Improved Survival and Renal Prognosis of Patients With Type 2 Diabetes and Nephropathy With Improved Control of Risk Factors

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OBJECTIVE

To evaluate long-term survival, development of renal end points, and decline in glomerular filtration rate (GFR) in patients with type 2 diabetes and diabetic nephropathy (DN) after renin-angiotensin system (RAS) inhibition and multifactorial treatment of cardiovascular risk factors have become standard of care.

RESEARCH DESIGN AND METHODS

All patients with type 2 diabetes and DN (*n* = 543) at Steno Diabetes Center were followed during 2000–2010. GFR was measured yearly with ^{51}Cr-EDTA plasma clearance. Annual decline in GFR was determined in patients with at least three measurements over a minimum of 3 years (ΔGFR cohort, *n* = 286). Results were compared with historical data, obtained using identical criteria at our hospital, before implementation of current treatment guidelines.

RESULTS

Baseline mean (SD) GFR was 74 (32) mL/min/1.73 m^2. More than 93% received RAS inhibition. During median 7.8 (interquartile range 5.7–9.8) years, mean (SE) annual GFR decline was 4.4 (0.24) compared with previously 5.2 (0.27) mL/min/1.73 m^2/year (*P* = 0.04). Doubling of plasma creatinine or end-stage renal disease (ESRD) developed in 19%, and 37% died during 5.7 (3.3–8.8) years. Mortality from onset of DN in the ΔGFR cohort was compared with that of our prior ΔGFR cohort from 1983 to 2003 (*n* = 227). Crude mortality risk was reduced by 42% and after age adjustment by 50% (*P* < 0.001 for both). In a multistate model accounting for competing risks of ESRD and death, prior cardiovascular disease and lower GFR were predictors of mortality, whereas albuminuria, HbA$_{1c}$, and low GFR predicted ESRD.

CONCLUSIONS

Overall prognosis has improved considerably with current multifactorial treatment of DN in type 2 diabetes, including long-term RAS inhibition.

Diabetic nephropathy (DN) is a major complication of type 2 diabetes, characterized by elevated urinary albumin excretion rate (UAER), increase in blood pressure (BP), and decline in renal function leading to end-stage renal disease (ESRD). In addition, these patients have a high risk of cardiovascular disease (CVD) (1), which further increases with deteriorating renal function (2,3). In the past, renal disease in type 2 diabetes was considered mild compared with type 1 diabetes (4) where mean

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survival after onset of persistent proteinuria was 5–7 years, preceding routine use of intensive antihypertensive therapy, including renin-angiotensin system (RAS) inhibition, and dialysis (5,6). However, subsequent studies also demonstrated poor prognosis for renal disease in type 2 diabetes (7), and despite better treatment, including the use of antihypertensive agents (8,9), DN is now the leading cause of ESRD in Europe and the U.S. and a rapidly increasing problem in the developing countries with the epidemic of type 2 diabetes (10).

The Steno-2 trial demonstrated that long-term multifactorial intervention with aggressive control of BP, lipids, and glucose, accompanied by acetylsalicylic acid and lifestyle advice, reduced progression of microvascular complications, CVD, and mortality by 50% in microalbuminuric patients with type 2 diabetes (11,12). Treatment based on this strategy was implemented in 2002 for all patients with type 2 diabetes at Steno Diabetes Center. In addition, inhibition of the RAS was recommended in patients with increased UAER. This recommendation is based on randomized double-blind controlled studies that have shown RAS inhibition to delay onset of the combined end point of doubling of serum creatinine, development of ESRD, or death (13,14). These studies have lasted up to 5 years, but the prognosis for deterioration of directly measured renal function over time and for survival with longer-term clinical use of RAS inhibition is inadequately evaluated. Furthermore, previous analyses in type 2 diabetes have not taken competing risk of ESRD and death into consideration (15).

In our current study, we evaluate the loss of renal function and the prognosis of patients with type 2 diabetes and DN from 2000 to 2010 by assessing change in ^{51}Cr-EDTA plasma clearance (glomerular filtration rate [GFR]), doubling of plasma creatinine or progression to ESRD, and mortality rate. Results were compared with patients identified and followed with the same criteria, the same methods, and at the same hospital (16) prior to the implementation of multifactorial treatment and extensive use of RAS inhibition. We applied a multistate model to account for CVD and the competing risks of ESRD and death.

RESEARCH DESIGN AND METHODS

Selection Criteria and End Points

Steno Diabetes Center offers patients with DN yearly measurement of GFR using ^{51}Cr-EDTA plasma clearance (17). In a retrospective setting, we identified all patients with type 2 diabetes and DN with at least one GFR measurement since 1 January 2000. Patients were followed from inclusion (date of first GFR determination after 1 January 2000) until 31 December 2010, death, or emigration. The date for fulfilling the DN criteria was set as the date of second albuminuric sample (>300 mg/24 h or albumin-to-creatinine ratio >300 mg/g). DN was defined as persistent macroalbuminuria in two of three consecutive urine samples without clinical or laboratory evidence of other kidney disease.

We analyzed development of either ESRD or doubling of plasma creatinine with the competing risk of death for all patients, as well as rate of decline in GFR for patients followed with a minimum of three GFR measurements over at least 3 years (ΔGFR cohort). Rate of decline in GFR and mortality were compared with our own cohort from 1983 to 2002 based on identical selection criteria and analyzed similarly (16).

Methods of Assessment

Our electronic medical records and laboratory database were sources of demographic, clinical, and laboratory information. The Danish National Registry on Regular Dialysis and Transplantation provided information on renal replacement therapy (RRT), and ICD codes from hospital contacts were supplied by the National Patient Registry. The Danish Register of Causes of Death provided information on date of death.

All patients were routinely examined with HbA_{1c}, BP, and UAER 3–4 times yearly in our clinic. GFR (17), plasma hemoglobin, plasma creatinine, and cholesterol were assessed annually. Intraindividual coefficient of variation in GFR is 3.9% (18). UAER was analyzed by immunologic methods (turbidimetry). Creatinine was changed from modified Jaffe to an enzymatic reaction in 2004. BP was measured in the sitting position after 5–10 min rest with a mercury sphygmomanometer or an oscillometric device (A&D Medical, San Jose, CA) using an appropriate cuff.

Baseline laboratory values were attained at the inclusion date. If unavailable, the closest measurement in time, within 1 year prior to baseline and 4 months after, was applied. To overcome day-to-day variation, we determined the weighted mean of BP and weighted geometric mean of UAER measurements from 1 year prior to baseline until 1 month after.

Rate of GFR decline was determined as the regression coefficient of all study measurements at time of measurement. Other follow-up values were expressed at weighted mean of all measurements. ESRD was defined as dialysis or renal transplantation. Doubling of plasma creatinine consisted of an increase of 100% from baseline to a minimum value of 150 μmol/L after conversion from Jaffe to standardized creatinine (19). CVD included stroke, acute myocardial infarction, ischemic heart disease, and heart failure based on ICD-10 and ICD-8 codes and on the operational codes for coronary artery bypass graft and percutaneous coronary intervention (Supplementary Table 1). Date of death was as reported in the Danish Register of Causes of Death.

Statistical Analysis

The *t* test, Kruskal-Wallis test, and χ^2 statistic were applied for the comparison of means, medians, and proportions. Linear regression was applied to assess associations for baseline and follow-up variables to rate of GFR decline. Continuous variables were standardized to show effect of 1 population SD change on GFR decline. Multivariate models with backward selection, as in prior ΔGFR study (16), of univariate factors with *P* value <0.2 were constructed, and adjusted corrected Akaike information criterion was used to select the final model. Age and sex were forced into the model of baseline variables. To avoid inclusion of related variables, we chose age rather than duration of diabetes or nephropathy, systolic BP over diastolic BP, GFR over chronic kidney disease stage or creatinine, and LDL-to-HDL ratio over total, LDL, and HDL cholesterol if more than one was eligible. For fulfillment of model assumptions, creatinine, UAER, triglyceride, and insulin per kilogram per day were log2 transformed. We plotted the cumulative mortality from baseline for our entire cohort. We

also fitted a Cox regression model with DN duration as the underlying time scale for a combined data set of both our ΔGFR cohorts (as data set for the prior cohort as a whole was unattainable), with cohort membership as the categorical variable. This was repeated with age as linear effect. We reported the hazard ratio of the new cohort versus the prior cohort. For the above-mentioned analysis and database management, SAS Enterprise Guide 4.3 (SAS Institute, Cary, NC) was used.

A multistate model classifying the follow-up (follow-up time and events) in the categories DN, CVD, and ESRD (including doubling of plasma creatinine), along with death from each of these states, was created (Fig. 1). Patients entered follow-up in the CVD state if they had CVD prior to DN; otherwise, all patients entered in the DN state. The ESRD state was subdivided by coexisting CVD. Occurrence of CVD and ESRD in conjunction was modeled together regardless of which event occurred first. Follow-up was split in intervals of 2 months' length, and the time scales age, diabetes duration and DN duration were computed at the beginning of each interval. A Poisson model with natural splines for time scales (age, diabetes duration, DN duration) using log length of the intervals as offset was used to model transition rates between states (20). The following baseline covariates were included for analysis of pre-ESRD death and ESRD, as they have previously been associated with the end points: systolic BP, GFR, UAER, hemoglobin, total cholesterol, smoking status (yes/no), BMI, and insulin per kilogram. Likelihood ratio tests were used to test proportionality of rates. We found a model with separate baseline intensities for rates of death and ESRD, and CVD as a time-dependent covariate with proportional effects along the three time scales, to be the most appropriate. Rate of CVD from DN was modeled using age, diabetes duration, sex, and HbA_{1c}. Age, time since ESRD, and previous CVD were used for modeling mortality rate in patients with ESRD.

We used the Lexis machinery implemented in the Epi package (version 1.1.52) (20,21) for R (version 3.0.1) (22) for the calculations. A full account of rate analyses including estimates of cumulative risk are available from http://bendixcarstensen.com/SDC/Nefro/DN2.pdf). The study was performed in accordance with ethics standards.

RESULTS

We identified 543 eligible patients, of whom 286 (53%) had three measurements of GFR over 3 years, which qualified for analyses of rate of decline in GFR (ΔGFR cohort). Table 1 shows characteristics for both the whole cohort and our ΔGFR cohort including comparison with our previous cohort (16). In the whole cohort, baseline mean (SD) GFR was 74 (32) mL/min/1.73 m^2 and HbA_{1c} was 8.4 (1.7)%, and median UAER was 485 mg/24 h (interquartile range [IQR] 256–938). At baseline, 76% received RAS inhibition, whereas 93% were prescribed RAS inhibition for at least half of the study period. RAS inhibition prescription in our ΔGFR cohort reached 95% in 2001 and remained between 90 and 97%

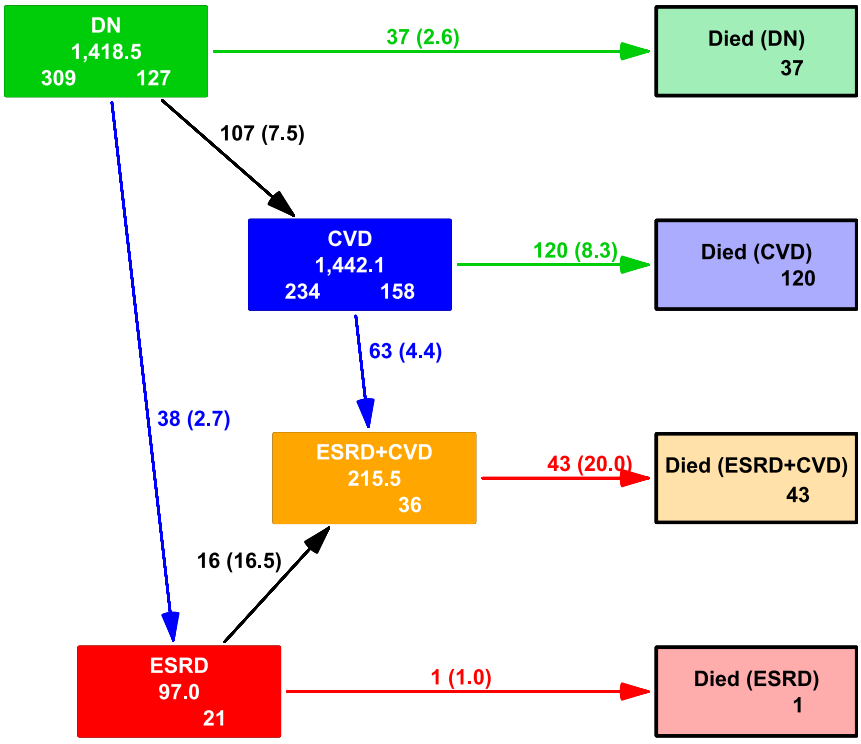

Figure 1—For patients with type 2 diabetes and DN, follow-up time was divided into time spent in the following clinical states: DN, CVD, and ESRD in chronologic order as shown in this multistate model with age, diabetes duration, and DN duration as underlying time scales. Numbers in boxes represent the sum of person-years in the state; numbers on the arrows are number of patients that change state with rates in % per year in the parentheses. Patients with CVD at baseline started in the CVD state (blue box); otherwise, all patients started in the DN state (green box). Green, DN only; blue, CVD; red, ESRD including doubling of p-creatinine; yellow, ESRD and CVD. Framed boxes with lighter colors represent those who died in the above-mentioned states.

Table 1—Characteristics for the whole current cohort, the group of patients eligible for rate of decline analysis (ΔGFR cohort), and the prior ΔGFR cohort used for comparison of rate of decline in GFR

	Current all	Current ΔGFR	Prior ΔGFR (16)	*P**
n	543	286	227	
Male (%)	76	76	74	0.61
Age (years)	60.6 (9.1)	59.2 (8.7)	57.0 (7.7)	<0.01
Diabetes duration (years)	12.8 (7.6)	12.4 (6.9)	10.8 (6.8)	<0.01
Nephropathy duration (years)	2 (1–4)	2 (1–4)	1 (0–2)	<0.001
Retinopathy: nil/simplex/proliferative (%)	27/56/17	29/54/17	30/49/21	0.41
Smoking (%)	27	27	36	0.03
BMI (kg/m^2)	27.2 (5.2)	27.4 (5.0)	30.0 (5.3)	<0.001
Prior CVD (%)	43	39	25†	
Insulin requirements (IE/kg/day)	0.8 (0.4–1.3)	0.8 (0.5–1.3)	N/A	
Baseline measurements				
GFR (mL/min/1.73 m^2)	74 (32)	80 (29)	83 (30)	0.22
Albuminuria (mg/24 h or mg/g)‡	485 (256–938)	414 (247–818)	734 (382–1,393)	<0.001
Systolic BP (mmHg)	149 (17)	149.2 (16.7)	157.7 (19.0)	<0.001
HbA_{1c} (%)	8.4 (1.7)	8.5 (1.6)	8.8 (1.5)	0.02
HbA_{1c} (mmol/mol)	68 (18)	69 (17)	73 (17)	0.02
Hemoglobin (mmol/L)§	8.3 (1.0)	8.4 (1.0)	8.7 (1.1)	0.001
Total cholesterol (mmol/L)	4.7 (1.2)	4.8 (1.3)	5.9 (1.5)	<0.001
HDL cholesterol (mmol/L)	1.1 (0.3)	1.2 (0.3)	N/A	
LDL cholesterol (mmol/L)	2.6 (1.1)	2.7 (1.1)	N/A	
LDL-to-HDL ratio	2.4 (1.1)	2.4 (1.1)	N/A	
Triglyceride (mmol/L)	1.9 (1.3–2.8)	1.9 (1.2–2.9)	N/A	
Plasma creatinine (μmol/L)‖	94 (75–120)	90 (74–108)	86 (73–105)	1.00
Other information				
Age at diabetes diagnosis (years)	47.8 (10.2)	46.8 (9.8)	46.2 (9.1)	0.47
Age at nephropathy debut (years)	57.5 (9.4)	56.2 (9.1)	55.4 (7.9)	0.27
Number of GFR measurements		6.1 (2.9)	7.2 (3.7)	<0.001
Total follow-up	5.7 (3.3–8.8)	7.8 (5.7–9.8)	6.1 (4.4–8.1)	<0.001
Follow-up measurements				
GFR (mL/min/1.73 m^2)	65 (29)	66 (28)		
Albuminuria (mg/24h or mg/g)‡	351 (138–872)	266 (125–705)		
Systolic BP (mmHg)	142.4 (14.4)	141.6 (12.5)		
HbA_{1c} (%)	8.1 (1.2)	8.1 (1.1)		
HbA_{1c} (mmol/mol)	65 (13)	65 (12)		
Cholesterol (mmol(mol)	4.4 (0.9)	4.3 (0.8)		
Prescribed medicine ≥50% of study duration (%)				
RAS inhibition	93	98	N/A	
ACE inhibitor	50	54	49	
Angiotensin receptor blocker	52	55	5	
β-Blocker	35	32	15	
Diuretics	79	85	67	
Calcium channel blocker	51	53	23	
Other antihypertensive drugs	11	9	4	
Lipid-lowering drugs	87	89	N/A	
Acetylsalicylic acid	86	89	N/A	

Data are presented as mean (SD) or median (IQR). *P* values from *t* test, Kruskal-Wallis test, or χ^2 statistic. *The *P* value represents comparison of the ΔGFR cohorts. †History of stroke, myocardial infarction, and percutaneous coronary intervention or coronary artery bypass graft. ‡All patients previously had sustained macroalbuminuria, expressed as minimum two of three measurements of 24-h albumin >300 mg or albumin-to-creatinine ratio >300 mg/g. At baseline, some patients had values <300. §To convert hemoglobin to g/dL, multiply the SI value by 1.611. ‖All creatinine measurements have been converted to isotope dilution mass spectrometry (IDMS) traceable values.

thereafter. In the ΔGFR cohort, 96% were prescribed RAS inhibition for at least half of the study duration compared with ~50% in the past (16). Improvements in cardiovascular risk factors were also evident in the present ΔGFR cohort, as total cholesterol, BMI, UAER, BP, HbA_{1c}, and smoking were all significantly lower, whereas age was higher and duration of diabetes and DN were longer (Table 1).

Mortality, ESRD, or Doubling of Plasma Creatinine

The combined kidney end point occurred in 19% (*n* = 101) of the entire cohort of 543 patients. In 16% (*n* = 89), creatinine doubled during follow-up, 8% (*n* = 42) developed ESRD, and 37% (*n* = 201) died during a median of 5.7 years (IQR 3.3–8.8). Cumulative mortality was 26% during the first 5 years of follow-up (Fig. 2).

In the present ΔGFR cohort, 23% (*n* = 66) died (Fig. 2), 22% (*n* = 64) doubled serum creatinine, and 6% (*n* = 16) developed ESRD over a median follow-up of

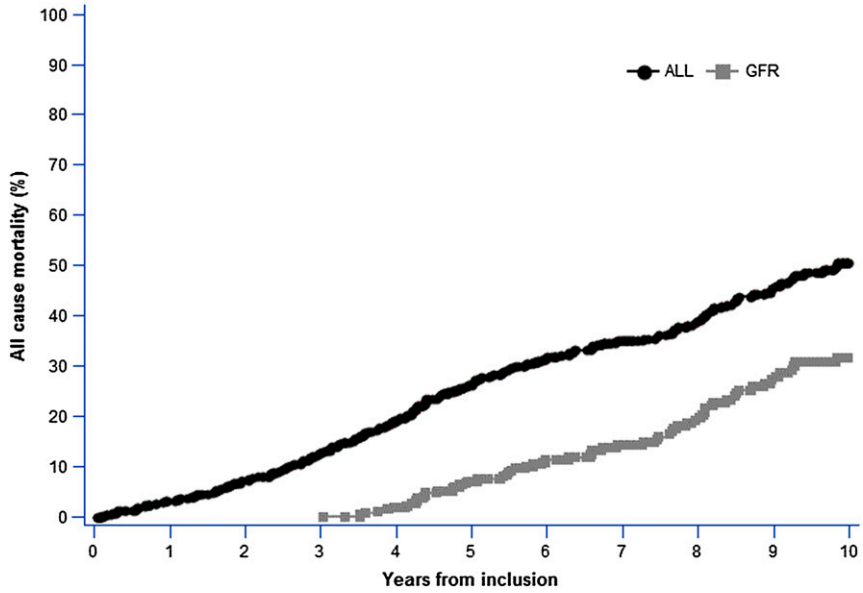

Figure 2—Cumulative mortality from inclusion. The entire cohort of patients with type 2 diabetes and DN is demonstrated by black dots. Their cumulative mortality after 5, 7, and 10 years of follow-up was 26.4%, 35.1%, and 50.1%, respectively. The mortality rate in the ΔGFR cohort is demonstrated by gray boxes. As follow-up for at least 3 years was a prerequisite for inclusion, no patients died during this time. (A high-quality color representation of this figure is available in the online issue.)

7.8 years (IQR 5.7–9.8). We compared mortality risk after onset of DN in the present ΔGFR cohort compared with our previous study (16), as both cohorts were selected with the same criteria where only patients with at least 3 years of follow-up were included. The mortality risk was markedly reduced in the current ΔGFR cohort. Thus, hazard ratio (95% CI) for death in the current ΔGFR cohort was 0.58 (0.42–0.81, $P = 0.001$) and further decreased to 0.50 (0.36–0.71, $P < 0.001$) after adjustment for age.

Rate of Decline in GFR

For the ΔGFR cohort, median follow-up time with GFR measurements was 7.8 years (IQR 5.7–9.8) and number of measurements was 5 (4–7). The mean (SE) rate of decline in GFR was 4.4 (0.24) mL/min/1.73 m^2/year. Compared with our prior cohort (16) the rate of decline in GFR was reduced by 14% (95% CI 4–28%, $P = 0.04$) from 5.2 (0.27) mL/min/1.73 m^2/year.

A total of 82 patients were included in both study periods (1983–2002 and 2000–2010). The mean (SE) GFR decline for these patients was 4.2 (0.48) in the former compared with 4.5 (0.47) mL/min/1.73 m^2/year in the latter period ($P = 0.66$), suggesting that the slower decline in GFR was sustainable.

We further considered patients from the prior ΔGFR cohort with new onset of DN during the last 10 years of their follow-up ($n = 182$) compared with new onset during our current follow-up period ($n = 170$). The annual mean (SE) decline was 5.2 (0.30) in the former vs. 4.3 (0.29) mL/min/1.73 m^2/year in the latter period ($P = 0.04$), again demonstrating a slower decline in GFR during the current study period compared with the prior study (16), undertaken at the same hospital with the same criteria.

Variables associated with annual rate of decline in GFR in univariate analyses are presented in Supplementary Fig. 1. Age was negatively and GFR, UAER, HbA_{1c}, BMI, hemoglobin, and diabetes duration were all positively associated with rate of decline in GFR in analyses of baseline variables. Follow-up values of BMI, UAER, HbA_{1c}, triglyceride, and LDL-to-HDL ratio were positively and diastolic BP and HDL negatively associated with decline in GFR. Furthermore, baseline retinopathy grade ($P = 0.03$) and chronic kidney disease stage ($P < 0.01$) were associated with faster decline in GFR in unadjusted analyses.

In separate multivariate models including baseline or follow-up variables, presence of retinopathy, elevated GFR, UAER, and HbA_{1c} at baseline were associated with faster decline in GFR, whereas elevated UAER, higher BMI, and lower diastolic BP during follow-up were associated with faster decline (Table 2).

Multistate Model

The multistate model with age, diabetes duration, and DN duration as underlying time scales (and thus built in the model) is presented in Fig. 1. The number of transitions between different clinical states and the corresponding progression rates in percentage/year are shown above the arrows. The annual mortality rate was 2.6% for DN only, 8.3% after a CVD event, 1.0% after ESRD, and 20.0% for ESRD and CVD in conjunction, as the majority of deaths after ESRD were preceded by CVD (Fig. 1). The rate for post-ESRD mortality (14.1%) can be derived by adding number of transitions from ESRD groups to death (the red arrows: 43 + 1 transitions) and dividing by person-years in the previous states (215.5 + 97 person-years). Similarly, pre-ESRD mortality, corresponding to the green arrows, equals 5.5% and the progression rate to ESRD (blue arrows) 3.5% per year. During follow-up, 123 patients without CVD at baseline experienced a CVD event; 6 patients had a percutaneous coronary intervention, 14 acute myocardial infarction, 15 stroke, and

Table 2—Adjusted effect of baseline and follow-up variables on annual decline in GFR for the ΔGFR cohort

	Difference of/between	Effect on decline in GFR (mL/min/year)	*P*
Baseline parameters			
Retinopathy*	Simplex/nil	1.86 (0.84–2.88)	<0.001
	Proliferative/nil	1.07 (−0.33 to 2.48)	0.13
Albuminuria	100%	0.62 (0.34–0.89)	<0.001
GFR	10 mL/min/1.73 m^2	0.44 (0.27– 0.61)	<0.001
HbA_{1c}	10 mmol/mol or 0.91%	0.35 (0.10–0.61)	<0.01
Sex†	Men/women	0.27 (−0.76 to 1.29)	0.61
Age†	10 years	0.26 (−0.29 to 0.81)	0.35
BMI	1 kg/m^2	0.09 (−0.01 to 0.18)	0.06
Follow-up parameters‡			
Diastolic BP	10 mmHg	−1.18 (−1.87 to −0.49)	<0.01
Albuminuria	100%	0.38 (0.13–0.63)	<0.01
HbA_{1c}	10 mmol/mol	0.30 (−0.09 to 0.68)	0.13
BMI	1 kg/m^2	0.12 (0.04 to 0.20)	<0.01

Adjusted r^2: baseline model = 0.19; follow-up model = 0.09. Two multivariate models explaining decline in GFR are represented. The top part demonstrates effect of different baseline variables on rate of decline in GFR and the bottom part the effect of follow-up variables in a separate model. The second column denotes the unit and the third column the effect on GFR decline rate (added to the "original" rate) for a given change in the parameter; e.g., a person with GFR of 70 mL/min/1.73 m^2 at baseline will be expected to have a decline in GFR that is 0.44 mL/min/1.73 m^2/year more rapid than if the baseline value were 60 mL/min/1.73 m^2. *Retinopathy overall *P* value = 0.01. †Forced into model. ‡ Weighted mean of all follow-up measurements.

37 heart failure, and 67 were diagnosed with ischemic heart disease. In few patients, these events coincided.

The multistate model was used to assess adjusted risk ratio of putative clinical predictors on the competing risk of either pre-ESRD mortality or ESRD (including doubling of plasma creatinine), demonstrated as the green and blue arrows in Fig. 1 (Supplementary Fig. 2). Previous CVD and lower GFR were predictors of pre-ESRD mortality with risk ratios of 3.01 (95% CI 1.81–5.01) and 1.14 (1.04–1.24) per −10 mL/min/1.73 m^2, respectively. Higher UAER and HbA_{1c} and lower GFR significantly predicted the development of ESRD. UAER of double magnitude resulted in a risk ratio of 1.51 (1.27–1.79), 1% higher HbA_{1c} in 1.22 (1.05–1.43), and 10 mL/min/1.73 m^2 lower GFR in 1.10 (1.00–1.20).

CONCLUSIONS

Our long-term observational study of patients with type 2 diabetes and DN followed during 2000–2010 showed significant improvement in prognosis compared with our prior but otherwise comparable cohort followed during 1983–2002. Multiple modifiable cardiovascular risk factors, total cholesterol, BMI, UAER, BP, HbA_{1c}, and smoking, were significantly improved compared with our previous cohort, and almost all patients were prescribed RAS inhibition in comparison with just about 50% in our prior study (16). Additionally, renal prognosis was better, with slower deterioration of renal function, and we found an almost 50% reduction in all-cause mortality after age adjustment in our ΔGFR cohort compared with the prior ΔGFR cohort (16).

In a previous observational cohort of 51 patients with DN at Steno followed from 1987, the cumulative mortality over 5 years was 33% (7) compared with 26% during the first 5 years of follow-up for our entire cohort (Fig. 2). Our more recent ΔGFR study (1983–2002) found overall mortality when patients not eligible for GFR analysis were included to be 53% (*n* = 194 of 366) during a median of 6 years (range 0–17) of follow-up (16), whereas in our current study this was 37% (201 of 543) during 5.7 years (range 0–11) for the entire cohort. This highlights improved survival over time.

Finally, we were able to compare data in more detail for the ΔGFR cohorts that only included patients with at least three GFR measurements and 3 years' follow-up and found the age-adjusted mortality risk to be halved in the current cohort compared with our prior study (16).

Randomized double-blind controlled trials of up to 5 years' duration have demonstrated benefits on a combined end point of doubling of serum creatinine, ESRD, or mortality in patients with type 2 diabetes and advanced DN by RAS inhibition, but overall mortality was not affected (13,14). This could be due to the short duration of these studies or because several risk factors were not addressed.

Along with multiple risk factors at baseline being improved compared with prior studies, mean follow-up variables of HbA_{1c}, cholesterol, UAER, and BP (Table 1) appeared lower than at baseline. BP declined 6.6 mmHg from baseline. General recommendations for BP treatment were RAS inhibition combined with diuretics (edema), calcium channel blockers, or β blockers (CVD) if needed.

Our findings of improvements in risk factors and outcome suggest that the benefits of multifactorial intervention described in the Steno-2 trial (11,12) may also apply after onset of established DN.

The slower deterioration of renal function was emphasized by the findings that 28% (*n* = 63) doubled serum creatinine and 7% (*n* = 15) received RRT during 6.5 years in our prior ΔGFR cohort (16) compared with 22% and 6% in our present and comparable ΔGFR cohort even though the follow-up was somewhat longer or 7.8 years. For minimization of bias, creatinine values attained prior to the assay change were converted and the minimum limit for doubling was lowered. Finally, the mean (SE) annual rate of decline in GFR improved by 14% from 5.2 (0.27) to 4.4 (0.24) mL/min/1.73 m^2/year.

By study design, long-time survivors were included in both cohorts. This strategy was applied to illustrate the composition of the patients attending our clinic. As patients included in both ΔGFR studies did had neither a lower rate in the latter study than in the former nor a rate below average, "survivor effect" is hardly causing the improvement. Further supporting improvement is the fact that patients with new-onset DN in our current ΔGFR cohort also had a significantly lower rate of decline than corresponding patients in the prior ΔGFR cohort.

The slower decline in GFR compared with prior studies fits well with the circumstance that incidence of RRT due to diabetes is stabilized or even decreased in Denmark since 2002 (23,24), despite diabetes prevalence having doubled between 1997 and 2007 (25). This is further supported by data from the U.S. and Catalonia, where age-specific incidences of ESRD in the diabetic population have decreased since the late 1990s (26) and 2002 (27), respectively.

Earlier studies including patients with DN not receiving antihypertensive treatment demonstrated decline in GFR ranging from 10 to 14 mL/min/1.73 m^2/year (28,29). Our previous study (16) demonstrated that early antihypertensive treatment reduced the rate of decline in GFR in patients with type 2 diabetes and DN but rather well preserved kidney function. This is in close agreement with the decline in estimated GFR (eGFR) reported in the angiotensin II receptor blocker group of the Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of End Points in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study: 5.5 and 4.4 mL/min/1.73 m^2/year, respectively (13,14).

We are not aware of recent studies that have used real GFR in unselected patients with DN. However, a few observational studies on decline in eGFR for patients with type 2 diabetes and DN were recently published. The reported rates were between 4.5 and 6.6 mL/min/1.73 m^2/year (30–33). It is well-known that eGFR and decline in eGFR underestimate the real GFR values (34,35). Furthermore, the studies differ in definition of DN.

Risk of mortality was affected by previous CVD and lower GFR, which is generally compatible with earlier studies (28). Elevated UAER, GFR, and HbA_{1c} were independent risk factors for the renal end point as well as rate of decline in GFR, whereas retinopathy degree, higher BMI, and lower diastolic BP were only associated with decline in GFR. These risk factors are well-known (16,28). Results from a post hoc study of RENAAL (36) support the influence of lower diastolic BP. Moreover, Leehey et al. (33) found a U-shaped association between diastolic BP (lowest risk at 75–79 mmHg) and GFR decline. The effect of lower diastolic BP probably reflects upon higher pulse pressure as a proxy for increased arterial stiffness. HbA_{1c} has in competing risk analysis of patients with type 1 diabetes been associated with ESRD but not death, suggesting that HbA_{1c} mainly contributes toward mortality risk through its effect on complications (15). The better control of risk factors including HbA_{1c} and thus an overall risk reduction could also explain the weakened impact of $HbA_{1c.}$

The fact that systolic BP and cholesterol did not have an impact in our study could be due to improved treatment, as 83% of patients in our cohort were in long-term statin treatment and >90% were in antihypertensive treatment, reducing variability and thus the impact as explaining variable. Exposure to statins for at least half the study period, which was not a significant factor for progression, may be too coarse a measure to detect an effect. Although cholesterol has been associated with decline in GFR, a randomized study with simvastatin and ezetimibe in more advanced DN and non-DM nephropathy failed to show benefits in renal function (37).

As thresholds for examination and intervention of CVD have probably changed and ascertainment differs in these cohorts due to improved registration using national registers, CVD rates may not be comparable.

Studies regarding the effects of longer-term RAS inhibition (>5 years) are sparse: A substudy of the UK Prospective Diabetes Study could not prove ACE inhibitors to have specific renoprotective effects in new-onset type 2 diabetes and found an insignificant increase in ESRD; however, events were very few (38). Similarly, a register-based study found an increase in renal events among long-term users of RAS inhibition (39), but the conclusions were challenged (40).

The current study was not designed to compare RAS inhibition with other antihypertensive treatments, as our study is not randomized and almost all received RAS inhibition, but it demonstrates that patients under current multifactorial treatment, which includes long-term RAS inhibition, have a better prognosis than previously. Comparing independent concurrent cohorts prescribed different treatments was not possible and would require a randomized study.

Although we applied the same criteria, we are comparing patients with many differences in clinical characteristics; the referral pattern to Steno Diabetes Center has not changed during this time, whereas treatment has improved. For comparison over time, incidence cohorts had been ideal, as inclusion of prevalent cases may introduce a bias from long-term survivors. Owing to low number of patients, this was feasible for neither death nor renal events—only for GFR decline.

In conclusion, the annual decline in GFR is significantly lower in our present cohort compared with an earlier cohort from our center, analyzed with similar methods, showing an improvement in the prognosis of patients with type 2 diabetes and DN. More importantly, mortality is greatly reduced, as are the renal end points compared with our earlier studies. These improvements coincide with and may depend upon better control of several modifiable cardiovascular risk factors and a marked rise in the use of RAS inhibition. We believe that current multifactorial treatment has led to better risk factor management and improved prognosis for patients with type 2 diabetes suffering from DN.

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Duality of Interest. G.A., M.L.J., and B.C. own shares in Novo Nordisk. H.-H.P. has participated in advisory boards for Abbvie, AstraZeneca, and Novartis and owns shares in Novo Nordisk. P.R. has participated in advisory boards for Abbvie, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, and Novo Nordisk and owns shares in Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.A. managed databases, researched data, performed statistics, wrote the manuscript, and reviewed the manuscript. M.L.J. prepared data for analysis, gave

programming advice, and reviewed the manuscript. B.C. performed advanced statistical analysis including interpretation of data and reviewed the manuscript. H.-H.P. gathered data, contributed toward drafting of the article, and reviewed the manuscript. K.R. gathered data and reviewed the manuscript. T.W.H. supervised the work, edited the manuscript repeatedly, and reviewed the manuscript. P.R. planned and supervised the work, contributed to the discussion, and edited and reviewed the manuscript. P.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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