SUPPLEMENTAL MATERIAL

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Antidiabetic regimens identified throughout patients' drug history

Combined SGLT2 inhibitor (SGLT2i) and GLP-1 receptor agonist (GLP-1RA) regimens	
SGLT2i/GLP-1RA	SGLT2i/GLP-1RA/Metformin/DPP-4i/Insulin
SGLT2i/GLP-1RA/Acarbose	SGLT2i/GLP-1RA/Metformin/DPP-4i/Meglitinide
SGLT2i/GLP-1RA/DPP-4i	SGLT2i/GLP-1RA/Metformin/Meglitinide/Insulin
SGLT2i/GLP-1RA/Insulin	SGLT2i/GLP-1RA/Metformin/SU/Acarbose
SGLT2i/GLP-1RA/Metformin	SGLT2i/GLP-1RA/Metformin/SU/DPP-4i
SGLT2i/GLP-1RA/SU	SGLT2i/GLP-1RA/Metformin/SU/Insulin
SGLT2i/GLP-1RA/TZD	SGLT2i/GLP-1RA/Metformin/SU/Meglitinide
SGLT2i/GLP-1RA/Meglitinide	SGLT2i/GLP-1RA/Metformin/SU/TZD
SGLT2i/GLP-1RA/DPP-4i/Insulin	SGLT2i/GLP-1RA/Metformin/TZD/DPP-4i
SGLT2i/GLP-1RA/Metformin/Acarbose	SGLT2i/GLP-1RA/Metformin/TZD/Insulin
SGLT2i/GLP-1RA/Metformin/DPP-4i	SGLT2i/GLP-1RA/Metformin/TZD/Meglitinide
SGLT2i/GLP-1RA/Metformin/Insulin	SGLT2i/GLP-1RA/SU/DPP-4i/Insulin
SGLT2i/GLP-1RA/Metformin/Meglitinide	SGLT2i/GLP-1RA/SU/TZD/DPP-4i
SGLT2i/GLP-1RA/Metformin/SU	SGLT2i/GLP-1RA/TZD/DPP-4i/Insulin
SGLT2i/GLP-1RA/Metformin/TZD	SGLT2i/GLP-1RA/Metformin/Acarbose/Meglitinide
SGLT2i/GLP-1RA/SU/Acarbose	SGLT2i/GLP-1RA/Metformin/DPP-4i/Meglitinide/Insulin
SGLT2i/GLP-1RA/SU/DPP-4i	SGLT2i/GLP-1RA/Metformin/SU/Acarbose/Insulin
SGLT2i/GLP-1RA/SU/Insulin	SGLT2i/GLP-1RA/Metformin/SU/DPP-4i/Acarbose
SGLT2i/GLP-1RA/SU/TZD	SGLT2i/GLP-1RA/Metformin/SU/DPP-4i/Insulin
SGLT2i/GLP-1RA/TZD/Insulin	SGLT2i/GLP-1RA/Metformin/SU/TZD/Acarbose
SGLT2i/GLP-1RA/SU/Meglitinide	SGLT2i/GLP-1RA/Metformin/SU/TZD/DPP-4i
SGLT2i/GLP-1RA/TZD/Meglitinide	SGLT2i/GLP-1RA/Metformin/SU/TZD/Insulin
SGLT2i/GLP-1RA/Metformin/Acarbose/Insulin	SGLT2i/GLP-1RA/Metformin/SU/TZD/Meglitinide
SGLT2i/GLP-1RA/Metformin/DPP-4i/Acarbose	SGLT2i/GLP-1RA/Metformin/SU/DPP-4i/Acarbose/Insulin
GLP-1RA regimens without SGLT2i agents	
Mono:GLP-1RA	GLP-1RA/DPP-4i/Meglitinide/Insulin
GLP-1RA/Acarbose	GLP-1RA/Metformin/Acarbose/Insulin
GLP-1RA/DPP-4i	GLP-1RA/Metformin/DPP-4i/Acarbose
GLP-1RA/Insulin	GLP-1RA/Metformin/DPP-4i/Insulin
GLP-1RA/Meglitinide	GLP-1RA/Metformin/DPP-4i/Meglitinide
GLP-1RA/Metformin	GLP-1RA/Metformin/Meglitinide/Insulin
GLP-1RA/SU	GLP-1RA/Metformin/SU/Acarbose
GLP-1RA/TZD	GLP-1RA/Metformin/SU/DPP-4i
GLP-1RA/Acarbose/Insulin	GLP-1RA/Metformin/SU/Insulin
GLP-1RA/Acarbose/Meglitinide	GLP-1RA/Metformin/SU/Meglitinide
GLP-1RA/DPP-4i/Insulin	GLP-1RA/Metformin/SU/TZD
GLP-1RA/DPP-4i/Meglitinide	GLP-1RA/Metformin/TZD/Acarbose
GLP-1RA/Meglitinide/Insulin	GLP-1RA/Metformin/TZD/DPP-4i
GLP-1RA/Metformin/Acarbose	GLP-1RA/Metformin/TZD/Insulin
GLP-1RA/Metformin/DPP-4i	GLP-1RA/Metformin/TZD/Meglitinide
GLP-1RA/Metformin/Insulin	GLP-1RA/SU/Acarbose/Insulin
GLP-1RA/Metformin/SU	GLP-1RA/SU/DPP-4i/Acarbose
GLP-1RA/Metformin/TZD	GLP-1RA/SU/DPP-4i/Insulin
GLP-1RA/Metformin/Meglitinide	GLP-1RA/SU/DPP-4i/Meglitinide
GLP-1RA/SU/Acarbose	GLP-1RA/SU/Meglitinide/Insulin
GLP-1RA/SU/DPP-4i	GLP-1RA/SU/TZD/DPP-4i
GLP-1RA/SU/Insulin	GLP-1RA/SU/TZD/Insulin
GLP-1RA/SU/Meglitinide	GLP-1RA/SU/TZD/Meglitinide
GLP-1RA/SU/TZD	GLP-1RA/TZD/DPP-4i/Acarbose
GLP-1RA/TZD/Acarbose	GLP-1RA/TZD/DPP-4i/Insulin
GLP-1RA/TZD/DPP-4i	GLP-1RA/TZD/DPP-4i/Meglitinide
GLP-1RA/TZD/Insulin	GLP-1RA/TZD/Meglitinide/Insulin
GLP-1RA/TZD/Meglitinide	GLP-1RA/Metformin/Acarbose/Meglitinide
GLP-1RA/DPP-4i/Acarbose/Meglitinide	GLP-1RA/SU/Acarbose/Meglitinide

GLP-1RA/Metformin/DPP-4i/Acarbose/Insulin	GLP-1RA/Metformin/TZD/DPP-4i/Insulin
GLP-1RA/Metformin/DPP-4i/Meglitinide/Insulin	GLP-1RA/Metformin/TZD/DPP-4i/Meglitinide
GLP-1RA/Metformin/SU/Acarbose/Insulin	GLP-1RA/Metformin/TZD/Meglitinide/Insulin
GLP-1RA/Metformin/SU/DPP-4i/Acarbose	GLP-1RA/SU/DPP-4i/Acarbose/Insulin
GLP-1RA/Metformin/SU/DPP-4i/Insulin	GLP-1RA/TZD/DPP-4i/Meglitinide/Insulin
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GLP-1RA/Metformin/SU/TZD/Meglitinide	GLP-1RA/Metformin/SU/TZD/DPP-4i/Insulin
GLP-1RA/Metformin/TZD/Acarbose/Insulin	GLP-1RA/Metformin/SU/TZD/Acarbose/Meglitinide
SGLT2i regimens without GLP-1RA agents	
Mono:SGLT2i	SGLT2i/Metformin/TZD/Insulin
SGLT2i/DPP-4i	SGLT2i/SU/DPP-4i/Acarbose
SGLT2i/Meglitinide	SGLT2i/SU/DPP-4i/Insulin
SGLT2i/Metformin	SGLT2i/SU/TZD/DPP-4i
SGLT2i/Insulin	SGLT2i/SU/TZD/Insulin
SGLT2i/SU	SGLT2i/TZD/DPP-4i/Acarbose
SGLT2i/TZD	SGLT2i/TZD/DPP-4i/Insulin
SGLT2i/Acarbose	SGLT2i/Metformin/Acarbose/Meglitinide
SGLT2i/DPP-4i/Acarbose	SGLT2i/Metformin/TZD/Meglitinide
SGLT2i/DPP-4i/Insulin	SGLT2i/SU/Acarbose/Meglitinide
SGLT2i/DPP-4i/Meglitinide	SGLT2i/SU/DPP-4i/Meglitinide
SGLT2i/Meglitinide/Insulin	SGLT2i/SU/Meglitinide/Insulin
SGLT2i/Metformin/Acarbose	SGLT2i/SU/TZD/Acarbose
SGLT2i/Metformin/DPP-4i	SGLT2i/SU/TZD/Meglitinide
SGLT2i/Metformin/Meglitinide	SGLT2i/TZD/Acarbose/Meglitinide
SGLT2i/Metformin/Insulin	SGLT2i/TZD/Meglitinide/Insulin
SGLT2i/Metformin/SU	SGLT2i/Metformin/DPP-4i/Meglitinide/Insulin
SGLT2i/Metformin/TZD	SGLT2i/Metformin/SU/Acarbose/Insulin
SGLT2i/SU/Acarbose	SGLT2i/Metformin/SU/DPP-4i/Acarbose
SGLT2i/SU/DPP-4i	SGLT2i/Metformin/SU/DPP-4i/Insulin
SGLT2i/SU/Insulin	SGLT2i/Metformin/SU/TZD/Acarbose
SGLT2i/SU/TZD	SGLT2i/Metformin/SU/TZD/DPP-4i
SGLT2i/TZD/DPP-4i	SGLT2i/Metformin/SU/TZD/Insulin
SGLT2i/TZD/Insulin	SGLT2i/Metformin/TZD/DPP-4i/Meglitinide
SGLT2i/Acarbose/Meglitinide	SGLT2i/Metformin/TZD/DPP-4i/Insulin
SGLT2i/SU/Meglitinide	SGLT2i/Metformin/Acarbose/Meglitinide/Insulin
SGLT2i/TZD/Acarbose	SGLT2i/Metformin/SU/Acarbose/Meglitinide
SGLT2i/TZD/Meglitinide	SGLT2i/Metformin/SU/DPP-4i/Meglitinide
SGLT2i/Metformin/Acarbose/Insulin	SGLT2i/Metformin/SU/Meglitinide/Insulin
SGLT2i/Metformin/DPP-4i/Acarbose	SGLT2i/Metformin/SU/TZD/Meglitinide
SGLT2i/Metformin/DPP-4i/Insulin	SGLT2i/Metformin/TZD/Acarbose/Meglitinide
SGLT2i/Metformin/DPP-4i/Meglitinide	SGLT2i/Metformin/TZD/Meglitinide/Insulin
SGLT2i/Metformin/Meglitinide/Insulin	SGLT2i/SU/Acarbose/Meglitinide/Insulin
SGLT2i/Metformin/SU/Acarbose	SGLT2i/SU/TZD/Acarbose/Meglitinide
SGLT2i/Metformin/SU/DPP-4i	SGLT2i/Metformin/SU/DPP-4i/Acarbose/Insulin
SGLT2i/Metformin/SU/Meglitinide	SGLT2i/Metformin/SU/TZD/DPP-4i/Insulin
SGLT2i/Metformin/SU/Insulin	SGLT2i/Metformin/SU/Acarbose/Meglitinide/Insulin
SGLT2i/Metformin/SU/TZD	SGLT2i/Metformin/SU/TZD/DPP-4i/Acarbose
SGLT2i/Metformin/TZD/Acarbose	SGLT2i/Metformin/SU/TZD/Acarbose/Meglitinide
SGLT2i/Metformin/TZD/DPP-4i	
Other combination regimens excluding GLP-1RA and SGLT2i agents	
Acarbose/Insulin	DPP-4i/Insulin
Acarbose/Meglitinide	DPP-4i/Meglitinide
DPP-4i/Acarbose	Meglitinide/Insulin

Metformin/Acarbose	Metformin/DPP-4i/Acarbose/Insulin
Metformin/DPP-4i	Metformin/DPP-4i/Acarbose/Meglitinide
Metformin/Insulin	Metformin/DPP-4i/Meglitinide/Insulin
Metformin/Meglitinide	Metformin/SU/Acarbose/Insulin
Metformin/SU	Metformin/SU/Acarbose/Meglitinide
Metformin/TZD	Metformin/SU/DPP-4i/Acarbose
SU/Acarbose	Metformin/SU/DPP-4i/Insulin
SU/DPP-4i	Metformin/SU/DPP-4i/Meglitinide
SU/Insulin	Metformin/SU/Meglitinide/Insulin
SU/Meglitinide	Metformin/SU/TZD/Acarbose
SU/TZD	Metformin/SU/TZD/DPP-4i
TZD/Acarbose	Metformin/SU/TZD/Insulin
TZD/DPP-4i	Metformin/SU/TZD/Meglitinide
TZD/Insulin	Metformin/TZD/Acarbose/Insulin
TZD/Meglitinide	Metformin/TZD/Acarbose/Meglitinide
DPP-4i/Acarbose/Insulin	Metformin/TZD/DPP-4i/Acarbose
DPP-4i/Acarbose/Meglitinide	Metformin/TZD/DPP-4i/Insulin
DPP-4i/Meglitinide/Insulin	Metformin/TZD/DPP-4i/Meglitinide
Acarbose/Meglitinide/Insulin	Metformin/TZD/Meglitinide/Insulin
Metformin/Acarbose/Insulin	SU/DPP-4i/Acarbose/Insulin
Metformin/Acarbose/Meglitinide	SU/DPP-4i/Meglitinide/Insulin
Metformin/DPP-4i/Acarbose	SU/TZD/Acarbose/Insulin
Metformin/DPP-4i/Insulin	SU/TZD/Acarbose/Meglitinide
Metformin/DPP-4i/Meglitinide	SU/TZD/DPP-4i/Acarbose
Metformin/Meglitinide/Insulin	SU/TZD/DPP-4i/Insulin
Metformin/SU/Acarbose	SU/TZD/DPP-4i/Meglitinide
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Metformin/SU/TZD	SU/DPP-4i/Acarbose/Meglitinide
Metformin/TZD/Acarbose	SU/Acarbose/Meglitinide/Insulin
Metformin/TZD/DPP-4i	Metformin/DPP-4i/Acarbose/Meglitinide/Insulin
Metformin/TZD/Insulin	Metformin/SU/Acarbose/Meglitinide/Insulin
Metformin/TZD/Meglitinide	Metformin/SU/DPP-4i/Acarbose/Insulin
SU/DPP-4i/Acarbose	Metformin/SU/DPP-4i/Acarbose/Meglitinide
SU/DPP-4i/Insulin	Metformin/SU/TZD/Acarbose/Insulin
SU/DPP-4i/Meglitinide	Metformin/SU/TZD/Meglitinide/Insulin
SU/Acarbose/Insulin	Metformin/SU/TZD/DPP-4i/Acarbose
SU/Acarbose/Meglitinide	Metformin/SU/TZD/DPP-4i/Insulin
SU/Meglitinide/Insulin	Metformin/SU/TZD/DPP-4i/Meglitinide
SU/TZD/Acarbose	Metformin/SU/TZD/Meglitinide/Insulin
SU/TZD/DPP-4i	Metformin/TZD/Acarbose/Meglitinide/Insulin
SU/TZD/Insulin	Metformin/TZD/DPP-4i/Acarbose/Insulin
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TZD/DPP-4i/Insulin	SU/TZD/Acarbose/Meglitinide/Insulin
TZD/DPP-4i/Meglitinide	SU/TZD/DPP-4i/Acarbose/Insulin
TZD/Acarbose/Insulin	Metformin/SU/DPP-4i/Acarbose/Meglitinide
TZD/Acarbose/Meglitinide	Metformin/SU/TZD/DPP-4i/Acarbose/Insulin
TZD/Meglitinide/Insulin	Metformin/SU/TZD/Acarbose/Meglitinide/Insulin
Metformin/Acarbose/Meglitinide/Insulin	Metformin/TZD/DPP-4i/Acarbose/Meglitinide/Insulin
Other monotherapy regimens	
Mono:Metforminformin	Mono:Meglitinide
Mono:SU	Mono:DPP-4i
Mono:TZD	Mono:Insulin
Mono:Acarbose	

The most commonly used combination regimens were metformin/sulphonylurea, metformin/DPP-4i, sulphonylurea/DPP-4i and metformin/sulphonylurea/DPP-4i.

Detailed description of sensitivity analyses

To assess the robustness of our results, we conducted several sensitivity analyses. First, we assessed how robust our observed associations were to potential unmeasured confounding using the E-value measure.[1] The E-value is defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates.[1] A large E-value implies considerable unmeasured confounding would be needed to explain away an effect estimate.[1] A small E-value implies little unmeasured confounding would be needed to explain away an effect estimate.[1] Second, we repeated our primary analysis determining the association between MACCE and antidiabetic regimen exposure in those without cardiovascular disease (defined as non-fatal myocardial infarction, acute coronary syndrome, stroke, transient ischaemic attack, unstable angina, heart failure and revascularisation) additionally excluding those with atrial fibrillation. Third, as SGLT2 inhibitors canagliflozin and dapagliflozin are not recommended in people with moderate to severe renal impairment (eGFR <60ml/min/1.73m^2), we excluded people with CKD stage 3+ from the primary analysis. Fourth, since sulphonylureas have previously been associated with a higher risk of MACCE, and thiazolidinediones (TZDs) and some DPP-4 inhibitors with higher risks of heart failure, we repeated the MACCE analysis excluding people with antidiabetic regimens containing sulphonylureas and the heart failure analysis excluding people with antidiabetic regimens containing TZDs and/or DPP-4 inhibitor agents. This involved censoring individuals from the source population upon a prescription for sulphonylureas, TZDs and DPP-4 inhibitors. Cases and controls were identified from those with a censor date beyond the index date. Fifth, we varied our definition of current exposure to antidiabetic regimens using grace periods of 30 and 60 days. Sixth, we restricted our MACCE outcome definition to events occurring in hospital or ONS mortality records. Seventh, we directly compared the association between MACCE and exposure to: (a.) GLP-1RA and combined GLP-1RA/SGLT2i regimens with SGLT2i regimens and (b.) SGLT2i and combined GLP-1RA/SGLT2i regimens with GLP-1RA regimens. Finally, our nested case-control analyses were supplemented by propensity-matched cohort analyses examining the risk of MACCE and heart failure associated with SGLT2i regimens and GLP-1RA regimens compared with other combination regimens. Due to the low prevalence of the SGLT2i/GLP-1RA regimen and outcome events, it was not feasible to analyse this regimen in the propensity-matched analysis.

In the propensity-matched cohort analyses, we identified the antidiabetic regimen which triggered entry into the cohort; defined as SGLT2i regimens, GLP-1RA regimens, SGLT2i/GLP-1RA regimens, other combination regimen and other monotherapy regimens. We then estimated the probability of treatment with each antidiabetic regimen using a multinomial logistic regression model with the antidiabetic regimens as the dependent variable and independent variables consisting of baseline patient characteristics; age, gender, region, Index of Multiple Deprivation (English IMD 2015 and Welsh IMD 2014), ethnicity, duration of type 2 diabetes, duration of treated diabetes, history of smoking, current smoker at cohort entry, history of renal disease, microvascular disease (nephropathy, retinopathy, neuropathy), cardiovascular disease, atrial fibrillation, COPD, dementia, liver disease, cancer, depression, bipolar disorder, schizophrenia, mean value over patient history and closest value in the year prior to cohort entry of biological variables (HbA1c, BMI, systolic and diastolic blood pressure, total cholesterol, creatinine, GFR) and binary variables indicating prescriptions for the following drugs in the year prior to cohort entry and count of the number of prescriptions in the year prior to cohort entry; antidiabetic medications (metformin, sulphonylurea, TZD, acarbose, meglitinides, GLP-1RA, DPP-4 inhibitors, SGLT2i), antihypertensive agents (ACE inhibitors, angiotensin II receptor blockers, beta blockers, calcium-channel blockers, diuretics, other), lipid-lowering agents (statins, fibrates, ezetimibe, other), antiplatelet agents (aspirin, clopidogrel, other), NSAIDs, steroids, anticoagulants, antipsychotics, antiosteoporotic agents. We used the missing indicator method for missing data in the biological variables, replacing missing values with a constant value and including a binary missing indicator variable in the model.

We then matched patients who were treated with SGLT2i and GLP-1RA regimens with patients who were treated with other combinations, but had similar model-based probabilities of being treated (maximum propensity score caliper ± 0.01).

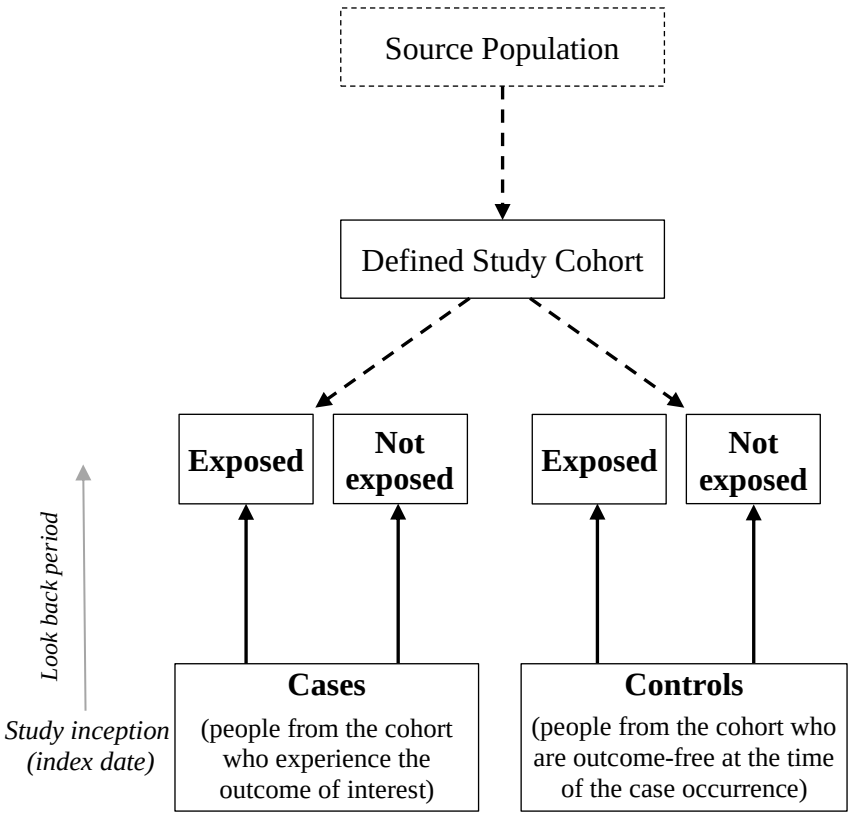
Patients were then followed until the endpoint (primary endpoint, MACCE; secondary endpoint, heart failure), death, transfer out of practice, or study end (31 November 2018); whichever occurred first. Cox Proportional Hazard models estimated the risk of the endpoints associated with the antidiabetic regimens. Estimates from each database (CPRD GOLD, CPRD Aurum, SAIL Databank) were meta-analysed using DerSimonian and Laird random-effects models.

Reference

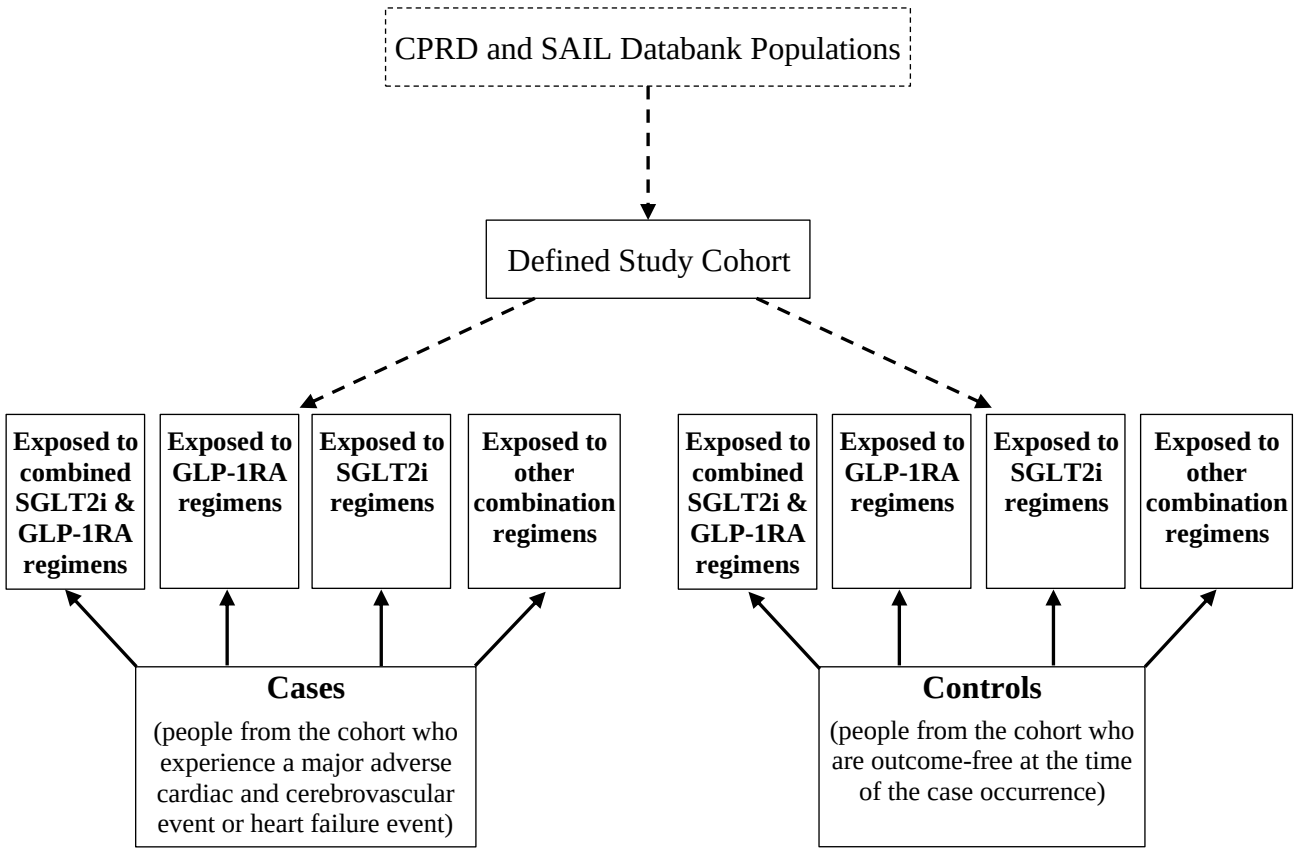
1. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med 2017;167(4):268.

Supplemental Figure 1. Nested case-control design

a. General



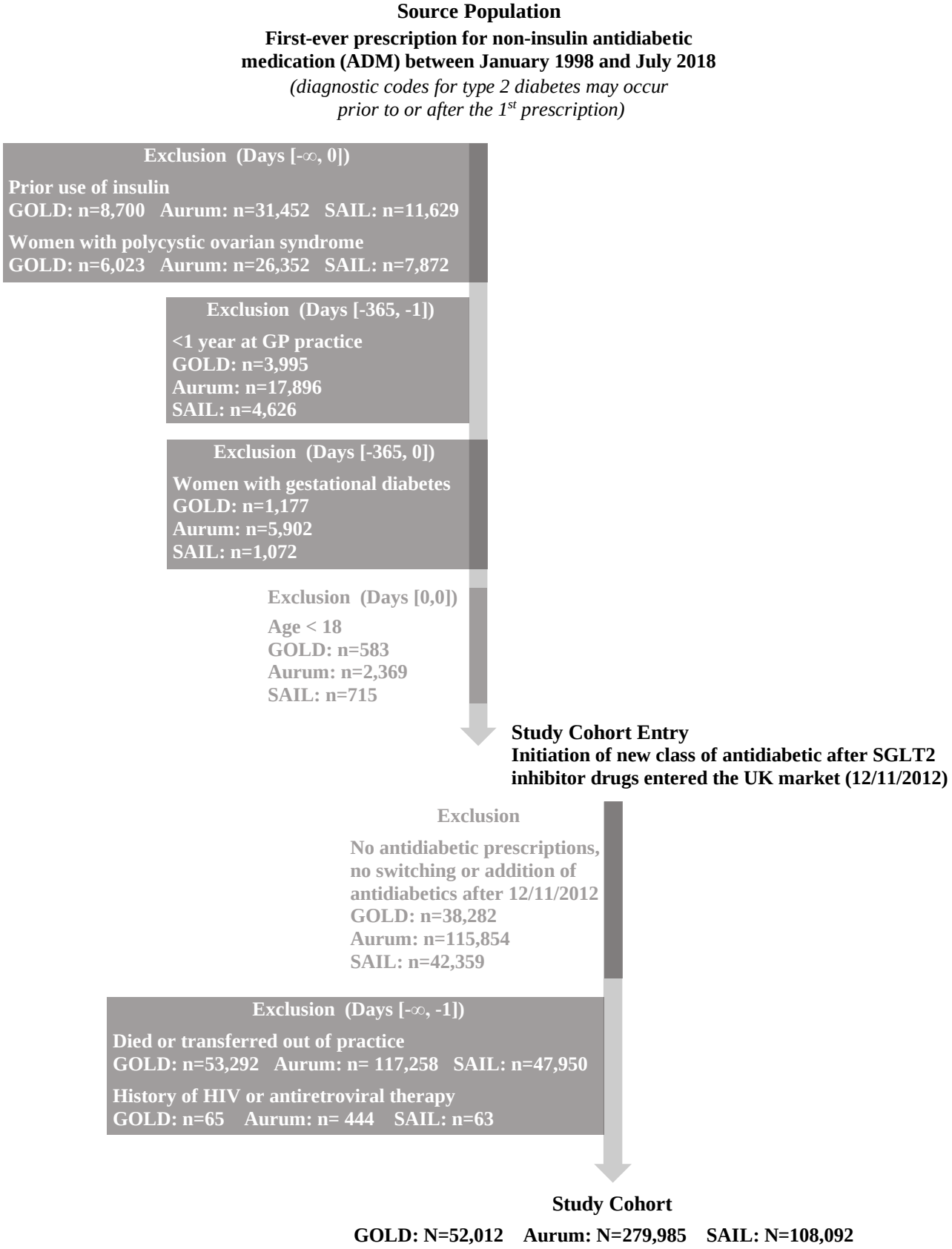
b. Study specific



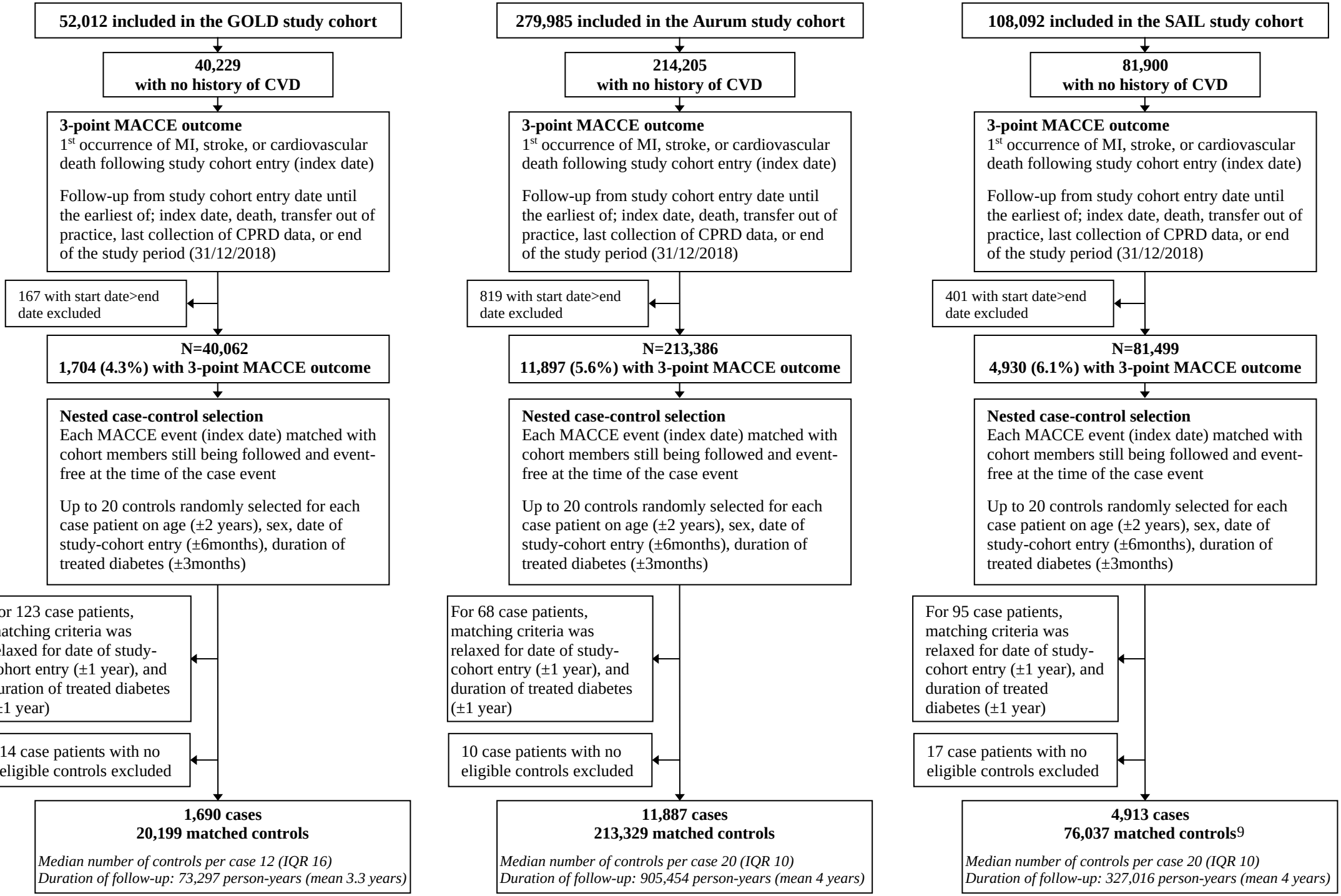
A nested case-control study is a case-control study "nested" within a cohort. In the first instance, a study cohort is defined from which cases and controls will be drawn. Cases are those from the defined cohort who develop the outcome of interest at a given point in time. Cases are matched to a random subset of people from the defined cohort who have not experienced the outcome of interest at that time. Controls are matched on potential confounders, along with a time element. This may include age, date of entry into the cohort, length of time in the cohort, or a combination of these. The controls may develop the outcome later and become a case themselves, and they may also act as a control for other cases.

In a specified look back window, the exposure status of cases and controls preceding the index date is identified, and the analysis establishes if an association between exposure and outcome exists.

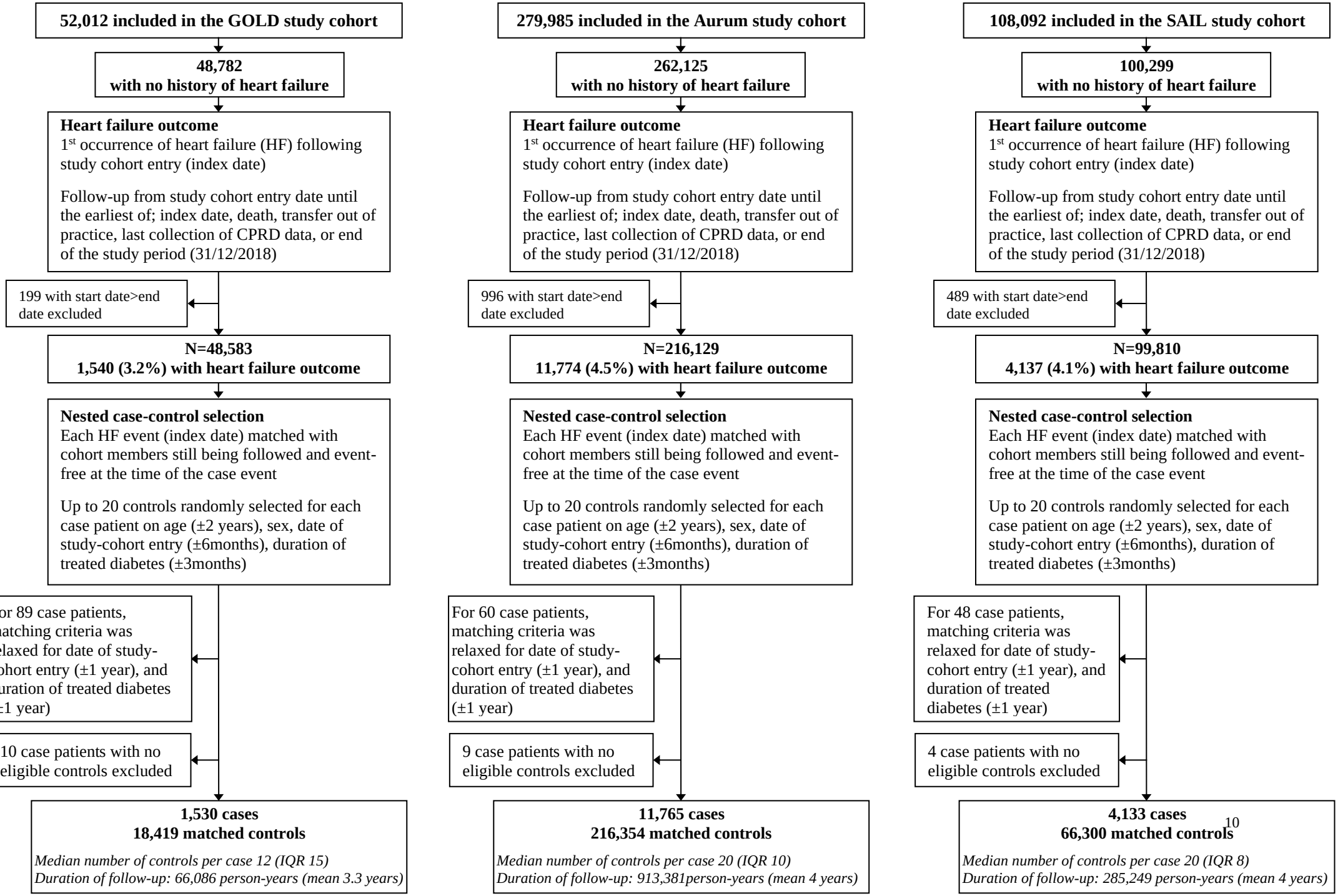
Supplemental Figure 2. Construction of the study cohort in CPRD GOLD, CPRD Aurum and the SAIL Databank



Supplemental Figure 3. Nested case-control selection for MACCE outcome in CPRD GOLD, CPRD Aurum and the SAIL Databank

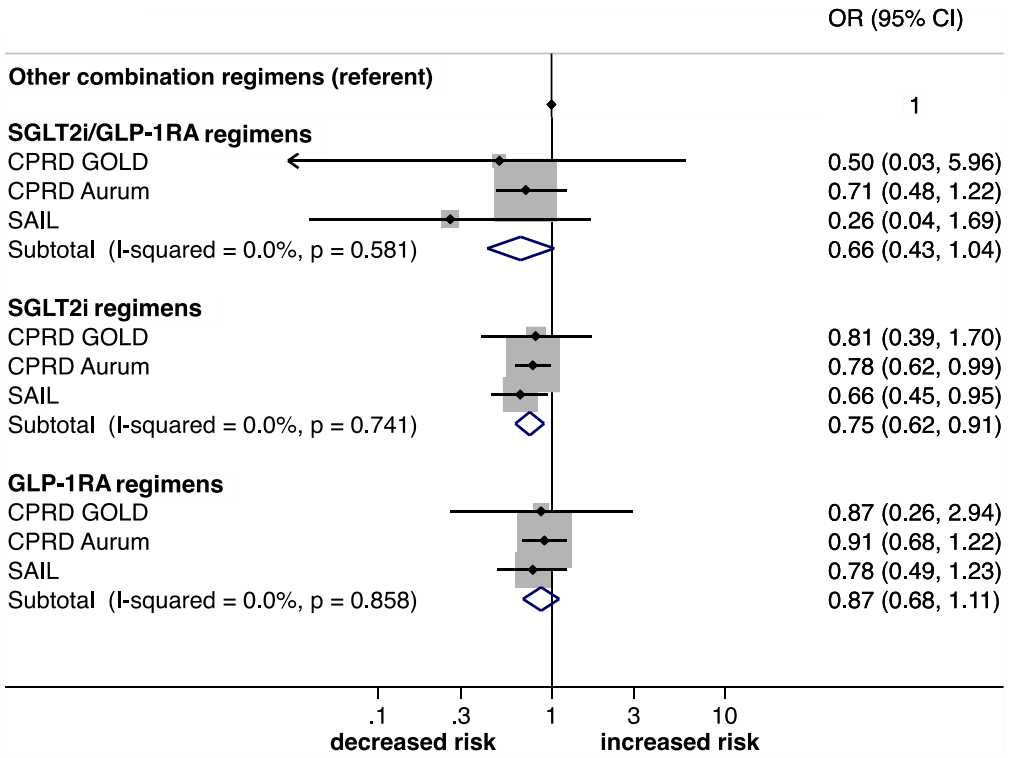


Supplemental Figure 4. Nested case-control selection for heart failure outcome in CPRD GOLD, CPRD Aurum and the SAIL Databank

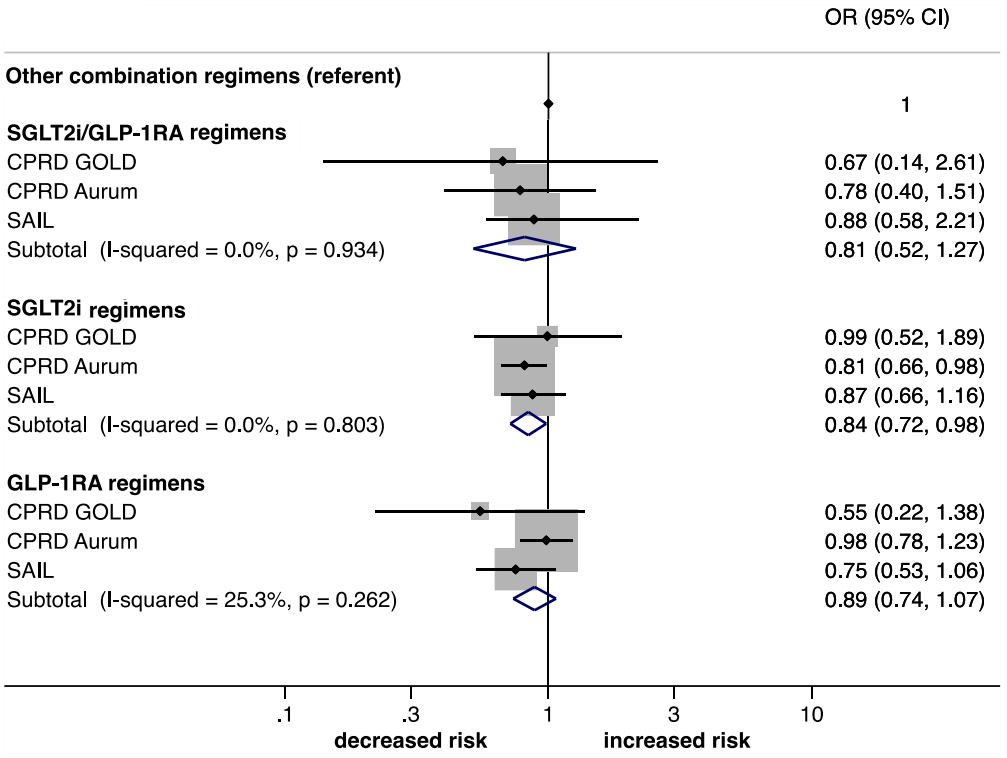


Supplemental Figure 5. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of individual components of 3-point major adverse cardiac and cerebrovascular events: a) myocardial infarction, b) stroke, c) cardiovascular death

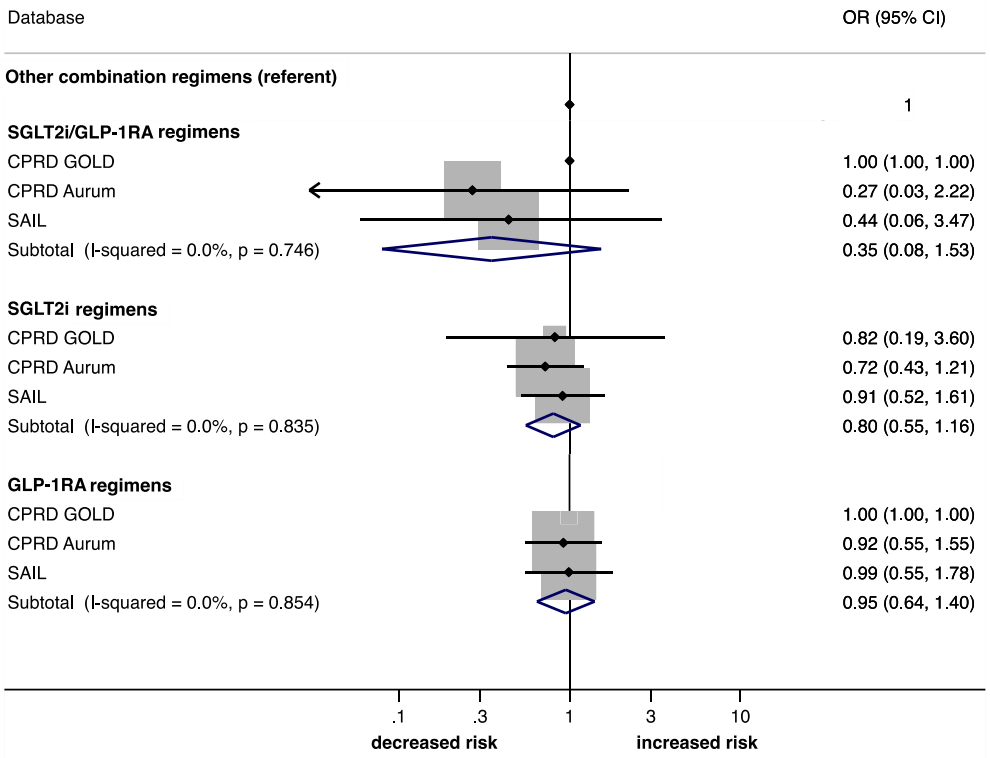
(a.) Myocardial infarction



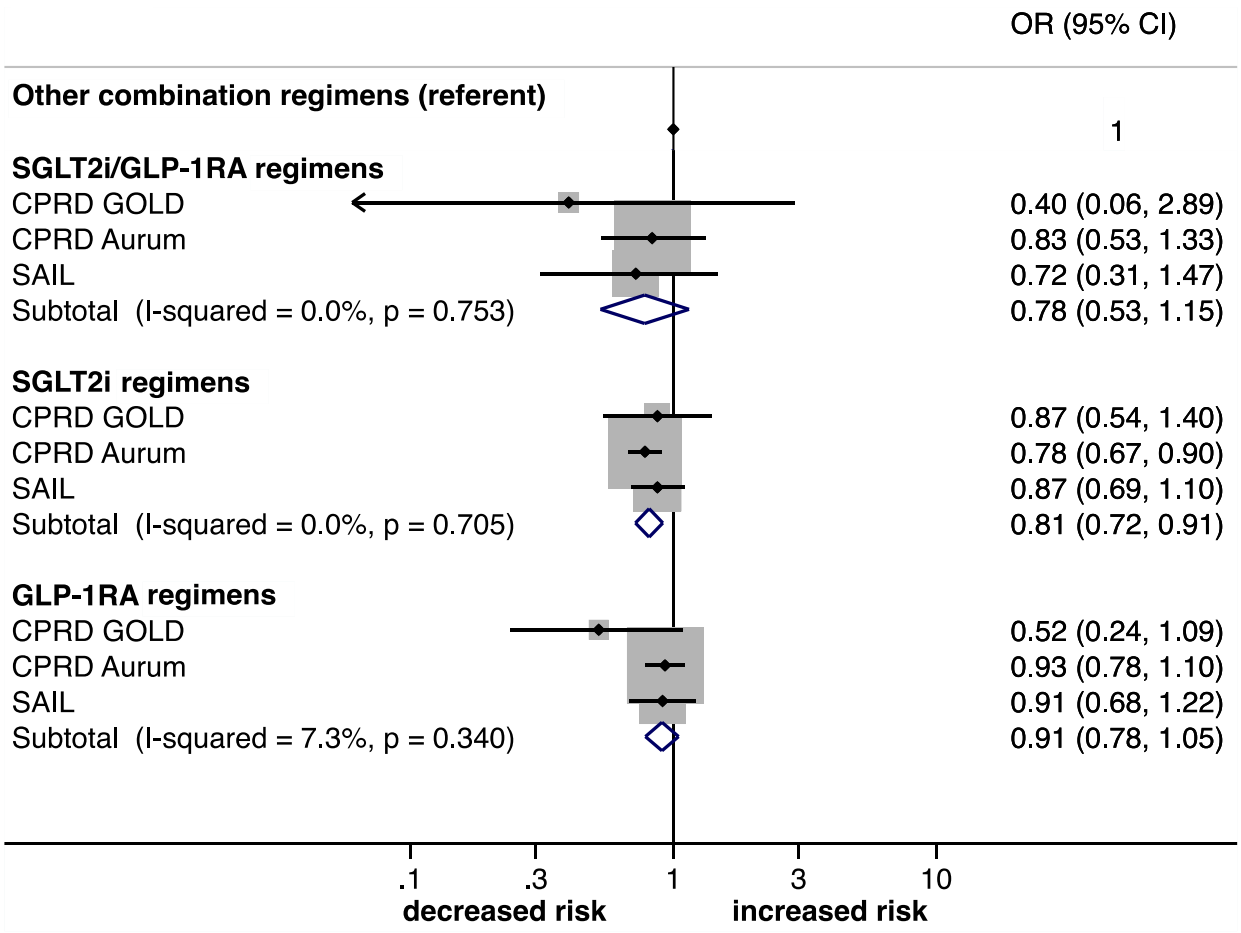
(b.) Stroke



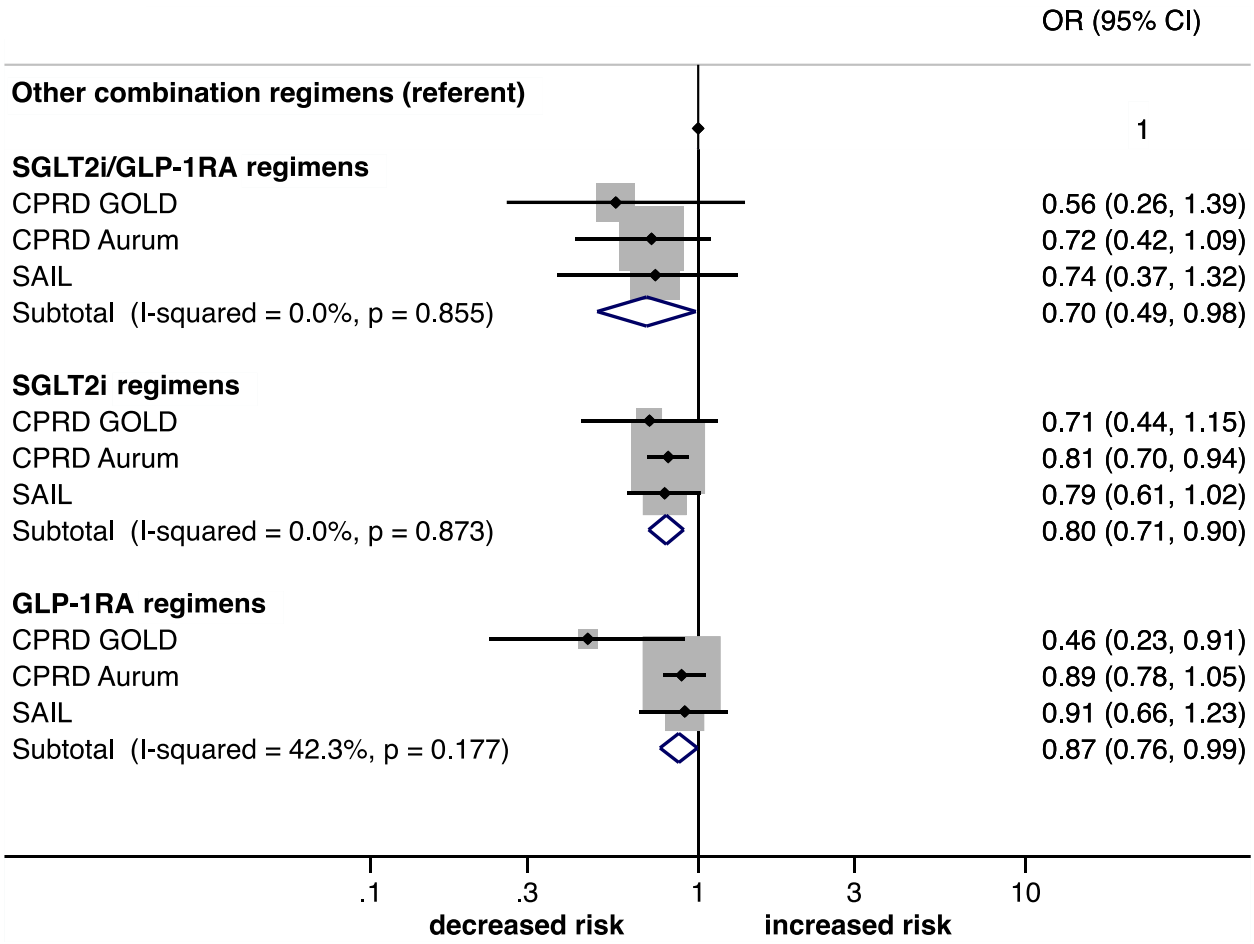
(c.) Cardiovascular death



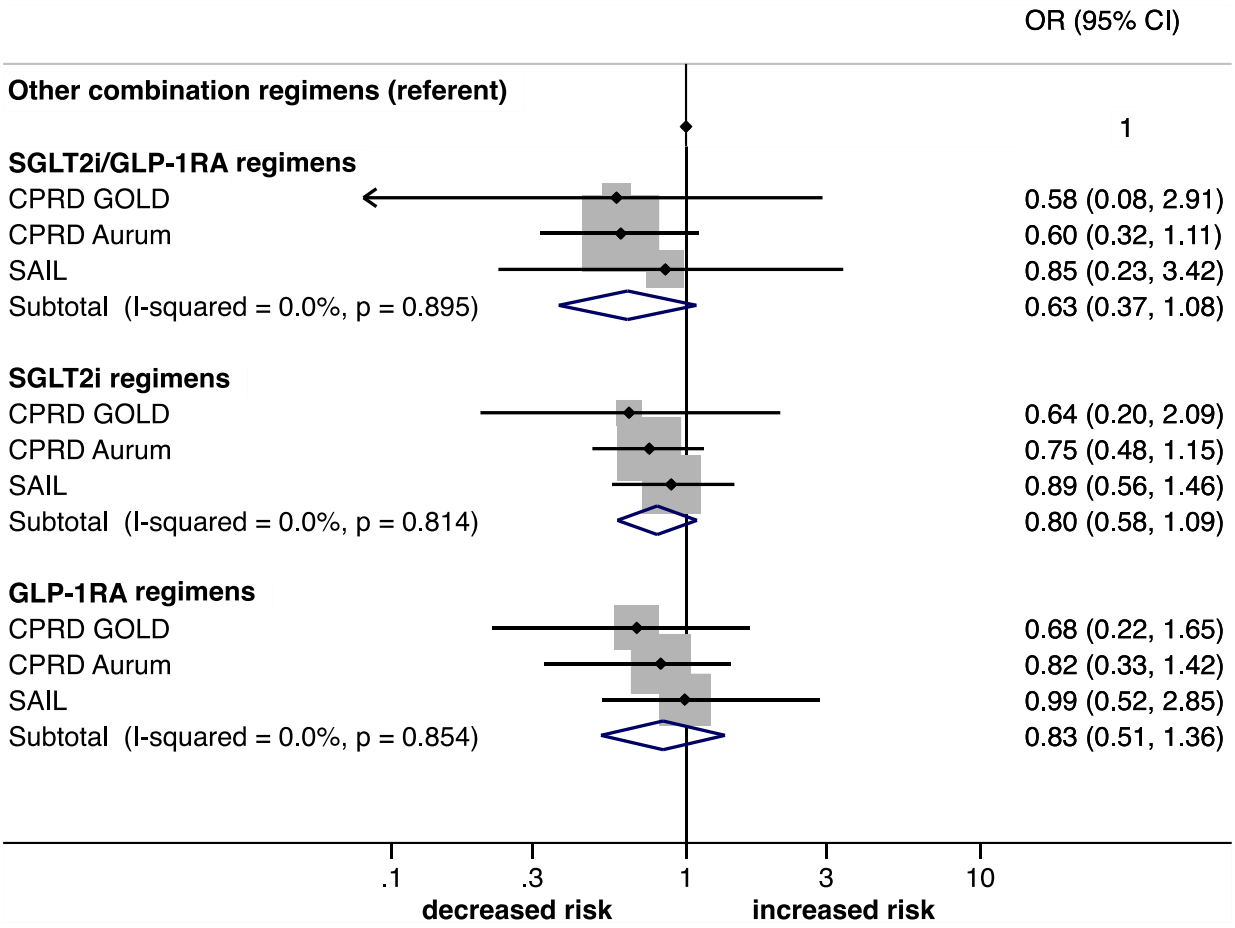
Supplemental Figure 6. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of 3-point major adverse cardiac and cerebrovascular events, after excluding people with a history of atrial fibrillation



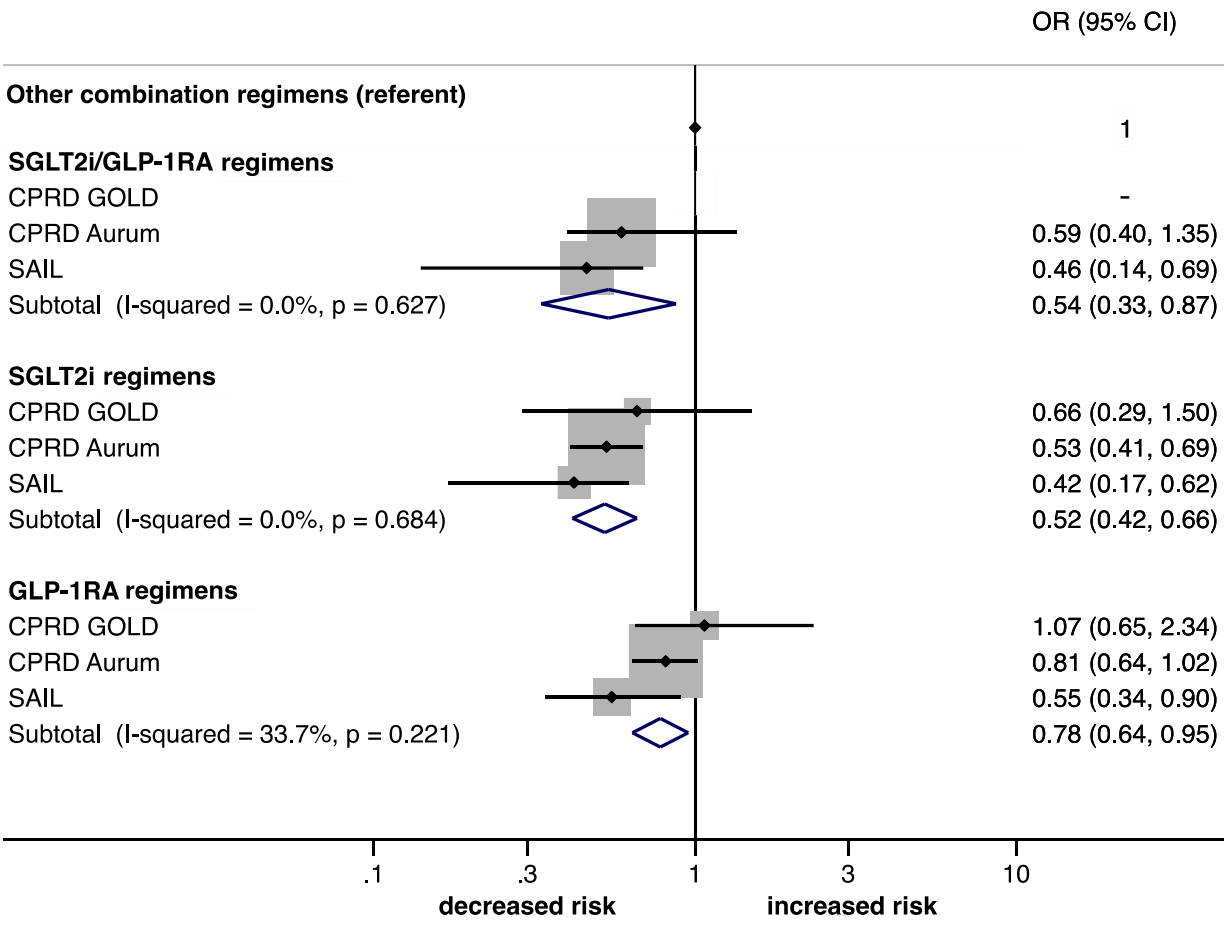
Supplemental Figure 7. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of 3-point major adverse cardiac and cerebrovascular events, after excluding people with CKD stage 3+



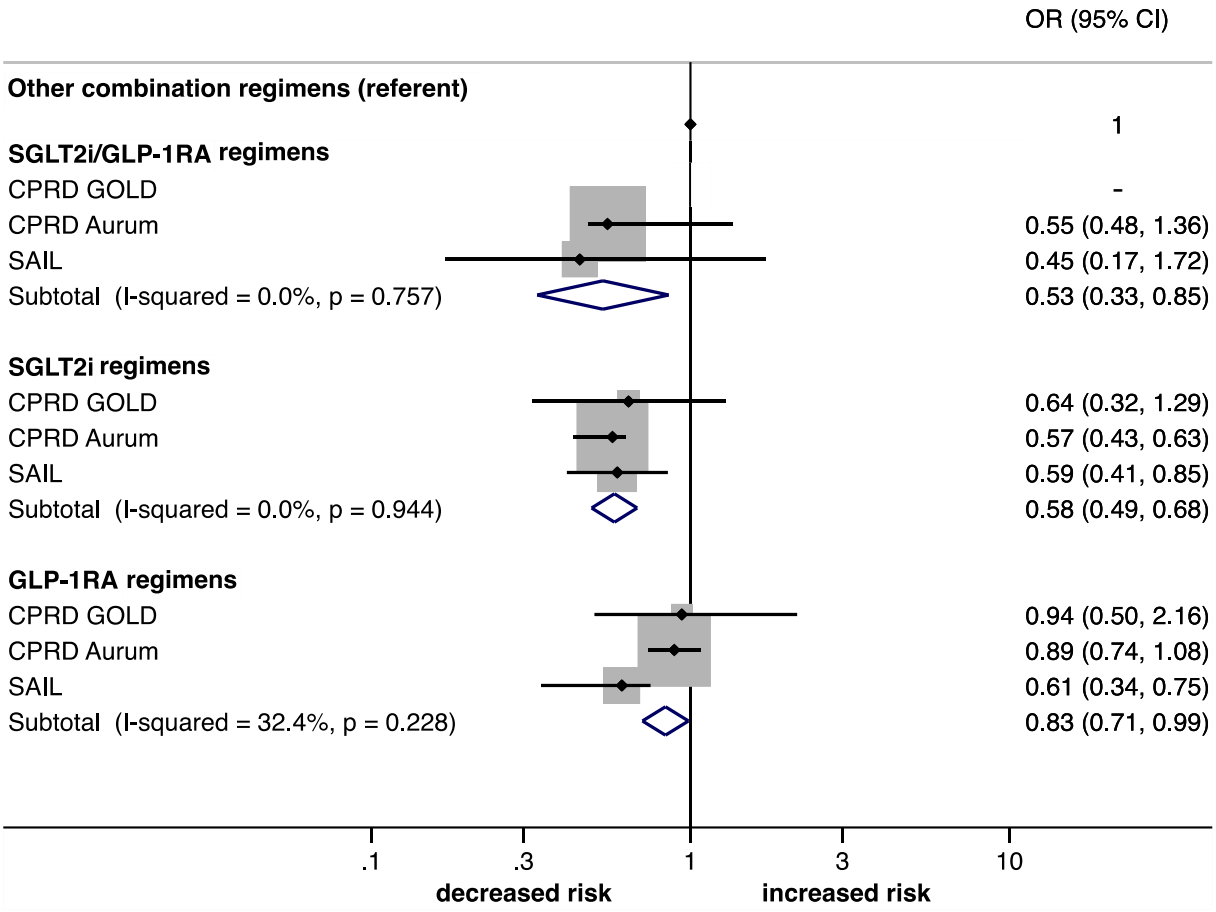
Supplemental Figure 8. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of 3-point major adverse cardiac and cerebrovascular events, after excluding regimens containing sulphonylureas



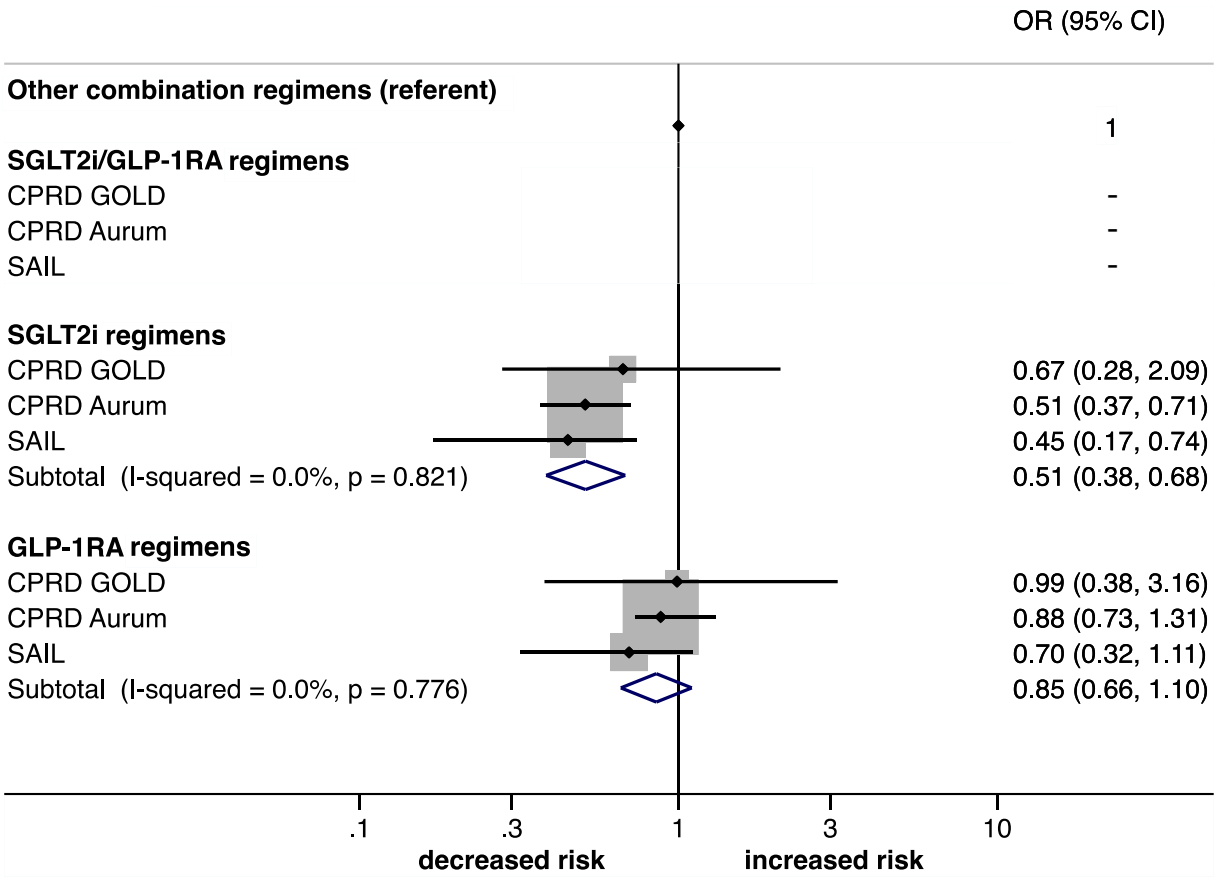
Supplemental Figure 9. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of heart failure, after excluding regimens containing DPP-4 inhibitors



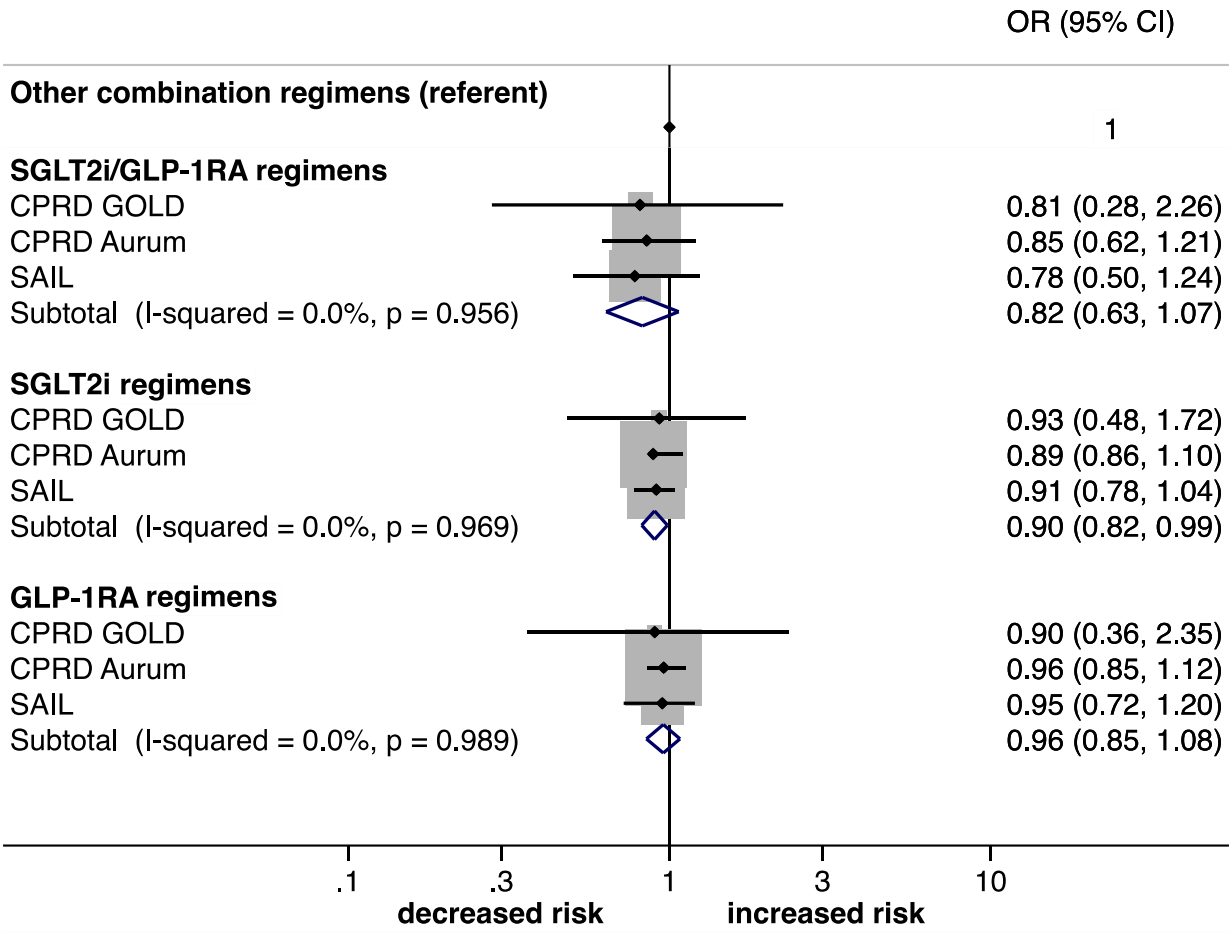
Supplemental Figure 10. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of heart failure, after excluding regimens containing TZDs



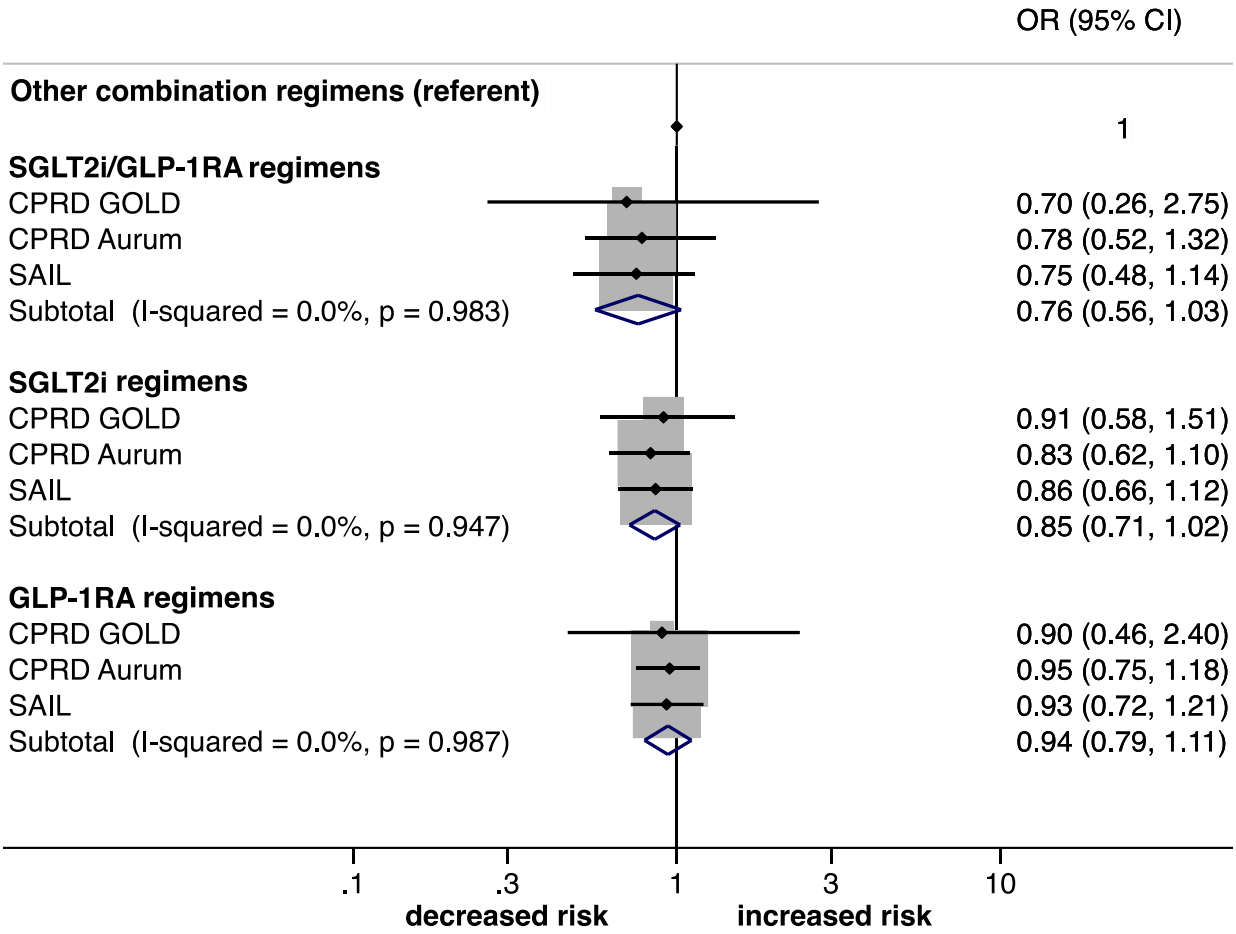
Supplemental Figure 11. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of heart failure, after excluding regimens containing TZDs or DPP-4 inhibitors



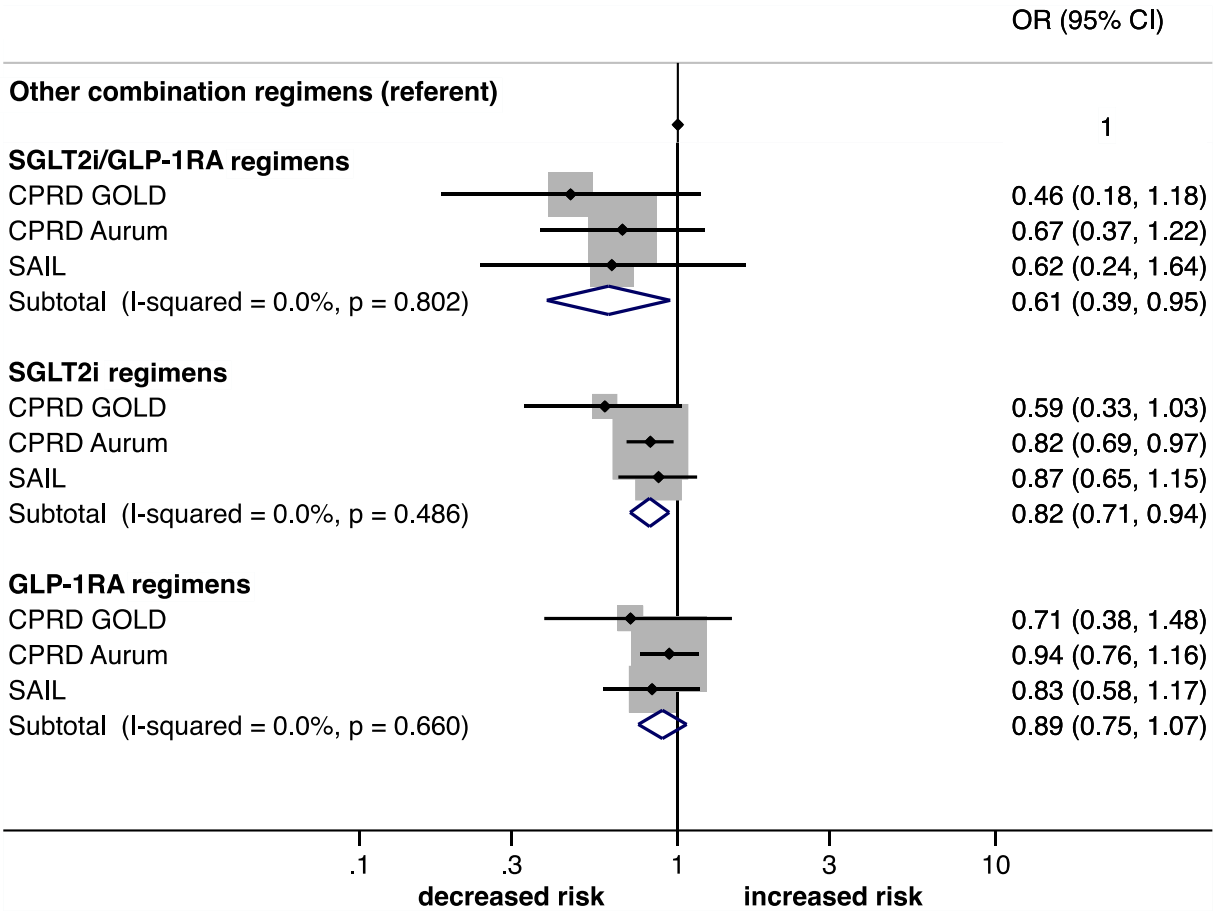
Supplemental Figure 12. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of 3-point major adverse cardiac and cerebrovascular events, with current exposure to ADM regimens defined as prescription + 30 days



Supplemental Figure 13. 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, with current exposure to ADM regimens defined as prescription + 60 days

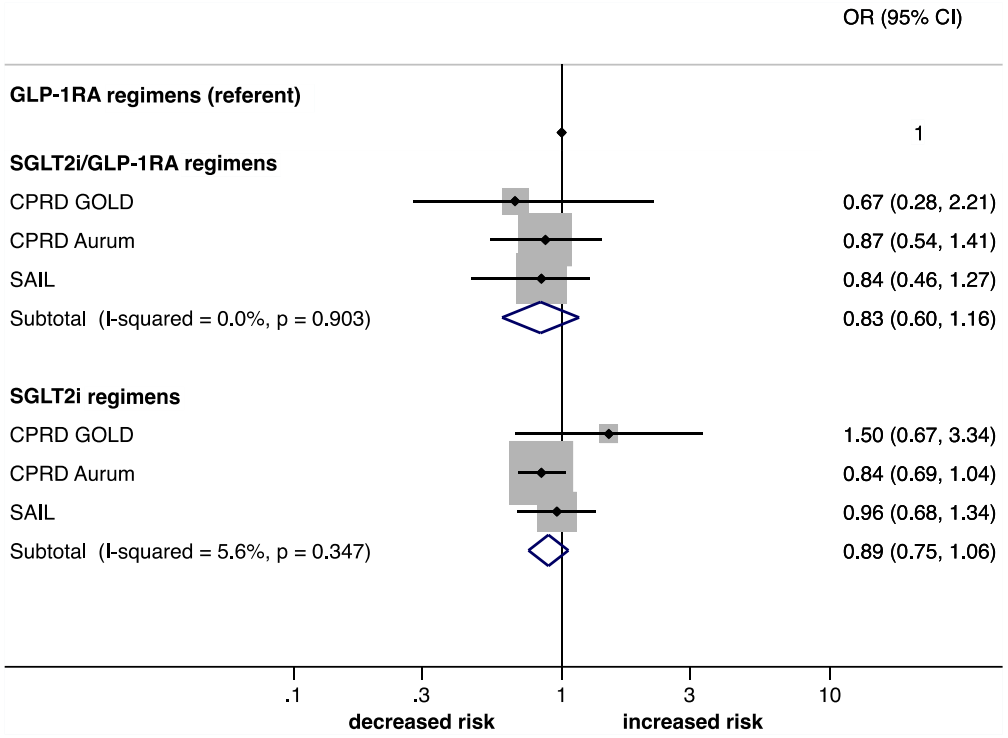


Supplemental Figure 14. Association between current use of SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and risk of 3-point major adverse cardiac and cerebrovascular events, when MACCE definition was restricted to events occurring in hospital and ONS mortality records

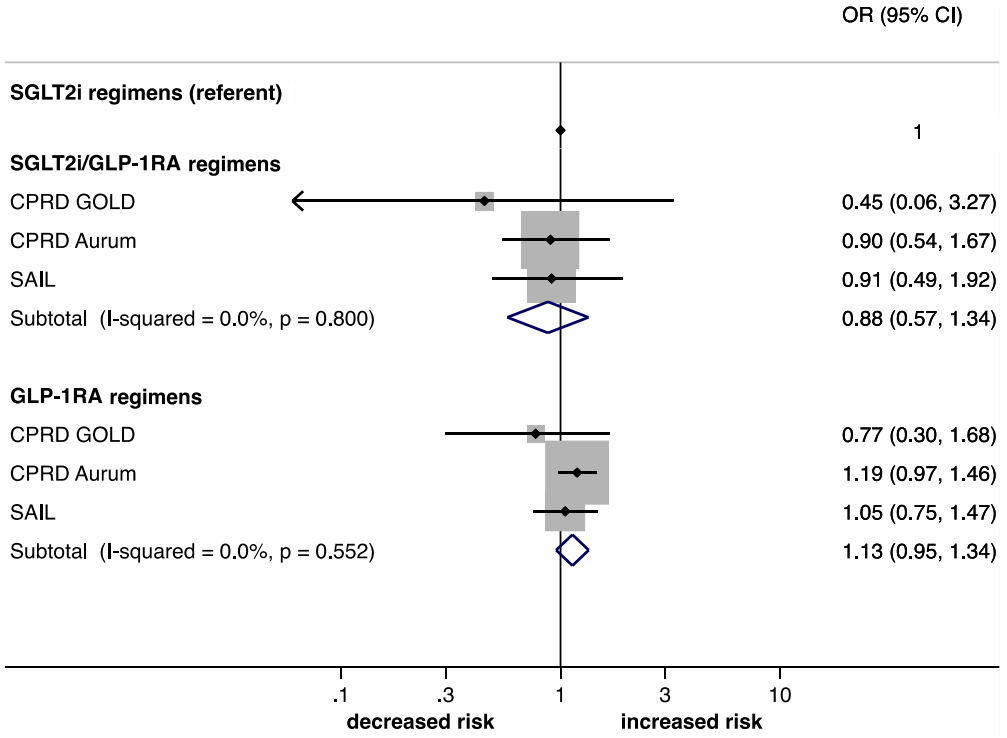


Supplemental Figure 15. Association between current use of (a.) SGLT2i and combined SGLT2i/GLP-1RA regimens compared with GLP-1RA regimens and (b.) GLP-1RA and combined SGLT2i/GLP-1RA regimens compared with SGLT2i regimens and risk of 3-point major adverse cardiac and cerebrovascular events

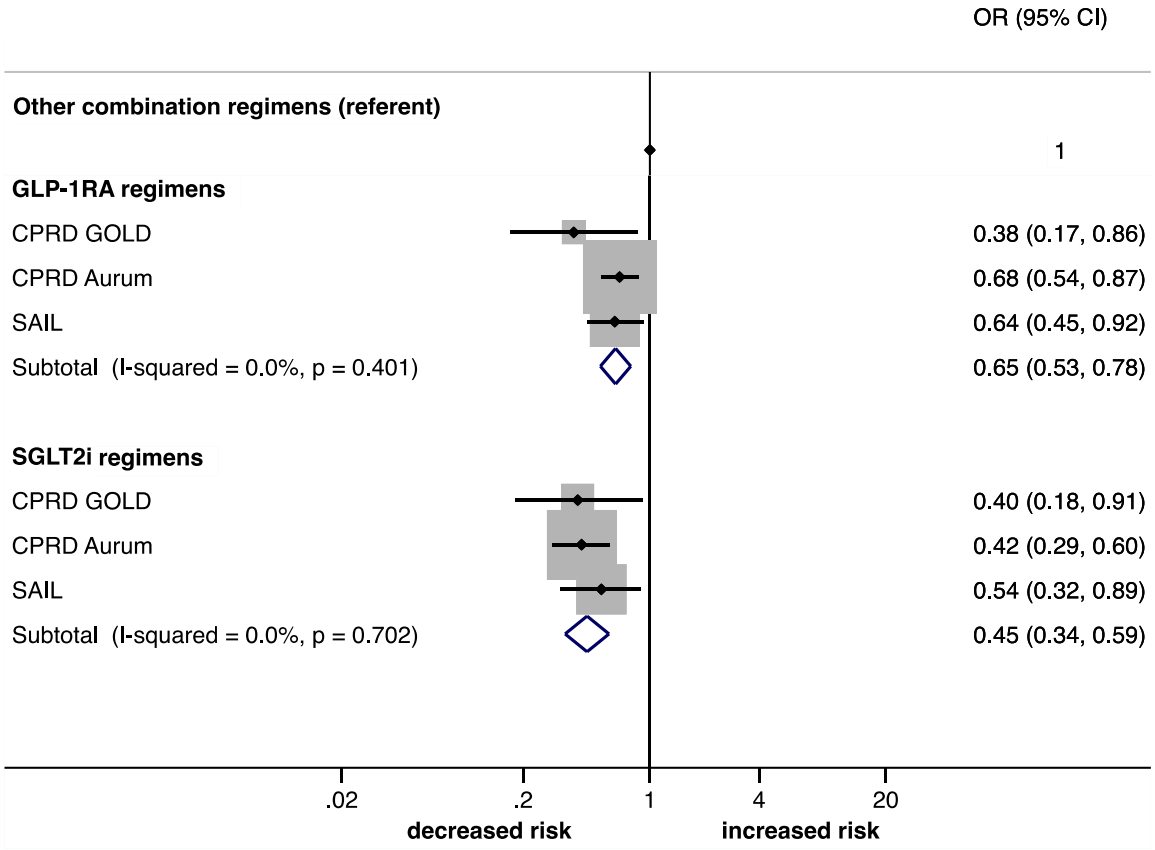
(a.)



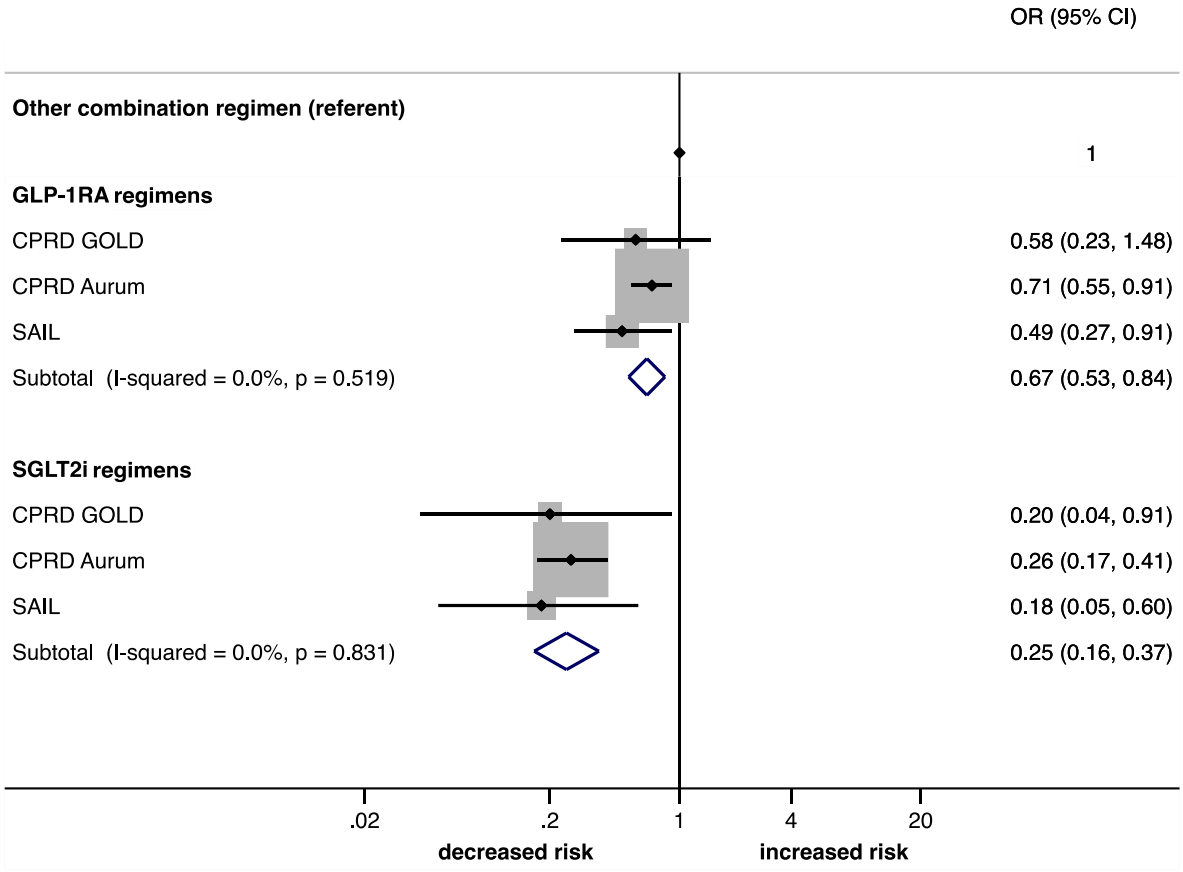
(b.)



Supplemental Figure 16. Propensity-matched cohort analysis of treatment with SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and the risk of MACCE



Supplemental Figure 17. Propensity-matched cohort analysis of treatment with SGLT2 inhibitor and GLP-1 receptor agonist regimens compared with other combination regimens and the risk of heart failure



Supplemental Table 1. Baseline clinical characteristics and medication use in MACCE cases and matched controls without a MACCE

	CPRD GOLD		CPRD Aurum		SAIL Databank	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
N	1,690	20,199	11,887	213,329	4,913	76,037
Sex, male	994 (58.8)	12,243 (60.6)	6,809 (57.3)	123,817 (58.0)	2,837 (57.7)	46,029 (60.5)
Age, years	69.3±12.3	67.2±11.8	69.4±12.6	68.2±11.9	68.1±12.2	66.4±11.4
Ethnicity						
White	1,450 (85.8)	15,489 (76.7)	9,889 (83.2)	164,684 (77.2)	1,151 (23.4)	17,788 (23.4)
South Asian	101 (6.0)	1,340 (6.6)	962 (8.1)	17,577 (8.2)	54 (1.1)	1,087 (1.4)
Black	40 (2.4)	626 (3.1)	408 (3.4)	8,808 (4.1)	7 (0.1)	197 (0.3)
Other	19 (1.1)	305 (1.5)	112 (0.9)	2,148 (1.0)	15 (0.3)	298 (0.4)
Unknown	80 (4.7)	2,439 (12.1)	516 (4.3)	20,112 (9.4)	3,686 (75.0)	56,667 (74.5)
Index of Multiple Deprivation						
1 *(least deprived quintile)*	339 (20.1)	4,507 (22.3)	2,222 (18.7)	42,923 (20.1)	708 (14.4)	12,996 (17.1)
2	296 (17.5)	3,877 (19.2)	2,263 (19.0)	44,028 (20.6)	876 (17.8)	13,295 (17.5)
3	347 (20.5)	4,197 (20.8)	2,342 (19.7)	43,633 (20.5)	944 (19.2)	15,770 (20.7)
4	376 (22.3)	4,178 (20.7)	2,457 (20.7)	42,191 (19.8)	1,094 (22.3)	15,851 (20.9)
5 *(most deprived quintile)*	332 (19.6)	3,435 (17.0)	2,595 (21.8)	40,412 (18.9)	1,256 (25.6)	17,367 (22.8)
Unknown	0	5 (<0.1)	8 (0.1)	141 (0.1)	35 (0.7)	758 (1.0)
Duration of treated diabetes, years	4.2±4.9	2.9±3.7	4.3±5.0	3.6±4.6	6.7±5.4	5.4±4.8
BMI, kg/m^2	31.5±7.3	31.4±6.5	30.5±6.6	30.9±6.3	31.8±6.9	31.9±6.6
HbA1c, % [mmol/mol]	8.7±1.9 [72±21]	8.4±1.8 [68±20]	8.6±1.9 [70±21]	8.3±1.8 [67±20]	8.9±2.0 [74±22]	8.7±1.8 [71±20]
Hypertension, >140/80mmHg	420 (24.9)	5,515 (27.3)	2,991 (25.2)	50,249 (23.6)	1,189 (24.2)	18,362 (24.2)
Smoking status						
Smoker (current/ex-smoker)	933 (55.2)	10,069 (49.9)	6,472 (54.5)	106,913 (50.1)	2,713 (55.2)	39,128 (51.5)
Never	695 (41.1)	9,243 (45.8)	4,984 (41.9)	100,094 (46.9)	1,964 (40.0)	33,423 (44.0)
Unknown	62 (3.7)	887 (4.4)	431 (3.6)	6,322 (3.0)	236 (4.8)	3,486 (4.6)
Microvascular complications						
Retinopathy	389 (23.0)	2,885 (14.3)	4,041 (34.0)	61,575 (28.9)	1,658 (33.8)	18,828 (24.8)
Peripheral neuropathy	160 (9.5)	1,116 (5.5)	1,286 (10.8)	15,391 (7.2)	486 (9.9)	4,649 (6.1)
Nephropathy/CKD≥stage 3	382 (22.6)	3,010 (14.9)	2,559 (21.5)	36,098 (16.9)	1,000 (20.4)	10,846 (14.3)
Charlson Comorbidity Score	1.5±1.6	1.0±1.4	18±1.6	1.4±1.5	1.7±1.6	1.3±1.5
Prescriptions in the year prior to cohort entry						
Antidiabetics						
Metformin	801 (47.4)	5,096 (25.2)	5,457 (45.9)	92,392 (43.3)	2,327 (47.4)	30,039 (39.5)
Sulphonylurea	550 (32.5)	3,077 (15.2)	3,720 (31.3)	57,585 (27.0)	1,494 (30.4)	17,270 (22.7)
Thiazolidinediones	143 (8.5)	819 (4.1)	817 (6.9)	14,224 (6.7)	293 (6.0)	4,276 (5.6)
Alpha-glucosidase	7 (0.4)	22 (0.1)	25 (0.2)	287 (0.1)	6 (0.1)	82 (0.1)
Meglitinides	5 (0.3)	25 (0.1)	46 (0.4)	877 (0.4)	18 (0.4)	263 (0.4)
DPP-4 inhibitors	198 (11.7)	1,265 (6.3)	1,268 (10.7)	20,877 (9.8)	591 (12.0)	7,447 (9.8)

GLP-1 receptor agonists	52 (3.1)	333 (1.7)	352 (3.0)	5,936 (2.8)	232 (4.7)	2,804 (3.7)
SGLT2 inhibitors	5 (0.3)	8 (<0.1)	11 (0.1)	224 (0.1)	5 (0.1)	50 (0.1)
Antihypertensives						
Angiotensin II receptor blocker	264 (15.6)	2,437 (12.1)	1,842 (15.5)	31,499 (14.8)	666 (13.6)	9,239 (12.2)
ACE inhibitor	609 (36.0)	6,032 (29.96)	4,257 (35.8)	75,637 (35.5)	1,863 (37.9)	27,820 (36.6)
Beta-blocker	320 (18.9)	2,799 (13.9)	2,215 (18.6)	32,813 (15.4)	960 (19.5)	11,874 (15.6)
Calcium channel blocker	555 (32.8)	5,404 (26.8)	3,690 (31.0)	60,761 (28.5)	1,467 (29.9)	20,578 (27.1)
Diuretic: thiazide, potassium sparing or loop	469 (27.8)	4,354 (21.6)	3,209 (27.0)	52,814 (24.8)	1,440 (29.3)	18,972 (25.0)
Other	216 (12.8)	1,713 (8.5)	1,499 (12.6)	22,476 (10.5)	541 (11.0)	7,089 (9.3)
Lipid-lowering agents						
Statin	895 (53.0)	9,644 (47.7)	2,904 (24.4)	52,339 (24.5)	2,775 (56.5)	43,540 (57.3)
Fibrate	21 (1.2)	202 (1.0)	1,682 (14.2)	31,677 (14.9)	125 (2.5)	1,539 (2.0)
Ezetimibe	26 (1.5)	294 (1.5)	100 (0.8)	1,563 (0.7)	92 (1.9)	1,198 (1.6)
Other	5 (0.3)	38 (0.2)	461 (3.9)	6,671 (3.1)	18 (0.4)	390 (0.5)
Antiplatelet agents						
Aspirin	382 (22.6)	3,017 (14.9)	2,755 (23.2)	41,502 (19.5)	1,248 (25.4)	15,634 (20.6)
Clopidogrel	22 (1.3)	154 (0.8)	5 (<0.1)	6 (<0.1)	99 (2.0)	943 (1.2)
Other	5 (0.3)	19 (0.1)	200 (1.7)	2,061 (1.0)	12 (0.2)	81 (0.1)
Glucocorticoids	242 (14.3)	1,908 (9.5)	1,282 (10.8)	20,436 (9.6)	607 (12.4)	6,990 (9.2)
NSAIDs	242 (14.3)	2,830 (14.0)	2,502 (21.1)	42,711 (20.0)	744 (15.1)	11,958 (15.7)
Anticoagulants	86 (5.1)	706 (3.5)	605 (5.1)	8,058 (3.8)	295 (6.0)	3,101 (4.1)
Ever exposure to antidiabetic drugs prior to cohort entry						
Number of antidiabetic prescriptions	66±98	29±66	65±102	52±83	148±261	166±329
Metformin	1,406 (83.2)	18,208 (90.1)	9,939 (83.6)	186,042 (87.2)	4,043 (82.3)	66,442 (87.4)
Sulphonylurea	254 (15.0)	1,710 (8.5)	1,749 (14.7)	24,145 (11.3)	768 (15.6)	8,158 (10.7)
Thiazolidinediones	9 (0.5)	75 (0.4)	51 (0.4)	712 (0.3)	25 (0.5)	357 (0.5)
Alpha-glucosidase	<10	15 (0.1)	10 (0.1)	142 (0.1)	8 (0.2)	96 (0.1)
Meglitinides	<10	11 (0.1)	12 (0.1)	205 (0.1)	10 (0.2)	143 (0.2)
DPP-4 inhibitors	15 (0.9)	155 (0.8)	106 (0.9)	1,771 (0.8)	51 (1.0)	705 (0.9)
GLP-1 receptor agonists	<10	13 (0.1)	17 (0.1)	214 (0.1)	<10	78 (0.1)
SGLT2 inhibitors	<10	12 (0.1)	<10	98 (0.1)	<10	58 (0.1)

Cases and controls were matched for age (±2 years), sex, date of study-cohort entry (±6months), duration of treated diabetes (±3months).
Presented as n (%) and mean±SD, where appropriate.

ACE, Angiotensin Converting Enzyme; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease defined as non-fatal myocardial infarction (MI), acute coronary syndrome (ACS), stroke, transient ischaemic attack (TIA), unstable angina, and revascularisation; GLP-1, Glucagon-like peptide-1; HbA1c, glycated haemoglobin; MACCE, Major Adverse Cardiac and Cerebrovascular Events defined as MI, ACS, stroke, TIA or cardiovascular death; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Supplemental Table 2. Baseline clinical characteristics and medication use in heart failure cases and matched controls without a heart failure event

	CPRD GOLD		CPRD Aurum		SAIL Databank	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
N	1,530	18,419	11,765	216,354	4,133	66,300
Sex, male	910 (59.5)	11,433 (62.1)	6,822 (58.0)	126,685 (58.6)	2,418 (58.5)	40,437 (61.0)
Age, years	72.5±11.6	70.8±11.5	72.6±11.5	71.7±10.9	71.4±11.1	69.9±10.4
Ethnicity						
White	1,369 (89.5)	15,046 (81.7)	10,179 (86.5)	174,127 (80.5)	1,002 (24.3)	15,688 (23.7)
South Asian	79 (5.2)	1,122 (6.1)	762 (6.5)	16,502 (7.6)	41 (1.0)	813 (1.2)
Black	25 (1.6)	489 (2.7)	347 (3.0)	7,774 (3.6)	5 (0.1)	110 (0.2)
Other	11 (0.7)	200 (1.1)	80 (0.7)	1,866 (0.9)	9 (0.2)	192 (0.3)
Unknown	46 (3.0)	1,562 (8.5)	397 (3.4)	16,085 (7.4)	3,076 (74.4)	49,497 (74.7)
Index of Multiple Deprivation *						
1 *(least deprived quintile)*	270 (17.7)	4,130 (22.4)	2,126 (18.1)	44,679 (20.7)	564 (13.7)	11,685 (17.6)
2	257 (16.8)	3,645 (19.8)	2,157 (18.3)	45,413 (21.0)	702 (17.0)	11,643 (17.6)
3	336 (22.0)	3,842 (20.9)	2,448 (20.8)	44,619 (20.6)	857 (20.7)	13,923 (21.0)
4	346 (22.6)	3,781 (20.5)	2,455 (20.9)	41,631 (19.2)	905 (21.9)	13,678 (20.6)
5 *(most deprived quintile)*	321 (21.0)	3,021 (16.4)	2,568 (21.8)	39,867 (18.4)	1,058 (25.6)	14,754 (22.3)
Unknown	0	0	11 (0.1)	145 (0.1)	47 (1.1)	617 (0.9)
Duration of treated diabetes, years	4.9±5.1	2.6±4.2	4.8±5.2	4.3±4.9	7.4±5.6	6.3±5.2
BMI, kg/m^2	32.4±7.4	30.9±6.3	31.7±7.1	30.3±6.1	32.5±7.5	31.3±6.3
HbA1c, % [mmol/mol]	8.4±1.9 [68±21]	8.3±1.8 [67±20]	8.4±1.9 [68±21]	8.2±1.7 [66±19]	8.7±2.0 [72±22]	8.6±1.8 [70±20]
Hypertension, >140/80mmHg	347 (22.7)	4,453 (24.2)	2,770 (23.5)	47,254 (21.8)	976 (23.6)	14,611 (22.0)
Smoking status						
Smoker (current/ex-smoker)	908 (59.4)	9,587 (52.1)	6,929 (58.9)	112,958 (52.2)	2,494 (60.3)	36,090 (54.4)
Never	558 (36.5)	7,912 (43.0)	4,425 (37.6)	96,620 (44.7)	1,446 (35.0)	27,280 (41.2)
Unknown	64 (4.2)	920 (5.0)	411 (3.5)	6,776 (3.1)	193 (4.7)	2,930 (4.4)
History of cardiovascular disease	584 (38.2)	4,060 (22.0)	4,522 (38.4)	49,298 (22.8)	1,445 (35.0)	12,939 (19.5)
Microvascular complications						
Retinopathy	429 (28.0)	3,159 (17.2)	4,411 (37.5)	71,309 (33.0)	1,521 (36.8)	19,703 (29.7)
Peripheral neuropathy	210 (13.7)	1,352 (7.3)	1,703 (14.5)	20,190 (9.3)	536 (13.0)	5,309 (8.0)
Nephropathy/CKD≥stage 3	488 (31.9)	3,848 (20.9)	3,822 (32.5)	49,321 (22.8)	1,294 (31.3)	13,106 (19.8)
Charlson Comorbidity Score	2.1±1.7	1.4±1.6	2.3±1.8	1.9±1.7	2.4±1.8	1.8±1.7
Prescriptions in the year prior to cohort entry						
Antidiabetics						
Metformin	777 (50.8)	5,918 (32.1)	5,686 (48.3)	101,830 (47.1)	2,103 (50.9)	30,281 (45.7)
Sulphonylurea	548 (35.8)	3,911 (21.2)	4,006 (34.1)	67,195 (31.1)	1,392 (33.7)	18,681 (28.2)

Thiazolidinediones	140 (9.2)	1,047 (5.7)	927 (7.9)	15,882 (7.3)	272 (6.6)	4,388 (6.6)
Alpha-glucosidase	5 (0.3)	28 (0.2)	32 (0.3)	390 (0.2)	15 (0.4)	101 (0.2)
Meglitinides	8 (0.5)	43 (0.2)	73 (0.6)	996 (0.5)	28 (0.7)	306 (0.5)
DPP-4 inhibitors	185 (12.1)	1,442 (7.8)	1,282 (10.9)	22,815 (10.6)	504 (12.2)	7,570 (11.4)
GLP-1 receptor agonists	55 (3.6)	348 (1.9)	432 (3.7)	5,812 (2.7)	203 (4.9)	2,680 (4.0)
SGLT2 inhibitors	5 (0.3)	7 (<0.1)	11 (0.1)	209 (0.1)	45 (0.1)	47 (0.1)
Antihypertensives						
Angiotensin II receptor blocker	295 (19.3)	2,665 (14.5)	2,271 (19.3)	36,075 (16.7)	706 (17.1)	9,477 (14.3)
ACE inhibitor	678 (44.3)	6,344 (34.4)	5,156 (43.8)	86,092 (39.8)	1,903 (46.0)	27,239 (41.1)
Beta-blocker	553 (36.1)	3,869 (21.0)	4,081 (34.7)	50,067 (23.1)	1,431 (34.6)	15,475 (23.3)
Calcium channel blocker	587 (38.4)	5,326 (28.9)	4,399 (37.4)	68,230 (31.5)	1,568 (37.9)	20,139 (30.4)
Diuretic: thiazide, potassium sparing or loop	660 (43.1)	4,577 (24.9)	5,018 (42.7)	60,711 (28.1)	1,874 (45.3)	19,181 (28.9)
Other	282 (18.4)	2,014 (10.9)	2,018 (17.2)	27,503 (12.7)	718 (17.4)	7,987 (12.1)
Lipid-lowering agents						
Statin	984 (64.3)	10,359 (56.2)	3,747 (31.9)	63,331 (29.3)	2,731 (66.1)	42,969 (64.8)
Fibrate	26 (1.7)	274 (1.5)	1,892 (16.1)	34,482 (15.9)	114 (2.8)	1,606 (2.4)
Ezetimibe	43 (2.8)	349 (1.9)	125 (1.1)	1,797 (0.8)	101 (2.4)	1,478 (2.2)
Other	16 (1.1)	86 (0.5)	1,242 (10.6)	16,072 (7.4)	40 (1.0)	514 (0.8)
Antiplatelet agents						
Aspirin	603 (39.4)	4,807 (26.1)	4,287 (36.4)	64,898 (30.0)	1,579 (38.2)	20,758 (31.3)
Clopidogrel	142 (9.3)	867 (4.7)	5 (<0.1)	8 (<0.1)	365 (8.8)	3,425 (5.2)
Other	23 (1.5)	172 (0.9)	1,074 (9.1)	11,675 (5.4)	70 (1.7)	821 (1.2)
Glucocorticoids	273 (17.8)	2,007 (10.9)	1,458 (12.4)	22,730 (10.5)	720 (17.4)	7,020 (10.6)
NSAIDs	175 (11.4)	2,388 (13.0)	2,389 (20.3)	43,552 (20.1)	506 (12.2)	9,374 (14.1)
Ever exposure to antidiabetic drugs prior to cohort entry						
Number of antidiabetic prescriptions	81±114	40±78	75±108	63±94	170±306	204±366
Metformin	1,243 (81.2)	16,064 (87.2)	9,522 (80.9)	182,346 (84.3)	3,258 (78.8)	55,564 (83.8)
Sulphonylurea	254 (16.6)	2,027 (11.0)	1,954 (16.6)	30,344 (14.0)	752 (18.2)	9,127 (13.8)
Thiazolidinediones	14 (0.9)	83 (0.5)	58 (0.5)	779 (0.4)	26 (0.6)	486 (0.7)
Alpha-glucosidase	<10	21 (0.1)	15 (0.1)	211 (0.1)	7 (0.2)	109 (0.2)
Meglitinides	0	15 (0.1)	22 (0.2)	320 (0.2)	11 (0.3)	172 (0.3)
DPP-4 inhibitors	14 (0.9)	187 (1.0)	181 (1.5)	2,120 (1.0)	67 (1.6)	768 (1.2)
GLP-1 receptor agonists	<10	15 (0.1)	11 (0.1)	159 (0.1)	8 (0.2)	35 (0.1)
SGLT2 inhibitors	<10	7 (0.1)	<10	75 (0.1)	<10	39 (0.1)

Cases and controls were matched for age (±2 years), sex, date of study-cohort entry (±6months), duration of treated diabetes (±3months).
Presented as n (%) and mean±SD, where appropriate

ACE, Angiotensin Converting Enzyme; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular; GLP-1, Glucagon-like peptide-1; HbA1c, glycated haemoglobin; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Supplemental Table 3. Clinical characteristics and medication use in current users of SGLT2i regimens, GLP-1 receptor agonist regimens and other combination regimens (CPRD GOLD)

	Antidiabetic regimen (N=21,889)					
	SGLT2i regimens	**GLP-1RA regimens**	**SGLT2i/GLP-1RA regimens**	**Other combination regimens**	**Other monotherapy regimens**	**No current exposure**
N (%)	643 (2.9)	372 (1.7)	49 (0.2)	4,684 (21.4)	11,242 (51.4)	4,898 (22.4)
Male, %	68.6	61.3	79.6	65.8	58.3	59.0
Age, years	60.1±8.8	61.0±9.4	57.3±9.2	67.2± 10.9	68.2±11.9	67.1±12.8
Ethnicity, %						
White	78.5	83.6	87.8	78.4	78.3	73.5
South Asian	5.8	4.6	<10	7.2	5.6	8.5
Black	2.2	<10	-	3.1	2.7	4.0
Other	1.9	-	-	1.1	1.5	1.9
Unknown	11.7	10.5	<10	10.2	11.9	12.0
Index of Multiple Deprivation, %						
1 *(least deprived quintile)*	27.5	24.5	16.3	20.2	22.9	21.5
2	19.8	15.9	24.5	19.2	18.9	19.3
3	19.4	21.8	24.5	20.8	21.0	20.2
4	16.5	19.4	14.3	21.1	21.0	20.8
5 *(most deprived quintile)*	16.8	18.6	20.4	18.7	16.2	18.2
Duration of treated diabetes, years	4.2±4.6	5.6±4.3	4.8±4.4	4.4±4.6	1.0±2.9	1.1±2.7
BMI, kg/m^2	34.7±6.5	36.4±6.2	35.7±4.8	31.1±6.2	31.3±6.5	30.9±6.8
HbA1c, % [mmol/mol]	9.2±1.7 [77±19]	9.1±1.8 [76±19]	9.7±1.6 [82±17]	8.9±1.9 [74±21]	8.2±1.8 [66±19]	8.4±1.9 [68±21]
Hypertension, >140/80mmHg	24.6	25.5	24.5	22.1	29.5	27.0
Smoking status, %						
Smoker (current/ex-smoker)	53.6	56.5	40.8	50.1	50.6	48.7
Never	42.8	41.1	59.2	44.8	45.7	45.9
Unknown	3.6	2.4	-	5.1	3.7	5.4
Microvascular complications, %						
Retinopathy	16.8	34.7	30.6	24.2	10.7	14.1
Peripheral neuropathy	7.2	12.9	<10	7.6	5.0	5.3
Nephropathy/CKD≥stage 3	5.6	12.6	<10	16.2	15.9	15.5
Charlson Comorbidity Score	0.7±1.0	1.3±1.4	1.1±1.1	1.3±1.5	1.0±1.4	1.1±1.4

Prescriptions in the year prior to cohort entry						
Antidiabetics, %						
Metformin	54.7	76.9	67.4	57.5	11.6	25.3
Sulphonylurea	31.0	46.0	26.5	35.6	7.1	16.1
Thiazolidinediones	8.6	14.5	12.2	10	1.7	3.9
Alpha-glucosidase	<10	-	-	0.4	0.1	<10
Meglitinides	<10	<10	-	0.3	0.1	0.1
DPP-4 inhibitors	19.1	26.3	24.5	14	2.4	6.3
GLP-1 receptor agonists	3.3	30.7	26.5	1.3	0.9	1.7
SGLT2 inhibitors	<10	-	<10	<10	<10	-
Antihypertensives, %						
Angiotensin II receptor blocker	12.3	18.6	16.3	14.8	11.4	11.7
ACE inhibitor	38.6	45.2	38.8	35.8	28.4	27.3
Beta-blocker	8.6	13.7	<10	12.1	15.7	13.8
Calcium channel blocker	26.6	30.1	20.4	27.3	27.8	25.7
Diuretic: thiazide, potassium sparing or loop	19.6	28.2	20.4	20.2	23.1	21.2
Other	6.8	11.0	<10	10.6	8.8	7.2
Lipid-lowering agents, %						
Statin	57.9	71.0	69.4	57.3	45.4	42.6
Fibrate	1.2	2.7	<10	1.2	1.0	0.9
Ezetimibe	2.0	3.0	<10	1.5	1.5	1.3
Other	<10	<10	-	0.2	0.2	0.1
Antiplatelet agents, %						
Aspirin	13.5	22.3	20.4	21.9	13.8	13.2
Clopidogrel	1.1	<10	-	0.8	0.9	0.5
Other	-	-	-	0.2	0.1	<10
Glucocorticoids, %	6.4	12.6	<10	8.0	10.6	10.2
NSAIDs, %	17.3	23.7	12.2	13.1	14.0	13.9
Anticoagulants, %	1.1	2.7	<10	3.4	4.0	3.3
Current exposure to other antidiabetic agents, %						
Metformin	85.5	85.2	85.7	93.5	87.4	-
Sulphonylurea	38.1	43.0	30.6	72.0	8.5	-
Thiazolidinediones	4.4	8.6	<10	10.3	0.2	-
Alpha-glucosidase	<10	0	0	0.5	0.1	-
Meglitinides	<10	0	0	0.5	0.1	-
DPP-4 inhibitors	23.6	3.0	<10	48.7	3.7	-

GLP-1 receptor agonists	-	100	100	-	-	-
SGLT2 inhibitors	100	-	100	-	-	-
Number of antidiabetics currently exposed to, %						
1	7.8	8.9	-	-	100	-
2	39.4	46.5	12.2	75.3	-	-
3	45.7	40.6	55.1	23.9	-	-
4+	7.2	1.0	32.7	0.8	-	-

Presented as mean±SD and %. Due to privacy concerns and possible patient identification following stratification by ADM exposure, precise proportions could not be presented for some characteristics.

ACE, Angiotensin Converting Enzyme; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular; GLP-1, Glucagon-like peptide-1; HbA1c, glycated haemoglobin; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Supplemental Table 4. Clinical characteristics and medication use in current users of SGLT2i regimens, GLP-1 receptor agonist regimens and other combination regimens (CPRD Aurum)

	Antidiabetic regimen (N=225,216)					
	SGLT2i regimens	**GLP-1RA regimens**	**SGLT2i/GLP-1RA regimens**	**Other combination regimens**	**Other monotherapy regimens**	**No current exposure**
N (%)	8,779 (3.9)	5,851 (2.6)	793 (0.4)	61,771 (27.4)	99,595 (44.2)	48,427 (21.5)
Male, %	66.6	60.0	68.0	70.0	55.5	57.4
Age, years	60.9±9.4	61.7±9.6	58.3±8.5	68.4±10.7	69.6±12.2	67.5±13.0
Ethnicity, %						
White	77.2	86.4	84.2	77.5	79.0	73.4
South Asian	8.4	3.9	3.9	8.9	7.4	9.7
Black	2.2	2.3	1.5	3.8	3.7	5.9
Other	0.9	0.7	0.9	0.9	0.9	1.3
Unknown	11.2	6.8	9.5	8.9	9.1	9.6
Index of Multiple Deprivation, %						
1 *(least deprived quintile)*	19.7	17.2	17.7	19.8	20.4	20.1
2	20.6	20.5	25.7	20.9	20.9	19.4
3	19.3	19.9	15.9	20.0	20.8	20.6
4	19.8	20.3	19.9	20.2	19.5	20.0
5 *(most deprived quintile)*	20.5	22.1	20.7	19.1	18.5	19.8
Duration of treated diabetes, years	5.8±4.5	6.8±4.5	7.0±4.5	5.9±4.6	1.9±3.9	3.4±4.6
BMI, kg/m^2	33.4±6.2	36.5±6.3	37.0±7.0	30.5±6.0	30.6±6.2	30.6±6.5
HbA1c, % [mmol/mol]	9.1±1.7 [76±18]	8.9±1.7 [73±18]	9.3±1.7 [77±18]	8.6±1.7 [70±18]	8.1±1.7 [64±18]	8.4±1.9 [68±20]
Hypertension, >140/80mmHg	21.6	24.1	21.8	19.8	26.1	23.9
Smoking status, %						
Smoker (current/ex-smoker)	53.0	56.9	57.5	50.8	50.2	48.7
Never	45.4	41.9	41.4	46.8	46.4	47.8
Unknown	1.6	1.2	1.1	2.4	3.4	3.5
Microvascular complications, %						
Retinopathy	38.5	43.0	41.6	40.5	21.1	27.5
Peripheral neuropathy	7.9	12.9	11.0	9.3	6.2	6.8
Nephropathy/CKD≥stage 3	4.8	13.5	6.6	18.4	17.9	17.1
Charlson Comorbidity Score	1.4±1.3	1.7±1.4	1.5±1.3	1.8±1.5	1.3±1.5	1.4±1.5

Prescriptions in the year prior to cohort entry						
Antidiabetics, %						
Metformin	73.2	80.6	80.6	72.5	21.9	40.2
Sulphonylurea	40.9	51.3	47.2	45.5	13.7	25.9
Thiazolidinediones	11.0	15.8	18.2	11.6	3.0	6.0
Alpha-glucosidase	0.1	0.3	0.6	0.3	0.1	0.2
Meglitinides	0.6	1.1	<10	0.7	0.2	0.4
DPP-4 inhibitors	23.8	23.1	21.1	16.1	3.9	9.7
GLP-1 receptor agonists	7.0	31.9	36.2	1.5	1.2	2.8
SGLT2 inhibitors	1.1	0.3	1.1	0.1	0.1	0.1
Antihypertensives, %						
Angiotensin II receptor blocker	14.8	20.2	19.6	16.1	13.9	14.2
ACE inhibitor	42.0	47.9	47.5	42.1	31.6	32.3
Beta-blocker	13.5	17.1	14.0	15.7	16.2	14.2
Calcium channel blocker	26.3	30.0	25.4	29.9	29.0	26.4
Diuretic: thiazide, potassium sparing or loop	19.7	31.2	26.1	24.5	26.1	23.1
Other	8.7	14.3	11.7	11.8	10.3	9.9
Lipid-lowering agents, %						
Statin	31.2	31.7	33.9	27.0	22.8	22.6
Fibrate	15.5	18.9	15.5	18.1	13.2	13.2
Ezetimibe	1.3	1.4	0.8	0.8	0.6	0.7
Other	2.8	3.6	2.1	3.7	3.0	2.9
Antiplatelet agents, %						
Aspirin	22.2	28.6	29.4	24.6	16.7	17.6
Clopidogrel	0	0	0	0	0	0
Other	0.8	1.0	0.6	1.1	1.0	0.9
Glucocorticoids, %	9.8	12.0	11.7	9.7	9.6	9.4
NSAIDs, %	20.8	23.5	20.6	19.5	20.3	19.7
Anticoagulants, %	1.8	3.3	2.7	3.7	4.4	3.5
Current exposure to other antidiabetic agents, %						
Metformin	85.1	84.1	87.9	92.9	83.1	-
Sulphonylurea	39.4	44.3	34.4	72.8	10.6	-
Thiazolidinediones	2.8	6.2	3.3	9.3	0.5	-
Alpha-glucosidase	0.1	<10	<10	0.2	0.1	-
Meglitinides	0.2	0.9	<10	0.6	0.1	-
DPP-4 inhibitors	27.8	5.0	3.7	52.0	5.7	-
GLP-1 receptor agonists	0.0	100.0	100.0	-	-	-

SGLT2 inhibitors	100.0	0.0	100.0	-	-	-
Number of antidiabetics currently exposed to, %						
1	7.7	9.3	-	-	100.0	-
2	38.3	44.7	8.5	72.9	-	-
3	45.0	41.5	55.5	26.4	-	-
4+	9.0	4.6	36.1	0.7	-	-

Presented as mean±SD and %. Due to privacy concerns and possible patient identification following stratification by ADM exposure, precise proportions could not be presented for some characteristics.

ACE, Angiotensin Converting Enzyme; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular; GLP-1, Glucagon-like peptide-1; HbA1c, glycated haemoglobin; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Supplemental Table 5. Clinical characteristics and medication use in current users of SGLT2i regimens, GLP-1 receptor agonist regimens and other combination regimens (SAIL Databank)

	Antidiabetic regimen (N=80,950)					
	SGLT2i regimens	**GLP-1RA regimens**	**SGLT2i/GLP-1RA regimens**	**Other combination regimens**	**Other monotherapy regimens**	**No current exposure**
N (%)	3,678 (4.5)	2,748 (3.4)	433 (0.5)	20,478 (25.3)	33,650 (41.6)	19,963 (24.7)
Male, %	67.1	58.4	68.4	63.4	58.6	59.1
Age, years	60.3±9.1	61.2±8.8	57.6±7.7	66.3±10.3	67.9±11.6	66.4±12.3
Ethnicity, %						
White	20.9	25.7	19.4	23.9	23.4	23.2
South Asian	1.6	0.7	1.2	1.4	1.2	1.9
Black	0.4	<10	<10	0.3	0.2	0.3
Other	0.3	<10	0	0.4	0.3	0.6
Unknown	76.9	73.3	79.2	74.1	74.9	74.1
Index of Multiple Deprivation, %						
1 *(least deprived quintile)*	16.8	14.3	18.2	15.5	16.9	18.8
2	14.3	16.2	15.0	17.2	17.9	18.0
3	18.7	20.9	14.1	20.9	20.9	20.4
4	22.0	23.2	20.1	21.2	21.1	19.9
5 *(most deprived quintile)*	27.4	25.1	32.1	24.3	22.2	21.7
Duration of treated diabetes, years	8.1±4.5	9.2±4.5	9.7±4.3	7.6±4.6	3.6±4.2	5.4±4.9
BMI, kg/m^2	34.2±6.2	37.0±6.7	37.6±6.1	31.4±6.1	31.5±6.5	31.8±6.8
HbA1c, % [mmol/mol]	9.4±1.7 [79±18]	9.3±1.7 [78±18]	9.5±1.6 [80±17]	9.0±1.8 [74±19]	8.4±1.8 [68±19]	8.7±1.9 [71±20]
Hypertension, >140/80mmHg	23.6	22.7	25.4	21.3	26.0	24.2
Smoking status, %						
Smoker (current/ex-smoker)	54.2	56.2	52.7	52.9	51.5	49.6
Never	43.8	40.5	43.9	43.2	43.6	44.8
Unknown	2.1	3.4	3.5	3.9	4.8	5.6
Microvascular complications, %						
Retinopathy	29.6	43.1	35.1	34.3	19.1	23.1
Peripheral neuropathy	8.2	10.6	11.3	7.1	5.4	6.0
Nephropathy/CKD≥stage 3	5.9	12.3	6.2	15.9	15.0	14.9
Charlson Comorbidity Score	1.2±1.3	1.7±1.4	1.5±1.3	1.6±1.5	1.2±1.5	1.3±1.5

Prescriptions in the year prior to cohort entry						
Antidiabetics, %						
Metformin	68.8	79.6	79.9	67.5	19.7	34.2
Sulphonylurea	38.6	50.2	50.6	40.3	10.5	19.8
Thiazolidinediones	7.3	13.2	12.0	10.6	2.4	4.6
Alpha-glucosidase	<10	<10	<10	0.2	0.1	0.1
Meglitinides	0.4	1.1	<10	0.5	0.2	0.3
DPP-4 inhibitors	25.0	25.6	27.7	16.3	3.7	8.5
GLP-1 receptor agonists	9.5	36.4	43.4	2.0	1.2	3.4
SGLT2 inhibitors	0.7	<10	<10	0.1	<10	0.1
Antihypertensives, %						
Angiotensin II receptor blocker	12.6	18.2	11.6	12.7	11.6	12.1
ACE inhibitor	45.6	50.8	57.5	42.9	32.9	32.6
Beta-blocker	14.4	18.7	14.6	15.8	16.4	15.0
Calcium channel blocker	25.9	32.7	30.0	28.0	27.5	25.4
Diuretic: thiazide, potassium sparing or loop	19.5	30.5	27.0	23.8	26.8	24.3
Other	9.0	13.1	11.8	10.6	9.0	8.5
Lipid-lowering agents, %						
Statin	68.8	75.2	74.8	66.5	51.7	52.0
Fibrate	2.4	4.3	5.1	2.4	1.7	1.8
Ezetimibe	1.5	3.2	2.5	1.7	1.4	1.5
Other	0.7	0.7	<10	0.6	0.4	0.5
Antiplatelet agents, %						
Aspirin	26.1	30.8	29.1	26.0	18.1	17.8
Clopidogrel	0.9	1.8	<10	1.3	1.3	1.2
Other	<10	0.3	-	0.1	0.1	0.2
Glucocorticoids, %	7.2	8.2	6.7	8.3	10.2	9.8
NSAIDs, %	19.6	19.0	19.6	14.4	15.8	15.4
Anticoagulants, %	2.6	3.3	1.4	3.7	4.8	4.3
Current exposure to other antidiabetic agents, %						
Metformin	83.9	83.2	86.6	92.5	83.8	-
Sulphonylurea	39.4	47.9	41.6	70.9	9.8	-
Thiazolidinediones	2.6	6.4	3.2	9.3	0.4	-
Alpha-glucosidase	<10	0.4	0	0.2	0.1	-
Meglitinides	0.2	0.3	<10	0.4	0.1	-
DPP-4 inhibitors	29.6	4.7	3.5	55.5	5.5	-

GLP-1 receptor agonists	0.0	100.0	100.0	-	-	-
SGLT2 inhibitors	100.0	0.0	100.0	-	-	-
Number of antidiabetics currently exposed to, %						
1	7.6	10.0	-	-	100.0	-
2	38.9	41.4	8.2	71.9	-	-
3	43.2	44.7	48.6	27.2	-	-
4+	10.3	3.9	43.2	0.8	-	-

Presented as mean±SD and %. Due to privacy concerns and possible patient identification following stratification by ADM exposure, precise proportions could not be presented for some characteristics.

ACE, Angiotensin Converting Enzyme; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular; GLP-1, Glucagon-like peptide-1; HbA1c, glycated haemoglobin; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Supplemental Table 6. Odds ratio (95% CI) for heart failure 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	1,530	18,419			11,765	216,354			4,133	66,300		
Combined SGLT2i & GLP-1RA regimens	5 (0.3)	33 (0.2)	0.31 (0.12-1.93)	0.24 (0.12-0.81)	23 (0.2)	645 (0.3)	0.69 (0.45-1.04)	0.52 (0.31-0.86)	14 (0.3)	289 (0.4)	0.79 (0.46-1.36)	0.38 (0.14-0.91)
SGLT2i regimens	25 (1.6)	395 (2.1)	0.62 (0.40-0.98)	0.51 (0.25-0.96)	198 (1.7)	7,245 (3.4)	0.54 (0.47-0.63)	0.49 (0.40-0.59)	76 (1.88)	2,586 (3.9)	0.50 (0.37-0.62)	0.49 (0.35-0.69)
GLP-1RA regimens	30 (2.0)	316 (1.7)	0.97 (0.64-1.47)	0.76 (0.40-1.46)	320 (2.7)	5,166 (2.4)	1.23 (1.09-1.39)	0.88 (0.74-1.04)	140 (3.4)	2,251 (3.4)	1.08 (0.90-1.31)	0.69 (0.52-0.94)
Other combination regimens	442 (28.9)	4,566 (24.8)	1	1	3,219 (27.4)	62,422 (28.9)	1	1	1,133 (27.4)	18,526 (27.9)	1	1
Other monotherapy regimens	687 (44.9)	9,002 (48.9)	1.25 (1.06-1.48)	1.20 (0.97-1.49)	5,389 (45.8)	95,608 (44.2)	1.17 (1.11-1.23)	1.08 (1.00-1.16)	1,703 (41.2)	26,812 (40.4)	1.20 (1.10-1.32)	1.03 (0.90-1.19)
No current regimen	341 (22.3)	4,107 (22.3)	1.32 (1.14-1.54)	1.20 (0.95-1.52)	2,616 (22.2)	45,268 (20.9)	1.18 (1.11-1.24)	1.19 (1.10-1.28)	1,067 (25.8)	15,836 (23.9)	1.22 (1.10-1.35)	1.32 (1.09-1.59)

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

Supplemental Table 7. Assessment of unmeasured confounders in the primary and secondary analyses

Database	Primary endpoint: MACCE		Secondary endpoint: Heart failure	
	OR (95% CI)	E-value (point estimate)	OR (95% CI)	E-value (point estimate)
SGLT2i/GLP-1RA				
CPRD GOLD	0.45 (0.15-1.39)	3.870	0.12 (0.02-0.85)	16.151
CPRD Aurum	0.70 (0.47-1.04)	2.211	0.53 (0.35-0.82)	3.180
SAIL	0.63 (0.34-1.15)	2.553	0.40 (0.17-0.92)	4.436
Pooled estimate	0.66 (0.48-0.90)	2.399	0.47 (0.33-0.69)	3.677
SGLT2i				
CPRD GOLD	0.92 (0.61-1.39)	1.394	0.50 (0.27-0.94)	3.414
CPRD Aurum	0.78 (0.69-0.89)	1.883	0.50 (0.43-0.59)	3.414
SAIL	0.80 (0.64-0.99)	1.809	0.55 (0.41-0.75)	3.038
Pooled estimate	0.79 (0.71-0.88)	1.845	0.51 (0.44-0.58)	3.333
GLP-1RA				
CPRD GOLD	0.79 (0.46-1.37)	1.846	0.82 (0.47-1.41)	1.737
CPRD Aurum	0.93 (0.80-1.08)	1.360	0.84 (0.73-0.97)	1.667
SAIL	0.87 (0.67-1.14)	1.564	0.67 (0.50-0.89)	2.350
Pooled estimate	0.91 (0.80-1.03)	1.429	0.80 (0.71-0.91)	1.809

Interpretation

As an example, considering the association between MACCE and exposure to SGLT2i/GLP-1RA regimens (pooled estimate), with an observed odds ratio of 0.66, an unmeasured confounder that was associated with both the outcome and the treatment by an odds ratio of 2.4-fold each, above and beyond the measured confounders, could explain away the estimate, but weaker confounding could not.