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Original Paper

A Prospective Cohort Study in Patients with Type 2 Diabetes Mellitus for Validation of Biomarkers (PROVALID) – Study Design and Baseline Characteristics

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Key Words
Diabetes mellitus type 2 • Diabetic kidney disease • Epidemiology • Treatment • Health care practise

Abstract
Background/Aims: The prevalence of diabetes mellitus type 2 and kidney disease in these patients varies widely between European countries. ***Methods:*** In addition to store biosamples the "Prospective cohort study in patients with type 2 diabetes mellitus for validation of biomarkers" collects information on history, physical status, laboratory measurements and medication in 4000 patients with diabetes mellitus type 2, being taken care of at the primary level of healthcare in 5 European countries (Austria, Hungary, Netherlands, Poland and Scotland). Next to comparing the rate of loss of eGFR between the countries, a further objective of the PROVALID study is to determine the 5-year cumulative incidence of renal and cardiovascular outcomes. ***Results:*** The mean age of the population recruited is 62.9±10 years, 54.6% are male and the mean BMI is 30.9±5.4 kg/m^2. Metabolic control (median HBA1c 6.8 % (6.2;7.5)) is achieved via administration of metformin in 67.4% of the patients and insulin

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in 30.3%. Median systolic and diastolic blood pressure at recruitment is 135 (125;146) and 80 (72;85) mmHg, 65.4% of subjects received RAAS blocking agents. Mean eGFR is 80.7±29.2 ml/min/1.73m^2 and median baseline albumin/creatinine ratio 8.3 mg (IQR: 3.8 and 25.1). ***Conclusion:*** PROVALID will provide information on incidence and progression of renal and cardiovascular disease and therapy in patients with type 2 diabetes mellitus in different European countries. Thus, in contrast to many other cohort studies we will be able to associate national clinical practise pattern with outcome in this highly vulnerable patient population.

Introduction

The number of adult patients suffering from diabetes mellitus in Europe is projected to increase from 48.4 million in 2003 to 58.6 million by the year 2025 but, interestingly, the prevalence varies significantly between countries. By 2025 11.9% of the population will be affected in Austria. Similar numbers are predicted for Hungary or Poland (11.2 and 11.0%), but much lower rates for the Netherlands or the United Kingdom (5.1 and 4.7%, respectively) [1]. Kidney disease is a devastating complication of diabetes mellitus, reducing the quality and quantity of life and putting an enormous socioeconomic burden on society. The mean annual incidence to renal replacement therapy due to any cause in 38 European countries in 2013 was 123±49 per million population (pmp). Diabetic patients contributed with a median of 28 pmp but again a large variability is observed (from 5 in the Ukraine to 83 in Israel), which is only partially explained by the background prevalence of diabetes in the specific populations [2, 3]. A remarkable regional difference in the prevalence of non-dialysis dependent chronic kidney disease in patients with diabetes mellitus has also been reported recently [4]. The reason(s) for this variability are unclear as no large scale databases are available reporting the incidence and rate of progression of renal disease as well as cardiovascular morbidity and mortality of diabetics with and without nephropathy on a regional or national level.

The PROVALID (PROspective cohort study in patients with type 2 diabetes mellitus for VALIDation of biomarkers) study prospectively collects information on patient history, physical status, laboratory measurements and medication and stores bio-samples (to allow analysis of new, emerging biomarkers) in patients with diabetes mellitus type 2, being taken care of at the primary level of healthcare in 5 European countries. The incidence of renal and cardiovascular events will be recorded and the study aims to establish novel ways to predict the course of the disease in individual patients or patient groups and explain regional variability. This report describes the baseline characteristics of the PROVALID population after recruitment is completed.

Materials and Methods

Design and setting

PROVALID is an observational, prospective cohort study in five European countries (Austria, Hungary, Netherlands, Poland and Scotland). Four thousand patients with type 2 diabetes mellitus were recruited between 2011 and 2015 at the primary level of healthcare. They are treated according to local practise and will be followed for at least 5 years. As defined in the protocol, recruitment was competitive between the countries after 2012, the recruitment strategies applied are described below. A coordinating centre is responsible for the study conduct in each country. Patients aged 18-75 years (the upper age limit was introduced via an amendment one year after the start of the study) and willing to sign informed consent were recruited if they have incident or prevalent type 2 diabetes mellitus (defined as treatment with hypoglycaemic drugs or according to ADA guidelines), irrespective of suffering from chronic kidney disease or not. Only subjects with active malignancy requiring chemotherapy were excluded. Detailed inclusion and exclusion criteria are given in Table 1.

Table 1. Inclusion- and exclusion criteria of PROVALID. * defined as treatment with hypoglycemic drugs or according to ADA guidelines

Inclusion	Exclusion
aged 18-75 years	active malignancy requiring chemotherapy
willing to sign informed consent form	
incident or prevalent type 2 diabetes mellitus* with or without chronic kidney disease	

Recruitment in Austria (n=629)

In Austria General Practitioners (GPs) manage patients with diabetes mellitus and send them to specialists for consultations only if deemed necessary. GPs were contacted in two regions (Upper Austria and Tyrol). In Upper Austria the GPs are part of a disease management program group formed by the regional social security institution, GPs in Tyrol were known to the Austrian PROVALID management team. In total 24 GPs agreed to participate (13 in Upper Austria, 11 in Tyrol); 460 patients were recruited in Upper Austria, 169 patients in Tyrol (32.9±22 patients per GPs practice in Upper Austria and 17±13.7 in Tyrol). A technician regularly visited the offices and assisted for data entry into the electronic data system as well as for bio-sample collection/work up.

Recruitment in Hungary (n=1420)

In Hungary patients with diabetes mellitus receive prescription medications from specialized centres and from GPs. Depending on the GPs request and/or site patients visit the diabetic centres every 3, 6 or 12 months, where a specialist prescribes/adjusts the medication for the next period and provides instructions for the GPs. Patients in PROVALID are being taken care by four of these centres and one GP network, where blood and urinary sample collection as well as clinical data allocation took place. These centres were chosen to represent Hungarian treatment.

Recruitment in the Netherlands (n=903)

GPs in the northern part of the Netherlands, who participate in the Groningen Initiative to Analyse Type 2 diabetes Treatment (GIANTT) project, were asked to participate also in PROVALID. Ambulatory patients with type 2 diabetes mellitus of cooperating GPs were then selected from the GIANTT database (a repository enabling identification of all known patients with type 2 diabetes) and received an invitation letter (n=2726). 903 patients decided to participate. Blood and urine tubes together with instructions were sent to these patients. They brought these tubes to the central laboratory during a regular diabetes care visit and additional blood and urine for the PROVALID study was collected while, data were provided from the GIANTT database

Recruitment in Scotland (n=511)

Patients were identified as potentially eligible from a list of general practitioners, who have signed up as sites for research with the Scottish Primary Care Research Network. All eligible patients were contacted with a brief letter (opt in sheet), a reply letter with pre-paid postage, telephone contact or email to contact the national coordinator if they wished to participate. Once the research nurse team received the indication of interest a study visit was arranged for obtaining blood tests and medical history as requested in the protocol. The recruitment process ensured that the patient management was exactly following the routine management of type 2 diabetes mellitus in Scotland. The population is likely to be representative of the general population of type 2 diabetics in Scotland rather than those with more complex comorbidities. Nonetheless some patients recruited may additionally be attending a secondary care diabetes service or nephrology clinic. 4192 patients were initially contacted, 611 responded and 511 took part.

Recruitment in Poland (n=537)

Patients with diabetes mellitus in Poland receive primary care by specialized institutions. In line with this the majority of participants were recruited in specialized Diabetic or Nephrology Outpatients Departments in Upper Silesia. About 30% of the cohort was provided by GPs directly, however even these

patients also received consultation by highly specialized centers periodically. Data were collected directly from the source documentation and blood and urine was collected by doctors appointed to this study

Data and sample collection

The clinical data are collected in the context of local established practice and already existing clinical data collection structures. A list of clinical parameters required from each patient was defined (so called minimal dataset, see Supplementary Table 1, for all supplementary material see: www.karger.com/doi/10.1159/000487500), but many other variables could be added: family history of diseases (renal disease, hypertension, type 2 diabetes mellitus, cardiovascular disease, malignancy) CRP/hsCRP, total serum cholesterol, serum LDL cholesterol, serum HDL cholesterol, serum triglycerides, serum potassium, hemoglobin, serum albumin. Parameters of the minimal dataset could be provided from all countries, additional variables were obtained from Austria, Hungary, Scotland and Poland. Blood and urine samples were obtained following strict SOPs (see Supplementary Table 2) and shipped to a central repository in Innsbruck/Austria. Data are de-personalized rather than permanently anonymized in the data retention process. Identifying information linking to the research database is printed out and kept at the local site. Data transferred between all local sites and the central data repository is encrypted.

Study outcomes

Next to comparing the rate of loss of eGFR between the countries, a further objective of the PROVALID study is to determine the 5-year cumulative incidence of renal outcomes (defined as progression from normoalbuminuria to microalbuminuria including > 30% increase in albuminuria from baseline; progression from microalbuminuria to macroalbuminuria including > 30% increase in albuminuria from baseline; progression to doubling of serum creatinine, end stage renal disease (ESRD) or death). Additionally the cumulative incidence of cardiovascular outcomes (cardiovascular death; non-fatal myocardial infarction or stroke; all cause hospitalization and hospitalization because of heart failure) is recorded. Finally bio-samples are collected at patient inclusion to allow validation of biomarkers potentially of use in renal disease diagnosis, prognosis, prevention and therapy at the genome, transcriptome, proteome, and metabolome level. Blood and urine is obtained also once a year allowing centralized analysis of laboratory parameters throughout the entire study.

Statistical analysis

Sample size estimation: Initially we assumed 5 participating countries of equal sample size and the calculation of sample size was based on the expected event rate after 5 years. We are interested in the 95% confidence interval for progression rate in each participating region. With a sample size of 800 per participating region and assuming a progression rate of 17 % within 3.5 years of follow-up (complete for all subjects), a 95% confidence interval will have an expected length of 7.5 percentage points, accounting for a drop-out rate (lost to follow-up) of 20% and correcting for multiplicity testing by the Bonferroni method. After completion of recruitment the expected precision of the prevalence estimates was recalculated, using the same assumption as in the initial study protocol. Because of the competitive recruitment and the subsequent unequal numbers of patients included in each country, the expected precision estimates varied as shown in Table 2. The analysis of other study endpoints will be reported elsewhere.

Description of baseline characteristics: Baseline characteristics are described by percentages for categorical variables, by means and standard deviations (SD) or medians and 25^{th} and 75^{th} percentiles for continuous variables after distributions were graphically inspected. Adjusted data were calculated by univariate linear regression after log transformation if appropriate. Comparisons between groups were performed using Chi^2-test or Kruskal-Wallis test.

Ethical approval: The PROVALID study protocol was approved in each participating country by the responsible local Institutional Review Board (IRB). Signing an informed consent was a prerequisite for study participation in all countries.

Results

Table 3, Table 4 and Table 5 show the general characteristics of the PROVALID population. Patients recruited were on average 63 years old and diabetic for 8 years, hypertension had preceded the diagnosis of diabetes by about 4 years. The comorbidity burden is typical for an outpatient population being taken care at non-specialized institutions.

Table 4 shows data on body weight, BMI, blood pressure and selected laboratory values. The population was obese and, on average metabolic and blood pressure control was acceptable, as was lipid management. Mean/median values for renal function showed preserved eGFR and normoalbuminuria.

Table 5 provides Information on selected glucose lowering, antihypertensive and lipid lowering therapy. The proportion of patients on glinides, glitazones, centrally acting antihypertensive agents and vasodilating drugs or aldosterone antagonists was below 5% and is not reported. Recruitment was finished before hard outcome trials with SGLT-2 inhibitors were published.

Table 6 shows renal function of the participants according to the KDIGO classification scheme. As expected, subjects with severe renal dysfunction were underrepresented as most likely they are usually referred to specialist care.

As one of the goals of PROVALID is to decipher differences in regional renal and cardiovascular disease prevalence and progression, we next analysed selected parameters by country. Due to significant differences between the countries in main risk factors for diabetic renal disease (age, gender and diabetes duration) we analysed unadjusted and respectively adjusted eGFR- and albuminuria levels in the different countries (Table 7).

Table 2. Expected precision estimates

	number of patients recruited	length of (Bonferroni-adjusted) 95% confidence interval for progression rate
Austria	629	7.8%
Hungary	1.420	5.2%
Netherlands	903	6.2 %
Poland	537	8.6%
Scotland	511	8.4%

Table 3. Study population characteristics

Characteristics	Value
Age (years)	62.9±10
Gender (% male)	54.6
History of diabetes mellitus (years)	8.0 (3;13)
History of hypertension (years)	12.0 (6;18)
History of coronary artery disease (%)	21.0
History of heart failure NYHA III or IV (%)	2.5
History of cerebrovascular disease (%)	6.7
History of peripheral artery disease (%)	7.1
History of malignancy (%)	4.5
Smoking (never) (%)	49.5

Table 4. Body weight, BMI, blood pressure and selected laboratory parameters of the study population

Characteristics	Value
Weight (kg)	88.6±18
BMI (kg/m²)	30.9±5.4
Systolic blood pressure (mmHg)	135 (125;146)
Diastolic blood pressure (mmHg)	80 (72;85)
eGFR (ml/min/1.73m²)	80.7±29.2
Albuminuria (mg albumin/g creatinine)	8.3 (3.8;25.1)
HBA1c (%)	6.8 (6.2;7.5)
Total serum cholesterol (mmol /L)	4.7 ± 1.23
Serum LDL cholesterol (mmol /L)	2.65 ± 1.00
Serum HDL Cholesterol (mmol /L)	1.27 ± 0.41
Serum triglycerides (mmol /L)	1.63 (1.18;2.31)

Table 5. Selected medical therapy of the study population

Glucose lowering agents	% of population
Biguanides	67.4
Insulin	30.3
Sulfonylureas	27.1
DPPIV inhibitors/GLP1 agonists	14.3
Blood pressure lowering agents	
ACE inhibitors/ARBs	65.4
β-blockers	43.3
Calcium antagonists	28.3
α-blockers	9.7
Diuretics (%)	
Thiazide diuretics	35.0
Loop diuretics	11.4
Lipid lowering agents	
Statins	59.6

Table 6. Renal function according to the KDIGO classification scheme of the study population (%). ACR: albumin/creatinine ratio in morning spot urine. G stages: glomerular filtration rate

	A1 ACR <30 mg/g	A2 ACR 30-300 mg/g	A3 ACR >300 mg/g	total
G1 >90 ml/min/1.73m²	27.4	5.7	0.6	33.7
G2 60-89 ml/min/1.73m²	37.7	7.9	1.3	47.0
G3a 45-59 ml/min/1.73m²	9.1	2.8	0.4	12.3
G3b 30-44 ml/min/1.73m²	2.9	1.4	0.6	5.0
G4 15-29 ml/min/1.73m²	0.8	0.6	0.5	1.9
G5 <15 ml/min/1.73m²	0.1	0.0	0.2	0.2
Total	78.0	18.5	3.4	100

Table 7. Comparison of main baseline parameters between the countries. * adjusted for age, gender, DM2 duration

	Austria n=629	Hungary n=1.420	Netherlands n=903	Poland n=537	Scotland n=511	p-value
Age (years)	64.3±9.6	63.2±10.3	65.0±8.7	59.5±10.9	59.4±9.3	<0.001
Gender (male, %)	56.9	51.7	59.5	41.0	65.6	<0.001
Diabetes duration (years)	8.0±6.9	12.5±9.1	7.5±5.0	6.5±7.8	7.3±5.6	<0.001
eGFR (ml/min/1.73m^2) unadjusted	77.2±23.9	75±27.8	83.1±32.3	91.0±35.4	85.6±19.8	<0.001
adjusted*	77.2±3.6	75±4.7	83.9±2.7	90.9±4.1	85.4±2.9	<0.001
Albuminuria (mg/g creatinine) unadjusted	12.5 (7.6; 29.4)	7.2 (2.7; 24.3)	5.0 (6.1; 39.7)	14.9 (6.1; 39.7)	8.4 (4.6; 25.7)	<0.001
adjusted*	11.6 (10.2; 29.4)	12.3 (10.8; 13.6)	11.7 (10.5; 12.8)	10.9 (9.4; 12.5)	11.1 (9.8; 12.5)	<0.001

Discussion

Observational prospective cohort studies play an important role in deriving evidence. In contrast to cross sectional analyses they offer a temporal dimension, which allows the recording of a sequence of events. Multiple outcomes for a given exposure can be examined and disease incidence in exposed and unexposed individuals over time be calculated. Nonetheless, study quality might be affected by selection, attrition or information bias [5]. As a consequence the „Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" group established guidelines on reporting observational research to improve the transparency of the methods [6]. We used their checklist to describe the design and baseline variables of the PROVALID study, a prospective observational cohort study that recruited patients with type 2 diabetes mellitus at the primary level of healthcare in 5 European countries (Austria, Hungary, Netherlands, Poland and Scotland). The cohort will be followed for at least 5 years to study the incidence and progression of kidney disease and define novel biomarkers and molecular pathways. Additionally, data on the effect of local practices of healthcare on the course of the disease will be studied. In this aspect it is interesting to note, that at baseline eGFR but not albuminuria values differed clinically meaningful between the countries even after adjustment for age, gender and diabetes duration. The reasons for this observation remain unclear (selection bias, difference in progression rate, variable local practise etc.). Follow up of the cohort will hopefully allow drawing more firm conclusions.

Several large cohort studies in patients with and without diabetes and a primary or secondary renal endpoint are currently being conducted. Some of these initiatives share some similarities with PROVALID while others differ significantly in design and patient population recruited.

Probably the best known prospective cohort involving subjects with early/moderately progressed CKD was recruited by the Chronic Renal Insufficiency Cohort (CRIC) study, which was established by the National Institute of Diabetes, Digestive, and Kidney Disease in 2001. Recruitment of 3939 participants by 7 specialized clinical centres was finished in 2008 with intentional oversampling of black and diabetic patients, the latter making up about half of the study population (n=1908). The cohort was started to be expanded by another 1500 subjects in 2015. The CRIC participants are followed until death or withdrawal of informed consent. The study contributed to the NIDDK´s CKD Biomarker Consortium, the CKD Prognosis Consortium and collaborates closely with the Chronic Kidney Disease Japanese cohort study and the German CKD study. Depending on the age, the eGFR limits for inclusion are between 20 and 70 ml/min/1.73m^2 and the renal endpoints considered are the need

for renal replacement therapy, a reduction of eGFR by 50% and/or a decline of eGFR by at least 25 ml/min/1.73m^2 [7, 8]. When compared to non-diabetic participants, patients with diabetes were more likely to suffer from comorbidities like myocardial infarction (28 vs 16%), congestive heart failure (14 vs 6%) or peripheral vascular disease (10 vs 3%) [9]. The mean eGFR in diabetic participants was 41 ml/min/1.73m^2, the mean HbA1c level 7.7% and about 80% were on RAS blocking agents [9].

The German Chronic Kidney Disease (GCKD) study recruited 5217 patients with CKD, who are under care of nephrologists. The inclusion criteria were an eGFR between 30 and 60 ml/min/1.73m^2 or a better preserved eGFR in the presence of urinary albumin excretion >300 or protein excretion >500 mg/day. 1844 subjects had diabetes and in 783 diabetic nephropathy is considered the leading cause of renal failure. The eGFR of diabetic patients in GCKD at baseline was 45 ml/min/1.73m^2 and the urinary albumin/creatinine ratio was 58 mg/g, their HbA1c level averaged 7% and 84% were on RAS blocking agents [10–12].

In Japan 17 clinical centres recruited 2977 patients (eGFR between 10 and 59 ml/min/1.73m^2) into the Chronic Kidney Disease Japan Cohort (CKD-JAC) [13, 14]. The primary endpoints of the study are cardiovascular events, at inclusion 37.6% of the subjects had diabetes and 20.6% were diagnosed with diabetic nephropathy. The eGFR of these two diabetic subgroups was 29 and 26 ml/min/1.73m^2 and urinary albumin excretion was 0.9 and 1.7 g/day, respectively. Blood pressure control was similar to the one in PROVALID (132/75 and 137/73 mmHg, respectively). The BMI in this Asian cohort was quite low (24 kg/m^2) and at least 80% of the population was treated with either ACE inhibitors or ARBs. 9% had a prior myocardial infarction and 5-8% had congestive heart failure, whereas 14-18% had a history of stroke. Recently the authors reported that after a follow up of about 4 years the risk of cardiovascular events was dramatically higher in diabetic subjects (41.3/1000 patient years) when compared to non-diabetics (12.6/1000 patient years) [15].

PROVALID complements from these studies in various aspects. First, PROVALID focused on subjects with type 2 diabetes exclusively recruited at the primary healthcare level. This selection resulted in a lower cardiovascular comorbidity burden when compared to CRIC, GCKD and JAC-CKD as patients with more advanced cardiovascular disease are usually referred to specialist care. In line with this idea is the fact that eGFR on average is much higher in the PROVALID population (81 ml/min/1.73m^2 in PROVALID versus 29-41 ml/min/1.73m^2 in the other cohorts). In contrast, the population recruited by the "Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study" shares many similarities with the PROVALID participants. 15.933 Caucasian patients with type 2 diabetes (defined by the American Diabetes Association criteria), attending consecutively 19 hospital-based Diabetes Clinics of the National Health Service throughout Italy in years 2007–2008 were recruited [16]. Next to the French SURDIAGENE study [17]. the German DIACORE project is another ongoing project with similarities to PROVALID [18]. However, DIACORE not only focuses on renal complications but rather aims to elucidate mechanisms involved in the development and progression of all type 2 diabetes mellitus associated complications. No baseline manuscript has been published so far and the same applies to other interesting cohorts like the French CKD-REIN [19] (n=3.600; eGFR 15-60 ml/min/1.73m^2) and the Chinese C-STRIDE [20] (n=3.600; eGFR 15-60 ml/min/1.73m^2) population. A unique feature of PROVALID when compared to others cohorts is the fact that it is conducted in 5 European countries with different healthcare systems. In addition the rate and risk factors for the *development* of renal disease as well as of renal endpoints (in those with established CKD) can be assessed in this general type 2 diabetes population. This is of importance since not all patients suffering from diabetes develop kidney disease. Besides clinical factors as glycaemic or blood pressure control, genetic factors seem to play a major role and can be exclusively examined in PROVALID. Thus the study will hopefully enable us to decipher the effect of regional healthcare practise on disease progression.

Complementary information on patients with CKD will be provided by registries [21] like the Australian CKD. OLD (Queensland) study [22], the US CKD Surveillance System

[23] or the initiatives of the EDTA ERA [4] in Europe and the NRHP programme in Uruguay [24]. Finally the recently initiated CKDopps programme has to be mentioned, which will recruit more than 12.000 patients with CKD [25]. By the recruitment of 4000 patients having type 2 diabetes in 5 European countries, PROVALID will provide further insight into the development of diabetic kidney disease, especially on a genetic level.

Disclosure Statement

The authors declare no conflicts of interest.

Acknowledgements

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