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RESEARCH LETTER

Risk of hospitalization with sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes lacking evidence of chronic kidney disease: Real-world data

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1 | INTRODUCTION

Patients with type 2 diabetes (T2D) have a high incidence of hospitalizations that reduce patients' quality of life and are translated into a significant burden on healthcare systems, accompanied by increased costs.[1,2] Randomized controlled trials (RCTs) showed that sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular events, heart failure (HF) hospitalizations, and kidney outcomes in patients with T2D, HF, or chronic kidney disease (CKD).[3] In some of these RCTs, SGLT2 inhibitors also modestly reduced the risk for any hospitalization.[4–11] However, these studies included patients with T2D and high cardiovascular risk,[4–6,11] or patients with CKD with and without T2D.[8,9] Whether SGLT2 inhibitor use is associated with a lower risk for any hospitalization in a general population of patients with T2D, especially patients without CKD, is unknown.

This was an observational, retrospective, cohort study of data from Maccabi Healthcare Services (MHS), Israel's seconds largest Health Maintenance Organization. We assessed the association of long-term, real-world use of SGLT2 inhibitors, versus that of dipeptidyl peptidase-4 (DPP-4) inhibitors, with risk for hospitalization in patients with T2D lacking evidence of CKD.

2 | METHODS

The database includes over 2.2 million patients, and approximately 180 000 are in the diabetes registry, with a 99% yearly retention rate. Patients with T2D, who initiated an SGLT2 inhibitor (empagliflozin or dapagliflozin) in an outpatient setting between August 2015 and December 2020 were propensity-scored matched with patients starting a DPP-4 inhibitor (sitagliptin, linagliptin, vildagliptin or saxagliptin). The presence of T2D was defined by an algorithm combining laboratory measurements (glycated haemoglobin [HbA1c] and fasting plasma glucose), purchased glucose-lowering agents, and diagnoses of diabetes made by expert physicians, as previously described.[12] The day of treatment initiation was defined as the index date, and the

preceding 12 months were defined as the baseline period. We included only adults with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2. We excluded patients with type 1 diabetes, defined by more than four insulin purchases per year following diabetes diagnosis without an oral glucose-lowering agent, and entry to the diabetes registry at age earlier than 26 years.[12] We also excluded patients with urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g, evidence of pregnancy within the prior 9 months, or with a record of SGLT2 inhibitor or DPP-4 inhibitor use in the baseline period in order to limit time-related biases. Comparable groups were created using propensity-score matching according to patients' demographics, medical history, background medications, and socioeconomic status, as previously described.[13] A multivariate logistic regression model was used to develop the propensity score, and the dependent binary variable indicated whether the indexed medication was an SGLT2 inhibitor or a DPP-4 inhibitor. Matching was performed by baseline eGFR layers (≥90 or 60 to <90 mL/min/1.73 m^2). The complete list of the 95 variables used for matching is presented in Appendix S1. Medical history was collected from validated MHS registries or using International Classification of Diseases-9 or Anatomical Therapeutic Chemical codes (Table S1). Laboratory and clinical values were collected only in outpatient settings to avoid changes in parameters that may occur during acute states. In the intention-to-treat analysis, patients were followed from the index date until September 2021, death, or end of data availability. In the as-treated definition, follow-up was also censored at the end of the last prescription duration with a 90–day grace period added to this, or at the initiation of the comparator study drug without a grace period. The study outcomes were the risks of first any hospitalization or prolonged hospitalization (≥3 nights). Cox proportional hazards regression models were applied to compare outcomes between the groups. We assessed subgroups of patients defined by their sex, age (<60 or ≥60 years), socioeconomic status[14] (1-4, 5-7, 8-10), index year of study entry (2015-2016, 2017, 2018, 2019, and 2020), body mass index (<30 or ≥30 kg/m^2), HbA1c (<8% or ≥8% [<64 mmol/mol or ≥64 mmol/mol]), history of cardiovascular disease (Appendix S1 and Table S2), history of HF,[12] eGFR (≥90 or 60 to <90 mL/min/1.73 m^2), urinary albumin (urine albumin below detectable levels or UACR >0 to <30 mg/g), and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use. The models were adjusted to the treatment arm, subgroups, and an interaction term between the treatment arm and the subgroups to assess heterogeneity. Analyses were performed using SAS version 9.4. The study received ethical approval from the institutional review board at MHS. Participants' informed consent was not required by the committee due to the anonymized nature of the dataset.

3 | RESULTS

After applying the inclusion and exclusion criteria, 10 090 and 15 238 patients initiated treatment with SGLT2 inhibitors and DPP-4 inhibitors, respectively (Tables S3 and S4; Figure S1). Following propensity-score matching, there were 6477 patients in each arm; 5431 patients (41.9%) were women and the mean (SD) patient age was 59.8 (10.9) years (Table 1). The mean baseline eGFR was 93.4 (14.2) mL/min/1.73 m^2, over half of the cohort did not have detectable albumin in urine, and 10 426 (80.5%) had no evidence of cardiovascular disease. Baseline characteristics were balanced between the matched cohorts (Table 1; Tables S3 and S4).

During a median (interquartile range) follow-up of 39.2 (21.9-54.9) months (Table S5), 2130 (32.9%) and 2211 (34.1%) of the participants were hospitalized in the SGLT2 inhibitor and DPP-4 inhibitor arms, respectively (13.1 vs. 14.1 hospitalized patients per 100 patient-years; hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.88-0.99). The risk of prolonged (≥3 nights) hospitalization was also lower with SGLT2 inhibitors compared to DPP-4 inhibitors (HR 0.91, 95% CI 0.84-0.98; Figure 1). There was no clear evidence for heterogeneity of the association between initiation of SGLT2 inhibitors versus DPP-4 inhibitors, with risk of any hospitalization by baseline subgroups, although the treatment effect was numerically more pronounced in patients with eGFR 60 to <90 mL/min/1.73 m^2 versus eGFR ≥90 mL/min/1.73 m^2 (HR 0.87, 95% CI 0.80-0.96 vs. HR 0.98, 95% CI 0.91-1.06, respectively; *P*-interaction = 0.051), and in those with detectable albumin in urine versus those with urinary albumin below detectable levels (HR 0.88, 95% CI 0.80-0.96 vs. HR 1.00, 95% CI 0.92-1.08, respectively; *P*-interaction = 0.053 [Figure 1; Table S6]). The association between treatment arms and the risk of prolonged hospitalization was more pronounced in patients with evidence of cardiovascular disease at baseline (*P*-interaction = 0.012; Figure 1). Similar findings were observed with the as-treated analysis, demonstrating lower risks of first any or prolonged hospitalization with the initiation of SGLT2 inhibitors versus that of DPP-4 inhibitors (Figure S2 and Table S6).

4 | DISCUSSION

Initiation of SGLT2 inhibitors versus DPP-4 inhibitors was associated with a 6% (95% CI 1-12) reduction in the risk of any hospitalization and a 9% (95% CI 2-16) reduction in the risk of prolonged (≥3 nights) hospitalizations. These findings are in line with cumulating data from RCTs.[4–10] In the EMPA-REG OUTCOME trial, treatment with empagliflozin compared with placebo resulted in a significant 11% (95% CI 4-19) reduction in the risk of first hospitalization in patients with T2D and previous cardiovascular disease.[4] In the CANVAS program, which also included patients with high risk but without established cardiovascular disease, the risk of first all-cause hospitalization was one of the prespecified outcomes. The effect of canagliflozin was marginally significant compared with placebo (HR 0.94, 95% CI 0.88-1.00).[6] A post hoc analysis of this trial found a significant 8% reduction in the rate of all (first and subsequent) hospitalizations, mainly driven by a reduction in cardiac-related hospitalizations.[5] Post hoc data of the DECLARE-TIMI 58 found a similar 11% reduction in risk of first hospitalizations in 17 160 patients with T2D, with creatinine clearance >60 mL/min, most of them (59.4%) with high risk for but without evidence of cardiovascular disease.[11] In the SOLOIST-WHF study involving patients

TABLE 1 Baseline characteristics of the participants after propensity-score matching

Variable	Level	SGLT2 inhibitors N = 6477	DPP-4 inhibitors N = 6477	STD
Demographic				
Age, years	Mean (SD)	59.9 (10.4)	59.8 (11.4)	0.01
Women	*n* (%)	2723 (42.0)	2708 (41.8)	0.00
Socioeconomic status[a]	Mean (SD)	6.0 (2.0)	6.0 (1.9)	−0.01
Medical history				
Years in diabetes registry	Mean (SD)	7.3 (5.7)	7.3 (5.7)	0.01
Body mass index, kg/m^2	Mean (SD)	31.6 (5.5)	31.8 (5.9)	−0.03
Systolic blood pressure, mmHg	Mean (SD)	131.6 (14.6)	131.5 (14.8)	0.01
Diastolic blood pressure, mmHg	Mean (SD)	78.2 (9.2)	78.2 (9.4)	0.00
HbA1c, %	Mean (SD)	7.9 (1.6)	7.9 (1.6)	0.02
eGFR	Mean (SD)	93.3 (13.9)	93.5 (14.6)	−0.02
	>90 mL/min/1.73 m^2, n (%)	4079 (63.0)	4079 (63.0)	0.00
	60-90 mL/min/1.73 m^2, n (%)	2398 (37.0)	2398 (37.0)	
UACR	Median [IQR]	0.0 [0.0-12.1]	0.0 [0.0-12.6]	−0.01
	Albumin below detectable	3424 (52.9)	3395 (52.4%)	
	>0–<15 mg/g, n (%)	1378 (21.3)	1405 (21.7)	0.03
	15-<30 mg/g, n (%)	1140 (17.6)	1162 (17.9)	
	Missing, n (%)	535 (8.3)	515 (8.0)	
eGFR slope mL/min/1.73 m^2/year (prior to index date)[b]	Mean (SD)	−0.6 (5.3)	−0.6 (5.5)	0.00
Established CV disease history[c]	n (%)	1256 (19.4)	1272 (19.6)	−0.01
Heart failure[c]	n (%)	88 (1.4)	95 (1.5)	−0.01
Hypertension registry[c]	n (%)	3583 (55.3)	3546 (54.7)	0.01
Baseline medications				
Metformin	n (%)	6118 (94.5)	6120 (94.5)	0.00
Insulin	n (%)	1043 (16.1)	981 (15.1)	0.03
Meglitinides	n (%)	326 (5.0)	322 (5.0)	0.00
Glucagon-like peptide-1 receptor agonists	n (%)	197 (3.0)	182 (2.8)	0.01
Thiazolidinediones	n (%)	245 (3.8)	221 (3.4)	0.02
ACE inhibitors/ARBs	n (%)	3622 (55.9)	3564 (55.0)	0.02
Beta blockers	n (%)	2009 (31.0)	1988 (30.7)	0.01
Loop diuretics	n (%)	225 (3.5)	233 (3.6)	−0.01
MRAs	n (%)	180 (2.8)	197 (3.0)	−0.02
Statins	n (%)	4874 (75.3)	4862 (75.1)	0.00
Antiplatelets	n (%)	2938 (45.4)	2935 (45.3)	0.00

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter-2; STD, standardized difference; UACR, urine albumin-to-creatinine ratio.

[a]Residential socioeconomic status was coded on a 1-10 scale developed by the Israeli Central Bureau of Statistics.[14]

[b]eGFR slope was calculated for the 2 years prior to index date for those with at least 180 days between the first and last measurement during this period. It was available in 11 668 (90.1%) of the participants.

[c]The presence of cardiovascular disease (Appendix S1), heart failure,[12] and hypertension were based on MHS registries.

with T2D and recent worsening HF, sotagliflozin increased the number of days alive and out of hospital.[10] Analyses from the EMPA-KIDNEY[9] and DAPA-CKD[8] trials found a lower risk of hospitalizations from any cause with empagliflozin and dapagliflozin, respectively, in patients with CKD with and without T2D. However, all these trials included specific populations with relatively high baseline cardiovascular or kidney risk, compared with the general populations of patients with T2D.

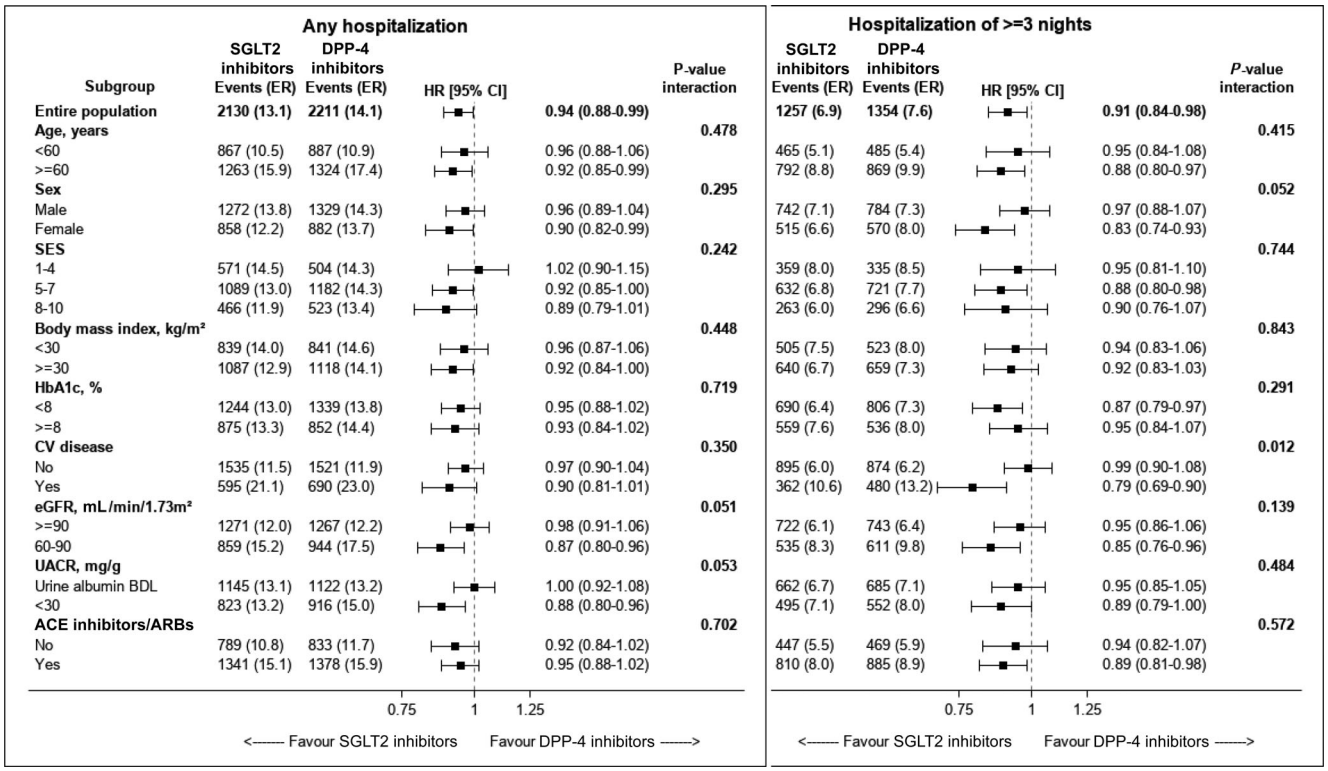

FIGURE 1 The risk of any hospitalization, or prolonged hospitalizations (≥3 nights) for any cause in initiators of sodium-glucose cotransporter-2 (SGLT2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors, overall and by baseline subgroups, in an intention-to-treat analysis. New initiators of SGLT2 inhibitors were propensity-scored matched with patients starting DPP-4 inhibitors. Cox proportional hazard regression models were used to compare the risk of any hospitalization or prolonged (≥3 nights) hospitalization in an intention-to-treat analysis, by baseline subgroups. Patients were followed from the index date until September 2021, death, or end of data availability. Event rates (ERs) are presented per 100 patient-years. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SES, socioeconomic status; UACR, urine albumin-to-creatinine ratio

Several real-world evidence studies also found an association between SGLT2 inhibitor use and a lower risk of hospitalization.[15–18] However, these studies had shorter follow-up duration,[15–17] fewer participants,[15,16] or high CV risk.[16] The long-term follow-up accompanied by a large number of participants in this analysis enabled us to show that SGLT2 inhibitor use is associated with reduced risk of any-cause hospitalization, even in patients with T2D without evidence of CKD.

The diabetes-attributed global annual expenditure rate was 1.3 trillion USD in 2015 and is expected to increase to 2.1 trillion USD in 2030.[19] In the United States, hospitalizations and inpatient care are responsible for approximately 30% of medical expenditure in patients with diabetes.[2] Thus, even a mild treatment effect on the relative risk of hospitalization may be translated into valuable cost benefits. How SGLT2 inhibitor-mediated reduction of hospitalization risk affects diabetes-related expenditures and patients' quality of life remains to be investigated.

This study has several limitations. It is an observational study, and while we used propensity-score matching, the presence of residual bias cannot be excluded, and no causation can be drawn. It is based on one registry, so the external validity remains to be tested, especially in different healthcare systems. We were unable to differentiate elective from non-elective hospitalizations in the dataset; however, we assessed the risk of prolonged (≥3 nights) hospitalizations—events that may have higher clinical relevance. The risk of hospitalization may fluctuate at different seasons and due to pandemics. Finally, although SGLT2 inhibitors in RCTs had varying effects on different causes of hospitalizations,[8,9,11] we did not assess the risk of specific hospitalization aetiologies, limiting discussion on potential mechanisms. Future studies are needed to evaluate the effect of SGLT2 inhibitors on cause-specific hospitalizations in real-world settings.

In conclusion, in a real-world setting, initiation of SGLT2 inhibitors versus DPP-4 inhibitors was associated with lower risks of any or prolonged (≥3 nights) all-cause hospitalization in patients with T2D lacking evidence of CKD.

AUTHOR CONTRIBUTIONS

Design: Meir Schechter, Cheli Melzer Cohen, Ilan Yanuv, Aliza Rozenberg, Avraham Karasik, and Ofri Mosenzon. Conduct/data collection: Meir Schechter, Cheli Melzer Cohen, Gabriel Chodick, Avraham Karasik and Ofri Mosenzon. Analysis: Cheli Melzer Cohen, Ilan Yanuv, Aliza Rozenberg and Gabriel Chodick. Writing manuscript: Meir Schechter, Tamir Zelter and Ofri Mosenzon.

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this report. This report was written by the investigators and the decision to submit for publication was made solely by the investigators.

CONFLICT OF INTEREST STATEMENT

Meir Schechter reports travel support from Novo Nordisk and AstraZeneca through Hadassah Medical Center, and lecturing fees from AstraZeneca. Cheli Melzer Cohen, Tamir Zelter and Gabriel Chodick have no conflict of interest to declare. Ilan Yanuv and Aliza Rozenberg receive hourly payment from AstraZeneca through Hadassah Medical Center and from Novo Nordisk. Avraham Karasik has received research grants and speaking honoraria from AstraZeneca, Novo Nordisk and Boehringer Ingelheim. Ofri Mosenzon reports Advisory Board membership for Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and BOL Pharma, research grant support through Hadassah Hebrew University Hospital from Novo Nordisk and AstraZeneca, and Speaker's Bureau participation for AstraZeneca, Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, and Boehringer Ingelheim. From May 1st, 2023, Ofri Mosenzon has been an employee of Regeneron Pharmaceuticals Inc.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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SUPPORTING INFORMATION

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

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