

SGLT2 Inhibitors vs GLP-1 Receptor Agonists for Kidney Outcomes in Individuals With Type 2 Diabetes

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 Supplemental content

IMPORTANCE No randomized clinical trial has directly compared the effectiveness of sodium-glucose cotransporter-2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment in reducing acute and chronic kidney outcomes.

OBJECTIVE To examine the comparative effectiveness of SGLT2i and GLP-1RA treatment for acute and chronic kidney outcomes in individuals with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS This comparative effectiveness study with a target trial emulation design used nationwide, population-based data from Denmark. Participants were individuals with metformin-treated type 2 diabetes who initiated SGLT2i or GLP-1RA treatment from January 2014 to November 2020, with follow-up through October 2024.

EXPOSURE Initiation of an SGLT2i or a GLP-1RA.

MAIN OUTCOMES AND MEASURES The 2 coprimary outcomes were chronic kidney disease (CKD; 40% reduction in estimated glomerular filtration rate [eGFR], severe albuminuria, or kidney failure) and acute kidney injury (AKI). Secondary outcomes included the individual components of CKD, albuminuria, and death. Intention-to-treat effects were estimated using inverse probability of treatment weights, comparing risks for CKD assessed by the Aalen-Johansen estimator, and AKI burden by mean cumulative counts (MCCs; mean number of events per individual as multiple AKI events were possible). Subgroup analyses included stratification by preexisting cardiovascular or kidney disease.

RESULTS The study included 36 279 individuals who initiated an SGLT2i and 18 782 who initiated a GLP-1RA (median [IQR] age, 63 [55-71] years vs 61 [52-70] years), with comparable diabetes duration, eGFR, and urine albumin-creatinine ratios. The weighted 5-year risk of CKD was 6.7% (95% CI, 6.4%-7.0%) for SGLT2i initiators and 8.2% (95% CI, 7.8%-8.6%) for GLP-1RA initiators (risk ratio: 0.81 [95% CI, 0.76-0.87]; risk difference: -1.5% [95% CI, -2.0% to -1.0%]). The 5-year MCC of AKI per 100 individuals was 25.2 (95% CI, 24.4-26.1) for SGLT2i initiators and 28.7 (95% CI, 27.4-30.0) for GLP-1RA initiators (MCC ratio: 0.88 [95% CI, 0.83-0.93]; MCC difference: -3.5 [95% CI, -5.0 to -2.0]). In contrast, the secondary outcomes of albuminuria and mortality were slightly reduced in GLP-1RA initiators. Results were consistent across subgroups, with the most pronounced CKD and AKI reductions with SGLT2i observed among individuals without preexisting kidney disease.

CONCLUSIONS AND RELEVANCE This comparative effectiveness study found that initiation of SGLT2i vs GLP-1RA treatment in individuals with type 2 diabetes was associated with a lower 5-year risk of CKD and a lower 5-year count of AKI. These findings underscore the potential of SGLT2i treatment for primary prevention of kidney disease in individuals with type 2 diabetes.

JAMA Intern Med. doi:10.1001/jamainternmed.2025.7409
Published online January 20, 2026.

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The prevention of adverse kidney outcomes in individuals with type 2 diabetes (T2D) has been redefined with the introduction of sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), which is reflected by their pivotal roles in current T2D treatment guidelines.¹⁻⁸ However, their comparative effectiveness for reducing acute and chronic kidney disease is uncertain. Indirect comparisons by network meta-analyses of randomized trials generally show a trend toward a larger reduction in composite kidney outcomes for SGLT2i compared with GLP-1RA treatment.⁹⁻¹⁴ Nonetheless, these comparisons could be skewed by a frequent lack of information on albuminuria, as GLP-1RAs may primarily prevent development of albuminuria, whereas SGLT2is mainly prevent worsening of estimated glomerular filtration rate (eGFR).^{12,15} Findings from observational studies remain inconsistent, with some reporting similar treatment outcomes between the 2 drug classes,^{16,17} while others point to improved kidney outcomes with SGLT2is.¹⁸⁻²² Importantly, prior studies are limited by the inclusion of small or selected patient populations,^{16,18-22} short follow-up (<2 years),^{16,17,20,21} and a lack of information on albuminuria.^{16,17,20-22}

In routine clinical care, SGLT2is and GLP-1RAs are used in populations with T2D who are younger and have fewer comorbidities than those represented in clinical trials. Therefore, the 2022 Consensus Report by the American Diabetes Association and the European Association for the Study of Diabetes called for more clinical evidence on the kidney-protective effects of SGLT2i and GLP-1RA in low-risk populations.²³ Moreover, evaluating the comparative effectiveness of SGLT2i vs GLP-1RA treatment in subgroups defined by cardiovascular and kidney disease is important for informing clinical decision-making based on clinical impact.²³

Emulating a target trial, we leveraged high-quality population-based data with long-term follow-up and information on routine measurements of eGFR and urine albumin-creatinine ratio (uACR) from primary care and hospital settings to compare acute and chronic kidney outcomes among SGLT2i and GLP-1RA initiators with T2D, overall and across subgroups with and without preexisting cardiovascular and kidney disease.

Methods

Study Design and Setting

We conducted this nationwide, population-based comparative effectiveness study in individuals with T2D in Denmark. Denmark has a universal, tax-supported health care system providing general and specialized care to all residents.²⁴ The use of a unique civil personal registry (CPR) number assigned to all Danish residents allows for linkage of health care databases at the individual level. According to Danish law, registry-based noninterventive studies do not require ethical approval or informed consent from participants. This study was reported to the Danish Data Protection Agency through registration at Aarhus University, and data were stored and analyzed in a protected data environment hosted by the Danish Health Data Authority. The manuscript was written in accor-

Key Points

Question Do kidney outcomes differ between initiating treatment with a sodium-glucose cotransporter-2 inhibitor (SGLT2i) vs glucagon-like peptide-1 receptor agonist (GLP-1RA) in individuals with type 2 diabetes?

Findings In this comparative effectiveness study with a target trial emulation including 36 279 SGLT2i initiators and 18 782 GLP-1RA initiators, SGLT2i initiation was associated with a lower 5-year risk of chronic kidney disease and a lower 5-year count of acute kidney injury compared with GLP-1RA initiation. Findings were consistent across subgroups and most pronounced among individuals without preexisting kidney disease.

Meaning These findings suggest that initiating treatment with an SGLT2i, compared with a GLP-1RA, is associated with improved kidney outcomes in individuals with type 2 diabetes.

dance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) reporting guidelines.^{25,26}

We emulated a target trial including initiators of SGLT2is (empagliflozin or dapagliflozin) and GLP-1RAs (liraglutide, semaglutide, or dulaglutide) from January 2014 to November 2020 based on health care databases covering the entire Danish population (5.8 million inhabitants in 2020) (eFigure 1 in Supplement 1).²⁷⁻²⁹ During this period, both SGLT2is and GLP-1RAs were second-line treatments to metformin for T2D in Denmark.³⁰

Applying the target trial framework, we first specified the hypothetical target trial protocol that would assess the comparative effectiveness of SGLT2i and GLP-1RA initiation for acute and chronic kidney outcomes and then carefully emulated the protocol using observational data.^{28,29} The key components of this process are presented in detail below and summarized in eTable 1 in Supplement 1.

Data Sources

Using the CPR number, we linked individual-level information from the following databases: The Civil Registration System, which includes information on age, sex, vital status, and residence of all Danish residents since 1968³¹; The Danish National Patient Registry, which holds information on all hospital diagnoses and treatments since 1995³²; The Danish National Prescription Registry, which holds information on all prescriptions filled at Danish pharmacies since 1995³³; The Clinical Laboratory Information System Research Database, which holds regional information on laboratory test results from North and Central Denmark since the 1990s^{34,35}; and The Register of Laboratory Results for Research, which holds complete nationwide information on laboratory test results since October 2015.^{35,36}

Eligibility Criteria

Eligible individuals included adult (≥ 18 years) Danish residents with metformin-treated T2D between January 1, 2014, and November 30, 2020 (eFigure 2 in Supplement 1). We excluded individuals with a prior dispensing of either an SGLT2i

or a GLP-1RA, type 1 diabetes (initiated insulin monotherapy before 30 years of age), a history of chronic dialysis, a kidney transplant, diagnosis of kidney failure with replacement therapy, median eGFR <30 mL/min/1.73 m² within the last year, or median uACR ≥300 mg/g within the last 2 years. To ensure appropriate covariate assessment, individuals were required to reside in Denmark for at least 12 months and have at least 1 recorded eGFR measurement.

Treatment Assignment and Strategies

Treatment assignment was defined by the first dispensing of either an SGLT2i or a GLP-1RA after fulfilling the eligibility criteria. As in the target trial, the treating physician would be allowed to individualize treatment dosage. Treatment with Saxenda (liraglutide), which was specifically approved for treatment of obesity in 2015, was not included.

Outcomes

The 2 coprimary outcomes of interest were chronic kidney disease (CKD) and acute kidney injury (AKI). Chronic kidney disease was defined as a composite of (1) a sustained reduction in eGFR (2 outpatient eGFR measurements separated by at least 90 days with a 40% reduction from eGFR at index, which was defined as the median of all outpatient eGFR measurements within the previous 365 days) or (2) kidney failure (diagnosis or procedure code related to chronic dialysis or transplant or 2 outpatient eGFR measurements <15 mL/min/1.73 m² separated by ≥90 days), or (3) severe albuminuria (2 outpatient uACR measurements of >300 mg/g separated by ≥90 days). AKI was defined as (1) an absolute increase in plasma creatinine (pCr) of ≥0.3 mg/dL (to convert to μmol/L, multiply by 88.4) within 48 hours or (2) a relative increase of at least 1.5 times the lowest pCr measurement within the last 7 days, or (3) a relative increase of at least 1.5 times the baseline pCr level, which was defined as the median of all outpatient pCr measurements within the previous 8 to 365 days.³⁷

Secondary outcomes included (1) the individual components of CKD; (2) incident or progressive albuminuria, ie, 2 outpatient uACR measurements of >30 mg/g separated by at least 90 days among individuals with normal to mildly increased albuminuria (<30 mg/g) at index and 2 outpatient uACR measurements of more than 300 mg/g separated by at least 90 days among individuals with moderately increased albuminuria (30-300 mg/g) at index; and (3) death. When assessing albuminuria, individuals with missing information on uACR at index were considered to have normal to mild albuminuria. To assess this premise, we compared the characteristics of individuals with missing uACR to those with normal to mildly increased albuminuria.

Follow-Up

For the primary intention-to-treat analyses, individuals were considered exposed from the date of initiation of SGLT2i or GLP-1RA treatment until outcome, date of death, emigration, 5 years of follow-up, or end of study on October 31, 2024. The outcome analyses were repeated using an on-treatment design, which censored individuals at the time of treatment cessation or initiation of a drug from the comparator study drug

class. Treatment duration was based on the estimated number of days covered by each filled prescription, calculated as the number of packages times the numerical volume of a package and adding a grace period of 180 days.

Covariates

To characterize the population at the time of treatment initiation, information on demographics, comorbidities, comedication, outpatient laboratory test results, country of origin, and social and frailty markers were included from the databases listed above (eTable 2 in Supplement 1). Comorbidities were defined using primary or secondary hospital diagnoses, except for hypertension, which was defined using a validated algorithm as at least 1 filled prescription for at least 2 different antihypertensive-specific drug classes in the previous year.³⁸ The look-back period was 90 days for comedication, 1 year for pCr and hemoglobin A_{1c} (HbA_{1c}), 2 years for uACR, and 10 years for comorbidities. eGFR was estimated using the CKD-EPI 2009 equation without correction for race.^{39,40}

Statistical Analysis

Population characteristics were described using medians with IQRs for continuous variables and as counts with percentages for categorical variables. For a balanced comparison of the 2 treatment groups, we applied stabilized inverse probability of treatment (IPT) weighting using propensity scores estimated from a logistic regression including 44 index covariates (Table).⁴¹ Covariate balance was assessed by standardized mean differences.

We estimated weighted cumulative incidences (risks) for CKD, sustained reduction in eGFR, severe albuminuria, kidney failure, and incident or progressive albuminuria, accounting for the competing risk of death using the Aalen-Johansen estimator.⁴² We similarly computed the cumulative incidence of death using the Kaplan-Meier estimator.⁴³ AKI was assessed using mean cumulative counts (MCCs), which reflect the mean number of events per individual, when each person can contribute with more than 1 event (eMethods in Supplement 1).⁴⁴

In the on-treatment analyses, we accounted for informative censoring, ie, differences in the probability of censoring, by time-dependent inverse probability of censoring weights, which were updated for each month of follow-up and used to reweight the treatment groups over time.⁴⁵ Weights were truncated at a value of 10.

We used multiple imputation (10 datasets) (eMethods in Supplement 1) to impute missing information on HbA_{1c} and uACR at index and used bootstrap methods with 200 samples to estimate standard errors for our estimates in each imputed dataset.⁴⁶ In analyses stratified by HbA_{1c} or uACR, the imputed value was used to classify individuals with missing data. The standard errors were combined across imputed datasets using the Rubin rule to provide 95% CIs of point estimates.⁴⁷

For the intention-to-treat analyses, we conducted subgroup analyses by sex, age (<65 or ≥65 years), eGFR (<60 or ≥60 mL/min/1.73 m²), uACR (<30 or 30-300 mg/g), HbA_{1c} (≤58 or >58 mmol/mol), atherosclerotic cardiovascular disease (ASCVD; coronary heart disease, peripheral artery disease, aortic

Table. Characteristics of SGLT2i and GLP-1RA Initiators

Characteristic	Initiators, No. (%) ^a		Absolute standardized mean difference ^b	
	SGLT2i (n = 36 279)	GLP-1RA (n = 18 782)	Crude	sIPTW
Age, median (IQR), y	63 (55-71)	61 (52-70)	0.167	0.001
Sex				
Female	13 135 (36)	7886 (42)	0.119	0.002
Male	23 144 (64)	10 896 (58)		
Calendar period				
2014-2017	11 154 (31)	6430 (34)	0.085	0.005
2018-2020	25 125 (69)	12 352 (66)		
Diabetes-related variables				
Diabetes duration, median (IQR), y	7 (3-11)	7 (3-11)	0.034	<0.001
HbA _{1c} , median (IQR), mmol/mol	64 (57-76)	66 (57-79)	0.070	0.005
Missing	659 (2)	286 (2)	NA	NA
Diabetic retinopathy	2843 (8)	1617 (9)	0.028	0.002
Diabetic neuropathy	1518 (4)	981 (5)	0.049	0.001
Diabetic nephropathy	1047 (3)	912 (5)	0.102	0.003
Glucose lowering drugs, median (IQR), No.	3 (2-5)	4 (2-6)	0.209	0.004
Insulin	3121 (9)	4138 (22)	0.380	0.003
DPP-4 inhibitors	11 441 (32)	4925 (26)	0.117	0.004
Sulfonylureas	4151 (11)	2078 (11)	0.012	0.001
eGFR, median (IQR), mL/min/1.73 m ²	90 (77-100)	91 (75-102)		
≥90	18 527 (51)	9911 (53)	0.035	<0.001
60-89	14 925 (41)	6403 (34)		
45-59	2294 (6)	1619 (9)		
<45	533 (1)	849 (5)		
eGFR measurements within the prior year, median (IQR), No.	3 (2-4)	3 (2-4)	0.057	0.001
uACR, median (IQR), mg/g	13 (7-33)	15 (7-37)		
Stage A1 (<30 mg/g)	20 574 (57)	10 377 (55)	0.053	0.002
Stage A2 (30-300 mg/g)	7768 (21)	4428 (24)		
Missing	7937 (22)	3977 (21)		
Albuminuria measurements within the prior 2 y, median (IQR), No.	2 (1-2)	2 (1-2)	0.053	0.003
Comorbidities				
ASCVD	8328 (23)	4062 (22)	NA	NA
Coronary heart disease	5877 (16)	2813 (15)	0.034	0.007
Peripheral artery disease	1103 (3)	625 (3)	0.016	0.001
Aortic aneurysm	327 (1)	149 (1)	0.012	0.005
Cerebrovascular disease	2423 (7)	1178 (6)	0.017	0.006
Heart failure	2215 (6)	1010 (5)	0.031	0.008
Atrial fibrillation or flutter	2887 (8)	1498 (8)	0.001	0.003
Venous thromboembolism	778 (2)	519 (3)	0.040	0.001
Hypertension	15 813 (44)	8546 (46)	0.039	0.004
Hypercholesterolemia	5095 (14)	2645 (14)	0.001	0.006
Medical obesity	4824 (13)	4303 (23)	0.252	0.001
Chronic obstructive pulmonary disease	2733 (8)	1763 (9)	0.067	0.001
Cancer	2573 (7)	1337 (7)	0.001	0.003

(continued)

Table. Characteristics of SGLT2i and GLP-1RA Initiators (continued)

Characteristic	Initiators, No. (%) ^a		Absolute standardized mean difference ^b	
	SGLT2i (n = 36 279)	GLP-1RA (n = 18 782)	Crude	sIPTW
Comedication				
ACE-I/ARB	19 834 (55)	10 257 (55)	0.001	0.004
Thiazide diuretics	3765 (10)	2196 (12)	0.042	0.003
Loop diuretics	2905 (8)	2111 (11)	0.110	0.003
Mineralocorticoid receptor antagonists	1642 (5)	889 (5)	0.010	0.001
β-Blockers	8374 (23)	4302 (23)	0.004	0.005
Calcium channel blockers	8261 (23)	4331 (23)	0.007	0.001
Statins	22 097 (61)	10 824 (58)	0.067	<0.001
Antiplatelets	9012 (25)	4345 (23)	0.040	0.005
Anticoagulants	2954 (8)	1567 (8)	0.007	0.001
NSAIDs	3319 (9)	2062 (11)	0.061	0.001
Country of origin				
Nordic countries	30 064 (83)	16 766 (89)	0.186	0.004
Non-Nordic European Union country, United Kingdom, and Switzerland	766 (2)	344 (2)	0.020	0.001
Other country	5449 (15)	1672 (9)	0.189	0.004
Social and frailty markers				
Marital status				
Unmarried	6183 (17)	3637 (19)	0.060	0.002
Married	20 737 (57)	10 286 (55)	0.048	0.003
Widowed or divorced	9359 (26)	4859 (26)	0.002	0.001
Psychoactive medication	5722 (16)	3503 (19)	0.076	0.001
Alcoholism	733 (2)	397 (2)	0.007	0.003
Hospitalization in the prior year	7111 (20)	4084 (22)	0.053	<0.001

Abbreviations: ACE-I, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; ASCVD, atherosclerotic cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, hemoglobin A_{1c}; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; sIPTW, stabilized inverse probability of treatment weighting; uACR, urine albumin-creatinine ratio.

^a Values are No. (%) unless indicated otherwise.

^b SGLT2i and GLP-1RA initiators were weighted according to the variables listed in the table and standardized mean differences were averaged across the imputations.

aneurysm, and cerebrovascular disease), heart failure, and diabetes duration (<7 or ≥7 years). New IPT weights were estimated in all subgroups. Effect modification was evaluated by assessing the ratio of risk ratios (RRs) or MCC ratios between subgroups.

Analyses were repeated in T2D populations treated solely with metformin prior to initiation of SGLT2i or GLP-1RA treatment; with an obesity diagnosis; and with complete information at index. Furthermore, we performed separate analyses comparing liraglutide and semaglutide to SGLT2i treatment. Statistical analyses were performed using SAS, version 9.4 (SAS Institute), and figures were produced using R, version 4.3.3 (R Foundation for Statistical Computing).

Results

Population Characteristics

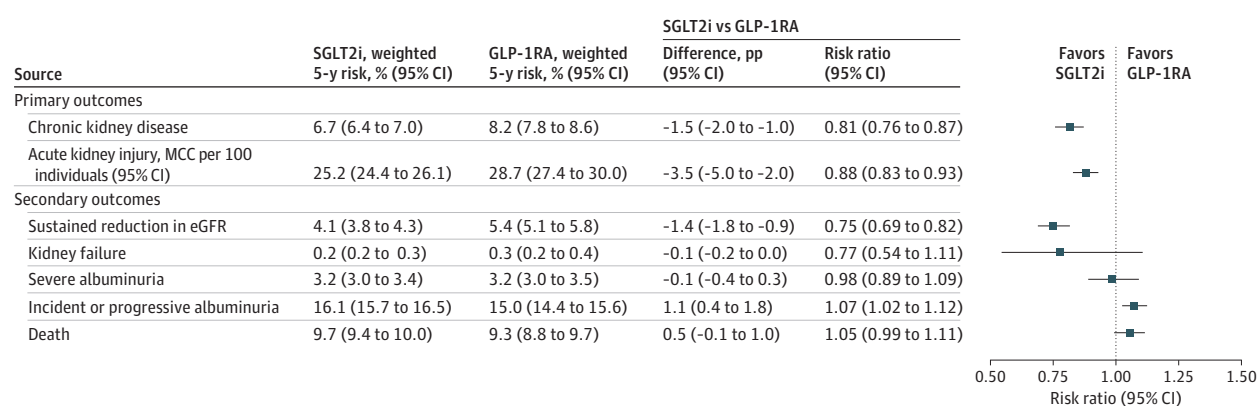
We identified 36 279 eligible SGLT2i initiator and 18 782 eligible GLP-1RA initiators (eFigure 2 in Supplement 1). Compared with GLP-1RA initiators, SGLT2i initiators were older (median, 63 [IQR, 55-71] years vs 61 [IQR, 52-70] years), more likely to be male (64% male and 36% female vs 58% male and 42% female), and less likely to have obesity (13% vs 23%) (Table). In contrast, diabetes duration, HbA_{1c}, eGFR, uACR, ASCVD, and

heart failure were overall comparable. Among SGLT2i users, 23 467 (65%) initiated empagliflozin and 12 812 (35%) initiated dapagliflozin. The majority of individuals using a GLP-1RA initiated liraglutide (9105 [48%]) or semaglutide (9049 [48%]), whereas only 628 (3%) initiated dulaglutide. The proportions of individuals with missing uACR (21%-22%) and HbA_{1c} (2%) were similar across treatment groups. Besides being slightly younger, individuals missing uACR had characteristics comparable with individuals with normal to mild albuminuria (eTable 3 in Supplement 1). After IPT weighting, the 2 treatment groups were balanced on all measured covariates with standardized mean differences below 0.01 (Table).

Outcomes

In the intention-to-treat analysis, the median follow-up time for CKD and AKI was 5.0 (IQR, 4.6-5.0) years among SGLT2i initiators and 5.0 (IQR, 4.5-5.0) years among GLP-1RA initiators (eTable 4 in Supplement 1). The frequency of eGFR and uACR measurements during follow-up were similar across treatment groups (eTable 4 in Supplement 1). The 5-year risk of CKD was 6.7% (95% CI, 6.4%-7.0%) for SGLT2i initiators and 8.2% (95% CI, 7.8%-8.6%) for GLP-1RA initiators, corresponding to an RR of 0.81 (95% CI, 0.76-0.87) and a risk difference (RD) of -1.5% (95% CI, -2.0% to -1.0%) (Figure 1 and Figure 2). The 5-year MCC of AKI per 100 individuals was 25.2 (95% CI,

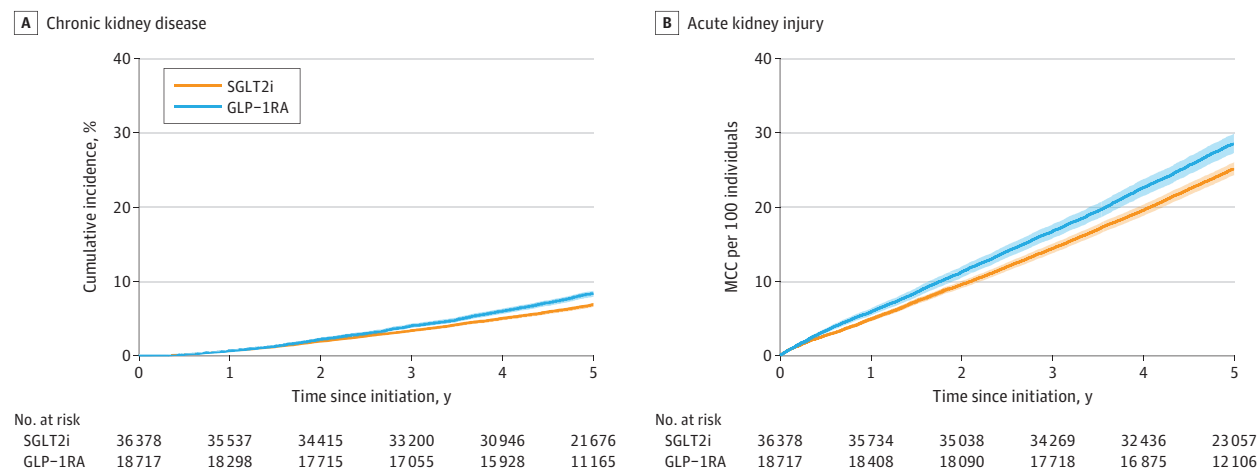
Figure 1. Five-Year Incidence of Primary and Secondary Outcomes—Intention-to-Treat Analyses



For acute kidney injury, the estimates are mean cumulative counts per 100 individuals, and the ratio displayed in the forest plot is the MCC ratio. For all other outcomes, estimates are risks (%), with risk ratios displayed in the forest

plot. eGFR indicates estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; MCC, mean cumulative count; pp, percentage point; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Figure 2. Cumulative Incidence of Primary Outcomes



Shaded areas represent 95% CIs. GLP-1RA indicates glucagon-like peptide-1 receptor agonist; MCC, mean cumulative count; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

24.4-26.1) for SGLT2i initiators and 28.7 (95% CI, 27.4-30.0) for GLP-1RA initiators, with an MCC ratio of 0.88 (95% CI, 0.83-0.93) and an MCC difference of -3.5 (95% CI, -5.0 to -2.0) per 100 individuals.

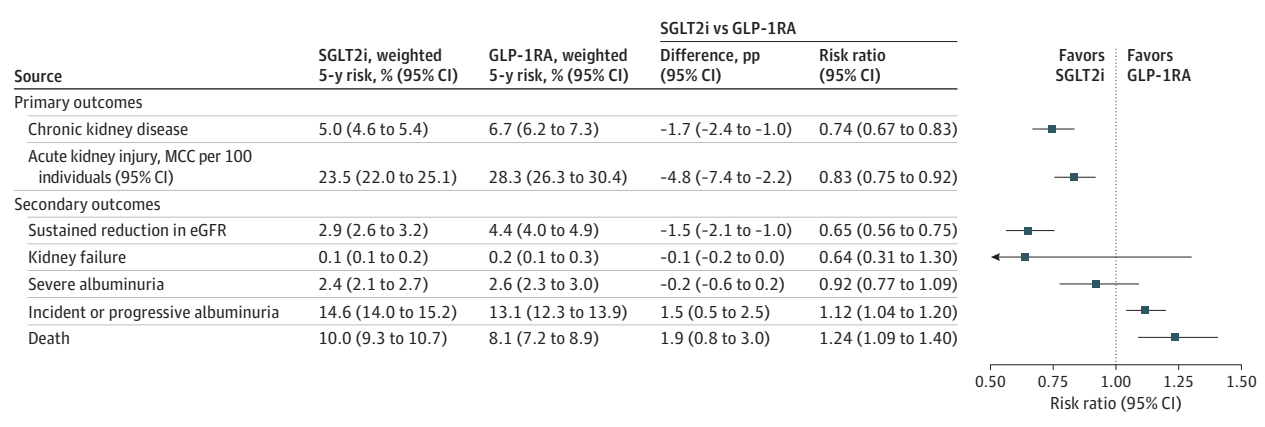
When assessing the individual components of CKD, SGLT2i initiation was associated with a lower risk of sustained reduction in eGFR (RR, 0.75 [95% CI, 0.69-0.82]; RD, -1.4% [95% CI, -1.8% to -0.9%]) and kidney failure (RR, 0.77 [95% CI, 0.54-1.11]; RD: -0.1% [95% CI, -0.2% to 0.0%]), compared with GLP-1RA initiation, while the risk of severe albuminuria was similar in the 2 treatment groups (RR, 0.98 [95% CI, 0.89-1.09]; RD, -0.1% [95% CI, -0.4% to 0.3%]) (Figure 1; eFigure 3 in Supplement 1).

The 5-years risks of incident or progressive albuminuria were 16.1% (95% CI, 15.7%-16.5%) for SGLT2i initiators and 15.0% (95% CI, 14.4%-15.6%) for GLP-1RA initiators, corresponding to an RR of 1.07 (95% CI, 1.02-1.12) and an RD of 1.1% (95% CI, 0.4%-1.8%) (Figure 1; eFigure 3 in Supplement 1). The

5-year mortality was 9.7% (95% CI, 9.4%-10.0%) for SGLT2i initiators and 9.3% (95% CI, 8.8%-9.7%) for GLP-1RA initiators, corresponding to an RR of 1.05 (95% CI, 0.99-1.11) and an RD of 0.5% (95% CI, -0.1% to 1.0%).

The on-treatment analyses reflected the intention-to-treat analyses with marginally larger relative differences across both primary and secondary outcomes (Figure 3). Thus, SGLT2i initiation was associated with a lower risk of CKD (RR, 0.74 [95% CI, 0.67-0.83]) and count of AKI (MCC ratio, 0.83 [95% CI, 0.75-0.92]), as well as lower risks of sustained reduction in eGFR (RR, 0.65 [95% CI, 0.56-0.75]) and kidney failure (RR, 0.64 [95% CI, 0.31-1.30]) when compared with GLP-1RA initiation. In contrast, severe albuminuria (RR, 0.92 [95% CI, 0.77-1.09]) did not differ materially, while risks of incident or progressive albuminuria (RR, 1.12 [95% CI, 1.04-1.20]) and death (RR, 1.24 [95% CI, 1.09-1.40]) were higher in SGLT2i initiators.

Figure 3. Five-Year Incidence of Primary and Secondary Outcomes—On-Treatment Analyses



For acute kidney injury, the estimates are mean cumulative counts per 100 individuals, and the ratio displayed in the forest plot is the MCC ratio. For all other outcomes, estimates are risks (%), with risk ratios displayed in the forest

plot. eGFR indicates estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; MCC, mean cumulative count; pp, percentage points; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Subgroup and Sensitivity Analyses

For CKD, RRs were similarly reduced with SGLT2i compared with GLP-1RA treatment across most subgroups, while the RR was lower for individuals with uACR below 30 mg/g vs 30 to 300 mg/g (eFigure 4 in Supplement 1). Similarly, the lower occurrence of AKI with SGLT2i initiation was more evident for individuals with eGFR of at least 60 mL/min/1.73 m² vs below 60 mL/min/1.73 m² (eFigure 5 in Supplement 1). In subgroup analyses of secondary outcomes, the results generally aligned with the overall results (eFigures 6-10 in Supplement 1). Likewise, sensitivity analyses showed results similar to those from the main analyses (eFigures 11-14 in Supplement 1).

Discussion

This comparative effectiveness study with target trial emulation used population-based health care data from routine clinical practice to compare acute and chronic kidney outcomes among SGLT2i and GLP-1RA initiators with T2D. We found a lower CKD risk and AKI count among individuals initiating SGLT2i compared with GLP-1RA treatment. The reduced risk of CKD was predominantly due to a lower risk of decline in eGFR and kidney failure with SGLT2i, while the risk of severe albuminuria was similar for the 2 treatment groups. The risk of incident or progressive albuminuria and death were slightly higher among SGLT2i initiators compared with GLP-1RA initiators. For CKD, differences in risks varied with uACR and were more pronounced among individuals with uACR below 30 mg/g, while the association with AKI was more evident among individuals with an eGFR of at least 60 mL/min/1.73 m². Collectively, these findings support a lower risk of acute and chronic kidney outcomes with SGLT2i vs GLP-1RA, especially among individuals with a low a priori risk of kidney disease.

To our knowledge, no head-to-head randomized clinical trials have directly compared the effectiveness of SGLT2is vs GLP-1RAs in reducing CKD and AKI. Network meta-analyses of randomized trials comparing SGLT2i and GLP-1RA treat-

ment have reported mixed results.⁹⁻¹⁴ Most included trials contained assessment of eGFR, while inclusion of albuminuria was less common. This could have affected the results as GLP-1RAs may exert their kidney-protective effects mainly by preventing albuminuria.^{10,15} In a meta-analysis of clinical trials comparing SGLT2i and GLP-1RA treatment to placebo, significant effects on hospitalization for kidney disease, including both severe albuminuria and reduction in eGFR, were reported for both drug classes.¹⁵ However, when severe albuminuria was excluded from the outcome, the effect of GLP-1RA treatment was markedly reduced, while the effect of SGLT2i treatment remained stable. This aligns with our findings, as development of incident or progressive albuminuria was less common among individuals treated with a GLP-1RA compared with an SGLT2i.

In addition to potentially divergent effects on albuminuria, GLP-1RAs appear more effective for stroke and peripheral artery disease, while SGLT2is seem superior in preventing heart failure.^{9,11,15} Although with limited statistical precision, our findings suggested a lower mortality with GLP-1RA treatment but reduced kidney outcomes with SGLT2i treatment. This finding corroborates a recent network meta-analysis by Wang et al¹⁴ and is consistent with an observational study by Edmonston et al¹⁷ that found a hazard ratio of 0.77 (95% CI, 0.65-0.91) for 40% eGFR decline and 1.08 (95% CI, 0.92-1.27) for death when comparing SGLT2is with GLP-1RAs. Collectively, this underscores that kidney outcomes are only one of several considerations when selecting treatment for individuals with T2D.^{11,15,17}

Observational studies have compared kidney outcomes in SGLT2i- and GLP-1RA-treated individuals. Lee et al²² performed a cohort study among individuals with CKD and found lower rates of kidney replacement therapy with SGLT2i vs GLP-1RA initiation. Conversely, Xie et al¹⁶ found no difference in CKD development in a predominantly male population based on data from the US Veterans Affairs database. Besides the use of selected patient populations, both studies were constrained by the absence of albuminuria data and short follow-

up. Other studies exhibit similar limitations, including small or selected patient populations,¹⁸⁻²¹ short follow-up,^{17,20,21} or a lack of information on albuminuria.^{17,20,21} In contrast, our study leveraged a large population-based cohort of all individuals with T2D initiating SGLT2i or GLP-1RA treatment in Denmark with long-term follow-up and comprehensive information on eGFR and uACR. This allowed for a representative and granular assessment of kidney outcomes, strengthening the relevance and impact of our findings for everyday clinical care.

Limitations

This study has some limitations. As the assignment of SGLT2i or GLP-1RA treatment was not random, there remains a potential for confounding despite accounting for 44 confounders. We lacked data on body mass index, yet a sensitivity analysis among individuals with an obesity diagnosis at index yielded results similar to the main analyses. Furthermore, the use of registers to identify the study population and define covariates comes with a risk of misclassification. We used a validated algorithm for identifying individuals with T2D with a positive predictive value of 95% and reduced the risk of misclassifying outcomes by using laboratory test results in accordance with current recommendations.⁴⁸⁻⁵⁰ Moreover, the reg-

istration of included comorbidities such as cardiovascular disease in the Danish National Patient Registry is high.³² Finally, the transportability of the findings may be limited by the inclusion of a general population cohort from the Nordic countries, as the risk of kidney outcomes may differ for other ethnicities and settings.

Conclusions

This comparative effectiveness study with population-based target trial emulation provides evidence for lower risks of acute and chronic kidney outcomes with SGLT2i compared with GLP-1RA initiation among individuals with T2D in a contemporary clinical care setting. The reduced risk of CKD with SGLT2i treatment was especially due to a lower risk of decline in eGFR, while GLP-1RA treatment was associated with lower risks of incident or progressive albuminuria and mortality. Notably, the differences in kidney outcomes were consistent across subgroups and most pronounced among individuals without preexisting kidney disease, which underscores a potential for primary prevention. Importantly, the divergent outcomes of eGFR and albuminuria suggest that combined treatment may offer additive benefits, which should be explored in future studies.

ARTICLE INFORMATION

Accepted for Publication: November 17, 2025.

Published Online: January 20, 2026.
doi:10.1001/jamainternmed.2025.7409

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Obtained funding: Jensen, Christiansen.

Administrative, technical, or material support: Jensen.

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Conflict of Interest Disclosures:

Drs Heide-Jørgensen and Andersen reported being involved, through the Department of Clinical Epidemiology, in studies with funding from various companies as research grants to (and administered by) Aarhus University; none of these studies are related to the current study. Dr Thomsen reported giving occasional presentations and lectures on medical epidemiological research (with or without financial compensation) for companies during the last 15 years, including AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi. No other disclosures were reported.

Funding/Support: Dr Jensen was supported by the Karen Elise Jensen Foundation and the Independent Research Fund Denmark (grant number 0134-00407B). Dr Christiansen was supported by the Karen Elise Jensen Foundation and the Independent Research Fund Denmark (grant numbers 0134-00407B and 4308-00245B). Dr Bonnesen was supported by a research grant from the Danish Diabetes and Endocrine Academy, which is funded by the Novo Nordisk Foundation under grant NNF225A0079901. Dr Fu was supported by a VENI grant from the Netherlands Organization of Scientific Research (#09150162310058), a Kolff grant from the Dutch Kidney Foundation (220K2026), and a Junior PI grant from Leiden University Medical Center.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

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