Prevalence and progression of chronic kidney disease among patients with type 2 diabetes: Insights from the DISCOVER study

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Abstract
We report the prevalence and change in severity of chronic kidney disease (CKD) in DISCOVER, a global, 3-year, prospective, observational study of patients with type 2 diabetes (T2D) initiating second-line glucose-lowering therapy. CKD stages were...
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defined according to estimated glomerular filtration rate (eGFR). Overall, 7843 patients from 35 countries had a baseline serum creatinine measurement. Of these (56.7% male; mean age: 58.1 years; mean eGFR: 87.5 mL/min/1.73 m²), baseline prevalence estimates for stage 0-1, 2, 3 and 4-5 CKD were 51.4%, 37.7%, 9.4% and 1.4%, respectively. A total of 5819 patients (74.2%) also had at least one follow-up serum creatinine measurement (median time between measurements: 2.9 years, interquartile range: 1.9-3.0 years). Mean eGFR decreased slightly to 85.7 mL/min/1.73 m² over follow-up. CKD progression (increase of ≥1 stage) occurred in 15.7% of patients, and regression (decrease of ≥1 stage) in 12.0%. In summary, a substantial proportion of patients with T2D developed CKD or had CKD progression after the initiation of second-line therapy. Renal function should be regularly monitored in these patients, to ensure early CKD diagnosis and treatment.

KEYWORDS
cohort study, diabetes complications, diabetic nephropathy, type 2 diabetes

1 | INTRODUCTION

Diabetes is the most common cause of chronic kidney disease (CKD), and the prevalence of CKD among patients with diabetes is reported to be up to 40%.1-5 However, data for many countries are scarce.1 DISCOVER is a global, 3-year, prospective, observational study of patients with type 2 diabetes (T2D) initiating second-line glucose-lowering therapy.6 Here, we report the baseline prevalence of CKD, and changes in CKD severity during follow-up.

2 | METHODS

The DISCOVER study methodology has been reported previously (ClinicalTrials.gov: NCT02226822/NCT02322762).6,7 Study sites in 38 countries were selected to be as representative as possible of T2D management in each country,8 and consecutive adult patients with T2D were enrolled at each site if they were initiating second-line glucose-lowering therapy (add-on or switch) after first-line oral therapy. Initiation of second-line therapy was chosen for study baseline because of the diversification of guideline-recommended medications available at this point in the treatment pathway.9,10 Exclusion criteria included type 1 diabetes, first-line treatment with an injectable agent or with natural medicines alone, and renal transplantation or dialysis (Table S1). Data were collected according to routine clinical practice at each site, at baseline, 6, 12, 24 and 36 months. The protocol did not mandate study visits, or data collection for any variable. The protocol complies with the Declaration of Helsinki, the International Conference on Harmonisation of Good Clinical Practice, and all local regulations for clinical research. The study protocol was approved by the appropriate clinical research ethics committees in each participating country, and the relevant institutional review boards at each site.

For the present analysis, patients from China were excluded because of regulatory changes during follow-up, and patients from Canada and France were excluded because they lacked serum creatinine data. Regions were defined according to World Health Organization categories. Estimated glomerular filtration rates (eGFRs) were derived for each patient from serum creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study equation.11,12 CKD stages were defined as follows:

- Stage 0-1: eGFR ≥ 90 mL/min/1.73 m²
- Stage 2: eGFR 60-89 mL/min/1.73 m²
- Stage 3: eGFR 30-59 mL/min/1.73 m²
- Stage 4-5: eGFR ≤ 29 mL/min/1.73 m².

Albuminuria and urine albumin-to-creatinine ratio (UACR) data were not assessed owing to rates of missing data of 80.0% or higher (either not recorded or test not performed). Disease change over follow-up was assessed in patients who had serum creatinine measurements at baseline and at least one follow-up time point. Progression and regression were defined as an increase or decrease, respectively, of at least one CKD stage from baseline to the last available measurement.

3 | RESULTS

In total, 14 041 patients were eligible for the analysis, of whom 7843 (55.9%) had a baseline serum creatinine measurement (Table 1). The availability of baseline measurements was greatest in the Western Pacific (76.1%), and lowest in Africa (37.2%). Among patients with a baseline measurement, 56.7% were male, mean age was 58.1 years (standard deviation [SD]: 12.0) and mean eGFR levels were 87.5 mL/min/1.73 m² (SD: 21.4; Table S2). The numbers of patients...
who had stage 0-1, 2, 3 and 4-5 CKD were 4038 (51.4%; across-region range [ARR]: 42.4%-63.0%), 2960 (37.7%; ARR: 30.7%-46.3%), 737 (9.4%; ARR: 6.0%-12.9%) and 108 (1.4%; ARR: 0.4%-4.1%), respectively. Stage 4-5 CKD was most prevalent in the Americas (4.1%), and was least prevalent in the Western Pacific (0.4%).

The proportion of women and Caucasians, prevalence of complications, and the use of concomitant medications increased with CKD severity, and the proportion of Asians decreased (Table S2).

A total of 5819 patients had baseline and at least one follow-up serum creatinine measurement (74.2% of those with a baseline measurement; ARR: 58.3%-86.8%; median time between measurements: 2.9 years [interquartile range: 1.9-3.0 years]; Table 1). Overall mean eGFR levels decreased slightly to 85.7 mL/min/1.73 m² during follow-up (SD: 21.2), while the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) increased slightly (Figure 1). Disease progressed during follow-up in 914 patients (15.7%; ARR: 12.3%-22.9%), and regressed in 699 (12.0%; ARR: 7.7%-22.0%). Disease progression was most common in Africa (22.9%), and regression was most common in South-East Asia (22.0%). A total of 636 patients (10.9%) progressed from stage 0-1 to stage 2 or greater, and 279 patients (4.8%) progressed from stage 0-1 or 2 to stage 3 or greater. The mean rate of change in eGFR in the overall population was $-0.3 \text{ mL/min/}1.73 \text{ m}^2 \text{ per year (SD: 23.4)}$. Patients whose disease progressed had higher levels of concomitant medication use than patients whose disease regressed or remained stable, but other characteristics were similar (Table S3).

### DISCUSSION

We observed a baseline prevalence of 48.5% for stage 2 or greater CKD among patients with T2D initiating second-line therapy, and a prevalence of 10.8% for stage 3 or greater CKD. This is in line with or higher than estimates reported in previous studies. For example, in the United States the prevalence of stage 1-5 CKD among patients with diabetes is reported to be 36.0%, while in the UK the prevalence of microalbuminuria 10 years after the diagnosis of T2D is 24.9%. The high prevalence of CKD may be explained by the quality of care in the countries included relative to those assessed in previous studies. Our results may also reflect some degree of selection bias, as the measurement of serum creatinine levels may have been more probable in patients with or at risk of CKD. In line with this, comparison of patient characteristics revealed a higher prevalence of prior...
microvascular complications, including CKD and albuminuria, as well as greater use of ACE inhibitors and ARBs among patients with than without a baseline serum creatinine measurement (data not shown). It should also be noted that patients who had undergone renal transplantation or dialysis were excluded from the study.

Although overall changes in mean eGFR during follow-up were small, we found that disease progressed in 15.7% and regressed in 12.0% of patients assessed. Comparison of patient characteristics showed greater use of concomitant medications among patients whose disease progressed than among those whose disease regressed or remained stable, reflecting the general increase in the use of ACE inhibitors and ARBs that was observed.

In summary, a substantial proportion of patients with T2D developed CKD or increased disease stage after the initiation of second-line glucose-lowering therapy. High rates of missing serum creatinine, albuminuria and UACR data are a limitation.
of the study, and indicate suboptimal disease management. Regular monitoring of patients would help to identify and manage CKD at an early stage.

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CONFLICT OF INTEREST

K.K., B.C., M.B.G., L.J., A.N., W.R., M.V.S., I.S., H.W. and M.K. are members of the DISCOVER Scientific Committee and received financial support from AstraZeneca to attend DISCOVER planning and update meetings. K.K. is supported by the National Institute for Health Research (NIHR), Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC). F.T. and M.K. are employees of Saint Luke’s Mid America Heart Institute, which has received research funding from AstraZeneca for participation in DISCOVER. H.C., A.C., P.F., J.M. and L.R. are employees of AstraZeneca. N.H. was an employee of AstraZeneca at the time the study was carried out. D.Z.C. and H.J.L.H. have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

K.K., B.C., M.B.G., L.J., A.N., W.R., M.V.S., I.S., H.W. and M.K. are members of the DISCOVER Scientific Committee and H.C., A.C., P.F., N.H. (at the time the study was carried out), J.M. and L.R. are employees of AstraZeneca and contributed to the design of the DISCOVER study programme. K.K. proposed the analysis carried out in this manuscript, and F.T and H.C. performed the statistical analysis. The general content of the manuscript was agreed upon by all authors, and all authors contributed to the manuscript development. All authors approved the final version of the manuscript before its submission. An AstraZeneca team reviewed the manuscript during its development and could make suggestions. However, the final content was determined by the authors. K.K is the guarantor of this work.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca’s data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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SUPPORTING INFORMATION

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

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