DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

# Addition or Switch to Insulin Therapy in People Treated with GLP-1 Receptor Agonists: A Real World Study in 66,583 Patients



| | |
|---|---|
| Journal: | *Diabetes, Obesity and Metabolism* |
| Manuscript ID | DOM-16-0402-OP.R2 |
| Manuscript Type: | Original Paper |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | Montvida, Olga; QIMR Berghofer Medical Research Institute<br>Klein, Kerenaftali; QIMR Berghofer Medical Research Institute<br>Kumar, Sudhesh; Warwick Medical School,<br>Khunti, Kamlesh; University of Leicester, Health Sciences<br>Paul, Sanjoy; QIMR Berghofer Medical research Institute, Clinical Trials & Biostatistics Unit |
| Key Words: | GLP-1 analogue, insulin therapy, pharmaco-epidemiology, type 2 diabetes |
| | |

**Title**: Addition or Switch to Insulin Therapy in People Treated with GLP-1 Receptor Agonists: A Real World Study in 66,583 Patients

**Short Title:** GLP-1 Receptor Agonists with or without Insulin

Olga Montvida, MSc[1,2]; Kerenaftali Klein, PhD[1]; Sudhesh Kumar, MD[3]; Kamlesh Khunti[4], PhD; Sanjoy K Paul, PhD[1]

[1]Clinical Trials and Biostatistics Unit, QIMR Berghofer Medical Research Institute, Brisbane, Australia

[2]School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia

[3]Warwick Medical School, University of Warwick, and University Hospitals Coventry and Warwickshire, United Kingdom

[4] Diabetes Research Centre, Leicester Diabetes Centre, University of Leicester, United Kingdom

Corresponding Author and person to whom reprint requests should be addressed:

Professor Sanjoy Ketan Paul

Clinical Trials and Biostatistics Unit,

QIMR Berghofer Medical Research Institute,

300 Herston Road, Herston, QLD 4006, Brisbane, Australia

Email: Sanjoy.Paul@qimrberghofer.edu.au

Phone: +61 7 3845 3020

Fax: +61 7 3845 3503

**Word Count, Abstract: 24~~50~~**
**Word Count, Main Body: ~~2852~~3011**
**Number of Tables: 4**
**Number of Figures: 1**
**Number of References: 2~~7~~8**
**Number of Supplementary Tables: 1**

**Abstract**

**Aims**

To ~~evaluate~~ evaluate the benefits of adding insulin therapy, or switching to insulin,~~real-world outcomes~~ in type 2 diabetes (T2DM) patients treated with Glucagon-like peptide-1 Receptor Agonist (GLP-1RA) with inadequately controlled hyperglycaemia. ~~of adding or switching to insulin therapy in patients with type 2 diabetes (T2DM) with inadequately controlled hyperglycaemia treated with Glucagon like peptide 1 Receptor Agonist (GLP-1RA)patients who failed to control HbA1cwith sub-optimal control of hyperglycaemia with Glucagon like peptide 1 Receptor Agonist (GLP-1RA) treatment.~~

**Materials and Methods**

T2DM patients (n=66,583) with minimum 6 months of GLP-1RA treatment, without previous insulin treatment were selected. Those who added insulin (n=39,599) ~~and those~~or switched to insulin upon GLP-1RA cessation (n=4,706) were identified. Adjusted changes in HbA1c, weight, systolic blood pressure (SBP), and LDL-C were estimated over 24 months' follow-up.

**Results**

Among those who continued with GLP-1RA treatment without adding or switching to insulin, the highest adjusted mean HbA1c change was achieved within six months, with no further glycaemic benefits observed during 24 months follow-up. ~~at 12 months.~~ ~~Patients who did not added/ or switched to insulin, reduced HbA1c by 0.73% (from the baseline 8.2%) at 6 months, with no further glycaemic benefits during 24 months follow-up. Addition/switch to insulin therapy occurred at median 3/14 months of follow-up at mean HbA1c of 8.8/9.3%.~~ Add~~ing~~ition of insulin within 6 months of GLP-1RA initiation was associated with 18%

higher odds to achieve HbA1c<7% at 24 months, compared to adding insulin later. At 24 months, those who added insulin reduced HbA1c significantly by 0.55%, while no glycaemic benefit was observed in those who ~~moving~~ switch~~ing~~ed to insulin ~~did not yield any glycaemic benefit~~. Irrespective of intensification with insulin, weight, SBP, and LDL-C were significantly reduced by 3 kg, 3 mmHg, and 0.2 mmol/L, respectively, over 24 months.

**Conclusions**

Significant delay in ~~intensifying~~ intensification of treatment by addition of ~~GLP-1RA treatment with~~ insulin ~~was~~ is observed in patients with T2DM~~Type 2 diabetes~~ inadequately controlled with GLP-1RA~~with elevated HbA1c~~. Earlier addition of insulin ~~resulted~~ is~~a~~ associated with ~~in~~ better ~~glucose~~ glycaemic control, while switching to insulin i~~wa~~s not clinically beneficial during 2 years of treatment. Non-responding patients on GLP-1RA would benefit by adding insulin therapy, rather than switching to insulin.

**Introduction**

People with diabetes are at increased risk of developing disabling and life-threatening health problems, including microvascular and macrovascular complications [1, 2]. Good control of hyperglycaemia and the associated risk factors in type 2 diabetes (T2DM) has been shown to reduce ~~-~~the risk of these complications [1, 3]. Thus anti-hyperglycaemic treatment strategies should ideally also address the management of cardiovascular risk factors, including body weight, blood pressure (BP) and lipids [4]. Novel anti-hyperglycaemic Glucagon-like peptide–1 receptor agonist (GLP-1RA) therapies, including Exenatide and Liraglutide, have the potential to address these challenges [5-9].

The combination of GLP-1RA and insulin treatments represents a promising glycaemic management strategy due to the complementary mechanisms of actions of these therapies [10]. Both therapies affect body weight, but in opposite directions: while significant weight reductions have been observed in patients treated with GLP-1RA, insulin is known to significantly increase body weight [11, 12]. A meta-analysis of clinical trials conducted by Eng and colleagues showed that the combination of GLP-1RA with basal insulin resulted in robust glycaemic control without increased risk of hypoglycaemia or weight gain ~~-~~[13]. ~~A number of observational and real-world data based studies have also evaluated the~~ The effectiveness of adding GLP-1RA to basal insulin therapy on glucose and weight control in patients with T2DM has also been evaluated in a number of observational and real-world data based studies [10, 14-20]. ~~Thus, i~~The intensification of ~~basal~~ insulin therapy ~~with~~ by addition of GLP-1RA, ~~instead of~~ rather than adding mealtime insulin, has ~~been widely investigated and~~ been shown ~~as~~ to be an attractive therapeutic option [13, 21], and is now recommended in international guidelines: "The available data now suggest that either a GLP-1 receptor agonist or prandial insulin could be used in this setting [in patients not achieving target HbA1c], with the former arguably safer, at least for short-term outcomes" [21]. ~~.~~

A significant number of patients treated with GLP1RA also intensify therapy by adding insulin, or switching to insulin therapy, primarily because of sub-optimal glycaemic ~~failure~~control. However, to the best of our knowledge, only three observational studies (n = 44 to 432) have evaluated the effectiveness of adding insulin to GLP-1RA therapy [20]. ~~However~~Moreover, these studies did not explore the HbA1c trajectories over time to understand the longitudinal patterns of glycaemic failure. Furthermore, no real-world study, to the best of our knowledge, has explored the dynamics of changes in glycaemic and cardiovascular risk factors from the time of GLP-1RA initiation ~~dynamics during~~through ~~-~~the transition phase of ~~of addition~~ adding or switching to insulin therapy ~~from the time of GLP-1RA initiation~~. The real-world patterns of adding or switching to insulin therapy from initial GLP-1RA treatment are also not well understood. ~~A~~Further, amongst patients with sub-optimal glycaemic control who intensify GLP-1RA therapy by addi~~ng~~tion of insulin ~~because of sub-optimal glycaemic control~~, it is not known whether earlier intensification is beneficial for a sustainable glucose control. ~~is also not know~~

From the time of initiation of GLP-1RA therapy in patients with T2DM, the aims of this longitudinal cohort study were to evaluate (1) changes in HbA1c, body weight, BP and LDL-cholesterol (LDL-C) over 6-, 12-, and 24-months of follow-up, (2) possible benefits of adding or switching to insulin treatment, and (3) the likelihood of clinically meaningful HbA1c reduction in those who intensified GLP-1RA treatment with insulin earlier, compared to those who added insulin later.

## Materials and Methods

### Data Source

The Centricity™ Electronic Medical Record (CEMR) database was used for this study. CEMR represents a variety of ambulatory medical practices from 49 US states, including solo practitioners, community clinics, academic medical centres, and large integrated delivery networks. The CEMR database consists of ~~over~~ more than 35,000 physicians and other providers, of whom approximately 75% are primary care providers. The database has been extensively used for academic research worldwide [22-25].

The CEMR database contains detailed prescription information with dates of prescription, including ~~All medications entered in the patient's medication list are stored in the CEMR. In such a way it contains data on medication prescriptions within EMR network, and also~~ information on medications that were purchased ~~may be used~~ over the counter or prescribed outside of the EMR network. ~~M~~The main medication information data set stores individual records in the form of start / stop dates, along with ~~it also contains~~ several specific ~~(i.e. chaining)~~ fields to track treatment adjustments and alterations over time.

From more than 2.4 million patients with confirmed diagnosis of T2DM, a cohort of 134,268 patients who received treatment with GLP-1RA from April 2005 to October 2014, was identified. The final study cohort of 66,583 patients was selected on the basis of the following criteria: (1) diagnosis of diabetes from January 1990, (2) age ≥ 18 years at the diagnosis of diabetes, (3) no insulin therapy prior to the initiation of GLP-1RA treatment, (4) no missing data on age, sex, HbA1c and body weight at GLP-1RA initiation, and (5) minimum six months of continuous treatment with GLP-1 RA from the first recorded prescription date.

In the final study cohort, those treated with Exenatide (EXE) and those treated with Liraglutide (LIRA) were identified. Those who added insulin therapy to existing GLP-1RA treatment (GLP+INS), and those who switched to insulin therapy upon the cessation of GLP-1RA treatment (GLP→INS), were identified by comparing insulin initiation dates and GLP-

1RA cessation dates. Time to addition of / switch to insulin therapy was calculated as the time difference between GLP-1RA and insulin initiation dates. Insulin therapy was identified by any insulin regimen (basal, biphasic or ~~,~~ prandial)~~., and with most~~The majority of the patients in the EXE group (94%) were treated with a twice daily Exenatide regimen.

Demographic, clinical and laboratory information included age, sex, ethnicity, and longitudinal measures of body weight, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), HbA1c, and lipids. ~~The clinical~~ Clinical and laboratory data at GLP-1RA treatment initiation (index date) were included on the basis of a three-month window, on or prior to index date. ~~The follow~~Follow-up clinical and laboratory measures were arranged longitudinally on the basis of non-overlapping six-monthly windows~~,~~ which were defined progressively from the time of GLP-1RA treatment initiation. Complete information on anti-hyperglycaemic agents, anti-hypertensive agents, cardio-protective medications (CPMs), weight-lowering and anti-depressant drugs was obtained along with dates of prescriptions. The CPMs included statins, angiotensin-converting enzyme inhibitors (ACE), and angiotensin II receptor blockers (ARB). The status of different medications intake was defined by whether it was taken during GLP-1RA treatment, and the treatment durations with such ~~these~~ medications were estimated.

**Statistical Methods**

While complete data on HbA1c and body weight were available at index date (by design), the ~~The~~ proportion~~s~~ of patients with missing longitudinal data on body weight, SBP, LDL-C and HbA1c ~~between 6 and 24~~over ~~-~~24 months of follow-up ranged ~~between~~ from 9% ~~and~~ to 19%. The missing longitudinal follow-up data were imputed using the multiple imputation ~~technique~~approach, with adjustments for age at index date and usage of oral anti-hyperglycaemic drugs during follow-up. All primary analyses were conducted using the

imputed data, with additional analyses conducted for sensitivity assessment based on complete cases ~~for sensitivity assessment~~.

The mean (95% CI) ~~of~~ changes in HbA1c, body weight, SBP and LDL-C at 6-, 12-, and 24-months from index date were estimated using multivariate regression models. ~~The changes in the risk~~ Risk factors changes were adjusted for age at index date, sex, ethnicity, and concomitant anti-hyperglycaemic, anti-hypertensive and weight lowering treatments, weighted by the respective baseline measures, ~~(~~as appropriate~~)~~. Separate analyses for HbA1c and weight changes were conducted for patients who continued to receive only GLP-1RA treatment over 6-, 12-, and 24- months, and for those who added or switched to insulin during follow-up. Robust estimates of the confidence intervals were obtained.

For patients with HbA1c above 7.5% at the time of GLP-1RA initiation, the proportions of patients who achieved HbA1c below 7% at 6-, 12-, and 24- months of treatment were evaluated for all groups. Proportions of those who achieved weight loss greater than or equal to 5% from initial body weight at 6-, 12-, and 24- months post GLP-1RA initiation were also calculated. The characteristics of the patients who added or switched to insulin were presented at the index date and at the time of transition to insulin.

**Results**

In the cohort of 66,583 patients with minimum six months of treatment with GLP-1RA, mean (SD) age was 56 (11) years, 28,959 (43%) were male, 45,291 (68%) were White Caucasians, 51,719 (87%) were obese, 3,404 (26%) / 858 (7%) had micro-/macro-albuminuria, and 17,415 (26%) had a history of hypertension at the time of initiation of GLP-1RA treatment ~~initiation~~ (Table 1). The use of different medications during GLP-1RA therapy, along with their durations of treatment, are presented in Table 1.

***Glycaemic Control***

With mean HbA1c of 8.2% at index date, among those who continued with GLP-1RA treatment without adding or switching to insulin, the highest adjusted mean HbA1c change was achieved within six months (-0.73%; CI: -0.73, -0.71), with no further glycaemic benefits at 12 months (-0.65%; CI: -0.65, -0.62) ~~and~~ or 24 months of follow-up (-0.59%; ~~,~~ CI: -0.60, -0.58; Table 2; ~~,~~ Figure 1A), all p<0.01. Among patients with HbA1c ≥ 7.5% at index date~~(n= )~~, who did not add or switch to insulin, and who continued with GLP-1RA treatment only for 12 and 24 months (n=14,682 and 6,825), 26% achieved HbA1c levels below 7% at 12 and 24 months respectively (Table 2).

Among those who added insulin during follow-up (GLP+INS, n=39,599), the mean HbA1c values at index date and at the time of adding insulin were 8.3% and 8.8% respectively. The median time to intensification with insulin was 3 months. Among these patients, those who had HbA1c above 7.5% and 8% at insulin initiation were 84% and 71% ~~had HbA1c above 7.5% and 8% at insulin initiation~~ respectively. Those who added insulin within six months of GLP-1RA initiation achieved significantly ~~higher~~greater (p<0.001)~~the highest~~ adjusted HbA1c reduction at 24 months of follow-up (-0.58%; CI: -0.61, -0.57), compared to those who added insulin after 12 months (-0.41%; CI: -0.43, -0.40;~~) (~~Figure 1A). Those who added insulin within six months of GLP-1RA initiation were 18% (odds ratio: 1.18; ~~95%~~ CI: 1.09, 1.28; p<0.001) more likely to achieve HbA1c below 7% at 24 months of follow-up, compared to those who added insulin treatment later.

The six monthly trajectories (mean, 95% CI) of HbA1c levels for those who switched to insulin therapy within 24 months (n=2,483; mean time to insulin: 14 month; Table 3) are presented in Figure 1B. In these patients the mean HbA1c ~~was~~ increased to 9.3% at the time to switching to insulin from mean HbA1c of 8.5% at GLP1-RA initiation, and 80% of them had HbA1c above 8% at insulin initiation (Table 3). Notably, these patients did not achieve better glycaemic control at 24 months, compared to their glycaemic status at index date

(Figure 1 B and C). ~~Meanwhile~~In contrast, patients who ~~had~~added ~~added~~ insulin ~~added~~ within 24 months of follow-up (n=36,113; mean time to insulin: 3 month; Table 3) experienced significant HbA1c reduction of 0.55% (CI: 0.54, 0.57) at 24 months compared to the index date (Figure 1C). The adjusted mean (95 % CI) of change in HbA1c and body weight at 6-, 12-, and 24- months post GLP-1RA initiation, for those who ceased GLP-1RA after 6 months of initiation and switched to insulin between 6-12, 12-18, and 18-24 months, are presented in Supplementary Table 1.

***Weight Change***

With a baseline body weight of 109 kg (Table 1), patients with a minimum 12 months of treatment with GLP-1RA ~~reduced~~ had ~~their body weight~~ significantly greater adjusted weight reduction (~~by adjusted~~ mean reduction 2.5 kg (~~95%~~ CI: 2.50, 2.51)), and 24% reduced their body weight by ≥ 5% (Table 4). Among those who ~~did not add or switch to insulin, and who~~ continued GLP-1RA treatment only (without addition or switch to insulin) for 24 months, the average weight reduction from index date was 3.31 kg (CI: 3.30, 3.32), and a third of patients achieved a weight loss of ≥ 5%. Patients who ~~had~~added ~~added~~ insulin ~~added~~ achieved marginally higher weight reduction (adjusted) at 12 months and 24 months (2.93 kg and 3.40 kg respectively, Table 4), compared to those who did not add or switch to insulin therapy (2.50 kg and 3.31 kg respectively~~, Table 4~~).

***Associations of glucose and weight loss***

Among patients with a minimum of 12 months of GLP-1RA treatment, 78% and 67% had reductions in HbA1c and body weight, respectively, from the index date, while 53% reduced both body weight and HbA1c ~~achieved simultaneous reductions~~ (similar between patients treated with LIRA ~~Liraglutide~~ and EXE~~xenatide~~, Figure 1D). At 12 months of follow-up, 8 %

and 7% failed to reduce both HbA1c and weight in the EXEExenatide and LIRAiraglutide groups, respectively.

***Cardiovascular risk factors***

With a mean 129 mmHg SBP level at index date, only 24% had SBP ≥ 140 mmHg. The adjusted average reduction in SBP was about 3 mmHg consistently over 6-, 12-, and 24-months of follow-up, and was similar across EXE and LIRA groups (Table 1 and Table 4). Among those who switched to insulin, the mean SBP levels at index date, at the time of moving to insulin, and at 24 month of follow-up remained stable at 130 mmHg.

In the study cohort 92% patients were on lipid lowering therapy. The average reduction in LDL-C was 0.18 mmol/L or greater consistently during 6-, 12-, and 24- months of follow-up (range of CI of reduction: 0.17 – 0.24 mmol/L-; Table 4), starting with a baseline LDL-C level of 2.43 mmol/L. Among patients who did not receive any statin (n= 15,949), mean reductions in LDL-C at 6-, 12-, and 24-months were 0.15 mmol/L, 0.14 mmol/L and 0.17 mmol/L, respectively (all p <0.001). Among those who switched to insulin, the mean LDL-C levels at index, at the time of moving to insulin, and at 24 month of follow-up were 2.47, 2.42, and 2.38 mmol/L, respectively.

**Discussion**

This longitudinal cohort study of 66,583 T2DM patients treated with GLP-1RA suggests that: (1) significant HbA1c reductions are may be obtained within six months from GLP-1RA treatment initiation, with no further glycaemic benefits likely over 24 months of follow-up; (2) earlier intensification with insulin therapy by six months (when added to GLP-1RA) is associated with 18% higher odds of lowering HbA1c below 7% within two years of treatment; and (3) adding insulin, rather than switching to it, is associated with significantly

lower glucose levels in a long-term outcome. We have also observed a clear indication of therapeutic inertia among patients who failed to respond to GLP-1RA therapy.

This study presents real world evidence of significant reductions in HbA1c, body weight, SBP and LDL-C over two years of follow-up in patients treated with GLP-1RA. Initiation of ~~It was observed that~~ GLP-1RA treatment ~~introduction~~ at lower HbA1c levels was associated with better glucose control over two years of follow-up. The observed ~~and the~~ . ~~o~~Observed HbA1c reductions were consistent with previous findings [15-19]. While glycaemic achievements observed within 6 months of GLP-1RA treatment initiation ~~in clinical trials~~ were higher in clinical trials, it is ~~well known~~recognised that ~~the~~ the effectiveness studies based on real world data generally provide lower estimates of glycaemic reduction or treatment effect(s) in general. The mean HbA1c reduction in patients treated with Liraglutide was marginally higher than those treated with Exenatide, although the proportions of patients who reduced HbA1c below 7% over 12 and 24 months of follow-up (ranging ~~between~~ from 26% ~~and~~ to 28%) were similar between these two therapies.

With initial response to GLP-1RA within 6 month of follow-up, patients who switched to insulin (by design after 6 months of GLP-1 RA treatment) experienced a significant rise in the glycaemic level at different points of follow-up, as evident from the Figure 1B. For example, those who switched to insulin within 18-24 months post index date, clearly experienced rising HbA1c levels consistently above 8% after 6 months of treatment with GLP-1RA. Furthermore, we observed that although switching to insulin prevented any further rise in HbA1c, no significant glycaemic reductions were achieved by the end of the 24 months follow-up period, compared to the index date (Figure 1 B and C). However, ~~in~~ those ~~who~~ patients ~~in whomadded~~who added insulin ~~was added~~ demonstrated significantly better glycaemic control by the end of the follow up period. After adjusting for the HbA1c levels at index date and at the time of insulin initiation, those who added insulin achieved a

significantly higher HbA1c reduction at 24 months by 0.48% (95% CI: 0.47, 0.50%), compared to those who switched to insulin (Figure 1 C).

This study revealed that addition of insulin and ~~, or and~~ switch to insulin ~~occurs~~ occurred at elevated HbA1c levels of 8.8% and 9.3% respectively, with a significant proportion of patients having HbA1c above 8 / 8.5% (71 / 58% in GLP+INS group and 80 / 68% in / GLP→INS group). This clearly ~~brings up~~raises the issue~~s~~ of therapeutic inertia [26, 27]. Given the high glycaemic burden in this population, the time to intensification of therapy requires further evaluation~~=~~. in conjunction with the factors that might prevent early intensification with insulin therapy, including fear of weight gain and hypoglycaemia. Notably, the distributions of body weight were similar between those who switched to, or added~~,~~ insulin, and those who remained on GLP-1RA treatment only (Table 1). Moreover, observed adjusted weight reductions in patients who added insulin~~,~~ were consistently and marginally greater than in those treated with GLP-1RA only during the follow-up period (Table 4). Our findings in terms of weight loss is consistent with a recent study reporting no weight gain post initiation of insulin in obese patients with T2DM [28] and the systematic review by Balena and colleagues [20].

The limitations of this study include non-availability of complete and reliable data on: (1) medication adherence; (2) dose adjustments in insulin treated patients; (3~~2~~) diet and exercise; (4~~3~~) socio-economic status; and (5~~4~~) potential residual confounders. The selection of patients with minimum 6 months treatment with GLP-1RA, excluding those who initiated insulin therapy earlier, could lead to a potential selection bias. However, the large analysis cohort from the validated CEMR database used in our study should be considered as a representative sample, and as such, provides a reliable picture of the state of risk factor management in routine practice. Complete risk factor data were available at index date, and imputations were conducted for only 9% to 19% missing longitudinal data. The results from complete case

analyses and imputed data were very similar. Finally, careful new-user design with a reasonable exposure time of two years, and appropriate adjustments for confounders are the primary strengths of the study.

In conclusion, this novel real world study provides evidence of significant delays in intensification of treatment in T2DM patients treated with GLP-1RA. Among HbA1c non-responders, early addition of insulin with GLP-1RA therapy within six months resulted in better and sustainable glycaemic control over two years. The findings from our study suggest that in people requiring treatment intensification on GLP-1RA, the preferred option should be addition of insulin rather than stopping GLP-1RA and switching to insulin therapy.



## Acknowledgements

SKP conceived the idea, and SKP and OM were responsible for the primary design of the study. The design concept was discussed and agreed with SK and KK. OM and Kere K conducted the data extraction. SKP, Kere K, and OM jointly conducted the statistical analyses. SK and KK worked on the analysis plan along with SKP. The first draft of the manuscript was developed by SKP and OM, and all authors contributed to the finalization of the manuscript. SKP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

QIMR Berghofer gratefully acknowledges the support from the Australian Government Department of Education's National Collaborative Research Infrastructure Strategy (NCRIS) initiative through Therapeutic Innovation Australia. No separate funding was obtained for this study. OM acknowledges the support from her associate supervisors Prof. Ross Young and Prof. Louise Hafner.

KK acknowledges support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – EM), and the NIHR Leicester Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit.

~~The Department of Health Sciences and Cardiovascular Sciences, University of Leicester is grateful for support from the NIHR Collaboration for Leadership in Applied Health Research & Care (CLAHRC) Scheme.~~

## Declaration of interests

SKP has acted as a consultant and/or speaker for Novartis, GI Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical and Amylin Pharmaceuticals LLC. He has received grants in support of investigator and investigator initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals, Sanofi-Avensis and Pfizer. KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen, Astra Zeneca and Boehringer Ingelheim. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme, Janssen and Roche. KK has received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk, Boehringer Ingelheim, Janssen and Astra Zeneca. SK has received research grants and been on advisory boards for Novo Nordisk. OM and Kere K have no conflict of interest to declare.

**References**


1. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009;52(11):2288-98.
2. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. The Lancet Diabetes & Endocrinology. 2015;3(2):105-13.
3. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: A scientific statement from the American Heart Association and the American Diabetes Association. Circulation. 2015;132(8):691-718.
4. American Diabetes Association. Standards of Medical Care in Diabetes—2015. Diabetes Care. 2015;38(Supplement 1).
5. Paul SK, Klein K, Maggs D, Best JH. The association of the treatment with glucagon-like peptide-1 receptor agonist exenatide or insulin with cardiovascular outcomes in patients with type 2 diabetes: A retrospective observational study. Cardiovascular Diabetology. 2015;14(1):10.
6. Smilowitz NR, Donnino R, Schwartzbard A. Glucagon-Like Peptide-1 Receptor Agonists for Diabetes Mellitus: A Role in Cardiovascular Disease. Circulation. 2014;129(22):2305-12.
7. Drucker DJ, Goldfine AB. Cardiovascular safety and diabetes drug development. The Lancet. 2011;377(9770):977-9.
8. Garber AJ. Novel GLP-1 receptor agonists for diabetes. Expert Opin Investig Drugs. 2012;21(1):45-57.
9. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes, obesity & metabolism. 2014;16(1):38-47.
10. Vora J. Combining incretin-based therapies with insulin: Realizing the potential in type 2 diabetes. Diabetes Care. 2013;36(SUPPL.2):S226-S32.
11. Shaefer CF, Reid TS, Dailey G, et al. Weight change in patients with type 2 diabetes starting basal insulin therapy: correlates and impact on outcomes. Postgraduate medicine. 2014;126(6):93-105.
12. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. Diabetes Care. 2014;37(8):2108-13.
13. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014;384(9961):2228-34.
14. Lee WC, Dekoven M, Bouchard J, Massoudi M, Langer J. Improved real-world glycaemic outcomes with liraglutide versus other incretin-based therapies in type 2 diabetes. Diabetes, obesity & metabolism. 2014;16(9):819-26.
15. Li Q, Chitnis A, Hammer M, Langer J. Real-world clinical and economic outcomes of liraglutide versus sitagliptin in patients with type 2 diabetes mellitus in the United States. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2014;5(2):579-90.
16. Rigato M, Avogaro A, Fadini GP. Effects of dose escalating liraglutide from 1.2 to 1.8 mg in clinical practice: a case-control study. Journal of endocrinological investigation. 2015;38(12):1357-63.
17. Gautier JF, Martinez L, Penfornis A, et al. Effectiveness and Persistence with Liraglutide Among Patients with Type 2 Diabetes in Routine Clinical Practice--EVIDENCE: A Prospective, 2-Year Follow-Up, Observational, Post-Marketing Study. Advances in therapy. 2015;32(9):838-53.
18. Ryder B, Thong K, editors. Findings from the Association of British Clinical Diabetologists (ABCD) nationwide exenatide and liraglutide audits. Diabetes UK Annual Professional Conference; 2012.
19. Thong KY, Jose B, Sukumar N, et al. Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit. Diabetes, obesity & metabolism. 2011;13(8):703-10.
20. Balena R, Hensley IE, Miller S, Barnett AH. Combination therapy with GLP-1 receptor agonists and basal insulin: A systematic review of the literature. Diabetes, Obesity and Metabolism. 2013;15(6):485-502.
21. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care. 2015;38(1):140-9.

22. Kamal KM, Chopra I, Elliott JP, Mattei TJ. Use of electronic medical records for clinical research in the management of type 2 diabetes. Research in social & administrative pharmacy~~-~~: Res Social Adm Pharm~~RSAP~~. 2014;10(6):877-84.
23. Davis KL, Tangirala M, Meyers JL, Wei W. Real-world comparative outcomes of US type 2 diabetes patients initiating analog basal insulin therapy. Curr Med Res Opin. 2013;29(9):1083-91.
24. Crawford AG, Cote C, Couto J, et al. Comparison of GE Centricity Electronic Medical Record database and National Ambulatory Medical Care Survey findings on the prevalence of major conditions in the United States. Population health management. 2010;13(3):139-50.
25. Paul S, Klein K, Maggs D, Best J. The association of the treatment with glucagon-like peptide-1 receptor agonist exenatide or insulin with cardiovascular outcomes in patients with type 2 diabetes: a retrospective observational study. Cardiovascular Diabetology. 2015;14(In Press).
26. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes, obesity & metabolism. 2016;18(4):401-9.
27. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovascular Diabetology. 2015;14(1):100.
28. Paul SK, Shaw J, Montvida O, Klein K. Weight gain in insulin treated patients by BMI categories at treatment initiation: New evidence from real-world data in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2016; Accepted manuscript online.

Table 1: Basic statistics on study parameters at the time of initiation of Exenatide or Liraglutide who continued GLP-1RA treatment for at-least six months, those who added insulin treatment during the follow-up, and those who switched to insulin treatment during the follow-up. The statistics are mean (SD) unless stated otherwise.

| | **ALL** | **EXE** | **LIRA** | **GLP+INS** | **GLP→INS** |
|---|---|---|---|---|---|
| N | 66583 | 44523 | 22060 | 39599 | 4706 |
| Age at GLP-1RA Initiation | 56 (11) | 56 (11) | 56 (11) | 56 (11) | 56 (11) |
| Male* | 28959 (43) | 18917 (42) | 10042 (46) | 17531 (44) | 2130 (45) |
| Ethnicity: Caucasian* | 45291 (68) | 29500 (66) | 15791 (72) | 27231 (69) | 3311 (70) |
| Ethnicity: Black* | 5021 (8) | 3118 (7) | 1903 (9) | 2971 (8) | 358 (8) |
| Ethnicity: Hispanic* | 1465 (2) | 943 (2) | 522 (2) | 1023 (3) | 89 (2) |
| Ethnicity: Asian* | 534 (1) | 326 (1) | 208 (1) | 312 (1) | 30 (1) |
| HbA1c at Diagnosis of Diabetes, % | 8 (1.4) | 8 (1.4) | 8.1 (1.5) | 8.1 (1.5) | 8.2 (1.5) |
| HbA1c at GLP-1RA Initiation, % | 8.2 (1.3) | 8.1 (1.3) | 8.3 (1.4) | 8.3 (1.4) | 8.4 (1.3) |
| HbA1c at GLP-1RA Initiation, %$^{\alpha}$ | 7.8 (7, 8.8) | 7.8 (7, 8.7) | 7.9 (7.1, 8.9) | 8 (7.1, 9.0) | 8.2 (7.4, 9.0) |
| HbA1c ≥ 7% at GLP-1RA Initiation* | 60351 (91) | 40180 (90) | 20171 (91) | 36130 (91) | 4388 (93) |
| HbA1c ≥ 7.5% at GLP-1RA Initiation* | 41045 (62) | 26700 (60) | 14345 (65) | 25691 (65) | 3388 (72) |
| HbA1c ≥ 8% at GLP-1RA Initiation* | 30599 (46) | 19777 (44) | 10822 (49) | 19859 (50) | 2628 (56) |
| Weight at GLP-1RA Initiation, kg | 109 (25) | 110 (25) | 109 (25) | 110 (25) | 108 (24) |
| BMI at GLP-1RA Initiation, kg/m$^2$ | 38 (8) | 38 (8) | 38 (8) | 38 (8) | 37 (8) |
| Obese at GLP-1RA Initiation* | 57927 (87) | 38753 (87) | 18971 (86) | 34847 (88) | 4000 (85) |
| SBP at GLP-1RA Initiation, mmHg | 129 (16) | 129 (16) | 129 (16) | 129 (16) | 130 (16) |
| SBP ≥ 140 mmHg at GLP-1RA Initiation* | 15728 (24) | 10628 (24) | 5100 (23) | 9487 (24) | 1184 (25) |
| DBP at GLP-1RA Initiation, mmHg | 77 (10) | 77 (10) | 77 (10) | 77 (10) | 77 (10) |
| LDL-C at GLP-1RA Initiation, mmol/L | 2.43 (0.72) | 2.44 (0.73) | 2.42 (0.72) | 2.42 (0.74) | 2.47 (0.74) |
| LDL-C ≥ 3.37 mmol/L at GLP-1RA Initiation* | 5780 (9) | 3951 (9) | 1829 (8) | 3652 (9) | 450 (10) |
| HDL-C at GLP-1RA Initiation, mmol/L | 1.10 (0.31) | 1.11 (0.30) | 1.10 (0.31) | 1.10 (0.30) | 1.09 (0.29) |
| Triglyceride at GLP-1RA Initiation, mmol/L$^{\alpha}$ | 1.69 (1.23, 2.28) | 1.69 (1.23, 2.27) | 1.71 (1.24, 2.31) | 1.71 (1.24, 2.29) | 1.75 (1.25, 2.35) |
| Triglyceride ≥ 1.69 mmol/L at GLP-1RA Initiation* | 15060 (51) | 9920 (50) | 5140 (51) | 10107 (51) | 967 (53) |
| Micro-albuminuria* | 3404 (26) | 2126 (25) | 1278 (29) | 2481 (26) | 167 (26) |

| | | | | | |
|---|---|---|---|---|---|
| Macro-albuminuria* | 858 (7) | 532 (6) | 326 (7) | 597 (6) | 49 (8) |
| Hypertension* | 17415 (26) | 12707 (29) | 4708 (21) | 11020 (28) | 1340 (28) |
| Metformin taken during the GLP-1RA Treatment* | 56035 (84) | 37645 (85) | 18390 (83) | 33837 (85) | 4129 (88) |
| Metformin Duration, month$^{\alpha}$ | 52.7 (28.2, 84.3) | 62.6 (34.9, 91.9) | 36.6 (20.8, 61.1) | 55.9 (30.3, 87.5) | 71.8 (43.6, 97.6) |
| Sulfonylurea taken during the GLP-1RA Treatment* | 38003 (57) | 26719 (60) | 11284 (51) | 23723 (60) | 3583 (76) |
| Sulfonylurea Duration, month$^{\alpha}$ | 32.5 (15, 60.3) | 36.8 (17, 66) | 25.4 (12.2, 45.8) | 33.5 (15.2, 61.9) | 39.8 (20.2, 67.9) |
| Antihypertensive taken during the GLP-1RA Treatment* | 53821 (81) | 36610 (82) | 17211 (78) | 32655 (82) | 4032 (86) |
| Antihypertensive Duration, month$^{\alpha}$ | 46.5 (23.8, 80.1) | 54.7 (28.4, 86.9) | 33.2 (17.5, 59.8) | 48.7 (25.2, 82.3) | 61.4 (33.9, 91.8) |
| CPM taken during the GLP-1RA Treatment* | 61145 (92) | 41273 (93) | 19872 (90) | 36861 (93) | 4462 (95) |
| CPM Duration, month$^{\alpha}$ | 51.1 (26.6, 84.9) | 59.9 (32.7, 91.6) | 35.7 (19.4, 64.5) | 53.8 (28.5, 87.5) | 68.3 (39, 96.3) |
| Weight lowering taken during the GLP-1RA Treatment* | 4591 (7) | 3297 (7) | 1294 (6) | 2831 (7) | 328 (7) |
| Weight lowering Duration, month$^{\alpha}$ | 12.6 (5.1, 28.2) | 13.1 (5.2, 29.4) | 11.9 (4.9, 25.5) | 12.1 (4.8, 27.5) | 12.6 (5.3, 28.7) |
| Anti-depressants taken during the GLP-1RA Treatment* | 28133 (42) | 19865 (45) | 8268 (37) | 16950 (43) | 2296 (49) |
| Anti-depressants Duration, month$^{\alpha}$ | 35.6 (15.4, 68.6) | 40.6 (17.4, 74.7) | 27.2 (12.6, 51.4) | 36.2 (15.5, 70.1) | 43.4 (19.5, 78.9) |

*N (%); $^{\alpha}$Median (IQR); CPM: Cardio-protective medication (statins, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers)

Table 2: Adjusted mean (95 % CI) of change in HbA1c at 6-, 12-, and 24- months post GLP-1RA initiation, for those who took GLP-1RA for at least 6-, 12-, and 24-months, by whether patients continued on GLP-1RA treatment only or added insulin therapy. For patients with HbA1c above 7.5% at GLP-1RA initiation, n (%) of those whose HbA1c reduced below 7% at 6-, 12-, and 24- months post GLP-1RA initiation by whether patients took GLP-1RA only or added insulin therapy.

| | On GLP-1RA for ≥ 6 months | | | On GLP-1RA for ≥ 12 months | | | On GLP-1RA for ≥ 24 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | ALL | EXE | LIRA | ALL | EXE | LIRA | ALL | EXE | LIRA |
| | 66583 | 44523 | 22060 | 50109 | 35085 | 15024 | 28422 | 22111 | 6311 |
| Δ HbA1c at 6 months | | | | | | | | | |
| GLP-1RA only | -0.73 (-0.73, -0.71) | -0.70 (-0.71, -0.70) | -0.80 (-0.80, -0.79) | -0.75 (-0.76, -0.75) | -0.72 (-0.73, -0.72) | -0.83 (-0.81, -0.83) | -0.75 (-0.75, -0.74) | -0.73 (-0.73, -0.72) | -0.85 (-0.86, -0.85) |
| GLP-1RA + INS | -0.83 (-0.84, -0.83) | -0.75 (-0.77, -0.75) | -0.95 (-0.96, -0.94) | -0.82 (-0.82, -0.81) | -0.75 (-0.76, -0.75) | -0.95 (-0.96, -0.95) | -0.81 (-0.81, -0.80) | -0.77 (-0.77, -0.76) | -0.93 (-0.93, -0.92) |
| HbA1c < 7% at 6 months for those whose HbA1c were ≥7.5% at GLP-1RA initiation | | | | | | | | | |
| GLP-1RA only | 5410 (25) | 3672 (24) | 1738 (27) | 3965 (27) | 2826 (26) | 1139 (29) | 2018 (30) | 1603 (29) | 415 (34) |
| GLP-1RA + INS | 4156 (21) | 2236 (19) | 1920 (24) | 3451 (22) | 1987 (20) | 1464 (25) | 2338 (24) | 1594 (22) | 744 (28) |
| Δ HbA1c at 12 months | | | | | | | | | |
| GLP-1RA only | - | - | - | -0.65 (-0.65, -0.62) | -0.62 (-0.62, -0.61) | -0.71 (-0.72, -0.71) | -0.67 (-0.68, -0.67) | -0.65 (-0.67, -0.65) | -0.74 (-0.74, -0.72) |
| GLP-1RA + INS | - | - | - | -0.73 (-0.73, -0.72) | -0.67 (-0.67, -0.66) | -0.85 (-0.86, -0.85) | -0.74 (-0.75, -0.74) | -0.71 (-0.71, -0.70) | -0.84 (-0.84, -0.83) |
| HbA1c < 7% at 12 months for those whose HbA1c were ≥7.5% at GLP-1RA initiation | | | | | | | | | |
| GLP-1RA only | - | - | - | 3829 (26) | 2770 (26) | 1059 (27) | 1960 (29) | 1577 (28) | 383 (32) |
| GLP-1RA + INS | - | - | - | 3462 (22) | 2083 (21) | 1379 (24) | 2401 (24) | 1679 (23) | 722 (27) |
| Δ HbA1c at 24 months | | | | | | | | | |
| GLP-1RA only | - | - | - | - | - | - | -0.59 (-0.60, -0.58) | -0.58 (-0.58, -0.57) | -0.63 (-0.64, -0.63) |
| GLP-1RA + INS | - | - | - | - | - | - | -0.65 | -0.63 | -0.70 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | (-0.66, -0.65) | (-0.64, -0.63) | (-0.71, -0.70) |
| HbA1c < 7% at 24 months for those whose HbA1c were ≥7.5% at GLP-1RA initiation | | | | | | | | | |
| GLP-1RA only | - | - | - | - | - | - | 1806 (26) | 1469 (26) | 337 (28) |
| GLP-1RA + INS | - | - | - | - | - | - | 2247 (23) | 1621 (23) | 626 (23) |

Table 3: HbA1c levels at GLP-1RA initiation and at insulin initiation, and the time to insulin therapy, for those who added insulin to existing GLP-1RA (GLP+INS) and those who switched to insulin treatment (GLP→INS) within two years of follow-up. Statistics are mean (SD) unless stated otherwise.

| | GLP+INS | | | GLP→INS | | |
|---|---|---|---|---|---|---|
| | ALL | EXE | LIRA | ALL | EXE | LIRA |
| N | 36113 | 22703 | 13410 | 2483 | 1856 | 627 |
| HbA1c at GLP-1RA Initiation, % | 8.3 (1.4) | 8.3 (1.4) | 8.4 (1.4) | 8.5 (1.4) | 8.5 (1.4) | 8.5 (1.4) |
| HbA1c at GLP-1RA Initiation, %[α] | 8 (7.1, 9) | 7.9 (7.1, 9) | 8.1 (7.2, 9.1) | 8.3 (7.5, 9.2) | 8.3 (7.5, 9.2) | 8.3 (7.6, 9.3) |
| HbA1c >= 7% at GLP-1RA Initiation[*] | 33032 (91) | 20649 (91) | 12383 (92) | 2351 (95) | 1761 (95) | 590 (94) |
| HbA1c >= 7.5% at GLP-1RA Initiation[*] | 23736 (66) | 14507 (64) | 9229 (69) | 1892 (76) | 1404 (76) | 488 (78) |
| HbA1c >= 8% at GLP-1RA Initiation[*] | 18436 (51) | 11202 (49) | 7234 (54) | 1489 (60) | 1119 (60) | 370 (59) |
| HbA1c at Insulin Initiation, % | 8.8 (1.3) | 8.8 (1.3) | 8.8 (1.3) | 9.3 (1.6) | 9.2 (1.5) | 9.5 (1.7) |
| HbA1c at Insulin Initiation, % [α] | 8.7 (7.8, 9.4) | 8.7 (7.8, 9.4) | 8.8 (7.9, 9.5) | 9.1 (8.2, 10) | 9 (8.1, 10) | 9.1 (8.4, 10.3) |
| HbA1c >= 7% at Insulin Initiation[*] | 36045 (100) | 22652 (100) | 13393 (100) | 2482 (100) | 1855 (100) | 627 (100) |
| HbA1c >= 7.5% at Insulin Initiation[*] | 30267 (84) | 18848 (83) | 11419 (85) | 2209 (89) | 1634 (88) | 575 (92) |
| HbA1c >= 8% at Insulin Initiation[*] | 25649 (71) | 15897 (70) | 9752 (73) | 1985 (80) | 1466 (79) | 519 (83) |
| Δ HbA1c (Insulin - GLP-1RA), %[α] | 0.46 (0.45, 0.47) | 0.49 (0.47, 0.50) | 0.42 (0.4, 0.44) | 0.73 (0.67, 0.79) | 0.67 (0.60, 0.73) | 0.91 (0.80, 1.03) |
| Time to Insulin Initiation, month[β] | 3 (0, 24) | 3 (0, 24) | 2 (0, 24) | 14 (6, 24) | 14 (6, 24) | 14 (6, 24) |
| Time to Insulin Initiation, month[α] | 0 (0, 3) | 0 (0, 4) | 0 (0, 2) | 13 (10, 18) | 14 (10, 19) | 12 (9, 18) |

[*]N (%); [α]Median (IQR); [β]Mean (Range)

Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish
Formatted: Danish

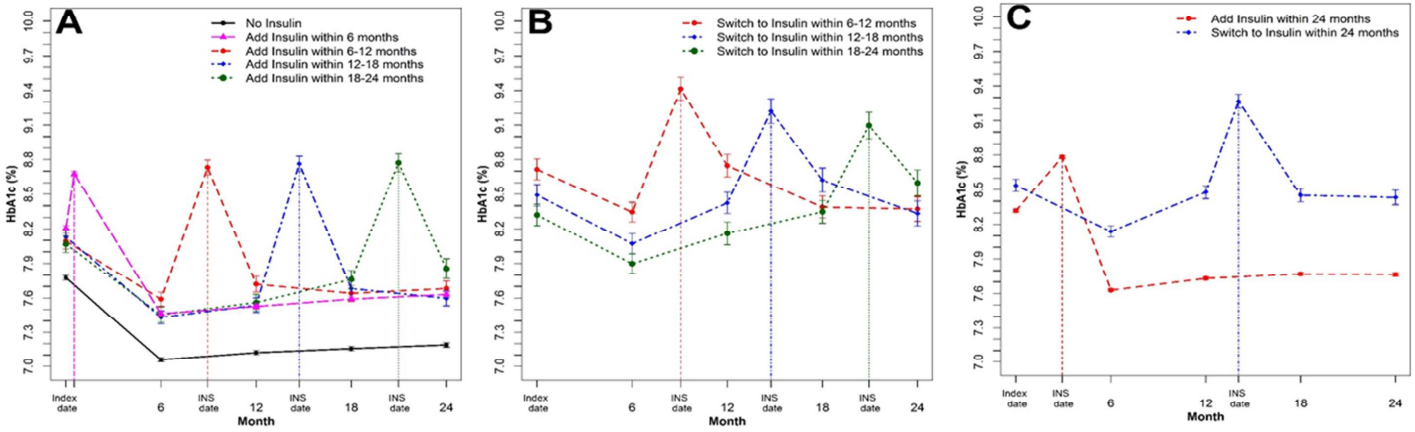
Table 4: Adjusted mean (95 % CI) of change in body weight at 6-, 12-, and 24- months post GLP-1RA initiation, for those who took GLP-1RA for at least 6-, 12-, and 24-months, by whether patients continued on GLP-1RA treatment only or added insulin therapy. n (%) of those who lost 5% or more of body weight during follow-up from GLP-1RA initiation. Adjusted mean (95 % CI) of changes in SBP and LDL-C at 6-, 12-, and 24- months post GLP-1RA initiation.

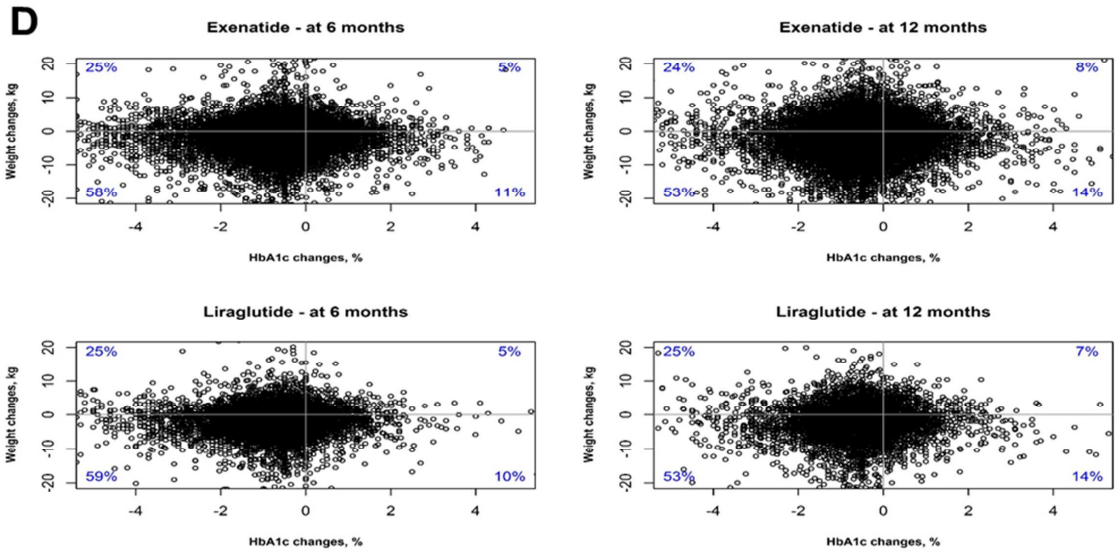
| | On GLP-1RA for ≥ 6 months | | | On GLP-1RA for ≥ 12 months | | | On GLP-1RA for ≥ 24 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | ALL | EXE | LIRA | ALL | EXE | LIRA | ALL | EXE | LIRA |
| Δ Weight at 6 months | | | | | | | | | |
| GLP-1RA only | -1.87 (-1.88, -1.87) | -1.90 (-1.91, -1.90) | -1.80 (-1.81, -1.80) | -1.96 (-1.97, -1.96) | -2.00 (-2.00, -1.99) | -1.86 (-1.87, -1.85) | -2.24 (-2.24, -2.23) | -2.23 (-2.24, -2.23) | -2.25 (-2.26, -2.23) |
| GLP-1RA + INS | -2.32 (-2.32, -2.31) | -2.20 (-2.20, -2.19) | -2.51 (-2.52, -2.51) | -2.41 (-2.41, -2.40) | -2.26 (-2.26, -2.25) | -2.68 (-2.68, -2.67) | -2.50 (-2.50, -2.49) | -2.38 (-2.39, -2.37) | -2.84 (-2.85, -2.83) |
| Weight loss ≥5% at 6 months | | | | | | | | | |
| GLP-1RA only | 5539 (15) | 3957 (15) | 1582 (15) | 3978 (15) | 2980 (15) | 998 (15) | 2050 (16) | 1684 (16) | 366 (17) |
| GLP-1RA + INS | 5241 (18) | 3085 (17) | 2156 (19) | 4413 (18) | 2729 (17) | 1684 (20) | 2985 (19) | 2124 (18) | 861 (21) |
| Δ Weight at 12 months | | | | | | | | | |
| GLP-1RA only | - | - | - | -2.50(-2.51, -2.50) | -2.54 (-2.55, -2.54) | -2.39 (-2.39, -2.38) | -2.83 (-2.84, -2.82) | -2.82 (-2.83, -2.82) | -2.87 (-2.88, -2.85) |
| GLP-1RA + INS | - | - | - | -2.93 (-2.93, -2.92) | -2.80 (-2.81, -2.80) | -3.16 (-3.16, -3.15) | -3.08 (-3.08, -3.07) | -3.00 (-3.00, -2.99) | -3.31 (-3.32, -3.30) |
| Weight loss ≥ 5% at 12 months | | | | | | | | | |
| GLP-1RA only | - | - | - | 6150 (24) | 4644 (24) | 1506 (23) | 3204 (25) | 2662 (26) | 542 (25) |
| GLP-1RA + INS | - | - | - | 6404 (26) | 4062 (26) | 2342 (28) | 4314 (27) | 3132 (27) | 1182 (29) |
| Δ Weight at 24 months | | | | | | | | | |
| GLP-1RA only | - | - | - | - | - | - | -3.31 (-3.32, | -3.3 (-3.31, - | -3.36 (-3.38, |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | -3.30) | 3.29) | -3.35) |
| GLP-1RA + INS | - | - | - | - | - | - | -3.40 (-3.41, -3.40) | -3.32 (-3.33, -3.31) | -3.63 (-3.64, -3.62) |
| Weight loss ≥ 5% at 24 months | | | | | | | | | |
| GLP-1RA only | - | - | - | - | - | - | 3884 (31) | 3210 (31) | 674 (31) |
| GLP-1RA + INS | - | - | - | - | - | - | 5104 (32) | 3747 (32) | 1357 (33) |
| Blood pressure changes | | | | | | | | | |
| Δ SBP at 6 months | -2.82 (-2.82, -2.81) | -2.78 (-2.78, -2.77) | -2.90 (-2.91, -2.89) | -2.95 (-2.96, -2.95) | -2.91 (-2.91, -2.90) | -3.05 (-3.06, -3.04) | -2.91 (-2.91, -2.90) | -2.87 (-2.87, -2.86) | -3.05 (-3.07, -3.04) |
| Δ SBP at 12 months | - | - | - | -2.79 (-2.79, -2.78) | -2.79 (-2.79, -2.78) | -2.79 (-2.80, -2.78) | -2.85 (-2.86, -2.85) | -2.78 (-2.78, -2.77) | -3.13 (-3.14, -3.11) |
| Δ SBP at 24 months | - | - | - | - | - | - | -2.64 (-2.64, -2.63) | -2.69 (-2.70, -2.69) | -2.44 (-2.46, -2.42) |
| LDL changes | | | | | | | | | |
| Δ LDL-C at 6 months | -0.19 (-0.20, -0.19) | -0.19 (-0.20, -0.19) | -0.19 (-0.19, -0.18) | -0.19 (-0.19, -0.18) | -0.19 (-0.20, -0.19) | -0.19 (-0.19, -0.18) | -0.19 (-0.21, -0.18) | -0.18 (-0.18, -0.17) | -0.20 (-0.21, -0.19) |
| Δ LDL-C at 12 months | - | - | - | -0.18 (-0.19, -0.18) | -0.18 (-0.19, -0.18) | -0.19 (-0.19, -0.18) | -0.19 (-0.20, -0.19) | -0.18 (-0.18, -0.17) | -0.20 (-0.21, -0.18) |
| Δ LDL-C at 24 months | - | - | - | - | - | - | -0.23 (-0.24, -0.23) | -0.23 (-0.24, -0.23) | -0.23 (-0.23, -0.22) |

**Figure Legend**

**Figure 1: (A)** Mean (95% CI) of longitudinal HbA1c measurements by whether patient added insulin within 6 / 6-12 / 12-18 / 18-24 months from the GLP-1RA initiation, or remained on GLP-1RA treatment only; **(B)** Mean (95% CI) of longitudinal HbA1c measurements by whether patient switched to insulin within 6-12 / 12-18 / 18-24 months from the GLP-1RA initiation; **(C)** Mean (95% CI) of longitudinal HbA1c measurements by whether patient added or switched to insulin within 24 months from GLP-1RA initiation; **(D)** Scatterplot of HbA1c change and body weight change at 6 and 12 months for patients treated with Exenatide and Liraglutide without adding or switching to insulin. The perpendicular dotted lines present the mean time to addition or switching to insulin by categories of timeline.


A
No Insulin
Add Insulin within 6 months
Add Insulin within 6-12 months
Add Insulin within 12-18 months
Add Insulin within 18-24 months
HbA1c (%)
Month
B
Switch to Insulin within 6-12 months
Switch to Insulin within 12-18 months
Switch to Insulin within 18-24 months
HbA1c (%)
Month
C
Add Insulin within 24 months
Switch to Insulin within 24 months
HbA1c (%)
Month


D
Exenatide - at 6 months
Exenatide - at 12 months
Liraglutide - at 6 months
Liraglutide - at 12 months
Weight changes, kg
HbA1c changes, %
25%
5%
58%
11%
24%
8%
53%
14%
59%
10%
25%
7%
53%
14%

Supplementary Table 1: Adjusted mean (95 % CI) of change in HbA1c and body weight at 6-, 12-, and 24- months post GLP-1RA initiation, for those who ceased GLP-1RA after 6 months of initiation and switched to insulin between 6-12, 12-18, and 18-24 months.

| | Switch to insulin within 6-12 months n= 1030 | Switch to insulin within 12-18 months n=776 | Switch to insulin within 18-24 months n=677 |
|---|---|---|---|
| Δ HbA1c at 6 months | -0.45 (-0.46, -0.45) | -0.50 (-0.50, -0.49) | -0.49 (-0.50, -0.49) |
| Δ HbA1c at 12 months | -0.08 (-0.08, -0.07) | -0.16 (-0.16, -0.15) | -0.23 (-0.23, -0.22) |
| Δ HbA1c at 24 months | -0.46 (-0.46, -0.45) | -0.24 (-0.25, -0.24) | 0.18 (0.17, 0.18) |
| Δ Weight at 6 months | -1.68 (-1.72, -1.64) | -1.32 (-1.32, -1.31) | -1.73 (-1.76, -1.71) |
| Δ Weight at 12 months | -1.69 (-1.71, -1.67) | -1.63 (-1.64, -1.62) | -1.92 (-1.95, -1.90) |
| Δ Weight at 24months | -0.93 (-0.95, -0.91) | -0.91 (-0.93, -0.89) | -1.98 (-1.99, -1.97) |