 fewer (10 fewer to 1 fewer) ⊕⊕○¶
GLP1 agonists vs. tirzepatide	*k* = 1; *n* = 1878 RR, 0.25 (0.03 to 1.92)‡ 6 fewer (8 fewer to 8 more) ⊕○○¶¶	NMA RR, 1.08 (0.68 to 1.73) ⊕○○‖¶**	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	GLP1 agonists and tirzepatide not in network	*k* = 2; *n* = 2143 RR, 0.57 (0.34 to 0.96)‡ 24 fewer (37 fewer to 2 fewer) ⊕⊕○§	*k* = 2; *n* = 2143 RR, 0.50 (0.11 to 2.23)‡ 4 fewer (7 fewer to 9 more) ⊕○○‡‡

Continued on following page

Table–Continued

Comparison	Trials, *k*; Participants, *n* RR (95% CI) Absolute Risk Difference per 1000 Persons (95% CI)* Certainty of Evidence†							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD Stage 3 +**	**Serious Adverse Event**	**Severe Hypoglycemia**
SGLT2 inhibitors (head-to-head)								
SGLT2 inhibitors vs. DPP4 inhibitors	*k* = 5; *n* = 3878 RR, 0.91 (0.3 to 2.78)‡ 0 fewer (1 fewer to 4 more) ⊕○○‡‡	NMA RR, 0.88 (0.80 to 0.97) ⊕⊕○‖**	NMA RR, 1.02 (0.85 to 1.22) ⊕⊕○‖**	NMA RR, 1.15 (0.87 to 1.52) ⊕⊕○‖**	NMA RR, 0.60 (0.48 to 0.74) ⊕○○‖¶**	NMA RR, 0.62 (0.52 to 0.74) ⊕⊕○‖**	*k* = 5; *n* = 3878 RR, 1.01 (0.76 to 1.32)‡ 1 more (13 fewer to 17 more) ⊕⊕⊕	*k* = 4; *n* = 3105 RR, 1.42 (0.26 to 7.59)‡ 0 fewer (1 fewer to 6 more) ⊕○○‡‡
SGLT2 inhibitors vs. GLP1 agonists	NMA RR, 0.98 (0.89 to 1.08) ⊕⊕○‖**	NMA RR, 0.99 (0.90 to 1.09) ⊕⊕○‖**	NMA RR, 1.01 (0.86 to 1.18) ⊕⊕○‖**	NMA RR, 1.30 (1.05 to 1.61) ⊕⊕○‖**	NMA RR, 0.69 (0.56 to 0.86) ⊕⊕○‖**	GLP1 agonists not in network	*k* = 2; *n* = 1249 RR, 1.08 (0.83 to 1.41)‡ 5 more (10 fewer to 24 more) ⊕⊕○¶	*k* = 3; *n* = 2068 RR, 1.00 (0.47 to 2.14)‡ 0 fewer (7 fewer to 14 more) ⊕⊕○¶
SGLT2 inhibitors vs. basal insulin	NMA RR, 0.70 (0.51 to 0.98) ⊕○○‖¶**	NMA RR, 0.81 (0.61 to 1.09) ⊕○○‖¶**	Basal insulin not in network	Basal insulin not in network	NMA RR, 0.64 (0.39 to 1.04) ⊕○○‖¶**	Basal insulin not in network	NMA RR, 0.79 (0.67 to 0.94) ⊕○○§§‖**	NMA RR, 0.22 (0.15 to 0.32) ⊕○○§§‖**
SGLT2 inhibitors vs. sulfonylurea	*k* = 4; *n* = 5134 RR, 1.09 (0.55 to 2.20)‡ 1 more (3 fewer to 9 more) ⊕⊕○¶	*k* = 2; *n* = 2995 RR, 0.57 (0.36 to 0.91)‡ 14 fewer (21 fewer to 3 fewer) ⊕⊕⊕	○○○††	○○○††	*k* = 1; *n* = 625 RR, 0.33 (0.01 to 8.13)‡ 2 fewer (3 fewer to 23 more) ⊕○○‡‡	Sulfonylurea not in network	*k* = 5; *n* = 5560 RR, 0.99 (0.87 to 1.14)‡ 0 fewer (20 fewer to 21 more) ⊕⊕⊕	*k* = 5; *n* = 5744 RR, 0.10 (0.07 to 0.15)‡ 83 fewer (86 fewer to 79 fewer) ⊕⊕⊕‖‖
Remaining comparisons								
Sulfonylurea vs. tirzepatide	NMA RR, 1.14 (0.64 to 2.02) ○○○‖‡‡**	NMA RR, 1.30 (0.81 to 2.07) ○○○‖‡‡**	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	NMA RR, 1.03 (0.83 to 1.28) ⊕○○§§‖**	NMA RR, 6.72 (4.25 to 10.62) ○○○‖‡‡**
Tirzepatide vs. sulfonylurea	NMA RR, 0.88 (0.50 to 1.56) ○○○‖‡‡**	NMA RR, 0.77 (0.48 to 1.23) ○○○‖‡‡**	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	NMA RR, 0.97 (0.78 to 1.20) ⊕○○§§‖**	NMA RR, 0.15 (0.09 to 0.24) ○○○‖‡‡**
Basal insulin vs. tirzepatide	*k* = 2; *n* = 3432 RR, 1.35 (0.82 to 2.21)‡ 5 more (3 fewer to 17 more) ⊕⊕⊕	*k* = 1; *n* = 1995 RR, 1.31 (0.91 to 1.90)‡ 15 more (4 fewer to 43 more) ⊕⊕⊕	Basal insulin and tirzepatide not in network	Basal insulin and tirzepatide not in network	Tirzepatide not in network	Basal insulin and tirzepatide not in network	*k* = 2; *n* = 3432 RR, 1.26 (1.05 to 1.51) 27 more (5 more to 54 more) ⊕○○§¶	*k* = 1; *n* = 1437 RR, 4.86 (2.64 to 8.96)‡ 57 more (24 more to 118 more) ⊕⊕○¶
Tirzepatide vs. basal insulin	*k* = 2; *n* = 3432 RR, 0.74 (0.45 to 1.22)‡ 7 fewer (15 fewer to 6 more) ⊕⊕⊕	*k* = 1; *n* = 1995 RR, 0.76 (0.53 to 1.10)‡ 15 fewer (29 fewer to 6 more) ⊕⊕⊕	Basal insulin and tirzepatide not in network	Basal insulin and tirzepatide not in network	Tirzepatide not in network	Basal insulin and tirzepatide not in network	*k* = 2; *n* = 3432 RR, 0.80 (0.67 to 0.96) 32 fewer (52 fewer to 6 fewer) ⊕○○§¶	*k* = 1; *n* = 1437 RR, 0.21 (0.11 to 0.38)‡ 57 fewer (64 fewer to 45 fewer) ⊕⊕○¶
Basal insulin vs. SGLT2 inhibitors	NMA RR, 1.42 (1.02 to 1.98) ⊕○○‖¶**	NMA RR, 1.23 (0.92 to 1.65) ⊕○○‖¶**	Basal insulin not in network	Basal insulin not in network	NMA RR, 1.57 (0.96 to 2.58) ⊕○○‖¶**	Basal insulin not in network	NMA RR, 1.26 (1.06 to 1.50) ⊕○○§§‖**	NMA RR, 4.51 (3.13 to 6.49) ⊕○○§§‖**

Continued on following page

Table–Continued

Comparison	Trials, *k*; Participants, *n* RR (95% CI) Absolute Risk Difference per 1000 Persons (95% CI)* Certainty of Evidence†							
	All-Cause Mortality	**MACE**	**MI**	**Stroke**	**CHF Hospitalization**	**CKD Stage 3+**	**Serious Adverse Event**	**Severe Hypoglycemia**
Basal insulin vs. sulfonylurea	*k* = 1; *n* = 2517 RR, 0.97 (0.64 to 1.14)‡ 1 fewer (12 fewer to 16 more) ⊕⊕⊕	*k* = 1; *n* = 2504 RR, 1.09 (0.78 to 1.54)‡ 4 more (10 fewer to 26 more) ⊕⊕⊕	Basal insulin not in network	Basal insulin not in network	*k* = 1; *n* = 2504 RR, 0.86 (0.51 to 1.45)‡ 3 fewer (12 fewer to 11 more) ⊕⊕⊕	Basal insulin not in network	NMA RR, 1.18 (0.99 to 1.41) ⊕◯◯§§‖**	*k* = 1; *n* = 2517 RR, 0.57 (0.31 to 1.04)‡ 10 fewer (15 fewer to 1 more) ⊕⊕◯¶
SGLT2 inhibitors vs. tirzepatide	◯◯◯††	◯◯◯††	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	Tirzepatide not in network	NMA RR, 0.96 (0.78 to 1.19) ⊕◯◯§§‖**	NMA RR, 0.76 (0.50 to 1.17) ⊕◯◯‖¶**

CHF = congestive heart failure; CKD = chronic kidney disease; DPP4 = dipeptidyl peptidase-4; GLP1 = glucagon-like peptide-1; MACE = major adverse cardiovascular event; MI = myocardial infarction; NMA = network meta-analysis; RR = risk ratio; SGLT2 = sodium–glucose cotransporter-2.
* Based on RR; estimates from direct comparisons.
† GRADE (Grading of Recommendations Assessment, Development and Evaluation) certainty of evidence: ⊕⊕⊕ = high; ⊕⊕◯ = moderate; ⊕◯◯ = low; ◯◯◯ = insufficient.
‡ Estimate from direct comparison because it has a higher certainty of evidence than the network estimate.
§ Rated down for inconsistency.
‖ Rated down for indirectness.
¶ Rated down for imprecision.
** Comparison informed by indirect evidence only.
†† Class comparison informed only by indirect evidence; indirect network path length >2.
‡‡ Rated down twice for imprecision.
§§ Rated down for risk of bias.
|||| This outcome met the prespecified minimally important difference.
¶¶ Rated down twice for imprecision.

underwent full-text review, and 130 citations summarizing findings from 84 trials were eligible for inclusion. On average, studies were large (mean *n* = 2600), were multinational, and enrolled mostly middle-aged adults (mean age, 58.7 years) with long-standing and previously treated T2DM (mean T2DM duration, 8.8 years). Mean baseline weight was 89.7 kg, and mean HbA_{1c} level was 8.1%. Most participants had comorbidities, including hypertension, CVD, or a history of tobacco use. Ethnicity was infrequently reported. Mean follow-up was 90.2 weeks (median study duration, 68.5 weeks), with a range of 52 to 328.5 weeks. For KQ2, we identified a total of 2108 citations, of which 6 underwent full-text review. Three reviews were eligible for data extraction (**Appendix Figure 2**, available at Annals.org).

The lowest allowed HbA_{1c} level for inclusion was 6.5%, although none had a mean baseline HbA_{1c} level below 7%. Three trials required participants to have CKD, 4 required them to have existing CVD or acute coronary syndrome, 3 required them to have obesity or overweight, and 11 required them to be "at risk for cardiovascular disease," with varying definitions. Of the 26 trials that allowed for monotherapy only, 21 allowed only metformin monotherapy. The remaining trials allowed for monotherapy or combinations. Fifty-seven trials allowed for a combination of therapies, often only specifying a drug that participants could not be taking. Review of inclusion criteria shows that trials were not completely jointly randomizable. However, the majority included a wide spectrum of prior treatment and thus the subnetwork of these trials was jointly randomizable, with exceptions having overlap with the broader trial population (**Table 4** of **Supplement 2**). In addition, there was no statistical heterogeneity, so combining of trials did not lead to statistical incoherence.

Mortality and Vascular Outcomes

All-Cause Mortality

Sixty (13–72) trials reported all-cause mortality and were included in the NMA. SGLT2 inhibitors (RR, 0.86 [95% CI, 0.80 to 0.93]; high CoE) and GLP1 agonists (RR, 0.88 [CI, 0.83 to 0.94]; high CoE) reduce all-cause mortality compared with usual care. Absolute effects did not reach the MID of 2 percentage points. In contrast, DPP4 inhibitors (RR, 1.01 [CI, 0.94 to 1.08]; high CoE), tirzepatide (RR, 0.98 [CI, 0.56 to 1.73]; low CoE), and insulin (RR, 1.23 [CI, 0.89 to 1.70]; low CoE) do not differ from usual care.

SGLT2 inhibitors may reduce all-cause mortality compared with insulin (RR, 0.70 [CI, 0.51 to 0.98]; low CoE), and GLP1 agonists probably reduce all-cause mortality compared with insulin (RR, 0.62 [CI, 0.41 to 0.93]; moderate CoE) and DPP4 inhibitors (RR, 0.61 [CI, 0.39 to 0.95]; moderate CoE). All other comparisons were not statistically significant or had insufficient CoE (**Tables 2** and **11** of **Supplement 1**; **Figure 1** of **Supplement 2**).

Major Adverse Cardiovascular Events

Twenty-one trials (13, 14, 19–22, 24, 32–36, 38, 51, 54, 60, 63, 68, 73–75) reported MACE and were included in the NMA. Compared with usual care, SGLT2 inhibitors (RR, 0.90 [CI, 0.83 to 0.98]; moderate CoE) and GLP1 agonists (RR, 0.91 [CI, 0.87 to 0.96]; high CoE) reduce MACE. The absolute effect did not reach the MID of 5 percentage points. DPP4 inhibitors (RR, 1.0 [CI, 0.94 to 1.06]; high CoE) and insulin (RR, 1.10 [CI, 0.83 to 1.46]; low CoE) do not reduce MACE compared with usual care. Evidence is insufficient for tirzepatide.

SGLT2 inhibitors reduce MACE compared with SU (RR, 0.57 [CI, 0.36 to 0.91]; high CoE) and probably reduce MACE compared with DPP4 inhibitors (RR, 0.88 [CI, 0.80 to 0.97]; moderate CoE). All other comparisons were not statistically significant or had insufficient evidence (Tables 3 and 12 of Supplement 1; Figure 2 of Supplement 2).

Myocardial Infarction

Ten studies (20, 21, 24, 32–34, 36, 38, 54, 60) reported on fatal and nonfatal MI and were included in the NMA. SGLT2 inhibitors (RR, 0.97 [CI, 0.85 to 1.12]; high CoE), GLP1 agonists (RR, 0.96 [CI, 0.89 to 1.04]; high CoE), and DPP4 inhibitors (RR, 0.95 [CI, 0.85 to 1.06]; high CoE) do not reduce MI compared with usual care. Evidence is insufficient for tirzepatide and insulin.

All head-to-head comparisons were not statistically significant or had insufficient evidence (Tables 4 and 13 of Supplement 1; Figure 3 of Supplement 2).

Stroke

Nine studies (21, 24, 32–34, 36, 38, 54, 60) reported on fatal and nonfatal stroke and were included in the NMA. GLP1 agonists reduce stroke (RR, 0.86 [CI, 0.77 to 0.95]; high CoE) compared with usual care. The absolute effect did not reach the MID of 5 percentage points. SGLT2 inhibitors (RR, 1.12 [CI, 0.93 to 1.34]; high CoE) and DPP4 inhibitors (RR, 0.97 [CI, 0.79 to 1.19]; high CoE) do not differ from usual care for stroke. Evidence is insufficient for tirzepatide and insulin.

GLP1 agonists probably reduce stroke compared with SGLT2 inhibitors (RR, 0.77 [CI, 0.62 to 0.95]; moderate CoE). All other comparisons were not statistically significant or had insufficient evidence (Tables 5 and 14 of Supplement 1; Figure 4 of Supplement 2).

CHF Hospitalizations

Twelve trials (13, 20, 21, 24, 32, 34, 36, 38, 51, 54, 74, 76) reported hospitalization due to CHF and were included in the NMA. SGLT2 inhibitors reduce CHF hospitalizations compared with usual care (RR, 0.64 [CI, 0.54 to 0.77]; high CoE), although the absolute effect did not reach the MID of 5 percentage points. GLP1 agonists (RR, 0.95 [CI, 0.85 to 1.06]; high CoE), DPP4 inhibitors (RR, 1.06 [CI, 0.96 to 1.17]; high CoE), and insulin (RR, 1.01 [CI, 0.64 to 1.60]; low CoE) do not differ from usual care for CHF hospitalizations. Evidence is insufficient for tirzepatide.

GLP1 agonists probably reduce CHF hospitalizations compared with DPP4 inhibitors (RR, 0.47 [CI, 0.25 to 0.88]; moderate CoE) and SU (RR, 0.47 [CI, 0.25 to 0.87]; moderate CoE). SGLT2 inhibitors probably reduce CHF hospitalizations compared with GLP1 agonists (RR, 0.69 [CI, 0.56 to 0.86]; moderate CoE) and may reduce CHF hospitalizations compared with DPP4 inhibitors (RR, 0.60 [CI, 0.48 to 0.74]; low CoE). All other comparisons were not statistically significant or had insufficient evidence (Tables 6 and 15 of Supplement 1; Figure 5 of Supplement 2).

Chronic Kidney Disease

Six trials (13, 20, 51–53, 60) included change in CKD from baseline and were included in the NMA. SGLT2 inhibitors reduce progression to CKD stage 3+ compared with usual care (RR, 0.66 [CI, 0.58 to 0.75]; high CoE). The absolute effect did not reach the MID of 5 percentage points. DPP4 inhibitors do not differ from usual care (RR, 1.07 [CI, 0.95 to 1.21]; high CoE). Evidence is insufficient for GLP1 agonists, tirzepatide, and insulin.

SGLT2 inhibitors probably reduce progression to CKD stage 3+ compared with DPP4 inhibitors (RR, 0.62 [CI, 0.52 to 0.74]; moderate CoE). All other comparisons were not statistically significant or had insufficient evidence (Tables 7 and 16 of Supplement 1; Figure 6 of Supplement 2).

Serious Adverse Events

Sixty-seven trials (13, 15–19, 21–27, 30–34, 36, 37, 39–73, 77–89) reported on serious adverse events and were included in the NMA. Compared with usual care, SGLT2 inhibitors reduce serious adverse events (RR, 0.93 [CI, 0.90 to 0.95]; high CoE), although the effect did not reach the MID of 5 percentage points. GLP1 agonists (RR, 0.98 [CI, 0.95 to 1.01]; high CoE), DPP4 inhibitors (RR, 0.96 [CI, 0.92 to 1.01]; high CoE), tirzepatide (RR, 0.79 [CI, 0.51 to 1.22]; high CoE), and insulin (RR, 1.17 [CI, 0.99 to 1.39]; moderate CoE) do not differ from usual care.

DPP4 inhibitors may reduce serious adverse events compared with insulin (RR, 0.82 [CI, 0.68 to 0.97]; low CoE) and probably reduce serious adverse events compared with SU (RR, 0.94 [CI, 0.91 to 0.99]; moderate CoE). GLP1 agonists probably reduce serious adverse events compared with tirzepatide (RR, 0.57 [CI, 0.34 to 0.96]; moderate CoE). SGLT2 inhibitors (RR, 0.79 [CI, 0.67 to 0.94]; low CoE) and tirzepatide (RR, 0.80 [CI, 0.67 to 0.96]; low CoE) may reduce serious adverse events compared with insulin. All other comparisons were nonsignificant or had insufficient evidence (Tables 8 and 17 of Supplement 1; Figure 7 of Supplement 2).

Severe Hypoglycemia

Fifty trials (13, 14, 17–25, 27, 28, 30, 32–34, 36–44, 47, 48, 50, 52–55, 59, 60, 64, 65, 67, 69, 70, 72, 73, 79, 80, 85, 89–93) reported on severe hypoglycemia and were included in the NMA. Compared with usual care, SGLT2 inhibitors reduce severe hypoglycemia

(RR, 0.85 [CI, 0.74 to 0.97]; high CoE), although the effect did not reach the MID of 5 percentage points. GLP1 agonists (RR, 1.02 [CI, 0.92 to 1.15]; moderate CoE), DPP4 inhibitors (RR, 1.14 [CI, 1.00 to 1.30]; high CoE), and tirzepatide (RR, 1.32 [CI, 0.78 to 2.22]; moderate CoE) do not differ from usual care for severe hypoglycemia. Evidence is insufficient for insulin.

DPP4 inhibitors reduce severe hypoglycemia compared with SU (RR, 0.14 [CI, 0.11 to 0.19]; high CoE). GLP1 agonists probably reduce severe hypoglycemia compared with insulin (RR, 0.23 [CI, 0.16 to 0.33]; moderate CoE) and SU (RR, 0.49 [CI, 0.26 to 0.92]; moderate CoE). SGLT2 inhibitors reduce severe hypoglycemia compared with SU (RR, 0.10 [CI, 0.07 to 0.15]; high CoE) and may reduce severe hypoglycemia compared with insulin (RR, 0.22 [CI, 0.15 to 0.32]; low CoE). Tirzepatide probably reduces severe hypoglycemia compared with insulin (RR, 0.21 [CI, 0.11 to 0.38]; moderate CoE). Only SGLT2 inhibitors compared with SU and tirzepatide compared with insulin had effects that reached the MID of 5 percentage points. All other comparisons were nonsignificant or had insufficient evidence (**Tables 9** and **18** of **Supplement 1**; **Figure 8** of **Supplement 2**).

See **Appendix B** of **Supplement 1** for additional class- and drug-specific harms (>5% adverse events), warnings and precautions, and contraindications from the FDA website to summarize overall harms.

Weight Loss

Reporting of change in body weight varied. Weight change as the percentage of participants who achieved at least a 10% reduction from baseline was reported in only 6 trials (70, 81, 82, 89, 94, 95), so we were unable to perform an NMA on this outcome. Thirty-seven trials (17, 18, 23, 26, 27, 29–31, 37, 38, 43, 45, 47, 48, 56–59, 61, 67–71, 73, 76, 79, 84, 85, 89, 90, 96–101) included the mean change in body weight from baseline. All were assessed as having low RoB or some concerns.

The 6 trials that reported the percentage of participants who achieved a 10% weight reduction (our predefined outcome of interest) included the following treatments: tirzepatide (3% to 67% of participants achieved a 10% weight reduction), liraglutide (15.9% to 25.2% achieved a 10% reduction), semaglutide (21% achieved a 10% reduction), dulaglutide (1.7% to 10% achieved a 10% reduction), usual care (6.7% achieved a 10% reduction), exenatide extended-release (4% achieved a 10% reduction), glargine (0% achieved a 10% reduction), and placebo (0% achieved a 10% reduction) (70, 81, 82, 89, 94, 95). The ranges include combining of trials and different treatment doses used within a trial.

The NMA found that, compared with usual care, GLP1 agonists (MD, −2.22 kg [CI, −2.86 to −1.58 kg]), SGLT2 inhibitors (MD, −2.48 kg [CI, −3.03 to −1.92 kg]), and tirzepatide (MD, −8.47 kg [CI, −9.49 to −7.45 kg]) resulted in a mean reduction in weight over the study period. DPP4 inhibitors resulted in no weight change (MD, 0.00 kg [CI, -0.61 to 0.61 kg]) over the study period, and insulin (MD, 2.90 kg [CI, 1.76 to 4.04 kg]) resulted in a mean increase in weight (**Table 10** of **Supplement 1**; **Figure 9** of **Supplement 2**).

Glycemic Control

Forty-nine trials (16, 17, 19, 22, 23, 25–27, 29–31, 37–40, 44, 45, 47, 49, 56–59, 61, 67–70, 73, 76, 79, 81, 82, 84–87, 89, 90, 92, 94, 96–103) reported change in HbA_{1c} level from baseline. Forty-eight trials were assessed as having either low RoB or some concerns, and 1 trial was assessed as having high RoB. The NMA for glycemic control had substantial heterogeneity and incoherence due to study design. Most trials allowed for postrandomization treatment with add-on medication in response to HbA_{1c} level. Given these factors, we are unable to accurately report glycemic control by drug class.

Treatment Effects According to Participant Characteristics

We required subgroup analysis to be prespecified by the investigators and planned with stratified randomization. Outcomes were rarely reported by participant characteristics, and evidence was insufficient for analysis of the predefined subgroups of interest.

Patient Values and Preferences

All 3 of the eligible reviews (104–106) (**Appendix Figure 2**) identified glycemic control, weight loss, frequency of use, hypoglycemic episodes, and gastrointestinal events as attributes patients consider when choosing medications. The review by González-González and colleagues (104) was the only one to assess the overall CoE; they reported very low CoE for GLP1 agonists and no evidence for SGLT2 inhibitors, resulting in a finding of insufficient CoE. Weekly GLP1 agonists were preferred to once-daily or twice-daily GLP1 agonists. The other 2 reviews reported low RoB in the included studies and identified glycemic control, weight loss, frequency of use, hypoglycemic episodes, and gastrointestinal events as attributes patients consider when choosing medications (105, 106). However, the reviews by Purnell and González-González and their respective colleagues (104, 106) both expressed concern about the number of industry-funded trials (**Appendix G** of **Supplement 1**).

DISCUSSION

SGLT2 inhibitors and GLP1 agonists reduce overall mortality compared with usual care and insulin in middle- aged, previously treated adults with T2DM. GLP1 agonists also reduce mortality compared with DPP4 inhibitors. SGLT2 inhibitors and GLP1 agonists reduce MACE compared with usual care, but neither drug reduces MI. Compared with usual care, GLP1 agonists but not SGLT2 inhibitors reduce stroke, and SGLT2 inhibitors reduce progression to CKD stage 3+, CHF hospitalizations, and severe hypoglycemia. Compared with each other, SGLT2 inhibitors reduce CHF hospitalizations and GLP1 agonists reduce stroke. DPP4 inhibitors and insulin did not reduce most outcomes of

interest, and evidence was mostly insufficient for tirzepatide. SGLT2 inhibitors and GLP1 agonists tended to cause fewer serious adverse effects and severe hypoglycemic events than DPP4 inhibitors, SU, and insulin.

Our review focused on large longer-term studies of clinical outcomes rather than intermediate or surrogate measures. Nevertheless, no study lasted longer than 5 years, and most assessed relative reductions in composite outcomes over short follow-up (mean duration <2 years). In contrast to older drugs such as SU or metformin in "treat-to-target" studies, reductions in mortality and MACE with SGLT2 inhibitors and GLP1 agonists occurred in a fairly short time. Relative effects were between 10% and 15% (except for SGLT2 inhibitors on CHF hospitalizations), and absolute risk reductions were about 1 percentage point and did not reach predefined MIDs. Subgroup data are limited and did not permit specific conclusions (**Tables 2** to **4** of **Supplement 2**).

Few studies enrolled treatment-naive patients or made a direct comparison with a nontreated control group. The majority involved metformin-based background therapy, but most did not require metformin and often allowed for various other baseline medications (**Table 4** of **Supplement 2**). These medications were often not reported, which is why we chose to combine placebo and metformin-based background therapy into a single treatment category defined as "usual care." Therefore, our review does not provide direct evidence on these newer drugs as first-line therapy in treatment-naive or newly diagnosed patients. Furthermore, although studies permitted enrollment of participants with an HbA_{1c} level as low as 6.5%, most enrolled participants had moderate glycemic control, with a baseline HbA_{1c} level of 8.1%. No study had a mean baseline HbA_{1c} level below 7%. Studies were not designed to reach a prespecified HbA_{1c} goal. All studies permitted enrollment of patients with existing CVD or CKD or those at high risk for CVD. However, as described in the Results section and in **Table 4** of **Supplement 2**, only a minority required patients to have these comorbidities for enrollment. Although we did not identify statistical heterogeneity across study comparisons, differences in usual care and in baseline characteristics of patients may be limitations in our decision to conduct an NMA.

The effect on weight and glycemic control was limited by study design and data reporting. Reporting of weight change varied, with most studies reporting the mean weight change rather than our outcome of interest (10% reduction). The NMA found that GLP1 agonists, SGLT2 inhibitors, and tirzepatide resulted in a mean weight reduction compared with usual care. In contrast, DPP4 inhibitors resulted in no weight change, and insulin and SU resulted in a mean increase in weight.

Only 2 studies specifically precluded use of nonstudy antidiabetic medications based on HbA_{1c} levels. Thus, the independent effect of these newer drugs on HbA_{1c} levels cannot be adequately assessed. However, the relatively small differences in HbA_{1c} level observed in these trials combined with multiple previous RCTs showing that intensive glycemic control with older drugs (target HbA_{1c} level <7%) did not improve key clinical outcomes suggests that the clinical effects of newer drugs are not mediated solely through glycemic effects (107). Older reviews of these diabetes medication classes have evaluated glycemic control effects and thus serve as a better data source for independent short-term drug effects on glucose level.

Our review strengthens findings from prior reviews. An NMA by Tsapas and colleagues (108) found favorable cardiovascular outcome effects for GLP1 agonists and SGLT2 inhibitors among patients with high preexisting cardiovascular risk but not among those with low cardiovascular risk. Subgroup data in our review were inadequate to draw conclusions about effects of the medications in preexisting cardiovascular risk groups or by age, sex, ethnicity, or kidney disease but did show a reduction in MACE and mortality with GLP1 agonists and SGLT2 inhibitors regardless of baseline CVD status.

Similar to the current findings, an NMA by Palmer and colleagues (109) found benefits for all-cause mortality, cardiovascular outcomes, and renal outcomes with GLP1 agonists and SGLT2 inhibitors when added to usual care and reductions in stroke with GLP1 agonists and CHF outcomes with SGLT2 inhibitors. Duan and colleagues (110) also reported an NMA that found cardiovascular benefit from GLP1 agonists and SGLT2 inhibitors. These previous meta-analyses included variable drug add-on comparators, sometimes including insulin and DPP4 inhibitors but not the range of comparators in the current report. Studies and drugs not evaluated in prior reviews, such as the GLP1/GIP agonist tirzepatide and the SGLT2 inhibitor bexagliflozin, were evaluated in the present report. We included the GRADE (Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness) trial, the only trial to directly assess clinical effectiveness and harms of 4 major, widely used classes of drugs: SU, insulin, GLP1 agonists, and DPP4 inhibitors (28, 74). Unfortunately, SGLT2 inhibitors were not evaluated in the GRADE trial.

SGLT2 inhibitors and GLP1 agonists consistently reduce severe hypoglycemia compared with either usual care or other medication classes, such as SU and insulin. This is consistent with previous reports and the mechanism of action of each medication class in that metformin, SGLT2 inhibitors, and GLP1 agonists do not independently cause hypoglycemia (108). For example, with the reduction in severe hypoglycemia with SGLT2 inhibitors compared with usual care, the hypoglycemia was likely caused by medications such as SU and insulin. We found that SGLT2 inhibitors reduce serious adverse events compared with usual care, whereas insulin increases serious adverse events compared with usual care. Serious adverse events were defined by authors, varied, and were not always fully reported. In general, they included events considered to be fatal or life-threatening. The reduction in serious adverse events seen with SGLT2 inhibitors compared with usual care is

likely due to study authors' definitions of serious adverse events, which could include death or MACE.

We evaluated antidiabetic medications as a class and not by individual drug. Although most of the benefits of antidiabetic medications are believed to be a class effect, it is worth noting that GLP1 agonists are a highly heterogeneous class of medications. The class includes older and less potent medications, such as exenatide; more potent daily injection medications, such as liraglutide; even more potent weekly injections, such as semaglutide; and less potent oral GLP1 agonists. Each medication has a range of doses, and outcomes, including glycemic control and weight loss, are dose-dependent. Our study does not report on outcomes with individual GLP1 agonists, but these factors should be considered when choosing a medication within this class.

Only 1 eligible study with insufficient data evaluated combination use of GLP1 agonists and SGLT2 inhibitors (83). Therefore, we are unable to comment on the evidence behind the use of this combination therapy. We are also unable to comment on medication dosing, specific medications within a class, or the route of administration (for example, oral compared with injectable GLP1 agonist) given our study design. Finally, we are unable to provide evidence on the order of use of medications (first-line, second-line) due to the lack of placebo-controlled studies of treatment-naive patients and our definition of background usual care.

We performed a bridge search from 1 January 2023 through 13 January 2024, which identified a total of 1311 references in the databases. Only 3 were likely to be eligible (111–113) (**Appendix H** of **Supplement 1**). One of these trials compared oral semaglutide with varying doses of oral semaglutide and therefore would not have contributed to our analysis (113). In the remaining 2 trials, Cherney and colleagues (112) compared sotagliflozin with placebo and found no evidence of difference in renal outcomes at 52 weeks, and Wexler and colleagues (111) compared liraglutide, sitagliptin, insulin glargine, and glimepiride, all added to metformin, and found no evidence of difference in renal outcomes. Overall, these findings are consistent with and would not change our findings.

We found limited evidence from existing systematic reviews on patient values and preferences. Three reviews met our criteria and qualitatively summarized their findings. A common theme across these 3 reviews was the recommendation to provide materials summarizing both benefits and harms of the antidiabetic medications for physician use with patients. All 3 reviews identified glycemic control, weight loss, frequency of use, hypoglycemic episodes, and gastrointestinal events as attributes patients consider when deliberating about medications. Although these overlap with our outcomes, which are prioritized by ACP public panel members and ACP CGC members, there are key differences: Mortality, CVD prevention, and CKD prevention were not identified in these reviews as key patient preferences and values.

Limitations include infrequent comparisons between drugs of interest and sparse data for NMA for most outcomes. Incoherence may be present due to differences in usual care and baseline patient characteristics among trials. Trial design did not allow for valid assessment of differences in glycemic control. There were insufficient data on predefined subgroups of interest, including demographic subgroups, patients with prior CVD, or treatment-naive persons.

In conclusion, in adults with T2DM, SGLT2 inhibitors and GLP1 agonists (but not DPP4 inhibitors, insulin, or tirzepatide) reduce all-cause mortality and MACE compared with usual care. SGLT2 inhibitors reduce CKD progression, CHF hospitalization, and severe hypoglycemia, and GLP1 agonists reduce stroke. Serious adverse events and severe hypoglycemia seem to be less frequent with SGLT2 inhibitors and GLP1 agonists compared with insulin or SU.

From Department of Medicine, VA Health Care System, and Department of Medicine, University of Minnesota, Minneapolis, Minnesota (T.D., C.J.B., A.K.); Center for Care Delivery & Outcomes Research, VA Health Care System, Minneapolis, Minnesota (A.L., R.M., M.A., C.K., K.U.); Department of Medicine, University of Minnesota; Center for Care Delivery & Outcomes Research, VA Health Care System; and Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota (L.L.); Department of Medicine, University of Minnesota, and Center for Care Delivery & Outcomes Research, VA Health Care System, Minneapolis, Minnesota (S.S.); and Department of Medicine, VA Health Care System; Department of Medicine, University of Minnesota; Center for Care Delivery & Outcomes Research, VA Health Care System; and Division of Health Policy & Management, School of Public Health, University of Minnesota, Minneapolis, Minnesota (T.J.W.).

Disclaimer: This article is the result of work supported by resources and use of facilities of the Minneapolis VA Health Care System. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the U.S. Department of Veterans Affairs or the U.S. government.

Acknowledgment: The authors thank Mr. Kyle Moen for technical and administrative assistance and members of their Topic Expert Panel (Daniel Bessesen, MD; Chester B. Good, MD, MPH; Angela M. Leung, MD, MSc; and Sandeep Vijan, MD, MS) for their input on the study protocol, feedback on interim conference calls, and review of earlier drafts of this manuscript.

Financial Support: By the American College of Physicians.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M23-1490.

Reproducible Research Statement: *Study protocol:* Available at www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=322129. *Statistical code and data set:* Interested individuals or organizations should contact the American College of Physicians (e-mail, clinicalpolicy@acponline.org).

Corresponding Author: Timothy J. Wilt, MD, MPH, Department of Medicine, VA Health Care System, One Veterans Drive (111-0), Minneapolis, MN 55417; e-mail, tim.wilt@va.gov.

Author contributions are available at Annals.org.

References

1. **Qaseem A, Wilt TJ, Kansagara D, et al; Clinical Guidelines Committee of the American College of Physicians.** Hemoglobin A_{1c} targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. Ann Intern Med. 2018;168:569-576. [PMID: 29507945] doi:10.7326/M17-0939

2. **American Diabetes Association Professional Practice Committee.** 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes–2022*. Diabetes Care. 2022;45:S125-S143. [PMID: 34964831] doi:10.2337/dc22-S009

3. **Qaseem A, Barry MJ, Humphrey LL, et al; Clinical Guidelines Committee of the American College of Physicians.** Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. Ann Intern Med. 2017;166:279-290. [PMID: 28055075] doi:10.7326/M16-1860

4. **Sterne JAC, Savović J, Page MJ, et al.** RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. [PMID: 31462531] doi:10.1136/bmj.l4898

5. **Gerta R.** Network meta-analysis, electrical networks and graph theory. Research Synthesis Methods. 2012;3:312-324. [PMID: 26053424] doi:10.1002/jrsm.1058

6. **Rücker G, Krahn U, König J, et al.** Package 'netmeta'. 11 January 2024. Accessed at https://cran.r-project.org/web/packages/netmeta/netmeta.pdf on 4 March 2024.

7. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime; 2015.

8. **Higgins JPT, Thomas J, Chandler J, et al, eds.** Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. J Wiley; 2019.

9. **Schünemann H, Brożek J, Guyatt G, et al, eds.** GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. The GRADE Working Group; Updated October 2013.

10. **Brignardello-Petersen R, Mustafa RA, Siemieniuk RAC, et al; GRADE Working Group.** GRADE approach to rate the certainty from a network meta-analysis: addressing incoherence. J Clin Epidemiol. 2019;108:77-85. [PMID: 30529648] doi:10.1016/j.jclinepi.2018.11.025

11. **Brignardello-Petersen R, Bonner A, Alexander PE, et al; GRADE Working Group.** Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol. 2018;93:36-44. [PMID: 29051107] doi:10.1016/j.jclinepi.2017.10.005

12. **Brignardello-Petersen R, Murad MH, Walter SD, et al; GRADE Working Group.** GRADE approach to rate the certainty from a network meta-analysis: avoiding spurious judgments of imprecision in sparse networks. J Clin Epidemiol. 2019;105:60-67. [PMID: 30253217] doi:10.1016/j.jclinepi.2018.08.022

13. **Rosenstock J, Perkovic V, Johansen OE, et al; CARMELINA Investigators.** Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA. 2019;321:69-79. [PMID: 30418475] doi:10.1001/jama.2018.18269

14. **White WB, Cannon CP, Heller SR, et al; EXAMINE Investigators.** Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369:1327-1335. [PMID: 23992602] doi:10.1056/NEJMoa1305889

15. **Williams-Herman D, Johnson J, Teng R, et al.** Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes Obes Metab. 2010;12:442-451. [PMID: 20415693] doi:10.1111/j.1463-1326.2010.01204.x

16. **Hollander PL, Li J, Frederich R, et al; CV181013 Investigators.** Safety and efficacy of saxagliptin added to thiazolidinedione over 76 weeks in patients with type 2 diabetes mellitus. Diab Vasc Dis Res. 2011;8:125-135. [PMID: 21562064] doi:10.1177/1479164111404575

17. **Chacra AR, Tan GH, Ravichandran S, et al; CV181040 Investigators.** Safety and efficacy of saxagliptin in combination with submaximal sulphonylurea versus up-titrated sulphonylurea over 76 weeks. Diab Vasc Dis Res. 2011;8:150-159. [PMID: 21562067] doi:10.1177/1479164111404574

18. **Bosi E, Ellis GC, Wilson CA, et al.** Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. Diabetes Obes Metab. 2011;13:1088-1096. [PMID: 21733058] doi:10.1111/j.1463-1326.2011.01463.x

19. **Yki-Järvinen H, Rosenstock J, Durán-Garcia S, et al.** Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a ≥52-week randomized, double-blind study. Diabetes Care. 2013;36:3875-3881. [PMID: 24062327] doi:10.2337/dc12-2718

20. **Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators.** Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317-1326. [PMID: 23992601] doi:10.1056/NEJMoa1307684

21. **Green JB, Bethel MA, Armstrong PW, et al; TECOS Study Group.** Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373:232-242. [PMID: 26052984] doi:10.1056/NEJMoa1501352

22. **Del Prato S, Camisasca R, Wilson C, et al.** Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. Diabetes Obes Metab. 2014;16:1239-1246. [PMID: 25132212] doi:10.1111/dom.12377

23. **Schernthaner G, Durán-Garcia S, Hanefeld M, et al.** Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). Diabetes Obes Metab. 2015;17:630-638. [PMID: 25761977] doi:10.1111/dom.12461

24. **Rosenstock J, Kahn SE, Johansen OE, et al; CAROLINA Investigators.** Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA. 2019;322:1155-1166. [PMID: 31536101] doi:10.1001/jama.2019.13772

25. **Filozof C, Gautier JF.** A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. Diabet Med. 2010;27:318-326. [PMID: 20536495] doi:10.1111/j.1464-5491.2010.02938.x

26. **Pérez-Monteverde A, Seck T, Xu L, et al.** Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin vs. pioglitazone in drug-naïve patients with type 2 diabetes. Int J Clin Pract. 2010;65:930-938. [PMID: 21849007] doi:10.1111/j.1742-1241.2011.02749.x

27. **Ferrannini E, Fonseca V, Zinman B, et al.** Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2009;11:157-166. [PMID: 19125777] doi:10.1111/j.1463-1326.2008.00994.x

28. **Nathan DM, Lachin JM, Balasubramanyam A, et al; GRADE Study Research Group.** Glycemia reduction in type 2 diabetes - glycemic outcomes. N Engl J Med. 2022;387:1063-1074. [PMID: 36129996] doi:10.1056/NEJMoa2200433

29. **Nauck M, Weinstock RS, Umpierrez GE, et al.** Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care. 2014;37:2149-2158. [PMID: 24742660] doi:10.2337/dc13-2761

30. **Pratley R, Nauck M, Bailey T, et al; 1860-LIRA-DPP-4 Study Group.** One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. Int J Clin Pract. 2011;65:397-407. [PMID: 21355967] doi:10.1111/j.1742-1241.2011.02656.x

31. **Pieber TR, Bode B, Mertens A, et al; PIONEER 7 investigators.** Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre,

open-label, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7:528-539. [PMID: 31189520]
32. **Holman RR, Bethel MA, Mentz RJ, et al; EXSCEL Study Group.** Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377:1228-1239. [PMID: 28910237] doi:10.1056/NEJMoa1612917
33. **Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Trial Investigators.** Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311-322. [PMID: 27295427] doi:10.1056/NEJMoa1603827
34. **Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators.** Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373:2247-2257. [PMID: 26630143] doi:10.1056/NEJMoa1509225
35. **Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators.** Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834-1844. [PMID: 27633186] doi:10.1056/NEJMoa1607141
36. **Husain M, Birkenfeld AL, Donsmark M, et al; PIONEER 6 Investigators.** Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381:841-851. [PMID: 31185157] doi:10.1056/NEJMoa1901118
37. **Zinman B, Aroda VR, Buse JB, et al; PIONEER 8 Investigators.** Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes: the PIONEER 8 trial. Diabetes Care. 2019;42:2262-2271. [PMID: 31530667] doi:10.2337/dc19-0898
38. **Gerstein HC, Colhoun HM, Dagenais GR, et al; REWIND Investigators.** Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394:121-130. [PMID: 31189511] doi:10.1016/S0140-6736(19)31149-3
39. **Davies M, Færch L, Jeppesen OK, et al; STEP 2 Study Group.** Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397:971-984. [PMID: 33667417] doi:10.1016/S0140-6736(21)00213-0
40. **Gallwitz B, Guzman J, Dotta F, et al.** Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. Lancet. 2012;379:2270-2278. [PMID: 22683137] doi:10.1016/S0140-6736(12)60479-6
41. **Garber A, Henry RR, Ratner R, et al; LEAD-3 (Mono) Study Group.** Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab. 2011;13:348-356. [PMID: 21205128] doi:10.1111/j.1463-1326.2010.01356.x
42. **Blonde L, Jendle J, Gross J, et al.** Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. Lancet. 2015;385:2057-2066. [PMID: 26009229] doi:10.1016/S0140-6736(15)60936-9
43. **Tuttle KR, Lakshmanan MC, Rayner B, et al.** Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol. 2018;6:605-617. [PMID: 29910024] doi:10.1016/S2213-8587(18)30104-9
44. **Giorgino F, Benroubi M, Sun J-H, et al.** Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). Diabetes Care. 2015;38:2241-2249. [PMID: 26089386] doi:10.2337/dc14-1625
45. **Roden M, Merker L, Christiansen AV, et al; EMPA-REG EXTEND™ MONO investigators.** Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naïve patients with type 2 diabetes: a double-blind extension of a phase III randomized controlled trial. Cardiovasc Diabetol. 2015;14:154. [PMID: 26701110] doi:10.1186/s12933-015-0314-0
46. **DeFronzo RA, Lewin A, Patel S, et al.** Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015;38:384-393. [PMID: 25583754] doi:10.2337/dc14-2364
47. **Pratley RE, Eldor R, Raji A, et al.** Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial. Diabetes Obes Metab. 2018;20:1111-1120. [PMID: 29266675] doi:10.1111/dom.13194
48. **Lavalle-González FJ, Januszewicz A, Davidson J, et al.** Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia. 2013;56:2582-2592. [PMID: 24026211] doi:10.1007/s00125-013-3039-1
49. **Schernthaner G, Gross JL, Rosenstock J, et al.** Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes Care. 2013;36:2508-2515. [PMID: 23564919] doi:10.2337/dc12-2491
50. **Neal B, Perkovic V, De Zeeuw D, et al; CANVAS Trial Collaborative Group.** Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care. 2015;38:403-411. [PMID: 25468945] doi:10.2337/dc14-1237
51. **Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators.** Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295-2306. [PMID: 30990260] doi:10.1056/NEJMoa1811744
52. **Wheeler DC, Stefánsson BV, Jongs N, et al; DAPA-CKD Trial Committees and Investigators.** Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021;9:22-31. [PMID: 33338413] doi:10.1016/S2213-8587(20)30369-7
53. **Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators.** Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347-357. [PMID: 30415602] doi:10.1056/NEJMoa1812389
54. **Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators.** Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-2128. [PMID: 26378978] doi:10.1056/NEJMoa1504720
55. **Häring HU, Merker L, Roux F, et al.** Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes. Diabetologie und Stoffwechsel. 2015;10:P45. doi:10.1055/s-0035-1549551
56. **Bailey CJ, Gross JL, Hennicken D, et al.** Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013;11:43. [PMID: 23425012] doi:10.1186/1741-7015-11-43
57. **Cefalu WT, Leiter LA, de Bruin TWA, et al.** Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Diabetes Care. 2015;38:1218-1227. [PMID: 25852208] doi:10.2337/dc14-0315
58. **Leiter LA, Cefalu WT, de Bruin TWA, et al.** Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc. 2014;62:1252-1262. [PMID: 24890683] doi:10.1111/jgs.12881
59. **Rosenstock J, Jelaska A, Frappin G, et al; EMPA-REG MDI Trial Investigators.** Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care. 2014;37:1815-1823. [PMID: 24929430] doi:10.2337/dc13-3055
60. **Cannon CP, Pratley R, Dagogo-Jack S, et al; VERTIS CV Investigators.** Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med. 2020;383:1425-1435. [PMID: 32966714] doi:10.1056/NEJMoa2004967
61. **Gallo S, Charbonnel B, Goldman A, et al.** Long-term efficacy and safety of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: 104-week

VERTIS MET trial. Diabetes Obes Metab. 2019;21:1027-1036. [PMID: 30614616] doi:10.1111/dom.13631
62. **Bode B, Stenlöf K, Harris S, et al.** Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55–80 years with type 2 diabetes. Diabetes Obes Metab. 2015;17:294-303. [PMID: 25495720] doi:10.1111/dom.12428
63. **Ridderstråle M, Andersen K, Zeller C, et al.** Empagliflozin (EMPA) compared with glimepiride (GLIM) as add-on to metformin (MET) for 2 years in patients with type 2 diabetes (T2DM). Can J Diabetes. 2014;38:S56. doi:10.1016/j.jcjd.2014.07.156
64. **Del Prato S, Nauck M, Duran-Garcia S, et al.** Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes Obes Metab. 2015;17:581-590. [PMID: 25735400] doi:10.1111/dom.12459
65. **Hollander P, Hill J, Johnson J, et al.** Results of VERTIS SU extension study: safety and efficacy of ertugliflozin treatment over 104 weeks compared to glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin. Curr Med Res Opin. 2019;35:1335-1343. [PMID: 30760125] doi:10.1080/03007995.2019.1583450
66. **Leiter LA, Yoon K-H, Arias P, et al.** Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care. 2015;38:355-364. [PMID: 25205142] doi:10.2337/dc13-2762
67. **Frías JP, Davies MJ, Rosenstock J, et al; SURPASS-2 Investigators.** Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385:503-515. [PMID: 34170647] doi:10.1056/NEJMoa2107519
68. **Del Prato S, Kahn SE, Pavo I, et al; SURPASS-4 Investigators.** Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet. 2021;398:1811-1824. [PMID: 34672967] doi:10.1016/S0140-6736(21)02188-7
69. **Ludvik B, Giorgino F, Jódar E, et al.** Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet. 2021;398:583-598. [PMID: 34370970] doi:10.1016/S0140-6736(21)01443-4
70. **Inagaki N, Takeuchi M, Oura T, et al.** Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 trial. Lancet Diabetes Endocrinol. 2022;10:623-633. [PMID: 35914543] doi:10.1016/S2213-8587(22)00188-7
71. **Matthews DR, Dejager S, Ahren B, et al.** Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes Obes Metab. 2010;12:780-789. [PMID: 20649630] doi:10.1111/j.1463-1326.2010.01233.x
72. **Göke B, Gallwitz B, Eriksson JG, et al.** Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. Int J Clin Pract. 2013;67:307-316. [PMID: 23638466] doi:10.1111/ijcp.12119
73. **Gallwitz B, Rosenstock J, Rauch T, et al.** 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012;380:475-483. [PMID: 22748821] doi:10.1016/S0140-6736(12)60691-6
74. **Nathan DM, Lachin JM, Bebu I, et al; GRADE Study Research Group.** Glycemia reduction in type 2 diabetes - microvascular and cardiovascular outcomes. N Engl J Med. 2022;387:1075-1088. [PMID: 36129997] doi:10.1056/NEJMoa2200436
75. **Patel CA, Bailey RA, Vijapurkar U, et al.** A post-hoc analysis of the comparative efficacy of canagliflozin and glimepiride in the attainment of type 2 diabetes-related quality measures. BMC Health Serv Res. 2016;16:356. [PMID: 27495291] doi:10.1186/s12913-016-1607-z
76. **Müller-Wieland D, Kellerer M, Cypryk K, et al.** Efficacy and safety of dapagliflozin or dapagliflozin plus saxagliptin versus glimepiride as add-on to metformin in patients with type 2 diabetes. Diabetes Obes Metab. 2018;20:2598-2607. [PMID: 29947099] doi:10.1111/dom.13437
77. **Ahrén B, Johnson SL, Stewart M, et al; HARMONY 3 Study Group.** HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care. 2014;37:2141-2148. [PMID: 24898304] doi:10.2337/dc14-0024
78. **Weinstock RS, Guerci B, Umpierrez G, et al.** Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes Obes Metab. 2015;17:849-858. [PMID: 25912221] doi:10.1111/dom.12479
79. **Ahrén B, Masmiquel L, Kumar H, et al.** Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5:341-354. [PMID: 28385659] doi:10.1016/S2213-8587(17)30092-X
80. **Rosenstock J, Allison D, Birkenfeld AL, et al; PIONEER 3 Investigators.** Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial. JAMA. 2019;321:1466-1480. [PMID: 30903796] doi:10.1001/jama.2019.2942
81. **Davies MJ, Bergenstal R, Bode B, et al; NN8022-1922 Study Group.** Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. JAMA. 2015;314:687-699. [PMID: 26284720] doi:10.1001/jama.2015.9676
82. **Frias JP, Nauck MA, Van J, et al.** Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet. 2018;392:2180-2193. [PMID: 30293770] doi:10.1016/S0140-6736(18)32260-8
83. **Jabbour SA, Frías JP, Ahmed A, et al.** Efficacy and safety over 2 years of exenatide plus dapagliflozin in the DURATION-8 study: a multicenter, double-blind, phase 3, randomized controlled trial. Diabetes Care. 2020;43:2528-2536. [PMID: 32816874] doi:10.2337/dc19-1350
84. **Lingvay I, Catarig A-M, Frias JP, et al.** Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7:834-844. [PMID: 31540867] doi:10.1016/s2213-8587(19)30311-0
85. **Kaku K, Araki E, Tanizawa Y, et al.** Superior efficacy with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with insulin degludec and liraglutide in insulin-naïve Japanese patients with type 2 diabetes in a phase 3, open-label, randomized trial. Diabetes Obes Metab. 2019;21:2674-2683. [PMID: 31407845] doi:10.1111/dom.13856
86. **Wang W, Nevárez L, Filippova E, et al.** Efficacy and safety of once-weekly dulaglutide versus insulin glargine in mainly Asian patients with type 2 diabetes mellitus on metformin and/or a sulphonylurea: a 52-week open-label, randomized phase III trial. Diabetes Obes Metab. 2019;21:234-243. [PMID: 30129089] doi:10.1111/dom.13506
87. **Halvorsen YD, Lock JP, Frias JP, et al.** A 96-week, double-blind, randomized controlled trial comparing bexagliflozin to glimepiride as an adjunct to metformin for the treatment of type 2 diabetes in adults. Diabetes Obes Metab. 2023;25:293-301. [PMID: 36178197] doi:10.1111/dom.14875
88. **Ishii H, Onishi Y, Oura T, et al.** Once-weekly dulaglutide with insulin therapy for type 2 diabetes: efficacy and safety results from a phase 4, randomized, placebo-controlled study. Diabetes Ther. 2020;11:133-145. [PMID: 31758520] doi:10.1007/s13300-019-00726-8
89. **Dahl D, Onishi Y, Norwood P, et al.** Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. JAMA. 2022;327:534-545. [PMID: 35133415] doi:10.1001/jama.2022.0078
90. **Rodbard HW, Rosenstock J, Canani LH, et al; PIONEER 2 Investigators.** Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care. 2019;42:2272-2281. [PMID: 31530666] doi:10.2337/dc19-0883

91. **ATLAS Study Group.** Titration of insulin glargine in patients with type 2 diabetes mellitus in Asia: physician- versus patient-led? Rationale of the Asian Treat to Target Lantus Study (ATLAS). Diabetes Technol Ther. 2011;13:67-72. [PMID: 21175274] doi:10.1089/dia.2010.0170

92. **Ridderstråle M, Andersen KR, Zeller C, et al; EMPA-REG H2H-SU trial investigators.** Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2:691-700. [PMID: 24948511] doi:10.1016/S2213-8587(14)70120-2

93. **Haering H-U, Merker L, Christiansen AV, et al; EMPA-REG EXTEND™ METSU investigators.** Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. Diabetes Res Clin Pract. 2015;110:82-90. [PMID: 26324220] doi:10.1016/j.diabres.2015.05.044

94. **Fuechtenbusch M, Aberle J, Heitmann E, et al.** Weight loss in patients with type 2 diabetes receiving once-weekly dulaglutide plus insulin lispro or insulin glargine plus insulin lispro: a post-hoc analysis of the AWARD-4 study across baseline body mass index subgroups. Diabetes Obes Metab. 2019;21:1340-1348. [PMID: 30737891] doi:10.1111/dom.13658

95. **Ahmann AJ, Capehorn M, Charpentier G, et al.** Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. 2018;41:258-266. [PMID: 29246950] doi:10.2337/dc17-0417

96. **Goke B, Gallwitz B, Eriksson J, et al; D1680C00001 Investigators.** Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. Int J Clin Pract. 2010;64:1619-1631. [PMID: 20846286] doi:10.1111/j.1742-1241.2010.02510.x

97. **Jabbour SA, Frías JP, Hardy E, et al.** Safety and efficacy of exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy: 52-week results of the DURATION-8 randomized controlled trial. Diabetes Care. 2018;41:2136-2146. [PMID: 30082326] doi:10.2337/dc18-0680

98. **Bode BW, Testa MA, Magwire M, et al; LEAD-3 Study Group.** Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. Diabetes Obes Metab. 2010;12:604-612. [PMID: 20590735] doi:10.1111/j.1463-1326.2010.01196.x

99. **Nauck M, del Prato S, Meier JJ, et al.** [Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin]. Dtsch Med Wochenschr. 2013;138 Suppl 1:S6-S15. [PMID: 23529570] doi:10.1055/s-0032-1305283

100. **Cefalu WT, Leiter LA, Yoon K-H, et al.** Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013;382:941-950. [PMID: 23850055] doi:10.1016/S0140-6736(13)60683-2

101. **Hollander P, Liu J, Hill J, et al.** Ertugliflozin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin: the VERTIS SU randomized study. Diabetes Ther. 2018;9:193-207. [PMID: 29282633] doi:10.1007/s13300-017-0354-4

102. **Nauck M, Frid A, Hermansen K, et al.** Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. Diabetes Obes Metab. 2013;15:204-212. [PMID: 22985213] doi:10.1111/dom.12012

103. **Zinman B, Nauck MA, Bosch-Traberg H, et al; LEADER Publication Committee on behalf of the LEADER Trial Investigators.** Liraglutide and glycaemic outcomes in the LEADER trial. Diabetes Ther. 2018;9:2383-2392. [PMID: 30392095] doi:10.1007/s13300-018-0524-z

104. **González-González JG, Díaz González-Colmenero A, Millán-Alanís JM, et al.** Values, preferences and burden of treatment for the initiation of GLP-1 receptor agonists and SGLT-2 inhibitors in adult patients with type 2 diabetes: a systematic review. BMJ Open. 2021;11:e049130. [PMID: 34244276] doi:10.1136/bmjopen-2021-049130

105. **Toroski M, Kebriaeezadeh A, Esteghamati A, et al.** Patient and physician preferences for type 2 diabetes medications: a systematic review. J Diabetes Metab Disord. 2019;18:643-656. [PMID: 31890689] doi:10.1007/s40200-019-00449-4

106. **Purnell TS, Joy S, Little E, et al.** Patient preferences for noninsulin diabetes medications: a systematic review. Diabetes Care. 2014;37:2055-2062. [PMID: 24963113] doi:10.2337/dc13-2527

107. **Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group.** Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545-2559. [PMID: 18539917] doi:10.1056/NEJMoa0802743

108. **Tsapas A, Avgerinos I, Karagiannis T, et al.** Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Ann Intern Med. 2020;173:278-286. [PMID: 32598218] doi:10.7326/M20-0864

109. **Palmer SC, Tendal B, Mustafa RA, et al.** 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;372:m4573. [PMID: 33441402] doi:10.1136/bmj.m4573

110. **Duan X-Y, Liu S-Y, Yin D-G.** Comparative efficacy of 5 sodium glucose cotransporter 2 inhibitor and 7 glucagon-like peptide 1 receptor agonists interventions on cardiorenal outcomes in type 2 diabetes patients: a network meta-analysis based on cardiovascular or renal outcome trials. Medicine (Baltimore). 2021;100:e26431. [PMID: 34397684] doi:10.1097/MD.0000000000026431

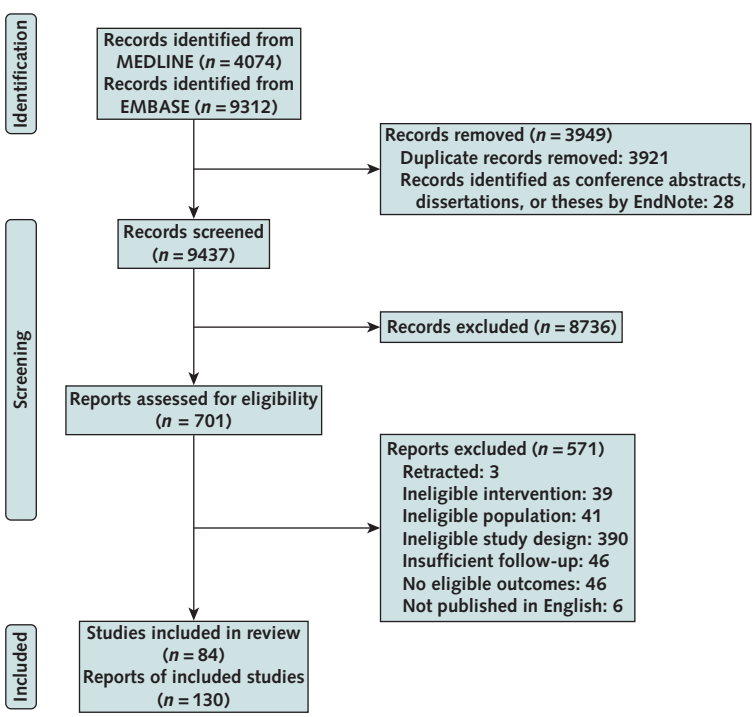
111. **Wexler D, de Boer I, Ghosh A, et al; GRADE Research Group.** Comparative effects of glucose-lowering medications on kidney outcomes in type 2 diabetes: the GRADE randomized clinical trial. JAMA Intern Med. 2023;183:705-714. [PMID: 37213109] doi:10.1001/jamainternmed.2023.1487

112. **Cherney D, Ferrannini E, Umpierrez G, et al.** Efficacy and safety of sotagliflozin in patients with type 2 diabetes and stage 3 chronic kidney disease. Diabetes Obes Metab. 2023;25:1646-1657. [PMID: 36782093] doi:10.1111/dom.15019

113. **Aroda V, Aberle J, Bardtrum L, et al.** Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in adults with type 2 diabetes (PIONEER PLUS): a multicentre, randomised, phase 3b trial. Lancet. 2023;402:693-704. [PMID: 37385279] doi:10.1016/S0140-6736(23)01127-3

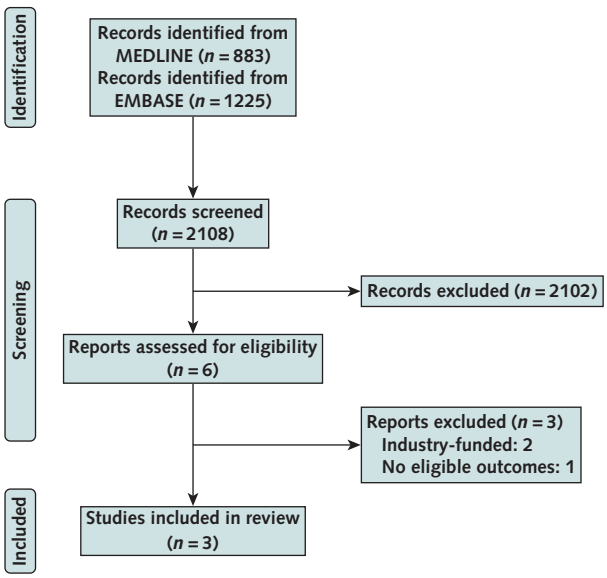
Author Contributions: Conception and design: T. Drake, A. Landsteiner, L. Langsetmo, C.J. Billington, S. Sultan, T.J. Wilt.
Analysis and interpretation of the data: T. Drake, A. Landsteiner, L. Langsetmo, R. MacDonald, C. Kalinowski, C.J. Billington, A. Kaka, S. Sultan, T.J. Wilt.
Drafting of the article: T. Drake, A. Landsteiner, L. Langsetmo, K. Ullman, C.J. Billington, S. Sultan, T.J. Wilt.
Critical revision for important intellectual content: T. Drake, A. Landsteiner, L. Langsetmo, C.J. Billington, A. Kaka, S. Sultan, T. J. Wilt.
Final approval of the article: T. Drake, A. Landsteiner, L. Langsetmo, R. MacDonald, M. Anthony, C. Kalinowski, K. Ullman, C.J. Billington, A. Kaka, S. Sultan, T.J. Wilt.
Statistical expertise: L. Langsetmo, R. MacDonald, T.J. Wilt.
Obtaining of funding: T.J. Wilt.
Administrative, technical, or logistic support: A. Landsteiner, M. Anthony, C. Kalinowski, K. Ullman, T.J. Wilt.
Collection and assembly of data: A. Landsteiner, L. Langsetmo, R. MacDonald, M. Anthony, C. Kalinowski, K. Ullman, T.J. Wilt.

Appendix Figure 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) study flow diagram: key question 1.



Key question 1: In adults with type 2 diabetes mellitus, what are the effectiveness and comparative effectiveness and harms of sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors, or long-acting insulins used either as monotherapy or in combination with other antidiabetic medications?

Appendix Figure 2. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) study flow diagram: key question 2.



Key question 2: What are patients' values and preferences regarding antidiabetic medications for type 2 diabetes mellitus management?