Comparative effects of sulfonylureas, DPP4is and SGLT2 inhibitors added to metformin monotherapy: a propensity-score matched cohort study in UK primary care

Short running title (46 characters): Comparative study of diabetes drugs in UK primary care

Author' names

Samantha Wilkinson[1], Elizabeth Williamson[1], Ana Pokrajac[2], Damian Fogarty[3], Heide Stirnadel-Farrant[4], Liam Smeeth[1], Ian J Douglas[1], Laurie A Tomlinson[1]

Address for each author

[1] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom
[2] West Herts Hospitals NHS Trust, Watford
[3] Belfast Health and Social Care Trust, Belfast BT9 7AB
[4] Epidemiology, GlaxoSmithKline, Stevenage, UK

Author' names and positions

Samantha Wilkinson, **PhD candidate**, Elizabeth Williamson, **Associate professor**, Ana Pokrajac, **Consultant,** Damian Fogarty, **Consultant Nephrologist,** Heide Stirnadel-Farrant, **Director Epidemiology & GSK Fellow,** Liam Smeeth, **Professor**, Ian J Douglas, **Associate professor,** Laurie A Tomlinson, **Associate professor**

Correspondence to: Samantha Wilkinson, Samantha.wilkinson@lshtm.ac.uk Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom. Telephone: 020 7927 2922

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.13970

Abstract

Aims - Sodium glucose co-transporter 2 inhibitors (SGLT2i), sulfonylureas (SU), and dipeptidyl peptidase-4 inhibitors (DPP4i) are added to treatment if metformin monotherapy does not achieve adequate glycaemic control. The comparative effects of these drugs on cardiometabolic risk factors in routine care are unknown.

Materials and Methods – Using primary care data of 10,631 new-users of SU, SGLT2i or DPP4i with metformin from the UK Clinical Practice Research Datalink. We created propensity-score matched cohorts and used linear mixed models to describe changes in HbA1c, estimated glomerular filtration rate (eGFR), systolic blood pressure (BP), and body mass index (BMI) over 96 weeks.

Results - HbA1c fell substantially after intensification for all drugs, mean change (mmol/mol), week 12: SGLT2i: -15.2 (95% CI-16.9,-13.5); SU: -14.3 (95% CI-15.5,-13.2); DPP4i: -11.9 (95% CI-13.1,-10.6)). Systolic BP fell for SGLT2i users throughout follow-up but not DPP4i or SU (Mean change (mmHg), week 12: SGLT2i: -2.3 (95% CI: -3.8,-0.8); SU: -0.8 (95% CI:-1.9,+0.4), DPP4i: -0.9 (95% CI: -2.1,+0.2)).

BMI decreased for SGLT2i and DPP4i treated patients, but not SU users (Mean change (kg/m^2), week 12: SGLT2i: -0·7 (95% CI: -0.9,-0.5); SU: 0.0 (95% CI: -0.3,+0.2), DPP4i: -0.3 (95% CI: -0.5,-0.1)). eGFR fell at 12 weeks for SGLT2i and DPP4i treated patients. At 60 weeks, the fall in eGFR from baseline was similar for each drug class.

Conclusions - In routine care, SGLT2is have greater effects on cardiometabolic risk factors than SUs. Routine care data closely replicates the effects of diabetes drugs on physiological variables measured in clinical trials.

Introduction

Type 2 Diabetes Mellitus is a leading cause of morbidity and mortality worldwide, resulting in one million deaths worldwide in 2017.(1) Drug treatments often provide benefits for glycaemic control and surrogate outcomes but recently clinical trials of sodium-glucose cotransporter 2 inhibitors (SGLT2is), have shown substantial reductions in adverse cardiovascular and renal outcomes.(2-5) In these major outcome trials SGLT2is have been compared to placebo, contrasting with the way the drugs have been recommended for use in clinical practice: international guidelines have recommended SGLT2i as an option to intensify glycaemic control after metformin monotherapy, but with sulfonylurea (SU), thiazolidinedione, DPP-4 inhibitor (DPP4i) or GLP-1 receptor agonists as alternate choices.(6, 7)

SGLT2is work by inhibiting reabsorption of glucose in the proximal renal tubule and thus lowering blood sugar levels. As well as improved glycaemic control, this results in weight loss, blood pressure reduction and diuresis.(8) In clinical trials of SGLT2is, the active treatment arm has shown lower blood pressure and better glycaemic control compared to patients receiving placebo.(2-5) However, there is limited evidence that lower blood pressure or tighter diabetic control is associated with better cardiovascular outcomes.(9, 10) Therefore, it is not clear if the improved clinical outcomes for SGLT2i treated patients are explained by improvements in known cardiovascular and renal risk

factors, which might also occur for other drug classes in direct comparator trials, or if other mechanisms exist.(11)

Observational studies have compared major outcomes between SGLT2i users and those with no additional treatment, and against active comparator agents.(12-17) These studies also report substantial outcomes benefits for SGLT2i users but have been criticised for failing to adequately account for sources of bias and confounding, in particular that SGLT2is are prescribed to younger patients with fewer comorbidities.(18) Few observational studies have examined the effects of first line intensification drugs for type 2 diabetes on biological parameters and these have mainly focussed on comparative effects of drug classes on glycaemic control.(19-21) The effects of SGLT2i drugs on physiological variables such as blood pressure measured in routine care, and how this relates to the results observed within the standardised setting of clinical trials, are currently unknown.

Use of both DPP4 and SGLT2i drugs for first stage intensification of control of type 2 diabetes have been increasing rapidly in routine clinical care over recent years with wide variation in prescribing patterns.(22) There has been relative equipoise for choice of intensification drug offered by current clinical guidelines, and limited differences in the characteristics of people prescribed different drugs which are well understood and measureable.(23) This combination of circumstances means that observational data lend themselves to a natural experiment, making direct comparisons of medication effects on

important diabetes outcomes in a routine care population at the first stage of treatment intensification when SGLT2is are commonly used.

Incentivised by the Quality Outcomes Framework, people with Type 2 diabetes are regularly monitored in United Kingdom primary care, and measures of diabetic control, cardiovascular risk and renal function are well recorded in routine data.(24) Therefore, we conducted a propensity score matched, new-user cohort study to determine the effects of the three most commonly used drugs for intensification of glycaemic control after metformin monotherapy, SGLT2i, DPP4 and SU, on measures of cardiovascular and renal risk.(22)

Materials and Methods

Data sources

We used data from the Clinical Practice Research Datalink (CPRD) which covers approximately seven percent of the UK population and is representative in terms of age, sex and ethnicity.(25) The data contains information collected by GPs and primary care practitioners for routine patient care in primary care settings. Data collected includes demographic information, medical diagnoses, prescriptions, laboratory test results and diagnoses made in secondary care. Our data were linked to patient-level quintiles of index of multiple deprivation scores (IMD) collated in 2015 as a measure of socioeconomic deprivation, provided by the Office of National Statistics.(26)

Study population

To reflect prescribing of drugs used to intensify treatment of type 2 diabetes in contemporary routine clinical practice, we selected a new-user cohort of adults adding additional treatment to metformin monotherapy (study population). We first identified a study population of individuals aged ≥18 years with a new record for metformin before any other antidiabetic medication, between Jan 2000 and July 2017. We restricted to people with a minimum of 12 months of prior registration in CPRD to allow complete data entry and ensure they were new-users of antidiabetic drugs. From this group we identified people prescribed one of the potential antidiabetic drug choices recommended by NICE at the first stage of treatment intensification, defined as the 'index' drug, between January 2014 and July 2017. Based on previous work we excluded people intensifying treatment with a thiazolidinedione, insulin or glucagon-like peptide-1 receptor agonists as these treatments have been infrequently used in recent years and/or fall outside the standard first-stage guidance.(22) We excluded patients who were pregnant before and after treatment change as guidelines are different whilst pregnant or breastfeeding.

To limit the study population to people who intensified rather than changed treatment, we required that a) a second prescription for the index drug was recorded within 60 days after the end of the first prescription, and b) that the individual received a further metformin prescription between the first and second prescription for an intensification drug. We used the date of the first prescription for the first stage intensification drug as baseline/study entry. ***Outcomes***

We chose four clinical measures that are associated with future risk of cardiovascular disease or diabetic complications: i) Glycosylated haemoglobin (HbA1c), ii) systolic blood pressure (BP), iii) body mass index (BMI) and iv) estimated glomerular filtration rate (eGFR).(27, 28) For each measure we extracted all test results for HbA1c, systolic BP, weight and height to calculate BMI, and serum creatinine to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.(29) We then created four cohorts which are subsets of the study population for each clinical measure (**Figure 1**). To be included in a cohort, patients required at least one record of the measure within 540 days prior to drug treatment intensification and at least one follow-up recording of the variable of interest. Participants in each cohort were followed until the first of: death, leaving the practice, prescription of an alternative drug treatment for type 2 diabetes, or end of study (1st July 2017).

Descriptive variables and covariates

Details of our cohort methodology have been published previously.(23) Baseline covariates are those recorded prior to index drug prescription. We only included measurements within 540 days prior to baseline as older values might not reflect the values at the point of treatment intensification. This time point was chosen pragmatically based on the Quality Outcomes Framework recommendation that patients with diabetes have full clinical review annually, with additional time for delays in arranging appointments and for data-entry.(30) Medical diagnoses such as cardiovascular disease (CVD) and retinopathy were defined as present if they were listed in the medical record on or before the date of drug intensification. We defined use of ACE Inhibitors/Angiotensin Receptor Blockers (ACEI/ARB) or statins as any prescription in the year before the start of follow-up.

Statistical analysis

Propensity score matching

Variables considered as potential confounders, based on previous work defining factors associated with drug prescription,(23) were: age, gender, ethnicity, baseline values of HbA1c, eGFR, BMI and systolic BP, baseline diagnosis of CVD, retinopathy or current smoking, quintile of IMD, time taking metformin before intensification, and the year that treatment was intensified.

Propensity score matching between the three classes of drugs was used to assemble a sample in which each patient receiving SGLT2i was matched to up to four DPP4i patients prescribed DPP4i and up to five patients prescribed SU. These matching goals were chosen to reflect the relative number of users in each group. Each matched set had to include a minimum of one patient from each of the three treatment groups being compared. Patients were matched without replacement on the propensity score within a calliper of 0·025, approximately 0·2 times the standard deviation of the propensity score. The estimated propensity scores were obtained from logistic regression. An iterative approach to the selection of confounders was taken, including a potential confounder in the model if required to obtain balance of the variable across treatment groups, as measured by the standardised mean difference, accepting imbalances up to 0·2. We matched cohorts on their baseline measures of BMI, systolic BP, eGFR or HbA1c by including additional 'exact' matching on each variable. To account for the variability in the number of individuals in the matched sets, patients in incomplete sets were up-weighted to give each matched set equal weight.(31) Separate propensity score models were fitted to each sub-cohort (one for each outcome measure). Missing data in confounders was handled using a missing category approach.(32)

Mixed effects linear regression

For each continuous outcome, we applied mixed effects linear regression models to the matched samples, with a random effect for patient, to estimate the mean of the measure

over time, for each treatment group. We fitted a cubic model for the outcome over time. Follow-up time was split at 12, 24, 36, 60, 84 and 96 weeks, with cut-offs based on commonly reported time periods in clinical trials. Treatment effects were estimated separately in each time band. We used these models to estimate differences in means at 12 and 60 weeks compared to week zero. Overall differences across the 96-week period were obtained by averaging the period-specific treatment effect estimates and weighting by the duration of the period. To explore differential drop out over follow up, we calculated mean baseline level of HbA1c, eGFR, systolic BP and BMI for all patients remaining in the analysis population at each follow up time point.

Sensitivity analyses

To assess the robustness of results to the assumptions made in our primary analysis we completed a series of sensitivity analyses. First, we applied the mixed effects models to 1:1:1 matched samples (rather than matched sets with varying numbers of matches). Second, we removed the censoring when patients were prescribed an additional or alternative diabetic medication, to obtain results analogous to an intention-to-treat-estimate. Third, we assessed the impact of conducting a complete case analysis by imputing missing data using chained equations . Fourth, we restricted the analysis to patients who had at least one baseline and one follow-up measure for all four outcome measures, to determine whether the primary results were influenced by inclusion of patients without select measures into different cohorts. Fifth, we excluded individuals

from the analysis if they had high numbers of tests for each measure (eGFR, HbA1c, BMI or systolic BP) during follow-up to assess whether frequent measurements had an impact on the findings.

Patient and Public Involvement statement

Patients were not involved in the design or conduct of the study. We plan to disseminate the results through peer-reviewed publication.

Results

Within the study population, of individuals who intensified from metformin monotherapy with an SU, DPP4i or SGLT2i, 40% were female and the mean age, BMI, eGFR and systolic BP was 60 years, 33 kg/m^2, 89 mls/min/1·73m^2 and 133 mmHg respectively. **(Table 1)** The subcohorts for each physiological variable of interest comprised: eGFR 5,067, HbA1c 5,392, BMI 6,587 and systolic BP 7,958 individuals. Details of the cohort selection are provided in **Figure 1**.

Propensity score matched analysis

Initial imbalances in baseline characteristics across treatment groups were minimised after propensity score matching, for each cohort (HbA1c, eGFR, BMI and systolic BP) (**Supplementary Figure 1**). The propensity scores for SGLT2i showed substantial overlap across the three treatment groups (**Supplementary Figure 2**).

Supplementary Table 1 describes the unmatched SGLT2i users and **Supplementary Table 2** shows the number of matches identified for each cohort. The number of SGLT2i users not matched ranged from 3% in the BMI cohort to 11% in the systolic BP cohort. The length of follow-up (days) and number of repeated measures did not vary substantially between each clinical variable (**Supplementary Table 3**).

Table 2 provides the baseline characteristics of the largest propensity score matched cohort, that for HbA1c. Baseline characteristics for the eGFR, systolic BP and BMI matched cohorts are shown in **Supplementary Tables 4-6.** After propensity score

matching, cohorts were well matched on baseline covariates, and closely matched on the baseline physiological variables of interest. **Supplementary Figure 2** show the percentage standardised mean difference in baseline covariates for unmatched and matched cohorts, for each measure.

Estimated mean values of each clinical measure for each treatment group at the analysed time points, and changes from baseline, from linear mixed models fitted within the propensity-score matched cohorts are shown in **Figure 2** and **Supplementary Table 7**.

HbA1c fell substantially after intensification from a baseline of 76-77 mmol/mol for all drugs, but fall was greatest for SGLT2i users. The mean fall (mmol/mol) at week 12 was -15·2 (95% CI: -16·9, -13.5) for SGLT2i users, SU -14.3 (95% CI: -15.5, -13.2) for SU users and -11.9 (95% CI: -13.1, -10.6) for DPP4i users. This fall compared to baseline was similar at 60 weeks of follow-up for all drug classes. The mean difference (mmol/mol) over 96 weeks of follow-up for SGLT2i users was -5.4 (95% CI: -7.4, -3.4) compared to DPP4i and -1.7 (95% CI: -3.7, +0.2) compared to SU.

Baseline systolic BP was 134-135 mmHg and fell for SGLT2i users throughout follow-up but not DPP4i or SU users. The mean fall (mmHg) at week 12 was -2.3 (95% CI: -3.8, -0.8) for SGLT2i users, -0.8 (95% CI: -1.9, +0.4) for SU users and -0.9 (95% CI: -2.1, +0.2) for DPP4i users. At 60 weeks, systolic BP remained lower than baseline for SGLT2i users but not for other drug classes. The mean difference

(mmHg) over 96 weeks of follow-up for SGLT2i users was -1.82 (95% CI: -3.18, -0.45) compared to DPP4i and -3.06 (95% CI: -4.43, -1.68) compared to SU.

Mean BMI at baseline was 36-37 kg/m^2 and fell compared to baseline over follow-up for SGLT2i and DPP4i treated patients. The mean fall (kg/m^2) at week 12 was -0.7 (95% CI: -0.9, -0.5) for SGLT2i users, 0.0 (95% CI: -0.3, +0.2) for SU users and -0.3 (95% CI: -0.5, -0.1) for DPP4i users. At 60 weeks, BMI remained lower than baseline for SGLT2i and DPP4i users but not SU users. These falls in BMI are equivalent to a weight loss of 2.3 kg for a DPP4i user and 5.0 kg for an SGLT2i user at 60 weeks of treatment for a person 1.7 m tall, the mean height of the cohort of patients prescribed SGLT2is. The mean difference (kg/m^2) over 96 weeks of follow-up for SGLT2i users was -0.92 (95% CI: -1.17, -0.66) compared to DPP4i and -1.67 (95% CI: -1.95, -1.38) compared to SU.

Baseline eGFR was 95 mls/min/1.73m^2 and fell at 12 weeks for SGLT2i and DPP4i treated patients. The mean fall (mls/min/1.73m^2) at week 12 was -3.1 (95% CI: -4.1, -2.0) for SGLT2i users, +0.5 (95% CI: -0.4, +1.3) for SU users and -1.0 (95% CI: -1.9, -0.2) for DPP4i users. At 60 weeks, the fall in eGFR from baseline was approximately 2 mls/min/1.73m^2 for each drug class. The mean difference (mls/min/1.73m^2) over 96 weeks of follow-up for SGLT2i users was -0.03 (95% CI: -1.01, 0.94) compared to DPP4i and -0.78 (95% CI: -1.82, -0.27) compared to SU.

During, and at the end of follow-up, participants who remained in the cohort were similar in their baseline measure to the entire cohort at baseline, suggesting that

differential loss to follow up of patients whose health status varied importantly from the entire cohort had not occurred **(Supplementary Tables 8-11).**

Results of all sensitivity analyses were all similar to the main analysis **(Supplementary Figures 3-7 and Supplementary Table 12)**. Distribution of baseline covariates for individuals dropped due to missing baseline or follow-up measures are similar to the study population (**Supplementary Tables 14-17**).

Discussion

Our research has robustly estimated and compared the effects of the three drug options commonly used to intensify metformin monotherapy; SUs, SGLT2is and DPP4is, on HbA1c, BMI, systolic BP and eGFR in UK primary care. In cohorts of people with similar baseline characteristics and levels of each clinical measure we show that all three drug options were associated with large falls in HbA1c, with better overall glycaemic control for people prescribed SGLT2is. People prescribed both DPP4i and SGLT2i experienced falls in BMI that were sustained over the study duration, with those prescribed SGLT2is experiencing about twice the weight loss seen for DPP4i users. Systolic BP fell compared to baseline at 12 weeks for SGLT2i users but not for other drug classes. Over the study duration, systolic BP was approximately 3mmHg lower for those prescribed SGLT2i compared to those prescribed SU. However, confidence intervals for the estimates of systolic blood pressure are large and overlap for the SGLT2i and DPP4i cohorts. Users of SGLT2i demonstrated falls in eGFR at 12 weeks of treatment but over time the fall in eGFR was small and similar for each drug class.

The major strength of this study is that it reflects recent clinical practice where relative equipoise about choice of drug class and wide national variation in choice create an opportunity for direct comparison of drug effects. Selecting patients having drug therapy intensified at the same stage of treatment reduces time related bias. We have previously examined the differences in patient characteristics prescribed each drug class in detail and, based on this, have used propensity score matching to

achieve cohorts of patients very similar in baseline characteristics. Regular monitoring of type 2 diabetic patients in UK primary care provided extensive data enabling us to use the vast majority of patients from our baseline cohort for modelling each clinical variable.

However, the relatively short period over which SGLT2is have been used in UK primary care means that the sample size is smaller than for many primary care database studies with a follow-up of two years, shorter than recent clinical trials. This means that we can only examine class effects and would be underpowered to detect drug-specific effects and endpoints such as cardiovascular disease mortality. We classified the start date of treatment for each intensification drug from the first record in primary care. For a proportion where the drugs were initiated in secondary care, this date would be misclassified. Our 'baseline' values of physiological variables may therefore have been measured after treatment had started. However, this would have led to underestimation of early differences and given the short duration of prescriptions issued in secondary care we would anticipate that this would affect only a very small proportion of our results. Proteinuria data was insufficiently complete to use as a variable in our analysis.

Our study design focussed on providing matches of patients prescribed DPP4i and SU to patients prescribed SGLT2i drugs. This means that the results are generalisable only to contemporary SGLT2i users in primary care who had, for example, high BMI and well preserved renal function compared to users of other drug classes. Patients with a relative contraindication for a drug, for example those

with poor renal function (and therefore prescribed DPP4i or SU) would not have been matched. Nonetheless, this study design does provide a robust comparison of the drug effects in routine care for patients for whom there was the possibility of patients being prescribed one of the three drug classes.

Finally, we sought to study the biological effects of the drug classes, so censored follow-up when patients commenced treatment with an alternative drug class, analogous to an 'as treated' analysis of a clinical trial. If a greater proportion of patients stopped treatment with one of the drug classes this would limit validity of between drug comparisons, particularly if decision to stop treatment was associated with an outcome variable (such as failure for glycaemic control to improve). However, we saw similar results in our simulated 'intention to treat' analysis, where we did not censor patients when they changed treatment, suggesting that this has not substantially impacted our results. A small proportion of the cohort (4%) stop the initial drug and do not restart a different diabetic treatment (which would lead to censoring), clinical measures early on in the study period are likely to most closely represent the 'as treated' drug effects'

As we have shown previously, SGLT2is are prescribed to a different population in UK primary care compared to patients enrolled in recent major outcome trials (**Supplementary Table 13**).(23) Participants in our study were younger with better renal function and lower proportion of cardiovascular disease, heart failure and retinopathy. Our study population had poorer glycaemic control and were heavier at baseline compared to participants in recent cardiovascular outcome studies. Perhaps

related to this they also showed greater improvement after initiating SGLT2i compared to trial patients. We found a fall in HbA1c equivalent to 1.4% after 12 weeks of treatment while clinical trial estimates ranged from -0.25% (95% CI: -0.31, -0.20) in CREDENCE to -0.58% (95% CI: 0.61, -0.56) in CANVAS.

For patients commencing SGLT2i, our study estimated falls in BMI compared to baseline equivalent to weight loss of 2 kg at 12 weeks for an individual 1.7m tall. Outcome studies showed weight loss ranging from 1 kg at 12 weeks in CREDENCE to 2 kg at 6 months in DECLARE-TIMI. At the end of our study mean weight loss compared to baseline was 5 kg for SGLT2i users compared to 2 kg in CREDENCE and 4 kg in DECLARE-TIMI.

Falls in blood pressure and eGFR on initiating treatment with SGLT2is are well recognised and here we found striking similarities between the effects seen in clinical trials and in this routine care population, although there is substantial uncertainty around our estimates. We found a mean fall in systolic BP of 2.3 mmHg (95% CI: -3.8, -0.8) compared to baseline at 12 weeks for SGLT2i users but no fall for those prescribed other drug classes. Trial falls in systolic BP compared to baseline ranged from 2.8 mmHg at 12 weeks in the CREDENCE study to 5.5 mmHg in EMPA-REG (10mg dose arm). Over the duration of the study our results showed a mean difference in systolic BP of -3.06 mmHg (95% CI: -4.43, -1.68) compared to SU treated patients. Estimates compared to placebo in clinical trials were very similar ranging from -2.7 mmHg (95% CI: -3.0, -2.4) in the DECLARE-TIMI study to -3.93mmHg (95% CI: -4.30, -3.56) in CANVAS.

For renal function we found a fall in eGFR of -3.1 mls/min/1.73 m^2 (95% CI: -4.1, -2.0) at 12 weeks, similar to that seen at three weeks (-3.72 ± 0.25 mls/min/1.73 m^2) in CREDENCE and the same as that seen in CANVAS at 12 weeks (-3.1 ± 0.1 mls/min/1.73 m^2). At 60 weeks we saw a fall of -2.2 mls/min/1.73 m^2 (95% CI: -3.6, -0.7), again very similar to estimates seen in clinical trials, for example a slope of 2.74 mls/min/1.73 m^2 /year (95% CI: 2.37, 3.11) seen in CREDENCE. However, unlike the clinical trials, falls in eGFR in our comparison patient group were not different to SGLT2i treated patients, approximately 2mls/min/1.73 m^2 at 60 weeks for patients treated with both SU and DPP4i. By contrast placebo treated patients in CREDENCE had a slope of decline of renal function of -4.59 mls/min/1.73 m^2 /year while in CANVAS they had a difference from baseline of -3.9 ± 0.2 mls/min/1.73 m^2 at a mean follow-up of 188 weeks in CANVAS.

These results demonstrate the huge value of primary care data for conducting observational research. Providing validation to our methods, estimates for both improvement in glycaemic control and HbA1c were very similar to those found in previous research on intensification of treatment for type 2 diabetes using CPRD.(19) This is the first study to examine how changes in BP and renal function relate to changes observed in clinical trials using CPRD data. Given the consistency of the results they are reassuring that the benefits of SGLT2i seen in clinical trials will be maintained in routine care, although given the lower risk profile of SGLT2i treated patients evidence of hard outcome benefits may take longer to accrue. This is particularly the case for outcomes related to renal function where our results suggest

that rate of renal decline is slower in non SGLT2i treated patients than in clinical trials which may reflect the overall lower risk profile (younger with higher baseline eGFR) or the tighter glycaemic control seen in patients treated with other active agents in routine care.

In conclusion, routine primary care data can be used to study the effect of the new classes of treatments for type 2 diabetes on a range of biological variables, and provides estimates that are directly comparable to those seen in controlled clinical trials. Although SGLT2is are associated with the largest reductions in glycaemic control, weight, and blood pressure, both SUs and DPP4is are also associated with beneficial changes, reinforcing the need for active comparator outcome trials of these drugs.

Acknowledgements

Funding

SW is funded by a GSK PhD scholarship. LT is funded by a Wellcome Trust Intermediate Clinical Fellowship (101143/Z/13/Z).

Authorship statement

SW, LAT, ID, HS-F, EW and LS conceived and devised the study, EW and SW analysed the data. All authors contributed to the interpretation of the data. SW drafted the article and all authors (SW, IJD, EW, HS-F, DF, AP, LS, LAT) reviewed and edited the manuscript, and approved the version to be published. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. LAT is the guarantor for the work and accepts full responsibility for the work, for the conduct of the study, had access to the data, and controlled the decision to publish.

Conflict of Interest Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: HS-F is an employee of and holds shares in GSK. IJD is funded by, holds stock in and has consulted for GSK. DF has consulted for clinical trial adjudication associated with oral hypoglycaemia medications (ACI clinical), and consulted for Boehinger-Ingelheim. AP reports personal fees from NovoNordisk, Boehringer Ingleheim and Lilly outside of the

submitted work. LS has received grants from GSK and has received grants from the Wellcome trust, the MRC, the NIHR, the British Heart foundation and Diabetes UK outside of the submitted work and is a Trustee of the British Heart Foundation. LAT and EW have no relevant conflicts of interest to disclose.

Ethics Approval

The research protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines & Healthcare products Regulatory Agency Database Research (number 16_267). This study was also approved by the London School of Hygiene and Tropical Medicine Ethics Committee, ref: 11923.

Data sharing

All codes used in this analysis are available on the Electronic Health Records Research Group Data Compass website: http://datacompass.lshtm.ac.uk/692/. Due to CPRD licence restrictions no further data sharing is available.

Role of the funding source

GSK provided unrestricted funding and did not influence in any aspect of the study.

References

1. G B D Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-88.
2. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28.
3. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644-57.
4. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57.
5. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2019.
6. National Institute for Health and Care Excellence (NICE). NG28: Type 2 diabetes in adults: management National Institute for Health and Care Excellence. 2015.
7. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85.
8. Kalra S. Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A Review of Their Basic and Clinical Pharmacology. Diabetes Ther. 2014;5(2):355-66.
9. Wright JT, Jr., Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002;288(19):2421-31.
10. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.
11. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61(10):2108-17.
12. Birkeland KI, Jorgensen ME, Carstensen B, Persson F, Gulseth HL, Thuresson M, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol. 2017;5(9):709-17.
13. Persson F, Nystrom T, Jorgensen ME, Carstensen B, Gulseth HL, Thuresson M, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observational study. Diabetes Obes Metab. 2018;20(2):344-51.
14. Nystrom T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes. Diabetes Obes Metab. 2017;19(6):831-41.

15. Patorno E, Goldfine AB, Schneeweiss S, Everett BM, Glynn RJ, Liu J, et al. Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study. BMJ. 2018;360:k119.
16. Toulis KA, Willis BH, Marshall T, Kumarendran B, Gokhale K, Ghosh S, et al. All-Cause Mortality in Patients With Diabetes Under Treatment With Dapagliflozin: A Population-Based, Open-Cohort Study in The Health Improvement Network Database. The Journal of Clinical Endocrinology & Metabolism. 2017;102(5):1719-25.
17. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, et al. Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL 2 Study. J Am Coll Cardiol. 2018;71(23):2628-39.
18. Raschi E, Poluzzi E, Fadini GP, Marchesini G, De Ponti F. Observational research on sodium glucose co-transporter-2 inhibitors: A real breakthrough? Diabetes, obesity & metabolism. 2018;20(12):2711-23.
19. Wilding J, Godec T, Khunti K, Pocock S, Fox R, Smeeth L, et al. Changes in HbA1c and weight, and treatment persistence, over the 18 months following initiation of second-line therapy in patients with type 2 diabetes: results from the United Kingdom Clinical Practice Research Datalink. BMC Med. 2018;16(1):116.
20. Khunti K, Godec TR, Medina J, Garcia-Alvarez L, Hiller J, Gomes MB, et al. Patterns of glycaemic control in patients with type 2 diabetes mellitus initiating second-line therapy after metformin monotherapy: Retrospective data for 10 256 individuals from the United Kingdom and Germany. Diabetes Obes Metab. 2018;20(2):389-99.
21. Mamza J, Mehta R, Donnelly R, Idris I. Important differences in the durability of glycaemic response among second-line treatment options when added to metformin in type 2 diabetes: a retrospective cohort study. Ann Med. 2016;48(4):224-34.
22. Wilkinson S, Douglas I, Stirnadel-Farrant H, Fogarty D, Pokrajac A, Smeeth L, et al. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017. BMJ Open. 2018;8(7).
23. Wilkinson S, Douglas IJ, Williamson E, Stirnadel-Farrant HA, Fogarty D, Pokrajac A, et al. Factors associated with choice of intensification treatment for type 2 diabetes after metformin monotherapy: a cohort study in UK primary care. Clin Epidemiol. 2018;10:1639-48.
24. Nitsch DC, B.; Hull, S. and Wheeler D.C. . on behalf of the National CKD Audit and Quality Improvement Programme in Primary Care. First National CKD Audit Report. 2017.
25. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.
26. Ministry of Housing Communities & Local Government. English indices of deprivation 2015 2015 [December 2017]. Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015.
27. Gæde P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. New England Journal of Medicine. 2003;348(5):383-93.
28. Oellgaard J, Gaede P, Rossing P, Persson F, Parving HH, Pedersen O. Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits. Kidney Int. 2017;91(4):982-8.
29. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

30. Doran T, Kontopantelis E, Valderas JM, Campbell S, Roland M, Salisbury C, et al. Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework. BMJ. 2011;342:d3590.
31. Rassen JA, Solomon DH, Glynn RJ, Schneeweiss S. Simultaneously assessing intended and unintended treatment effects of multiple treatment options: a pragmatic "matrix design". Pharmacoepidemiol Drug Saf. 2011;20(7):675-83.
32. Groenwold RHH, White IR, Donders ART, Carpenter JR, Altman DG, Moons KGM. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2012;184(11):1265-9.

		SU N = 5,010	SGLT2i N = 1,187	DPP4i N = 4,434
Age (years)		61 (13)	55 (10)	61 (12)
Female		1988 (39.7)	474 (39.9)	1745 (39.4)
BMI (kg/m^2)		32 (6)	37 (7)	33 (7)
Missing		470 (9.4)	54 (4.5)	285 (6.4)
eGFR (mls/min/1.73m^2)		89 (18)	96 (13)	88 (18)
Missing		1683 (33.6)	493 (41.5)	1568 (35.4)
Systolic BP (mmHg)		133 (14)	134 (14)	133 (14)
Missing		837 (16.7)	293 (24.7)	880 (19.8)
HbA1c (mmol/mol)		80 (21)	77 (17)	73 (16)
Missing		2180 (43.5)	629 (53)	2085 (47)
Metformin treatment (months)		40 (37)	36 (33)	44 (37)
Cardiovascular disease		707 (14.1)	119 (10)	601 (13.6)
Heart failure		194 (3.9)	24 (2)	146 (3.3)
Retinopathy		868 (17.3)	181 (15.2)	861 (19.4)
ACEI/ARB treatment		2711 (54.1)	670 (56.4)	2490 (56.2)
Statin treatment		3530 (70.5)	819 (69)	3387 (76.4)
Index of multiple deprivation	LEAST deprived 1	467 (9.3)	93 (7.8)	398 (9.0)
	2	485 (9.7)	99 (8.3)	378 (8.5)
	3	567 (11.3)	117 (9.9)	449 (10.1)

	4	643 (12.8)	99 (8.3)	427 (9.6)
	MOST deprived 5	589 (11.8)	81 (6.8)	479 (10.8)
Missing		2259 (45.1)	698 (58.8)	2303 (51.9)
		SU	**SGLT2i**	**DPP4i**
		N = 5,010	**N = 1,187**	**N = 4,434**
Smoking status	Non-smoker	1883 (37.6)	462 (38.9)	1642 (37.0)
	Current	818 (16.3)	193 (16.3)	688 (15.5)
	Ex-smoker	2297 (45.8)	532 (44.8)	2102 (47.4)
Missing		12 (0.2)	N<5	N<5
Ethnicity	White	2052 (41.5)	500 (42.1)	1944 (43.8)
	South Asian	229 (4.6)	31 (2.6)	146 (3.3)
	Black	122 (2.4)	9 (0.8)	61 (1.4)
	Other	59 (1.2)	5 (0.4)	26 (0.6)
	Mixed heritage	14 (0.3)	N<5	16 (0.4)
Missing		2534 (50.6)	640 (53.9)	2241 (50.5)

Table 1. Description of the study population at baseline for individuals intensifying treatment from metformin monotherapy with SU, SGLT2i or DPP4i between 2014-2017

Values for continuous values are mean (standard deviation) and categorical values are n (%). % are of entire cohort. Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4 inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Haemoglobin A1c, eGFR: estimated glomerular filtration rate, BMI: Body mass index, BP: Blood pressure,

ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin 2 receptor blockers.

Frequencies below five not stated as per MHRA Database Research policy.

		SU	SGLT2i	DPP4i
Number of individuals*		1,691	481	1,445
Counts after weighting		481	481	481
Age (years)		56.4 (11.3)	56.3 (9.6)	56.6 (10.6)
Female		191 (40)	191 (40)	190 (39)
BMI (kg/m^2)		34.4 (5.4)	34.8 (5.5)	34.3 (5.4)
eGFR (mls/min/1.73m^2)		93.5 (15.4)	93.3 (12.2)	93.3 (14.7)
Systolic BP (mmHg)		133.9 (13.3)	133.7 (12.4)	133.7 (13.2)
HbA1c (mmol/mol)		76.7 (18.2)	76.4 (16.8)	76.7 (16.6)
Metformin treatment (months)		36.1 (34.4)	38.0 (32.9)	38.2 (35.2)
Cardiovascular disease		57 (12)	45 (9)	51 (11)
Heart failure		14 (3)	12 (2)	11 (2)
Retinopathy		79 (16)	75 (16)	88 (18)
ACEI/ARB treatment		252 (52)	278 (58)	252 (52)
Statin treatment		337 (70)	339 (70)	360 (75)
Index of multiple deprivation	LEAST deprived 1	50 (10)	51 (11)	50 (10)
	2	51 (11)	54 (11)	51 (11)
	3	59 (12)	60 (12)	61 (13)
	4	41 (9)	40 (8)	37 (8)
	MOST deprived 5	35 (7)	37 (8)	36 (7)
Missing		245 (51)	239 (50)	246 (51)

		SU	SGLT2i	DPP4i
Smoking status	Non-smoker	178 (37)	199 (41)	182 (38)
	Current	87 (18)	75 (16)	73 (15)
	Ex-smoker	213 (44)	207 (43)	225 (47)
Missing		<5	< 5	< 5
Ethnicity	White	202 (42)	194 (40)	192 (40)
	South Asian	9 (2)	11 (2)	11 (2)
	Black	6 (1)	7 (1)	6 (1)
	Other	< 5	< 5	< 5
	Mixed heritage	< 5	< 5	< 5
Missing		261 (54)	267 (56)	269 (56)

Table 2. Description of the propensity score matched and weighted HbA1c cohort at baseline for individuals intensifying treatment from metformin monotherapy with SU, SGLT2i or DPP4i between 2014-2017

*****Number of individuals contributing data to the HbA1c analysis, before weighting was applied. Values for categorical values are weighted mean (standard deviation) and categorical values are n (%) of entire cohort. After iteration of the propensity score model, the following covariates were included in the model: age, HbA1c, eGFR, BMI, systolic BP, patient-level IMD, ethnicity. The groups were further matched on deciles of baseline HbA1c. Figures provided are weighted means or counts. Abbreviations: SU: Sulfonylurea, DPP4i: dipeptidyl peptidase 4 inhibitors, SGLT2i: Sodium-glucose co-transporter-2 inhibitors, HbA1c: Haemoglobin A1c, eGFR: estimated glomerular filtration rate, BMI: Body mass index, BP: Blood pressure, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin 2 receptor blockers. Frequencies below five not stated as per MHRA Database Research policy.

Figures

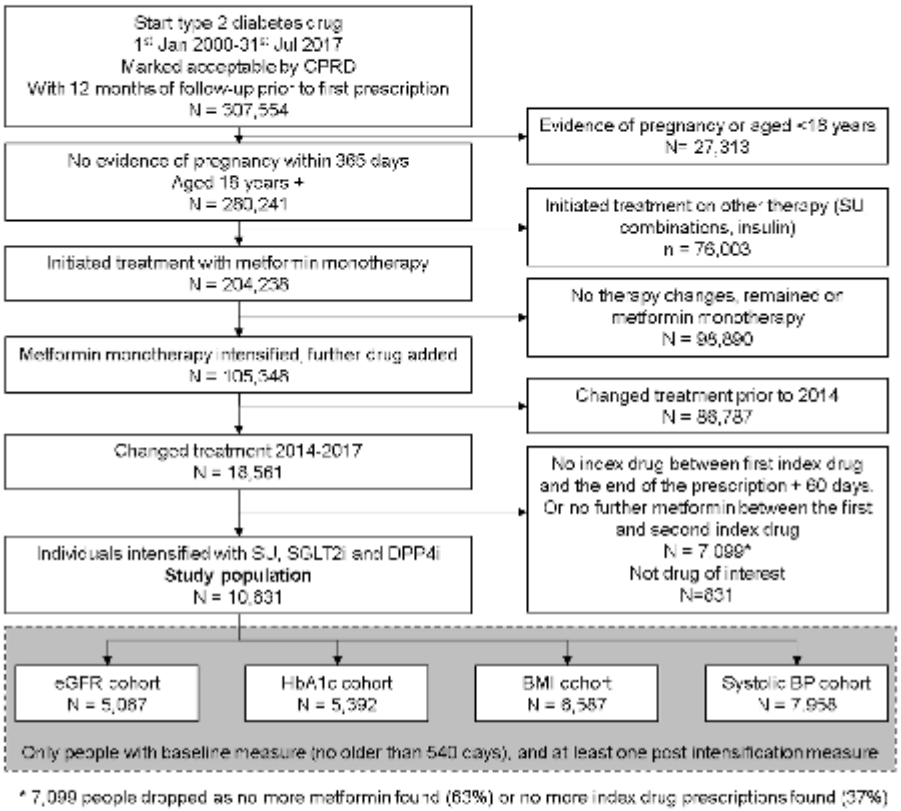

Figure 1: Flow diagram of identification of study participants

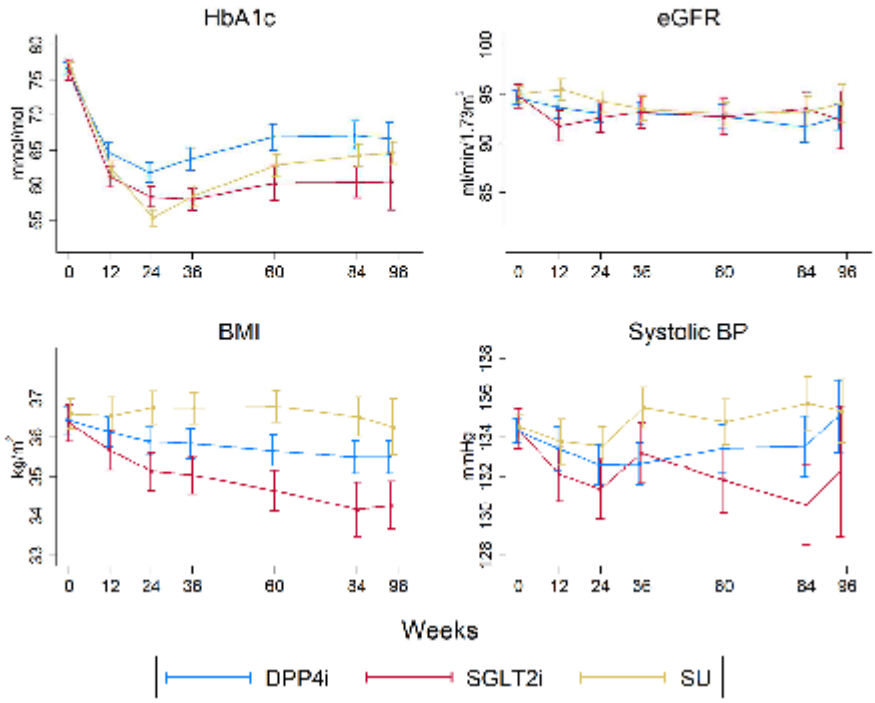

Figure 2. Mean (95% confidence intervals) of each clinical measure during treatment, for propensity score matched cohorts of individuals following intensification with DPP4i, SGLT2i and SU after metformin monotherapy.