Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes

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OBJECTIVE

To assess associations between current use of sodium–glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists (GLP-1RAs), and their combination and risk for major adverse cardiac and cerebrovascular events (MACCE) and heart failure (HF) in people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

In three nested case-control studies involving patients with type 2 diabetes in England and Wales (primary care data from the Clinical Practice Research Datalink and Secure Anonymised Information Linkage Databank with linkage to hospital and mortality records), we matched each patient experiencing an event with up to 20 control subjects. Adjusted odds ratios (ORs) for MACCE and HF among patients receiving SGLT2i or GLP-1RA regimens versus 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. In a cohort of 411,206 with type 2 diabetes and without HF, 17,451 (4.2%) experienced an HF event. Compared with other combination regimens, the adjusted pooled OR and 95% CI for MACCE associated with SGLT2i regimens was 0.82 (0.73, 0.92), with GLP-1RA regimens 0.93 (0.81, 1.06), and with the SGLT2i/GLP-1RA combination 0.70 (0.50, 0.98). Corresponding data for HF were SGLT2i 0.49 (0.42, 0.58), GLP-1RA 0.82 (0.71, 0.95), and SGLT2i/GLP-1RA combination 0.43 (0.28, 0.64).

CONCLUSIONS

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

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 inhibitors (SGLT2is) have important cardiovascular benefits in people with

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type 2 diabetes; however, there are notable differences (1,2). A network meta-analysis suggested that SGLT2is reduce admission to the hospital for heart failure (HF) more than GLP-1RAs, whereas GLP-1RAs reduce the risk for nonfatal stroke more than SGLT2is (2). In a meta-analyses of placebo-controlled clinical trials, GLP-1RAs and SGLT2is 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 HF hospitalization by 30–37% in people with and without prior atherosclerotic CVD, whereas GLP-1RAs provided a more modest reduction of 11% (1,3,4). However, trial cohorts did not exclude people with prior HF, and they largely consisted of people with established CVD and individually were not adequately powered to demonstrate superiority in primary prevention settings.

We hypothesized 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 SGLT2is and GLP-1RAs offers superior reductions in CVD risk factors compared with using either medication alone (5,6), we hypothesized that the combination would provide additive reductions in MACCE and HF risks. Using linked electronic primary and secondary care health records from England and Wales, we aimed to assess whether GLP-1RA and SGLT2i use, individually or combined, is associated with lower rates of MACCE or HF compared with not using such therapies in the primary prevention setting.

RESEARCH DESIGN AND METHODS

Study Design and Data Source

We conducted nested case-control (NCC) studies (Supplementary Fig. 1) using data obtained from three medical record databases: the Clinical Practice Research Datalink (CPRD) GOLD (data contributed by U.K. practices using Vision electronic patient record system software), CPRD Aurum (data contributed by U.K. practices using EMIS software), and the Secure Anonymised Information Linkage (SAIL) Databank (practices contributing data in Wales). Patients who transferred from CPRD GOLD to Aurum were excluded from GOLD. Because 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 anonymized, 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 are coded using Read version 2 codes in GOLD and Systematized Nomenclature of Medicine–Clinical Terms (U.K. edition), Read version 2 and local EMIS Web codes in Aurum (7,8). Prescribing data are recorded using the Gemscript product code system (an integrated National Health Service [NHS] dictionary of medicines and devices) in GOLD and dictionary of medicines and devices prescribing codes in Aurum (7,8). The CPRD data sets 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 (IMD) 2015 for all eligible patients in the English practices consenting to linkage.

The SAIL Databank provides anonymized health and administrative data covering ∼80% of Welsh general practices (9). The data sets available within the SAIL Databank include general practice medical records, including prescriptions issued (without dispensing information), hospital inpatient and outpatient records, ONS deaths, and the Welsh IMD 2014 (9). Clinical and prescribing data are coded using Read version 2.

The NCC study design was chosen for its statistical efficiency because exposure does not need to be classified for each person-moment of follow-up (10). Although a time-dependent Cox proportional hazards regression model can account for time-varying exposure, the NCC study design can be used as an alternative approach because the exposure and covariate information for control subjects correspond to the time of selection of their respective case subjects (11). By matching cases and controls from the same population at the time of the outcome event, this creates a comparable sample of control subjects with respect to important clinical and confounding factors, minimizing 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 a methodological approach to delineate each NCC study as described by Filion et al. (13) for study population construction across the databases (Fig. 1). The defined study cohorts consisted of patients with first-ever prescriptions for noninsulin antidiabetic medications (ADMs) between January 1998 and July 2018 who initiated at least one new class of ADM (first-line initiation, switch, or addition to treatment regimen) between November 2012 (when SGLT2is became available in the U.K.) and July 2018 (end of study period), conditional on the following exclusions at the time of the first ADM prescription (see Fig. 1 and Supplementary Fig. 2 for database specifics): *1*) <365 days current registration at the general practice, *2*) <18 years of age, *3*) prior use of insulin (because patients with type 2 diabetes initiating ADM with insulin are more likely to be at a different stage of the condition and to have a worse global risk profile), *4*) women with a history of polycystic ovarian syndrome, and *5*) women with a diagnosis of gestational diabetes mellitus in the year before the first ADM prescription. We further excluded patients with a history of HIV or antiretroviral therapy (due to the effect on glucose metabolism, body fat, and diabetes-related complications) and patients with type 2 diabetes treated with diet only.

Within each database, we examined incident events by restricting study cohorts to those without a history of CVD for the primary end point and those without prior HF for the secondary end point, as identified from primary care and hospital records. We defined prior CVD as nonfatal myocardial infarction, acute coronary syndrome, stroke, transient ischemic attack, unstable angina, HF, and revascularization procedures. Prior HF was defined as a previous hospital admission for HF (including HF with normal, reduced, and preserved ejection fraction). Individuals within each database cohort were followed from cohort entry until the end point (defined below), death, transfer out of practice, or study end (31 November 2018), whichever occurred first.

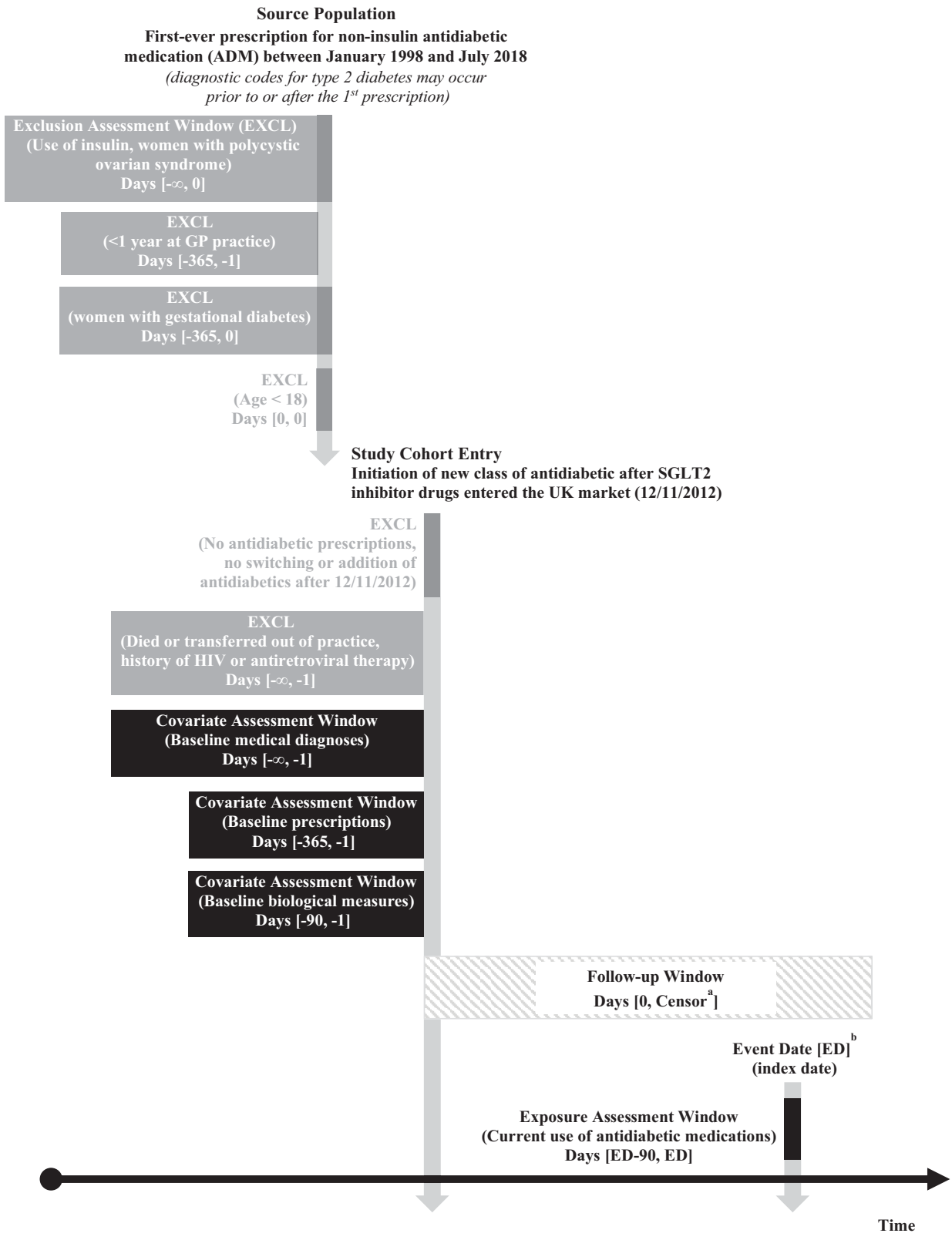

Figure 1—Study population. [a]Censored at minimum of event date, death, last collection of data, transfer out of practice, or end of study period. [b]Controls risk set matched on age (±2 years), sex, cohort entry (±1 year), and duration of treated diabetes (±1 year). GP, general practitioner.

Definition of Outcomes

MACCE and HF were identified from primary care, hospital (primary and secondary diagnoses captured from HES Admitted Patient Care data files; hospitalization/spell, episode, and primary diagnoses across a hospitalization), and/or ONS mortality records. The primary composite end point was the first record of the following MACCE after cohort entry: *1*) myocardial infarction/acute coronary syndrome; *2*) stroke/transient ischemic attack, including intracerebral and subarachnoid hemorrhage; and/or *3*) cardiovascular death. The secondary end point was the first record of HF after cohort entry.

Case and Control Subject Selection

For the primary end point, within each database, cases were identified as patients in the study cohort who experienced a MACCE during follow-up (Supplementary Fig. 3). The index date for cases was defined as the date of the first MACCE. For the secondary end point, cases were identified as patients in the study cohort who experienced HF during follow-up (Supplementary Fig. 4). The index date for cases was defined as the date of the first HF event.

Risk set sampling from the study cohort was used to match each case with up to 20 control subjects, 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 time scale 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 subject selection are provided in Supplementary Figs. 3 and 4.

Exposure

Current exposure to ADMs, including insulin, was defined as two consecutive drug prescriptions for each ADM class issued before the index date (MACCE or HF event) with a prescription length plus a 90-day grace period (defined as continuous use, accounting for nonadherence/nonpersistence), which included the index date. The grace period is the permissible time gap for patients to obtain a subsequent prescription after discontinuation or the end of the previous prescription coverage (14). This approach accounts for variability among prescription durations and remaining stockpiled medications (14,15). For ADM treatment in type 2 diabetes, a permissible gap of 90 days is typically implemented (15–17).

Exposure to ADMs (including insulin) was categorized as *1*) combined SGLT2i and GLP-1RA regimens, *2*) GLP-1RA regimens without SGLT2i agents, *3*) SGLT2i regimens without GLP-1RA agents, *4*) other combination regimens excluding GLP-1RA and SGLT2i agents, *5*) other monotherapy regimens, or *6*) no current exposure. A full list of the ADM regimens contained within each exposure group is provided in the Supplementary 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, HbA_{1c}, 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 before cohort entry and ever exposure to ADMs as all prescriptions before cohort entry. In CPRD, ethnicity was identified from primary care records using Read codes and through linkage with HES (18). In the SAIL Databank, ethnicity was identified from primary care records. Socioeconomic deprivation (English IMD 2015 or Welsh IMD 2014), an aggregated area-level measure of deprivation domains based on the patient's residential locality, was categorized into quintiles (1 = least deprived to 5 = most deprived).

Statistical Analysis

We determined the association between incident MACCE and incident HF with current exposure to SGLT2i regimens, GLP-1RA regimens, and their combination compared with other combination regimens. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% CIs, 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, HbA_{1c}, blood pressure, total cholesterol), and drug history (prescriptions for ADMs, antihypertensive agents, lipid-lowering agents, antiplatelet agents, corticosteroids, nonsteroidal anti-inflammatory drugs, and anticoagulants in the year before cohort entry; ever exposure to ADMs; number of ADMs prescribed before cohort entry), as detailed in Supplementary Tables 1 and 2. Because of the nature of risk set sampling, generated ORs 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 using 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 patients with atrial fibrillation, excluding patients with chronic kidney disease stage $\geq$3, excluding patients with current ADM regimens containing sulfonylureas in the MACCE analysis and regimens containing thiazolidinediones and/or dipeptidyl peptidase 4 (DPP-4) inhibitors in the HF analysis, conducting propensity-matched cohort analyses to examine the risk of MACCE and HF associated with SGLT2is and GLP-1RAs compared with other combination regimens, and assessing the robustness of observed associations to unmeasured confounding through calculation of the E value (21) (see the Supplementary Material). Analyses were performed using Stata 16.1 (StataCorp, College Station, TX) statistical software. We followed Reporting of Studies Conducted Using Observational Routinely Collected Health Data for Pharmacoepidemiological Research guidance (22).

Ethical Approval

This study is based in part on data from the CPRD obtained under license from the U.K. Medicines and Healthcare Products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. ONS and HES data are subject to Crown copyright (2018) protection and reused with the permission of the Health and Social Care Information Centre, all rights reserved. The Office of Population Censuses and Surveys Classification of Interventions and Procedures, codes, terms,

 The interpretation and conclusions contained in this study are those of the authors alone. The study and use of CPRD data were approved by the Independent Scientific Advisory Committee for CPRD research (ref. 19_024A). Approval for SAIL Databank access was granted from the Information Governance Review Panel (project approval no. 0907), an independent body overseeing study approvals in line with permissions already granted for conducting data analysis in the SAIL Databank.

RESULTS

Study Population

The cohorts included 440,089 patients with type 2 diabetes (CPRD GOLD *n* = 52,012, CPRD Aurum *n* = 279,985, SAIL *n* = 108,092) treated with noninsulin ADMs. After excluding those with prior CVD, the unadjusted incidence rate of MACCE was 18.1/1,000 person-years of follow-up (CPRD GOLD 17.7/1,000 person-years, CPRD Aurum 17.9/1,000 person-years, SAIL 18.9/1,000 person-years) (Supplementary Fig. 3). After separately excluding those with a history of HF from the study cohorts, the unadjusted incidence rate of HF was 13.9/1,000 person-years of follow-up (CPRD GOLD 13.2/1,000 person-years, CPRD Aurum 14.4/1,000 person-years, SAIL 13.0/1,000 person-years) (Supplementary Fig. 4).

For the primary end point (MACCE), case subjects were more likely than control subjects to be White, living in deprived areas, and smokers and to have diabetes-related microvascular complications, other comorbidities, and prescriptions for ADMs, antihypertensives, statins, and antiplatelets (Supplementary Table 1). Clinical characteristics for the HF cohorts are provided in Supplementary Table 2. Case subjects with HF were more likely than control subjects to be older, White, living in more deprived areas, and smokers and to have more comorbidities. A higher proportion of case subjects had prescriptions for multiple ADMs, antihypertensive agents, statins, antiplatelets, and anticoagulants.

SGLT2is and GLP-1RAs and MACCE

Of the final cohort of 18,490 patients with MACCE, 599 (3.2%) used SGLT2i regimens, 469 (2.5%) used GLP-1RA regimens, 53 (0.3%) used a combination of SGLT2is and GLP-1RAs, and 4,893 (26.5%) used other combination regimens (Table 1). The remaining patients used other monotherapy regimens (43.1%) or were not on an ADM regimen at the time of the MACCE (24.4%). Supplementary Tables 3–5 provide database-specific clinical characteristics of patients in each current ADM exposure group. Across all the current exposure regimens, metformin was the most commonly prescribed other ADM (∼85% in SGLT2i, GLP-1RA, and combined SGLT2i/GLP-1RA regimens; 92% in other combination regimens; 84% in other monotherapy regimens). Exposure to sulfonylureas 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 and other combination regimens. In SGLT2i, GLP-1RA, and other combination exposure groups, regimens primarily consisted of two or three different ADMs. Patients in the combined SGLT2i/GLP-1RA exposure groups were more likely to be currently exposed to three or more different agents.

In patients without prior CVD, treatment with an SGLT2i was associated with a lower odds of MACCE compared with other combination regimens (adjusted pooled OR 0.82 [95% CI 0.73, 0.92]), whereas treatment with a GLP-1RA was not associated with a significantly lower odds of MACCE (0.93 [0.81, 1.06]) (Fig. 2). The combined SGLT2i and GLP-1RA regimen was associated with 30% lower odds of MACCE compared with other combination regimens (0.70 [0.50, 0.98]) (Fig. 2).

Supplementary Fig. 5 presents the estimates for individual components of MACCE. The MACCE risks were largely driven by reductions in risk for myocardial infarction.

SGLT2is and GLP-1RAs and HF

Of the final cohort of 17,428 patients with HF, 299 (1.7%) used SGLT2i regimens, 490 (2.8%) used GLP-1RA regimens, 42 (0.2%) used a combination of SGLT2is and GLP-1RAs, and 4,352 (25.0%) used other combination regimens (Supplementary Table 6). Treatment with an SGLT2i or a GLP-1RA regimen was associated with lower odds of incident HF compared with other ADM combinations (adjusted pooled ORs 0.49 [95% CI 0.42, 0.58] and 0.82 [0.71, 0.95], respectively) (Fig. 3). The combined SGLT2i and GLP-1RA regimen was associated with a 57% lower odds of HF compared with other combination regimens (0.43 [0.28–0.64]) (Fig. 3).

Sensitivity Analyses

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

CONCLUSIONS

In this study focusing on the primary prevention of clinical events, our results suggest that compared with other ADM combination regimens, *1*) current use of SGLT2is, but not GLP-1RAs, was associated with significantly lower odds of incident MACCE; *2*) current use of SGLT2is, GLP-1RAs, and their combination was associated with significantly lower odds of incident HF; and *3*) current use of the SGLT2i/GLP-1RA combination was nominally associated with lower odds of MACCE than SGLT2is and GLP-1RAs alone.

Primary Prevention of MACCE

SGLT2is

A trial with dapagliflozin and two meta-analyses of other placebo-controlled trials indicated no significant benefit of SGLT2is in reducing the risk for MACCE in primary prevention settings (4). Although the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial considered a special population with type 2 diabetes and albuminuric chronic kidney disease, in the primary prevention subgroup, canagliflozin reduced the risk by 32% (HR 0.68 [95% CI 0.49, 0.94]) (23). Whether these primary

Table 1—MACCE associated with current treatment with SGLT2is and/or GLP-1RAs 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)
Patients, *n*	1,690	20,199			11,887	213,329			4,913	76,037		
Combined SGLT2i and 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)

Data are *n* (%) unless otherwise indicated. aOR, adjusted odds ratio. *Adjusted for case-control matching factors (age, duration of treated diabetes); ethnicity; IMD, microvascular complications, Charlson comorbidity index, smoking status, BMI, HbA_{1c}, blood pressure, and total cholesterol at cohort entry; prescriptions for medications in the year before cohort entry (ADMs, antihypertensive agents, lipid-lowering agents, antiplatelet agents, corticosteroids, nonsteroidal anti-inflammatory drugs, and anticoagulants); ever exposure of ADMs; and number of ADMs prescribed before cohort entry.

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 multinational cohort showing that in patients with type 2 diabetes (27% with CVD), SGLT2i use was associated with lower risks of individual MACCE compared with 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. In recent observational studies comparing SGLT2is with GLP-1RAs, cardiovascular risks appeared similar (26,29,30), with cardioprotective benefits observed in secondary prevention (26). Compared with DPP-4 inhibitors and sulfonylureas (the first-choice drugs for treatment intensification after metformin) or placebo, short-term use of an SGLT2i was associated with reduced risks of MACCE (specifically myocardial infarction and cardiovascular death), HF, and all-cause mortality, with modest or neutral effects on stroke (31–33). With >3 years of follow-up, we report an 18% (OR 0.82 [95% CI 0.73, 0.92]) reduction in the adjusted risk for MACCE with SGLT2i therapy compared with other ADMs. The apparent benefits of SGLT2is that we demonstrate in the primary prevention setting appear to be similar to those reported from randomized controlled trials (RCTs) in the secondary prevention setting (HR 0.86 [95% CI 0.80, 0.93]) (1), with overlapping CIs and the pooled RCT effect estimate being contained within our study's CI.

GLP-1RAs

Except for the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial, the proportion of participants in primary prevention GLP-1RA trials has been low to modest, and the benefits of GLP-1RAs on MACCE risk have been inconsistent; however, in the latest meta-analysis, which included Effect of Efpelgenatide on Cardiovascular Outcomes (AMPLITUDE-O) data, GLP-1RAs reduced MACCE risk by 14% (HR 0.86 [95% CI 0.80, 0.93]), with low heterogeneity with The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) excluded in sensitivity analyses (3). This MACCE benefit appeared to be driven by a 15% risk

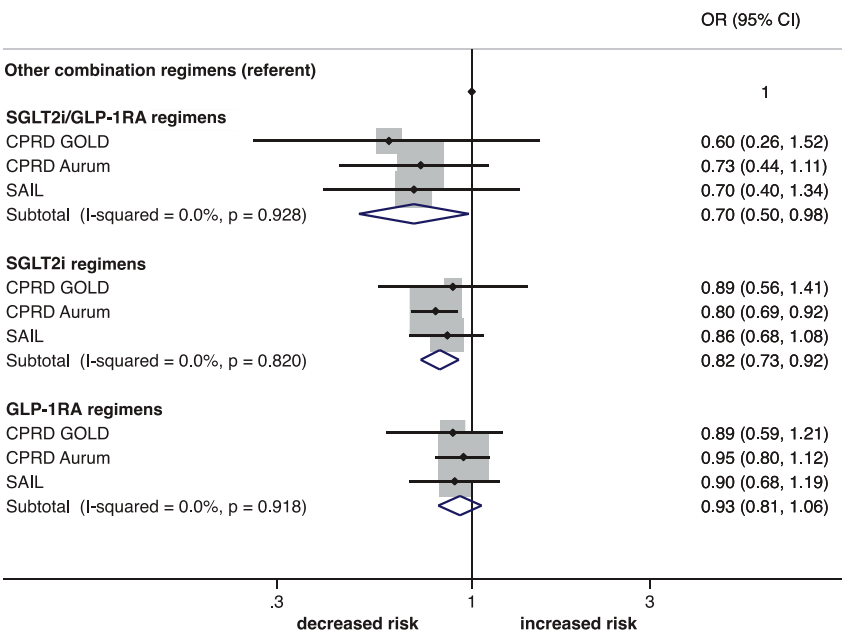

Figure 2—Association between current use of SGLT2is and GLP-1RAs compared with other combination regimens and risk of three-point MACCE. Adjusted for case-control matching factors (age, duration of treated diabetes); ethnicity; IMD, microvascular complications, Charlson comorbidity index, smoking status, BMI, HbA_{1c}, blood pressure, and total cholesterol at cohort entry; prescriptions for medications in the year before cohort entry (ADMs, antihypertensive agents, lipid-lowering agents, antiplatelet agents, corticosteroids, nonsteroidal anti-inflammatory drugs, and anticoagulants); ever exposure to ADMs, and number of ADMs prescribed before cohort entry.

reduction in patients 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 aforementioned meta-analysis of clinical trials (3).

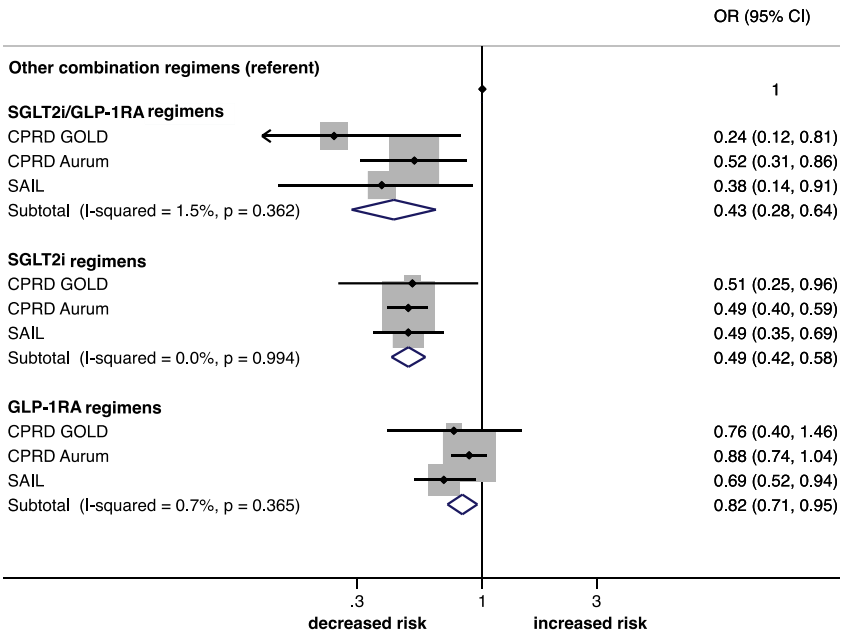

Figure 3—Association between current use of SGLT2is and GLP-1RAs compared with other combination regimens and risk of HF. Adjusted for case-control matching factors (age, duration of treated diabetes); ethnicity; IMD, history of CVD, microvascular complications, Charlson comorbidity index, smoking status, BMI, HbA_{1c}, blood pressure, and total cholesterol at cohort entry; prescriptions for medications in the year before cohort entry (ADMs, antihypertensive agents, lipid-lowering agents, antiplatelet agents, corticosteroids, nonsteroidal anti-inflammatory drugs, and anticoagulants); ever exposure of antidiabetic drugs; and number of ADMs prescribed before cohort entry.

Primary Prevention of HF

SGLT2is

RCTs have shown clear benefits of SGLT2is on HF risk, although data in patients without prior HF have been inconsistently reported (1,36). In patients 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 patients with type 2 diabetes and no prior history of atherosclerotic CVD, SGLT2is reduce the risk for HF (HR 0.63 [95% CI 0.50, 0.80]), but corresponding data in patients without prior HF are lacking (4). Consistent with our data, observational studies have suggested reductions in the risk of hospitalization for HF (25,29,30), ranging from 17 to 40% lower risk in SGLT2i users compared with GLP-1RA or other ADM users (29,30), with no interaction by baseline CVD status (28).

GLP-1RAs

Although there are consistent data for SGLT2is reducing MACCE and HF risk, the consensus on GLP-1RAs has been less clear. New data from the AMPLITUDE-O trial showed significant reductions in HF risk with exendin-4–based GLP-1RA efpeglenatide (HR 0.61 [95% CI 0.38, 0.98]) (37). Consequently, the latest meta-analysis of RCTs reported a statistically significant 11% reduction (HR 0.89 [95% CI 0.82, 0.98]) in the risk of hospitalization for HF with GLP-1RAs (3), which is not dissimilar to our reported estimate (OR 0.82 [95% CI 0.71, 0.95]). This benefit was largely driven by the risk reduction in patients with established CVD; no significant benefit was observed in those without CVD. The only positive observational study showed that GLP-1RAs are associated with a 49% lower risk of hospitalization for HF (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 an 18% lower risk

of first HF episodes in 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 because of potential safety concerns from small RCTs, they may be better avoided in patients with HF with reduced ejection fraction until robust evidence of benefit is generated in this group (39–41).

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

Mechanisms of Benefit With SGLT2is and GLP-1RAs

SGLT2is and GLP-1RAs have well-documented overlapping and distinct mechanisms of action, as summarized recently (46), that could explain their beneficial effects on MACCE and HF 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 HbA_{1c}, weight, and systolic blood pressure compared with use of either medication alone (5,6). HbA_{1c} reductions of up to 2% Diabetes Control and Complications Trial (DCCT) units accompanied by a >3-kg 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 hypoglycemia, 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 SGLT2is (49–52), and therefore, combination therapy could negate this adverse effect (51). We show that the SGLT2i/GLP-1RA combination appears to be associated with lower rates of MACCE and HF compared with SGLT2is and GLP-1RAs alone, although with overlapping CIs. 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

Our study has several strengths. First, we maximized statistical power by acquiring data from three sources on 440,089 patients and analyzed these as separate NCC studies. Second, we linked to hospital and mortality records, providing greater capture of outcomes and covariates. Third, the NCC study design minimized the potential lack of comparability of cases and controls and was a practical approach to assessing associations with the drugs of interest, especially combined SGLT2is and GLP-1RAs, which would not have been feasible in a cohort design because of low prevalence of these exposure groups and more limited follow-up to observe outcomes. Fourth, we used 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-1RAs and SGLT2is are generally regarded as second- and third-line therapies, as are combination regimens (44,53). Therefore, our primary reference group, patients receiving other ADM regimens (excluding GLP-1RAs and SGLT2is), provided a clinically relevant treatment comparison. Finally, we performed several sensitivity analyses to assess the robustness of our findings, including a propensity-matched cohort analysis to estimate the probability of treatment with each ADM regimen and match those treated with SGLT2is or GLP-1RAs to those treated with other combination regimens.

Our study also has several limitations. First, we assessed associations with drug classes rather than individual SGLT2is and GLP-1RAs. Second, ADMs potentially included agents that have, in some studies, been associated with elevated HF risks, which could explain differences in findings compared with placebo-controlled RCTs (54,55). However, in several sensitivity analyses, we excluded case and control subjects whose regimen contained sulfonylureas, thiazolidinediones, or DPP-4 inhibitors; these results were consistent with those of our primary analysis. Third, having a 90-day grace period might have failed to capture a minority of people switching between GLP-1RAs and SGLT2is, leading to some misclassification of the exposure; however, to minimize misclassification of current drug exposure, we required that patients have two consecutive prescriptions for the ADM 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 (Supplementary Figs. 12 and 13). Fourth, making comparisons between second- and third-line therapies could have theoretically introduced time-lag biases because of 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. Fifth, the potential beneficial effects of GLP-1RAs may be underestimated because of 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). Sixth, the potential for prescriber bias and clinical inertia existed, 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. Finally, it was not feasible to stratify by duration of exposure to current regimens because of the large number of strata from covariate adjustment and small sample sizes within strata, and interpretation of treatment effects on

individual MACCE is cautioned because of limited statistical power.

Clinical Implications of Prescribing Guidelines

American Diabetes Association/European Association for the Study of Diabetes guidelines were recently updated to reflect current evidence, with a new recommendation to use SGLT2is and GLP-1RAs in high-risk patients (44). The guidelines highlight that no studies have assessed CVD or renal benefits in low-risk patients with type 2 diabetes. We show that in primary prevention, use of these agents is associated with lower odds of MACCE (SGLT2is) and HF (SGLT2is and GLP-1RAs) 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 to evaluate the 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. Although GLP-1RAs and SGLT2is 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).

In conclusion, this study of real-world data from clinical practice in type 2 diabetes suggests that in primary prevention, current use of SGLT2is is associated with an 18% lower odds of MACCE, and the odds of HF were 51% lower with current use of SGLT2is and 18% lower with current use of GLP-1RAs. Clinical trials of these agents and their combination are called for in the primary prevention setting to evaluate efficacy and cost-effectiveness.

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Data Sharing. Read and ICD-10 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 U.K. 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 CPRD (https://www.cprd.com), secondary care data can be requested via application to the hospital episode statistics from the U.K. Health and Social Care Information Centre (https://www.hscic.gov.uk/hesdata), and mortality data are available by application to the U.K. ONS (https://www.ons.gov.uk/ons/index.html).

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