FAVOURABLE KIDNEY OUTCOMES ARE ASSOCIATED WITH EMPAGLIFLOZIN VS DPP-4i THERAPY IN PATIENTS WITH DIABETES AND NORMAL KIDNEY FUNCTION – REAL-WORLD EVIDENCE

Meir Schechter[1,2] MD PhD, Cheli Melzer-Cohen[3] MSc, Aliza Rozenberg[1,2] MA, Ilan Yanuv[1,2] MSc, Gabriel Chodick[3,4] PhD MHA, Ofri Mosenzon[1,2] MD MSc, Avraham Karasik[3,5] MD

[1]Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Jerusalem, Israel; [2] Faculty of Medicine, Hebrew University of Jerusalem, Israel; [3] Maccabi Institute for Research and Innovation, Maccabi Healthcare Services, Tel Aviv, Israel; [4] School of Public Health Sackler, Faculty of Medicine, Tel Aviv University, Israel; [5] Tel Aviv University, Israel

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BACKGROUND

SGLT2i therapies were proven to improve kidney outcomes both as a primary outcome in kidney outcomes trials[1–3] and as secondary outcomes in CVOTs.[4–6]

However, patient populations in these trials, had relatively high kidney and / or CV risk compared to the 'general' T2D population.

Several studies have assessed kidney outcomes with SGLT2i therapy using RW data; however, these studies had relatively limited follow-up.[7,8]

DPP-4i are considered neutral from CV and kidney aspects.[1–5] Like SGLT2i, DPP-4i are often initiated as second- or third-line treatment in patients with T2D, providing appropriate comparators to investigate SGLT2i-associated kidney effects.

MHS is the second largest health maintenance organisation in Israel.

The database includes over 3 million people, with highly granular, all inclusive electronic medical records, and <1% yearly abandonment rate, providing an excellent source for long-term RW data.

We assessed long-term kidney outcomes among patients with T2D initiated on empagliflozin or any SGLT2i (empagliflozin and dapagliflozin) compared with those initiated on DPP-4i in the MHS (2015–2021), with specific emphasis on those with normal kidney function at baseline.

OBJECTIVES

Compare the risk for the following outcomes between those initiated on empagliflozin or dapagliflozin versus DPP-4i in patients with low KDIGO risk.

PRIMARY OUTCOMES

A composite **'kidney-specific' outcome:**
- First occurrence of confirmed-sustained ≥40% reduction from baseline estimated glomerular filtration rate (eGFR)
- New ESKD

A composite **'kidney or death' outcome:**
- All the above or death from any cause

SECONDARY OUTCOMES

Confirmed-sustained[*] declines from baseline eGFR **≥30%, ≥40%, ≥50% or ≥57%**

Change in eGFR over time = eGFR slope

METHODS

STUDY DESIGN *and* POPULATION

Non-interventional, retrospective cohort.

Adult patients with T2D initiating treatment with empagliflozin or dapagliflozin were compared with **PS-matched patients** initiating treatment with any **DPP-4i.**

Inclusion criteria

- Dispensation of at least one package of empagliflozin, dapagliflozin, or any DPP-4i during the study period
- Diagnosed with T2D before index date
- At least one eGFR measurement in the year before index date

The current analyses included only patients with low KDIGO risk defined as baseline eGFR >60 mL/min/1.73 m^2 and UACR <30 mg/g

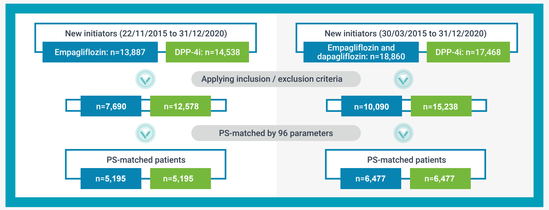
Exclusion criteria

- **Age <18 years**
- Defined as having **T1D**
- A record of **SGLT2i or DPP-4i use during the preceding 12 months**
- Patients prescribed with **both an SGLT2i and a DPP-4i** on index date
- **On dialysis treatment or after kidney transplantation**
- **<12 months of available data** before index date
- **Pregnancy** during the study

Definitions of exposure period

Exposure periods were defined based on drugs dispensations data in MHS.
- 'Intention to treat' (ITT) analysis: follow-up is censored at occurrence of an effectiveness outcome (for the specific outcome), death, or end of data availability.
- 'As-treated' (AT) analysis: follow-up is censored also at drug discontinuation, or initiation of the comparator drug.
- The AT definition is composed of a supply period and a grace period of additional 90 days after end of drug supply.

Number of participants



Follow-up duration

Empagliflozin and dapagliflozin (n=6,477) versus DPP-4i (n=6,477)

		Median FU (IQR), months	Patient year
ITT	Empagliflozin and dapagliflozin DPP-4i	39.2 (21.9–54.9) 36.0 (21.3–54.9)	20,852.3 20,660.3
AT	Empagliflozin and dapagliflozin DPP-4i	14.3 (6.0–31.1) 12.6 (5.7–26.6)	11,215.8 9959.0

Empagliflozin (n=5,195) versus DPP-4i (n=5,195)

		Median FU (IQR), months	Patient year
ITT	Empagliflozin DPP-4i	35.9 (20.6–52.4) 34.6 (21.1–51.9)	15,745.7 15,713.2
AT	Empagliflozin DPP-4i	14.3 (6.0–30.6) 12.7 (5.7–26.6)	8808.2 7817.4

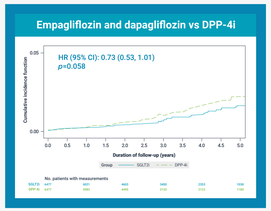
Baseline characteristics

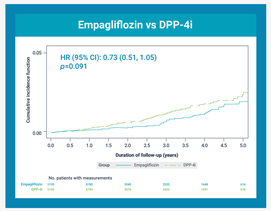
CHARACTERISTICS	LEVEL	EMPAGLIFLOZIN (n=5195)	DPP-4i (n=5195)	SMD	EMPA and DAPA (n=6477)	DPP-4i (n=6477)	SMD
Demographic characteristics							
Age, years	**Mean (SD)**	60.1 (10.4)	60.0 (11.6)	0.01	59.9 (10.4)	59.8 (11.4)	0.01
Women	**n (%)**	2100 (40.4)	2082 (40.1)	0.01	2723 (42.0)	2708 (41.8)	0.00
Medical history							
Years in diabetes registry	**Mean (SD)**	7.4 (5.7)	7.3 (5.7)	0.02	7.3 (5.7)	7.3 (5.7)	0.01
Established CVD history	**n (%)**	1099 (21.2)	1119 (21.5)	0.01	1256 (19.4)	1272 (19.6)	0.01
BMI kg/m²	**Mean (SD)**	31.6 (5.4)	31.7 (5.9)	0.03	31.6 (5.5)	31.8 (5.9)	0.03
HbA_{1c} (%)	**Mean (SD)**	7.9 (1.6)	7.9 (1.6)	0.00	7.9 (1.6)	7.9 (1.6)	0.02
Medications							
Metformin	**n (%)**	4896 (94.2)	4928 (94.9)	0.03	6118 (94.5)	6120 (94.5)	0.00
Sulfonylureas	**n (%)**	588 (11.3)	571 (11.0)	0.01	800 (12.4)	778 (12.0)	0.01
Basal insulin	**n (%)**	741 (14.3)	704 (13.6)	0.02	968 (14.9)	926 (14.3)	0.02
RAAS inhibitors	**n (%)**	2900 (55.8)	2891 (55.6)	0.00	3622 (55.9)	3564 (55.0)	0.02
Kidney markers							
eGFR (mL/min/1.73 m²), n (%)	**>90**	3217 (61.9)	3217 (61.9)	0.00	4079 (63.0)	4079 (63.0)	0.00
	60–90	1978 (38.1)	1978 (38.1)		2398 (37.0)	2398 (37.0)	
	Mean (SD)	93.0 (14.0)	93.3 (14.5)	0.02	93.3 (13.9)	93.5 (14.6)	0.02
UACR (mg/g), n (%)	**Below detectable**	2719 (52.3)	2687 (51.7)	0.00	3424 (52.9)	3395 (52.4)	0.03
	<15	1131 (21.8)	1159 (22.3)		1378 (21.3)	1405 (21.7)	
	15–<30	931 (17.9)	952 (18.3)		1140 (17.6)	1162 (17.9)	
	Missing	414 (8.0)	397 (7.6)		535 (8.3)	515 (8.0)	
	Median (IQR)	0.0 (0.0–12.3)	0.0 (0.0–12.7)	0.01	0.0 (0.0–12.1)	0.0 (0.0–12.6)	0.01
eGFR slope (mL/min/1.73 m² per year) at baseline	**Mean (SD)**	−0.7 (5.2)	−0.7 (5.4)	0.00	−0.6 (5.3)	−0.6 (5.5)	0.00

RESULTS

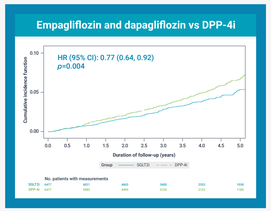
Risk for the primary outcomes in initiators of empagliflozin or dapagliflozin versus DPP-4i (ITT analysis)

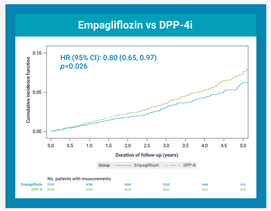
***KIDNEY-SPECIFIC* OUTCOME** ≥40% reduction in eGFR or ESKD



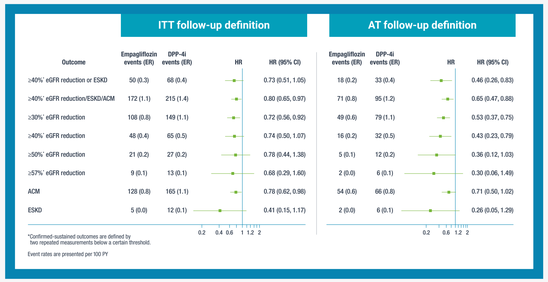


***KIDNEY OR DEATH* OUTCOME** ≥40% reduction in eGFR, ESKD or all-cause death





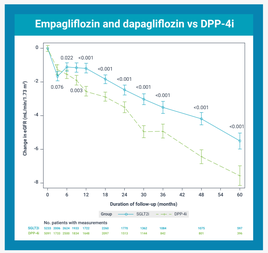
Risk for categorical eGFR declines in initiators of empagliflozin versus DPP-4i

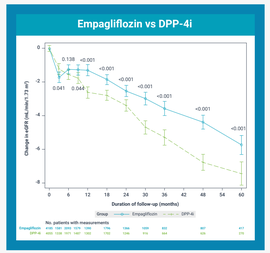


*Confirmed-sustained outcomes are defined by two repeated measurements below a certain threshold.

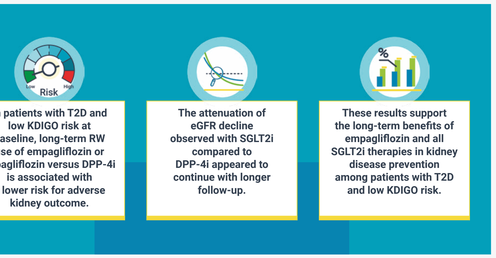
Event rates are presented per 100 PY

Change in eGFR over time in patients treated with empagliflozin only or empagliflozin and dapagliflozin versus DPP-4i (AT analysis)





Conclusion



In patients with T2D and low KDIGO risk at baseline, long-term RW use of empagliflozin or dapagliflozin versus DPP-4i is associated with a lower risk for adverse kidney outcome.

The attenuation of eGFR decline observed with SGLT2i compared to DPP-4i appeared to continue with longer follow-up.

These results support the long-term benefits of empagliflozin and all SGLT2i therapies in kidney disease prevention among patients with T2D and low KDIGO risk.

Footnotes

ACM, all-cause mortality; **AT**, as treated; **BMI**, body mass index; **CI**, confidence interval; **CV**, cardiovascular; **CVD**, cardiovascular disease; **CVOT**, cardiovascular outcome trial; **DPP-4(i)**, dipeptidyl peptidase-4 inhibitor; **eGFR**, estimated glomerular filtration rate; **EMPA**, empagliflozin; **ESKD**, end-stage kidney disease; **FU**, follow up; **HbA_{1c}**, glycated haemoglobin; **HR**, hazard ratio; **IQR**, interquartile range; **ITT**, intention-to-treat; **KDIGO**, Kidney Disease: Improving Global Outcomes; **MHS**, Maccabi Healthcare Services; **PS**, propensity score; **RAAS**, renin–angiotensin–aldosterone system; **RW**, real-world; **SD**, standard deviation; **SGLT2i**, sodium-glucose co-transporter 2 inhibitor; **SMD**, standardised mean difference; **T1D**, Type 1 diabetes; **T2D**, Type 2 diabetes; **UACR**, urine albumin:creatinine ratio.

[*]Confirmed-sustained outcomes are defined by two repeated measurements below a certain threshold.

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