IMPORTANT DIFFERENCES IN THE DURABILITY OF GLYCEMIC RESPONSE AMONG SECOND-LINE TREATMENT OPTIONS WHEN ADDED TO METFORMIN IN TYPE 2 DIABETES: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Importance: There is limited information about the durability of glycemic control when different oral glucose-lowering therapies (GLTs) are used as add-on treatments to metformin (MET) in patients with type 2 diabetes mellitus (T2DM).

Objective: To compare time to treatment failure between different classes of oral GLT when used as second line (add-on) treatments to MET monotherapy at HbA1c $\geq$ 7.5%.

Design, setting and participants: A retrospective cohort study on 20,070 patients who were newly treated with a sulphonylurea (SU), dipeptidyl-peptidase-4 (DPP-4) inhibitor or thiazolidinedione (TZD) following MET therapy failure (2007-2014). Patients' data was sourced from UK General Practices via The Health Improvement Network (THIN) database. The risk of dual therapy failure was compared between 3 treatment groups: MET+SU (reference group, n=15,508), MET+DPP-4 inhibitor (n=3,080) and MET+TZD (n=1,482). Follow-up was until treatment substitution or intensification with a 3rd GLT, or for up to 5 years (totalling 46,430 person-years). Propensity score weighting and Cox proportional hazard regression analyses were employed.

Main outcomes and measures: Risk of dual therapy failure was compared between treatment groups while adjusting for baseline covariates.

Results: Unadjusted survival analysis showed the incidence of dual therapy failure at 1 year was 15% with SU, 23% with DPP-4 inhibitor and 8% with TZD. Corresponding failure rates at 2 years were 26%, 38% and 12% respectively. Adjusted multivariate models showed that, compared to the SU group, adding a DPP-4 inhibitor was associated with an increased risk of treatment failure (adjusted hazard ratio, aHR, 1.58; 95% CI: 1.48-1.68), while adding a TZD was associated with a reduced hazard (aHR, 0.45; 95% CI: 0.41-0.50). Baseline parameters associated with an increased hazard of intensification included HbA1c, diabetes duration, gender, smoking status and the use of statins.

Conclusions and relevance: In routine clinical practice, adding a DPP-4 inhibitor to MET is associated with an increased, earlier requirement for treatment intensification compared to adding an SU or TZD. Adding a TZD to MET resulted in the most durable glycemic response.

Introduction

There is evidence that tight glucose control, especially in the early years after diagnosis, reduces the risk of long-term cardiovascular (CV) complications in patients with type 2 diabetes mellitus (T2DM).[1,2] International guidelines therefore recommend an individualized treatment strategy to achieve and maintain target levels of glycemic control.[3] Metformin (MET) is the usual first-line therapy when diet and exercise are insufficient, but due to the progressive decline in beta cell function many patients fail to maintain adequate levels of glycated hemoglobin (HbA1c) with monotherapy and require treatment intensification by adding a second oral agent.[3,4]

For most patients in whom MET alone is no longer sufficient, the options include adding a sulphonylurea (SU), a dipeptidyl-peptidase-4 (DPP-4) inhibitor or a thiazolidinedione (TZD). While these drugs have shown broadly similar reductions in HbA1c in randomized trials, the durability of glycemic responses when added as dual therapy with MET in everyday practice is unknown. Recent observational studies,[5,6] and randomized controlled trials,[7] have mainly reported on the durability of glucose lowering therapies (GLTs) when used as initial monotherapy rather than as add-on treatments in patients with longer duration T2DM.

Thus, the aim of this study was to compare the time to treatment failure among patients who added a DPP-4 inhibitor, SU or TZD to MET monotherapy in routine clinical practice, and to assess the glycemic and body weight responses over time.

Methods

Study design and data source

We conducted retrospective cohort analyses of data from The Health Improvement Network (THIN) database, which contains anonymous patient data from more than 400 General

Practices throughout England and Wales. THIN has been used previously to evaluate diabetes-related outcomes in routine clinical practice.[8]

Study population

The study population comprised a cohort of patients identified to have T2DM and registered to a practice for more than 12 months before the index date (January 1st 2007 - May 30th 2014). The cohort included patients ≥ 18 years old who were newly treated with an SU, DPP-4 inhibitor or TZD following MET therapy failure. Patients who were administered other GLTs such as glucagon-like peptide 1 receptor (GLP-1) agonists, sodium glucose co-transporter 2 (SGLT2) inhibitors, glinides and acarbose were excluded from the study due to the small numbers of user cases. Also excluded were patients who added insulin treatment to MET monotherapy in order to enable us to compare different oral GLTs. Standardized computerized routines were used to identify and extract information on patients' prescriptions for GLTs using British National Formulary (BNF) codes, and patients' diagnosis of disease conditions using Read codes.

Exposure

The exposures were incident intensification prescription of any SU (gliclazide, glimepiride, glipizide, glibenclamide or tolbutamide), a DPP-4 inhibitor (sitagliptin, vildagliptin, saxagliptin or linagliptin), or TZD (pioglitazone) as 2nd line GLT following MET monotherapy failure. Pioglitazone constitute 100% of TZDs in the data. The follow-up period commenced from the index date (the date of incident intensification prescription) through to the date of a censoring addition or substitution of another GLT at HbA1c ≥ 7.5%, up to 5 years after the index date. The study end date was May 30th 2014. Patients were segregated into three treatment groups based on the GLTs they received at baseline: MET + SU (reference/control group) vs. MET + DPP-4 inhibitor or MET + TZD.

Outcome

The primary composite outcome was time to dual therapy failure. This was defined as time to substitution or intensification of treatment with a 3rd agent at HbA1c ≥ 7.5%. Secondary outcomes included the glycemic effectiveness and body weight responses. The risks of treatment failure in the study population were compared across the three treatment groups.

Covariates

Covariates were selected *a priori* on the basis of clinical significance. These are baseline demographic and medical parameters, and include: age, gender, social deprivation (measured using Townsend's index scores), body weight, body mass index (BMI), baseline HbA1c, total cholesterol levels, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, systolic and diastolic BP, smoking status, duration of T2DM, glomerular filtration rate (GFR), serum albumin levels and urinary albumin-creatinine ratio (ACR). Others included the use of lipid-lowering drugs (mainly statins), antihypertensive drugs, aspirin and the following comorbidities at baseline: coronary heart diseases (CHD), peripheral arterial disease (PAD), hypoglycemia and heart failure.

Statistical analyses

Primary analyses include descriptive statistical analysis using Chi squared tests and logistic regression to assess all variables. We estimated a multinomial propensity score based on all the baseline covariates in our study.[9] This was designed to estimate the probability that a patient's initial 2nd line therapy was an SU (MET+SU was the treatment group with the largest number of patients).[10] Propensity score (PS) was estimated via inverse-probability-weighted regression adjustments (IPWRA)[11] using a logistic regression model in which the treatment status (indicator variable) was regressed on the baseline covariates.[12]

Balance in baseline covariates was assessed between the treatment groups by estimating the absolute standardized differences before and after propensity score weighting. A standardized

effect size ≥ 10% indicated serious imbalance.[13] The variations in mean and frequency distribution of measured baseline covariates between treatment groups with the same estimated propensity score was summarized.

Crude and adjusted Kaplan–Meier estimates of survival functions were calculated to evaluate the association of the treatment groups, and differences in survival were assessed via the log rank tests. From the survival curves, we computed the probability of dual therapy failure occurring within a 5-year follow-up. We constructed Cox proportional hazards models adjusting for all covariates while including propensity score as a prognostic covariate. The marginal hazard ratios were estimated to enable us to quantify the adjusted risk of requiring intensification with a 3rd line glucose lowering agent in DPP-4 inhibitor or TZD treated groups compared to the SU group.

We tested for violations of the proportional hazards assumptions using Schoenfeld residuals test.[14] Point estimates with 95% confidence intervals (CI) at the conventional statistical significance level of 0.05 were used in the regression models. Missing data among covariates was accounted for with multiple imputations using the chained equation (MICE) model.[15] All analyses were conducted using R[16] and Stata Software, version 13.[17]

Sensitivity Analyses

Additional sensitivity analyses were carried out to evaluate the robustness of our results by examining the assumption of no unmeasured confounding variable.[18,19] Assumption was made for an unmeasured covariate that would influence the measure of effect.[12] In addition, sensitivity analysis was carried out to compare results of covariates with missing data with those having multiple-imputed data to assess the reliability of the outcomes and the impact of missing data.

Biases

Our analysis employed the "new user" design to minimize biases associated with prevalent use of intensification regimens.[18] In an approach similar to that used in as-treated analyses, we used the intensification regimen to define drug exposure; post index date exposure to any GLT other than SU, DPP-4 inhibitor or TZD was not permitted in our study to reduce confounding by indication. In addition, to eliminate bias that may occur from Kaplan–Meier estimates of survival functions due to an unbalanced distribution of covariates, we used the adjusted log-rank test to compare the equality of the survival curves in the propensity score weighted cohort.[20]

Results

General patient characteristics

After screening 23,090 patients who intensified MET treatment with a 2nd line therapy, 20,070 patients made the criteria for cohort entry and were assigned to one of three treatment groups as outlined in the Supplement eFigure 1. The number (proportion) of patients assigned to each treatment group included 15,508 (77%) who added a SU ~~therapy (median follow-up 2.1 yrs, IQR: 0.8-4.0 yrs)~~, 3,080 (15%) added a DPP-4 inhibitor ~~(median follow-up 1.3 yrs, IQR: 0.5-2.4 yrs),~~ and 1,482 (7%) added a TZD ~~(median follow-up 3.7 yrs, IQR: 1.8-4.9 yrs)~~. ~~Their corresponding median time before treatment failure was 1.7, 0.9 and 2.6 yrs, respectively.~~

Overall, patients had a mean age of 59 yrs and were predominantly male (59%). Compared with patients who added other GLTs, those who added an SU appeared to be older (60 vs 57 yrs), had higher mean HbA1c levels (9.1% vs 8.6%), lower BMI and lower diabetes duration (Table 1). The patients' socioeconomic status was similar across the treatment groups. Before PS weighting, many of the measured covariates had a standardized difference above the 0.10 level (Table 1). However, the application of PS weighting brought into balance the

distributions of the measured covariates (See Supplementary eTable 1). Apart from previous hypoglycemia and a diagnosis of other CHD, the baseline characteristics of the weighted sample were not statistically different; as a result, the systematic differences between subjects in the treatment groups in the original cohort have been substantially reduced in the weighted sample (eTable 1). This shows that the differences between the treatment groups have been reduced by PS weighting and adequate balance on baseline covariates has been induced by the specification of the PS model used.

Time to dual therapy failure

The average time to treatment failure in the cohort of patients who added a 2nd line oral glucose lowering agent after MET is summarised in Table 2. Overall, 6,891 (44%) of patients who received a SU, 1,360 (44%) who received a DPP-4 inhibitor and 438 (30%) of patients who received TZD had to add or switch to another glucose lowering therapy during the study period. The mean time to treatment failure among TZD users was the longest at 3.3 years, followed by SU users (2.4 years) and then DPP-4 inhibitor (1.6 years). The unadjusted survival analysis showed the incidence of dual therapy failure at 1 year was 15% with SU, 23% with DPP-4 inhibitor and 8% with TZD. Corresponding failure rates at 2 years were 26%, 38% and 12%, respectively (Figure 1).

~~*Estimating survival curves for treatment failure*~~

Crude Kaplan–Meier (KM) survival curves for subjects who added SU, DPP-4 inhibitor or TZD in the unadjusted ~~original (unweighted)~~ cohort are shown in Figure 1. The result shows there was a significant difference between the three curves; log-rank test $p<0.001$. The adjusted KM survival curves obtained from the PS weighted cohort were also significantly different (adjusted log-rank test $p< 0.001$) (See eFigure 2 in the supplement). From the estimated survival curves, our data showed that the rates of dual therapy failure were significantly different. Second line use of a TZD was associated with the most durable

glycemic response, followed by the SU and then a DPP-4 inhibitor. ~~The unadjusted survival analysis showed the incidence of dual therapy failure at 1 year was 15% with SU, 23% with DPP-4 inhibitor and 8% with TZD. Corresponding failure rates at 2 years were 26%, 38% and 12% respectively (Figure 1).~~ Thus, patients who added a DPP-4 inhibitor or SU to MET monotherapy were more likely to require a 3rd line glucose lowering agent than those who added a TZD.

These results were consistent and remained significant in the adjusted multivariable Cox proportional hazards models, with DPP-4 inhibitor use (adjusted hazard ratio, aHR, 1.58; 95%CI, 1.48-1.68) being associated with an increased hazard of dual therapy failure and TZD use (aHR, 0.45; 95%CI, 0.41-0.50) associated with a decreased hazard of treatment failure compared with SU, respectively (Table 2).

In addition, factors predicting earlier failure of dual therapy on any of the glucose lowering agents were led by use of a lipid lowering drug, mainly statins (aHR = 1.57). Other significant risk factors included being female (aHR = 1.38), current smoking status (aHR = 1.07), T2DM duration (aHR = 1.07), body weight (aHR = 1.02) and HbA1c (aHR = 1.02) (see eTable 2~~1~~ in the supplement).

Glycemic and body weight responses

Results of the descriptive analysis showed that, overall, the co-administration of SU, DPP-4 inhibitor and TZD to patients who had inadequate glycemic control with MET were associated with significant HbA1c reductions of -1.3%, -0.9% and -1.2%, respectively ($p<0.001$). Over the course of therapy, the addition of a SU produced between 0.3 and 0.5% greater reduction in HbA1c compared to the addition of a DPP-4 inhibitor whereas the addition of a TDZ appears to show a fluctuating pattern of reduction that was not significantly different from the SU (Figure 2). In addition, the data show that addition of a 2nd line oral agent to MET was associated with an overall 15% of patients meeting the HbA1c

target ≤6.5% and about 27% meeting the HbA1c target <7% after 1 year of dual therapy. In terms of comparative responses at 1 year, the proportion of patients attaining HbA1c targets below 7% after using SU, DPP-4 inhibitor and TZD include 29%, 22% and 26%, respectively (Figure 4). ~~resulted in similar proportions attaining HbA1c target of <7% had the best rate of HbA1c goal (HbA1c<7%) attainment (21%), followed by a DPP-4 inhibitor (5%) and then a TZD (1%) (Figure 4)~~

In terms of overall changes in body weight, the addition of a TZD was associated with significant weight gain (1.8kg, p<0.001), while add-on DPP-4 inhibitor produced a significant weight reduction (-1.8kg, p<0.001). A very small reduction in body weight was observed with the SU (-0.2kg, p<0.001) (Figure 3).

Sensitivity analyses

We tested for violations of the proportional hazards assumptions using Schoenfeld residuals test, which tests the null hypothesis that the hazard ratio is constant over time. There is no evidence (P=0.5) to reject the assumption of proportional hazards for the treatment groups. The sensitivity analysis on missing data yielded comparable results to complete case models; the estimated aHR for DPP-4 inhibitor was 1.47 (95% CI: 1.34-1.60) and 0.50 for TZD (95% CI: 0.43-0.58), which reflects results that are unlikely to be attributable to bias from missing information. The probability density functions of the PS weighting of the treatment groups show there was no violation of the overlap assumption.[21] (eFigure 3 in the supplement)

Discussion

This study has shown that in routine clinical practice, among patients with T2DM receiving a 2nd line GLT as add-on to MET, the addition of a TZD is associated with the most durable glycemic response, followed by a SU and then a DPP-4 inhibitor. Factors associated with earlier dual therapy failure included concomitant use of statin therapy, being female, a

smoker, those with longer diabetes duration and higher baseline HbA1c levels. Adding an SU to MET as the 2nd line treatment gave the best chance of attaining an HbA1c goal of <7.5%.

The Agency for Healthcare Research and Quality has suggested that the durability of glycemic response after treatment intensification is best investigated using well-designed long-term observational studies.[22] Previous studies, however, have mainly focused on the durability of initial monotherapies, often in drug-naïve patients.[5-7] The present study has focused on the most commonly prescribed add-on therapies to MET. The results are similar to those in the ADOPT (A Diabetes Outcomes Progression) trial,[7] which showed that 'time to monotherapy failure' was longer with rosiglitazone, a TZD no longer widely used, ~~a TZD (rosiglitazone)~~ compared with MET and a SU, glyburide.[7] The ADOPT study which involved 4,360 patients followed for a median of 4 years also reported rosiglitazone showed a significant greater reduction in HbA1c compared to SU (between-group absolute difference of -0.4%), which contrasts the HbA1c changes observed in our study. Combination therapies have been shown to have additive effects and are better at reducing HbA1c compared with monotherapy regimens. A recent review of 140 clinical trials and 26 observational studies on head-to-head comparisons of GLTs (MET, second-generation SU, TZD, meglitinides, DPP-4 inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists) as monotherapy and combination therapy[23] reported most medications decreased the HbA1c level by about 1% (absolute reduction). A study conducted by the Quartet study group examined the long-term sustained effects of adding pioglitazone or gliclazide to failing MET monotherapy.[24] The 2-year, randomised, multicentre trial were performed in patients with inadequately controlled HbA1c (7.5-11% inclusive) and the mean reduction in HbA1c from baseline was 0.9% for TZD vs 0.8% for SU (p = 0.2). The SU group showed an initial better efficacy compared to TZD users, however, a progressive rise in HbA1c was observed by week 24 in both groups, with the SU group showing a more prominent increase. A similar initial pattern of reduction

was observed in our study. However, SU and TZD groups showed progressive increase after 2 years of treatment.

Observational studies have also shown that patients initially prescribed MET are significantly less likely to require treatment intensification than those who initiated treatment with other GLTs.[5,6, 23] However, therapeutic responses to GLTs may be different when used as add-on to MET compared with monotherapy.[25] The results of this real-world observational study are different to those of a previous randomized, controlled trial in which better durability of glycemic response was observed over 2 years with a DPP-4 inhibitor (sitagliptin) added to MET compared with a SU (glipizide).[26] In addition, a recent real-world study by Inzucchi et al[27] showed the opposite result to our study; patients treated with MET + sitagliptin showed a 24% lower risk of insulin initiation over a 6-year period compared with MET + SU users (HR 0.76; 95% CI 0.65–0.90). We speculate that one of the reasons for this disparity could be as a result of the different A1c levels characterised by the different cohorts. The study population examined by Inzuuchi et al had a mean A1c of approximately 8% compared to our study population with approximately 9% at baseline, moreover, the outcome of their stratification analysis which examined patients with A1c ≥9% was not statistically different between sitagliptin vs SU users, and results from their Cox model also showed that a 1% increase in A1c level was associated with a 20% increase in the risk of insulin initiation. The pattern of HbA1c reduction observed across the treatment groups over time was similar for SU and DPP-4 users, even though SU users maintained between -0.3% and -0.5% more reduction in HbA1c compared to DPP-4 inhibitor users. However, there was no consistent pattern seen with TZD users, which showed fluctuations in glycemic response after 48 weeks. It appears the initial decline in HbA1c among TZD users was not as prominent as that seen with SU or DPP-4 inhibitor within the first 24 weeks of treatment. We assume the reason for this initial slow response could be explained by certain uncontrollable factors. For example, SU is an insulin secretagogue that acts to increase insulin secretion, whereas TZD acts by activating a

nuclear receptor thereby altering genetic transcription, however, TZDs also act without increasing insulin secretion. Therefore, the slow initial glycemic response observed with TZD is consistent with the response that should occur within the first 3 months of TZD administration.

All 3 classes of GLTs assessed were associated with significant reductions in HbA1c. ~~but~~ The overall absolute 5-year mean change in HbA1c between SU, DPP-4 inhibitor and TZD was -1.3%, -0.9% and -1.2%, respectively. ~~–1.2%, –0.8% and –0.9%, respectively at 2 years.~~ The respective 2-year mean change obtained in our study (-1.2%, -0.8% and –0.9%) ~~These results~~ are consistent with previous evidence that an SU is superior to a TZD when added to MET,[25] while other studies have concluded that the efficacy of an SU is not superior to a DPP-4 inhibitor[28] or TZD[23,28] when added to MET. In terms of goal attainment , most prospective randomized head-to-head trials of SU vs DPP-4 inhibitor co-administered with MET have 1 to 2 years study duration and have similar proportions of patients who are lost to follow-up due to lack of efficacy. ~~In terms of goal attainment,~~ Similar proportions of patients attained glycemic efficacy (HbA1c < 7%) in our data; ~~a higher proportion of patients on~~ SU (29%~~28%~~) ~~reached HbA1c <7%~~ compared to ~~those on~~ DPP-4 inhibitor (22%) and TZD (26%) ~~6% vs 4%, respectively). Fewer patients treated with DPP-4 inhibitor and TZD reached this target at 1 year (5% vs 1%, respectively) as compared to SU (21%).~~ ~~In contrast,~~ A similar result was obtained from a randomised active-comparator study, which showed the proportion of patients who achieved this target at 1 year was similar between SU and DPP-4 inhibitors as add-on to MET (22.7% vs 23.1%, respectively).[29] It is well known that the higher the HbA1c, the greater the reduction in HbA1c with all agents. Therefore, the higher HbA1c recorded for SU users at baseline (9.1%) compared to DPP-4 inhibitor vs TZD (8.6% vs 8.6%) may add more weight to the absolute mean change observed among SU users. Results obtained from RCTs and real-world data in the area of superiority between SU and

DPP-4inhibitor as the add-on therapies to MET vary, meaning that a definitive conclusion cannot be made on the superiority of either SU over DPP-4 inhibitor in controlling HbA1c in patients with T2DM. The results of this real-world data imply that future robust research should examine efficacy in subgroup of patients over time and what influences a clinician's choice of treatment option.

When used in combination with MET, weight loss was observed with DPP-4 inhibitor (-1.8kg) vs. weight gain with TZD (1.8kg). ~~The weight loss accompanying use of a DPP-4 inhibitor appeared to be consistent 3 years from commencement of therapy.~~ TZD-related weight gain was evident after 24 weeks and was progressive over 3 years. Placebo-controlled trials have shown TZD and SU increased body weight by 1 to 5kg.[30] In a study of direct comparisons of monotherapies with TZD and SU, increased body weight was recorded with SU, even though this was lesser than that observed with TZD. Combinations of MET plus a TZD or MET plus SU increased weight more than MET monotherapy.[23] In contrast, SU was associated with borderline weight loss in our study. The reason for this disparity cannot be explained from our data. However, we assume that underlying factors such as education, lifestyle changes and combination therapy with MET might have contributed to the weight loss observed. Moreover, the greater amount of weight gain induced by TZD compared with SU in our data is consistent with data from another RCT – the ADOPT study, where patients administered SU monotherapy gained weight during the first year of treatment and thereafter experienced a gradual decline in body weight during the subsequent years.[7] On the other hand, the weight loss accompanying use of a DPP-4 inhibitor appeared to be consistent 3 years from commencement of therapy. A previous study showed the co-administration of a DPP-4 inhibitor with MET is associated with similar weigh loss effect when compared with MET monotherapy, although the strength of evidence was low due to fewer studies on DPP-4 inhibitors.[23] In contrast, previous overviews have concluded there is no significant weight

change with a DPP-4 inhibitor (-0.14kg, 95%CI: -0.94 to 0.63kg), while SU and TZD were associated with 2.06kg vs 2.08kg weight gain, when used in combination with MET, respectively.[28] Additional analysis conducted to investigate the correlation between change in body weight and change in HbA1c showed a significantly negative but weak association between change in HbA1c and change in weight in the cohort. (Pearson's correlation coefficient, $r = -0.03$; $p<0.001$). Change in weight accounted for approximately 0.1% of the total variation in HbA1c change; for every 1kg increase in weight, HbA1c increased by an estimated 0.01%, which is clinically irrelevant.

The risk for hypoglycemia with an SU has been reported to increase by 6-fold, compared with other GLT.[23] Newer agents such as DPP-4 inhibitor when added to MET was also reported to reduce HbA1c levels, but without additional risk for hypoglycemia.[23] Unfortunately, we were not able to assess the incidence of hypoglycemia in our data due to inadequate reporting of hypo events. However, we were also able to identify other factors that may independently predict earlier need for treatment intensification. These include diabetes duration, gender, smoking status, body weight and the use of statins. These findings may be particularly relevant for evaluating whether the adherence to glucose lowering therapy could be influenced by individual patient characteristics and foster research on the characteristics of patients that benefit most from SU, DPP-4 inhibitors and other newer second line agents. Our observation that statin therapy is an independent predictor of an earlier need for treatment intensification is particularly interesting. The adverse metabolic effects of statins on insulin secretion and insulin sensitivity is being recognised.[31]

Our analyses were subject to a number of limitations that are inherent to observational studies. Firstly, we cannot be certain that the patients were fully compliant with their

medication. ~~However, any overestimation of exposure to the medications in our analysis such a misclassification would be non-differential and only bias results towards unity~~. Other factors apart from HbA1c may also influence the decision to intensify treatment in everyday practice. These may include unknown compliance, tolerability, safety, cost, physician's reason for adding/substituting with a third oral agent and a patient's preference. Unfortunately, ~~but~~ we were ~~our analysis is~~ unable to evaluate how these factors might have influenced the findings. These information are useful in the management of type 2 diabetes in routine clinical practice and can be best obtained through qualitative research studies. Other newer agents being added to MET monotherapy such as GLP-1receptor agonists and SGLT-2 inhibitors were not assessed due to limited number of patients using them in our data. The failure to obtain similar data on SGLT-2 inhibitors and GLP-1receptor agonists is a major limitation of the present study. Although we could not account for potential residual confounders such as compliance, indications for intensification treatments, markers of β-cell deterioration and differences in dosages, we were able to account for differences in the observed covariates and used robust analytical techniques to control confounding that may bias the results of the estimated treatment effects. Our use of propensity score analysis to estimate average treatment effect in a large dataset contributed to the balancing of treatment and comparison groups on the available covariates without the loss of observations. However, the limitation to this technique is that it only accounts for observed covariates. Hence, other factors that may influence a physician's choice of therapy that cannot be accounted for in the study or any other hidden biases that may remain after PS weighting l overlap between treatment and control groups. Furthermore, we ensured a thoughtful and thorough specification of the selection model was employed to successfully apply the propensity score weighting technique.

Conducting a randomized trial to compare the durability of different 2nd line GLTs would be challenging and there are none, to date, in the literature. In this study, we observed that in routine clinical practice, among patients with T2DM, the rates of dual therapy failure were significantly different between commonly used 2nd line oral GLTs. A TZD was associated with the most durable glycemic response at the expense of greater weight gain, followed by the SU and DPP-4 inhibitor. The study highlights important differences in glycemic outcomes among different 2nd line treatment options used in everyday practice.

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Table 1: Characteristics of Patients at Treatment Intensification

Baseline variable	Total (N = 20,070)	MET + SU (n = 15,508)	MET + DPP-4i (n = 3,080)	MET + TZD (n = 1,482)	Effect Size [a]	Effect Size [b]
Demographics						
Age (yrs), Mean (SD)	59.2 (12.9)	59.8 (13.1)	57.2 (12.0)	56.8 (11.5)	0.23	0.07
Gender, No. (%)						
Male	11741 (59)	9097 (59)	1767 (57)	877 (59)	0.04	0.02
Female	8329 (41)	6411 (41)	1313 (43)	605 (41)	0.04	0.02
Townsend deprivation, No. (%)						
Least deprived	4210 (21)	3140 (20)	751 (24)	319 (22)	0.10	0.03
Less	3950 (20)	3036 (20)	625 (20)	289 (20)	0.02	0.01
Average	4328 (22)	3388 (22)	644 (21)	296 (20)	0.05	0.04
More	4297 (21)	3381 (22)	588 (19)	328 (22)	0.07	0.02
Most deprived	3285 (16)	2563 (17)	472 (15)	250 (17)	0.04	0.02
Clinical Parameters, Mean (SD)						
HbA1c (%)	9.0 (2.2)	9.1 (2.3)	8.6 (1.6)	8.6 (1.7)	0.24	0.07
BMI (kg/m2)	31.7 (6.6)	31.1 (6.5)	33.8 (6.8)	33.3 (6.6)	0.41	0.05
Weight (Kg)	90.9 (21.4)	89.0 (20.9)	97.8 (22.0)	96.0 (21.6)	0.41	0.06
SBP (mmHg)	134.8 (15.6)	135.0 (15.9)	133.7 (14.6)	135.3 (14.4)	0.10	0.04
DBP (mmHg)	79.4 (9.7)	79.4 (9.8)	79.6 (9.3)	79.8 (9.0)	0.05	0.01
TC (mmol/l)	4.7 (1.3)	4.8 (1.4)	4.6 (1.2)	4.5 (1.2)	0.19	0.06
HDL (mmol/l)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	0.05	0.02
LDL (mmol/l)	2.6 (1.1)	2.7 (1.1)	2.5 (1.0)	2.5 (1.0)	0.20	0.05
Triglyceride (mmol/L)	2.4 (2.5)	2.5 (2.7)	2.3 (1.9)	2.4 (2.5)	0.05	0.03
GFR (mls/min/1.73m2)	73.8 (17.2)	73.4 (17.3)	75.7 (16.4)	74.7 (16.8)	0.13	0.02
ACR (mg/mol)	4.1 (9.3)	4.3 (9.4)	3.9 (9.3)	3.2 (8.5)	0.12	0.05
Diabetes duration (yrs) [c]	2.9 (3.6)	2.8 (3.6)	3.4 (3.3)	3.0 (3.2)	0.17	0.02
Smoking status, No. (%)						
Non-smoker	8706 (43)	6787 (44)	1315 (43)	604 (41)	0.06	0.04
Current smoker	3750 (19)	2935 (19)	534 (17)	281 (19)	0.04	0.01
Ex-smoker	7614 (38)	5786 (37)	1231 (40)	597 (40)	0.06	0.03
Use of Medications, No. (%)						
Aspirin	3803 (19)	2861 (18)	544 (18)	398 (27)	0.23	0.06
Antihypertensive	10592 (53)	7985 (51)	1803 (59)	804 (54)	0.14	0.02
LLT	11588 (58)	8506 (55)	2138 (69)	944 (64)	0.29	0.06
Comorbidities, No. (%)						
Hypoglycemia	509 (3)	463 (3)	32 (1)	14 (1)	0.13	0.10
CHD	270 (1)	230 (1)	21 (1)	19 (1)	0.07	0.06
PAD	210 (1)	178 (1)	14 (0)	18 (1)	0.07	0.04
Heart Failure	458 (2)	406 (3)	41 (1)	11 (1)	0.13	0.11
Stroke	297 (1)	261 (2)	19 (1)	17 (1)	0.09	0.08

Abbreviations: MET (metformin); SU (sulphonylurea); DPP-4 (dipeptidyl peptidase-4 inhibitor); INS (insulin); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); HbA1c (hemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); GFR (glomerular filtration rate); LLT (lipid lowering therapy); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (urinary albumin creatinine ratio); SD (standard deviation)

Effect size (ES) is the absolute standardised mean difference of means or percentages divided by the standard deviation.
[a] Unweighted ES

[b] ES after propensity score weighted cohort based on average treatment effect in the population (ATE). Differences between treatment groups have been reduced by weighting using the propensity score

[c] Diabetes duration is time from first diagnosis of diabetes to date of intensification with 2nd line drug (index date)

Table 2: Rates, Hazard Ratios of Dual Therapy Failure and Glycemic and Weight Changes

	MET + SU	MET + DPP-4i	MET + TZD
Person-years	36,643	4,964	4,823
Average time to treatment failure (yrs)	2.4 (1.7)	1.6 (1.3)	3.3 (1.7)
Unadjusted failure rate (95% CI)			
Year 1	0.15 (0.14-0.16)	0.23 (0.22-0.25)	0.08 (0.07-0.10)
Year 2	0.26 (0.25-0.27)	0.38 (0.37-0.41)	0.12 (0.10-0.14)
Year 3	0.36 (0.35-0.37)	0.51 (0.48-0.53)	0.17 (0.15-0.19)
Year 4	0.45 (0.44-0.46)	0.61 (0.59-0.64)	0.23 (0.21-0.26)
Year 5	0.90 (0.88-0.91)	-	0.64 (0.56-0.72)
Adjusted hazard ratio (95% CI) [a]	1.0 [Reference]	1.58 (1.48-1.68)	0.45 (0.41-0.50)
Mean (SD) HbA1c at endpoint (%)	7.8 (1.7)	7.7 (1.5)	7.3 (1.4)
Mean (SD) HbA1c change, % [b]	-1.3 (2.4)	-0.9 (1.6)	-1.2 (1.9)
(mmol/mol)	-14 (26)	-10 (18)	-13 (21)
Year 1	-1.0 (2.0)	-0.6 (1.4)	-0.6 (1.7)
	-11 (22)	-7 (15)	-7 (19)
Year 2	-1.2 (2.3)	-0.8 (1.6)	-0.9 (1.9)
	-13 (25)	-9 (18)	-10 (21)
Mean (SD) Weight change, ~~K~~kg [b]	-0.2 (6.7)	-1.8 (6.3)	+1.8 (8.8)
Year 1	-0.4 (5.1)	-0.7 (3.9)	+0.2 (4.7)
Year 2	-0.1 (5.8)	-1.1 (4.8)	+0.5 (6.1)

Abbreviation: MET (metformin); SU (sulphonylurea); DPP-4i (dipeptidylpeptidase-4 inhibitor); TZD (thiazolidinedione); SD (standard deviation); HbA1c (glycated hemoglobin)

[a] Adjusted for all baseline covariates and propensity score

[b] Overall change in absolute value (values are running average)

Figure 1: Full cohort survival curves

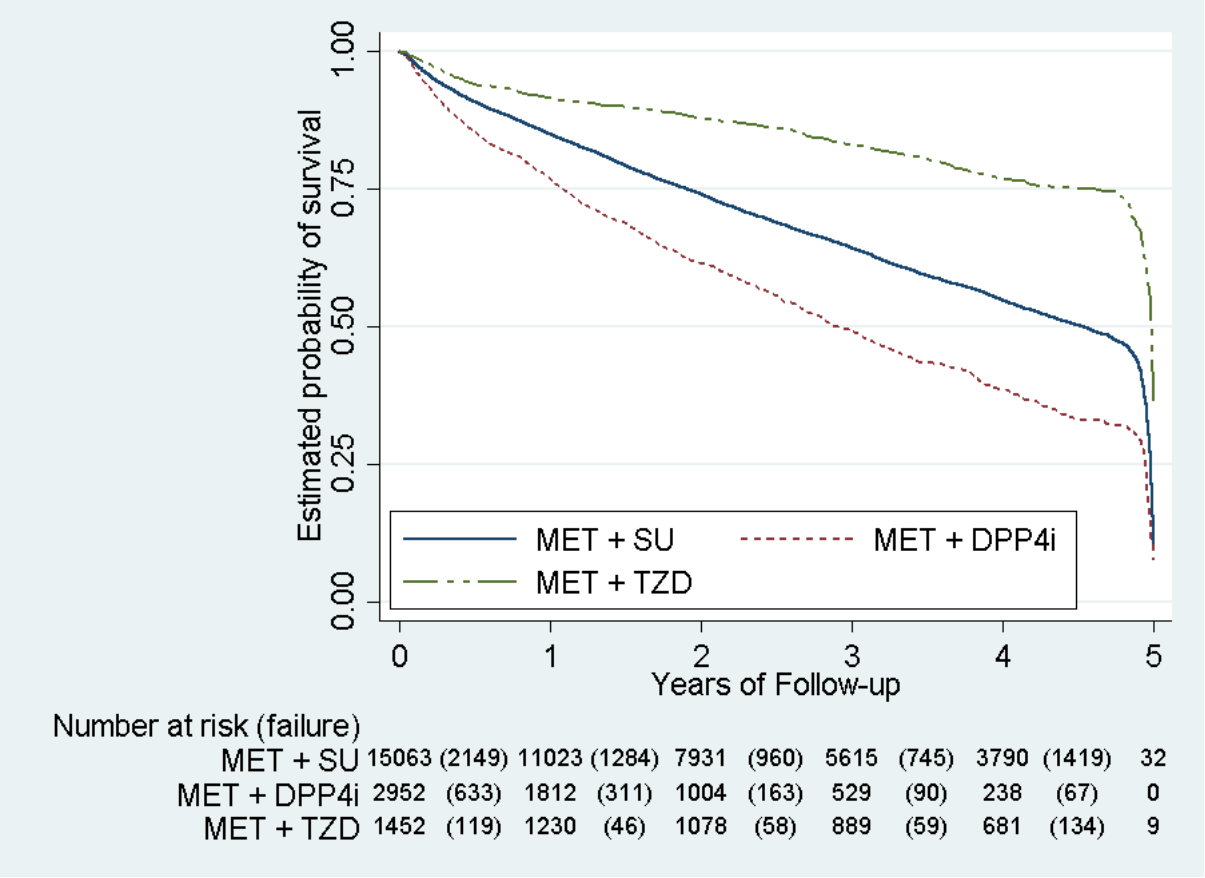

Figure 1 depicts the Kaplan-Meier survival curves for the treatment group (SU, DPP-4 inhibitor and TZD) participants in the original sample. The three survival curves are significantly different from one another (log-rank test P value < 0.001)

Figure 2: Glycemic responses – HbA1c over time

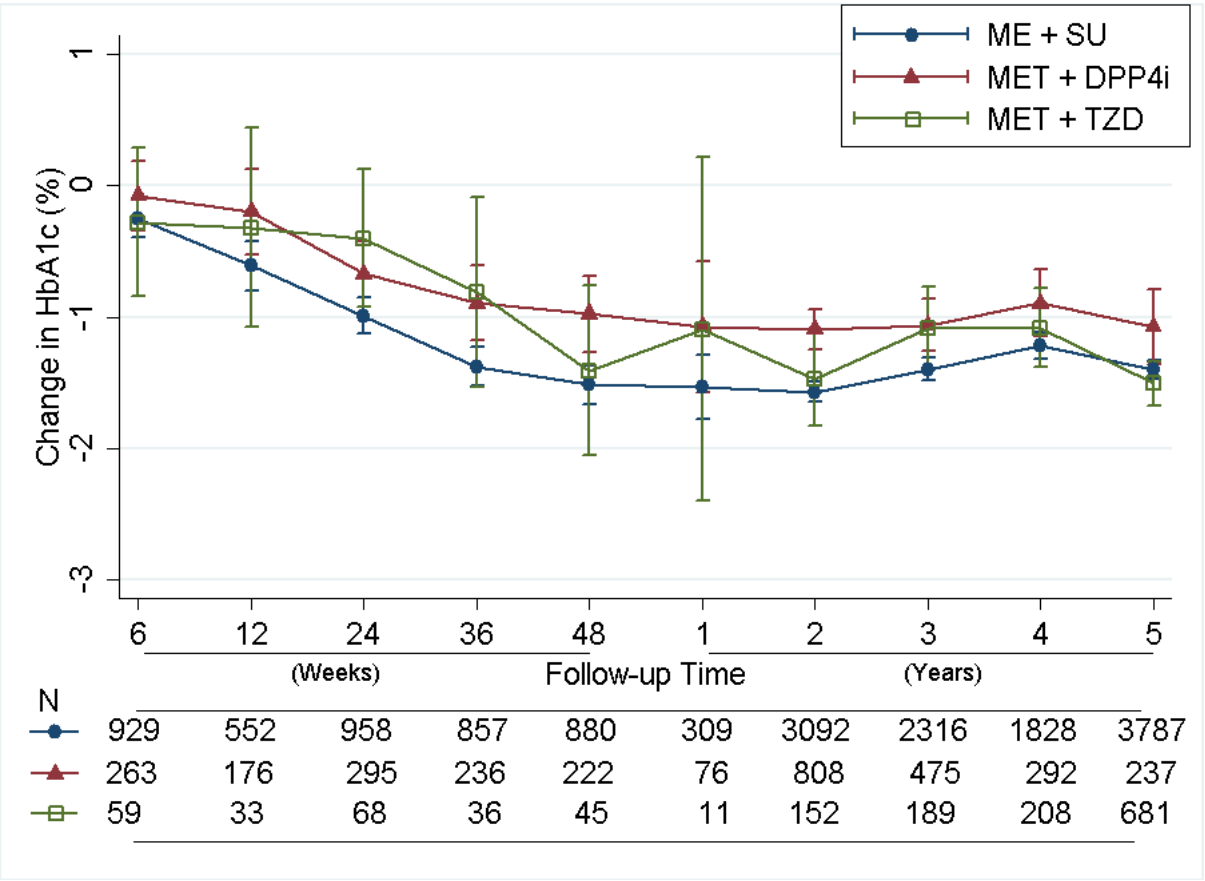

Figure 2 shows SU added to MET maintained a 0.3 to 0.5% greater reduction in HbA1c compared to MET plus DPP-4 inhibitor. There was no clear or consistent difference in HbA1c changes between SU and TZD when added to MET over time. (Note: Mean HbA1c changes are not running averages)

Figure 3: Body weight changes over time

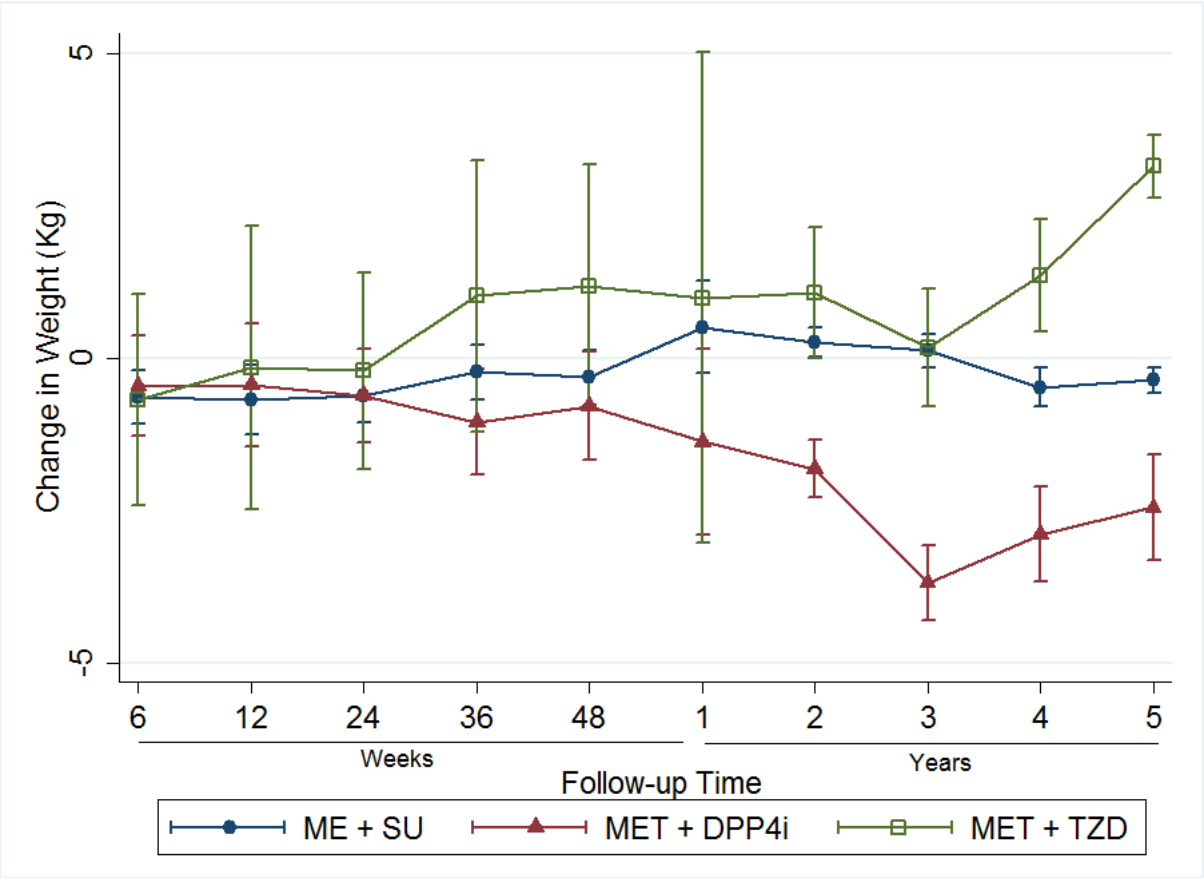

Figure 3 shows intensifying MET therapy with TZD was associated with weight gain over time, while DPP-4 inhibitor was associated with weight loss over time. SU was associated with neutral weight changes over time

Figure 1: Patients achieving HbA1c targets at 1 year

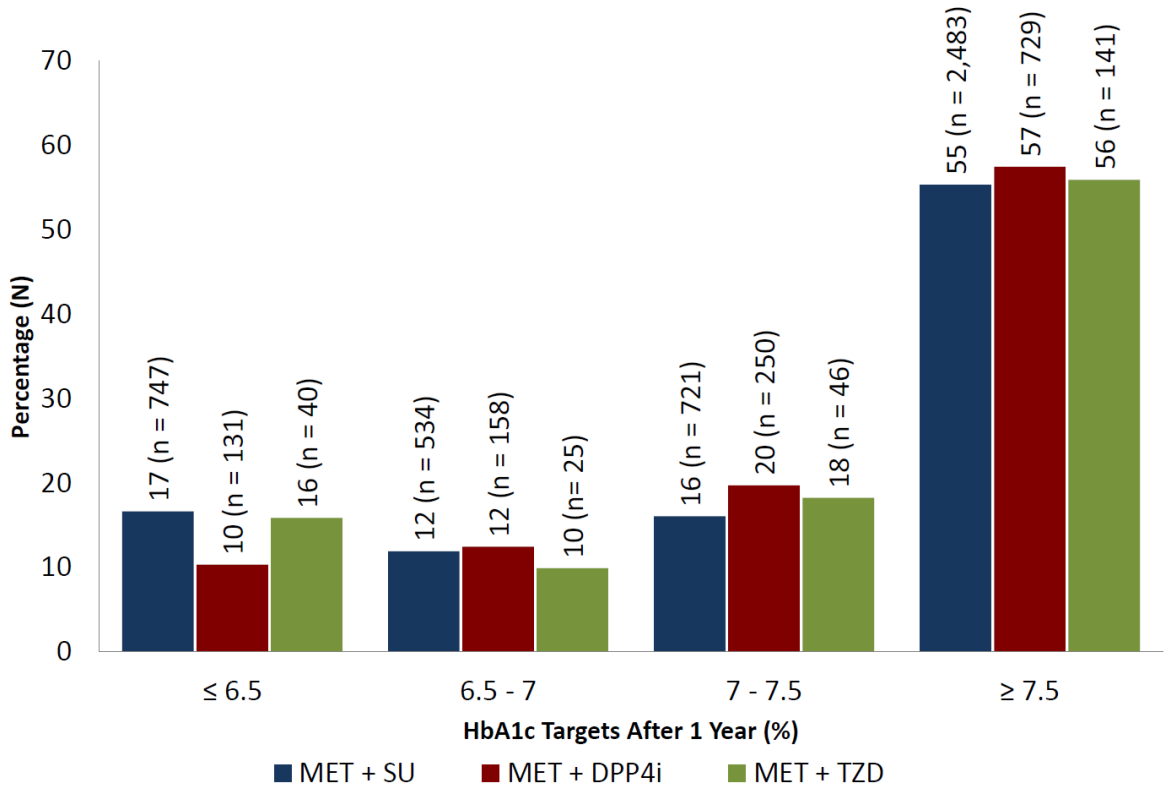

Figure 4 shows HbA1c goal achievement was quite low for all dual therapies studied. The addition of SUs second line to MET had the best rate of HbA1c goal attainment, followed by DPP-4 inhibitors, and then TZDs