Pharmacoepidemiological study report synopsis ER-9489

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

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Study ID: ER-9489

Sponsor: AstraZeneca Nordic Baltic

Report version: 1.0

Report date: 14 November 2017

Study Information

Title	**A retrospective nationwide cohort study to investigate the treatment of type 2 diabetic patients in Finland – DAHLIA**
Study ID	ER-9489
Report synopsis version	1.0
Report synopsis date	14 November 2017
EU PAS register number	ENCEPP/SDPP/8202
Sponsor	AstraZeneca Nordic Baltic SE-151 85 Södertälje, Sweden
Sponsor contact person	Susanna Jerström, Medical Evidence Manager Medical Nordic-Baltic SE-151 85 Södertälje, Sweden
Active substance	ATC codes A10 (Drugs used in diabetes)
Medicinal product	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)
Country of study	Finland
Authors of the report synopsis	Solomon Christopher, Anna Lundin, Minna Vehkala, Fabian Hoti

Table of contents

1 Study report summary (Abstract)

Rationale: The overall objective of this study was to describe type 2 diabetes mellitus (T2DM) patients in Finland, especially their antidiabetic medication use, and to discuss the progression of the disease in terms of comorbidities, mortality and drug treatment. In addition, evaluation of treatment practices, cost for concomitant use and cost-benefit assessments for selected new blood glucose-lowering drugs (GLD) were conducted.

Methods: This was a retrospective observational database linkage cohort study using patient level data from different nationwide registers in Finland. The target population comprised of over 18 years old T2DM patients with purchase of any GLD during 1998-2015 or a special reimbursement for diabetes by the end of 2015. Patients with type 1 diabetes mellitus were excluded from the study population.

Information on drug purchase, diagnoses during in-patient hospitalization, outpatient hospital visit and primary care visits, and mortality was obtained from the Finnish national registries of Social Insurance Institution (SII), National Institute for Health and Welfare (THL), and Statistics Finland (SF), respectively. In addition, data on rehabilitations, sick leaves and retirements were provided by SII while data on institutionalizations were provided by THL. Linkage among different sources of data at individual level was based on unique personal identification numbers.

The T2DM study population was described during 1998-2015 using annual values of incidence, prevalence, GLD usage and usage of drugs other than GLD. The drug usage and comorbidities were also described at the latest time available time point (End of 2015). Treatment intensification and disease progression was described through summaries of drug usage and comorbidities at different levels of antidiabetic treatments and second-line medication. Specific cardiovascular (CV) comorbidities and all-cause mortality were further described using annual age-standardized risk ratios in comparison to the general population.

Costs of GLDs were presented in relation to specific new GLDs of interest. In addition, costs of health-related events such as hospitalizations, sick leaves, rehabilitation and institutionalizations were presented in resource-time utilization units.

Results: The study included all T2DM patients in the nationwide Finnish Prescription Register during 1998-2015. The final study cohort consisted of 523 292 patients. The annual incidence and prevalence have increase about 1.6 times over the study duration. The annual risk of mortality and CV comorbidities have decreased during the study duration. Trends in annual usage of GLDs were observed where some GLDs such as DPP-4 inhibitors increased while some other GLDs such as Sulfonylureas have decreased over the study duration.

The most frequent second-line treatment addition to biguanides were DPP-4 inhibitors and Sulfonylureas. CV risk treatment constituted the largest proportion of other drugs used by T2DM patients in 2015.

Over the study duration, the risk of other health-related events such as institutionalizations, rehabilitations and sick-leaves have decreased in the T2DM patients. However, the risk of in- and outpatient hospitalizations did not change markedly.

Conclusion: Increase in incidence and prevalence of T2DM signifies the increasing burden of disease and importance for diabetes care. Reduction in annual risks of all-cause mortality, CV comorbidities and other health-related events indicate overall improvement in diabetes care.

The increasing and decreasing trends in annual usage of different GLDs signifies the change in treatment and management of T2DM, and reflect changes in health policies such as reimbursement policies affecting treatment patterns.

2 List of abbreviations

ATC code	Anatomical therapeutic chemical classification system code
DDD	Defined daily dose
DPP-4	Dipeptidyl peptidase 4
DPS	Finnish Diabetes Prevention Study
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
GLD	Blood glucose-lowering drug
GLP-1	Glucagon-like peptide-1
HILMO	Finnish Hospital Care Register
ICD-10	International classification of diseases, 10th revision
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 (Kela)
SPC	Summary of product characteristics
SF	Statistics Finland (Tilastokeskus – TK)
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)

3 Approvals

We have reviewed this study report synopsis (ER-9489 Version 1.0, dated 14th November 2017) and confirm it by signing it.

Principal investigator:

Signature 12.12.2017 Date

Fabian Hoti

EPID Research, Metsänneidonkuja 12, FI-02130 Espoo

Sponsor project lead/On behalf of the sponsor:

Signature 05.12.2017 Date

Johan Bodegård

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4 Responsible parties

Sponsor: AstraZeneca Nordic Baltic

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

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

Principal investigator: Fabian Hoti, PhD

Co-investigators: Tuire Prami, PhD, Principal Investigator until May 3, 2017

Solomon Christopher, MSc, Statistician

Minna Vehkala, PhD, Statistician

Study scientific committee: Principal investigator: Fabian Hoti (PhD), EPID Research

Tuire Prami, PhD, EPID Research, until May 3, 2017

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

5 Amendments and updates

No.	Date	Section of study protocol	Amendment or update	Reason
1.	03 MAY 2017	2 Responsible parties	Name of the Principal investigator changed from Tuire Prami to Fabian Hoti	Administrative changes
2.	03 MAY 2017	2 Responsible parties	Name of the member of Study scientific committee changed from Tuire Prami to Fabian Hoti	Administrative changes
3.	03 MAY 2017	8.2 Setting and population	Method changes - Excluded those with no GLD purchase during study period - Excluded those with: <18 years at first GLD purchase and <30 years at first insulin purchase - Performed 2 sub-group analyses for periods in line with data from registers of other Nordic countries to allow comparability	Comparability with studies from other Nordic countries
4.	03 MAY 2017	8.5 Study size	Method changes - Extension of the study period with year 2015	- Increasing the novelty value of the upcoming study results; making researching of the newest drugs possible
5.	03 MAY 2017	8.7 Data analysis plan	Method changes - In addition to treatment levels (number of concomitant GLDs), describe second line treatments for those using metformin only	Comparability with studies from other Nordic countries

6 Milestones

Milestone	Date
Registration in the EU PAS register	13 APR 2015
Ethics Committee approval (Protocol v. 1.0)	27 APR 2015
Start of data collection	15 OCT 2016
End of data collection	15 FEB 2017
Data permit approvals based on protocol 2.1 + amendment v1.0	15 JUN 2017
Ethics Committee approval (Protocol v. 2.1 + amendment v1.0)	12 SEP 2017
Statistical analysis completed	29 SEP 2017
Final report synopsis of study results	15 OCT 2017

7 Rationale and background

In patients with T2DM, diminishing beta-cell function leads to a progressive decrease in insulin secretion, increased hepatic glucose production and reduced insulin sensitivity. T2DM prevention is managed by life style changes (education, diet and physical activity), and lifestyle factors are important in managing hyperglycaemia through all the phases of the disease [1]. Patients often fail to achieve adequate blood glucose control with lifestyle changes and progress to oral antidiabetic medication at a very early stage of the therapy, metformin being the first-line drug. According to the Finnish Diabetes Prevention Study (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 already at the time of diagnosing T2DM [1].

Oral anti-diabetics (OADs) can be used in several treatment levels: either by a stepwise increase in dose adjustments of individual drugs within a specific range to achieve the desired response or through combination of multiple drugs to achieve appropriate blood glucose control [1]. However, at some point in time the OADs might not have the sufficient effect, explained by the progressive nature of T2DM, and an injectable GLD, glucagon-like peptide-1 (GLP-1) receptor agonist or insulin, will be added to the treatment.

Several new classes of GLDs, including the GLP-1 receptor agonists, also known as incretin mimetics, have entered the market. They are used as add-on drugs to metformin (the most commonly used OAD), and in some cases as monotherapy [1]. The newest international guidelines enable the use of several different GLDs as second-line add-on to metformin. This is, however, frequently limited by national regulations because of high costs.

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

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. Parallel studies are conducted in Sweden, Norway, and Denmark, which make between-country comparisons possible.

8 Research questions 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. The study also includes analysis of health economic characteristics.

8.1 Primary Objectives

1. Annual incidence and prevalence of T2DM 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 GLDs and the treatment journey in T2DM patients
    a) Time to initiation, persistence, discontinuation, concomitance, and switching of GLDs
    b) Different treatment levels (from 1st line treatment to higher level combination treatments)
    c) Changes in dosing of GLDs

d) Initiation, discontinuation, switching and changes in relation to the comorbidity during follow-up

e) Describe how well GLD treatment practices follow the current care guidelines in terms of using treatment levels 1, 2 and 3, 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 GLD

9 Research methods

9.1 Study design

This was a retrospective observational database linkage cohort study using patient level data from multiple nation-wide registers in Finland. The study aimed at describing drug utilization in T2DM patients.

The linkage of different nation-wide register databases results in an open (dynamic) cohort of incident and prevalent T2DM patients, as identified by diagnosis codes, reimbursement decision and /or drug purchases. Exposure to blood GLDs were defined using prescription database.

Drug utilization was described for GLDs at the ATC group level, specific GLD of interest and drugs other than GLDs as numbers (percentages) of annual users. In addition, second-line GLDs and treatment levels were further described in a separate section.

The study also describes all-cause mortality and selected comorbidity in the T2DM cohort annually. Age-standardized mortality and incidence ratios were used to describe the annual mortality and comorbidity, respectively, in comparison to the general population within the same age-groups. Mortality with reference to T2DM was further described using life-years lost as compared to Finnish population at the same age.

Costs of drugs and other health-related events such as hospitalizations, rehabilitation, institutionalizations, sick leaves and early retirements were described with references to GLDs of interest.

9.2 Data sources

Registers used in the study and the respective 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
Care Register for Health Care (HILMO)	National Institute for Health and Welfare	In- and outpatient diagnoses Hospitalization periods
Primary Care Register (AvoHILMO) *	National Institute for Health and Welfare	Primary care diagnoses Date of visit
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	≥10 days sick leaves Rehabilitations periods
Statistical pension register	Social Insurance Institution	Date of retirements

* Data available since 2011

9.2.1 Data permit process and data linkage

Approval of the 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 were requested from each registry holder based on the study protocol and ethical approval. Ethical approval and data permits were updated according to the latest protocol (version 2.1 with amendment 1.0).

9.3 Population and setting

Study population consists of T2DM patients in Finland during the study period from 1998 to 2015. A brief description of the data sources, the national registers and regional databases, within Finland is provided in Section 9.2. The study population will be identified by the following inclusion and exclusion criteria:

Inclusion criteria:

- A purchase of any GLD (ATC: A10) drug from 1998 to 2015 **or** a special reimbursement for diabetes (refund code 103) by the end of 2015.

Exclusion criteria:

- Patients with no GLD purchase during the study period
- 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
- Patients with a type 1 diabetes diagnosis (E10) and only insulin use during the first year of treatment
- Age <30 at the start of insulin treatment
- Age <18 at the start of any GLD
- Polycystic ovary syndrome (PCOS) defined by the ICD-10 code O28.2 or combination treatment with G03GB02 and metformin. However, patients with Metformin therapy after 45 years of age will be considered as type 2 diabetic.
- Gestational diabetes defined by ICD-10 code O24.4 will have a wash out window of one year. The first dispense of GLD after one year from diagnosis date will classify a patient as a type 2 diabetic patient (unless criteria for type 1 is fulfilled)

Patients re-entering T2DM population: For those patients who were excluded based on diabetes types other than type 2, the patient was re-included as type 2 diabetic at the first start of GLD (non-insulin drug for type 1 diabetes patients).

9.3.1 Definitions

Index date: For each patient, the index date was defined as the date of the first purchase of any GLD during the study period.

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 GLDs were defined as patients with no purchase of GLD (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) were included.

Drug exposure period: Drug exposure starts at the time of the drug purchase. The length of the drug exposure period was defined by the amount of DDDs included in the purchase and the estimated daily dosage. For the first purchase the daily dosage was assumed to be 1 DDD and for consecutive purchases the daily dose is estimated as the amount of DDDs in the previous purchase divided by the time differences between the two purchases. If a drug purchase date occurred during on-going exposure of the same drug, the start of the drug exposure period may be moved forward for maximum of 30 days.

If there was a time difference of more than 180 days between two drug purchases, the estimated daily dosage was adopted from the previous estimated daily dose. The estimated daily usage was rounded off to half a DDD as the minimum daily dosage.

Second-line medication: All patients with metformin as monotherapy in first line were selected. In a second step, all patients with another GLD class (switch or add-on) was defined as second line. In order to be included as second line the date of second line must be at least 6 months after the first line date. In addition, at least one dispense/prescription of metformin during the year preceding the second line date must be found.

Second-line medication is classified in a hierarchical manner, starting with insulin, followed by Sulfonylureas, DPP4 inhibitors, SGLT2 inhibitors, GLP1 receptor agonists and other medications. For

example patients who initiate simultaneously both insulin and Sulfonylureas will be classified as an insulin patient.

Treatment levels: Treatment levels in this study are defined as the number of unique GLDs simultaneously used at a given time irrespective of which line of treatment they belong to (insulin as a rescue treatment is ignored). The treatment levels also include as separate levels insulin use with and without other GLDs.

9.4 Variables

The variable definition criteria are described in this section. The exact variable definitions using ATC, VNR, ICD-10 and ICPC-2 codes are provided in annex 1 (Tables 1 - 6).

9.4.1 Variables for population identification

- Purchases of GLDs: 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, O28.2

9.4.2 Demographics

- Age in years and age-groups 18-19 followed by 5 year intervals (18-19, 20-24, 25-29, 30-34, and so on)
- Sex (Male/Female)

9.4.3 Comorbidities and mortality

- Comorbidities (Annex 1, Table 5)
    - In- and outpatient hospital visits (ICD-10 codes), primary care visits (ICPC-2 codes)
    - Special reimbursement codes with related ICD-10 diagnoses
    - Drug treatment: ATC codes
- Mortality: death dates

9.4.4 Exposure variables

- GLD utilization (Annex 1, Tables 1-4)
    - ATC codes
    - VNR numbers (Nordic article numbers)
- Other concomitant drug utilization (Annex 1, Table 6)
    - ATC codes

9.4.5 Disease progression

- Antidiabetic drug treatment
- Cardiovascular, microvascular and chronic kidney diseases, and amputations using comorbidity definitions (Section 9.4.3)
- Retirements
- Rehabilitation periods
- Institutionalizations
- Sick leaves
- Hospitalization periods (inpatient periods and outpatient visits)

9.4.6 Costs & resource use

Drugs: Drug cost for each purchase was provided from prescription register

- GLDs:

Health-related events: Costs were not provided for the following events. The starting day and end day / length of duration for each episode of event was provided. This information was used to calculate resource utilization.

- In- and outpatient hospitalizations
- Primary care visits
- ≥10 days sick leaves
- Rehabilitations
- Retirements
- Institutionalizations

9.5 Events of interest

As a drug utilization study, this study does not involve predefined outcomes for evaluating their risk due to any drug exposure. The outcomes are described for the T2DM population.

9.5.1 Mortality

All-cause mortality is described for the T2DM population annually and by age-groups. Annual age-standardized mortality ratios are also calculated.

9.5.2 Comorbidities

In this study, the following comorbidities are of interest: Cardiovascular, microvascular, kidney-related, lower-limb amputations and other diseases. These diseases are described at baseline and with relevance to drug utilization (at initiation of second-line treatments, treatment level 1 and initiation of new GLDs of interest identified at VNR levels).

Four cardiovascular diseases of specific interest namely myocardial infarction (MI), stroke, atrial fibrillation (AF) and heart failure (HF) are further described for T2DM population by crude incidence annually and by age-groups. Annual age-standardized incidence ratios are also calculated for these diseases.

9.5.3 Other health-related events

Health-related events associated with in-patient hospitalizations, out-patient hospital visits, primary care visits, rehabilitations, institutionalizations, sick leaves and early retirements are described by annual incidence and in relation to initiation of GLDs of interest identified by VNR numbers.

9.5.4 Economic aspects

The economic aspects are described with reference to drug utilization using costs for drugs and resource utilization for hospital care, sick-leaves, rehabilitations and institutionalizations. All health-related costs other than drug costs are presented as resource-time utilization.

9.6 Study size

The study aimed to include all T2DM patients in the nationwide Finnish Prescription Register in 1998-2015. The estimated study population size was approximately 350 000 patients. The actual study cohort size was 523 292 patients. The population flowchart (Figure 1) presents the flow of study participants starting from the number of individuals included in the study based on GLD purchase and/or reimbursement decisions. The numbers excluded from there onwards due to criteria defined in section 9.3 are also displayed.

9.7 Data management

R language [3] (www.r-project.org, read 25 Sep 2014) was 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.

All study data will be retained until 5th May 2020 and then destroyed. All supporting documents will be retained for five years after the report finalization. As the register holder of the study register EPID Research is in charge of deleting the data. 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 the protocol. All requests to use the study data for other purposes than mentioned in the study protocol must be subjected to appropriate data permit processes.

9.8 Statistical methods

The principles of the statistical analysis are outlined below.

9.8.1 Population summaries

The annual incidence and prevalence of T2DM population was described from 1998 to 2015. Incidence was defined by index date (first purchase of a GLD) in each year and T2DM-free population at the beginning of the year. Prevalence was defined as the size of T2DM population in each year by mid-year population size.

Population summaries were described at end of 2015 for those who are alive at the end of 2015. The summaries include distributions of age and sex, usage of GLDs, other drugs and comorbidities. Drug usage was described based on drugs used only in 2015 (one year history). Comorbidities were described using all available history. In addition, annual drug usage for GLDs and other drugs were also presented annually.

Comorbidities, GLDs and other drugs were described at initiation of second-line treatments. The second-line treatments were also described annually for those initiating second-line treatment in the respective years. Second-line treatment summaries were reported only for incident T2DM population during 1998-2015.

Comorbidities, GLDs and other drugs were described at first initiation of treatment level 1. The change in GLDs at the initiation of treatment level 2 from level 1 was also described. Treatment level summaries were reported only for incident T2DM population during 1998-2015.

Comorbidities, GLDs and other drugs were described at first initiation of new GLDs of interest (grouped at VNR level).

9.8.2 Main statistical methods

Part-I

Annual crude mortality rates were estimated for predefined age-groups using Poisson regression. Annual age-standardized mortality ratios were computed using indirect standardization. The annual mortality rates of the Finnish population for the same age-groups were used for standardization. Crude mortality rates along with the number at risk, person-years, events and rates (95% CI) were presented separately, both annually and by age-groups.

Life-expectancy and life-years lost were computed using Chiang's method [4]. Life-years lost were presented for the Finnish and Swedish (for comparison) mean age for T2DM patients. Life-years lost from ages 40 to 80 were also plotted for men and women separately. Annual numbers and percentages of known causes of death were presented at ICD-10 code group levels.

Four CV comorbidities of special interest (myocardial infarction (I21), stroke (I63), heart failure (I50), atrial fibrillation (I48)) were analysed separately. These comorbidity events were included if they were the main diagnosis for an in-patient hospitalization episode with at least one overnight stay. Only one comorbidity event per person per year was included in the analysis. Annual crude incidence rates for these four comorbidities of interest were estimated for predefined age-groups using Poisson regression. Annual age-standardized incidence ratios were also computed using indirect standardization. The annual incidence rates of these comorbidities for the Finnish population for the same age-groups were used for standardization. Crude incidence rates along with the number at risk, person-years, events and rates (95% CI) are presented separately, both annually and by age-groups.

Part-II

Incidence of rehabilitation, institutionalization, sick leaves, and retirements are calculated per 100,000 person-years. Number of events, follow-up time and incidence rates are provided annually. Incidence rates and the 95% confidence intervals were computed using Poisson regression.

GLD costs 6 months before and after initiation of selected new GLDs: Drug costs were computed annually at the ATC group level. The data for 2010-2015 were used for these analyses due to availability of the new drugs of interest during this period. For combination drugs, the cost corresponding to each component was divided proportional to the costs of the corresponding individual drugs within that year.

If the first initiation of a drug of interest was after 1 July 2015, the individual was excluded in the cost analyses with respect to that drug. This was performed only when analysing drug costs before and after 6 months from initiation of drugs of interest. Wilcoxon signed-rank tests were used to compute the p-values for differences in costs. Costs are presented in euros.

Average annual total drug cost analysis Annual average costs of GLDs were presented for the years when the new GLDs of interest were available. Costs were presented both as averaged over individuals who had any GLD purchase within the year and over number of purchases within the year.

For combination drugs, the cost corresponding to each component was divided proportional to the costs of the corresponding individual drugs within that year.

Resource use for events: Resource utilization for sick-leaves, in-patient and outpatient hospitalizations were presented for 6 months before and after initiation of drugs of interest. All health-related costs other than drug costs are presented as resource-time utilization.

9.8.3 Missing values

The data for some events such as retirements, institutionalizations, sick-leaves and rehabilitations were not completely available for 2015. Therefore, the events data in 2015 were not included in the cost analysis.

9.8.4 Subgroup analyses

For purposes of comparison with similar studies conducted in Sweden, Denmark and Norway, two sub-groups were defined for analyses: (i) dataset for GLD users between 2007 and 2015 (along with their drug and comorbidity history) was used to compute incidence, prevalence of T2DM and baseline summaries drug use and comorbidities for the T2DM population. (ii) dataset for initiators of second-line treatment between 2006 and 2015 was used to compute summaries for drug use and comorbidities at initiation of second-line treatment. These results are presented in two separate appendices (appendices 3 and 4).

9.9 Quality control

The study was performed by following the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct [5] and the Guideline for Good Pharmacoepidemiology Practices (GPP) [6] by the International Society for Pharmacoepidemiology (ISPE).

The study has been registered in the ENCePP E-register of Studies (www.encepp.eu/encepp/studiesDatabase.jsp, read 03 Jun 2015). The ENCePP Seal has been obtained as encouraged by ENCePP when registering the study. Results will be published in the EU PAS register maintained by EMA.

10 Results

10.1 Participants

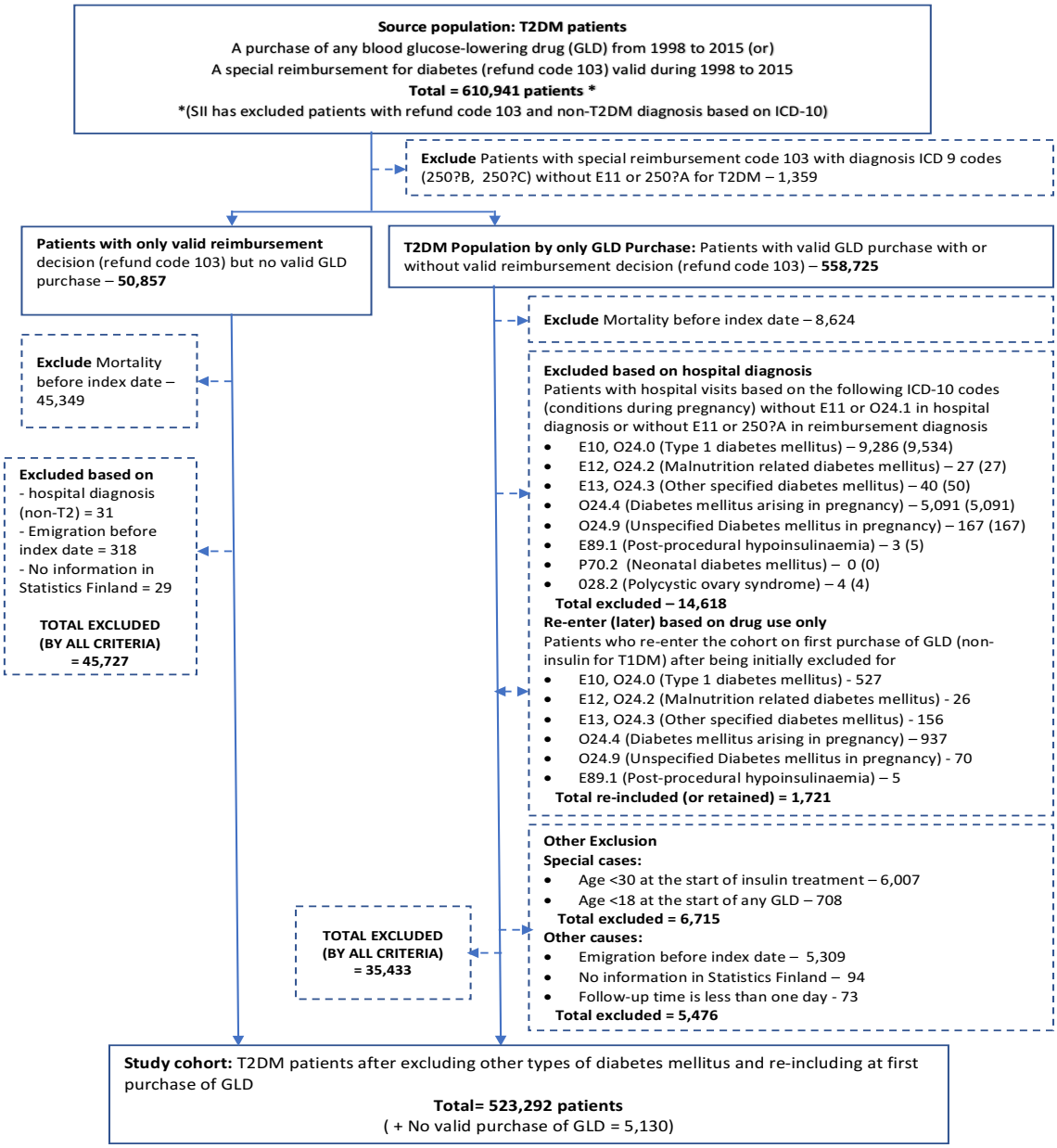

Figure 1. The flow of participants starting from the target population to the study cohort by inclusion and exclusion criteria

10.2 Incidence and prevalence of T2DM

10.2.1 Annual incidence of T2DM

Annual incidence of T2DM from 1998 to 2015 are presented (Table 1.1). The incidence is based on the number of new cases of T2DM during each year and the T2DM-free population in the beginning of the year. The new cases are defined by medication database only (first purchase of a GLD). This analysis is also presented stratified by sex in Figure 2, and Tables 1.2 and 1.3, Appendix 1.

The annual incidence gradually increased about 1.6 times from 276 in 1998 to 439 in 2015, per 100,000 person-years. The annual incidence of T2DM for men was consistently higher than for women throughout the study period. Starting in 2006 there was a rise in the annual incidence of T2DM defined by first purchase of a GLD with a subsequent peak during 2008.

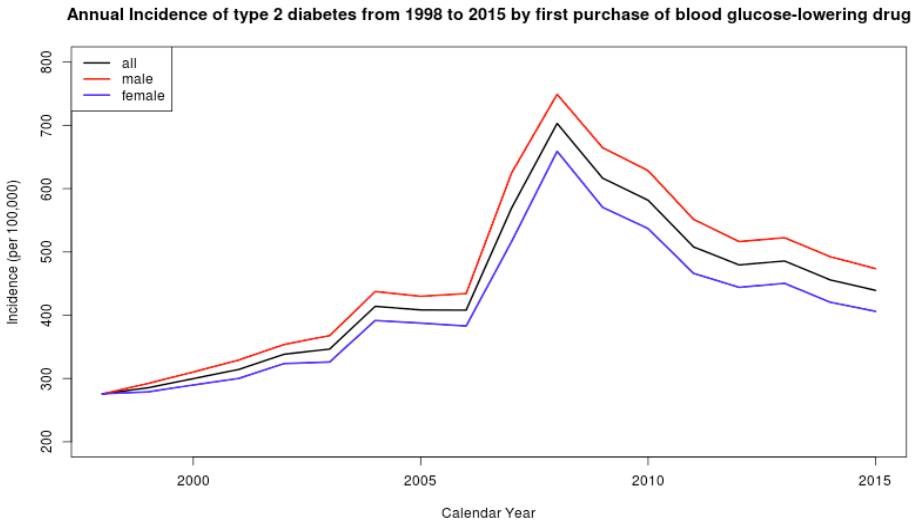

Figure 2. Annual Incidence of T2DM by first GLD purchase from 1998 to 2015

10.2.2 Annual prevalence of T2DM

Annual prevalence of T2DM from 1998 to 2015 are presented (Table 1.4). The prevalence is based on the number of cases of T2DM and mid-year national population. This analysis is also presented stratified by sex in Figure 3, and Table 1.5 and 1.6, Appendix 1.

The annual number and prevalence gradually increased about 60% during the study period from 2.6% in 1998 to 6.7% in 2015. The observed increase in prevalence was bigger in men than in women where the increase in prevalence was 75% in men compared to 41%% in women.

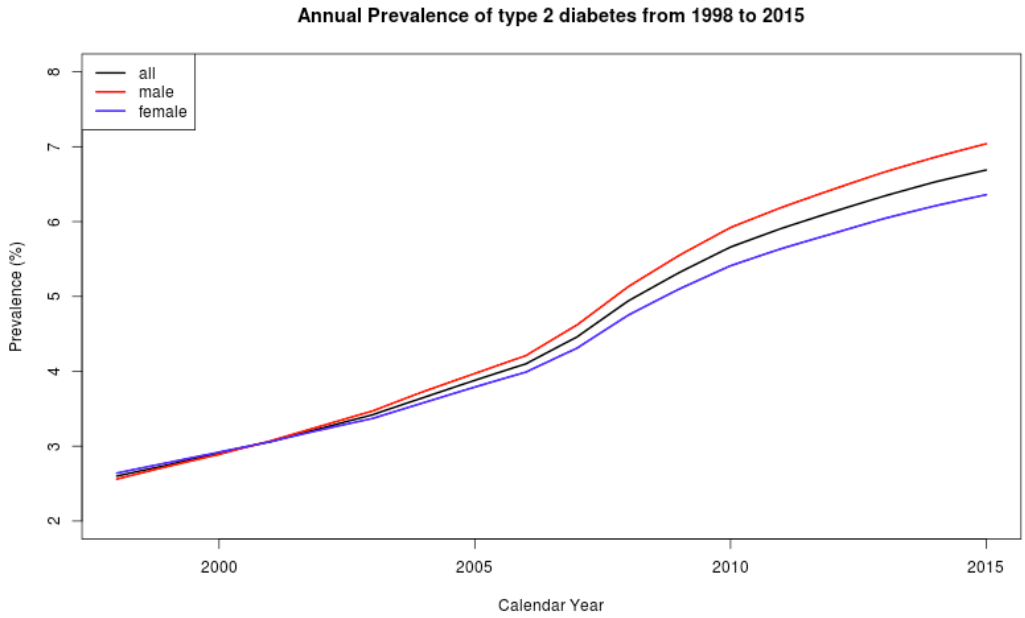

Figure 3. Annual Prevalence of T2DM from 1998 to 2015

Table 2 combines Tables 1.1 and 1.4, Appendix 1 and presents the annual incidence and prevalence of T2DM from 1998 to 2015.

Table 2. Annual numbers, incidence (per 100,000 person years) and prevalence (%) of type 2 diabetes from 1998 to 2015. Incidence is defined by first purchase of GLD

Year	Incidence of T2DM			Prevalence of T2DM		
	New cases (N)	Finnish population at risk	Incidence	All cases (N)	Finnish population size	Prevalence (%)
1998	13895	5039285	275.73	134256	5159646	2.60
1999	14373	5037046	285.35	142442	5171302	2.75
2000	15105	5038673	299.78	150650	5181115	2.91
2001	15855	5044251	314.32	159128	5194901	3.06
2002	17079	5047167	338.39	168748	5206295	3.24
2003	17504	5050984	346.55	178318	5219732	3.42
2004	20945	5058293	414.07	191188	5236611	3.65
2005	20681	5064392	408.36	203886	5255580	3.88
2006	20700	5073069	408.04	216171	5276955	4.10
2007	28958	5084313	569.56	236502	5300484	4.46

2008	35786	5089812	703.09	262922	5326314	4.94
2009	31372	5088505	616.53	284576	5351427	5.32
2010	29612	5090700	581.69	304200	5375276	5.66
2011	25885	5097067	507.84	319209	5401267	5.91
2012	24490	5107465	479.49	332702	5426674	6.13
2013	24861	5118568	485.70	345709	5451270	6.34
2014	23368	5126044	455.87	357151	5471753	6.53
2015	22535	5130157	439.27	367356	5487308	6.69

10.2.3 Summary of study population of T2DM patients

A total of 523,292 T2DM patients were identified between 1998-2015. The mean age of the patients alive in the end of 2015 were 66.6 years ranging from 18 to 108. (Table 2.1, Appendix 1). The proportion of female T2DM patients were approximately 48%. The majority of the T2DM patients alive at the end of 2015 were in the age ranges of 60-64 (13.46%), 65-69 (17.91%) and 70-74 (14.54%).

10.3 Drug utilization and treatment intensification

The distribution of GLD usage in T2DM patients alive at the end of 2015 is described in Table 3 (Table 2.2, Appendix 1). The majority of T2DM patients were users of Biguanides (83%). During the study period the Biguanide use were steadily increasing from 1998 (46%) until 2007 (76.4%) and has subsequently been at a steady level from 2008 at approximately 80-84% (Table 2.5-2.7, Appendix 1).

The insulin use during the study period dropped from 36.5% in 1998 to 26.3% in 2015. In contrast, after their intoduction on the market in 2006 the use of DPP-4 inhibitors rose from 0.4% in 2007 to 38.6% by the end of 2015.

Table 3. Usage of GLDs in 2015 in T2DM patients who are alive at the end of 2015

Glucose-lowering drugs	Users N (%)
Biguanides	255533 (83.23)
Sulfonylureas	16389 (5.34)
Dipeptidyl Peptidase 4 (DPP-4) inhibitors	118533 (38.61)
Sodium/Glucose Co-transporter 2 (SGLT-2) inhibitors	7309 (2.38)
Glucagon-like Peptide (GLP-1) receptor agonist	12272 (4.00)
Meglitinides	2340 (0.76)
Thiazolidinediones	8495 (2.77)
Insulin (all)	80644 (26.27)

Other (non-diabetic) drug usage

Tables 2.8-2.10, Appendix 1 describes the annual use of drugs other than GLDs in T2DM patients alive at the end of each year during the entire study period, respectively. At the end of 2015 the largest proportion of other non-diabetic drugs belonged to the group of CV risk treatment where 85% of all patients were users as displayed in Table 4, reproduced from Table 2.3, Appendix 1. It increased from 60% in 1998 to 85% in 2015. Antihypertensives increased from 57% in 1998 to 78% in 2015.

Table 4. Usage of other (non-diabetic) drugs in 2015 in T2DM patients who are alive at the end of 2015

Non-diabetic drugs	Users N (%)
CV risk treatment	300661 (85.07)
Statins	196831 (55.69)
Antihypertensives	275947 (78.08)
ACE inhibitors	104659 (29.61)
ARB	122109 (34.55)
Dihydropyridines (calcium channel blockers)	102956 (29.13)
Low ceiling diuretics (thiazides)	0 (0.00)
Beta blockers	172080 (48.69)
Non-hydropyridines (calcium channel blockers)	3083 (0.87)
High ceiling diuretics (loop-diuretics)	52162 (14.76)
Aldosterone antagonists	11212 (3.17)
Digoxin	10970 (3.10)
Warfarin	43820 (12.40)
Receptor P2Y12 antagonists	14060 (3.98)
Direct factor Xa inhibitors	3275 (0.93)
Direct thrombin inhibitor	1277 (0.36)
Other antiplatelets	1684 (0.48)
Weight loss drugs	0 (0.00)

10.3.1 Second line treatment

The average age of T2DM patients initiating second level treatment was 63.6 years ranging from 20-100 years with the largest proportion of patients being in the age group of 60-69 years (Table 5.1, Appendix 1). The proportion of female T2DM patients initiating second line treatment were 45%. The mean time since diagnosis of T2DM until initiating second line treatment were 3.5 years.

Table 5.2, Appendix 1, describes baseline comorbidities at initiation of second line treatment. The highest proportion falls in the cardiovascular diseases group. Of the patients starting second line treatment 58% were using statins and a majority of patients were using one or more drugs belonging to antihypertensives (Table 5.3, Appendix 1).

The second line treatment initiated after metformin were represented by DPP-4 inhibitors in more than half of the patients (55.4%). Sulfonylureas were initiated as a second line treatment by 23.2%. The drug groups that had the lowest proportion of second line users after metformin were the SGLT-2 inhibitors (0.3%) and GLP-1 receptor agonists (0.2%). Insulin as a second line treatment initiated after metformin were used by 7.6% of the patients (Table 5.5, Appendix 1).

Tables 5.6-5.8, Appendix 1 present the second line treatment initiated after metformin in each year. For the year 2015, DPP-4 inhibitors were the highest proportion (89.5%). Over the study period from 1998-2015 the number of patients initiating second line treatment after metformin in the form of sulfonylureas has declined from 92.1% in 1998 to 49.6% in 2005 and subsequently to 1.3% in 2015 (Table 5.8, Appendix 1). In contrast, from 2007 to 2015 the initiation of DPP-4 inhibitors as a second line treatment after metformin has increased from 2.4% to 89.5%.

10.3.2 Treatment levels

The treatment levels (number of concomitant GLDs used) and general characteristics for incidence T2D patients have been described in Table 6.1-6.7 in Appendix 1.

In short, the age of initiation of treatment level 1, 2 or 3 showed little variation with an average ranging from 62.3 to 63.1 years. Age group categorization were consistent with these findings where the average age did not vary between treatment levels. The proportion of males initiating 3rd level treatment was larger than for women (58% vs 42%) compared to those initiating 1st level treatment where the proportions were 52 and 48% for men and women, respectively. The average time to initation of treatment level 1 and 3 after diagnosis of T2DM were 0.02 and 5.66 years respectively (Table 6.1, Appendix 1)

The highest proportion of comorbidities among T2DM patients at the time of first initiation of treatment level were in the category of cardiovascular diseases. The percentage of cardiovascular disease events were consistenly equal to or lower in the patients initiating 1, 2 and 3 treatment levels compared to insulin only and insulin with others groups (Table 6.2, Appendix 1). The difference was most pronounced for heart failure (6-8% vs 14-17%) and stroke (7% vs 11-12%).

Some of the other comorbidities that were higher in the insulin groups were severe hypoglycemia (1-6% vs 9-10%), cancer (8-9% vs 13-21%) and chronic kidney disease (0.5% vs 2-5%) for treatment level 1-3 compared to insulin only or insulin and others.

The highest proportion of concomitant medication other than GLDs were observed in the drug groups statins and antihypertensives for all treatment levels (Table 6.3, Appendix 1). The use of both statins and antihypertensives were generally higher in patients in treatment level 3 compared to the other treatment levels. Statins were used in 70% of treatment level 3 patients compared to 44% and 36% in treatment level 1 and insulin only respectively.

At initiation of treatment level 1, the GLDs with highest proportions were biguanides (79%) and sulfonylureas (15%) (Table 6.5, Appendix 1)

The number and percentage of patients moving from treatment level 1 to level 2 were studied for eight different drug groups (Table 6.6-7, Appendix 1). Analysis showed that if starting on biguanides as level 1 the second level treatment addition was most commonly a DPP-4 inhibitor (55.6%) or a drug from the sulfonylureas group (29%). If starting on any of the other groups as level 1 the most common addition for level 2 treatment were a biguanide.

10.3.3 Drug groups at VNR level

Patients starting on GLDs of interest as identified by VNR numbers were generally younger, especially in comparison to those initiating different levels of teatment (Tables 7.1 and 6.1, Appendix 1).

The time since T2DM diagnosis until the first use of drug groups analysed at VNR level show that it takes an average of 8.8-13.2 years until initiating anti-diabetic drugs Byetta, Bydureon, Forxiga, Jardiance, Lyxumia, Victoza and Xigduo (Table 7.1, Appendix 1). In addition, the patients initiating these drugs also have an average of 3 or more GLDs in their existing therapy. The gender distribution in users of the different drug groups showed that Xigduo, Lyxumia and Jardiance are more frequently used by men (67, 70 and 62%) compared to a more even distribution in the use of Forxiga, Byetta, Bydureon and Victoza with 59, 53, 54 and 54% respectively for men.

Calendar year data presents the proportion of individuals starting the drug at each year among those who ever used the drug (Table 7.1, Appendix 1). These new GLDs of interest were introduced and/or initiated only during the years 2011-2015.

CV comorbidities for patients initiating treatment with drugs from the different drug group show that atrial fibrilation is more frequent within Byetta, Bydureon, Forxiga, Victoza and Xigduo users, while angina pectoris is more common within Lyxumia and Jardiance users (Table 7.2, Appendix 1). COPD was present as a prevalent comorbidity for all of the drug groups studied ranging from 43.1% in Forxiga and Jardiance users to 65.2% in Lyxumia users.

The highest proportion of concomitant medication other than GLDs at first initiation of drug groups analysed at VNR level were observed in the drug groups statins and antihypertensives for all drugs studied (Table 7.3, Appendix 1). It was less frequent with concomitant use of weight loss drugs when using Forxiga, Jardiance and Xigduo compared to the other groups.

When starting treatment with any of the drugs studied at the VNR level patients were to a high extent, >93%, using biguanides in their existing therapy. Pre-existing use was also common for DPP-4 inhibitors, insulins, as well as sulfonylureas with proportions ranging from 70-85%, 35-87% and 38-60% for the three drug groups respectively (Table 7.4, Appendix 1).

10.4 Comorbidity and Mortality in T2DM

10.4.1 Comorbidities

A list of comorbidities in T2DM patients alive at the end of 2015 is presented in Table 5 (reproduced from Table 2.4, Appendix 1). Approximately 25% of T2DM patients had some cardiovascular complications, in particular myocardial infarction (4%) , stroke (7%), heart failure (7%), atrial fibrillation (9%) and others. Approximately one fourth of the T2DM patients had experienced microvascular complications. Less than 1% of the population had ever had a lower limb amputation.

Table 5. Comorbidities (using all available history) in T2DM patients who are alive at the end of 2015

Comorbidities	N (%)
Cardiovascular disease (CVD)	88645 (25.08)
Myocardial Infarction	14331 (4.05)
CABG	7519 (2.13)
PCI with stent	240 (0.07)
Unstable angina	11398 (3.23)
Angina pectoris	19395 (5.49)
Heart failure	23104 (6.54)
Atrial fibrillation	32102 (9.08)
Stroke (Total)	26428 (7.48)
Hemorrhagic stroke	2778 (0.79)
Ischaemic stroke	16027 (4.53)
Transitory ischemic attack (TIA)	13276 (3.76)
Peripheral artery disease	18556 (5.25)
Major organ specific bleeding	12670 (3.58)
Chronic kidney disease	8403 (2.38)
Dialysis	1086 (0.31)
Microvascular complications	87878 (24.86)
Diabetic mono / poly-neuropathy	12494 (3.54)
Diabetic eye complication	24118 (6.82)
Diabetic foot / peripheral angiopathy	11205 (3.17)
Diabetic kidney disease	16344 (4.62)
Diabetes with several unspecified complications	60880 (17.23)
Severe hypoglycemia	22928 (6.49)
Keto- lactate acidosis	2783 (0.79)
Cancer	30291 (8.57)
COPD	47133 (13.34)
Lower limb amputations	3180 (0.90)
Total number of patients	353423

Age-adjusted incidence rates and standardized incidence ratios for the four cardiovascular comorbidities of interest (MI, stroke, HF and AF) in T2DM patients show a reduction over the study period, 1998-2015, for all events (Tables 4.1-4, Appendix 1). The standardized incidence ratios for stroke was reduced from 2.01 (1.93, 2.09) in 1998 to 1.23 (1.19, 1.28) in 2015 which is a 39% decrease (Figure 4). Similar decreases in the standardized incidence ratios were also observed for MI (30%) and heart failure (29%). However, the decrease for atrial fibrilation (8%) was marginal (Table 6).

These reductions were also evident from the annual crude incidence rates for these comorbidities. All of the four comorbidities showed gradual decrease in the annual crude incidence rates during 1998-2015 (Tables 4.5-4.6, Appendix 1).

The crude incidence rates by age-groups showed a gradual increase in risk with increasing age for all of the four comorbidities (Tables 4.9-4.11, Appendix 1). This also confirms that the use of age-standardization was appropriate.

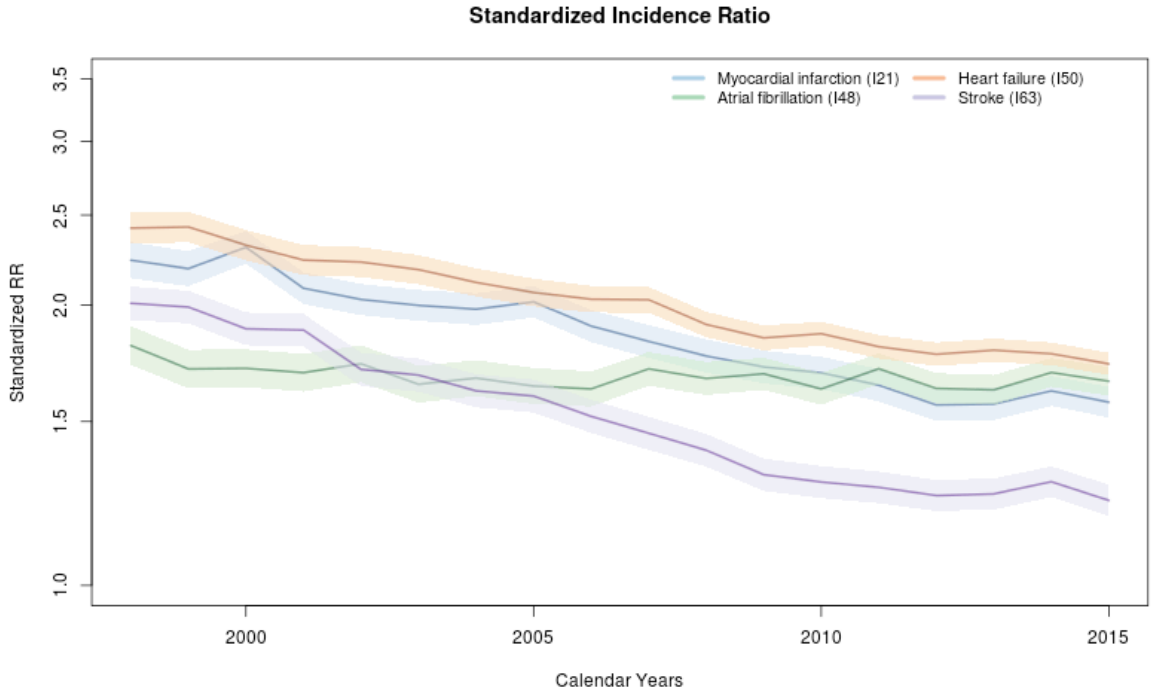

Figure 4. Annual standardized incidence ratios for 4 comorbidities of interest from 1998 to 2015

10.4.2 Incidence of overall mortality in T2DM patients

Age-standardized mortality ratio for T2DM patients for the years 1998-2015 are presented for all-cause mortality in Table 3.1, Appendix 1. The standardized mortality ratio decreased over the years from 1.43 in 1998 to 1.24 in 2015 which is about 13% reduction (Table 6).

Crude mortality rates for all-cause mortality by calendar year and age are presented in Tables 3.2 and 3.3, Appendix 1. The crude mortality rates in the T2DM patients decreased over the period 1998-2015 and increased with age.

Table 6. Annual age-standardised risk ratios (95% CI) for all-cause mortality, myocardial infarction, stroke, heart failure and atrial fibrillation in T2DM patients from 1998 to 2015

Year	All-cause Mortality	Myocardial infarction	Stroke	Heart failure	Atrial fibrillation
1998	1.43 (1.40, 1.47)	2.24 (2.14, 2.34)	2.01 (1.93, 2.09)	2.42 (2.33, 2.52)	1.81 (1.73, 1.90)
1999	1.49 (1.46, 1.53)	2.19 (2.10, 2.29)	1.99 (1.91, 2.07)	2.43 (2.34, 2.52)	1.71 (1.63, 1.79)
2000	1.52 (1.48, 1.55)	2.31 (2.22, 2.40)	1.89 (1.81, 1.97)	2.32 (2.24, 2.41)	1.71 (1.63, 1.79)
2001	1.49 (1.45, 1.52)	2.09 (2.01, 2.17)	1.88 (1.81, 1.96)	2.24 (2.16, 2.32)	1.69 (1.62, 1.77)
2002	1.48 (1.45, 1.51)	2.03 (1.95, 2.11)	1.71 (1.64, 1.78)	2.23 (2.15, 2.31)	1.73 (1.65, 1.81)
2003	1.47 (1.44, 1.50)	2.00 (1.92, 2.08)	1.68 (1.62, 1.75)	2.18 (2.11, 2.26)	1.65 (1.57, 1.72)
2004	1.44 (1.41, 1.47)	1.98 (1.91, 2.06)	1.62 (1.55, 1.69)	2.12 (2.04, 2.19)	1.67 (1.60, 1.75)
2005	1.45 (1.42, 1.48)	2.02 (1.94, 2.10)	1.60 (1.53, 1.66)	2.06 (1.99, 2.14)	1.64 (1.57, 1.71)
2006	1.40 (1.38, 1.43)	1.90 (1.83, 1.98)	1.52 (1.46, 1.58)	2.03 (1.96, 2.10)	1.63 (1.56, 1.70)
2007	1.43 (1.40, 1.46)	1.83 (1.76, 1.90)	1.46 (1.40, 1.52)	2.03 (1.96, 2.09)	1.71 (1.64, 1.78)
2008	1.38 (1.36, 1.41)	1.76 (1.69, 1.84)	1.40 (1.34, 1.45)	1.91 (1.85, 1.97)	1.67 (1.60, 1.74)
2009	1.30 (1.28, 1.33)	1.72 (1.65, 1.79)	1.32 (1.26, 1.37)	1.85 (1.79, 1.90)	1.69 (1.62, 1.76)
2010	1.30 (1.28, 1.33)	1.69 (1.63, 1.76)	1.29 (1.24, 1.34)	1.86 (1.81, 1.92)	1.63 (1.56, 1.69)
2011	1.27 (1.25, 1.30)	1.64 (1.58, 1.71)	1.27 (1.23, 1.33)	1.81 (1.75, 1.86)	1.71 (1.65, 1.78)
2012	1.29 (1.26, 1.31)	1.56 (1.50, 1.63)	1.25 (1.20, 1.30)	1.77 (1.72, 1.82)	1.63 (1.57, 1.69)
2013	1.26 (1.24, 1.29)	1.57 (1.51, 1.63)	1.25 (1.21, 1.30)	1.79 (1.74, 1.84)	1.62 (1.56, 1.68)
2014	1.24 (1.22, 1.26)	1.62 (1.56, 1.68)	1.29 (1.24, 1.34)	1.77 (1.73, 1.82)	1.69 (1.63, 1.75)
2015	1.24 (1.21, 1.26)	1.57 (1.52, 1.63)	1.23 (1.19, 1.28)	1.73 (1.68, 1.78)	1.66 (1.60, 1.72)

The life-expectancy and life-years lost at the ages 62 and 67 for the following reasons: the mean age of the T2DM population in 2015 is 67, and the mean age at index date for the T2DM population is 62 (Table 3.4, Appendix 1). The life-years lost for the T2DM population at age 67 in comparison the general population decreased by 0.95 years from 3.6 years in 1998 to 2.81 in 2015. For the age 62, the decrease was 1.2 years. The life years lost for ages 40 to 80 for the T2DM population comparted to the general population is presented for males and females separately in Figure 5.

The annual numbers and percentages of known primary causes of death in T2DM population were presented in Tables 3.5-3.7, Appendix 1. Deaths related to circulatory system (ICD-10: I00-I99) were the highest proportion in all years and decreased from 58% in 1998 to 44% in 2014 which is a 23% reduction. This class also includes the CV deaths. On the other hand, deaths related to neoplasms increased from 16.5% in 1998 to 22.3% in 2014 which is a 35% increase. Death with ICD-10 codes E00-E90 which include endocrine, nutritional and metabolic disorders decreased from 6.4 in 1998 to 3.8 in 2014 which is a 40% reduction. This class also includes T2DM.

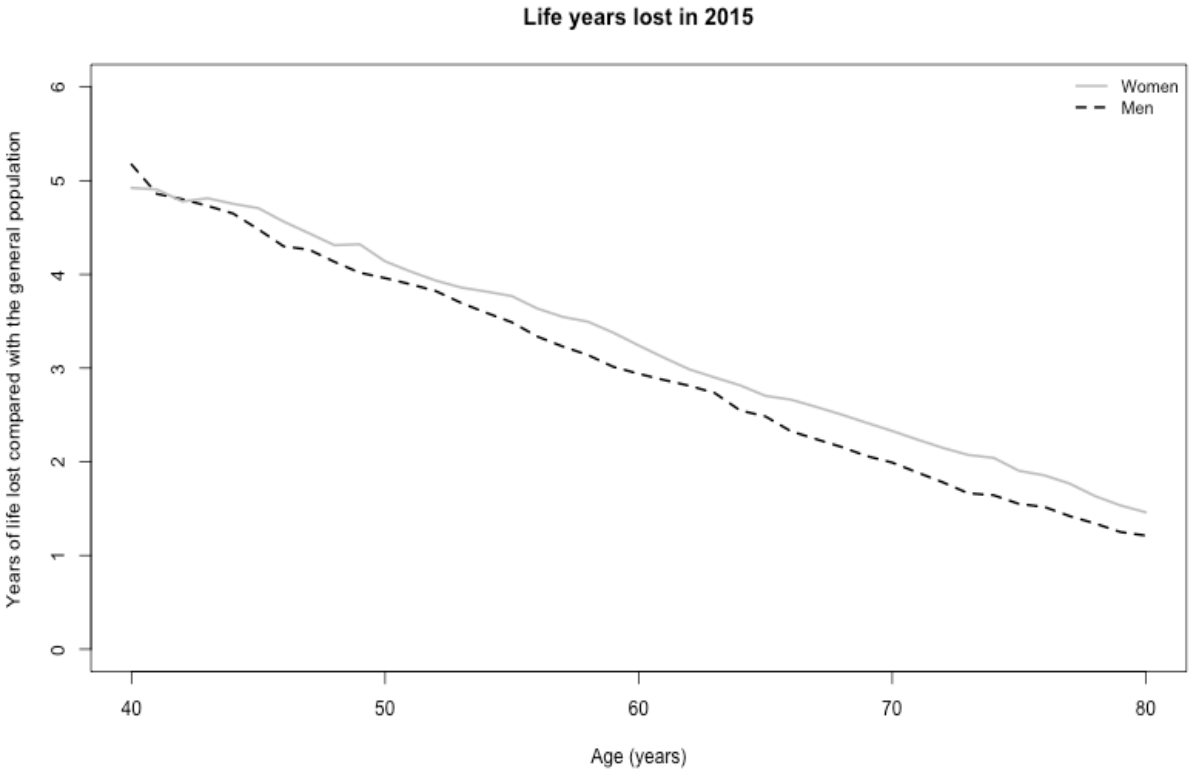

Figure 5. Life-years lost by gender for those with T2DM between the ages of 40 and 80 years

10.5 Economic aspects in relation to T2DM and Drugs of interest

The results of the economic aspects are presented as part-II analyses in Appendix 2.

10.5.1 Incidence of health-related events

Tables 1-6, Appendix 2 present incidence of rehabilitation, institutionalization, sick leaves, retirements in-patient hospitalizations and out-patient hospital visits are calculated per 100,000 person-years. There is a decreasing trend over the years for incidences of rehabilitation (9,661 to 2,262 from 1998 to 2014, respectively), institutionalization (35,421 to 14,321 from 1998 to 2014, respectively), sick leaves (21,589 to 12,854 from 1998 to 2014, respectively) and retirements (9,999 to 1,426 from 1998 to 2014, respectively).

The incidence of in- and outpatient hospitalizations did not change much over the years (365,922 to 358,465 from 1998 to 2015, respectively).

When calculating incidence of rehabilitations, 1,862 short episodes that occurred within a longer episode of the individual were not considered.

10.5.2 Cost of GLDs

Tables 7-8, Appendix 2 present the cost of other GLDs 6 months before and after initiation of new GLDs of interest. Table 7, Appendix 2 presents cost of GLDs other than the GLD of interest 6 months before and after initiation. Table 8, Appendix 2 presents cost of GLDs including the GLD of interest 6 months before and after its initiation. Initiation of a new GLD marks treatment intensification making the increase in overall drug cost a natural consequence.

Tables 9-10, Appendix 2 present the annual average cost of GLDs groups (ATC level) during the years when drugs of interest are available. Averages were calculated for both all users of any GLD in the respective year and only those who purchased the GLD group in the respective year.

10.5.3 Resource use

Health related resource utilization is presented with reference to usage of drugs of interest. The cost of events are presented in health resource time (for example, number of days of hospitalization) and can be multiplied by a relevant average cost to obtain the actual cost.

Tables 11-13, Appendix 2 present costs of sick leaves, in- and outpatient hospitalizations, and primary care visits 6 months before and after initiation of GLDs of interest. The costs of these events did not differ too much between before and after initiation of GLDs of interest.

Table 14, Appendix 2 provides the annual average number of days of in- and outpatient hospitalizations, institutionalizations, sick leaves and rehabilitations from 1998 to 2014. Average annual number of hospitalizations and rehabilitations have decreased over the years.

10.6 Sub-group analyses

10.6.1 GLD users between 2007 and 2015

The dataset for GLD users between 2007 and 2015 (along with their drug and comorbidity history) was used to compute incidence, prevalence of T2DM and baseline summaries drug use and comorbidities for the T2DM population. The results from this sub-population had similar findings and annual trends to the 1998-2015 T2MD population for incidence and prevalence of T2DM, and drug usage for both GLDs and other drugs. The results from this sub-population analysis is presented in Appendix 3.

The annual number and incidence of new T2D defined by purchase of GLDs during 2007-2015 is presented in Table 8, Appendix 3. The incidence of new T2D patients decreased from 2008 to 2015 reflecting similar trends as for the 1998-2015 population with a peak incidence value in 2008. The annual number and prevalence of T2DM during 2007-2015 is presented in Table 7, Appendix 3. The prevalence of T2D increased from 4.08% in 2007 to 6.42% in 2015.

In a subpopulation analysis for patients dispensed with GLDs during 2007-2015, the average age was 67.5 years in 2015 (Table 1, Appendix 3). The mean time since the first GLD also increased during the study period from 5.7 to 8.1 years. The use of Biguanides in the subpopulation were similar to the pattern seen in the later phase of the 1998-2015 population with values ranging between 73.4-78.5% of patients using biguanides during 2007-2015 (Table 2-3, Appendix 3). DPP-4 inhibitors increased steadily from 0.4% in 2007 up to 34.9% in 2015, while sulfonylureas decreased from 36.4% in 1998 to 4.8% in 2015. GLP-1 receptor agonist and SGLT-2 inhibitors also steadily increased since their introductions in 2011 and 2013, respectively.

The annual usage of other (non-diabetic) drug groups during 2007-2015 are presented in tables 4-5, Appendix 3. The history of comorbidities for those patients alive in the ned of 2015 is presented in Table 6, Appendix 3.

10.6.2 Second-line treatment intiators between 2006 and 2015

The dataset for initiators of second-line treatment between 2006 and 2015 was used to compute summaries for drug use and comorbidities at initiation of second-line treatment. The results from this sub-population had similar findings to the 1998-2015 T2MD population. The results from this sub-population analysis is presented in Appendix 4.

The annual age and gender distribution of patients initiating second line treatment during 2006-2015 is presented in table 1.1, Appendix 4. The mean age increased from 62.4-65.3 during the 10 year study period with a female proportion of patients ranging between 43.1-45.1%.

The number and percentage of patients initiating different GLDs at the initiation of second line treatment betweeen 2011-2015 is presented in table 2.1, Appendix 4. The percentage of patients initiating a DPP-4 inhibitor as a second line treatment in the subpopulation was 84.9-89.5% between 2011-2015. The GLP-1 receptor agonists and SGLT-2 inhibitors were initiated as a second line treatment in 0.5% and 2.12% of the TD2 patients respectively in 2015.

Table 5.1, Appendix 4 describes comorbidites at time of first initiation of second line treatment in year 2015. Table 4.1, Appendix 4 describes use of other drugs at time of first initition of second line treatment in year 2015. Analysis looking at the number of patients initiating second line treatment and use of CV drugs at time of first initiation of second line treatment during 2006-2015 is presented in table 3.1, Appendix 4.

10.7 Protection of human subjects

This is a fully register-based study and patients were not contacted in any phase of the study. The protocol all versions 1.0, 2.0 and 2.1 (with amendment 1.0) were approved by Ethics Committee of Hospital District of Helsinki and Uusimaa.

10.8 Adverse events

This study does not meet the criteria for adverse event reporting [7].

11 Discussion

11.1 Key results

Both the prevalence and the incidence of T2DM gradually increased about 1.6 times from 1998 to 2015. The observed increase and subsequent peak in annual incidence of T2DM during the years 2006 to 2008 occurred during a period where a diabetes screening programme in Finland was conducted simultaneously [8]. The increased effort of identifying diabetic patients from the population in this programme could possibly have had some impact on the annual prevalence and incidence of T2DM observed in the study population during this time.

With respect to GLD usage, Biguanide use were steadily increasing from 1998 (46%) until 2007 (76.4%) and subsequently been at a steady level from 2008 (80%) while sulfonylureas steadily decreased from 69% in 1998 to 5% in 2015. DPP-4 inhibitors steady increased from 2007 up to 39% in 2015. GLP-1 receptor agonist and SGLT-2 inhibitors also steadily increased since their introductions in 2011 and 2013, respectively.

For the second-line treatment after metformin, DPP-4 inhibitor was observed with highest proportion overall (55%) and in 2015 (90%). Treatment levels that include insulin (insulin only and insulin + others) were associated with higher proportions of certain comorbidities. However, this only confirms that insulin use is associated with severity of diabetes and hence associated with other comorbidity [1].

With respect to treatment levels, most T2DM patients started with biguanides at level 1. DPP-4 inhibitors and Sulfonylureas were added to biguanides the most at level 2. CV risk treatment constituted the largest proportion of other drugs used by T2DM patients in 2015.

The annual age-standardized mortality ratio decreased over the years from 1.43 in 1998 to 1.24 in 2015 which is about 13% reduction. The annual age-standardized incidence ratios for the four comorbidities of

interest were observed to decrease from 1998 to 2015 by 39% for stroke, 30% for MI, 29% for heart failure and 8% for atrial fibrillation.

Incidence of health-related events such as rehabilitation, institutionalization, sick leaves, and retirements decreased over the study duration 1998-2015, while in- and outpatient hospitalizations remained the same.

11.2 Limitations

The eligibility for reimbursements for the cost of reimbursable drugs prescribed by a doctor or dentist applies to all permanent residents of Finland. Coverage of the Prescription Register containing reimbursement information is nearly complete [9,10] with some minor missing data including e.g. over the counter medications that are not reimbursed, prescribed medications that is not reimbursed at a reasonable market price or has not been approved for reimbursement by the pharmaceutical board. The missing data may include some drugs of interest other than GLDs (Annex 2, table 6). Medications used during hospitalizations are not available.

11.3 Generalisability

As a retrospective cohort study utilizing individual level data from nation-wide registers during the study period, this study represents the Finnish T2DM population well. Identifying T2DM patients using GLD use and reimbursement decision codes as well as employing carefully chosen exclusion criteria to exclude non-T2DM patients using hospital diagnoses is a strength of this study. The inclusion and exclusion criteria are also similar to those used in studies from other Nordic countries and allows comparability. The results from the two sub-populations: (i) trends in annual incidence and prevalence of T2DM, baseline comorbidities, and annual drug use (GLD and other) among GLD users during 2007-2015 and (ii) second-line initiators during 2006-2015 and their annual drugs use have findings similar to other studies from Nordic countries such as Sweden, Denmark and Norway [11,12].

12 Conclusion

Increase in incidence and prevalence of T2DM signifies the increasing burden of disease and importance for diabetes care.

Reduction in standardized morality ratio for all-cause mortality, standardized incidence ratios for the four CV diseases of specific interest, and incidence of other health-related events such as rehabilitation, institutionalization, sick leaves, and retirements over the study duration 1998-2015 indicate overall improvement in diabetes care. This also reflects in the increase in primary care over the study duration.

The increasing and decreasing trends in annual usage of different GLDs signifies the change in treatment and management of T2DM. They also reflect health policies such as reimbursement policies that affect treatment pattern.

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Annex 1. Definitions for drugs and comorbidities

Definitions for drugs and comorbidities using various codes (VNR, ATC, ICD-10, ICPC, NCSP, special reimbursement)

Annex 1, table 1. List of blood glucose-lowering drugs of interest analysed at VNR code group level

Product name	VNR	Substance	ATC	Mode of action
Bydureon	088891 495854	exenatide	A10BX04	GLP-1 receptor agonist
Byetta	072978 072996	exenatide	A10BX04	GLP-1 receptor 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 receptor agonist
Trulicity	391550 564626	dulaglutide	A10BX (not assigned yet)	GLP-1 receptor 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

Annex 1, table 2. Blood glucose-lowering drugs analysed at ATC code group level

Group	ATC	Drug
1. Biguanides, A10BA		
	A10BA01	Phenformin
	A10BA02	Metformin
	A10BA03	Buformin
2. Sulfonamides, urea derivatives, A10BB		
	A10BB01	Glibenclamide
	A10BB02	Chlorpropamide
	A10BB03	Tolbutamide
	A10BB04	Glibornuride
	A10BB05	Tolazamide
	A10BB06	Carbutamide
	A10BB07	Glipizide
	A10BB08	Gliquidone
	A10BB09	Gliclazide
	A10BB10	Metahexamide
	A10BB11	Glisoxepide
	A10BB12	Glimepiride
	A10BB31	Acetohexamide
3. Alpha glucosidase inhibitors, A10BF		
	A10BF01	Acarbose
	A10BF02	Miglitol
	A10BF03	Voglibose
4. Thiazolidinediones, A10BG		
	A10BG01	Troglitazone
	A10BG02	Rosiglitazone
	A10BG03	Pioglitazone
5. Dipeptidyl Peptidase 4 (DPP-4) inhibitors, A10BH		
	A10BH01	Sitagliptin
	A10BH02	Vildagliptin

	A10BH03	Saxagliptin
	A10BH04	Alogliptin
	A10BH05	Linagliptin
	A10BH06	Gemigliptin
	A10BH51	Sitagliptin and simvastatin
6. Meglitinides		
	A10BX02	Repaglinide
	A10BX03	Nateglinide
7. Glucagon-like Peptide-1 (GLP-1) receptor agonist		
	A10BX04	Exenatide
	A10BX07	Liraglutide
	A10BX10	Lixisenatide
	A10BX14	Dulaglutide
8. Sodium-Glucose Co-transporter 2 (SGLT-2) inhibitors		
	A10BX09	Dapagliflozin
	A10BX11	Canagliflozin
	A10BX12	Empagliflozin
9. Other oral blood lowering drugs, other A10B		

Annex 1, table 3. Blood glucose-lowering combination drugs included in the ATC code group level analyses based on individual components

ATC code level groups	ATC	Drug
Biguanides, Sulfonamides	A10BD01	Phenformin and sulfonamides
Biguanides, Sulfonamides	A10BD02	Metformin and sulfonamides
Biguanides, Thiazolidinediones	A10BD03	Metformin and rosiglitazone
Sulfonamides, Thiazolidinediones	A10BD04	Glimepiride and rosiglitazone
Biguanides, Thiazolidinediones	A10BD05	Metformin and pioglitazone
Sulfonamides, Thiazolidinediones	A10BD06	Glimepiride and pioglitazone
Biguanides, DPP-4 inhibitor	A10BD07	Metformin and sitagliptin
Thiazolidinediones, DPP-4 inhibitor	A10BD09	Pioglitazone and alogliptin
Biguanides, DPP-4 inhibitor	A10BD10	Metformin and saxagliptin
Biguanides, DPP-4 inhibitor	A10BD11	Metformin and linagliptin
Thiazolidinediones, DPP-4 inhibitor	A10BD12	Pioglitazone and sitagliptin
Biguanides, DPP-4 inhibitor	A10BD13	Metformin and alogliptin
Biguanides, Meglitinides	A10BD14	Metformin and repaglinide
Biguanides, SGLT-2 inhibitor	A10BD15	Metformin and dapagliflozin
Biguanides, SGLT-2 inhibitor	A10BD16	Metformin and canagliflozin
Biguanides, SGLT-2 inhibitor	A10BD20	Metformin and empagliflozin

Annex 1, table 4. Insulin and analogues at the ATC code group level

Group	ATC	Drug
1. Insulins and analogues for injection, fast-acting, A10AB		
	A10AB01	Insulin (human)
	A10AB02	Insulin (beef)
	A10AB03	Insulin (pork)
	A10AB04	Insulin lispro
	A10AB05	Insulin aspart
	A10AB06	Insulin glulisine
	A10AB30	Combinations
2. Insulins and analogues for injection, intermediate-acting, A10AC		
	A10AC01	Insulin (human)
	A10AC02	Insulin (beef)
	A10AC03	Insulin (pork)
	A10AC04	Insulin lispro
	A10AC30	Combinations
3. Insulins and analogues for injection (intermediate- or long-acting combined with fast-acting), A10AD		
	A10AD01	Insulin (human)
	A10AD02	Insulin (beef)
	A10AD03	Insulin (pork)
	A10AD04	Insulin lispro
	A10AD05	Insulin aspart
	A10AD06	Insulin degludec and insulin aspart
	A10AD30	Combinations
4. Insulins and analogues for injection, long-acting, A10AE		
	A10AE01	Insulin (human)
	A10AE02	Insulin (beef)
	A10AE03	Insulin (pork)
	A10AE04	insulin glargine
	A10AE05	Insulin detemir
	A10AE06	Insulin degludec

	A10AE30	Combinations
5. Insulins and analogues for inhalation		
A10AF	A10AF01	Insulin (human)

Annex 1, table 5. Comorbidities (One code on each line is sufficient for classification)

Comorbidity	ICD-10	ATC	Special reimbursement code	ICPC-2	NCSP
Cardiovascular diseases					
Myocardial infarction	I21 – I22			K75	
CABG					FNA-FNE
PCI with stent					FNG
Unstable angina	I20.0			K74	
Angina pectoris	I20.1, I20.8, I20.9				
Stroke total	I60-I66, G45x			K89, K90	
Hemorrhagic	I60-I62				
Ischaemic stroke	I63-I64				
Transitory ischemic attack (TIA)	G45				
Heart failure	I50		201	K77	
Atrial fibrillation	I48			K78	
Peripheral artery disease	I70-I79				
Kidney diseases					
Chronic kidney disease	N18				
Dialysis	Z49				JAK10, TJA20, TJA33, DJ008, DR015-24, QF006
Microvascular complications					
Diabetic kidney disease	N08.3, E10.2, E11.2, E12.2, E13.2, E14.2,				
Diabetic mono- / polyneuropathy	E10.4, E11.4, E12.4, E13.4, E14.4, G99.0, G59.0, G63.2				
Diabetic eye complications	H28.0, H35.8, H36.0, E10.3, E11.3, E12.3, E13.3, E14.3,				CKC12, CKD65
Diabetic foot / Peripheral angiopathy	E11.6B, M14.2, M14.6, M90.8, L98.4, E10.5, E11.5, E12.5, E13.5, E14.5				QDGX10

Diabetes with several / unspecified complications	E11.6, E10.6, E13.6, E14.6, E10.7, E11.7, E12.7, E13.7, E14.7, E10.8, E11.8, E12.0, E12.8, E13.8, E14.8				
Severe hypoglycemia	E10.0, E11.0, E12.0, E13.0, E14.0, E11.6A, E16.0-2				
Keto- / lactate acidosis	E10.1, E11.1, E12.1, E13.1, E14.1, E87.2				
Lower limb amputations					
Amputations of the lower extremities					NGQ, NFQ, NHQ
Other					
COPD	J44	R03			
Cancer	C00-C99				
Major organ specific bleeding	D629, I60, I61, I62, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922				
Bariatric surgery					JDF10, JDF11, JDF20, JDF21
Abbreviations: STEMI, ST elevation myocardial infarction; NSTEMI, Non-ST elevation myocardial infarction; COPD, chronic obstructive pulmonary disease					

Annex 1, table 6. Other drugs of interest

Drug class	ATC
DRUGS FOR PEPTIC ULCER AND GORD	A02B
• H2-receptor antagonists	A02BA
• Prostaglandins	A02BB
• Proton pump inhibitors	A02BC
Propulsives	A03F
ANTIOBESITY PREPARATIONS	A08A
• Centrally acting antiobesity products	A08AA
• Peripherally acting antiobesity products	A08AB
• Other antiobesity drugs	A08AX
ANTITHROMBOTIC AGENTS	B01A
• Warfarin	B01AA03
• Clopidogrel	B01AC04
• Ticlopidine	B01AC05
• Acetylsalicylic acid	B01AC06
• Dipyridamole	B01AC07
• Prasugrel	B01AC22
• Ticagrelor	B01AC24
• Platelet aggregation inhibitors combinations	B01AC30
• Direct thrombin inhibitors	B01AE
• Direct factor Xa inhibitors	B01AF
Antiarrhythmics, classes I and III	C01B
Adenosine	C01EB10
Antihypertensives	C02
Diuretics	C03
Beta blocking agents	C07
Calcium channel blockers	C08
Verapamil	C08DA01
Diltiazem	C08DB01
ACE inhibitors	C09A, C09B

Angiotensin II antagonists	C09C, C09D
Renin-inhibitors	C09XA
Statins	C10AA, C10B
Fibrates	C10B
Thyroid preparations	H03A
Antibacterials for systemic use	J01
Antimycotics for systemic use	J02
Antimycobacterials	J04
Antigout preparations	M04
Aenzodiazepine derivatives	N05CD
Benzodiazepine related drugs	N05CF
Antidepressants	N06A
Drugs for obstructive airway diseases	R03

Annex 1, table 7. ICD-10 codes for exclusion criteria diagnosis

ICD-10 Code	Diagnosis for exclusion criteria
E10	Type 1 diabetes mellitus
E11	Type 2 diabetes mellitus
E12	Malnutrition-related diabetes mellitus
E13	Other specified diabetes mellitus
E14	Unspecified diabetes mellitus
O28.2	Polycystic ovarian syndrome (Abnormal cytological finding on antenatal screening of mother)
E89.1	Postprocedural hypoinsulinaemia
O24	Diabetes mellitus in pregnancy
O24.0	Pre-existing type 1 diabetes mellitus
O24.1	Pre-existing type 2 diabetes mellitus
O24.2	Pre-existing malnutrition-related diabetes mellitus
O24.3	Pre-existing diabetes mellitus, unspecified
O24.4	Diabetes mellitus arising in pregnancy
O24.9	Diabetes mellitus in pregnancy, unspecified

P70.2	Neonatal diabetes mellitus