Cardiovascular events and all-cause mortality with Insulin vs Glucagon-like peptide-1 analogue in Type 2 Diabetes

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Abstract

Objectives: To analysed time to cardiovascular events and mortality in patients with T2DM who received treatment intensification with insulin or a Glucagon like peptide-1 (GLP-1ar) analogue following dual therapy failure with metformin (MET) and sulphonylurea (SU).

Methods: A retrospective cohort study was conducted in 2,003 patients who were newly treated with a GLP-1ar or insulin following dual therapy (MET+SU) failure between 2006-2014. Data was sourced from The Health Improvement Network (THIN) database. Risks of major adverse cardiovascular events (MACE) (non-fatal myocardial infarction, non-fatal stroke and all-cause mortality) was compared between MET+SU+Insulin (N=1584) vs MET+SU+GLP-1ar (N=419). Follow-up was for 5 years (6614 person-years). Propensity score matching analysis and Cox proportional hazard models were employed.

Results: Mean age was 52.8±14.1 years. Overall, the number of MACE was 231 vs 11 for patients who added insulin vs GLP-1ar respectively, (44.5 vs 7.7 per-1000-person-years adjusted Hazard Ratio (aHR): 0.27; 95%CI: 0.14-0.53; p<0.0001). Insulin was associated with significant increase in weight compared with GLP-1ar; (1.78 vs -3.93kg; p <0.0001) but HbA1c reduction was similar between both treatment groups; (-1.29 vs -0.98; p= 0.156). In a subgroup analysis of obese patients, (BMI>30kg/m2) there were 84 vs 11 composite outcomes (38.6 vs 8.1 per 1000 person-years; aHR: 0.31; 95%CI: 0.16-0.61; p=0.001) in the Insulin and GLP-1ar groups respectively.

Conclusion: In this cohort of obese people with T2DM, intensification of dual oral therapy by adding GLP-1ar analogue is associated with a lower MACE outcome in routine clinical practice, compared with adding insulin therapy as the third glucose-lowering agent.

Key messages

What is already known about this subject?

Insulin therapy is widely used to manage hyperglycaemia in people with type 2 diabetes. Its use however is well recognised to be associated with weight gain and increased risk of hypoglycaemia – two known risk factors for cardiovascular events. More recently, concerns have been raised regarding the cardiovascular safety of insulin in people with type 2 diabetes.

What does this study add?

This study compares the cardiovascular safety of insulin with an alternative injectable glucose lowering therapy, the GLP-1 analogues in routine clinical practice. The later treatment is known to induce weight loss without any increased risk of hypoglycaemia.

How might this impact on clinical practice

In people with type 2 diabetes who require intensification of glucose lowering therapy following failure of metformin and sulfonylurea, GLP-1 analogues should be considered first before insulin treatment, especially in patients who are overweight. The use of GLP-1ar appears to be associated with a reduction in cardiovascular events and mortality compared with insulin.

Introduction:

The achievement of tight glucose control has been shown to reduce the risk of long term vascular complications in patients with type 2 diabetes (T2D).[1, 2] Following the initiation of antidiabetic medication with metformin (MET), about 40-60% of patients with T2D fail to achieve their glycaemic target, requiring intensification with a second-line agent, typically, with a sulphonylurea (SU).[3, 4] For many patients, failure to maintain optimal HbA1c level despite up-titration to maximal doses of dual therapy (MET+SU) will necessitate the need for further intensification with a third-line agent. Although a variety of treatment options are available following failure of MET+SU dual therapy, limited data is available on the cardiovascular (CV) safety and diabetes related outcomes on the most appropriate third line antidiabetic therapy.[5, 6] Moreover, in the last 7 years, questions regarding the long term cardiovascular (CV) safety of insulin have been raised.[7, 8] These epidemiological studies however have mainly investigated the use of insulin as monotherapy or in combination with metformin.[9-11] Conversely, the cardiovascular benefits of the Glucagon like peptide-1 analogues,[12, 13] a novel glucose lowering therapy with favourable effects on weight reduction and low risks of hypoglycaemia are an active area of clinical investigations (http://www.clinicaltrials.gov). GLP-1 analogues are hypothesized to have pleiotropic effects on the cardiovascular system based on evidence from experimental studies.[14] Furthermore, since insulin is known to be associated with weight gain and increased risk of hypoglycaemia, adding a GLP-1 analogue to MET+SU is an attractive alternative to lower HbA1c in patients with T2D. No comparative outcome data versus insulin in patients with dual therapy failure are however available. Further work is therefore needed to explore the CV safety of insulin compared with GLP-1 analogues when used as a third line (injectable) therapy in patients with longer duration disease and higher CV risk.

The aim of the present study therefore was to compare the real-world composite cardiovascular and mortality outcomes in UK clinical practice amongst patients with T2D following intensification of MET+SU dual-therapy with either insulin or a GLP-1 analogue.

Methods:

Study Design and Data Sources:

This was a retrospective cohort study using the UK primary care database- The Health Improvement Network (THIN). THIN is the UK computerised longitudinal anonymised primary care records with information systematically entered by primary care physicians. It contains details of over 10.5 million patients derived from 532 general practices. THIN has been validated and shown to be demographically representative of the dynamics of the UK population in terms of demography, major conditions prevalence, and mortality rate[15, 16] and has been used previously to evaluate diabetes-related outcomes in routine clinical practice.[17, 18] Ethics approval was provided by South East Research Ethics committee.

Study Population:

This comprised of patients with T2D aged 18 and above, whose MET+SU dual-therapy was intensified with either insulin or GLP-1 agonist analogues from January 2006 to May 2014. We selected patients whose index date (treatment intensification with insulin or GLP-1ar) was at least 90 days after the baseline date (registration into the database). Patients who started insulin or GLP-1 analogue first before MET+SU commenced; previously on other antidiabetic medication; on more than triple therapy; with any form of CV; who died before intensification of dual-therapy; or those with type1 diabetes were excluded.

Exposures and Outcomes:

Our exposures of interest were insulin (either ultra-short/short acting, premixed or long-acting) and GLP-1 agonist analogues (Exenatide, Liraglutide or Lixisenatide) with a follow up period of 5 years from index date. The study was exposure-based and participants were censored following the addition of another therapy; change of either GLP-1ar or Insulin; loss to follow-up (transfer out of practice) or at the of study.

The primary composite outcome was time to the risk of composite MACE (major adverse cardiac events which include non-fatal myocardial infarction (MI), non-fatal stroke and cardiovascular death). These were as identified by their appropriate read codes in the THIN database and must have occurred at least 180 days after the intensification of MET+SU with either insulin or GLP-1 analogue. Cases were censored in event of intensification with a fourth-line therapy or final records in the data (transfer out), or at the end of the study.

Covariates:

The study covariates were collected at least 180 days before intensification of metformin. These time-varying covariates included the baseline demographic parameters as age, sex, socioeconomic deprivation and smoking status; clinical measures as body weight, body mass index (BMI) and blood pressure (systolic and diastolic); biochemical parameters as baseline HbA1c, creatinine level, total cholesterol levels, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides; and medications as statins, aspirin, antihypertensive drugs, and oral antidiabetic drugs; comorbidities; the duration of diabetes treatment; and duration of MET+SU dual-therapy before intensification.

Statistical Analyses:

Primary analysis was time to the composite outcome of non-fatal AMI, non-fatal stroke or all-cause death in a propensity score-matched cohort. A propensity score (PS) model was used to adjust for allocation bias and was estimated using a logistic regression model in which the treatment status was regressed on the baseline covariates. We assessed the balance in baseline covariates between the treated (INS) and reference (GLP-1ar) subjects using standardized differences before and after matching. 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 the estimated treatment probabilities; 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, at the nearest distance measured by the estimated propensity score. 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, the absolute reduction in the probability of an event occurring within a 5-year follow-up was calculated. 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 GLP-1 analogue group. Proportional hazards assumptions were confirmed through Schoenfeld residuals test. 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 were accounted for with multiple imputations using the chained equation (MICE) model. All analyses were conducted using Stata Software, version 13.[19]

Subgroup Analyses:

Cox proportional hazard models were fitted to adjust for baseline and time-varying demographics, comorbidities, medications and metabolic indices for those with BMI of 30kg/m^2 and above and 40kg/m^2 in order to explore the impact of obesity in influencing the primary outcomes.

Statistical significance was put at a p-level of 0.05. To avoid the probability of type II error, the study was powered to 0.9 and the sample size of 412 in each treatment group was found to detect a true difference of 0.1 between the two treatment groups at 5% significance level. The study fulfilled the STROBE criteria for reporting observational studies.

Results:

Cases and Total Follow up:

From the THIN database, we identified 2,003 eligible patients in the UK Primary care, whose MET+SU dual-therapy was intensified with the addition of either Insulin (1,584) or GLP-1ar (419). The flow diagram (Figure 1) shows how our cohort was derived. The median treatment duration was 8.33 (IQR: 6.63 to 8.34) years. The median follow up was 3.74 years (IQR: 2.10–4.93) representing a total follow-up period of 6614.12 person-years. The

Patients' Characteristics:

In the full cohort, the overall median age was 53.0 (IQR: 43.0-63.0) years. 50.2% were females. The mean BMI and HbA1c level were 31.8 (7.9)kg/m^2 and 9.7(2.9)% respectively. One-on-one propensity score matching yielded 419 patients each in both treatment arms. The baseline characteristics in both treatment groups were compared between the full and matched cohort of patients with their standardised differences shown in Table 1.

Crude Event Rates:

Survival analyses at 5 years were 95.8% vs 99.3% for insulin and GLP-1ar intensified therapies respectively (Figure 2). Overall, there were 242 composite events with a crude incidence rate of 36.9 per 1,000 person-years (95%CI: 32.3 – 41.5). There were 231 vs 11 composite events in the insulin vs GLP-1ar groups respectively, with unadjusted incidence MACE rates of 44.5 vs 7.7 per 1,000 person-yrs (Table 2). Among the obese population (BMI $\geq$ 30kg/m^2), there were 84 vs 11 composite MACE events, accounting for an unadjusted incidence rates of 38.6 vs 8.1 per 1,000 person-years in patients intensified with insulin vs GLP-1 respectively. Similarly, when stratified for morbid obesity (BMI $\geq$ 40kg/m^2), 30 vs 7 events (29.6 vs 7.1 per 1,000 person-years) occurred (Table 2).

Table 3 shows the components of MACE- mortality, non-fatal MI and stroke. In the insulin vs GLP-1ar treatment groups, there were 151 vs 5; 38 vs 3; and 42 vs 3 events of mortality, MI and stroke respectively. Higher events of all the component outcomes were also reported in the insulin group than in the GLP-1ar groups for all the components.

Risk of Composite Cardiovascular Outcomes and Mortality:

Table 2 shows the comparison of number of composite cardiovascular events, crude incidence rate and hazard ratio between the treatment groups in the propensity score-matched cohort. In the unadjusted model, the risk of composite cardiovascular outcomes was 80% less (HR: 0.20, 95%CI: 0.11-0.37) in patients whose dual therapies were intensified with GLP-1 analogue compared to insulin. Following adjustment for gender, there was a slight reduction to 73% (aHR: 0.27, 95%CI: 0.14–0.53). Similar patterns were shown when stratified for obesity (BMI $\geq$30 kg/m^2) and morbid obesity (BMI $\geq$40 kg/m^2) with the risks being lower in the GLP-1 group (aHR: 0.31, 95%CI: 0.16-0.61 and aHR: 0.31, 95%CI: 0.13-0.75 respectively).

Of all the individual components of MACE, adjusted hazard ratio was only significant for mortality. There was a 71% reduced risk of mortality (aHR: 0.21, 95%CI: 0.08-0.51), similar to that of the composite outcome. The risks of stroke and MI were also 61 and 55% less in the GLP-1ar group compared to insulin. However, this was not significant. This trend was also observed when stratified for obesity and morbid obesity (Table 3).

Changes in HbA1c and Weight:

In figure 3, the trend in changes in HbA1c and weight per year in both treatment groups within the 5-year follow up period is highlighted. There was no statistically significant change in the mean HbA1c levels in both treatment group although reduction in HbA1c was seen more in the insulin group throughout the follow up period (-1.27 vs -1.0%, p=0.117). Conversely, the insulin group recorded more weight gain than the observed weight loss in the GLP-1ar group (1.19 vs -3.35kg, p<0.0001) during the study period.

Sensitivity analyses comparing changes in weight and HbA1c between both treatment groups, using both complete and missing data reported similar trend in both groups; showing that the imputation robustly addressed the missing data.

Discussion:

This study showed that, among patients who are taking MET+SU, intensification of glucose lowering therapy with GLP-1 agonist in routine clinical practice was associated with a significant 73% risk reduction in the risk of adverse composite CV events and mortality compared with intensification with insulin therapy. HbA1c reduction was similar between the two groups but significant difference in weight response was observed between the two groups, i.e. weight gain with insulin and significant weight reduction with GLP-1 agonist.

Many trials comparing GLP-1 with insulin or other comparators including placebo have reported conflicting findings with those with placebo comparators showing CV benefits. Two recent meta-analyses however reported cardiovascular benefits of GLP-1 agonist.[12, 13] A similar recent observational study in a large cohort of 39,225 T2D patients reported a similar reduced risk of heart failure, MI and stroke in three treatment groups comparing exenatide- and exenatide + insulin to insulin only (61/56%, 50/38% and 52/63% respectively).[20] This collaborates with other reports showing the novel pleiotropic cardio-protective effects of GLP-1 agonist have also been described.[21] A further possible explanation for the observed reduction in CV events with GLP-1 compared with insulin in our study could be due to the effects of GLP-1 agonist in reducing hyperglycaemia with limited increased risks of hypoglycaemia, as well as the beneficial effects of GLP-1 agonist in inducing weight loss.[22] Both hypoglycaemia[23] and weight gain[24], which are commonly associated with insulin therapy, are known risk factors for adverse cardiovascular events. While further exploring the possible effect of obesity in our study cohort, we demonstrated a greater reduction of cardiovascular events with GLP-1 compared with insulin therapy in the subgroup of obese (BMI ≥30kgm-2) and morbidly obese (BMI ≥40kgm-2) patients with type 2 diabetes.

The CV safety of insulin is a controversial issue. Despite methodological adjustments, it is hard to exclude in observational studies all the potential bias. In the ORIGIN study, a randomized clinical trial with glargina insulin in a high CV risk population, insulin therapy was not associated with higher CV events. On the other hand, although preclinical studies and some meta-analysis suggest that GLP-1 analogues could have a protective CV effect, the ELIXA study (the only CV randomized clinical trial with a GLP-1 analogue published so far) showed that lixisenatide had a neutral CV effect compared with other antidiabetic therapies.

Our study showed comparable reductions in HbA1c levels in the patients on either GLP-1 or Insulin. Clinical trials[25, 26] involving Exenatide and Liraglutide[27] have reported similar HbA1c reduction compared with insulin. Similarly, among patients on MET+SU, a recent randomized clinical trial reported similar HbA1c reduction between the GLP-1 analogue, Taspoglutide and insulin glargine.[28] Insulin therapy has been known to be associated with weight gain and this was consistent throughout the study period in contrast to GLP-1 which showed consistent decline in weight. The observed increase in body weight following insulin therapy is in conformity with previous studies.[4, 29, 30] Although the baseline BMI in our matched cohort was close to the morbid obesity range, our findings can be generalised to all type 2 diabetes patients because sub-analyses in the obese and morbidly obese subgroups showed very similar findings.

The main strength of our study derives from the inclusion of a large cohort of T2DM patients receiving anti-diabetic medications in a real-world population which is largely representative of the UK population. This implies that our findings will be generalizable to the UK population and other countries that share similar demographics. Being derived from the UK primary care data, our findings mirror common clinical practice in the UK than the results of clinical trials. The large cohort from which the study participants were derived from provides adequate statistical power and also contains information on other time-varying covariates to adjust for possible confounders.

We adjusted for a large set of factors that could have differed at the baseline through propensity score matching. This would have been a major drawback in our study because GLP-1 analogues, being relatively newly introduced, had very fewer patients but more with CV risk factors as obesity, hypertension, hyperlipidaemia and greater weight than insulin. A potential source bias was the inconsistency in the measurement of HbA1c levels according to

guidelines (3-6 monthly). Due to this, many patients had no recordings for weight and HbA1c beyond the baseline. Some residual confounding in our study could be from our inability to measure and adjust for the dosage of the glucose-lowering therapies used in this study as well as the reliability of diabetes duration due to the ongoing issue of identifying incident versus prevalent diabetes. In addition, while there was a trend towards a lower DBP in the GLP-1 group compared to insulin, this difference was not significantly different. Also, the classification of exposure into two broad drug groups could have possibly masked the effects of individual drugs and could have driven our study away or closer to the null hypothesis.

In summary, the evidence from this large cohort study, tracking outcomes in routine clinical practice suggests that intensification of dual oral therapy by adding insulin is associated with a higher risk of CV events, compared to adding a GLP-1ar therapy as the third glucose-lowering agent especially among obese patients with type 2 diabetes. This observation needs to be confirmed in a randomised clinical trial setting.

I.I. and R.D conceived the idea for the study. U.A and J.M drafted the study proposal. I.I sought and obtained THIN Ethical Advisory board's approval. Data analyses were conducted by U.A, J.M and R.M. U.A wrote the first draft. All authors reviewed and contributed to subsequent drafts and approved the final version of the manuscript

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Legend (Tables/Figures)

Table 1: Baseline patient characteristics

Table 2: Comparison of Number of Events, Incidence Rate and Hazard Ratio between the treatment groups in the Propensity Score-Matched Cohort

Table 3: Comparison of Number of Events, Incidence Rate and Hazard Ratio between the treatment groups by the components of MACE

Figure 1: Selection of Study Cohort

Figure 2: Kaplan Meier Survival Analysis Plot for Matched cohort

Figure 3a: Mean Changes in HbA1c

Trend in mean changes in HbA1c level (%) between the treatment groups (Met+SU+Insulin vs Met+SU+GLP-1ar). There was no significant change in both group treatment groups throughout the study period.

Figure 3b: Mean Changes in Weight

Trend in mean changes in weight (Kg) between the treatment groups (Met+SU+Insulin vs Met+SU+GLP-1ar). For all the years of the follow-up duration, the p-values were less than 0.05

Table 1

	Cohort					
	Full			Propensity Matched		
Baseline variable	MET + SU + INS (n = 1584)	MET + SU + GLP-1ar (n = 419)	Std. diff [a]	MET + SU + INS (n = 419)	MET + SU + GLP-1ar (n = 419)	Std. diff [b]
Demographics						
Age (yrs), Mean (SD)	53.8 (14.8)	49.6 (10.5)	- 0.33	49.0 (13.3)	49.6 (10.5)	0.05
Gender, No. (%)						
Male	770 (49.0)	227 (54.0)	0.12	193 (46.1)	227 (54.2)	0.16
Female	814 (51.0)	192 (46.0)	-0.12	226 (53.9)	192 (45.8)	-0.16
Townsend deprivation, No. (%)						
Least deprived	294 (18.6)	78 (18.6)	-0.01	86 (20.5)	78 (18.6)	-0.05
Less	300 (18.9)	84 (20.1)	-0.09	81 (19.3)	84 (20.1)	0.02
Average	333 (21.0)	75 (17.9)	-0.16	70 (16.7)	75 (17.9)	0.03
More	352 (22.2)	98 (23.4)	0.11	109 (26.0)	98 (23.4)	-0.06
Most deprived	305 (19.3)	84 (20.0)	0.17	73 (17.5)	84 (20.0)	0.07
Clinical Parameters, Mean (SD)						
HbA1c (%)	9.9 (2.9)	9.4 (2.0)	-0.13	9.4 (2.3)	9.4 (2.0)	-0.02
BMI (kg/m2)	29.8 (6.70)	39.6 (7.1)	1.28	39.7 (7.5)	39.6 (7.1)	-0.02
Weight (Kg)	84.6 (20.5)	115.4 (23.8)	1.31	114.4 (23.0)	115.4 (23.8)	0.04
SBP (mmHg)	132.6 (17.5)	136.1 (15.0)	0.37	136.8 (16.3)	136.1 (15.0)	-0.05
DBP (mmHg)	79.6 (10.5)	82.6 (10.1)	0.33	83.6 (11.2)	82.6 (10.1)	-0.10*
TC (mmol/l)	5.1 (1.6)	4.8 (1.5)	-0.03	5.0 (1.5)	4.8 (1.5)	-0.11
HDL (mmol/l)	1.2 (0.4)	1.1 (0.3)	-0.34	1.0 (0.3)	1.1 (0.3)	0.07
LDL (mmol/l)	2.8 (1.1)	2.6 (1.1)	-0.08	2.7 (1.0)	2.6 (1.1)	-0.07
Triglyceride (mmol/L)	2.9 (5.8)	3.2 (4.0)	0.10	3.1 (3.0)	3.2 (4.0)	0.01*
Albumin (g/L)	42.0 (4.3)	42.5 (3.7)	0.13	42.7 (3.9)	42.5 (3.7)	-0.06
eGFR (mls/min/1.73m2)	74.1 (19.0)	78.5 (16.2)	0.32	77.6 (16.9)	78.5 (16.2)	0.05
ACR (mg/mol)	4.8 (11.4)	4.0 (8.6)	0.01	4.2 (12.5)	4.0 (8.6)	-0.02
Diabetes duration (yrs)	2.6 (4.6)	2.7 (3.0)	0.19	2.9 (5.6)	2.7 (3.0)	-0.04
Smoking status, No. (%)						
Non-smoker	619 (39.0)	164 (39.2)	0.08	159 (38.0)	164 (39.2)	0.03
Current smoker	435 (27.5)	94 (22.4)	-0.16	86 (20.5)	94 (22.4)	0.05
Ex-smoker	530 (33.5)	161 (38.4)	0.07	174 (41.5)	161 (38.4)	-0.06
BMI Categories, No. (%)						
$\leq 30 kg/m^2$	918 (58.0)	19 (4.5)	-1.30	20 (4.8)	19 (4.5)	-0.01
$30\text{-}34.9 kg/m^2$	354 (22.3)	110 (26.3)	0.07	105 (25.0)	110 (25.3)	0.03
$\geq 35 kg/m^2$	312 (19.7)	290 (69.2)	1.06	294 (70.2)	290 (69.2)	-0.02
Use of Medications, No. (%)						
Aspirin	220 (13.9)	82 (19.6)	0.10	84 (10.1)	82 (19.6)	-0.01*
Antihypertensive	587 (37.1)	212 (50.6)	0.23	201 (48.0)	212 (50.6)	0.05
LLT	608 (38.4)	240 (57.4)	0.28	227 (54.2)	240 (57.3)	0.06
Comorbidities, No. (%) [c]						
Other CHD	38 (2.4)	7 (1.6)	-0.05	3 (0.7)	7 (1.7)	0.09
PAD	29 (1.8)	7 (1.6)	-0.05	5 (1.2)	7 (1.7)	0.04
Heart Failure	31 (2.0)	4 (1.0)	0.03	1 (0.2)	4 (1.0)	0.09
Hypoglycaemia	124 (7.8)	13 (3.1)	-0.01	8 (1.9)	13 (3.1)	0.08

MET (metformin); SU (sulphonylurea); GLP-1 (Glucagon-like peptide 1); 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 (albumin creatinine ratio); SD (standard deviation)

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

[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

[c] Comorbidities: other recorded medical disorders

* In the matched cohort, only Aspirin and Triglyceride had statistically significant standardized difference at 0.01 level

Table 2:

	MET + SU + INS (n = 419)	**MET + SU + GLP-1ar (n = 419)**
Follow-up period (years)	5.19	1.42
Sample population		
Composite outcome (No. of events) [a]	231	11
Incidence Rate (95% CI)[b]	44.5 (39.1-50.6)	7.7 (4.5-14.0)
Unadjusted hazard ratio (95% CI)	1.0 [Reference]	0.20 (0.11-0.37)
Adjusted hazard ratio (95% CI)[c]	1.0 [Reference]	0.27 (0.58-0.97)
Subgroup population		
BMI $\geq$ 30Kg/m^2		
Composite outcome (No. of events) [a]	84	11
Incidence Rate (95% CI)[b]	38.6 (31.2-47.8)	8.1 (4.5–14.6)
Unadjusted hazard ratio (95% CI)	1.0 [Reference]	0.26 (0.14-0.49)
Adjusted hazard ratio (95% CI)[c]	1.0 [Reference]	0.31 (0.16-0.61)
BMI $\geq$ 35Kg/m^2		
Composite outcome (No. of events) [a]	30	7
Incidence Rate (95% CI)[b]	29.6 (20.7 - 42.4)	7.1 (3.4-14.8)
Unadjusted hazard ratio (95% CI)	1.0 [Reference]	0.32 (0.14-0.73)
Adjusted hazard ratio (95% CI)[c]	1.0 [Reference]	0.31 (0.13-0.75)

Abbreviation: MET (metformin); SU (sulphonylurea); GLP-1 (Glucagon-like Peptide analogue); INS (insulin); BMI (body mass index)
[a] Composite outcome includes: non-fatal acute myocardial infarction (AMI), non-fatal stroke or all-cause death
[b] Rates are calculated per 1000 person-years
[c] Adjusted for gender

Table 3

	Mortality		Myocardial Infarction		Stroke	
Met + SU	**INS**	**GLP-1ar**	**INS**	**GLP-1ar**	**INS**	**GLP-1ar**
Sample population						
No. of events	151	5	38	3	42	3
Incidence Rate (95% CI)[a]	31.0 (26.6 – 36.2)	4.2 (1.9 – 9.4)	8.1 (6.0 – 11.0)	2.1 (0.7 – 6.5)	8.9 (6.6 – 11.8)	7.7 (0.7 – 6.5)
Unadjusted hazard ratio (95% CI)	1.0	0.21 (0.09 – 0.52)*	1.0	0.45 (0.12 – 1.67)	1.0	0.39 (0.11 – 1.43)
Adjusted hazard ratio (95% CI)[b]	1.0	0.21 (0.08 – 0.51)*	1.0	0.45 (0.12 – 1.69)	1.0	0.39 (0.10 – 1.44)
Subgroup population						
BMI ≥ 30kg/m^2						
Composite outcome (No. of events)	55	5	17	3	16	3
Incidence Rate (95% CI)[a]	25.3 (19.4 – 32.9)	4.4 (2.0 – 9.8)	7.8 (4.9 – 12.6)	2.2 (0.71 – 6.85)	7.4 (4.5 – 12.0)	2.2 (0.70 – 6.80)
Unadjusted hazard ratio (95% CI)	1.0	0.24 (0.10 – 0.59)*	1.0	0.56 (0.15 – 2.11)	1.0	0.45 (0.12 – 1.70)
Adjusted hazard ratio (95% CI)[b]	1.0	0.24 (0.10 – 0.59)*	1.0	0.57 (0.15 – 2.14)	1.0	0.45 (0.12 - 1.72)
BMI ≥ 40kg/m^2						
Composite outcome (No. of events)	23	5	4	1	5	2
Incidence Rate (95% CI)[a]	22.7 (15.1 – 34.2)	5.0 (2.1 – 12.1)	4.0 (1.5 – 10.5)	1.0 (0.2 – 7.2)	4.9 (2.1 – 11.9)	2.0 (0.50 - 8.10)
Unadjusted hazard ratio (95% CI)	1.0	0.34 (0.12 – 0.94)*	1.0	0.36 (0.04 – 3.65)	1.0	0.50 (0.09 – 2.89)
Adjusted hazard ratio (95% CI)[b]	1.0	0.33 (0.12 – 0.92)*	1.0	0.33 (0.03 – 3.29)	1.0	0.48 (0.8 – 2.8)

Abbreviation: MET (metformin); SU (sulphonylurea); GLP-1ar (Glucagon-like Peptide analogue); INS (insulin); BMI (body mass index)

[a] Incidence rates are calculated per 1,000 person-years

[b] Adjusted for gender; * P-values <0.05