The effects of dual-therapy intensification

THE EFFECTS OF DUAL THERAPY INTENSIFICATION WITH INSULIN OR DPP-4 INHIBITOR ON CARDIOVASCULAR EVENTS AND ALL-CAUSE MORTALITY IN PATIENTS WITH TYPE 2 DIABETES: A RETROSPECTIVE COHORT STUDY

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Abstract

Purpose

To compare time to a composite endpoint of non-fatal acute myocardial infarction, non-fatal stroke or all-cause mortality in patients with type 2 diabetes mellitus (T2DM) who had their treatment intensified with a dipeptidylpeptidase-4 (DPP-4) inhibitor or insulin (INS) following dual therapy (metformin, MET plus sulfonylurea, SU) failure.

Methods

A retrospective cohort study was conducted on 5,238 patients newly treated with either a DPP-4 inhibitor or INS following dual therapy failure (2007-2014). Data was sourced from UK General Practices. The risk of the composite outcome was compared between 2 treatment groups: MET+SU+INS (n=1,584) and MET+SU+DPP-4 inhibitor (n=3,654), while adjusting for baseline covariates. Follow-up was for up to 5 years. Propensity score matching analysis and Cox proportional hazard models were employed.

Results

Overall, 123 and 171 composite outcome events occurred among patients who added INS vs. DPP-4 inhibitor, respectively (44.5 vs 14.6 events per 1000 person-years). Addition of INS was associated with a significantly higher hazard ratio (HR) vs. the addition of a DPP-4 inhibitor (adjusted HR 2.6 (95%CI: 1.9–3.4; $p<0.01$), an effect that was more pronounced in obese (BMI 30-34.9kg/m^2) patients (corresponding aHR 3.6, 95%CI: 2.3-5.6, $p< 0.01$).

Conclusion

In routine clinical practice, intensification of MET+SU therapy by adding INS is associated with increased risk of cardiovascular events and death compared with adding a DPP-4 inhibitor.

These findings are in line with suggestions from previous studies regarding the cardiovascular safety of insulin in T2DM, but should be interpreted with caution.

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 glycaemic control. [3] Metformin (MET) is the usual first-line drug therapy when diet and exercise alone are insufficient. [3, 4] It used to be the case during the period of this retrospective analysis, that the recommended second-line therapy after MET was sulfonylurea (SU), [4] and because of the progressive decline in beta cell function many patients failed to maintain adequate levels of HbA1c despite up-titration to maximum tolerated doses of dual therapy (MET+SU). However, recent guidelines give more flexibility in prescribing choices.[5]

Several treatment options are available when MET and SU dual therapy is insufficient, [3] but there is very limited data on cardiovascular (CV) and diabetes-related outcomes in this group of patients to inform decision-making about third-line treatments. For many patients the choice includes adding basal insulin (INS) or a DPP-4 inhibitor as a third oral agent. There are concerns about the CV safety of INS in T2DM, [6-10] but these studies have mainly investigated the use of INS *per se*, as monotherapy or in combination with metformin. [6-10] On the other hand, the UKPDS [11] and ORIGIN [12] trials have demonstrated the safety of INS, while recent prospective RCTs have shown the CV outcomes of DPP-4 inhibitors are non-inferior to placebo. [13, 14] However, no RCT has compared INS with DPP-4 inhibitors either in terms of their CV safety or effectiveness as a third option after MET plus SU fails. Further work is needed to explore the CV safety of INS when used as a third line therapy, often in patients with longer duration disease and higher CV risk. Insulin is known to exert antiatherogenic effects [15] and many patients prefer to delay INS treatment because of fear of

injections, weight gain and the risk of hypoglycaemia. Therefore, adding a DPP-4 inhibitor to MET+SU is an effective alternative to lower HbA1c. Prior to recent RCTs which have demonstrated the safety of DPP-4 inhibitor, there has been some uncertainty about CV outcomes with DPP-4 inhibitors [13, 16] and till date, there are no comparative outcome studies available on DPP-4 inhibitor versus INS in patients with dual therapy failure. Therefore, the aim of the present study is to compare CV outcomes and mortality among patients with T2DM who, in routine clinical practice, intensified their treatment with the addition of INS or a DPP-4 inhibitor following dual therapy (MET+SU) failure.

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. [17]

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 a DPP-4 inhibitor or INS following MET+SU therapy failure. Patients who were administered other glucose-lowering therapies (GLTs) such as pioglitazone, glucagon-like peptide 1 receptor (GLP-1) agonists, sodium glucose co-transporter 2 (SGLT2) inhibitors, glinides and acarbose

were excluded from the study. Also excluded were patients with a baseline diagnosis of a CV condition. Standardised 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. Read codes used in defining the outcome of events are summarized as electronic supplementary material (ESM).

Exposure

The exposures were incident intensification prescription of INS (long-acting, short or fast-acting, or biphasic) or a DPP-4 inhibitor (sitagliptin, vildagliptin, saxagliptin, linagliptin) as 3rd line GLT following dual (MET+SU) treatment failure. The follow-up period commenced from the index date (the date of incident intensification prescription) through to the date of a censoring outcome event until a switch to, or addition of, another anti-diabetic drug, up to 5 years after the index date. The study end date was May 30th 2014. Patients were segregated into two treatment groups based on the GLTs they received at baseline: MET + SU + INS vs. MET + SU + DPP-4 inhibitor (reference/control group).

Outcome

The primary composite outcome was time to diagnosis of predefined events. These included non-fatal acute myocardial infarction (AMI), non-fatal stroke and all-cause mortality. Secondary outcomes included CV events (non-fatal AMI, non-fatal stroke and CV-related deaths combined), all-cause deaths and CV-related deaths. Read codes used for identifying AMI and strokes are included in ESM Table 1. CV-related deaths were included where the cause of death was documented. Subjects whose cause of death could not be verified were

ignored in the CV deaths analysis. The risks of events in the study population were compared between the two treatment groups. In addition, descriptive analysis of the glycaemic and body weight responses of patients in each treatment group was conducted.

Covariates

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

Statistical analyses

Descriptive analysis of baseline characteristics was conducted for all patients and compared between the INS and DPP-4 inhibitor treated groups using t test for continuous variables and chi-squared test for categorical variables. Primary analysis estimated the time to the composite outcome of non-fatal AMI, non-fatal stroke or all-cause death in the entire cohort as well as propensity score-matched cohort. A propensity score (PS) model was estimated using a logistic regression model in which the treatment status was regressed on the baseline covariates. [18] We assessed the balance in baseline covariates between the treated (INS) and

reference (DPP-4 inhibitor) subjects using standardized differences before and after matching. [19] An absolute standardized difference > 10% indicated serious imbalance. The mean and frequency distribution of measured baseline covariates between treatment groups with the same estimated PS was examined and summarized. Pairs of treated group and reference subjects were matched based on their estimated treatment probabilities using logistic regression. The average treatment effect on the treated (ATT) was estimated by finding at least 1 match for each of the treated subjects from the reference group. PS was considered as a prognostic covariate and included in a Cox proportional hazards regression model.

Crude and adjusted Kaplan–Meier estimates of survival functions were obtained for the treatment groups in the full cohort and PS-matched cohort. From these survival functions, we computed the absolute reduction in the probability of an event occurring within a 5-year follow-up. The marginal hazard ratios were also estimated to enable us to quantify the adjusted hazard of an event occurring in the INS treated group compared to the DPP-4 inhibitor group. Proportional hazards assumptions were confirmed through Schoenfeld residuals test. [20] 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. [21] All analyses were conducted using Stata Software, version 13. [22]

Subgroup and Sensitivity Analyses

We examined the hazard ratio of an event occurring in subgroups of patients with BMI between 30 to 34.9kg/m^2 and those with BMI ≥ 35kg/m^2. BMI categories were broken down into BMI <30, 30-34.9, and >35kg/m^2 distinguishing overweight, obese and morbidly obese

because NICE refer to BMI >35 as arbitrary cut off for certain prescribing choices rather than patient numbers in each group. Sensitivity analysis was aimed at examining the assumption of no unmeasured binary confounding variable. [23, 24] Assumption was made for an unmeasured covariate that would increase the odds of assigned treatment. [18] Sensitivity analysis was applied to Kaplan-Meier survival functions in the PS-matched cohort. In addition, a 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. [23] 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 a DPP-4 inhibitor or INS was not permitted in our study to reduce confounding by indication.

Immortal-time bias was also addressed by ensuring subjects diagnosed with outcome events on or before the index date were excluded. 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 stratified log-rank test to compare the equality of the survival curves in the matched sets (Kaplan-Meier survival curves were estimated separately for INS treated and compared with DPP-4 inhibitor treated participants in the PS-matched sample). [25]

Results

General patient characteristics

After screening 8,654 patients who intensified MET+SU treatment with a 3rd line drug, 5,238 patients made the criteria for cohort entry and were assigned to one of two treatment groups as outlined in Figure 1. The number (proportion) of patients assigned to each treatment group included: n=1,584 (30%) for MET + SU + INS and n=3,654 (70%) for MET + SU + DPP-4 inhibitor.

Patients had a mean age of 56 yrs and constituted of 56% male. Compared with patients who added a DPP-4 inhibitor, those who added INS to MET+SU before PS matching had higher mean HbA1c levels of 9.9% (85mmol/mol) vs 9.2% (77mmol/mol), respectively and many of the measured covariates had a standardized difference above the 0.10 level (Table 1). The application of PS matching resulted in the inclusion of 3,168 patients (1,584 MET+SU+INS matched 1:1 with MET+SU+DPP-4 inhibitor) and brought into balance the distributions of the measured covariates. Apart from previous hypoglycaemia and a diagnosis of other CHD, the baseline characteristics of the matched sample were not statistically different; as a result, the systematic differences between INS and DPP-4 inhibitor subjects in the original sample have been substantially reduced or eliminated in the matched sample (Table 1). This shows that the differences between the treatment groups have been reduced by PS matching and adequate balance on baseline covariates has been induced by the specification of the PS model used.

Time to composite outcome

The time to a composite outcome in the cohort of patients is summarised in Table 2. The median time before the composite outcome among the DPP-4 inhibitor users was longer at

2.4 years (IQR: 1.1-3.8) compared to INS users (2.1 years, IQR: 0.9-3.6). The survival analysis showed the 5-year cumulative incidence of composite outcome was 9% with DPP-4 inhibitor and 23% with INS.

Estimating survival curves and survival effects

Crude Kaplan–Meier (KM) survival curves for INS subjects and the reference DPP-4 inhibitor subjects in the full original sample are reported in Figure 2a. The result showed there was a significant difference between the two curves; log-rank test $p<0.001$. The KM survival curves obtained from the PS matched sample are summarized (stratified log-rank test $p< 0.001$) (Figure 2b). From the estimated survival curves, our data showed that patients who intensified treatment with INS were significantly more likely to experience a composite outcome than those who added a DPP-4 inhibitor. For example, from the matched sample, the probability of dying or experiencing a CV event at 3 yrs was 0.11 (95% CI, 0.10-1.03) with INS and 0.03 (95% CI, 0.02-0.04) with a DPP-4 inhibitor.

Overall, there were 123 and 171 composite outcome events among patients who added INS vs. a DPP-4 inhibitor, respectively (44.5 vs 14.6 events per 1000 person-yrs). The rate of occurrence remained the same after matching. The adjusted hazard ratio (aHR) from the PS-matched model was 2.6 (95% CI: 1.9–3.4; $p< 0.01$) (Table 2). A breakdown of the number of component outcome events showed the following: the number of CV events (non-fatal AMI, non-fatal stroke or CV-related deaths) was 95 and 94 among patients who added INS vs. a DPP-4 inhibitor, respectively (18 vs 8 events per 1000 person-yrs; $p<0.01$); all-cause deaths were 124 vs 64 events, respectively (23 vs 5 events per 1000 person-yrs) (Table 2).

Subgroup and other analyses

Our data showed that in the normal BMI group (BMI <30kg/m^2), the composite outcomes were 147 and 90 among patients who added INS vs a DPP-4 inhibitor, respectively (49 vs 20 events per 1000 person-yrs; aHR 2.32 (1.75-3.10); p< 0.001). In a subgroup of patients with BMI 30-34.9kg/m^2, the composite outcomes were 54 and 44 among patients who added INS vs a DPP-4 inhibitor, respectively (46 vs 12 events per 1000 person-yrs; aHR 3.6 (2.3-5.6); p< 0.01). The subgroup with BMI ≥ 35kg/m^2 had 30 and 37 composite events from intensification with INS vs a DPP-4 inhibitor (30 vs 11 events per 1000 person-yrs; aHR 2.4 (1.4-4.0); p< 0.01) (Table 2).

Stratification analysis across baseline BMI categories showed the risk of composite outcome among obese (BMI 30-34.9kg/m^2) patients was not significantly different to those of normal BMI category (BMI <30kg/m^2) patients. The risk of composite outcome between the morbidly obese group (BMI ≥35kg/m^2) was also not significantly different to that of obese BMI (BMI 30-34.9kg/m2) cohort (HR 0.77, 95%CI; 0.56-1.05, P=0.1). However, the morbidly obese BMI group was associated with a reduced risk of composite outcome compared to the normal BMI category (HR 0.61; 95% CI, 0.45-0.81, p=0.001).

In terms of glycaemic response, INS vs DPP-4 inhibitor users showed absolute mean reduction in HbA1c of -1.3% (14mmol/mol) vs -1.0% (11mmom/mol), respectively (P < 0.001). With the exception of the period between 48 weeks and 1 year, the mean reduction in HbA1c was not significantly different between INS and DPP-4 inhibitor over time. (ESM Figure 1) The glycaemic response was also examined across the three subgroups of BMI categories. Among patients who intensified their treatment with INS, the greatest glycaemic response was observed in the subgroup with normal BMI category (-1.5%, p<0.001) while the subgroup of obese and morbidly obese patients exhibited lesser but similar level of

glycaemic response (-0.9% and -0.9%, respectively). The greatest glycaemic response observed among patients who added a DPP-4 inhibitor was observed in the subgroup with normal BMI level (-1.8%). This was followed by obese and morbidly obese subgroup (-1.1% and -0.8%, respectively). (ESM Figure 2)

An absolute significant body weight increase was observed with INS (1.2kg, $P < 0.001$), whereas DPP-4 inhibitor showed a non-significant weight loss (-0.1kg, $P = 0.5$). From our data, INS users appeared to have consistently gained weight after the first year of treatment intensification. (ESM Figure 3) An assessment of the body weight changes across the BMI categories show that in both INS vs DPP-4 inhibitor treatment groups only the morbidly obese BMI subgroup experienced a reduction in body weight (-2kg vs -2.3kg, respectively, ESM Figure 4).

Further analysis on gender related outcomes showed that within the female population, the number of composite outcomes were 105 and 67 among patients who added INS vs a DPP-4 inhibitor, respectively (39 vs 14 events per 1000 person-yrs; aHR 2.34 (1.68-3.28); $p< 0.001$). Whereas within the male population, the number of composite outcomes were 126 and 104 in patients who added INS vs a DPP-4 inhibitor, respectively (50 vs 15 events per 1000 person-yrs; aHR 3.08 (2.32-4.09); $p< 0.001$). (Table 2) Nevertheless, comparative analysis results show the risk of composite outcome in female population was not significantly different to the risk in males (HR 0.84, 95%CI; 0.69-1.03, P=0.1).

Sensitivity analyses

One of the analyses was to assess how strongly an unmeasured confounder would have to be associated with treatment selection in order for a previously statistically significant treatment effect to become statistically non-significant if the unmeasured confounder had been accounted for. However, a large majority of estimated effects of covariates in our study were not statistically significant. Therefore, we did not employ this sensitivity analysis. Moreover, the p value for the stratified log-rank test in the matched cohort was $p<0.001$. Hence, the small p-value obtained in the primary analysis cannot be taken as an indication that the study is insensitive to unmeasured confounders. The sensitivity analysis on missing data yielded comparable results to complete case models (aHR 2.3 (1.7-3.0); $p< 0.001$), which reflects results that are unlikely to be attributable to bias from missing information. The probability density functions of the PS matching of the treatment groups show there was no violation of the overlap assumption. [26] (ESM Figure 6)

Discussion

This study has shown that in people who may need to have more therapy to lower their glycaemia, those who are selected by their GP to have DPP-4 inhibitor were less likely to experience the composite outcome of non-fatal AMI, non-fatal stroke or death. Furthermore, the increased risk with INS was even higher among the subgroup of patients who were obese (BMI>30). In the absence of a consensus on which third-line treatment is most appropriate when maximum tolerated doses of MET+SU fail to maintain adequate glycaemic control, this study identifies important differences in CV and mortality outcomes between two treatment options that are frequently used in patients with dual therapy failure.

The risk-benefit balance and overall safety of a more intensive treatment strategy in T2DM has recently been questioned, [27] and in particular the use of INS has been associated with an

increase in life-threatening hypoglycaemia risk and mortality. [6] Other observational studies have also raised concerns about INS use in T2DM. For example, a dose-response relationship between INS exposure and all-cause deaths was reported in a large Canadian population, [7] and worse survival was reported among INS treated patients (relative to those on MET+SU) in a study exploring the relationship between HbA1c and CV disease. [8] More recently, adverse CV events and increases in all-cause mortality were reported in a cohort of patients who received INS compared with other agents, [9] and among those whose treatment was intensified to INS (compared with adding a SU) following failure of metformin monotherapy. [10] However, an important limitation of these observational studies was their inability to control for differences in HbA1c, [7] hidden confounders or allocation bias [8-10] because they compared INS therapy with either MET or SU, both of which are often used much earlier in the course of the disease. The present study overcomes many of these limitations and specifically compared outcomes in a cohort of dual therapy failure patients without prior evidence of CV disease.

The observation of an even higher hazard ratio for the composite of non-fatal AMI, non-fatal stroke and all-cause death among the obese subgroup is clinically important. Insulin therapy is associated with weight gain, thereby increasing the amount of insulin required to control hyperglycaemia, [28, 29] at the expense of further weight gain, increased insulin resistance and potentially increased risk of CHD. [30] Our study population still had suboptimal glucose control (HbA1c > 8% or 64mmol/mol) despite treatment intensification with insulin. Our data shows patients in our study population have poor response to diabetes management, although this may not apply to most other populations. Therefore, patient factors associated with persistently high HbA1c might be an important determinant of increased mortality risks and may need to be further investigated. We would speculate that patients in our study may have

required high dose insulin treatment in order to achieve glycaemic targets. We have previously shown that the effectiveness of insulin therapy to lower HbA1c levels among overweight patients with diabetes is reduced. [31]

Research evidence has shown that increasing obesity typically confers an increased risk of CV diseases and CHD and there is the general idea that more marked obesity may be associated with a worse prognosis. A systematic review of over 250,000 patients in 40 cohort studies followed patients for up to 3.8 years and reported that overweight and obese CHD patients have a lower risk for total and CV mortality compared with underweight and normal-weight CHD patients and in morbidly obese patients with a BMI ≥35 kg/m^2, there was an excess risk for CV mortality without any increase in total mortality.[32] However, data from our study contrasts this evidence as the morbidly obese group is observed to be associated with a reduced risk of composite outcome compared to normal BMI. Another study by Galal et al assessed 4.4-year mortality in 2,392 patients with PAD who had a high mortality risk, showed progressive reductions in mortality in obese groups, overweight and normal BMI groups compared to underweight patients.[33] Although their results showed BMI was an independent predictor of greater mortality in the entire cohort, there was still a relationship between higher BMI and lower mortality in the overweight and obese PAD group. Lavie et al documented the inverse relationship between BMI and all-cause mortality in over 30,000 patients with preserved left ventricular systolic function. This study found the highest mortality in underweight patients, yet overweight, obese, and morbidly obese patients (BMI ≥35 kg/m^2) had significantly lower mortality than those with ideal BMI (18.5 to 25 kg/m^2).[34] A limitation to our data meant we could not examine the risk of CV outcomes or mortality outcomes within subgroups with specific CV co-morbidities. Therefore, we speculate that although obesity may be a powerful risk factor for all-cause

mortality events, patients with different cardiovascular co-morbidities may paradoxically have varying prognosis depending on the level of systemic vascular resistance and plasma renin activity. We therefore recommend that further studies to examine the factors that may influence the variation in CV and mortality risks across BMI categories.

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. Other factors apart from HbA1c may also influence the decision to intensify treatment in everyday practice. These may include tolerability, cost and patient's preference. In addition, covariates were mainly included as baseline parameters and their effects were not assessed during the follow-up period, some of these variables are relevant during the entire observation period for monitoring outcomes. For example, the use of other medications such as antihypertensive drugs are shown to have significant benefits on CV and renal outcomes in people with diabetes, independently of their blood pressure lowering efficacy.[35] In addition, evidence from recently published real-world data showed that sitagliptin-persistent treatment for a medium–long period is associated with an improved metabolic control, as well as to a reduction on CV risk.[36] Unfortunately, the relationship between the different types of antihypertensive drugs or adherence to statin use cannot be explained from our data. 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 matching to estimate average treatment effect in the dataset contributed to the balancing of treatment and comparison groups on the available covariates. However, this technique only accounts for observed covariates.

Although we ensured a thoughtful and thorough specification of the selection model was employed to successfully apply the propensity score matching technique and minimise bias, our study findings must be interpreted with caution in light of the above limitations. Furthermore, there are other newer agents which will most likely be used in place of insulin after MET+SU combination therapy such as GLP-1 agonist and SGLT-2 inhibitors given their benefit in weight and hypoglycaemia risk. The changing landscape of diabetes management could undermine the relevance of the clinical implications of findings from this study.

Conclusion

Patients with T2DM fail to maintain adequate levels of HbA1c despite up-titration to maximum tolerated doses of dual therapy (MET+SU). Comparative effectiveness studies and RCTs which examine the risks of cardiovascular events or deaths from the co-administration of INS or DPP-4 inhibitor as 3rd line regimens are not reported. Conducting RCTs at this level of treatment is not without its numerous challenges. We observed that among patients with diabetes who are receiving MET and SU therapy, the addition of insulin compared with DPP-4 inhibitor was associated with an increased risk of a composite of non-fatal cardiovascular outcomes and all-cause mortality. The observed excess risk of adverse cardiovascular events was increased in patients who are obese. Insulin is a still a very important treatment option in the management of T2DM and our data is not clinically applicable until RCTs comparing insulin with DPP-4 inhibitors have been conducted. These findings require further investigation to clarify the risk associated with insulin, especially among obese patients with T2DM, in view of the increasing availability of other therapies.

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Compliance with ethics guidelines

This article is based on anonymous patient data and does not involve any new studies of human or animal subjects performed by any of the authors. Ethical approval was obtained as part of the Specialist Research committee approval by The Health Improvement Network, provided by the National Research Ethics Committee South East Research Ethics Committee.

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Table 1: Characteristics of Patients at Treatment Intensification

	Cohort					
	Full			Propensity Matched		
Baseline variable	MET + SU + INS (n = 1584)	MET + SU + DPP-4 (n = 3654)	Std. diff [a]	MET + SU + INS (n = 1584)	MET + SU + DPP-4 (n = 1584)	Std. diff [b]
Demographics						
Age (yrs), Mean (SD)	53.7 (14.8)	56.6 (11.5)	-0.18	53.7 (14.8)	54.4 (12.8)	-0.05
Gender, No. (%)						
Male	770 (49)	2163 (59)	-0.16	770 (49)	768 (48)	0.00
Female	814 (51)	1491 (41)	0.16	814 (51)	816 (52)	0.00
Townsend deprivation, No. (%)						
Least deprived	294 (19)	802 (22)	-0.07	294 (19)	302 (19)	-0.01
Less	300 (19)	733 (20)	-0.03	300 (19)	336 (21)	-0.06
Average	333 (21)	782 (21)	0.00	333 (21)	295 (19)	0.06
More	352 (22)	711 (19)	0.05	352 (22)	349 (22)	0.01
Most deprived	305 (19)	626 (17)	0.04	305 (19)	302 (19)	0.01
Clinical Parameters, Mean (SD)						
HbA1c (%)	9.9 (2.9)	9.2 (2.7)	0.18	9.9 (2.9)	9.8 (3.7)	0.03
BMI (kg/m2)	29.8 (6.7)	32.3 (6.3)	-0.30	29.8 (6.7)	29.8 (6.1)	0.00
Weight (Kg)	84.6 (20.4)	93.1 (20.3)	-0.32	84.6 (20.4)	84.5 (19.7)	0.00
SBP (mmHg)	132.6 (17.5)	135.0 (15.2)	-0.11	132.6 (17.5)	132.7 (15.6)	-0.01
DBP (mmHg)	79.6 (10.5)	80.4 (9.3)	-0.07	79.6 (10.5)	79.8 (9.2)	-0.03
TC (mmol/l)	5.1 (1.6)	4.8 (1.3)	0.16	5.1 (1.6)	5.1 (1.8)	0.00
HDL (mmol/l)	1.2 (0.4)	1.1 (0.3)	0.12	1.2 (0.4)	1.2 (0.3)	0.00
LDL (mmol/l)	2.8 (1.1)	2.7 (1.0)	0.14	2.8 (1.1)	2.8 (1.1)	0.04
Triglyceride (mmol/L)	2.9 (5.8)	2.5 (3.2)	0.06	2.9 (5.8)	2.8 (6.0)	0.01
Serum albumin (g/L)	42.0 (4.3)	42.8 (3.7)	-0.17	42.0 (4.3)	42.0 (3.9)	-0.01
eGFR (mls/min/1.73m2)	74.1 (19.0)	75.8 (16.7)	-0.08	74.1 (19.0)	74.4 (17.3)	-0.02
ACR (mg/mol)	4.8 (11.4)	3.6 (9.0)	0.11	4.8 (11.4)	4.2 (9.7)	0.06
Diabetes duration (yrs) [c]	2.6 (4.6)	2.7 (3.1)	-0.03	2.6 (4.6)	2.5 (3.8)	0.01
Smoking status, No. (%)						
Non-smoker	619 (39)	1604 (44)	-0.07	619 (39)	602 (38)	0.02
Current smoker	435 (27)	669 (18)	0.16	435 (27)	458 (29)	-0.03
Ex-smoker	530 (33)	1381 (38)	-0.07	530 (33)	524 (33)	0.01
BMI Categories, No. (%)						
$\leq 30 kg/m^2$	918 (58)	1447 (40)	0.29	918 (58)	910 (57)	0.01
$30\text{-}34.9 kg/m^2$	354 (22)	1167 (32)	-0.18	354 (22)	368 (23)	-0.02
$\geq 35 kg/m^2$	312 (20)	1040 (28)	-0.16	312 (20)	306 (19)	0.01
Use of Medications, No. (%)						
Aspirin	220 (14)	734 (20)	-0.14	220 (14)	242 (15)	-0.04
Antihypertensive	587 (37)	1873 (51)	-0.22	587 (37)	581 (37)	0.01
LLT	608 (38)	2136 (58)	-0.31	608 (38)	585 (37)	0.03
Comorbidities, No. (%) [d]						
Other CHD [e]	38 (2)	71 (2)	0.00	38 (2)	63 (4)	-0.10*
PAD	29 (2)	49 (1)	0.02	29 (2)	40 (3)	-0.05
Heart Failure	31 (2)	36 (1)	0.05	31 (2)	39 (2)	-0.03
Hypoglycaemia [e]	124 (8)	142 (4)	0.10	124 (8)	158 (10)	-0.09*

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 (haemoglobin 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)

[a] Standardized differences are the absolute difference in means or percentage divided by the standard deviation of the treated group

[b] Resulting standardized difference after 1:1 matching based on average treatment effect on treated (ATT) propensity score technique and robust variance estimation. See ESM Figure 5 for graphical illustration of balance

[c] Diabetes duration is time from first diagnosis of diabetes to date of intensification with 3rd line drug (index date)

[d] Comorbidities are defined in the Supplement (see Table 1 in the ESM)

[e] In the matched cohort, only CHD and hypoglycaemia had statistically significant standardized difference at 0.10 level

Table 2: Numbers of Events, Rates and Adjusted Hazard Ratios

	MET + SU + INS	MET + SU + DPP-4 inhibitor
Person-years	5,193	11,694
Sample population		
Composite outcome (No. of events) [a]	231	171
Median time to composite outcome (IQR)	2.1 (0.9-3.6)	2.4 (1.1-3.8)
Unadjusted rate of outcome (95% CI)	44.5 (39.1-50.6)	14.6 (12.6-17.0)
Adjusted hazard ratio (95% CI)	2.6 (1.9-3.4)	1.0 [Reference]
Cardiovascular events (No. of events) [b]	95	94
Unadjusted rate (95% CI)	18.4 (15.1-22.5)	8.1 (6.6-9.9)
Adjusted hazard ratio (95% CI)	2.0 (1.5-2.8)	1.0 [Reference]
All-cause deaths (No. of events) [c]	124	64
Unadjusted rate (95% CI)	23.2 (19.5-27.7)	5.4 (4.2-6.9)
Adjusted hazard ratio (95% CI)	3.7 (2.7-5.2)	1.0 [Reference]
Cardiovascular deaths (No. of events) [d]	9	5
Unadjusted rate (95% CI)	1.7 (0.9-3.3)	0.4 (0.2-1.0)
Adjusted hazard ratio (95% CI)	2.6 (0.8-8.9)	1.0 [Reference]
Subgroup population		
BMI <30kg/m^2		
Composite outcome (No. of events) [a]	147	90
Unadjusted rate (95% CI)	48.8 (41.2-57.4)	19.6 (16.0-24.1)
Adjusted hazard ratio (95% CI)	3.08 (2.2-4.3)	[Reference]
BMI 30-34.9kg/m^2		
Composite outcome (No. of events) [a]	54	44
Unadjusted rate (95% CI)	46.4 (35.5-60.5)	11.8 (8.8-15.9)
Adjusted hazard ratio (95% CI)	3.6 (2.3-5.6)	1.0 [Reference]
BMI ≥ 35kg/m^2		
Composite outcome (No. of events) [a]	30	37
Unadjusted rate (95% CI)	29.6 (20.7-42.4)	11.2 (8.1-15.5)
Adjusted hazard ratio (95% CI)	2.4 (1.4-4.0)	1.0 [Reference]
Females		
Composite outcome (No. of events) [a]	105	67
Unadjusted rate (95% CI)	39 (32.2-47.3)	14.4 (11.3-18.2)
Adjusted hazard ratio (95% CI)	2.3 (1.7-3.3)	1.0 [Reference]
Males		
Composite outcome (No. of events) [a]	126	104
Unadjusted rate (95% CI)	50.4 (42.3-60)	14.8 (12.2-17.9)
Adjusted hazard ratio (95% CI)	3.08 (2.32-4.09)	1.0 [Reference]

Abbreviation: MET (metformin); SU (sulphonylurea); DPP-4 (dipeptidylpeptidase-4 inhibitor); INS (insulin); BMI (body mass index)

[a] Composite outcome include: non-fatal acute myocardial infarction (AMI), non-fatal stroke or all-cause death. For full regression model of sample population, see ESM Table 2

[b] Cardiovascular events relate to non-fatal AMI, non-fatal stroke or cardiovascular related deaths

[c] All-cause deaths only include records with confirmed cause of death. Patients whose cause of death could not be verified were not included

[d] Cardiovascular deaths refer to deaths from all cardiovascular causes

Rates are calculated per 1000 person-years in all cases.