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ORIGINAL ARTICLE

Observational Study

Using real world data to assess cardiovascular outcomes of two antidiabetic treatment classes

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Informed consent statement: This was an observational study based on analyses of anonymized electronic medical records describing real world treatment. No intervention or any study specific activity was done. Therefore, no informed consent was necessary and would even have been not feasible considering the anonymized and retrospective character of the analysis.

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Abstract

AIM

To evaluate the effect on cardiovascular outcomes of sodium-glucose co-transporter-2 (SGLT2) inhibitors in a real world setting by analyzing electronic medical records.

METHODS

We used TriNetX, a global federated research network providing statistics on electronic health records (EHR). The analytics subset contained EHR from approximately 38 Million patients in 35 Health Care Organizations in the United States. The records of 46,909 patients who had taken SGLT2 inhibitors were compared to 189,120 patients with dipeptidyl peptidase (DPP) 4 inhibitors. We identified five potential confounding factors and built respective strata: elderly, hypertension, chronic kidney disease (CKD), and co-medication with either insulin or metformin. Cardiovascular events were counted

as stroke (ICD10 code: I63) or myocardial infarction (ICD10: I21) occurring within three years after the first instance of the respective medication in the patients' records.

RESULTS

Of the 46909 patients with SGLT2 inhibitors in their EHR, 1667 patients (3.6%) had an ICD code for stroke or for myocardial infarction within the first three years after the first instance of the medication. In the control group, there were 10680 events of 189120 patients (5.6%), which represents a risk ratio of 0.63 (95%CI: 0.60-0.66). The overall incidence of stroke or myocardial infarction in the strata with a potential confounding risk factor reached from 4.9% in patients taking metformin to 12.5% in the stratum with the highest risk (concomitant CKD). In all strata, the difference in risk of experiencing a cardiovascular event was similarly in favor of SGLT2 *vs* control, with Risk Ratio ranging from 0.62 to 0.81.

CONCLUSION

Real world data replicated the results from randomized clinical trials, confirmed the cardiovascular advantages of SGLT2 inhibitors, and showed its applicability to the US population.

Key words: Sodium-glucose co-transporter-2 inhibitors; Cardiovascular events; Clinical trials; Electronic medical records; Dipeptidyl peptidase 4 inhibitors; Real world evidence; Diabetes

Core tip: Cardiovascular advantages of sodium-glucose co-transporter-2 (SGLT2) inhibitors were shown in complex clinical trials or in countries with large registries. However, it was unclear whether these findings could be applied to routine medical practice in the US. This real world analysis from 46909 patients with SGLT2 inhibitors revealed a 0.63 (95%CI: 0.60-0.66) risk ratio of SGLT2 inhibitors compared to 189120 patients with dipeptidyl peptidase 4 inhibitors. This analysis of electronic health records could replicate the results of randomized clinical trials, which supports the usefulness of such real world studies (*e.g.,* for long-term outcome or safety observations).

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INTRODUCTION

An estimated 30.3 million people of all ages (or 9.4% of the United States population) had diabetes in 2015[1]. It is expected that the world prevalence of diabetes among adults will increase to 7.7%, or 439 million adults, by 2030. Between 2010 and 2030, there will be a 69% increase in the number of adults with diabetes in developing countries, and a 20% increase in developed countries[2].

While short-term treatment targets focus on the normalization of values for glucose and hemoglobin A1c, the long-term objective is to avoid late-stage complications of diabetes and end-organ damage. Up to 70% of patients with diabetes type Ⅱ (T2DM) also have arterial hypertension[1] and are thus exposed to an increased risk of experiencing a stroke or heart attack. It is therefore important that treatment paradigms for T2DM consider the long-term cardiovascular risk.

In 2015, the EMPA-REG OUTCOME trial found a significant mortality benefit of sodium-glucose co-transporter-2 (SGLT2) inhibitors *vs* placebo[3]. Because the findings were unexpected, unprecedented and not linked to obvious mechanistic pathways, it was suggested that the results be replicated in future investigations[4]. Recently, CVD-REAL Nordic, a multinational observational study, analyzed the cardiovascular mortality and morbidity in patients with T2DM following initiation SGLT2 inhibitors[5]. CVD-REAL Nordic was an observational analysis of individual patient-level data from national registries in three Scandinavian countries, showing that SGLT2 inhibitor use was associated with reduced cardiovascular disease and cardiovascular mortality.

The objective of the following analysis was to support or contradict the results of EMPA-REG OUTCOME and CVD-REAL Nordic by using electronic medical records (EMR) from a predominately United States-based research network, thus evaluating the representativity of these results outside the experimental setting of a randomized clinical trial and beyond a European population, respectively.

MATERIALS AND METHODS

We used TriNetX, a global federated research network providing access to statistics on EMR (diagnoses, procedures, medications, laboratory values, genomic information). The analytics subset allowed the analysis of approximately 38 million patients in 35 large Health Care Organizations predominately in the United States. As a federated network, TriNetX received a waiver from Western IRB, since only aggregated counts, statistical summaries of de-identified information, and no protected health information is received. In addition, no study-specific activities are performed in retrospective analyses. Details of the network have been described elsewhere[6-8]. All analyses were done in the TriNetX "Analytics" network using the browser-based real-time analytics features. At the time of the analysis in June 2018, we analyzed the EMR of 46909 patients in the network who had an instance of any SGLT2 inhibitor

Table 1 Patient characteristics and results before correcting for potential confounding factors

	SGLT2	Control
n	46909	189120
Mean age	59	66
SD age	11	13
Percent male	53%	52%
Comorbidities		
Hypertension (I10)	45%	41%
CKD (N18)	4%	8%
Co-medication		
On insulin	32%	19%
On metformin	52%	33%
LDL cholesterol (mg/dL)	91.6	93.1
HDL cholesterol (mg/dL)	43.6	43.2
After index event		
Total stroke (I63) or MI (I21)	12347 (5.2%)	
n in group	1667	10680
Percent in group	3.60%	5.60%
RR SGLT2 *vs* control	0.63	

SGLT2: Sodium-glucose co-transporter-2; RR: Risk ratio; SD: Standard deviation; CKD: Chronic kidney disease; LDL: Low density lipoprotein; HDL: High density lipoprotein; MI: Myocardial infarction.

(empagliflozin, dapagliflozin or canagliflozin) any time within the past ten years in their electronic medical record. As a comparison group, we chose patients who had taken dipeptidyl peptidase (DPP) 4 inhibitors (linagliptin, alogliptin, sitagliptin or saxagliptin) during the same time, and found 189120 patients. Using a Bayesian statistical approach[9] on demographics and pre-existing (baseline) comorbidities of the two groups, we identified five potential confounding factors and built strata with the following criteria: age ⩾ 60 years, presence of hypertension [International Classification of Diseases (ICD)10 code I10], presence of CKD (ICD10 code N18), co-medication with insulin, and co-medication with metformin. Separately analyzing strata allowed us to address potential bias in the federated data model without direct access to the individual data sets on the patient level.

Cardiovascular events were counted by selecting any stroke (ICD10 code I63) or myocardial infarction (ICD10 code I21) occurring during a three-year observation period after the first instance of the above mentioned medications in the patients' records.

The risks of experiencing an event in each stratum were calculated by dividing the number of patients with an event (numerator) by the total number of patients with the respective medication in each stratum (denominator). The risk ratios for SGLT2 inhibitors *vs* the comparison group were calculated by dividing the risk for each SGLT2 stratum by the risk in each corresponding DPP4 stratum.

RESULTS

Of the 46909 patients taking SGLT2 inhibitors, 1667 patients (3.6%) had an ICD code for stroke or myocardial infarction during their three-year observation period, compared to 10680 of 189120 (5.6%) in the control group (Table 1). This translates into a risk ratio of 0.63 without any correction for potential bias ($P < 0.001$; 95%CI: 0.60-0.66).

SGLT2 inhibitors carry a contra-indication for renal insufficiency[10]. Indeed, the percentage of patients with CKD was only 4% in the SGLT2 group, compared to 8% in the control group. While the groups were similar in gender distribution (53% and 52% male, respectively) and low density lipoprotein, as well as high density lipoprotein levels, the SGLT2 group was younger than the control group (mean age 59 *vs* 66) and had more patients with concomitant hypertension (45% *vs* 41%). There were also differences in the use of insulin (32% *vs* 19%) and metformin (52% *vs* 33%). To balance for these potential confounding factors, strata were built for age ⩾ 60 years, CKD, hypertension, and antidiabetic co-medication (insulin and metformin). The overall incidence of stroke or myocardial infarction in each stratum reached from 4.9% to 12.5%. In all strata, the difference in the risk of experiencing a cardiovascular event in the SGLT2 group *vs* control was similarly in favor of SGLT2, with risk ratios ranging from 0.62 (co-medication insulin) to 0.81 (patients with CKD) (Table 2).

DISCUSSION

Drug therapy of type Ⅱ diabetes mellitus should both bring glucose and hemoglobin A1c values into an acceptable and stable range, and reduce the likelihood of end organ damage or cardiovascular events.

Several studies and meta-analyses have suggested a positive effect on cardiovascular outcomes by the SGLT2 inhibitor class[11,12]. EMPA-REG OUTCOME and CANVAS were randomized placebo controlled prospective trials that used empagliflozin[4] and canagliflozin[13], respectively.

A recent observational cohort study observed protective effects of SGLT2 inhibitors compared to sulfonylureas by a database analysis[14]. Another study, CVD-REAL Nordic, was the first large observational analysis performed in real world settings in three Scandinavian countries that evaluated the cardiovascular benefits of this class, which also showed that SGLT2 inhibitor use was associated with reduced cardiovascular disease and cardiovascular mortality compared with the use of other glucose-lowering drugs[4]. Such real-world studies are less complicated and significantly less costly than traditional prospective randomized clinical outcomes trials. In addition, the reduced number of eligibility criteria ensures that the study results are representative and applicable to a much wider population. Recently, another study confirmed that real-world data analyses of patients receiving routine care provide findings similar to those found in a randomized clinical trial, and may even support (supplemental) regulatory applications[15]. Real world evidence can sometimes complement or

Table 2 Results from the patient subgroups (strata) with potential confounding factors

	Stratum 1 > 60 yr		Stratum 2 hypertension		Stratum 3 CKD		Stratum 4 insulin		Stratum 5 metformin	
	SGLT2	control	SGLT2	control	SGLT2	control	SGLT2	control	SGLT2	control
n	23594	131219	27499	115703	3786	34388	24395	90978	37762	136569
patients with stroke or MI	9784 (6.3%)		10827 (7.6%)		4755 (12.5%)		8976 (7.8%)		8629 (4.9%)	
n in group	1077	8707	1452	9375	391	4364	1275	7701	1394	7235
percent in group	4.60%	6.60%	5.30%	8.10%	10.30%	12.70%	5.20%	8.50%	3.70%	5.30%
RR SGLT2 *vs* control	0.69		0.65		0.81		0.62		0.7	

SGLT2: Sodium-glucose co-transporter-2; MI: Myocardial infarction; RR: Risk ratio; CKD: Chronic kidney disease.

even replace randomized controlled trials, but prejudices and reservations so far have limited their acceptance[16].

Therefore, the underlying data sources must be reliable, and the methods used have to be defined in advance to avoid "data dredging" based on the findings[17]. Furthermore, the data usually come from non-consented patients and therefore the highest standards of data privacy must be ensured.

The present study was undertaken to evaluate whether the results of the EMPA-REG OUTCOME and CVD-REAL Nordic studies can be replicated in a federated network of EHR, and if they can be applied to a predominantly United States American population. As controls, we chose DPP4 inhibitors that represent another homogeneous and relatively new non-metformin class. We found a significantly lower incidence of stroke or myocardial infarction in the SGLT2 group within the three-year observational period compared with the control group.

In a federated data network, individual data sets never leave the source (*i.e.*, the data warehouse of a healthcare organization). Instead, the analyses are done based on aggregated statistical counts. At the time of this analysis, our platform limited the methods that could be applied to correct for potential confounding factors, such as pair matching or propensity score matching (PSM). While PSM is a popular method of preprocessing data for causal inference, it is controversial since it may accomplish the opposite of its intended goal, such as increasing imbalance or bias[18]. In addition, the censoring by PSM that excludes certain patients from the analysis, reduces the sample size and the representation of a diverse patient population, thus reintroducing the criticism often applied to randomized clinical trials regarding their very restrictive eligibility criteria.

We therefore chose to build subgroups of the study population according to the presence of potentially confounding factors, and to test these strata individually. SGLT2 inhibitors have a contraindication for renal insufficiency and are a relatively new class of antidiabetics with less long-term experience than comparator classes, such as metformin or DPP4 inhibitors. One can therefore assume that the treatment decision by prescribing physicians may be driven by a patient's renal function, patient age, and other potential risk factors. Indeed, we found a lower mean age in the SGLT2 group, similar to CVD-REAL Nordic before matching. Furthermore, the SGLT2 group had fewer patients with CKD than the comparison group. In prospective randomized clinical trials, such factors usually get balanced by randomization, which must be corrected for when a retrospective analysis is done. We therefore created five strata, based on age $\geqslant$ 60 years, hypertension, CKD, insulin therapy or metformin therapy, and tested the event rates individually in each of these subgroups. The fact that the overall highest event rate was found in the higher risk stratum (patients with CKD) provides internal validation for the selection of the strata.

All strata showed very similar hazard ratios for cardiovascular events (according to our definition using ICD10 codes for myocardial infarction or stroke), which were consistently in favor of the SGLT2 inhibitor group, *i.e.*, between 0.62 and 0.81. This generally confirms the findings of the CVD-REAL Nordic study, where the risk ratio for cardiovascular mortality and for major cardiovascular events was in a similar range of 0.53 and 0.78, respectively.

Limitations

Due to the nature of the design (retrospective, non-randomized) and data analysis (federated, aggregated strata), this study could be done very quickly, simplistically and with minimal cost, but may have several limitations. Non-randomized comparisons bear the risk that patients' disease state influence the treatment decision and thus introduce imbalances. We limited balancing for confounders to five major factors and did not further correct for residual, potentially confounding factors like other co-morbidities, duration of diabetes, glucose or HBa1c values, concomitant medications or length of exposure to concomitant treatment. Our outcome criteria were simply the ICD10 codes for myocardial infarction or stroke, relying on correct coding at the source without differentiation between morbidity and mortality. Despite the fact that one specific compound numerically dominated in each group (SGLT2: canagliflozin 78%, DPP4: sitagliptin 69%), we consider the results as representative of a class but not robust enough for a comparison of two individual compounds.

Real world studies depend on the prescribing and documentation behavior of the data-providing institutions. We used EHR in structured form rather than

Table 3 Data density in the two comparator cohorts

	SGLT2	Control
Total facts	54852092	261813664
Avg facts per patient	1143	1325
Avg diagnosis facts per patient	231	262
Eastern United States, patients (%)	68	69
Western United States, patients (%)	32	31

SGLT2: Sodium-glucose co-transporter-2; Avg: Average.

claims data. This has the advantage of complete medical information coming from the respective Health Care Organization, but data may be lacking if a patient visits another institution. This especially applies to medication and prescription refills. While we defined an observational period of three years, we could not validate whether the patients actually stayed with their medication for the whole period, as we defined the treatment group based on one documentation of SGLT2 or DPP4 in their records. Insofar as a difference in compliance or persistence between the groups could introduce a potential imbalance, the approach would be similar to the intent-to treat principle, which is applied to randomized clinical trials.

Furthermore, differences in the completeness of medical records between comparison groups need to be taken into consideration as well. In searching for a potential documentation bias, we found similar data density in the SGLT2 cohort compared to control (Table 3).

Theoretically, one could assume that more events had been found in the control group simply because this patient cohort was better documented. In real world studies, consideration of different therapeutic settings and documentation completeness is important, *e.g.,* when comparing oral *vs* injectable medication, or inpatient *vs* outpatient procedures. However, SGLT2 inhibitors and DPP4 inhibitors are both taken orally and prescribed in similar settings. In addition, our data overall found about 20% more events in the DPP4 group, but the density of facts per patient in the documentation of this group was only 6% higher. Therefore, a documentation bias as an explanation for the difference in CV events in this study is very unlikely.

In conclusion, this study was conducted by analyzing EHR of approximately 38 million patients from 35 healthcare organizations, mainly from the United States. This real world clinical setting allows the analysis of data from patients with a much broader cardiovascular risk profile than the highly selective population in randomized clinical trials. The federated structure of this network ensures the highest level of data privacy standards, but poses some restrictions on the possible analytics, such as matching by propensity scores. Despite these limitations: (1) this analysis could replicate the results from much more complex and costly studies on the same topic, which validates our methods and the quality of data in the network; (2) our analysis shows that the cardiovascular advantages of SGLT2 inhibitors found in the Scandinavian CVD-REAL Nordic study can be applied to the United States American population.

ARTICLE HIGHLIGHTS

Research background

Therapy for diabetes mellitus intends to control blood glucose values, to prevent or delay diabetic complications such as chronic kidney disease or retinopathy, and to reduce the likelihood of cardiovascular events like myocardial infarction or stroke. Several randomized clinical trials and sophisticated European registries have suggested that sodium-glucose co-transporter-2 (SGLT2) inhibitors may have an advantage in preventing cardiovascular events.

Research motivation

Randomized clinical trials are conducted on highly selected patient populations and follow very artificial treatment protocols. This makes it sometimes questionable whether the results are representative and can be applied to routine medical practice.

Research objectives

To determine whether positive results from randomized clinical trials with SGLT2 inhibitors can be confirmed by real world data from actual routine medical practice in the United States.

Research methods

A federated research network was used, allowing analyses of electronic medical records (EMR) from 38 million patients in 35 large Health Care Organizations predominately in the United States. Cardiovascular events occurring during a three-year observation period after start of a therapy with an SGLT2 inhibitor were counted and compared to a control group starting dipeptidyl peptidase 4 inhibitors. Comorbidity strata were created to address potential confounders.

Research results

In the overall cohort and in all comorbidity strata, the risk of experiencing a cardiovascular event was similarly in favor of SGLT2, with risk ratios ranging from 0.62 to 0.81.

Research conclusions

The analysis of data from patients with a much broader cardiovascular risk profile than the selected population in randomized clinical trials could replicate the results of such trials. This validates the methods and quality of data in the network, and allows extrapolation of the trial results to the general patient population.

Research perspectives

Sophisticated analyses of high quality EMR can complement costly, complex and lengthy randomized clinical trials, can assess their representativity for actual medical practice in the real world, and may even, in certain instances, be able to replace them.

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