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DERP Surveillance: Newer Diabetes Drugs and Cardiovascular Disease Outcomes

December 2021

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Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the last systematic review on Newer Diabetes Drugs and Cardiovascular Disease (CVD) Outcomes.[1] The literature search for this report focuses on new randomized controlled trials (RCTs), large prospective and retrospective cohort studies, and actions taken by the US Food and Drug Administration (FDA) since the last report, including approval of new drugs, formulations, or indications, and identification of serious harms. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participants commission an update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the second surveillance document on this topic since the completion of the last systematic review update in February 2020.[1] The search strategy for that systematic review was through October 2, 2019.

Table 1. Topic History and Search Dates

Document Type	Date Presented	Search Dates
Surveillance Report	December 2020	10/02/19 to 11/02/20
Systematic Review Update #4	February 2020	01/01/17 to 10/02/19
Systematic Review Update #3	September 2017	02/01/16 to 07/01/17
Systematic Review Update #2	July 2016	01/01/13 to 02/01/16
Systematic Review	February 2011	07/01/07 to 07/01/10

PICOS

Population

Adults with type 2 diabetes

Interventions

Table 2. Included Interventions

Class	Generic Names	Brand Names	FDA Approval Date
Oral drugs			
SGLT-2 inhibitors	Ertugliflozin Empagliflozin Dapagliflozin Canagliflozin	Steglatro Jardiance Farxiga Invokana	12/19/17 8/1/14 1/8/14 3/29/13
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia	1/25/13 5/2/11 7/31/09 10/16/06
GLP-1 agonists	Semaglutide (oral)	Rybelsus	9/20/19
Fixed-dose combination products of oral drugs			
SGLT-2 inhibitor with DPP-4 inhibitor and metformin	Empagliflozin-linagliptin-metformin hydrochloride ER	Trijardy XR	01/27/20
SGLT-2 inhibitor with DPP-4 inhibitor	Dapagliflozin-saxagliptin Empagliflozin-linagliptin	Qtern Glyxambi	2/27/17 1/30/15
SGLT-2 inhibitor with metformin	Ertugliflozin-metformin Empagliflozin-metformin ER Canagliflozin-metformin ER Empagliflozin-metformin Dapagliflozin-metformin ER Canagliflozin-metformin	Segluromet Synjardy XR Invokamet XR Synjardy Xigduo XR Invokamet	12/19/17 12/9/16 9/20/16 8/26/15 10/29/14 8/8/14
DPP-4 inhibitor with TZD	Alogliptin-pioglitazone	Oseni	1/25/13
DPP-4 inhibitor with metformin	Linagliptin-metformin ER Alogliptin-metformin Sitagliptin-metformin ER Linagliptin-metformin Saxagliptin-metformin ER Sitagliptin-metformin	Jentadueto XR Kazano Janumet XR Jentadueto Kombiglyze XR Janumet	5/27/16 1/25/13 2/2/12 1/30/12 11/5/10 3/30/07
Subcutaneous injection drugs			
GLP-1 agonists	Semaglutide Lixisenatide Dulaglutide Albiglutide Exenatide ER Liraglutide Exenatide	Ozempic Adlyxin Trulicity Tanzeum Bydureon Victoza Byetta	12/5/17 7/27/16 9/18/14 4/15/14 1/27/12 1/25/10 4/28/05
GLP-1 agonist with long-acting insulin	Liraglutide-insulin degludec U100/3.6 mg Lixisenatide-insulin glargine U100/33 mg	Xultophy Soliqua	11/21/16 11/21/16

Abbreviations. DPP-4: dipeptidyl peptidase 4; ER: extended release; FDA: US Food and Drug Administration; GLP-1: glucagon-like peptide 1; SGLT-2: sodium-glucose cotransporter-2; TZD: thiazolidinediones; XR: extended release.

Comparators

- Another listed intervention (head-to-head comparisons)
- Combination therapies versus monotherapy of included intervention types
- Placebo

Outcomes

- Mortality (e.g., all-cause and cardiovascular-related [CV-related])
- CVD outcomes (e.g., fatal or nonfatal myocardial infarction [MI], fatal or nonfatal stroke, hospitalization for heart failure [hHF], major adverse cardiovascular event [MACE])
- Serious adverse events (SAEs; e.g., investigator-determined SAEs including events related to study treatment, events causing permanent discontinuation, and prespecified events of interest [e.g., pancreatitis, hypoglycemia, neoplasm, allergic reaction, genital infection])

Study Designs

- RCTs
- Large prospective and retrospective cohort studies
  - Sample size of ≥ 10,000 participants

Key Questions

KQ1. What is the effectiveness of newer diabetes medications for CV events, including mortality, in adults with type 2 diabetes?

  a. Does the effect differ when used as monotherapy versus combination therapy?
  b. Does the effect differ in patients with and without prior cardiovascular disease?
  c. Is there evidence of a class effect?
  d. What are the harms associated with treatment?

KQ2. What are the characteristics of ongoing studies for newer diabetes medications and CVD outcomes?

Methods

Using the PICOS outlined above, Center for Evidence-based Policy (Center) researchers searched for eligible RCTs and large cohort studies in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Epub Ahead of Print, Ovid MEDLINE, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from November 2, 2020 to October 19, 2021. We used the Google search engine to identify studies published since the implementation of the search strategy in the surveillance (December 2020). We used limits for English language and human participants. We also searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. To identify new drugs, we used Google and searched CenterWatch, a privately owned database of clinical trials information, and IPD Analytics, a privately owned database of pharmaceutical information.

Findings

New Drugs or Formulations

Subcutaneous exenatide ER (extended release), originally marketed as Bydureon and Bydureon Pen, was discontinued by AstraZeneca in March 2021 for business reasons.[2,3] Exenatide ER will continue to be sold under the brand name Bydureon BCise, with the same formulation and a new auto-injector pen that does not require titration or reconstitution.[3]

New Indications

We identified 2 new indications (Table 3) for sodium-glucose cotransporter-2 (SGLT-2) inhibitors since the last surveillance. Additionally, 2 glucagon-like peptide 1 (GLP-1) agonists gained expanded indications for chronic weight management, which is beyond the scope of the report. Liraglutide subcutaneous (SC) sold under the brand name Saxenda is now indicated for chronic weight management in adults with obesity and type 2 diabetes in December 2020.[4] Semaglutide SC sold under the brand name Ozempic gained an indication for chronic weight management in adults with obesity or overweight with at least 1 weight-related condition (e.g., type 2 diabetes) in June 2021.[5]

Table 3. New Indications of Newer Diabetes Drugs for CVD Outcomes

Drug Name	Class	Indication	Approval Date
Dapagliflozin	SGLT-2 inhibitor	To reduce the risk of kidney function decline, kidney failure, CV death and hHF in adults with chronic kidney disease, with or without type 2 diabetes.[6,7]	April 2021
Empagliflozin	SGLT-2 inhibitor	To reduce the risk of CV death plus hHF in adults with HFrEF, with or without type 2 diabetes.[8,9]	August 2021

Abbreviations. CV: cardiovascular; CVD: cardiovascular disease; HFrEF: heart failure with reduced ejection fraction; hHF: hospitalization for heart failure; SGLT-2: sodium-glucose cotransporter-2.

New Serious Harms or Warnings

In June 2021, the FDA removed a warning for risk of increased low-density lipoprotein (LDL) cholesterol from the prescribing label of fixed-dose combination empagliflozin with metformin products (i.e., Synjardy, Synjardy XR [extended release]).[10,11] As of June 16, 2021, the FDA is evaluating the need for regulatory action for a potential signal of drug-induced liver injury for GLP-1 agonists and GLP-1 agonists with long-acting insulin.[12]

We identified 9 new serious harms or warnings (Table 4) since the last surveillance including 1 for dipeptidyl peptidase 4 (DPP-4) inhibitors, 4 for GLP-1 agonists, 3 for SGLT-2 inhibitors, and 1 for fixed-dose combination products.

Table 4. New Serious Harms or Warnings of Newer Diabetes Drugs for CVD Outcomes

Drug	New Serious Harms or Warnings	Date
DPP-4 inhibitors		
Sitagliptin, sitagliptin-metformin	New warning for risk of acute renal failure and hypoglycemia with concomitant insulin or insulin secretagogue use was added to the sitagliptin line of products (i.e., Januvia, Janumet)[13-15]	December 2020
GLP-1 agonists		
Semaglutide (oral, subcutaneous)	New warnings for increased risk of hypersensitivity reaction and risk of hypoglycemia with concomitant insulin or insulin secretagogue use were added to semaglutide (i.e., Rybelsus, Ozempic).[16,17]	April 2021
Liraglutide	New warnings for increased risk of hypoglycemia with concomitant insulin or insulin secretagogue use were added to liraglutide products (i.e., Saxenda, Victoza).[4,18] Additional warnings for increased risk of acute pancreatitis, heart rate increase, and suicidal ideation or behavior were added to liraglutide (i.e., Saxenda).[4]	November 2020 December 2020
Exenatide	New warnings for increased risk of hypoglycemia with concomitant insulin or insulin secretagogue use were added to exenatide (i.e., Byetta) products.[19]	June 2021
SGLT-2 inhibitors		
Empagliflozin, empagliflozin-linagliptin, empagliflozin-metformin	New warnings for increased risk of ketoacidosis and volume depletion were added to the empagliflozin line of products (i.e., Jardiance, Glyxambi, Synjardy, Synjardy XR).[10,11,20,21]	June 2021
Empagliflozin	Additional new warnings for increased risk of urosepsis and pyelonephritis, and necrotizing fascitis of the perineum were added to single agent empagliflozin (i.e., Jardiance).[20]	June 2021
Empagliflozin with metformin	A new boxed warning for lactic acidosis was added to empagliflozin with metformin products (i.e., Synjardy, Synjardy XR).[10,11]	June 2021
Empagliflozin-linagliptin-metformin ER	New warning for increased risk of volume depletion was added to empagliflozin-linagliptin-metformin ER (i.e., Trijardy XR)[22]	June 2021

Abbreviations. CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase 4; ER: extended release; GLP-1: glucagon-like peptide 1; SGLT-2: sodium-glucose cotransporter-2; XR: extended release.

Published Studies

Overall, we identified 20 new eligible studies[23-38] in this surveillance period (Table 5), all of which were large cohort studies. Sample sizes for the cohorts ranged from 11,014 to 714,582.

Of the 20 eligible cohort studies, outcomes were compared among:

- GLP-1 agonists and SGLT-2 inhibitors in 5 studies[33-35,37,39]
- GLP-1 agonists or SGLT-2 inhibitors to other diabetic treatments in 2 studies[24,40]
- GLP-1 agonists or SGLT-2 inhibitors as add-on therapies to metformin in 1 study[26]
- SGLT-2 inhibitors alone in 1 study[30]
- SGLT-2 inhibitors and DPP-4 inhibitors in 3 studies[28,31,41]

- SGLT-2 inhibitors to other diabetic treatments in 4 studies[27,36,38,42]
- SGLT-2 inhibitors or DPP-4 inhibitors to other diabetic treatments in 1 study[32]
- DPP-4 inhibitors to other diabetic treatments in 3 studies[23,25,29]

Table 5. Included Published Studies of Newer Diabetes Drugs for CVD Outcomes

Author, Year Trial Number Trial Name	Enrollment Study Country	Treatment Groups	Eligible Outcomes
Prospective and retrospective studies: *GLP-1 agonists vs. other diabetic treatments*			
Lugner et al., 2021[33]	N = 21,745 Sweden	• GLP-1 agonists • SGLT-2 inhibitors	• MACE • Fatal or non-fatal CVD including MI and stroke • HF • Severe renal disease • Hyper- or hypoglycemia • Ketoacidosis • Diabetic nephropathy or retinopathy • All-cause mortality
Norgaard et al., 2021[34]	N = 13,468 Denmark	• GLP-1 agonist • SGLT-2 inhibitors	• CV death, MI, or stroke • CV death • MI • Stroke • hHF
Poonawalla et al., 2021[35]	N = 11,014 United States	• GLP-1 agonists • SGLT-2 inhibitors	• MI, stroke, or all-cause mortality • All-cause mortality or HF • All-cause mortality • MI • Stroke • HF
Thomsen et al., 2021[37] NCT03993132 EMPLACE	N = 27,204 Denmark	• Liraglutide • Empagliflozin	• MACE including stroke, MI, UA, coronary revascularization, hHF • hHF or all-cause mortality • First hHF • First initiation of loop-diuretic therapy • All-cause mortality or hospitalization
Patorno et al., 2021[39]	N = 372,080 United States	• GLP-1 agonists • SGLT-2 inhibitors	• Composite of hospitalization for acute MI, ischemic or hemorrhagic stroke, or hHF • MI • Ischemic or hemorrhagic stroke • All-cause mortality

Author, Year Trial Number Trial Name	Enrollment Study Country	Treatment Groups	Eligible Outcomes
			• MI, ischemic or hemorrhagic stroke, or all-cause mortality
Prospective and retrospective studies: *SGLT-2 inhibitors vs. other diabetic treatments*			
Ryan et al., 2018[42] NCT03492580 OBSERVE-4D	N = 714,582 United States	• Canagliflozin • Empagliflozin • Dapagliflozin • DPP-4 inhibitors • GLP-1 agonists • AHAs • Thiazolidinediones • Sulfonylureas • Insulin	• Number of hHF • Number of below-knee lower extremity amputations
Han et al., 2020[28]	N = 408,506 South Korea	• SGLT-2 inhibitors • DPP-4 inhibitors	• hHF • All-cause mortality • MI • Stroke • Diabetic ketoacidosis • Bone fracture • Severe hypoglycemia • Genital infection • UTI
Horii et al., 2020[30]	N = 171,622 Japan	• SGLT-2 inhibitors	• Hypoglycemia
Seong et al., 2021[41]	N = 260,336 South Korea	• Dapagliflozin • DPP-4 inhibitors	• MACE
Fralick et al., 2021[27]	N = 19,928 United States	• SGLT-2 inhibitors • Metformin	• Composite of hospitalization for HF, MI, or stroke • Hypoglycemia • Diabetic ketoacidosis • Genital infection • Lactic acidosis • Acute kidney injury
Idris et al., 2021[31]	N = 24,438 United Kingdom	• SGLT-2 inhibitors • DPP-4 inhibitors	• All-cause mortality • CV death • hHF • CKD diagnosis
Komuro et al., 2021[32]	N = 108,362 Japan	• SGLT-2 inhibitors • DPP-4 inhibitors • Other glucose-lowering drugs	• Diagnosis of HF and/or CKD • HF • CKD • All-cause mortality • Stroke • MI

Author, Year Trial Number Trial Name	Enrollment Study Country	Treatment Groups	Eligible Outcomes
Real et al., 2021[36] CVD-Real Catalonia	N = 25,834 Spain	• SGLT-2 inhibitors • Other glucose-lowering drugs	• All-cause mortality • hHF • CKD • MACE
Xie et al., 2021[38]	N = 128,293 United States	• SGLT-2 inhibitors • Sulfonylureas	• All-cause mortality
Prospective and retrospective studies: *DPP-4 inhibitors vs. other diabetic treatments*			
Baksh et al., 2021[23]	N = 113,296 United States	• DPP-4 inhibitors • Sulfonylureas • Metformin	• MACE including MI, cardiac arrest, CAB, coronary angioplasty, HF, stroke, inpatient death • Acute MI • Stroke • HF
Cristiano et al., 2021[25]	N = 81,116 United States	• DPP-4 inhibitors • Other treatments excluding pioglitazone, SGLT-2 inhibitors or GLP-1 agonists	• All-cause mortality • Acute kidney injury • Angioplasty • Atrial fibrillation • CABG • CAD • Cerebrovascular attack • HF • MI • PAD
Herrera Comoglio et al., 2021[29]	N = 123,260 Spain	• DPP-4 inhibitors • Sulfonylureas • Meglitinides • Metformin	• MACE • MI • Stroke • All-cause mortality • HF • PAD
Prospective and retrospective studies: *newer diabetes drugs vs. other diabetic treatments*			
Franklin et al., 2021[40]			
NCT03936049 DUPLICATE-LEADER	N = 168,690 United States	• Liraglutide vs. DPP-4 inhibitor	• Composite of stroke, MI, and mortality
NCT03936062 DUPLICATE-TECOS	N = 349,476 United States	• Sitagliptin vs. sulfonylurea	• Composite of ACS/UA, stroke, MI, and mortality
NCT03936036 DUPLICATE-CARMELINA	N = 101,830 United States	• Linagliptin vs. sulfonylurea	• Composite of stroke, MI, and mortality
NCT03936023 DUPLICATE-SAVOR-TIMI	N = 182,126 United States	• Saxagliptin vs. sulfonylurea	• Composite of stroke, MI, and mortality
NCT04215536 DUPLICATE-EMPAREG	N = 103,752 United States	• Empagliflozin vs. DPP-4 inhibitor	• Composite of stroke, MI, and mortality
NCT04215523 DUPLICATE-DECLARE	N = 49,790 United States	• Dapagliflozin vs. DPP-4 inhibitor	• Composite of stroke, MI, and mortality

Author, Year Trial Number Trial Name	Enrollment Study Country	Treatment Groups	Eligible Outcomes
NCT03936010 DUPLICATE-CANVAS	N = 152,202 United States	• Canagliflozin vs. DPP-4 inhibitor	• Composite of stroke, MI, and mortality
Baviera et al.[24] (2021)	N = 92,434 Italy	• GLP-1 agonists or SGLT-2 inhibitors • Other AHAs	• All-cause mortality • Hospital admission for cerebrovascular disease • CVD • Ischemic stroke • ACS • HF • PVD • Lower limb complications • SAEs including hospital admission for hypoglycemia, ketoacidosis, amputation, acute renal failure, syncope, fracture, and diabetes with coma
Prospective and retrospective studies: *newer diabetes drugs as add-on therapies to metformin vs. other diabetic treatments as add-on therapies to metformin*			
DeRemer et al.[26] (2021)	N = 13,006 United States	• GLP-1 agonists or SGLT-2 inhibitors as add on to metformin • Metformin	• First major CV composite including stroke, MI, CHF • Stroke • MI • CHF

Abbreviations. ACS: acute coronary syndrome; AHA: antihyperglycemic agent; CAB: coronary artery bypass; CABG: coronary artery bypass graft; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; HF: heart failure; hHF: hospitalization for heart failure; MACE: major adverse cardiovascular event; MI: myocardial infarction; PAD: peripheral arterial disease; PVD: peripheral vascular disease; SAE: serious adverse events; SGLT-2: sodium glucose co-transporter 2; UA: unstable angina; UTI: urinary tract infection.

Ongoing Studies

We identified 31 ongoing studies[43-73] evaluating CVD outcomes (Table 6), including 1 head-to-head RCT, 1 RCT comparing semaglutide to dietary intervention, 8 RCTs comparing newer diabetes drugs to standard of care (SOC), 12 placebo-controlled RCTs, and 9 cohort studies.

The 1 head-to-head RCT[72] we identified is comparing insulin glargine-lixisenatide to dulaglutide with an estimated sample size of 40 participants, and estimated completion date of December 2022. The 1 RCT[70] comparing semaglutide to dietary intervention has an estimated enrollment of 100 participants, and is expected to be completed by March 2023.

The 8 RCTs[49,50,52,54-56,64,66] comparing newer diabetes drugs to SOC have sample sizes ranging from 40 to 12,500 and are evaluating CVD outcomes in:

- 5 studies of SGLT-2 inhibitors[49,50,52,64,66]
- 3 studies of GLP-1 agonists[54-56]

Of the 8 RCTs comparing newer diabetes drugs to SOC, 2 RCTs[49,66] are expected to be completed in 2022, 2 RCTs[50,54] in 2023, 1 RCT[56] in 2024, and 1 RCT[52] in 2025. One RCT[64] comparing a SGLT-1 inhibitor to SOC was expected to be completed in 2020 and 1 RCT[55] comparing a GLP-1 agonist to SOC was completed in August 2020, but we did not identify any publications related to these trials.

The 12 placebo-controlled RCTs[44-47,53,57,60,61,65,67,68,71] have sample sizes ranging from 52 to 9,642 and are evaluating CVD outcomes in:

- 9 studies of SGLT-2 inhibitors[44-47,53,61,65,67,68]
- 3 studies of GLP-1 agonists[57,60,71]

Of the 12 placebo-controlled RCTs, 1 RCT[61] is expected to be completed in November 2021, 3 RCTs[44-46] in 2022, 4 RCTs[47,53,65,71] in 2023, and 4 RCTs[57,60,67,68] in 2024.

The 9 cohort studies[43,48,51,58,59,62,63,69,73] have sample sizes ranging from 20,000 to 232,000 and are evaluating CVD outcomes in:

- 6 studies of SGLT-2 inhibitors[48,51,62,63,69,73]
- 2 studies of GLP-1 agonists[43,58]
- 1 study of DPP-4 inhibitors[59]

Of the 9 cohort studies, 3 studies[62,69,73] are estimated to be completed in 2021, 2 studies[48,63] in 2022, and 1 study[43] in 2024. Two cohort studies[51,58] were expected to be completed in 2020 and 1 cohort study[59] completed in 2019, but we did not identify any publications related to these trials.

Table 6. Included Ongoing Studies of Newer Diabetes Drugs for CVD Outcomes

Trial Number Trial Name Estimated Completion	Estimated Enrollment Treatment Groups	Eligible Outcomes
GLP-1 agonists		
NCT01919489[55] August 2020 (actual) *No publications have been identified*	N = 273 (actual) • Liraglutide + OAD • Insulin glargine + OAD	• Hypoglycemic episodes • ER visits and readmissions • Acute renal failure
NCT04034524[58] December 2020	N = 20,000 Retrospective cohort • GLP-1 agonists except liraglutide • Basal insulin	• Composite of MI, stroke • MI • Stroke • Serious hypoglycemia • Acute pancreatitis • Acute cholecystitis

Trial Number Trial Name Estimated Completion	Estimated Enrollment Treatment Groups	Eligible Outcomes
NCT04893148[72] GLP1RA2021 December 2022	N = 40 • Insulin glargine/lixisenatide • Dulaglutide	• Incidence of hypoglycemia
NCT04938388[70] March 2023	N = 100 • Semaglutide (oral) • Fresh organic vegetables	• Number of participants with treatment-related AEs
NCT03948347[54] LAMP May 2023	N = 1,708 • Liraglutide 1.8 mg • SOC	• New ischemic or hemorrhagic stroke events • New vascular events (stroke, TIA, MI, or vascular death)
NCT04916470[71] STEP HFpEF DM August 2023	N = 610 • Semaglutide • Placebo	• Number of treatment-emergent severe or clinically significant hypoglycemia episodes
NCT03914326[60] SOUL July 2024	N = 9,642 • Semaglutide 3, 7, or 14 mg • Placebo	• MACE • All-cause mortality • CV-related death • Nonfatal MI • Nonfatal stroke • hHF
NCT03819153[57] FLOW August 2024	N = 3,508 • Semaglutide 1mg • Placebo	• Composite of eGFR decline, ESRD, renal death, or CV death • MACE • All-cause mortality • Major adverse limb event • Severe hypoglycemia
NCT04572165[43] August 2024	N = 200,000 Retrospective cohort • Semaglutide • Sulfonylureas • SGLT-2 inhibitors • Insulin	• Occurrence of first time malignant pancreatic neoplasm
NCT04255433[56] SURPASS-CVOT October 2024	N = 12,500 • Tirzepatide SC • Dulaglutide SC	• MACE • All-cause mortality • CV death • MI • Stroke • Revascularization • UA
DPP-4 inhibitors		
NCT02197078[59] February 2019 (actual) *No publications have been identified*	N = 189,426 (actual) Retrospective cohort • Linagliptin • Glitazones • Sulfonylurea • Other DPP-4 inhibitors	• MACE • Coronary revascularization • ACS • Stroke • hHF

Trial Number Trial Name Estimated Completion	Estimated Enrollment Treatment Groups	Eligible Outcomes
SGLT-2 inhibitors		
NCT01001962[64] PREHYPD January 2020	N = 1,054 • Empagliflozin 25 mg • Metformin 2,000 mg	• CV-related mortality and morbidity
NCT03627039[51] MACES August 2020	N = 20,000 Retrospective cohort • SGLT-2 inhibitor • Metformin	• MACE • Hypoglycemia • Diabetic ketoacidosis • Lactic acidosis • Acute kidney injury • Genital infection
NCT04882813[73] DUPLICATE-DAPA-CKD June 2021	N = 87,727 (actual) Retrospective cohort • Dapagliflozin • Sitagliptin	• Composite of ESRD or all-cause mortality • Relative hazard of ESRD • Relative hazard of all-cause mortality
NCT03817463[62] November 2021	N = 171,808 (actual) Prospective cohort • Empagliflozin or an SGLT-2 inhibitor • DPP-4 inhibitors	• All-cause mortality • hHF • MACE • CV-related death
NCT03794518[61] December 2021	N = 648 • Dapagliflozin 10 mg + pioglitazone 15 mg • Placebo and SOC	• First hHF • All-cause mortality
NCT03464045[69] December 2021	N = 98,000 (actual) Prospective cohort • Empagliflozin • DPP-4 inhibitors • SGLT-2 inhibitors	• Occurrence of urinary tract cancer • Occurrence of bladder cancer • Occurrence of renal cancer
NCT04298229[49] DICTATE-AHF March 2022	N = 240 • Dapagliflozin 10 mg + protocolized diuretic therapy • Protocolized diuretic therapy	• Worsening HF • Hospital readmission
NCT03087773[44] EMMY April 2022	N = 476 (actual) • Empagliflozin 10 mg • Placebo	• hHF • All-cause mortality
NCT03363464[63] EMPRISE June 2022 *Published preliminary results are addressed in previous report, no full publications have been identified*	N = 232,000 Retrospective cohort • Empagliflozin • DPP-4 inhibitor • GLP-1 agonist	• Hospitalization for MI, stroke, or CV death • hHF • All-cause mortality

Trial Number Trial Name Estimated Completion	Estimated Enrollment Treatment Groups	Eligible Outcomes
NCT02864914[48] August 2022	N = 99,000 (actual) Retrospective cohort • Empagliflozin • DPP-4 inhibitor	• Severe UTI complications • Genital infections • Diabetic ketoacidosis • Chronic kidney disease • Acute kidney injury
NCT03594110[46] EMPA-KIDNEY December 2022	N = 6,609 (actual) • Empagliflozin • Placebo	• Composite of kidney disease progression or CV death • First hHF or CV death • All-cause hospitalizations • All-cause mortality • CV death • CV death or ESRD
NCT04509674[45] EMPACT-MI December 2022	N = 3,312 • Empagliflozin • Placebo	• hHF or all-cause mortality • CV hospitalizations or all-cause mortality • MI hospitalizations or all-cause mortality • CV death
NCT05037695[66] SAFE-PCI December 2022	N = 40 • Empagliflozin 25 mg • SOC	• CV death • MI • Hospitalization for UA • Stroke • Death from CV causes, MI, or UA
NCT04340908[53] June 2023	N = 500 • Dapagliflozin 10 mg • Placebo	• Postoperative all-cause mortality • Hypoglycemia • Hospitalization • Diabetic ketoacidosis • Lactic acidosis • Postoperative AF • Postoperative infection • Postoperative kidney injury
NCT04249778[47] July 2023	N = 392 • Dapagliflozin 10 mg • Placebo	• Composite of hospital admissions, ER visits, urgent visits for HF, death after admission with ADHF • CV death • Nonfatal MI • Stroke • Acute kidney injury
NCT04523064[50] POST-CABGDM November 2023	N = 144 • Empagliflozin 25 mg • SOC	• Acute kidney injury • AF • Pulmonary infection • Surgical site infection • ICU readmission • MI type 5
NCT04906213[65] CREST-KT December 2023	N = 72 • Empagliflozin 10 mg • Placebo	• Number of UTI • Number of genital tract infections • AEs

Trial Number Trial Name Estimated Completion	Estimated Enrollment Treatment Groups	Eligible Outcomes
NCT04583813[68] EMPA-AF April 2024	N = 400 • Empagliflozin • Placebo	• Composite of MACE • Hospitalizations for CV events • Incidence of AEs
NCT04965935[67] INFINITI2019 June 2024	N = 52 • Dapagliflozin 10 mg • Placebo	• AEs
NCT03982381[52] SMARTEST September 2025	N = 4,300 • Dapagliflozin 10 mg • Metformin 1,000 to 3,000 mg	• Composite of death, MI, stroke, HF, diabetic nephropathy, retinopathy, or foot ulcer • MACE • HF or CV death • Mortality

Abbreviations. ACS: acute coronary syndrome; ADHF: acute decompensated heart failure; AE: adverse event; AF: atrial fibrillation; CV: cardiovascular; CVD: cardiovascular disease; DPP-4: dipeptidyl peptidase 4; eGFR: estimated glomerular filtration rate; ER: emergency room; ESRD: end-stage renal disease; GLP-1: glucagon-like peptide 1; hHF: hospitalization for heart failure; HF: heart failure; ICU: intensive care unit; MACE: major adverse cardiovascular event; MI: myocardial infarction; OAD: other antidiabetic agents; SC: subcutaneous; SGLT-2: sodium-glucose cotransporter-2; SOC: standard of care; TIA: transient ischemic attack; UA: unstable angina; UTI: urinary tract infection.

Summary

Since the completion of the DERP systematic review presented in February 2020, we identified:

- 40 new published studies (20 in this surveillance document)
  - 0 head-to-head studies
  - 1 RCT assessing liraglutide as add-on therapy
  - 4 placebo-controlled RCTs
  - 35 cohort studies (20 in this surveillance document)

- 31 ongoing studies
  - 1 head-to-head study
  - 1 trial comparing newer diabetes drugs to dietary intervention
  - 8 trials comparing newer diabetes drugs to SOC
  - 12 placebo-controlled trials
  - 9 cohort studies

- 1 new drug (0 in this surveillance document)
  - Empagliflozin-linagliptin-metformin hydrochloride extended release (Trijardy XR) for treatment of adults with type 2 diabetes

- 6 new indications (2 in this surveillance document)
  - Dulaglutide for MACE in adults with type 2 diabetes and established CVD or at CV risk
  - 2 doses of dulaglutide (3.0 mg and 4.5 mg) for treatment of type 2 diabetes
  - Semaglutide for MACE in adults with type 2 diabetes and known heart disease

    - Dapagliflozin for CV death and hHF in adults with heart failure with reduced ejection fraction (HFrEF) with or without type 2 diabetes
    - Dapagliflozin for kidney function decline, kidney failure, CV death, and hHF in adults with chronic kidney disease with or without type 2 diabetes
    - Empagliflozin for CV death plus hHF in adults with HFrEF with or without type 2 diabetes

- 11 new warnings (9 in this surveillance document)
    - GLP-1 agonists: potential signal of serious risk of diabetic ketoacidosis
        - Sitagliptin products: risk of acute renal failure or hypoglycemia with concomitant insulin or insulin secretagogue use
        - Semaglutide: risk of hypersensitivity reaction or hypoglycemia with concomitant insulin or insulin secretagogue use
        - Liraglutide: risk of acute pancreatitis, heart rate increase, suicidal ideation or behavior, or hypoglycemia with concomitant insulin or insulin secretagogue use
        - Exenatide: risk of hypoglycemia with concomitant insulin or insulin secretagogue use
    - SGLT-2 inhibitors: risk of diabetic ketoacidosis after surgery
        - Empagliflozin products: risk of ketoacidosis or volume depletion
        - Empagliflozin only: risk of ketoacidosis, volume depletion, urosepsis and pyelonephritis, and necrotizing fascitis of the perineum
    - Empagliflozin-linagliptin-metformin ER (Trijardy XR): risk of volume depletion

- 2 updated safety labels (1 in this surveillance document)
    - Empagliflozin: black box warning of leg and foot amputation was removed
    - Empagliflozin-metformin: black box warning for risk of lactic acidosis added

Using the *Is There a There There Scale* (ITS; Table 7), we rated this topic as *Maybe* (see Appendix B for ratings and definitions).

Table 7. Summary and ITS Rating

Clinical Evidence	Yes How many?	No
New Comparative Trial		☒
New Placebo-Controlled Trial (if needed)	☑ 5 studies (0 in this surveillance)	
New Meaningful[a] Study	☑ 1 study for ertugliflozin and CVD outcomes (0 in this surveillance)	
Ongoing Study Likely to be Published in the Next Year	☑ 7 studies (2 RCTs, 5 cohort studies)	
FDA Actions	**Yes Description**	**No**
New Drug or Formulation	☑ Trijardy XR (0 in this surveillance)	
New Indication	☑ 6 indications (2 for dulaglutide, 2 for dapagliflozin, 1 for semaglutide, 1 for empagliflozin)	
New Serious Harm or Warning	☑ 11 warnings (6 for GLP-1 agonists, 5 for SGLT-2 inhibitors)	
ITS Rating: *Maybe*		

Note. [a] *Large studies (≥ 1,000 participants), studies with long-term follow-up (≥ 24 months), studies comparing one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies including an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.*
Abbreviation. CVD: cardiovascular disease; FDA: US Food and Drug Administration; GLP-1: glucagon-like peptide 1; ITS: Is There a There There Scale; RCT: randomized controlled trial; SGLT-2: sodium-glucose cotransporter-2; XR: extended release.

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Appendix A. Abstracts of New Eligible Studies

Baksh S, Wen J, Mansour O, et al. Dipeptidyl peptidase-4 inhibitor cardiovascular safety in patients with type 2 diabetes, with cardiovascular and renal disease: a retrospective cohort study. *Sci Rep*. 2021;11(1):16637. doi: 10.1038/s41598-021-95687-z.

Clinical trials investigating cardiovascular safety of dipeptidyl peptidase-IV inhibitors (DPP-4i) among patients with cardiovascular and renal disease rarely recruit patients with renal impairment, despite associations with increased risk for major adverse cardiovascular events (MACE). We investigated the risk of MACE associated with the use of DPP-4i among these high-risk patients. Using a new-user, retrospective, cohort design, we analyzed 2010-2015 IBM MarketScan Commercial Claims and Encounters for patients with diabetes, comorbid with cardiovascular disease and/or renal impairment. We compared time to first MACE for DPP-4i versus sulfonylurea and versus metformin. Of 113,296 individuals, 9146 (8.07%) were new DPP-4i users, 17,481 (15.43%) were new sulfonylurea users, and 88,596 (78.20%) were new metformin users. Exposure groups were not mutually exclusive. DPP-4i was associated with lower risk for MACE than sulfonylurea (aHR 0.84; 95% CI 0.74, 0.93) and similar risk for MACE to metformin (aHR 1.07; 95% CI [1.04, 1.16]). DPP-4i use was associated with lower risk for MACE compared to sulfonylureas and similar risk for MACE compared to metformin. This association was most evident in the first year of therapy, suggesting that DPP-4i is a safer choice than sulfonylurea for diabetes treatment initiation in high-risk patients.

Baviera M, Genovese S, Lepore V, et al. Lower risk of death and cardiovascular events in patients with diabetes initiating glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors: a real world study in two Italian cohorts. Diabetes Obes Metab. 2021;23(7):1484-1495. doi: 10.1111/dom.14361.

AIM: To examine the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors compared with other antihyperglycaemic agents (AHAs) in large and unselected populations of the Lombardy and Apulia regions in Italy.

MATERIALS AND METHODS: An observational cohort study of first-time users of GLP-1RAs, SGLT2 inhibitors or other AHAs was conducted from 2010 to 2018. Death and cardiovascular (CV) events were evaluated using conditional Cox models in propensity-score-matched populations. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for each region and in a meta-analysis for pooled risks.

RESULTS: After propensity-score matching, the Lombardy cohort included 18 716 and 11 683 patients and the Apulia cohort 9772 and 6046 patients for the GLP-1RA and SGLT2 inhibitor groups, respectively. Use of GLP-1RAs was associated with lower rates of death (HR 0.61, CI 0.56-0.65, Lombardy; HR 0.63, CI 0.55-0.71, Apulia), cerebrovascular disease and ischaemic stroke (HR 0.70, CI 0.63-0.79; HR 0.72, CI 0.60-0.87, Lombardy), peripheral vascular disease (HR 0.72, CI 0.64-0.82, Lombardy; HR 0.80, CI 0.67-0.98, Apulia), and lower limb complications (HR 0.67, CI 0.56-0.81, Lombardy; HR 0.69, CI 0.51-0.93, Apulia). Compared with other AHAs, SGLT2 inhibitor use decreased the risk of death (HR 0.47, CI 0.40-0.54, Lombardy; HR 0.43, CI 0.32-0.57, Apulia), cerebrovascular disease (HR 0.75, CI 0.61-0.91, Lombardy; HR 0.72, CI 0.54-0.96, Apulia), and heart failure (HR 0.56, CI 0.46-0.70, Lombardy; HR 0.57, CI 0.42-0.77, Apulia). In the pooled cohorts, a reduction in heart

failure was also observed with GLP-1RAs (HR 0.89, 95% CI 0.82-0.97). Serious adverse events were quite low in frequency.

CONCLUSION: Our findings from real-world practice confirm the favourable effect of GLP-1RAs and SGLT2 inhibitors on death and CV outcomes across both regions consistently. Thus, these drug classes should be preferentially considered in a broad type 2 diabetes population beyond those with CV disease.

Cristiano EA, Miles JM, Worsham S, et al. Decreased mortality after long term treatment with DPP-4 inhibitors: a retrospective study of US veterans with type 2 diabetes. *Endocr Pract.* 2021;06:06. doi: 10.1016/j.eprac.2021.07.017.

IMPORTANCE: The prevalence of chronic kidney disease (CKD) in the United States is 13% of the general population. Among those with CKD, diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD).

OBJECTIVE: This is a retrospective study examining the effect of long-term use of DPP-4 inhibitors on all-cause mortality and progression of renal disease in the veteran population.

METHODS: Data was extracted using the Veterans Administration Informatics and Computing Infrastructure (VINCI). Data from a large cohort of veterans diagnosed with type 2 diabetes mellitus (T2DM) were used to identify patients on DPP-4 inhibitors (treatment group) and without DPP-4 inhibitors (control group). Groups were compared to determine the effect of DPP-4 inhibitors on the progression of CKD, microalbuminuria and all-cause mortality. Increase in serum creatinine (mg/dl) over time (days) was taken as a measure of progression of CKD. Data were analyzed using SAS. Results were compared using t-tests, frequency tables, Kaplan Meier survival curves and odds ratios (OR).

RESULTS: Subjects in the treatment group (N=40,558) had baseline variables (age, BMI, race) similar to the control group (N=40,558). Diabetes control improved in the treatment group (HgbA1c 8.3% (67mmol/mol) to 7.8% (62mmol.mol), $p < 0.001$) but not in the control group (7.4% (57mmol/mol) to 7.3% (56mmol/mol)). New diagnoses of heart failure and CABG were clinically significant (OR 0.66 and 0.52). No change in progression of CKD was seen in either group. All-cause mortality was reduced by 59%.

CONCLUSION: We conclude that DPP-4 inhibitors are associated with a significant reduction in all-cause mortality independent of glucose control, albeit with no clear cause, including obtainable cardiovascular outcomes. Our data is consistent with prior trials in that DPP-4 inhibitors did not show a significant change in serum creatinine or microalbuminuria.

DeRemer CE, Vouri SM, Guo J, Donahoo WT, Winterstein AG, Shao H. Comparing cardiovascular benefits between GLP-1 receptor agonists and SGLT2 inhibitors as an add-on to metformin among patients with type 2 diabetes: a retrospective cohort study. *J Diabetes Complications.* 2021;35(9):107972. doi: 10.1016/j.jdiacomp.2021.107972.

AIMS: This study aimed to compare cardiovascular benefits associated with the use of GLP-1RA versus SGLT2i as add-on therapies to metformin among adults with type 2 diabetes (T2D) with and without a history of cardiovascular complications, using real-world data.

METHODS: Using data from the IBM R MarketScan R Commercial Claims Databases, metformin users above 18years with T2D who initiated GLP-1RA or SGLT2i were identified. The study endpoints include MI, stroke, CHF, and a cardiovascular composite of these three

outcomes. Cox proportional hazard regression models were used to compare the risks of cardiovascular endpoints while controlling for demographics and clinical characteristics.

RESULTS: We identified 13,006 adults with T2D who initiated a GLP-1RA or SGLT2i as an add-on therapy to metformin and followed for a maximum of 5years. No difference in the endpoints was observed between users of two drugs who did not have established cardiovascular disease at baseline. However, significantly lower CHF risks (HR: 0.47, 95% CI: 0.28-0.79) and cardiovascular composite (HR: 0.67, 95% CI: 0.47-0.97) were observed in SGLT2i users compared with GLP-1RA users, among individuals with established cardiovascular diseases.

CONCLUSIONS: Results suggest greater cardioprotective benefit from SGLT2i compared to GLP-1RA when used for secondary prevention among adults with T2D.

Fralick M, Schneeweiss S, Redelmeier DA, Razak F, Gomes T, Patorno E. Comparative effectiveness and safety of sodium-glucose cotransporter-2 inhibitors versus metformin in patients with type 2 diabetes: an observational study using data from routine care. *Diabetes Obes Metab*. 2021;23(10):2320-2328. doi: 10.1111/dom.14474.

AIM: To assess the effectiveness and safety of sodium-glucose cotransporter-2 (SGLT2) inhibitors in treatment-naive patients compared with metformin.

PARTICIPANTS AND METHODS: We conducted a cohort study of US adults with type 2 diabetes mellitus who had not filled a prescription for a diabetes medication in the preceding year. We then identified patients who newly filled a prescription for an SGLT2 inhibitor or metformin between 2013 and 2018. The primary outcome was a composite of heart failure, myocardial infarction or stroke. Safety outcomes included hypoglycaemia, diabetic ketoacidosis, genital infection, lactic acidosis and acute kidney injury. After 1:1 propensity-score (PS) matching, proportional hazards models were fit to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

RESULTS: We identified 9964 individuals newly prescribed an SGLT2 inhibitor who were PS-matched to 9964 individuals newly prescribed metformin. The mean age was 54 years, 52% were women, and the duration of follow-up was 213 days for metformin and 147 days for SGLT2 inhibitors. The primary outcome occurred in 54 patients (7.2 events per 1000 person-years) who received an SGLT2 inhibitor, compared to 84 patients (8.5 per 1000 person-years) who received metformin (HR 0.82, 95% CI 0.58, 1.15). Similar results (HR 0.87, 95% CI 0.69, 1.09) were observed in an analysis with longer follow-up (ie, approximately 600 days). The rates of genital infection (HR 2.28, 95% CI 1.87, 2.78) and diabetic ketoacidosis (HR 1.58, 95% CI 0.92, 2.70) were higher for patients prescribed an SGLT2 inhibitor compared to metformin, while the rates of acute kidney injury (HR 0.94, 95% CI 0.60, 1.47) or hypoglycaemia (HR 0.83, 95% CI 0.48, 1.42) were not.

CONCLUSIONS: We observed a numerically lower rate of short-/mid-term cardiovascular events for patients newly prescribed an SGLT2 inhibitor compared to metformin, albeit with wide CIs that include the possibility of a null effect. SGLT2 inhibitors were associated with a higher rate of genital infection and diabetic ketoacidosis. Larger cohort studies and long-term clinical trials powered to assess cardiovascular events are necessary to understand the risk-benefit profile of SGLT2 inhibitors as first-line therapy for adults with type 2 diabetes mellitus.

Franklin JM, Patorno E, Desai RJ, et al. Emulating randomized clinical trials with nonrandomized real-world evidence studies: first results from the RCT DUPLICATE initiative. *Circulation*. 2021;143(10):1002-1013. doi: 10.1161/circulationaha.120.051718.

BACKGROUND: Regulators are evaluating the use of noninterventional real-world evidence (RWE) studies to assess the effectiveness of medical products. The RCT DUPLICATE initiative (Randomized, Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology) uses a structured process to design RWE studies emulating randomized, controlled trials (RCTs) and compare results. We report findings of the first 10 trial emulations, evaluating cardiovascular outcomes of antidiabetic or antiplatelet medications.

METHODS: We selected 3 active-controlled and 7 placebo-controlled RCTs for replication. Using patient-level claims data from US commercial and Medicare payers, we implemented inclusion and exclusion criteria, selected primary end points, and comparator populations to emulate those of each corresponding RCT. Within the trial-mimicking populations, we conducted propensity score matching to control for >120 preexposure confounders. All study measures were prospectively defined and protocols registered before hazard ratios and 95% CIs were computed. Success criteria for the primary analysis were prespecified for each replication.

RESULTS: Despite attempts to emulate RCT design as closely as possible, differences between the RCT and corresponding RWE study populations remained. The regulatory conclusions were equivalent in 6 of 10. The RWE emulations achieved a hazard ratio estimate that was within the 95% CI from the corresponding RCT in 8 of 10 studies. In 9 of 10, either the regulatory or estimate agreement success criteria were fulfilled. The largest differences in effect estimates were found for RCTs where second-generation sulfonylureas were used as a proxy for placebo regarding cardiovascular effects. Nine of 10 replications had a standardized difference between effect estimates of <2, which suggests differences within expected random variation.

CONCLUSIONS: Agreement between RCT and RWE findings varies depending on which agreement metric is used. Interim findings indicate that selection of active comparator therapies with similar indications and use patterns enhances the validity of RWE. Even in the context of active comparators, concordance between RCT and RWE findings is not guaranteed, partially because trials are not emulated exactly. More trial emulations are needed to understand how often and in what contexts RWE findings match RCTs. Registration: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT03936049, NCT04215523, NCT04215536, NCT03936010, NCT03936036, NCT03936062, NCT03936023, NCT03648424, NCT04237935, NCT04237922.

Han SJ, Ha KH, Lee N, Kim DJ. Effectiveness and safety of sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: a nationwide population-based study. *Diabetes Obes Metab*. 2021;23(3):682-691. doi: 10.1111/dom.14261.

AIM: To examine the real-world cardiovascular effectiveness and safety associated with sodium-glucose co-transporter-2 (SGLT2) inhibitor compared with dipeptidyl peptidase-4 (DPP-4) inhibitor treatment in older adults with type 2 diabetes.

MATERIALS AND METHODS: In this retrospective cohort study, older adults with type 2 diabetes (aged >=65 years) were identified in the Korean National Health Insurance Service

database from September 2014 to December 2016. In total, 408 506 new users of an SGLT2 inhibitor or DPP-4 inhibitor were propensity score matched. Cox regression was used to estimate the hazard ratios (HR) and 95% confidence interval (CI) for outcomes of interest: hospitalization for heart failure (HHF), all-cause death, myocardial infarction, stroke, diabetic ketoacidosis (DKA), bone fracture, severe hypoglycaemia, genital infection and urinary tract infection (UTI).

RESULTS: Compared with DPP-4 inhibitors, new users of SGLT2 inhibitors had a lower risk of HHF (HR 0.86; 95% CI 0.76-0.97), all-cause death (HR 0.85; 95% CI 0.75-0.98) and stroke (HR 0.86; 95% CI 0.77-0.97), but a similar risk of myocardial infarction (HR 0.95; 95% CI 0.77-1.19). The risks of DKA, bone fracture and severe hypoglycaemia were similar between both groups, although genital infection (HR 2.44; 95% CI 2.22-2.67) and UTI (HR 1.05; 95% CI 1.00-21.11) were more frequent among new users of SGLT2 inhibitors compared with DPP-4 inhibitors.

CONCLUSION: Our findings suggest that initiation of SGLT2 inhibitors offers cardiovascular disease protection and can be used safely in older adults with type 2 diabetes.

Herrera Comoglio R, Vidal Guitart X. Cardiovascular events and mortality among type 2 diabetes mellitus patients newly prescribed first-line blood glucose-lowering drugs monotherapies: a population-based cohort study in the Catalan electronic medical record database, SIDIAP, 2010-2015. *Prim Care Diabetes.* 2021;15(2):323-331. doi: 10.1016/j.pcd.2020.11.002.

AIM: To assess cardiovascular (CV) events and all-cause mortality in type 2 diabetes mellitus (T2DM) patients treated with first-line monotherapies of non-insulin antidiabetic drugs (NIADs).

METHODS: Longitudinal retrospective cohort study in the Catalan database SIDIAP (Information System for the Development of Research in Primary Care). T2DM patients >=18 years newly prescribed first-line monotherapies during 2010-2015 were followed since their first prescription until the composite of major adverse CV events, MACE (myocardium infarction [MI], stroke and all-cause death), its components, heart failure (HF) and peripheral artery disease (PAD) or censoring. Cox proportional hazard models were used to estimate hazard ratios 95% confidence interval (HR [95%CI]).

RESULTS: Compared with metformin, the use of sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP-4 i) and meglitinides were significantly associated with higher risk for MACE (1.55 [1.42-1.68]); 1.49 [1.22-1.84] and 2.01 [1.29-3.12]) and all-cause mortality (1.67 [1.52-1.84], 1.65 [1.30-2.] and 2.08 [1.26-3.42]). Sulfonylureas users had increased risk of MI (1.38 [1.03-1.85]) stroke (1.31 [1.11-1.54]), HF (1.49 [1.28-1.72]) and PAD (1.24 [1.02-1.51]). Meglitinides users were at increased risks of MI, HR 2.03 (1.10-3.74).

CONCLUSION: In first-line monotherapies, compared with metformin, sulfonylureas were associated with increased risks in all the outcomes; DPP-4 i and repaglinide showed increased risks of MACE and mortality. Residual confounding cannot be ruled out.

Horii T, Oikawa Y, Kunisada N, Shimada A, Atsuda K. Real-world risk of hypoglycemia-related hospitalization in Japanese patients with type 2 diabetes using SGLT2 inhibitors: a nationwide cohort study. *BMJ open diabetes res.* 2020;8(2):11. doi: 10.1136/bmjdrc-2020-001856.

INTRODUCTION: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are believed to lower glucose levels and inhibit cardiovascular events related to type 2 diabetes (T2D). To maximize their benefits, the risk of resultant hypoglycemia has to be minimized; however, the magnitude of this risk remains unclear. Here, we aimed to identify clinical factors linked to an increased risk of hypoglycemia among Japanese patients with T2D and treated with SGLT2 inhibitors.

RESEARCH DESIGN AND METHODS: This was a real-world retrospective cohort study conducted using the Japanese Medical Data Vision database. We identified patients with T2D and treated with SGLT2 inhibitors who were enrolled in the database from April 2014 to October 2019. Cox multivariate regression analyses were performed to determine demographical and clinical factors linked to SGLT2 inhibitor-associated hypoglycemia-related hospitalization.

RESULTS: Of 171 622 patients prescribed SGLT2 inhibitors, hypoglycemia-related hospitalization occurred in 216 (0.13%), with 0.60 incidences per 100 person-years. The risk of SGLT2 inhibitor-associated hypoglycemia was higher with each 10-year increase in age (HR 1.49; 95% CI 1.32 to 1.68) and high in patients with body mass index <25 kg/m^2 (HR 1.98; 95% CI 1.50 to 2.61), insulin use (HR 3.26; 95% CI 2.43 to 4.38), and sulfonylurea use (HR 1.44; 95% CI 1.02 to 2.03). The risk was lower in women than in men (HR 0.73; 95% CI 0.54 to 0.98) and low in concomitant metformin users (HR 0.52; 95% CI 0.37 to 0.74).

CONCLUSIONS: These findings may help minimize the risk of hypoglycemia-related hospitalization due to T2D treatment with SGLT2 inhibitors. We revealed that the risk of hypoglycemia may be higher when combining SGLT2 inhibitors with sulfonylureas and/or insulin. Furthermore, we discovered a high risk of hypoglycemia in older and non-obese patients. These findings may assist in maximizing the benefits of SGLT2 inhibitors for the treatment of T2D.

Idris I, Zhang R, Mamza JB, et al. Lower risk of hospitalization for heart failure, kidney disease and death with sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in type 2 diabetes regardless of prior cardiovascular or kidney disease: a retrospective cohort study in UK primary care. *Diabetes Obes Metab.* 2021;23(10):2207-2214. doi: 10.1111/dom.14437.

AIM: To assess if sodium-glucose co-transporter-2 inhibitors (SGLT2is) reduce the risk of all-cause mortality, cardiovascular death and hospitalization for heart failure (HF) or chronic kidney disease (CKD) to a greater extent than dipeptidyl peptidase-4 inhibitors (DPP4is) in people with type 2 diabetes (T2D) with or without established cardiovascular and/or renal disease (CVRD).

METHODS: This retrospective cohort study propensity-matched 24 438 patients receiving an SGLT2i 1:1 to a patient receiving a DDP4i, stratified based on the presence of CVRD. The primary outcomes were the time to each of the following: all-cause mortality, cardiovascular death or hospitalization for HF, myocardial infarction, stroke and CKD.

RESULTS: Overall, SGLT2is were associated with reductions in all-cause mortality, cardiovascular mortality, hospitalization for HF and hospitalization for CKD compared with

DPP4is. In patients with no CVRD history, SGLT2is were associated with reductions in all-cause mortality (HR 0.71, 95% CI 0.57-0.88; P = .002), hospitalization for HF (HR 0.76, 95% CI 0.59-0.98; P = .035) and hospitalization for CKD (HR 0.75, 95% CI 0.63-0.88; P < .001). In patients with established cardiovascular disease (CVD) or at high risk, SGLT2is were associated with reductions in all-cause mortality (HR 0.69, 95% CI 0.59-0.82; P < .001), cardiovascular mortality (HR 0.76, 95% CI 0.62-0.95; P = .014), hospitalization for HF (HR 0.73, 95% CI 0.63-0.85; P < .001), hospitalization for stroke (HR 0.75, 95% CI 0.59-0.94; P = .013) and hospitalization for CKD (HR 0.49, 95% CI 0.43-0.54; P < .001).

CONCLUSION: There was consistency across subgroups and sensitivity analyses. SGLT2is were associated with a reduced risk of all-cause mortality and hospitalization for HF and CKD compared with DPP4-is, highlighting the need to introduce SGLT2is early in the management of patients with T2D.

Idris I, Zhang R, Mamza JB, et al. Lower risk of hospitalization for heart failure, kidney disease and death with sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in type 2 diabetes regardless of prior cardiovascular or kidney disease: a retrospective cohort study in UK primary care. *Diabetes Obes Metab*. 2021;23(10):2207-2214. doi: 10.1111/dom.14437.

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CONCLUSION: There was consistency across subgroups and sensitivity analyses. SGLT2is were associated with a reduced risk of all-cause mortality and hospitalization for HF and CKD compared with DPP4-is, highlighting the need to introduce SGLT2is early in the management of patients with T2D.

Komuro I, Kadowaki T, Bodegard J, Thuresson M, Okami S, Yajima T. Lower heart failure and chronic kidney disease risks associated with sodium-glucose cotransporter-2 inhibitor use in Japanese type 2 diabetes patients without established cardiovascular and renal diseases. *Diabetes Obes Metab.* 2021;23 Suppl 2:19-27. doi: 10.1111/dom.14119.

AIMS: To examine heart failure (HF) and chronic kidney disease (CKD) risks reduction associated with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) compared to other glucose-lowering drugs (oGLD) in the early stage of type 2 diabetes patients without established cardiovascular or renal diseases (CVRD-free T2D).

MATERIALS AND METHODS: We performed an observational cohort study using a Japanese hospital claims registry, Medical Data Vision. CVRD-free T2D patients were identified between 1 April 2014 and 30 September 2018. SGLT-2i and oGLD new users (and dipeptidyl peptidase 4 inhibitors [DPP-4i] separately) were subjected to 1:1 propensity-score matching analysis. Hazard ratios (HRs) of cardiorenal disease (HF and/or CKD), HF, CKD, stroke, myocardial infarction (MI), and all-cause mortality, were estimated using unadjusted Cox regression.

RESULTS: A total of 108 362 CVRD-free patients including 54 181 SGLT-2i and 54 181 oGLD users were matched. Baseline characteristics were well balanced (mean age 59.1 years, 63% male, and follow-up 1.50 years [162 970 patient-years]). Compared to oGLD group, SGLT-2i group had lower risk of cardiorenal disease, HF, CKD, stroke, and all-cause mortality with HRs (95% confidence intervals) 0.55 (0.49-0.61), 0.73 (0.61-0.87), 0.45 (0.39-0.52), 0.69 (0.59-0.81), and 0.52 (0.46-0.58), respectively, while no difference in MI. These were consistent in 1:1 propensity-score matching analysis between SGLT-2i and DPP-4i users (n = 17 232 in each group).

CONCLUSIONS: In Japanese CVRD-free T2D patients, SGLT-2i initiation was associated with lower risk of cardiorenal diseases, stroke, and all-cause mortality compared to oGLD, suggesting preventive effect of SGLT-2i treatment in the early stage of T2D patients without CVRD manifestation.

Lugner M, Sattar N, Miftaraj M, et al. Cardiorenal and other diabetes related outcomes with SGLT-2 inhibitors compared to GLP-1 receptor agonists in type 2 diabetes: nationwide observational study. *Cardiovasc Diabetol.* 2021;20(1):67. doi: 10.1186/s12933-021-01258-x.

BACKGROUND: Major prospective randomized clinical safety trials have demonstrated beneficial effects of treatment with glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i) in people with type 2 diabetes and elevated cardiovascular risk, and recent clinical treatment guidelines therefore promote early use of these classes of pharmacological agents. In this Swedish nationwide observational study, we compared cardiorenal outcomes and safety of new treatment with GLP-1RA and SGLT-2i in people with type 2 diabetes.

METHODS: We linked data from national Swedish databases to capture patient characteristics and outcomes and used propensity-score based matching to account for differences between the two groups. The treatments were compared using Cox regression models.

RESULTS: We identified 9648 participants starting GLP-1RA and 12,097 starting SGLT-2i with median follow-up times 1.7 and 1.1 years, respectively. The proportion of patients with a history of MACE were 15.8%, and 17.0% in patients treated with GLP-1RA and SGLT-2i,

respectively. The mean age was 61 years with 7.6 years duration of diabetes. Mean HbA1c were 8.3% (67.6 mmol/mol) and 8.3% (67.2 mmol/mol), and mean BMI 33.3 and 32.5 kg/m^2 in patients treated with GLP-1RA or SGLT-2i, respectively. The cumulative mortality risk was non-significantly lower in the group treated with SGLT-2i, HR 0.78 (95% CI 0.61-1.01), as were incident heart failure outcomes, but the risks of cardiovascular or renal outcomes did not differ. The risks of stroke and peripheral artery disease were higher in the SGLT-2i group relative to GLP-1RA, with HR 1.44 (95% CI 0.99-2.08) and 1.68 (95% CI 1.04-2.72), respectively.

CONCLUSIONS: This observational study suggests that treatment with GLP-1RA and SGLT-2i result in very similar cardiorenal outcomes. In the short term, treatment with GLP-1RA seem to be associated with lower risks of stroke and peripheral artery disease, whereas SGLT-2i seem to be nominally associated with lower risk of heart failure and total mortality.

Norgaard CH, Starkopf L, Gerds TA, et al. Cardiovascular outcomes with GLP-1 receptor agonists versus SGLT-2 inhibitors in patients with type 2 diabetes. *Eur Heart J Cardiovasc Pharmacother*. 2021;02:02. doi: 10.1093/ehjcvp/pvab053.

AIMS: We examined cardiovascular outcomes associated with initiation of GLP-1RA versus SGLT-2i treatment in a real-world setting among patients with type 2 diabetes.

METHODS AND RESULTS: This Danish nationwide registry-based cohort study included patients with type 2 diabetes with a first ever prescription of either GLP-1RA or SGLT-2i from 2013 through 2015 with follow-up until end of 2018. All analyses were standardized with respect to age, sex, diabetes duration, comorbidity, and comedication. The main outcome was a composite of cardiovascular death, myocardial infarction, and stroke. Furthermore, the components of the composite outcome and hospitalization for heart failure were evaluated. Standardized average 3-year risks of outcomes and differences thereof were estimated using doubly robust estimation combining cause-specific Cox regression with propensity score regression. We identified 8,913 new users of GLP-1RA and 5,275 new users of SGLT-2i. The standardized 3-year risk associated with initiating GLP-1RA and SGLT-2i, respectively, was for the composite cardiovascular outcome, 5.6% (95% confidence interval (CI): 5.2-6.1) versus 5.6% (95% CI: 4.8-6.3); cardiovascular mortality, 1.6% (95% CI: 1.3-1.9) versus 1.5% (95% CI: 1.1-1.8); hospitalization for heart failure, 1.7% (95% CI: 1.5-2.0) versus 1.8% (95% CI: 1.2-2.5); myocardial infarction, 2.1% (95% CI: 1.8-2.4) versus 2.1% (95% CI: 1.5-2.6); and stroke, 2.5% (95% CI: 2.2-2.9) versus 2.6% (95% CI: 2.2-3.1).

CONCLUSION: In this nationwide study of patients with type 2 diabetes, initiating GLP-1RA versus SGLT-2i was not found to be associated with significant differences in cardiovascular risk.

Poonawalla IB, Bowe AT, Tindal MC, Meah YA, Schwab P. A real-world comparison of cardiovascular, medical and costs outcomes in new users of SGLT2 inhibitors versus GLP-1 agonists. *Diabetes Res Clin Pract*. 2021;175:108800. doi: 10.1016/j.diabres.2021.108800.

AIMS: To compare SGLT2 inhibitors and GLP-1 agonists on cardiovascular (CV) outcomes, treatment persistence/discontinuation, healthcare utilization and costs.

METHODS: This retrospective cohort study utilized medical and pharmacy claims to identify new SGLT2 inhibitor or GLP-1 agonist users from January 2015 to June 2017. A total of 5,507 patients were included in each treatment group after 1:1 propensity score matching. Cox proportional hazards models were used to compare CV outcomes and treatment

discontinuation. Healthcare utilization and costs were compared using Wilcoxon signed rank test.

RESULTS: No differences in the primary composite CV outcome or secondary CV outcome were observed. Patients using GLP-1 agonists were more likely to discontinue treatment (hazard ratio 1.15, 95% confidence interval 1.10-1.21) and more likely to have an inpatient hospitalization (14.4% vs. 11.9%, P < 0.001) or emergency department visit (27.4% vs. 23.5%, P < 0.001) compared to patients on SGLT2 inhibitors. The average per-person per-month cost difference was +$179 for total cost (P < 0.001), +$70 for medical cost (P < 0.001) and +$108 for pharmacy cost (P < 0.001) for GLP-1 agonists compared to SGLT2 inhibitors.

CONCLUSIONS: Differences in composite CV outcomes were not established. However, other findings that favored SGLT2 inhibitors should be weighed against the known risks associated with this therapeutic class.

Real J, Vlacho B, Ortega E, et al. Cardiovascular and mortality benefits of sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes mellitus: CVD-Real Catalonia. *Cardiovasc Diabetol*. 2021;20(1):139. doi: 10.1186/s12933-021-01323-5.

BACKGROUND: Evidence from prospective cardiovascular (CV) outcome trials in type 2 diabetes (T2DM) patients supports the use of sodium-glucose co-transporter-2 inhibitors (SGLT2i) to reduce the risk of CV events. In this study, we compared the risk of several CV outcomes between new users of SGLT2i and other glucose-lowering drugs (oGLDs) in Catalonia, Spain.

METHODS: CVD-REAL Catalonia was a retrospective cohort study using real-world data routinely collected between 2013 and 2016. The cohorts of new users of SGLT2i and oGLDs were matched by propensity score on a 1:1 ratio. We compared the incidence rates and hazard ratio (HR) for all-cause death, hospitalization for heart failure, chronic kidney disease, and modified major adverse CV event (MACE; all-cause mortality, myocardial infarction, or stroke).

RESULTS: After propensity score matching, 12,917 new users were included in each group. About 27% of users had a previous history of CV disease. In the SGLT2i group, the exposure time was 60% for dapagliflozin, 26% for empagliflozin and 14% for canagliflozin. The use of SGLT2i was associated with a lower risk of heart failure (HR: 0.59; 95% confidence interval [CI] 0.47-0.74; p < 0.001), all-cause death (HR = 0.41; 95% CI 0.31-0.54; p < 0.001), all-cause death or heart failure (HR = 0.55; 95% CI 0.47-0.63; p < 0.001), modified MACE (HR = 0.62; 95% CI 0.52-0.74; p < 0.001), and chronic kidney disease (HR = 0.66; 95% CI 0.54-0.80; p < 0.001).

CONCLUSIONS: In this large, retrospective observational study of patients with T2DM from a Catalonia, initiation of SGLT-2i was associated with lower risk of mortality, as well as heart failure and CKD.

Ryan PB, Buse JB, Schuemie MJ, et al. Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: a real-world meta-analysis of 4 observational databases (OBSERVE-4D). *Diabetes Obes Metab.* 2018;20(11):2585-2597. doi: 10.1111/dom.13424.

AIMS: Sodium glucose co-transporter 2 inhibitors (SGLT2i) are indicated for treatment of type 2 diabetes mellitus (T2DM); some SGLT2i have reported cardiovascular benefit, and some have reported risk of below-knee lower extremity (BKLE) amputation. This study examined the real-world comparative effectiveness within the SGLT2i class and compared with non-SGLT2i antihyperglycaemic agents.

MATERIALS AND METHODS: Data from 4 large US administrative claims databases were used to characterize risk and provide population-level estimates of canagliflozin's effects on hospitalization for heart failure (HHF) and BKLE amputation vs other SGLT2i and non-SGLT2i in T2DM patients. Comparative analyses using a propensity score-adjusted new-user cohort design examined relative hazards of outcomes across all new users and a subpopulation with established cardiovascular disease.

RESULTS: Across the 4 databases (142 800 new users of canagliflozin, 110 897 new users of other SGLT2i, 460 885 new users of non-SGLT2i), the meta-analytic hazard ratio estimate for HHF with canagliflozin vs non-SGLT2i was 0.39 (95% CI, 0.26-0.60) in the on-treatment analysis. The estimate for BKLE amputation with canagliflozin vs non-SGLT2i was 0.75 (95% CI, 0.40-1.41) in the on-treatment analysis and 1.01 (95% CI, 0.93-1.10) in the intent-to-treat analysis. Effects in the subpopulation with established cardiovascular disease were similar for both outcomes. No consistent differences were observed between canagliflozin and other SGLT2i.

CONCLUSIONS: In this large comprehensive analysis, canagliflozin and other SGLT2i demonstrated HHF benefits consistent with clinical trial data, but showed no increased risk of BKLE amputation vs non-SGLT2i. HHF and BKLE amputation results were similar in the subpopulation with established cardiovascular disease. This study helps further characterize the potential benefits and harms of SGLT2i in routine clinical practice to complement evidence from clinical trials and prior observational studies.

Thomsen RW, Knudsen JS, Kahlert J, et al. Cardiovascular events, acute hospitalizations, and mortality in patients with type 2 diabetes mellitus who initiate empagliflozin versus liraglutide: a comparative effectiveness study. *J Am Heart Assoc.* 2021;10(11):e019356. doi: 10.1161/JAHA.120.019356.

BACKGROUND: In cardiovascular outcome trials, the sodium glucose cotransporter 2 inhibitor empagliflozin and glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide caused similar reductions in major adverse cardiac events (MACE). We compared clinical outcomes in routine clinical care.

METHODS AND RESULTS: EMPLACE (Cardiovascular and Renal Outcomes, and Mortality in Danish Patients with Type 2 Diabetes Who Initiate Empagliflozin Versus GLP-1RA: A Danish Nationwide Comparative Effectiveness Study) is an ongoing nationwide population-based comparative effectiveness cohort study in Denmark. For the present study, we included 14 498 new users of empagliflozin and 12 706 new users of liraglutide, 2015 to 2018. Co-primary outcomes were expanded major adverse cardiac events (stroke, myocardial

infarction, unstable angina, coronary revascularization, hospitalization for heart failure [HHF], or all-cause death); HHF or all-cause death; and first HHF or first initiation of loop-diuretic therapy. Secondary outcomes included all-cause hospitalization or death. We applied propensity score balancing and Cox regression to compute adjusted hazard ratios (aHRs) in on-treatment (OT) and intention-to-treat (ITT) analyses. Cohorts were well balanced at baseline (median age 61 years, 59% men, diabetes mellitus duration 6.6 years, 30% with preexisting cardiovascular disease). During mean follow-up of 1.1 years in OT and 1.5 years in ITT analyses, empagliflozin versus liraglutide was associated with a similar rate of expanded major adverse cardiac events (OT aHR, 1.02; 95% CI, 0.91-1.14; ITT aHR, 1.06; 95% CI, 0.96-1.17), and HHF or all-cause death (OT aHR, 0.97; 95% CI, 0.85-1.11; ITT aHR, 1.02; 95% CI, 0.91-1.14); and a decreased rate of a first incident HHF or loop-diuretic initiation (OT aHR, 0.80; 95% CI, 0.68-0.94; ITT aHR, 0.87; 95% CI, 0.76-1.00), and of all-cause hospitalization or death (OT aHR, 0.93; 95% CI, 0.89-0.98; ITT aHR, 0.93; 95% CI, 0.90-0.97).

CONCLUSIONS: Empagliflozin and liraglutide initiators had comparable rates of expanded major adverse cardiac events, and HHF or all-cause death, whereas empagliflozin initiators had a lower rate of a first HHF or loop-diuretic initiation.

Xie Y, Bowe B, Gibson AK, McGill JB, Maddukuri G, Al-Aly Z. Comparative effectiveness of sodium-glucose cotransporter 2 inhibitors vs sulfonylureas in patients with type 2 diabetes. *JAMA Intern Med.* 2021;181(8):1043-1053. doi: 10.1001/jamainternmed.2021.2488.

IMPORTANCE: In the treatment of type 2 diabetes, evidence of the comparative effectiveness of sodium-glucose cotransporter 2 (SGLT2) inhibitors vs sulfonylureas-the second most widely used antihyperglycemic class after metformin-is lacking.

OBJECTIVE: To evaluate the comparative effectiveness of SGLT2 inhibitors and sulfonylureas associated with the risk of all-cause mortality among patients with type 2 diabetes using metformin.

DESIGN, SETTING, AND PARTICIPANTS: A cohort study used data from the US Department of Veterans Affairs compared the use of SGLT2 inhibitors vs sulfonylureas in individuals receiving metformin for treatment of type 2 diabetes. A total of 23870 individuals with new use of SGLT2 inhibitors and 104423 individuals with new use of sulfonylureas were enrolled between October 1, 2016, and February 29, 2020, and followed up until January 31, 2021.

EXPOSURES: New use of SGLT2 inhibitors or sulfonylureas.

MAIN OUTCOMES AND MEASURES: This study examined the outcome of all-cause mortality. Predefined variables and covariates identified by a high-dimensional variable selection algorithm were used to build propensity scores. The overlap weighting method based on the propensity scores was used to estimate the intention-to-treat effect sizes of SGLT2 inhibitor compared with sulfonylurea therapy. The inverse probability of the treatment adherence weighting method was used to estimate the per-protocol effect sizes.

RESULTS: Among the 128 293 participants (mean [SD] age, 64.60 [9.84] years; 122 096 [95.17%] men), 23870 received an SGLT2 inhibitor and 104423 received a sulfonylurea. Compared with sulfonylureas, SGLT2 inhibitors were associated with reduced risk of all-cause mortality (hazard ratio [HR], 0.81; 95% CI, 0.75-0.87), yielding an event rate difference of -5.15 (95% CI, -7.16 to -3.02) deaths per 1000 person-years. Compared with sulfonylureas, SGLT2 inhibitors were associated with a reduced risk of death, regardless of

cardiovascular disease status, in several categories of estimated glomerular filtration rate (including rates from >90 to <=30 mL/min/1.73 m2) and in participants with no albuminuria (albumin to creatinine ratio [ACR] <=30 mg/g), microalbuminuria (ACR >30 to <=300 mg/g), and macroalbuminuria (ACR >300 mg/g). In per-protocol analyses, continued use of SGLT2 inhibitors was associated with a reduced risk of death compared with continued use of sulfonylureas (HR, 0.66; 95% CI, 0.60-0.74; event rate difference, -10.10; 95% CI, -12.97 to -7.24 deaths per 1000 person-years). In additional per-protocol analyses, continued use of SGLT2 inhibitors with metformin was associated with a reduced risk of death compared with SGLT2 inhibitor treatment without metformin (HR, 0.70; 95% CI, 0.50-0.97; event rate difference, -7.62; 95% CI, -17.12 to -0.48 deaths per 1000 person-years).

CONCLUSIONS AND RELEVANCE: In this comparative effectiveness study analyzing data from the US Department of Veterans Affairs, among patients with type 2 diabetes receiving metformin therapy, SGLT2 inhibitor treatment was associated with a reduced risk of all-cause mortality compared with sulfonylureas. The results provide data from a real-world setting that might help guide the choice of antihyperglycemic therapy.

Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe*, and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers will use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require DERP participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

No

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of No is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of Maybe is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of Yes is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.

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