

# Endocrinology: What You May Have Missed in 2025

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During 2025, endocrinology witnessed the expansion of pharmacotherapeutic options for type 2 diabetes (T2DM), obesity, and metabolic dysfunction-associated steatohepatitis (MASH); increasing complexity of treatment algorithms, including choices for intensification of therapy; and heightened concern about emerging side effects of commonly used medications. From the wealth of studies published in 2025, this article notes 9 studies that offer critical information for clinicians who manage or co-manage patients with endocrine and metabolic disorders, including T2DM, obesity, and MASH. One of the 9 articles reviews the effectiveness of diabetes self-management education and support interventions, an important component of diabetes care, in improving hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>). Another is focused on comparing HbA<sub>1c</sub> lowering when escalating the dose of dulaglutide versus switching to tirzepatide in people with T2DM. Two of the 9 articles are focused on potential side effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs), including gastrointestinal side effects and nonarteritic anterior ischemic optic neuropathy. One article summarizes the risk for life-threatening pituitary immune-related adverse events caused by immune checkpoint inhibitors; another explores the use of GLP-1RAs in MASH. One additional study explores the risk for urogenital infections in patients with diabetes receiving sodium-glucose cotransporter-2 inhibitors (SGLT-2is) versus GLP-1RAs. Another study explores cardiovascular, kidney, and safety outcomes with canagliflozin (an SGLT-2i). The last article explores the efficacy and safety of finerenone in T2DM. The results of each study have a direct effect on clinical care for patients who often present to physicians who are not endocrinologists.

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The approach to the care of common endocrine disorders increased in complexity and intensity over the past year. The dizzying pace of publication of practice-changing evidence can make keeping up to date difficult. This overview includes 9 studies whose results provide insight into common clinical dilemmas in the approach to treatment of type 2 diabetes (T2DM), obesity, and metabolic dysfunction-associated steatohepatitis (MASH). In addition, 1 study sheds light on the risk for life-threatening immune-related pituitary disease associated with commonly used immunotherapies. In this article, we summarize key points that can assist clinicians who are not endocrinologists in the care of patients with common endocrine disorders and patients treated with immune checkpoint inhibitors (ICIs).

## THE PROCESS BEHIND THIS ARTICLE

This article was produced from a collaboration with *Annals of Internal Medicine*, the Health Information

Research Unit at McMaster University, and internal medicine subspecialty fellows at McMaster University. The same literature surveillance process that is used for ACP Journal Club was used to retrieve and assess the scientific soundness of the new evidence relevant to endocrinology from more than 120 journals as it was published. If necessary, the authors identified additional journals relevant to the field that they thought were missing from the journals routinely screened and could also propose additional articles captured through other relevant channels, such as professional conferences. The critical appraisal process relies on highly trained staff at McMaster University and a worldwide panel of more than 3600 physicians, including experts in endocrinology, to assess the clinical relevance and newsworthiness of the evidence. A web-based platform was created to allow the authors to screen articles potentially relevant to endocrinology published in 2025. Content criteria used to select the featured articles were relevance to internal medicine

This article is part of the Annals supplement "What You May Have Missed in 2025." Alfonso Iorio, MD, PhD (Department of Research Methods, Evidence, and Impact and Department of Medicine, McMaster University), and Christine Laine, MD, MPH (Editor in Chief, *Annals of Internal Medicine*), served as editors for this supplement.

physicians who are not specialists in endocrinology and actionable clinical information.

The Health Information Research Unit staff produced standardized summaries of the selected articles (see the Appendix, which is available at the end of this article). The authors, who include fellows in endocrinology and the *Annals* Associate Editor for endocrinology, provide a narrative built around addressing the following 5 questions:

- *Why should internal medicine physicians know about this article?*
- *What is the main message for physicians who are not endocrinology specialists?*
- *How do these findings fit in the context of existing knowledge?*
- *Are there any important limitations or caveats to recognize?*
- *What evidence gaps remain?*

### **Diabetes self-management education or support delivered by mobile health interventions may improve hemoglobin A<sub>1c</sub> in adults with T2DM**

(See Summary 1 in the Appendix)

#### ***Why should internal medicine physicians know about this article?***

The American Diabetes Association recommends structured diabetes self-management education and support (DSME/S) to reinforce self-management behaviors and improve glycemic outcomes for persons with diabetes (1). However, the number of persons with T2DM is increasing beyond the capacity of specialty clinics that provide DSME/S (2). Internal medicine and primary care clinics may lack the resources to consistently deliver face-to-face DSME/S and could benefit from mobile health (mHealth) tools to support diabetes self-management.

#### ***What is the main message for physicians who are not endocrinology specialists?***

This systematic review and meta-analysis assessed the effects of varied mHealth interventions for DSME/S compared with standard care in 9328 persons with T2DM across 43 clinical trials (3). These interventions improved hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) by 0.4 percentage point without increasing hypoglycemia, with the greatest effect observed in interventions that incorporated diabetes self-management support. Subgroup analyses suggested that mobile DSME/S may additionally improve medication adherence, glucose monitoring frequency, and weight loss. mHealth interventions offer a patient-led, cost-effective avenue to support providers in delivering DSME/S to patients with T2DM.

#### ***How do these findings fit in the context of existing knowledge?***

Previous literature on mHealth interventions for T2DM has consisted of pilot and feasibility studies.

Prior reviews have similarly found statistically significant HbA<sub>1c</sub> lowering with the use of virtual (mobile or computer-based) self-management interventions (4, 5). This study builds on existing literature by incorporating randomized controlled trial (RCT)-level data to demonstrate a significant glycemic benefit from patient-led, automated mHealth DSME/S interventions.

#### ***Are there any important limitations or caveats to recognize?***

Several of the included studies had high risk of publication bias, lack of blinding, and incomplete objective outcome data. The article contains discrepancies in the reporting of sample sizes and CIs for HbA<sub>1c</sub>. These limitations should be considered when interpreting the effect of DSME/S on HbA<sub>1c</sub>.

#### ***What evidence gaps remain?***

There is a need for larger-scale RCTs that directly assess the effect of mHealth interventions on glycemic outcomes and patient-reported outcomes, such as health-related quality of life or treatment satisfaction. Existing mHealth interventions have significant heterogeneity and have not been tailored to meet individual patients' needs or barriers to their diabetes self-management.

### **In patients with T2DM, overweight or obesity, or MASH or steatotic liver disease, GLP-1RAs increase risk for cholelithiasis and gastroesophageal reflux disease, but not other gastrointestinal or biliary adverse events, versus placebo**

(See Summary 2 in the Appendix)

#### ***Why should internal medicine physicians know about this article?***

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are commonly used for glycemic management and weight reduction (6). Providers may hesitate to prescribe GLP-1RAs in patients with underlying gastrointestinal (GI) disease due to concern about GI adverse events. As GLP-1RAs are approved for broader applications, including cardiovascular disease and MASH, understanding their GI safety profile will be increasingly relevant to clinical practice for internal medicine physicians.

#### ***What is the main message for physicians who are not endocrinology specialists?***

Chiang and colleagues (7) conducted a systematic review and meta-analysis of 55 RCTs including 106 395 participants with T2DM, obesity, or MASH or metabolic dysfunction-associated steatotic liver disease (MASLD) who were administered a GLP-1RA. Compared with placebo, GLP-1RAs increased the risk

for cholelithiasis (risk ratio, 1.46 [95% CI, 1.09 to 1.97]) and gastroesophageal reflux disease (GERD) (risk ratio, 2.19 [CI, 1.48 to 3.25]). This increased risk was more likely present in trials including participants with overweight, obesity, or MASLD and trials using high-dose formulations. There was no increased risk for pancreatitis, intestinal obstruction, cholecystitis, or other serious adverse GI events compared with placebo.

#### ***How do these findings fit in the context of existing knowledge?***

Literature on GI and biliary adverse events associated with GLP-1RA use is inconsistent, causing hesitancy to prescribe these therapies in at-risk populations. Prior studies have suggested increased risk for serious GI adverse events, such as pancreatitis, intestinal obstruction, or cholecystitis, whereas more recent RCTs do not support these findings (8-10). This study clarifies the current evidence on the safety profile of GLP-1RAs and may inform clinical decision making around GLP-1RA use in patients with T2DM, overweight or obesity, or MASH or MASLD.

#### ***Are there any important limitations or caveats to recognize?***

The included studies are heterogeneous in trial design, GLP-1RA agent selection, dosing regimens, and outcome definitions. Subgroup analyses did not reach statistical significance, limiting the ability to delineate dosing formulations or populations with higher risk.

#### ***What evidence gaps remain?***

Future research should focus on longitudinal assessment of biliary or GI adverse events beyond 2 years of GLP-1RA use. In addition, no RCT-level data exist evaluating GLP-1RAs in persons with a history of pancreatitis or biliary disease. Although retrospective studies to date have found no difference in GI adverse events for those with a history of pancreatitis or biliary disease using GLP-1RAs (11), prospective studies are needed to validate these findings.

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### **In patients who had inadequately controlled T2DM with lower-dose dulaglutide, switching to tirzepatide reduced HbA<sub>1c</sub> and body weight more than escalating dulaglutide at 40 weeks**

(See Summary 3 in the Appendix)

#### ***Why should internal medicine physicians know about this article?***

Incretin-based treatments, including GLP-1RAs and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RAs, are highly effective in reducing both HbA<sub>1c</sub> and body weight (12). Tirzepatide, a GIP/GLP-1RA, has been shown to have a greater effect on

glycemic control and weight reduction than a GLP-1RA alone (13). This article examines the efficacy and safety of the maximum or maximally tolerated dose of a GLP-1RA (dulaglutide) compared with switching from dulaglutide to the maximum or maximally tolerated dose of a GIP/GLP-1RA (tirzepatide) (14).

#### ***What is the main message for physicians who are not endocrinology specialists?***

This large, multicenter, randomized, phase 4 trial showed that switching to tirzepatide is more effective than increasing doses of dulaglutide in improving both HbA<sub>1c</sub> and body mass index. Participants who were transitioned to tirzepatide (15 mg or maximum tolerated dose) achieved an HbA<sub>1c</sub> reduction of 1.44 percentage points and weight loss of 10.5 kg. Participants who received dose increases of dulaglutide (to the maximum tolerated dose) achieved an HbA<sub>1c</sub> reduction of 0.67 percentage point and weight loss of 3.6 kg. Side effect profiles were similar in each group.

#### ***How do these findings fit in the context of existing knowledge?***

In the SURPASS-SWITCH (A Phase 4, Randomized, Open-Label, Active-Controlled Study to Investigate the Efficacy and Safety of Switching from Weekly Dulaglutide to Weekly Tirzepatide in Adults with Type 2 Diabetes) trial, participants who switched to tirzepatide showed improved weight loss and glycemic control. However, the trial had a short follow-up time (12 weeks) and no comparator group (15). In addition, a previous study showed that tirzepatide was noninferior to dulaglutide on a composite of death from cardiovascular causes, myocardial infarction, or stroke (16). This randomized, open-label, phase 4 trial provides clarity that transitioning to tirzepatide versus continuing with dulaglutide over 40 weeks improved HbA<sub>1c</sub> and weight loss without increasing the risk for side effects.

#### ***Are there any important limitations or caveats to recognize?***

This was an open-label study that was industry-funded, and participants and investigators were aware of the drug participants were receiving. The GLP-1RA studied was dulaglutide despite published data showing semaglutide to be more efficacious (17). The study population had a relatively narrow HbA<sub>1c</sub> range of 7.0% or greater to 9.5% or less; therefore, results may not be generalizable to patients with very poorly controlled diabetes.

#### ***What evidence gaps remain?***

Long-term weight reduction and sustained weight loss after switching therapy will be an important area of future study. Of note, participants receiving tirzepatide did not have a weight loss plateau at the end of the study (week 40) despite starting on the maximum

dosage at week 20. Further study is indicated to understand the sustainability of weight loss achieved with tirzepatide compared with other GLP-1RA agents, as well as weight change after transitioning off incretin mimetic therapy.

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**In patients with malignant tumors, ICI therapy is associated with pituitary immune adverse reactions**

(See Summary 4 in the Appendix)

**Why should internal medicine physicians know about this article?**

Immune checkpoint inhibitors are cornerstones of immunotherapy and are increasingly becoming first-line treatments in cancer types including melanoma, non-small cell lung cancer, and renal cell carcinoma (18-20). Therefore, ICI-induced endocrine toxicities are also becoming increasingly common adverse events, and they vary widely in severity (21). Primary care physicians and endocrinologists are at the forefront of diagnosing life-threatening pituitary disease in patients treated with ICIs. This systematic review and meta-analysis of both RCTs and single-group trials aimed to analyze the incidence and relative risk for ICI-related pituitary endocrine toxicities, including hypophysitis (a rare inflammatory condition of the thyroid) and hypopituitarism.

**What is the main message for physicians who are not endocrinology specialists?**

The study included patients older than 18 years with any type of malignant tumor receiving an ICI therapy (22). Overall, risk for hypophysitis or hypopituitarism varied by drug class; however, cytotoxic T lymphocyte-associated protein 4 inhibitors showed the highest incidence of hypophysitis and caused the highest severity of adverse pituitary events. Programmed cell death 1 inhibitor monotherapy showed the lowest incidence of hypophysitis. Of note, the risk for hypophysitis was increased for those receiving ICI combination therapy compared with monotherapy.

**How do these findings fit in the context of existing knowledge?**

This study highlights that as ICIs are increasingly used in the treatment of cancer, they are associated with significant autoimmune endocrinopathies that pose diagnostic and treatment challenges to clinicians (23). Although this article focuses on central processes, including hypophysitis and hypopituitarism, there is a growing body of evidence that documents the incidence of multiple endocrinopathies, including hypothyroidism, hyperthyroidism, primary adrenal insufficiency, and type 1 diabetes, especially when ICIs are used in combination (24).

**Are there any important limitations or caveats to recognize?**

This review included both RCTs and single-group prospective trials, which led to significant heterogeneity between the studies and could reflect differences in patient populations or monitoring practices. Treatment guidelines about ICI therapy are rapidly evolving, and some of the studies used here included now-outdated therapies. Fewer studies explored hypopituitarism than hypophysitis; therefore, a detailed subgroup analysis could not be done.

**What evidence gaps remain?**

Treatment regimens for ICI therapy are rapidly evolving, and further large systematic investigations are needed to inform a definitive approach to diagnosis and treatment (23). The literature reviewed in these studies was aimed at capturing the incidence of adverse reactions in various organ systems. A significant amount of the primary literature did not include descriptions of details, including age, gender, or time course, that could help clinicians better identify patients on the basis of risk factors or clinical presentation patterns.

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**In patients with T2DM, initiating SGLT-2i treatment was linked to increased risk for genital tract infections but not urinary tract infections compared with initiating GLP-1RA treatment at up to 5 years**

(See Summary 5 in the Appendix)

**Why should internal medicine physicians know about this article?**

Since their approval in 2013 for the management of T2DM, sodium-glucose cotransporter-2 inhibitors (SGLT-2is) have been widely used in clinical practice. This trend increased after 2020, when evidence demonstrated cardiorenal benefits in participants with no history of diabetes but a history of heart failure (HF) or chronic kidney disease (CKD) (25, 26). However, the U.S. Food and Drug Administration warned about an increased risk for severe urinary tract infections (UTIs) and genital tract infections (GTIs) (27), a concern especially relevant to persons with diabetes, who are at higher risk for UTI and GTI than the general population (28). This article provides real-world data to contextualize urogenital infection risk when prescribing SGLT-2is in routine outpatient practice, especially among high-risk patients.

**What is the main message for physicians who are not endocrinology specialists?**

This large Danish population-based cohort study (28) found that UTI risk was similar at 1 year of follow-up between patients starting SGLT-2i treatment and those starting GLP-1RA treatment, regardless of analytic approach. These findings were consistent across subgroups of patients with an HbA<sub>1c</sub> greater than 7.5% and those with baseline urogenital pathologies. In

contrast, initiation of SGLT-2i treatment was associated with a higher risk for GTI, peaking in the first 3 months of treatment. Although GTI risk declined over time, risk remained elevated throughout follow-up for those receiving SGLT-2is compared with GLP-1RAs.

***How do these findings fit in the context of existing knowledge?***

Although these findings are consistent with existing knowledge, this study addresses an important knowledge gap by including patients at high risk for UTI and GTI, who are typically excluded from randomized clinical trials (29). Specifically, this study evaluated clinically relevant patient subgroups, including persons with a history of UTI or GTI, benign prostatic hyperplasia, urinary incontinence, urogenital surgery, history of urinary stones, obesity, and frailty-related conditions.

***Are there any important limitations or caveats to recognize?***

Danish health registries do not capture diagnoses from general practices. However, researchers used prescription data for urogenital-specific antibiotics and antifungals as an indirect method to identify UTIs and GTIs diagnosed in these settings. Cases treated with non-first-line antibiotics or GTIs managed with over-the-counter treatments may not have been identified. Despite the robust study design, residual confounding from unmeasured variables, such as lifestyle or sociodemographic characteristics, may be present.

***What evidence gaps remain?***

Additional studies in other geographic regions may be needed to assess the generalizability of these findings.

**In patients with T2DM, new use of semaglutide was linked to increased risk for NAION compared with new use of SGLT-2is at up to 5 years**

(See Summary 6 in the Appendix)

***Why should internal medicine physicians know about this article?***

General internal medicine physicians often prescribe GLP-1RAs for the management of T2DM because of their glucose-lowering properties and established cardiovascular, renal, and weight loss benefits (30). Recent studies have identified a potential association between GLP-1RAs and nonarteritic anterior ischemic optic neuropathy (NAION), a rare but potentially serious adverse event (31, 32). Consequently, clinicians require reliable evidence to contextualize this potential risk when counseling patients about initiating or continuing GLP-1RA therapy.

***What is the main message for physicians who are not endocrinology specialists?***

In this large retrospective cohort study using national health registries from Denmark (2018 to

2024) and Norway (2018 to 2022), semaglutide use was associated with a higher incidence of NAION compared with SGLT-2i use among patients with T2DM (pooled adjusted hazard ratio, 2.81 [CI, 1.67 to 4.75]; incidence rate difference, 1.41 additional cases per 10 000 person-years) (33). These findings were consistent across multiple supplemental analyses, including those focused on medication adherence and T2DM duration. Despite the increased relative risk, the absolute risk was low, estimated at 0.3% to 0.5% over 20 years, and should be considered in the context of the established cardiometabolic benefits of semaglutide.

***How do these findings fit in the context of existing knowledge?***

These findings are consistent with multiple previous studies (31, 32, 34) but differ from other cohort studies that did not identify a statistically significant association (35, 36). Of note, most prior studies compared NAION risk in GLP-1RA users with no treatment and did not do extensive supplemental analyses to adjust for additional potential confounding variables.

***Are there any important limitations or caveats to recognize?***

The absolute incidence of NAION was low in the included cohort, limiting the statistical power of subgroup analyses. Although the authors accounted for most available potential confounding variables, the retrospective design may have led to residual confounding. The notable difference in relative risk between the Norwegian and Danish populations also raises concern for unmeasured population-level, genetic, or health system factors that may have influenced the observed association.

***What evidence gaps remain?***

The association should be evaluated in prospective studies conducted to account for established NAION risk factors, including optic disc morphology, sleep apnea, and baseline retinopathy, which cannot be adequately assessed using retrospective registry data.

**In adults with T2DM and high cardiorenal risk, canagliflozin versus placebo reduced major adverse cardiovascular events, HF hospitalization, and kidney disease progression, with consistent effects across age groups**

(See Summary 7 in the Appendix)

***Why should internal medicine physicians know about this article?***

The prevalence of diabetes is projected to reach 60.6 million cases by 2060, with 69.8% of affected persons expected to be older than 65 years (37).

Clinicians managing T2DM in aging populations need evidence on the efficacy and safety of glucose-lowering therapies, particularly SGLT-2is given their cardiorenal protective benefits. However, clinicians are often hesitant to initiate treatment with these agents in older adults because of potential complications from osmotic diuresis, volume depletion, and other serious side effects (38). This study integrates data from RCTs and uses age-stratified analyses to evaluate risks and benefits in older populations.

***What is the main message for physicians who are not endocrinology specialists?***

This pooled analysis of 14 543 participants from the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program and the CREDENCE (Canagliflozin Tand Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) RCTs (39) showed that canagliflozin consistently reduced major adverse cardiovascular events, HF hospitalizations, and adverse kidney outcomes across all age groups, including those aged 75 years or older. Age did not affect the risk for serious adverse events, hypoglycemia, acute kidney injury, or serious UTIs. The main safety concern was an increased risk for genital mycotic infections, which were seen in all age groups in both sexes and were more notable in men aged 75 years or older.

***How do these findings fit in the context of existing knowledge?***

These findings are consistent with previous evidence demonstrating the efficacy and safety of SGLT-2is across all age groups (40). However, the use of individual data from 2 large RCTs increases statistical power and allows for more robust analyses in age groups that have been underrepresented in prior studies.

***Are there any important limitations or caveats to recognize?***

*P* values for trend were not adjusted for multiple comparison correction; therefore, some statistically significant trends may be due to chance. In addition, the pooled data were obtained from RCTs that enrolled patients with established cardiovascular disease or CKD with albuminuria, which may limit the generalizability of the results (3). Finally, the RCTs were funded by a pharmaceutical company, a factor that should be considered when interpreting the results.

***What evidence gaps remain?***

Additional studies evaluating safety in patients aged 80 years or older are necessary because the sample for this group was smaller than for other age groups.

**In patients with MASH and moderate or advanced liver fibrosis, weekly semaglutide improved histologic steatohepatitis and fibrosis at 72 weeks**

(See Summary 8 in the Appendix)

***Why should internal medicine physicians know about this article?***

Therapeutic options for management of MASH and liver fibrosis remain limited. Although GLP-1RAs have shown reduction of steatohepatitis in phase 2 studies, phase 3-level data demonstrating sustained efficacy and safety in larger samples are necessary (41).

***What is the main message for physicians who are not endocrinology specialists?***

In a phase 3, randomized, double-blind, placebo-controlled trial, the authors showed the effectiveness of weekly semaglutide in reducing MASH and liver fibrosis compared with placebo (42). The 72-week interim analysis of 800 patients found that 29% more patients receiving semaglutide had resolution of steatohepatitis without worsening fibrosis and 14% more patients receiving semaglutide had resolution of fibrosis without worsening steatohepatitis. Secondary analyses showed 16% greater combined resolution of steatohepatitis and histologic reduction in liver fibrosis, as well as 8.5% greater reduction in mean body weight compared with placebo.

***How do these findings fit in the context of existing knowledge?***

Prior literature consisting of phase 2 trials and cohort studies demonstrated improvement in steatohepatitis and inconclusive effects on fibrosis with GLP-1RA use. This trial shows significant reduction in histologic measures of steatohepatitis and fibrosis in a large population receiving semaglutide. The findings support the use of GLP-1RAs for treatment of MASH, which is consistent with its well-established role in reducing weight, insulin resistance, and other glucometabolic variables that coexist with MASH development (43).

***Are there any important limitations or caveats to recognize?***

This study presents interim trial results from 72 weeks, which is short of the planned 240-week follow-up period. It will be of value to see longitudinal liver-related outcomes, such as progression to cirrhosis and key safety outcomes. With regard to limitations, the predominantly White study population (67.6%) limits generalizability, and the study lacked data on biomarkers of alcohol consumption or genetic polymorphisms as a determinant of therapeutic response.

**What evidence gaps remain?**

Future research should examine the long-term clinical outcomes of GLP-1RA use in MASH, including progression to cirrhosis, transplant-free survival, and mortality. It would additionally be important to delineate population subgroups that would most benefit from GLP-1RA use, as well as how this therapy might interact with or compare with other emerging MASH treatments. Finally, although GLP-1RAs are safe to use in cirrhosis, data on their efficacy in this population are lacking (44).

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**In patients with T2DM and CKD or HF with preserved or reduced ejection fraction, finerenone had consistent cardiovascular and kidney effects across baseline HbA<sub>1c</sub> levels**

(See Summary 9 in the Appendix)

**Why should internal medicine physicians know about this article?**

Cardiovascular disease is the principal cause of morbidity, mortality, and increasing health care costs in patients with T2DM (45, 46). Heart failure, T2DM, and CKD are increasingly recognized as both interrelated and undertreated, and significant overlap among these conditions is associated with increased risk for hospitalization and death (47). Treatment plans for T2DM should address comorbid conditions like CKD and HF. This pooled analysis evaluated the efficacy and safety of finerenone, a highly selective nonsteroidal mineralocorticoid receptor antagonist, in participants with T2DM and either CKD or HF.

**What is the main message for physicians who are not endocrinology specialists?**

In this pooled analysis of 3 phase 3, global, multicenter, double-blind, placebo-controlled RCTs of finerenone (FINE-HEART), the efficacy and safety of finerenone versus placebo were evaluated over a median follow-up of 2.9 years (46). The analysis included 15 365 participants with T2DM (mean HbA<sub>1c</sub>, 7.6% [SD, 1.4%]). Patients used various glucose-lowering regimens, including insulin, metformin, sulfonylureas, SGLT-2is, and GLP-1RAs. The analysis showed reduction for the treatment group in the composite kidney outcome, HF hospitalizations, major adverse cardiovascular events, and all-cause mortality. These results occurred independently of glucose-lowering regimen and baseline HbA<sub>1c</sub> levels. Cardiovascular death was not significantly reduced.

**How do these findings fit in the context of existing knowledge?**

Finerenone is a highly selective nonsteroidal mineralocorticoid receptor antagonist that reduces inflammation and fibrosis in the heart, kidney, and vasculature (48). It has been shown to slow CKD

progression and decrease cardiovascular events in patients with T2DM and both early- and advanced-stage CKD (49, 50). In addition, FINE-HEART showed that finerenone reduced the composite of total worsening HF events and cardiovascular death in those with mildly reduced or preserved ejection fraction regardless of T2DM status, although cardiovascular death was not significantly reduced (51). Because GLP-1RAs and SGLT-2is improve cardiovascular outcomes, this study pooled data from these trials to examine whether the cardiorenal benefits of finerenone were shown regardless of glucose-lowering regimen and baseline HbA<sub>1c</sub> (52, 53).

**Are there any important limitations or caveats to recognize?**

Although the study aimed to describe the cardiorenal benefit of finerenone, regardless of glucose-lowering regimen, the use of therapies known to affect cardiorenal outcomes was limited by sample size and therefore limited in the analysis. The most common glucose-lowering treatment regimens were insulin alone or insulin with metformin. The uptake of SGLT-2is (9.6%) and GLP-1RAs (7.2%) was low. This analysis used composite outcomes. As such, worsening HF events contributed most significantly to the composite outcome. Of note, the primary end point of cardiovascular death was not a significant outcome in the FINE-HEART analysis; therefore, this pooled analysis should be interpreted with caution. Finerenone did modestly increase hyperkalemia, and both trials required serum potassium levels of 4.8 mmol/L or lower for enrollment. The within-subgroup estimates had wide CIs, which indicates less statistical power within subgroups.

**What evidence gaps remain?**

There is growing interest in treatment of cardiovascular-kidney-metabolic health in addition to targeting excellent glycemic control to improve outcomes in patients with T2DM, CKD, and HF. Both GLP-1RAs and SGLT-2is have helped patients achieve improved glycemic control and shown cardiorenal benefits. More research is necessary to understand the subgroup populations that will derive the greatest benefit from finerenone in addition to GLP-1RAs. Although the composite outcomes described in the study are promising, future research should aim to quantify the risk for drug-drug interactions as well as excess cost to patients and health care systems.

**CONCLUSIONS**

The 9 presented studies address critical questions related to the care of patients with T2DM, obesity, and MASLD or MASH. One study highlighted a need for increased awareness of hypophysitis or hypopituitarism in patients treated with ICIs. Another reviewed the

effect of DSME/S interventions: Support of healthy lifestyle choices and self-care through programs that include DSME/S are of increasing importance as providers and patients contemplate how to prevent weight gain after discontinuing GLP-1RA and GLP-1RA/GIP treatment.

Four articles focused on GLP-1RAs, including one designed to understand efficacy and adverse effects in patients receiving dulaglutide (a GLP-1RA) versus switching to tirzepatide (a GLP-1RA/GIP). Another study explored the efficacy of semaglutide (a GLP-1RA) in reducing MASH and liver fibrosis. Two others focused on GI side effects and NAION in persons prescribed a GLP-1RA.

Two additional studies focused on SGLT-2is: One explored the risk for urogenital infections in patients with diabetes receiving SGLT-2is versus GLP-1RAs, and the other focused on cardiovascular, kidney, and safety outcomes with canagliflozin (an SGLT-2i). The last article explored the efficacy and safety of finerenone in T2DM.

The results of each study provided evidence that extended current knowledge or influenced clinical care for patients with T2DM, obesity, or MASLD or MASH and those treated with ICLs. Future research should focus on maximizing use of DSME/S to support glycemic control, refining risk assessment when determining diabetes and obesity treatment regimens, considering the cost of multidrug therapy for diabetes, and expanding treatment options that improve outcomes in persons with multiple, simultaneous comorbid conditions.

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**Disclosures:** Disclosure forms are available with the article online.

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Collection and assembly of data: B. Batch, C. Escudero.

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APPENDIX: SUMMARIES

Summary 1

**Diabetes self-management education or support delivered by mobile health interventions may improve hemoglobin A<sub>1c</sub> in adults with T2DM**

Versluis A, Boels AM, Huijden MCG, et al. Diabetes self-management education and support delivered by mobile health (mHealth) interventions for adults with type 2 diabetes—a systematic review and meta-analysis. *Diabet Med.* 2025;42:e70002. [PMID: 40007461] doi:10.1111/dme.70002

**Design:** Systematic review and meta-analysis. Latest search date: 31 January 2023.

**Inclusion Criteria:** RCTs comparing diabetes self-management education (DSM-E), DSM support (DSM-S), or combined DSME/S delivered by mHealth interventions with usual care or an attention placebo in adults with T2DM. Interventions were delivered through device-based mobile platforms (for example, SMS, text messaging, automated calls, or smartphone applications). Exclusions: interventions involving nonautomated communication with health care providers (for example, telephone calls or tailored feedback), remote monitoring or patient-provider communication systems, or mHealth tools functioning primarily as data records or diaries.

**Primary Outcome:** HbA<sub>1c</sub>.

**Results:** 43 RCTs (*n* = 9328; intervention duration, 1 to 52 weeks) were included. All trials had at least 1 methodological limitation, 19 had low risk of selection bias, and only 2 reported blinded assessors (Cochrane Risk of Bias Tool).

**Table.** Meta-analysis of DSM-E, DSM-S, or Combined DSME/S Versus Usual Care or Attention Placebo in Adults With T2DM\*

Outcome and Intervention	Trials (Patients), <i>n</i> ( <i>n</i> )	Mean Difference Versus Usual Care or Attention Placebo (95% CI), mmol/mol†	<i>I</i> <sup>2</sup> , %
<b>HbA<sub>1c</sub></b>			
DSM-E	8 (1289)	-4 (-6 to -1)	53
DSM-S	16 (1326)	-4 (-7 to -2)	58
Combined DSME/S	18 (3636)	-2 (-3 to -0)	21

DSM-E = diabetes self-management education; DSME/S = DSM education and support; DSM-S = DSM support; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; T2DM = type 2 diabetes.

\* Moderate certainty of evidence.

† Clinically meaningful difference, ≥4 mmol/mol. Follow-up duration varied across trials (range, 2 to 104 wk).

## Summary 2

### In patients with T2DM, overweight or obesity, or MASH or steatotic liver disease, GLP-1RAs increase risk for cholelithiasis and gastroesophageal reflux disease, but not other gastrointestinal or biliary adverse events, versus placebo

Chiang CH, Jaroenlapnopparat A, Colak SC, et al. Glucagon-like peptide-1 receptor agonists and gastrointestinal adverse events: a systematic review and meta-analysis. *Gastroenterology*. 2025;169:1268-1281. [PMID: 40499738] doi:10.1053/j.gastro.2025.06.003

**Design:** Systematic review and meta-analysis. Latest search date: May 2025.

**Inclusion Criteria:** Double-blind, placebo-controlled RCTs evaluating clinically available GLP-1RAs approved by the U.S. Food and Drug Administration for use in adults with T2DM, overweight or obesity, or MASH or MASLD that reported at least 1 GI or biliary condition. Open-label trials were excluded.

**Primary Outcomes:** GI and biliary adverse events associated with GLP-1RA use.

**Results:** 55 RCTs ( $n = 106\,395$ ; treatment duration, 24 to 277 weeks) met inclusion criteria. 50 RCTs had low overall risk of bias, and 5 RCTs had some concerns in the Cochrane Risk of Bias Tool 2. Most trials evaluated semaglutide (40%) and liraglutide (22%).

**Table.** Meta-analysis of GLP-1RAs Versus Placebo in Patients With T2DM, Overweight or Obesity, or MASH or MASLD

Outcome*	Trials (Patients), <i>n</i> ( <i>n</i> )	Risk Ratio (95% CI)	Absolute Risk Increase per 1000 Patients	GRADE Certainty	$I^2$ , %
Cholelithiasis	37 (89 703)	1.46 (1.09 to 1.97)	2 (0 to 4)	High	29
GERD	33 (84 457)	2.19 (1.48 to 3.25)	4 (2 to 7)	Moderate	59

GERD = gastroesophageal reflux disease; GLP-1RA = glucagon-like peptide-1 receptor agonist; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MASH = metabolic dysfunction-associated steatohepatitis; MASLD = metabolic dysfunction-associated steatotic liver disease; T2DM = type 2 diabetes.

\* Outcomes were not prespecified primary end points in the included trials and were collected through routine adverse event reporting; definitions and ascertainment varied across trials. Follow-up duration ranged from 24 to 277 wk.

**Summary 3**

**In patients who had inadequately controlled T2DM with lower-dose dulaglutide, switching to tirzepatide reduced HbA<sub>1c</sub> and body weight more than escalating dulaglutide at 40 weeks**

Billings LK, Winne L, Sharma P, et al. Comparison of dose escalation versus switching to tirzepatide among people with type 2 diabetes inadequately controlled on lower doses of dulaglutide. A randomized clinical trial. *Ann Intern Med.* 2025;178:609-619. [PMID: 40183678] doi:10.7326/ANNALS-24-03849

**Design:** RCT.

**Blinding:** Blinded (medical director, regulatory scientist, lead statistician, health outcomes scientist, and outcome adjudication committee).

**Setting:** 38 sites in 5 countries (United States, Mexico, Belgium, Germany, and Romania).

**Patients:** 282 adults (mean age, 58 years; 52% men; 81% White) who had T2DM, HbA<sub>1c</sub> between 7% and 9.5%, body mass index of 25 kg/m<sup>2</sup> or higher, and stable body weight and had been receiving a stable weekly dose of dulaglutide, 0.75 or 1.5 mg, for at least 6 months and 0 to 3 oral antihyperglycemic medications at stable doses for at least 3 months. Key exclusions: type 1 diabetes, previous insulin use (unless used for <14 days or for gestational diabetes), or previous dulaglutide dose reduction for intolerance without successful reescalation.

**Interventions:** Once-weekly subcutaneous tirzepatide, started at 2.5 mg for 4 weeks and escalated in 2.5-mg increments every 4 weeks to 15 mg or maximum tolerated dose (*n* = 139), or once-weekly subcutaneous dulaglutide, escalated every 4 weeks to 4.5 mg or maximum tolerated dose (*n* = 143). All patients received diabetes management counseling, and background oral antihyperglycemic medication treatment continued unless hypoglycemia occurred or was likely. Treatment continued for 40 weeks.

**Table.** Tirzepatide Versus Escalation of Dulaglutide in Patients With Inadequately Controlled T2DM (mITT Analysis; *n* = 282)\*

Outcome	Least-Squares Mean Change From Baseline† (SE) at 40 Weeks		Estimated Treatment Difference† (95% CI) at 40 Weeks
	Tirzepatide	Dulaglutide	
HbA <sub>1c</sub> , %	-1.44 (0.07)	-0.67 (0.08)	-0.77 (-0.98 to -0.56)
Weight, kg‡	-10.5 (0.5)	-3.6 (0.5)	-6.9 (-8.3 to -5.5)

HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; mITT = modified intention-to-treat; T2DM = type 2 diabetes.

\* Patients who received ≥1 dose of study drug. 80% vs. 90% achieved maximum tolerated dose at 40 wk. Serious adverse events at 44 wk: 7.2% vs. 7.0%; adverse event discontinuation: 2.9% vs. 0.7%.

† Adjusted for baseline HbA<sub>1c</sub> or weight, dulaglutide dose at screening, number of oral antihyperglycemic medications, and region. Negative values favor tirzepatide.

‡ Tested only if the primary end point was significant (hierarchical testing).

**Summary 4****In patients with malignant tumors, ICI therapy is associated with pituitary immune adverse reactions**

Li Z, Liu Z, Wei H, et al. Risk of pituitary immune-related adverse events caused by immune checkpoint inhibitors: a systematic review and meta-analysis. *Endocr Pract.* 2025;31:1177-1184. [PMID: 40532761] doi:10.1016/j.eprac.2025.06.008

**Design:** Systematic review and meta-analysis. Latest search date: 31 October 2024.

**Inclusion Criteria:** Studies assessing ICI therapy in adults with any type of malignant tumor. The investigators excluded case reports, reviews, and studies in which ICIs were combined with other therapies.

**Primary Outcome:** ICI-related pituitary immune adverse reactions.

**Results:** 17 RCTs were included (21 single-group studies were also included but are not reported here). Risk of bias was low for all trials (Cochrane Risk of Bias Tool).

**Table.** Meta-analysis of Association Between ICI Therapy and ICI-Related Pituitary Immune Adverse Reactions in Adults With Any Type of Malignant Tumor

Comparison	Trials (Patients), <i>n</i> ( <i>n</i> )	Risk Ratio (95% CI)	<i>I</i> <sup>2</sup> , %
Any ICI therapy vs. control	17 (12 978)	10.09 (6.90 to 14.75)	25
ICI monotherapy vs. control	11 (8134)	16.12 (7.90 to 32.92)	0
ICI combination therapy vs. control	6 (4844)	7.78 (4.96 to 12.20)	47
ICI combination therapy vs. ICI monotherapy	3 (2109)	5.42 (3.36 to 8.73)	38

ICI = immune checkpoint inhibitor.

**Summary 5**

**In patients with T2DM, initiating SGLT-2i treatment was linked to increased risk for genital tract infections but not urinary tract infections compared with initiating GLP-1RA treatment at up to 5 years**

Ljungberg C, Kristensen FPB, Dalager-Pedersen M, et al. Risk of urogenital infections in people with type 2 diabetes initiating SGLT2is versus GLP-1RAs in routine clinical care: a Danish cohort study. *Diabetes Care*. 2025;48:945-954. [PMID: 40173095] doi:10.2337/dc24-2169

**Design:** Population-based cohort study with linkage from national databases and follow-up for at most 5 years.

**Setting:** Denmark.

**Patients:** Adults (median age, 63 years; 62% men) who had T2DM, had a first filled prescription for an SGLT-2i or GLP-1RA between January 2016 and December 2021, and had received at least 1 prescription for metformin in the past year. Key exclusions: filled prescription for liraglutide, estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m<sup>2</sup>, or residency in Denmark for less than 12 months before the filled prescription. The main analysis was done in 79 453 patients who were included in the inverse probability of treatment-weighted cohorts.

**Risk Factors:** First filled prescription for an SGLT-2i (n = 52 488) or GLP-1RA (n = 26 965).

*Table.* Association Between Use of SGLT-2is Versus GLP-1RAs and Risk for UTIs or GTIs in Adults With T2DM (ITT Analysis)\*

Outcome and Follow-up	Cumulative Risk, %		Risk Ratio (95% CI)†
	SGLT-2i	GLP-1RA	
<b>UTI</b>			
1 y	10.0	10.2	0.98 (0.94 to 1.03)
5 y	26.3	27.3	0.96 (0.94 to 0.99)
<b>GTI</b>			
1 y	2.0	0.7	2.95 (2.52 to 3.44)
5 y	4.6	2.8	1.64 (1.49 to 1.80)

GLP-1RA = glucagon-like peptide-1 receptor agonist; GTI = genital tract infection; ITT = intention-to-treat; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; T2DM = type 2 diabetes; UTI = urinary tract infection.

\* Analysis censored at an outcome event, death, emigration, end of study, or a maximum of 5 y.

† Inverse probability of treatment-weighted with covariates including age, sex, T2DM duration and complications, hemoglobin A<sub>1c</sub> level, estimated glomerular filtration rate, urogenital pathology, social and frailty markers, use of other glucose-lowering medications, and other comorbid conditions and medications, with death as a competing event.

## Summary 6

### In patients with T2DM, new use of semaglutide was linked to increased risk for nonarteritic anterior ischemic optic neuropathy compared with new use of SGLT-2is at up to 5 years

Simonsen E, Lund LC, Ernst MT, et al. Use of semaglutide and risk of non-arteritic anterior ischemic optic neuropathy: a Danish-Norwegian cohort study. *Diabetes Obes Metab.* 2025;27:3094-3103. [PMID: 40098249] doi:10.1111/dom.16316

**Design:** Population-based cohort study using data from linked national databases, with up to 5 years of follow-up.

**Setting:** Denmark and Norway.

**Patients:** Patients (55% men; 41% aged 50 to 64 years) who had T2DM and were new users of semaglutide or SGLT-2is between 2018 and May 2022 (Norway) or June 2024 (Denmark). Key exclusions: previous anterior ischemic optic neuropathy, previous use of SGLT-2is or other GLP-1RAs in new initiators of semaglutide or previous use of GLP-1RAs in new initiators of SGLT-2is, and migration in the 2 years before study entry. The main analysis was done in 121 650 patients who were included in the standardized, mortality ratio-weighted analysis.

**Risk Factors:** First-ever filled prescription for semaglutide ( $n = 60\,887$ ) or an SGLT-2i ( $n = 60\,763$ ).

**Table.** Association Between New Use of Semaglutide Versus SGLT-2is and Risk for NAION in Patients With T2DM (ITT Analysis)\*

Cohort	Incidence Rate per 10 000 Person-Years†		Hazard Ratio (95% CI)†	Pooled Hazard Ratio (95% CI)†
	Semaglutide	SGLT-2i		
Denmark	2.18	1.02	2.17 (1.20 to 3.92)	2.81 (1.67 to 4.75)
Norway	2.90	0.40	7.25 (2.34 to 22.4)	-

ITT = intention-to-treat; NAION = nonarteritic anterior ischemic optic neuropathy; SGLT-2i = sodium-glucose cotransporter-2 inhibitors; T2DM = type 2 diabetes.

\* Censored at diagnosis of NAION, death, emigration, end of data availability, or 5 y.

† Propensity score-weighted with age, sex, calendar time, prescriber type for initial prescription (Denmark only), markers of diabetes severity, systemic risk factors for NAION, and specific comorbid conditions and concurrent medications. Standardized mortality ratio weights were calculated using propensity scores. Inverse probability weighting of complete cases was used to account for potential selection bias due to missing covariate information.

**Summary 7**

**In adults with T2DM and high cardiorenal risk, canagliflozin versus placebo reduced major adverse cardiovascular events, HF hospitalization, and kidney disease progression, with consistent effects across age groups**

Siriwardana A, Buizen L, Jun M, et al. Cardiovascular, kidney and safety outcomes with canagliflozin in older adults: a combined analysis from the CANVAS Program and CREDENCE trial. *Diabetes Obes Metab.* 2025;27:1972-1979. [PMID: 39781601] doi:10.1111/dom.16190

**Design:** Post hoc pooled analysis of individual patient data from 3 RCTs: CANVAS, CANVAS-Renal, and CREDENCE trials.

**Description of Individual Studies:** Randomized, double-blind, placebo-controlled trials of adults with T2DM (mean age, 64 years; most were White). CANVAS included 10 142 patients who were aged 30 years or older and had an eGFR of at least 30 mL/min/1.73 m<sup>2</sup> and established atherosclerotic cardiovascular disease or were aged 50 years or older and had at least 2 cardiovascular disease risk factors. CREDENCE included 4401 patients aged 30 years or older with T2DM and CKD (eGFR, ≥30 to <90 mL/min/1.73 m<sup>2</sup> and urinary albumin-creatinine ratio, >300 to ≤5000 mg/g).

**Interventions:** Canagliflozin versus placebo, added to usual care. Dosage of canagliflozin was 100 or 300 mg/d in CANVAS; 100 mg/d, with optional titration to 300 mg/d, in CANVAS-Renal; and 100 mg/d in CREDENCE.

**Primary Outcomes:** Cardiovascular and kidney outcomes from the CANVAS and CREDENCE trials.

**Table.** Pooled Individual Patient Data Analysis of Canagliflozin Versus Placebo in Patients With T2DM and High Cardiorenal Risk (ITT Analysis; n = 14 543)

Age	Patients, n	HR (95% CI) for MACE*	P for Interaction	HR (95% CI) for KCE†	P for Interaction
<b>All</b>	14 543	0.84 (0.76 to 0.93)		0.63 (0.53 to 0.77)	
<b>Subgroup</b>			0.66		0.14
<65 y	7927	0.85 (0.73 to 0.99)		0.67 (0.53 to 0.84)	
65 to 75 y	5281	0.82 (0.69 to 0.96)		0.53 (0.36 to 0.78)	
>75 y	1335	0.84 (0.63 to 1.13)		0.63 (0.30 to 1.32)	

HR = hazard ratio; ITT = intention-to-treat; KCE = kidney composite end point; MACE = major adverse cardiovascular events; T2DM = type 2 diabetes.

\* Nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

† Doubling of serum creatinine, kidney failure, or death due to kidney disease.

## Summary 8

### In patients with MASH and moderate or advanced liver fibrosis, weekly semaglutide improved histologic steatohepatitis and fibrosis at 72 weeks

Sanyal AJ, Newsome PN, Kliers I, et al; ESSENCE Study Group. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med*. 2025;392:2089-2099. [PMID: 40305708] doi:10.1056/NEJMoa2413258

**Design:** Planned interim analysis of the first 800 patients enrolled in an RCT.

**Blinding:** Blinded (patients, health care providers, pathologists, and adverse events assessment committee).

**Setting:** 253 clinical sites in 37 countries.

**Patients:** 800 adults (mean age, 56 years; 57% women; 68% White; 56% with T2DM) who had histologically confirmed MASH, Nonalcoholic Steatohepatitis Clinical Research Network liver fibrosis stage 2 (31%) or 3 (69%), and a nonalcoholic fatty liver disease activity score of at least 4. Key exclusions: chronic liver disease, alcohol consumption above 20 g/d for women or 30 g/d for men, hepatic decompensation or Model for End-Stage Liver Disease score above 12, eGFR less than 30 mL/min/1.73 m<sup>2</sup>, history of acute pancreatitis, or treatment with a GLP-1RA in the past 90 days.

**Interventions:** Weekly subcutaneous semaglutide, titrated from 0.25 mg to 2.4 mg at 16 weeks (*n* = 534), or placebo (*n* = 266), added to standard MASH care.

**Table.** Semaglutide Versus Placebo in Patients With MASH and Stage 2 or 3 Liver Fibrosis (Planned Interim ITT Analysis of the First 800 Patients Enrolled)\*

Outcome	Event Rate, %		RBI (95% CI), %†	NNT (95% CI)†
	Semaglutide	Placebo		
Resolution of steatohepatitis without worsening fibrosis at 72 wk‡	62.9	34.3	84 (55 to 121)	4 (3 to 5)
Reduction in fibrosis without worsening steatohepatitis at 72 wk§	36.8	22.4	66 (30 to 115)	7 (5 to 13)

ITT = intention-to-treat; MASH = metabolic dysfunction-associated steatohepatitis; NNT = number need to treat; RBI = relative benefit increase.

\* Adverse event rates for semaglutide vs. placebo: any adverse event, 86% vs. 80%; serious adverse event, 13% vs. 13%; fatal adverse event, 0% vs. 2%; nausea, 36% vs. 13%; diarrhea, 27% vs. 12%; constipation, 22% vs. 8%; and vomiting, 19% vs. 6%.

† RBI, NNT, and CI calculated from event rates in supplemental file.

‡ Nonalcoholic fatty liver disease activity score of 0 for ballooning and 0 to 1 for inflammation.

§ ≥1-stage reduction on Nonalcoholic Steatohepatitis Clinical Research fibrosis scale; score range, 0 to 4 (cirrhosis).

**Summary 9**

**In patients with T2DM and CKD or HF with preserved or reduced ejection fraction, finerenone had consistent cardiovascular and kidney effects across baseline HbA<sub>1c</sub> levels**

Ostrominski JW, Claggett BL, Miao ZM, et al. Efficacy and safety of finerenone in type 2 diabetes: a pooled analysis of trials of heart failure and chronic kidney disease. *Diabetes Care*. 2025;48:745-755. [PMID: 40019856] doi:10.2337/dc24-1873

**Design:** Prespecified pooled individual patient analysis of 3 phase 3 RCTs (FIDELIO-DKD [Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease], FIGARO-DKD [Finerenone in reducing cardiovascular mortality and morbidity in Diabetic Kidney Disease], and FINEARTS-HF [Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure]).

**Description of Individual Studies:** Placebo-controlled RCTs of adults (mean age, 66 years; 68% men; 70% White; mean HbA<sub>1c</sub>, 7.6% [among 15 365 analyzed]) with T2DM and CKD, or with HF with preserved or mildly reduced ejection fraction with or without T2DM. FIDELIO-DKD and FIGARO-DKD enrolled adults with T2DM and proteinuric CKD (eGFR ≥25 mL/min/1.73 m<sup>2</sup>) and excluded patients with symptomatic HF with reduced ejection fraction. FINEARTS-HF enrolled adults aged 40 years or older with symptomatic HF with preserved or mildly reduced ejection fraction (left ventricular ejection fraction ≥40%), elevated natriuretic peptide levels, recent diuretic use, and eGFR of at least 25 mL/min/1.73 m<sup>2</sup>.

**Interventions:** Once-daily finerenone or placebo. Finerenone treatment was started at 10 mg and titrated to 20 mg as tolerated in patients with a baseline eGFR less than 60 mL/min/1.73 m<sup>2</sup> (FIDELIO-DKD and FIGARO-DKD) or less than or equal to 60 mL/min/1.73 m<sup>2</sup> (FINEARTS-HF). For patients with a baseline eGFR of at least 60 mL/min/1.73 m<sup>2</sup> (FIDELIO-DKD and FIGARO-DKD) or greater than 60 mL/min/1.73 m<sup>2</sup> (FINEARTS-HF), finerenone treatment was started at 20 mg once daily; further titration to 40 mg once daily was permitted only in FINEARTS-HF.

**Primary Outcome:** Cardiovascular death.

**Table.** Pooled Individual Patient Data Analysis of Finerenone Versus Placebo in Patients With T2DM and CKD or HFmrEF or HFpEF (ITT Analysis; n = 15 365)\*

Baseline HbA <sub>1c</sub>	HR (95% CI) for CV Death	P for Interaction	HR (95% CI) for MACE†	P for Interaction	HR (95% CI) for KCE‡	P for Interaction
<b>All</b>	0.89 (0.78 to 1.01)		0.91 (0.85 to 0.98)		0.80 (0.72 to 0.90)	
<b>Subgroup</b>		0.75		0.99		0.14
<6.9%	0.89 (0.68 to 1.16)		0.88 (0.77 to 1.02)		0.92 (0.76 to 1.11)	
≥7.0 to 8.0%	0.86 (0.64 to 1.15)		0.90 (0.77 to 1.05)		0.69 (0.56 to 0.85)	
≥8.1%	0.77 (0.59 to 1.00)		0.90 (0.78 to 1.03)		0.74 (0.61 to 0.90)	

CKD = chronic kidney disease; CV = cardiovascular; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; ITT = intention-to-treat; KCE = kidney composite end point; MACE = major adverse cardiovascular events; T2DM = type 2 diabetes.

\* Median follow-up of 2.9 y for patients with T2DM and available baseline HbA<sub>1c</sub> levels.

† Nonfatal myocardial infarction, nonfatal stroke, HF hospitalization, or CV death.

‡ Sustained ≥50% decline in estimated glomerular filtration rate (eGFR), sustained eGFR <15 mL/min/1.73 m<sup>2</sup>, end-stage kidney disease, or death due to kidney failure.