JAMA Internal Medicine | Original Investigation

Effectiveness of Empagliflozin vs Dapagliflozin for Kidney Outcomes in Type 2 Diabetes

Kasper Bonnesen, PhD; Uffe Heide-Jørgensen, PhD; Diana H. Christensen, PhD; Christian F. Christiansen, PhD; Timothy L. Lash, DSc; Sean Hennessy, PharmD, PhD; Anthony A. Matthews, PhD; Lars Pedersen, PhD; Reimar W. Thomsen, PhD; Morten Schmidt, DMSc

IMPORTANCE No large randomized clinical trial has directly compared empagliflozin with dapagliflozin, leaving their comparative effectiveness regarding kidney outcomes unknown.

OBJECTIVE To compare kidney outcomes between initiation of empagliflozin vs dapagliflozin in adults with type 2 diabetes who were receiving antihyperglycemic treatment.

DESIGN, SETTING, AND PARTICIPANTS This target trial emulation used nationwide, population-based routinely collected Danish health care data to compare initiation of empagliflozin vs dapagliflozin in adults with type 2 diabetes who received antihyperglycemic treatment between June 1, 2014, and October 31, 2020. Data were analyzed from October 2023 to August 2024. Persons were followed up until an outcome, emigration, death, 6 years, or December 31, 2021, whichever occurred first.

EXPOSURE Initiation of empagliflozin vs dapagliflozin.

MAIN OUTCOMES AND MEASURES Outcomes included acute kidney injury, incident chronic kidney disease (stages G3 to G5 or stage A2 or A3), and progression of chronic kidney disease (≥40% decrease in estimated glomerular filtration rate from baseline). Risks of kidney outcomes were estimated in intention-to-treat and per-protocol analyses using an Aalen-Johansen estimator that adjusted for 56 potential confounders and considered death as a competing event.

RESULTS A total of 32 819 individuals who initiated treatment with empagliflozin and 17 464 with dapagliflozin were included (median [IQR] age, 63 [54-71] years; 18 872 female individuals [37.5%]; median [IQR] estimated glomerular filtration rate, 88 [73-104] mL/min/1.73 m^2). After weighting, all measured covariates were well balanced between the groups. In intention-to-treat analyses, people who initiated treatment with empagliflozin and dapagliflozin exhibited comparable 6-year risks of acute kidney injury (18.2% vs 18.5%; risk ratio, 0.98; 95% CI, 0.91-1.06), chronic kidney disease stages G3 to G5 (11.8% vs 12.1%; risk ratio, 0.97; 95% CI, 0.89-1.05), chronic kidney disease stage A2 or A3 (14.8% vs 14.3%; risk ratio, 1.04; 95% CI, 0.93-1.15), and progression of chronic kidney disease (5.3% vs 5.7%; risk ratio, 0.94; 95% CI, 0.56-1.58). The primary analyses were supported by corresponding per-protocol analyses.

CONCLUSIONS AND RELEVANCE The results of this cohort study suggest that people with type 2 diabetes who initiated treatment with empagliflozin and dapagliflozin had comparable long-term kidney outcomes.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Kasper Bonnesen, PhD, Aarhus University, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark (bonnesen@clin.au.dk).

JAMA Intern Med. 2025;185(3):314-323. doi:10.1001/jamainternmed.2024.7381
Published online January 21, 2025.

Type 2 diabetes is a leading cause of kidney disease globally.[1] People with diabetes-related kidney disease face a higher risk of kidney failure, cardiovascular disease, and death.[1] Early diagnosis and treatment of type 2 diabetes, along with associated metabolic and vascular issues, are the most effective strategies to mitigate kidney disease in patients with type 2 diabetes.

The sodium-glucose cotransporter 2 inhibitors (SGLT2is) empagliflozin and dapagliflozin reduce cardiovascular and kidney outcomes in patients with type 2 diabetes[2-5]; thus, they are widely used.[6,7] The effects of SGLT2is are generally considered class effects.[8] Consequently, Danish,[9] European,[10,11] and US[11] guidelines do not favor any agent vs others when treating type 2 diabetes. Yet, European and US guidelines stress that "within-class differences should be considered."[11] As to our knowledge only 1 small trial that focused on changes in estimated glomerular filtration rate (eGFR) has directly compared these agents,[12] examining differences in their long-term effects is important.[13] Such differences might exist due to variations in their chemical structure and pharmacodynamic effects.[14-16] This study compared the effectiveness of empagliflozin vs dapagliflozin in reducing kidney outcomes in persons with type 2 diabetes according to baseline kidney function.

Key Points

Question Do kidney outcomes differ between treatment initiation of empagliflozin and dapagliflozin in persons with type 2 diabetes who are receiving antihyperglycemic treatment?

Findings This nationwide cohort study of 32 819 individuals who initiated treatment with empagliflozin and 17 464 with dapagliflozin, all with type 2 diabetes and who were receiving antihyperglycemic treatment, found no clinically important differences in the risks of acute kidney injury, incident chronic kidney disease, or chronic kidney disease progression over 6 years between people who initiated treatment with empagliflozin vs dapagliflozin.

Meaning The study results support the current clinical practice of not recommending empagliflozin vs dapagliflozin, or vice versa, when treating type 2 diabetes.

Methods

Research Question and Study Design

This prospective new-user, active-comparator cohort study used nationwide, population-based routinely collected Danish health care data[17] to emulate a target trial (ie, a hypothetical pragmatic trial that would address the causal question of interest) of empagliflozin vs dapagliflozin, in addition to standard care, for preventing kidney outcomes in persons with type 2 diabetes.[18] The key population or patient, intervention, comparison, outcome, and time (PICOT) components of the target trial and its emulation are presented in this article and summarized in eTable 1 in Supplement 1. The data sources used for emulation are described elsewhere,[19-25] and their content is summarized in eTable 2 in Supplement 1. eTable 3 in Supplement 1 presents all codes used in the study.

In Denmark, national health care services provide tax-financed access to general practitioners, private practice specialists, and hospitals, as well as partial reimbursement for prescription medication expenses.[17] Individual-level linkage of Danish health registries was provided by the unique Civil Personal Registration number given to all Danish citizens at birth or to persons arriving on legal immigration.[19] In Denmark, registry-based research using health care data does not require informed consent from included individuals.

Population

In the target trial, inclusion criteria would include having type 2 diabetes treated with antihyperglycemic medication (monotherapy treatment with metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 agonists, or thiazolidinediones or combination treatment with the same agents and/or insulin) and being 18 years or older. Exclusion criteria would include previous SGLT2i treatment in Denmark and preexisting kidney failure.

The emulation applied similar eligibility criteria. Antihyperglycemic treatment was defined as at least 1 dispensing within 365 days before empagliflozin or dapagliflozin initiation. Insulin monotherapy was an insufficient inclusion criterion because dapagliflozin was briefly approved for type 1 diabetes, and the Danish National Prescription Registry cannot differentiate type 1 from type 2 diabetes as the indication for treatment.[20] Kidney failure was defined as a previous kidney failure diagnosis, chronic dialysis or kidney transplant procedure, or a median eGFR of less than 15 mL/min/1.73 m^2 within 365 days before initiation of empagliflozin or dapagliflozin.[20,26,27] To ensure that the registry captured everyone's creatinine measurements and identified the creatinine-defined outcomes (explained later),[21] we required people to have lived in a municipality with presumed complete laboratory registry data coverage for creatinine for at least 365 days[27] and to have had at least 1 creatinine measurement registered during this period.

Intervention and Comparator

Eligible patients in the target trial would be randomly assigned, 1-to-1, to either adjunct treatment with empagliflozin (intervention) or dapagliflozin (comparator) at their maximal tolerated doses. Participants and treating physicians would be aware of the assigned treatment. Treating physicians would be allowed to adjust antihyperglycemic treatment according to clinical guidelines and judgment. In the emulation, individuals were assigned to the empagliflozin or dapagliflozin group based on their first time ever dispensing during the enrollment period.[20]

Outcomes

In the target trial, the outcomes would follow the Kidney Disease Improving Global Outcomes (KDIGO) definitions[28,29] and include acute kidney injury (creatinine increase within 48 hours, ≥26.5 μmol/L or ≥1.5 times baseline), first occurrence of chronic kidney disease (CKD) (eGFR <60 mL/min/1.73 m^2 or urine

albumin-to-creatinine ratio [uACR] ≥30 mg/g), and CKD progression (≥40% decline in eGFR). The eGFR-defined CKD outcome would be examined in patients with an eGFR of 60 mL/min/1.73 m^2 or higher at enrollment, the uACR-defined CKD outcome would be examined in patients without albuminuria at enrollment, and the CKD progression outcome would be examined in patients with an eGFR of less than 60 mL/min/1.73 m^2 at enrollment. The outcomes would be assessed during scheduled follow-up by a masked adjudication committee.

The emulation applied similar outcomes, but we required a confirmatory test at least 90 days apart without a normal test result in between for the CKD and CKD progression outcomes (eTable 1 in Supplement 1). The outcomes were prospectively identified via routinely collected creatinine or uACR measurements from outpatient clinics and general practice,[30] making differential misclassification unlikely.

Time

The inclusion period in the target and emulated trials was from June 1, 2014, to October 31, 2020, reflecting the time before SGLT2is obtained European approval for congestive heart failure and CKD treatment in individuals without type 2 diabetes. Baseline was the time of randomization in the target trial and the time of the first empagliflozin or dapagliflozin dispensing in the emulation. Individuals were followed up from baseline until the outcome of interest, emigration, 6 years of follow-up, death, or the end of the study period (December 31, 2021), whichever occurred first, accounting for death as a competing event.[31]

Statistics

In the target trial, the causal estimands would be intention-to-treat and per-protocol effects. The Aalen-Johansen estimator would be used to estimate cumulative incidences for the empagliflozin and dapagliflozin groups,[32] along with 6-year risks, risk differences, and risk ratios between the groups.[32] For per-protocol analyses, individuals would be censored on nonadherence to their assigned treatment strategy, and time-varying inverse probability weights would be used to adjust for selection bias potentially induced by this censoring.[33] Covariates associated with nonadherence that would be used to estimate these weights would include all baseline covariates, with time-updated age, diabetes duration, hemoglobin A_{1c} (HbA_{1c}) levels, eGFR, uACR, low-density and high-density lipoprotein cholesterol levels, triglyceride levels, diagnosis of morbidities, initiation of antihyperglycemic and other medications, and follow-up time. Intention-to-treat analyses would include subgroup analyses according to the presence of atherosclerotic cardiovascular disease or heart failure, age, sex, duration of diabetes, HbA_{1c} levels, the number of antihyperglycemic medications used, and index year. Missing data would be accounted for using multiple imputation, with 10 imputations.[34]

In the emulation, the causal estimands were the observational analogues to the intention-to-treat and per-protocol effects. The analyses were performed as specified in the target trial, except we controlled for confounding using baseline inverse probability of treatment weights estimated from all baseline covariates in the **Table** (see eTable 4 in Supplement 1

Table. Baseline Characteristics of the Target Trial Emulation Cohort Before Weighting[a,b]

Characteristic	No. (%)	
	Initiated treatment with empagliflozin (n = 32 819)	Initiated treatment with dapagliflozin (n = 17 464)
Age, median (IQR), y	62.6 (54.2-70.6)	62.7 (54.3-70.6)
Sex		
Female	12 182 (37.1)	6690 (38.3)
Male	20 637 (62.9)	10 774 (61.7)
Duration of diabetes, median (IQR), y	8.4 (4.1-13.3)	7.9 (4.1-12.4)
Hemoglobin A_{1c} level, median (IQR), %	8.2 (7.2-9.7)	8.1 (7.2-9.5)
eGFR, median (IQR), mL/min/1.73 m^2	87.5 (72.5-103.6)	88.0 (73.1-104.2)
eGFR		
≥60 mL/min/1.73 m^2	29 351 (89.4)	15 660 (89.7)
45-59 mL/min/1.73 m^2	2750 (8.4)	1342 (7.7)
30-44 mL/min/1.73 m^2	653 (2.0)	411 (2.4)
15-29 mL/min/1.73 m^2	65 (0.2)	51 (0.3)
uACR, median (IQR), mg/g	16.4 (7.5-49.0)	16.0 (7.0-46.0)
uACR, mg/g		
≤29 mg/g	15 163 (46.2)	7572 (43.4)
30-299 mg/g	6775 (20.6)	3205 (18.4)
≥300 mg/g	1364 (4.2)	608 (3.5)
Low-density lipoprotein cholesterol, median (IQR), mg/dL	73.4 (57.9-100.4)	77.2 (57.9-100.4)
High-density lipoprotein cholesterol, median (IQR), mmol/L	42.5 (34.7-50.2)	42.5 (34.7-50.2)
Triglyceride, median (IQR), mg/dL	185.8 (132.7-265.5)	185.8 (132.7-265.5)
Coexisting cardiovascular morbidities		
Arterial claudication	712 (2.2)	323 (1.8)
Ischemic stroke	690 (2.1)	267 (1.5)
Myocardial infarction	1249 (3.8)	492 (2.8)
Stable angina pectoris	2568 (7.8)	1073 (6.1)
Unstable angina pectoris	428 (1.3)	158 (0.9)
Heart failure	823 (2.5)	392 (2.2)
Aortic aneurysm/dilation	228 (0.7)	112 (0.6)
Aortic dissection	12 (0.0)	6 (0.0)
Aortic regurgitation/stenosis	718 (2.2)	296 (1.7)
Atrial fibrillation/flutter	2365 (7.2)	1106 (6.3)
Bradycardia	262 (0.8)	93 (0.5)
Mitral regurgitation/stenosis	146 (0.4)	63 (0.4)
Coexisting noncardiovascular morbidities		
Chronic obstructive pulmonary disease	1308 (4.0)	651 (3.7)
Coagulopathy and other blood disorders	896 (2.7)	433 (2.5)
Deep vein thrombosis	253 (0.8)	145 (0.8)
High-risk cancer (5-y survival <30%)	303 (0.9)	146 (0.8)
Hypercholesterolemia	3928 (12.0)	1717 (9.8)
Hypertension	18 461 (56.3)	9319 (53.4)
Liver disease	526 (1.6)	246 (1.4)
Obesity	3774 (11.5)	1867 (10.7)
Pulmonary embolism	233 (0.7)	97 (0.6)

(continued)

Table. Baseline Characteristics of the Target Trial Emulation Cohort Before Weighting[a,b] (continued)

Characteristic	No. (%)	
	Initiated treatment with empagliflozin (n = 32 819)	Initiated treatment with dapagliflozin (n = 17 464)
Antihyperglycemic medication use		
Metformin	31 161 (94.9)	16 624 (95.2)
Insulin	7715 (23.5)	2596 (14.9)
Sulfonylureas	5740 (17.5)	3361 (19.2)
Dipeptidyl peptidase-4 inhibitors	10 553 (32.2)	6978 (40.0)
Glucagon-like peptide 1 agonists	7345 (22.4)	3267 (18.7)
Thiazolidinediones	21 (0.1)	17 (0.1)
No. of used antihyperglycemic medications		
SGLT2i + 1 other	11 341 (34.6)	5947 (34.1)
SGLT2i + several other	21 478 (65.4)	11 517 (65.9)
Other medication use		
ACE inhibitors	9531 (29.0)	4986 (28.6)
Angiotensin 2-receptor blockers	8078 (24.6)	4105 (23.5)
Anticoagulants[c]	3262 (9.9)	1574 (9.0)
Antidepressants	5128 (15.6)	2589 (14.8)
Antiplatelets[d]	11 885 (36.2)	5925 (33.9)
Antipsychotics	1530 (4.7)	871 (5.0)
β Blockers	9721 (29.6)	4773 (27.3)
Calcium channel blockers	10 846 (33.0)	5551 (31.8)
Diuretics	9859 (30.0)	5114 (29.3)
Glucocorticoids	1880 (5.7)	1018 (5.8)
Nitrates	1861 (5.7)	769 (4.4)
Opioids	5626 (17.1)	2808 (16.1)
Statins	25 581 (77.9)	13 270 (76.0)
Nonaspirin NSAIDs	7357 (22.4)	4260 (24.4)
Respiratory medications	4610 (14.0)	2383 (13.6)
Socioeconomic position		
Civil status		
Married	21 371 (65.1)	11 480 (65.7)
Divorced	5651 (17.2)	2948 (16.9)
Single	5771 (17.6)	3024 (17.3)
Employment		
Employed	12 793 (39.0)	6816 (39.0)
Unemployed	2010 (6.1)	1066 (6.1)
Early retirement	5787 (17.6)	3016 (17.3)
State pension	12 228 (37.3)	6566 (37.6)
Income[e]		
Low	8125 (24.8)	4488 (25.7)
Moderate, low	8334 (25.4)	4318 (24.7)
Moderate, high	8219 (25.0)	4310 (24.7)
High	8141 (24.8)	4348 (24.9)
Education		
Primary	11 760 (35.8)	6265 (35.9)
Secondary	14 230 (43.4)	7681 (44.0)
Tertiary	5686 (17.3)	2882 (16.5)
Index year		
2014-2015	1088 (3.3)	2785 (15.9)
2016-2018	18 272 (55.7)	8377 (48.0)
2019-2020	13 459 (41.0)	6302 (36.1)
≥2 General practice visits ≤180 d	30 740 (93.7)	16 729 (95.8)

Abbreviations: ACE, angiotensinogen-converting enzyme; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; SGLT2i, sodium-glucose cotransporter 2 inhibitor; uACR, urine albumin-creatinine ratio.

SI conversion factors: to convert cholesterol to mmol/L, multiply by 0.0259; for hemoglobin A1c to the proportion of total hemoglobin, multiply by 0.01; for triglycerides to mmol/L, multiply by 0.0113.

[a] Those who initiated treatment with empagliflozin and dapagliflozin were weighted according to age, sex, duration of diabetes, hemoglobin A_{1c} level, estimated glomerular filtration rate, uACR, low-density lipoprotein level, high-density lipoprotein level, triglyceride level, coexisting morbidities, antihyperglycemic medication use, other medication use, health care–seeking behavior, and calendar year.

[b] The table presents the numbers after imputation; the numbers of missing values for the empagliflozin and dapagliflozin groups before imputation were as follows: hemoglobin A_{1c} level (688 [2.1%] and 400 [2.3%]), uACR (9517 [29.0%] and 6079 [34.8%]), low-density lipoprotein cholesterol level (7791 [23.7%] and 3912 [22.4%]), high-density lipoprotein cholesterol level (2850 [8.7%] and 1346 [7.7%]), triglyceride level (2877 [8.8%] and 1396 [8.0%]), civil status (26 [0.1%] and 12 [0.1%]), employment (≤5 in both groups), and education (1143 [3.5%] and 636 [3.6%]).

[c] Includes vitamin K antagonists, heparin, direct thrombin inhibitors, and direct factor Xa inhibitors.

[d] Includes acetylsalicylic acid and adenosine diphosphate receptor inhibitors.

[e] Income was categorized according to the quartiles of the total eligible population for female and male individuals independently within each year.

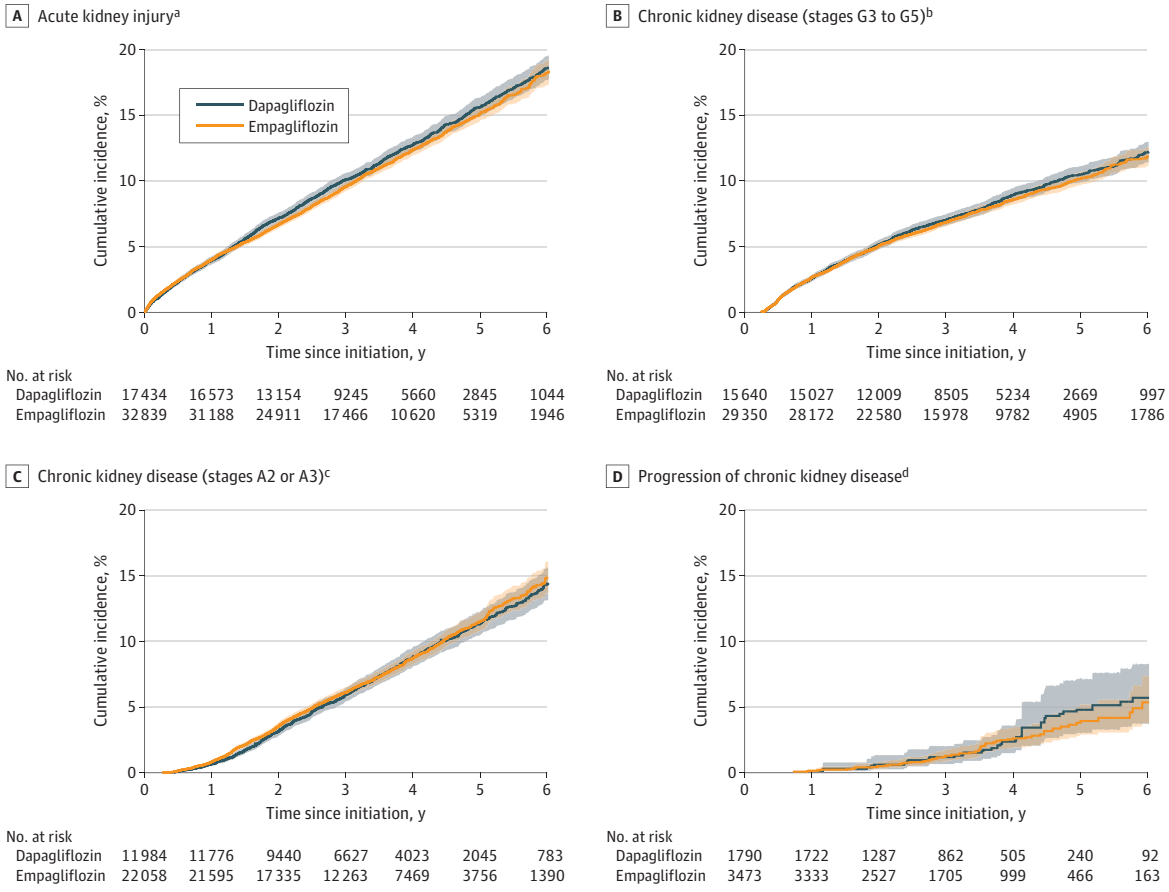
for details on definitions). Subgroup analyses compared the estimated absolute risks for each exposure group using weights calculated independently within each subgroup. Covariate balances after weighting were evaluated by plotting the absolute standardized mean differences.[35] In per-protocol analyses, nonadherence was defined as either 6 months without any dispensing of the initiated SGLT2i or dispensing of another SGLT2i. Nonparametric bootstrapping with 200 samples was used to calculate 95% CIs for all estimates.[36] Analyses were performed using SAS, version 9.4 (SAS Institute).

Results

Study Population

The study included 32 819 individuals who initiated treatment with empagliflozin and 17 464 with dapagliflozin (eFigure 1 in Supplement 1). Before weighting, the empagliflozin and dapagliflozin groups were not notably different regarding their distributions of age (median [IQR], 62.6 [54.2-70.6] years vs 62.7 [54.3-70.6] years), sex (12 182 female individuals [37.1%] vs 6690 [38.3%]), duration of diabetes (median [IQR], 8.4 [4.1-13.3] years vs 7.9 [4.1-12.4] years), HbA_{1c} level (median [IQR], 8.2% [7.2%-9.7%] vs 8.1% [7.2%-9.5%]; to convert to the proportion of total

Figure 1. Cumulative Incidences of Kidney Outcomes in Persons With Type 2 Diabetes Initiating Empagliflozin or Dapagliflozin



Those who initiated treatment with empagliflozin or dapagliflozin were weighted according to age, sex, duration of diabetes, hemoglobin A_{1c} level, estimated glomerular filtration rate, urine albumin-creatinine ratio, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, coexisting morbidities, antihyperglycemic medication use, other medication use, health care–seeking behavior, and calendar year. The shaded areas represent 95% CIs.

[a]In all eligible persons.

[b]In persons with an estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or greater when initiating treatment; we required the outcome to be confirmed by a second test 30 to 180 days after its first indication (eTable 1 in Supplement 1), and the time of the outcome was set to the date of the confirmatory test; therefore, no events were observed during the first 30 days of follow-up.

[c]In persons without albuminuria when initiating treatment; we required the outcome to be confirmed by a second test 30 to 180 days after its first indication (eTable 1 in Supplement 1) and the time of the outcome is set to the date of the confirmatory test; therefore, no events were observed during the first 30 days of follow-up.

[d]In persons with an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 when initiating treatment.

hemoglobin, multiply by .01), eGFR (median [IQR], 87.5 [72.5-103.6] mL/min/1.73 m^2 vs 88.0 [73.1-104.2] mL/min/1.73 m^2), uACR (median [IQR], 16.4 [7.5-49.0] mg/g vs 16.0 [7.0-46.0] mg/g), blood lipid levels, nonantihyperglycemic medication use, and socioeconomic position (Table). Coexisting morbidities were also comparable between the groups, although the prevalence of cardiovascular diseases was generally higher in those who initiated empagliflozin than dapagliflozin. Compared with those who initiated treatment with dapagliflozin, more who initiated empagliflozin were using insulin (7715 [24%] vs 2596 [15%]) and glucagon-like peptide-1 receptor agonists (7345 [22%] vs 3267 [19%]), while fewer were using dipeptidyl peptidase-4 inhibitors (10 553 [32%] vs 6978 [40%]). After weighting, all measured covariates were well-balanced between the groups (eFigures 2-5 in Supplement 1). eTable 5 in Supplement 1 presents the distribution of these weights.

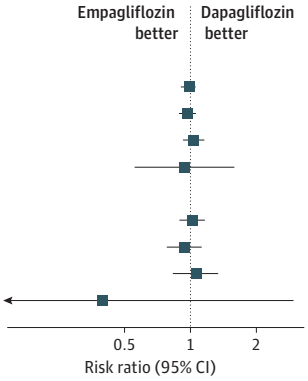
The median (IQR) follow-up in the empagliflozin and dapagliflozin groups, respectively, ranged from 2.8 (1.8-4.0) years vs 3.0 (1.8-4.6) years when studying CKD stage A2 or A3 to 3.2 (2.2-4.3) years vs 3.6 (2.2-5.1) years when studying CKD progression (eTable 6 in Supplement 1). eTable 7 in Supplement 1 presents the number of creatinine or uACR measurements during follow-up, the time receiving treatment, and the proportion of people discontinuing treatment.

Kidney Outcomes

Figure 1 presents the cumulative incidences of kidney outcomes for the intention-to-treat analyses; eTable 6 in Supplement 1 presents the unweighted number of events and incidence rates. During 6 years, empagliflozin and dapagliflozin initiators exhibited comparable risks of acute kidney injury (18.2% vs 18.5%; risk difference, −0.4%; 95% CI, −1.7% to 1.0%; risk

Figure 2. Comparative Effectiveness Regarding Kidney Outcomes of Initiating Empagliflozin or Dapagliflozin

Outcome	6-y Risk (95% CI), %		Risk difference, (95% CI)	Risk ratio (95% CI)
	Empagliflozin initiators	Dapagliflozin initiators		
Intention-to-treat analysis				
AKI[a]	18.2 (17.3 to 19.1)	18.5 (17.6 to 19.5)	-0.4 (-1.7 to 1.0)	0.98 (0.91 to 1.06)
CKD (stages G3 to G5)[b]	11.8 (11.1 to 12.5)	12.1 (11.4 to 12.9)	-0.4 (-1.4 to 0.6)	0.97 (0.89 to 1.05)
CKD (stage A2 or A3)[c]	14.8 (13.6 to 16.1)	14.3 (13.1 to 15.6)	0.5 (-1.1 to 2.1)	1.04 (0.93 to 1.15)
Progression of CKD[d]	5.3 (3.7 to 7.3)	5.7 (3.7 to 8.2)	-0.3 (-3.1 to 2.5)	0.94 (0.56 to 1.58)
Per-protocol analysis				
AKI[a]	15.0 (13.7 to 16.3)	14.7 (13.4 to 16.2)	0.2 (-1.7 to 2.2)	1.02 (0.89 to 1.16)
CKD (stages G3 to G5)[b]	9.6 (8.6 to 10.7)	10.3 (8.9 to 11.8)	-0.7 (-2.5 to 1.2)	0.94 (0.78 to 1.12)
CKD (stage A2 or A3)[c]	14.6 (12.0 to 17.5)	13.8 (11.6 to 16.3)	0.8 (-2.5 to 4.1)	1.06 (0.83 to 1.34)
Progression of CKD[d]	1.9 (0.3 to 6.7)	4.7 (1.2 to 11.8)	-2.8 (-8.1 to 2.4)	0.40 (0.05 to 2.94)



Those who initiated treatment with empagliflozin or dapagliflozin were weighted according to age, sex, duration of diabetes, hemoglobin A_{1c} level, estimated glomerular filtration rate, urine albumin-creatinine ratio, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, coexisting morbidities, antihyperglycemic medication use, other medication use, health care–seeking behavior, and calendar year.
AKI indicates acute kidney injury; CKD, chronic kidney disease.

[a]In all eligible persons.

[b]In persons with an estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or greater when initiating treatment.

[c]In persons without albuminuria when initiating treatment.

[d]In persons with an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 when initiating treatment.

ratio, 0.98; 95% CI, 0.91-1.06) (**Figure 2**). In persons with an eGFR of 60 mL/min/1.73 m^2 or higher at baseline, the 6-year risk of CKD stages G3 to G5 was also comparable between those who initiated treatment with empagliflozin vs dapagliflozin (11.8% vs 12.1%; risk difference, −0.4%; 95% CI, −1.4% to 0.6%; risk ratio, 0.97; 95% CI, 0.89-1.05). In persons without albuminuria at baseline, the 6-year risk of CKD stage A2 or A3 was likewise comparable between those who initiated empagliflozin vs dapagliflozin (14.8% vs 14.3%; risk difference, 0.5%; 95% CI, −1.1% to 2.1%; risk ratio, 1.04; 95% CI, 0.93-1.15). In persons with an eGFR of less than 60 mL/min/1.73 m^2 at baseline, the 6-year risk of 40% or greater progression of their kidney disease was also comparable between those who initiated empagliflozin vs dapagliflozin (5.3% vs 5.7%; risk difference, −0.3%; 95% CI, −3.1% to 2.5%; risk ratio, 0.94; 95% CI, 0.56-1.58).

In per-protocol analyses, empagliflozin and dapagliflozin initiators did not exhibit notably different 6-year risks of acute kidney injury (15.0% vs 14.7%; risk difference, 0.2%; 95% CI, −1.7% to 2.2%; risk ratio, 1.02; 95% CI, 0.89-1.16), CKD stages G3 to G5 (9.6% vs 10.3%; risk difference, −0.7%; 95% CI, −2.5% to 1.2%; risk ratio, 0.94; 95% CI, 0.78-1.12), CKD stage A2 or A3 (14.6% vs 13.8%; risk difference, 0.8%; 95% CI, −2.5% to 4.1%; risk ratio, 1.06; 95% CI, 0.83-1.34), and CKD progression (1.9% vs 4.7%; risk difference, −2.8%; 95% CI, −8.1% to 2.4%; risk ratio, 0.40; 95% CI, 0.05-2.94) (Figure 2). For intention-to-treat analyses, no notable differences in 6-year outcomes were observed within the prespecified demographic and comorbidity subgroups (**Figure 3** and **Figure 4**; eTable 8 in Supplement 1).

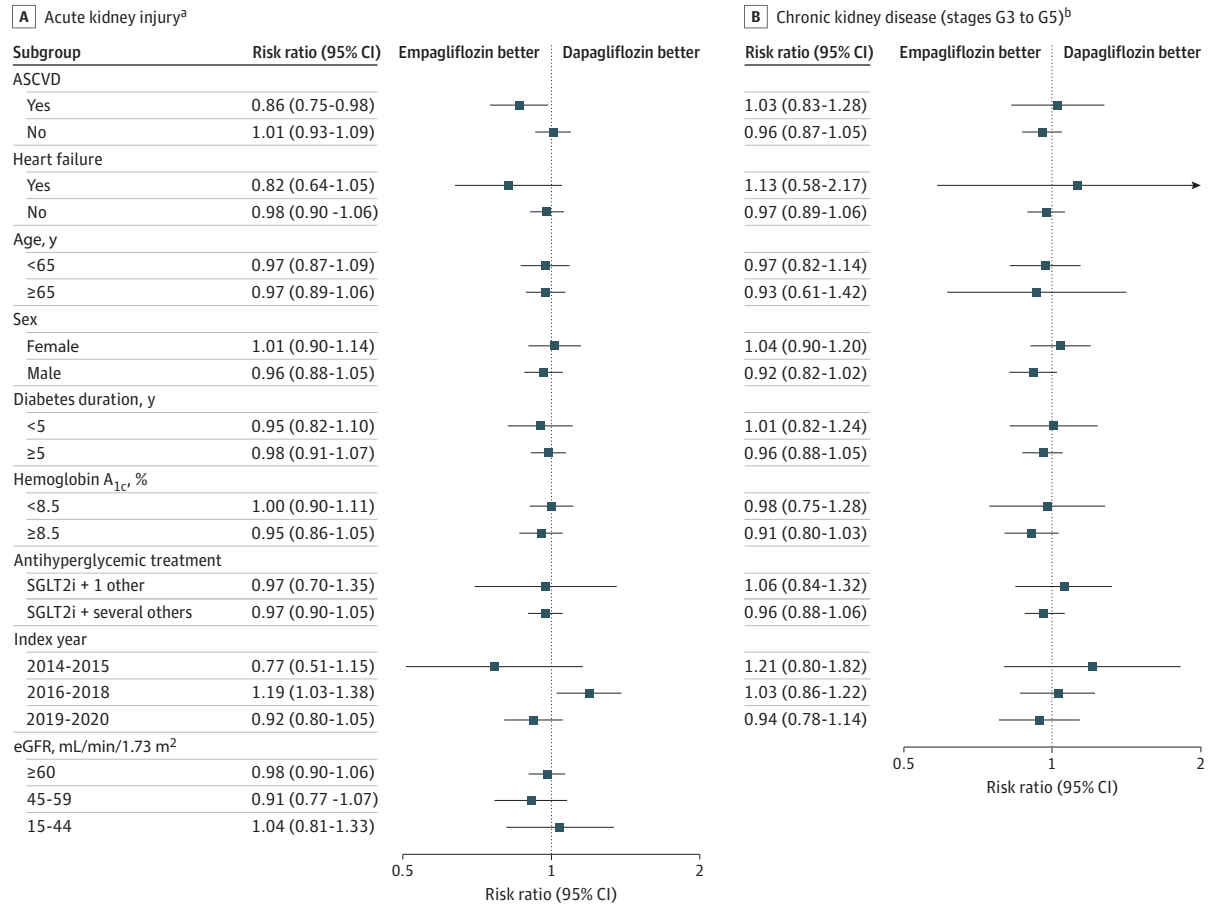
Discussion

In this nationwide cohort study, using the target trial emulation framework, we found no clinically important differences in 6-year kidney outcomes in persons with type 2 diabetes initiating treatment with empagliflozin or dapagliflozin. The findings were consistent in intention-to-treat and per-protocol analyses. In the absence of a large, randomized clinical trial directly comparing kidney outcomes between empagliflozin and dapagliflozin, this emulation of such a target trial provides what is to our knowledge the best currently available evidence for guiding clinical decision-making. The findings do not indicate a kidney advantage of initiating empagliflozin vs dapagliflozin or vice versa as an adjunct therapy in persons with type 2 diabetes, supporting the current clinical practice of not recommending either drug vs the other.[2,3] Given the lack of SGLT2i preference in the KDIGO guidelines for type 2 diabetes management in CKD[37] and the absence of SGLT2i recommendations in the KDIGO guidelines for general CKD management,[29] our study provides insights into selecting an appropriate SGLT2i for managing these conditions. Although the findings indicate a class effect of SGLT2is, this cannot be confirmed before comparing the remaining SGLT2is.

Previous Literature

As comparisons between empagliflozin and dapagliflozin trials have been limited by differences in study cohorts, absolute risks of outcomes, and median follow-up,[2-5] this study's findings potentially extend the understanding of the effectiveness between these agents. Compared with placebo, the EMPA-REG OUTCOME and DECLARE-TIMI trials indicated risk reductions of acute kidney injury of 0.6 percentage points for empagliflozin and 0.5 percentage points for dapagliflozin for patients with type 2 diabetes.[2,3] For patients with CKD treated with empagliflozin vs placebo, the EMPA-KIDNEY trial reported a relative risk reduction of kidney disease progression of 29%.[4] For patients with CKD treated with dapagliflozin vs placebo, the DAPA-CKD trial reported a relative risk reduction of at least a

Figure 3. Comparative Effectiveness Regarding Kidney Outcomes of Initiating Empagliflozin or Dapagliflozin in Acute Kidney Injury and Chronic Kidney Disease (Stages G3 to G5)



Those who initiated treatment with empagliflozin or dapagliflozin were weighted according to age, sex, duration of diabetes, hemoglobin A_{1c} level (to convert to the proportion of total hemoglobin, multiply by 0.01), estimated glomerular filtration rate, urine albumin-creatinine ratio, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, coexisting morbidities, antihyperglycemic medication use, other medication use, health care–seeking behavior, and calendar year. ASCVD indicates atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

[a]In all eligible persons.

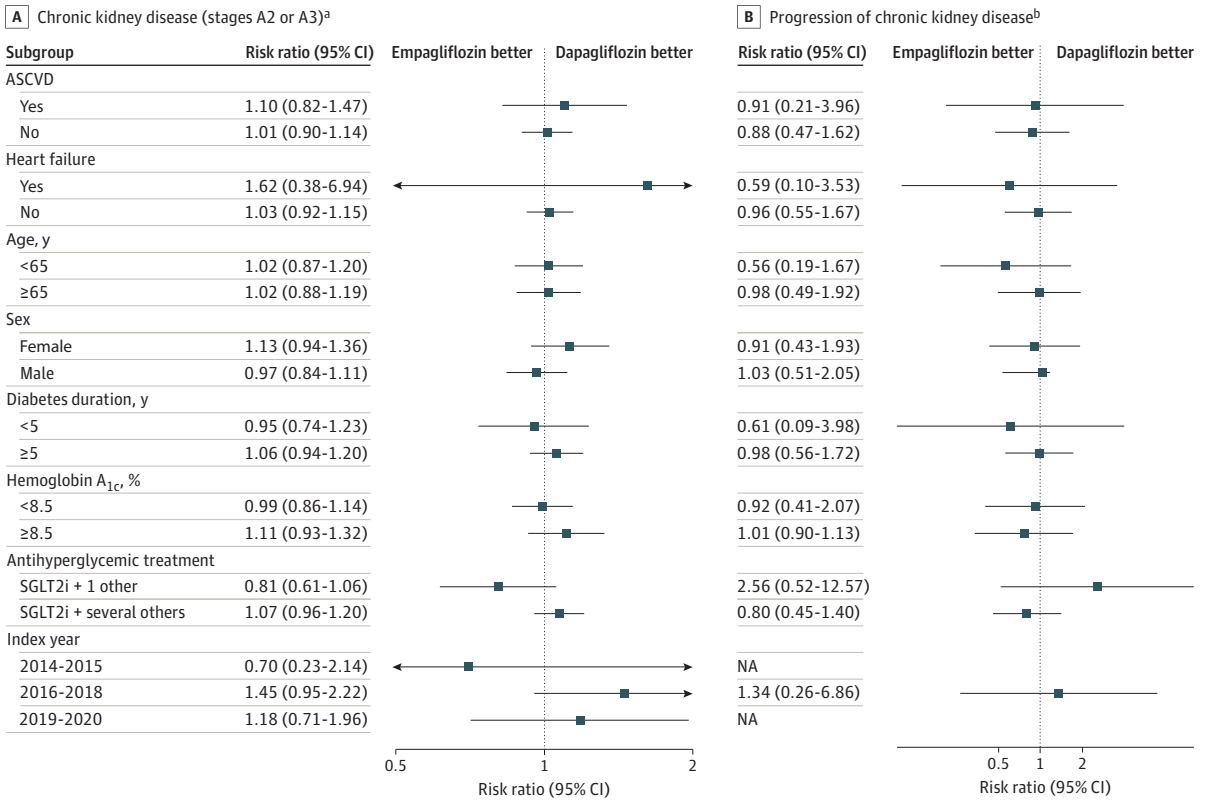
[b]In persons with an estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or greater when initiating treatment.

50% decline in the eGFR of 47% and a relative risk reduction of kidney failure of 36%.[5] A meta-analysis of randomized clinical trials pooled data to make indirect comparisons between individual SGLT2is.[38] When comparing empagliflozin with dapagliflozin for reducing kidney outcomes in patients with type 2 diabetes (4 trials), the analysis found no difference between empagliflozin and dapagliflozin in the risk of acute kidney injury (hazard ratio [HR], 0.99; 95% CI, 0.77-1.26) or kidney disease progression (HR, 1.01; 95% CI, 0.79-1.29).[38] These findings were consistent in persons without type 2 diabetes.[38]

The DAPA-CKD trial reported an incidence rate of kidney failure of 25 per 1000 person-years in the treated arm.[5] In the treated arm, the incidence rate of kidney disease progression was reported to be 61 per 1000 person-years in the EMPA-KIDNEY trial[4] and 26 per 1000 person-years in the DAPA-CKD trial.[5] In our study, the incidence rates for CKD ranged from 48 to 69 per 1000 person-years, and the rates for CKD progression were 2.9 and 3.0 per 1000 person-years in the empagliflozin and dapagliflozin groups, respectively. These differences from trial findings may stem from differences in study populations and outcome definitions.[4,5] For instance, the EMPA-KIDNEY trial included patients with and without type 2 diabetes,[4] and the EMPA-KIDNEY and DAPA-CKD trials required participants to be taking renin-angiotensin-aldosterone inhibitors.[4,5] Additionally, the more complete assessment of kidney disease progression in the trials, due to planned systematic follow-up, may explain the differences compared with the less systematic monitoring in routine care.

Only 1 trial directly compared the effectiveness of reducing kidney outcomes between empagliflozin and dapagliflozin for patients with type 2 diabetes.[12] This open-label trial from South Korea compared adding empagliflozin (n = 160) vs dapagliflozin (n = 156) to metformin, glimepiride, and dipeptidyl peptidase-4 inhibitor treatment in patients with dysregu-

Figure 4. Comparative Effectiveness Regarding Kidney Outcomes of Initiating Empagliflozin or Dapagliflozin in Chronic Kidney Disease (Stages A2 or A3) and Progression of Chronic Kidney Disease



Those who initiated treatment with empagliflozin or dapagliflozin were weighted according to age, sex, duration of diabetes, hemoglobin A_{1c} level (to convert to the proportion of total hemoglobin, multiply by 0.01), estimated glomerular filtration rate, urine albumin-creatinine ratio, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, coexisting morbidities, antihyperglycemic medication use, other medication use, health care–seeking behavior, and calendar year. ASCVD indicates atherosclerotic cardiovascular disease; NA, not applicable; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

[a]In persons without albuminuria when initiating treatment.

[b]In persons with an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 when initiating treatment.

lated type 2 diabetes.[12] Within 52 weeks, eGFR changes were similar between the empagliflozin and dapagliflozin groups (−1.2 mL/min/1.73 m^2 vs −1.3 mL/min/1.73 m^2).[12] The study did not report on other kidney end points.[12] Two observational studies compared kidney outcomes between empagliflozin and dapagliflozin initiators.[39,40] A Scandinavian study using in-hospital data found comparable rates of serious kidney events and diabetic ketoacidosis between people initiating treatment with empagliflozin vs dapagliflozin using antihyperglycemic medication without heart failure or CKD at baseline (HR for serious kidney events, 0.97; 95% CI, 0.87-1.07; HR for ketoacidosis, 1.12; 95% CI, 0.94-1.33).[39] A Japanese study using health checkups and insurance claims data reported comparable eGFR declines across all SGLT2is.[40] Unlike the Scandinavian study, we used outpatient and general practice data on creatinine and uACR to define the outcomes and examined different kidney outcomes in different populations.[39] Unlike the Japanese study, we examined several kidney outcomes, used the target trial emulation framework, and included a population-based cohort of people with type 2 diabetes.[40] Another study showed comparable 6-year risks of major adverse cardiovascular outcomes between those who initiated treatment with empagliflozin vs dapagliflozin with type 2 diabetes (10.0% vs 10.0%; risk ratio, 1.00; 95% CI, 0.91-1.10).[41] Together with our findings, these results support that empagliflozin and dapagliflozin provide comparable cardiorenal protection in patients type 2 diabetes.

Limitations

Treatment assignment was not randomized, leaving the potential for unmeasured or residual confounding. The EMPA-REG OUTCOME trial (published in November 2015) included persons with an eGFR of 30 mL/min/1.73 m^2 or higher, whereas the DECLARE-TIMI trial (published in January 2019) excluded persons with a creatinine clearance less than 60 mL/min, resulting in only 7% having an eGFR less than 60 mL/min/1.73 m^2.[2,3] Thus, physicians might have preferred empagliflozin when treating persons with poorer kidney function, making empagliflozin look harmful compared with dapagliflozin in the analyses including persons with CKD. However, no group differences in baseline kidney function were observed, neither overall nor within index year periods, and the risk of acute kidney injury

was comparable between those who initiated empagliflozin vs dapagliflozin in subgroups according to eGFR. Later empagliflozin and dapagliflozin trials in patients with CKD were first published after this study's inclusion period.[4,5] Confounding by indication from heart failure was also not a concern, as the study was conducted during a period before SGLT2is obtained European approval for treating congestive heart failure and CKD in patients without type 2 diabetes. During the study period, Danish guidelines for type 2 diabetes evolved. Initially, metformin was the sole first-line treatment, with other glucose-lowering medications as second-line or third-line options. In 2018, SGLT2is were recommended as add-ons for patients with atherosclerotic cardiovascular disease, heart failure, or kidney disease. By 2022, SGLT2is were recommended alongside metformin as first-line treatments for patients with these conditions, regardless of glycemic control.[9] For patients without these conditions, SGLT2is were recommended as adjuncts for those at high cardiovascular risk who needed additional glycemic control or as second-line treatments for others.[9] Empagliflozin was briefly favored in 2018, but to our knowledge, since then, no specific preference has existed,[9] although some might have favored empagliflozin, as it demonstrated cardiovascular benefits earlier.[2,3] Empagliflozin and dapagliflozin have been consistently available in Denmark. The cohort was limited to persons with a routine creatinine measurement at baseline, introducing the possibility of selection bias. However, few persons lacked a routine creatinine measurement, and no noteworthy disparity was observed between those who initiated empagliflozin (7.6%) vs dapagliflozin (6.0%). Few CKD progression outcomes were associated with imprecise estimates, leaving the possibility of meaningful differences between those who initiated empagliflozin vs dapagliflozin unresolved. Further research is needed to determine whether this study's findings are generalizable to other countries with different ethnic distributions, health care settings, or reimbursement schemes.

Conclusions

The results of this cohort study suggest that people with type 2 diabetes who initiated treatment with empagliflozin and dapagliflozin had comparable long-term kidney outcomes. These findings support the current clinical practice of not recommending either drug vs the other when used for treating type 2 diabetes.

ARTICLE INFORMATION

Accepted for Publication: November 9, 2024.

Published Online: January 21, 2025. doi:10.1001/jamainternmed.2024.7381

Author Affiliations: Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark (Bonnesen, Heide-Jørgensen, Christensen, Christiansen, Pedersen, Thomsen, Schmidt); Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (Bonnesen, Heide-Jørgensen, Christensen, Christiansen, Pedersen, Thomsen, Schmidt); Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark (Christensen); Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia (Lash); Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Hennessy); Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Matthews); Department of Cardiology, Gødstrup Hospital, Herning, Denmark (Schmidt).

Author Contributions: Dr Schmidt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bonnesen, Heide-Jørgensen, Christensen, Christiansen, Hennessy, Matthews, Pedersen, Thomsen, Schmidt.
Acquisition, analysis, or interpretation of data: Bonnesen, Heide-Jørgensen, Christensen, Christiansen, Lash, Matthews, Schmidt.
Drafting of the manuscript: Bonnesen.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Bonnesen, Heide-Jørgensen, Matthews, Pedersen.
Obtained funding: Bonnesen, Schmidt.
Administrative, technical, or material support: Schmidt.
Supervision: Heide-Jørgensen, Christensen, Christiansen, Lash, Schmidt.

Conflict of Interest Disclosures: Dr Bonnesen reported grants from the Danish Diabetes and Endocrine Academy, Danish Cardiovascular Academy, Helge Peetz og Verner Peetz og Hustru Vilma Peetz Legat, Danish Data Science Academy, Christian og Ottilia Brorsons Rejselegat, and Karl G. Andersen Fond during the conduct of the study. Dr Heide-Jørgensen reported involvement in studies with funding from various companies as research grants to (and administered by) Aarhus University. Dr Christensen reported grants from the Danish Diabetes and Endocrine Society, Danish Diabetes and Endocrine Academy, and Novo Nordisk Foundation during the conduct of the study as well as Independent Research Fund Denmark outside the submitted work. Dr Lash reported that he is a member of the Amgen Epidemiology Methods Advisory Council, for which he receives consulting fees and travel support. Dr Hennessy reported personal fees from the Medullary Thyroid Carcinoma Registry Consortium (Novo Nordisk, AstraZeneca, and Eli Lilly) outside the submitted work. Dr Thomsen reported that the Department of Clinical Epidemiology of Aarhus University and Aarhus University Hospital receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. No other disclosures were reported.

Funding/Support: Drs Bonnesen and Christensen were supported by research grants from the Danish Diabetes and Endocrine Academy, which is funded by the Novo Nordisk Foundation under grant number NNF22SA0079901. Dr Schmidt was supported by the Novo Nordisk Foundation under grant number NNF19OC0054908. Dr Matthews receives funds from the Swedish Research Council (2018-03028 and 2021-02236) and Forte (2020-00029). Dr Christiansen received funding from Independent Research Fund Denmark under grant number 0134-00407B.

Role of the Funder/Sponsor: The funding organizations 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.

REFERENCES

1. International Diabetes Federation. Diabetes atlas. Accessed December 13, 2023. https://diabetesatlas.org/

2. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720

3. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. doi:10.1056/NEJMoa1812389

4. Herrington WG, Staplin N, Wanner C, et al; The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233

5. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816

6. Pottegård A, Andersen JH, Søndergaard J, Thomsen RW, Vilsbøll T. Changes in the use of glucose-lowering drugs: a Danish nationwide study. *Diabetes Obes Metab*. 2023;25(4):1002-1010. doi:10.1111/dom.14947

7. Adhikari R, Jha K, Dardari Z, et al. National trends in use of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists by cardiologists and other specialties, 2015 to 2020. *J Am Heart Assoc*. 2022;11(9):e023811. doi:10.1161/JAHA.121.023811

8. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134(10):752-772. doi:10.1161/CIRCULATIONAHA.116.021887

9. Danish Endocrine Society. Type 2 diabetes—national treatment guideline. Accessed 12 May, 2024. https://endocrinology.dk/nbv/diabetes-melitus/behandling-og-kontrol-af-type-2-diabetes/

10. Marx N, Federici M, Schütt K, et al; ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023;44(39):4043-4140. doi:10.1093/eurheartj/ehad192

11. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2022;65(12):1925-1966. doi:10.1007/s00125-022-05787-2

12. Ku EJ, Lee DH, Jeon HJ, Oh TK. Empagliflozin versus dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin, glimepiride and dipeptidyl peptide 4 inhibitors: A 52-week prospective observational study. *Diabetes Res Clin Pract*. 2019;151:65-73. doi:10.1016/j.diabres.2019.04.008

13. Patorno E. Well-conducted real-world evidence studies can complement essential evidence from clinical trials. *Circulation*. 2024;150(18):1412-1415. doi:10.1161/CIRCULATIONAHA.124.069220

14. Bhattacharya S, Rathore A, Parwani D, et al. An exhaustive perspective on structural insights of SGLT2 inhibitors: a novel class of antidiabetic agent. *Eur J Med Chem*. 2020;204:112523. doi:10.1016/j.ejmech.2020.112523

15. Wright EM. SGLT2 inhibitors: physiology and pharmacology. *Kidney360*. 2021;2(12):2027-2037. doi:10.34067/KID.0002772021

16. Sokolov V, Yakovleva T, Chu L, et al. Differentiating the sodium-glucose cotransporter 1 inhibition capacity of canagliflozin vs. dapagliflozin and empagliflozin using quantitative systems pharmacology modeling. *CPT Pharmacometrics Syst Pharmacol*. 2020;9(4):222-229. doi:10.1002/psp4.12498

17. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591. doi:10.2147/CLEP.S179083

18. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758-764. doi:10.1093/aje/kwv254

19. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3

20. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-798f.

21. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

22. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health*. 2011;39(7)(suppl):95-98. doi:10.1177/1403494811408483

23. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011;39(7)(suppl):103-105. doi:10.1177/1403494811405098

24. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health*. 2011;39(7)(suppl):91-94. doi:10.1177/1403494810394715

25. Andersen JS, Olivarius NdeF, Krasnik A. The Danish national health service register. *Scand J Public Health*. 2011;39(7)(suppl):34-37. doi:10.1177/1403494810394718

26. Arendt JFH, Hansen AT, Ladefoged SA, Sørensen HT, Pedersen L, Adelborg K. Existing data sources in clinical epidemiology: laboratory information system databases in Denmark. *Clin Epidemiol*. 2020;12:469-475. doi:10.2147/CLEP.S245060

27. Jensen SK, Heide-Jørgensen U, Vestergaard SV, Sørensen HT, Christiansen CF. Routine clinical care creatinine data in Denmark—an epidemiological resource for nationwide population-based studies of kidney disease. *Clin Epidemiol*. 2022;14:1415-1426. doi:10.2147/CLEP.S380840

28. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179-c184. doi:10.1159/000339789

29. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2024;105(4S):S117-S314.

30. Gravesen HV, Jensen SK, Vestergaard SV, Heide-Jørgensen U, Christiansen CF. Defining baseline creatinine for identification of AKI in population-based laboratory databases: a Danish nationwide cohort study. *Kidney360*. 2021;3(2):232-241. doi:10.34067/KID.0006082021

31. Rojas-Saunero LP, Young JG, Didelez V, Ikram MA, Swanson SA. Considering questions before methods in dementia research with competing events and causal goals. *Am J Epidemiol*. 2023;192(8):1415-1423. doi:10.1093/aje/kwad090

32. Aalen O. Nonparametric estimation of partial transition probabilities in multiple decrement models. *Ann Stat*. 1978;6(3):534-545. doi:10.1214/aos/1176344198

33. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664. doi:10.1093/aje/kwn164

34. Harel O, Mitchell EM, Perkins NJ, et al. Multiple imputation for incomplete data in epidemiologic studies. *Am J Epidemiol*. 2018;187(3):576-584. doi:10.1093/aje/kwx349

35. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. *Psychol Methods*. 2010;15(3):234-249. doi:10.1037/a0019623

36. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. *Stat Med*. 2016;35(30):5642-5655. doi:10.1002/sim.7084

37. Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes management in chronic kidney disease: synopsis of the KDIGO 2022 clinical practice guideline update. *Ann Intern Med*. 2023;176(3):381-387. doi:10.7326/M22-2904

38. Kani R, Watanabe A, Miyamoto Y, et al. Comparison of effectiveness among different sodium-glucose cotransoporter-2 inhibitors according to underlying conditions: a network meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2024;13(3):e031805. doi:10.1161/JAHA.123.031805

39. Engström A, Söderling J, Hviid A, et al. Comparative cardiovascular and renal effectiveness of empagliflozin and dapagliflozin: Scandinavian cohort study. *Eur Heart J Cardiovasc Pharmacother*. 2024;10(5):432-443. doi:10.1093/ehjcvp/pvae045

40. Suzuki Y, Kaneko H, Okada A, et al. Kidney outcomes in patients with diabetes mellitus did not differ between individual sodium-glucose cotransporter-2 inhibitors. *Kidney Int*. 2022;102(5):1147-1153. doi:10.1016/j.kint.2022.05.031

41. Bonnesen K, Heide-Jørgensen U, Christensen DH, et al. Comparative cardiovascular effectiveness of empagliflozin versus dapagliflozin in adults with treated type 2 diabetes: a target trial emulation. *Circulation*. 2024;150(18):1401-1411. doi:10.1161/CIRCULATIONAHA.124.068613