Comparative effects of oral anti-diabetic agents after metformin monotherapy in UK primary care: a propensity-score matched cohort study

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Introduction

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) may reduce risk of cardiovascular disease and other outcomes for people with type 2 diabetes mellitus (T2DM). However, many randomised studies are trialled against placebo. In current UK primary care guidance, SGLT2i, sulphonylureas (SU), and dipeptidyl peptidase-4 inhibitors (DPP4i) are all recommended for treatment intensification after metformin monotherapy. The comparative effects of these drugs on outcomes in routine care are not known. We used the natural experiment of variation in treatment choice to compare the effect of these drugs on clinical measures of diabetic control and cardiorenal risk factors, within propensity score-matched cohorts of people intensifying treatment for T2DM.

Methods

Using primary care data from the United Kingdom Clinical Practice Research Datalink, we identified adults who intensified treatment using an SU, an SGLT2i or a DPP4i after a period of metformin monotherapy, between 2014 and 2017. We used propensity score matching to create cohorts of individuals closely matched for baseline characteristics. Using linear mixed models, we described changes in haemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), systolic blood pressure (BP), and body mass index (BMI) up to 96 weeks after treatment intensification.

Results

For each measurement cohort (HbA1c, systolic BP, eGFR and BMI) imbalance in baseline characteristics were minimised after propensity score matching. Table 1 shows these for the largest of the cohorts, HbA1c. The mean values over time for each clinical variable and drug in matched cohorts are shown in Figure 1. Mean HbA1c fell substantially at intensification for all drugs, with the greatest fall during follow-up among those treated with SGLT2i. Systolic BP fell at 12 weeks by 2.3mmHg compared to baseline for patients treated with SGLT2i and went on to remain significantly lower at most time points during follow up. Mean systolic BP among patients treated with SU and DPP4i remained similar during follow-up. As seen in clinical trials, for patients treated with SGLT2i eGFR fell at 12 weeks, (3mls/min/1.73m2), and was lower than for SU and DPP4i treated patients, but then remained stable. Over the duration of follow-up mean eGFR fell for each drug class, by approximately 2mls/min/1.73m2 at 60 weeks. BMI decreased substantially for patients treated with SGLT2i, and also for DPP4i, but remained similar for those treated with SU. By 60 weeks, the mean BMI in the DPP4i and SGLT2i cohorts were lower than for SU users although absolute change was low at 1-2kg/m2.

Discussion

Our results demonstrate excellent ability for data from routine care to replicate the effects on physiological variables observed in landmark clinical trials. Improvements for glycaemic control are seen for all agents, and for BMI and systolic BP among patients prescribed both DPP4i as well as SGLT2i. Estimated GFR falls to a similar but small extent in all groups over 96 weeks of follow-up. This strongly reinforces the need for active comparator trials to establish the true long-term cardiovascular and renal benefits of novel anti-diabetic drugs as prescribed in routine care.