# Safety and Efficacy of Liraglutide in Patients With Type 2 Diabetes and End-Stage Renal Disease: An Investigator-Initiated, Placebo-Controlled, Double-Blind, Parallel-Group, Randomized Trial

*Thomas Idorn,[1] Filip K. Knop,[2,3] Morten B. Jørgensen,[1] Tonny Jensen,[4] Marsela Resuli,[5] Pernille M. Hansen,[5] Karl B. Christensen,[6] Jens J. Holst,[3] Mads Hornum,[1] and Bo Feldt-Rasmussen[1]*

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## OBJECTIVE

**To evaluate parameters related to safety and efficacy of liraglutide in patients with type 2 diabetes and dialysis-dependent end-stage renal disease (ESRD).**

## RESEARCH DESIGN AND METHODS

**Twenty-four patients with type 2 diabetes and ESRD and 23 control subjects with type 2 diabetes and normal kidney function were randomly allocated to 12 weeks of double-blind liraglutide (titrated to a maximum dose of 1.8 mg) or placebo treatment (1:1) injected subcutaneously once daily as add on to ongoing antidiabetic treatment. Dose-corrected plasma trough liraglutide concentration was evaluated at the final trial visit as the primary outcome measure using a linear mixed model.**

## RESULTS

**Twenty patients with ESRD (1:1 for liraglutide vs. placebo) and 20 control subjects (1:1) completed the study period. Dose-corrected plasma trough liraglutide concentration at the final visit was increased by 49% (95% CI 6–109, $P = 0.02$) in the group with ESRD compared with the control group. Initial and temporary nausea and vomiting occurred more frequently among liraglutide-treated patients with ESRD compared with control subjects ($P < 0.04$). Glycemic control tended to improve during the study period in both liraglutide-treated groups as assessed by daily blood glucose measurements ($P < 0.01$), and dose of baseline insulin was reduced in parallel ($P < 0.04$). Body weight was reduced in both liraglutide-treated groups (−2.4 ± 0.8 kg [mean ± SE] in the group with ESRD, $P = 0.22$; −2.9 ± 1.0 kg in the control group, $P = 0.03$).**

## CONCLUSIONS

**Plasma liraglutide concentrations increased during treatment in patients with type 2 diabetes and ESRD, who experienced more gastrointestinal side effects. Reduced treatment doses and prolonged titration period may be advisable.**


*[1]Department of Nephrology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*
*[2]Center for Diabetes Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark*
*[3]The Novo Nordisk Foundation Center for Basic Metabolic Research and Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*
*[4]Department of Endocrinology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*
*[5]Department of Internal Medicine, Hillerød Hospital, University of Copenhagen, Hillerød, Denmark*
*[6]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark*

*Corresponding author: Thomas Idorn, thomas.idorn@regionh.dk.*

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Diabetic nephropathy is the most common cause of dialysis-dependent end-stage renal disease (ESRD). Forty-five percent of U.S. patients with ESRD have diabetes compared with 23% of patients in Denmark (1,2). Several antidiabetic drugs are cleared renally. Accordingly, only a limited number of antidiabetic treatment options exist for this group of patients. Currently, insulin is the cornerstone of treatment; however, dose reduction may be required due to reduced renal clearance of circulating insulin (3–5). Hence, the risk of hypoglycemia is high, and unawareness, often associated with autonomous neuropathy, frequently further impedes insulin treatment in patients with ESRD and diabetes (6). The oral antihyperglycemic agents biguanides, α-glucosidase inhibitors, and sodium-glucose cotransporter 2 inhibitors are not usable in patients with ESRD and type 2 diabetes (4,5). Some second-generation sulphonylureas and meglitinides can be used with caution, and thiazolidinediones may be used to treat patients with ESRD and diabetes without cardiac disease (4,5). The dipeptidyl peptidase 4 (DPP-4) inhibitors have expanded the limited armamentarium; linagliptin can be administered to patients with ESRD without dose reduction (7), and saxagliptin, vildagliptin, and sitagliptin can be used in reduced doses (8–12). The efficacy of DPP-4 inhibitors is, however, often inadequate. Glucagon-like peptide-1 (GLP-1) receptor agonists possess a potent antihyperglycemic effect with a low risk of hypoglycemia. Nevertheless, these agents have been less thoroughly investigated and are currently not recommended for patients with ESRD due to lack of data (13–18). The primary objectives of the current study were to evaluate plasma liraglutide concentrations and adverse events (AEs) during treatment in patients with type 2 diabetes and ESRD. We hypothesized that patients with type 2 diabetes and ESRD tolerate treatment with liraglutide in doses that accord with the recommendations of the European Medicines Agency (13), without causing significant accumulation in plasma.

## RESEARCH DESIGN AND METHODS

The protocol has been published previously (19), and a summary is provided below.

### Trial Design and Registration

The study was conducted as an investigator-initiated, multicenter (three sites), placebo-controlled, double-blind, parallel-group, randomized trial in Denmark. Two groups were investigated: *1*) patients with type 2 diabetes and ESRD and *2*) patients with type 2 diabetes and normal kidney function (control group). Participants in both groups were randomized to liraglutide or placebo (1:1). The intervention period was 12 weeks and inclusion was continued until 20 participants in each group had completed a minimum of 6 weeks of treatment. The Danish Medicines Agency (EudraCT number 2010-021922-36), the Scientific Ethics Committee of the Capital Region of Denmark (H-3-2011-032), and the Danish Data Protection Agency (2007-58-0015) approved the study, which was registered at clinicaltrials.gov (NCT01394341) prior to study start. The study was carried out in compliance with the International Conference on Harmonization and good clinical practice (GCP) guidelines under the surveillance of the GCP unit at Copenhagen University Hospital. The study was conducted in accordance with the latest revision of the Helsinki Declaration.

### Participants and Study Settings

Patients with ESRD were recruited among chronic dialysis patients at the Departments of Nephrology at Rigshospitalet and Hillerød Hospital, Denmark, from September 2011 to October 2013. Control subjects were recruited from the outpatient clinic at the Department of Endocrinology, Rigshospitalet. Eligibility criteria for participants in the dialysis group were men and women aged 18–85 years, chronic hemodialysis or peritoneal dialysis treatment, type 2 diabetes diagnosed at least 3 months prior to screening, and preserved β-cell function as evaluated by a glucagon test. Inclusion criteria in the control group were men and women aged 18–85 years, normal kidney function (plasma creatinine $<$105 μmol/L for men and $<$90 μmol/L for women), type 2 diabetes diagnosed at least 3 months prior to screening, glycated hemoglobin ($HbA_{1c}$) $>$6.5% ($>$48 mmol/mol), and preserved β-cell function.

### Experimental Design

Participants in both groups followed the same study plan. On an initial screening day, a 6-min glucagon test was performed for documentation of preserved β-cell function. After screening, all included participants attended nine planned visits: randomization (week 0), week 1, week 2, week 4, week 6, week 8, week 10, week 12, and follow-up (week 13). At each visit, blood sampling was performed, AEs were reported, glycemic control was assessed, trial medication was dispensed, used packages were collected to estimate compliance, and doses of antidiabetic drugs, including trial medication, were adjusted. Blood glucose was measured (using a Contour glucose meter; Bayer HealthCare, Copenhagen, Denmark) three times daily (fasting in the morning, before dinner, and before bedtime) throughout the study period. Participants did not inject trial medication in the morning prior to the trial visits, and time since last dose was registered at each trial visit. Participants attended in a fasting state (8 h overnight) for the randomization, week 6, and week 12 visits.

### Intervention

Trial medication was initiated on the day of randomization in a dosage of 0.6 mg s.c. once daily. All participants were requested to inject the medicine in the abdomen before breakfast. Depending on glycemic control and side effects, dose was escalated by up to 0.6 mg per week to a maximum of 1.8 mg. Doses of baseline antidiabetic medication were individually adjusted in parallel with trial medication according to prespecified treatment goals. To minimize the risk of hypoglycemia, basal insulin dose was reduced by 20–50% at randomization and sulphonylureas were paused, while metformin was continued in unchanged doses.

### Outcomes

The primary end point was the dose-corrected trough concentration of liraglutide in plasma at the final trial visit (week 12). Secondary end points included severe AEs (SAEs), AEs, glycemic control, change in baseline insulin dose, body weight, hypoglycemic episodes (divided into minor [blood glucose $<$3.1 mmol/L and no need for assistance] and major [blood glucose $<$3.1 mmol/L and requiring assistance from third person]), and cardiovascular parameters (heart rate, blood pressure, lipid profile, and prohormone brain natriuretic peptide [proBNP] concentration in plasma).

### Sample Size

The power calculation was based on the primary end point. On the basis of previous

trials with liraglutide, the trough value was estimated to be 20,000 pmol/L during steady state and the SD was estimated to be 8,000 pmol/L in people with normal kidney function (20,21). Ten completers in each liraglutide treatment arm and a significance level of 5% ($\alpha = 0.05$) would enable us to detect a difference of 10,600 pmol/L with a power of 80% ($1 - \beta = 0.80$) using a two-sample Student *t* test. Further statistical power was obtained by analyzing data from all visits using a linear mixed model.

### Randomization and Blinding

Patients and control subjects were assigned to receive either liraglutide or placebo according to a computer-generated randomization list provided by Novo Nordisk A/S (Bagsværd, Denmark). Simple randomization was used consecutively in both groups, and an unblinded, impartial person from Rigshospitalet was informed in the case of withdrawals or exclusions in order to ensure 10 completers in each treatment arm. Participants, investigators, and healthcare staff were blinded for the allocated treatment and remained so until last patient last visit.

### Analyses and Statistical Methods

The primary end point was reported based on a modified per-protocol (PP) analysis, i.e., restricted to participants who completed a minimum of 6 weeks of intervention with a compliance >80% of the prescribed trial medication. If the full intervention period was not completed, the last observation carried forward method was applied. Secondary end points related to efficacy were reported based on data from the PP population, and data related to safety were reported based on intention-to-treat analyses. We used a linear mixed model to address our primary end point. Group, trial visit day, and treatment dose since last trial visit were used as explanatory variables, and a model with interaction between group and trial visit day was applied to model two different trajectories: differences in dose-corrected liraglutide concentrations between groups and changes in dose-corrected liraglutide concentrations within groups during the study period. The primary end point was calculated as the difference in estimated, dose-corrected plasma trough liraglutide concentrations between the two liraglutide-treated groups at the final trial visit (week 12). Plasma liraglutide concentrations were measured by a validated liraglutide-specific ELISA method at Huntingdon Life Sciences Ltd. (Alconbury, U.K.) as previously described (22). Distribution of data and homogeneity of variance were assessed using graphical evaluation of residuals from the linear mixed model. The empirical distribution of the liraglutide concentrations was well approximated by a log-normal distribution, and, hence, liraglutide concentrations and treatment doses were log transformed prior to analysis. Otherwise, normally distributed data were evaluated using parametric testing, and for data that did not follow a normal distribution or exhibited unequal variance, nonparametric testing was applied. For group comparisons of categorical data, we used $\chi^2$ or Fisher exact tests, and continuous data were analyzed with a one-way ANOVA using Tukey honestly significant difference test as post hoc test. A Poisson regression analysis was used for evaluation of AEs, and the placebo-treated control group was used as references. Blood glucose measurements were analyzed using a linear mixed effects model, taking the variation between participants and the serial correlation into account. All tests were two tailed, and a *P* value <0.05 was considered significant.

## RESULTS

### Demographic and Baseline Clinical Data

Eligibility was assessed in 176 patients with ESRD and 215 control subjects; 24 patients with ESRD were randomized (14 to liraglutide treatment and 10 to placebo treatment) and 23 control subjects were randomized (11 to liraglutide treatment and 12 to placebo treatment). In both groups, potential study participants were screened based on computer-generated lists of patients registered with diabetes, without further specification. Thus, the group of patients assessed for eligibility also included patients with type 1 diabetes. In the group with ESRD, the main reasons for noneligibility and refusing to participate were type 1 diabetes, cardiac disease, and time consumption, and in the control group, the main reasons were type 1 diabetes, ongoing treatment with an incretin-based agent, renal insufficiency, and time consumption. Twenty participants in each group (10 treated with liraglutide and placebo, respectively) completed the study period, with the exception of one patient with ESRD (liraglutide group) who dropped out after 8 weeks of treatment due to the summer holidays. Figure 1*A* and B shows study flowcharts. Groups were matched according to age, sex, and BMI. Ethnicity, smoking, and diabetes history were comparable between groups. The majority of patients with ESRD and control subjects were treated with insulin (75 and 70%, respectively; PP population); none of the patients with ESRD received metformin compared with 80% in the control group. Two patients with ESRD and one control subject were treated with sulphonylureas at baseline. The majority of patients with ESRD received standard medical care for dialysis patients, including erythropoietin, iron substitution, vitamins B, C, and D, and phosphate binders. Demographic and baseline clinical and biochemical data are summarized in Table 1.

### Liraglutide Doses and Plasma Concentrations

Liraglutide-treated patients with ESRD were titrated more slowly than liraglutide-treated control subjects but ended at comparable doses after 12 weeks ($1.33 \pm 0.13$ and $1.26 \pm 0.06$ mg/day, $P = 0.61$) (Fig. 2*A*). The dose-corrected plasma trough liraglutide concentration at the final visit was increased by 49% (95% CI 6–109, $P = 0.02$) in liraglutide-treated patients with ESRD compared with liraglutide-treated control subjects (Fig. 2*D*). Estimated geometric means of plasma liraglutide concentrations were 11,980 (95% CI 9,379–15,290) and 8,057 (6,306–10,290) pmol/L $\times$ $mg^{-1}$, respectively, at week 12 (Fig. 2*D*). The dose-corrected plasma trough liraglutide concentration was increased in the liraglutide-treated group with ESRD throughout the intervention period compared with the liraglutide-treated control group. The increase ranged from 30.4% (−9.4 to 87.6) to 70.4% (5.4 to 175.3) at individual trial visits, and there were no signs of progressive accumulation of liraglutide in the group with ESRD as evaluated from the slope of the dose-corrected liraglutide concentration curve, which was similar to that of the control group ($P = 0.78$) (Fig. 2*D*). Compliance was high in all four treatment arms at all visits (>94.8%), with no differences between groups ($P = 0.95$).

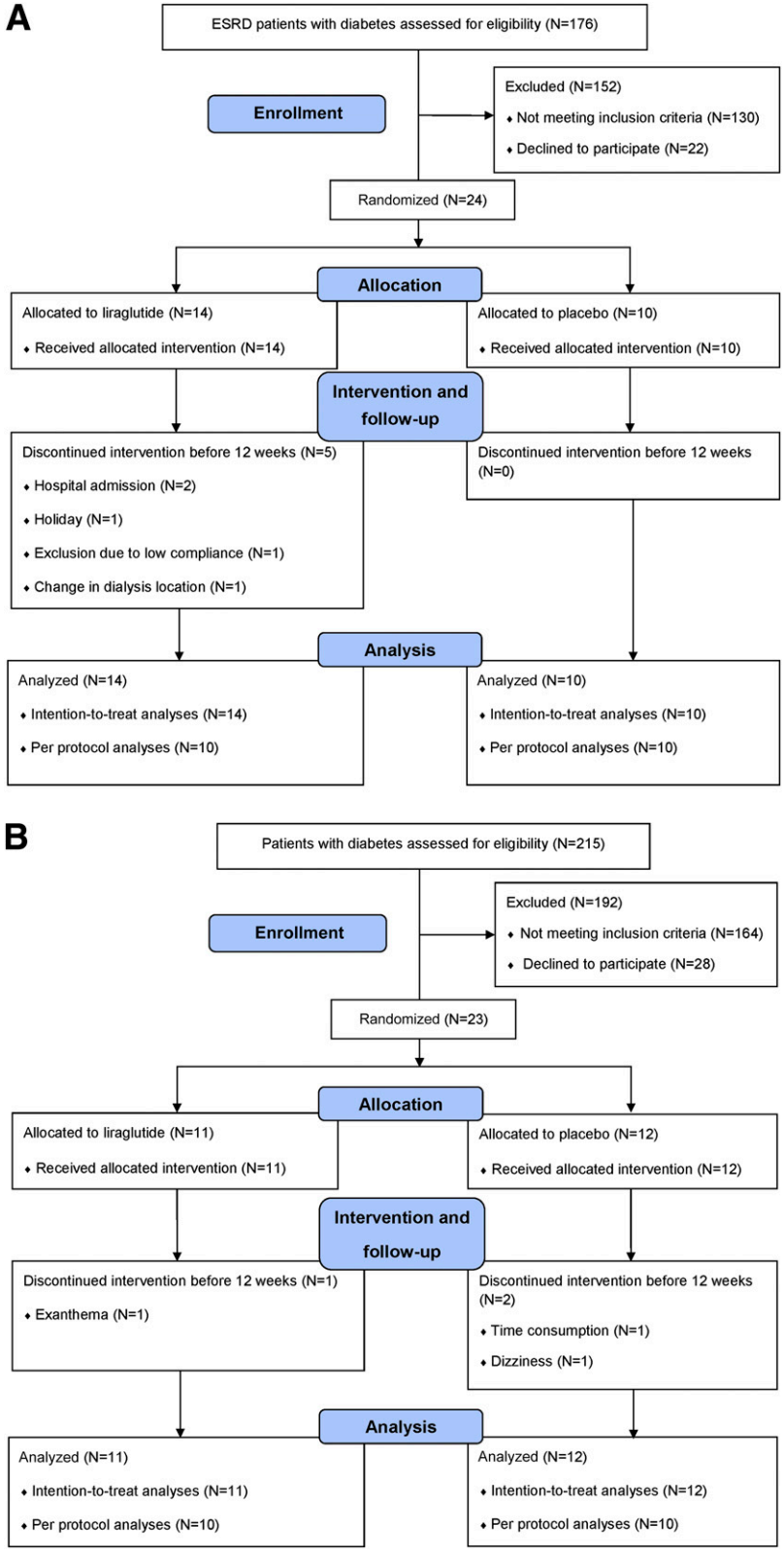


**Figure 1**—Study flowchart of participants diagnosed with diabetes and ESRD (*A*) and diabetes and normal kidney function (*B*).

### Glycemic Control and Change in Baseline Antidiabetic Treatment

$HbA_{1c}$ was reduced in both liraglutide groups: patients with ESRD, $-0.5 \pm 0.3\%$ ($-6 \pm 3$ mmol/mol) from $6.7 \pm 0.4\%$ ($50 \pm 4$ mmol/mol) at baseline, $P = 0.71$ compared with placebo-treated patients with ESRD; control subjects, $-1.3 \pm 0.4\%$ ($-14 \pm 4$ mmol/mol) from $7.9 \pm 0.4\%$ ($63 \pm 4$ mmol/mol) at baseline, $P = 0.03$ compared with placebo-treated control subjects (Supplementary Table 1). Likewise, blood glucose was reduced from baseline to week 12 in all groups ($P < 0.01$) (Supplementary Fig. 1B). In parallel, doses of basal insulin were significantly reduced in both liraglutide-treated groups during the study period ($P < 0.04$) (Supplementary Fig. 1A).

### AEs and SAEs

Gastrointestinal side effects constituted the dominant AE. Nausea and vomiting occurred more frequently in liraglutide-treated patients with ESRD than in the other treatment arms ($P < 0.04$) (Fig. 3 and Supplementary Table 2). Both nausea and vomiting were, however, temporary in most patients and primarily related to initiation of treatment and dose escalation (Fig. 3). Both liraglutide-treated groups experienced significantly more dyspepsia compared with the placebo groups, whereas only liraglutide-treated control subjects had excess abdominal discomfort and diarrhea ($P < 0.03$). The number of episodes with hypoglycemia did not differ between treatment arms ($P = 0.34$). AEs are summarized in Supplementary Table 2. More SAEs occurred in the group with ESRD ($n = 7$, including $n = 6$ among liraglutide-treated patients with ESRD) compared with the control group ($n = 1$ from the liraglutide group), although none was assessed to be related to trial medication. All SAEs led to admission, and in all cases the patient was discharged within 6 days in a good clinical condition without permanent injuries. There were no deaths. Two cases of admission caused exclusion from the study due to interrupted use of trial medication. SAEs, their causes, and short descriptions are reported in Supplementary Table 3.

### Changes in Clinical and Biochemical Parameters During Treatment

Changes in clinical and biochemical parameters during the study period are summarized in Supplementary Table 1.

**Table 1—Baseline clinical and demographic data**

| | ESRD + liraglutide | ESRD + placebo | Control + liraglutide | Control + placebo | *P* |
|---|---|---|---|---|---|
| *n* | 10 | 10 | 10 | 10 | |
| Age (years) | 68.3 ± 3.1 | 65.9 ± 4.4 | 60.7 ± 3.2 | 63.1 ± 2.1 | 0.40 |
| Sex (male/female) | 8/2 | 9/1 | 7/3 | 8/2 | 0.74 |
| BMI (kg/m$^2$) | 31.6 ± 2.4 | 31.5 ± 2.4 | 30.2 ± 1.3 | 30.8 ± 1.0 | 0.95 |
| Smoking (present/previous/never; *n*) | 0/6/4 | 0/4/6 | 3/6/1 | 6/2/2 | 0.01 |
| Ethnicity (Caucasian/African American/Asian; *n*) | 10/0/0 | 7/0/3 | 9/1/0 | 9/1/0 | 0.07 |
| Diabetes | | | | | |
| Duration since diagnosis of type 2 diabetes (years) | 15.3 ± 2.3 | 13.0 ± 2.4 | 9.9 ± 3.0 | 16.0 ± 2.7 | 0.36 |
| Treatment (OAD/insulin/insulin and OAD/diet; *n*) | 1/7/1/1 | 0/7/0/3 | 5/1/4/0 | 1/3/6/0 | <0.01 |
| Comorbidity and treatment | | | | | |
| Ischemic heart disease (previous MI or revascularization/none; *n*) | 3/7 | 4/6 | 1/9 | 2/8 | 0.45 |
| Peripheral vascular disease (previous amputation/foot ulcers or intermittent claudication/none; *n*) | 1/3/6 | 1/0/9 | 0/1/9 | 0/4/6 | 0.22 |
| Retinopathy (proliferative or previous laser treatment/simplex/none; *n*) | 3/2/5 | 3/1/6 | 1/1/8 | 1/4/5 | 0.42 |
| Antihypertensive treatment (*n*) | 10 | 9 | 7 | 9 | 0.23 |
| Lipid-lowering treatment (*n*) | 6 | 7 | 10 | 10 | 0.03 |
| Blood samples | | | | | |
| $HbA_{1c}$ [% (mmol/mol)] | 6.7 ± 0.4 (50 ± 4) | 6.6 ± 0.4 (49 ± 4) | 7.9 ± 0.4 (63 ± 4) | 7.8 ± 0.4 (62 ± 4) | 0.04 |
| Creatinine (μmol/L) | 535 ± 44 | 643 ± 67 | 63 ± 4# | 61 ± 3§ | <0.01 |
| Albumin (g/L) | 40 ± 1 | 43 ± 1 | 43 ± 1 | 42 ± 1 | 0.14 |
| Alanine aminotransferase (units/L) | 24 ± 4 | 21 ± 2 | 34 ± 6 | 28 ± 4 | 0.13 |
| Calcitonin (pmol/L) | 6.0 ± 2.2 | 3.0 ± 1.0 | 0.7 ± 0.2# | 0.6 ± 0.2§ | 0.01 |
| ProBNP (pmol/L) | 429 ± 107 | 228 ± 140 | 5 ± 1# | 10 ± 2§ | <0.01 |
| Total cholesterol (mmol/L) | 4.0 ± 0.4 | 4.7 ± 0.4 | 3.8 ± 0.3 | 3.9 ± 0.4 | 0.23 |
| LDL cholesterol (mmol/L) | 2.1 ± 0.4 | 2.7 ± 0.4 | 1.9 ± 0.2 | 2.2 ± 0.3 | 0.34 |
| HDL cholesterol (mmol/L) | 1.5 ± 0.2 | 1.2 ± 0.1 | 1.3 ± 0.1 | 1.2 ± 0.1 | 0.17 |
| Triglyceride (mmol/L) | 1.14 ± 0.13* | 2.26 ± 0.27† | 1.97 ± 0.24 | 1.24 ± 0.24 | 0.01 |

Data are presented as means ± SE or numbers (*n*). For those biochemical parameters reported with a lower detection limit, an exact result was estimated as half the lower detection limit (calcitonin 0.3 pmol/L; proBNP 2.95 pmol/L). MI, myocardial infarction; OAD, oral antidiabetic agent. Post hoc statistical testing for continuous data: *ESRD + liraglutide vs. ESRD + placebo: $P < 0.05$. #ESRD + liraglutide vs. control + liraglutide: $P < 0.05$. §ESRD + liraglutide vs. control + placebo: $P < 0.05$. †ESRD + placebo vs. control + placebo: $P < 0.05$.

Liraglutide treatment caused weight loss in the control group (from 89.5 ± 3.7 to 86.6 ± 3.5 kg, $P = 0.03$), whereas weight was reduced insignificantly in the group with ESRD (from 91.1 ± 4.9 to 88.7 ± 5.2 kg, $P = 0.22$). Pulse rate increased 6.9 ± 2.4 min$^{-1}$ in liraglutide-treated patients with ESRD from 69.9 ± 2.9 min$^{-1}$ at randomization ($P < 0.01$ when compared with the placebo group) and 5.5 ± 2.3 min$^{-1}$ in liraglutide-treated control subjects from 77.8 ± 3.8 min$^{-1}$ at randomization ($P = 0.35$). Liraglutide treatment changed neither systolic nor diastolic blood pressure significantly in the two groups ($P > 0.33$). The majority of biochemical markers were not affected by liraglutide treatment. ProBNP was significantly reduced in the group with ESRD treated with liraglutide, which was not the case in the liraglutide-treated control group. However, significant reductions in total LDL and HDL cholesterol were observed only in the control group. None of the clinical and biochemical changes observed during intervention differed between liraglutide-treated patients with ESRD and liraglutide-treated control subjects ($P > 0.10$). Changes in clinical and biochemical parameters are summarized in Supplementary Table 1.

## CONCLUSIONS

In this investigator-initiated, multicenter, placebo-controlled, double-blind, parallel-group, randomized trial, we found that *1*) dose-corrected liraglutide concentration was significantly increased in patients with type 2 diabetes and ESRD throughout 12 weeks of liraglutide treatment as compared with patients with type 2 diabetes and normal kidney function, *2*) progressive accumulation of liraglutide did not occur in patients with ESRD during treatment, *3*) liraglutide treatment allowed significant reduction in basal insulin doses in insulin-treated patients with type 2 diabetes and ESRD without causing deterioration of glycemic control, and *4*) patients with ESRD seemed more prone to liraglutide's gastrointestinal side effects than patients with type 2 diabetes with normal kidney function.

Few studies have examined safety and efficacy of GLP-1 receptor agonists in the setting of renal insufficiency. Five GLP-1 receptor agonists are approved by the European Medicines Agency to treat type 2 diabetes: exenatide (twice-daily and once-weekly formulations), lixisenatide, albiglutide, dulaglutide, and liraglutide (13–18). Exenatide and lixisenatide are primarily eliminated by glomerular filtration and subsequent proteolytic degradation in the tubules; therefore, in the currently recommended doses, they are unsuitable for patients with advanced stages of renal insufficiency (11,12,14,15,17,23–26). Albiglutide and dulaglutide are thought to be degraded in vivo by ubiquitous proteolytic enzymes and general protein catabolism

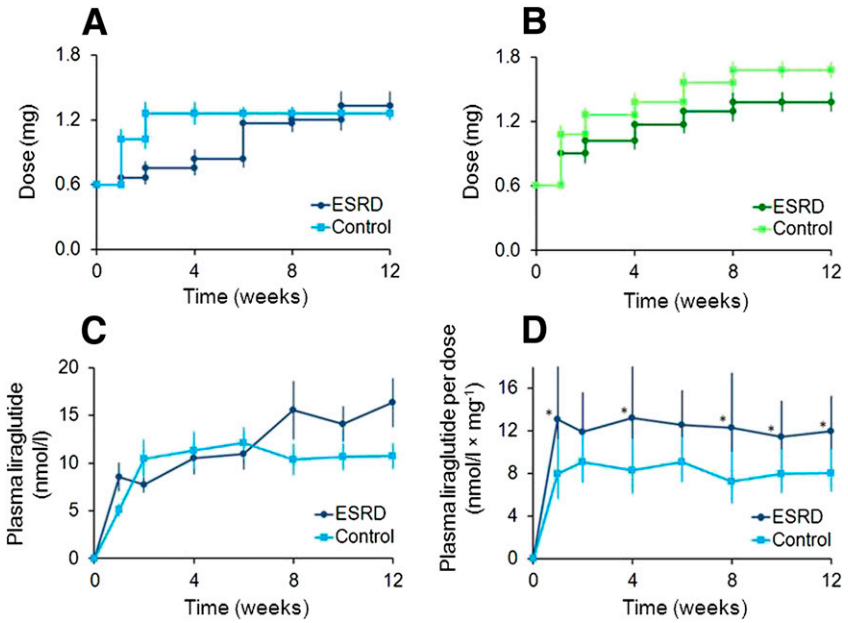


**Figure 2**—Doses of trial medication in the liraglutide groups (*A*) and in the placebo groups (*B*). Concomitant plasma trough liraglutide concentrations (*C*) (only liraglutide groups are shown) and dose-corrected plasma trough liraglutide concentrations (*D*) (only liraglutide groups are shown). Data are means ± SE (*A–C*) and estimated geometric means with 95% CIs (*D*) based on data from the PP population. Asterisks (*) in *D* indicate significance ($P < 0.05$).

pathways; however, due to very limited experience, treatment is not recommended in patients with severe renal insufficiency (creatinine clearance <30 mL/min) (16,18). Liraglutide is extensively bound to plasma proteins (>98%) and is thought to be metabolized the same way as large proteins without a specific organ having been identified as the major site of elimination. Intact liraglutide cannot be demonstrated in the urine, and only a small fraction (6%) is thought to be excreted as metabolites in the urine (13,27). Thus, existing knowledge indicates that the kidneys do not represent a key route for elimination of liraglutide. Malm-Erjefält et al. (28) suggested that liraglutide is degraded completely within the body, and Davidson et al. (29) concluded in a meta-analysis that mild renal insufficiency (creatinine clearance 60−89 mL/min) does not affect the efficacy or safety of liraglutide treatment. A study by Jacobsen et al. (30) evaluated pharmacokinetic properties of liraglutide after subcutaneous injection of a single dose (0.75 mg) in patients with various degrees of renal insufficiency and found no signs of accumulation or delayed elimination, even in those with ESRD. In a newly published 4-day open-label pilot study by Osonoi et al. (31), 10 Japanese patients with type 2 diabetes and ESRD were treated with two injections of liraglutide (0.6 or 0.9 mg s.c./day on days 2 and 3). The study had no control group. Nonetheless, the authors suggested that dose reduction of liraglutide is not required in patients with ESRD (31). Another recent randomized controlled trial examined efficacy and safety of 26 weeks of liraglutide treatment (1.8 mg s.c./day) in 140 patients with type 2 diabetes and moderate renal insufficiency (estimated GFR 30–59 mL/min). Liraglutide was not measured in plasma, but results showed no unexpected safety or tolerability issues (32). Few case reports have suggested an association between liraglutide therapy and acute kidney injury in patients with none or mild to moderate preexisting renal insufficiency (33); however, the aforementioned study by Umpierrez et al. (32) did not report any such cases. The European Medicines Agency states that no dose adjustment of liraglutide is required in patients with mild or moderate renal insufficiency (creatinine clearance >30 mL/min), but because there is no therapeutic experience in patients with severe renal insufficiency (creatinine clearance <30 mL/min), liraglutide cannot currently be recommended for use in these patients (13). Likewise, the U.S. Food and Drug Administration advises that liraglutide should be used with caution in patients with renal insufficiency owing to limited experience (34). The current study brings novel data to this poorly illuminated area.

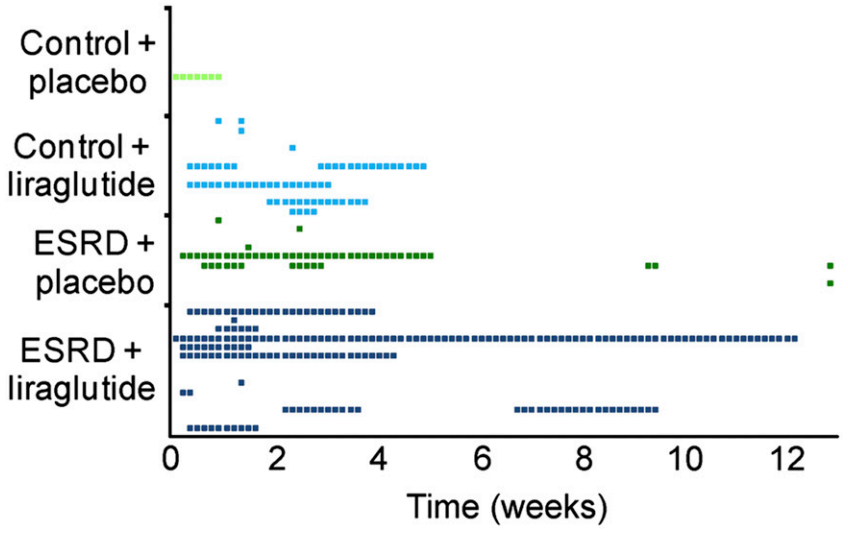


**Figure 3**—Occurrence of nausea and vomiting in the four groups during treatment. Each line represents one patient and each square represents one day or episode with nausea and/or vomiting.

Plasma trough liraglutide concentrations are dose dependent and would be expected to increase during continuous treatment in patients with ESRD if the kidneys play a significant role in degradation and/or elimination of intact liraglutide (22,28,30). Accordingly, our results suggest that the degradation and/or elimination of liraglutide is significantly impaired in patients with dialysis-dependent ESRD, which is in contrast to

the aforementioned studies (13,28,30). Nonetheless, we did not observe progressive accumulation in the group with ESRD during treatment (Fig. 2*D*), indicating that the kidneys are not exclusively responsible for elimination and/or degradation of liraglutide. Our findings suggest that doses should be reduced if liraglutide treatment is considered for those with severe renal insufficiency. Further studies are needed to confirm this.

Plasma liraglutide concentrations correlate with the frequency and intensity of AEs related to treatment with liraglutide (22), and elderly patients and patients with mild renal impairment are known to be more prone to its gastrointestinal side effects (13). These facts might explain the increased incidences of nausea and vomiting occurring in the liraglutide-treated group with ESRD in our study. Nausea and vomiting were generally temporary phenomena related to initiation of treatment and dose escalation, and few patients experienced these side effects in the second half of the treatment period. Therefore, it is likely that dose reduction and slow dose escalation will reduce occurrence and duration of these side effects.

The safety profile was overall good in the group with ESRD. The SAEs were in excess in the liraglutide-treated part of the group with ESRD; however, none was considered related to liraglutide treatment, and in all cases of admission, the patients were discharged in a good clinical condition within 6 days without permanent disabilities. Only few cases of hypoglycemia were observed (all minor) despite combination with insulin in several patients. We observed an excess number of withdrawals and exclusions in the liraglutide-treated part of the group with ESRD ($n = 5$); however, with the exception of one patient, who was excluded due to low compliance, none of these was assessed to be caused by liraglutide treatment. Liraglutide-treated patients with ESRD and control subjects expectedly lost weight during treatment with no difference between groups ($P = 0.39$) (35). We observed no cases of severe dehydration, even in those with the most gastrointestinal side effects, i.e., the weight losses observed were not assessed to be due to dehydration. We reported two SAEs due to clotted arteriovenous fistulas; neither patient was clinically dehydrated and both were above their ideal "dry weight" at admission.

A high BMI is associated with lower mortality in patients with ESRD including the range of obesity ($\geq$30 kg/m$^2$), the so-called obesity paradox (36–38). Moreover, weight loss at any BMI is associated with increased mortality among patients receiving maintenance dialysis (39). Even though the aforementioned studies were only observational and did not specifically examine patients with ESRD and type 2 diabetes during intervention, individual evaluation of an acceptable weight loss must be performed prior to initiation of liraglutide treatment in patients with ESRD.

The study was not powered to conclude on most of our secondary end points. Nevertheless, data on $HbA_{1c}$, blood glucose, and change in doses of baseline antidiabetic treatment suggest that the blood glucose–lowering effect of liraglutide is not impeded by severe uremia. Earlier studies by our group indicated that endogenous GLP-1 might have a reduced β-cell stimulatory effect in patients with ESRD (40,41), but the present results suggest that high plasma levels of a GLP-1 receptor agonist can circumvent this. Further studies testing the efficacy of liraglutide in patients with advanced stages of renal insufficiency are warranted.

Our study has several limitations. The study population was relatively small, which allows us to draw statistically supported conclusions only on our primary end point. Likewise, evaluation of potential severe, rare AEs, e.g., pancreatitis (11), requires larger-scale studies with longer follow-up. The primary end point in our study is nonclinical; however, it is strictly objective and, therefore, representative of the population with ESRD, although our patients represent a selected part of the population with diabetes and ESRD with the least comorbidity. Gastrointestinal symptoms, including nausea and occasionally vomiting, occur frequently in the population with ESRD in general (Fig. 3). This impedes evaluation of gastrointestinal side effects related to liraglutide to some extent. However, inclusion of a placebo arm in the group with ESRD facilitated differentiation. Hemodialysis patients were examined immediately prior to a dialysis session, i.e., often with excess body fluid. This affects weight and blood pressure measurements and complicates the evaluation of liraglutide-induced weight loss and change in blood pressure.

In conclusion, our data suggest that continuous liraglutide treatment is applicable in patients with type 2 diabetes and ESRD, although larger-scale studies are needed to confirm this. Dose reduction and prolongation of the titration period may be advisable to reduce nausea and vomiting, which occurred more frequently in patients with ESRD. Few SAEs were reported, all seemingly unrelated to liraglutide treatment. Glycemic control did not deteriorate during liraglutide treatment in the group with ESRD, despite a significant reduction in basal insulin doses. We observed a nonsignificant weight loss in the group with ESRD, which may be an untoward effect in some dialysis patients.

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**Author Contributions.** T.I. designed the study; wrote the study protocol; screened, recruited, and treated all study participants; performed data analyses and statistical calculations; and wrote the initial draft of the manuscript. F.K.K., J.J.H., M.H., and B.F.-R. designed the study. M.B.J. screened, recruited, and treated all study participants and performed data analyses and statistical calculations. T.J. designed the study and screened,

recruited, and treated all study participants. M.R. and P.M.H. screened, recruited, and treated all study participants. K.B.C. designed the study and performed data analyses and statistical calculations. All authors contributed to the interpretation of the data and the revision of the paper and approved the final version of the manuscript. The study data are the property of T.I., B.F.-R., and Rigshospitalet. T.I. and B.F.-R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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