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ORIGINAL ARTICLE

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Exenatide once weekly decreases urinary albumin excretion in patients with type 2 diabetes and elevated albuminuria: Pooled analysis of randomized active controlled clinical trials

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Abstract

Aims: To examine the albuminuria-lowering effect of exenatide once weekly (EQW) compared with active glucose-lowering comparators in patients with type 2 diabetes and elevated urinary albumin-to-creatinine ratio (uACR).

Methods: Six randomized double-blind and open-label phase III studies were pooled in a *post hoc*, exploratory analysis to evaluate the efficacy and safety of EQW versus non-glucagon-like peptide-1 receptor agonist comparators in patients with type 2 diabetes and baseline uACR ≥30 mg/g. Treatment groups were EQW versus all comparators pooled. Efficacy outcomes were percent change from baseline to week 26/28 in uACR and absolute change in glycated haemoglobin (HbA1c), systolic blood pressure (SBP), body weight and estimated glomerular filtration rate (eGFR).

Results: Baseline characteristics were generally similar between the two treatment groups (EQW: N = 194, all comparators: N = 274). Relative to the comparator group, EQW changed albuminuria by −26.2% (95% confidence interval [CI] −39.5 to −10). Similar improvements were observed with EQW versus oral glucose-lowering drugs (−29.6% [95% CI −47.6 to −5.3) or insulin (−23.8% [95% CI −41.8 to −0.2]). The effect of EQW on uACR was independent of baseline renin-angiotensin system inhibitor usage. Adjusted mean decreases in HbA1c, SBP and body weight were more pronounced in the EQW versus the comparator group. Adjustment for changes in HbA1c, eGFR and SBP did not substantially affect the uACR-lowering effect of EQW.

When also adjusting for changes in body weight, the uACR-lowering effect was reduced to (−13.0% [95% CI −29.9 to 7.8]).

Conclusion: Exenatide once weekly reduced uACR in patients with type 2 diabetes and elevated albuminuria compared to commonly used glucose-lowering drugs.

KEYWORDS

diabetic kidney disease, exenatide, GLP-1RA, glucagon-like peptide-1 receptor agonists, pooled analysis

1 | INTRODUCTION

Diabetic kidney disease develops in approximately 40% of all patients with diabetes. It is the leading cause of end-stage kidney disease (ESKD) worldwide and associated with an increased risk of cardiovascular morbidity and mortality.[1,2] Despite intensive glucose and blood pressure control, many patients with diabetic kidney disease progress to ESKD, highlighting the need for novel treatment strategies.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) stimulate insulin secretion by pancreatic β cells in a glucose-dependent way, suppress glucagon release, and delay gastric emptying. GLP-1RAs have been shown to significantly improve glycaemic control and reduce body weight.[3] Data from large cardiovascular outcome trials suggest that GLP-1RAs may also beneficially impact renal outcomes like albuminuria and decline in estimated glomerular filtration rate (eGFR).[4–8] This potential renal protective effect may be mediated by improvements in glycaemic and metabolic control although other effects such as increases in natriuresis and diuresis or anti-inflammatory effects may also be involved.[9]

The cardiovascular outcome trials enrolled patients at high cardiovascular risk and compared the efficacy and safety of GLP-1RAs against placebo. Few studies are available on the comparative effects of GLP-1RAs versus other glucose-lowering drugs in patients with diabetes and albuminuric kidney disease. We therefore assessed the effect of the GLP-1RA exenatide once weekly (EQW) on urinary albumin-to-creatinine ratio (uACR) and eGFR versus other glucose-lowering drugs in patients with type 2 diabetes and elevated albuminuria.

2 | METHODS

2.1 | Study design and patient population

In this *post hoc*, exploratory pooled analysis, six randomized double-blind and open-label phase III studies were included that evaluated the efficacy and safety of exenatide 2 mg administered subcutaneously once weekly (EQW; aqueous formulation or non-aqueous suspension) versus all comparators pooled including insulin (insulin glargine, insulin detemir) or oral antidiabetic drugs (OADs; sitagliptin, metformin or pioglitazone) in patients with type 2 diabetes (Table S1). The study designs, populations and primary results of all these studies have been previously reported.[10–15] In five studies, the controlled treatment period was 26 weeks; in one study,[13] it was 28 weeks. Results were combined for the week 26/28 timepoint.

Patients with a baseline urinary albumin to creatinine ratio (uACR) ≥30 mg/g were included for analysis. Studies were performed on a broad range of background drugs. All study protocols were approved by the institutional review boards and central ethics committees, and informed consent was obtained from all patients. All studies complied with the Declaration of Helsinki and other relevant ethical guidelines.

2.2 | Outcome measures

The main endpoint in the present analysis was the uACR percent change from baseline to week 26/28. Urinary albumin and creatinine were determined in a single spot urine sample available at baseline and week 26/28 only.

In addition, the effects of EQW versus all comparators on absolute mean changes from baseline to week 26/28 in glycated haemoglobin (HbA1c), systolic blood pressure (SBP), body weight and eGFR were evaluated. eGFR was estimated with the four-variable Modification of Diet in Renal Disease (MDRD-4) formula for five of the six pooled studies.[16] One study[14] was performed in Japan and used a modified MDRD equation according to Matsuo et al.[17]

The proportions of patients with adverse events (AEs), AEs leading to discontinuation from study, serious AEs, and AEs of special interest (acute renal failure and dehydration-related events, hypoglycaemic events, and gastrointestinal events) during the 26-/28-week controlled treatment period were calculated and presented by treatment group. AEs were recorded throughout the studies and AEs of special interest were evaluated by summarizing AEs using standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (for dehydration and acute renal failure) or by system organ class and preferred terms (for gastrointestinal AEs).

2.3 | Statistical analysis

Two patient populations were defined for these analyses: (a) a modified intention-to-treat analysis set, defined as all randomized patients who received at least one dose of study medication, had baseline

uACR ≥30 mg/g and had week 26/28 uACR assessments, and (b) a safety analysis set, defined as all patients who were randomized, had baseline uACR ≥30 mg/g, and took at least one dose of the study medication.

Baseline characteristics, demographics and safety data of patients in the pooled analyses were summarized with descriptive statistics. For the primary efficacy analysis of uACR percent change from baseline to week 26/28, uACR values were log-transformed and change from baseline to week 26/28 (ln [week 26/28 uACR/baseline uACR]) was analysed using an analysis of covariance (ANCOVA) model including fixed categorical effects of treatment group and study and a continuous covariate of log-transformed baseline uACR. The ANCOVA results were inverse-transformed using exponentiation to present the uACR percent change from baseline point estimates (least squares geometric mean estimates, standard errors) and corresponding two-sided 95% confidence intervals (CIs). Results were presented for all six studies combined and also separately for the three studies with OADs and for the three studies with insulin comparator treatment groups. Baseline was defined as the latest non-missing assessment prior to the first dose of study medication. For post-baseline, only efficacy results collected during the week 26/28 controlled period were included in the analysis (ie, an all-completers analysis). No imputation was carried out for missing week 26/28 results. All results after treatment discontinuation were excluded.

To assess the consistency of the effects of exenatide on uACR across important patient subgroups, the ANCOVA model was also run for several baseline subgroups (uACR category, eGFR category, and renin-angiotensin system inhibitor category). The model was also run including the categorical subgroup variable as a covariate and subgroup by treatment group interaction in the model. A P value ≤0.100 was considered to indicate a significant interaction. An ANCOVA model was also used for the efficacy analysis of absolute changes from baseline to week 26/28 in eGFR, HbA1c, body weight and SBP, with treatment group and study as fixed effects and the corresponding continuous baseline value as a covariate. To explore the influence of metabolic and cardiovascular variables on uACR percent change, covariates of changes from baseline to week 26/28 (in natural logarithm scale) of each continuous variable HbA1c, eGFR and SBP were added to the primary ANCOVA model.

A third ANCOVA model additionally included body weight change from baseline to week 26/28 (in natural logarithm scale) as a covariate. Metabolic variables included in the two ANCOVA models as covariates were pre-specified.

The proportions of patients with certain percent reductions in uACR from baseline to week 26/28 (≥30%, ≥40% and ≥50%) were calculated, where percent change was determined by (week 26/28 uACR – baseline uACR)/ baseline uACR × 100.

The proportion of patients experiencing AEs was calculated based on either a crude incidence rate or a study size-adjusted incidence rate. Comparisons of the crude and study size-adjusted incidence rates showed only small differences; thus, only crude AE incidence rates are presented. MedDRA version 21.1 was used to code AEs.

All statistical analyses were performed using SAS/STAT version 9.4 (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Baseline characteristics

A total of 674 patients had uACR ≥30 mg/g at baseline and were included in the safety analysis (EQW, N = 284; comparators, N = 390). Week 26/28 uACR results were available for 468 patients (EQW, N = 194; comparators, N = 274); these patients were included in the efficacy analyses. In the comparator treatment group, 127/274 patients (46%) received insulin and 147/274 (54%) received oral glucose-lowering drugs.

Baseline demographics and clinical characteristics of this group are summarized in Table 1 and were generally balanced between treatment groups. The median uACR in the EQW and comparator group was 68.2 and 72.2 mg/g, respectively, and mean baseline eGFR in the EQW and comparator group was 78.9 and 79.6 mL/min/1.73m^2, respectively. A total of 41 patients (21.1%) in the EQW and 48 patients (17.5%) in the comparator group were classified as stage 3 chronic kidney disease (CKD). Mean HbA1c was 8.6% versus 8.5%, and the mean duration of diabetes was 7.4 and 7.0 years in the EQW and comparator groups, respectively. In both treatment groups, approximately half of the patients were using a renin-angiotensin system (RAS) inhibitor at baseline. The proportion of patients taking glucose-lowering medication prior to entering the study was higher for the EQW treatment group. This imbalance was due to the DURATION-4 trial, in which drug-naïve patients were randomized to either exenatide, metformin, pioglitazone or sitagliptin. In the other five studies, all but one patient in both treatment groups were treated with at least one glucose-lowering agent prior to randomization.

3.2 | Renal effects of exenatide

Overall, patients in both treatment groups with baseline uACR ≥30 mg/g experienced an adjusted mean percent decrease in uACR from baseline to week 26/28 (least squares mean change: EQW, −55.5% [95% CI −62.1 to −47.7], comparators, −39.7% [95% CI −47.8 to −30.2]). After 26/28 weeks of treatment, adjusted mean percent uACR was reduced by 26.2% (95% CI −39.5 to −10.0) in the EQW compared to the comparator group (Figure 1 and Table 2).

Three studies administered OADs for the comparator group while the other three studies administered insulin. Considering oral glucose-lowering drugs and insulin separately, similar results in uACR adjusted mean percent change from baseline to week 26/28 were observed for EQW compared to oral glucose-lowering drugs (−29.6% [95% CI −47.6 to −5.3]) and EQW compared to insulin (−23.8% [95% CI −41.8 to −0.2]; Figure 1).

The uACR analysis results were also presented for several different subgroups of patients. For each subgroup investigated, both

TABLE 1 Baseline demographics and clinical characteristics: intention-to-treat analysis set

	EQW (N = 194)	All comparators (N = 274)
Age, years	55.0 (11.1)	55.2 (10.8)
Sex: male, n (%)	118 (60.8)	184 (67.2)
Race, n (%)		
White	79 (40.7)	119 (43.4)
Asian	88 (45.4)	119 (43.4)
Black/African American	10 (5.2)	5 (1.8)
Other	17 (8.8)	31 (11.3)
Weight (kg)	84.4 (20.1)	84.4 (20.4)
BMI (kg/m^2)	30.7 (5.8)	30.3 (5.6)
BMI ≥30, n (%)	94 (48.5)	118 (43.1)
SBP (mm Hg)	134 (14.9)	134 (15.5)
DBP (mm Hg)	81 (9.7)	81 (8.9)
Type 2 diabetes duration, years	7.4 (5.4)	7.0 (5.7)
HbA1c, %	8.6 (1.1)	8.5 (1.0)
HbA1c, mmol/mol	70.4 (11.6)	69.7 (11.2)
Background antiglycaemic medications, n (%)		
None[a]	24 (12.4)	73 (26.6)
Background insulin	0 (0)	0 (0)
Background OAD[b]		
Metformin	169 (87.1)	201 (73.4)
Sulphonylureas	17 (8.8)	18 (6.6)
Thiazolidinediones	24 (12.4)	21 (7.7)
Baseline RAS inhibitor use, n (%)	100 (51.5)	142 (51.8)
eGFR, mL/min/1.73m^2[c]	78.9 (22.0)	79.6 (21.1)
eGFR ≥ 30 to <60 mL/min/1.73m^2 (moderate CKD), n (%)[c]	41 (21.1)	48 (17.5)
eGFR ≥ 60 to <90 mL/min/1.73m^2 (mild CKD), n (%)[c]	93(47.9)	144(52.6)
eGFR ≥ 90 mL/min/1.73m^2 (normal), n (%)[c]	60 (30.9)	82 (29.9)
Median (min, max) uACR, mg/g	68.2 (30.1, 2938.0)	72.2 (30.1, 4211.7)
uACR ≥30 to ≤300 mg/g (moderate), n (%)[d]	163 (84.0)	234 (85.4)
uACR >300 mg/g (severe), n (%)[d]	31 (16.0)	40 (14.6)

Data are mean (SD) unless stated otherwise.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EQW, exenatide once weekly; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; RAS, renin-angiotensin system; SBP, systolic blood pressure; uACR, urine albumin-to-creatinine ratio.

[a]Patients in DURATION 4 study were required to be antihyperglycaemic drug-naïve to enter the study.

[b]One additional patient took repaglinide, which was not permitted background antiglycaemic medication per the protocol.

[c]eGFR calculated using Modification of Diet in Renal Disease-4 formula or three variable Japanese equation (for study GWBX) which adjusts for other body composition.

[d]Albuminuria category.

treatment groups experienced adjusted mean percent decreases in uACR from baseline to week 26/28 with greater numerical reductions in the EQW group (Figure 1B and Table 3). The effect of EQW on albuminuria was generally consistent across various subgroups. However, the effect of the comparators varied among subgroups and therefore the adjusted mean percent change in uACR with EQW compared to the comparator group also varied. EQW compared to comparators changed uACR by −29.7% (95% CI −43.5 to −12.7) and by −5.8% (95% CI −42.7 to 54.9; subgroup by treatment group interaction *P* value = 0.292) in patients with baseline uACR ≥30 to

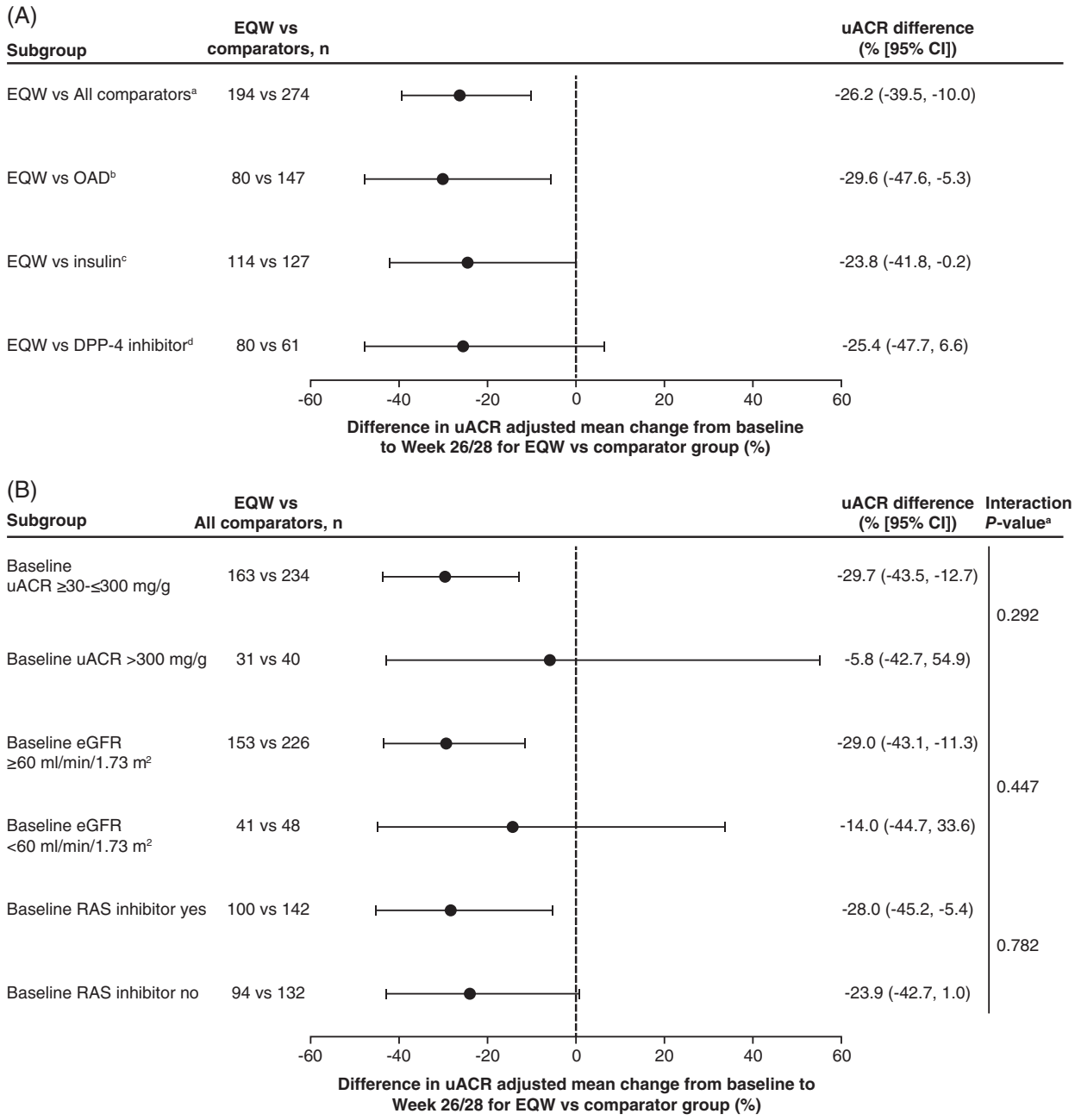

FIGURE 1 **A**, Effect of exenatide versus comparators on urine albumin-to-creatinine ratio (uACR) from baseline to week 26/28. ANCOVA model adjusted for ln(baseline uACR), study, and treatment group; analysis performed on ln(week 26/28 uACR/baseline uACR), then inverse-transformed to present percent change from baseline results. Baseline = last non-missing value prior to the first study medication dose. Geometric means are presented. [a]All six studies. [b]Pooled studies DURATION 2,[10] DURATION 4,[12] DURATION-NEO-2.[13] Oral antidiabetic drug (OAD) group includes sitagliptin, pioglitazone and metformin. [c]Pooled studies DURATION 3,[11] H8O-JE-GWBX[14] and H8O-EW-GWDL.[15] Insulin includes insulin glargine and insulin detemir. [d]Pooled studies DURATION 2,[10] DURATION 4,[12] DURATION-NEO-2.[13] Dipeptidyl peptidase-4 (DPP-4) inhibitor includes only sitagliptin. **B**, Subgroup analysis of the relative effect of exenatide versus comparators on uACR from baseline to week 26/28. ANCOVA model adjusted for ln(baseline uACR), study, treatment group, subgroup, and subgroup by treatment group interaction; analysis performed on ln(week 26/28 uACR/baseline uACR), then inverse-transformed to present percent change from baseline results. Baseline = last non-missing value prior to the first study medication dose. Geometric means are presented. [a]Subgroup by treatment group interaction term *P* value. ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; EQW, exenatide once weekly; n, number of patients with observed baseline and week 26/28 values; RAS, renin-angiotensin system

≤300 mg/g and baseline uACR >300 mg/g, respectively. In patients with baseline eGFR ≥60 or < 60 mL/min/1.73m^2, EQW changed adjusted mean percent uACR compared to the comparator group by −29.0% (95% CI −43.1 to −11.3) and − 14.0% (95% CI −44.7 to 33.6; *P* value for interaction = 0.447). When assessed by baseline RAS inhibitor use, the adjusted mean percent change in uACR with EQW

TABLE 2 ANCOVA analysis of percent change in urinary albumin-to-creatinine ratio (uACR) from baseline to week 26/28 for patients with baseline uACR ≥30 mg/g and week 26/28 uACR results

Summary statistics	uACR, mg/g					
	Adjusting for ln(baseline uACR), study and treatment group[a]		Adjusting for ln(baseline uACR), study and treatment group and log changes in HbA1c, eGFR and SBP[a]		Adjusting for ln(baseline uACR), study and treatment group and log changes in HbA1c, eGFR, SBP and body weight[a]	
	EQW	Comparators	EQW	Comparators	EQW	Comparators
N	194	274	194	274	194	274
Baseline, mean (SD)	207.2 (374.5)	199.4 (410.6)	207.2 (374.5)	199.4 (410.6)	207.2 (374.5)	199.4 (410.6)
Adjusted % change from baseline to week 26/28						
LS mean (95% CI)	−55.5 (−62.1, −47.7)	−39.7 (−47.8, −30.2)	−54.0 (−60.9, −45.8)	−41.4 (−49.3, −32.3)	−51.2 (−58.8, −42.3)	−43.9 (−51.6, −35.0)
Difference from comparators at week 26/28						
LS mean (95% CI)	−26.2 (−39.5, −10.0)		−21.5 (−35.8, −3.9)		−13.0 (−29.9, 7.8)	

Baseline = last non-missing value prior to the first study medication dose. Geometric means are presented.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; EQW, exenatide once weekly; HbA1c, glycated haemoglobin; LS, least squares; N, number of patients with observed baseline and week 26/28 values; SBP, systolic blood pressure; uACR, urinary albumin-to-creatinine ratio.

[a]ANCOVA analysis performed on ln (week 26/28 uACR/baseline uACR), then inverse-transformed to present percent change from baseline results.

compared to the comparator group was −28.0% (95% CI −45.2 to −5.4) for patients using an RAS inhibitor versus −23.9 (−42.7 to 1.0) for patients not using an RAS inhibitor (*P* value for interaction = 0.782; Figure 1B and Table 3).

The proportions of patients with at least a 30% reduction in the actual uACR value from baseline to week 26/28 were 67.0% for EQW and 49.6% for the comparators. Similarly, the proportions of patients with at least 40% reduction in uACR from baseline were 56.7% for EQW and 44.5% in the comparator group, and the proportions of patients with at least 50% reduction were 48.5% and 36.9%, respectively (Figure 2).

From baseline to week 26/28, adjusted mean eGFR increased by 1.10 mL/min/1.73m^2 (95% CI −1.32 to 3.51) for patients in the EQW group compared to 2.86 mL/min/1.73m^2 (95% CI 0.66 to 5.07) for patients in the comparator group. Accordingly, the between-group difference for adjusted mean change was −1.77 mL/min/1.73m^2 (95% CI −4.76 to 1.23).

3.3 | Effect of exenatide on metabolic and cardiovascular variables

The adjusted mean change in HbA1c from baseline to week 26/28 was −1.4% (95% CI −1.6 to −1.3) in the EQW group and − 1.0% (95% CI −1.1 to −0.9) in the comparator group. Relative to the comparator group, EQW changed HbA1c by −0.41% (95% CI −0.58 to −0.23) after 26/28 weeks. Patients treated with EQW also experienced an adjusted mean decrease in body weight as opposed to patients in the comparator group (−2.3 kg [95% CI −2.8 to −1.8] compared to 0.5 kg [95% CI 0.1 to 0.9], relative change −2.8 kg [95% CI −3.4 to −2.2]). In addition, treatment with EQW versus comparators resulted in a change in adjusted mean SBP of −3.0 (95% CI −4.8 to −1.3) and − 0.4 (95% CI −2.0 to 1.2), respectively, and a relative change of −2.6 mm Hg (95% CI −4.8 to −0.5) in favour of EQW.

In an attempt to explore whether concomitant reductions in metabolic variables influenced the beneficial effects of EQW on uACR compared to the comparators, the EQW treatment effect on uACR was adjusted for changes (on log scale) in HbA1c, eGFR, SBP and body weight. After adjustment for changes in HbA1c, eGFR and SBP from baseline to week 26/28, the uACR-lowering effect of EQW versus comparators persisted (adjusted mean percent change in uACR −21.5% [95% CI −35.8, −3.9]; Table 2). However, when also adjusted for changes in body weight, the uACR-lowering effect of EQW was reduced to −13.0% (95% CI −29.9 to 7.8) compared to comparators (Table 2). Notably, however, the 95% CIs for differences from the comparators in the adjusted mean percent changes for analyses without adjustment and with adjustments for the metabolic variables all overlapped.

3.4 | Safety

The proportion of patients experiencing any AE (EQW, 71.8%; all comparators, 68.2%) during the 26-/28-week controlled treatment

TABLE 3 Subgroup ANCOVA analysis of percent change in urinary albumin-to-creatinine ratio (uACR) from baseline to week 26/28 for patients with baseline uACR ≥30 mg/g and week 26/28 uACR results

	uACR (mg/g) adjusting for ln(baseline uACR), study, treatment group, subgroup, and subgroup by treatment interaction[a]											
	Baseline uACR 30–300 mg/g		Baseline uACR >300 mg/g		Baseline eGFR ≥60 mL/min/1.73m^2		Baseline eGFR <60 mL/min/1.73m^2		Baseline RAS inhibitor use		No baseline RAS inhibitor use	
Summary statistics	EQW	Compa-rators	EQW	Compa-rators	EQW	Compa-rators	EQW	Compa-rators	EQW	Compa-rators	EQW	Compa-rators
N`	163	234	31	40	153	226	41	48	100	142	94	132
Baseline mean (SD)	85.0 (65.8)	83.9 (60.0)	850.1 (608.8)	875.1 (781.1)	196.3 (319.1)	172.7 (288.8)	247.8 (536.4)	325.1 (748.6)	226.4 (438.5)	225.6 (458.9)	186.8 (292.5)	171.2 (350.9)
Adjusted % change from baseline to week 26/28												
LS mean (95% CI)	−58.5 (−65.3, −50.2)	−40.9 (−50.0, −30.1)	−34.1 (−59.5, 7.1)	−30.0 (−55.1, 8.9)	−56.3 (−63.3, −47.9)	−38.4 (−47.3, −28.1)	−52.8 (−67.2, −32.2)	−45.1 (−61.1, −22.7)	−53.8 (−63.1, −42.1)	−35.8 (−47.2, −21.9)	−56.6 (−65.2, −46.1)	−43.0 (−53.0, −30.9)
Difference from comparators at week 26/28												
LS mean (95% CI)	−29.7 (−43.5, −12.7)		−5.8 (−42.7, 54.9)		−29.0 (−43.1, −11.3)		−14.0 (−44.7, 33.6)		−28.0 (−45.2, −5.4)		−23.9 (−42.7, 1.0)	
Subgroup by treatment group interaction *P* value	0.292				0.447				0.782			

Baseline = last non-missing value prior to the first study medication dose. Geometric means are presented.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; EQW, exenatide once weekly; LS, least squares; N, number of patients with observed baseline and week 26/28 values; RAS, renin-angiotensin system; uACR, urine albumin-creatinine ratio.

[a]ANCOVA analysis performed on ln(week 26/28 uACR/baseline uACR), then inverse-transformed to present percent change from baseline results.

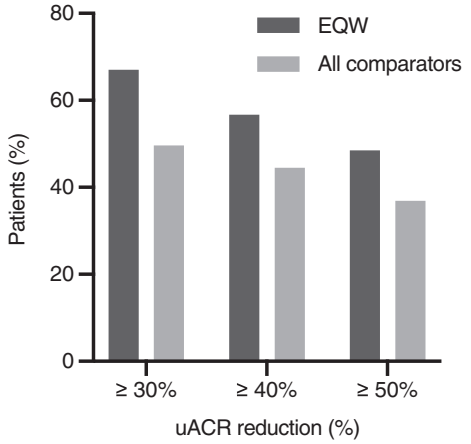

FIGURE 2 Proportion of patients with ≥30%, ≥40% and ≥50% reduction in urine albumin-to-creatinine ratio (uACR) from baseline to week 26/28. Exenatide once weekly (EQW), N = 194; all comparators, N = 274. Percent change = (week 26/28 uACR – baseline uACR)/baseline uACR × 100. N, number of patients with observed baseline uACR ≥30 mg/g and week 26/28 uACR values

TABLE 4 Summary of adverse events (patients with baseline uACR ≥30 mg/g[a]). (safety analysis set)

Number (%) of patients[b]	EQW (N = 284)	Comparators (N = 390)
Any AE	204 (71.8)	266 (68.2)
Any serious AE	8 (2.8)	16 (4.1)
Any AE with outcome of death	1 (0.4)	1 (0.3)
Any AE leading to study discontinuation	11 (3.9)	11 (2.8)
AE of special interest		
Acute renal failure[c]	0 (0.0)	0 (0.0)
Dehydration[c]	0 (0.0)	0 (0.0)
Any hypoglycaemic events	26 (9.2)	51 (13.1)
Gastro-intestinal AE	99 (34.9)	70 (17.9)

Abbreviations: AE, adverse event; EQW, exenatide once weekly; MedDRA, Medical Dictionary for Regulatory Activities, N, number patients in the pooled treatment group.

The 26- or 28-week treatment period AEs occured on or after the first randomized study drug dose day through to the end of the controlled treatment period. Patients with multiple events are counted once per category but can be counted in more than one category.

[a]Safety analysis set includes all randomized patients who took at least one dose of study medication.

[b]Number (%) patients (crude AE incidence rate) = total number of patients with AEs/total number of patients in the pooled treatment group.

[c]Standardized MedDra Query (narrow), MedDRA version 21.1.

period was of a similar magnitude in both treatment groups. The proportion of patients with serious AEs and AEs leading to study discontinuation or death were low and similar between the treatment groups. No patients experienced acute renal failure or dehydration-related AEs during the 26-/28-week controlled treatment period. The proportion of patients experiencing any hypoglycaemic event was also similar between the groups (EQW, 9.2%; all comparators, 13.1%). A higher proportion of patients in the EQW group experienced at least one gastrointestinal AE than in the comparators group (34.9% vs. 17.9%; Table 4).

4 | DISCUSSION

This exploratory pooled analysis of six randomized phase III studies investigated the renal effects of EQW in patients with type 2 diabetes and elevated albuminuria. The results suggest that treatment with EQW consistently reduced adjusted mean percent uACR over a 6-month controlled treatment period compared with commonly used oral glucose-lowering drugs and insulin. The uACR-lowering effect of EQW was largely independent of changes in HbA1c, eGFR and SBP, suggesting that albuminuria reductions may not be influenced by these variables. After additional adjustment for changes in body weight, the uACR-lowering effect of EQW compared to the comparator treatments attenuated.

Cardiovascular outcome trials have suggested a potential benefit of GLP-1RAs relative to placebo treatment in slowing progression of CKD, although definitive evidence is lacking. In the LEADER[5] and SUSTAIN-6[6] trials, liraglutide and semaglutide reduced the incidence of a composite renal outcome (macroalbuminuria, doubling of serum creatinine and eGFR <45 mL/min/m^2, ESKD, death from kidney disease) compared to placebo. A renal composite endpoint of sustained 40% eGFR drop, end-stage renal disease, and new macroalbuminuria was improved in the EXSCEL trial by exenatide compared to placebo, although the effect was only statistically significant after multivariable adjustment.[18] Other GLP-1RA trials have also suggested beneficial kidney effects, although the benefits were mainly driven by reductions in albuminuria.[7,8,19] Interestingly, the potential kidney benefits seem to be stronger in patients with established CKD. In a combined analysis of the LEADER and SUSTAIN trials, treatment with liraglutide or semaglutide slowed progression of eGFR decline with a stronger effect in patients with baseline eGFR <60 mL/min/1.73m^2.[20] In addition, the AWARD-7 trial that compared dulaglutide to insulin glargine in patients with stages 3–4 CKD demonstrated benefits on eGFR decline as well as a clinically relevant endpoint of doubling of serum creatinine or ESKD.[21] However none of these trials were designed to characterize the long-term efficacy of GLP-1RAs on major kidney outcomes. The ongoing FLOW trial, investigating the effect of semaglutide versus placebo on the progression of renal impairment in people with type 2 diabetes and chronic kidney disease, will deliver more definitive evidence about the efficacy and safety of GLP-1RAs in reducing major kidney outcomes in patients with type 2 diabetes and CKD (NCT03819153).

Although emerging data suggest that GLP-1RAs can improve renal outcomes in patients with type 2 diabetes, the magnitude of this effect compared to other glucose-lowering drugs has not been characterized in most studies. The present analysis shows that the adjusted percent mean reduction in uACR was greater for patients taking EQW

compared with patients taking other active glucose-lowering drugs in patients with moderately or severely increased albuminuria. None of the six studies in our analysis included SGLT2 inhibitors. The DURATION 8 clinical trial included a dapagliflozin treatment group, but that study did not collect uACR and was therefore not included in the analysis.[22] As far as we know, there are no other head-to-head studies that compare the albuminuria-lowering effects – or other renal outcomes – of GLP-1RAs against SGLT2 inhibitors. However, evidence from cardiovascular outcome trials suggests that the magnitude of the effects on uACR of both drug classes is similar.[19,21,23–25]

This analysis provides more insight into the mechanisms underlying the albuminuria-lowering effect of GLP-1RAs. Reductions in albuminuria have been hypothesized to be a result of improvements in glycaemic and blood pressure control. However, in the present analysis, concurrent adjustment for changes in HbA1c, eGFR and systolic blood pressure did not substantially affect the exenatide-induced reduction in albuminuria, suggesting that other mechanisms are involved. However, adjustment for concomitant changes in body weight reduced the uACR-lowering effect of exenatide compared to the comparator group, suggesting that the beneficial renal effects of exenatide may be influenced, at least partially, by weight loss. In contrast to our findings however, in a cardiovascular outcome trial with liraglutide, the effects on renal function decline were not mediated by change in body weight.[23]

The relationship between weight gain or obesity and the development of albuminuria, CKD and ESRD has been well established in epidemiological studies.[26,27] Obesity has direct pathophysiological effects on the kidney but may also indirectly affect kidney disease through its frequently occurring comorbidities such as type 2 diabetes, hypertension and cardiopulmonary disease. Obesity alters renal haemodynamics, causing intraglomerular hypertension, activation of the renin-angiotensin-aldosterone system and increased sympathetic activity. Obesity also increases inflammation and oxidative stress, attenuates the bioactivity of nitric oxide and influences podocyte biology through altered levels of adipokines.[28] Bariatric surgery is currently the most effective way to achieve lasting weight loss, and has been shown to substantially reduce the incidence of ESRD.[29]GLP-1RAs reduce appetite and food intake, resulting in weight loss that could counteract the aforementioned negative effects and thereby decrease albuminuria. Alternatively, GLP-1RAs induce natriuresis and diuresis, which may also contribute to weight loss and possibly improvements in albuminuria. Ongoing studies, such as the DECADE study (Netherlands Trial Register Identifier NL6662) aim to better delineate the underlying mechanisms of GLP-1RA-induced reductions in albuminuria.

The overall safety profile of exenatide in this analysis is consistent with other exenatide studies. The proportion of patients experiencing any AE was slightly higher in the EQW treatment group than the all-comparators group; this difference was mainly attributable to gastrointestinal AEs.

The present study has several limitations. First, this was a *post hoc* analysis of six randomized trials that were not designed to evaluate the renal effect of EQW. The results of this analysis should therefore be interpreted as hypothesis-generating rather than conclusive. Also, of the 468 patients included in the efficacy analysis, two studies[12,14] contributed 52% of the patients and thus had a large influence on the results across the six studies. uACR was determined from single, random urine samples, whereas the 'gold standard' for the evaluation of proteinuria is 24-hour urine collection. This may have resulted in more variability in the uACR results. Furthermore, uACR was determined at baseline and at week 26/28. Hence, it is not possible to observe a trend for uACR over the controlled treatment period. Since we selected patients with UACR >30 mg/g from a single visit at randomization we cannot exclude the possibility of a regression to the mean effect in both the exenatide and comparator groups. As a result the absolute effect sizes in both groups may be overestimated; therefore, the exenatide effect sizes should be interpreted in the context of the comparator effect. Nevertheless, this still resulted in an effect size of more than 25%, which has been shown to be associated with a high likelihood to infer benefit on clinical kidney endpoints.[30] Importantly, caution should be taken when interpreting the results of the subgroup analyses. Sample sizes in some of the subgroups, such as the subgroup of patients with eGFR <60 mL/min/1.73m^2, are quite small and, because they are essentially subgroups of the subset of patients with baseline albuminuria, may not be representative of all patients randomized to these six studies. Because of the small subgroups, we recognize that tests for interaction effects were also underpowered. We also acknowledge that the 26-/28-week follow-up period was too short to comprehensively characterize the effect of EQW on eGFR and may explain the discrepancy between reductions in uACR with EQW and neutral effects on eGFR. Finally, it is important to note that the patients included in the EQW-versus-OADs and EQW-versus-insulin comparisons came from different studies. Thus, differences in study design or conduct may have influenced these results.

In conclusion, in this pooled analysis EQW was well tolerated and reduced uACR in patients with type 2 diabetes and elevated albuminuria compared to commonly used oral glucose-lowering drugs and insulin. These data add to the body of evidence suggesting that GLP-1RAs may exert kidney-protective effects in patients with type 2 diabetes.

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CONFLICTS OF INTEREST

A.B.v.d.A. has nothing to disclose. D.H.v.R. has consulting relationships with Boehringer Ingelheim, Eli Lilly, Merck and Sanofi, and receives research operating funding from AstraZeneca, Boehringer Ingelheim-Eli Lilly Diabetes Alliance and MSD. C.G. has consulting relationships with AstraZeneca, Boehringer Ingelheim, Egis, Eli Lilly, MSD, Novo Nordisk, Sanofi and Zentiva. K.H. has consulting relationships with Novo Nordisk and Sanofi, and receives research operating funding from Novo Nordisk. L.S. is an employee of Kelly Services for AstraZeneca, a former employee of AstraZeneca, and a stockholder of AstraZeneca, Merck and Express Scripts. E.H. and C.D.S. are employees and stockholders of AstraZeneca. H.J.L.H has consulting

relationships with AbbVie, AstraZeneca, Boehringer Ingelheim, CSL Pharma, Fresenius, Gilead, Janssen, Merck, Mitsubishi Tanabe, Mundi Pharma and Retrophin.

AUTHOR CONTRIBUTIONS

H.J.L.H., C.D.S. and L.S. designed the *post hoc* analysis, and interpreted the data. A.B.v.d.A. and H.J.L.H wrote the first draft of the manuscript. D.H.v.R., C.G., K.H, L.S. and E.H. participated in the interpretation of the data and revised the manuscript critically for important intellectual content. L.S. performed statistical analyses. All authors gave final approval to submit the article for publication.

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REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report. 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed January 17, 2020.
2. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886. https://doi.org/10.1053/j.ajkd.2012.07.005.
3. Drab SR. Glucagon-like Peptide-1 receptor agonists for type 2 diabetes: a clinical update of safety and efficacy. *Curr Diabetes Rev*. 2016;12(4):403-413. https://doi.org/10.2174/1573399812666151223093841.
4. Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators.Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373(23):2247-2257. https://doi.org/10.1056/NEJMoa1509225.
5. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee., LEADER Trial Investigators.Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322. https://doi.org/10.1056/NEJMoa1603827.
6. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844. https://doi.org/10.1056/NEJMoa1607141.
7. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (harmony outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157):1519-1529. https://doi.org/10.1016/S0140-6736(18)32261-X.
8. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet*. 2019;394(10193):131-138. https://doi.org/10.1016/S0140-6736(19)31150-X.
9. Muskiet MHA, Tonneijck L, Smits MM, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. *Nat Rev Nephrol*. 2017;13(10):605-628. https://doi.org/10.1038/nrneph.2017.123.
10. Bergenstal RM, Wysham C, MacConell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet*. 2010;376(9739):431-439. https://doi.org/10.1016/S0140-6736(10)60590-9.
11. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet*. 2010;375(9733):2234-2243. https://doi.org/10.1016/S0140-6736(10)60406-0.
12. Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care*. 2012;35(2):252-258. https://doi.org/10.2337/dc11-1107.
13. Gadde KM, Vetter ML, Iqbal N, Hardy E, Öhman P. DURATION-NEO-2 study investigators. Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: the DURATION-NEO-2 randomized clinical study. *Diabetes Obes Metab*. 2017;19(7):979-988. https://doi.org/10.1111/dom.12908.
14. Inagaki N, Atsumi Y, Oura T, Saito H, Imaoka T. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. *Clin Ther*. 2012;34(9):1892-1908.e1. https://doi.org/10.1016/j.clinthera.2012.07.007.
15. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. *Diabetes Care*. 2013;36(5):1368-1376. https://doi.org/10.2337/dc12-1333.
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med*. 1999;130(6):461-470. https://doi.org/10.7326/0003-4819-130-6-199903160-00002.
17. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53(6):982-992. https://doi.org/10.1053/j.ajkd.2008.12.034.
18. Bethel MA, Mentz RJ, Merrill P, et al. Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly Exenatide: insights from the EXSCEL trial. *Diabetes Care*. 2019;43:446-452. https://doi.org/10.2337/dc19-1065.
19. Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(11):859-869. https://doi.org/10.1016/S2213-8587(18)30268-7.
20. Perkovic V, Bain S, Bakris G, et al. FP482EGFR loss with glucagon-like PEPTIDE-1 (GLP-1) analogue treatment: data from sustain 6 and leader. *Nephrol Dial Transplant*. 2019;34(Suppl. 1). https://doi.org/10.1093/ndt/gfz106.FP482.
21. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. 2018;6(8):605-617. https://doi.org/10.1016/S2213-8587(18)30104-9.
22. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4(12):1004-1016. https://doi.org/10.1016/S2213-8587(16)30267-4.
23. Mann JFE, Ørsted DD, Brown-Frandsen K, et al; LEADER Steering Committee and Investigators.Liraglutide and renal outcomes in type

2 diabetes. *N Engl J Med*. 2017;377(9):839-848. https://doi.org/10.1056/NEJMoa1616011.
24. Wanner C, Inzucchi SE, Lachin JM, et al; EMPA-REG OUTCOME Investigators.Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334. https://doi.org/10.1056/NEJMoa1515920.
25. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group.Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. https://doi.org/10.1056/NEJMoa1611925.
26. Chang AR, Grams ME, Ballew SH, et al. Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ*. 2019;364:k5301. https://doi.org/10.1136/bmj.k5301.
27. Hsu C, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Ann Intern Med*. 2006;144(1):21-28. https://doi.org/10.7326/0003-4819-144-1-200601030-00006.
28. Tang J, Yan H, Zhuang S. Inflammation and oxidative stress in obesity-related glomerulopathy. *Int J Nephrol*. 2012;2012:608397-608311. https://doi.org/10.1155/2012/608397.
29. Shulman A, Peltonen M, Sjöström CD, et al. Incidence of end-stage renal disease following bariatric surgery in the Swedish obese subjects study. *Int J Obes 2005*. 2018;42(5):964-973. https://doi.org/10.1038/s41366-018-0045-x.
30. Heerspink HJL, Coresh J, Gansevoort RT, Inker LA. Change in albuminuria as a surrogate endpoint in chronic kidney disease – authors' reply. *Lancet Diabetes Endocrinol*. 2019;7(5):336-337. https://doi.org/10.1016/S2213-8587(19)30080-4.

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