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**Effect of adding GLP-1RA on mortality, cardiovascular events and metabolic outcomes  
among insulin-treated patients with Type 2 Diabetes: A Large Retrospective UK  
Cohort Study**

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## Abstract

**Aim:** Combining a GLP-1 receptor agonist (GLP-1RA) with insulin is often an effective treatment strategy for overweight patients with Type 2 diabetes, but little is known about the longer term effects on cardiovascular and mortality outcomes in routine clinical practice in the UK. We therefore compared the times to a major non-fatal CV event and all-cause mortality among overweight patients with Type 2 diabetes (T2D) treated with insulin alone versus insulin+GLP-1RA in a large UK database.

**Methods:** A retrospective cohort study was conducted in 18,227 patients with insulin-treated T2D from UK General Practices using The Health Improvement Network (THIN) database. The 5-year risk of mortality and a three-point composite of all-cause mortality and non-fatal CV outcomes (MI or stroke) was compared between a propensity score-matched cohort of those on insulin alone (N=1793) and insulin+GLP-1RA (N=1,793), irrespective of other diabetes therapies, providing a total of 12,682 person-yrs of follow up. Cox proportional hazard models were used to estimate the hazard ratios of the outcomes.

**Results:** HbA1c reduction was similar between both groups (-0.42 vs -0.33%,  $p=0.089$  at 12 months). Overall, three-point composite events of all-cause mortality and CV events (MACE) were 98 vs 55 for the insulin alone vs insulin+GLP-1RA groups respectively (14.7 vs 9.2 per 1000 person-yrs; adjusted Hazard Ratio (aHR): 0.64; 95%CI: 0.42-0.98;  $p=0.038$ ). Corresponding composite non-fatal CV events were 33 vs 28 (6.0 vs 5.6 per 1000 person-yrs; aHR: 0.76; 95%CI: 0.41- 1.42;  $p=0.393$ ) while all-cause mortality events were 49 vs 13 (6.9 vs 2.0 per 1000 person-yrs; aHR: 0.35; 95%CI: 0.17- 0.73;  $p=0.005$ )

**Conclusion:** Based on a large UK cohort in routine clinical practice, adding a GLP-1RA to insulin therapy is associated with a reduction in risk of composite CV events and all-cause mortality, but non-significant higher risk of hospitalisation for heart failure in overweight patients with Type 2 diabetes.

## **Key messages**

### **What is already known about this subject?**

The use of insulin therapy 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 (CV) safety of insulin in people with type 2 diabetes. The CV benefit of GLP-1 Receptor Antagonist (GLP-1RA) has recently been reported and combining GLP-1RA with Insulin therapy in overweight patients with Type 2 diabetes is already widely used in routine clinical practice, primarily, to facilitate HbA1c and weight reduction.

### **What does this study add?**

Previous studies (RCT or observational) have not investigated the comparative CV and mortality as well as the real world metabolic (HbA1c and weight) outcome of adding a GLP-1RA to ongoing insulin therapy in overweight patients with Type 2 diabetes. This study showed that adjuvant use of GLP-1RA to insulin therapy is associated with significant reduction in composite of CV events and mortality, and also in all-cause mortality and weight loss compared with no GLP-1 RA.

### **How might this impact on clinical practice**

In overweight people with insulin treated type 2 diabetes who require intensification of glucose lowering therapy due to suboptimal HbA1c levels, the addition of a GLP-1 RA is associated with reductions in composite of CV events and mortality. The use of GLP-1RA in routine practice was associated with a greater weight reduction, but no difference in HbA1c when compared insulin therapy without adding a GLP-1RA.

## **Introduction:**

For many patients with T2D, insulin treatment will be required to control hyperglycaemia and to reduce the risk of long-term vascular complications in patients with type 2 diabetes (T2D). [1-5]. Typically, this will involve the initiation of a basal or a biphasic insulin regimen, with some patients requiring multiple daily insulin injections with basal and prandial insulin.

However, insulin therapy is known to induce ~4-9 kg weight gain in the first year of treatment. [6] Furthermore, recent evidence from randomized controlled trial, epidemiological and observational studies have questioned the long-term cardiovascular (CV) safety of insulin therapy.[7-12]

Conversely, the CV benefits of the Glucagon like peptide-1 analogues (GLP-1RA), a novel injectable glucose lowering therapy, with favourable effects on weight and low risks of hypoglycaemia, are an active area of research (<http://www.clinicaltrials.gov>). Preclinical studies have already demonstrated the pleotropic effects of GLP-1RA on myocardium and vascular endothelium, [13,14] and many clinical studies have reported improvement in surrogate markers of CV disease. [15] More recently, The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial showed that liraglutide, a GLP-1RA, is associated with significant reductions of CV events and death from CV causes. [16]

Thus, since insulin therapy is known to be associated with weight gain and increased risk of hypoglycaemia, adding a GLP-1RA to insulin therapy is an attractive option to lower HbA1c levels in overweight patients with T2D. [17] No comparative 'real world' metabolic outcome data of insulin versus Insulin plus GLPRA is available and further work is required to explore the CV effects of insulin compared with insulin plus GLP-1RA in overweight patients with T2D, who are at an inherent risk of developing CV disease.

The aim of the present study therefore was to determine the real-world composite CV and mortality outcomes in UK clinical practice amongst insulin-treated patients with T2D who received adjunctive treatment with a GLP-1RA, compared with those who did not.

## **Methods:**

### **Study Design and Data Sources:**

A retrospective cohort study was conducted using The Health Improvement Network (THIN) – a UK computerised longitudinal anonymised Primary Care database in which information is systematically entered by Primary Care physicians. With details of over 10.5 million patients from about 532 general practices, it has been validated and shown to be demographically representative of the UK population in terms of demography, major conditions prevalence, and mortality rates. [18,19] It has been validated by many studies and in our previous studies, used extensively to evaluate diabetes-related outcomes in routine clinical practice [20, 21].

### **Study Population:**

We obtained data of all insulin users with T2D from the THIN database who were aged 18 and above, who initiated insulin therapy (as dual, triple or more therapy) between January 2006 and May 2014 and went on to have their insulin therapy intensified with either an add-on of GLP-1RA or not, independent of the use of other GLTs. We excluded participants who commenced GLP-1RA before insulin therapy and those with type1 diabetes. From this main cohort, we excluded all patients with a prior history of CV events (stroke or AMI) before, or within 180 days after, insulin initiation in a subgroup analysis on CV events.

### **Exposures and Outcomes:**

**Exposure:** The main exposure was the initiation of any GLP-1RA or otherwise among insulin users. Insulin regimen can be ultra-short/short acting, premixed or long-acting; while GLP-1RA are exenatide, liraglutide, or lixinatide. The study was exposure-based. Insulin users on dual, triple or more therapies who went on to add GLP-1RA were at that point included and then compared with patients who did not have GLP-1RA as an add on therapy.

From this stage, participants were followed up for a maximum of 5 years, and were censored at the earliest of the following: discontinuation or substitution of GLP-1RA or insulin; loss to follow-up (transfer out of practice); first occurrence of any of the study outcomes; or at the end of the study after 5 years. This implies that if no records of prescriptions of GLP-RA or insulin were found after one year in the electronic records, such medication was considered stopped and the patient censored at this point.

**Outcome:** In the main cohort, the primary outcomes were time to the risk of a three-point composite event of Major Adverse Cardiovascular Event (MACE) which comprises all-cause mortality, non-fatal MI and non-fatal stroke. The time to the risk of two-point composite CV event (non-fatal myocardial infarction (MI) or non-fatal stroke) was estimated in a subgroup of patients from the main cohort, with no prior CV history. These outcomes and their dates of occurrence were identified by their appropriate Read Codes in the THIN database. The secondary outcomes were the mean changes in HbA1c (glycemic control) and weight between both treatment groups from baseline at 6, 12, 24 and 36 months.

### **Covariates:**

Important time-varying clinical baseline covariates were extracted and included in the data. These were fitted in our regression models to adjust for their confounding effects on the study outcome. These include baseline demographic parameters as age, gender, socioeconomic status (measured by the Townsend deprivation scores and ranked in quintiles), alcohol and smoking status and clinical measures like body mass index (BMI), weight, height, systolic (SBP) and diastolic blood pressure (DBP). Also, other important biochemical parameters as baseline HbA1c, lipid-profile, glomerular filtration rate (GFR), creatinine level, albumin-creatinine ratio (ACR), the use of other medications including GLTs; comorbidity status; the duration of diabetes treatment; and insulin use, were included and adjusted for in our analyses.

### **Statistical Analyses:**

We summarised baseline variables within the treatment groups (INS+GLP-1RA vs INS+Non-GLP-1RA) using mean values and standard deviation (SD) for continuous variables; and frequencies (%) for categorical variables (Table 1). We therefore estimated the propensity score (PS) for treatment with GLP-1RA using logistic regression as the conditional probability of being treated with GLP-1RA with the baseline covariates as age, gender, socioeconomic status, alcohol and smoking status, BMI, weight, height, systolic and diastolic blood pressure, HbA1c, lipid-profile, GFR, creatinine level, ACR, the use of other medications, comorbidity status and the duration of diabetes treatment. We matched both treatment groups (GLP-1RA vs Non-GLP-1RA) based on their estimated treatment probabilities, with the average treatment effect on the treated (ATT) computed by 1:1 matching for each group at the nearest distance, measured by the estimated propensity score.

The standardised differences between the treatment groups following adjustment with the PS and all the baseline variables were calculated using linear regression models with their p values

determined. A difference > 10% was considered significant. In the summary table (Table 1) as well, the distribution of the covariates between the treatment groups in the PS matched group was also summarised.

Using the Kaplan-Meier survival estimate, we obtained the crude and adjusted 5-year estimates of survival functions for both treatment groups (INS+GLP-1RA vs INS+Non-GLP-1RA). We calculated the absolute reduction in the probability of the incidence of the outcome within a 5-year follow-up from these survival functions. Also, we estimated the marginal hazard ratios to quantify the adjusted hazard of MACE and the incidence of mortality and CV events in the GLP-1RA group (treated group) compared to the non-GLP-1RA group. Having considered PS a prognostic covariate, it was included in the final Cox proportional hazards regression model. To test for violations of the proportional hazard assumption of the Cox regression analyses by adding an interaction term of the predictor and log time and by analysing the Schoenfeld residuals. We did not observe any violations of the proportional hazard assumption because both were found to be non-significant. We used maximum likelihood estimation to explore if there is any possible interactions between the treatment groups and the baseline variables which were included in the propensity score but found no interactions with any of the covariates.

Finally, we compared glycaemic efficacy (measured by change in HbA1c from baseline at different follow-up timelines) and changes in weight and blood pressure (systolic and diastolic) between the two treatment groups using Student's t-test and linear regression while adjusting for significant baseline covariates. Ethical approval for this study was obtained by The South-East Research Ethics Committee.

### **Subgroup and Sensitivity Analyses:**

We compared the study outcomes between the full data and PS-matched population to compare the confounding effect of selection bias could have on the full cohort. Also, we did further subgroup analyses to estimate the hazards of the components of CV events – non-fatal stroke and MI in patients with no prior history of any CV event. We also estimated the hazard of MACE, all-cause mortality and CV events in the subtypes of GLP-1RA identified in the dataset (liraglutide, exenatide and lixinatide), using the non-GLP-1RA group as the comparator.

Statistical significance was put at a p-level of 0.05 and to avoid the probability of type II error, we powered the study to 0.9 with a minimum sample size of 400 in each arm was estimated to be adequate to detect a true difference of 0.1 between the two treatment groups at 5% significance level. In the regression models and all other analyses, the point estimates were



computed, with 95% confidence intervals (CI), at the conventional statistical significance level of 0.05. We used multiple imputations using the chained equation (MICE) model to account for any missing data among covariates. All analyses were conducted using Stata Software, version 14[22].

**Sources of funding:** No extramural funding was used to support this work.

**Conflict of Interest:** The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

## **Results:**

### **Cases and Total Follow up:**

A total of 18,227 adults with insulin treated T2D whose standard care with insulin was intensified with either GLP-RA (1,943) or not (16,284) were selected from the THIN database. Furthermore, as shown in Figure 1, after propensity-score-matching in both cohorts, the total population was reduced to 3,586 (N= 1793 in each arm) in the main cohort. The mean follow up duration was 3.2 (SD: 3.07) years), representing a total follow-up period of 12,681.9 person-years.

### **Patients' Characteristics:**

Table 1 is a summary of the distribution of the baseline characteristics of the study participants between the treatment groups in the full and matched cohorts respectively. The overall mean age was 62.7 (13.8) years. A slightly higher proportion (53.2%) was composed of males while the mean baseline HbA1c level was 8.6 (1.8) %. Furthermore, the overall baseline weight and BMI were 90.8 (18.7) kg and 32.4(6.9) kg/m<sup>2</sup> respectively.

Significant differences in the distribution of the baseline variables between the treatment groups in the full cohort were observed. These were in baseline HbA1c, BMI, weight, diabetes duration, current alcohol-intake, among others which were higher in the GLP-1RA group, while age and SBP were significantly higher in the non-GLP-1RA group. Following one-on-one propensity score matching, 1,793 patients were matched to each other in both treatment groups and no differences in baseline variables were noted. Table 1 shows the distribution of the baseline variables between both treatment groups with these baseline compared between the full and matched cohort of patients, with their standardised differences shown.

### **Crude Event Rates:**

**Composite Outcome (MACE):** The probability of survival for a three-point composite MACE was similar (99%) in both treatment groups after one year, but was significantly reduced at 5 years to 96% and 93% in the GLP-1RA and non-GLP-1RA groups respectively (log-rank test p-value = 0.0055). The unadjusted crude incidence rate was 12.1 per 1,000 person-years (9.1 vs 14.7) signifying a total of 153 events (55 vs 98) in the GLP-1RA vs non-GLP-1RA groups respectively (Table 2).

**Mortality:** Also in the main cohort, the probability of survival was 100% in both treatment groups after one year, but at the end of the 5-year follow-up period, this was significantly reduced to 98% and 96% in the GLP-1RA and non-GLP-1RA groups respectively (log-rank test p-value = 0.0001) (Figure 2). There was a total of 62 (13 vs 49) mortality events with a crude incidence rate of 4.6 (2.0 vs 6.9) per 1,000 person-years in the GLP-1RA vs non-GLP-1RA groups respectively. These are summarised in Table 2.

**Cardiovascular events:** Among the 2,820 matched participants in the subgroup with no prior history of CV events, the probability of survival for the two-point cardiovascular event of non-fatal MI and stroke fell from 99.5% and 99.3% after one year in the GLP-1RA vs non-GLP-1RA groups respectively to 97% in both groups at 5 years (log-rank test p-value = 0.7880). Additionally, there was a total 61 CV events, with an unadjusted crude incidence rate of 5.8 per 1,000 person-years with 28 and 33 events in the GLP-1RA vs Non-GLP-1RA groups respectively (crude incidence rates: 5.6 vs 6.0 per 1,000 person-years).

In the subgroup analysis for non-fatal MI, there were 7 events (3 vs 4 events in the GLP-1RA vs non-GLP-1RA groups respectively (crude incidence rates: 0.6 vs 0.7 per 1,000 person years), while Similarly, a total of 25 vs 29 non-fatal stroke events was reported, signifying an unadjusted crude incidence rate of 5.0 vs 5.2 per 1,000 person-years (Table 2).

### **Risk of MACE, All-cause mortality and Composite Cardiovascular Outcomes**

The summary of the hazard of MACE, all-cause mortality and CV events between the treatment groups is presented in Table 2. The unadjusted risk of MACE was 37% less (HR: 0.63, 95%CI: 0.45 – 0.86) in the GLP-1RA treatment group compared to the non-GLP-1RA group. Following adjustment for age, duration of diabetes and insulin use, gender, socioeconomic stats, alcohol use, eGFR, lipid profile, and events of hypoglycaemia, this slightly reduced to 36% (aHR: 0.64,

95%CI: 0.42 – 0.98). Similarly, the risk of all-cause mortality was 65% less (HR: 0.35, 95%CI: 0.17 – 0.73) in the GLP-1RA group, following adjustment.

Compared to the non-GLP-1RA group, the risk of composite cardiovascular outcomes was 24% less (aHR: 0.76, 95%CI: 0.41 – 1.42) in patients whose insulin therapy was intensified with GLP-1RA. . Specifically, the risks of non-fatal MI and stroke were 38% and 7% non-significantly lower in the GLP-1RA group compared to the non-GLP-1RA group after adjustment for significant confounders (Table 2).

### **Glycaemic Control (Change in HbA1c) and Change in Weight.**

Both treatment groups showed a significant reduction in HbA1c throughout the study period, but there was no significant difference between the groups at any of the study timelines (-0.32% vs -0.39%,  $p = 0.08$  at 6 months; and -0.34% vs -0.41%,  $p = 0.33$  at 36 months).

Conversely, there were significant increases in weight in both treatment groups in the first 6 months, up to 12 months in the non-GLP-1RA group. From 12 in the GLP-1-RA group, and 24 to 36 months in both groups, there were significant reductions in weight (Figure 3). Between both treatment groups, there were significant differences of -0.37kg and -0.57kg in the mean weight recorded at 6 and 12 months respectively. However, beyond 12 months, no significant differences in changes in weight were observed between the groups: -0.17kg vs -0.55kg (mean diff: -0.38kg;  $p = 0.325$ ) at 24 months and -0.99kg vs -0.85kg (mean diff: -0.13kg;  $p = 0.768$ ) at 36 months in the non-GLP-1RA vs GLP1-RA groups respectively.,

### **Subgroup and Sensitivity analyses:**

Table 3 shows the risk of composite MACE, all-cause mortality and CV events in the different GLP-1RA subtypes – liraglutide, exenatide and lixinatide. Compared to the insulin users who had no GLP-1RA add-on, the risk of MACE was 47% (aHR: 0.53; 95%CI: 0.32 – 0.89) and 19% (aHR: 0.81; 95%CI: 0.50 – 1.31) less in liraglutide and exenatide respectively, while no event was recorded for lixinatide. Similarly, all-cause mortality was 83% (aHR: 0.17; 95%CI: 0.06 – 0.47) and 51% less (aHR: 0.49; 95%CI: 0.24 – 0.99) with no event for lixinatide. No difference was observed between the drug subtypes on CV events.

Another sensitivity was conducted to explore the association between the intensification of insulin therapy with GLP-1RA vs none on hospitalisations for heart failure. There were 70

events of heart failure recorded (34 vs 36 events for the insulin alone vs insulin+GLP-1RA groups respectively (3.7 vs 4.4 per 1000 person-yrs; aHR: 1.22; 95%CI: 0.76-1.94; p=0.415) (Table 2). When stratified by the different subtypes of GLP-1RA, there were 15, 20 and 1 events of heart failure in exenatide, liraglutide and lixisenatide respectively; giving a crude incidence rate of 4.5 vs 4.4 vs 5.7 per 1000 person-yrs. The risks of hospitalisation for heart failure were 22%, 20% and 66% non-significantly higher in exenatide, liraglutide and lixisenatide respectively compared to none use of GLP-1RA (Table 3).

Further sensitivity analyses to compare the risks of the study outcomes in the full and matched cohorts showed no difference in the magnitudes of the effect sizes. Also, we compared the differences in change in HbA1c between both treatment groups, using both complete and missing data and reported similar trend in both groups. This affirmed that the imputation robustly addressed the missing data.

## **Discussion:**

This study showed that, among overweight patients with insulin-treated T2D in routine clinical practice, adding a GLP-1RA was associated with a significant 36% risk reduction in a three-point composite of all-cause mortality, non-fatal MI and stroke; a 65% reduction in all-cause mortality and a non-significant 24% reduction in CV events, compared with no adjunctive GLP-1RA treatment. HbA1c reduction was similar between the two groups while the use of GLP-1RA with insulin was associated with significant weight reduction compared with none.

Our findings were similar in pattern with that major clinical trials as SUSTAIN-6 [23] and LEADER.[16] In the LEADER trial, liraglutide (a GLP-1RA) was compared to placebo, A similar but smaller (13% and 15%) reductions in the risk of composite outcomes and all-cause mortality respectively, was observed. These were replicated too in the SUSTAIN-6 trial. As shown in our study, the risks of non-fatal myocardial infarction, and nonfatal stroke were non-significantly lower as shown in these trials, but we reported a non-significant higher risk of hospitalization for heart failure in the GLP-1RA group which was persisted for each type of GLP-1RA.

Evidence from RCT have shown that the complementary mechanism of actions of GLP-1RA and insulin therapy offers a unique advantage to patients with T2D, and is associated with

significant reduction in HbA1c (mean ~0.8%), fasting and postprandial glucose, lower risk of hypoglycaemia, prevention of weight gain and concurrent reduction of insulin doses[24-27].

It is conceivable that the weight reduction from GLP-1RA may be partly responsible for an increased effect of exogenous insulin delivered by insulin injections in study participants. However, the discrepancies in the HbA1c reduction observed in RCT following the addition of GLP-1RA to insulin therapy, compared with our neutral effect on HbA1c levels from real world practice may reflect 'real life' patients fear of hypoglycaemia and weight gain, as well as the complexities of insulin dose reduction when adding a GLP-1RA to ongoing insulin therapy. Of note, most RCT have employed a treat to target design, where insulin doses were optimized by investigators simultaneous to adding a GLP-1RA. A previous study comparing the results from RCT and real world studies on the efficacy of vildagliptin versus sulfonylureas, for example, showed that the decrease in HbA1c from baseline with sulfonylurea treatment is smaller in real life than in RCTs, whereas the reduction with vildagliptin is essentially the same, suggesting that the full power of treatment is retained in real life for vildagliptin but not for sulfonylureas, possibly due to fear of hypoglycaemia [28].

Our observation of reduced composite of CV events and all-cause mortality of adding a GLP-1RA to insulin therapy, independent of HbA1c reduction supports novel pleiotropic cardio-protective effects of GLP-1 agonist, which have been previously described.[13,14] A further possible explanation for the observed reduction in the composite events with GLP-1RA could be due to the reduced risks of hypoglycaemia as well as the beneficial effects of GLP-1 agonist in inducing weight loss – both via the addition of a GLP-1RA and concurrent reductions in insulin doses.[17] Both hypoglycaemia[29] and weight gain[30] , which are commonly associated with insulin therapy, are known risk factors for adverse CV events and mortality.

Insulin therapy has been known to induce weight gain. In contrast to evidence from RCT, where weight loss of between 0.4-1.8kg was observed in the first 24-30 weeks of adding a GLP-1RA to insulin therapy, significant weight loss was only observed after 12 months of adding a GLP-1RA in routine clinical practice. At 24 months of follow up however, we observed a non-significant weight loss of -0.55kg with adjuvant GLP-1RA compared with -0.17kg without a GLP-1RA. The delay in weight response in this observational study may reflect in a delay in down-titration of insulin doses in routine clinical practice due to the lack of regular follow up or a rigid treat-to-target treatment protocol. Of note, the baseline weight of our cohort is

comparable to that from RCT. The observed increase in body weight with insulin therapy (without adjuvant GLP-1RA) however is in conformity with previous studies.[24-27]

The main strength of our study derives from the inclusion of a large cohort of T2DM patients receiving insulin therapy in a real-world population which is largely representative of the UK population. This implies that our findings will be generalizable to various population that share similar demographics. The large cohort of patients studied here 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 is crucial since the decision to add a GLP-1RA in routine clinical practice is often based on the fact that patients are overweight as per UK NICE guidelines[31], also confirmed by this study in Table 1 (where baseline weight in the full cohort (before matching) was significantly greater in the GLP-1RA group (96.6kg vs 90.6kg;  $p < 0.0001$ )). Nevertheless, some residual confounding in our study could persist due to our inability to measure and adjust for the dosage of the insulin therapy as well as the reliability of diabetes duration due to the ongoing issue of identifying incident versus prevalent diabetes. 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. Finally, the low outcomes recorded in the subgroup analysis could be a reflection of poor recording or coding of these outcomes in the dataset, while there was no validated data on the specific causes of mortality in the dataset.

In summary, the evidence from this large cohort study, tracking outcomes in routine clinical practice suggests that adding a GLP-1RA as an adjunct to insulin therapy in overweight patients with T2D is associated with a significant reduction in a composite of all-cause mortality and CV events (MACE) and all-cause mortality, and a non-significant higher risk of hospitalisation for heart failure compared with not adding a GLP-1RA therapy. The mechanism for this cardio-protective effects remained speculative but further study in a randomised clinical trial setting is required to confirm this observation.

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## Legend

### Tables

Table 1 – Baseline characteristics in the full and propensity-matched cohorts

Table 2: Events, Crude Incidence Rates and Hazard Ratios of MACE, all-cause mortality and cardiovascular events in the two treatment groups.

Table 3: Subgroup analysis for events, crude incidence rates and hazard ratios of MACE, all-cause mortality and cardiovascular events in the GLP-1RA subtypes.

### Figures:

Figure 1 - Selection of study cohort

Figure 2 - Kaplan-Meier curves showing the 5-year probability of survival for [A]. Three-point composite of all-cause mortality, non-fatal MI and stroke (MACE) between INS +/- GLP1-RA treatment groups. Log-rank test p-value = 0.0055. [B] All-cause mortality between INS +/- GLP1-RA treatment groups. Log-rank test p-value = 0.0001. [C] Two-point composite of CV events (non-fatal MI and stroke) between INS +/- GLP1-RA treatment groups. Log-rank test p-value = 0.829

Figure 3A - Comparison of glycaemic efficacy (measured by change in HbA1c) in INS+GLP-1RA vs INS+non-GLP1-RA treatment groups throughout the study duration. (*md* = mean difference, *p* = p-value)

Figure 3B- Comparison of changes in weight in INS+GLP-1RA vs INS+non-GLP1-RA treatment groups throughout the study duration. (*md* = mean difference, *p* = p-value)

Figure 3C - Comparison of changes in systolic blood pressure in INS+GLP-1RA vs INS+non-GLP1-RA treatment groups throughout the study duration. (*md* = mean difference, *p* = p-value)

Figure 3D- Comparison of changes in diastolic blood pressure in INS+GLP-1RA vs INS+non-GLP1-RA treatment groups throughout the study duration. (*md* = mean difference, *p* = p-value)

Table 1: Baseline characteristics in the full and propensity-matched cohorts

Baseline variables	Cohort					
	Full			Propensity Matched		
	INS + Others (n = 16,284)	INS+GLP-1RA (n = 1,943)	Std diff	INS + Others (n = 1,793)	INS+GLP-1RA (n = 1,793)	Std diff
<b>Demographics</b>						
Age (yrs), Mean (SD)	62.4 (13.6)	54.6 (11.7)	0.048	54.9 (12.9)	54.9 (11.5)	0.007
Gender, No. (%)						
Male	8683 (53.0)	1012 (52.0)	0.015	990 (55.0)	937 (52.0)	0.010
Female	7601 (47.0)	931 (48.0)	-0.015	803 (45.0)	856 (48.0)	-0.010
Townsend dep, No. (%)						
Least deprived	3219 (20.1)	368 (20.0)	0.054	373 (21.0)	349 (19.0)	0.035
2nd quintile	3139 (20.0)	358 (19.1)	0.035	342 (19.0)	343 (19.0)	0.020
3rd quintile	3302 (21.9)	428 (22.9)	-0.020	427 (24.0)	406 (23.0)	-0.023
4th quintile	3353 (22.0)	410 (22.0)	-0.026	375 (21.0)	392 (22.0)	-0.010
Most deprived	2543 (16.0)	316 (16.0)	-0.046	276 (15.0)	303 (17.0)	-0.023
<b>Clinical Parameters, Mean (SD)</b>						
HbA1c (%)	8.6 (1.8)	8.9 (1.9)	-0.014	8.9 (1.8)	8.9 (1.9)	-0.007
BMI (kg/m <sup>2</sup> )	32.3 (6.8)	33.9 (7.3)	0.016	33.5 (7.1)	33.8 (7.3)	-0.008
Weight (Kg)	90.6 (18.5)	96.6 (19.8)	0.069	96.1 (19.6)	96.5 (19.7)	-0.018
Height (m)	1.7 (0.1)	1.7 (0.1)	0.069	1.7 (0.1)	1.7 (0.1)	-0.013
SBP (mmHg)	136.5 (23.1)	135.0 (22.9)	0.004	134.7 (22.6)	134.9 (23.0)	-0.012
DBP (mmHg)	75.8 (10.9)	77.5 (10.4)	0.084	77.9 (11.1)	77.5 (10.5)	-0.002
TC (mmol/l)	4.5 (1.3)	4.6 (1.2)	0.009	4.6 (1.3)	4.6 (1.2)	0.001
HDL (mmol/l)	1.2 (0.4)	1.2 (0.4)	-0.061	1.2 (0.4)	1.2 (0.4)	0.021
LDL (mmol/l)	2.4 (1.1)	2.4 (1.1)	0.027	2.4 (1.1)	2.4 (1.1)	0.009
Triglyceride (mmol/L)	2.0 (1.2)	2.1 (1.2)	0.019	2.1 (1.2)	2.1 (1.2)	-0.023
Albumin (g/L)	4.0 (0.4)	4.1 (0.4)	0.004	4.1 (0.5)	4.1 (0.4)	0.003
eGFR (mls/min/1.73m <sup>2</sup> )	62.2 (21.3)	68.2 (20.0)	0.056	66.8 (21.6)	68.0 (19.8)	0.003
ACR (mg/mol)	5.8 (8.5)	5.7 (8.3)	0.014	6.0 (8.4)	5.7 (8.4)	-0.009
Diabetes duration (yrs)	4.2 (4.9)	4.9 (4.5)	0.262	4.9 (4.8)	5.0 (4.5)	0.013
Smoking status, No. (%)						
Non-smoker	7916 (49.0)	945 (49.0)	-0.034	849 (47.0)	865 (48.0)	-0.021
Current smoker	2358 (14.0)	267 (14.0)	0.009	267 (15.0)	242 (13.0)	0.002
Ex-smoker	6010 (37.0)	731 (38.0)	0.035	677 (38.0)	686 (38.0)	0.027
Alcohol status, No. (%)						
Non-drinker	6183 (38.0)	623 (32.1)	-0.030	569 (32.0)	568 (32.0)	-0.051
Current drinker	9061 (56.0)	1182 (61.2)	-0.092	1117 (62.0)	1096 (61.0)	0.054
Ex-drinker	1040 (6.0)	138 (6.7)	0.097	107 (6.0)	129 (7.0)	-0.019
BMI Categories, No. (%)						
≤ 24.9kg/m <sup>2</sup>	2248 (14.0)	207 (11.0)	0.004	193 (11.0)	191 (11.0)	-0.006
25-29.9kg/m <sup>2</sup>	3975 (24.0)	368 (19.0)	-0.006	373 (21.0)	342 (19.0)	0.004
≥ 30kg/m <sup>2</sup>	10061 (62.0)	1368 (70.0)	0.003	1227 (68.0)	1260 (70.0)	0.001
<b>Other GLTs, No. (%)</b>						
Metformin	13670 (84.2)	1923 (99.0)	0.058	1738 (97.2)	1773 (99.1)	-0.038
Sulphonylurea	12191 (75.1)	1603 (83.4)	0.041	1472 (82.0)	1485 (83.0)	0.081
Thiazolidinedione	4646 (29.3)	1108 (57.6)	0.180	699 (39.0)	1030 (57.0)	0.062
SGLT2	39 (0.5)	46 (2.1)	0.001	5 (0.3)	42 (2.0)	-0.002
Glinides	657 (4.9)	133 (7.9)	0.050	103 (6.0)	125 (7.0)	0.032
DPP4	1900 (12.1)	669 (34.2)	0.256	292 (16.0)	620 (35.4)	0.187*
<b>Use of Medications, No. (%)</b>						
Aspirin	14596 (90.1)	1911 (99.8)	-0.007	1723 (99.6)	1723 (99.6)	-0.008
Antihypertensive	14223 (91)	1713 (90)	-0.030	1608 (90.0)	1608 (90.0)	-0.036
LLT	14156 (91.7)	1820 (95.5)	-0.059	1717 (96.0)	1708 (95.0)	0.015
<b>Comorbidities, No. (%)<sup>c</sup></b>						
CHD	5062 (31.0)	398 (20.0)	-0.213*	361 (20.0)	367 (20.0)	-0.147
PAD	2259 (14.1)	149 (8.2)	-0.148*	144 (8.0)	133 (7.0)	-0.105*
Heart Failure	2324 (14.8)	133 (7.5)	-0.151*	110 (6.0)	120 (7.0)	0.001

Hypoglycaemia	2995 (18.2)	190 (10.1)	-0.239*	156 (9.0)	169 (9.0)	-0.036
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GLP-1RA (Glucagon-like peptide 1 receptor agonist); INS (insulin); SGLT2 (Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors); DPP4 (Dipeptidyl peptidase-4 (DPP-4) inhibitors); 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 insulin (index date)

<sup>a</sup> Standardized differences are the absolute difference in means or percentage divided by the standard deviation of the treated group

<sup>b</sup> Resulting standardized difference after 1:1 matching based on average treatment effect on treated (ATT) propensity score technique and robust variance estimation

\* In the matched cohort, only DPP4 and PAD had statistically significant standardized difference at 0.10 level

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Table 2

	<b>INS + Non-GLP-1RA</b>	<b>INS + GLP-1RA</b>	<b>Total</b>
<b>Population</b>	1,793	1,793	3,586
<b>Composite Outcomes*</b>			
No. of events	98	55	153
Crude Incidence Rate (95% CI) <sup>a</sup>	14.7 (12.0 – 17.9)	9.2 (7.0 – 11.9)	12.1 (10.3 – 14.1)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.63 (0.45 – 0.86)	-
Adjusted Hazard Ratio (95% CI) <sup>b</sup>	1.0 [Ref]	0.64 (0.42 – 0.98)	-
<b>All-cause Mortality</b>			
No. of events	49	13	62
Crude Mortality Rate (95% CI)	6.9 (5.2 – 9.1)	2.0 (1.2 – 3.5)	4.6 (3.6 – 5.9)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.30 (0.16 – 0.56)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.35 (0.17 – 0.73)	-
<b>Population**</b>	1,410	1,410	2,820
<b>Composite Cardiovascular events***</b>			
No. of events/population	33	28	61
Crude Incidence Rate (95% CI)	6.0 (4.2 – 8.4)	5.6 (3.8 – 8.0)	5.8 (4.5 – 7.4)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.93 (0.56 – 1.54)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.76 (0.41 – 1.42)	-
<b>Acute Myocardial infarction (MI)</b>			
No. of events	4	3	7
Crude Incidence Rate (95% CI)	0.7 (0.3 – 1.9)	0.6 (0.2 – 1.8)	0.7 (0.3 – 1.4)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.87 (0.19 – 3.88)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.62 (0.06 – 6.53)	-
<b>Non-fatal Stroke</b>			
No. of events	29	25	54
Crude Incidence Rate (95% CI) <sup>a</sup>	5.2 (3.6 – 7.5)	5.0 (3.4 – 7.3)	5.1 (3.9 – 6.7)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.94 (0.55 – 1.61)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	0.93 (0.54 – 1.61)	-
<b>Heart Failure</b>			
No. of events	34	36	70
Crude Incidence Rate (95% CI) <sup>a</sup>	3.7 (2.6 – 5.2)	4.4 (3.2 – 6.2)	4.1 (3.2 – 5.2)
Unadjusted Hazard Ratio (95% CI)	1.0 [Ref]	1.21 (0.76 – 1.93)	-
Adjusted Hazard Ratio (95% CI)	1.0 [Ref]	1.22 (0.76 – 1.94)	-

Abbreviation: GLP-1RA (Glucagon-like Peptide analogue receptor); INS (insulin); CI (Confidence Interval)

\* MACE includes a composite of all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke

\*\* This population excludes patients with prior history of CV events (as defined below) at insulin initiation

\*\*\* Composite cardiovascular events include non-fatal AMI and non-fatal stroke

<sup>a</sup> Crude incidence rates are calculated per 1,000 person-years

<sup>b</sup> Adjusted for age, duration of diabetes, duration of insulin use, gender, Townsend deprivation score, alcohol, albumin, Lipid profile, medication (Lipid-lowering therapy, antihypertensives), eGFR (glomerular filtration rate), events of hypoglycaemia, and number of glucose-lowering therapies.

Table 3: Subgroup analysis for events, crude incidence rates and hazard ratios of MACE, all-cause mortality and cardiovascular events in the GLP-1RA subtypes

	<b>None</b>	<b>Exenatide</b>	<b>Liraglutide</b>	<b>Lixinatide</b>	<b>Total</b>
<b>Population</b>	<b>1,793</b>	<b>751</b>	<b>1008</b>	<b>34</b>	<b>3,586</b>
<b>Composite Outcomes (MACE)*</b>					
No. of events/person-time	<b>98/6674</b>	<b>30/2552</b>	<b>25/3340</b>	<b>0/116</b>	<b>153/12682</b>
Crude Incidence Rate (95% CI) <sup>a</sup>	<b>14.7 (12.0 – 17.9)</b>	<b>11.8 (8.2 – 16.8)</b>	<b>7.5 (5.1 – 11.1)</b>	-	<b>12.1 (10.3 – 14.1)</b>
Adjusted Hazard Ratio (95% CI) <sup>b</sup>	<b>1.0 [Ref]</b>	<b>0.81 (0.50 – 1.31)</b>	<b>0.53 (0.32 – 0.89)</b>	-	-
<b>All-cause Mortality</b>					
No. of events/person-time	<b>49 / 7125</b>	<b>9/2757</b>	<b>4/3561</b>	<b>0/118</b>	<b>62/13561</b>
Crude Mortality Rate (95% CI)	<b>6.9 (5.2 – 9.1)</b>	<b>3.3 (1.70 – 6.3)</b>	<b>1.1 (0.42 – 3.0)</b>	-	<b>4.6 (3.6 – 5.9)</b>
Adjusted Hazard Ratio (95% CI)	<b>1.0 [Ref]</b>	<b>0.49 (0.24 – 0.99)</b>	<b>0.17 (0.06 – 0.47)</b>	-	-
<b>Population**</b>	<b>1,410</b>	<b>576</b>	<b>806</b>	<b>28</b>	<b>2,820</b>
<b>Composite Cardiovascular events***</b>					
No. of events/person-time	<b>33/5541</b>	<b>16/2093</b>	<b>12/2840</b>	<b>0/107</b>	<b>61</b>
Crude Incidence Rate (95% CI)	<b>5.5 (4.2 – 8.4)</b>	<b>7.6 (4.7 – 12.5)</b>	<b>4.2 (2.4 – 7.4)</b>	-	<b>5.8 (4.5 – 7.4)</b>
Adjusted Hazard Ratio (95% CI)	<b>1.0 [Ref]</b>	<b>0.75 (0.36 – 1.56)</b>	<b>0.48 (0.22 – 1.04)</b>	-	-
<b>Acute Myocardial infarction (MI)</b>					
No. of events/person-time	<b>4/5612</b>	<b>1/2127</b>	<b>2/2863</b>	<b>0/108</b>	<b>7</b>
Crude Incidence Rate (95% CI)	<b>0.7 (0.3 – 1.9)</b>	<b>0.5 (0.1 – 3.3)</b>	<b>0.7 (0.2 - 2.8)</b>	-	<b>0.7 (0.3 – 1.4)</b>
Adjusted Hazard Ratio (95% CI)	<b>1.0 [Ref]</b>	<b>0.44 (0.05 – 4.01)</b>	<b>0.71 (0.13 – 3.91)</b>	-	-
<b>Non-fatal Stroke</b>					
No. of events/person-time	<b>29/5550</b>	<b>15/2094</b>	<b>10/2841</b>	<b>0/107</b>	<b>54</b>
Crude Incidence Rate (95% CI) <sup>a</sup>	<b>5.2 (3.6 – 7.5)</b>	<b>7.2 (4.3 – 11.9)</b>	<b>3.5 (1.9 – 6.5)</b>	-	<b>5.1 (3.9 – 6.7)</b>
Adjusted Hazard Ratio (95% CI)	<b>1.0 [Ref]</b>	<b>1.33 (0.72 – 2.49)</b>	<b>0.64 (0.31 – 1.32)</b>	-	-
<b>Heart Failure</b>					
No. of events/person-time	<b>34/9087</b>	<b>15/3341</b>	<b>20/4535</b>	<b>1/176</b>	<b>70/17140</b>
Crude Incidence Rate (95% CI)	<b>3.7 (2.7 – 5.2)</b>	<b>4.5 (2.7 – 7.4)</b>	<b>4.4 (2.8 – 6.8)</b>	<b>5.7 (0.80 – 40.4)</b>	<b>4.1 (3.2 – 5.2)</b>
Adjusted Hazard Ratio (95% CI)	<b>1.0 [Ref]</b>	<b>1.22 (0.66 – 2.24)</b>	<b>1.20 (0.69 – 2.08)</b>	<b>1.66 (0.23 – 12.13)</b>	-

\* MACE includes a composite of all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke

\*\* This population excludes patients with prior history of CV events (as defined below) at insulin initiation

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\*\*\* Composite cardiovascular events include non-fatal AMI and non-fatal stroke

<sup>a</sup> Crude incidence rates are calculated per 1,000 person-years

<sup>b</sup> Adjusted for age, duration of diabetes, duration of insulin use, gender, Townsend deprivation score, alcohol, albumin, Lipid profile, medication (Lipid-lowering therapy, antihypertensives), eGFR (glomerular filtration rate), events of hypoglycaemia, and number of glucose-lowering therapies.

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