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Original Investigation

Kidney Disease End Points in a Pooled Analysis of Individual Patient–Level Data From a Large Clinical Trials Program of the Dipeptidyl Peptidase 4 Inhibitor Linagliptin in Type 2 Diabetes

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Background: Although assessment of cardiovascular safety is mandated by regulatory agencies for the development of new drugs to treat type 2 diabetes, evaluation of their renal safety has been relatively neglected.

Study Design: Individual patient–level data pooled analysis of 13 phase 2 or 3 randomized, double-blind, placebo-controlled, clinical trials of the dipeptidyl peptidase 4 inhibitor linagliptin.

Setting & Participants: Participants who participated in any of 13 randomized clinical trials and fulfilled predefined inclusion/exclusion criteria, such as being drug-naive (hemoglobin A_{1c}, 7.0%-11.0% [53-97 mmol/mol]) or being on background glucose-lowering therapy (hemoglobin A_{1c}, 6.5%-10.5% [48-91 mmol/mol]).

Intervention: Of 5,466 consenting individuals with inadequately controlled type 2 diabetes, 3,505 received linagliptin, 5 mg/d, and 1,961 received placebo.

Outcomes: The primary kidney disease outcome was defined as first occurrence during the study of 6 predefined safety end points: new onset of moderate elevation of albuminuria (urinary albumin-creatinine ratio [ACR] >30 mg/g with baseline values ≤ 30 mg/g), new onset of severe elevation of albuminuria (ACR > 300 mg/g with baseline values ≤ 300 mg/g), reduction in kidney function (serum creatinine increase to ≥250 μmol/L from a baseline value < 250 μmol/L), halving of estimated glomerular filtration rate (loss of baseline eGFR > 50%), acute renal failure (ascertained from diagnostic codes), or death from any cause.

Measurements: Albuminuria was assessed using ACR. GFR was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

Results: Cumulative exposure (person-years) was 1,751 for linagliptin and 1,055 for placebo. The primary composite outcome occurred in 448 (12.8%) and 306 (15.6%) participants in the linagliptin and placebo groups, respectively. Linagliptin treatment significantly reduced the hazard of kidney disease events by 16% compared with placebo (HR, 0.84; 95% CI, 0.72-0.97; $P = 0.02$).

Limitations: Retrospective and hypothesis-generating study involving short- to midterm clinical trials.

Conclusions: Linagliptin was not associated with increased kidney disease risk in patients with type 2 diabetes. The potential of this drug to improve kidney disease outcomes warrants further investigation.

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INDEX WORDS: Dipeptidyl peptidase 4 (DPP-4) inhibition; linagliptin; kidney disease end points; albuminuria; renal function; renal risk; type 2 diabetes mellitus (T2DM); hyperglycemia; glucose control; glucose-lowering therapy; pooled analysis.

The number of new medications available for the treatment of type 2 diabetes has substantially increased over the past 2 decades.[1] The primary goal of these agents is to effectively lower elevated blood glucose concentrations in order to reduce the risk of long-term complications that result from chronic hyperglycemia.[2,3] However, it is equally critical for any new agent to also be proved to be safe. Although specific aspects of toxicology, including renal handling of drugs likely to be administered for years, are routinely evaluated in the very early stages of drug development, it is only after sufficient clinical exposure that potential safety concerns might become apparent. As an example, systematic reviews and

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meta-analyses of clinical trials pointed out the potential for increased risks of myocardial infarction associated with the thiazolidinedione rosiglitazone.[4,5] Largely as a result of these types of concerns, regulatory requirements issued by the US Food and Drug Administration (FDA) in 2008 stipulate that new type 2 diabetes drugs should rule out an unacceptable increase in cardiovascular risk in phase 2 and phase 3 clinical trials prior to drug approval.[6-8]

Microvascular complications, such as retinopathy, nephropathy, and neuropathy, are widespread in type 2 diabetes and account for significant morbidity and mortality.[9] Therefore, current treatment goals in diabetes include prevention of microvascular complications such as preservation of kidney function.[2,3] However, an approach to assess kidney disease end points for novel diabetes drugs is not generally applied. More commonly, specific renal data have been obtained from secondary analyses of cardiovascular outcome trials with several studies identifying effects on glomerular filtration rate (GFR), although this was not the primary end point of those trials.[10-12] Despite the value of acquiring these important data, such long-term renal safety evidence has often not been a priority of the clinical trial program, but has only become available several years after drug approval.

Linagliptin, a novel member of the dipeptidyl peptidase 4 (DPP-4) inhibitor class, has previously been shown to significantly improve glucose control without causing weight gain or increasing hypoglycemia risk.[13-15] In accordance with the guidance by the FDA, an early cardiovascular meta-analysis was performed that ruled out an unacceptable increase in cardiovascular risk for this drug and linagliptin was consequently approved in the United States in May 2011.[16] Unlike other members of the DPP-4 inhibitor class, linagliptin is not primarily cleared by the kidney and can be prescribed to patients with type 2 diabetes at one single dose irrespective of kidney function.[15,17] Such pharmacologic qualities support the use of linagliptin in a broad range of patients with type 2 diabetes, including those with increased prevalence and risk of renal microvascular complications, as well as in patients with declining kidney function.[18] The objective of this study was to explore kidney disease end points in a large set of patients with type 2 diabetes treated with linagliptin. Comprehensive assessments of safety events were performed by developing a systematic and innovative approach based on individual-patient data from a large clinical trials program.

METHODS

Study Design and Data Source

This pooled kidney disease analysis included all randomized, double-blind, and placebo-controlled clinical trials of linagliptin of 12-week or longer duration for which database lock of either predefined interim or final analysis was completed before February 13, 2011. Individual-patient data from 2 phase 2 and 11 phase 3 trials were included in the data set only if they received either linagliptin at a dose of 5 mg once daily or placebo. Studies were conducted globally over periods of 12 to 76 weeks as monotherapy or in combination with other glucose-lowering agents in patients with inadequately controlled type 2 diabetes. Open-label extension periods of primary double-blind randomized clinical trials were not considered (Table S1, available as online supplementary material).

Detailed study designs and primary and secondary efficacy and safety results of the individual studies have been published previously (Table S1).[19]

All patients provided written informed consent. Local ethics committees/institutional review boards reviewed and approved all study protocols. All studies were conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Setting and Participants

Eligibility criteria for each of the 13 trials were similar. Most relevant common inclusion criteria were age 18 years or older or 21 years or older, diagnosis of type 2 diabetes, and body mass index $\leq$ 40 or $\leq$45 kg/m^2. At screening, hemoglobin A_{1c} levels ranged either from 7.0% to 11.0% (53-97 mmol/mol) in treatment-naive participants or from 6.5% to 10.5% (48-91 mmol/mol) in participants previously treated with one or more glucose-lowering therapy. In the majority of trials, previous glucose-lowering therapies, if any, had to be unchanged for at least 8 weeks prior to informed consent. Most relevant common exclusion criteria at screening included the following: decreased hepatic function defined by serum levels of either alanine transaminase, aspartate transaminase, or alkaline phosphatase more than 3 times the upper limit of normal; myocardial infarction, stroke, or transient ischemic attack within the previous 3 or 6 months; any requirement for hemodialysis within the previous 3 months; and kidney transplantation.

Individuals whose blood glucose levels were not adequately controlled during each of the 13 trials received additional rescue therapy to ensure overall safety, as appropriate.

The pooled population consisted of all randomly assigned individuals (n = 5,466) who received at least one dose of study drug (treated set: linagliptin group, n = 3,505; placebo group, n = 1,961).

Kidney Disease End Points

Based on clinical guidelines or recommendations made by medical associations and regulatory bodies,[2,3,7,20] we defined the primary composite outcome as first occurrence of 6 individual and clinically relevant kidney disease end points: (1) new onset of moderate elevation of albuminuria (urinary albumin-creatinine ratio [ACR] $>$ 30 mg/g at any time during study conduct with baseline values $\leq$ 30 mg/g), (2) new onset of severe elevation of albuminuria (ACR $>$ 300 mg/g at any time during study conduct with baseline values $\leq$ 300 mg/g), (3) reduction in kidney function (serum creatinine increase to $\geq$250 μmol/L [$\geq$2.8 mg/dL] from a baseline value $<$ 250 μmol/L as defined by European Medicines Agency; increase observed at a minimum of 2 consecutive visits during study conduct with a between-visit time window of at least 4 weeks), (4) halving of estimated GFR (eGFR; loss of baseline eGFR $>$ 50% as defined by the FDA, and observed at a minimum of 2 consecutive visits during study conduct with a between-visit time window of at least 4 weeks), (5) incidence of acute renal failure, and (6) death from any cause. Although similar end points have previously been interpreted as efficacy parameters in renal studies,[10,11] they were assessed as safety outcomes in the linagliptin program.

Individual components of the primary composite outcome were defined as secondary outcomes.