Variations in Risk of End-Stage Renal Disease and Risk of Mortality in an International Study of Patients With Type 1 Diabetes and Advanced Nephropathy

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OBJECTIVE

Patients with type 1 diabetes and diabetic nephropathy are targets for intervention to reduce high risk of end-stage renal disease (ESRD) and deaths. This study compares risks of these outcomes in four international cohorts.

RESEARCH DESIGN AND METHODS

In the 1990s and early 2000s, Caucasian patients with type 1 diabetes with persistent macroalbuminuria in chronic kidney disease stages 1–3 were identified in the Joslin Clinic (U.S., 432), Finnish Diabetic Nephropathy Study (FinnDiane) (Finland, 486), Steno Diabetes Center Copenhagen (Denmark, 368), and INSERM (France, 232) and were followed for 3–18 years with annual creatinine measurements to ascertain ESRD and deaths unrelated to ESRD.

RESULTS

During 15,685 patient-years, 505 ESRD cases (rate 32/1,000 patient-years) and 228 deaths unrelated to ESRD (rate 14/1,000 patient-years) occurred. Risk of ESRD was associated with male sex; younger age; lower estimated glomerular filtration rate (eGFR); higher albumin/creatinine ratio, HbA_{1c}, and systolic blood pressure; and smoking. Risk of death unrelated to ESRD was associated with older age, smoking, and higher baseline eGFR. In adjusted analysis, ESRD risk was highest in Joslin versus reference FinnDiane (hazard ratio [HR] 1.44, $P = 0.003$) and lowest in Steno (HR 0.54, $P < 0.001$). Differences in eGFR slopes paralleled risk of ESRD. Mortality unrelated to ESRD was lowest in Joslin (HR 0.68, $P = 0.003$ vs. the other cohorts). Competing risk did not explain international differences in the outcomes.

CONCLUSIONS

Despite almost universal renoprotective treatment, progression to ESRD and mortality in patients with type 1 diabetes with advanced nephropathy are still very high and differ among countries. Finding causes of these differences may help reduce risk of these outcomes.

Patients with type 1 diabetes with advanced diabetic nephropathy defined as macroalbuminuria are at high risk of end-stage renal disease (ESRD) and death (1–4). These patients are targets for aggressive interventions with both existing and new renoprotective therapies. Studies on the natural history of advanced diabetic

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nephropathy are limited. Some of these studies provide descriptive data about historical cohorts not subjected to current interventions and frequently consider only ESRD or total mortality, not distinguishing risk of ESRD from risk of deaths unrelated to ESRD (1–4). In more recent studies, lack of standardization regarding study design, risk factors, and definition of outcomes did not allow for comparisons among centers and countries (5–7).

Recent publications described an experience of specific inception cohorts (registries) of patients with type 1 diabetes and showed significant differences among countries (8–12). Those studies were nicely reviewed in a recent editorial (13). However, the studies did not allow the determination of probable causes of such differences. For example, could the differences be due to better primary prevention, mainly good glycemic control before patients developed diabetic nephropathy, secondary interventions in patients with diabetic nephropathy, differences in study designs, or distributions of risk factors? Or, finally, if all factors are considered and the differences persist, are they due to genetic or environmental factors?

The opportunity to answer the above questions with regard to patients with type 1 diabetes with advanced diabetic nephropathy subjected to the contemporary therapeutic protocols was provided by the recent JDRF Diabetic Nephropathy Collaborative Research Initiative (DNCRI). This study dissects the genetic architecture of diabetic nephropathy in type 1 diabetes. The subproject entitled "Genes determining time of onset of ESRD in type 1 diabetes" contributes to the DNCRI through studies of the genetics of time to ESRD and of rate of estimated glomerular filtration rate (eGFR) loss as a quantitative phenotype, rather than by the traditional case-control study design. For the subproject, participants were assembled from 3–18 years of follow-up studies of cohorts of patients with type 1 diabetes and proteinuria from Finland (Finnish Diabetic Nephropathy Study [FinnDiane]), U.S. (Joslin Diabetes Center), Denmark (Steno Diabetes Center Copenhagen), and France/Belgium (Institut National de la Santé et de la Recherche Médicale [INSERM]). In this report, we compare the natural history of advanced diabetic nephropathy in type 1 diabetes among these four cohorts by comparing distributions of eGFR slopes and risk of ESRD and mortality unrelated to ESRD, controlling for different distributions of risk factors.

RESEARCH DESIGN AND METHODS

The study protocols and informed consent procedures for recruitment, examination, and follow-up of the study participants were concordant with the Declaration of Helsinki and were approved by the relevant institutional review boards or bioethics committees.

Patients and Eligibility Criteria

All cohorts were ascertained for the purpose of follow-up studies to investigate the natural history of diabetic nephropathy in type 1 diabetes, including characterizing standard and novel biomarkers and the role of genetic factors of renal decline (5–7,14–21). Enrollment and baseline examinations took place through the 1990s and early 2000s, with follow-up through 2013. We included individuals with baseline eGFR $\geq$30 mL/min/1.73 m^2 who were alive within 1 year of follow-up and had at least a 42-month follow-up if free from ESRD.

Joslin Proteinuria Cohort

A total of 3,500 adult individuals with type 1 diabetes remain under the care of Joslin Clinic, an institution established in 1898 and devoted to treatment of diabetes (6). The majority come to the clinic within the first 5 years of diabetes diagnosis, and they remain under care for a long period of time, frequently for life (14,15). Between 1991 and 2004, we monitored the occurrence of persistent macroalbuminuria, and patients with established type 1 diabetes diagnosis in medical records, residence in New England, and age at enrollment between 21 and 54 years were approached by trained recruiters. Between 1991 and 2004, out of 784 patients, 432 consented for participation and met eligibility criteria for the current study. Enrolled participants were followed until 2013, with the goal of obtaining blood and urine specimens at least every 2 years. Collection of research specimens occurred during routine clinic visits. Patients with less frequent clinic visits or those who stopped coming to the clinic were examined at their homes.

FinnDiane Proteinuria Cohort

FinnDiane was initiated in 1997 with the aim of studying clinical, biochemical, environmental, and genetic risk factors for diabetes complications in patients with type 1 diabetes (16). Prior to that, a pilot study was conducted between 1994 and 1997. The FinnDiane is a nationwide prospective multicenter study including 93 centers in Finland. All university hospitals (n = 5), all central hospitals (n = 16), all district hospitals that treat patients with type 1 diabetes (n = 28), and the largest health care centers (n = 44) are involved. Adult patients (aged >18 years) with type 1 diabetes defined based on age at onset of diabetes <40 years and insulin treatment initiated within 1 year of diagnosis were asked to participate in the study. Although the study is not by definition a population-based study, the patient distribution follows that of the general Finnish population.

So far, more than 5,000 patients have participated in the FinnDiane study. Patients were initially studied between 1994 and 2013 and were thereafter followed either by prospective FinnDiane visits at the local centers or by following them through medical files and registries. Follow-up data, including serial measurements of serum creatinine, were available for 630 out of 898 patients with

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macroalbuminuria (7,17), and 486 met further eligibility criteria.

Steno Proteinuria Cohort

Steno Diabetes Center Copenhagen is a tertiary highly specialized diabetes center in the Capital Region of Denmark. The patients included in the cohort are participants in the previously described study of patients with type 1 diabetes and diabetic nephropathy and a matched control group with long duration of diabetes (18). This cohort was supplemented with patients included up to 2009 according to the same protocol.

From 1993 to 2009, adult Caucasian (self-declared) patients with type 1 diabetes and diabetic nephropathy attending the outpatient clinic at Steno Diabetes Center Copenhagen were invited to participate in a study of genetic risk factors for the development of diabetes complications. Type 1 diabetes was considered present if age at onset of diabetes was <35 years and time to definite insulin therapy was <1 year. In total, 540 patients with persistent macroalbuminuria, the presence of diabetic retinopathy, and the absence of other kidney or urinary tract disease were enrolled. Eligibility criteria of the current study were met by 368 patients.

INSERM Proteinuria Cohort

The cohort details were recently published (21). Briefly, individuals of Europid ethnicity (based on genetic identification) were recruited on the occasion of the GENEDIAB (Genétique de la Nephropathie Diabétique) and GENESIS (Genetics Nephropathy and Sib Pair Study) studies (19,20). In addition, consecutive nonduplicate patients in enrollment centers in Corbeil-Essonnes, Nantes, Paris Saint-Louis, Poitiers, and Toulouse were recruited (21). Inclusion criteria for the GENEDIAB study included severe diabetic retinopathy (proliferative or severe nonproliferative requiring panphotocoagulation), while patients with retinopathy and diabetes duration >15 years were eligible for the GENESIS study. Type 1 diabetes was defined as the age of onset <35 years (GENESIS and GENEDIAB) or <40 years (other centers) and a definitive requirement for insulin treatment <1 year following diagnosis. Ascertainment of study participants was all hospital based. There were 232 patients meeting eligibility criteria for the current study.

The comparison of the ascertainment of the four cohorts is shown in Table 1. In total, 2,678 patients with macroalbuminuria and an additional 523 with prevalent ESRD had available DNA samples and were initially recruited in the JDRF DNCRI project. For the current study, 1,518 Caucasian participants from the four cohorts met the inclusion criteria.

Assessment of Abnormalities in Urinary Albumin Excretion

In the Joslin Clinic laboratory, albumin concentrations were measured with immunonephelometry in spot urines at least once a year. Creatinine measurements in urine were assayed by the Jaffe modified picrate method to calculate albumin/creatinine ratio. (The persistent macroalbuminuria status was established if at least two out of three measurements collected during a 2-year interval preceding study enrollment were >300 mg/g (6). In FinnDiane, macroalbuminuria was defined as urinary albumin excretion rate (AER) ≥200 μg/min or ≥300 mg/24 h or an ACR ≥25 mg/mmol in men and ACR ≥35 mg/mmol in women in at least two out of three overnight, 24-h urine collections (AER) or first morning void urine samples (ACR). Persistent macroalbuminuria was established if at least two out of three consecutive urine collections were within the macroalbuminuria range (7). In Steno Diabetes Center Copenhagen, urinary AER was measured at least once per year by an enzyme immunoassay in 24-h urine collections. In addition, urinary ACRs were also available. AER >300 mg/24 h in at least two out of three consecutive measurements was considered persistent macroalbuminuria. Arbitrarily, the date for fulfilling the persistent macroalbuminuria criterion was set as the date of the second sample within the range of macroalbuminuria. In the GENESIS and GENEDIAB cohorts, baseline urinary albumin concentration was centrally determined using immunonephelometry, while the patients recruited through five hospital centers had their AER determined locally. To determine persistent macroalbuminuria, at least two out of three consecutive AER measurements in sterile urine collections had to fall in the range of macroalbuminuria (>300 mg/24 h). ACR was not available in all study patients.

Assessment of Renal Function

In Joslin Clinic, Steno Diabetes Center Copenhagen (until 2004), and FinnDiane (at the central laboratory of the Helsinki University Central Hospital until January 2002), serum creatinine was measured with the Jaffe modified picrate method

Table 1—Patients enrolled in the four type 1 diabetes cohorts with macroalbuminuria or prevalent ESRD and numbers of eligible patients in the current study

	Participating center				
	Joslin	FinnDiane	Steno	INSERM	Total
Years of recruitment*	1993–2002	1998–2001	1993–1999	1993–1998	
Number of patients recruited	784	898	540	456	2,678
Number of eligible patients in CKD stages 1–3¶	432 (199)†	486 (253)†	368 (182)†	232 (99)†	1,518 (733)†
Number of patients in CKD stages 4–5	69 (68)†	66 (63)†	32 (31)†	71 (61)†	238 (223)†
Number of noneligible patients	283	346	140	153	922
Number of patients with prevalent ESRD	220	268	35	0	523

*Years of recruitment indicate calendar years during which 25th and 75th percentiles of the patients were enrolled into the follow-up study. ¶Patients were eligible for the study if they *1*) had type 1 diabetes, had persistent macroalbuminuria at baseline, and had at least a 42-month follow-up time with eGFR determinations; *2*) had type 1 diabetes, had persistent macroalbuminuria at baseline, and developed ESRD during follow-up; *3*) had type 1 diabetes, had persistent macroalbuminuria at baseline, and had at least a 12-month follow-up time before death unrelated to ESRD. †Data in parentheses show the number of patients who progressed to ESRD or died due to causes unrelated to ESRD during follow-up.

and with an enzymatic method thereafter. In the FinnDiane study, most serum creatinine determinations came from local hospital laboratories. In 2010 in FinnDiane and in 2011–2014 in Joslin, a subset of serum specimens were reassayed in the Advanced Research and Diagnostic Laboratory at the University of Minnesota using the Roche enzymatic assay (product no. 11775685) on a Roche/Hitache Mod P analyzer. This method has been calibrated to be traceable to an isotope dilution mass spectrometry (IDMS) reference assay and was verified by measuring National Institute of Standards and Technology Standard Reference Material (NIST SRM) no. 967. These duplicate measurements were used to calibrate the clinical measurements (22). In Steno, the measurements performed with the Jaffe method were transformed to an IDMS traceable standard, as described previously (23). Baseline samples from patients in the GENEDIAB and GENESIS cohorts were assayed centrally for serum creatinine, while the measurements were performed locally in the five recruiting centers. During follow-up, serum creatinine was measured using colorimetric methods with different appliances according to the local practice. In all cohorts, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to estimate eGFR (24). Only serum creatinine determinations prior to ESRD diagnosis were taken into account in the analysis of eGFR trajectories.

Ascertainment of Onset of ESRD and Mortality Unrelated to ESRD

All patients from the Joslin cohort were queried against rosters of the United States Renal Data System and the National Death Index covering all events up to the end of 2013. In the FinnDiane cohort, data regarding onset of ESRD were obtained from the Care Register for Health Care (HILMO) in Finland and were then verified using patients' medical files. No patients in the FinnDiane study received a preemptive kidney transplantation without prior dialysis. Data on mortality and causes of death were retrieved from Statistics Finland and were confirmed using death certificates. Both queries covered all events up to the end of 2013 (17). In Steno Diabetes Center Copenhagen, information about ESRD was obtained from patient records or discharge letters from other hospitals. The Danish Register of Causes of Death provided information on deaths. In the INSERM cohort, hospital records were analyzed for identification of the presence and date of onset of ESRD or death, and, in cases of missing data, general practitioners were interviewed by telephone. The national death certificate registry was consulted when no data were available.

The onset of ESRD was given as the date of first dialysis or transplantation or the date of death for those captured by death certificate. In all cohorts, if ESRD did not develop and death was ascertained, the outcome was defined as "death unrelated to ESRD."

Clinical Characteristics at Baseline Examination

All patients enrolled into the study had a standardized examination performed at baseline. This examination included an interview regarding past history of type 1 diabetes, its complications and history of treatment (specifically with renoprotective and antihypertensive drugs), and presence of standard risk factors, such as smoking history. In addition, patients had standardized measurements of blood pressure, height, and weight and measurements of HbA_{1c} (performed locally with high-performance liquid chromatography and Diabetes Control and Complications Trial–adjusted) and serum lipids (lipids were not available for all INSERM patients).

Statistical Analysis

Continuous variables were summarized as medians and quartiles while categorical variables were presented as counts, proportions, and percentages. Incidence rates of ESRD and mortality rates due to deaths unrelated to ESRD were used to describe the follow-up results in each cohort. The cumulative incidence function of ESRD and cumulative incidence of mortality unrelated to ESRD were determined accounting for competing risks. To adjust for baseline differences in covariates within the framework of competing risks, multivariate Fine and Gray proportional subhazards survival regression models were used, with ESRD and deaths unrelated to ESRD as competing events (25). Deviations from proportionality of hazards were tested with interaction terms of tertiles of follow-up time (not statistically significant, $P > 0.05$). To account for informative censoring of follow-up time in patients with rapid eGFR loss, a joint longitudinal-survival model was used to describe renal function decline (26,27). Both the eGFR time-series data and times to ESRD or censoring were used to obtain estimates of mean rates of renal (eGFR) decline in the cohorts, an approach that is robust with regard to heterogeneity of baseline renal function (eGFR) at enrollment and variable duration of follow-up (27). Statistical significance was set at a $P < 0.05$. Analyses were performed in SAS for Windows, version 9.3 (SAS Institute, Cary, NC) and R software version 3.3.1 with 'cmprsk' package (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the Study Cohorts

There were 1,518 eligible patients with type 1 diabetes with persistent macroalbuminuria and in chronic kidney disease (CKD) stages 1–3 enrolled from Joslin, FinnDiane, Steno, and INSERM to the follow-up study on natural history of advanced diabetic nephropathy. Baseline characteristics of these patients according to study cohort are presented in Table 2. Patients for two cohorts, Joslin and Steno, were ascertained at single specialty clinics with a long tradition of providing long-term care for patients with diabetes. In contrast, FinnDiane enrolled patients who remained under care of multiple local clinics nationwide. A large number of subjects in INSERM were patients initially enrolled in the GENEDIAB and GENESIS projects in 38 diabetes or nephrology clinics in France and Belgium.

The cohorts did not differ with respect to male and female proportions and serum cholesterol level. There were statistically significant but clinically small differences in age at enrollment and age at diagnosis of type 1 diabetes. Joslin cohort subjects had shorter diabetes duration before study enrollment, higher baseline eGFR, and lower systolic blood pressure. Blood pressure control was good (median systolic 130–140 mmHg) across the cohorts, while glycemic control was largely inadequate (median HbA_{1c} ranging from 8.7% or 72 mmol/mol in the INSERM to 9.2% or 77 mmol/mol in the Steno cohort).

Table 2—Baseline characteristics of the four study cohorts of patients with type 1 diabetes with persistent macroalbuminuria in CKD stages 1–3 at baseline

Characteristic	Joslin cohort (*n* = 432)	FinnDiane cohort (*n* = 486)	Steno cohort (*n* = 368)	INSERM cohort (*n* = 232)	*P* value
Men (%)	57.2	60.3	61.1	59.9	0.68
Age (years)	37 (32, 43)	39 (32, 48)	40 (33, 48)	41 (32, 50)	<0.001
Age at diabetes diagnosis (years)	12 (8, 20)	10 (7, 15)	10 (7, 15)	13.5 (8.5, 21)	<0.001
Duration of diabetes (years)	23 (17, 30)	27 (22, 31)	27 (22, 32.5)	26 (18.5, 33)	<0.001
Urinary ACR (mg/g)	718 (420, 1,337)	321 (122, 786)	581 (273, 1,489)		<0.001*
Urinary albumin (mg/L)				497 (181, 1,110)	
eGFR (mL/min/1.73 m^2)	88 (69, 109)	70 (49, 93)	75 (58, 96)	74 (56, 94)	<0.001
Systolic blood pressure (mmHg)	131 (120, 142)	141 (130, 155)	140.5 (127.5, 154.5)	140 (130, 155)	<0.001
Antihypertensive treatment (%)	74.8	94.8	81.5	82.3	<0.001
HbA_{1c}					
%	9.0 (7.9, 10.2)	8.8 (8.0, 10.0)	9.2 (8.2, 10.1)	8.7 (7.7, 9.8)	
mmol/mol	75 (63, 88)	73 (64, 86)	77 (66, 87)	72 (61, 84)	0.002
Total cholesterol (mmol/L)	5.3 (4.5, 6.1)	5.3 (4.7, 6.0)	5.5 (4.7, 6.2)		0.19*
Smoking status					
Never (%)	46.1	38.4		47.4	
Former (%)	29.9	29.0		16.4	<0.001*
Current (%)	24.0	32.6	44.0	36.2	<0.001†

Data are median (1st, 3rd) quartile unless otherwise indicated. The statistical tests compare medians across the four cohorts. *Comparison of three cohorts. †Comparison of current smoking prevalence between four cohorts.

The prevalence of renoprotective treatment, predominantly with ACE inhibitors or angiotensin receptor blockers, was very high, ranging from ~95% in FinnDiane to ~75% in the Joslin cohort.

By design, all patients had persistent macroalbuminuria, but the cohorts differed by extent of albuminuria, with lowest rate in FinnDiane (median 321 mg/g) and highest in the Joslin cohort (median 718 mg/g). Baseline albuminuria was below the threshold for macroalbuminuria in some patients, as at least two of three consecutive albumin measurements had to be in the macroalbuminuria range. In the INSERM cohort, ACR was unavailable so urinary albumin concentration was used for defining albuminuria. Current smoking prevalence was highest in the Steno (44%) and FinnDiane (36%) cohorts and lowest (26%) in the Joslin cohort.

Comparison of Risk of ESRD in Study Cohorts

There were 505 cases of ESRD in 1,518 patients followed for a total of 15,685 patient-years. This accounted for an overall incidence rate of ESRD 32.2 per 1,000 patient-years. The summary of events and follow-up time is shown for each cohort in Table 3. The median follow-up time in patients who remained alive ranged from 11–12 years in the FinnDiane, Joslin, and INSERM cohorts to ~16 years in the Steno cohort. The follow-up time was much shorter in patients who developed ESRD or died, with medians ranging from 6 to 9 years. Since the cohorts differed significantly by eGFR at baseline, the incidence rates in Table 3 are stratified by CKD stages. The relationship between CKD stage and incidence of ESRD was observed in every cohort. The highest incidence rate of ESRD in CKD stages 1 and 2 was in the Joslin cohort, while the highest incidence of ESRD in CKD stage 3 was in the FinnDiane cohort. With CKD stages combined,

Table 3—Analysis of incidence rates of ESRD and rates of mortality unrelated to ESRD in the four study cohorts

Characteristic	Joslin cohort	FinnDiane cohort	Steno cohort	INSERM cohort
No. of ESRD	159	186	99	61
No. of non-ESRD deaths	40	67	83	38
No. of alive without ESRD	233	233	186	133
Follow-up for ESRD and deaths in years	7.3 (5.0, 10.8)	8.6 (5.1, 11.5)	8.2 (5.5, 11.6)	6.5 (4.1, 12.6)
Follow-up for alive in years	10.7 (7.2, 14.7)	11.6 (7.2, 13.3)	15.8 (13.5, 18.5)	11.9 (7.2, 15.7)
Incidence rate of ESRD (per 1,000 patient-years)				
CKD 1	25.9	13.1	10.1	11.9
CKD 2	46.3	33.3	14.8	24.1
CKD 3	53.7	75.0	53.4	45.2
Rate of mortality unrelated to ESRD (per 1,000 patient-years)				
CKD 1	10.8	13.1	17.1	11.9
CKD 2	7.8	16.6	17.0	16.4
CKD 3	8.1	13.9	23.3	21.0

Follow-up times are presented as median (1st, 3rd quartile).

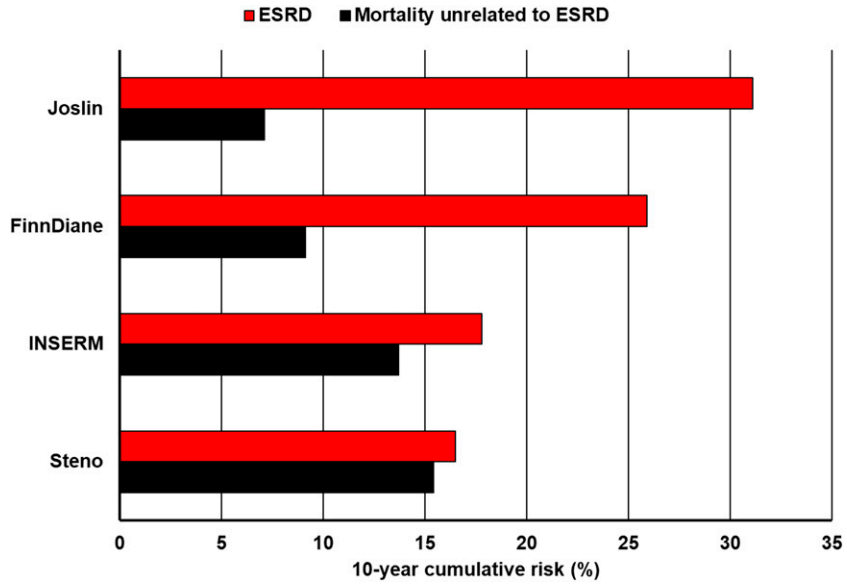

Figure 1—Comparison of cumulative risk of ESRD and mortality unrelated to ESRD after 10 years of follow-up among the four study cohorts ordered by decreasing risk of ESRD.

the incidence rates of ESRD were 37.2 per 1,000 patient-years in Joslin, 40.5 per 1,000 patient-years in FinnDiane, 22.0 per 1,000 patient-years in Steno, and 26.2 per 1,000 patient-years in INSERM. Cumulative incidence of ESRD among the study cohorts as of the 10th year of follow-up is shown in Fig. 1. It was 31.1% in Joslin, 25.9% in FinnDiane, 17.8% in INSERM, and 16.5% in Steno cohorts.

Comparison of Mortality Unrelated to ESRD

In the four cohorts, 228 deaths unrelated to ESRD occurred, which accounted for an overall rate of mortality unrelated to ESRD of 14.5 per 1,000 patient-years, two times lower than the incidence rate of ESRD. The majority of these deaths were due to cardiovascular causes. Mortality rates were not related to CKD stage (Table 3) but were different among cohorts. The nonstratified mortality rates were 9.4 per 1,000 patient-years in Joslin, 14.6 per 1,000 patient-years in FinnDiane, 18.5 per 1,000 patient-years in Steno, and 16.3 per 1,000 patient-years in INSERM. The cumulative incidence of deaths unrelated to ESRD is shown in Fig. 1. At 10 years they were 7.1% in the Joslin cohort, 9.1% in FinnDiane, 13.7% in INSERM, and 15.4% in Steno.

Competing Risk Regression for ESRD and Mortality Unrelated to ESRD

Table 4 presents the results from proportional subhazards models for the risk of ESRD (on the left) and mortality unrelated to ESRD (on the right). Risk factors associated with ESRD were lower baseline eGFR, higher baseline ACR, higher HbA_{1c} and systolic blood pressure, younger age at study entry (or shorter type 1 diabetes duration), and male sex. Risk factors for mortality were older age, smoking, and higher baseline eGFR.

The differences in ESRD risk among the study cohorts remained in the presence of covariates. ESRD risk was highest in the Joslin cohort, hazard ratio (HR) and 95% CI 1.44 (1.14, 1.84), while the risk was lowest in the Steno (HR 0.54, 95% CI 0.42, 0.69) and INSERM (HR 0.67, 95% CI 0.49, 0.92) in comparison with FinnDiane, the largest cohort, as the reference. After adjusting for covariates, no significant differences in mortality unrelated to ESRD were observed between the three European cohorts and the adjusted HRs with FinnDiane as reference were numerically small. For Steno it was 1.01 with 95% CI 0.73, 1.41 and for INSERM HR was 0.93, 95% CI 0.61, 1.42. In contrast, risk of deaths unrelated to ESRD in Joslin remained lower, with HR versus FinnDiane 0.67, 95% CI 0.44, 1.02, $P = 0.063$. In comparison with the three European cohorts, combined HR was 0.68, 95% CI 0.53, 0.87, $P = 0.003$.

Table 4—Proportional subhazards models for the risk of ESRD and for mortality unrelated to ESRD in the four study cohorts (FinnDiane as reference) adjusted for sex, age, baseline eGFR, HbA_{1c}, systolic blood pressure, and smoking status

	Risk of ESRD		Mortality unrelated to ESRD*	
Covariates	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male sex	1.37 (1.13, 1.68)	0.002	1.23 (0.92, 1.63)	0.17
Age (10-year increase)	0.66 (0.59, 0.74)	<0.001	2.12 (1.84, 2.44)	<0.001
Baseline eGFR (10 mL/min increase)	0.73 (0.70, 0.77)	<0.001	1.08 (1.02, 1.14)	0.008
HbA_{1c} (1% increase)	1.22 (1.15, 1.29)	<0.001	1.10 (1.00, 1.21)	0.059
Systolic blood pressure (10 mmHg increase)	1.14 (1.08, 1.20)	<0.001	0.99 (0.92, 1.06)	0.74
Current smoking	1.21 (1.00, 1.47)	0.048	1.78 (1.36, 2.33)	<0.001
Joslin vs. FinnDiane	1.44 (1.14, 1.84)	0.003	0.67 (0.44, 1.02)**	0.063**
Steno vs. FinnDiane	0.54 (0.42, 0.69)	<0.001	1.01 (0.73, 1.41)	0.94
INSERM vs. FinnDiane	0.67 (0.49, 0.92)	0.013	0.93 (0.61, 1.42)	0.74

Adjusting for serum cholesterol and ACR in cohorts with available data had a small impact on the differences in ESRD risk or mortality unrelated to ESRD between cohorts and did not influence statistical inferences. Adjusting for age at type 1 diabetes diagnosis or diabetes duration instead of age did not change the statistical inferences on the differences between the cohorts. *In Joslin, 69% of deaths were due to CVD. In FinnDiane, 55% of deaths were due to CVD. In Steno, 67% of deaths were due to CVD. In INSERM, causes of deaths were not available. **In comparison with three other cohorts HR 0.68, $P = 0.003$.

Table 5—Estimated mean slopes of renal decline expressed in mL/min/1.73 m^2/year in the four study cohorts with the crude and covariate-adjusted differences between them

		Differences between cohorts (relative to FinnDiane cohort)			
		Unadjusted		Covariate-adjusted	
Cohort	Unadjusted mean slope (95% CI)	Estimate	*P* value	Estimate	*P* value
FinnDiane (reference)	−4.0 (−4.4, −3.6)				
Joslin	−5.2 (−5.7, −4.8)	−1.2 (−1.8, 0.7)	<0.001	−1.0 (−1.6, −0.5)	<0.001
Steno	−3.3 (−3.7, −2.8)	0.7 (0.2, 1.3)	0.012	0.9 (0.3, 1.4)	0.002
INSERM	−4.1 (−4.6, −3.5)	−0.1 (−0.7, 0.6)	0.92	−0.2 (−0.8, 0.5)	0.57

Adjusted for sex, age, HbA_{1c}, systolic blood pressure, antihypertensive treatment, and smoking status. Further adjusting for serum cholesterol and ACR in cohorts with available data did not influence statistical inferences about the differences between the cohorts. Baseline eGFR is not included in the covariate set, as it is already present in joint model specification.

Comparison of Slopes of eGFR Loss Between Cohorts

Unadjusted estimates (with 95% CI) of mean rate of renal function (eGFR) decline in each cohort were −5.2 (−5.7, −4.8) mL/min/1.73 m^2/year (Joslin), −4.0 (−4.4, −3.6) mL/min/1.73 m^2/year (FinnDiane), −4.1 (−4.6, −3.5) mL/min/1.73 m^2/year (INSERM), and −3.3 (−3.7, −2.8) mL/min/1.73 m^2/year (Steno). Estimated differences between cohorts from joint longitudinal-survival model, which incorporates informative censoring of the eGFR data in patients with fast renal function decline, are provided in Table 5. After adjusting for covariates (sex, age, HbA_{1c}, systolic blood pressure, antihypertensive treatment, and current smoking), the differences between cohorts remained largely unchanged, with the steepest slopes observed in the Joslin cohort and negligible difference between the FinnDiane and INSERM cohorts, while slopes in the Steno cohort were significantly shallower. The adjusted differences from the reference (FinnDiane) were 1.0 (95% CI 0.5, 1.6) mL/min steeper in Joslin, 0.2 (95% CI −0.5, 0.8) mL/min steeper in INSERM, and 0.9 (95% C: 0.3, 1.4) mL/min shallower in the Steno cohort. Additional adjustment for ACR and serum cholesterol in a model with the INSERM cohort excluded (as no data were available) did not significantly change estimated differences in slopes.

CONCLUSIONS

In this international follow-up study of four large cohorts of patients with type 1 diabetes with macroalbuminuria, we examined differences among countries in the risk of progression to ESRD and mortality unrelated to ESRD. There are several major findings of our study. First, despite almost universal treatment with renoprotective drugs, ESRD risk is high and varied dramatically among the study cohorts: the Joslin cohort from New England, U.S., had the highest risk of ESRD, whereas the Steno Copenhagen cohort from Denmark had the lowest, and the other cohorts, FinnDiane and INSERM, had an intermediate ESRD risk. The second finding is related to our long-term follow-up with serial eGFR measurements. We were able to show that international differences in ESRD risk are very well reflected in differences in average slopes of renal decline many years before onset of ESRD. The third finding is that the pattern of ESRD risk was virtually reversed for mortality unrelated to ESRD, which was mainly due to cardiovascular disease (CVD) causes. The mortality was highest in the Steno cohort and lowest in the Joslin cohort. Both institutions are considered the world excellence centers for treatment of type 1 diabetes.

In contrast to recently expressed opinion (13), striking international differences in ESRD risk and mortality unrelated to ESRD could not be explained by so-called "competing risks." It was postulated that in populations with higher deaths unrelated to ESRD, patients with proteinuria and CKD 3 would die before developing ESRD, while lower mortality could allow more patients to progress from CKD stage 3 to ESRD. In our study, the differences among centers in deaths unrelated to ESRD occurred mainly in patients with CKD stages 1–2 and were unrelated to baseline eGFR and eGFR slopes. Differences in eGFR slopes among cohorts were present many years before ESRD onset. This indicates that the international variation in risk of ESRD is due to different intensity of disease process that underlies progression of diabetic nephropathy. As a result of that, in the Joslin cohort, there were almost twice as many fast progressors to ESRD as in the Steno cohort (28). On the other hand, Steno had more than two times more frequent deaths unrelated to ESRD in comparison with Joslin.

From our findings, we can consider progression to ESRD and mortality unrelated to ESRD, mainly due to CVD, as independent disease processes. We identified two sets of risk factors for them, and they overlapped only partially. Interestingly, the distributions of risk factors varied between the countries; however, controlling for them in regression models did not materially change the pattern of differences in eGFR decline, in risks of ESRD and in mortality unrelated to ESRD. Therefore, the international differences in both outcomes could be due to unknown genetic or environmental factors that vary among populations, different health attitudes, or alternatively, they might be attributed to gene-environment interactions. The nature of genetic factors is being explored in the recent JDRF DNCRI, which dissects the genetic architecture of diabetic nephropathy in type 1 diabetes. The research on the role of environmental factors determining variation in risk of progression to ESRD and mortality in patients with type 1 diabetes with advanced diabetic nephropathy needs to be developed. It should provide new knowledge that could facilitate the development of new, more effective interventions to reduce risk of these two life-limiting outcomes.

Some recent publications showed variation in risk of ESRD among several

countries (8–13). Whereas those studies aimed to examine lifetime risk of ESRD since the onset of diabetes, our study focused specifically on patients with type 1 diabetes who had advanced diabetic nephropathy at baseline and were subjected to specialized care and treatment for 3–18 years in four different health care systems. Unlike those epidemiological observations, our study provides more specific insight into disease mechanisms that underlie renal decline in patients with advanced nephropathy during follow-up, and it assessed mortality as an additional outcome. Overall combined risk of ESRD and mortality unrelated to ESRD was very high in our cohorts. Optimistic conclusions from the national registry studies should not obscure the opposite prognosis in high-risk patients. These individuals need new, effective, possibly aggressive interventions targeting both kidney and cardiovascular diseases. These two important clinical problems have different determinants, risk factors, and mechanisms but should be addressed simultaneously.

Our study has considerable strengths, such as a very large sample size, prospective design, and long follow-up with serial eGFR determinations. We also have to acknowledge its limitations. The cohorts varied by designs and patient ascertainment procedures, and many biochemical measurements were performed locally in study centers. The INSERM cohort lacked complete data on lipid profile and urinary creatinine. Due to the design of GENESIS and GENEBIAB studies, prospective follow-up was unavailable in some of study participants.

The follow-up outcomes in the study were ascertained in a prospective manner. Patients in the Joslin and Steno Copenhagen clinics, most under care early in course of their type 1 diabetes, seem to well represent populations of eastern Massachusetts and the Copenhagen metropolitan area. The FinnDiane cohort has excellent external validity for the whole population of Finland, and INSERM patients are a sample from populations of France and Belgium. Thus, the limitations cannot undermine the main message of our study and its external validity, that the natural history of advanced diabetic nephropathy and burden of mortality in type 1 diabetes is very high and variable among countries.

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