# Liraglutide Use in A Real-World Setting: Patient Characteristics at Antidiabetic Treatment Initiation Modulate Cardiovascular Safety Outcomes

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**Research article**

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# Abstract

**Background:** Generation of real-world cardiovascular drug safety evidence in patients with type 2 diabetes (T2D) warrants robust methodology. Regulatory authorities are increasingly seeking to support their decision making through real-world evidence. At the time of marketing authorization, this study was required by regulatory authorities to further characterize the liraglutide safety profile in routine real-world clinical practice (external validity). Safety outcomes were compared to those of other non-insulin antidiabetic (NIAD) treatments in patients with T2D initiating NIADs in a UK real-word setting. The design was endorsed by health regulatory authorities. This paper analyzes the methodology and study results, and postulates that it was the differences in patient characteristics at NIAD initiation, not the treatment itself, that modulated the observed differences in cardiovascular risk between NIAD cohorts.

**Methods:** Data were obtained from linked UK electronic repositories: the Clinical Practice Research Datalink primary care database (CPRD GOLD) and Hospital Episode Statistics (HES). Risks of selected outcomes with current liraglutide use were compared to current use of other NIADs. Rates of each outcome and corresponding crude and adjusted incidence rate ratios were examined using Poisson regression analysis.

**Results**: Overall, 149 788 patients met the study inclusion criteria; of these, 3432 initiated liraglutide. Components of the metabolic syndrome were more common among liraglutide initiators than those initiating other NIADs. The risk of some macrovascular conditions was increased in liraglutide initiators versus other NIAD initiators; following stepwise adjustment, this was only seen in liraglutide initiators when compared to biguanide initiators (incidence rate ratio: 1.33 [99% confidence interval (CI): 1.11;1.59]).

**Conclusions**: The observed increase of macrovascular outcomes in liraglutide initiators compared with other NIAD initiators emphasizes the importance of countering potential selection bias when designing studies comparing cardiovascular outcomes across treatment initiator cohorts in heterogenous populations, such as patients with T2D. Baseline differences in the NIAD cohort may have modulated cardiovascular outcomes and likely explain the observed increased cardiovascular risk in liraglutide initiators. Selection bias, channeling bias and residual confounding, inherent in such observational studies, must be considered early when designing the study if the real-world data are to support decision-making.


# Background

Type 2 diabetes (T2D) is a highly heterogeneous condition, encompassing several subgroups with differing disease progression and comorbidities/complications [1]. T2D is primarily characterized by abnormal carbohydrate, lipid and protein metabolism, involving multiple pathophysiological disturbances within multiple organs. Insulin resistance, beta-cell dysfunction and impairment of incretin hormone action contribute to the development and progression of hyperglycemia [2].

Cardiovascular (CV) disease accounts for approximately half of all deaths in patients with T2D [3]. The subgroup of patients with T2D who present the metabolic syndrome (MetS) is at higher risk of developing CV outcomes than the rest of the population [4]. MetS is a clustering of cardiometabolic risk factors including hypertension, dyslipidemia and visceral obesity [4, 5], and is closely associated with the pre-existence of hypersinsulinemia and insulin resistance [6]. Persons with MetS have elevated rates and severity of CV outcomes, including microvascular dysfunction, coronary atherosclerosis and calcification, cardiac dysfunction, myocardial infarction and heart failure [7].

International guidelines recommend an individualized approach to guide the choice of subsequent pharmacotherapies, when treatment intensification is required in patients with T2D [5]. The choice of antidiabetic pharmacotherapy is based on the comorbiditites presented by the patient (e.g. components of the MetS) and the stage of disease progression, thus leading to differential therapy choices among patients with T2D.

Optimal glycemic control is one of the cornerstones in the multifactorial treatment approach in patients with T2D to prevent long-term complications associated with chronic hyperglycemia [8–10]. Diet, exercise and education are the established first-line treatment of T2D, together with initiation of metformin in patients who are unlikely to achieve their individualized glycated hemoglobin (HbA1c) target without pharmacotherapy. At the time of this study, diabetes treatment guidelines recommended glucagon-like peptide-1 receptor agonists (GLP-1RAs) as second-line after metformin, on equal terms with other oral glucose-lowering agents and insulin, as part of a multifactorial risk-reduction strategy in the management of T2D [11].

Liraglutide is a human GLP-1RA analog approved for treatment of T2D in the European Union on 30 June 2009. The safety and efficacy of liraglutide were established through a rigorous and comprehensive phase 3 clinical trial program, demonstrating improvement of glycemic control, reduction in body weight and a low risk of hypoglycemic events [12].

Due to these drug characteristics, the UK National Institute for Health and Care Excellence (NICE) guidelines recommended limiting the use of liraglutide to patients with a body mass index (BMI) $\geq 35$ kg/m$^2$ who require optimization of their glycemic control [13]. Furthermore, liraglutide could be taken concomitantly with other glucose-lowering drugs, including insulin. Thus, liraglutide use in the UK real-world setting differed from its use in the pre-authorization randomized clinical trials (RCTs), where patients were not necessarily obese and were not taking insulin.

Generally, RCTs are often short in duration, include restricted populations, are conducted in specialized centers, and treatment is mandated by study protocol. Consequently, real-world data are needed to ascertain external validity and complement RCT data, further supporting regulatory decision-making.

Accordingly, regulatory authorities required a liraglutide post-authorization safety study (PASS) at the time of marketing authorization (2009). The study was to further characterize the safety profile of liraglutide after market launch, as well as to explore events identified as of special interest during the marketing authorization application review in the real-world setting. Hence, in order to fulfill this regulatory requirement, a database PASS was set up comparing safety outcomes (including CV outcomes) in initiators of the newly marketed liraglutide with outcomes in initiators of the most commonly used non-insulin antidiabetics (NIADs) in the UK population. The study design was endorsed by health regulatory authorities at a time before the establishment of the Pharmacovigilance Risk Assessment Committee (PRAC).

This paper evaluates the methodology used to collect and perform comparative drug CV safety assessments in a real-world UK population initiating liraglutide and other NIADs.

## Methods

# Data sources

In this real-world, observational, safety surveillance study of adult patients prescribed NIADs, data were obtained using individually linked UK electronic repositories: the Clinical Practice Research Datalink (CPRD) primary care database (GOLD) and Hospital Episode Statistics (HES).

# Clinical Practice Research Datalink (CPRD) GOLD

The CPRD collects anonymized medical records from general practitioners (GPs). CPRD GOLD is based on GP records using the Vision software system within the UK [14]. Patients are semi-permanently affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals and hospitalizations.

The data recorded in CPRD GOLD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. All information is recorded by staff at the GP

practice and not necessarily validated externally, although the database has generally been shown to be of high quality [4, 15]. The database currently includes more than 13 million patients, from 1987 onwards [16].

## Hospital Episode Statistics (HES)

HES contains details of all admissions to UK National Health Service (NHS) hospitals in England. All NHS trusts in England, including acute hospitals, primary care trusts and mental health trusts, are included. HES data are collected during a patient's stay at a hospital to allow hospitals to be reimbursed for the care they deliver. As the data are extracted from patients' notes, they may also reflect the quality of clinical record-keeping. HES data have been collected for admitted patients since 1989 and outpatient attendances since 2003. At the time of this study, linked CPRD GOLD and HES data were available from 1 April 1997 to 31 March 2014.

## Study design and patient population

Patients in CPRD GOLD who were considered 'new NIAD users' were eligible for inclusion. New users for each class of drug were identified by the first time each drug was prescribed, with no prescription record of that drug in the previous 12 months. Excluded patients were those aged < 18 years with a history of cancer or human immunodeficiency virus/acquired immunodeficiency syndrome, or with a history of liraglutide use, and any patient in any comparator group who had initiated liraglutide during the study. Patients were only included in each outcome analysis if they had no record of that outcome in the previous 12 months.

The study period was between 1 January 2005 and the end of follow-up time for a patient. End of follow-up was defined as the earliest of: the date of the last data collection from the GP practice; transfer out of the practice; death; or the end of data collection from HES (31 March 2014). Patients without any follow-up were excluded. All patients initiating NIADs after the end of follow-up were excluded from the analyses, as were any outcomes recorded in CPRD GOLD after this time.

## NIAD treatment groups

NIAD treatment groups included patients who initiated (new users) the following: liraglutide, exenatide, dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, saxagliptin, sitagliptin, vildagliptin), sulfonylureas, biguanides, acarbose, glinides (nateglinide, repaglinide) or glitazones (rosiglitazone, pioglitazone).

## Outcomes assessed

As part of post-marketing safety surveillance activity, outcomes captured included macrovascular conditions overall, consisting of acute myocardial infarction, ischemic heart disease (IHD), percutaneous transluminal coronary angioplasty, coronary artery bypass graft, lower limb amputation, stroke, transient ischemic attack and heart failure. These sub-outcomes were also studied separately. Other captured outcomes included malignant neoplasms (overall) and separately thyroid and pancreatic cancer and acute pancreatitis.

This manuscript focuses on the CV outcomes in the study population fulfilling the inclusion/exclusion criteria in CPRD GOLD and eligible for linkage with HES.

## Statistical analysis

Rates of each outcome and corresponding crude- and adjusted-incidence rate ratios (IRRs) were examined using Poisson regression analysis and expressed for liraglutide versus each of the comparators. The Poisson model was considered adequate for analyzing the number of occurred outcomes during the study period for each exposure in a database. Only variables contributing to the model were included using a forward stepwise procedure. Baseline characteristic measurements and confounding factor adjustments were as follows: baseline characteristics for groups of patients initiating liraglutide and other NIADS were examined at the index date; duration of diabetes was calculated based on the

patient's date of the first diabetes record; laboratory test data were used to assess HbA1c; insulin prescription (as an indicator of the burden/progression of diabetes and its comorbidities/complications) was assessed at various time points.

The number of prior antidiabetes medication types was assessed by looking at the number of antidiabetes medications prescribed in the previous year. Patients who initiated various NIADs may have continued to use these medications after index date.

Where possible, the following confounding factors were selected for adjustment: age, gender, duration of diabetes, HbA1c, insulin prescription, smoking status, alcohol consumption status and BMI.

For the crude analyses, where the number of outcome events in the liraglutide cohort was < 5, the model was not run due to the CPRD small cell data governance regulations. Where the number of outcome events in patients initiating liraglutide was < 10, further adjusted analyses could not be made, as there was not enough information to make a meaningful comparison. Adjustment for age and gender, and further adjusted analyses, could be made for outcomes with at least 10 patient events among those initating liraglutide, with convergence achieved. This included macrovascular events, IHD and heart failure.

## Results

# Patient population

There were 149 788 patients fulfilling the inclusion criteria in CPRD GOLD and eligible for linkage with HES. Table 1 shows the definition of the study population. Of these, 3432 patients initiated liraglutide.

Table 1
Definition of the study population.

| | Number of patients |
|---|---|
| Acceptable male or female patients with at least 1 day of follow-up time[¶] in CPRD GOLD | 11 673 099 |
| Patients with at least one prescription for a NIAD drug during the study period | 313 544 |
| Aged at least 18 years | 313 281 |
| Eligible for linkage with HES data, with at least 1 day of follow-up,[¶] excluding those who start treatment after the end of follow-up | 174 883<br>149 910 |
| With no history of malignant neoplasm[†] | 149 788 |
| With no history of HIV/AIDs recorded in HES[‡] | 149 788 |
| Total in the study population | |

[¶]The start of follow-up was defined as the latest date of the start of HES collection (1 April 1997), or the start of UTS follow-up. The end of follow-up was defined as the earliest date of the end of HES collection (31 March 2014), the date of the last collection from the GP practice, transfer out of the practice or death. [†]Previous cancer was assessed using the CPRD GOLD clinical and referral files and HES records. [‡]HIV/AIDS was identified from a prescription of HIV medication in the therapy file, a positive record of HIV/AIDS in the CPRD GOLD clinical, referral or test files or a HES record.

AIDS, acquired immunodeficiency syndrome; CPRD, Clinical Practice Research Datalink; GP, general practitioner; HES, Hospital Episode Statistics database; HIV, human immunodeficiency virus; NIAD, non-insulin antidiabetic; UTS, up-to-standard.

# NIAD treatment groups

Characteristics of the patients initiating each of the NIADs are shown in Table 2. Compared with patients initiating other NIADs, other than exenatide, patients initiating liraglutide were younger, had a longer mean diabetes duration and higher mean HbA1c level, were more overweight or obese, more had been prescribed insulin > 1 year prior to index date, more had a greater frequency of any microvascular complications, more had a history of hypertension at index date, and had a greater number of concomitant antidiabetic medications.

Table 2
Baseline characteristics of patients initiating treatment with each NIAD.

| Characteristic | Liraglutide | Exenatide | DPP-4 inhibitors | Acarbose | Biguanides | Glinides | Glitazones | SUs |
|---|---|---|---|---|---|---|---|---|
| Total | 3 432 | 3 252 | 17 279 | 600 | 74 067 | 964 | 16 749 | 33 142 |
| Follow-up, years, mean (SD) | 2.6 (1.3) | 3.6 (1.8) | 2.8 (1.6) | 5.2 (2.8) | 4.1 (2.6) | 4.6 (2.6) | 5.3 (2.7) | 4.1 (2.5) |
| Female sex | 1 569 (45.7%) | 1 481 (45.5%) | 7 325 (42.4%) | 259 (43.2%) | 34 604 (46.7%) | 437 (45.3%) | 6 931 (41.4%) | 13 854 (41.8%) |
| Age, years, mean (SD) | 56.2 (10.6) | 55.8 (10.6) | 61.8 (12.2) | 63.0 (12.9) | 58.2 (15.3) | 62.1 (13.5) | 61.2 (12.2) | 61.6 (13.4) |
| BMI, kg/$m^2$, mean (SD) | 38.1 (7.1) | 38.5 (7.1) | 32.7 (6.6) | 31.5 (7.2) | 32.0 (6.7) | 30.7 (6.4) | 31.7 (6.4) | 31.4 (6.6) |
| Obese (BMI ≥ 30 kg/$m^2$) | 3 127 (91.1%) | 2 989 (91.9%) | 10 776 (62.4%) | 305 (50.8%) | 41 825 (56.5%) | 475 (49.3%) | 9 348 (55.8%) | 17 674 (53.3%) |
| Duration of diabetes, years, mean (SD) | 9.7 (6.1) | 9.1 (5.7) | 8.4 (6.2) | 8.5 (6.7) | 2.8 (4.9) | 7.6 (6.7) | 6.7 (5.8) | 4.4 (4.6) |
| Smoking status | | | | | | | | |
| Non-smoker | 1 203 (35.1%) | 1 107 (34.0%) | 6 215 (36.0%) | 193 (32.2%) | 28 574 (38.6%) | 361 (37.4%) | 5 972 (35.7%) | 11 806 (35.6%) |
| Ex-smoker | 1 659 (48.3%) | 1 593 (49.0%) | 8 250 (47.7%) | 297 (49.5%) | 30 553 (41.3%) | 438 (45.4%) | 7 762 (46.3%) | 14 963 (45.1%) |
| Smoker | 570 (16.6%) | 551 (16.9%) | 2 808 (16.3%) | 105 (17.5%) | 14 490 (19.6%) | 164 (17.0%) | 2 959 (17.7%) | 6 225 (18.8%) |
| Unknown smoking status | 0 (0.0%) | 1 (< 0.1%) | 6 (< 0.1%) | 5 (0.8%) | 450 (0.6%) | 1 (0.1%) | 56 (0.3%) | 148 (0.4%) |
| Alcohol | | | | | | | | |
| Non-drinker | 362 (10.5%) | 405 (12.5%) | 2 043 (11.8%) | 90 (15.0%) | 9 322 (12.6%) | 136 (14.1%) | 2 226 (13.3%) | 4 112 (12.4%) |
| Ex-drinker | 664 (19.3%) | 565 (17.4%) | 3 069 (17.8%) | 98 (16.3%) | 8 358 (11.3%) | 176 (18.3%) | 2 425 (14.5%) | 4 593 (13.9%) |
| Drinker | 2 304 (67.1%) | 2 143 (65.9%) | 11 622 (67.3%) | 378 (63.0%) | 50 417 (68.1%) | 571 (59.2%) | 11 213 (66.9%) | 22 314 (67.3%) |
| Unknown drinking status | 102 (3.0%) | 139 (4.3%) | 545 (3.2%) | 34 (5.7%) | 5 970 (8.1%) | 81 (8.4%) | 885 (5.3%) | 2 123 (6.4%) |

Data are n (%), unless stated otherwise stated. †Calculated, not measured. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; NIAD, non-insulin antidiabetic; SD, standard deviation; SU, sulfonylurea.

| Characteristic | Liraglutide | Exenatide | DPP-4 inhibitors | Acarbose | Biguanides | Glinides | Glitazones | SUs |
|---|---|---|---|---|---|---|---|---|
| Diabetes complications in the 12 months prior to index date | 1 947 (56.7%) | 1 152 (35.4%) | 9 437 (54.6%) | 112 (18.7%) | 11 508 (15.5%) | 201 (20.9%) | 2 944 (17.6%) | 8 548 (25.8%) |
| Any microvascular complication | 387 (11.3%) | 385 (11.8%) | 1 748 (101.1%) | 58 (9.7%) | 2 039 (2.8%) | 71 (7.4%) | 1 086 (6.5%) | 1 737 (5.2%) |
| Ophthalmic complications | 61 (1.8%) | 35 (1.1%) | 196 (1.1%) | 9 (1.5%) | 262 (0.4%) | 16 (1.7%) | 111 (0.7%) | 225 (0.7%) |
| Neurological complications | 16 (0.5%) | 30 (0.9%) | 126 (0.7%) | 5 (0.8%) | 198 (0.3%) | 6 (0.6%) | 161 (1.0%) | 196 (0.6%) |
| Kidney complications | 17 (0.5%) | 12 (0.4%) | 68 (0.4%) | 3 (0.5%) | 73 (< 0.1%) | 0 (0.0%) | 17 (0.1%) | 79 (0.2%) |
| Circulatory complications | 1 730 (50.4%) | 843 (25.9%) | 8 426 (48.8%) | 54 (9.0%) | 9 760 (13.2%) | 128 (13.3%) | 1 819 (10.9%) | 7 102 (21.4%) |
| Diabetic foot or arthropathy complications | | | | | | | | |
| Other comorbidities | 2 747 (80.0%) | 2 615 (80.4%) | 12 980 (75.1%) | 456 (76.0%) | 43 236 (58.4%) | 696 (72.2%) | 12 408 (74.1%) | 22 803 (68.8%) |
| History of hypertension | 136 (4.0%) | 136 (4.2%) | 801 (4.6%) | 38 (6.3%) | 2 244 (3.0%) | 66 (6.8%) | 438 (2.6%) | 1 599 (4.8%) |
| History of congestive heart failure | | | | | | | | |
| HbA1c (%), mean (SD) | 9.4 (1.7) | 9.3 (1.7) | 8.9 (1.5) | 8.8 (1.7) | 8.6 (1.9) | 8.7 (1.7) | 8.9 (1.5) | 9.0 (1.8) |
| HbA1c (mmol/mol)[†], mean (SD) | 79.2 (18.6) | 78.1 (18.6) | 73.8 (16.4) | 72.7 (18.6) | 70.5 (20.8) | 71.6 (18.6) | 73.8 (16.4) | 74.9 (19.7) |
| Insulin prescribed > 1 year before index | 974 (28.4%) | 945 (29.1%) | 1 495 (8.7%) | 58 (9.7%) | 2 526 (3.4%) | 110 (11.4%) | 833 (5.0%) | 822 (2.5%) |

Data are n (%), unless stated otherwise stated. [†]Calculated, not measured. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; NIAD, non-insulin antidiabetic; SD, standard deviation; SU, sulfonylurea.

| Characteristic | Liraglutide | Exenatide | DPP-4 inhibitors | Acarbose | Biguanides | Glinides | Glitazones | SUs |
|---|---|---|---|---|---|---|---|---|
| No insulin prescribed before or on index date | 2 354 (68.6%) | 2 193 (67.4%) | 15 617 (90.4%) | 533 (88.8%) | 70 724 (95.5%) | 799 (82.9%) | 15 809 (94.4%) | 32 029 (96.6%) |
| Number of diabetes medications prescribed in the year prior to index date, mean (SD) | 2.3 (1.0) | 2.1 (0.9) | 1.7 (0.7) | 1.8 (1.0) | 0.1 (0.3) | 1.7 (0.9) | 1.5 (0.6) | 0.9 (0.6) |

Data are n (%), unless stated otherwise stated. †Calculated, not measured. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated hemoglobin; NIAD, non-insulin antidiabetic; SD, standard deviation; SU, sulfonylurea.

Baseline patient characteristics for exenatide were similar to those initiating liraglutide.

# Clinical outcomes

For macrovascular outcomes overall, adjustments could be made for all eight confounders (age, gender, duration of diabetes, HbA1c, insulin prescribing, smoking status, alcohol consumption status and BMI). For IHD and heart failure, the stepwise regression resulted in differing predictive variables. For IHD, HbA1c did not meet the threshold in the comparison with glitazones, nor BMI for sulfonylureas. Patients with a previous history of a given CV outcome were excluded, and important baseline characteristics and confounders can be seen in Table 2.

An increased risk of IHD and heart failure was observed with liraglutide use compared to NIADs (Table 3). For macrovascular conditions overall, the estimated unadjusted IRRs were significantly higher for liraglutide versus biguanides or glitazone initiators (Table 3). After age and gender adjustment, the IRRs for liraglutide initiators were also significantly higher versus DPP-4 inhibitor or sulfonylurea initiators. However, after stepwise adjustment of the IRR, adjusting for age, smoking, alcohol, gender, insulin prescription, BMI, HbA1c and diabetes duration, liraglutide initiators only had an increased risk of macrovascular conditions versus biguanide initiators (IRR: 1.33 [99% confidence interval (CI): 1.11;1.59]).

Table 3
Risk of macrovascular conditions for patients initiating liraglutide compared with other NIADs.

| Treatment | Number of patients | Number of outcome events | Person-years | Incidence (99% CI)[†] | Unadjusted IRR (99% CI) | Age- and gender-adjusted IRR (99% CI) | Stepwise adjusted IRR (99% CI) |
|---|---|---|---|---|---|---|---|
| **Risk of macrovascular conditions overall** | | | | | | | |
| Liraglutide | 3 323 | 263 | 4 009 | 6.56 (5.60;7.69) | N/A | N/A | N/A |
| Exenatide | 3 153 | 242 | 3 762 | 6.43 (5.45;7.59) | 1.02 (0.81;1.28) | 1.02 (0.81;1.29) | 1.04 (0.82;1.30)[a,b,d,e] |
| DPP-4is | 16 656 | 1 540 | 2 3973 | 6.42 (6.02;6.86) | 1.02 (0.86;1.21) | 1.38 (1.16;1.65)* | 1.07 (0.88;1.29)[a,b,c,d,e,f,g,h] |
| Acarbose | 563 | 53 | 730 | 7.26 (5.10;10.34) | 0.90 (0.61;1.33) | 1.25 (0.83;1.88) | 0.99 (0.65;1.52)[a,d,e,f] |
| Biguanides | 71 445 | 7 549 | 17 0581 | 4.43 (4.30;4.56) | 1.48 (1.26;1.74)* | 1.92 (1.63;2.26)* | 1.33 (1.11;1.59)*[,a,b,c,d,e,f,g,h] |
| Glinides | 903 | 114 | 1 307 | 8.72 (6.85;11.10) | 0.75 (0.56;1.00) | 1.00 (0.74;1.35) | 0.80 (0.56;1.12)[a,b,d,e] |
| Glitazones | 16 290 | 2 040 | 40 845 | 4.99 (4.72;5.29) | 1.31 (1.11;1.55)* | 1.73 (1.45;2.05)* | 1.19 (0.98;1.45)[a,b,c,d,e,f,g,h] |
| Sulfonylureas | 31 379 | 4 037 | 67 929 | 5.94 (5.71;6.19) | 1.10 (0.94;1.30) | 1.55 (1.31;1.83)* | 1.06 (0.88;1.29)[a,b,c,d,e,f,g,h] |
| **Risk of ischemic heart disease** | | | | | | | |
| Liraglutide | 3369 | 230 | 4 078 | 5.64 (4.76;6.68) | N/A | N/A | N/A |
| Exenatide | 3182 | 206 | 3823 | 5.39 (4.50;6.45) | 1.05 (0.82;1.34) | 1.04 (0.82;1.34) | 1.06 (0.83;1.36)[a,b,d,e] |
| DPP-4is | 16 959 | 1254 | 24 633 | 5.09 (4.73;5.47) | 1.11 (0.92;1.33) | 1.50 (1.24;1.81)* | 1.15 (0.94;1.41)[a,b,c,d,e,f,g,h] |
| Acarbose | 574 | 42 | 762 | 5.51 (3.70;8.20) | 1.02 (0.66;1.58) | 1.38 (0.88;2.17) | 1.18 (0.75;1.87)[a,d,e] |
| Biguanides | 72 537 | 5777 | 17 6250 | 3.28 (3.17;3.39) | 1.72 (1.45;2.04)* | 2.19 (1.84;2.60)* | 1.45 (1.20;1.76)*[,a,b,c,d,e,f,g,h] |
| Glinides | 930 | 97 | 1363 | 7.12 (5.48;9.24) | 0.79 (0.58;1.08) | 1.04 (0.75;1.44) | 0.75 (0.52;1.09)[a,d,e,f,g] |
| Glitazones | 16 453 | 1524 | 41 853 | 3.64 (3.41;3.89) | 1.55 (1.29;1.86)* | 1.99 (1.66;2.40)* | 1.40 (1.13;1.73)*[,a,b,c,d,e,f,h] |
| Sulfonylureas | 32 198 | 3145 | 71 068 | 4.43 (4.23;4.63) | 1.27 (1.07;1.52)* | 1.77 (1.48;2.12)* | 1.13 (0.92;1.40)[a,b,c,d,e,g,h] |

All IRRs are for the comparator vs liraglutide. [†]Per 100 person-years.*$P < 0.01$. Bonferroni correction applied. Adjusted for [a]age, [b]smoking, [c]alcohol use, [d]gender, [e]insulin prescribing, [f]BMI, [g]HbA1c, [h]diabetes duration. BMI, body mass index; CI, confidence interval; DPP-4is, dipeptidyl peptidase-4 inhibitors; HES, Hospital Episode Statistics database; IRR, incidence rate ratio; NIAD, non-insulin antidiabetic; N/A, not applicable.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Risk of macrovascular conditions overall** | | | | | | | |
| **Risk of heart failure** | | | | | | | |
| Liraglutide | 3405 | 66 | 4290 | 1.54 (1.12;2.11) | N/A | N/A | N/A |
| Exenatide | 3229 | 52 | 4062 | 1.28 (0.90;1.83) | 1.20 (0.75;1.94) | 1.22 (0.76;1.97) | 1.26 (0.78;2.03)[a,c,d,e,f,h] |
| DPP-4is | 17087 | 436 | 25 944 | 1.68 (1.49;1.90) | 0.92 (0.65;1.29) | 1.47 (1.03 ;2.08)* | 0.97 (0.67;1.41)[a,b,d,e,f,g,h] |
| Acarbose | 591 | 17 | 805 | 2.11 (1.13;3.95) | 0.73 (0.36;1.47) | 1.14 (0.54;2.41) | 0.67 (0.30;1.48)[a,d,e,f,h] |
| Biguanides | 73 613 | 2187 | 18 7903 | 1.16 (1.10;1.23) | 1.32 (0.96;1.82) | 2.00 (1.45;2.77)* | 1.28 (0.90;1.81)[a,b,c,d,e,f,g,h] |
| Glinides | 951 | 43 | 1494 | 2.88 (1.94;4.26) | 0.53 (0.32;0.88)* | 0.83 (0.49;1.43) | 0.63 (0.36;1.11)[a,d,e,f,h] |
| Glitazones | 16 682 | 664 | 44 246 | 1.50 (1.36;1.66) | 1.02 (0.73;1.43) | 1.59 (1.13;2.22)* | 0.99 (0.68;1.45)[a,b,c,e,f,g] |
| Sulfonylureas | 32 660 | 1487 | 75 832 | 1.96 (1.83;2.10) | 0.78 (0.57;1.08) | 1.33 (0.96;1.85) | 0.84 (0.58;1.21)[a,b,c,d,e,f,g] |

All IRRs are for the comparator vs liraglutide. [†]Per 100 person-years.*$P < 0.01$. Bonferroni correction applied. Adjusted for [a]age, [b]smoking, [c]alcohol use, [d]gender, [e]insulin prescribing, [f]BMI, [g]HbA1c, [h]diabetes duration. BMI, body mass index; CI, confidence interval; DPP-4is, dipeptidyl peptidase-4 inhibitors; HES, Hospital Episode Statistics database; IRR, incidence rate ratio; NIAD, non-insulin antidiabetic; N/A, not applicable.

A total of 230 IHD events were observed, leading to an estimated incidence per 100 person years of 5.64 (99% CI: 4.76;6.68). The estimated unadjusted and age- and gender-adjusted IRRs were significantly higher for patients initiating liraglutide versus biguanide, glitazone or sulfonylurea initiators (Table 3). After adjusting for age and gender, the IRR was signficantly higher for liraglutide initiators versus DPP-4 inhibitor, biguanide, glitazone or sulfonylurea initiators. The comparison to biguanide and gliatazone initiators remained significant for the stepwise-adjusted IRR after adjusting for age, smoking, alcohol, gender, insulin prescription, BMI, HbA1c and diabetes duration (IRR: 1.45 [99% CI: 1.20;1.76] and IRR: 1.40 [99% CI:1.13;1.73], respectively).

For heart failure, the estimated age- and gender-adjusted IRRs were significantly higher for liraglutide initiators versus DPP-4 inhibitor, biguanide and glitazone initiators (Table 3). However, none of the stepwise-adjusted IRRs were statistically significant (see Table 3 for specific adjustments).

# Discussion

An increased risk of some macrovascular conditions was observed in liraglutide initiators, compared with those initiating most other NIADs. However, after performing a stepwise adjustment, increased risk was only seen in liraglutide initiators compared with biguanide initators. These findings are likely explained by the differential drug choice applied to the different subpopulations of T2D. Compared with other NIAD initiators at baseline, liraglutide initiators had more advanced and longer duration of T2D, reflected by having more microvascular complications, more concomitant NIAD and insulin use and higher HbA1c levels. In addition, more components of the MetS were captured for liraglutide initiators. These findings suggest that UK physicians prescribed liraglutide to a selected T2D subpopulation who presented with MetS (selection bias) and/or had a more advanced stage of T2D, poorly controlled with the marketed antidiabetics available at the time liraglutide entered the market (chanelling bias).

The observed increase of macrovascular outcomes in the liraglutide initiator cohort may rather be due to the population's baseline metabolic risk profile and not to liraglutide exposure itself (confounding). In addition, liraglutide initiators may have had other inherent residual baseline characteristics which have not been measured but increase CV risk (residual confounding), e.g. higher levels of hyperinsulinemia/insulin resistance (which are associated with MetS and independently associated with increased risk of CV outcomes [17]) or diabetic dyslipidemia (increased triglyceride levels, decreased high-density lipoprotein-cholesterol levels and increased small dense low-density lipoprotein particle levels), which is a component of the MetS and independently associated with increased risk of CV outcomes [2, 5, 18].

This study´s real-world findings on pre-liraglutide patient characteristics are in line with those reported by the UK Association of British Clinical Diabetologists' audits, which examined data on 6238 liraglutide-treated patients from 2009 to 2013 [19]. Liraglutide users from diabetes centers across the UK were found to be heavier and with poorer glycemic control than patients from liraglutide phase 3 RCTs. The conclusion was that the baseline characteristics of liraglutide-treated patients were influenced by the UK NICE guidelines, which recommend liraglutide for patients with high BMI (≥ 35 kg/$m^2$) [19]. Patients with higher BMIs inherently have a higher probability of having more cardiometabolic risk factors [12]. In addition, UK reimbursement conditions add to further confounding by indication, reinforcing that patients initiating liraglutide have higher CV risk [20].

In this study, liraglutide initiation itself appears to be an indicator for the presence of a higher clustering of cardiometabolic risk and more advanced disease stage within the continuum of T2D. The same appears to apply to exenatide, which can be expected, as both belong to the same drug class (GLP-1RAs).

Non-interventional database studies lack randomization, with resulting bias and confounding. This is a specific problem in T2D, where increasing diabetes severity (comorbidities/complications and stage of progression) is followed by treatment steps, and lack of response leads to treatment intensification. Thus, separating disease severity from treatment exposure as the causal agent for increased incidences of CV outcomes in a heterogeneous T2D population, as in the presented study, can be challenging. Baseline treatment characteristics must be balanced between cohorts to achieve homogeneity across cohorts. In order to finalize a study design with homogeneity across treatment cohorts, thorough background knowledge is required, encompassing the disease and its natural history, complications and comorbidities, the likely real-world target population of the drug and current local pharmacotherapy guidelines, and the feasibility of obtaining required data from the chosen source.

The presented study highlights that comparative analysis of treatment initiator cohorts, without thoroughly balancing baseline characteristics, is not suited to addressing new drug safety. In this study, patient baseline characteristics had not been matched among cohorts. In addition, it was not possible to adjust for all of the a priori planned covariates, owing in part to the rarity of the outcomes under investigation. Risk estimates for liraglutide initiators are likely to have been increased when adjusting for age, since liraglutide users were younger. Even with a relatively large database such as the CPRD, the comparison of a new drug to existing therapies was challenging due to the heterogeneity of the populations treated with different drugs, and the relatively low numbers of new drug initiators.

Of note, real-world liraglutide observational data emerging from comparative studies based on cohorts which had been matched (baseline characteristics were equally weighted across cohorts) have shown that liraglutide use was associated with significantly lower major adverse CV event (MACE) risk [21]. Additionally, CV outcomes trials with GLP-1RAs have not reported increased CV risk [13]. The blinded, randomized, placebo-controlled LEADER trial demonstrated that MACE risk was signficantly reduced in liraglutide- versus placebo-treated patients [22]. These findings support our interpretation that selection bias, confounding and possibly channelling bias drive the observed increased CV risk in liraglutide initiators in the UK real-world setting in the presented study.

Observational studies provide external validity of a drug's safety and effectiveness in everyday clinical practice, thus supporting decision-makers and key stakeholders regarding treatment options to be carried out in the real world [23].

Observational PASS are key in gathering this type of real-world evidence. However, as patients are not randomized, the study design for investigating the safety of newly marketed products should, to the extent possible, account for confounding and bias. This requires the feasibility of aquiring sufficient data quantity and quality to obtain true homogeneity among cohorts. These considerations are in line with the Guidelines for Good Pharmacoepidemiology Practice [24] and should be taken into account also when designing and interpreting studies that seek to support regulatory decisions.

This regulatory health authorityrequired PASS sought to investigate the safety of liraglutide in the UK realworld setting. CPRD GOLD reflects the UK real-world clinical practice setting [16]. Patients prescribed liraglutide had higher components of the MetS and markedly more advanced T2D than NIAD initiators. It was not always possible to adjust for all confounders and, in some cases, this may have modulated safety outcomes, although in others, significant results persisted despite adjustment for all confounders (e.g. comparison with biguanides). The study design allows for a descriptive analysis of the cohort populations initiating different antidiabetic medications. An improved study design to assess CV safety with liraglutide would require equally weighting the baseline characteristics. This study was endorsed by the health regulatory authorities at a time before the establishment of the Pharmacovigilance Risk Assessment Committee (PRAC). PRAC is responsible for reviewing the design and for the evaluation of post-authorisation safety studies. In addition, this observational real world study was thought to complement the the liraglutide Cardiovascular Outcome Trial (CVOT), LEADER, which was also a regulatory authority required PASS at the time of marketing authorization (2009).

## Conclusions

The methodology for this study was insufficient to generate reliable real-world CV safety data to compare liraglutide initiators with other NIAD initiators. An increased risk of some macrovascular conditions was observed in patients initiating liraglutide compared to those initiating other NIADs. However, the observed difference in CV risk is likely due to differences in baseline characteristics between the NIAD cohorts, and not to the specific NIAD initiated. These results emphasize the importance of countering selection bias and confounding when designing a study comparing CV outcomes across treatment initiator cohorts in heterogenous populations, in order to generate robust real-world evidence to support regulatory and health providers' decisions, enhancing patient safety.

## Abbreviations

BMI, body mass index; CI, Confidence Interval ; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; GP, general practitioner; HES, Hospital Episode Statistics; IHD, ischemic heart disease; IRR, incidence rate ratios; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; NHS, National Health Service; NIAD, non-insulin antidiabetic; PASS, post authorization safety study; RCT, randomized clinical trial; T2D, type 2 diabetes; SU, sulphonylurea

## Declarations

*Ethics approval and consent to participate:* This study was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency, under reference number 10_044. This work uses data provided by patients and collected by the NHS as part of their care and support.

*Consent for publication:* Not applicable.

*Availability of data and materials:* The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

*Competing interests:* HG, TJ and AMP are employees of and stockholders in Novo Nordisk. AG has no potential conflicts of interest to declare.

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*Authors' contributions*: AG, HG, TJ and AMP analyzed the data and wrote the manuscript.

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