Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events

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Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study

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ABSTRACT

OBJECTIVE

To determine whether the combined use of glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors is associated with a decreased risk of major adverse cardiovascular events and serious renal events compared with either drug class alone among patients with type 2 diabetes, and to assess the effect of the combination on the individual components of major adverse cardiovascular events, heart failure, and all cause mortality.

DESIGN

Population based cohort study using a prevalent new-user design, emulating a trial.

SETTING

UK Clinical Practice Research Datalink linked to Hospital Episode Statistics Admitted Patient Care and Office for National Statistics databases.

PARTICIPANTS

Two prevalent new-user cohorts were assembled between January 2013 and December 2020, with follow-up until the end of March 2021. The first cohort included 6696 patients who started GLP-1 receptor agonists and added on SGLT-2 inhibitors, and the second included 8942 patients who started SGLT-2 inhibitors and added on GLP-1 receptor agonists. Combination users were matched, in a 1:1 ratio, to patients prescribed the same background drug, duration of background drug, and time conditional propensity score.

MAIN OUTCOME MEASURES

Cox proportional hazards models were fitted to estimate the hazard ratios and 95% confidence intervals of major adverse cardiovascular events and serious renal events, separately, comparing the GLP-1 receptor agonist-SGLT-2 inhibitor combination with the background drug, either GLP-1 receptor agonists or SGLT-2 inhibitors, depending on the cohort. Secondary outcomes included associations with the individual components of major adverse cardiovascular events (myocardial infarction, ischaemic stroke, cardiovascular mortality), heart failure, and all cause mortality.

RESULTS

Compared with GLP-1 receptor agonists, the SGLT-2 inhibitor-GLP-1 receptor agonist combination was associated with a 30% lower risk of major adverse cardiovascular events (7.0 *v* 10.3 events per 1000 person years; hazard ratio 0.70, 95% confidence interval 0.49 to 0.99) and a 57% lower risk of serious renal events (2.0 *v* 4.6 events per 1000 person years; hazard ratio 0.43, 0.23 to 0.80). Compared with SGLT-2 inhibitors, the GLP-1 receptor agonist-SGLT-2 inhibitor combination was associated with a 29% lower risk of major adverse cardiovascular events (7.6 *v* 10.7 events per 1000 person years; hazard ratio 0.71, 0.52 to 0.98), whereas serious renal events generated a wide confidence interval (1.4 *v* 2.0 events per 1000 person years; hazard ratio 0.67, 0.32 to 1.41). Secondary outcomes generated similar results but with wider confidence intervals.

CONCLUSIONS

In this cohort study, the GLP-1 receptor agonist-SGLT-2 inhibitor combination was associated with a lower risk of major adverse cardiovascular events and serious renal events compared with either drug class alone.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors reduce the risk of cardiovascular and renal events in patients with type 2 diabetes

These drug classes are increasingly used in combination when previous therapy with other antihyperglycaemic drugs fails

Whether the combined use of these drug classes results in improved cardiovascular and renal outcomes in the real world setting, compared with the use of either drug class alone, remains unclear

WHAT THIS STUDY ADDS

This population based cohort study aimed at emulating a randomised controlled trial

The combined use of a GLP-1 receptor agonist and an SGLT-2 inhibitor was associated with a lower risk of cardiovascular and serious renal events, compared with either drug class alone

These findings highlight the potential benefit of combining these two effective drug classes in preventing cardiovascular and renal events in the treatment of type 2 diabetes

Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are second to third line antihyperglycaemic drugs commonly prescribed for the treatment of type 2 diabetes.[1 2] Individually, these drugs have been shown to reduce the risk of cardiorenal events and mortality in large cardiovascular outcome trials.[3-9] However, the combined effect of these drug classes on these outcomes has not been extensively studied.

GLP-1 receptor agonists and SGLT-2 inhibitors are often combined in clinical settings when monotherapy fails to maintain glycaemic targets.[10 11] Given their different mechanisms of action, the combination of the drugs may improve clinical outcomes through additive effects. Observational studies among patients with type 2 diabetes have shown that the GLP-1 receptor agonist-SGLT-2 inhibitor combination results in more significant improvements in haemoglobin A_{1c} and blood pressure while lowering body weight than either drug class alone.[12-17] However, these represent surrogate outcomes, and whether this combination is associated with a reduced risk of macrovascular and microvascular complications remains unclear. To date, observational studies investigating the cardiovascular effectiveness of the combination have either been underpowered or had important methodological limitations, such as immortal time bias.[12 15 18-20] Importantly, none compared the combination with either drug class alone or investigated serious renal events, which are clinically relevant outcomes in this patient population.[12 15 18-20]

The primary objective of this study was to determine whether the combined use of GLP-1 receptor agonists and SGLT-2 inhibitors is associated with a decreased risk of two co-primary outcomes, major adverse cardiovascular events and serious renal events, compared with the use of either drug class alone among patients with type 2 diabetes. The secondary outcomes included the association with the individual components of major adverse cardiovascular events (myocardial infarction, ischaemic stroke, cardiovascular mortality), heart failure, and all cause mortality.

Methods

Data sources

This population based cohort study was conducted using data from the UK Clinical Practice Research Datalink (CPRD) GOLD and Aurum databases, linked with the Hospital Episode Statistics Admitted Patient Care (HES APC) and the Office for National Statistics (ONS) databases. The CPRD is a large primary care database with data for more than 60 million patients from approximately 2000 general practices across the UK.[21] These 60 million patients were born, living, and deceased during the study period while registered with a general practice in the UK. Read codes and SNOMED-CT terms are used to code clinical data such as diagnoses and procedures, and prescriptions are recorded using drug codes linked to the British National Formulary.[21] More than 90% of patients in the CPRD are linkable to other datasets.[22 23] The HES APC database contains hospital admission records from English National Health Service hospitals and includes information such as admission and discharge dates, diagnoses (recorded using ICD-10 (international classification of diseases, 10th revision) codes), specialists seen, and procedures undertaken for all linked patients.[23] The ONS database is a vital statistics database that contains data on registered deaths in the UK, including the official date and causes of death.[23]

Study population

We used a prevalent new-user design,[24] a design that emulates a randomised controlled trial,[25] to investigate the effect of the GLP-1 receptor agonist-SGLT-2 inhibitor combination on cardiorenal outcomes compared with either drug class alone or with other antihyperglycaemic drugs. Essentially, this design emulated a randomised controlled trial, in which participants on a background therapy with one of the drug classes of interest (GLP-1 receptor agonists or SGLT-2 inhibitors) are randomised to either continue the background drug or add on the other drug of interest (SGLT-2 inhibitor or GLP-1 receptor agonist, respectively). Thus, we constructed two cohorts. One cohort included patients with a background treatment of a GLP-1 receptor agonist who added on an SGLT-2 inhibitor and were compared with those who continued a background treatment of GLP-1 receptor agonists. The second cohort included patients with a background treatment of an SGLT-2 inhibitor who added on a GLP-1 receptor agonist; these patients were compared with those who continued a background treatment of SGLT-2 inhibitors.

We first assembled two separate base cohorts of new users of the drug classes of interest (GLP-1 receptor agonists (dulaglutide, exenatide, liraglutide (except the 3 mg/0.5 mL formulation indicated for weight loss), lixisenatide, semaglutide) and SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)). These cohorts consisted of patients who received their first prescription for one of these drug classes between 1 January 2013 (the year SGLT-2 inhibitors were introduced in the UK market) and 31 December 2020. To be included in these cohorts, patients had to be at least 18 years of age and have at least one year of medical history in the CPRD before the first prescription. We excluded patients who used either GLP-1 receptor agonists or SGLT-2 inhibitors in the year before the first prescription in order to identify new users. For the base cohort of new GLP-1 receptor agonist users, we excluded patients with a history of SGLT-2 inhibitors and vice versa for the base cohort of new SGLT-2 inhibitor users. We also excluded patients with no diagnosis of type 2 diabetes ever before cohort entry, as well as those with diagnosed contraindications for the study drugs—namely, end stage renal disease and multiple endocrine neoplasia syndrome, assessed ever before cohort entry. Using an on-treatment approach, we followed the new users of the drug classes of interest while they remained continuously exposed. Continuous use was defined as having overlapping successive prescriptions, with a 60 day grace period to bridge consecutive non-overlapping prescriptions. We followed patients until treatment discontinuation, death, end of registration with the CPRD, end of the follow-up period (29 March 2021) or add-on of one of the drugs of interest (described below), whichever occurred first.

Using the base cohorts defined above, we created the study cohorts. We divided the follow-up period into 30 day intervals. Within each 30 day interval, we identified new users of the GLP-1 receptor agonist-

SGLT-2 inhibitor combination. These included patients who started their treatment with both drug classes on the same day at the start of follow-up and those who added on a GLP-1 receptor agonist or an SGLT-2 inhibitor for the first time at some point during the follow-up (up until 29 March 2021). The comparator consisted of patients who had never used a GLP-1 receptor agonist-SGLT-2 inhibitor combination up until the time of the interval and had received a prescription for the background drug at that 30 day interval. As part of the design, patients initially in the comparator group could enter the combination group, but only after receiving the add-on drug.

We then calculated time conditional propensity scores by using conditional logistic regression, conditional on the covariates listed below and stratifying on two variables: time interval and specific background drug. The second variable was to account for possible heterogeneity in the effectiveness within a drug class (for example, for empagliflozin, this variable grouped all patients who used that drug; these included patients who used empagliflozin in combination with a GLP-1 receptor agonist or empagliflozin alone). See the supplementary appendix for SAS codes.

Finally, in both study cohorts, we matched combination users in chronological order, in a one to one ratio without replacement, to GLP-1 receptor agonist or SGLT-2 inhibitor users (depending on the cohort) with the same background drug, duration of use of the background drug, and propensity score. Study cohort entry was defined by the date of the add-on prescription in the combination group and the prescription date of the comparator drug in a given interval. Thus, this matching procedure ensured that combination users and their comparators used the same background drug for the same duration and had a similar probability of receiving the treatment combination. See supplementary figure A for a graphical depiction of the design. Supplementary table A compares the methods of a target trial of the question and our emulated trial using real world data.

Exposure definition

We used an on-treatment approach in which patients were followed while being continuously exposed to the study drugs. For patients receiving a combination of a GLP-1 receptor agonist and an SGLT-2 inhibitor, continuous use was determined by overlapping prescription durations of both drug classes and allowing a 60 day grace period to bridge consecutive non-overlapping prescriptions. Hence, we considered patients to be combination users if their GLP-1 receptor agonist and SGLT-2 inhibitor prescriptions overlapped each other during the follow-up period. As such, treatment discontinuation for combination users was defined by the absence of either drug class by the end of the 60 day grace period. For patients on the background drug, treatment discontinuation was defined by the absence of a prescription by the end of the 60 day grace period. Thus, all patients were followed from study cohort entry until one of the study outcomes (described below), treatment discontinuation, initiation of a study drug in the comparator group, death from any cause (depending on the outcome), end of registration, or the end of the study period (29 March 2021), whichever came first.

Primary and secondary outcomes

We assessed two co-primary outcomes, which we identified by using inpatient diagnostic codes and mortality codes in the primary position (ICD-10 codes for the outcomes can be found in supplementary table B**).** They included major adverse cardiovascular events, which included myocardial infarction, ischaemic stroke, and cardiovascular mortality; and serious renal events, which included acute kidney injury, chronic kidney disease, hypertensive chronic renal disease, unspecified kidney failure, and renal complications of diabetes. Additionally, we examined secondary outcomes such as the individual components of major adverse cardiovascular events (myocardial infarction, ischaemic stroke, cardiovascular mortality), heart failure, and all cause mortality.

Potential confounders

We considered a wide range of potential confounders measured at or before study cohort entry. This corresponded to the time of new drug in combination users and the matched time in comparators. Hence, all covariates were updated at each exposure set in a time varying fashion. The covariates included age (modelled as a continuous variable using cubic splines with five knots at the 5th, 27.5th, 50th, 72.5th, and 95th centiles), sex, smoking status, body mass index, alcohol related disorders, and cohort entry year (2013-15, 2016-18, 2019-21). We also considered proxies for severity of diabetes, including duration of diabetes (calculated by the time difference between cohort entry date and date of the first of either a haemoglobin A_{1c} >6.4%, a diagnosis of type 2 diabetes, or prescription for an antihyperglycaemic drug ever before cohort entry), haemoglobin A_{1c} level (≤7.0%, 7.1-8.0%, or >8.0%), types of antihyperglycaemic drugs used in the year before cohort entry (metformin, sulfonylureas, thiazolidinediones, meglitinides, α-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, and insulin), microvascular (nephropathy, neuropathy, retinopathy) and macrovascular complications of diabetes (myocardial infarction, ischaemic stroke, peripheral vascular disease, coronary artery disease, coronary revascularisation, heart failure, all measured in ever before study cohort entry). Additionally, we considered common comorbidities (cancer (other than non-melanoma skin cancer), atrial fibrillation, thyroid diseases, and chronic obstructive pulmonary disease), as well as common prescription drugs (antihypertensives (diuretics, β blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and others), non-steroidal anti-inflammatory drugs, paracetamol, acetylsalicylic acid, other antiplatelet agents, statins, fibrates, digoxin, opioids), and markers

of healthcare seeking behaviour (colorectal cancer screening, prostate specific antigen screening, and influenza vaccination). These potential confounders were identified by Read and SNOMED-CT codes in the CPRD and ICD-10 codes in HES APC. We used an unknown category for variables that contained missing data (for example, body mass index, smoking status, haemoglobin A_{1c}).

Statistical analysis

We summarised patients' characteristics by using descriptive statistics in each cohort. An absolute standardised difference of <0.10 between the matched exposure groups was indicative of good balance. We calculated incidence rates of the outcomes for each exposure group, with confidence intervals based on the Poisson distribution. We used Kaplan-Meier curves to plot the cumulative incidence of the co-primary outcomes for the different exposure groups over the follow-up period. We fitted Cox proportional hazards regression models to estimate the hazard ratios and 95% confidence intervals for each outcome, comparing the GLP-1 receptor agonist-SGLT-2 inhibitor combination with the background drug. We calculated the number needed to treat to prevent one event at one year and three years of use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination by using the Kaplan-Meier method.[26]

Secondary analyses

We did three secondary analyses to examine the effect of the combined GLP-1 receptor agonist-SGLT-2 inhibitor treatment in patient subgroups of interest. Firstly, we did separate stratified analyses based on cardiovascular and chronic renal disease history at study cohort entry. Secondly, we stratified the analysis on the basis of the individual GLP-1 receptor agonist-SGLT-2 inhibitor combinations. Finally, we did effect measure modification analyses for age (>65 and ≤65 years) and sex. For these analyses, we included interaction terms between the exposure variable and these variables in the models.

Sensitivity analyses

We did several sensitivity analyses to examine whether our results were robust to varying assumptions. Firstly, given uncertainties about the grace period between consecutive prescriptions, we repeated our analyses using grace periods of 30 and 90 days. Secondly, to assess the impact of potential informative censoring, we did an analysis using time varying inverse probability of censoring weighting. We calculated this by taking the product of the weights calculated from the conditional probabilities of treatment discontinuation or switching, administrative censoring (end of study period/end of registration with practice), and death by using the covariates listed above. SAS codes for the calculation of these weights can be found in the supplementary appendix. Thirdly, given that insulin use has been associated with adverse cardiovascular effects, we did a separate analysis in which we excluded patients who had used insulin at study cohort entry and censored on insulin use during follow-up. We used new cohorts and propensity matching for this analysis. Fourthly, to assess the impact of missing data on our findings, we did an analysis using multiple imputation. Multiple regression models were fitted to impute variables that contained missing data, and the resulting datasets were combined using Rubin's rules.[27-29] Finally, we did an analysis repeating the process using one to two matching. We used SAS version 9.4 for all analyses.

Patient and public involvement

Our study was a secondary data analysis and did not include patients as study participants. No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. This is because no specific funding had been allocated for this purpose. Moreover, the CPRD data are not publicly available, and the analysis plan requires specialised training.

Results

GLP-1 receptor agonist-SGLT-2 inhibitor combination versus GLP-1 receptor agonists

Supplementary table C shows the distribution of the characteristics of both exposure groups before matching. The cohort included 6696 patients who added an SGLT-2 inhibitor to their GLP-1 receptor agonist treatment, who were matched to an equal number of patients who continued their treatment with GLP-1 receptor agonists (fig 1). The most common combinations were liraglutide and dapagliflozin (1380 users), liraglutide and empagliflozin (1240 users), dulaglutide and empagliflozin (963 users), and by liraglutide and canagliflozin (562 users).

Table 1 shows the characteristics of the GLP-1 receptor agonist-SGLT-2 inhibitor combination users and GLP-1 receptor agonist users after matching. The exposure groups were well balanced across all covariates, with all standardised differences below 0.05. The mean durations of diabetes and previous use of GLP-1 receptor agonists was around 11 and 1.6 years, respectively, at cohort entry. We assessed the positivity assumption within each exposure set and observed good overlap between the propensity score distributions (supplementary figure B).

Table 2 shows the results of the analyses for the primary and secondary outcomes. Overall, the use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination was associated with a 30% lower risk of MACE (7.0 *v* 10.3 per 1000 person years; hazard ratio 0.70, 95% confidence interval 0.49 to 0.99) compared with the use of GLP-1 receptor agonists after a median follow-up time of 9.0 months. Figure 2 shows the cumulative incidence curves for major adverse cardiovascular events, with a lower cumulative incidence for the GLP-1 receptor agonist-SGLT-2 inhibitor combination and the curves diverging after eight months of use. The number needed to treat to prevent one major adverse cardiovascular event after one and three years of use was 378 and 131, respectively.

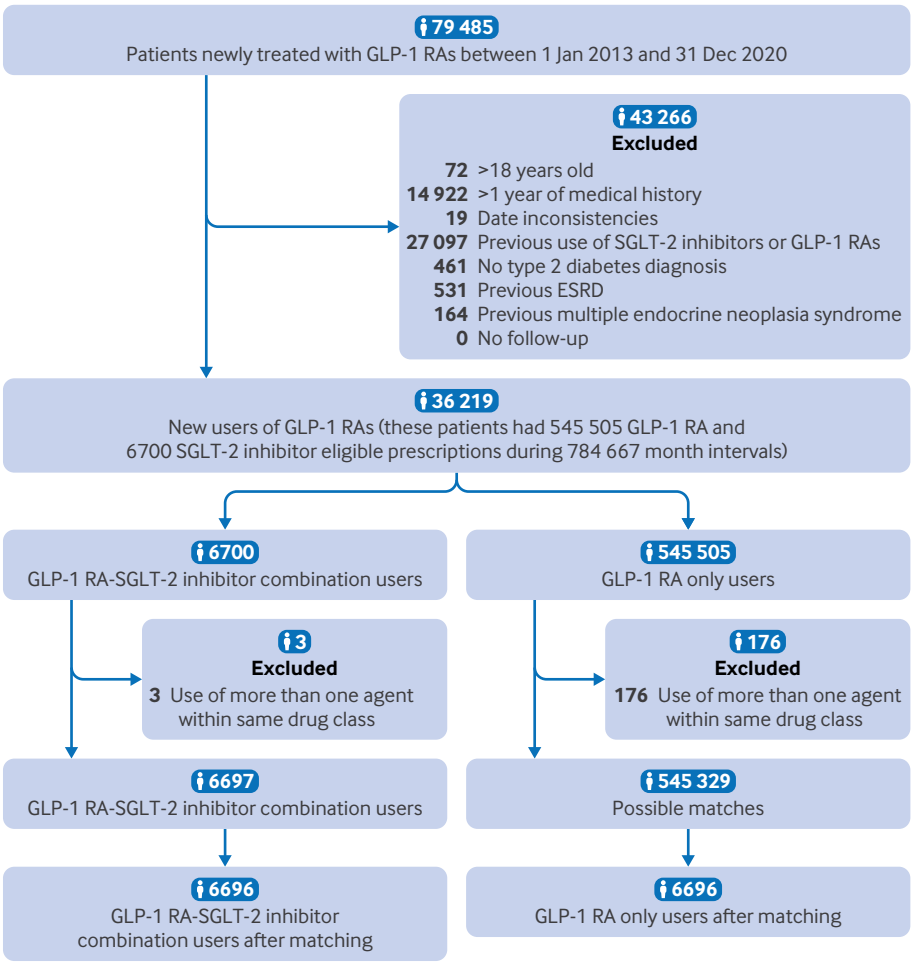

Fig 1 | Study flowchart for construction of glucagon-like peptide-1 (GLP-1) receptor agonist (RA)-sodium-glucose cotransporter-2 (SGLT-2) inhibitor combination users versus GLP-1 RA users cohort. An individual can represent multiple matching opportunities at different times during follow-up period; thus, number of possible matches exceeds total number of patients. ESRD=end stage renal disease

For the secondary outcomes, the GLP-1 receptor agonist-SGLT-2 inhibitor combination was associated with a 65% lower risk of cardiovascular mortality (1.1 *v* 2.9 per 1000 person years; hazard ratio 0.35, 0.15 to 0.80) and a 43% lower risk of heart failure (3.6 *v* 6.1 per 1000 person years; 0.57, 0.35 to 0.91) compared with GLP-1 receptor agonists. Hazard ratios were below the null value for myocardial infarction, ischaemic stroke, and all cause mortality but generated wide confidence intervals. When patients were stratified by history of cardiovascular disease, the use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination in patients with previous cardiovascular disease was associated with a lower hazard ratio with respect to all cause mortality (0.46, 0.26 to 0.80) than in patients without a history of cardiovascular disease (1.04, 0.64 to 1.71; supplementary table D). After stratification by specific GLP-1 receptor agonist-SGLT-2 inhibitor combinations, the hazard ratios ranged from 0.64 for the liraglutide-dapagliflozin combination to 1.18 for the liraglutide-empagliflozin combination with confidence intervals overlapping each other (supplementary table E). We observed no effect measure modification for age and sex (supplementary tables F and G). Finally, the results of the sensitivity analyses were consistent with those of the primary analysis (supplementary tables H-L).

After a median follow-up time of 9.1 months, the use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination was associated with a 57% lower risk of serious renal events (2.0 *v* 4.6 per 1000 person years; hazard ratio 0.43, 0.23 to 0.80) compared with the use of GLP-1 receptor agonists (table 2). Supplementary figure C shows the cumulative incidence curves for serious renal events, with a lower cumulative incidence for the GLP-1 receptor agonist-SGLT-2 inhibitor combination and the curves diverging after nine months of use. We observed no effect measure modification after stratifying patients by history of renal disease (supplementary table M).

GLP-1 receptor agonist-SGLT-2 inhibitor combination versus SGLT-2 inhibitors

Supplementary table N shows the distribution of the characteristics of the exposure groups before

Table 1 | Characteristics of GLP-1 receptor agonist-SGLT-2 inhibitor combination users and GLP-1 receptor agonist users after matching. Values are numbers (percentages) unless stated otherwise

Characteristics	GLP-1 receptor agonist-SGLT-2 inhibitor combination users (n=6696)	GLP-1 receptor agonist users (n=6696)	Absolute standardised difference
Mean (SD) age, years	56.7 (10.4)	57.3 (10.4)	0.05
Male sex	3652 (54.5)	3643 (54.4)	0.00
Body mass index:			
30	837 (12.5)	840 (12.5)	0.00
≥30	5782 (86.4)	5790 (86.5)	0.00
Unknown	77 (1.1)	66 (1.0)	0.02
Smoking status:			
Ever	5384 (80.4)	5434 (81.2)	0.02
Never	1302 (19.4)	1251 (18.7)	0.02
Unknown	10 (0.1)	11 (0.2)	0.00
Alcohol related disorders	566 (8.5)	567 (8.5)	0.00
Mean (SD) duration of GLP-1 receptor agonist use, years	1.6 (1.4)	1.6 (1.4)	0.00
Mean (SD) duration of diabetes, years	11.0 (6.1)	11.2 (6.3)	0.03
Haemoglobin A_{1c}:			
≤7.0%	323 (4.8)	281 (4.2)	0.03
7.1-8.0%	983 (14.7)	994 (14.8)	0.00
>8.0%	5374 (80.3)	5409 (80.8)	0.01
Unknown	16 (0.2)	12 (0.2)	0.01
Type of antihyperglycaemic drugs:			
Metformin	6048 (90.3)	6035 (90.1)	0.01
Thiazolidinediones	469 (7.0)	467 (7.0)	0.00
Meglitinides	26 (0.4)	21 (0.3)	0.01
α glucosidase inhibitors	7 (0.1)	4 (0.1)	0.02
Sulfonylureas	3411 (50.9)	3386 (50.6)	0.01
DPP-4 inhibitors	1705 (25.5)	1695 (25.3)	0.00
Insulin	1705 (25.5)	1701 (25.4)	0.00
Peripheral vascular disease	652 (9.7)	689 (10.3)	0.02
Ischaemic stroke	240 (3.6)	252 (3.8)	0.01
Myocardial infarction	438 (6.5)	444 (6.6)	0.00
Coronary artery disease	1088 (16.2)	1131 (16.9)	0.02
Coronary revascularisation	472 (7.0)	485 (7.2)	0.01
Heart failure	354 (5.3)	383 (5.7)	0.02
Renal disease	659 (9.8)	755 (11.3)	0.05
Retinopathy	2992 (44.7)	3064 (45.8)	0.02
Neuropathy	1890 (28.2)	1974 (29.5)	0.03
Cancer	1502 (22.4)	1537 (23.0)	0.01
Atrial fibrillation/flutter	349 (5.2)	394 (5.9)	0.03
Thyroid disease	764 (11.4)	806 (12.0)	0.02
Chronic obstructive pulmonary disease	812 (12.1)	840 (12.5)	0.01
Diuretics	1119 (16.7)	1171 (17.5)	0.02
β blockers	1591 (23.8)	1632 (24.4)	0.01
Calcium channel blockers	2123 (31.7)	2142 (32.0)	0.01
Angiotensin converting enzyme inhibitors	3304 (49.3)	3278 (49.0)	0.01
Angiotensin II receptor blockers	1365 (20.4)	1390 (20.8)	0.01
Other antihypertensive drugs	97 (1.4)	94 (1.4)	0.00
Non-steroidal anti-inflammatory drugs	1524 (22.8)	1539 (23.0)	0.01
Paracetamol	2245 (33.5)	2306 (34.4)	0.02
Acetylsalicylic acid	1656 (24.7)	1697 (25.3)	0.01
Other antiplatelets	393 (5.9)	379 (5.7)	0.01
Statins	5470 (81.7)	5530 (82.6)	0.02
Digoxin	87 (1.3)	101 (1.5)	0.02
Fibrates	219 (3.3)	208 (3.1)	0.01
Opioids	150 (2.2)	159 (2.4)	0.01
Colorectal cancer screening	1122 (16.8)	1133 (16.9)	0.00
Prostate specific antigen testing	372 (5.6)	397 (5.9)	0.02
Influenza vaccination	126 (1.9)	119 (1.8)	0.01
Year of study cohort entry:			
2013-15	1473 (22.0)	1443 (21.6)	0.01
2016-18	2921 (43.6)	2955 (44.1)	0.01
2019-21	2302 (34.4)	2298 (34.3)	0.00

DPP-4=dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter-2; SD=standard deviation.

matching. The cohort included 8942 patients who added a GLP-1 receptor agonist to their SGLT-2 inhibitor treatment, who were matched to an equal number of patients using SGLT-2 inhibitors only (fig 3). No patients on the combination treatment were lost in the matching process. The most common

Table 2 | Hazard ratios for primary and secondary outcomes comparing GLP-1 receptor agonist-SGLT-2 inhibitor combination with GLP-1 receptor agonist use alone

Exposure	No of patients	Events	Person years	Incidence rate (95% CI)*	Hazard ratio (95% CI)†
Primary outcomes					
MACE:					
GLP-1 RAs	6696	113	10 971	10.3 (8.5 to 12.4)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	45	6417	7.0 (5.1 to 9.4)	0.70 (0.49 to 0.99)
Serious renal events:					
GLP-1 RAs	6696	51	10 992	4.6 (3.5 to 6.1)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	13	6453	2.0 (1.1 to 3.4)	0.43 (0.23 to 0.80)
Secondary outcomes					
Myocardial infarction:					
GLP-1 RAs	6696	60	10 971	5.5 (4.2 to 7.0)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	24	6417	3.7 (2.4 to 5.6)	0.73 (0.45 to 1.17)
Ischaemic stroke:					
GLP-1 RAs	6696	30	10 971	2.7 (1.8 to 3.9)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	15	6417	2.3 (1.3 to 3.9)	0.90 (0.48 to 1.67)
Cardiovascular mortality:					
GLP-1 RAs	6696	32	10 971	2.9 (2.0 to 4.1)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	7	6417	1.1 (0.4 to 2.3)	0.35 (0.15 to 0.80)
Heart failure:					
GLP-1 RAs	6696	67	10 979	6.1 (4.7 to 7.8)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	23	6446	3.6 (2.3 to 5.4)	0.57 (0.35 to 0.91)
All cause mortality:					
GLP-1 RAs	6696	102	11 056	9.2 (7.5 to 11.2)	1.00 (reference)
GLP-1 RA-SGLT-2 inhibitor combination	6696	41	6459	6.4 (4.6 to 8.6)	0.71 (0.49 to 1.02)

CI=confidence interval; GLP-1=glucagon-like peptide 1; MACE=major adverse cardiovascular events; RA=receptor agonist; SGLT-2=sodium-glucose cotransporter-2.
*Per 1000 person years.
†Patients were matched on duration of GLP-1 RA use, GLP-1 RA drug type, and propensity score.

combinations were dapagliflozin and dulaglutide (1865 users), empagliflozin and dulaglutide (1633 users), dapagliflozin and liraglutide (1119 users), and empagliflozin and semaglutide (784 users).

Table 3 shows the characteristics of the GLP-1 receptor agonist-SGLT-2 inhibitor combination users and SGLT-2 inhibitor users after matching. The exposure groups were well balanced across all covariates, with no standardised difference above 0.02. The mean duration of diabetes was 10.8 years at cohort entry, and the mean duration of SGLT-2 inhibitor use at study cohort entry was 1.5 years. We assessed the positivity assumption within each exposure set and observed good overlap between the propensity score distributions (supplementary figure D).

Table 4 shows the results of the analyses for the primary and secondary outcomes. Overall, the use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination was associated with a 29% lower risk of major adverse cardiovascular events (7.6 *v* 10.7 per 1000 person years; hazard ratio 0.71, 0.52 to 0.98) compared with the use of SGLT-2 inhibitors after a median follow-up time of 8.4 months. Figure 4 shows the cumulative incidence curves for major adverse cardiovascular events, with a lower cumulative incidence for the GLP-1 receptor agonist-SGLT-2 inhibitor combination and the curves diverging after three months of use. The number needed to treat to prevent one major adverse cardiovascular event after one and three years of use was 221 and 86, respectively.

For the secondary outcomes, the hazard ratios were below the null value for myocardial infarction, ischaemic stroke, cardiovascular mortality, heart failure, and all cause mortality, but with wide confidence intervals that included the null. The hazard ratios were similar after stratification of patients by history of cardiovascular disease (supplementary table O). After stratifying by specific GLP-1 receptor agonist-SGLT-2 inhibitor combination, we observed similar hazard ratios between the different types of combinations (supplementary table P). No

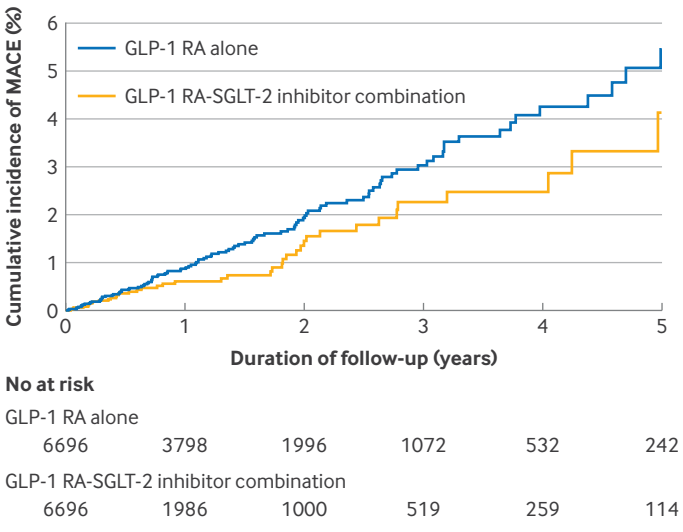

Fig 2 | Cumulative incidence curves of major adverse cardiovascular events (MACE) for glucagon-like peptide-1 (GLP-1) receptor agonist (RA)-sodium-glucose cotransporter-2 (SGLT-2) inhibitor combination versus GLP-1 RAs

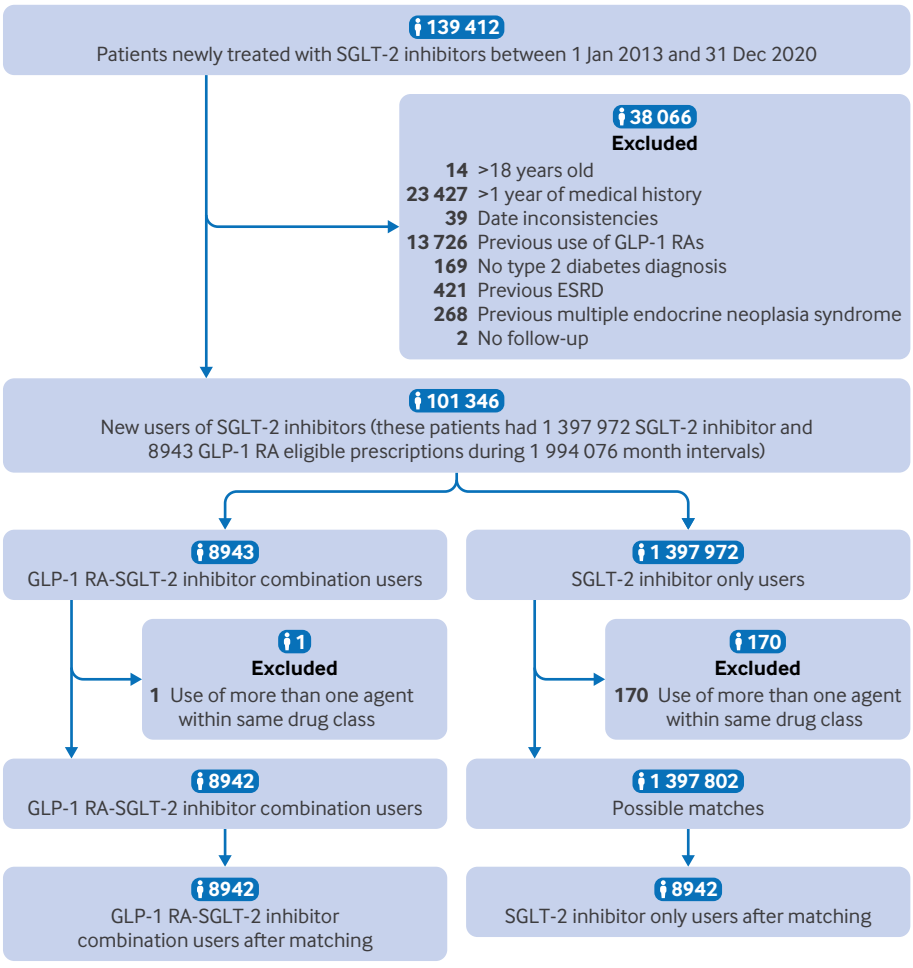

Fig 3 | Study flowchart for construction of glucagon-like peptide-1(GLP-1) receptor agonist (RA)-sodium-glucose cotransporter-2 (SGLT-2) inhibitor combination users versus SGLT-2 inhibitor users cohort. An individual can represent multiple matching opportunities at different times during follow-up period; thus, number of possible matches exceeds total number of patients. ESRD=end stage renal disease

effect measure modification by age was apparent (supplementary table Q). With respect to major adverse cardiovascular events, the use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination in female patients was associated with a lower hazard ratio (0.39, 0.22 to 0.71) compared with male patients (0.96, 0.66 to 1.40; supplementary table R). The results of the sensitivity analyses are presented in supplementary tables S-W, and they are consistent with those of the primary analysis.

After a median follow-up of 8.5 months, the cohort generated 36 serious renal events. The use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination was associated with a hazard ratio below the null with a wide confidence interval (1.4 *v* 2.0 per 1000 person years; hazard ratio 0.67, 0.32 to 1.41). Supplementary figure E shows the cumulative incidence curves for serious renal events, with a lower cumulative incidence for the GLP-1 receptor agonist-SGLT-2 inhibitor combination up to two years and the crossing thereafter. When we stratified patients by history of renal disease, the use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination in patients with a history of renal disease was associated with a lower hazard ratio for major adverse cardiovascular events (0.41, 0.18 to 0.94) compared with patients without previous renal disease (0.80, 0.57 to 1.12; supplementary table X).

Discussion

The results of this population based cohort study, designed to emulate a randomised controlled trial, suggest that the combined use of GLP-1 receptor agonists and SGLT-2 inhibitors is associated with a reduced risk of major adverse cardiovascular events and serious renal events, compared with using either drug class alone. The addition of an SGLT-2 inhibitor to existing GLP-1 receptor agonist use was also associated with a reduced risk of cardiovascular mortality and heart failure compared with GLP-1 receptor agonists alone. Overall, the results remained robust in several sensitivity analyses.

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Table 3 | Characteristics of GLP-1 receptor agonist-SGLT-2 inhibitor combination users and SGLT-2 inhibitor users after matching. Values are numbers (percentages) unless stated otherwise

Characteristics	SGLT-2 inhibitor-GLP-1 receptor agonist combination users (n=8942)	SGLT-2 inhibitor users (n=8942)	Absolute standardised difference
Mean (SD) age, years	57.6 (10.2)	57.5 (10.3)	0.00
Male sex	4676 (52.3)	4752 (53.1)	0.02
Body mass index:			
30	1567 (17.5)	1628 (18.2)	0.02
≥30	7296 (81.6)	7235 (80.9)	0.02
Unknown	79 (0.9)	79 (0.9)	0.00
Smoking status:			
Ever	7177 (80.3)	7149 (79.9)	0.01
Never	1758 (19.7)	1787 (20.0)	0.01
Unknown	7 (0.1)	6 (0.1)	0.00
Alcohol related disorders	759 (8.5)	756 (8.5)	0.00
Mean (SD) duration of GLP-1 receptor agonist use, years	1.5 (1.4)	1.5 (1.4)	0.01
Mean (SD) duration of diabetes, years	10.8 (6.3)	10.8 (6.4)	0.00
Haemoglobin A_{1c}:			
≤7.0%	344 (3.8)	319 (3.6)	0.01
7.1-8.0%	1661 (18.6)	1652 (18.5)	0.00
>8.0%	6924 (77.4)	6959 (77.8)	0.01
Unknown	13 (0.1)	12 (0.1)	0.00
Type of antihyperglycaemic drugs:			
Metformin	8099 (90.6)	8044 (90.0)	0.02
Thiazolidinediones	504 (5.6)	491 (5.5)	0.01
Meglitinides	32 (0.4)	40 (0.4)	0.01
α glucosidase inhibitors	13 (0.1)	11 (0.1)	0.01
Sulfonylureas	3845 (43.0)	3832 (42.9)	0.00
DPP-4 inhibitors	3834 (42.9)	3820 (42.7)	0.00
Insulin	1550 (17.3)	1571 (17.6)	0.01
Peripheral vascular disease	913 (10.2)	904 (10.1)	0.00
Ischaemic stroke	351 (3.9)	377 (4.2)	0.01
Myocardial infarction	573 (6.4)	545 (6.1)	0.01
Coronary artery disease	1464 (16.4)	1472 (16.5)	0.00
Coronary revascularisation	600 (6.7)	599 (6.7)	0.00
Heart failure	396 (4.4)	406 (4.5)	0.01
Renal disease	824 (9.2)	813 (9.1)	0.00
Retinopathy	3743 (41.9)	3771 (42.2)	0.01
Neuropathy	2274 (25.4)	2277 (25.5)	0.00
Cancer	2271 (25.4)	2287 (25.6)	0.00
Atrial fibrillation/flutter	482 (5.4)	490 (5.5)	0.00
Thyroid disease	1018 (11.4)	1022 (11.4)	0.00
Chronic obstructive pulmonary disease	1104 (12.3)	1122 (12.5)	0.01
Diuretics	1372 (15.3)	1360 (15.2)	0.00
β blockers	2060 (23.0)	2049 (22.9)	0.00
Calcium channel blockers	2690 (30.1)	2700 (30.2)	0.00
Angiotensin converting enzyme inhibitors	4383 (49.0)	4445 (49.7)	0.01
Angiotensin II receptor blockers	1677 (18.8)	1664 (18.6)	0.00
Other antihypertensive drugs	114 (1.3)	115 (1.3)	0.00
Non-steroidal anti-inflammatory drugs	2004 (22.4)	2059 (23.0)	0.01
Paracetamol	2887 (32.3)	2818 (31.5)	0.02
Acetylsalicylic acid	1917 (21.4)	1890 (21.1)	0.01
Other antiplatelets	567 (6.3)	612 (6.8)	0.02
Statins	7383 (82.6)	7353 (82.2)	0.01
Digoxin	85 (1.0)	75 (0.8)	0.01
Fibrates	260 (2.9)	232 (2.6)	0.02
Opioids	166 (1.9)	176 (2.0)	0.01
Colorectal cancer screening	1653 (18.5)	1675 (18.7)	0.01
Prostate specific antigen testing	543 (6.1)	561 (6.3)	0.01
Influenza vaccination	143 (1.6)	154 (1.7)	0.01
Year of study cohort entry:			
2013-15	707 (7.9)	697 (7.8)	0.00
2016-18	3388 (37.9)	3381 (37.8)	0.00
2019-21	4847 (54.2)	4864 (54.4)	0.00

DPP-4=dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter-2; SD=standard deviation.

Comparison with previous studies

The results of this study indicate that the combined use of GLP-1 receptor agonists and SGLT-2 inhibitors is associated with a lower risk of major adverse cardiovascular events, compared with the use of either drug class alone. These findings are concordant with

Table 4 | Hazard ratios for primary and secondary outcomes comparing GLP-1 receptor agonist-SGLT-2 inhibitor combination with SGLT-2 inhibitor use alone

Exposure	No of patients	Events	Person years	Incidence rate (95% CI)*	Hazard ratio (95% CI)†
Primary outcomes					
MACE:					
SGLT-2 inhibitor	8942	141	13 160	10.7 (9.0 to 12.6)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	55	7250	7.6 (5.7 to 9.9)	0.71 (0.52 to 0.98)
Serious renal events:					
SGLT-2 inhibitor	8942	26	13 243	2.0 (1.3 to 2.9)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	10	7278	1.4 (0.7 to 2.5)	0.67 (0.32 to 1.41)
Secondary outcomes					
Myocardial infarction:					
SGLT-2 inhibitor	8942	75	13 160	5.7 (4.5 to 7.1)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	30	7250	4.1 (2.8 to 5.9)	0.73 (0.48 to 1.12)
Ischaemic stroke:					
SGLT-2 inhibitor	8942	33	13 160	2.5 (1.7 to 3.5)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	15	7250	2.1 (1.2 to 3.4)	0.86 (0.46 to 1.59)
Cardiovascular mortality:					
SGLT-2 inhibitor	8942	44	13 160	3.3 (2.4 to 4.5)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	13	7250	1.8 (1.0 to 3.1)	0.54 (0.29 to 1.01)
Heart failure:					
SGLT-2 inhibitor	8942	43	13 235	3.3 (2.4 to 4.4)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	17	7274	2.3 (1.4 to 3.7)	0.70 (0.40 to 1.23)
All cause mortality:					
SGLT-2 inhibitor	8942	130	13 259	9.8 (8.2 to 11.6)	1.00 (reference)
SGLT-2 inhibitor-GLP-1 RA combination	8942	50	7284	6.9 (5.1 to 9.1)	0.73 (0.52 to 1.01)

CI=confidence interval; GLP-1=glucagon-like peptide 1; MACE=major adverse cardiovascular events; RA=receptor agonist; SGLT-2=sodium-glucose cotransporter-2
*Per 1000 person years.
†Patients were matched on duration of SGLT-2 inhibitor use, SGLT-2 inhibitor drug type, and propensity score.

those of observational studies that have also observed a decreased risk of major adverse cardiovascular events when comparing the GLP-1 receptor agonist-SGLT-2 inhibitor combination with different types of comparators: sulfonylurea-GLP-1 receptor agonist combination (hazard ratio 0.67, 0.59 to 0.89),[30] metformin-sulfonylurea combination (hazard ratio 0.53, 0.35 to 0.80),[31] and other combination regimens (odds ratio 0.70, 0.50 to 0.98).[19] As these studies compared the GLP-1 receptor agonist-SGLT2 inhibitor combination with other drug combinations, they were designed to answer different clinical questions.[19 30 31] By contrast, our study was specifically designed to determine whether the add-on of a GLP-1 receptor agonist or an SGLT-2 inhibitor versus either drug class alone results in additional benefits on cardiovascular and renal outcomes. This is particularly relevant given the increasing combined use of these effective drug classes.[10 11]

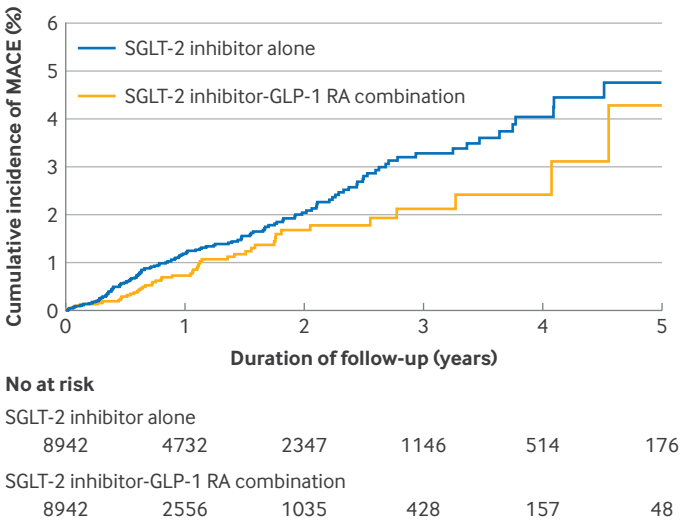

Fig 4 | Cumulative incidence curves of major adverse cardiovascular events (MACE) for glucagon-like peptide-1(GLP-1) receptor agonist (RA)-sodium-glucose cotransporter-2 (SGLT-2) inhibitor combination versus SGLT-2 inhibitors

Biological mechanisms

The associations observed with the GLP-1 receptor agonist-SGLT-2 inhibitor combination in this study can be attributed to an additive effect resulting from their different yet complementary mechanisms of action. Both drug classes have been shown to confer clinical benefits such as glycaemic control, body mass reduction, and improved systolic blood pressure and lipid profiles, which may collectively contribute to their cardiorenal protective effect.[32] However, these drug classes use different mechanisms to achieve these effects. GLP-1 receptor agonists bind to and stimulate GLP-1 receptors, which augments insulin secretion and inhibits glucagon release by the pancreas in a glucose dependent manner, leading to reductions in plasma glucose.[33 34] This drug class also promotes satiety by delaying gastric emptying and acting on appetite regions of the hypothalamus, resulting in decreased food intake and sustained weight loss.[33] Furthermore, GLP-1 receptor agonists may impart additional cardiovascular benefits by alleviating atherosclerosis

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through improving inflammatory markers.[35] The anti-inflammatory and anti-oxidative effects of GLP-1 receptor agonists may also result in decreased albuminuria, reduced mesangial expansion, and improved glomerular hyperfiltration and endothelial function, explaining their renoprotective effects.[36 37]

SGLT-2 inhibitors, on the other hand, exert their antihyperglycemic effects by inhibiting the reabsorption of glucose in the proximal tubules of the kidneys, resulting in urinary glucose excretion.[38] The excretion of calories in the form of glucose in the urine also promotes weight loss.[39] An interesting finding from our study was that adding an SGLT-2 inhibitor to existing GLP-1 receptor agonist treatment was associated with a decreased risk of heart failure, but this was not seen when GLP-1 receptor agonists were added to a background of SGLT-2 inhibitors. This finding corresponds to observations from the cardiovascular outcome trials for SGLT-2 inhibitors, in which they have been consistently associated with reduced risks of heart failure,[6-9] whereas this effect was not observed in the cardiovascular outcome trials for GLP-1 receptor agonists. The decreased risk of heart failure associated with SGLT-2 inhibitors may be imparted by their haemodynamic effects on the heart, such as reduced intravascular volume, improved arterial elasticity, and decreased cardiac preload and afterload.[40 41] Concerning their renoprotective effects, SGLT-2 inhibitors ameliorate hyperfiltration in the proximal tubules, which reduces intraglomerular pressure.[42]

Thus, the decreased cardiorenal risk associated with the combined use of GLP-1 receptor agonists and SGLT-2 inhibitors may be attributed to an additive effect, achieved by the distinct mechanisms and sites of action for these different drug classes. Further laboratory research is needed to elucidate better the mechanisms by which GLP-1 receptor agonists and SGLT-2 inhibitors impart their cardiorenal protective effects.

Strengths and limitations of study

This study has several strengths. Firstly, using the CPRD allowed for the ability to adjust for important potential confounders, including cardiovascular risk factors, microvascular and macrovascular complications, body mass index, and laboratory measures, which are often unavailable in other datasets. Secondly, we used an active comparator, prevalent new-user design that closely emulates a randomised controlled trial, a methodological approach best suited for this study question.[25] Thirdly, our study investigated not only cardiovascular outcomes but also serious renal events, which are clinically relevant outcomes in the type 2 diabetes population.

This study also has some limitations. Firstly, CPRD captures only data on prescriptions written by general practitioners, so information on patients' adherence to treatment regimens is unknown, potentially introducing exposure misclassification. However, using an on-treatment exposure definition that followed patients while they were continuously exposed to the study drugs likely mitigated this bias. Additionally, given that the CPRD is a general practice database, prescriptions written by specialists are not captured, which may be another source of exposure misclassification. The impact of this potential bias is unlikely to be significant as general practitioners in the UK are primarily responsible for the long term management of patients with type 2 diabetes.[43] Secondly, outcome misclassification is also possible. However, validation studies have shown that hospital admission for cardiovascular events in the CPRD linked HES database has a high positive predictive value.[44 45] Although the recording of the components of serious renal events (for example, renal complications of diabetes, chronic kidney disease) has not been validated in the CPRD, we do not expect any outcome misclassification to be differential between the exposure groups. Thirdly, residual confounding is a possibility owing to the observational nature of the study. However, by matching patients on specific background drug, duration of use of the background drug, and propensity scores generated on the basis of 46 potential confounders, we likely minimised the likelihood of significant confounding. Fourthly, the follow-up time for the combination therapy group was shorter than that for the monotherapy group in both cohorts. We anticipated the follow-up to be differential between the exposure groups but not likely to be associated with the outcome. For this reason, we did an inverse probability of censoring weighting sensitivity analysis, which yielded point estimates that were very similar to those of the primary analysis. Furthermore, the differences in follow-up periods are reflective of the real world experience with these drugs. Lastly, several secondary analyses were underpowered, generating few exposed events and wide confidence intervals. Thus, these results should be interpreted with caution.

Conclusion

In summary, the results of this population based study, designed to closely emulate a randomised controlled trial, suggest that the use of the GLP-1 receptor agonist-SGLT-2 inhibitor combination is associated with a lower risk of major adverse cardiovascular events and serious renal events among patients with type 2 diabetes compared with each drug class alone. Additional studies, including randomised controlled trials, will be needed to corroborate our findings and to explore the full therapeutic potential of the GLP-1 receptor agonist-SGLT-2 inhibitor combination among patients with type 2 diabetes.

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Ethics approval: The study protocol was approved by the Research Data Governance of the CPRD (protocol 22_002276) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada. The study was a secondary data analysis and did not include patients as study participants. Hence the Research Data Governance of the Clinical Practice Research Datalink and the Research Ethics Board deemed it to be exempt from the need to obtain patient consent.

Data sharing: This study is based on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the UK National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. Because electronic health records are classified as "sensitive data" by the UK Data Protection Act, information governance restrictions (to protect patient confidentiality) prevent data sharing via public deposition. Data are available with approval, through the individual constituent entities controlling access to the data. Specifically, the primary care data can be requested via application to the Clinical Practice Research Datalink (https://www.cprd.com).

Transparency: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Dissemination to participants and related patient and public communities: We will disseminate the results through our general media communications plan, by organising a press release through the Public Relations Department of the Lady Davis Institute. Finally, we will directly communicate our results to diabetes associations and regulatory agencies.

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Web appendix: Supplementary materials