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Published in:
Diabetes, Obesity and Metabolism

DOI (link to publication from Publisher):
10.1111/dom.15185

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Received: 9 February 2023 | Revised: 4 June 2023 | Accepted: 5 June 2023

DOI: 10.1111/dom.15185

WILEY

ORIGINAL ARTICLE

All-cause mortality and cardiovascular outcomes with sodium-glucose Co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and with combination therapy in people with type 2 diabetes

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Abstract

Aim: To assess the relationship of sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor analogues (GLP-1RA) and their combination (SGLT2i + GLP-1RA) with 5-year risk of all-cause mortality, hospitalization and cardiovascular/macrovascular disease in people with type 2 diabetes.

Materials and Methods: Retrospective cohort analysis of 2.2 million people with type 2 diabetes receiving insulin across 85 health care organizations using a global federated health research network. Three intervention cohorts (SGLT2i, GLP-1RA and SGLT2i + GLP-1RA) were compared against a control cohort (no SGLT2i/GLP-1RA). Propensity score matching for age, ischaemic heart disease, sex, hypertension, chronic kidney disease, heart failure and glycated haemoglobin was used to balance cohorts 1:1 (SGLT2i, n = 143 600; GLP-1RA, n = 186 841; SGLT-2i + GLP-1RA, n = 108 504). A sub-analysis comparing combination and monotherapy cohorts was also performed.

Results: The intervention cohorts showed a reduced hazard ratio (HR, 95% confidence interval) over 5 years compared with the control cohort for all-cause mortality (SGLT2i 0.49, 0.48-0.50; GLP-1RA 0.47, 0.46-0.48; combination 0.25, 0.24-0.26), hospitalization (0.73, 0.72-0.74; 0.69, 0.68-0.69; 0.60, 0.59-0.61) and acute myocardial infarct (0.75, 0.72-0.78; 0.70, 0.68-0.73; 0.63, 0.60-0.66), respectively. All other outcomes showed a significant risk reduction in favour of the intervention cohorts. The sub-analysis showed a significant risk reduction in all-cause mortality for combination therapy versus SGLT2i (0.53, 0.50-0.55) and GLP-1RA (0.56, 0.54-0.59).

Conclusions: SGLT2i, GLP-1RAs or combination therapy confers mortality and cardiovascular protection in people with type 2 diabetes over 5 years. Combination therapy was associated with the greatest risk reduction in all-cause mortality versus a propensity matched control cohort. In addition, combination therapy offers a

reduction in 5-year all-cause mortality when compared directly against either monotherapy.

KEYWORDS
cardiovascular disease, chronic kidney disease, glucagon-like peptide-1 receptor agonists, hospitalization, mortality, sodium-glucose cotransporter 2 inhibitors, type 2 diabetes

1 | INTRODUCTION

Cardiovascular disease is the most common cause of death in people living with type 2 diabetes mellitus.[1] In 2017, over 1 million deaths were directly attributed to type 2 diabetes, with cardiovascular death responsible for half of these.[2,3] In the same year it was estimated that 462 million live with type 2 diabetes, with the prevalence expected to rise significantly from 6059 to 7079 cases per 100 000 by 2030.[2]

Historically, clinicians had a limited ability to reduce the risk of cardiovascular disease in people with type 2 diabetes through the modification of cardiovascular risk factors (dysglycaemia, hyperlipidaemia, blood pressure and smoking) and promotion of a healthy lifestyle. Metformin has been considered cardioprotective, primarily based on data from UKPDS.[4] In a recent meta-analysis in patients with type 2 diabetes with coronary artery disease, metformin reduced cardiovascular and all-cause mortality, and cardiovascular events.[5] However, this effect has not been true for all hypoglycaemic therapies as the thiazolidinedione, rosiglitazone, was withdrawn in the late 2000s because of excess cardiovascular risk.[6] Because of growing concerns relating to cardiovascular safety of novel glucose-lowering therapies, regulatory authorities stipulated that future therapies must show cardiovascular safety. Consequently, we saw the emergence of large, international, randomized controlled cardiovascular outcome trials (CVOT) assessing incident major adverse cardiovascular events (MACE) in patients taking novel glucose-lowering therapies. More recently, two classes of glucose-lowering therapies, namely sodium glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RA) showed both cardiovascular and renal benefit.[7,8] SGLT2i have ubiquitously also shown a significant reduction in hospitalization from heart failure, with varying SGLT2i showing a neutral or positive effect on cardiovascular events, all-cause mortality[8] and atrial fibrillation.[9] In addition, dapagliflozin became the first SGLT2i to be approved in Europe for the treatment of chronic kidney disease (CKD), irrespective of the presence or absence of type 2 diabetes, based on findings from the DAPA-CKD renal outcomes trial.[10] In addition, meta-analysis of randomized trials by Sattar et al. showed that GLP-1RA are associated with a reduced risk for all MACE events, all-cause mortality, hospital admission for heart failure, and worsening kidney function in people with type 2 diabetes.[11]

In this study, we review the real-world impact of SGLT2i and GLP-1RA therapy, on all-cause mortality, hospitalization, cardiovascular outcomes and CKD when given either alone or together over 5 years following the initiation of treatment. Given the limited data regarding the impact of combination therapy on 'hard clinical endpoints' from clinical trials, we evaluated such combination therapy using a large real-world dataset and include a comparison of combination therapy versus monotherapy with either SGLT2i or GLP-1RA.

2 | MATERIALS AND METHODS

2.1 | Study population

This study was conducted with anonymized data from TriNetX, a global federated health research network that has access to both inpatient and outpatient electronic medical records (EMRs) from health care organizations (HCOs) from all over the world. This analysis was conducted on the Global Collaborative Network, which contains data from over 114 million patients with access to diagnoses, procedures, medications, laboratory values and genomic information worldwide. The global collaborative network collects data from across 14 different countries, from predominately US HCOs. In particular, for this retrospective cohort analysis, approximately 2.2 million patients with type 2 diabetes receiving insulin from 85 HCOs were included. Data recorded between 1 January 2010 and 24 March 2023 were used in the subsequent analyses. As part of the data ingestion process when HCOs joins the network, data are mapped to a common data model to reflect individual institution, country and regional standards with regard to electronic health record data. All data collection, processing and transmission are performed in compliance with all Data Protection laws applicable to the contributing HCOs, including the EU Data Protection Law Regulation 2016/679, the General Data Protection Regulation on the protection of natural persons regarding the processing of personal data and the Health Insurance Portability and Accountability Act, the US federal law, which protects the privacy and security of health care data. The TriNetX Global Collaborative Network is a distributed network (with the majority of HCOs located in the United States), and analytics are performed at the HCO with only aggregate results being surfaced and returned to the platform. Data usage and publication agreements are in place with all HCOs.

2.2 | Building cohorts in TriNetX

Patients with type 2 diabetes were identified in each cohort based on the inclusion of the ICD-10-CM code E11 in their EMR. To avoid the potential of patients with type 1 diabetes being included and skewing

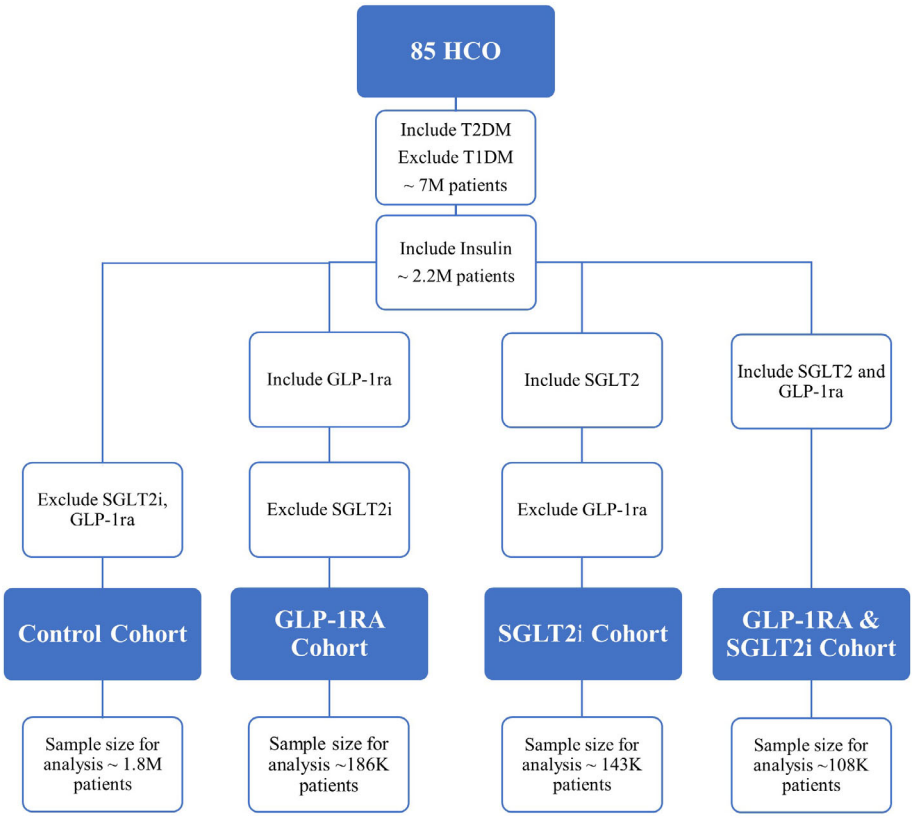

FIGURE 1 Diagram of inclusion and exclusion criteria used to develop the different cohorts in the study. GLP-1RA, glucagon-like peptide 1 receptor agonist; HCO, health care organization; SGLT2is, sodium glucose cotransporter-2 inhibitors; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

the analysis, EMR code E10 was used as an exclusion criterium when building the cohorts. This analysis was conducted on four cohorts: (a) control, no SGLT2i/GLP-1RA treatment; (b) SGLT2i treatment; (c) GLP-1RA treatment; and (d) SGLT2i + GLP-1RA combination treatment, in either order. They were built using inclusion/exclusion criteria leveraging the available EMR data in TriNetX, specifically the diagnosis and medications codes (Figure 1). Patients that fulfil the respective inclusion/exclusion criteria are included in the relevant cohort. Three analyses were conducted from the four cohorts with each analysis propensity score matched (PSM) for age, presence of ischaemic heart disease (IHD) (ICD-CM-10, I20-25), sex, hypertension (ICD-CM-10, I10-I16), CKD (ICD-CM-10, E11.22 and N18), heart failure (ICD-CM-10, I50) and glycated haemoglobin (HbA1c) value to balance the analysis (1:1 matching) being undertaken. It was not possible to match HbA1c to a mean value between cohorts, instead patients were matched in to two HbA1c categories: ≤7% and >7%. The three analyses were: (a) SGLT2i versus control; (b) GLP-1RA versus control; and (c) combination of SGLT2i + GLP-1RA versus control (all 1:1 PSM). All cohorts included patients with type 2 diabetes specifically treated with insulin, a common late line therapy for type 2 diabetes, along with other hypoglycaemic pharmacological agents (see Tables S1-S5 for the complete list of pharmacological agents). This was done to ensure the people in each cohort were at a similar disease stage.

As this study was comparing specifically SGLT2i versus GLP-1RA effects on cardiovascular outcomes a control cohort excluding these medications was used as a standard reference point for comparison. The analysis on the respective cohorts was based on the following outcomes over 5 years from the index event: all-cause mortality, any hospitalization, cardiovascular outcomes including acute-myocardial infarct, unstable angina, IHD, heart failure, atrial fibrillation, stroke, peripheral vascular disease (PVD), lower limb amputation and CKD. Mortality data were collected directly from the electronic health records of HCOs, and were not collected from a government source, such as a registered persons database.

Using the above cohorts, a sub-analysis was performed comparing the combination cohort to both SGLT2i cohort and GLP-1RA cohort. The same PSM was performed between these cohorts as has previously been described, and the same outcomes by 5 years were recorded.

2.3 | Index event

The initiation of insulin was used as the index event for the control group and was incorporated into the index criteria for the treatment cohorts. The index events for the SGLT2i cohort were when both insulin and SGLT2i were prescribed, for the GLP-1RA cohort when both insulin and GLP-1RA were prescribed, and for the combination cohort when all three of insulin, SGLT2i and GLP-1RA were prescribed. The data collection started once all index criteria were met, which prevented the immortal time bias from affecting the cohorts. The inclusion of insulin across the cohorts was undertaken to ensure the cohorts contained people with type 2 diabetes who were at a similar disease stage.

2.4 | Statistical analysis

The control cohort was considered the reference cohort (HR = 1) when compared with the SGLT2i, GLP-1RA and SGLT2i + GLP-1RA cohorts. Using the TriNetX software a survival analysis was performed, which estimates the probability of an outcome at a respective time interval (daily time interval was used in these analyses) over 5 years from the index event and generates a hazard ratio (HR), log rank test and Kaplan-Meier survival curve. TriNetX uses the R Survival package v3.2-3 for its analysis. Patients were excluded from an outcome analysis if they had already experienced the outcome before the time window.

To account for patients who dropped out of the analysis, censoring is applied. A patient was removed (censored) from the analysis after the last event in their electronic record.

3 | RESULTS

3.1 | Propensity score matching

After propensity matching for age, gender, presence of IHD, hypertension, heart failure, CKD and HbA1c value, each pair of cohorts (SGLT2i vs. control, GLP-1RA vs. control and combination vs. control) were deemed well matched with almost all differences between these characteristics being non-significant. PSM was also performed in the sub-analysis, using the same characteristics as in the primary analysis, each pair of cohorts (combination vs. SGLT2i and combination vs. GLP-1RA) were deemed to be well matched; however, some variables remained statistically significant between cohorts. Tables S1-S5 list the race and medication breakdowns of the different cohorts after propensity matching (Table 1).

3.2 | Survival analysis

3.2.1 | Sodium-glucose cotransporter 2 inhibitor versus control

In all the analysed events, treatment with SGLT2i reduced the hazard rate of that event occurring over 5 years when compared with the propensity matched control cohort's hazard rate, this is evidenced in the HRs below. The greatest reduction in risk was for all-cause mortality (HR 0.49, 95% CI 0.48, 0.50). SGLT2i treatment also reduced the risk of hospitalization (HR 0.73, 95% CI 0.72, 0.74), acute myocardial infarct (HR 0.75, 95% CI 0.72, 0.78), unstable angina (HR 0.79, 95% CI 0.73, 0.85), IHD (HR 0.91, 95% CI 0.88, 0.93), heart failure (HR 0.73, 95% CI 0.71, 0.75), atrial fibrillation (HR 0.74, 95% CI 0.71, 0.77), stroke (HR 0.75, 95% CI 0.72, 0.78), PVD (HR 0.79, 95% CI 0.76, 0.82), lower limb amputation (HR 0.69, 95% CI 0.64, 0.73) and CKD (HR 0.79, 95% CI 0.77, 0.81).

3.2.2 | Glucagon-like peptide-1 receptor agonist versus control

In all the analysed events, treatment with GLP-1RA reduced the hazard rate of that event occurring over 5 years when compared with the propensity matched control cohort's hazard rate, this is evidenced in the HRs below. The greatest reduction in risk was for all-cause mortality (HR 0.47, 95% CI 0.46, 0.48). GLP-1RA treatment also reduced the risk of hospitalization (HR 0.69, 95% CI 0.68, 0.69), acute myocardial infarct (HR 0.70, 95% CI 0.68, 0.73), unstable angina (HR 0.73, 95% CI 0.68, 0.79), IHD (HR 0.85, 95% CI 0.83, 0.87), heart failure (HR 0.73, 95% CI 0.71, 0.74), atrial fibrillation (HR 0.77, 95% CI 0.75, 0.79), stroke (HR 0.77, 95% CI 0.75, 0.80), PVD (HR 0.89, 95% CI 0.86, 0.92), lower limb amputation (HR 0.66, 95% CI 0.63, 0.70) and CKD (HR 0.90, 95% CI 0.88, 0.92).

3.2.3 | Combination sodium-glucose cotransporter 2 and glucagon-like peptide-1 receptor agonist versus control

In all the analysed events, treatment with combination therapy (SGLT2i + GLP-1RA) reduced the hazard rate of that event occurring over 5 years compared with a propensity matched control cohort's hazard rate, this is evidenced in the HRs below. The greatest reduction in risk was for all-cause mortality (HR 0.25, 95% CI 0.24, 0.26). Combination treatment also reduced the risk of hospitalization (HR 0.60, 95% CI 0.59, 0.61), acute myocardial infarct (HR 0.63, 95% CI 0.60, 0.66), unstable angina (HR 0.75, 95% CI 0.69, 0.82), IHD (HR 0.84, 95% CI 0.81, 0.86), heart failure (HR 0.60, 95% CI 0.58, 0.62), atrial fibrillation (HR 0.65, 95% CI 0.62, 0.68), stroke (HR 0.69, 95% CI 0.66, 0.72), PVD (HR 0.84, 95% CI 0.80, 0.87), lower limb amputation (HR 0.59, 95% CI 0.55, 0.64) and CKD (HR 0.72, 95% CI 0.70, 0.74).

3.3 | Log rank test

For all of the survival analyses between these cohorts, SGLT2i versus control, GLP-1RA versus control and combination versus control, the log rank test evidenced a significant difference between the survival curves for each outcome (see Table 2 for each log rank test).

3.4 | Combination versus monotherapy treatment

3.4.1 | Combination sodium-glucose cotransporter 2 inhibitor and glucagon-like peptide-1 receptor agonist versus sodium-glucose cotransporter 2 inhibitor

The combination cohort showed a modest reduction in risk for IHD (HR 0.91, 95% CI 0.88, 0.94), heart failure (HR 0.81, 95% CI 0.78, 0.84), atrial fibrillation (HR 0.90, 95% CI 0.86, 0.95), stroke (HR 0.90, 95% CI 0.85, 0.94), lower limb amputation (HR 0.81, 95% CI 0.74,

TABLE 1 Propensity score matching

		Pre-propensity matching SGLT2i	Control	*p*-Value	Post-propensity matching SGLT2i	Control	*p*-Value
Sample size[a]		143 740	1 848 971		143 600	143 600	
Age, years; mean ± SD		62.8 ± 12.2	62.9 ± 15.1	.026	62.8 ± 12.2	62.8 ± 12.2	.936
Sex, %							
Female		40.3	48.2	<.001	40.4	40.4%	.613
Male		59.6	51.8	<.001	59.6	59.7	.621
IHD[a]		57 248 (39.8%)	514 912 (27.8%)	<.001	57 108 (39.8%)	57 117 (39.8%)	.973
Hypertension[a]		112 527 (78.3%)	1 225 039 (66.3%)	<.001	112 387 (78.3%)	112 466 (78.3%)	.721
Heart failure[a]		37 794 (26.3%)	313 412 (17.0%)	<.001	37 657 (26.2%)	37 579 (26.2%)	.741
CKD[a]		33 392 (23.2%)	363 172 (19.6%)	<.001	33 289 (23.2%)	33 157 (23.1%)	.559
T2DM with CKD[a]		28 063 (19.5%)	206 441 (11.2%)	<.001	19 751 (13.8%)	19 588 (13.6%)	.376
HbA1c[a], %	≤7	56 593 (39.4%)	508 989 (27.5%)	<.001	56 463 (39.3%)	56 377 (39.3%)	.742
	>7	79 892 (55.6%)	415 774 (22.5%)	<.001	79 752 (55.5%)	79 765 (55.5%)	.961
		GLP-1	**Control**	***p*-Value**	**GLP-1**	**Control**	***p*-Value**
Sample size[a]		186 844	1 848 971		186 841	186 841	
Age, years; mean ± SD		58.7 ± 13.0	62.9 ± 15.1	<.001	58.7 ± 13.0	58.7 ± 13.1	.397
Sex, %							
Female		56.4	48.2	<.001	56.4	56.3	.810
Male		43.6	51.8	<.001	43.6	43.7	.792
IHD[a]		45 831 (24.5%)	514 912 (27.80%)	<.001	45 831 (24.5%)	45 588 (24.4%)	.355
Hypertension[a]		137 015 (73.30%)	1 225 039 (66.3%)	<.001	137 012 (73.3%)	137 019 (73.3%)	.979
Heart failure[a]		23 936 (12.8%)	313 412 (17.0%)	<.001	23 936 (12.8%)	23 712 (12.7%)	.272
CKD[a]		37 195 (19.9%)	363 172 (19.6%)	.006	37 192 (19.9%)	37 012 (19.8%)	.460
T2DM with CKD[a]		19 488 (10.4%)	159 346 (8.6%)	<.001	19 485 (10.4%)	19 164 (10.3%)	.085
HbA1c[a], %	≤7	74 141 (39.7%)	508 989 (27.5%)	<.001	74 138 (39.7%)	73 838 (39.5%)	.316
	>7	105 509 (56.5%)	415 774 (22.5%)	<.001	105 506 (56.5%)	105 516 (56.5%)	.974
		SGLT2i + GLP-1	**Control**	***p*-value**	**SGLT2i + GLP-1**	**Control**	***p*-Value**
Sample size[a]		108 507	1 848 971	<.001	108 504	108 504	
Age, years; mean ± SD		58.7 ± 11.5	62.9 ± 15.1	<.001	58.7 ± 11.5	58.6 ± 11.6	.207
Sex, %							
Female		49.0	48.2	<.001	49.0	48.9	.571
Male		50.9	51.8	<.001	50.9	51.1	.553
IHD[a]		32 944 (30.4%)	514 912 (27.8%)	<.001	32 941 (30.4%)	32 836 (30.3%)	.624
Hypertension[a]		86 483 (79.7%)	1 225 039 (66.3%)	<.001	86 480 (79.7%)	86 438 (79.7%)	.823
Heart failure[a]		17 314 (16.0%)	313 412 (17.0%)	<.001	17 313 (16.0%)	17 006 (15.7%)	.071
CKD[a]		22 003 (20.3%)	363 172 (19.6%)	<.001	22 003 (20.3%)	21 922 (20.2%)	.665
T2DM with CKD[a]		12 267 (11.3%)	159 346 (8.6%)	<.001	12 265 (11.3%)	11 953 (11.0%)	.033
HbA1c[a], %	≤7	45 925 (42.3%)	508 989 (27.5%)	<.001	45 923 (42.3%)	45 913 (42.3%)	.965
	>7	76 877 (70.8%)	415 774 (22.5%)	<.001	76 874 (70.8%)	76 877 (70.9%)	.989
Sub-analysis of combination therapy vs. SGLT-2i or GLP-1RA							
		SGLT2i + GLP-1	**SGLT2i**	***p*-Value**	**SGLT2i + GLP-1**	**Control**	***p*-Value**
Sample size[a]		108 507	143 740		96 291	96 291	
Age, years; mean ± SD		58.7 ± 11.5	62.8 ± 12.2	<.001	60.0 ± 11.0	59.7 ± 11.6	<.001
Sex, %							
Female		49.0	40.3	<.001	45.9	44.8	<.001
Male		50.9	59.6	<.001	54.1	55.2	<.001
IHD[a]		32 944 (30.4%)	57 248 (39.8%)	<.001	31 624 (32.8%)	31 183 (32.4%)	.032

(Continues)

TABLE 1 (Continued)

Sub-analysis of combination therapy vs. SGLT-2i or GLP-1RA							
		SGLT2i + GLP-1	SGLT2i	*p*-Value	SGLT2i + GLP-1	Control	*p*-Value
Hypertension[a]		86 483 (79.7%)	112 527 (78.3%)	<.001	76 280 (79.2%)	75 244 (78.1%)	<.001
Heart failure[a]		17 314 (16.0%)	37 794 (26.3%)	<.001	17 176 (17.8%)	16 840 (17.5%)	.045
CKD[a]		22 003 (20.3%)	33 392 (23.2%)	<.001	20 219 (21.0%)	19 734 (20.5%)	.006
T2DM with CKD[a]		12 267 (11.3%)	19 880 (13.8%)	<.001	11 518 (12.0%)	11 311 (11.7%)	.144
HbA1c[a], %	≤7	45 925 (75.7%)	56 593 (67.0%)	<.001	39 550 (41.1%)	37 764 (39.2%)	<.001
	>7	76 877 (70.8%)	79 892 (55.6%)	<.001	64 923 (67.4%)	64 310 (66.8%)	.003
		SGLT2i + GLP-1	GLP-1	*p*-Value	SGLT2i + GLP-1	Control	*p*-Value
Sample size[a]		108 507	186 844		107 643	107 643	
Age, years; mean ± SD		58.7 ± 11.5	58.7 ± 13.0	.516	58.7 ± 11.5	58.7 ± 11.8	.474
Sex, %							
Female		49.0	56.4	<.001	49.4	49.2	.191
Male		50.9	43.6	<.001	50.5	50.8	.184
IHD[a]		32 944 (30.4%)	45 831 (24.5%)	<.001	32 098 (29.8%)	31 279 (29.1%)	<.001
Hypertension[a]		86 483 (79.7%)	137 015 (73.30%)	<.001	85 619 (79.5%)	85 809 (79.7%)	.309
Heart failure[a]		17 314 (16.0%)	23 936 (12.8%)	<.001	16 658 (15.5%)	15 865 (14.7%)	<.001
CKD[a]		22 003 (20.3%)	37 195 (19.9%)	.015	21 963 (20.4%)	21 415 (19.9%)	.003
T2DM with CKD[a]		12 267 (11.3%)	19 488 (10.4%)	<.001	12 208 (11.3%)	11 719 (10.9%)	.001
HbA1c[a], %	≤7	45 925 (75.7%)	74 141 (39.7%)	<.001	45 681 (42.4%)	44 910 (41.7%)	.001
	>7	76 877 (70.8%)	105 509 (56.5%)	<.001	76 013 (70.6%)	76 013 (70.6%)	1

[a]Number of patients. Abbreviations: CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated haemoglobin; IHD, ischaemic heart disease; SGLTI2i, sodium-glucose cotransporter-2 inhibitors; T2DM type 2 diabetes mellitus. $p \leq .05$ was considered statistically significant.

0.88), CKD (HR 0.92, 95% CI 0.89, 0.95), acute myocardial infarct (HR 0.83, 95% CI 0.79, 0.88) and hospitalization (HR 0.81, 95% CI 0.80, 0.83) over 5 years when compared with a PSM SGLT2i cohort. The greatest reduction in risk was seen in all-cause mortality (HR 0.53, 95% CI 0.50, 0.55). There was no significant difference in the risk of unstable angina (HR 0.95, 95% CI 0.86, 1.05) and PVD (HR 1.01, 95% CI 0.96, 1.06). These results are summarized in Figure 2B.

3.4.2 | Combination sodium-glucose cotransporter 2 inhibitor and glucagon-like peptide-1 receptor agonist versus glucagon-like peptide-1 receptor agonist

The combination cohort showed a significant reduction in risk compared with a PSM GLP-1RA cohort for several events. The greatest reduction in risk was seen in the event all-cause mortality (HR 0.56, 95% CI 0.54, 0.59). The other events that showed a modest reduction in risk were heart failure (HR 0.84, 95% CI 0.80, 0.87), atrial fibrillation (HR 0.89, 95% CI 0.85, 0.93), stroke (HR 0.92, 95% CI 0.88, 0.96), lower limb amputation (HR 0.87, 95% CI 0.81, 0.95), CKD (HR 0.80, 95% CI 0.77, 0.83), acute myocardial infarct (HR 0.93, 95% CI 0.89, 0.98) and hospitalization (HR 0.87, 95% CI 0.85, 0.88). There was no significant difference in the risk of unstable angina (HR 1.08, 95% CI 0.97, 1.19), IHD (HR 1.00, 95% CI 0.97, 1.03) and PVD (HR 0.96, 95% CI 0.92, 1.01). These results are summarized in Figure 2C.

3.5 | Log rank test

For each survival analysis performed between the combination versus SGLT2i cohorts the log rank test showed a significant difference between all survival curves except for the outcomes for unstable angina ($p = .327$) and PVD ($p = 1$). For the combination versus GLP-1RA cohorts the log rank test showed a significant difference between all survival curves except for the outcomes for unstable angina ($p = 1$), IHD ($p = 1$) and PVD ($p = .090$) (Table 3).

4 | DISCUSSION AND CONCLUSION

Our study showed that treatment with SGLT2i or GLP-1RA, both as monotherapy and combination, confer prognostic cardiovascular benefit on people with type 2 diabetes when compared with people who are treatment naïve, over 5 years. Second, our data suggests that combination therapy confers a greater all-cause mortality benefit than either monotherapy. Finally, combination therapy appears to provide a greater benefit for most cardiovascular and CKD outcomes than monotherapy with GLP-1RA or SGLT2i.

TABLE 2 Summary of outcome incidence, survival probability and Log rank test for each cohort and event in the primary analysis

Outcome		Sample Size[a]	Patients with Outcome	5-year Survival Probability (%)	Log rank test	*p* value
All-cause mortality						
SGLT2i vs control	SGLT2i	142 704	7883	86.4	2934	<0.001
	Control	142 390	20 390	76.0		
GLP-1RA vs control	GLP-1RA	185 502	8691	89.3	3666.31	<0.001
	Control	185 446	20 318	81.7		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	107 718	2653	94.1	4776.287	<0.001
	Control	107 697	12 121	81.4		
Unstable Angina						
SGLT2i vs control	SGLT2i	137 984	1103	97.9	36.953	<0.001
	Control	138 988	1818	97.5		
GLP-1RA vs control	GLP-1RA	182 981	1224	98.5	73.004	<0.001
	Control	183 264	1843	98.1		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	105 151	780	98.2	39.214	<0.001
	Control	105 711	1227	97.9		
Ischaemic Heart Disease						
SGLT2i vs control	SGLT2i	86 492	9400	75.4	49.654	<0.001
	Control	86 483	12 695	74.4		
GLP-1RA vs control	GLP-1RA	141 010	14 583	79.3	215.942	<0.001
	Control	141 253	18 526	77.5		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	75 563	7194	79.2	131.099	<0.001
	Control	75 668	9757	77.8		
Heart Failure						
Control vs SGLT-2	SGLT2i	105 943	7093	84.3	438.436	<0.001
	Control	106 021	11 894	80.0		
GLP-1RA vs control	GLP-1RA	162 905	10 823	85.9	671.953	<0.001
	Control	163 129	16 163	82.6		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	91 191	4718	88.4	827.687	<0.001
	Control	91 498	8936	82.9		
Atrial Fibrillation						
SGLT2i vs control	SGLT2i	119 327	5155	89.5	294.659	<0.001
	Control	120 761	8848	86.7		
GLP-1RA vs control	GLP-1RA	170 127	6741	91.4	269.705	<0.001
	Control	168 773	9493	90.0		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	97 570	3126	92.7	376.605	<0.001
	Control	97 136	5545	89.8		
Stroke						
SGLT2i vs control	SGLT2i	129 369	4530	90.7	231.388	<0.001
	Control	128 059	7617	89.2		
GLP-1RA vs control	GLP-1RA	172 757	6773	91.9	262.524	<0.001
	Control	170 100	9345	90.4		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	100,020	3295	92.2	286.014	<0.001
	Control	98 001	5444	90.2		

(Continues)

TABLE 2 (Continued)

Outcome		Sample Size[a]	Patients with Outcome	5-year Survival Probability (%)	Log rank test	*p* value
Peripheral Vascular Disease						
SGLT2i vs control	SGLT2i	129 459	4768	90.1	165.878	<0.001
	Control	131 102	7915	88.5		
GLP-1RA vs control	GLP-1RA	172 762	7234	91.1	53.342	<0.001
	Control	174 903	8962	90.6		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	98 967	3836	90.7	69.466	<0.001
	Control	100 676	5434	90.1		
Lower Limb Amputation						
SGLT2i vs control	SGLT2i	140 508	1593	97.4	145.558	<0.001
	Control	140 594	2891	96.3		
GLP-1RA vs control	GLP-1RA	183 399	2100	97.6	221.003	<0.001
	Control	183 816	3419	96.8		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	106 637	1062	97.7	193.831	<0.001
	Control	106 479	2051	96.7		
Chronic Kidney Disease						
SGLT2i vs control	SGLT2i	109 460	9324	79.9	327.684	<0.001
	Control	109 621	14 671	75.8		
GLP-1RA vs control	GLP-1RA	148 850	14 378	80.2	82.461	<0.001
	Control	149 130	17 363	79.4		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	85 946	6533	83.5	434.926	<0.001
	Control	86 154	10 165	79.1		
Acute-Myocardial Infarct						
SGLT2i vs control	SGLT2i	124 687	4270	91.4	218.693	<0.001
	Control	127 103	7404	89.2		
GLP-1RA vs control	GLP-1RA	175 799	5306	93.4	404.374	<0.001
	Control	174 321	8218	91.4		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	99 318	2696	93.7	381.766	<0.0001
	Control	99 130	4996	90.9		
Hospitalisation						
SGLT2i vs control	SGLT2i	143 600	54 638	35.2	3119.935	<0.001
	Control	143 600	75 358	26.7		
GLP-1RA vs control	GLP-1RA	186 841	74 247	37.9	6008.484	<0.001
	Control	186 841	97 293	28.2		
SGLT2i + GLP-1RA vs control	SGLT2i + GLP-1	108 504	37 816	41.4	6027.887	<0.001
	Control	108 504	56 531	28.3		

[a]Patients were excluded from each result if they had experienced an outcome prior to the time window. *p* value taken to be significant if ≤0.05. Log rank test calculated against one degree of freedom.

Wright et al.[12] has showed similar protective effects from an analysis of three databases in the UK, with either SGLT2i alone or combination therapy with both SGLT2i + GLP-1RAs, conferring lower odds for MACE and heart failure compared with other treatment regimens. However, this study focused on primary prevention, whereas we did not exclude baseline cardiovascular events rather we matched for IHD, thus representing a 'typical' type 2 diabetes population. In addition, a meta-analysis by Li et al.,[13] has showed the glycaemic efficacy (HbA1c, fasting plasma glucose, 2 h plasma glucose), favourable improvements in body composition (body weight, body mass index) and favourable safety profile in those with combination therapy.

Previously published data on SGLT2i monotherapy from the TriNetX platform also confirmed beneficial effects of SGLT2i on cardiovascular events (RR for treatment with SGLT2i of 0.62-0.81),

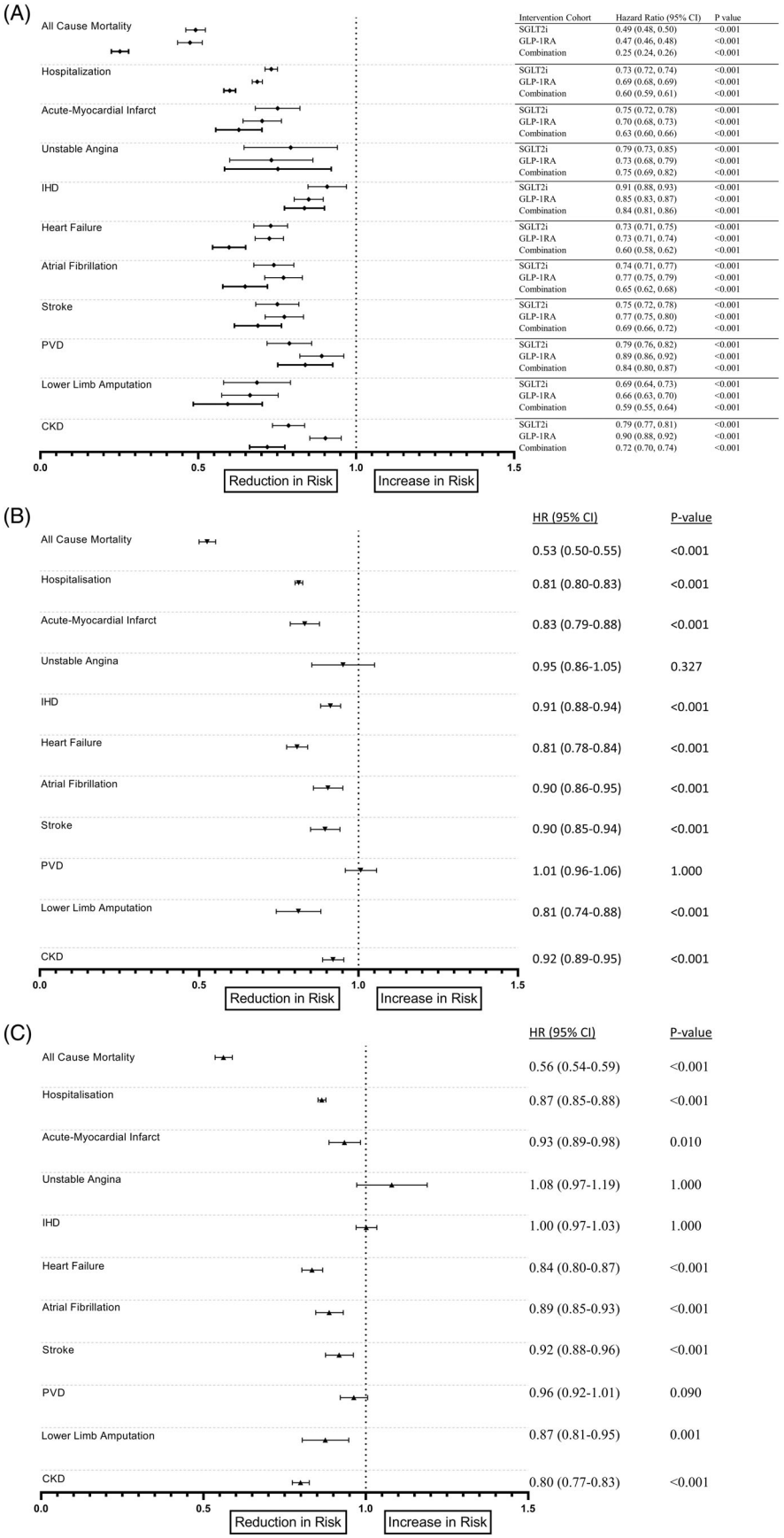

FIGURE 2 (A) Hazard ratio (HR) of each outcome occurring, comparing the intervention cohorts to control cohort with 95% confidence intervals (CIs). (B) HR of each outcome comparing the combination cohort to the sodium glucose cotransporter-2 inhibitor (SGLT2i) cohort with 95% CIs. (C) HR of each outcome comparing the combination cohort to the glucagon-like peptide 1 receptor agonist (GLP-1RA) cohort with 95% CIs. CKD, chronic kidney disease; IHD, ischaemic heart disease; PVD, peripheral vascular disease

TABLE 3 Summary of outcome incidence, survival probability and Log rank test for each cohort and event in the sub-analysis

Outcome		Sample Size[a]	Patients with Outcome	5-year Survival Probability (%)	Log rank test	*p* value
All-cause mortality						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	95 628	2508	93.7	673.782	<0.001
	SGLT2i	95 719	4219	89.0		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	106 869	2620	94.1	586.997	<0.001
	GLP-1RA	106 848	5044	89.3		
Unstable Angina						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	93 077	745	98.0	0.991	0.319
	SGLT2i	93 067	693	98.0		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	104 393	763	98.2	2.107	0.147
	GLP-1RA	104 773	765	98.4		
Ischaemic Heart Disease						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	64 667	6470	78.2	26.930	<0.001
	SGLT2i	65 108	6309	77.7		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	75 545	7193	79.2	0.010	0.921
	GLP-1RA	76 364	7585	79.8		
Heart Failure						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	79 115	4334	87.7	104.447	<0.001
	GLP-1RA	79 451	4801	85.7		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	90 985	4702	88.4	85.886	<0.001
		91 778	5933	86.2		
Atrial Fibrillation						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	85 656	2980	92.0	14.986	<0.001
	SGLT2i	84 796	2909	91.5		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	96 940	3092	92.7	24.185	<0.001
	GLP-1RA	97 107	3712	91.6		
Stroke						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	88 493	2974	92.0	18.208	<0.001
	SGLT2i	87 569	2909	91.3		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	99 277	3262	92.2	12.870	<0.001
	GLP-1RA	98 826	3778	92.0		
Peripheral Vascular Disease						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	87 428	3486	90.4	0.071	0.790
	SGLT2i	88 169	3070	90.8		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	98 260	3799	90.8	2.863	0.091
	GLP-1RA	98 552	4220	91.0		
Lower Limb Amputation						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	94 568	980	97.5	22.808	<0.001
	SGLT2i	94 277	1077	97.5		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	105 801	1050	97.7	10.456	0.001
	GLP-1RA	105 276	1279	97.5		
Chronic Kidney Disease						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	75 576	6013	82.6	20.239	<0.001
	SGLT2i	76 092	5784	82.0		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	85 145	6440	83.6	182.880	<0.001
	GLP-1RA	85 823	8308	80.0		

TABLE 3 (Continued)

Outcome		Sample Size[a]	Patients with Outcome	5-year Survival Probability (%)	Log rank test	*p* value
Acute-Myocardial Infarct						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	87 482	2486	93.3	43.863	<0.001
	SGLT2i	86 069	2610	92.5		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	98 746	2666	93.7	6.572	0.010
	GLP-1RA	99 759	3086	93.1		
Hospitalisation						
SGLT2i +GLP-1RA vs SGLT2i	SGLT2i + GLP-1RA	96 291	33 349	41.5	745.751	<0.001
	SGLT2i	96 291	35 871	36.5		
SGLT2i +GLP-1RA vs GLP-1RA	SGLT2i + GLP-1RA	107 643	37 455	41.5	420.107	<0.001
	GLP-1RA	107 643	42 910	37.7		

[a]Patients were excluded from each result if they had experienced an outcome prior to the time window. *p* value taken to be significant if ≤ 0.05. Log rank test calculated against one degree of freedom.

reproducing positive clinical trial data.[14] Importantly, the downstream cardiovascular benefits of SGLTI2i have been shown in high-quality randomized control trials in the type 2 diabetes (EMPA-REG OUTCOME trial with empagliflozin,[15] CANVAS Program with canagliflozin,[16] and DECLARE-TIMI 58 with dapagliflozin[17]). Importantly, the EMPA-REG OUTCOME trial (empagliflozin) showed a significantly reduced all-cause mortality rate.[15] These results have paved the way for randomized controlled trials (RCTs) evaluating the utility of SGLT2i in heart failure with reduced ejection fraction (in people without type 2 diabetes), which yielded positive results (DAPA-HF with dapagliflozin,[18] EMPREOR-REDUCED with empagliflozin,[19] SOLOIST-WHF with sotagliflozin[20]). However, these beneficial cardiovascular effects are not observed across all SGLT2i (VERTIS-CV with ertugliflozin[21]; not showing all medications within this class have the same effects). Finally, SGLT2i have also showed a marked reduction in the progression in CKD in patients with or without type 2 diabetes (CREDANCE with canagliflozin,[22] DAPA-CKD with dapagliflozin[10] and SCORED with sotagliflozin[23] and EMPA-KIDNEY with empagliflozin[24]). These landmark RCTs showed the pleiotropic benefits of SGLT2i[25] resulting in licensing authorizations in those with type 2 diabetes, heart failure with reduced ejection fraction and CKD. The results of our study further support the ubiquitous mortality and cardiovascular benefits of SGLT2i therapy in people with type 2 diabetes through showing these effects in the real world.

Comparing our results directly with the CVOTs we see a greater reduction in risk for all-cause mortality HR 0.49 to 0.68-0.93[15–17] and a superior reduction in risk for cardiovascular outcomes, myocardial infarction HR 0.75 to 0.87-0.89[15–17] and stroke HR 0.75 to 0.87-1.18.[15–17] Our heart failure risk reduction is in keeping with previous studies, HR 0.73 to 0.65-0.73.[15–17] The variation between our results and that of the CVOTs is probably explained by the nature of our study, a real-world study using non-randomized, non-controlled data versus controlled and randomized data. This is in addition to our study populations being markedly different as we focused only on people with type 2 diabetes treated with insulin and CVOTs focused on people with type 2 diabetes with established cardiovascular disease.

SGLT2i have unexpectedly provided a paradigm shift in the management of, and prognosis in, heart failure, atherosclerotic cardiovascular disease and CKD. Comparatively, results for GLP-1RA in improving cardiovascular outcomes exhibit greater heterogeneity and currently have limited evidence in the population without type 2 diabetes. While specific GLP-1RA have showed positive cardiovascular benefits in patients with type 2 diabetes (SUSTAIN-6 with subcutaneous Semaglutide[26]; LEADER with Liraglutide[27]; AMPLITUDE with Efpeglenatide[28]; Harmony Outcomes with Albiglutide[29]; and REWIND with Dulaglutide[30]), other GLP-1RA CVOTs showed neutral results (EXSCEL with Exenatide[31]; ELIXA trial with Lixisenatide[32]; and PIONEER 6 oral Semaglutide[33]). Allowing for the same limitations in a direct comparison between CVOTs and our data as previously mentioned, we can see that our data showed a greater reduction in all-cause mortality HR 0.47 to 0.78-1.05 and myocardial infarction HR 0.70 to 0.74-0.86.[26–30] The reduction in stroke (HR 0.77 to 0.74-0.86) and heart failure (HR 0.73 to 0.61-1.11) risk were similar to the CVOT studies.[26–30]

There are limited data on cardiovascular outcomes with GLP-1RA and SGLT2i combination. A post-hoc analysis of the EXSCEL trial showed combination therapy may provide additional cardiovascular benefit compared with Exenatide alone.[34] However, given the post-hoc nature and moderate size of the study cohort this should be interpreted as a hypothesis generating trend. Stronger evidence for combination therapy came from the SCALE trial,[35] where concomitant use of an SGLT2i was seen in roughly 15% of the study population showing overlapping confidence intervals between both cohorts. This suggests that the benefit of a GLP-1RA is independent of SGLT2i. In a large metanalysis (eight RCTs with 1895 patients) showed significant improvement in body weight and blood pressure but no difference in cardiovascular events above monotherapy.[13] This is in contrast to a previous meta-analysis in 2020 (five RCTs and six non-RCTs of 1604 patients) that showed improved outcomes with combination therapy as compared with monotherapy with either GLP-1RA or SGLT2i.[36]

Previous similar retrospective studies have been limited by small sample sizes in heterogeneous patient cohorts with limited duration of

data.[37–39] This is a large real-world study undertaken to evaluate the benefit of monotherapy and combination therapy on mortality and cardiovascular outcomes. Our study was able to leverage data from 7 million patients with type 2 diabetes from 85 different HCOs in multiple countries and our final analysis included approximately 108 000 dual therapy patients compared with 186 000 in the GLP-1RA cohort and 143 000 in the SGLT2i cohort. The population size of our study and the long duration of the analysis adds credible evidence to the literature as to the beneficial effects of combination therapy on all-cause mortality.

Given the retrospective nature of the study, several limitations exist. First, these are real world data, which are not randomized comparisons nor are they controlled. Specifically, the effect of socioeconomic status on access to novel anti-glycaemic treatments cannot be accounted for in this study. Second, as data are extracted from the EHR from an administrative database, there is a potential for a lack of data completeness, data may not be recorded by the HCO or recorded in free text that we are unable to extrapolate. Specifically, mortality data were extracted only from the electronic health records of the participating HCOs and not a government source, such as a registered persons database. In addition, should participants move between HCO, it is possible that some of their data may not be available to us as one or more of their HCOs may not form part of the global collaborative network. Therefore, this retrospective cohort analysis requires interpretation in the context of a lack of ideal control and higher risk of confounding, showing associations and not causality.

In conclusion, SGLT2i, GLP-1RA and combination therapy of SGLT2i + GLP-1RA are more effective than other therapies for type 2 diabetes with a prognostic mortality and cardiovascular benefit based on real-world practice data. Combination therapy also appears to provide a greater all-cause mortality and cardiovascular benefit than monotherapy with either drug class. These findings should be confirmed by monotherapy versus combination therapy trials with multifactorial risk modification in high-risk type 2 diabetes populations.

AUTHOR CONTRIBUTIONS

DRR contributed to the generation of the results and analysis using the TriNetX platform, and took lead on writing the manuscript. HE and FP contributed to the writing of the manuscript. PA, GH, IK and RG facilitated access to the TriNetX platform and assisted in generating the results and analysis, PA also contributed to the writing of the manuscript. DJC and GYHL provided senior author review of the manuscript and UA oversaw the study development, manuscript writing and provided senior author review of the manuscript. UA is also the guarantor of this work and had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGEMENTS

No funding was received for this work.

CONFLICT OF INTEREST STATEMENT

DC has received investigator-initiated grants from Astra Zeneca and Novo Nordisk and support for education from Perspectum. PA, IK, GH and RG are employees of TriNetX LLC. GYHL is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthem. No fees are received personally. GYHL is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 899871. UA has received honoraria from Procter and Gamble, Viatris and Sanofi for educational meetings. UA has also received investigator-led funding by Procter and Gamble. HE, FP and DRR have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15185.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from TriNetX, LLC, https://trinetx.com/, but third-party restrictions apply to the availability of these data. The data were used under license for this study with restrictions that do not allow for the data to be redistributed or made publicly available. However, for accredited researchers, the TriNetX data are available for licensing at TriNetX, LLC. Data access may require a data sharing agreement and may incur data access fees. Data used in the generation of this paper was collected from the global TriNetX network and local data at LUHFT were not used.

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SUPPORTING INFORMATION

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

How to cite this article: Riley DR, Essa H, Austin P, et al. All-cause mortality and cardiovascular outcomes with sodium-glucose Co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and with combination therapy in people with type 2 diabetes. *Diabetes Obes Metab*. 2023; 25(10):2897-2909. doi:10.1111/dom.15185