Pharmacoepidemiological study protocol ER-9489

A retrospective nationwide cohort study to investigate the treatment of type 2 diabetic patients in Finland - DAHLIA

Authors: Ilona Iso-Mustajärvi, Houssem Khanfir, Fabian Hoti, Tuire Prami

Protocol number: ER-9489

Sponsor: AstraZeneca Nordic Baltic

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Study Information

Title	A retrospective nationwide cohort study to investigate the treatment of type 2 diabetic patients in Finland – DAHLIA
Protocol identifier	ER-9489
Date of last version of protocol	24 Feb 2015 (This is the first version of the protocol.)
EU PAS register number	Study registration in European Network of Centres for Pharmacoepidemiology and Pharmacovigilance will be performed after the study protocol approval.
Active substances	Antidiabetic drugs (ATC group A10)
Marketing authorization holder financing the study	The following AstraZeneca products are available on the Finnish market: Bydureon (exenatide A10BX04), Byetta (exenatide A10BX04), Forxiga (dapagliflozin A10BX09), Komboglyze (metformine and saxagliptin A10BD10), Onglyza (saxagliptin A10BH03), Xigduo (dapagliflozin and metformin A10BD15)
Joint PASS	No
Research question and objectives	The purpose of the study is to describe type 2 diabetes mellitus patients in Finland, especially their antidiabetic medication use (e.g. persistence, concomitance and switching), and to discuss the progression of the disease in terms of comorbidities and drug treatment. As a secondary objective the study includes health economic characteristics.
Country of study	Finland
Author	Ilona Iso-Mustajärvi, Houssem Khanfir, Fabian Hoti, Tuire Prami

Sponsor

Marketing authorization holder financing the study	AstraZeneca Nordic Baltic SE-151 85 Södertälje Sweden
MAH contact person	Susanna Pozarek

Table of contents

1 List of abbreviations

ATC code	Anatomical therapeutic chemical classification system code
DPP-4	Dipeptidyl peptidase 4
DPS	Finnish Diabetes Prevention Study
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
GLP-1	Glucagon-like peptide-1
ICMJE	International Committee of Medical Journal Editors
HILMO	Finnish Hospital Care Register

ICD-10
- E10
- E11
- E12
- E13
- E14
- E89.1
- O24
  - O24.0
  - O24.1
  - O24.2
  - O24.3
  - O24.4
  - O24.9
- P70.2
	International classification of diseases, 10th revision
	- Type 1 diabetes mellitus
	- Type 2 diabetes mellitus
	- Malnutrition-related diabetes mellitus
	- Other specified diabetes mellitus
	- Unspecified diabetes mellitus
	- Postprocedural hypoinsulinaemia
	- Diabetes mellitus in pregnancy
	  - Pre-existing type 1 diabetes mellitus
	  - Pre-existing type 2 diabetes mellitus
	  - Pre-existing malnutrition-related diabetes mellitus
	  - Pre-existing diabetes mellitus, unspecified
	  - Diabetes mellitus arising in pregnancy
	  - Diabetes mellitus in pregnancy, unspecified
	- Neonatal diabetes mellitus

ID	Identification number
OAD	Oral antidiabetic drug
SID	Study identification number
SII	Social Insurance Institution
SPC	Summary of product characteristics
T2DM	Type 2 diabetes mellitus
THL	National Institute for Health and Welfare

2 Responsible parties

Sponsor: AstraZeneca Nordic Baltic

Sponsor study team: Johan Bodegård (Medical Evidence Scientific Leader), Susanna Pozarek (Medical Evidence Manager) and Joni Alvesalo (Medical Advisor)

Study conduct: EPID Research Oy, Metsänneidonkuja 12, FI-02130 Espoo, Finland

Principal investigator: Tuire Prami (PhD)

Co-investigators: Pasi Korhonen (Ph.D., Adj. prof. biostatistics) and Fabian Hoti (Ph.D.) from EPID Research

Study scientific committee (elsewhere also Steering committee):

Principal investigator Tuire Prami (PhD), EPID Research

Medical expert prof. Jorma Lahtela (MD, PhD), Tampere University Hospital / University of Tampere

Representative of the sponsor Johan Bodegård (MD, PhD), AstraZeneca Nordic Baltic

3 Abstract

Title: A retrospective nationwide cohort study to investigate the treatment of type 2 diabetic patients in Finland – DAHLIA

Rationale and background: There are about 280,000 people diagnosed with diabetes receiving medical treatment in Finland, most of them (85%) with type 2 diabetes mellitus (T2DM). T2DM is initially managed by life style changes only, but patients failing to control their blood glucose levels start eventually also using oral antidiabetic drugs (OADs). When the disease proceeds, many patients will need treatment with an injectable glucose-lowering drug (glucagon-like peptide-1 receptor agonist or insulin) in addition to OADs. Many new medicines have conquered the market in the recent years, but it is not completely known in detail how the glucose-lowering agents are used in a real-life setting.

Research question and objectives: The purpose of the study is to describe type 2 diabetes mellitus patients in Finland, especially their antidiabetic medication use (e.g. persistence, concomitance and switching), and to discuss the progression of the disease in terms of comorbidities and drug treatment. As a secondary objective the study includes health economic characteristics.

Study design: Descriptive retrospective study using nationwide data from the Finnish National Registers.

Study setting and population: Study population consists of T2DM patients with a filled prescription for use of any blood glucose-lowering (anatomical therapeutic chemical classification system (ATC) code: A10) drug between 1998 and 2013 or a special reimbursement for diabetes (refund code 103) by end of 2013. The study size will be about 240 000 T2DM patients.

Data sources: The cohort will be identified from the prescription register of the Social Insurance Institution. Follow-up information will be requested from nationwide registers maintained by the National Institute for Health and Welfare, Social Insurance Institution, and Statistics Finland.

4 Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1.	None	None	None	None
2.	None	None	None	None

5 Milestones

Milestone	**Planned date**
ENCePP registration	13 March 2015
Ethics Committee approval	14 April 2015
Data permit approvals	31 August 2015
Start of data collection	30 September 2015
End of data collection	30 November 2015
Statistical analysis completed	29 February 2016
Draft report	31 March 2016
Final report	30 April 2016
Manuscript sent for a peer-reviewed journal	30 April 2016

6 Rationale and background

There are some 280,000 people diagnosed with diabetes receiving treatment in Finland, most of them (85%) with type 2 diabetes mellitus (1). In recent years diabetes has been one of the most rapidly spreading diseases in Finland according to the Health Insurance registers of Social Insurance Institution of Finland (SII). Finnish Diabetes Prevention Study (DPS), a prospective follow-up survey by the Finnish Diabetes Association has shown that the incidence of diabetes was 15 % in 2000-2001 as well as in 2009-2010 (2).

In patients with T2DM, diminishing beta-cell function leads to a progressive decrease in insulin secretion, increased internal glucose production and reduced insulin sensitivity. T2DM is initially managed by life style changes (education, diet and physical activity) (3). Patients often fail to achieve adequate blood glucose control with lifestyle changes and progress to therapy with oral antidiabetic drugs. According to DPS, in 2000-2001 16% of the T2DM patients were treated with diet but by 2009-2010 this proportion had decreased to 7% (2).

OADs can be used in several treatment levels, either be uptitrated or combined with each other to achieve appropriate blood glucose control (3). However, at some point in time the OADs might not have the sufficient effect, explained by the progressive nature of T2DM, and an injectable glucose-lowering drug, glucagon-like peptide-1 (GLP-1) receptor agonist or insulin, will be added to the treatment.

Several new classes of glucose-lowering drugs, including the GLP-1 agonists, also known as incretin mimetics, have entered the market in the last few years. They are used as add-on drugs to metformin (the most commonly used OAD), and in some cases as mono-treatment (3). The newest international guidelines enable the use of several different glucose-lowering drugs as second add-on to metformin. This is, however, frequently limited by national regulations because of high cost.

The availability of new classes of glucose-lowering drugs with updated guidelines has had an impact on the glucose-lowering treatment practices of T2DM during the last years. It would be important to understand the treatment journey in relation to disease progression and switches between different treatment levels in practice.

The latest Finnish Statistics on Medicines from 2012 reports that the consumption of the antidiabetic drugs has remained more or less the same during the past years, but there was a 9% increase in sales in 2012 compared to year 2011 (4). This was mainly due to OAD sale increase by 18% while their consumption remained the same. Metformin was the most used antidiabetic with a 59% proportion. For the first time in 2012 dipeptidyl peptidase 4 (DPP-4) inhibitors, gliptins, were more commonly used than sulphonylureas. The use of GLP-1 agonists was still rare in 2012.

The aim of the study is to describe the treatment reality of type 2 diabetes patients in relation to the recent changes on the drug market in Finland using administrative health care data. As the study period lasts until 2013 (the latest year currently available from nationwide registers), the study setting includes also the newest drug groups on the market. A parallel study is conducted in Sweden, which makes between-country comparison possible. The enrolment of similar studies also in Norway and Denmark is under planning and therefore it would be feasible to compare the results from four Nordic countries in near future.

This study also gives support for the study sponsor as a marketing authorization holder when answering to the drug utilization requirements presented by the authorities.

7 Research questions and objectives

The objectives of this study are to describe:

1. Annual incidence and prevalence of T2DM patients in 1998-2013
2. Annual overall and cause-specific mortality in T2DM patients in 1998-2013
3. Annual incidence and prevalence of cardiovascular, microvascular and chronic kidney diseases and amputations in T2DM patients in 1998-2013
4. Use of blood glucose-lowering drugs and the treatment journey in T2DM patients
    a) Time to initiation, persistence, discontinuation, concomitance, and switching of blood glucose-lowering drugs
    b) Different treatment levels (from 1st line treatment to higher level combination treatments)
    c) Changes in dosing of blood glucose-lowering drugs
    d) Initiation, discontinuation, switching and changes in relation to the comorbidity during follow-up (independent from specific drug treatment)
    e) Describe how well blood glucose-lowering drug treatment practices follow the current care guidelines in terms of using the 1st, 2nd, 3rd and 4th line treatments and use of insulin
    f) Describe how patient demographics and disease history affect prescribing practices compared with current care guidelines (e.g. renal failure in patients not starting with metformin)
5. Disease progression:
    a) Describe incidence and prevalence of diabetes complications at different stages of disease as defined by usage of blood glucose-lowering drugs (independent from specific drug treatment)
    b) Describe the incidence of retirements and sick leaves in study population (independent from specific drug treatment)
6. Costs of drugs, hospital care, sick leaves, rehabilitation and early retirement before and after initiation of blood glucose-lowering drug

Local protocol requirements:

The Pharmaceuticals Pricing Board, subordinated to the Ministry of Social Affairs and Health in Finland, has requested detailed data about treatment practices and drug utilization including cost calculations from the study sponsor, AstraZeneca Nordic Baltic acting as a marketing authorization holder for T2DM products. This requirement is due to local reimbursement issues.

As the documentation presented for the pricing board will not become published in the routine process of this authority, the results produced for the Pharmaceutical Pricing Board will be considered confidential in this study. The specific aims of these subanalyses will be presented to the register holders of the source data and to the ethics committee in the study permit process.

8 Research methods

8.1 Study Design

This is a retrospective observational database linkage cohort study using patient level data from different nationwide registers in Finland.

8.2 Setting and population

Study population consists of T2DM patients in Finland identified by the following inclusion and exclusion criteria:

Inclusion criteria:

- A filled prescription for use of any blood glucose-lowering (ATC: A10) drug between 1998 and 2013 **or** a special reimbursement for diabetes (refund code 103) by end of 2013.

Exclusion criteria:

- Patients who are entitled to special reimbursement for diabetes (refund code 103) with ICD-10 diagnosis E10, E12, E13, E14 or E89.1 indicative of type 1 diabetes, diabetes related to malnutrition, other specified diabetes, unspecific diabetes or postprocedural hypoinsulinaemia, respectively, without refund 103 for E11 (i.e. other precondition for 103 than T2DM: ICD-10 E11).
- Patients with hospital visits based on ICD-10 E10, O24.0, E12, O24.2, E13, O24.3, O24.4, O24.9, E89.1 or P70.2 (referring to other diabetes mellitus than T2DM also during pregnancy or at birth) without E11 or O24.1

Index date: For each patient the index date is defined as the date of the first T2DM diagnosis or filled prescription of any blood glucose-lowering drug, whichever occurs first.

Follow-up: Follow-up starts at index date and ends at date of moving abroad, death, or the end of the year 2013, whichever occurs first.

Incident user: Incident users of blood glucose-lowering drugs are defined as patients with no filled prescription for use of any blood glucose-lowering (ATC: A10) prior to initiation, with a minimum history of two years available in the prescription database.

8.3 Data sources

Registers used in the study and the relative register holders are presented in Table 1.

Table 1. Registers used in the study with the register holders and relevant register contents

Register	Register holder	Content
Finnish Prescription Register	Social Insurance Institution	Drug purchases Reimbursement statuses Place of domicile * Drug costs
Finnish Hospital Care Register (HILMO)	National Institute for Health and Welfare	In- and outpatient diagnoses Hospitalization periods ** Treatment costs
Finnish Institutional Care Register (Social HILMO)	National Institute for Health and Welfare	Institutionalization (other than hospitalization) periods **
Finnish Causes of Death Registry	Statistics Finland	Time and causes of death
Sickness allowance register	Social Insurance Institution	Sickness allowances ≥10 days sick leaves Rehabilitation
Statistical pension register	Social Insurance Institution	Retirements

* For taking moving abroad during the follow-up period into account.** To censor periods with unknown drug use.

The variables related to different registers are listed in Annex 1.

Data permit process and data linkage:

Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) will be requested to cover the nationwide study. Data permits will be requested from each registry holder based on the study protocol and ethical approval. If the ethical approval is not received EPID Research will not proceed with the permit process, and the study is considered to be ceased. Neither can the study be completed if one of the register holders dismisses a permit application.

Patients will be identified by the Social Insurance Institution. SII will then convert the patient identification numbers (IDs) to study IDs (SIDs) and send the IDs and the SIDs to other register holders: National Institute for Health and Welfare (THL) and Statistics Finland. All the three register holders will then extract the study data based on the variable lists presented in the Annex 1 and send the raw data to EPID Research without IDs (including SIDs only). EPID Research will be the register holder for the study database and also responsible of destroying the data after the study.

8.4 Study Variables

8.4.1 Variables for population identification

- Filled prescriptions for blood glucose-lowering drugs: ATC code A10
- Special reimbursement for diabetes: refund code 103 with related ICD-10 diagnoses
- ICD-10 diagnoses: E10-E14, E89.1, 024, P70.2

8.4.2 Demographics

- Age
  - Continuous (years)
  - Categorical (categories to be defined based on data)
- Gender (Male/Female)

8.4.3 Comorbidities and causes of death

- Comorbidities: ICD-10 codes
- Special reimbursement codes with related ICD-10 diagnoses
- Causes of death: ICD-10 codes

See Annex 2 (Annex table 4) for details.

8.4.4 Exposure variables

- Blood glucose-lowering drug utilization
  - ATC codes

- Other concomitant drug utilization
  - ATC codes

See Annex 1 (Annex table 1) for details.

8.4.5 Costs

- Glucose-lowering drugs: costs from prescription register
- Other drugs: costs from prescription register
- In- and outpatient hospitalizations: national averages for unit costs of health care services in Finland will be based on pricing in a single representative hospital district
- Sickness allowance
- ≥10 days sick leaves
- Rehabilitation
- Retirement: average cost for early retirement will be defined and applied for all

8.5 Study size

The study aims to include all T2DM patients in the nationwide Finnish Prescription Register in 1998-2013. The estimated study population size is about 240 000 patients.

8.6 Data management

R language (www.r-project.org, read 25 Sep 2014) will be used for in data management for creating the analysis database and in statistical analysis for creating tabulations and graphics as well as in all statistical modelling. R language is described more detailed in report "R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (www.r-

project.org/doc/R-FDA.pdf, read 25 Sep 2014). Full audit trail starting from raw data obtained from register holders, and ending to statistical tables and graphs in reports will be maintained. Source code of data management and data analyses is kept for inspection for five years after publication of results. The study may be inspected by the sponsor's independent representative(s), study scientific committee, or by the competent authorities.

All study data and supporting documents will be retained for five years after the end of the study and then destroyed. As the register holder of the study register EPID Research is in charge of archiving and deleting the data. Secure archives will be maintained for the orderly storage and retrieval of all study-related material. An index shall be prepared to identify the archived contents and their location. Access to the archives will be controlled and limited to authorised personnel only. Access to the study data cannot be given to any third parties, neither the study data can be used to other purposes than prescribed in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

8.7 Data analysis plan

The principles of the statistical analysis are outlined below. More detailed statistical analysis plans will be written separately.

8.7.1 Missing data

If a variable is totally missing it is excluded from the analysis. If a variable is missing for only some of the patients a missing data category is added and used in the analysis.

8.7.2 Population summaries

The annual prevalent and incident population will be described on yearly basis from 1998 to end of follow-up (year 2013). The summaries will include patient demographics, comorbidities, use of blood glucose-lowering drugs and use of other drugs. Incident population will be described on index date and prevalent population on the 1st of July. Both counts and percentages will be given.

8.7.3 Study objectives 1-3

- The annual incidence and prevalence of T2DM in Finland will be presented by age and gender during 1998-2013 using counts and percentages
- The annual overall and cause-specific mortality in the prevalent T2DM study population will be presented by gender and by age during 1998-2013
- The annual incidence and prevalence of cardiovascular-, microvascular, chronic kidney diseases and amputations in the prevalent T2DM study population will be presented by age and gender during 1998-2013

8.7.4 Study objective 4

- Time from initiation of 1st line treatment (first blood glucose-lowering drug) to change of medication and type of change (add-on, switch, discontinuation) will be described stratified by type of 1st line treatment. Short-term use of insulin as first treatment will be reported but will not be considered 1st line treatment
- Time from initiation of 2nd line treatment to change of medication and type of change (add-on, switch, discontinuation) will be described stratified by type of 2nd line treatment. If applicable the similar analysis will be done for 3rd and 4th line treatments
- For 1st and 2nd line treatments dosing will be described against time since start of treatment
- Comorbidities (diagnosis- and medication-based) will be described at time of initiation of 1st, 2nd, 3rd and 4th line treatment. Comorbidities at initiation of insulin will be described separately

- For patients on different treatment stages (1st ,2nd, 3rd and 4th line), the percentage that move to next level (add-on), modify medication within stage (switch) and initiate insulin treatment will be reported
- The percentages mentioned above will be stratified by gender, age and selected comorbidities

8.7.5 Study objective 5

The incidence and prevalence of diabetes complications and the incidence of retirements and sick leaves will be described by

- number of ongoing treatments
- number of treatments in history

The description will be presented separately for treatment combinations with and without insulin, i.e., two ongoing treatments including insulin and two ongoing treatments without insulin.

8.7.6 Study objective 6

Costs of drugs, hospital care, sick leaves, rehabilitation and early retirement before and after initiation of blood glucose-lowering drug will be estimated one year before and after initiation and stratified by 1st and 2nd line treatments. Drug costs and sickness allowances will be obtained from the prescription register and unit costs for hospitalizations, outpatient visits and rehabilitation will be based on individual-level cost accounting data from one hospital district. For early retirements average cost will be defined and applied for all.

8.8 Quality control

The study will be conducted as specified in this protocol. All revisions to the protocol must be approved by the sponsor, the principal investigator and the co-authors of the study. All changes to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to register holders.

The study protocol has been written by following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (www.encepp.eu/code_of_conduct/documents/ ENCePPCodeofConduct_Rev3.pdf, read 25 Sep 2014). The protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices by International Society for Pharmacoepidemiology (www.pharmacoepi.org/resources/guidelines_08027.cfm, read 25 Sep 2014).

The study protocol will be registered in the ENCePP E-register of Studies (www.encepp.eu/encepp/ studiesDatabase.jsp, read 25 Sep 2014). Study results will also be published in ENCePP pages.

About storage of records and archiving of the statistical programming performed to generate the results, and possible audits, see section 8.6. Due to the study type (register study using administrative databases) on-site monitoring will not be performed.

8.9 Limitations of the research methods

Data on weight, laboratory analyses (e.g. glycohemoglobin, lipids, albumin in urea), blood pressure, smoking, physical exercise and dietary habits are not available for the study population.

Coverage of the Prescription Register containing reimbursement information of all permanent residents of Finland is about 97%. Missing data includes e.g. relatively inexpensive packages and over the counter medications that are not reimbursed.

Medications used during hospitalizations are not available. However, based on the hospital care register the hospitalization periods can be taken into account to define gaps in the drug treatment periods. Also moving abroad or institutionalization during the follow-up period will be taken into account.

9 Protection of human subjects

This is a fully register-based study and patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

EPID Research will receive pseudonymized data including study identification numbers (SIDs) only. EPID Research employees have undertaken professional secrecy and are aware of their concern with the Act on the Openness of Government Activities 621/1999 (based on which the data can be received from the register holders). The study registers are formed on the basis mentioned in the Personal Data Act (523/1999) §12 and the data is handled as described in §14 therein.

The sponsor will not have access to the patient level data. Being a member of the study scientific committee does not repeal this rule to benefit the sponsor employees.

The protocol will be subjected to Ethics Committee of Hospital District of Helsinki and Uusimaa for review and approval. Register notification of the forming study registers will be sent to the Office of the Data Protection Ombudsman.

10 Management and reporting of adverse events/adverse reactions

This study does not meet the criteria for adverse event reporting.

11 Plans for disseminating and communicating study results

The principal investigator together with the co-investigators will write a study report. This report will be delivered to the sponsor and members of the study scientific committee. The report does not include personal level data.

Based on the study report, the principal investigator and co-investigators with co-authors (members of the study scientific committee and possible other contributors approved by the study scientific committee) will prepare (a) scientific manuscript(s) for academic publication. The study scientific committee decides the publication forums. The principal investigator and the study scientific committee shall always have the right to prepare publications of the study results independently of AstraZeneca.

The sponsor is entitled to view the final results prior to submission for publication. AstraZeneca also has the right to comment the results and interpretations thereof without unjustifiably delaying the publication. In this particular study the commenting time for the sponsor during the review rounds is agreed to be maximum of one month. The principal investigator is free not to take the comments of the sponsor into account. Changes in the presentations must be based on scientific reasons only.

The principal investigator and AstraZeneca are committed to ensuring that authorship for all publications should comply with the criteria defined by the International Committee of Medical Journal Editors (ICMJE). It is stated that each author should have participated sufficiently in the work to take public responsibility for the content (www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html, read 27 Jan 2015). AstraZeneca believes that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to AstraZeneca employees.

An abstract of the study findings will be provided through the ENCePP e-register of studies within three months following the final study report. According to the ENCePP Code of Conduct the principal investigator is responsible for publication of the results. The abstract of the main results of the study will be

published, whether positive or negative. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests.

12 References

1. Sund R, Koski S. FinDM II. On the register-based measurement of the prevalence and incidence of diabetes and its long-term complications. A technical report. Tampere: The Finnish Diabetes Association, 2009. [Internet, cited 2014 Sep 25]. Available from: www.diabetes.fi/files/1167/DehkoFinDM_Raportti_ENG.pdf

2. Valle T, Eriksson J, Peltonen M, Aarne M, Koski S. Dehko-raportti 2010:5: Diabeetikkojen hoitotasapaino Suomessa vuosina 2009-2010 [Internet, cited 2015 Feb 2]. In Finnish. Available from: www.diabetes.fi/d-kauppa/dehko/dehko-raportit/2010_5_diabeetikkojen_hoitotasapaino_suomessa_vuosina_2009-2010.616.shtml

3. Diabetes (online). Current Care Guidelines. Working group appointed by the Finnish Medical Society Duodecim, the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society. Helsinki: The Finnish Medical Society Duodecim, 2013 [Internet, cited 2014 Sep 25]. Available from: www.kaypahoito.fi/web/kh/suositukset/suositus?id=hoi50056#s10

4. Finnish Medicines Agency Fimea, Social InsuSocial Insurance Institutionrance Institution. Finnish Statistics on Medicine 2012 [Internet, cited 2015 Feb 2]. Available from: www.fimea.fi/instancedata/prime_product_julkaisu/fimea/embeds/fimeawwwstructure/24954_SLT_2012_net.pdf

13 Approvals

We have reviewed this study protocol (ER-9489, Version 1.0, dated 24 Feb 2015) and agree to its terms by signing it.

Principal investigator:

Tuire Prami 24.2.2015

Signature Date

Tuire Prami

EPID Research, Metsänneidonkuja 12, FI-02130 Espoo

Medical expert of the study scientific committee:

Signature Date

Jorma Lahtela

Tampere University Hospital, Internal Medicine, P.O. Box 2000 FI-33521 Tampere

On behalf of the sponsor:

Signature Date

Susanne Skovgaard Nickelsen, MD VP Medical/Regularory AstraZeneca Nordic-Baltic

Medical Nordic-Baltic, AstraZeneca Nordic-Baltic, Arne Jacobsens Allé 13 DK-2300 Copenhagen S Denmark

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We have reviewed this study protocol (ER-9489, Version 1.0, dated 24 Feb 2015) and agree to its terms by signing it.

Principal investigator:

Signature Date

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EPID Research, Metsänneidonkuja 12, FI-02130 Espoo

Medical expert of the study scientific committee:

25-Feb-2015

Signature Date

Jorma Lahtela

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On behalf of the sponsor:

Signature Date

Susanne Skovgaard Nickelsen, MD VP Medical/Regularory AstraZeneca Nordic-Baltic

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Medical expert of the study scientific committee:

Signature Date

Jorma Lahtela

Tampere University Hospital, Internal Medicine, P.O. Box 2000 FI-33521 Tampere

On behalf of the sponsor:

9. March 2015

Signature Date

Susanne Skovgaard Nickelsen, MD VP Medical/Regularory AstraZeneca Nordic-Baltic

Medical Nordic-Baltic, AstraZeneca Nordic-Baltic, Arne Jacobsens Allé 13 DK-2300 Copenhagen S Denmark

14 List of stand alone documents

- Statistical analysis plan
- ENCePP checklist for study protocols.

Annex 1. Variable lists according to data sources

The Social Insurance Institution

SII will identify the population by searching the special reimbursement decisions for diabetes (refund code 103) by end of 2013, and by listing the patients with a prescription for any blood glucose-lowering drug (ATC: A10) between 01 Jan 1998 and 31 Dec 2013.

For the population identified SII will deliver the data about

- Drug purchases in years 1996-2013
    - ATCs
        - Listed in Annex table 1
    - Purchase dates
    - VNR numbers
    - Package sizes
    - Number of packages
    - Total amount purchased in defined daily doses
    - Cost variables
- Reimbursement statuses until end of year 2013
    - Special reimbursement codes (listed in Annex table 2) with related ICD-10 codes
    - Starting and stopping dates
- Place of domicile if abroad at the end of the years 1996-2013
- Sickness allowances in 1998-2013
    - ≥10 days sick leaves
    - Rehabilitation
- Retirement

Annex table 1: ATC codes of the study drugs by drug class

Drug class	ATC
drugs for acid related disorders	A02
propulsives	A03F
antiemetics and antinauseants	A04
intestinal antiinfectives	A07A
antiobesity preparations, excl. diet products	A08A
antidiabetic drugs	A10
antithrombotic agents	B01
cardiac therapy	C01
antihypertensives	C02
diuretics	C03
beta blocking agents	C07
calcium channel blockers	C08
agents acting on the renin-angiotensin system	C09
lipid modifying agents	C10
thyroid preparations	H03A
antibacterials for systemic use	J01
antimycotics for systemic use	J02
antimycobacterials	J04
antigout preparations	M04
benzodiazepine derivatives	N05CD
benzodiazepine related drugs	N05CF
antidepressants	N06A
drugs for obstructive airway diseases	R03

Annex table 2: Special reimbursement categories included in the study

Category	Disease in Latin
103	Diabetes mellitus
104	Hypothyreosis
124	Cystinuria, morbus Wilson, acrodermatitis enteropathica
137	Insufficientia renis chronica
138	Anemia insufficientialis renalis
201	Insufficientia cordis, incompensatio cordis chronica
205	Hypertonia chronica
206	Angina pectoris, infarctus myocardii inveteratus, morbi ischaemici alii
207	Arrhythmiae cordis chronici
211	Hypercholesterolaemia familialis
212	Arthritis urica, diathesis urica

The National Institute for Health and Welfare (THL)

For history and follow-up information (years 1996-2013) THL will deliver the data from the HILMO register about

- All diagnoses (ICD-10 codes and dates)
- Surgical codes mentioned in the Annex table 3 (and dates)
- Hospitalization periods (starting and stopping days)
    - Costs of each hospitalization (if available)
    - Medical specialty (to exclude primary care if possibly present in HILMO)

For follow-up (years 1998-2013) the data from the Social HILMO register about

- Institutionalizations (starting and stopping days)
    - Type of service (inpatients vs outpatients)

Annex table 3: Surgical codes for comorbidities and causes of death

Procedure	NCSP code
Coronary arteries	FN
Severe ischemic arrhythmia	FPE-FPG
Dialysis	KA_4
Lower limb amputations	NGQ, NHQ

The above-mentioned data should include the information about the patient (SID codes created by SII, age and sex) and the hospital.

Statistics Finland

For the population identified in this study Statistics Finland will deliver data about deaths:

- Date of death
- Causes of death (all levels)
    - ICD-10 codes

SII converts the patient IDs to SIDs and sends the ID – SID pairs to other register holders THL and Statistics Finland. The data sent to EPID Research will include SIDs only.

Annex 2. Comorbidity variables

Annex table 4: ICD-10 codes for comorbidities and causes of death

Disease	ICD-10
Cardiovascular diseases	
Myocardial infarction	I21-I22
Angina pectoris	I20
Chronic ischaemic heart disease	I25
Coronary revascularisation	Z95
Heart failure	I50, I11.0
Severe ischemic arrhythmias	I46-I49
Cerebrovascular disease	
Hemorrhagic/embolic stroke	I60-I64, G45
Diseases of arteries, arterioles and capillaries	I70-I79
Kidney diseases	
Glomerular dysfunction	N08.3
Chronic kidney disease	N18
Unspecified kidney disease	N19
Acute kidney disease	N17
Dialysis	Z49
Microvascular complications	
Diabetic mononeuropathy	G59.0
Diabetic polyneuropathy	G63.2
Diabetic retinopathy	H36.0
Diabetic cataract	H28.0
Diabetic glaucoma	H40.9
Diabetic artropathy	M14.2, M14.6
Peripheral angiopathy	I79.2

Autonomic neuropathy	G99.0
Diabetic nephropathy	N08.3
Diabetes with neuropathy	E10.4, E11.4, E12.4, E13.4, E14.4
Diabetes with nephropathy	E10.2, E11.2, E12.2, E13.2, E14.2
Diabetes with eye complications	E10.3, E11.3, E12.3, E13.3, E14.3
Diabetes with circulatory disturbance	E10.5, E11.5, E12.5, E13.5, E14.5
Diabetes with several complications	E10.7, E11.7, E12.7, E13.7, E14.7
Diabetes with unspecified complications	E10.8, E11.8, E12.8, E13.8, E14.8
Diabetes without complications	E10.9, E11.9, E12.9, E13.9, E14.9
Metabolic complications	
Hypoglycaemia - Diabetic coma	E10.0, E11.0, E12.0, E13.0, E14.0, E16.0-E16.2
Ketoacidosis	E10.1, E11.1, E12.1, E13.1, E14.1
Gastrointestinal diseases	
Oesophagitis	K20
Gastro-oesophageal reflux disease	K21
Other disease of oesophagus	K22
Peptic ulcers disease	K25-K28
Gastritis and duodenitis	K29
GI bleeding	K92.0, K92.1, K92.2
Dyspepsia	K30
Nausea	R11
Other diseases	
Hypertension	I10
Hypercholesterolemia	E78
Hypothyreosis	E03
Cancer	C00-C99
COPD	J44

Urinary tract infection	N34, N39
Gout	M10
Pregnancy	Z32
Diabetes mellitus in pregnancy	O24
Diabetic counselling	Z71.3