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Published in:
Diabetes Care

DOI:
10.2337/dc18-0999

Publication date:
2018

Document version
Accepted manuscript

Citation for pulished version (APA):
Knudsen, J. S., Thomsen, R. W., Pottegård, A., Knop, F. K., & Sørensen, H. T. (2018). Differences Between Randomized Clinical Trial Patients and Real-World Initiators of the Glucagon-Like Peptide 1 Receptor Agonist Liraglutide. *Diabetes Care*, *41*(9), e133-e135. https://doi.org/10.2337/dc18-0999

Differences between Randomized Clinical Trial Patients and Real-World Initiators of the Glucagon-Like Peptide 1 Receptor Agonist Liraglutide

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Word count: 611, tables: 1

Randomized controlled trials (RCTs) are considered the gold standard to determine efficacy and safety of new drugs. Successful randomization addresses known and unknown confounding when assessing a drug's effect among trial patients selected on strict inclusion and exclusion criteria (1). However, treatment results have been shown on occasion to be much less favorable than expected outside trial populations, often related to differences in age, comorbidity, disease severity, drug compliance and/or co-medication among patients treated in everyday clinical practice (1). The risk of adverse drug effects may also be higher among patients treated in routine clinical care.

Liraglutide, a glucagon-like peptide 1 receptor agonist, was quickly adopted by clinicians following approval by the European Medicines Agency in 2009 and by the US Food and Drug Administration in 2010. Approval was based on a number of phase III RCTs called the LEAD 1-5 trials (2).

We used data from Danish population-based medical databases to examine whether routine clinical care liraglutide initiators, would have been eligible for participation in the phase III trials. Furthermore, their HbA1c reduction on liraglutide was evaluated. We included all individuals who lived in Northern Denmark and redeemed a first-time liraglutide prescription from 2009-2015 (n=9,251). We adapted each LEAD 1-5 trial eligibility criterion (such as age, comorbid conditions, current drug use, level of HbA1c, etc.), to the Danish National Patient Registry, the Danish Prescription Registry, and the clinical laboratory information system, as appropriate (Table 1) (3). Exclusion criteria were largely similar in the LEAD 1-5 trials, and we used only exclusion criteria that were shared in all five trials. When exact information was unavailable in our databases (i.e. BMI and blood pressure), we assumed that patients would be eligible for trial participation.

Routine clinical care liraglutide users frequently had comorbidities that would have made them ineligible for the LEAD 1-5 trials, including 'clinically significant cardiovascular disease' (29%) or 'other significant disease' (11%) (Table 1). Further, 27% had HbA_{1c} levels outside the values needed for inclusion in the LEAD 1-5 trials, and 37% were on current insulin, another exclusion criterion in the LEAD 1-5 trials. Overall, 73% of all real-world liraglutide users would have been ineligible for any of the LEAD trials (Table 1). Approved indications expanded during 2009-2015 allowing for liraglutide therapy together with more glucose-lowering drug regimens (e.g., with insulin or as monotherapy), and a beneficial liraglutide effect in patients with cardiovascular disease emerged shortly after our study period (4). When we disregarded both previous glucose-lowering drug use and pre-existing cardiovascular disease as exclusion criteria, we found that 45% of real-world users would have been ineligible for RCT participation.

Overall, patients ineligible for LEAD 1-5 participation had a higher HbA1c before initiating liraglutide (8.7% [72 mmol/mol])) than eligible patients (8.4% [68 mmol/mol]) (Table 1), but experienced similar HbA1c reductions after six months (-1.0% [-11mmol/mol] vs. -0.9% [10mmol/mol]).

We found that liraglutide users treated in clinical care settings in Northern Denmark did not resemble patients included in the LEAD 1-5 trials, with almost three out of four routine clinical care initiators being classified as ineligible for the RCTs. Nevertheless, our findings suggest that the efficacy of liraglutide on HbA_{1c} seen in the LEAD trials translates into real-world effectiveness, both for eligible and non-eligible patients. The LEAD 1-5 trials thus found similar reductions in HbA1c after six months (12 months in LEAD 3), i.e.; between -0.8% (-9 mmol/mol) (LEAD 3) and -1.5% (-17 mmol/mol) (LEAD 4). However, our findings also

underscore the importance of post-marketing observational studies based on real-world data. While subsequent RCTs and the present study have established the efficacy of liraglutide in patients ineligible for the LEAD 1-5 trials, safety data are needed for patients with common comorbidities.

ACKNOWLEDGEMENTS

Funding: Aarhus University funded the study.

Author Contributions**:** JSK, AP, FKK and RWT designed the study. JSK reviewed the literature. JSK, AP, RWT and HTS directed the analyses. All authors participated in the discussion and interpretation of the results. JSK organized the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. RWT is the guarantor.

Conflict of interests: AP has received funding from Novo Nordisk for unrelated projects, with funding paid to his institution (no personal fees). FKK has served on scientific advisory panels and/or been part of speaker's bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gubra, MedImmune, MSD/Merck, Norgine, Novo Nordisk, Sanofi and Zealand Pharma.. All other authors declare that they have no personal potential competing interests. None of the authors received support from any organization for the submitted work.

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Table 1. Real-world liraglutide initiators that would have been excluded from participation in the LEAD 1-5 trials and their HbA1c reduction.

Exclusion criteria for participation in LEAD 1-5 trials	Number of real-world patients that would have been excluded based on each criterion		Mean (95% CI) HbA_{1c} (% / mmol/mol) before liraglutide initiation	Mean (95% CI) HbA_{1c} (% / mmol/mol) six months after liraglutide initiation	Mean (95% CI) HbA_{1c} reduction (% / mmol/mol) (95% CI)
	n	%			
All patients	9,251	(100)	8.6 (8.6-8.6)/ 70 (70,70)	7.6 (7.6,7.7)/ 60 (60,61)	-1.0 (-1.0,-0.9)/ -11 (-11,-10)
Excluded for any of the following	6,768	(73.2)	8.7 (8.7:8.7)/ 72 (72,72)	7.7 (7.7,7.7)/ 61 (61,61)	-1.0 (-1.0,-0.9)/ -11 (-11,-10)
Not excluded for any of the following	2583	(26.9)	8.4 (8.3-8.4)/ 68 (67,68)	7.5 (7.4,7.5)/ 58 (57,58)	-0.9 (-1.0,-0.9)/ -10 (-11,-10)
Ongoing non-insulin GLD therapy for less than 3 months	1,051	(11.4)	8.8 (8.7,8.9)/ 73 (73,74)	7.7 (7.6,7.8)/ 61 (60,62)	-1.1 (-1.2,-1.0)/ -12 (-13,-11)
HbA_{1c} level outside range*	2,522	(27.3)	9.1 (9.0,9.2)/ 76 (75,77)	7.8 (7.7,7.9)/ 62(61,63)	-1.3 (-1.4,-1.2)/ -14 (-16,-13)
Age <18 years	8	(0.1)	8.6 (6.0,11.1)/ 70 (42,98)	6.7 (-1.0,14.4)/ 50 (<0,134)	-2.5 (-16.3,11.3)/ -28 (-155,100)
Age >80 years	147	(1.6)	8.5 (8.2,8.7)/ 69 (66,72)	7.6 (7.4,7.8)/ 60 (57,62)	-0.9 (-1.1,-0.6)/ -10 (-12,-7)
Current Insulin treatment	3,414	(36.9)	8.8 (8.7,8.8)/ 73 (72,73)	8.00 (7.9:8.0)/ 64 (63,64)	-0.8 (-0.8,-0.7)/ -9 (-9,-8)
Impaired liver function	86	(0.9)	9.2 (8.8,9.6)/ 77 (73,81)	7.7 (7.3:8.0)/ 61 (56,64)	-1.7 (-2.1,-1.2)/ -19 (-23,-13)
Hepatitis B or C positive	27	(0.3)	9.1 (8.5,9.7)/ 76 (69,82)	8.5 (7.6,9.3)/ 69 (60,78)	-0.6 (-1.3,0.1)/ -7 (-14,1)
Impaired renal function	395	(4.3)	8.6 (8.5,8.8)/ 70 (69,74)	7.7 (7.6,7.8)/ 61 (60,62)	-0.9 (-1.0,-0.7)/ -10(-11,-8)
Clinically significant active CVD	2,646	(28.6)	8.7 (8.6,8.7)/ 72 (70,72)	7.7 (7.7,7.8)/ 61 (61,62)	-0.9 (-1.0,-0.9)/ -10 (-11,-10)
Cancer	326	(3.5)	8.5 (8.4,8.7)/ 69 (68,72)	7.6 (7.5:7.8)/ 60 (58,62)	-0.9 (-1.1,-0.8)/ -10 (-12,-10)
Clinically significant disease	1,029	(11.2)	8.6 (8.4,8.6)/ 70 (68,70)	7.6 (7.5,7.7)/ 60 (58,61)	-1.0 (-1.1,-1.0)/ -11 (-12,-11)
Recurrent hypoglycaemia	46	(0.5)	8.5 (8.0,9.0)/ 69 (64,75)	8.1 (7.7,8.5)/ 65 (61,69)	-0.5 (-0.9,0.0)/ -6 (-10,0)
Use of drugs that interferes with glucose	439	(4.8)	8.6 (8.4,8.7)/ 70 (68,72)	7.5 (7.4,7.6)/ 58 (57,60)	-1.0 (-1.2,-0.9)/ -11 (-13,-10)
Alcohol or substance abuse	389	(4.2)	8.9 (8.6,9.1)/ 74 (70,76)	7.8 (7.6,7.9)/ 62 (60,63)	-1.1 (-1.3,-0.9)/ -12 (-14,-10)

Mental incapacity	246	(2.6)	8.9 (8.6,9.1)/ 74 (70,76)	7.8 (7.5,8.0)/ 62 (58,64)	-1.1 (-1.4,-0.9)/ -12 (-14,-10)
Current/ intention of breastfeeding or pregnant	25	(0.3)	7.8 (7.1,8.5)/ 62 (54,69)	7.1 (6.5,7.7)/ 54 (48,61)	-0.9 (-1.5,0.2)/ -10 (-17,2)

Among 9,251 real-world initiators of liraglutide in Northern Denmark. *Last measured HbA_{1c} outside 7-11%/7-11%/7-10% (53-97mmol/mol/ 53-97mmol/mol/ 53-86mmol/mol) range among patients receiving no/mono/combi non-insulin GLD prescriptions before liraglutide initiation. Exclusion criteria: As present in all LEAD 1-5 studies. Abbreviations: GLD, Glucose Lowering Drugs; CVD, Cardiovascular Disease; CI, Confidence Intervals.