Cardiovascular Diabetology

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The impact of metformin on kidney disease progression and mortality in diabetic patients using SGLT2 inhibitors: a real-world cohort study

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Abstract

Background Selecting the optimal first-line therapy for type 2 diabetes is essential for achieving glycemic control and providing cardio-renal protection, though the combined benefits of metformin with SGLT2 inhibitors, remain uncertain.

Methods This retrospective cohort study analyzed data from Clalit Health Services (2016–2021), to compare outcome in adults with type 2 diabetes treated with SGLT2 inhibitors alone versus in combination with metformin. Propensity score matching was applied to balance baseline characteristics between groups. Primary outcomes were a composite kidney outcome (40% decline in eGFR, or progression to ESRD), and all-cause mortality. Safety outcomes included hospitalizations, acute kidney injury and metabolic acidosis.

Results The study included 45,545 patients, with 6774 patients in each group following propensity score matching. The median follow-up time was 1166 days. Combination therapy with metformin and SGLT2 inhibitors was associated with significantly reduced risk of all-cause mortality (aHR 0.74, 95% CI 0.64–0.84), and composite kidney outcomes (aHR 0.65 95% CI 0.48–0.87) even after accounting for mortality as a competing risk (aHR 0.67; 95% CI 0.5–0.9). Furthermore, combination therapy was associated with reduced risks of hospitalization (aHR 0.93 95% CI 0.87–0.99), severe acute kidney injury events (aHR 0.72 95% CI 0.54–0.96) and metabolic acidosis events (aHR 0.58 95% CI 0.4–0.83), compared with SGLT2 inhibitors alone.

Conclusions Patients receiving combination therapy with metformin and SGLT2 inhibitors showed significantly reduced risks of kidney disease progression and mortality compared to those treated with SGLT2 inhibitors alone. These findings support the use of metformin with SGLT2 inhibitors as a first-line treatment strategy for type 2 diabetes irrespective of glycemic control or cardio-renal risk factors.

Keywords Metformin, SGLT2 inhibitors, Chronic kidney disease, All-cause mortality, Diabetes mellitus, Diabetic kidney disease

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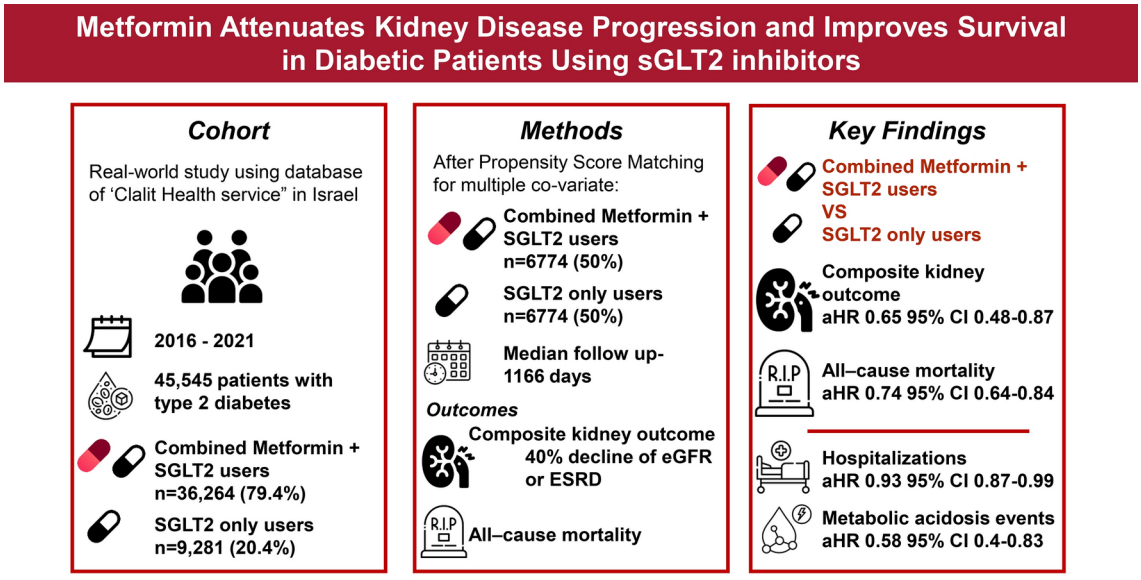
Graphical Abstract



Introduction

Cardiovascular disease (CVD) and chronic kidney disease (CKD) are the leading causes of mortality in patients with type 2 diabetes (T2D) and significantly contribute to ongoing morbidity [1, 2]. For the past two decades, the American Diabetes Association (ADA) has recommended metformin as the first-line therapy for T2D, owing to its efficacy, affordability, weight neutrality, and benefits in cardiovascular outcomes as well as its potential role in slowing kidney disease progression [3]. However, the latest 2022 consensus on Diabetes Management in Chronic Kidney Disease, joint issued by ADA and Kidney Disease: Improving Global Outcomes (KDIGO), also advocates for the inclusion of sodium-glucose -cotransporter-2 inhibitors (SGLT2i) in all diabetes patients as part of the comprehensive approach to managing glucose levels and reducing cardiovascular and renovascular risk [4]. Specifically, the use of SGLT2 inhibitors is recommended for all T2D patients with diabetic kidney disease and an estimated Glomerular Filtration Rate (eGFR) above 20 ml/min/1.73 m^2, to mitigate CKD progression and reduce cardiovascular events, regardless of baseline HbA1c, or metformin use. These recommendations are particularly crucial for patients with multiple atherosclerotic cardiovascular disease (ASCVD) risk factors, established ASCVD, or diabetic kidney disease [5].

Substantial evidence indicates that inadequate glycemic control within the initial years following T2D diagnosis is strongly correlated with a higher risk of future microvascular and macrovascular complications, as well as increased mortality. This "glycemic legacy" effect, consistently observed in both randomized controlled trials and real-world observational studies, underscores the critical importance of selecting first-line medications or combination therapies for T2D that not only optimize glycemic control but also provide significant cardiovascular and renal protective benefits [6].

In recent years, accumulating data has reinforced the benefits of metformin in improving cardiovascular and renal outcomes, even in patients with progressive CKD and eGFR levels below 60 ml/min/1.73 m^2 [2, 7–9]. Nevertheless the 2022 joint ADA and KDIGO guidelines, while recognizing metformin's superior efficacy in glycemia control, highlight a reduced efficacy in cardiovascular and renal protection when compared with SGLT2 inhibitors [5]. Whether metformin offers additional renal protection and survival benefits when combined with SGLT2 inhibitors remains uncertain.

Therefore, this study aims to evaluate the real-world impact of a combined metformin and SGLT2 inhibitors regimen, compared to treatment with SGLT2 inhibitors alone, on renal progression outcomes and all-cause mortality in T2D patients.

Research design and methods

Study participants and design

We conducted a retrospective observational cohort study involving patients with T2D, utilizing data from the repositories of Clalit Health Services (CHS), the largest healthcare provider in Israel, serving approximately 4.7 million individuals. A detailed description of the datasets used in this study is available in previous publication [10].

Patients were categorized based on their treatment regimen at the time of their first SGLT2 inhibitors prescription (study inclusion time) into two groups: those receiving SGLT2 inhibitors monotherapy or SGLT2 inhibitors in combination with other anti-diabetic medications excluding metformin, and those receiving SGLT2 inhibitors in combination with metformin, with or without additional anti-diabetic medications. Eligible participants included adults (age ≥ 18 years) diagnosed with T2D who were treated with SGLT2 inhibitors with or without metformin between 2016 and 2021. Exclusion criteria included individuals who lacked essential data required for propensity scoring matching (PSM) at time of the study enrolment, those with a history of organ transplantation, and patients with advanced CKD at baseline, defined as an eGFR < 15 ml/min/1.73m^2 or undergoing dialysis.

Given the retrospective study design, the inherent unreliability of some reports and our aim to provide real-world data, we employed an 'intension to treat' approach, defining treatment composition at a specific time point. Since current guidelines recommend a sequential medication strategy with SGLT2 inhibitors added to metformin, we assumed that during the study period—when SGLT2 inhibitors were relatively new, patients were primarily treated with either combination therapy or SGLT2 inhibitors monotherapy, without a subsequent, late addition of older medications such as metformin.

De-identified patient data were extracted from electronic medical records, encompassing demographic information, clinical data, laboratory results, and prescriptions records. Notably, patients prescribed dipeptidyl peptidase 4 (DPP-4) inhibitors were excluded from this study, as the same database was being utilized for a concurrent study involving these patients.

Patients treated with a combination of metformin and SGLT2 inhibitors were matched, in a 1:1 ratio with controls receiving SGLT2 inhibitors alone, using PSM. The matching process accounted for variables associated with mortality risk and the risk of kidney disease progression. These variables included age, sex, socioeconomic scale based on place of residence [11], eGFR as calculated using CKD- EPI 2021 equation, urine albumin/creatinine ratio (uACR) categorized as no proteinuria (< 30 mg/gr), 30–300 mg/gr, or > 300 mg/gr, baseline hemoglobin (Hb), hemoglobin A1c (HbA1c) grouped in 1% increments (including a category for missing data in cases where baseline HbA1c was unavailable), smoking status, comorbidities, blood pressure, and medications for diabetes and CKD. The propensity score was derived from logistic regression analysis with metformin use as the dependent variable. Patients were matched according to the propensity score with a caliper of 0.05.

Outcomes

The primary endpoints of the study were a composite kidney outcome and all-cause mortality. The composite kidney outcome was defined as a 40% decline in eGFR from baseline value, or progression to end-stage renal disease (ESRD), which was defined as an eGFR less than 15 mL/min/1.73m^2 or the need for renal replacement therapy.

Secondary endpoints included the combined outcome of the kidney composite and all-cause mortality. Safety outcomes were also assessed, and included hospitalizations within one-year, events of all-cause metabolic acidosis, ketoacidosis, non-ketotic metabolic acidosis, urinary tract infections (UTIs) and acute kidney injury (AKI) events, AKI events were defined based on the severity of serum creatinine level increase between two laboratory measurements, taken within a one-year interval. Specifically, AKI was defined as a serum creatinine increase exceeding 50%, while severe AKI was defined as an increase exceeding 100%. Additionally, anemia events were evaluated as a falsification outcome, with anemia defined as a hemoglobin level below 12 g/dl in women and 13 g/dl in men for more than three months.

Outcomes were assessed over a five-year period starting from the date of the first SGLT2 inhibitors prescription, except for hospitalizations, which were evaluated over a one-year period.

Statistical analysis

Between-group comparisons of normally distributed continuous variables were performed using a T-test, while non-normally distributed variables were analyzed using the Mann–Whitney U-test. Discrete variables were compared using the χ^2 test. To compare eGFR slopes between groups, a multivariate mixed linear model with random slope and intercept was employed. This model was stratified by baseline eGFR and proteinuria, and incorporated the same variables used in the survival model, as detailed below.

A propensity score was calculated using logistic regression to predict baseline metformin use. The variables included in the propensity score were age, sex, socioeconomic scale (SES), BMI, initial eGFR, albumin-to-creatinine ratio, initial HbA1c level, baseline hemoglobin, co-morbidities (e.g., dyslipidemia, ischemic heart disease [IHD], hypertension), and the use of other antidiabetic medications as well as ACE inhibitors (ACEI) or angiotensin receptor blockers (ARBs). Matching was performed using a caliper distance of 0.05, chosen after testing various caliper distances (ranging from 0.08 to 0.02) for optimal sample size and similarity between matched groups. The same propensity score was utilized to conduct inverse probability-weighted (IPW) analyses using the crude cohort.

Kaplan–Meier survival curves were generated to illustrate difference between the groups, with log-rank tests used for between-group comparisons. Crude and adjusted hazard ratios (HRs) for the matched pairs were estimated using Cox proportional hazards or competing risk models, as detailed below. To mitigate indication bias, all analyses were stratified by CKD stage and proteinuria. The proportional hazards assumption was assessed using Schoenfeld residuals. To further minimize confounding, multivariate analyses were conducted, adjusting for all variables considered to potentially influence both exposure and outcome events. A comprehensive list of variables included in the model is provided in Supplementary Table S1. Interactions between subgroups and metformin use were evaluated using Cox regression models, incorporating metformin use, subgroup variables, and interaction terms to determine the significance of subgroup effects. To further validate the matching within each subgroup stratum, an additional inverse probability weighting (IPW) analysis was performed within each subgroup.

Sensitivity analyses were conducted to address potential residual confounding. These analyses were restricted to patients with complete datasets used in the propensity score calculation, including baseline HbA1c values. Additionally, sensitivity analyses were conducted for matched patients with BMI differences of less than 7 kg/m^2 and on patients receiving only SGLT2 inhibitors and metformin, without other glucose-lowering treatments.

Competing-risk models using the Fine and Gray method were applied to account for the risk of death prior to the occurrence of the composite kidney outcome. These models estimated cause-specific sub-hazard ratios (sub-HRs), including death as a competing risk and were adjusted for the same covariates as the primary Cox analyses.

Ethics

The study protocol received approval from the Rabin Medical Center (RMC) Institutional Review Board and was conducted according to the Declaration of Helsinki (approval number RMC-0133-22). Patient consent exemptions were granted owing to the observational and non-interventional design of the study. Reporting adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [18].

Results

Baseline characteristics

During the follow-up period from January 1st, 2016, to December 31st, 2021, a total of 45,545 were included in the study. Among them, 36,264 (79.4%) received a combined therapy with SGLT2 inhibitors and metformin (combination group), while 9,281 patients (20.4%) were treated with SGLT2 inhibitors alone (non-metformin group) at the time of study inclusion. Before matching, the two unmatched groups had substantially different characteristics. Compared with the non-metformin group, patients who managed with a combination of SGLT2 inhibitors plus metformin were younger, had a higher baseline eGFR, and were less likely to have a diagnosis of progressive CKD with eGFR < 60 ml/min/ 1.73 m^2. Additionally, they had a higher mean BMI and elevated mean HbA1c levels. This group was also more frequently treated with GLP-1 receptor agonists, MRA and furosemide (Table 1).

After PSM for multiple variables, baseline differences between groups were eliminated, except for BMI, which retained a standardized mean difference (SMD) of 0.15 (Table 1 and Supplementary Fig. S1). The number of patients was reduced to 6774 patients in each group. The median follow-up period was 1216 days in the crude cohort, and 1166 in the matched cohort. Figure 1 summarizes patient breakdown.

Correlation between metformin use and incidence of kidney disease progression and all-cause mortality before PSM

During the follow-up period, 494 patients (1.08%) experienced a composite kidney outcome, and 2644 patients (5.8%) died in the crude cohort.

Multivariate Cox analyses, stratified by CKD stage and proteinuria, revealed a significantly lower all-cause mortality rate in the combination treatment group compared to the non-metformin group ([HR]: 0.73; 95% confidence interval [CI]: 0.67–0.8; $P < 0.001$). Similarly, the incidence of the composite kidney outcome was significantly lower in patients receiving the combination therapy than in those not treated with metformin (HR 0.79; 95% CI 0.64–0.97; $P = 0.025$). However, the association was no longer statistically significant when mortality was included as a competing risk (HR 0.83; 95% CI 0.67–1.03; $P = 0.094$). The risk of the combined outcome encompassing both the composite kidney event and all-cause mortality, remained significantly reduced in the group receiving the combination therapy that included metformin (HR 0.73; 95% CI 0.67–0.8; $P < 0.001$). Sensitivity analysis using inverse probability weighting in the crude cohort demonstrated results consistent with the primary analysis (Supplementary Table S2).

Correlation between metformin use and Incidence of kidney disease progression and all-cause mortality after PSM

Patients receiving combination therapy with metformin and SGLT2 inhibitors demonstrated a significantly lower risk of all-cause mortality compared to non-metformin users (aHR 0.74 95% CI 0.64–0.84; $P < 0.001$). Similarly,

Table 1 Demographics before and after PSM

	Before matching				After matching			
	All	**Combination therapy of SGLT2i + metformin**	**Metformin non-users**	**SMD**	**All**	**Combination therapy of SGLT2i + metformin**	**Metformin non-users**	**SMD**
N	45,545	36,264	9281		13,548	6774	6774	
Demographics								
Age	65.6 ± 10.82	65.02 ± 10.68	67.87 ± 11.03	0.26	66.72 ± 10.68	66.51 ± 10.46	66.94 ± 10.90	0.04
Male sex	27,622 (60.6%)	21,639 (59.7%)	5983 (64.5%)	0.10	8468 (62.5%)	4182 (61.7%)	4286 (63.2%)	0.03
SES	3.18 ± 1.13	3.15 ± 1.13	3.29 ± 1.11	0.12	3.27 ± 1.1	3.24 ± 1.11	3.3 ± 1.09	0.05
Physical exam								
Systolic BP	130.76 ± 14.87	131 ± 14.63	129.81 ± 15.73	0.08	130.59 ± 15.05	130.93 ± 14.72	130.25 ± 15.36	0.05
Diastolic BP	74.51 ± 9.84	74.86 ± 9.75	73.15 ± 10.07	0.17	74.04 ± 9.83	74.29 ± 9.71	73.79 ± 9.94	0.05
BMI	30.48 ± 5.48	30.81 ± 5.51	29.21 ± 5.15	0.30	29.5 ± 4.95	29.87 ± 4.99	29.13 ± 4.87	0.15
Kidney function								
Mean eGFR	88.26 ± 20.55	90.07 ± 19.41	81.2 ± 23.18	0.41	85.9 ± 19.32	85.45 ± 19.72	86.36 ± 18.91	0.05
eGFR < 60 ml/min/1.73 m^2 (%)	4952 (10.9%)	3029 (8.4%)	1923 (20.7%)	0.36	1583 (11.7%)	873 (12.9%)	710 (10.5%)	0.07
Albuminuria < 300 mg/dL	14,614 (32.1%)	11,712 (32.3%)	2902 (31.3%)	0.02	4216 (31.1%)	2138 (31.6%)	2078 (30.7%)	0.02
Albuminuria > 300 mg/dL	4937 (10.8%)	3801 (10.5%)	1136 (12.2%)	0.06	1387 (10.2%)	766 (11.3%)	621 (9.2%)	0.07
Laboratory exams								
Baseline Hb	13.8 ± 1.65	13.81 ± 1.64	13.75 ± 1.69	0.04	13.83 ± 1.65	13.81 ± 1.68	13.85 ± 1.63	0.03
HbA1c	8.17 ± 1.54	8.23 ± 1.54	7.91 ± 1.48	0.21	8.01 ± 1.49	8.04 ± 1.52	7.98 ± 1.47	0.04
Medical history								
IHD	12,830 (28.2%)	9823 (27.1%)	3007 (32.4%)	0.12	4125 (30.4%)	2005 (29.6%)	2120 (31.3%)	0.04
PVD	2800 (6.1%)	2093 (5.8%)	707 (7.6%)	0.07	853 (6.3%)	426 (6.3%)	427 (6.3%)	0.00
CVA	2527 (5.5%)	1930 (5.3%)	597 (6.4%)	0.05	768 (5.7%)	391 (5.8%)	377 (5.6%)	0.01
Heart failure	1259 (2.8%)	856 (2.4%)	403 (4.3%)	0.11	421 (3.1%)	192 (2.8%)	229 (3.4%)	0.03
Atrial fibrillation	4853 (10.7%)	3410 (9.4%)	1443 (15.5%)	0.19	1581 (11.7%)	766 (11.3%)	815 (12%)	0.02
Dyslipidemia	40,838 (89.7%)	32,407 (89.4%)	8431 (90.8%)	0.05	12,208 (90.1%)	6056 (89.4%)	6152 (90.8%)	0.05
Hypertension	34,629 (76%)	27,436 (75.7%)	7193 (77.5%)	0.04	10,254 (75.7%)	5148 (76%)	5106 (75.4%)	0.01
Former smokers	13,019 (28.6%)	10,245 (28.3%)	2774 (29.9%)	0.04	3911 (28.9%)	1947 (28.7%)	1964 (29%)	0.01
Current smokers	6929 (15.2%)	5614 (15.5%)	1315 (14.2%)	0.04	2042 (15.1%)	1024 (15.1%)	1018 (15%)	0.00
COPD	6131 (13.5%)	4798 (13.2%)	1333 (14.4%)	0.03	1808 (13.3%)	929 (13.7%)	879 (13%)	0.02
Pulmonary HTN	1403 (3.1%)	949 (2.6%)	454 (4.9%)	0.12	464 (3.4%)	225 (3.3%)	239 (3.5%)	0.01
Gout	3309 (7.3%)	2494 (6.9%)	815 (8.8%)	0.07	974 (7.2%)	508 (7.5%)	466 (6.9%)	0.02
Hypothyroidism	5557 (12.2%)	4344 (12%)	1213 (13.1%)	0.03	1670 (12.3%)	855 (12.6%)	815 (12%)	0.02
Medications								
Insulin	12,418 (27.3%)	10,179 (28.1%)	2239 (24.1%)	0.09	3045 (22.5%)	1564 (23.1%)	1481 (21.9%)	0.03
GLP1 agonists	6909 (15.2%)	6294 (17.4%)	615 (6.6%)	0.33	635 (4.7%)	318 (4.7%)	317 (4.7%)	0.00
Sulfonylurea	5894 (12.9%)	4628 (12.8%)	1266 (13.6%)	0.03	1291 (9.5%)	585 (8.6%)	706 (10.4%)	0.06
Repaglinide	4182 (9.2%)	3124 (8.6%)	1058 (11.4%)	0.09	1385 (10.2%)	696 (10.3%)	689 (10.2%)	0.00
ACE inhibitors	16,250 (35.7%)	13,092 (36.1%)	3158 (34%)	0.04	4689 (34.6%)	2313 (34.1%)	2376 (35.1%)	0.02
ARBs	13,405 (29.4%)	10,656 (29.4%)	2749 (29.6%)	0.01	3983 (29.4%)	2058 (30.4%)	1925 (28.4%)	0.04
MRAs	2867 (6.3%)	1889 (5.2%)	978 (10.5%)	0.20	978 (7.2%)	427 (6.3%)	551 (8.1%)	0.07

Table 1 (continued)

	Before matching				After matching			
	All	Combination therapy of SGLT2i + metformin	Metformin non-users	SMD	All	Combination therapy of SGLT2i + metformin	Metformin non-users	SMD
Fusid	4243 (9.3%)	2820 (7.8%)	1423 (15.3%)	0.24	1309 (9.7%)	647 (9.6%)	662 (9.8%)	0.01
Thiazide	8171 (17.9%)	6691 (18.5%)	1480 (15.9%)	0.07	2277 (16.8%)	1188 (17.5%)	1089 (16.1%)	0.04
CCBs	13,005 (28.6%)	10,350 (28.5%)	2655 (28.6%)	0.00	3848 (28.4%)	1981 (29.2%)	1867 (27.6%)	0.04
Beta blockers	19,885 (43.7%)	15,331 (42.3%)	4554 (49.1%)	0.14	6137 (45.3%)	3039 (44.9%)	3098 (45.7%)	0.02
Alpha blockers	1921 (4.2%)	1474 (4.1%)	447 (4.8%)	0.04	529 (3.9%)	288 (4.3%)	241 (3.6%)	0.04

Data are mean (SD) or n (%). SMD, standardized mean difference; SES, socioeconomic status; eGFR, estimated glomerular filtration rate; BP, blood pressure; BMI, body mass index; IHD, ischemic heart disease; CVA, cerebrovascular disease; PVD, peripheral vascular disease; HTN, hypertension; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; CCB, calcium channel blocker

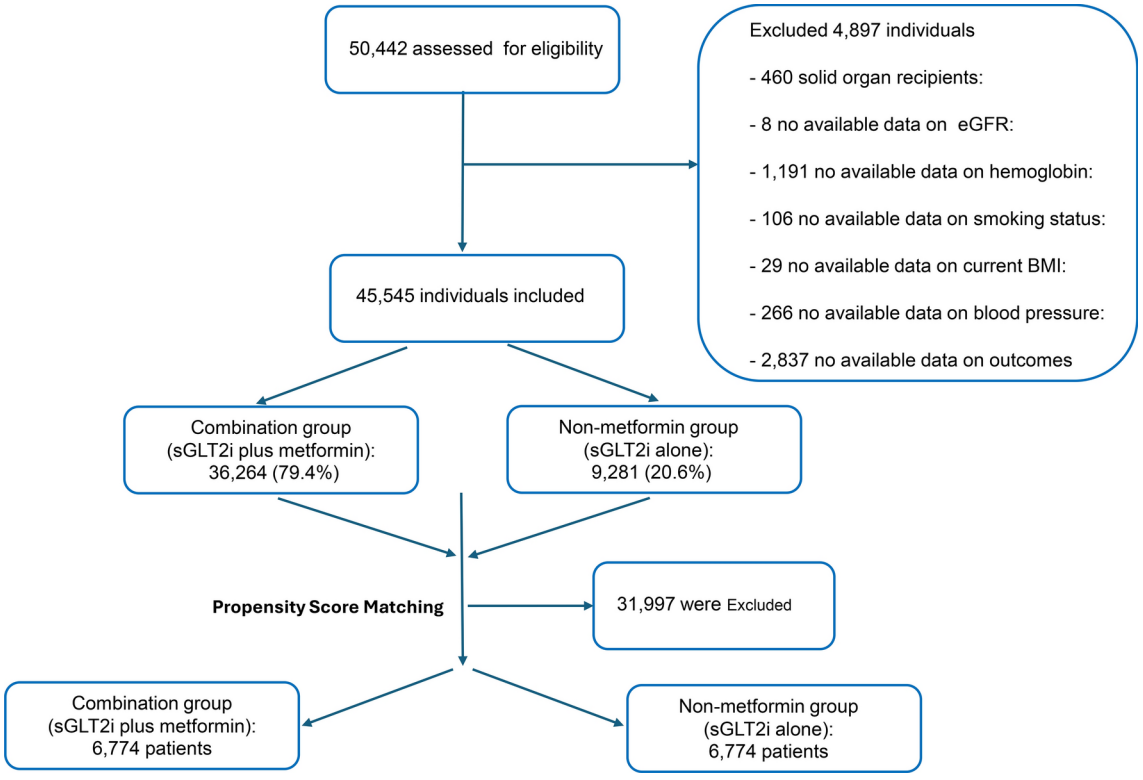


Fig. 1 Flow chart of study

the incidence of the composite kidney outcome was significantly lower in the combination therapy group (aHR 0.65 95% CI 0.48–0.87; $P = 0.004$). This risk reduction of composite kidney outcome remained significant even after accounting for mortality as a competing risk (and aHR 0.67; 95% CI 0.5–0.9; $P = 0.007$). Moreover, the combined outcome of composite kidney and all-cause mortality, was significantly reduced in the patients receiving metformin-inclusive combination therapy (aHR 0.71; 95% CI 0.63–0.81; $P < 0.001$) (Fig. 2A and Supplementary Table S3).

Kaplan Meier analysis revealed a significantly reduced risk of all-cause mortality, while the reduction in composite kidney outcome showed only a trend and did not reach statistical significance ($P = 0.00095$, $P = 0.065$, respectively). Additionally, Kaplan Meier analysis revealed a significant risk reduction for the combined outcome of composite kidney and mortality ($P = 0.00016$). (Supplementary Fig. S2).

An assessment of eGFR decline over the study period demonstrated that combination therapy with metformin and SGLT2 inhibitors was associated with a significantly slower decline in eGFR, with a reduction of 0.21 (95% CI

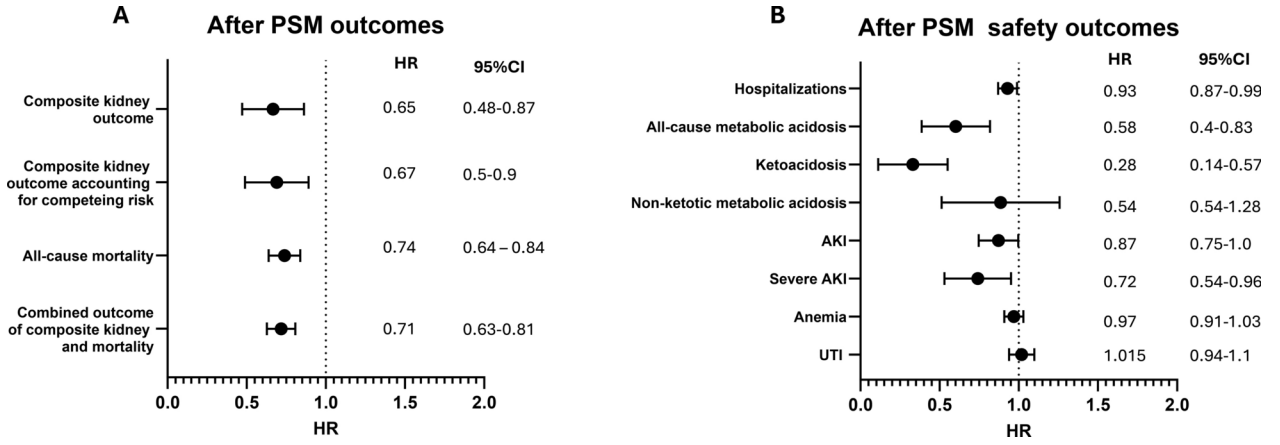


Fig. 2 Correlation between metformin use and Incidence of **A** CKD progression and all-cause mortality and **B** safety outcomes after PSM. The composite kidney outcome was defined as a 40% decline in eGFR from baseline value, or progression to ESRD, which was defined as an eGFR < 15 mL/min/1.73m^2 or the need for RRT; Competing-risk model were used to account for the risk of death prior to occurrence of the composite kidney outcome; The X axis in linear scale; HR, hazard ratio; CI, confidence interval

0.13–0.29) ml/min/1.73 m^2 per year compared to SGLT2 inhibitors monotherapy (Supplementary Fig. S3).

Sensitivity analyses for matched cohort

A sensitivity analysis limited to patients from the matched cohort with complete datasets included a total of 12,249 patients. This analysis confirmed that patients receiving combination therapy with metformin and SGLT2 inhibitors had a significantly lower risk of all-cause mortality compared to non-metformin users (aHR 0.74 95% CI 0.64–0.85; $P < 0.001$). Similarly, the incidence of the composite kidney outcome remained significantly lower in the combination therapy group, (aHR 0.71 95% CI 0.52–0.96; $P = 0.028$). However, after accounting for mortality as a competing risk, only a strong trend toward risk reduction was observed, which did not reach statistical significance (aHR 0.74 95% CI 0.55–1; P –0.053) (Supplementary Table S3).

A separate sensitivity analysis excluding patients from the matched cohort with a substantial BMI difference (> 7 kg/mr^2) included 9742 patients. This analysis corroborated the lower risk of all-cause mortality associated with the combination therapy compared to non-metformin users (aHR 0.8, 95% CI 0.68–0.94; $P = 0.007$). Furthermore, the incidence of the composite kidney outcome remained significantly lower in the combination therapy group, even after accounting for mortality as a competing risk (aHR 0.58 95% CI 0.49–0.69; $P < 0.001$) (Supplementary Table S3).

An additional sensitivity analysis included only patients receiving either metformin and SGLT2 inhibitors combination therapy or SGLT2 inhibitors monotherapy, without any other anti-glycemic treatment. This analysis confirmed the significant benefits of combination therapy in reducing all-cause mortality (aHR 0.69 95% CI 0.56–0.86; $P < 0.001$). While a strong trend toward a reduced risk of the composite kidney outcome was observed after accounting for competing risk, statistical significance was not achieved (aHR 0.625 95% CI 0.39–1; $P = 0.051$) (Supplementary Table S3).

Association between metformin use and safety outcomes risk

In the matched cohort, 3492 (25.8%) patients were hospitalized for any reason within one year, and 528 (4%) hospitalized due to metabolic acidosis events within five years, including 125 cases of ketoacidosis (0.9%). Overall, there were 788 AKI events (5.8%), including 197 severe AKI events (1.46%), along with 4066 UTI events (30.1%) and 2446 anemia events (18.3%).

The risk of hospitalization was significantly lower in patients treated with combination of metformin and SGLT2 inhibitors compared to non-metformin users (aHR 0.93 95% CI 0.87–0.99; $P = 0.032$). Furthermore, combination therapy was associated with a significant reduction in the risk of all-cause metabolic acidosis and ketoacidosis events, while no difference was observed in the risk of non-ketotic metabolic acidosis events compared to non-metformin users (aHR 0.58 95% CI 0.4–0.83; $P = 0.003$, aHR 0.28 95% CI 0.14–0.57; $P < 0.001$, aHR 0.83 95% CI 0.54–1.28; $P = 0.404$, respectively) (Fig. 2B and Supplementary Table S3).

Similarly, Kaplan Meier analysis revealed a significant risk reduction in incidence of all-cause metabolic acidosis ($P = 0.0049$, respectively. (Supplementary Fig. S2).

A trend toward a reduced risk of AKI was observed in the combination therapy group, though it did not reach statistical significance. However, the reduction in severe AKI events was significant (aHR 0.87 95% CI

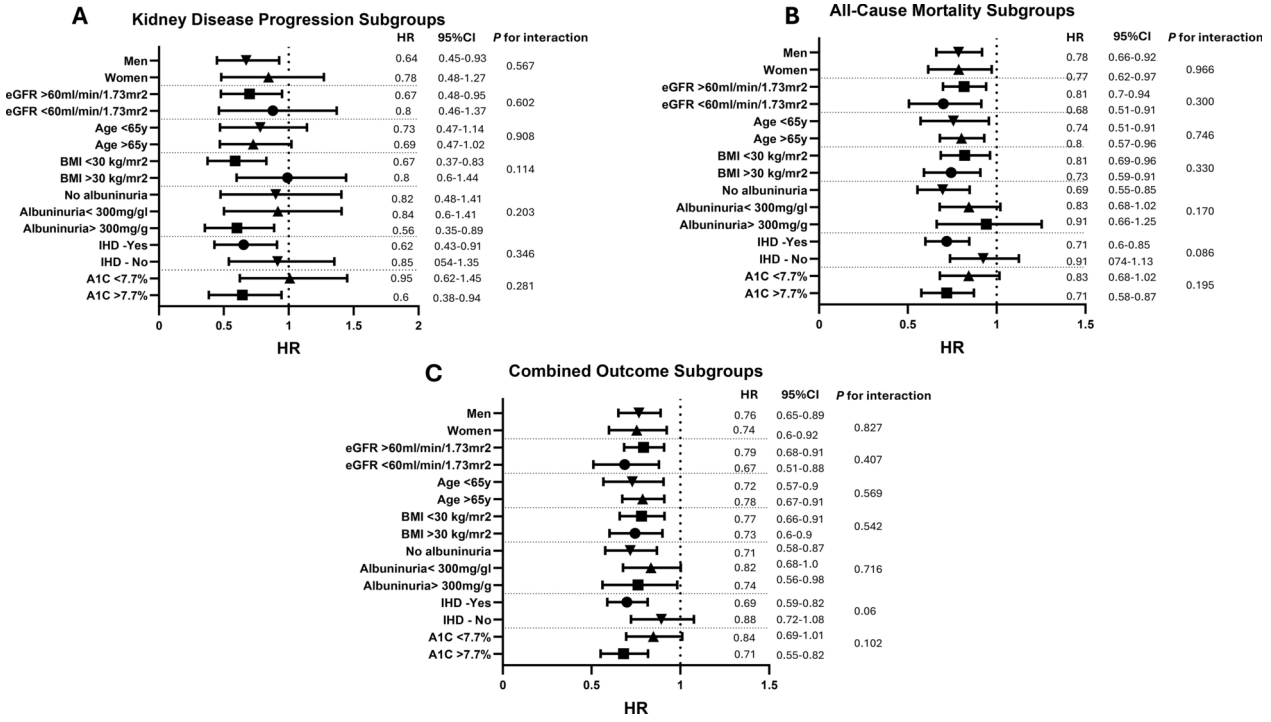


Fig. 3 Subgroup analysis of the correlation between metformin use and Incidence of **A** CKD progression, **B** all-cause mortality and **C** combined outcome of CKD progression and mortality. HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; BMI, body mass index; IHD, ischemic heart disease; The X axis in logarithmic scale

0.75–1; $P = 0.05$, aHR 0.72 95% CI 0.54–0.96; $P - 0.027$, respectively).

No significant difference was observed in the risk of UTI or anemia events in the combination therapy group compared to non-metformin users (aHR 1.015 95% CI 0.94–1.1; $P = 0.72$, aHR 0.97 95% CI 0.91–1.03; $P - 0.308$, respectively) (Fig. 2B and Supplementary Table S3). (S3D)

Subgroup analysis of the correlation between metformin use and Incidence of kidney disease progression and all-cause mortality

The observed reduction in all-cause mortality, kidney progression and the composite outcome, was consistent across all examined patient subgroups, including those stratified by age, sex, CKD stage, albuminuria, BMI, pre-existing IHD and glycemic control (Fig. 3).

Discussion

This study found that combination therapy with metformin and SGLT2 inhibitors in patients with T2D was associated with significantly improved survival rates and kidney disease outcomes, compared to treatment with SGLT2 inhibitors alone. We investigated the associations between metformin use and both kidney disease progression and mortality within a large cohort of 45,545 T2D patients over an extended follow-up period. After comprehensive propensity-score matching that included multiple covariates, we retained two well-matched groups of 6774 patients each. Compared to the regimen excluding metformin, the combined therapy of SGLT2 inhibitors plus metformin was associated with a significantly reduced risk of composite kidney disease outcome as well as all-cause mortality. The renal and survival benefits of metformin use remained robust after adjusting for established clinical and demographic risk factors. Furthermore, the therapy was associated with lower rates of adverse events, including hospitalizations, severe AKI episodes, and metabolic acidosis.

CKD is highly prevalent among patients with T2D, affecting up to 61% of U.S. diabetic patients aged 65 years and older [12]. Since its approval by the United States Food and Drug Administration (UAS-FDA) in 1994, metformin has been the recommended first-line therapy for T2D [13]. Metformin is a biguanide diabetic drug that reduce hepatic glucose production and intestinal glucose absorption while enhancing insulin sensitivity, making it a preferred treatment for T2D owing to its efficacy, affordability, and favorable safety profile [14]. Research indicates that beyond glycemic control, metformin is associated with improved cardiovascular, and survival outcomes in patients with T2D [2, 7, 15–18]. The FDA initially recommended against the use of metformin in patients with serum creatinine levels above 1.5 mg/dL due to concerns regarding drug accumulation and potential risk of lactic acidosis [1]. Nevertheless, recent data suggests a low risk of lactic acidosis in patients

with moderate CKD (eGFR 30–60 ml/min per 1.73 m^2) and indicates potential reno-protective benefits of metformin, leading to more flexible guideline recommendations. The 2022 consensus on Diabetes Management in Chronic Kidney Disease, from the ADA and KDIGO recommends metformin for all T2D patients with an eGFR above 30 ml/min per 1.73 m^2, with a dose adjustments suggested for eGFR below 45 ml/min per 1.73 m^2 [3, 5, 9].

Beyond its anti-glycemic effects and role in achieving tight glucose control in the early stages following diabetes diagnosis, experimental studies indicate that metformin may exert antifibrotic effects, offering potential benefits for kidney and cardiovascular health independently of its direct glycemic impact [19]. CKD is now assumed to be a process involving glomerulosclerosis and tubulointerstitial fibrosis, driven by the epithelial-to-mesenchymal transition, regardless of the underlying cause [20]. Metformin may mitigate this process by activating AMP-activated protein kinase (AMPK) and downregulating transforming growth factor beta 1 (TGF-β1), as well as by AMP-independent mechanisms including the suppression of pro-inflammatory cytokines, reduction of oxidative stress, and inhibition of apoptosis [21–24]. Various animal models have highlighted metformin's potential in improving both diabetic and non-diabetic CKD through these pleotropic mechanisms [25–30].

While metformin has been associated with cardioprotective and nephroprotective effects, recent large-scale, high quality randomized controlled trials (RCTs) have highlighted the superior cardiovascular and renal benefits of SGLT2 inhibitors compared with all other treatments for T2D [31–35]. Collectively, these landmark trials have influenced recent guidelines updates, repositioning SGLT2 inhibitors as a recommended second-line therapy after metformin or as first-line option in patients with ASCVD, CKD, heart failure or high/very high cardiovascular risk [5]. Given that significant proportion of patients with newly diagnosed T2D are likely to develop ASCVD and renal complications in the future, there is pressing question whether a combined first-line therapy of metformin and SGLT2i might be beneficial to maximize the therapeutic advantages of both medications.

In the current study, we demonstrated that patients treated with a combination of metformin and SGLT2 inhibitors have significantly lower risk of mortality and kidney disease progression compared to those treated with SGLT2 inhibitors alone. Notably, we defined kidney disease progression based on stringent criteria including a decline in eGFR by at least 40% or the development of ESRD. Even after a thorough PSM with adjustment for multiple covariates and validation through several sensitivity analyses, the addition of metformin to SGLT2 inhibitors therapy was associated with a nearly 33% reduction in the risk of kidney disease progression and almost 30% reduction in all-cause mortality. This risk reduction remained consistent across all patient subgroups, regardless of age, sex, CKD stage, glycemic control or other risk factors and comorbidities.

Several experimental studies have suggested potential anti-senescence benefits of metformin and SGLT-2 beyond their glycemic effects, contributing to their cardioprotective and reno-protective actions [19]. Corremans et al. demonstrated that both metformin and SGLT2 inhibitors (canagliflozin), provided similar renal protection in a rat model of diabetic kidney disease (DKD). Notably, canagliflozin's renoprotection correlated with reduced hyperglycemia, whereas metformin benefits even without strict glycemic control [26]. Intriguingly, in a non-diabetic CKD model only metformin, but not canagliflozin, successfully halted kidney function decline and further CKD progression [27].

Additional preclinical studies suggest the benefits of combination therapy of metformin and SGLT2 inhibitors over monotherapy. Harada et al. demonstrated in a leptin receptor-deficient (db/db) mice model that SGLT2 inhibitors prompts a significant metabolic shift, enhancing fatty acid oxidation and increasing levels of 3-hydroxybutyric acid (3HBA) which may suppress GSK3 activity and improve diabetic kidney outcomes. However, this metabolic activation could also result in excessive protein catabolism and muscle loss, especially in non-obese individuals. The combination of SGLT2 inhibitors with metformin mitigates these effects and raises antioxidant pipecolate levels, offering anti-inflammatory benefits and enhancing cell survival through mTOR1 modulation [36]. Additional studies in DKD rat model also support the potential benefit of low-dose combination therapy with SGLT2 inhibitors and metformin, particularly in managing renal dysfunction and improving energy homeostasis by modulating the key pathways such as AMPK, mTOR, and SIRT1. This synergistic approach not only attenuates renal dysfunction but also reduces oxidative stress and activates renal autophagy, emphasizing its broader therapeutic benefits [37, 38].

Despite nearly 10% of our large cohort comprised patients with eGFR below 60 ml/min/1.73 m^2, the addition of metformin did not increase hospitalization rate. Additionally, contrary to concerns regarding a heightened risk of metabolic acidosis in CKD patients, combination therapy with SGLT2 inhibitors and metformin was associated with a significantly lower risk of both all-cause metabolic acidosis and ketoacidosis events. No significant difference was observed in the risk of non-ketotic metabolic acidosis compared to the regimen without metformin.

Indeed, although initial concerns were raised regarding potential exacerbation of metabolic acidosis with the combination of metformin and SGLT2 inhibitors due to

the distinct mechanisms of lactic acidosis (metformin) and ketoacidosis (SGLT2 inhibitors), emerging evidence suggests that this combination may mitigate these risks. SGLT2 inhibitors promote euglycemic diabetic ketoacidosis (EDKA) by increasing glucosuria, stimulating glucagon, and shifting metabolism from glucose to lipid and protein utilization, mimicking starvation state [4]. Conversely, metformin enhances insulin sensitivity and suppresses glucagon activity, potentially mitigating SGLT2 inhibitors-induced ketosis [39]. Harada et al. furthermore demonstrated that combination therapy with SGLT2 inhibitors and metformin counterbalance the risks of SGLT2 inhibitors-induced EDKA as well as metformin associated lactic acidosis. Their study revealed that combination therapy attenuates SGLT2 inhibitors-induced metabolic shifts, including ketogenesis and protein catabolism, particularly in renal tissue. Plasma lactate levels were also significantly lower with combination therapy compared to metformin monotherapy, accompanied by reductions in glucose and pyruvate levels, lactate precursors, further supporting a decreased risk of lactic acidosis [36]. Additionally, since lactic acidosis is dose-dependent, combination therapy allows for lower doses of both drugs, improving glycemic control while reducing the risk of adverse effects [37, 40]. Likewise, combination therapy enables the use of reduced doses of metformin to achieve effective glucose control, potentially lowering the incidence of other dose-dependent adverse effects, such as gastrointestinal disturbance [41].

Consistent with this, we observed a trend toward a lower risk of AKI in the combination therapy group although this reduction did not reach statistical significance, whereas the reduction in severe AKI events was significant. Furthermore, no significant difference was observed in the risk of other falsification outcomes, such UTIs or anemia, between the combination therapy group and non-metformin users. Collectively, these findings suggest that dual therapy not only optimizes glycemic control and clinical outcomes but may also provide synergistic benefits in reducing the risk of adverse complications.

A limited number of studies have focused on the benefits of first-line combination therapy in newly diagnosed patients with T2D compared to the traditional sequential additive treatment strategy [4, 42]. Real-world evidence underscores that delay in treatment intensification following monotherapy failure leads to prolonged periods of glycemic variability, which can impede optimal disease management [4, 43]. Early initiation of a combination therapy with DPP4 inhibitors plus metformin has demonstrated greater and more durable long-term benefits compared to the current standard-of-care approach of initial monotherapy in patients with newly diagnosed T2D [44]. Furthermore, a real-world cohort study by Anson et al., with a three year follow-up period, showed that Initiating combination therapy with metformin and SGLT2 inhibitors in newly diagnosed patients, without prior ASCVD, significantly improved cardiometabolic, renal and survival outcomes, compared to standard metformin monotherapy [45]. The authors suggested that the potent anti-glycemic effects of this combination therapy may mitigate vascular damage and reduce long-term risks of cardiovascular and kidney complications, even though these outcomes often take longer than three years to fully manifest [6]. Our findings further highlight, through consistent data supported by robust multivariate and sensitivity analyses, along with biologically plausible mechanisms of action, the additive reno-protective and survival benefits of combining metformin and SGLT2 inhibitors as first-line therapy, beyond its glucose-lowering impact.

Our study provides valuable insights, but also contains several limitations. Firstly, while retrospective cohort studies like ours provide valuable insights, they carry the potential for residual confounding, and causality cannot be definitively established. Although RCTs are considered the gold standard for determining causality, they often lack the statistical power to assess long-term and specific outcomes individually, rather than composite outcomes. Furthermore, for well-established medications such as metformin, the evidence of cardio-reno protective effects remains uncertain in the absence of large-scale RCTs. Nevertheless, extensive cohort studies that leverage general population databases and real-world clinical data, enhanced by robust statistical methods, can offer valuable predictions regarding the risks associated with long-term and distinct outcomes [4]. Selection bias is an inherent limitation of retrospective design and is even more significant in the current study, as the reason for not prescribing metformin-potentially due to serious clinical event– remain unknown. However, considering the significant risk of EDKA associated with SGLT-2 inhibitors, these medications are often prescribed under a "sick day protocol" similar to metformin, which may help reduce the selection bias.

Second, while we have no specific reason to believe that our findings would differ based on race, most of the Clalit Health System population is Caucasian. This may limit the generalizability of our results to more diverse populations. Nevertheless, both metformin and sGLT2 inhibitors have been demonstrated to be safe and effective in improving outcomes across non-Caucasian and susceptible populations [45, 46].

Third, as a real-world study, this research primarily included patients with an eGFR > 60 ml/min/1.73 m^2, with only a small subgroup (10% of the cohort) having moderate CKD (eGFR < 60 ml/min/1.73 m^2). Due to the limited sample size of this subgroup, we are unable to

draw definitive conclusions regarding the impact of eGFR stage on the association between combination therapy and kidney outcomes. Nevertheless, previous studies, along with biologically plausible mechanisms, suggest that the benefits of metformin are more pronounced in the early stages of kidney disease, as opposed to advanced stages where fibrosis is more extensive and less responsive to anti-fibrotic treatments [2, 4].

Finally, our study relied on the recorded use of specific anti-diabetic medications at particular time points. As a result, we were unable to assess the cumulative dose of metformin for each individual, limiting our ability to evaluate potential dose-dependent effects of metformin on risk reduction and safety outcomes. Nevertheless, our findings were consistent across propensity-matched analyses, several sensitivity analyses and multivariable adjustment within multiple subgroups, strengthening the validity of our conclusions and their important clinical implications.

To our knowledge, this is the first study to demonstrate the additive renal protective and survival benefits of combining metformin with SGLT2 inhibitors. In a large, well-matched cohort, we observed that patients treated with the combination of metformin and SGLT2 inhibitors had a significantly lower risk of mortality and kidney disease progression compared to those treated with SGLT2 inhibitors alone. This substantial reduction in both mortality and kidney disease progression risk was consistent across nearly all patient subgroups and was associated with reduced risk of adverse events. These findings support the use of metformin in combination with SGLT2 inhibitors as a first-line therapy in T2D patients, regardless of glycemic control level and cardio-renal risk factors.

Abbreviations

AMPK	Activating AMP-activated protein kinase
ACEI	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blocker
BMI	Body mass index
CI	Confidence interval
CVA	Cerebrovascular disease
CVD	Cardiovascular disease
COPD	Chronic obstructive pulmonary disease
CCB	Calcium channel blocker
DKD	Diabetic kidney disease
EDKA	Euglycemic diabetic ketoacidosis
eGRF	Estimated glomerular filtration rate
HTN	Hypertension
HR	Hazard ratio
IHD	Ischemic heart disease
MRA	Mineralocorticoid receptor antagonist
PVD	Peripheral vascular disease
IHD	Ischemia heart disease
RCT	Randomized control trial
RMC	Rabin Medical Center
T2D	Type 2 diabetes mellitus
TGF-β1	Transforming growth factor beta 1

Supplementary Information

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Additional file 1.

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Author contributions

All the authors contributed significantly to this work and have approved the submission of this manuscript. TA—Investigation, Data Curation, and Writing– Original Draft Preparation. BRZ—Conceptualization, Methodology, Investigation, Formal Analysis, Supervision, Review & Editing. TS, EM- Data Curation, Review & Editing, BZ, DB, IF, EN- Review & Editing.

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Data availability

The data that support the findings of this study are available from the repositories of Clalit Health Services (CHS). Data is not publicly available as it contains private participants' information. Data from this study can be obtained upon request by contacting the corresponding author, Dr. Timna Agur at timna.agur@clalit.org.il.

Declarations

Ethical approval

This study protocol was reviewed and approved by the local Ethics Committee of the Rabin Medical Center, Israel, approval number RMC.

Informed consent

Due to the retrospective nature of the research, patient consent was not required according to the Rabin Medical Center ethics committee.

Conflict of interest

BRZ reports a consulting fee from Fresenius Medicare and lecturer fee from AstraZeneca plc. BZ reports consulting fee from Fresenius Medicare. All other authors have no conflicts of interest to disclose as described by the 'Kidney and Blood pressure research' Journal.

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References

1. Collins AJ, Li S, Gilbertson DT, Liu J, Chen SC, Herzog CA. Chronic kidney disease and cardiovascular disease in the Medicare population. Kidney Int Suppl. 2003;64(87):S24–31.
2. Charytan DM, Solomon SD, Ivanovich P, Remuzzi G, Cooper ME, McGill JB, et al. Metformin use and cardiovascular events in patients with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2019;21(5):1199–208.
3. Kwon S, Kim YC, Park JY, Lee J, An JN, Kim CT, et al. The long-term effects of metformin on patients with type 2 diabetic kidney disease. Diabetes Care. 2020;43(5):948–55.
4. Lim LL, Chow E, Chan JCN. Cardiorenal diseases in type 2 diabetes mellitus: clinical trials and real-world practice. Nat Rev Endocrinol. 2023;19(3):151–63.

5. de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and kidney disease: improving global outcomes (KDIGO). Kidney Int. 2022;102(5):974–89.
6. Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, et al. The legacy effect in type 2 diabetes: Impact of early glycemic control on future complications (the diabetes & aging study). Diabetes Care. 2019;42(3):416–26.
7. Hu Y, Lei M, Ke G, Huang X, Peng X, Zhong L, et al. Metformin use and risk of all-cause mortality and cardiovascular events in patients with chronic kidney disease-a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2020;11:559446.
8. El-Damanawi R, Stanley IK, Staatz C, Pascoe EM, Craig JC, Johnson DW, et al. Metformin for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2024;6(6):CD013414.
9. Yi Y, Kwon EJ, Yun G, Park S, Jeong JC, Na KY, et al. Impact of metformin on cardiovascular and kidney outcome based on kidney function status in type 2 diabetic patients: a multicentric, retrospective cohort study. Sci Rep. 2024;14(1):2081.
10. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021.
11. Filc D, Davidovich N, Novack L, Balicer RD. Is socioeconomic status associated with utilization of health care services in a single-payer universal health care system? Int J Equity Health. 2014;13:115.
12. Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on kidney disease: improving global outcomes (KDIGO) staging. BMC Res Notes. 2014;7:415.
13. Standards of Medical Care in Diabetes-2016: Summary of revisions. Diabetes Care. 2016;39 (Suppl 1):S4–S5.
14. Foretz M, Guigas B, Viollet B. Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. Nat Rev Endocrinol. 2019;15(10):569–89.
15. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854–65.
16. Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron CB, Stanifer JW, Mock CK, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med. 2017;166(3):191–200.
17. Ekström N, Schiöler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open. 2012;2(4):e001076.
18. Marcum ZA, Forsberg CW, Moore KP, de Boer IH, Smith NL, Boyko EJ, et al. Mortality associated with metformin versus sulfonylurea initiation: a cohort study of veterans with diabetes and chronic kidney disease. J Gen Intern Med. 2018;33(2):155–65.
19. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. Cell Metab. 2020;32(1):15–30.
20. Nogueira A, Pires MJ, Oliveira PA. Pathophysiological mechanisms of renal fibrosis: a review of animal models and therapeutic strategies. In Vivo. 2017;31(1):1–22.
21. Lee M, Katerelos M, Gleich K, Galic S, Kemp BE, Mount PF, et al. Phosphorylation of Acetyl-CoA carboxylase by AMPK reduces renal fibrosis and is essential for the anti-fibrotic effect of metformin. J Am Soc Nephrol. 2018;29(9):2326–36.
22. Lu J, Shi J, Li M, Gui B, Fu R, Yao G, et al. Activation of AMPK by metformin inhibits TGF-β-induced collagen production in mouse renal fibroblasts. Life Sci. 2015;127:59–65.
23. Corremans R, Vervaet BA, D'Haese PC, Neven E, Verhulst A. Metformin: a candidate drug for renal diseases. Int J Mol Sci. 2018;20(1).
24. Song A, Zhang C, Meng X. Mechanism and application of metformin in kidney diseases: an update. Biomed Pharmacother. 2021;138:111454.
25. Shen Y, Miao N, Xu J, Gan X, Xu D, Zhou L, et al. Metformin prevents renal fibrosis in mice with unilateral ureteral obstruction and inhibits Ang II-Induced ECM production in renal fibroblasts. Int J Mol Sci. 2016;17(2).
26. Corremans R, Vervaet BA, Dams G, D'Haese PC, Verhulst A. Metformin and canagliflozin are equally renoprotective in diabetic kidney disease but have no synergistic effect. Int J Mol Sci. 2023;24(10).
27. Corremans R, Neven E, Maudsley S, Leysen H, De Broe ME, D'Haese PC, et al. Progression of established non-diabetic chronic kidney disease is halted by metformin treatment in rats. Kidney Int. 2022;101(5):929–44.
28. Takiar V, Nishio S, Seo-Mayer P, King JD, Li H, Zhang L, et al. Activating AMP-activated protein kinase (AMPK) slows renal cystogenesis. Proc Natl Acad Sci U S A. 2011;108(6):2462–7.
29. Omachi K, Kaseda S, Yokota T, Kamura M, Teramoto K, Kuwazuru J, et al. Metformin ameliorates the severity of experimental Alport syndrome. Sci Rep. 2021;11(1):7053.
30. Lin CX, Li Y, Liang S, Tao J, Zhang LS, Su YF, et al. Metformin attenuates cyclosporine a-induced renal fibrosis in rats. Transplantation. 2019;103(10):e285–96.
31. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
32. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.
33. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57.
34. Ingelfinger JR, Rosen CJ. Clinical credence - SGLT2 inhibitors, diabetes, and chronic kidney disease. N Engl J Med. 2019;380(24):2371–3.
35. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388(2):117–27.
36. Harada M, Han S, Shi M, Ge J, Yu S, Adam J, et al. Metabolic effects of SGLT2i and metformin on 3-hydroxybutyric acid and lactate in db/db mice. Int J Biol Macromol. 2024;265(Pt 1):130962.
37. Jaikumkao K, Thongnak L, Htun KT, Pengrattanachot N, Phengpol N, Sutthasupha P, et al. Dapagliflozin and metformin in combination ameliorates diabetic nephropathy by suppressing oxidative stress, inflammation, and apoptosis and activating autophagy in diabetic rats. Biochim Biophys Acta Mol Basis Dis. 2024;1870(1):166912.
38. Madhag Z, Al-Isawi Z. Empagliflozin alone and in combination with metformin mitigates diabetes-associated renal complications. J Med Life. 2024;17(5):530–5.
39. Yu X, Zhang S, Zhang L. Newer perspectives of mechanisms for euglycemic diabetic ketoacidosis. Int J Endocrinol. 2018;2018:7074868.
40. Chow E, Clement S, Garg R. Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. BMJ Open Diabetes Res Care. 2023;11(5).
41. Donnan K, Segar L. SGLT2 inhibitors and metformin: dual antihyperglycemic therapy and the risk of metabolic acidosis in type 2 diabetes. Eur J Pharmacol. 2019;846:23–9.
42. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab. 2014;16(5):410–7.
43. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care. 2013;36(11):3411–7.
44. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S, et al. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet. 2019;394(10208):1519–29.
45. Anson M, Zhao SS, Essa H, Austin P, Ibarburu GH, Lip GYH, et al. Metformin and SGLT2i as first-line combination therapy in type 2 diabetes: a real-world study with a focus on ethnicity. Clin Ther. 2023;45(12):1259–65.
46. Li X, Zhang Q, Zhou X, Guo S, Jiang S, Zhang Y, et al. The different hypoglycemic effects between East Asian and non-Asian type 2 diabetes patients when treated with SGLT-2 inhibitors as an add-on treatment for metformin: a systematic review and meta-analysis of randomized controlled trials. Aging (Albany NY). 2021;13(9):12748–65.

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