Open access • Journal Article • DOI:10.1111/1753-0407.12919

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Published on: 01 Aug 2019 - Journal of Diabetes (J Diabetes)

Topics: Liraglutide, Medical prescription and Population

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Published in:
Journal of Diabetes

DOI:
10.1111/1753-0407.12919

Publication date:
2019

Document version:
Accepted manuscript

Citation for pulished version (APA):
Knudsen, J. S., Thomsen, R. W., Pottegård, A., Knop, F. K., & Sørensen, H. T. (2019). Clinical characteristics and glucose-lowering drug utilization among patients initiating liraglutide in Denmark: a routine clinical care prescription study. *Journal of Diabetes*, *11*(8), 690-694. https://doi.org/10.1111/1753-0407.12919

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

Running title: **Liraglutide initiators in Denmark**

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1753-0407.12919

Highlights

In this population-based real-world prescription study, we characterized all new users of liraglutide in Northern Denmark 2009-2015. More than half (57%) of the patients had liraglutide prescribed as part of drug combinations outside the originally approved indications. Comorbidities or diabetes complications were present in the majority of all patients, with the highest prevalences observed among the 73% of initiators who would have been ineligible for the LEAD 1-5 trials that lead to liraglutide registration, underscoring the need for further post-marketing studies.

Keywords: diabetes pharmacology; drug utilization; liraglutide; cross-sectional studies; glucagon-like peptide-1 receptor; Denmark.

To the Editor

The number of users of the glucagon-like peptide 1 receptor agonist (GLP-1RA) liraglutide has grown substantially since its approval in Europe (2009) and the USA (2010). Routine clinical care drug users often differ considerably from randomized trial participants with regard to age, comorbidities, and comedications - factors that may be of importance for the 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].

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 9,251 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 previous 100 days before liraglutide initiation. We then examined 100 day post-initiation treatment combinations. Finally, we ascertained diabetes complications and comorbidities present at the time of liraglutide initiation, based on patients' complete history of drug prescriptions, hospital procedures and diagnoses, and laboratory tests. We stratified patient characteristics by eligibility (yes/no) to participation in the LEAD 1-5 trials (Liraglutide Effect and Action in Diabetes 1–5 [the phase III trials that liraglutide approval was based upon]) using definitions

described in more detail elsewhere[5]. When reporting HbA1c and eGFR we used the latest measurement within one year before liraglutide initiation.

Results

We found that the glucose-lowering drug regimens preceding liraglutide initiation were most often the following: metformin in combination with other non-insulin glucose-lowering drugs (34%), metformin + insulin (21%), metformin monotherapy (20%), and insulin monotherapy (9%) (Figure 1). After liraglutide initiation, liraglutide was most often used in combination with metformin (40%) and metformin + 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 value before liraglutide initiation was 8.4% (IQR 7.5%-9.5%). (Table 1).

More than half of 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 (> 1 positive test) (39%), and/or estimated glomerular filtration rate (eGFR) ≤60 ml/min/1.73m2 (12%). A proportion of 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 liraglutide initiators, with much higher prevalences in the 73% of initiators who were ineligible for the LEAD trials versus the 27% patients who would have been eligible (macrovascular complications: 41% vs 6%, microvascular complication: 62% vs 46%, conditions in the Charlson comorbidity index: 49% vs 13%, Table 1).

Comment

The initial indications for liraglutide approved by the European Medicines Agency (EMA) in 2009 were 1) use in combination with metformin or sulphonylurea, among patients with insufficient glycemic control despite maximum tolerated dose of monotherapy with metformin or sulphonylurea or 2) use in combination with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycemic control despite dual therapy[6]. During 2009-2015, less than half (43%) of our routine clinical care patients initiated liraglutide in accordance with these original indications (Figure 1, left-hand side), 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 + insulin users during 2009-2015 were naïve to insulin at the time of liraglutide initiation; *i.e.*, liraglutide was used as an add-on to previous insulin treatment, not as co-therapy in tandem with insulin initiation.

In conclusion, we found that liraglutide initially was prescribed off-label in more than half of liraglutide initiators. Moreover, comorbidities or complications were present in more than half of liraglutide initiators, with a distribution skewed towards the 73% of initiators 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 has been observed among randomized trial patients. 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.

Acknowledgements

Funding: Aarhus University Research Foundation funded the study. The sponsor had no role in study design, data collection, analysis or interpretation of the data, writing of the manuscript, or in the decision to submit the paper for publication. All authors had full access to the study data and had final responsibility for the decision to submit for publication.

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 speaker's 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 (CMBU) 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).

Ethics approval: Under Danish law, no ethical approval is required for register based studies.

The project was approved by the Danish Data Protection Agency (file number 2014-54-0922).

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Figure 1. Glucose-lowering drugs used 100 days before (left-hand side of figure) and 100 days after (right-hand side of figure) first-time redemption of a liraglutide prescription

Liraglutide initiators most often transitioned from therapy with metformin + another non-insulin glucose-lowering drug (GLD) (33.9%), metformin monotherapy (19.5%), metformin + insulin (20.7%), insulin monotherapy (8.7%), or no GLD (6.1%). Percentages show the proportion of all patients within different drug groups before (left-hand side of figure) and after (right-hand side of figure) first-time redemption of a liraglutide prescription.

Abbreviations: DPP4i, dipeptidyl peptidase 4 inhibitors; lira: liraglutide; mono: monotherapy; NIGLD: non-insulin glucose-lowering drugs; SGLT2i: sodium-glucose transporter 2 inhibitors; SU: sulphonylurea drugs

Table 1 Clinical characteristics of 9,251 real-world initiators of liraglutide in Northern Denmark, 2009-2015.

	Total		Would have been excluded from LEAD 1-5 trials		Would have been included in LEAD 1-5 trials	
	n	%	n	%	n	%
Overall	9,251	100	6,768	73.2	2,483	26.8
Gender						
Female	3,815	41.2	2,788	41.2	1,027	41.4
Male	5,436	58.8	3,980	58.8	1,456	58.6
Age						
0-30	134	1.4	99	1.5	35	1.4
31-59	4,702	50.8	3,262	48.2	1,440	58.0
60-69	3,106	33.6	2,354	34.8	752	30.3
70+	1,309	14.1	1,053	15.6	256	10.3
Median age (IQR)	59.2	(50.2,66.4)	60.1	(51.1, 67.1)	56.8	(48.7, 66.4)
Calendar period of liraglutide initiation						
2009-2011	4,810	52.0	3,631	53.6	1,179	47.5
2012-2013	2,571	27.8	1,828	27.0	743	29.9
2014-2015	1,870	20.2	1,309	19.3	561	22.6
Baseline HbA_{1c}, % (latest within one year)						
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	1,108	12.0	658	9.7	450	18.1
7.5-7.9	1,297	14.0	785	11.6	512	20.6
8-8.9	2,357	25.5	1544	22.8	813	32.7
9-9.9	1,595	17.2	1,075	15.9	520	20.9
≥10 s	1,602	17.3	1,479	21.9	123	5.0
Median HbA_{1c} (IQR)	8.4	(7.5, 9.5)	8.5	(7.4, 9.8)	8.2	(7.6, 9.0)
Diabetes duration						
<1 year	622	6.7	484	7.2	138	5.6
1-<2 years	534	5.8	336	5.0	198	8.0
2-<3 years	597	6.5	380	5.6	217	8.7
≥3 years	7,498	81.1	5,568	82.3	1,930	77.7
Macrovascular complications	2,898	31.3	2,752	40.7	146	5.9
Ischaemic heart disease	2,127	23.0	2,001	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	5,358	57.9	4,223	62.4	1,135	45.7

(eye, neurological or renal)						
Eye complications	2,414	26.1	1,972	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 (>= 2 positive tests)	3,648	39.4	2,865	42.3	783	31.5
eGFR<60	1,107	12.0	994	14.7	113	4.6
Charlson Comorbidity Index (CCI) † score						
0	5,652	61.1	3,481	51.4	2,171	87.4
1	1,909	20.6	1,697	25.1	212	8.5
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	3,614	39.1	3,019	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	1,520	16.4	1,172	17.3	348	14.0
Osteoporosis/fracture	239	2.6	206	3.0	33	1.3
History of infections requiring hospitalisation	3,640	39.3	2,952	43.6	688	27.7
Obesity	2,833	30.6	2,275	33.6	558	22.5
Mental disorders	3,860	41.7	3,047	45.0	813	32.7
Thrombocyte aggregation	4,339	46.9	3,527	52.1	812	32.7
Prophylaxis						
Statins	7,228	78.1	5,320	78.6	1,908	76.8
ACE inhibitors	4,385	47.4	3,265	48.2	1,120	45.1
ATII antagonists	2,997	32.4	2,276	33.6	721	29.0
Antihypertensive treatment	7,567	81.8	5,677	83.9	1,890	76.1
Marital status						
Unmarried	1,490	16.1	1,054	15.6	436	17.6
Widowed	651	7.0	494	7.3	157	6.3
Divorced	1,371	14.8	1,058	15.6	313	12.6
Married	5,557	60.1	4,023	59.4	1,534	61.8
Unknown	182	2.0	139	2.1	43	1.7

All categories are cross-sectional or retrospective as appropriate. †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.

Abbreviations: COPD, chronic obstructive pulmonary disorder; IQR, 25th and 75th percentiles; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ATII, angiotensin II; LEAD, Liraglutide Effect and Action in Diabetes 1–5 (phase III trials that liraglutide approval was based upon).