Multinational, prospective cohort-study in patients with type 2 diabetes for validation of biomarkers

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Observational invasive

Summary

ID

NL-OMON38296

Source
ToetsingOnline

Brief title
PROVALID

Condition

- Diabetic complications
- Nephropathies

Synonym
Type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Univ. Prof. Dr. Gert Mayer, Universitätsklinik für Innere Medizin IV (Nephrologie und Hypertensiologie)

Source(s) of monetary or material Support: European Union grant

Intervention

Keyword: Biomarkers, End-stage Renal Disease (ESRD), Nephropathy, Type 2 Diabetes

Outcome measures

Primary outcome

Renal outcomes are 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.

Cut-off values indicating normoalbuminuria, microalbuminuria, and

macroalbuminuria are defined as:

24 hour timed

overnight first morning sample

mg / 24 hour

ug / min mg / g creatinin

Normoalbuminuria < 30 <

20 < 30

Microalbuminuria 30 - 300 20

- 200 30 - 300

Macroalbuminuria > 300

> 200 > 300

Secondary outcome

Cardiovascular outcomes are defined as

• cardiovascular death

• non fatal myocardial infarction or non fatal stroke

• hospitalization because of heart failure

The diagnosis of cardiovascular events is made based on the treating physician*s judgement and checked by the adjudication endpoint committee. The adjudication endpoint committee consists of members located in each participating country. The national coordinator is responsible for annual random check of the quality of data entry. He/she is also responsible for correct patient follow up in case the treating physician changes.

Study description

Background summary

48.4 million Europeans aged 20 and 79 years had diabetes in 2003; by the year 2025 this number will reach 58.6 million. Interestingly a high variability is observed between countries. By 2025 11.9% of the population will be affected in Austria. The numbers for Hungary or Poland are expected to be similar (11.2 and 11.0%), but the prevalence will be much lower in the Netherlands and the UK (5.1 and 4.7% respectively) (www.heartstats.org). One of the most devastating complications of diabetes is nephropathy and despite diabetes being the main cause of end stage renal disease in industrialzed nations the incidence also varies considerably within Europe. In 2008 in Austria 29% of incident dialysis patients had diabetic nephropathy, a number much different from the one observed in the Netherlands (14.6%) or Scotland (6.5%). Whereas in Austria the prevalence of patients with type 1 diabetes on dialysis was 52.9 pmp, the number for subjects with type 2 disease was 149.3. In the Netherlands the corresponding figures were 35.9 and 57.9 and in Scotland 80.7 and 25.5 (EDTA-ERA Annual Report 2008). The reasons for these discrepancies are unclear as no large scale national epidemiological databases are available reporting

the exact incidence and rate of progression of diabetic nephropathy as well as cardiovascular morbidity and mortality of diabetics with and without nephropathy. PROVALID will be an indefinite, prospective cohort study in patients with type II diabetes in five European countries (Austria, Hungary, Netherlands, Poland and Scotland). The patients will be treated according to local practice and followed for the incidence of renal and cardiovascular outcomes as well as mortality.
Diabetic nephropathy occurs in both, type 1 and 2 diabetes mellitus. In type 1 disease approximately 20 to 30 percent of the patients develop microalbuminuria (MIA, the excretion of 30 to 300 mg of albumin per day) after a mean disease duration of 15 years (Newman DJ, Mattock, MB, Dawnay AB, Kerry, S, McGuire, A, Yaqoob, M, Hitman, GA, Hawke, C: Systematic review on urine albumin testing for early detection of diabetic complications. Health Technol Assess 2005; 9:iii-vi,xiii-163). In contrast to earlier studies currently less than half of individuals with MIA will progress to overt nephropathy and end stage renal disease due to better metabolic control, more aggressive blood pressure reduction and the use of agents that block the renin angiotensin system (Finne P, Reunanen A, Stenman S, Groop PH, Grönhagen-Riska C: Incidence of end stage renal disease in patients with type 1 diabetes. JAMA 2005; 294:1782-1787). In type 2 diabetes the most robust data on the incidence and progression of nephropathy were derived from the United Kingdom Prospective Diabetes Study. Among the 5.100 patients with newly diagnosed diabetes enrolled the prevalence of MIA, macroalbuminuria and either an elevated plasma creatinine concentration or requirement of renal replacement therapy after 10 years was 25, 5 and 0.8 % respectively (Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR: Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003; 63:225-232). Unfortunately especially in patients with type II diabetes the sensitivity and specificity of MIA for the progression of renal disease is low even though it is generally accepted that it confers a decreased cardiovascular prognosis (Newman DJ, Mattock, MB, Dawnay AB, Kerry, S, McGuire, A, Yaqoob, M, Hitman, GA, Hawke, C: Systematic review on urine albumin testing for early detection of diabetic complications. Health Technol Assess 2005; 9:iii-vi,xiii-163). Hence more specific and / or sensitive biomarkers to identify patients at risk for renal disease or those whose nephropathy will progress despite state of the art therapy are urgently needed. Therefore in the PROVALID study blood and urine will be collected at regular intervals and the specimen will be available for analysis on a genome, transcriptome, proteome and metabolome level. As cardiovascular morbidity and mortality will also be registered PROVALID will also serve as a source of information in the area of cardiovascular research.

Study objective

PROVALID will have 3 major objectives:

Primary: Determine the cumulative incidence of renal outcomes in patients with type II diabetes in different European countries.

Renal outcomes are 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

Secondary:
• Annual collection of blood and urine specimen for 5 years to allow validation of biomarkers potentially of use in renal disease diagnosis, prognosis, prevention and therapy at the genome, transcriptome, proteome and metabolome level
• Collection of serum and urine at least once a year allowing centralized analysis of routine laboratory parameters throughout the entire study

Tertiary: Determine the cumulative incidence of cardiovascular outcomes in patients with type II diabetes in different European countries.
Cardiovascular outcomes are defined as:
* Cardiovascular death
* Non fatal myocardial infarction or non fatal stroke
* Hospitalization because of heart failure

Study design

PROVALID is a prospective cohort study in at least 4.000 individuals with type II diabetes in five European countries (Austria, Hungary, Netherlands, Poland and Scotland). The patients will be followed and treated according to local practice.

Study burden and risks

The clinical data will be collected in the context of local established practice and already existing clinical data collection structures. All necessary procedures to correctly diagnose the progression of albuminuria or renal disease will be done at the recruiting site. A minimal list of clinical parameters required for our purpose will be collected. Any other clinical parameter or outcome parameter that will be collected is advantageous. General practitioners or colleagues working at other recruitment sites will also collect annual blood and urine samples from their patients.

There are no risks other than the ones relative to the venapunction.
Patients will not have a direct benefit from the study. However PROVALID will likely contribute to the discovery of biomarkers potentially of use in renal disease diagnosis, prognosis, prevention and therapy at the genome, transcriptome, proteome and metabolome level.

Contacts

Public
Univ. Prof. Dr. Gert Mayer, Universitätsklinik für Innere Medizin IV (Nephrologie und Hypertensiologie)

Medizinische Universität Innsbruck, Anichstrasse 35
A - 6020 Innsbruck
AT
Scientific
Univ. Prof. Dr. Gert Mayer, Universitätsklinik für Innere Medizin IV (Nephrologie und Hypertensiologie)

Medizinische Universität Innsbruck, Anichstrasse 35
A - 6020 Innsbruck
AT

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient age > 18 years
2. Incident or prevalent patients with type II diabetes mellitus
3. Patients who are willing to sign informed consent to provide blood and urine samples

Exclusion criteria

1. Patients with malignancy on current active treatment

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-06-2012
Enrollment:	800
Type:	Actual

Ethics review

Approved WMO Date:	01-03-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-09-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL35350.042.11