



Wright, A. K. et al. (2022) Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes. *Diabetes Care*. (Early Online Publication)

(doi: [10.2337/dc21-1113](https://doi.org/10.2337/dc21-1113))

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Deposited on: 18 January 2022

Full title: Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists and their combination in type 2 diabetes

Short running title: MACCE & heart failure risk with antidiabetics

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Total word count: 4,599

Number of Tables: 1

Number of Figures: 3

Abstract (235 words)

Objective: To assess associations between current use of SGLT2i, GLP-1RA and their combination and risk for MACCE and heart failure (HF) in people with type 2 diabetes.

Research Design and Methods: In three nested case-control studies involving people with type 2 diabetes in England and Wales (primary care data from CPRD and SAIL Databank with linkage to hospital and mortality records), we matched each patient experiencing an event with up to 20 controls. Adjusted odds ratios for MACCE and HF among patients receiving SGLT2i or GLP-1RA regimens vs other combinations were estimated using conditional logistic regression and pooled using random-effects meta-analysis.

Results: Among 336,334 people with type 2 diabetes and without cardiovascular disease, 18,531 (5.5%) experienced a MACCE. 17,451 (4.2%) experienced a HF event in a cohort of 411,206 with type 2 diabetes and without HF. Compared with other combination regimens, the adjusted pooled odds ratio and 95% confidence interval (CI) for MACCE associated with SGLT2i regimens was 0.82 (95% CI 0.73-0.92); with GLP-1RA regimens 0.93 (95% CI 0.81-1.06), and with the SGLT2i/GLP-1RA combination 0.70 (95% CI 0.50-0.98). Corresponding data for HF were: SGLT2i, 0.49 (95% CI 0.42-0.58); GLP-1RA, 0.82 (95% CI 0.71-0.95); and SGLT2i/GLP-1RA combination, 0.43 (95% CI 0.28-0.64).

Conclusions: SGLT2i and SGLT2i/GLP-1RA combination regimens may be beneficial in primary prevention of MACCE and heart failure and GLP-1RA for heart failure. These data call for primary prevention trials using these agents and their combination.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT2i) have important cardiovascular benefits in people with type 2 diabetes; however, there are notable differences.(1,2) A network meta-analysis suggested that SGLT-2 inhibitors reduced admission to hospital for heart failure more than GLP-1 receptor agonists, whereas GLP-1 receptor agonists reduced risk for non-fatal stroke more than SGLT-2 inhibitors.(2) In a meta-analyses of placebo-controlled clinical trials, GLP-1RA and SGLT2i reduced the risk of major adverse cardiac and cerebrovascular events (MACCE) by ~14% in people with established cardiovascular disease (CVD) but provided no significant benefits in primary prevention settings.(1,3) Meta-analyses have suggested that SGLT2is reduce the risk for heart failure hospitalization by 30-37%, in people with and without prior atherosclerotic CVD, whereas GLP-1RA provided a more modest reduction of 11%.(1,3,4) However, trial cohorts did not exclude people with prior heart failure and they largely consisted of people with established CVD and individually were not adequately powered to demonstrate superiority in primary prevention settings.

We hypothesised that the CVD benefits observed in “high-risk” trial participants would also be apparent in lower-risk primary care populations *without* known CVD. Moreover, since the combination of SGLT2i and GLP-1RA offers superior reductions in CVD risk factors when compared to using either medication alone,(5,6) we hypothesised that the combination would provide additive reductions in MACCE and heart failure risks. Using linked electronic primary and secondary care health records from England and Wales (UK), we aimed to assess whether GLP-1RA and SGLT2i use, individually or combined, was associated with lower rates of MACCE or heart failure, compared to not using such therapies, in the primary prevention setting.

RESEARCH DESIGN AND METHODS

Study design and data source

We conducted nested case-control studies (Supplemental Figure 1) using data obtained from three medical record databases: the Clinical Practice Research Datalink (CPRD) GOLD (data contributed by UK practices using Vision electronic patient record system software), CPRD Aurum (data contributed by UK practices using EMIS software), and the Secure Anonymised Information Linkage (SAIL) Databank (practices contributing data in Wales, UK). Patients who transferred from CPRD GOLD to Aurum were excluded from GOLD. As we only identified people attending English general practices in CPRD, there was no overlap with the SAIL Databank which only contains patients attending Welsh general practices.

The CPRD databases contain anonymised, longitudinal primary care medical records and prescribing data (containing information on prescriptions issued but not on dispensing information) from English general practices.(7,8) Clinical data is coded using Read Version 2 codes in GOLD and SNOMED CT (UK edition), Read Version 2 and local EMIS Web[®] codes in Aurum.(7,8) Prescribing data is recorded using the Gemscript product code system (an integrated NHS Dictionary of Medicines and Devices [dm+d] drug dictionary) in GOLD and dm+d prescribing codes in Aurum.(7,8) The CPRD datasets were linked to Hospital Episodes Statistics (HES) for admitted patients and outpatients, Office for National Statistics (ONS) death registration, and the Index of Multiple Deprivation 2015 for all eligible patients in the linkage-consenting English practices.

The SAIL databank provides anonymised health and administrative data covering ~80% of Welsh general practices.(9) The datasets available within the SAIL databank include: GP practice medical records including prescriptions issued by general practices (without

dispensing information), hospital in-patient and out-patient records, ONS deaths, and the Welsh Index of Multiple Deprivation 2014.(9) Clinical and prescribing data is coded using Read Version 2.

The nested case-control (NCC) design was chosen for its statistical efficiency as exposure does not need to be classified for each person-moment of follow-up.(10) Whilst a time-dependent Cox Proportional Hazards regression model can account for time-varying exposure, the NCC can be used as an alternative approach as the exposure and covariate information for controls correspond to the time of selection of their respective case.(11) By matching cases and controls from the same population at the time of the outcome event, this creates a comparable sample of controls with respect to important clinical and confounding factors, minimising potential selection bias and time-lag bias whereby cases and controls may be at different stages of diabetes progression.(11,12)

Study population

We followed the methodological approach to delineate each nested case-control study as described by Filion et al.(13) for study population construction across the databases (Figure 1). The defined study cohorts consisted of individuals with first-ever prescriptions for non-insulin antidiabetic medications between January 1998 and July 2018 who initiated at least one new class of antidiabetic drug (first-line initiation, switch or addition to treatment regimen) between November 2012 (when SGLT2 inhibitors became available in the UK) and July 2018 (end of study period), conditional on a number of exclusions at the time of the first antidiabetic prescription (Figure 1 and Supplemental Figure 2 for database specifics); i. less than 365 days current registration at the GP practice, ii. less than 18 years of age, iii. prior use of insulin (as patients with type 2 diabetes initiating on insulin are more likely to be at a

different stage in the condition and have a worse global risk profile), iv. women with a history of polycystic ovarian syndrome (PCOS), and v. women with a diagnosis of gestational diabetes in the year prior to first antidiabetic prescription. We further excluded patients with a history of HIV or antiretroviral therapy prior to cohort entry (due to the effect on glucose metabolism, body fat and diabetes-related complications). People with type 2 diabetes who were diet only treated at cohort entry were excluded.

Within each database, we examined incident events by restricting study cohorts to those *without a history of CVD* for the primary endpoint and *those without prior heart failure* for the secondary endpoint, as identified from primary care and hospital records. We defined prior CVD as non-fatal myocardial infarction (MI), acute coronary syndrome (ACS), stroke, transient ischaemic attack (TIA), unstable angina, heart failure and revascularisation procedures. Prior heart failure was defined as a previous admission for heart failure (including heart failure with normal, reduced and preserved ejection function). Individuals within each database cohort were followed from cohort entry until the endpoint (defined below), death, transfer out of practice, or study end (31 November 2018); whichever occurred first.

Definition of outcomes

MACCE and heart failure events were identified from primary care, hospital (primary and secondary diagnoses captured from Admitted Patient Care [HES APC] data files; hospitalisation/spell, episode and primary diagnoses across a hospitalisation) and/or ONS mortality records. The primary composite endpoint was the first record of the following MACCE after cohort entry: a) MI/ACS; b) stroke/TIA including intracerebral and

subarachnoid haemorrhage; and/or b) cardiovascular death. The secondary endpoint was the first record of heart failure after cohort entry.

Case and control selection

For the primary endpoint, within each database, cases were identified as those in the study cohort who experienced a MACCE during follow-up (Supplemental Figure 3). The index date for cases was defined as the date of the first MACCE event. For the secondary endpoint, cases were identified as those in the study cohort who experienced heart failure during follow-up (Supplemental Figure 4). The index date for cases was defined as the date of the first heart failure event.

Risk-set sampling from the study cohort was used to match each case with up to 20 cohort members from the same practice and of the same sex who were at risk of an event but were event-free at the index date on the follow-up timescale using the following criteria: age (± 2 years), date of cohort entry (± 1 year), and duration of treated diabetes (± 1 year). Cases without any eligible controls were excluded. Details of case and control selection are provided in Supplemental Figures 3 and 4.

Exposure

Current exposure to antidiabetic medications (ADMs), including insulin, was defined as 2 consecutive drug prescriptions for each antidiabetic class issued prior to the index date (MACCE or heart failure event) with a prescription length, plus a 90-day grace period (defined as continuous use, accounting for non-adherence/non-persistence), which included the index date. The grace period is the permissible time gap for patients to get a subsequent prescription following a discontinuation or the end of the previous prescription coverage.(14)

This approach accounts for the variability among prescription durations and remaining stockpiled medications.(14,15) For antidiabetic treatment in type 2 diabetes, a permissible gap of 90 days is typically implemented.(15–17)

Exposure to ADMs (including insulin) was categorised as: a) combined SGLT2 inhibitor (SGLT2i) and GLP-1 receptor agonist (GLP-1RA) regimens, b) GLP-1RA regimens without SGLT2i agents, c) SGLT2i regimens without GLP-1RA agents, d) other combination regimens excluding GLP-1RA and SGLT2i agents, e) other monotherapy regimens, or f) no current exposure. A full list of the antidiabetic regimens contained within each exposure group is provided in the Supplemental Material.

Patient demographics and clinical characteristics

Patient characteristics and prescriptions were measured at cohort entry. Medical diagnoses were defined as any history of Read codes from primary care or ICD-10 codes from HES before cohort entry. Cardiovascular risk factors (BMI, HbA1c, blood pressure, total cholesterol) were identified from the closest recording up to 3 months before the cohort entry date. Drug history was defined as prescriptions in the year prior to cohort entry and ever exposure of antidiabetics as all prescriptions prior to cohort entry. In CPRD, ethnicity was identified from primary care records using Read codes and through linkage with HES.(18) In SAIL, ethnicity was identified from primary care records. Socio-economic deprivation (2015 English Index of Multiple Deprivation or 2014 Welsh Index of Multiple Deprivation [IMD]), an aggregated area-level measure of deprivation domains based on the patient's residential locality, was categorised into quintiles: 1 (least deprived) to 5 (most deprived).

Statistical analysis

We determined the association between incident MACCE and incident heart failure with current exposure with SGLT2i regimens, GLP-1RA regimens, and their combination as compared with other combination regimens. Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals (CI), stratifying on matched sets. We adjusted all models for the case-control matching factors (age, duration of treated diabetes), clinical characteristics (ethnicity, IMD, microvascular complications, Charlson Comorbidity Index, smoking status, BMI, HbA1c, blood pressure, total cholesterol) and drug history; prescriptions for antidiabetic medications, antihypertensive agents, lipid-lowering agents, antiplatelet agents, corticosteroids, NSAIDs and anticoagulants in the year prior to cohort entry, ever exposure of antidiabetic drugs and number of antidiabetic drugs prescribed prior to cohort entry, as detailed in Supplemental Tables 1 and 2. Due to the nature of risk-set sampling, odds ratios generated are unbiased estimators of the hazard ratio (HR).(19) Database-specific study estimates were pooled using DerSimonian and Laird random-effects meta-analysis. Between-study heterogeneity was assessed through the I^2 statistic.(20) A value of 0% indicates no observed heterogeneity.(20)

We conducted several sensitivity analyses to assess the robustness of our findings including: varying the length of the current exposure grace period to 30 and 60-days; excluding people with atrial fibrillation; excluding people with chronic kidney disease stage 3+; excluding people with current antidiabetic regimens containing sulphonylureas in the MACCE analysis and regimens containing TZDs and/or DPP-4 inhibitor agents in the heart failure analysis; conducting propensity-matched cohort analyses to examining the risk of MACCE and heart failure associated with SGLT2i regimens and GLP-1RA regimens compared with other combination regimens; and assessing the robustness of observed associations to unmeasured

confounding through calculation of the E-value(21) (see the Supplemental Material).

Analyses were performed using Stata 16.1 (StataCorp LP, College Station, TX). We followed RECORD-PE (REporting of studies Conducted using Observational Routinely collected health Data for PharmacoEpidemiological research) guidance.(22)

RESULTS

Study population

The cohorts included 440,089 people with type 2 diabetes (CPRD GOLD n=52,012, CPRD Aurum n=279,985, SAIL n=108,092) treated with non-insulin ADMs. After excluding those with prior CVD, the unadjusted incidence rate (IR) of MACCE was 18.1 per 1,000 person-years of follow-up (CPRD GOLD IR=17.7/1,000 person-years, CPRD Aurum IR=17.9/1,000 person-years, SAIL IR=18.9/1,000 person-years); Supplemental Figure 3. After separately excluding those with a history of heart failure from the study cohorts, the unadjusted IR of heart failure was 13.9 per 1,000 person-years of follow-up (CPRD GOLD IR=13.2/1,000 person-years, CPRD Aurum IR=14.4/1,000 person-years, SAIL IR=13.0/1,000 person-years); Supplemental Figure 4.

For the primary endpoint (MACCE), cases were more likely than controls to be: White, living in deprived areas, smokers and have diabetes-related microvascular complications, other comorbidities, and prescriptions for antidiabetic medications, antihypertensives, statins and antiplatelets; Supplemental Table 1. Clinical characteristics for the heart failure cohorts are provided in Supplemental Table 2. Heart failure cases were more likely than controls to be older, White, more deprived, smokers, have co-existing conditions (CVD, microvascular complications) and more comorbidities. A higher proportion of cases had prescriptions for multiple ADMs, antihypertensive agents, statins, antiplatelets and anticoagulants.

SGLT2 inhibitor and GLP-1 receptor agonist regimens and MACCE

Of the final cohort of 18,490 MACCE cases, 599 (3.2%) were users of SGLT2i regimens, 469 (2.5%) GLP-1RA regimen users, 53 (0.3%) were using a combination of SGLT2i and GLP-1RA and 4,893 (26.5%) were users of other combination regimens; Table 1. The remaining patients were users of other monotherapy regimens (43.1%) or were not on a current ADM regimen at the time of the MACCE event (24.4%). Supplemental Tables 3-5 provide database-specific clinical characteristics of people on each current antidiabetic regimen exposure group. Across all the current exposure regimens, metformin was the most commonly prescribed other antidiabetic agent (~85% in SGLT2i, GLP-1RA and combined SGLT2i/GLP-1RA regimens; 92% in other combination regimens; 84% in other monotherapy regimens). Exposure to sulphonylureas was more common in other combination regimens compared with the SGLT2i, GLP-1RA and combined SGLT2i/GLP-1RA regimens (72% vs. 30-47%). DPP-4 inhibitors were largely observed in the SGLT2i regimens and other combination regimens. In SGLT2i, GLP-1RA and other combination exposure groups, regimens primarily consisted of 2 or 3 different antidiabetic agents. People in the combined SGLT2i/GLP-1RA regimens exposure groups were more likely to be currently exposed to 3 or more different agents.

In people without prior CVD, treatment with a SGLT2i regimen was associated with lower odds of MACCE, when compared to other combination regimens; adjusted pooled odds ratio 0.82 (95% CI 0.73-0.92), whereas treatment with a GLP-1RA regimen was not associated with significantly lower odds of MACCE; pooled odds ratio 0.93 (95% CI 0.81-1.06); Figure 2. The combined SGLT2i and GLP-1RA regimen was associated with 30% lower odds of MACCE, compared with other combination regimens: 0.70 (95% CI 0.50-0.98); Figure 2.

Supplemental Figure 5 reports the estimates for individual components of MACCE. The MACCE risks were largely driven by reductions in risk for myocardial infarction.

SGLT2 inhibitor and GLP-1 receptor agonist regimens and heart failure

Of the final cohort of 17,428 heart failure cases, 299 (1.7%) individuals were users of SGLT2i regimens, 490 (2.8%) GLP-1RA regimen users, 42 (0.2%) on a combination of SGLT2i and GLP-1RA and 4,352 (25.0%) were users of other combination regimens; Supplemental Table 6.

Treatment with a SGLT2i regimen or a GLP-1RA regimen was associated with lower odds of incident heart failure, when compared to other antidiabetic combination regimens (Figure 3); adjusted pooled odds ratios 0.49 (95% CI 0.42-0.58) and 0.82 (95% CI 0.71-0.95), respectively. The combined SGLT2i and GLP-1RA regimen was associated with 57% lower odds of heart failure when compared with other combination regimens: 0.43 (95% CI 0.28-0.64), (Figure 3).

Sensitivity analyses

Generally, E-values indicated that unmeasured confounders would have to have much larger effects on endpoints than most risk factors to explain the reported associations (Supplemental Table 7). The results of all other sensitivity analyses were consistent with our main results, Supplemental Figures 6-17.

CONCLUSIONS

In this study focussing on the primary prevention of clinical events, our results suggest that when compared with other antidiabetic combination regimens: a) current use of SGLT2i, but

not GLP-1RA, was associated with significantly lower odds of incident MACCE; b) current use of SGLT2i, GLP-1RA and their combination was associated with significantly lower odds of incident heart failure; and c) current use of the SGLT2i/GLP-1RA combination was nominally associated with lower odds of MACCE than the SGLT2i and GLP-1RA regimens alone.

Primary prevention of MACCE

SGLT2i: A trial with dapagliflozin and two meta-analyses of other placebo-controlled trials indicated no significant benefit of SGLT2i in reducing risk for MACCE in primary prevention settings.(4) Whilst the CREDENCE trial considered a special population with type 2 diabetes and albuminuric chronic kidney disease, in the primary prevention subgroup, canagliflozin reduced risk by 32% (HR 0.68; 95% CI 0.49-0.94).(23) Whether these primary prevention MACCE benefits would be observed in a general type 2 diabetes population remain unclear.

Observational studies assessing MACCE risks associated with SGLT2is have also been inconclusive.(24–27) The most convincing data come from a large multi-national cohort showing that in type 2 diabetes patients (27% with CVD), SGLT2i use was associated with lower risks of individual MACCE events when compared to other ADMs.(28) However, this work did not report primary prevention data, the propensity score used did not account for important confounders and follow-up was only 1 year.(28) In recent observational studies comparing SGLT2i with GLP-1RA, cardiovascular risks appeared similar (26,29,30) with cardioprotective benefits observed in secondary prevention.(26) Compared with DPP-4 inhibitors and sulphonylureas (the first-choice drugs for treatment intensification after metformin) or placebo, short term use of SGLT2i was associated with reduced risks of MACCE (specifically myocardial infarction and cardiovascular death), heart failure and all-

cause mortality with modest or neutral effects on stroke.(31–33) Here we advance the field, with over 3-years of follow-up, we report a 18% (OR 0.82; 95% CI 0.73-0.92) reduction in the adjusted risk for MACCE with SGLT2i therapy compared to other ADMs. The apparent benefits of SGLT2i that we demonstrate in the primary prevention setting appear to be similar to those reported from RCTs in the secondary prevention setting (HR 0.86; 95% CI, 0.80–0.93),(1) with overlapping confidence intervals and the pooled RCT effect estimate being contained within our study’s confidence interval.

GLP-1RA: Except for the REWIND trial, the proportion of participants in primary prevention GLP-1RA trials has been low to modest and the benefits of GLP-1RA on MACCE risk have been inconsistent; however, in the latest meta-analyses which includes AMPLITUDE-O data, GLP-1RAs reduced MACE risk by 14% (HR 0.86; 95% CI 0.80-0.93), with low heterogeneity with ELIXA excluded in sensitivity analyses.(3) This MACE benefit appeared to be driven by 15% risk reduction in people with established CVD. Observational studies assessing MACCE risks associated with individual GLP-1RAs have been underpowered and inconclusive.(34,35) We show a numerically lower risk of MACCE associated with GLP-1RA therapy in primary prevention (OR 0.93; 95% CI 0.81-1.06), which is similar to the result obtained in the most recent meta-analysis of clinical trials.(3)

Primary prevention of heart failure

SGLT2i: Clinical trials have shown clear benefits of SGLT2is on heart failure risk although data in people without prior heart failure have been inconsistently reported.(1,36) In people with multiple CVD risk factors, a meta-analysis of SGLT2i trials suggested that these agents might have clinical benefits although summary results were not significant (HR 0.84; 95% CI 0.69-1.01).(36) A recently reported meta-analysis of RCTs suggested that in people with type

2 diabetes and no prior history of atherosclerotic CVD, SGLT2i reduced the risk for heart failure (HR 0.63; 95% CI 0.50-0.80), but corresponding data in people without prior heart failure is lacking.(4) Consistent with our data, observational studies have suggested reductions in the risk for heart failure hospitalisation,(25,29,30) ranging from 17-40% lower risk in SGLT2i users compared to people using GLP-1RA or other diabetes therapies,(29,30) with no interaction by baseline CVD status.(28)

GLP-1RA. Whilst there is consistent data for SGLT2i reducing MACCE and HF risk, the consensus on GLP-1RA has been less clear. New data from the AMPLITUDE-O trial showed significant reductions in heart failure risk with exendin-4 based GLP-1RA, efpeglenatide (HR 0.61; 95% CI 0.38-0.98).(37) Consequently, in the latest meta-analysis of RCTs, Sattar et al. reported a statistically significant 11% reduction (HR 0.89; 95% CI 0.82-0.98) in the risk for heart failure hospitalisation with GLP-1RAs, which is not dissimilar to our reported estimate (OR 0.82; 95% CI 0.71-0.95).(3) This benefit was largely driven by the risk reduction in people with established CVD; no significant benefit was observed in those without CVD. In the only positive observational study, Velez et al. showed that GLP-1RA prescribing was associated with a 49% lower risk of heart failure hospitalisation.(38) However, the analysis was based on 128 events, follow-up was only 2 years and the analysis accounted for a limited number of covariates. Here, we show a 18% lower risk of first heart failure episodes with GLP-1RA users over ~4 years (mean) of follow-up after adjusting for many more potential confounders. At this time, expert consensus is that GLP-1RAs may be appropriate in patients at risk for HF but due to potential safety concerns from small clinical trials they may be better avoided in people with HF with reduced ejection fraction until robust evidence of benefit is generated in this group.(39–41)

Whilst some trial and observational data and the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus report have indicated GLP-1RAs as the preferred drugs to prevent atherosclerotic events rather than heart failure in the secondary prevention setting,(1,42–44) the heart failure benefits we showed in the primary prevention setting may relate to metabolic changes. There is growing evidence that myocardial metabolic abnormalities, including impaired fatty acid, glucose metabolism and myocardial insulin resistance, contribute to heart failure with reduced ejection fraction (left ventricular ejection fraction [LVEF]≤40%).(45) The GLP-1 hormone stimulates insulin secretion, increases insulin sensitivity and enhances glucose uptake and thus GLP-1RA agents could be a potential modulator to enhance myocardial glucose metabolism.(45) Additionally, GLP-1RA therapy has been shown to significantly improve LVEF.(45) Therefore GLP-1RA agents could be important in heart failure, particularly primary prevention.

Mechanisms of benefit with SGLT2i and GLP-1RA

SGLT2i and GLP-1RAs have well documented overlapping and distinct mechanisms of action, as summarised recently,(46) that could explain their beneficial effects on MACCE and heart failure risk as well as the combination having potential additive benefits.

The combined use of these agents is of significant interest because we are not aware of any trials investigating their effectiveness. The combination has demonstrated superior reductions in HbA1c, weight and systolic blood pressure compared to using either medication alone.(5,6) HbA1c reductions of up to 2% DCCT units accompanied by over 3kg of weight loss and 4 mmHg reductions in systolic blood pressure have been observed with combination therapy, (5,6,47) with safety profiles consistent with those of individual classes.(48) Clinical

studies have reported low risks of hypoglycaemia, pancreatitis, acute renal failure, amputations, diabetic ketoacidosis, and medullary thyroid cancer.(47,48) The potential adverse effect of GLP-1RAs promoting adipose tissue inflammation is attenuated by SGLT2 inhibitors,(49–52) and therefore combination therapy could negate this adverse effect.(51) We showed that the SGLT2i/GLP-1RA combination appeared to be associated with lower rates of MACCE and heart failure when compared to SGLT2i and GLP-1RA regimens alone, although with overlapping confidence intervals. However, with a limited sample size receiving combined therapy, caution in interpretation must be applied. RCTs are needed to assess the efficacy of the combined treatment and to confirm these findings.

Strengths and limitations

Strengths include: a) maximising statistical power by acquiring data from three sources on 440,089 people, analysed as separate nested-case control studies; b) linking to hospital and mortality records, providing greater capture of outcomes and covariates; c) using the nested case-control design which minimises the potential lack of comparability of the cases and controls and as a practical approach to assess associations with these drugs of interest, especially combined SGLT2i and GLP-1RA, which would not have been feasible in a cohort design due to low prevalence of these exposure groups and more limited follow-up to observe outcomes; d) using a relevant comparator group to reduce confounding by indication. As suggested by clinical guidelines, people diagnosed with type 2 diabetes generally initiate treatment with metformin, switching or adding agents if this monotherapy fails to control blood glucose levels.(44,53) GLP-1RA and SGLT2i are generally regarded as second- and third-line therapies as are combination regimens.(44,53) Therefore our primary reference group, patients receiving other antidiabetic combination regimens (excluding GLP-1RA and SGLT2i), is a clinically relevant treatment comparison; e) performing several sensitivity

analyses to assess the robustness of our findings including a propensity-matched cohort analysis (estimating the probability of treatment with each antidiabetic regimen and matching those treated with SGLT2i or GLP-1RA regimens to those on other combination regimens).

Limitations include: a) assessing associations with drug classes rather than individual SGLT2is and GLP-1RAs; b) antidiabetic regimens potentially included agents that have, in some studies, been associated with elevated heart failure risks, which could explain differences in findings compared to placebo-controlled RCTs.(54,55) However, in several sensitivity analyses we excluded cases and controls whose regimen contained sulphonylureas, TZDs or DPP-4 inhibitors, these results were consistent with those of our primary analysis; c) having a 90-day grace period could fail to capture a minority of people switching between GLP-1RA and SGLT2i agents leading to some misclassification of the exposure; however, to minimise misclassification of current drug exposure, we required individuals to have 2 consecutive prescriptions for the antidiabetic class. We observed a similar trend in risk estimates associated with the exposure groups when grace periods were defined as 30 days and 60 days in sensitivity analyses (Supplemental Figures 12-13); d) making comparisons between second- and third-line therapies could theoretically introduce time-lag biases due to patients being at different disease stages, but we reduced these impacts by matching cases and controls on diabetes duration and accounting for comorbidities and other drug treatments; e) the potential beneficial effects of GLP-1RA may be underestimated due to the drug latency period and the length of time patients were exposed to these regimens in our study. In clinical trials, clinical benefits were generally more evident with longer-term GLP-1RA treatment(56); f) the potential for prescriber bias and clinical inertia affecting drug-type initiation and exposure time; however, we mitigated some of these effects through the study design including matching patients from within the same general practice and adjusting for

patient demographics and clinical characteristics; g) it was not feasible to stratify by duration of exposure to current regimens due to the large number of strata from covariate adjustment and small sample sizes within strata; h) interpretation of treatment effects on individual MACCE components is cautioned due to having limited statistical power.

Clinical implication on prescribing guidelines

ADA and EASD guidelines were recently updated reflecting current evidence, with a new recommendation to use these agents in high-risk patients.(44) The guidelines highlight that no studies have assessed CVD or renal benefits in low-risk type 2 diabetes patients. We show that in primary prevention, use of these agents is associated with lower odds of MACCE (SGLT2i) and heart failure (SGLT2i and GLP-1RA) and that combination therapy could be especially useful to prevent MACCE. Ideally, confirmation of these results is needed before they can be incorporated into clinical decision-making frameworks. These data call for trials evaluating efficacy and cost-effectiveness of these interventions and their combination in the primary prevention setting. In view of the practical and economic issues associated with traditional trial designs, performing adequately powered pragmatic trials embedded within health care systems would be an attractive option. Whilst GLP-1RA and SGLT2i are expensive, the cost-effectiveness of such treatment options in the primary prevention setting will need to be examined as 80% of diabetes care costs cover managing complications, mostly CVD.(57)

Summary

This study of real-world data from clinical practice in type 2 diabetes, suggests that in primary prevention, current use of SGLT2i was associated with 18% lower odds of MACCE, and the odds of heart failure were 51% lower with current use of SGLT2i and 18% lower

with current use of GLP-1RA therapy. Clinical trials of these agents and their combination are called for in the primary prevention setting to evaluate efficacy and cost-effectiveness.

ACKNOWLEDGMENTS

Author Contributions: MKR conceptualised the research question. MKR, DMA, AKW and MJC contributed to the development of the idea, study design and statistical analysis. EK, LL, HT, RE, IB, MAM, TVS and NS advised on the study design and statistical analysis plan. AKW drafted the study protocol; MKR, DMA, EK, RE, IB, MM, TVS and NS contributed to the study protocol. AKW extracted the data, AKW and MJC performed the statistical analysis. AKW had access to, and verified, the underlying data. AKW and MKR drafted the manuscript. All authors interpreted the data, reviewed and revised the manuscript and approved the final version to be published. The guarantor, AKW, affirms that the 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 have been explained.

Sources of Funding: This study was funded by Diabetes UK (BDA: 14/0004971). We also acknowledge financial support from Medical Research Council (MRC) Health eResearch Centre Grant MR/K006665/1 and Methodology award MR/T025085/1. MJC and DMA are funded by the National Institute for Health Research (NIHR) Greater Manchester Patient Safety Translational Research Centre (award number: PSTRC-2016-003). The views expressed are those of the authors and not necessarily those of Diabetes UK, MRC, NIHR or the Department of Health and Social Care. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript and decision to submit the manuscript for publication.

Conflict of interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. DMA reports research funding from AbbVie, Almirall, Celgene, Eli Lilly, Janssen, Novartis, UCB and the Leo Foundation outside the submitted work. MKR has received non-promotional speaker fees from Novo Nordisk, consultancy fees from Cell Catapult and Roche Diabetes Care, and modest owning of shares in GlaxoSmithKline, outside the submitted work. IB reports grants from the National Institute for Health Research during the conduct of the study and personal fees from AstraZeneca (chief data scientist advisor) outside the submitted work. NS reports grants and personal fees from Boehringer Ingelheim and personal fees from Amgen (advisory board and speaker honoraria), AstraZeneca (advisory board and speaker honoraria), Eli Lilly (advisory board and speaker honoraria), Merck Sharp & Dohme (advisory board), Novartis (advisory board), Novo Nordisk (advisory board and speaker honoraria), Pfizer (advisory board) and Sanofi (advisory board and speaker honoraria), outside the submitted work. All other authors declare no competing interests. There are no other relationships or activities that could appear to have influenced the submitted work.

Data Sharing: Read and ICD codes used are publicly available at The ClinicalCodes repository and can be accessed at <https://clinicalcodes.rss.mhs.man.ac.uk/>. Electronic health records are, by definition, considered “sensitive” data in the UK by the Data Protection Act and cannot be shared via public deposition because of information governance restriction in place to protect patient confidentiality. Access to data is available only once approval has been obtained through the individual constituent entities controlling access to the data. The primary care data can be requested via application to the Clinical Practice Research Datalink (<https://www.cprd.com>); secondary care data can be requested via application to the hospital

episode statistics from the UK Health and Social Care Information Centre (www.hscic.gov.uk/hesdata); and mortality data are available by application to the UK Office for National Statistics (www.ons.gov.uk/ons/index.html).

Ethical Approval: This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. ONS and HES data is subject to Crown copyright (2018) protection, re-used with the permission of The Health, & Social Care Information Centre, all rights reserved. The OPCS Classification of Interventions and Procedures, codes, terms and text is Crown copyright (2018) published by Health and Social Care Information Centre, also known as NHS Digital and licensed under the Open Government Licence available at www.nationalarchives.gov.uk/doc/open-government-licence/open-government-licence.htm.

The interpretation and conclusions contained in this study are those of the authors alone. The study and use of CPRD data was approved by the Independent Scientific Advisory Committee (ISAC) for CPRD research, ref. 19_024A. Approval for SAIL Databank access was granted from the Information Governance Review Panel (project approval number 0907), an independent body overseeing study approvals in line with permissions already granted for conducting data analysis in the SAIL Databank.

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Table 1. Odds ratio (95%CI) for MACCE associated with current treatment with SGLT2 inhibitor and/or GLP-1 receptor agonist regimens compared with other combination regimens

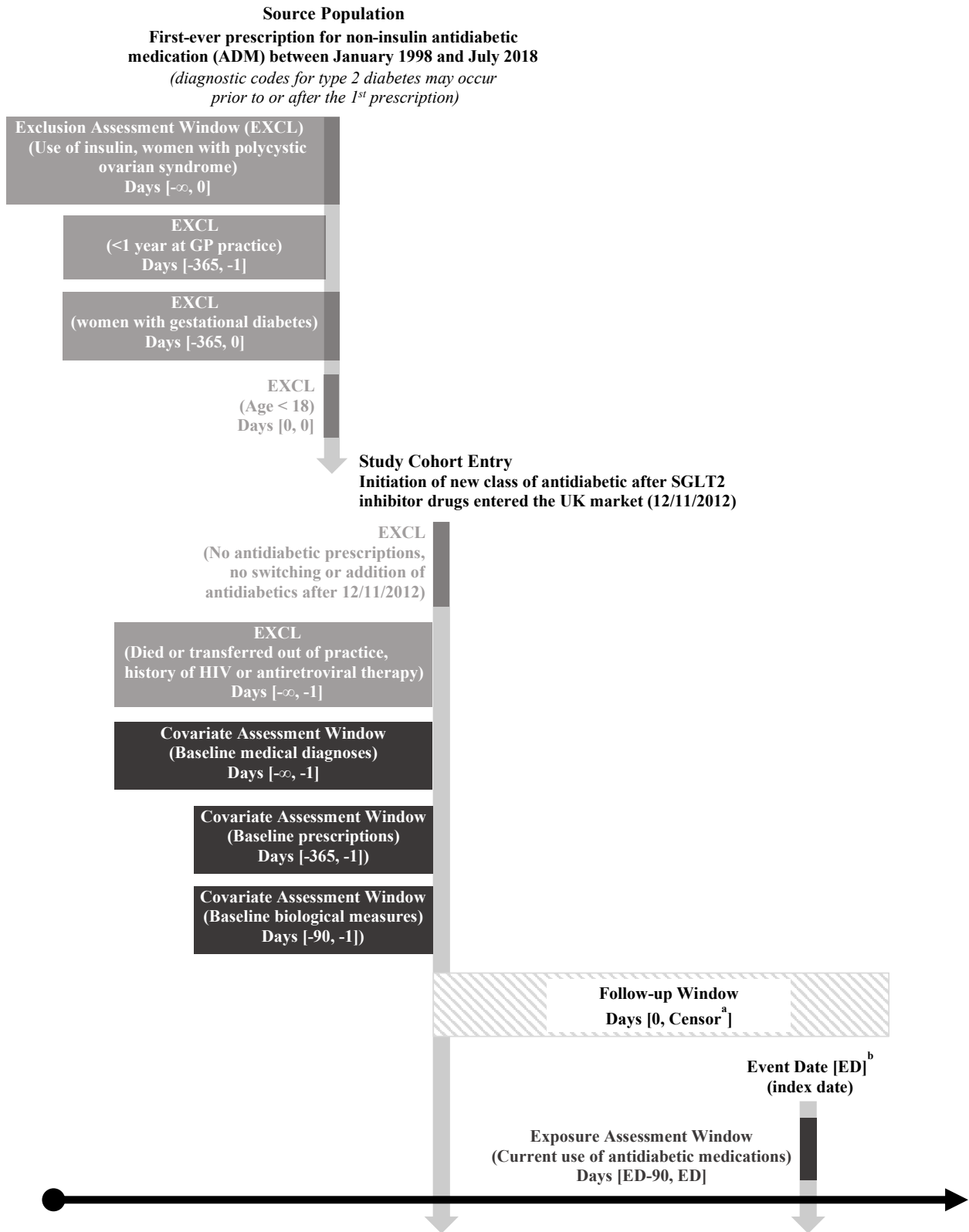
Treatment	CPRD GOLD				CPRD Aurum				SAIL Databank			
	Cases	Controls	Unadjusted OR (95% CI)	aOR* (95% CI)	Cases	Controls	Unadjusted OR (95% CI)	aOR* (95% CI)	Cases	Controls	Unadjusted OR (95% CI)	aOR* (95% CI)
N	1,690	20,199			11,887	213,329			4,913	76,037		
Combined SGLT2i & GLP-1RA regimens	6 (0.4)	45 (0.2)	0.66 (0.22-1.98)	0.60 (0.26-1.52)	25 (0.2)	768 (0.4)	0.81 (0.54-1.08)	0.73 (0.44-1.11)	22 (0.5)	411 (0.5)	0.85 (0.55-1.31)	0.70 (0.40-1.34)
SGLT2i regimens	58 (3.4)	585 (2.9)	0.93 (0.68-1.26)	0.89 (0.56-1.41)	355 (3.0)	8,424 (4.0)	0.82 (0.71-0.87)	0.80 (0.69-0.92)	186 (3.8)	3,492 (4.6)	0.85 (0.72-0.99)	0.86 (0.68-1.08)
GLP-1RA regimens	28 (1.7)	344 (1.7)	0.80 (0.53-1.21)	0.89 (0.59-1.21)	289 (2.4)	5,562 (2.6)	0.99 (0.88-1.15)	0.95 (0.80-1.12)	152 (3.1)	2,596 (3.4)	0.94 (0.78-1.12)	0.90 (0.68-1.19)
Other combination regimens	436 (25.8)	4,249 (21.0)	1	1	3,169 (26.7)	58,602 (27.5)	1	1	1,288 (26.2)	19,190 (25.2)	1	1
Other monotherapy regimens	757 (44.8)	10,483 (51.9)	1.28 (1.11-1.48)	1.37 (1.10-1.71)	5,250 (44.2)	94,345 (44.2)	1.14 (1.08-1.20)	1.13 (1.06-1.21)	1,953 (39.8)	31,697 (41.7)	1.13 (1.03-1.22)	1.06 (0.84-1.13)
No current regimen	405 (24.0)	4,493 (22.3)	1.33 (1.14-1.56)	1.47 (1.15-1.88)	2,799 (23.6)	45,628 (21.4)	1.31 (1.15-1.44)	1.28 (1.19-1.38)	1,312 (26.7)	18,651 (24.5)	1.23 (1.12-1.36)	1.11 (0.89-1.31)

MACCE, Major Adverse Cardiac and Cerebrovascular Events; GLP-1RA, Glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor; aOR, adjusted odds ratio.

* Adjusted for case-control matching factors (age, duration of treated diabetes), ethnicity, Index of Multiple Deprivation, microvascular complications, Charlson Comorbidity Index, smoking status, BMI, HbA1c, blood pressure and total cholesterol at cohort entry, prescriptions for medications in the year prior to cohort entry (antidiabetic medications, antihypertensive agents, lipid-lowering agents, antiplatelet agents, corticosteroids, NSAIDs, and anticoagulants), ever exposure of antidiabetic drugs and number of antidiabetic drugs prescribed prior to cohort entry

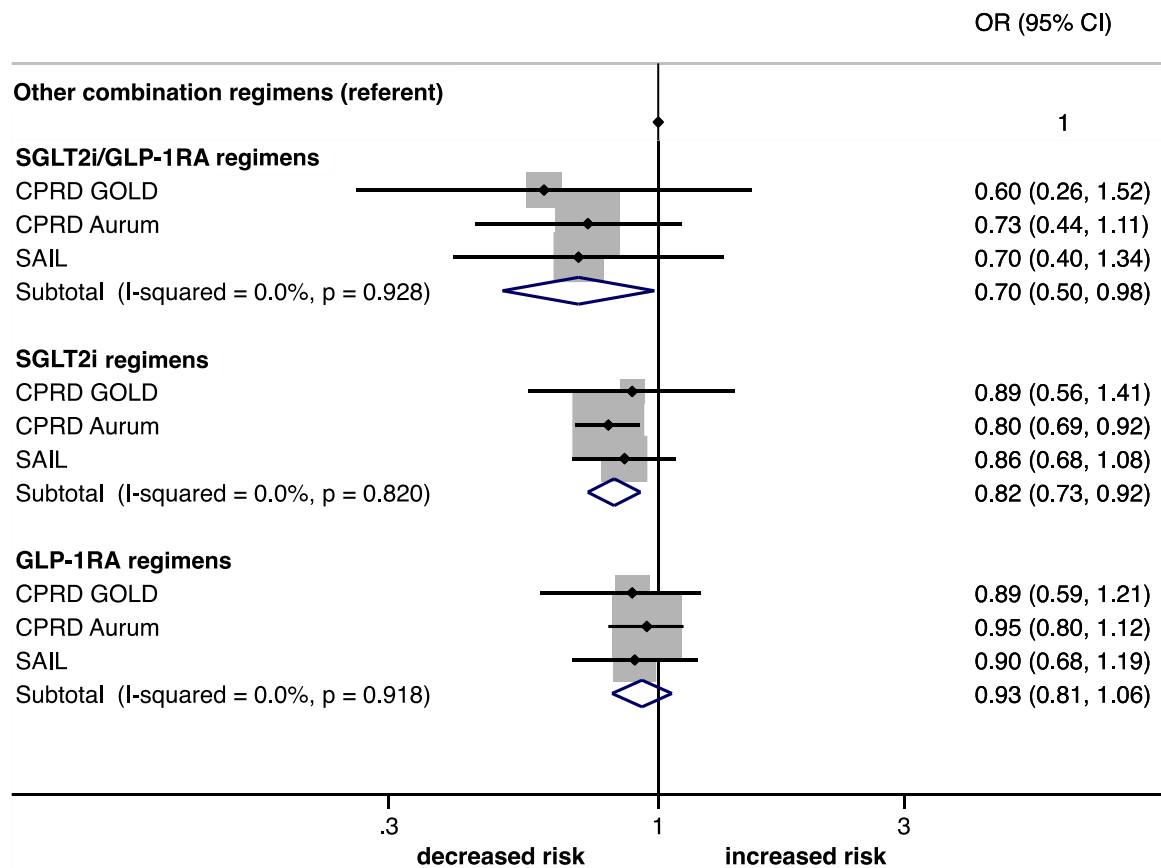
FIGURES

Figure 1. Defining the study population



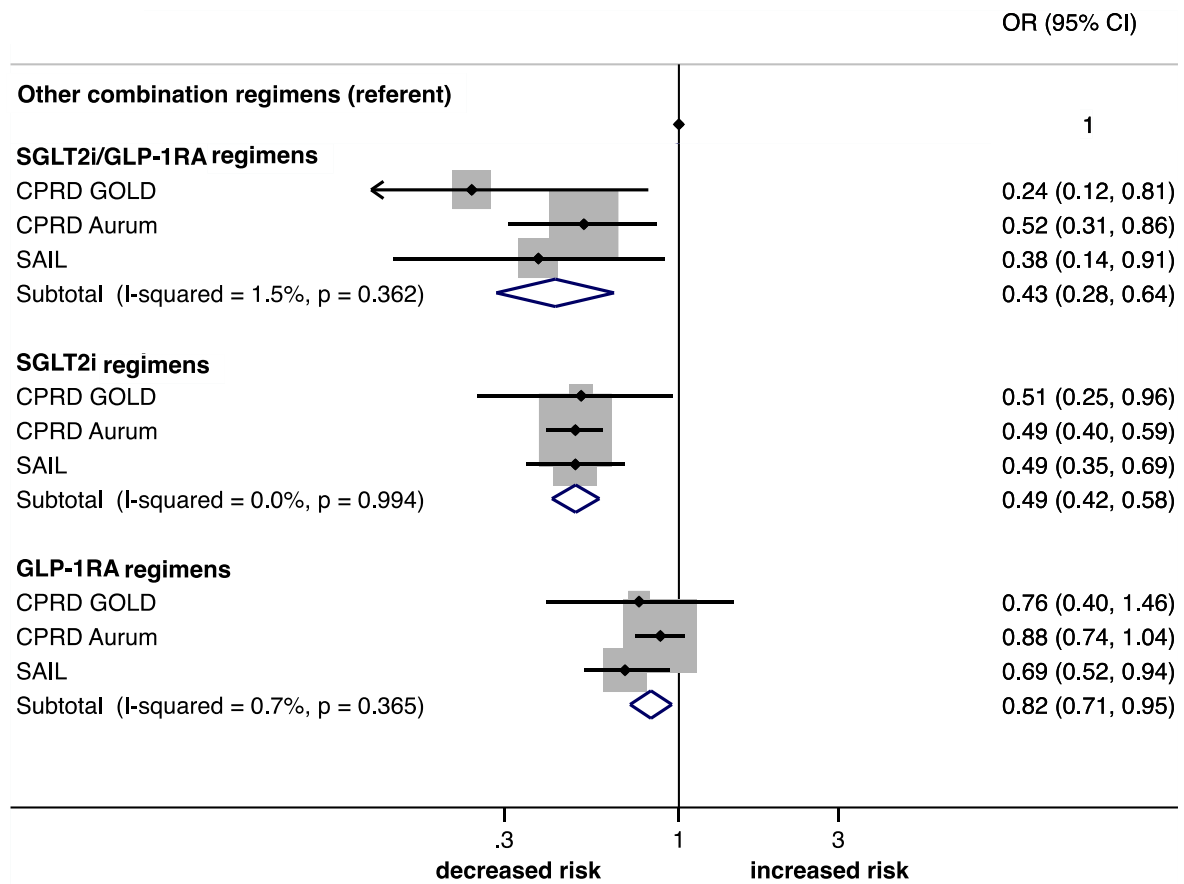
- a. Censored at minimum of event date, death, last collection of data, transfer out of practice or end of study period
- b. Controls risk-set matched on age (± 2 years), sex, cohort entry (± 1 year), duration of treated diabetes (± 1 year)

Figure 2. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of 3-point major adverse cardiac and cerebrovascular events



Adjusted for case-control matching factors (age, duration of treated diabetes), ethnicity, Index of Multiple Deprivation, microvascular complications, Charlson Comorbidity Index, smoking status, BMI, HbA1c, blood pressure and total cholesterol at cohort entry, prescriptions for medications in the year prior to cohort entry (antidiabetic medications, antihypertensive agents, lipid-lowering agents, antiplatelet agents, corticosteroids, NSAIDs and anticoagulants), ever exposure of antidiabetic drugs and number of antidiabetic drugs prescribed prior to cohort entry

Figure 3. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of heart failure



Adjusted for case-control matching factors (age, duration of treated diabetes), ethnicity, Index of Multiple Deprivation, history of CVD, microvascular complications, Charlson Comorbidity Index, smoking status, BMI, HbA1c, blood pressure and total cholesterol at cohort entry, prescriptions for medications in the year prior to cohort entry (antidiabetic medications, antihypertensive agents, lipid-lowering agents, antiplatelet agents, corticosteroids, NSAIDs and anticoagulants), ever exposure of antidiabetic drugs and number of antidiabetic drugs prescribed prior to cohort entry