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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

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Abstract

Aim: To assess the effectiveness and safety of sodium-glucose cotransporter-2 (SGLT2) inhibitors in treatment-naïve 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.

KEYWORDS
antidiabetic drug, cohort study, metformin, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Metformin has been the recommended first-line treatment for patients with type 2 diabetes mellitus for the past 30 years.[1-3] The main justification is that metformin, unlike other medications for diabetes, was shown to reduce the risk of cardiovascular events, although this has not been consistently observed in subsequent clinical trials.[4-7] Metformin is also inexpensive, well tolerated, does not cause hypoglycaemia, and reduces microvascular complications. Furthermore, it effectively reduces glycated haemoglobin (HbA1c), promotes weight loss, and has very few absolute contraindications. Until recently, the remaining medications available to treat type 2 diabetes have generally only shown efficacy for reducing HbA1c, which is a surrogate for the risk of microvascular and macrovascular complications, with no cardiovascular or mortality endpoints.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce HbA1c[8,9] and were approved by the US Food and Drug Administration in 2013. Randomized trials identified additional benefits, including a reduced risk of stroke, myocardial infarction and cardiovascular mortality.[8-10] Similarly to metformin, SGLT2 inhibitors do not cause hypoglycaemia.[11,12] Unlike metformin, SGLT2 inhibitors lower blood pressure, albuminuria and the risk of both renal failure and heart failure.[12-15] In two recent trials, dapagliflozin and empagliflozin were each shown to reduce the risk of heart failure hospitalization among adults with heart failure, regardless of whether they had diabetes.[16,17] These data suggest that SGLT2 inhibitors may have cardiovascular benefits even in adults without diabetes mellitus and provide further impetus for considering them as first-line agents for adults with diabetes.

Randomized clinical trials have compared metformin to SGLT2 inhibitors among adults with diabetes who are treatment-naïve, but the primary outcome was change in HbA1c.[14,18] In the absence of a head-to-head clinical trial, studies based on existing real-world data may provide insights into the cardiovascular effectiveness of SGLT2 inhibitors compared to metformin. These data have limitations, yet recent advances in pharmacoepidemiology methods have improved the validity of studies using real-world data for assessing comparative effectiveness.[19-21] The objective of the present study was to compare the effectiveness and safety of SGLT2 inhibitors relative to metformin for reducing cardiovascular events in treatment-naïve patients with type 2 diabetes mellitus using data from routine care.

2 | METHODS

2.1 | Study design

We conducted a new-user cohort study using population-based claims data from commercially insured patients in the United States (IBM MarketScan).[19] US insurance claims databases typically include adults under the age of 65 years who have either purchased health insurance or had the insurance provided through their employer. Thus, such databases typically do not include patients receiving Medicare fee-for-service (eg, people aged over 65 years) or people of low socioeconomic status who receive healthcare through Medicaid. IBM MarketScan provided longitudinal, individual-level data on patient demographics, healthcare utilization, medical diagnoses, medication cost, diagnostic tests, clinical procedures, outpatient laboratory results, and pharmacy dispensing of drugs to over 50 million people in the United States.[19]

We compared adults over the age of 18 years who were diagnosed with type 2 diabetes mellitus and newly prescribed an SGLT2 inhibitor or metformin between March 29, 2013 (date of US approval of the first SGLT2 inhibitor) and December 31, 2018 (most recent available data). Patients with type 2 diabetes mellitus were identified using International Classification of Diseases, ninth and tenth revision codes (Appendix S1, Table S1). A systematic review of validation studies demonstrated that the positive predictive value (PPV) of using these diagnostic codes to identify adults with diabetes generally exceeds 80%.[22] Because the present study required a diagnosis of diabetes and a prescription fill for metformin or an SGLT2 inhibitor we anticipated the PPV to be even higher. We only included patients who were not taking any medications for their diabetes during the 365 days before cohort entry and henceforth refer to this population as being treatment-naïve (Appendix S1, Table S2 and S3). Cohort entry was the date of the first prescription for an SGLT2 inhibitor or metformin (Figure 1).

Patients who were dispensed both an SGLT2 inhibitor and metformin on the cohort entry date were excluded. Patients with any of the following characteristics in the 365 days before cohort entry were also excluded: enrolment for less than 365 days, dialysis, cancer, type 1 diabetes, and patients who received a combination pill including either metformin or an SGLT2 inhibitor on the index date (Appendix S1, Figure S1).

The Brigham and Women's Hospital Institutional Review Board provided ethics approval and a valid data use agreement was in place.

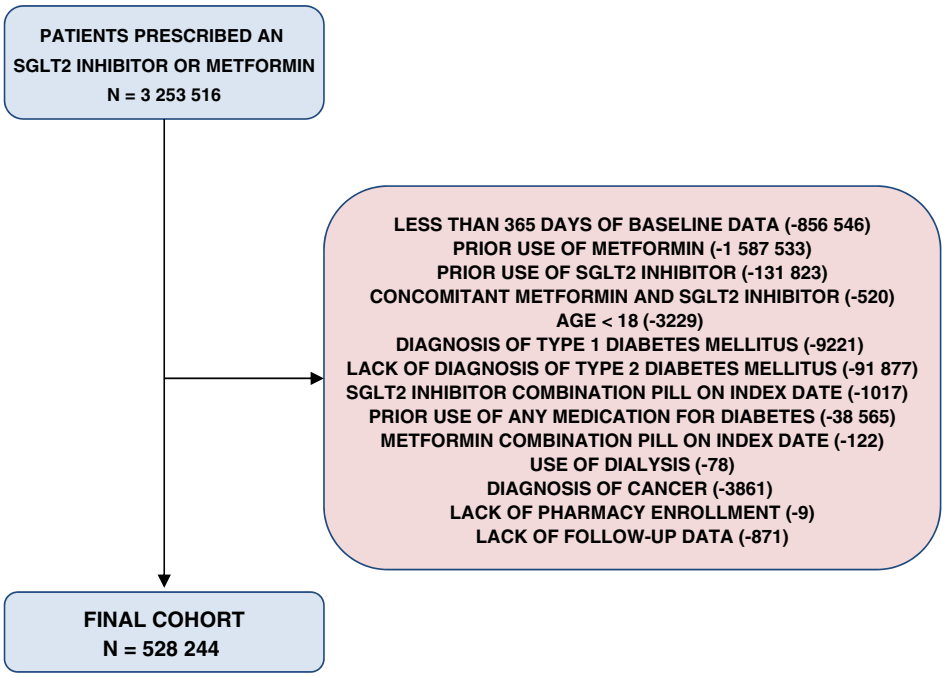

FIGURE 1 Cohort entry diagram legend: SGLT2, sodium glucose co-transporter 2

2.2 | Cohort follow-up

Follow-up began the day after cohort entry and continued until the end of the first of either study period (December 31, 2018), end of continuous health plan enrolment, occurrence of a study outcome, discontinuation of the initial medication, switching to or adding the comparator medication, or death. A medication was considered discontinued if 90 days had elapsed after the expiration of the last prescription's supply without the prescription being refilled.[19]

2.3 | Study outcomes

The primary outcome for this study was a composite of hospitalization with a primary diagnosis, as opposed to a secondary listed diagnosis, of heart failure, myocardial infarction or stroke (Appendix S1, Table S4). This differed from the outcome definition of most cardiovascular outcome trials, which typically assessed a composite of myocardial infarction, stroke or cardiovascular death. Cardiovascular death was not included in the present study because cause of death is not available through the MarketScan database. The diagnosis codes used for our primary outcome generally have a PPV of more than 80%.[23-25] Safety outcomes included the risk of each of the following: hypoglycaemia; diabetic ketoacidosis; genital infection; lactic acidosis; or acute kidney injury (Appendix S1, Table S5). As a negative tracer outcome, we assessed all-cause hospitalization. We also calculated the average co-pay for SGLT2 inhibitors compared to metformin using data available in IBM MarketScan. Co-pay reflects the out-of-pocket cost paid by someone with health insurance for their prescription medication.

2.4 | Baseline characteristics

Covariates were assessed during the 365 days prior to cohort entry unless otherwise stated. Data were collected for each patient (Table 1 and Appendix S1, Table S3) reflecting diagnoses and procedures recorded during health encounters, including chronic medical conditions, proxies for diabetes severity, medications, overall healthcare utilization, contact with healthcare providers, potential indicators of cardiac risk (eg, recent electrocardiogram, stress test or echocardiogram) and medications.[26,27]

2.5 | Statistical analysis

Propensity score (PS) matching was used to adjust for confounding. The probability of initiating an SGLT2 inhibitor versus metformin was calculated by fitting a logistic regression model which contained nearly all baseline covariates without further selection. Laboratory values were not included in calculating the PS due to a large amount of missing data, and calculating a PS generally requires no missing data. After calculating a PS for each included patient, patients prescribed an SGLT2 inhibitor were matched 1:1 with patients prescribed metformin using a caliper of 0.05 on the probability scale. Covariate balance between the matched cohorts was assessed using standardized differences.[28] A standardized difference of 0.1 or less indicated adequate balance between groups.[28]

After PS matching we computed the incidence rate of the outcomes and fit proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the primary outcome without further adjustments. As a predefined sensitivity analysis, we performed an analysis similar to an intention-to-treat analysis in which

TABLE 1 Baseline characteristics before and after matching

Variable	Metformin	SGLT2 inhibitors	Standardized difference	Metformin	SGLT2 inhibitors	Standardized difference
Number of patients	518 280	9964		9964	9964	
Women, n (%)	250 225 (48.3)	5128 (51.5)	0.064	5135 (51.5)	5128 (51.5)	0.001
Mean age, years	54.32 (11.69)	53.50 (10.00)	0.075	53.51 (11.50)	53.50 (10.00)	0.001
Mean (SD) HbA1c, %	7.59 (1.86)	7.87 (1.81)	0.155	7.36 (1.64)	7.87 (1.81)	0.293
Missing, n (%)	484 478 (93.5)	9208 (92.4)		9186 (92.2)	9208 (92.4)	
Mean (SD) creatinine	0.88 (0.22)	0.88 (0.24)	0.004	0.87 (0.20)	0.88 (0.24)	0.061
Missing, n (%)	482 515 (93.1)	9133 (91.7)		9159 (91.9)	9133 (91.7)	
Medical history, n (%)						
Ischaemic stroke or TIA	11 161 (2.2)	187 (1.9)	0.02	176 (1.8)	187 (1.9)	0.008
Ischaemic heart disease	49 400 (9.5)	1042 (10.5)	0.031	1037 (10.4)	1042 (10.5)	0.002
Hypertension	330 210 (63.7)	7036 (70.6)	0.147	7069 (70.9)	7036 (70.6)	0.007
Dyslipidaemia	304 640 (58.8)	6810 (68.3)	0.2	6824 (68.5)	6810 (68.3)	0.003
Smoking	43 868 (8.5)	673 (6.8)	0.065	693 (7.0)	673 (6.8)	0.008
Heart failure	14 298 (2.8)	271 (2.7)	0.002	252 (2.5)	271 (2.7)	0.012
Obese or overweight	149 071 (28.8)	3293 (33.0)	0.093	3266 (32.8)	3293 (33.0)	0.006
Chronic kidney injury	12 214 (2.4)	320 (3.2)	0.052	310 (3.1)	320 (3.2)	0.006
Diabetic retinopathy	6875 (1.3)	293 (2.9)	0.112	295 (3.0)	293 (2.9)	0.001
Diabetic nephropathy	10 152 (2.0)	316 (3.2)	0.077	324 (3.3)	316 (3.2)	0.005
Diabetic neuropathy	21 337 (4.1)	796 (8.0)	0.163	784 (7.9)	796 (8.0)	0.004
Acute kidney injury	6324 (1.2)	87 (0.9)	0.034	92 (0.9)	87 (0.9)	0.005
Hypoglycaemia	1471 (0.3)	38 (0.4)	0.017	39 (0.4)	38 (0.4)	0.002
Diabetic ketoacidosis	1323 (0.3)	21 (0.2)	0.009	20 (0.2)	21 (0.2)	0.002
Genital infection	10 925 (2.1)	246 (2.5)	0.024	270 (2.7)	246 (2.5)	0.015
Medications, n (%)						
Angiotensin-converting enzyme inhibitor	167 255 (32.3)	2340 (23.5)	0.197	2407 (24.2)	2340 (23.5)	0.016
Angiotensin receptor blocker	94 541 (18.2)	2017 (20.2)	0.051	1947 (19.5)	2017 (20.2)	0.018
Beta blocker	95 273 (18.4)	1487 (14.9)	0.093	1437 (14.4)	1487 (14.9)	0.014
Calcium channel blocker	67 098 (12.9)	1025 (10.3)	0.083	991 (9.9)	1025 (10.3)	0.011
Antiplatelet	26 425 (5.1)	449 (4.5)	0.028	434 (4.4)	449 (4.5)	0.007
Statin	228 836 (44.2)	3816 (38.3)	0.119	3715 (37.3)	3816 (38.3)	0.021
Diuretic	83 908 (16.2)	1402 (14.1)	0.059	1386 (13.9)	1402 (14.1)	0.005
Mean (SD) number of medications	4.12 (2.59)	3.74 (2.60)	0.148	3.72 (2.38)	3.74 (2.60)	0.009
Healthcare utilization, n (%)						
Endocrinologist visit	25 181 (4.9)	1044 (10.5)	0.212	1053 (10.6)	1044 (10.5)	0.003
Cardiac stress test	34 957 (6.7)	780 (7.8)	0.042	777 (7.8)	780 (7.8)	0.001
Electrocardiogram	172 452 (33.3)	3396 (34.1)	0.017	3390 (34.0)	3396 (34.1)	0.001
Echocardiogram	45 384 (8.8)	988 (9.9)	0.04	998 (10.0)	988 (9.9)	0.003
Emergency department visit	113 884 (22.0)	2007 (20.1)	0.045	1982 (19.9)	2007 (20.1)	0.006
Mean (SD) outpatient visits	6.55 (5.90)	7.56 (6.00)	0.171	7.48 (7.14)	7.56 (6.00)	0.013
Inpatient hospitalization, n (%)	45 429 (8.8)	649 (6.5)	0.085	638 (6.4)	649 (6.5)	0.004
HbA1c ordered, n (%)	393 496 (75.9)	8398 (84.3)	0.211	8348 (83.8)	8398 (84.3)	0.014
Flu shot, n (%)	65 702 (12.7)	1163 (11.7)	0.031	1129 (11.3)	1163 (11.7)	0.011
Pneumococcal vaccine, n (%)	25 205 (4.9)	369 (3.7)	0.057	367 (3.7)	369 (3.7)	0.001
Cardiologist visit, n (%)	98 030 (18.9)	1970 (19.8)	0.022	1968 (19.8)	1970 (19.8)	0.001

Abbreviations: HbA1c, glycated haemoglobin; SD, standard deviation; SGLT2, sodium glucose cotransporter-2; TIA, transient ischaemic attack.

the censoring criteria of drug discontinuation, switching or augmentation were removed. We also assessed the outcome rates in a cohort restricted to patients at high risk of cardiovascular events. This subgroup was selected a priori because the clinical indications for empagliflozin and canagliflozin were expanded in 2016.[29,30] Specifically, both are indicated to reduce the risk of cardiovascular events in adults with type 2 diabetes mellitus who have cardiovascular disease. We used two different definitions of cardiovascular disease: (1) having a diagnosis of both hypertension and hyperlipidaemia, or (2) having a diagnosis of hypertension or hyperlipidaemia and one of coronary artery disease (including recent coronary artery bypass graph or percutaneous coronary intervention), stroke, heart failure, or peripheral vascular disease. All analyses were performed using the Aetion Evidence Platform v4.9 (incl. R v3.4.2), which has been scientifically validated by its accurate repetition of a range of previously published studies and by its replication or prediction of clinical trial findings.[19,31,32]

3 | RESULTS

3.1 | Study population

We identified 528 244 patients who satisfied study inclusion and exclusion criteria including 518 280 who received metformin and 9964 who received an SGLT2 inhibitor (Table 1). Patients who received an SGLT2 inhibitor generally had higher baseline cardiovascular risk (eg, higher rates of hypertension, dyslipidaemia) and characteristics suggestive of worse diabetes control (ie, higher rates of diabetic neuropathy, higher HbA1c, more likely to have seen an endocrinologist) compared to those who received metformin. After PS matching, we matched 100% of SGLT2 inhibitor users to metformin initiators; baseline characteristics were well balanced with the exception of HbA1c (Table 1). Overall, the average age was 54 years, 52% were women, most had a diagnosis of hypertension, and few had a diagnosis of ischaemic heart disease, heart failure or cerebral vascular disease (Table 1). The overall median (interquartile range [IQR]) duration of follow-up was 213 (91 500) days for patients prescribed metformin and 147 (58 360) days for patients prescribed SGLT2 inhibitors (Appendix S1, Table S6). The mean (standard deviation [SD]) co-pay for metformin was $3 (6.8) and the mean (SD) co-pay for SGLT2 inhibitors was $49 (64.5).

3.2 | Primary outcome

In the PS-matched cohort, the primary outcome occurred in 54 patients (7.2 events per 1000 person-years) among 9964 PS-matched new users of an SGLT2 inhibitor, compared to 84 patients (8.5 per events 1000 person-years) among 9964 PS-matched new users of metformin, resulting in an HR of 0.82 (95% CI 0.58, 1.15; Table 2). In regards to the components of the primary outcome, this included heart failure (HR 0.81 [95% CI 0.40, 1.63]), myocardial infarction (HR 0.91 [95% CI 0.54, 1.52]) and stroke (HR 0.76 [95% CI 0.42, 1.39]). When we carried forward the exposure to the first-used medication without accounting for possible treatment discontinuation, the median duration of follow-up was approximately 600 days (SGLT2 inhibitors: 610 days; metformin: 579 days) and the PS-matched result for the primary outcome was consistent with our primary analysis (HR 0.87, 95% CI 0.69, 1.09). This result is consistent with our primary analysis and suggests no major issues with regard to informative censoring.

3.3 | Primary outcome restricted to patients at higher risk of cardiovascular disease

In the cohort of patients with a diagnosis of both hypertension and hyperlipidaemia, we identified 5299 patients prescribed an SGLT2 inhibitor who were PS-matched to 5299 patients prescribed metformin. Within this group, the primary outcome occurred in 28 patients (6.8 events per 1000 person-years) prescribed an SGLT2 inhibitor compared to 45 patients (8.1 events per 1000 person-years) prescribed metformin. This event rate suggested a potentially lower HR

TABLE 2 Propensity score-matched rate of cardiovascular composite outcome and its components

	Entire cohort		Patients with HTN and HLD		Patients with HTN or HLD and cardiovascular disease	
	Metformin	SGLT2 inhibitors	Metformin	SGLT2 inhibitors	Metformin	SGLT2 inhibitors
Composite outcome						
Number of patients	9964	9964	5299	5299	5137	5137
Number of events	84	54	45	28	51	33
Rate per 1000 PY	8.52	7.19	8.10	6.75	9.66	8.18
HR (95% CI)	Ref.	0.82 (0.58, 1.15)	Ref.	0.81 (0.50, 1.30)	Ref.	0.83 (0.54, 1.30)
Unadjusted HR (95% CI)	Ref.	0.88 (0.67, 1.14)	Ref.	0.73 (0.51, 1.05)	Ref.	0.73 (0.53, 1.02)

Note: Unadjusted refers to results in the unmatched population (ie, propensity score matching was not performed).
Abbreviations: CI, confidence interval; HLD, hyperlipidaemia; HR, hazard ratio; HTN, hypertension; PY, person-years; Ref., referent group; SGLT2, sodium glucose cotransporter 2.

for patients prescribed an SGLT2 inhibitor compared to metformin (HR 0.81, 95% CI 0.50, 1.30; Table 2), albeit with wide 95% confidence intervals that included the possibility of a null effect. For the PS-matched cohort of patients with a diagnosis of hypertension or hyperlipidaemia and cardiovascular disease, similar findings were observed (HR 0.83, 95% CI 0.54, 1.30; Table 2).

3.4 | Adverse events

Overall, the PS-matched rate of genital infections was higher for patients prescribed an SGLT2 inhibitor compared to metformin (HR 2.28, 95% CI 1.87, 2.78), as was the rate numerically higher for diabetic ketoacidosis (HR 1.58, 95% CI 0.92, 2.70; Table 3). The PS-matched rate of acute kidney injury (HR 0.94, 95% CI 0.60, 1.47) and hypoglycaemia (HR 0.83, 95% CI 0.48, 1.42) was not higher among patients prescribed an SGLT2 inhibitor. Lactic acidosis was rare (12 events in total), which precluded any formal statistical analysis. The rate of our tracer outcome of all-cause inpatient hospitalization was, as anticipated, nearly identical between the two groups of patients (HR 0.97, 95% CI 0.87, 1.08).

TABLE 3 Propensity score-matched rate of adverse events

	Metformin	SGLT2 inhibitors
Hypoglycaemia		
Number of patients	9964	9964
Number of events	33	22
Rate per 1000 PY	3.33	2.92
HR (95% CI)	Ref.	0.83 (0.48, 1.42)
Unadjusted HR (95% CI)	Ref.	0.95 (0.62, 1.44)
Acute kidney injury		
Number of patients	9964	9964
Number of events	46	34
Rate per 1000 PY	4.65	4.51
HR (95% CI)	Ref.	0.94 (0.60, 1.47)
Unadjusted HR (95% CI)	Ref.	0.73 (0.53, 1.02)
Diabetic ketoacidosis		
Number of patients	9964	9964
Number of events	23	32
Rate per 1000 PY	2.32	4.25
HR (95% CI)	Ref.	1.58 (0.92, 2.70)
Unadjusted HR (95% CI)	Ref.	1.57 (1.11, 2.23)
Genital infections		
Number of patients	9964	9964
Number of events	153	282
Rate per 1000 PY	15.64	38.31
HR (95% CI)	Ref.	2.28 (1.87, 2.78)
Unadjusted HR (95% CI)	Ref.	2.80 (2.49, 3.15)
Lactic acidosis[a]		
Number of patients	9964	9964
Number of events	9	3
Rate per 1000 PY	0.91	0.40

Note: Unadjusted refers to results in the unmatched population (ie, propensity-score matching was not performed).
Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years; Ref., referent group; SGLT2, sodium glucose cotransporter 2 inhibitor.
[a]Too few events to reliably calculate the hazard ratio.

4 | DISCUSSION

In this cohort study of nearly 20 000 PS-matched adults with type 2 diabetes mellitus who were treatment-naïve in the preceding year, patients newly prescribed an SGLT2 inhibitor had a numerically lower rate of short-/mid-term cardiovascular events compared to patients newly prescribed metformin. While the effect estimate, an 18% reduction in cardiovascular events, is promising, the wide 95% CIs preclude a definitive assertion of benefit. Adults prescribed an SGLT2 inhibitor also had a higher rate of genital infection and diabetic ketoacidosis compared to those prescribed metformin, but not hypoglycaemia or acute kidney injury. These results help provide timely exploratory data to add to the debate about the role of SGLT2 inhibitors as first-line therapy for some patients with type 2 diabetes mellitus.[3,14,33] However, the relatively low number of events in our primary outcome, as expressed in the wide CIs of many of our outcomes, means these findings require replication.

The strengths of our study were its relatively large sample size compared to the available clinical trials of treatment-naïve patients with type 2 diabetes mellitus, the inclusion of only patients who had not received diabetes medications in the preceding 1 year, and the evaluation of clinically relevant endpoints. Our results did not definitively identify cardiovascular benefits of SGLT2 inhibitors compared with metformin among patients at relatively low baseline risk of cardiovascular disease. While the cardiovascular outcome trials demonstrated clear cardiovascular benefits for patients randomized to SGLT2 inhibitors, those trials have three important differences compared to the present study.[8,9]

First, the comparator group for the cardiovascular outcome studies was placebo while in the present study we used an active comparator. Second, the included patients in the cardiovascular outcome trials generally had more advanced diabetes as evidenced by the fact that approximately 50% were taking insulin. Thus, the results from the cardiovascular outcome trials established the efficacy of SGLT2 inhibitors in patients with more advanced diabetes, but not their comparative effectiveness in treatment-naïve patients.

Third, the patients in the cardiovascular outcome trials generally had a greater burden of cardiovascular risk factors (eg, mean age 63 years, 60% had coronary artery disease and 10% had heart failure) compared to the patients in the present study.[9] This probably explains why our event rate was lower than that detected in the cardiovascular outcome trials. Our preplanned subgroup analysis of patients at higher cardiovascular risk identified a numerically lower rate of cardiovascular events for those who received an SGLT2 inhibitor, although future

studies with a larger sample size and longer duration of follow-up may provide greater clarity regarding the comparative effectiveness of these medications in patients at higher baseline risk of cardiovascular events.

The relatively short duration of follow-up observed in the present study is a reflection of real-world use of diabetes medications, where adherence is lower than that observed in clinical trials. This short duration of follow-up and imperfect adherence may also explain why the CIs for our primary outcome included the null. This means that our data help to address the short- and mid-term risk of cardiovascular events, but do not address the long-term risk. Other explanations for our null finding include outcome misclassification (ie, if a study participant was assigned to the incorrect outcome category) or a lack of statistical power.[8,9] The former is problematic because outcome misclassification can result in bias to the null. The latter is an important limitation and thus additional larger studies are needed in addition to randomized trials.

A recently published 6-month randomized clinical trial of 1186 treatment-naïve patients with type 2 diabetes mellitus compared the safety and efficacy of combined metformin and canagliflozin, canagliflozin alone, or metformin alone.[14] The reduction in HbA1c with metformin (−1.3%) was comparable to that achieved with canagliflozin (−1.4%). Canagliflozin was also associated with greater reductions in body weight (−3.5 kg) compared to metformin (−2.1 kg), slightly lower rates of hypoglycaemia, and a higher rate of mycotic genital infection and renal-related adverse events. [14] Rates of diabetic ketoacidosis were not reported in the trial, and neither were cardiovascular outcomes evaluated.

Both cardiovascular outcomes and adverse events were evaluated in the present study. We did not observe a higher rate of acute kidney injury or hypoglycaemia for patients prescribed an SGLT2 inhibitor compared to metformin. The higher rates of genital infections and diabetic ketoacidosis with SGLT2 inhibitors that we observed are consistent with prior studies.[12,34,35] Because genital infection commonly occurred with SGLT2 inhibitors in the present study and because diabetic ketoacidosis can be life-threatening, these two important risks justify counselling patients accordingly and monitoring for both.

An important limitation of the present study is unmeasured confounding. Most physicians prescribe metformin as the first-line agent, and thus the patients we identified who were prescribed an SGLT2 inhibitor may have been at higher cardiovascular risk (eg, higher body mass index, total cholesterol, systolic blood pressure) or had more severe diabetes (eg, higher HbA1c, longer duration of diabetes) even after PS matching. While these markers of cardiovascular risk and diabetes severity are important unmeasured confounders that may have been more common among those prescribed an SGLT2 inhibitor, this would bias our results towards an increased risk of cardiovascular events, rather than a null finding or decreased risk. Another important unmeasured confounder is race and socioeconomic status. Both influence the likelihood of receiving an SGLT2 inhibitor and the risk of our primary outcome. The higher co-pay for SGLT2 inhibitors that we observed suggests that socioeconomic status impacts prescribing of SGLT2 inhibitors. Thus, some of the difference we observed may be related to these unmeasured confounders and this will be an important area of future research.

Another important limitation is that we could not definitively establish that the patients were treatment-naïve. However, this problem also exists in clinical trials since complete pharmacy records dating back to the time of diagnosis of diabetes are rarely available. Clinical trials of diabetes medications typically define "treatment-naïve" as patients who self-report no prior treatment or those who have not received a diabetes medication in the past 12 weeks or more.[14,36] For the present study, we had access to pharmacy records and excluded patients who had previously received a diabetes medication in the preceding 52 weeks (ie, 12 months), which is considerably longer than the definition used in clinical trials. Another limitation is the low incidence rate of cardiovascular outcomes relative to the cardiovascular outcome trials, which is expected in a healthier population. Another category of limitations for this study is incomplete data. For example, HbA1c was missing in the vast majority of included patients. As another example, insurance claims databases in the United States capture in-hospital mortality but generally do not capture out-of-hospital mortality.

An important consideration for prescribing an SGLT2 inhibitor first-line is cost and our data show a higher co-pay for SGLT2 inhibitors compared to metformin. In the United States, the out-of-pocket costs for those without insurance for a 1-month supply of metformin and an SGLT2 inhibitor are approximately $4 and $600, respectively. In healthcare settings where the price of an SGLT2 inhibitor is markedly lower (eg, the United Kingdom) the cost would not be a major barrier to considering an SGLT2 inhibitor for first-line therapy.

In conclusion, the present study provides preliminary evidence that SGLT2 inhibitors are not associated with an increased risk of short- or mid-term cardiovascular events and might be associated with a lower risk compared to patients who are treatment-naïve and prescribed metformin. The study also confirmed that SGLT2 inhibitors are associated with an increased risk of diabetic ketoacidosis and genital infections in this population. Conducting a randomized trial of the cardiovascular effectiveness of metformin versus an SGLT2 inhibitor in treatment-naïve patients will require a sufficiently large sample size because most patients who are treatment-naïve will have low rates of cardiovascular events. Until such a trial is conducted, we rely on observational studies such as the present study and available clinical trial data on surrogate endpoints such as HbA1c.

CONFLICTS OF INTEREST

E.P. is an investigator of investigator-initiated grants to the Brigham and Women's Hospital from GSK, not related to the topic of the submitted work. S.S. participates in investigator-initiated grants to the Brigham and Women's Hospital from Boehringer Ingelheim unrelated to the topic of this study. He is a consultant to Aetion Inc., a software manufacturer in which he owns equity. His interests were declared, reviewed, and approved by the Brigham and Women's Hospital and Partners HealthCare System in accordance with their institutional compliance policies.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data are not available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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