Differences between randomized clinical trial patients and real world initiators of the glucagon-like peptide-1 receptor agonist liraglutide

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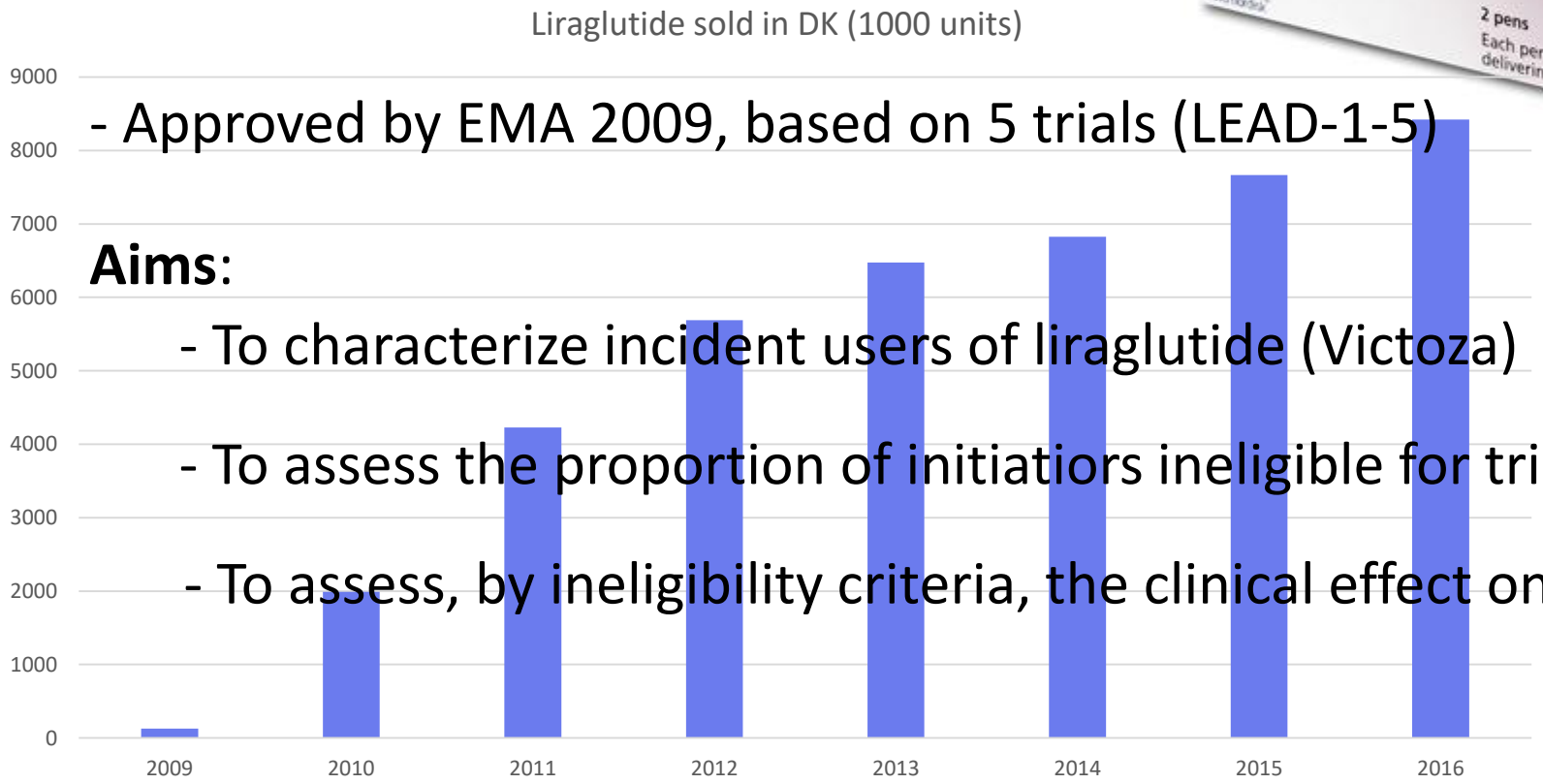
- Randomized controlled trials are the gold standard used to determine efficacy of new drugs.

- When real-world patients differ from trial patients, real-world effectiveness and safety may differ from trial results.



- Approved by EMA 2009, based on 5 trials (LEAD-1-5)

Aims:

- To characterize incident users of liraglutide (Victoza)
- To assess the proportion of initiatiors ineligible for trial participation.
- To assess, by ineligibility criteria, the clinical effect on HbA_{1c}

Methods:

Design: Population-based cross-sectional study.

Setting: All residents in Northern Denmark during 2009-2015.

Participants: We identified 9,251 patients who initiated therapy with liraglutide.

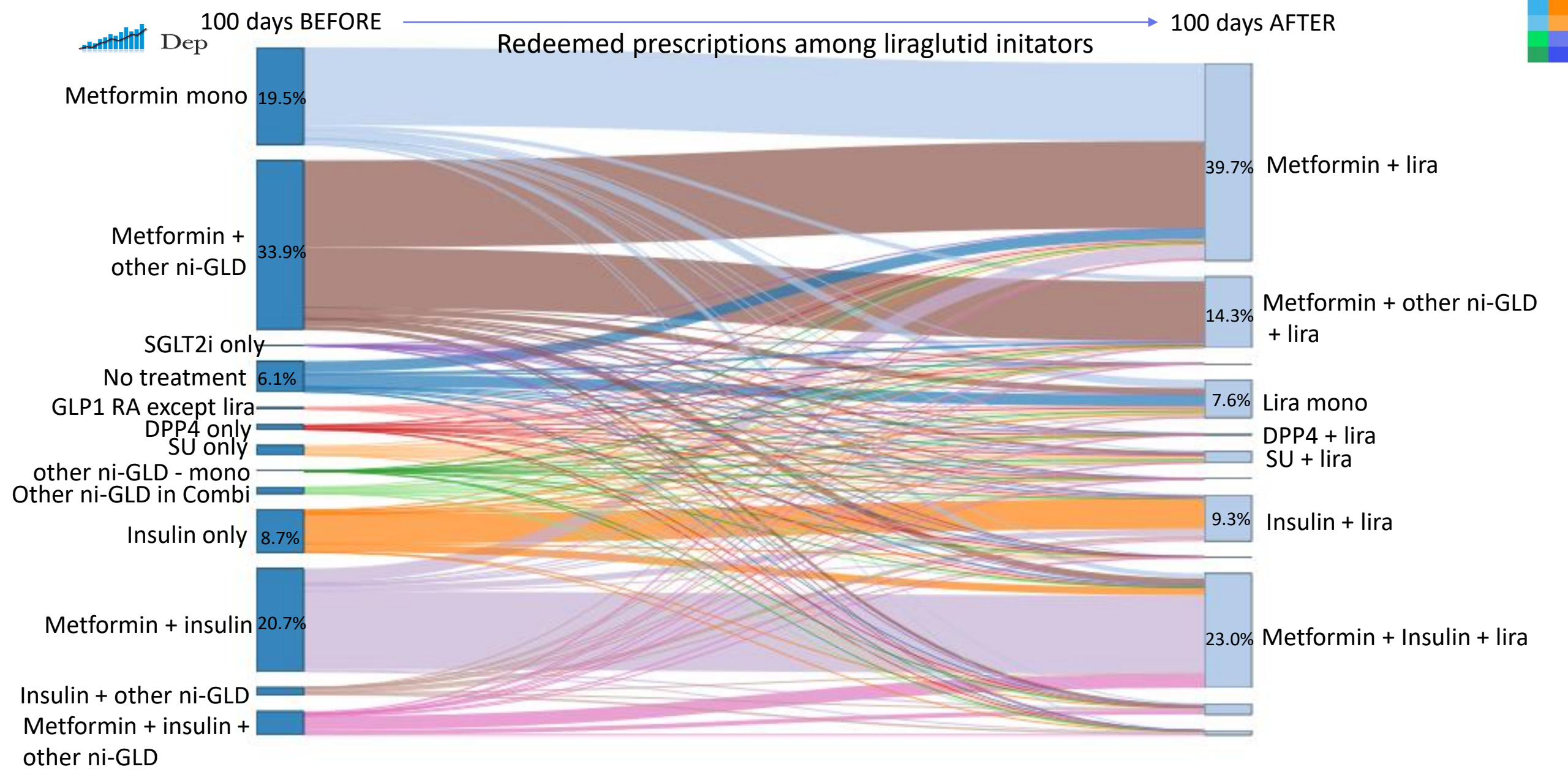
Data sources:

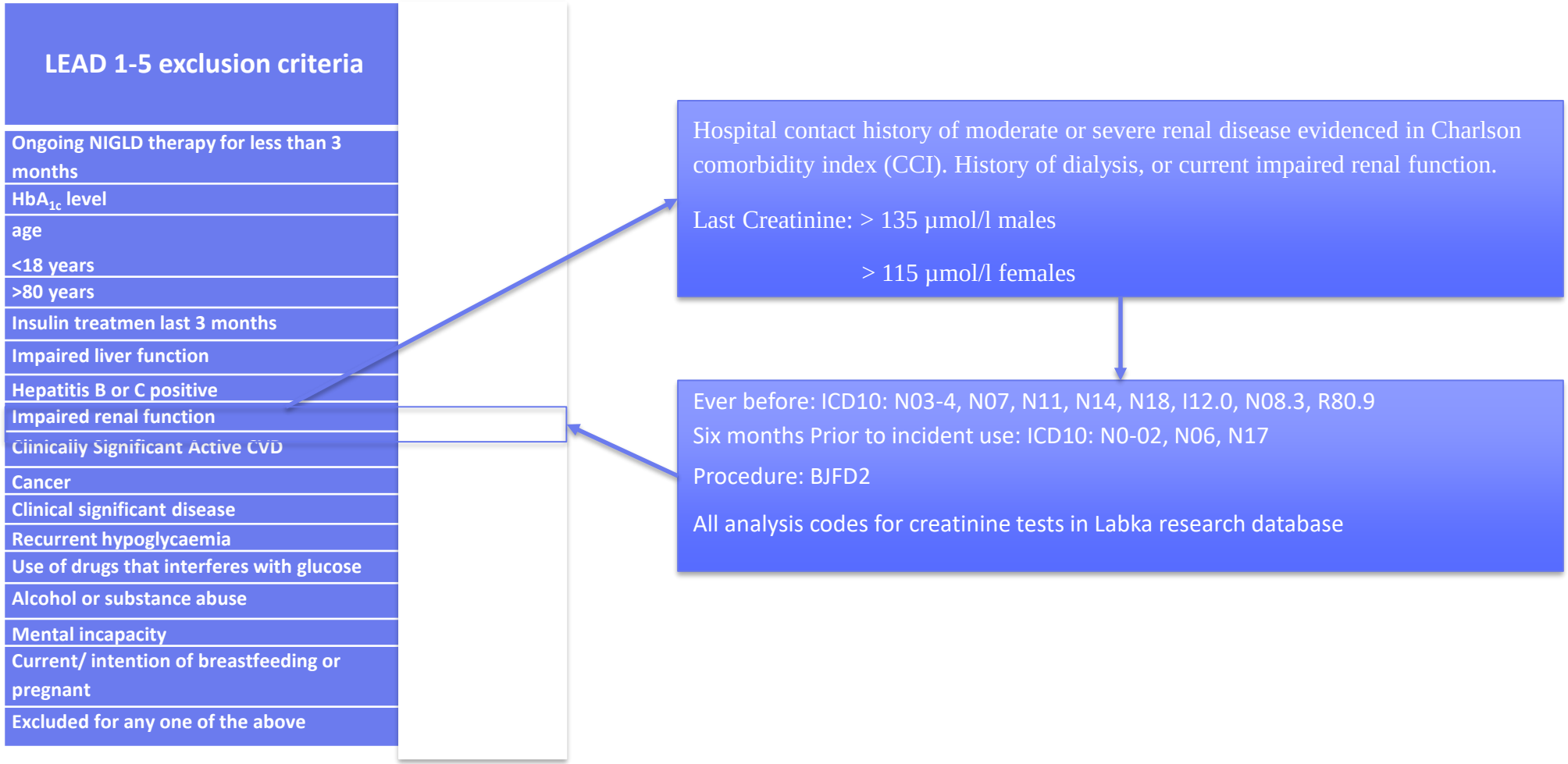
National Danish Registries:

- Civil Registration System
- Danish National Prescription Registry
- Danish National Patient Registry

Regional Danish Registry:

- Clinical Laboratory Information System


100 days BEFORE
100 days AFTER
Redeemed prescriptions among liraglutid initators
Metformin mono
19.5%
Metformin + other ni-GLD
33.9%
SGLT2i only
No treatment
6.1%
GLP1 RA except lira
DPP4 only
SU only
other ni-GLD - mono
Other ni-GLD in Combi
Insulin only
8.7%
Metformin + insulin
20.7%
Insulin + other ni-GLD
Metformin + insulin + other ni-GLD
39.7%
Metformin + lira
14.3%
Metformin + other ni-GLD + lira
7.6%
Lira mono
DPP4 + lira
SU + lira
9.3%
Insulin + lira
23.0%
Metformin + Insulin + lira


LEAD 1-5 exclusion criteria
Ongoing NIGLD therapy for less than 3 months
HbA1c level
age
<18 years
>80 years
Insulin treatmen last 3 months
Impaired liver function
Hepatitis B or C positive
Impaired renal function
Clinicaiiy Significant Active CVD
Cancer
Clinical significant disease
Recurrent hypoglycaemia
Use of drugs that interferes with glucose
Alcohol or substance abuse
Mental incapacity
Current/ intention of breastfeeding or pregnant
Excluded for any one of the above
Hospital contact history of moderate or severe renal disease evidenced in Charlson comorbidity index (CCI). History of dialysis, or current impaired renal function.
Last Creatinine: > 135 µmol/l males
> 115 µmol/l females
Ever before: ICD10: N03-4, N07, N11, N14, N18, I12.0, N08.3, R80.9
Six months Prior to incident use: ICD10: N0-02, N06, N17
Procedure: BJFD2
All analysis codes for creatinine tests in Labka research database

- Important causes for exclusion:

- Insulin use (37%)
- HbA_{1c} outside limits (27%)
- Existing cardiovascular disease (29%)
- Clinically Significant disease (not CVD) (11%)

- Changes in knowledge of liraglutid 2009-2015:

- Good choice to patients with CVD (LEADER trial)

- Approved for treatment in combination with insulin

- Important causes for exclusion:

- Insulin use (37%)

- HbA_{1c} outside limits (27%)

- Existing cardiovascular disease (29%)

- Clinically Significant disease (not CVD) (11%)

- 45 % of patients still ineligible for trial participation

- Did the LEAD-trials suffer from a flawed design?

  No! Not to answer trial aim:

- The purpose with RCTs is to examine the effect in ideal circumstances **(efficacy)**

  - Selection may reduce generalizability of results

- The effect on real world patients (**effectiveness**) **may differ markedly from RCTs**

- Effect on HbA_{1c} after 6 months after initiation of Liraglutide

	Mean HbA_{1c} % change. (95% CI)
Ongoing non-insulin GLD therapy for less than 3 months	-1.4 (-1.6:-1.1)
HbA_{1c} level	-1.3 (-1.4:-1.2)
Age <18 years	-2.5 (-16.3:11.3)
Age >80 years	-0.9 (-1.1:-0.6)
Insulin treatment last 3 months	-0.8 (-0.8:-0.7)
Impaired liver function	-1.7 (-2.1:-1.2)
Hepatitis B or C positive	-0.6 (-1.3:0.1)
Impaired renal function	-0.9 (-1.0:-0.7)
Clinically significant active CVD	-0.9 (-1.0:-0.9)
Cancer	-0.9 (-1.1:-0.8)

	Mean HbA_{1c} % change. (95% CI)
Clinically significant disease	-1.0 (-1.0:-1.0)
Recurrent hypoglycaemia	-0.5 (-0.9:0.0)
Use of drugs that interferes with glucose	-1.0 (-1.2:-0.9)
Alcohol or substance abuse	-1.1 (-1.3:-0.9)
Mental incapacity	-1.1 (-1.4:-0.9)
Current/ intention of breastfeeding or pregnant	-0.9 (-1.5-0.2)
Excluded for any one of the above	-1.0 (-1.0:-0.9)
Not excluded for any of the above	-0.9 (-1.0:-0.9)
All patients	-1.0 (-1.0:-0.9)

- Our findings suggest that the efficacy of liraglutide on HbA_{1c} seen in RCTs translates into real-world effectiveness both for patients that would have been eligible as well as ineligible for participation in the LEAD 1-5 trials.

- Safety and adverse effects are not examined in a large proportion of treated patients

- Register based studies can be carried out in real world settings

- Despite limitations, register based studies may be the best possible tool for adressing questions not feasible to adress by RCTs