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# Improved survival in patients obtaining remission of nephrotic range albuminuria in diabetic nephropathy

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*Background.* The level of albuminuria is related to progression of diabetic nephropathy, and patients with nephrotic range albuminuria have advanced renal structural changes and the fastest decline in glomerular filtration rate (GFR). We have previously demonstrated that the rate of decline in GFR is diminished in patients obtaining remission of nephrotic range albuminuria, but information is scarce concerning the impact of remission of nephrotic range albuminuria on the long-term prognosis.

*Methods*. At the Steno Diabetes Center, we performed a prospective cohort study of all type 1 diabetic patients with nephrotic range albuminuria ($N = 125$), who had annual measurement of GFR [$^{51}$chromium-ethylenediaminetetraacetic acid ($^{51}$Cr-EDTA) plasma clearance] carried out for at least 3 years. Patients were followed from onset of nephrotic range albuminuria until death or the end of year 2003. Nephrotic range albuminuria was defined as persistent albuminuria above 2.5 g/24 hours, remission of nephrotic range albuminuria was defined as sustained albuminuria <0.6 g/24 hours for at least 1 year.

*Results.* Nephrotic range albuminuria occurred in 90 men and 35 women, age [mean (SD)] 34 (8) years, duration of diabetes 22 (8) years, and follow-up time from onset of nephrotic range albuminuria [median (range)] 12.4 (3.0 to 24.9) years. Remission was induced in 32 patients (26%), 25 predominantly treated with angiotensin-converting enzyme (ACE) inhibitors, seven with non-ACE inhibitors. The remission lasted 5.5 (1.0 to 22.4) years. At the end of follow-up, 25% in the remission group and 74% in the no remission group had reached the composite end point of end-stage renal disease (ESRD) (dialysis, transplantation) or death. A Cox proportional hazard regression analysis with gender and age as fixed covariates and remission as time-dependent covariate revealed that obtaining remission was associated with a lower risk of dialysis, transplantation, or death, relative risk (95% CI) 0.28 (0.13 to 0.59), $P = 0.001$, whereas older age at onset of nephrotic range albuminuria (per 10-year increase) was associated with higher risk of reaching the end point, 1.42 (1.08 to 1.87), $P = 0.01$.

*Conclusion.* Our prospective study suggests that remission of nephrotic range albuminuria in type 1 diabetic patients, induced by aggressive antihypertensive treatment with and without ACE inhibitors, is associated with a slower progression in diabetic nephropathy and a substantially improved survival.

**Key words:** nephrotic range albuminuria, antihypertensive treatment, diabetic nephropathy, remission, type 1 diabetes, mortality, end-stage renal disease.

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Diabetic nephropathy is a chronic progressive kidney disease with high morbidity and mortality [1], and is characterized by an early elevation of arterial blood pressure, increasing albuminuria, and a relentless mean decline in glomerular filtration rate (GFR) of approximately 10 to 12 mL/min/year and extremely high risk of cardiovascular disease without antihypertensive treatment [2–5]. The degree of albuminuria is closely related to the progression of diabetic nephropathy as reviewed by Rossing [6]. The most advanced renal structural changes, the fastest decline in GFR, the highest risk of cardiovascular disease, and the shortest survival time are seen in the group of diabetic patients with diabetic nephropathy and the highest levels of albuminuria (i.e., nephrotic range albuminuria) [7–9]. We have previously demonstrated that remission of nephrotic range albuminuria, defined as reduction of albuminuria from above 2500 mg per 24 hours to below 600 mg per 24 hours, is associated with a slower deterioration of kidney function [10]. However, whether remission of nephrotic range albuminuria will transfer in to a better long-term prognosis and survival remains to be elucidated. To evaluate the impact of remission of nephrotic range albuminuria on the composite end point: end-stage renal disease (ESRD) (dialysis or transplantation) or death, we analyzed data from our long-term prospective observational study of 125 consecutive type 1 diabetic patients with nephrotic range albuminuria due to diabetes.

## METHODS

The patients with nephrotic range albuminuria have been described in detail previously [10]. In brief, we evaluated all type 1 diabetic patients with diabetic

nephropathy at the Steno Diabetes Center, who had their kidney function monitored with at least one yearly determination of GFR and a minimum of 3 years follow-up ($N = 321$). Of the total cohort (200 men), nephrotic range albuminuria developed in 125 patients (90 men) [10]. In the present study, the follow-up was extended to the end of the year 2003. Diabetic nephropathy was diagnosed clinically if the following criteria were fulfilled: persistent albuminuria > 300 mg/24 hours in at least two out of three consecutive 24-hour urine collections, presence of diabetic retinopathy, and absence of any other evidence of kidney or renal tract disease [11]. As previously reported, nephrotic range albuminuria was defined as persisting albuminuria above 2500 mg/24 hours in at least two out of three consecutive 24-hour urine collections, and remission was accordingly defined as a reduction in albuminuria from nephrotic range albuminuria to below 600 mg/24 hours, sustained for at least 1 year during the follow-up period [10]. ESRD was defined as commencement of renal replacement therapy. All definitions were pre specified prior to data analysis.

At onset of nephrotic range albuminuria (baseline), 67 patients (54%) were without antihypertensive treatment, 24 (19%) treated predominately with angiotensin-converting enzyme (ACE) inhibitors and 34 (27%) patients were treated with other antihypertensive agents than ACE inhibitors [10]. During follow-up, all 125 patients except one started antihypertensive treatment, 103 (82%) patients predominately with ACE inhibitors, and 21 (17%) with other antihypertensive agents. Patients were classified as taking ACE inhibitors if this class of antihypertensive agents were prescribed before or during the individual follow-up time. During the entire follow-up period, we strived to keep blood pressure below 140/90 mm Hg. Fourteen percent of the patients received monotherapy, 44% received two agents, 35% received three agents, and 7% were treated with four or more antihypertensive drugs.

All patients took at least two daily injections of insulin and had a diabetic diet containing 45% to 55% carbohydrates, 30% to 35% fat, and 15% to 20% protein. No sodium or protein restrictions were applied during the study. Lipid-lowering treatment and aspirin were used as secondary prevention in patients with concomitantly cardiovascular disease.

## Procedures

GFR was measured after a single intravenous injection of 3.7 mBq $^{51}$chromium-ethylenediaminetetraacetic acid ($^{51}$Cr-EDTA) by determination of the radioactivity in venous blood samples taken 180, 200, 220, and 240 minutes after the injection [12]. The mean variability in GFR of each patient from day to day was 4%. Results are standardized to 1.73 $m^2$ body surface. Number of GFR measurements ranged from 3 to 41 (median 12) in each patient, and follow-up from 3 to 24.9 years (median 12.4) [10]. All patients visited the outpatient clinic every 3 to 4 months during the study. Blood glucose concentration, glycosylated hemoglobin $A_{1c}$ ($Hb_{1c}$), albuminuria, blood pressure, and body weight was monitored, and the insulin dose and antihypertensive treatment were adjusted.

Albuminuria was measured in 24-hour urine collections as well as in timed urine collections, obtained during the 4-hour clearance period [10]. Glycosylated $HbA_{1c}$ was measured from venous blood samples by isoelectric focusing and high-performance liquid chromatography (HPLC) [10]. The normal range was 4.1% to 6.4%. Serum cholesterol was measured with standard laboratory techniques. Arterial blood pressure was measured at each visit with a standard mercury sphygmomanometer and appropriate cuff size. The measurements were performed twice, on the right arm, after at least 10 minutes rest and averaged. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase V). Arterial hypertension was diagnosed according to the World Health Organization (WHO) criteria (≥160/95 mm Hg) until 1995 and thereafter according to the American Diabetes Association criteria (≥140/90 mm Hg) [13]. Retinopathy was assessed after pupillary dilatation by ophthalmoscopy. From 1991, evaluation was performed by fundus photography and graded nil, simplex, or proliferative diabetic retinopathy.

Date of death was recorded, and information on the cause of death obtained from death certificates. Follow-up ended December 31, 2003. All death certificates were reviewed independently by two observers and the primary cause of death recorded. If patients had entered renal replacement therapy, the cause of death was coded as ESRD independently of the causes given on the death certificate. Available additional information from necropsy reports was included.

## Statistical analysis

Results are expressed as means and standard deviation (SD) for descriptive information. Albuminuria is given as median (range) and was logarithmically transformed before analysis. Linear regression analysis, least squares method, was used to determine the slope of GFR for each patient. Two Cox proportional hazards regression analyses were performed: one with the combined end point of ESRD or death as end point, the other with death only as end point. A proportional hazards model with time since nephrotic range albuminuria as timescale was used. Fixed covariates in the analyses were gender, and age at onset of nephrotic range albuminuria. A model with glycosylated $HbA_{1c}$ included as fixed covariate was also performed in the patients where this parameter was measured at baseline. Remission of nephrotic range albuminuria was

**Table 1.** Baseline data in 125 type 1 diabetic patients with diabetic nephropathy at onset of nephrotic range albuminuria

| | At onset of nephrotic range albuminuria ($N = 125$) |
|---|---|
| Gender *male/female* | 90/35 |
| Height[a] *cm* | 173 ± 8 |
| Age at onset of nephrotic range albuminuria[a] *years* | 34 ± 8 |
| Age at onset of diabetes[a] *years* | 12 ± 8 |
| Retinopathy *simplex/proliferative* | 28/97 |
| Smoking *yes/no* | 68/57 |
| Glomerular filtration rate[a] *mL/min/1.73 m²* | 78 ± 24 |
| Systolic blood pressure[a] *mm Hg* | 145 ± 15 |
| Diastolic blood pressure[a] *mm Hg* | 89 ± 8 |
| Mean arterial blood pressure[a] *mm Hg* | 108 ± 9 |
| Albuminuria[b] *mg/24 hours* | 2647 (515–7448) |
| Glycosylated hemoglobin $A_{1c}$[a] % | 9.3 ± 1.4 |
| Serum cholesterol[a] *mmol/L* | 6.4 ± 1.5 |

Mean of values during the first year after onset of nephrotic range albuminuria are given. Consequently, some patients with previously persistent nephrotic range albuminuria receiving antihypertensive treatment had baseline albuminuria below 2500 mg/24 hours.
[a]Mean ± SD; [b]Median (range).

**Table 2.** Baseline data and treatment during follow-up in 125 type 1 diabetic patients with diabetic nephropathy and nephrotic range albuminuria divided in those subsequently obtaining remission or not obtaining remission

| | Remission group ($N = 32$) | No remission group ($N = 93$) | $P$ value |
|---|---|---|---|
| Baseline data | | | |
| Gender *male/female* | 18/14 | 72/21† | <0.05 |
| Body mass index[a] *kg/m²* | 24.4 ± 2.8 | 23.7 ± 3.1 | NS |
| Age at onset of nephrotic range albuminuria[a] *years* | 33 ± 7 | 35 ± 9 | NS |
| Smoking *yes/no* | 15/17 | 53/40 | NS |
| History of ischemic heart disease *yes/no* | 0/32 | 6/87 | NS |
| History of stroke *yes/no* | 0/32 | 5/88 | NS |
| Glomerular filtration rate[a] *mL/min/1.73 m²* | 81 ± 25 | 78 ± 23 | NS |
| Systolic blood pressure[a] *mm Hg* | 144 ± 12 | 146 ± 16 | NS |
| Diastolic blood pressure[a] *mm Hg* | 90 ± 8 | 89 ± 8 | NS |
| Albuminuria[b] *mg/24 hours* | 2577 (515–4800) | 2677 (893–7448) | NS |
| Glycosylated hemoglobin $A_{1c}$[a] % | 9.0 ± 1.6 | 9.4 ± 1.3 | NS |
| Serum cholesterol[a] *mmol/L* | 6.4 ± 1.8 | 6.3 ± 1.3 | NS |
| Treatment during follow-up | | | |
| Mean number of antihypertensive agents[a] | 2.5 | 2.3 | NS |
| Antihypertensive treatment (nil/non-ACEinhibitors/ ACE inhibitors) | 0/7/25 | 1/14/78 | NS |
| Diuretics *yes/no* | 26/32 | 71/22 | NS |
| Lipid-lowering treatment *yes/no* | 6/26 | 17/76 | NS |
| Total follow-up time[b] *years* | 14.6 (7.2–24.9) | 11.2 (3.0–24.9) | <0.05 |

ACE is angiotensin-converting enzyme. Baseline values are mean of values during the first year after onset of nephrotic range albuminuria. Consequently, some patients with previously persistent nephrotic range albuminuria receiving antihypertensive treatment had baseline albuminuria below 2500 mg/24 hours.
[a]Mean ± SD; [b]Median (range).

entered as time-dependent covariate with value 0 up to the time of remission, and after that a value of 1. Delayed entry was used due to the inclusion criterion of annual GFR measurement for at least 3 years. Cox proportional hazards regression analysis was performed by the freely available software R (*http://www.ci.tuwien.ac.at/R*).

## RESULTS

We analyzed data from 125 patients (90 men and 35 women) with a median follow-up time of 12.4 (3.0 to 24.9) years from onset of nephrotic range albuminuria. Baseline data for all 125 patients are shown in Table 1. Clinical and laboratory data at baseline are calculated as mean of values during the first year after onset of nephrotic range albuminuria. Risk factors for cardiovascular disease at baseline, grouped by patients subsequently obtaining or not obtaining remission of nephrotic range albuminuria, are shown in Table 2.

Clinical and laboratory data during follow-up are presented in details elsewhere [10]. Arterial blood pressure and serum cholesterol was lower in the patients obtaining remission, while no difference was demonstrated in glycemic control during follow up, measured as $HbA_{1c}$, between groups. Per definition, albuminuria was significantly lower in the remission group. The present analysis confirms previous findings, as patients obtaining remission had a significantly lower rate of decline in GFR during the entire follow-up period as compared to patients not obtaining remission (3.2 mL/min/year vs. 7.4 mL/min/year, $P < 0.001$).

Remission was induced in 32 patients (26%), and lasted 5.5 (1.0 to 22.4) years. Of these 32 patients, 25 patients were treated with ACE inhibitors, and seven patients with non-ACE inhibitors. The occurrence of remission was 24% (95% CI 16 to 32) in all patients treated with ACE inhibitors versus 33% (95% CI 13 to 53) in the non-ACE inhibitor–treated patients, NS. There was no difference in the use of diuretics (81% in the remission group versus 76% in the no remission group, NS). During follow-up, similar numbers of antihypertensive agents was used in patients obtaining or not obtaining remission, NS. The proportion of patients treated with lipid-lowering drugs, predominately statins, was 19% in the remission group and 18% in the no remission group, NS.

During the 12.4 years of follow-up, four patients progressed to ESRD and four died in the remission group (25% of the patients in the remission group reached the composite end point), whereas 31 patients progressed to ESRD and 38 died in the no remission group (74% of the patients in the no remission group reached the composite end point). In the remission group, one patient died after initiation of renal replacement therapy, resulting in a total of five deceased patients in this group (two due to

**Table 3.** Cox proportional hazard regression analysis of the impact of remission of nephrotic range albuminuria on the composite end point of end-stage renal disease (ESRD) or death in 125 type 1 diabetic patients with diabetic nephropathy

| | | Remission | |
|---|---|---|---|
| | Total | Yes | No |
| Number of patients | 125 | 32 | 93 |
| Number of events | 77 | 8 | 69 |
| Follow-up time *years* | 8.7 | 8.1 | 8.9 |
| Cox model | | | |
| Outcome | ESRD or death | | |
| Time scale | Time since nephrotic range albuminuria | | |
| Entry | 2.5 years after nephrotic range albuminuria | | |
| Estimates | | Relative risk (95% CI) | *P* value |
| Fixed covariates | | | |
| Gender (female vs. male) | | 0.92 (0.53 to 1.57) | 0.740 |
| Age at entry (per 10 years) | | 1.42 (1.08 to 1.87) | 0.011 |
| Time-dependent covariate | | | |
| Obtained remission | | 0.28 (0.13 to 0.59) | 0.001 |

**Table 4.** Cox proportional hazard regression analysis of the impact of remission of nephrotic range albuminuria on mortality in 125 type 1 diabetic patients with diabetic nephropathy

| | | Remission | |
|---|---|---|---|
| | Total | Yes | No |
| Number of patients | 125 | 32 | 93 |
| Number of events | 50 | 5 | 45 |
| Follow-up time *years* | 10.2 | 8.3 | 10.8 |
| Cox model | | | |
| Outcome | Death | | |
| Time scale | Time since nephrotic range albuminuria | | |
| Entry | 2.5 years after nephrotic range albuminuria | | |
| Estimates | | Relative risk (95% CI) | *P* value |
| Fixed covariates | | | |
| Gender (female vs. male) | | 0.93 (0.48 to 1.80) | 0.830 |
| Age at entry (per 10 years) | | 1.60 (1.14 to 2.23) | 0.006 |
| Time-dependent covariate | | | |
| Obtained remission | | 0.37 (0.14 to 0.94) | 0.036 |

cardiovascular disease, two died of infections, while one died of unknown cause). In the no remission group, seven patients died after commencement of renal replacement therapy. The main cause of death was cardiovascular disease, accounting for 64% of deaths in this group. Twenty-five patients died from acute myocardial infarction or ischemic heart disease and four died of cerebrovascular disease.

The estimates of the Cox proportional hazard regression analysis for both the combined end point of death and ESRD, and for death alone are given in Tables 3 and 4. The effect of gender is nonsignificant, but does not exclude substantial differences between the genders. Age has a substantial effect, as rates increases about 50% per 10 years. The effect of remission of nephrotic range albuminuria is strong, with a reduction of both ESRD and mortality by some 60%. The confidence limits are such that the minimally tenable reduction is 40% (upper 95% confidence limit for relative risk is 0.59).

Glycosylated $HbA_{1c}$ at baseline was only determined in a subset of the patients (97 of the 125 patients), since this method was not available in the remaining patients at baseline examnation. A sub-analysis, including glycosylated $HbA_{1c}$ as fixed covariate, was performed (Table 5). The effect of glycosylated $HbA_{1c}$ on the combined end point as well as death only is statistically significant. The estimated effect of remission is essentially unaffected after glycosylated $HbA_{1c}$ inclusion in analysis as compared with analysis performed in all 125 patients without glycosylated $HbA_{1c}$. However the reduced number of patients in this sub analysis makes the confidence limits wider (Table 5).

## DISCUSSION

Our prospective observational study demonstrates long lasting remission of nephrotic range albuminuria, obtained by aggressive antihypertensive therapy with and without ACE inhibitors, is associated with a significantly slower progression of diabetic nephropathy, and a substantially reduction in patients progressing to ESRD or death during the 12 years of follow-up.

Originally, Watkins et al [7] performed a follow-up study in proteinuric type 1 diabetic patients and reported that patients with proteinuria above 3000 mg per 24 hours all died after 2 to 6 years of follow-up, thus identifying a subset of patients with a very poor prognosis. In a retrospective study, Kussman, Goldstein, and Gleason [9] demonstrated diabetic kidney disease to be a chronic, progressive and irreversible disease with an accelerated loss in kidney function in the later stages of the disease. Furthermore, it has been demonstrated that patients with nephrotic range albuminuria have the fastest decline in GFR and more advanced structural changes as compared to patients with non-nephrotic range albuminuria [8]. In an observational study of 301 type 1 diabetic patients, we have previously demonstrated that patients with the highest levels of albuminuria have the fastest decline in GFR [14]. Thus, a subset of diabetic patients with diabetic nephropathy with a particular poor prognosis can be identified by the level of albuminuria. Long-term remission of nephrotic range proteinuria was originally demonstrated by Wilmer et al [15], where antihypertensive treatment induced remission in a small subset (6 of 103 patients) of type 1 diabetic patients with diabetic nephropathy and nephrotic range proteinuria. We confirmed and extended these findings by demonstrating that patients obtaining remission of nephrotic range albuminuria have a significantly lower decline in GFR as compared to patients not obtaining remission.

Albuminuria is a clinical marker of kidney damage, and reduction in albuminuria is used as a surrogate parameter for renoprotection in clinical trials, with the exception of remission of massive proteinuria (i.e., nephrotic

**Table 5.** Cox proportional hazard model, including glycosylated hemoglobin $A_{1c}$ in the subanalysis of the impact of remission of nephrotic range albuminuria on death or end-stage renal disease (ESRD), or mortality alone, in 97 type 1 diabetic patients with diabetic nephropathy

| | ESRD or death | | Death alone | |
|---|---|---|---|---|
| Cox model | | | | |
| Outcome | ESRD or death | | Death | |
| Time scale | Time since nephrotic range albuminuria | | Time since nephrotic range albuminuria | |
| Entry | 2.5 years after nephrotic range albuminuria | | 2.5 years after nephrotic range albuminuria | |
| Estimates | Relative risk (95% CI) | *P* value | Relative risk (95% CI) | *P* value |
| Fixed covariates | | | | |
| Gender (female vs. male) | 0.72 (0.36 to 1.46) | 0.370 | 0.89 (0.38 to 2.09) | 0.790 |
| Age at entry (per 10 years) | 1.34 (0.99 to 1.82) | 0.061 | 1.50 (1.02 to 2.20) | 0.039 |
| Glycosylated hemoglobin $A_{1c}$ | 1.32 (1.11 to 1.57) | 0.002 | 1.40 (1.13 to 1.72) | 0.002 |
| Time-dependent covariate | | | | |
| Obtained remission | 0.28 (0.10 to 0.78) | 0.016 | 0.40 (0.12 to 1.33) | 0.130 |

syndrome), which may be used as a principal end point [16]. Development of persistent proteinuria is a major life-threatening complication in patients with type 1 diabetes [17], and in that perspective even the rate of decline in GFR may be regarded as a surrogate end point as opposed to ESRD and mortality. In the RENAAL Study in type 2 diabetes, the baseline levels as well as the initial reduction in proteinuria has been demonstrated to be a strong predictor of ESRD and cardiovascular morbidity [18]. Every 50% reduction in proteinuria within the first 6 months halved the risk for cardiovascular end points and heart failure during follow-up [18]. However, no studies in type 1 diabetic patients have so far evaluated the impact of remission of nephrotic range albuminuria on the hard end points, ESRD and mortality. In the present study, we demonstrate for the first time that remission from nephrotic range albuminuria is associated with a reduction in patients progressing to ESRD, and a substantially improved survival in type 1 diabetic patients with diabetic nephropathy.

In a prospective observational study including 939 type 1 diabetic patients followed for 10 years, glycemic control was found to be an independent predictor of all-cause mortality with a relative risk of 1.11 (95% CI 1.03 to 1.20) [19]. Our study confirm and extend this observation, as glycemic control was found to be associated with the combined end point of death or ESRD as well as mortality alone in the subset of patients with the poorest prognosis (i.e., patients with nephrotic range albuminuria). Development of overt diabetic nephropathy has for many years been regarded as "a point of no return" in relation to glycemic control and progression of diabetic kidney disease. However, successful pancreatic transplantation resulting in normoglycemia for 10 years induced reversal of established diabetic glomerular lesions in type 1 diabetic patients. In summary, to improve the prognosis in patients with diabetic nephropathy the available data suggest that improved glycemic control is of importance, and implies vigorous efforts to normalize hyperglycemia.

In epidemiologic studies dealing with the natural history of diabetic nephropathy, the median survival time after onset of persistent proteinuria has been reported to be from 5 to 10 years [22–24]. After aggressive antihypertensive treatment has been introduced in patients with diabetic nephropathy, the median survival time now exceeds 16 years in these patients [25]. Although the relative cardiovascular mortality in proteinuric type 1 diabetic patients is 37-fold that in the general population [5], uremia has been the main cause of death in the earlier studies performed before [22–24] as well as after [25] the use of antihypertensive treatment was generally established in patients with diabetic nephropathy. In the subset of patients with nephrotic range albuminuria, well known to have a high risk of progressing to ESRD, we report that even though uremia still is the main cause of progressing to the composite end point, cardiovascular disease has become increasingly more prevalent. Thus, suggesting that the improved kidney prognosis reveals a new great challenge in these patients: prevention, early detection, and treatment of cardiovascular disease.

In the present study, approximately one out five patient obtained remission, and may be therefore be regarded as responders. Identifying factors with impact on a beneficial response is not only of academic interest, since identification of such factors would have huge impact on the treatment and prognosis in patients. Classical and established risk factors for progression of diabetic kidney disease (i.e., arterial blood pressure, albuminuria, $HbA_{1c}$, and lipids), measured at onset of nephrotic range albuminuria were similar at onset of nephrotic range albuminuria in responders and nonresponders [10], thus other determinants of remission must be taken in to consideration. As previously discussed, variation in dietary salt intake and activity of the renin-angiotensin system could contribute to the difference between responders and nonresponders [10]. Furthermore, in observational studies such as ours the compliance concerning adherence to prolonged antihypertensive treatment are not assessed directly, although the number of antihypertensive

agents prescribed in responders and nonresponders was similar in our study. Patient compliance with drug therapy has been recognized as one of the major reasons why antihypertensive therapy fails in the United States and elsewhere [26], and subsequently noncompliers may be misclassified as nonresponders. The use of several antihypertensive agents in order to control blood pressure may reduce compliance even further. Poor adherence to antihypertensive treatment can be observed in patients with uncontrolled hypertension as well as in well controlled blood pressure [27], which may imply that even at the same blood pressure level, nonadherence to ACE inhibitor therapy will render the patients without the nonhemodynamic beneficial effects of these compounds [28, 29].

Although many non genetic factors may influence the effects of medications, there is now growing evidence for genetic factors being responsible for individual response to therapy. Exner et al [30] demonstrated differences in response to ACE inhibitor treatment between black and white patients with left ventricular dysfunction. However, racial categorization is only a surrogate marker for different inherited determinants of drug response. There are now examples of cases in which interindividual differences in drug response are due to sequence variants in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets as reviewed by Evans and McLeod [31]. It is estimated that genetics can account for 20% to 95% of variability in drug deposition and effects [32]. Unfortunately, DNA for genotyping was only available in a subset of the investigated patients. However in the future, genetic factors of importance for the progression of diabetic nephropathy could possibly differentiate between the responders and nonresponders.

## CONCLUSION

Our prospective study demonstrates that remission of nephrotic range albuminuria, induced by antihypertensive treatment with and without ACE inhibitors, is associated with a slower progression in diabetic nephropathy and a substantially improved survival in type 1 diabetic patients with diabetic nephropathy. The improved kidney prognosis with longer survival free of ESRD reveals the urgent need for targeting early prevention, detection, and treatment of cardiovascular disease. The beneficial results observed in our study were obtained despite the fact that only a minority of patients received statins and low dose aspirin, and more than 50% were smokers. At present time, we at the Steno Diabetes Center have changed the treatment strategy to include statins and low dose aspirin in all our patients with albuminuria. Furthermore, an aggressive approach toward smoking cessation has been introduced.

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