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

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Randomized controlled trials (RCTs) are considered the gold standard for determining 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 comedication 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 its approval by the European Medicines Agency in 2009 and by the U.S. Food and Drug Administration in 2010. Approval was based on a number of phase III RCTs called the Liraglutide Effect and Action in Diabetes (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 HbA_{1c} 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, HbA_{1c} level, 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 other 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 HbA_{1c} before initiating liraglutide (8.7% [72 mmol/mol]) than eligible patients (8.4% [68 mmol/mol]) (Table 1) but experienced similar HbA_{1c} reductions after 6 months (−1.0% [−11 mmol/mol] vs. −0.9% [−10 mmol/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 noneligible patients. The LEAD 1–5 trials thus found similar reductions in HbA_{1c}

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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 HbA_{1c} reduction

Exclusion criteria for participation in LEAD 1–5 trials	Real-world patients that would have been excluded based on each criterion		Mean (95% CI) HbA_{1c} before liraglutide initiation		Mean (95% CI) HbA_{1c} 6 months after liraglutide initiation		Mean (95% CI) HbA_{1c} reduction	
	n	%	%	mmol/mol	%	mmol/mol	%	mmol/mol
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	2,583	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 noninsulin GLD therapy for <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 hypoglycemia	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 interfere 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. Exclusion criteria as present in all LEAD 1–5 studies. CVD, cardiovascular disease; GLD, glucose-lowering drugs. *Last measured HbA_{1c} outside 7–11% (53–97 mmol/mol)/7–11% (53–97 mmol/mol)/7–10% (53–86 mmol/mol) range among patients receiving no/monotherapy/combination noninsulin glucose-lowering drug prescriptions before liraglutide initiation.

after 6 months (12 months in LEAD 3): between −0.8% (−9 mmol/mol) (LEAD 3) and −1.5% (−17 mmol/mol) (LEAD 4). However, our findings also underscore the importance of postmarketing observational studies based on real-world data. Although subsequent RCTs and the current 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.

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