
بسم الله الرحمن الرحیم

Liraglutide and Renal Outcomes in Type ٢ Diabetes

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Liraglutide (Victoza)

Liraglutide and Renal Outcomes in Type ٢ Diabetes

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- Original article
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DMII and CKD

- Persons with type ٢ diabetes mellitus, particularly those with evidence of cardiovascular disease, are at high risk for chronic kidney disease.

- Diabetic kidney disease is reported to be the leading cause of dialysis-dependent chronic kidney disease.

- Prevention of new-onset diabetic nephropathy and the prevention of progression of established diabetic nephropathy.

Diabetic Nephropathy

- Improved glycemic control
- blood-pressure control
- Inhibition of the renin–angiotensin system

Effects of glucose-lowering agents

- Some glucose-lowering agents have glucose-independent effects on diabetic nephropathy and its progression
- Dipeptidyl peptidase ۴ (DPP-۴) inhibitor linagliptin
- Human glucagon-like peptide ۱ (GLP-۱) analogue liraglutide
- Sodium-glucose co-transporter ۲ (SGLT۲) inhibitors

Effects of glucose-lowering agents

- However, in long-term studies, no clinically meaningful benefits on renal outcomes have emerged

- Except for SGLT٢ inhibitor empagliflozin.

Liraglutide

- In short-term studies, liraglutide improved glycemic control, reduced urinary albumin excretion, and increased urinary sodium excretion.

- However, the long-term effects of liraglutide on the development and progression of diabetic kidney disease are unknown.

Liraglutide

- The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial recently showed lower risks of cardiovascular outcomes, death from any cause, and microvascular outcomes with liraglutide than with placebo.

Methods

- Double-blind
- Placebo controlled trial
- Patients with type ٢ diabetes and a high risk of cardiovascular disease were randomly assigned, in a ١:١ ratio, to receive liraglutide or matching placebo, in addition to usual care.

Microvascular Outcomes

- The pre-specified secondary microvascular outcome was a composite of renal and retinal outcomes.

- Focus was on the renal outcomes, which were more common than the retinal events.

Renal Outcome

- The composite renal outcome consisted of:
  ۱. New-onset persistent macroalbuminuria

  ۲. Persistent doubling of the serum creatinine level (an estimated GFR of ۴۵ ml or less per minute per ۱٫۷۳ m۲ of body surface area (hereafter referred to as persistent doubling of the serum creatinine level),

  ۳. The need for continuous renal-replacement therapy (end stage renal disease) with no reversible cause of the renal disease

  ۴. Death from renal disease.

Macroalbuminuria

- Macroalbuminuria was defined as a concentration of more than ٣٠٠ mg of albumin in a ٢٤-hour urine sample or as a concentration of more than ٣٠٠ mg of albumin per gram of creatinine in a first morning sample.

- To confirm the presence of persistent macroalbuminuria or doubling of the serum creatinine level, a second measurement was mandatory.

Laboratory Assessments

- Creatinine levels (both urinary and serum) were measured enzymatically
- Urinary albumin concentration was assessed by means of immuno precipitation
- The serum creatinine level and the albumin-to-creatinine ratio were measured and calculated at randomization annually, and at trial completion;
- The serum creatinine level was also measured at month ۶.

Laboratory Assessments

- Microalbuminuria (or a high urinary albumin level) was defined as a concentration of ٣٠ to ٣٠٠ mg of albumin per gram of creatinine, and macroalbuminuria (or a very high urinary albumin level) as a concentration of more than ٣٠٠ mg of albumin per gram of creatinine.

- If the urinary albumin measurements were below the lower limit of quantification (٥ mg per liter), a value of ٢,٥ mg per liter was imputed for statistical analysis.

Statistical Analysis

- All the patients who underwent randomization were included and followed from the time of randomization until death or the end of follow up, whichever came first.

- Pre-specified between-group comparisons were performed at ۳۶ months, which was the last trial visit at which laboratory testing was performed at the same time point in the entire population.

Results

Trial Population:

- A total of ۹۳۴۰ patients underwent randomization, with ۴۶۶۸ patients to receive liraglutide and ۴۶۷۲ to receive placebo.

- The median follow-up of the patients was ۳٫۸۴ years

- The mean percentage of time of patients taking the trial regimen was ۸۳٫۰%.

- The characteristics of the patients at baseline were generally balanced between the trial groups.

Results

- The mean age of the patients was ۶۴ years,
- The mean blood pressure ۱۳۶/۷۷ mm Hg.
- The mean estimated GFR was ۸۰ ml per minute per ۱,۷۳ m۲
- A total of ۲۰,۷% of the patients with GFR of ۳۰ to ۵۹ ml per minute per ۱,۷۳ m۲,
- ۲,۴% had an estimated GFR of less than ۳۰ ml per minute per ۱,۷۳ m۲.
- Microalbuminuria and macroalbuminuria were present in ۲۶,۳% and ۱۰,۵% of the patients, respectively.
- A total of ۸۶۳۲ patients received antihypertensive agents
- ۷۷۴۱ patients received renin–angiotensin system blockers.

Composite Renal Outcome

- The pre-specified composite renal outcome occurred in fewer patients in the liraglutide group (۲۶۸ patients [۵,۷%] vs ۳۳۷ [۷,۲%]; hazard ratio, ۰,۷۸; ۹۵% confidence interval [CI], ۰,۶۷ to ۰,۹۲; P=۰,۰۰۳) (Table ۱ and Fig. ۱A).
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- New-onset persistent macroalbuminuria occurred in fewer patients in the liraglutide group than in the placebo group (۱۶۱ patients [۳,۴%] vs. ۲۱۵ [۴,۶%]; hazard ratio, ۰,۷۴; ۹۵% CI, ۰,۶۰ to ۰,۹۱; P=۰,۰۰۴) (Fig. ۱B).

Composite Renal Outcome

- The risks of persistent doubling of the serum creatinine level and of end-stage renal disease (use of renal replacement therapy) did not differ significantly between groups (Table ١ and Fig. ١C and ١D).

- There were few cases of death due to renal disease (٨ patients in the liraglutide group and ٥ in the placebo group).

Composite Renal Outcome

Table 1. Composite Renal Outcome and Individual Components of the Composite Outcome.*

Outcome	Liraglutide (N=4668)	Placebo (N=4672)	Total (N=9340)	Hazard Ratio (95% CI)	P Value
	no. of patients (rate per 1000 patient-yr of observation)				
Composite renal outcome	268 (15.0)	337 (19.0)	605 (17.0)	0.78 (0.67–0.92)	0.003
Components of composite renal outcome†					
New-onset persistent macroalbuminuria	161 (9.0)	215 (12.1)	376 (10.6)	0.74 (0.60–0.91)	0.004
Persistent doubling of serum creatinine level	87 (4.9)	97 (5.5)	184 (5.2)	0.89 (0.67–1.19)	0.43
Renal-replacement therapy	56 (3.1)	64 (3.6)	120 (3.4)	0.87 (0.61–1.24)	0.44
Death due to renal disease	8 (0.4)	5 (0.3)	13 (0.4)	1.59 (0.52–4.87)	0.41

* There were 17,822 patient-years of observation in the liraglutide group and 17,741 in the placebo group. All the events were adjudicated. Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with trial group as a covariate.

† The composite renal outcome consisted of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level and an estimated glomerular filtration rate of 45 ml or less per minute per 1.73 m^2 of body-surface area (referred to as persistent doubling of the serum creatinine level), the need for continuous renal-replacement therapy (end-stage renal disease), or death due to renal disease. One patient who had macroalbuminuria at baseline had an event of new-onset persistent macroalbuminuria that was confirmed by adjudication after the patient had regression to microalbuminuria earlier in the trial.

Renal Function over Time (GFR)

- The estimated GFR declined continuously (Fig. ٣A), but the decline was slightly slower in the liraglutide group than in the placebo group (estimated trial-group ratio at ٣٦ months, ١,٠٢; ٩٥% CI,١,٠٠ to ١,٠٣; P=٠,٠١, corresponding to a ٢% less decrease with liraglutide).

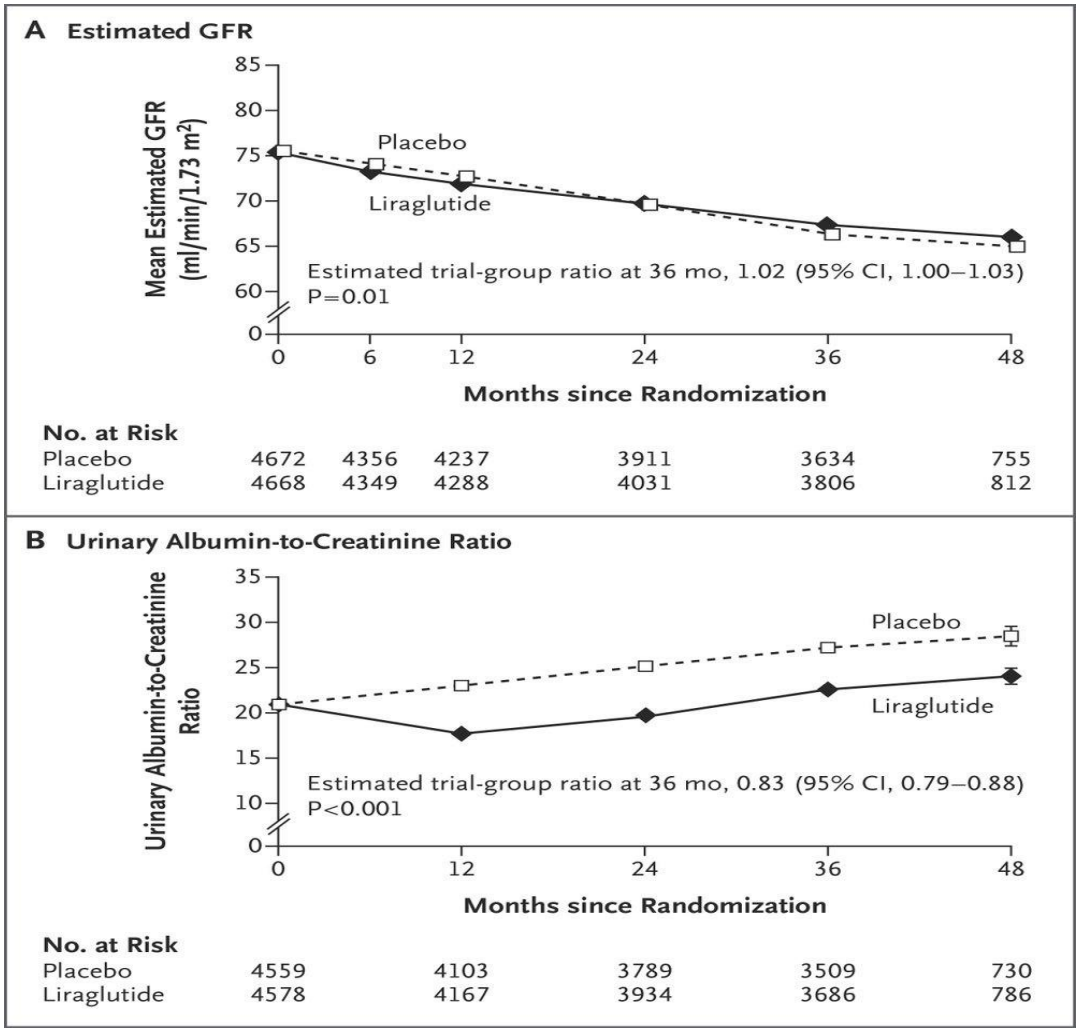
- The decrease in the estimated GFR at ٣٦ months was ٧,٤٤ ml per minute per ١,٧٣ m٢ in the liraglutide group, as compared with ٧,٨٢ ml per minute per ١,٧٣ m٢ in the placebo group.

Renal Function over Time (Alb/Cr)

- The urinary albumin-to creatinine ratio increased less in the liraglutide group, yielding a ١٧% lower urinary albumin-to creatinine ratio at ٣٦ months in favor of liraglutide (estimated trial-group ratio, ٠,٨٣; ٩٥% CI, ٠,٧٩ to ٠,٨٨; P<٠,٠٠١) (Fig. ٣B).

- The estimated increase in the urinary albumin-to-creatinine ratio at ٣٦ months was ١,٨ mg of albumin per gram of creatinine in the liraglutide group, as compared with ٦,٣ mg of albumin per gram of creatinine in the placebo group (Fig. ٣B);

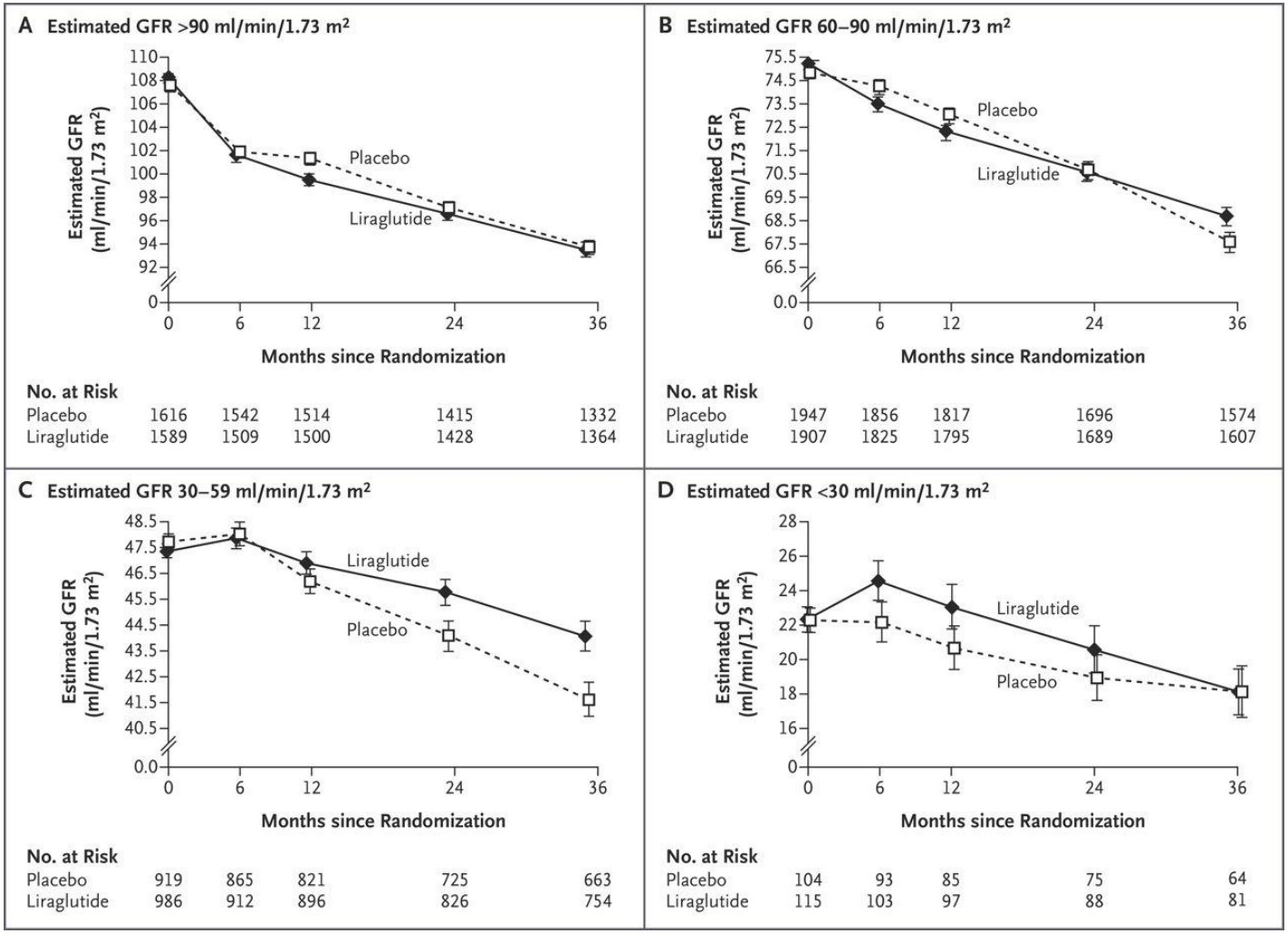
Renal Function over Time



GFR Decrease Rate

- When results were stratified according to the estimated GFR at baseline, the decrease in the estimated GFR in patients with a baseline estimated GFR of ۳۰ to ۵۹ ml per minute per ۱٫۷۳ m۲ was ۲ ml per minute per ۱٫۷۳ m۲ in the liraglutide group, as compared with ۴ ml per minute per ۱٫۷۳ m۲ in the placebo group (estimated trial group ratio in favor of liraglutide, ۱٫۰۷; ۹۵% CI,

GFR Decrease Rate in Subgroups



GFR Decrease Rate

- Results did not differ significantly between groups in patients with a baseline estimated GFR of ۶۰ ml or more per minute per ۱,۷۳ m۲ or with an estimated GFR of less than ۳۰ ml per minute per ۱,۷۳ m۲ (there were few patients in the latter group).

- When analyzed according to albuminuria at baseline, the decrease in the estimated GFR was smaller in the liraglutide group than in the placebo group in patients with macroalbuminuria (P=۰,۰۱) but did not differ significantly in those with microalbuminuria (P=۰,۲۴) or normoalbuminuria (P=۰,۶۰) (data not shown).

Other Outcomes and Adverse Events

- Outcomes that were not pre-specified included the composite of the doubling of the serum creatinine level or the use of renal-replacement therapy;

- there were no significant differences between the randomized groups

- New-onset microalbuminuria occurred in fewer patients in the liraglutide group than in the placebo group
- (۲۲۹۳ patients [۴۹,۱%] vs. ۲۴۹۸ [۵۳,۵%]; hazard ratio, ۰,۸۷; ۹۵% CI, ۰,۸۳ to ۰,۹۳; P<۰,۰۰۱).

- The rates of renal adverse events were similar

Discussion

- Among patients who were receiving usual care, liraglutide resulted in significantly lower rates of renal outcomes than placebo among patients with type ٢ diabetes who were at high cardiovascular risk.

- This result was driven mainly by a lower incidence of macroalbuminuria in the liraglutide group than in the placebo group.

- There were non-significantly lower risks of the doubling of the serum creatinine level and of end-stage renal disease with liraglutide than with placebo during up to ٥ years of follow-up.

Discussion

- New-onset persistent macroalbuminuria is an effect that is typically associated with subsequent progressive reductions in the GFR in patients with type ٢ diabetes.
- ONTARGET
- TRANSCEND
- new-onset macroalbuminuria was associated with a risk of end-stage renal disease or doubling of the serum creatinine level that was ٣ to ٥ times as high as the risk among patients in whom new-onset macroalbuminuria did not develop.

Discussion

- Similar renal outcomes associated with new-onset macroalbuminuria were reported in the ADVANCE trial and supported by meta-regression analyses. Macroalbuminuria is also a risk factor for cardiovascular events.

Discussion

- In this present trial, the risks of doubling of the serum creatinine level and end-stage renal disease did not differ significantly between the liraglutide group and the placebo group

- The initial changes in the estimated GFR are difficult to interpret, but there may be a potential slowing in the reduction in the estimated GFR with liraglutide in patients with a low baseline estimated GFR.

Discussion

- Intensified glucose control associated with a lower incidence of new macroalbuminuria than was usual care

- (UKPDS) consistent benefit on microvascular outcomes only, after ١٠ years of follow up

Discussion

- ACCORD, much earlier benefit on macroalbuminuria but no change in the risks of doubling of the serum creatinine level or end-stage renal disease with ۴ years of follow-up

- ADVANCE substantial benefit with regard to new-onset albuminuria over a ۵-year follow-up with no significant change in the risk of a doubling of the serum creatinine level but a tendency toward a lower risk of end-stage renal disease

Discussion

- As in the present trial, these trials have shown between-group differences in the glycated hemoglobin level of between ٠,٢ and ٠,٤ percentage points, and benefits of active compounds on albuminuria, but not on other renal outcomes.

- In contrast, the EMPA-REG OUTCOME trial showed that Empagliflozin resulted in significantly lower risks than placebo of progression to macroalbuminuria, the doubling of the serum creatinine level, and despite small numbers, end-stage renal Disease.

Discussion

- It appears to be unlikely that the moderate between-group differences in systolic blood pressure and body weight can fully explain the effect on renal outcomes. In an analysis that took into account those differences, the composite renal outcome still occurred less frequently with liraglutide than with placebo. The mechanisms behind the renal effects of liraglutide are probably multifactorial.

Discussion

- Most studies investigating the effect of GLP-١ treatment on renal hemodynamic variables in patients with type ٢ diabetes have shown neutral effects. Preclinical studies have shown convincingly that GLP-١ therapy decreases the level of inflammation and oxidative stress and prevents diabetic nephropathy and acute kidney injury.

Discussion

- Furthermore, a recent randomized trial involving patients with type ٢ diabetes and albuminuria showed that liraglutide treatment reduced levels of inflammatory biomarkers. Hence, it is possible that preservation of renal function and the antialbuminuric effects of liraglutide may be due to anti-inflammatory effects rather than renal hemodynamic effects.

Conclusion

- In conclusion, in this secondary analysis, among patients with type ۲ diabetes at high risk for cardiovascular disease who were receiving usual care, liraglutide resulted in a lower risk of the composite renal outcome and thus lower rates of the development and progression of diabetic kidney disease than placebo, primarily owing to a lower rate of new-onset persistent macroalbuminuria.

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Citation

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