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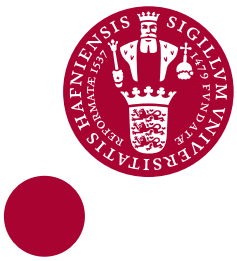

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Individual effects of treatment

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WILEY

BRIEF REPORT

Pleiotropic effects of liraglutide in patients with type 2 diabetes and moderate renal impairment: Individual effects of treatment

Emilie H. Zobel MD[1] | Bernt J. von Scholten DMSc[1,2] | Bryan Goldman MS[2] | Frederik Persson DMSc[1] | Tine W. Hansen PhD[1] | Peter Rossing DMSc[1,3]

[1]Complications Research, Steno Diabetes Center Copenhagen, Gentofte, Denmark

[2]Novo Nordisk A/S, Søborg, Denmark

[3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence
Emilie H. Zobel, Steno Diabetes Center Copenhagen, Niels Steensens Vej 2, 2820, Gentofte, Denmark.
Email: emilie.hein.zobel@regionh.dk

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Liraglutide has pleiotropic effects favouring cardiovascular and renal risks. We investigated individual responses to liraglutide in six cardio-renal risk factors to examine whether responses in one risk factor are associated with changes in other risk factors (cross-dependency). We performed secondary analysis of the LIRA-RENAL trial (n = 279) in type 2 diabetes. HbA1c, body weight, systolic blood pressure (SBP), low density lipoprotein (LDL)-cholesterol, urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) were measured at baseline and after 26 weeks of liraglutide/placebo treatment: "Good responders" had a change within the best quartile. In the liraglutide-treated group, good HbA1c responders showed similar changes in other risk factors analysed to low responders ($P \geq 0.17$). Good body weight responders had a larger reduction in HbA1c than low body weight responders (−1.6 ± 0.94 vs. −1.0 ± 0.82%; $P = 0.003$), but similar changes in the other risk factors ($P \geq 0.11$). Good and low responders in SBP, UACR, LDL-cholesterol or eGFR showed similar changes in other risk factors ($P \geq 0.07$). Treatment response to liraglutide is largely individual; aside from an association between body weight and HbA1c reduction, there are no obvious cross-dependencies in risk factor response.

KEYWORDS

diabetic nephropathy, liraglutide, type 2 diabetes.

1 | INTRODUCTION

Several newer antihyperglycaemic drugs have pleiotropic effects[1] favouring cardiovascular and renal risk in type 2 diabetes.

Liraglutide, a once-daily human glucagon-like peptide-1 (GLP-1) analogue, lowers glucose, body weight, blood pressure, lipids and albuminuria.[2–4] The long-term Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) clinical trial established that liraglutide reduces cardiovascular events and offers long-term renoprotection in patients with type 2 diabetes and established cardiovascular disease.[5]

We explored the pleiotropic effects of liraglutide on an individual level in the Efficacy and Safety of Liraglutide versus Placebo as Add-on to Glucose-Lowering Therapy in Patients with Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL) study. We investigated individual responses to liraglutide in six cardio-renal risk factors (HbA1c, body weight, systolic blood pressure [SBP], low density lipoprotein [LDL]-cholesterol, urine albumin-to-creatinine ratio [UACR] and estimated glomerular filtration rate [eGFR]) to examine whether beneficial responses in one risk factor are associated with changes in other risk factors (cross-dependency).

2 | MATERIALS AND METHODS

2.1 | Study design and participants

A secondary analysis of LIRA-RENAL, which was a 26-week, randomized, double-blind, placebo-controlled, parallel group trial, aimed to assess superiority of liraglutide 1.8 mg versus placebo as an add-on to

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existing glucose-lowering treatment (oral glucose-lowering agents and/or insulin therapy) in participants with type 2 diabetes and moderate renal impairment (stage 3 chronic kidney disease, defined as eGFR of 30-59 mL/min/1.73m^2). Patients were to maintain their background diabetes medication throughout the trial but the dose of insulin or sulphonylurea could be reduced in case of hypoglycaemic episodes.[6]

The study was conducted according to the Declaration of Helsinki and was approved by the relevant authorities. Trial registration: ClinicalTrials.gov identifier NCT01620489.

2.2 | Measurement of risk factors

HbA1c, body weight, SBP, LDL-cholesterol and UACR were measured and eGFR was calculated (based on the Modification of Diet in Renal Disease [MDRD] formula) at baseline, at regular intervals during the trial, and after 26 weeks of treatment, using routine methods.[6] UACR was calculated as the mean of the morning urine samples from the day before the visit and the day of the visit.

2.3 | Statistical analyses

Good response was defined as an observed change from baseline (ratio to baseline for UACR and LDL-cholesterol) at week 26 at or below the first quartile of the distribution in the liraglutide group (ie, greatest reduction). For eGFR, good response was defined as an observed ratio to baseline at or above the third quartile of the distribution in the liraglutide group (ie, increase or smallest reduction).

We evaluated separately in the liraglutide and placebo groups the association of good response among the six risk factors using Fisher's exact test.

Furthermore, we evaluated (a) linear correlations among changes in the six risk factors to investigate treatment response on a continuous scale, and (b) associations between baseline values and responder status for each of the six risk factors in the liraglutide-treated group.

Within each treatment group, a two-sample t-test using Satterthwaite's approximation was used to compare good and low responders for each risk factor in terms of both baseline values and change from baseline in the other risk factors. Pairwise associations in change from baseline among the six risk factors were also evaluated using scatterplots, and Pearson's correlation coefficients were calculated.

For all analyses, LDL-cholesterol, UACR and eGFR values were log-transformed. Because all analyses are exploratory, no correction for multiplicity was applied.

3 | RESULTS

Of 279 participants exposed to study medication, 220 who had at least one of the six variables measured at baseline and after 26 weeks of liraglutide (n = 109) or placebo (n = 111) treatment were included in the present analysis.

Participants had a mean ± standard deviation (SD) age of 66.7 (±8.5) years, diabetes duration of 15.0 (±8.3) years, and 48.6% were female. At baseline, mean (±SD) HbA1c was 8.0 (±0.8)%, body weight 94.6 (±17.7) kg and SBP 136 (±15) mm Hg. Participants had a geometric mean (coefficient of variation) UACR of 7.1 (6.6) mg/mmol, LDL-cholesterol of 2.3 (0.5) mmol/L and eGFR of 47.2 (0.2) mL/min/1.73m^2. Baseline characteristics (Supporting Information Table S1) were generally well balanced by treatment group.

3.1 | Cross-dependency for response in risk factors

Changes in risk factors for good versus low responders, for the liraglutide-treated participants, are presented in Table 1. Good (reduction ≥1.7%) and low HbA1c responders showed similar changes from baseline to end of trial in other risk factors analysed ($P \geq 0.17$; Figure 1A). Good body weight responders (reduction ≥4.6 kg) had a significantly larger reduction in HbA1c than low body weight responders ($P = 0.003$), but similar changes in the other risk factors (Figure 1B). No significant difference was seen between good and low responders in SBP (reduction ≥10 mm Hg), UACR (≤54% of baseline value), LDL-cholesterol (≤85% of baseline value) or eGFR (≥107% of baseline value) from baseline to end of trial in any of the other risk factors ($P \geq 0.07$).

Results for good versus low responders in the six risk factors, for placebo-treated participants, are presented in Supporting Information Table S2. Overall, findings were similar to the liraglutide-treated group, with few associations between changes in the six risk factors.

We further investigated whether a good response in one risk factor was associated with good response in each of the other risk factors, using the cut-offs stated for a good response. Results of these analyses of binary response variables were largely consistent with the analyses of continuous change from baseline (Supporting Information Table S3A and B).

3.2 | Linear correlations between changes in the six risk factors

We analysed linear correlation between observed changes in the six risk factors after 26 weeks of treatment with liraglutide. HbA1c reduction was associated with body weight reduction ($r = 0.24$; $P = 0.01$) but changes in the other risk factors were not significantly correlated ($P \geq 0.11$).

3.3 | Association between baseline value and response for each risk factor

For each risk factor, we analysed the association between the baseline value and response to liraglutide treatment. This association was significant for HbA1c ($P < 0.001$), SBP ($P < 0.001$) and LDL-cholesterol ($P = 0.002$), but not for body weight, eGFR or UACR ($P \geq 0.051$).

4 | DISCUSSION

Liraglutide treatment has pleiotropic effects that favourably change both cardiovascular and renal risk variables. We observed no obvious cross-dependency in the risk factor response, except for

TABLE 1 Good versus low responders in risk factors for the liraglutide-treated group

Variable	Q4	Q1–Q3	*P* value
(A) HbA1c good versus low responders (Q4 [n = 29] vs. Q1–Q3 [n = 76])			
HbA1c (%)	−2.2 (0.48)	−0.77 (0.67)	—
Body weight (kg)	−3.3 (3.4)	−2.2 (3.8)	0.17
SBP (mm Hg)	1 (17)	−3 (15)	0.28
UACR (%)[a]	0.81 [1.6]	0.91 [1.2]	0.67
eGFR (%)[a]	0.97 [0.17]	0.98 [0.18]	0.75
LDL-cholesterol (%)[a]	1.1 [0.29]	1.0 [0.31]	0.22
(B) Body weight good versus low responders (Q4 [n = 29] vs. Q1–Q3 [n = 77])			
HbA1c (%)	−1.6 (0.94)	−1.0 (0.82)	0.003
Body weight (kg)	−7.0 (2.3)	−0.8 (2.5)	—
SBP (mm Hg)	−3 (15)	−1 (15)	0.51
UACR (%)[a]	0.67 [1.1]	0.97 [1.3]	0.12
eGFR (%)[a]	0.98 [0.14]	0.98 [0.19]	0.99
LDL-cholesterol (%)[a]	1.0 [0.34]	1.0 [0.29]	0.89
(C) SBP good versus low responders (Q4 [n = 33] vs. Q1–Q3 [n = 73])			
HbA1c (%)	−1.1 (0.71)	−1.2 (0.97)	0.69
Body weight (kg)	−3.3 (3.8)	−2.1 (3.7)	0.13
SBP (mm Hg)	−18 (10)	6 (11)	—
UACR (%)[a]	0.69 [1.1]	0.98 [1.4]	0.13
eGFR (%)[a]	0.97 [0.13]	0.98 [0.20]	0.94
LDL-cholesterol (%)[a]	1.0 [0.32]	1.0 [0.30]	0.81
(D) UACR good versus low responders (Q4 [n = 21] vs. Q1–Q3 [n = 61])			
HbA1c (%)	−1.4 (0.80)	−1.0 (0.96)	0.17
Body weight (kg)	−2.9 (3.8)	−2.4 (3.9)	0.63
SBP (mm Hg)	−3 (18)	−0.3 (16)	0.57
UACR (%)[a]	0.29 [0.69]	1.3 [0.88]	—
eGFR (%)[a]	0.98 [0.28]	0.96 [0.13]	0.79
LDL-cholesterol (%)[a]	1.0 [0.23]	1.0 [0.30]	0.69
(E) eGFR good versus low responders (Q4 [n = 27] vs. Q1–Q3 [n = 78])			
HbA1c (%)	−1.3 (0.89)	−1.1 (0.89)	0.40
Body weight (kg)	−2.4 (3.3)	−2.6 (3.8)	0.82
SBP (mm Hg)	0 (16)	−3 (15)	0.46
UACR (%)[a]	1.2 [2.5]	0.76 [0.87]	0.18
eGFR (%)[a]	1.20 [0.17]	0.91 [0.11]	—
LDL-cholesterol (%)[a]	1.0 [0.29]	1.0 [0.31]	0.72
(F) LDL-cholesterol good versus low responders (Q4 [n = 24] vs. Q1–Q3 [n = 71])			
HbA1c (%)	−0.92 (0.77)	−1.3 (0.87)	0.07
Body weight (kg)	−2.9 (4.7)	−2.7 (3.1)	0.88
SBP (mm Hg)	−5 (13)	−0.8 (16)	0.26
UACR (%)[a]	0.75 [1.4]	0.89 [1.3]	0.56
eGFR (%)[a]	0.95 [0.3]	0.99 [0.14]	0.56
LDL-cholesterol (%)[a]	0.71 [0.15]	1.16 [0.23]	—

Abbreviations: eGFR, estimated glomerular filtration rate; LDL, low density lipoprotein; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio.

[a] Relative change of log-transformed values. Values are mean (standard deviation) or geometric mean [coefficient of variation]. Two-sample t-test using the Sattertwhaite approximation.

association of a good response in body weight with a greater reduction in HbA1c. The same association was not seen among placebo-treated patients.

We have recently published data from a small study (n = 31) examining the pleiotropic effects of liraglutide. Surprisingly, a pronounced body weight loss was not associated with a greater reduction in HbA1c, and a pronounced reduction in HbA1c was not associated with a greater reduction in urinary albumin excretion rate. We had expected a cross-dependency between reduction in SBP and urinary albumin excretion rate, but this was also not seen.[7] With the obvious limitations of a small open-label study, we wished to confirm our findings.

The present analysis of LIRA-RENAL confirms the highly individual treatment response to liraglutide. Aside from a good response in body weight being associated with a greater reduction in HbA1c, there was no obvious cross-dependency in risk factor response in the liraglutide-treated group. Overall changes in the placebo group were smaller (vs. the liraglutide group) but, interestingly, there were several cross-dependencies in risk factor response in this group, suggesting that the population size and length of study were sufficient to detect possible associations. An HbA1c reduction following body weight reduction may be more evident over time, and therefore we speculate that the longer study duration in LIRA-RENAL (26 weeks vs. 7 weeks for the open-label study) may partly explain this observed difference. The association was not seen in the placebo-treated group.

We had originally hypothesized that in some individuals liraglutide treatment would lead to a response in all risk factors, whereas other individuals would not respond in any risk factor. Our findings, from analysing cross-dependency in liraglutide response in two different populations with type 2 diabetes, do not support this hypothesis.

Individual characteristics may influence the magnitude of the treatment response to liraglutide.[8] We showed that a high baseline level of HbA1c, SBP and LDL-cholesterol was associated with a greater response in the corresponding variable. We acknowledge that regression towards the mean can contribute to these associations. Interestingly, a high baseline body weight was not linked to a good body weight response. In accordance with our finding, Berkovic et al. showed that higher baseline HbA1c was related to a greater reduction in HbA1c after liraglutide treatment for 6 months in 207 participants with type 2 diabetes.[9]

Studies showing the beneficial effect of GLP-1 receptor agonists on hard outcomes are available, and future analysis of the link between individual patient risk factor responses and occurrence of renal and cardiovascular events could ultimately enhance the opportunity to personalize treatment. Other mechanisms such as inflammation that are not directly reflected in the cardio-renal risk factors may also be involved.

4.1 | Clinical implications

We found substantial heterogeneity in the individual risk factor response to liraglutide treatment. This may help guide clinicians to not just take into account treatment response in one variable (ie, HbA1c or body weight), but to also consider a number of other variables when assessing the effect of liraglutide, in anticipation of a beneficial clinical outcome. Furthermore, a good response in one risk factor does not appear to predict response in other variables, except for an association between body weight and glycaemic control.

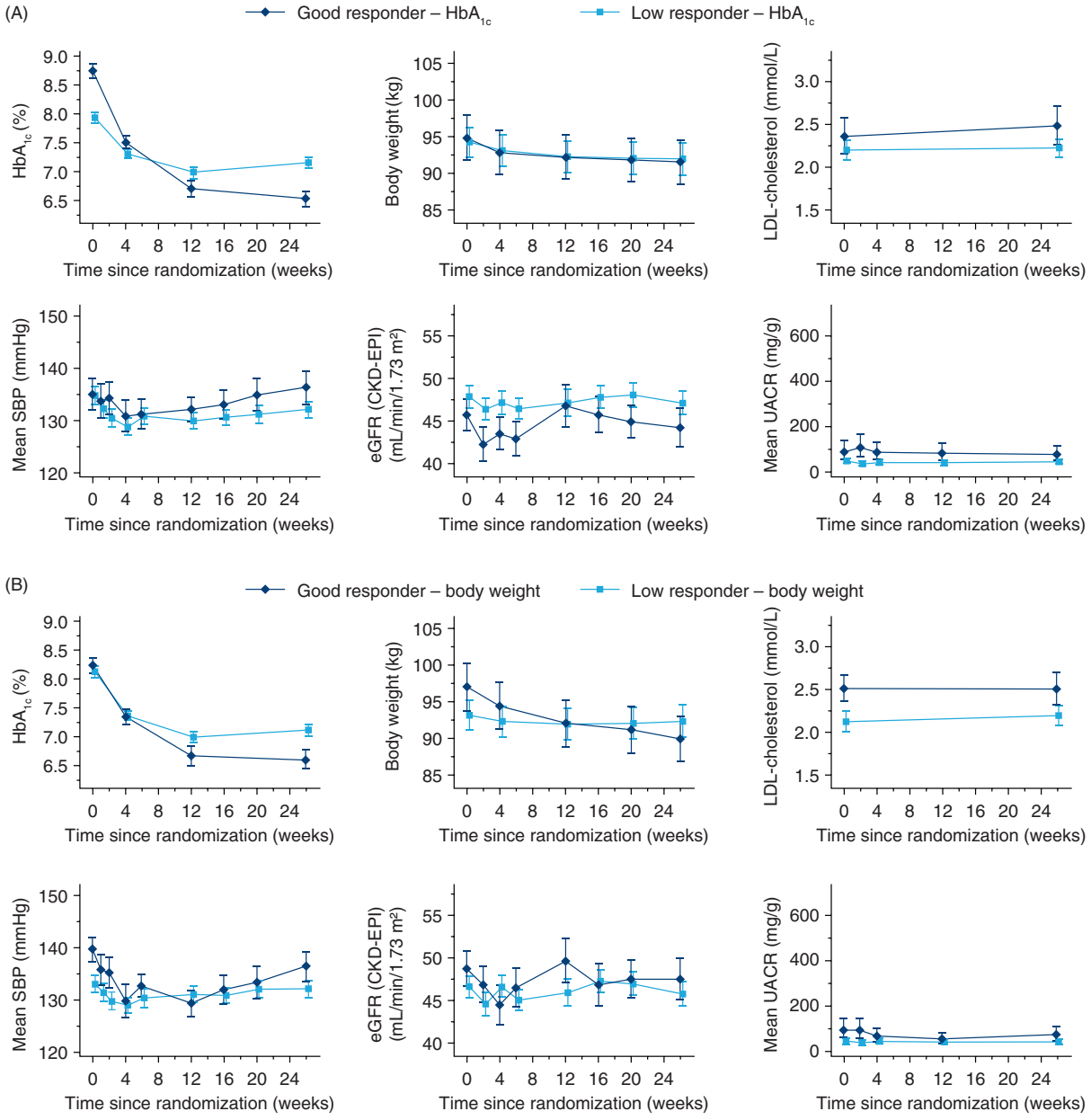

FIGURE 1 Cross-dependency in risk factor response. A, Changes in risk factors for good versus low HbA1c responders for liraglutide-treated participants. B, Changes in risk factors for good versus low body weight responders for liraglutide-treated participants. Good responders were defined as having a change from baseline to week 26 within the best quartile in the liraglutide-treated group. Good responders in HbA1c (reduction ≥1.7%) had similar changes in the other risk factors compared with low responders in HbA1c ($P \geq 0.17$). Good body weight responders had a significantly greater reduction in HbA1c (−1.6 ± 0.94 vs. −1.0 ± 0.82%) compared with low body weight responders ($P = 0.003$), but no difference in change of other risk factors between responder groups ($P \geq 0.11$). Observed mean ± standard error (SE). For log-transformed data of low density lipoprotein (LDL)-cholesterol, urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR), observed means and SE were calculated on the log-transformed values and then back-transformed to the original scale

4.2 | Strengths and limitations

The strength of this study is that we confirmed our previous findings from a small open-label study[7] in a secondary analysis of a large, randomized, controlled trial. As this is still an exploratory analysis, however, we cannot exclude the possibility that significant associations between risk factor responses may exist. An important limitation is the day-to-day variation in the cardio-renal risk factors, which could obscure a true correlation among the risk factors. In particular, UACR, SBP and serum creatinine vary from day to day and this variation may hamper detection of a true correlation. The aim of the present analysis was to determine cross-dependency in risk factor response. Future analyses of a dedicated liraglutide outcome trial are required to assess if the changes in risk factors translate into renal and cardiovascular events.

In conclusion, liraglutide treatment has pleiotropic effects that favourably change cardiovascular and renal risk. We show that treatment response to liraglutide is largely individual and, aside from an association between body weight reduction and HbA1c reduction, there are no obvious cross-dependencies in the risk factor response. Future analysis of the link between risk factor responses and occurrence of renal and cardiovascular events could ultimately lead to

personalized treatment and help elucidate which effects are most important for optimal outcomes.

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CONFLICT OF INTEREST

E. H. Z. declares no duality of interest associated with this manuscript. B. J. v. S. and B. G. are Novo Nordisk employees and B. J. v. S. has equity interest in Novo Nordisk. F. P. reports research grants received from AstraZeneca, lecture fees from AstraZeneca, MSD, Janssen, Lily, Boehringer Ingelheim, Novo Nordisk and Novartis, and being consultant/advisory board member for AstraZeneca, Bayer, Amgen and MSD. T. W. H. has equity interest in Novo Nordisk. P. R. received lecture fees (to his institution) from Bayer, Novo Nordisk, AstraZeneca and Boehringer Ingelheim, research grants from AstraZeneca and Novo Nordisk, has served as a consultant for Bayer, AstraZeneca, Astellas, Boehringer Ingelheim, AbbVie and Novo Nordisk (all honoraria to his institution), and has equity interest in Novo Nordisk.

Author contributions

E. H. Z., F. P., T. W. H. and P. R. conceived and designed the research, analysed and interpreted the data; B. G. performed the statistical analysis; E. H. Z. and T. W. H. drafted the manuscript; E. H. Z., B. J. v. S., F. P. and P. R. critically revised the manuscript for key intellectual content; all authors approved the final version of the manuscript. E.H.Z. is responsible for the integrity of the work as a whole.

Data sharing

The subject level analysis datasets for the research presented in the publication are available from the corresponding author on reasonable request.

ORCID

Emilie H. Zobel https://orcid.org/0000-0003-3318-7070

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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