Pharmacoepidemiological study protocol ER-9489

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

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Study Information

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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
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Sponsor

Marketing authorization holder financing the study	AstraZeneca Nordic Baltic SE-151 85 Södertälje Sweden
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1 List of abbreviations

ATC code	Anatomical therapeutic chemical classification system code
DDD	Defined daily doses
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

ICPC-2	International Classification of Primary Care
ID	Identification number
OAD	Oral antidiabetic drug
SGLT2	Sodium/glucose cotransporter 2
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
Vnr	Nordic article number (an identification code for a specific article of medicine)

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), University of Tampere / Tampere University Hospital

Medical expert Prof. Johan Eriksson (MD, PhD), University of Helsinki / Hospital District of Helsinki and Uusimaa

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: Diabetes is one of the most rapidly spreading diseases in Finland. There are about 350,000 people receiving antidiabetic medical treatment (6.5% of population), most of them (85%) with type 2 diabetes mellitus (T2DM). Patients often fail to control their blood glucose levels with lifestyle changes and start using oral antidiabetic drugs (OADs) at very early stage of the therapy. When the disease proceeds, many patients need 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 T2DM 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 2015 or a special reimbursement for diabetes (refund code 103) by end of 2015. The study size will be about 350 000 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

The following substantial changes have been made compared to the protocol version 1.0 dated 24 Feb 2015.

Number	Section of study protocol	Amendment or update	Reason
1.	1 List of abbreviations	DDD, ICPC-2, SGLT2 and Vnr added	Insertion of new terms in the document
2.	2 Responsible parties	Prof. Johan Eriksson added	New member in the Steering committee
3.	3 Abstract	- Population size - Treatment vs. disease progression - Study years	According to the changes elsewhere in the document
4.	5 Milestones	Further milestones postponed	Delay in permit process
5.	6 Rationale and background	- Size of the diabetes population - Updating the role of nutrition and OAD treatment during the disease progression - Enlargement of the study setting in terms of study years and aims	- Update of the background information (based on the discussion with SII) - Line of the present Current Case Guideline - Inclusion of one more year (2014) to the study period and specification of the sub-aims of the study
6.	7 Research questions and objectives	- Enlargement of the study setting in terms of study years (study questions 1-3) and aims (study questions 5-6) - Local requirements sub-chapter withdrawn	- Inclusion of one more year (2014) to the study period; specification of the aims of the study (this need raised up in data permit process of SII) - Inclusion of all aims in objectives
7.	8.3 Data sources	Primary Care Register added as a data source	- Progression of the study process
8.	8.3.1 Data linkage and permit process	- Heading numbering - Update of the study status	- Style issue - Progression of the study process
9.	8.4 Study variables	- Small changes in variable definitions - Variables related to primary care data added - Institutionalizations added to the Disease progression and Costs analyses - A new sub-chapter: “8.4.5 Disease progression” created	- Clarification - A new data source - Progression of the study process - This sub-chapter was missing in protocol version 1.0
10.	8.5 Study size	- Increment of the study population size - Enlargement of the study period with year 2014	- Discussion with SII during the data permit process - Increasing the novelty value of the upcoming study results; making researching of the newest drugs possible
11.	8.7 Data analysis plan	Table 2 added	Specification in data analysis

			plan, use of Vnrs in particular analysis
12.	8.7.2 Population summaries	Mentioning year 2014 as follow-up end	Enlargement of the study period with year 2014
13.	8.7.3- 8.7.6 Study objectives 1-6	Changes in statistical analysis plan according to the changes in research questions and objectives	Clarification; changes in research questions and objectives; requested by SII in data permit process
14.	8.7.5-8.7.6 Study objectives 5-6	Changes in statistical analysis plan according to the changes in handling data related to primary care and institutionalizations	A new data source; Progression of the study process
15.	8.8 Quality control	Updates based on the study status	Progression of the study process
16.	9 Protection of human subjects	Updates in Ethics Committee contacting based on the study status	Progression of the study process
17.	13 Approvals	Prof. Johan Eriksson added	New member in the Steering committee
18.	14 List of stand alone documents	Mention about statistical analysis plan withdrawn	Statistical analysis plan is not directly linked to this protocol but is an independent document
19.	Annex 1 Variable lists according to data sources	- Mentioning year 2014 as follow-up end - Clarification of the variable list addressed to the SII - AvoHILMO variables added to the list of required data from THL	- Enlargement of the study period with year 2014 - Requested by SII in data permit process - A new data source
20.	Annex 2 Comorbidity variables	Annex 2 (Annex table 4) withdrawn	Not needed for the data request, as all primary and secondary care diagnoses and treatment periods are included in it. This table will be included in the statistical analysis plan.

Compared to the protocol version 2.0 dated 27 Aug 2015, the study period extension (last year 2014 changed to be 2015) caused amendments in the following chapters in protocol version 2.1:

- Abstract
- Rationale and background
- Research questions and objectives
- Research methods
- Annex 1

Also the Milestones and Approvals were updated in version 2.1 due to the delay in study process (data delivery from SII). List of stand alone documents (including ENCePP check list for study protocols) was not applicable for the changes from study protocol version 2.0 to 2.1.

5 Milestones

Milestone	Planned date
ENCePP registration	13 Apr 2015 (actual date)
Ethics Committee approval (Protocol v. 1.0)	27 Apr 2015 (actual date)
Ethics Committee approval (Protocol v. 2.0)	22 Sep 2015 (actual date)
Protocol 2.1 approval	07 Jun 2016
Data permit approvals based on protocol 2.1	31 Jul 2016
Start of data collection	30 Sep 2016
End of data collection	31 Dec 2016
Statistical analysis completed	28 Feb 2017
Draft report	31 Mar 2017
Final report	31 May 2017
First manuscript sent to a peer-reviewed journal	30 Jun 2017
End of the study, destruction of the person level data	28 Feb 2022

6 Rationale and background

The latest large report by The Finnish Diabetes Association (2009) stated that there were some 280,000 people diagnosed with diabetes receiving treatment in Finland, most of them (85%) with type 2 diabetes mellitus (T2DM) (1). In recent years, however, diabetes has been one of the most rapidly spreading diseases in Finland. Finnish Diabetes Prevention Study (DPS), a prospective follow-up survey by the Finnish Diabetes Association has shown that the incidence of diabetes among T2DM patients was 15% in 2000-2001 as well as in 2009-2010 (2). In 2014 the population receiving antidiabetic drug treatment was assumed to be already 350 000 people (6.5% of the Finnish population).

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 prevention is managed by life style changes (education, diet and physical activity), and the nutrition is a cornerstone of hyperglycaemia through all the phases of the disease (3). Patients often fail to achieve adequate blood glucose control with lifestyle changes and progress oral antidiabetic medication at very early stage of the therapy, metformin being the first-line drug. According to DPS, in 2000-2001 16% of the T2DM patients were treated with diet only, but by 2009-2010 this proportion had decreased to 7% (2). According to the present Current Care Guideline metformin is recommended to be added to the regimen at the time of diagnosing T2DM (3).

Despite of the guideline statements to start the treatment with metformin, an American study in 15 516 patients showed that only 57.8% of the patients using oral antidiabetic drugs (OADs) started the therapy with metformin (4). Drug treatment initiation with metformin was associated with reduced subsequent treatment intensification. Another U.S. study with a ten-year study period found that 45% of metformin treatments were used as monotherapy (5).

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 costs.

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. Only little comparative effectiveness evidence exist worldwide (4), and especially the effects of the glucose-lowering drugs on long-term clinical outcomes are uncertain (6).

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 (7). 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 2015 (the latest year available from nationwide registers), the study setting includes also the newest drug groups on the market, which increases the novelty value of the study. 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. The present Finnish protocol includes also local characteristics that are based on requests from the Pharmaceuticals Pricing Board, subordinated to the Ministry of Social Affairs and Health in Finland.

7 Research questions and objectives

The objectives of this study are to describe:

1. Annual incidence and prevalence of T2DM patients in 1998-2015
2. Annual overall and cause-specific mortality in T2DM patients in 1998-2015
3. Annual incidence and prevalence of cardiovascular, microvascular and chronic kidney diseases, and amputations in T2DM patients in 1998-2015
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
    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 in study population at different treatment levels
    b) Describe the incidence of retirements, rehabilitation periods, sick leaves and hospitalization periods in study population at different treatment levels
6. Costs of drugs, hospital care, sick leaves, rehabilitations and early retirements in relation to initiation of a new blood glucose-lowering drug

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 from 1998 to 2015 **or** a special reimbursement for diabetes (refund code 103) by end of 2015.

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), and/or
- 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 (in the hospital data), the special reimbursement status for T2DM or filled prescription of any blood glucose-lowering drug during the study period, whichever occurs first. In case of the entitlement for T2DM in special reimbursement register prior to study start, the index date is defined to be 01 Jan 1998.

Follow-up: Follow-up starts at index date and ends at date of moving abroad, death, or the end of the year 2015, whichever occurs first.

Incident cases: 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 (i.e. no living abroad within two years prior to initiation).

Also when analysing incident cases of comorbidities, only the patients with a minimum history of two years available (i.e. no living abroad within two years prior to the event) will be included.

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
Primary Care Register (AvoHILMO) *	National Institute for Health and Welfare	Diagnoses Visits
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 Rehabilitations
Statistical pension register	Social Insurance Institution	Retirements

* Data available since 2011

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

8.3.1 Data permit process and data linkage

Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) to cover the nationwide study was received based on the protocol version 1.0. Data permits have been requested from each registry holder based on the study protocol and ethical approval. All the relative authorities were informed about protocol version 2.0. Study permit process will be updated according to protocol version 2.1.

If any of the register holders dismisses a permit application, the study is considered to be ceased. Neither could the study be completed without ethical approval.

Patients will be identified by the Social Insurance Institution according to the inclusion criteria. 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 (based on year of birth)
  - Continuous (years)
  - Categorical (categories to be defined based on data)
- Sex (Male/Female)
- Characterization of the patients as insulin dependent / non-insulin dependent in the Primary Care Register data (International Classification of Primary Care, ICPC-2, codes T89 / T90, respectively)

8.4.3 Comorbidities and causes of death

- Comorbidities: ICD-10 codes, ICPC-2 codes
- Special reimbursement codes with related ICD-10 diagnoses
- Drug treatment: ATC codes
- Causes of death: ICD-10 codes

8.4.4 Exposure variables

- Blood glucose-lowering drug utilization
  - ATC codes
  - Vnr numbers (Nordic article numbers)
- Other concomitant drug utilization
  - ATC codes
  - See Annex 1 (Annex table 1) for details.

Inpatient hospitalizations and institutionalizations as well as moving abroad will be taken into account when analysing the gaps in drug exposures based on reimbursed drug purchases.

8.4.5 Disease progression

- Antidiabetic drug treatment
- Cardiovascular, microvascular and chronic kidney diseases, and amputations
  - ICD-10 codes
  - Special reimbursement codes with related ICD-10 diagnoses
  - ICPC-2 codes
  - ATC codes
- Retirements
- Rehabilitation periods
- Institutionalizations
- Sick leaves
- Hospitalization periods
  - Inpatient periods
  - Outpatient visits
- Primary care
  - Inpatient periods
  - Outpatient visits

8.4.6 Costs

- Glucose-lowering drugs: costs from prescription register
- Other drugs: costs from prescription register
- In- and outpatient hospitalizations: actual costs or national averages for unit costs of health care services in Finland based on pricing in a single representative hospital district (depending on the data available)
    - Primary care
    - Secondary care
- Sickness allowance
- ≥10 days sick leaves
- Rehabilitation: an average cost will be defined and applied for all patients
- Retirement: an average cost for early retirement will be defined and applied for all patients
- Institutionalization: an average cost for early long-term institutionalization will be defined and applied for all patients

8.5 Study size

The study aims to include all T2DM patients in the nationwide Finnish Prescription Register in 1998-2015. The estimated study population size is about 350 000 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 report finalization and then destroyed. As the register holder of the study register EPID Research is in charge of 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 has been 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 2015). 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 sex during 1998-2015 using counts and percentages.
- The annual overall and cause-specific mortality in the prevalent T2DM study population will be presented by sex and by age during 1998-2015. The results will be presented separately for:
    - The whole cohort
    - Different treatment levels
- The annual incidence and prevalence of cardiovascular, microvascular and chronic kidney diseases, and lower limb amputations in the prevalent T2DM study population will be presented by age and sex during 1998-2015. The results will be presented separately for:
    - The whole cohort
    - Different treatment levels

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. In these analyses new blood glucose-lowering drugs listed in Table 2 will be analysed at Vnr level.
- 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. In these analyses new blood glucose-lowering drugs listed in Table 2 will be analysed at Vnr level.
- Dosing and changes in dosing against time since start of treatment will be described. The dosing definition is based on purchased amount of a particular drug in defined daily doses (DDDs) and time difference between consecutive purchases during the follow-up. In these analyses new blood glucose-lowering drugs listed in Table 2 will be analysed at Vnr level.
- Comorbidities (diagnosis- and medication-based) will be described at time of initiation of 1st, 2nd, 3rd and 4th line treatment. Analysis for particular drugs or drug groups (such as insulin, sulphonylureas or GLP-1 agonists) will be described separately.
- For patients on different treatment levels (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 will be stratified by sex, age, selected comorbidities and calendar year.

8.7.5 Study objective 5

The disease progression will be described by

- Comorbidity (incidence and prevalence)
    - Cardiovascular, microvascular and chronic kidney diseases, and amputations
- Retirements (incidence, person years)
- Rehabilitation periods (incidence, person years)
- Institutionalizations (incidence, person years)
- Sick leaves (incidence, person years)

- Hospitalization periods
    - Inpatient periods (incidence, person years)
    - Outpatient visits (incidence)
- Primary care
    - Inpatient periods (incidence, person years)
    - Outpatient visits (incidence)

These results will be stratified by sex, age, calendar year and different treatment levels.

8.7.6 Study objective 6

Costs of drugs (at Vnr level), hospital care, sick leaves and rehabilitation one year before and after initiation of a new blood glucose-lowering drug listed in Table 2 (and the change between these two time periods compared to the other patients at the same treatment level) will be estimated and stratified by sex, age and calendar year, and treatment levels. Patients with an index day in 2015 or living abroad a year prior to their index day in 1998-2014 will be excluded from this analysis.

Drug costs will be obtained from the prescription register (actual costs for each purchase), and sick leaves as periods and by sickness allowances. For rehabilitations an average cost will be defined and applied for all.

Costs for hospitalizations and outpatient visits will be extracted from the original data if available. Alternatively a unit cost will be based on cost accounting data from one hospital district. This decision will be based on the quality of the data.

For early retirements and early long-term institutionalizations of the patients using new blood glucose-lowering drugs (Table 2) during the study period, an average cost for a person-year will be defined and applied for all. The mean time of retirement/institutionalization under consideration is compared to the mean time of retirement/institutionalization of the whole cohort and other patients at the same treatment level at one particular calendar year. These will be stratified by sex.

Table 2. GLP-1 analogs and agonists, and SGLT2 inhibitors currently on the Finnish market separated at Vnr code level (8)

Product name	Vnr	Substance	ATC	Mode of action
Bydureon	088891 495854	exenatide	A10BX04	GLP-1 agonist
Byetta	072978 072996	exenatide	A10BX04	GLP-1 agonist
Forxiga	041140 492107 507959 596876	dapagliflozin	A10BX09	SGLT2 inhibitor
Jardiance	106581 110972 526918 541084	empagliflozin	A10BX12	SGLT2 inhibitor
Lyxumia	376568 464765	lixisenatide	A10BX10	GLP-1 agonist
Trulicity	391550 564626	dulaglutide	A10BX (not assigned yet)	GLP-1 agonist
Victoza	050365 080629	liraglutide	A10BX07	GLP-1 analog
Xigduo	052071 054950 379097 393404	dapagliflozin (and metformin)	A10BD15	SGLT2 inhibitor

Abbreviations: Vnr, Nordic article number; ATC, Anatomical therapeutic chemical; GLP-1, Glucagon-like peptide-1; SGLT2, sodium/glucose cotransporter 2

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 has been registered in the ENCePP E-register of Studies (www.encepp.eu/encepp/studiesDatabase.jsp, read 03 Jun 2015). At the time of submitting the protocol version 2.0 to ENCePP, an ENCePP Seal will be applied as encouraged by ENCePP when registering the study. Study results will published in ENCePP pages (See also chapter 11).

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 versions 1.0 and 2.0 were approved by Ethics Committee of Hospital District of Helsinki and Uusimaa. 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

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13 Approvals

I have reviewed this study protocol (ER-9489, Version 2.1, dated 07 Jun 2016) and agree to its terms by signing it.

Principal investigator:

Tuire Prami
EPID Research, Metsänneidonkuja 12, FI-02130 Espoo, Finland

Tuire Prami 07 Jun 2016

Signature Date

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 2015, and by listing the patients with a reimbursed prescription for any blood glucose-lowering drug (ATC: A10) between 01 Jan 1998 and 31 Dec 2015.

For the population identified SII will deliver the data about

- Drug purchases in years 1996-2015
    - ATCs
        - Listed in Annex table 1
    - Purchase dates
    - Vnr numbers (sufficient for antidiabetics, ATC: A10, only)
    - Package sizes
    - Number of packages
    - Total amount purchased in DDDs
    - Cost variables
- Reimbursement statuses until end of year 2015
    - Special reimbursement codes (listed in Annex table 2) with related ICD-10 codes
    - Starting and stopping dates
- Sex of the patient
- Year of birth
- Information about place of domicile abroad at the end of the years 1996-2015
- Sickness allowances in 1997-2015
- ≥10 days sick leaves in 1997-2015
    - Starting day
    - Stopping day / the length of the period
- Rehabilitation periods 1997-2015
    - Starting day
    - Stopping day / the length of the period
- Retirements 1998-2015
    - Starting day (the first during the study period)

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 1996-2015) 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 history and follow-up information (years 2011-2015) THL will deliver the data from the AvoHILMO register about

- All diagnoses (ICPC-2 codes and dates)
- Visit start and visit end time points
- Type of contact
- Professional involved
- Costs of the service (if available)

For follow-up (years 1998-2015) 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, NFQ, NHQ

The above-mentioned data should include the information about the patient: SID codes created by SII, and the hospital/health centre/institution.

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.