Longitudinal Estimated GFR Trajectories in Patients With and Without Type 2 Diabetes and Nephropathy

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Background: In clinical practice and clinical trials, changes in serum creatinine concentrations are used to evaluate changes in kidney function. It has been assumed that these changes follow a linear pattern when serum creatinine concentration is converted to estimated glomerular filtration rate (eGFR). However, the paradigm that kidney function declines linearly over time has been questioned by studies showing either linear or nonlinear patterns. To verify how this impacts on kidney end points in intervention trials, we analyzed eGFR trajectories in multiple clinical trials of patients with and without diabetes.

Study Design: Longitudinal observational study.

Setting & Participants: 6 clinical trials with repeated measurements of serum creatinine.

Predictor: Patient demographic and clinical parameters.

Outcomes: Probability of nonlinear eGFR function trajectory calculated for each patient from a Bayesian model of individual eGFR trajectories.

Results: The median probability of a nonlinear eGFR decline in all trials was 0.26 (interquartile range, 0.13-0.48). The median probability was 0.28 in diabetes versus 0.09 in nondiabetes trials ($P < 0.01$). The percentage of patients with a >50% probability of nonlinear eGFR decline was generally low, ranging from 19.3% to 31.7% in the diabetes trials and from 15.1% to 21.2% in the nondiabetes trials. In the pooled data set, multivariable linear regression showed that higher baseline eGFR, male sex, diabetes status, steeper eGFR slope, and non–renin-angiotensin-aldosterone-system antihypertensives were independently associated with a greater probability of a nonlinear eGFR trajectory.

Limitations: Relatively short follow-up and no measured GFR.

Conclusions: In both diabetes and nondiabetes trials, the majority of patients show a more or less linear eGFR decline. These data support the paradigm that in diabetic and nondiabetic kidney disease, eGFR decline progresses linearly over time during a clinical trial period. However, in diabetes, one should take the nonlinearity proportion into account in the design of a clinical trial.

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To evaluate the effectiveness of interventions on delaying the progression of chronic kidney disease (CKD), clinical trials enroll patients who are likely to reach end-stage renal disease (ESRD) in the near future. Landmark clinical trials have used this clinically meaningful end point.[1,2] By definition, glomerular filtration rate (GFR) must decline to reach ESRD. Accordingly, a couple of trials have used the rate of GFR decline over time (GFR slope) as clinical trial end point.[3-7] The advantage of using rate of change in GFR as end point is that it provides greater statistical power than binary outcomes such as ESRD. However, a key assumption to use GFR slope as clinical trial end point is that the decline in GFR is linear over time.[8]

An early relatively small study showed that in patients with diabetic nephropathy, kidney function declines linearly over time.[9] However, this study had a relatively short follow-up and a study group consisting of only 9 individuals. In contrast, a more contemporary and larger study concluded that many African American patients with hypertensive nephrosclerosis have a nonlinear estimated GFR (eGFR) trajectory or an extended period of nonprogression.[10] Another study reported that 46% of patients show a nonlinear kidney function decline before reaching dialysis therapy.[11] These data challenge the existing paradigm of linear kidney function trajectories, which may have important implications for the analysis and interpretation of clinical trials using eGFR slope as end point. However, these prior studies investigated the linearity of eGFR trajectories in single cohorts with specific characteristics using different analytical methods.

To overcome these limitations, we undertook a pooled analysis of 6 clinical trials comparing eGFR trajectories in clinical trials of patients with and without diabetes, at different stages of CKD, using a uniform analytical approach.

Methods

Study Design

We included 6 clinical trials with longitudinal measurements of serum creatinine. Study selection criteria included randomized controlled clinical trials with sequential serum creatinine measurements enrolling patients with nondiabetic CKD or type 2 diabetes and CKD and availability of individual patient data. The selected studies enrolled patients with type 2 diabetes in the early (BENEDICT [Bergamo Nephrologic Diabetes Complications Trial]) and

advanced stage of renal disease (RENAAL [Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan] and IDNT [Irbesartan Type II Diabetic Nephropathy Trial]).[1,2,12] In addition, patients without diabetes and nephropathy participating in the REIN [Ramipril Efficacy In Nephropathy], ROAD [Renoprotection of Optimal Antiproteinuric Doses], and ESBARI [Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency] clinical trials were also included.[6,7,13,14] The details of all trials have been described previously; the main inclusion and exclusion criteria are summarized in Table 1.[1,2,6,7,12-14]

The first 3 of the 6 included trials related to diabetes. BENEDICT tested the effect of the angiotensin-converting enzyme inhibitor trandolapril alone or in combination with the calcium channel blocker verapamil on preventing microalbuminuria in patients who had normal urinary albumin excretion (urinary albumin excretion rate < 20 μg/min) with eGFRs > 60 mL/min/1.73 m^2. Median follow-up was 3.6 years. Serum creatinine was measured every 3 months.[12] The RENAAL trial and IDNT assessed the effect of angiotensin receptor blockers (losartan and irbesartan) in protecting against the progression of diabetic nephropathy in patients with overt proteinuria (protein excretion at least 50 and 900 mg/d for RENAAL and IDNT, respectively) with eGFRs between 30 and 60 mL/min/1.73 m^2. Patients were followed up over a treatment period of 3.4 and 2.6 years for RENAAL and IDNT, respectively, and serum creatinine was measured at baseline, month 1, and every 3 months thereafter.[1,2] IDNT also included a calcium channel blocker arm (amlodipine).

The 3 remaining trials were nondiabetes trials. The REIN trial assessed whether the angiotensin-converting enzyme inhibitor ramipril slows the progression of GFR decline in patients with nondiabetic kidney disease and proteinuria (protein excretion ≥ 1 g/d for ≥3 months).[6,7] The ROAD trial assessed whether the optimal antiproteinuric dosages of the angiotensin-converting enzyme inhibitor benazepril or angiotensin receptor blocker erlosartan, as compared with their conventional antihypertensive dosages, could improve kidney outcomes in patients without diabetes and with proteinuria (protein excretion > 1.0 g/d for ≥3 months).[13] The ESBARI trial examined the efficacy of benazepril in patients without diabetes and proteinuria (protein excretion > 0.3 g/d for ≥3 months).[14] The ROAD and ESBARI trials were both conducted in China. All nondiabetes trials enrolled patients with a creatinine clearance between 20 and 70 mL/min. Median follow-ups in REIN, ROAD, and ESBARI were 2.6, 3.7, and 3.4 years, respectively.[7,13,14] Serum creatinine was measured in the REIN trial at baseline; months 1, 3, 6; and every 6 months thereafter. It was measured every 3 months in the ESBARI trial and every 4 months in the ROAD trial.

All trials were conducted according to the principles outlined in the Declaration of Helsinki. All patients gave

Table 1. Inclusion and Exclusion Criteria for Included Trials

	BENEDICT	RENAAL	IDNT	REIN	ROAD	ESBARI
Inclusion criteria						
Age range	≥40 y	31-70 y	30-70 y	18-70 y	18-70 y	18-70 y
Diagnosis of T2DM	Yes	Yes	Yes	No	No	No
Kidney function	Scr ≤ 1.5 mg/dL	Scr 1.3-3.0 mg/dL (F) Scr 1.5-3.0 mg/dL (M)	Scr 1.3-3.0 mg/dL (F) Scr 1.2-3.0 mg/dL (M)	eCL_{cr}, 20-70 mL/min/1.73 m^2	Scr 1.5-5.0 mg/dL	Scr 1.5-5.0 mg/dL
Albuminuria	UAE < 20 μg/min	ACR ≥ 300 mg/g UPE > 500 mg/24 h	UPE > 900 mg/24 h	UPE > 1.0 g/24 h	UPE > 1.0 g/24 h	UPE > 0.3 g/24 h
Exclusion criteria						
Other diseases	Nondiabetic kidney disease	History of nondiabetic kidney disease or T1DM diagnosis	T2DM onset at age < 20 y or T1DM diagnosis	Renovascular disease or T1DM	Renovascular disease or immediate need for dialysis	Renovascular disease or immediate need for dialysis
CV disease	MI, stroke, TIA, unstable AP within past 3 mo or HF	MI or CABG within past 1 mo; CVA or PTCA within past 6 mo or HF history	MI, CABG, CVA, or PTCA within past 3 mo or HF history	HF, MI, or CVA within past 6 mo or severe uncontrolled HTN (DBP ≥ 115 mm Hg and/or DBP ≥ 220 mm Hg)	MI or CVA within past 1 y	MI or CVA within past 1 y

Abbreviations: ACR, albumin-creatinine ratio; AP, angina pectoris; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; CABG, coronary artery bypass graft; CV, cardiovascular; CVA, cerebrovascular accident; DBP, diastolic blood pressure; eCL_{cr}, estimated creatinine clearance; ESBARI, Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency; F, female; HF, heart failure; HTN, hypertension; IDNT, Irbesartan Type II Diabetic Nephropathy Trial; M, male; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; REIN, Ramipril Efficacy In Nephropathy; RENAAL, Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan; ROAD, Renoprotection of Optimal Antiproteinuric Doses; Scr, serum creatinine; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack; UAE, urinary albumin excretion; UPE, urinary protein excretion.