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RESEARCH LETTER

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Clinical characteristics and glucose-lowering drug utilization among patients initiating liraglutide in Denmark: a routine clinical care prescription study

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Highlights

- This population-based real-world prescription study characterized all new users of liraglutide in northern Denmark from 2009 to 2015.
- More than half (57%) the patients had liraglutide prescribed as part of drug combinations outside the originally approved indications.
- Comorbidities or diabetes complications were present in most patients, with the highest prevalence observed among the 73% of initiators who would have been ineligible for the Liraglutide Effect and Action in Diabetes (LEAD) 1-5 trials that led to liraglutide registration, underscoring the need for further post-marketing studies.

KEYWORDS
cross-sectional studies, diabetes pharmacology, drug utilization, glucagon-like peptide-1 receptor, liraglutide

To the Editor

The number of users of the glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) liraglutide has grown substantially since its approval in Europe in 2009 and in the US in 2010. Routine clinical care drug users often differ considerably from participants of randomized trials in terms of age, comorbidities, and comedications, factors that may be of importance for a drug's, effect including cardiovascular outcomes, mortality, and risk of adverse events.[1] Thus, there is a need for post-marketing information on the prevalence and extent of comorbidity and off-label drug use among liraglutide users in everyday clinical practice.[2]

1 | METHODS

In this population-based cross-sectional study we linked existing population-based medical databases covering all redeemed prescriptions,[3] laboratory data, and hospital

outpatient and inpatient diagnoses for the 1.8 million inhabitants of northern Denmark, as described in more detail elsewhere.[4] The study cohort included 9251 individuals who initiated liraglutide between 2009 and 2015 and who had lived in northern Denmark continuously during the year prior to initiation. Liraglutide accounts for more than 90% of all GLP-1RA use in Denmark.[2] We first examined each patient's baseline glucose-lowering therapy use in the 100 days before liraglutide initiation. We then examined 100-day post-treatment initiation combinations. Finally, we ascertained diabetes complications and comorbidities present at the time of liraglutide initiation, based on patients' complete histories of drug prescriptions, hospital procedures, diagnoses, and laboratory tests. Patients were stratified based on eligibility (yes/no) to participate in the Liraglutide Effect and Action in Diabetes (LEAD) 1-5 trials (the Phase III trials that liraglutide approval was based upon) using definitions described in more detail elsewhere.[5] When reporting HbA1c and estimated glomerular filtration rate (eGFR), we used the most recent measurement within the 1-year period before liraglutide initiation.

1.1 | Ethics approval

Under Danish law, no ethics approval is required for register-based studies. This project was approved by the Danish Data Protection Agency (File no. 2014-54-0922).

2 | RESULTS

As shown in Figure 1, the most common glucose-lowering drug regimens preceding liraglutide initiation were as follows: metformin in combination with other non-insulin glucose-lowering drugs (34%); metformin + insulin (21%); metformin monotherapy (20%); and insulin monotherapy (9%). After liraglutide initiation, liraglutide was most often used in combination with metformin (40%), followed by metformin plus insulin (23%; Figure 1).

Liraglutide initiators were mostly male (59%) and had a median age of 59 years (interquartile range [IQR] 50-66 years). The median HbA1c before liraglutide initiation was 8.4% (IQR 7.5%-9.5%; Table 1).

More than half the patients (58%) had one or more microvascular complications, including previous hospital-diagnosed retinopathy (26%), neuropathy (7%), hospital-coded renal complications (8%), history of microalbuminuria (more than one positive test; 39%), and/or eGFR ≤60 mL/min per 1.73 m^2 (12%). A proportion of patients (29%) had a history of clinically significant hospital-diagnosed cardiovascular disease, including previous ischemic heart disease (23%), cerebrovascular disease (8%), heart failure (5%), and/or abdominal and/or peripheral vascular disease (11%). In total, comorbidities or complications were present in more than half of all liraglutide initiators, with prevalences much higher in the 73% of initiators who were ineligible for the LEAD trials than among the 27% patients who would have been eligible (macrovascular complications: 41% vs 6%; microvascular

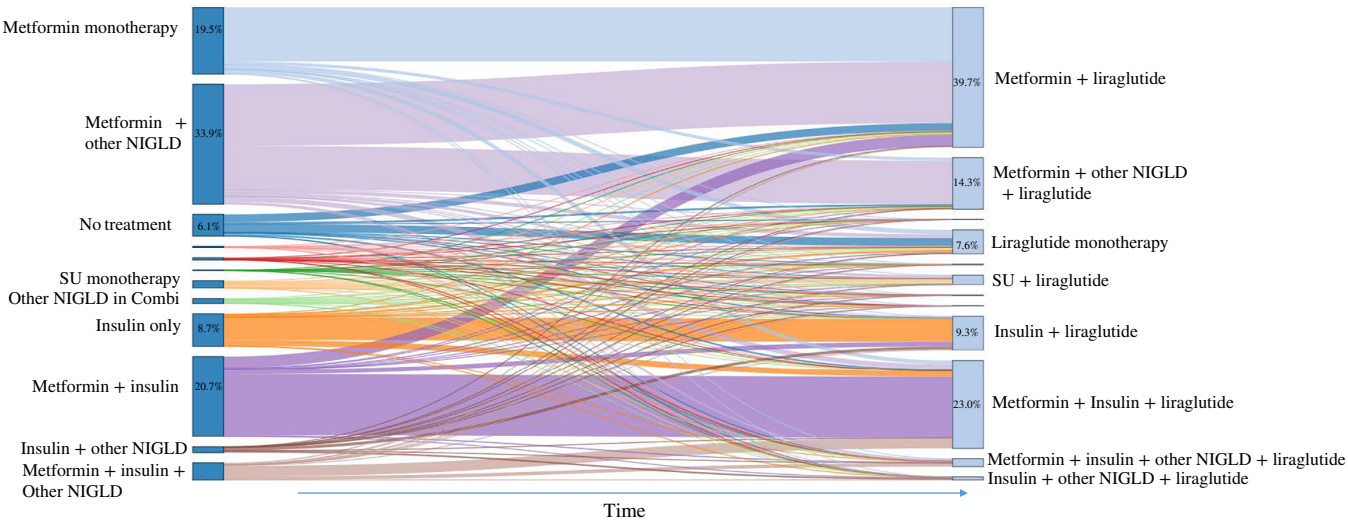

FIGURE 1 Glucose-lowering drugs used 100 days before (left-hand side) and 100 days after (right-hand side) first-time redemption of a liraglutide prescription. Liraglutide initiators most often transitioned from therapy with metformin plus another non-insulin glucose-lowering drug (NIGLD; 33.9%), metformin monotherapy (19.5%), metformin plus insulin (20.7%), insulin monotherapy (8.7%) or no glucose-lowering drug (6.1%). Percentages show the proportion of all patients within different drug groups before (left-hand side) and after (right-hand side) first-time redemption of a liraglutide prescription. DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; SGLT2i: sodium-glucose cotransporter 2 inhibitors; SU, sulfonylurea drugs

TABLE 1 Clinical characteristics of 9251 real-world initiators of liraglutide in northern Denmark, 2009 to 2015

	Total	Would have been excluded from LEAD 1-5 trials	Would have been included in LEAD 1-5 trials
Overall	9251 (100)	6768 (73.2)	2483 (26.8)
Sex			
Female	3815 (41.2)	2788 (41.2)	1027 (41.4)
Male	5436 (58.8)	3980 (58.8)	1456 (58.6)
Age (y)			
0-30	134 (1.4)	99 (1.5)	35 (1.4)
31-59	4702 (50.8)	3262 (48.2)	1440 (58.0)
60-69	3106 (33.6)	2354 (34.8)	752 (30.3)
≥ 70	1309 (14.1)	1053 (15.6)	256 (10.3)
Median [IQR] age (y)	59.2 [50.2-66.4]	60.1 [51.1-67.1]	56.8 [48.7-66.4]
Calendar period of liraglutide initiation			
2009-11	4810 (52.0)	3631 (53.6)	1179 (47.5)
2012-13	2571 (27.8)	1828 (27.0)	743 (29.9)
2014-15	1870 (20.2)	1309 (19.3)	561 (22.6)
Baseline HbA1c (%; most recent in past 1 y)			
No measurement	221 (2.4)	170 (2.5)	51 (2.1)
< 6.5	408 (4.4)	408 (6.0)	0 (0)
6.5-6.9	663 (7.2)	649 (9.6)	14 (0.6)
7-7.4	1108 (12.0)	658 (9.7)	450 (18.1)
7.5-7.9	1297 (14.0)	785 (11.6)	512 (20.6)
8-8.9	2357 (25.5)	1544 (22.8)	813 (32.7)
9-9.9	1595 (17.2)	1075 (15.9)	520 (20.9)
≥ 10	1602 (17.3)	1479 (21.9)	123 (5.0)
Median [IQR] HbA1c (%)	8.4 [7.5-9.5]	8.5 [7.4-9.8]	8.2 [7.6-9.0]
Diabetes duration (y)			
< 1	622 (6.7)	484 (7.2)	138 (5.6)
1-<2	534 (5.8)	336 (5.0)	198 (8.0)
2-<3	597 (6.5)	380 (5.6)	217 (8.7)
≥ 3	7498 (81.1)	5568 (82.3)	1930 (77.7)
Macrovascular complications	2898 (31.3)	2752 (40.7)	146 (5.9)
Ischemic heart disease	2127 (23.0)	2001 (29.6)	126 (5.1)
Cerebrovascular disease	736 (8.0)	729 (10.8)	7 (0.3)
Abdominal and peripheral vascular disease	982 (10.6)	966 (14.3)	16 (0.6)
Microvascular complications[a]	5358 (57.9)	4223 (62.4)	1135 (45.7)
Eye complications	2414 (26.1)	1972 (29.1)	442 (17.8)
Neurological complications	657 (7.1)	582 (8.6)	75 (3.0)
Renal	726 (7.8)	646 (9.5)	80 (3.2)
Microalbuminuria[b]	3648 (39.4)	2865 (42.3)	783 (31.5)
eGFR <60 mL/min per 1.73 m^2	1107 (12.0)	994 (14.7)	113 (4.6)
CCI score[c]			
0	5652 (61.1)	3481 (51.4)	2171 (87.4)
1	1909 (20.6)	1697 (25.1)	212 (8.5)

TABLE 1 (Continued)

	Total	Would have been excluded from LEAD 1-5 trials	Would have been included in LEAD 1-5 trials
2	986 (10.7)	903 (13.3)	83 (3.3)
≥ 3	704 (7.6)	687 (10.2)	17 (0.7)
Atrial fibrillation	609 (6.6)	541 (8.0)	68 (2.7)
Hypertension	3614 (39.1)	3019 (44.6)	595 (24.0)
COPD	904 (9.8)	804 (11.9)	100 (4.0)
Renal disease	224 (2.4)	216 (3.2)	8 (0.3)
Rheumatic disease	305 (3.3)	283 (4.2)	22 (0.9)
Osteoarthritis	1520 (16.4)	1172 (17.3)	348 (14.0)
Osteoporosis or fracture	239 (2.6)	206 (3.0)	33 (1.3)
History of infections requiring hospitalization	3640 (39.3)	2952 (43.6)	688 (27.7)
Obesity	2833 (30.6)	2275 (33.6)	558 (22.5)
Mental disorders	3860 (41.7)	3047 (45.0)	813 (32.7)
Thrombocyte aggregation prophylaxis	4339 (46.9)	3527 (52.1)	812 (32.7)
Statins	7228 (78.1)	5320 (78.6)	1908 (76.8)
ACE inhibitors	4385 (47.4)	3265 (48.2)	1120 (45.1)
ARBs	2997 (32.4)	2276 (33.6)	721 (29.0)
Antihypertensive treatment	7567 (81.8)	5677 (83.9)	1890 (76.1)
Marital status			
Unmarried	1490 (16.1)	1054 (15.6)	436 (17.6)
Widowed	651 (7.0)	494 (7.3)	157 (6.3)
Divorced	1371 (14.8)	1058 (15.6)	313 (12.6)
Married	5557 (60.1)	4023 (59.4)	1534 (61.8)
Unknown	182 (2.0)	139 (2.1)	43 (1.7)

Note. Unless indicated otherwise, data are given as n (%). All categories are cross-sectional or retrospective, as appropriate.

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LEAD, Liraglutide Effect and Action in Diabetes 1-5 (Phase III trials that liraglutide approval was based upon).

[a]Eye, neurological, or renal.

[b]Two or more positive tests.

[c]The Charlson Comorbidity Index (CCI) includes 19 major disease categories, ascertained from each individual's complete hospital contact history before the date of initial liraglutide treatment. Diabetes was excluded.

complication: 62% vs 46%; conditions in the Charlson comorbidity index: 49% vs 13%; Table 1).

3 | COMMENT

The initial indications for liraglutide approved by the European Medicines Agency in 2009 were: (a) use in combination with metformin or sulfonylurea, among patients with insufficient glycemic control despite a maximum tolerated dose of monotherapy with metformin or sulfonylurea; or (b) use in combination with metformin and a sulfonylurea or metformin and a thiazolidinedione in patients with insufficient glycemic control despite dual therapy.[6] In the present study, between 2009 and 2015, less than half (43%) of the routine clinical care patients initiated liraglutide in accordance with these original indications (see left-hand side of Figure 1), and there was little change during this period. The indication for liraglutide has since been broadened to include treatment in combination with basal insulin (2014) and as monotherapy (2016), covering all drug combinations shown in Figure 1. As seen in Figure 1, virtually no liraglutide plus insulin users during the period 2009 to 2015 were naïve to insulin at the time of liraglutide initiation (ie, liraglutide was used as an add-on to previous insulin treatment, not as cotherapy in tandem with insulin initiation).

In conclusion, we found that liraglutide was initially prescribed off-label for more than half of all liraglutide initiators. Moreover, comorbidities or complications were present

in more than half of all liraglutide initiators, with a distribution skewed towards the 73% of those we previously showed would have been ineligible for the LEAD 1-5 trials.[5] These data are important because the risk of potential adverse drug effects may be higher among multimorbid patients treated in everyday clinical practice, and in those with off-label drug treatment, than what has been observed among patients in randomized trials. Our aim was not to investigate drug safety, and our findings may not necessarily represent an increased risk to treated patients, yet these results underscore the need for further post-marketing observational and safety studies.

DISCLOSURE

AP has received funding from Novo Nordisk for unrelated projects, with funding paid to his institution (no personal fees). FKK has served as consultant to, received research support for unrelated research projects from, and/or been part of scientific advisory panels and/or speakers bureaus for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Norgine, Sanofi, and Zealand Pharma. FKK is academically affiliated with, not employed by, the Novo Nordisk Foundation Center for Basic Metabolic Research at Copenhagen University. All other authors declare that they have no personal potential competing interests. The Department of Clinical Epidemiology at Aarhus University is involved in other studies with funding from various companies as research grants to (and administered by) Aarhus University, not including the submitted work. None of the authors received support from any organization for the submitted work. All authors have completed the ICMJE Uniform Disclosure at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

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