Pharmacoepidemiological study protocol ER12-9451

Realization of the clinical practice guidelines for diabetes in Finland – A case study of the usability of electronic patient information systems and national registers to support evidence based decision making in health care

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Study Information

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Joint PASS	No
Research question and objectives	The overall objective of the study is to evaluate whether the electronic patient information systems and national registers can be used to support evidence based decision making in health care. The specific scientific objectives are to evaluate how the key elements of the Current Care guideline for diabetes (by the Finnish Medical Society Duodecim) are realized in practice and to investigate which factors explain successful implementation of treatment recommendations.
Country(-ies) of study	Finland
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Sponsor

Sponsor	Pharma Industry Finland (Lääketeollisuus ry)
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2 List of abbreviations

ACE inhibitor	Angiotensin converting enzyme inhibitor
APR	Ambulatory and primary care related patient groups
ARB	Angiotensin receptor blockers
ATC code	Anatomical therapeutic chemical classification system code
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DDD	Defined daily dose
DRG	Diagnosis-related group
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICD-10	International classification of diseases, 10th revision
ICPC-2	International Classification of Primary Care
ISPE	International Society for Pharmacoepidemiology
NCSP code	NOMESCO classification of surgical procedures code
PHC	Primary health care
SID	Study identification number
SII	Social Insurance Institution
SPAT	Finnish classification for procedures in primary care (*Suomalainen perusterveydenhuollon avohoidon toimintoluokitus*)
TIA	Transient ischemic attack

3 Responsible parties

Study funding:	Lääketeollisuus ry (Pharma Industry Finland)
Study conduct:	EPID Research Oy and AT Medical Affairs Consulting Oy
Principal investigator:	Pasi Korhonen (Ph.D., Adj. prof. biostatistics), EPID Research
Co-investigators:	Miika Linna (D.Sc., Adj. prof. health economics), University of Helsinki, Aalto University
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	Fabian Hoti (Ph.D.), EPID Research
	Tuire Tirkkonen (Ph.D.), EPID Research
Project manager:	Anu Sulamaa (M.Sc.), Pharma Industry Finland
Steering committee:	Pasi Korhonen, Tatu Miettinen, Jarmo Hahl, Anu Sulamaa (affiliations above), prof. Jaakko Tuomilehto (University of Helsinki), Leo Niskanen (Fimea), Hannes Enlund (Fimea), Miika Linna (Aalto University, HEMA Institute), Jari Haukka (EPID Research), Raija Sipilä (Finnish Medical Society Duodecim), Elli Leppä (Pharmaceutical Information Centre)
Study sites:	Selected primary and specialty health care organizations from Finland (possible include but are not limited to Helsinki/Uusimaa, Hämeenlinna, Rauma, Oulu, Keski-Pohjanmaa, Pohjois-Pohjanmaa, Kainuu, Pohjois-Karjala, Sipoo, Hanko, Porvoo)

Contact details of the principal investigator and co-investigators are given separately in Annex 1.

4 Abstract

Title:

Realization of the clinical practice guidelines for diabetes in Finland – A case study of the usability of electronic patient information systems and national registers to support evidence based decision making in health care

Rationale and background:

The Finnish Current Care guideline for diabetes gives advice to physicians in treating patients comprehensively. The efficacious treatment of diabetes is of utmost importance in order to prevent the diabetic complications as effectively as possible. How this guideline realizes in practice is not fully known.

Local and nationwide patient information systems and health care registers contain routinely saved patient information important for pharmacoepidemiologic research. However, in practice the use of this information has been limited to nationwide registers while the use of patient and laboratory information systems has been scarce. This is due to difficult and lengthy research permission processes when acquiring data from several different sites using various information systems.

Combination of both two source types would serve as a valuable resource in studies evaluating risks, benefits and costs. Also the implementation of clinical practice guidelines could be assessed. The need for the evaluation of medicines in real-life setting has been increasing e.g. due to post-authorization safety and efficacy studies. Rare outcomes (e.g. cancer) or special populations (e.g. elderly or pregnant women) can be studied by proper pharmacoepidemiological methods with access to patient level data from large populations.

The aim of this study is to identify whether and how the electronic patient information systems and national registers can be used for research purposes in Finland. This aim is piloted in patients with type 2 diabetes, a disease of great public health importance.

Research question and objectives:

The overall objective of the study is to evaluate whether and how the electronic patient information systems and national registers can be used to support evidence based decision making in health care.

The specific objectives are

- to identify the research permission processes for accessing patient level data both from electronic patient information systems from different health care organizations and from the nation-wide health care registers,
- to evaluate how the key elements of the Current Care guideline are realized in practice in type 2 diabetes mellitus patients, and to investigate which factors explain successful implementation of treatment recommendations,
- to evaluate the equality of data in local and nationwide medication registers, and
- to evaluate the cost and use of resources and to explore the costs of different outcomes in the implementation of recommendations.

Study design:

This is a retrospective database linkage study using patient information system data from selected primary and specialty health care organisations with linkage to nationwide registers.

Population:

Selected primary and specialty health care organizations from Finland (possible include but are not limited to Helsinki/Uusimaa, Hämeenlinna, Rauma, Oulu, Keski-Pohjanmaa, Pohjois-Pohjanmaa, Kainuu, Pohjois-Karjala, Sipoo, Hanko, Porvoo). These are called as the ***study sites***. These sites use patient information systems provided either by Tieto Oyj, CGI Oy (former Logica Oy) or Mediconsult Oy.

Inclusion criteria:

- The broad study population comprises all patients who have a diagnosis for diabetes (ICD-10 code E10*, E11*, E13* or E14*, or ICPC-2 code T89 or T90), a written prescription for diabetic medication (ATC code A10A* or A10B*), HbA_{1c} value ≥ 6.5%, glucose tolerance test ≥ 11 mmol/L or nutrition counselling related to diabetes in the electronic patient information systems within the selected study sites, or patients who have purchased prescriptions for diabetic medication (ATC code A10A* or A10B*) or who have special reimbursement for diabetes (refund code 103) in the Social Insurance Institution (SII) registers during 2009-2012.

For each patient the first date of such event mentioned above is called ***index date***. The following exclusion criteria are used to identify patients with an ***incident*** (first time) diagnosis for ***type 2 diabetes***.

Exclusion criteria:

- Patients with a diagnosis for diabetes (ICD-10 code E10*, E11*, E13* or E14*, or ICPC-2 code T89 or T90) or a written prescription for diabetic medication (ATC code A10A* or A10B*) in the electronic patient information systems **within two years prior to index date**.
- Patients with a purchased prescription for diabetic medication (ATC code A10A* or A10B*) in the prescription register of the SII within two years prior to index date.
- Patients with special reimbursement decisions for diabetes (reimbursement category no 103) in the reimbursement register of the SII within two years prior to index date.
- Patients with abroad place of domicile within two years prior to index date.
- Patients with place of domicile not including in the study site areas at the end of any of the study years.
- Patients carrying **only** diagnosis for type 1 diabetes (ICD-10 code E10* or ICPC-2 code T89) in the electronic patient information systems (without codes E11*, E13*, E14* or T90 = clear type 1 diabetes mellitus patients).
- Patients with special reimbursement decision 103 for diagnosis E10* (type 1 diabetes) **only** in the reimbursement register of the SII (without codes E11*, E13* or E14* = clear type 1 diabetes mellitus patients).

Variables:

Variables for population characterization at baseline:

- Age
- Gender
- Concomitant diseases
- Concomitant medications
- Smoking
- Body-Mass Index (BMI)
- Dietary habits
- Physical exercise

Variables for diabetes medications to evaluate the realization of the Current Care guideline:

- Start of metformin at 1st line treatment
- Treatment intensification during follow-up by adding 2nd or 3rd line treatment (i.e. sulphonylureas, glinides, gliptines, glitazones or insulin)

Variables for laboratory parameters to evaluate the realization of the Current Care guideline:

- Follow-up of HbA_{1c}
  - Frequency of follow-up of HbA_{1c}
  - HbA_{1c} values being on target
- Follow-up of lipids (S-LDL)
  - S-LDL being on target
  - S-LDL measurement taken within 12 to 36 months after index date
- P/S-Crea measurements taken within 12 to 15 months after index date
- U-Alb measurement taken within 12 to 15 months after index date
- P/S-ALAT measurement taken within 12 to 36 months after index date

Other variables to evaluate the realization of the Current Care guideline:

- Dietary advice and exercise consultation provided
- Visit to foot therapist or similar health care professional within 12/15/>15 months after index date
- At least one visit to dentist within 12 months after index date
- At least one fundus photography taken within 36 months after index date

Variables for treatment decisions (other than diabetes treatment) based on follow-up measurements:

- Blood pressure > 140 / 90 mmHg
- Renal insufficiency
- Microalbuminuria
- LDL > 2.5 mmol/L
- LDL > 1.8 mmol/L with prior diagnosis for coronary artery disease/stroke/TIA/periferal arterial disease

Variables for other endpoints:

- Mortality
- Health care resource use: Visits and other primary health care contacts, hospital discharges
    - Total costs of primary health care services
    - Total costs of secondary and tertiary care
    - Total costs of due to use of pharmaceuticals
- Amputations of the lower extremities
- Absence from work
- Severe hypoglycemic events

Data sources:

- Patient information systems from the study sites
- Prescription register, Register for reimbursed medications and Sickness allowance register (SII)
- Hospital care register and Primary care register (National Institute for Health and Welfare)
- Causes of death registry (Statistics Finland)

Study size:

Type 2 diabetes patients from the selected primary and specialty health care organizations (i.e. study sites) from Finland. The size of the study population depends on the number and size of the selected study sites. The sites use patient information systems provided either by Tieto Oyj, CGI Oy (former Logica Oy) or Mediconsult Oy who jointly have over 95% of the market share in Finland. Thus it is anticipated that a large proportion of type 2 diabetes patients from the selected sites are captured in the study population.

Data analysis:

The baseline characteristics will be presented as number of cases and percentages separately for each study site and for all sites combined. Appropriate statistical tests will be applied to statistically quantify any between site differences. Realization of current care guidelines will be evaluated for each site separately and for all sites combined. A logistic regression model will be used to model the study end-points with respect to the baseline covariates and study sites.

5 Amendments and updates

Changes in the approved protocol must be reviewed the Steering committee before subsequent approval by the authors.

Number	Date	Section of the study protocol	Amendment or update	Reason
none	none	none	none	none

6 Milestones

Milestone	Planned date
Start of study permit process	04/2013
End of study permit process	09/2013
Start of data collection	09/2013
End of data collection	11/2013
Start of data analysis	11/2013
End of data analysis	04/2014
Start of study reporting process	02/2014
End of study reporting process	04/2014
Start of scientific reporting process	04/2014

7 Rationale and background

Diabetes is a chronic and progressive disease, that affects already more than 500 000 people in Finland (Diabetes, Current Care Summary, 2011). It is characterized by dysfunctions in insulin secretion and sensitivity, and by hyperglucagonemia resulting increased levels of blood sugar. Type 2 diabetes patients, and particularly those who are have uncontrolled diabetes, are at increased risk of vascular complications. These include both microvascular (diabetic nephropathy, retinopathy and neuropathy) and macrovascular (peripheral vascuar disease, coronary heart disease and cerebrovascular) complications. It has been shown that intensive drug treatment policy decreases these complications when compared to less intensive treatment policy (UKPDS 33 and 34, 1998).

Life-style interventions were previously recommended as the first treatment choice in patients with new type 2 diabetes. However, as life-style interventions are difficult to put successfully into effect, the Current Care guideline for diabetes recommends that metformin should be initiated concomitantly with life-style interventions (Diabetes, Current Care Summary, 2011). The Current Care guideline also includes a clear algorithm of treatment choices after initiation of metformin treatment as well as detailed guidance for the holistic treatment of a type 2 diabetes patients.

It is not well established how the Current Care guideline is realized in practice and whether there are national variations in following this guideline. This study aims to investigate the realization of the guideline in practice by using different patient information sources.

Patient information systems and nationwide health care registers contain information on diagnoses, prescriptions, medical treatments and procedures, home care, first aid care, and laboratory measurements. This information is recorded on patient level during normal daily routines when treating patients in hospitals and health care centers or filling in prescriptions from pharmacies. The nation-wide health care registers are currently used in pharmacoepidemiologic research. The use of patient and laboratory information systems has

been limited due to difficult and lengthy research permission processes when acquiring data from several different sites using various information systems. Combination of these two sources for research purposes would serve as a valuable resource for evaluation of risks, benefits and costs of various treatments and assessing how clinical practice guidelines are realized in practice in large populations. Such research would in turn support evidence based decision making in health care and potentially guide better use of resources.

There is an increasing need for the evaluation of medicines in real-life setting. Due to limited knowledge of the effects of new medical treatments after clinical trial experimentation the competent authorities may require further post-authorization safety and efficacy studies (PASS and PAES) or drug utilization studies from the marketing authorization holder. This may involve evaluation of the effect the treatment on a rare outcome (e.g. cancer) or in a special population (e.g. elderly or pregnant women) requiring access to reliable patient level information on treatments and outcomes in large populations.

The aim of this study is to identify whether and how the electronic patient information systems and national registers can be used for research purposes in Finland. This aim is piloted in patients with type 2 diabetes, a disease of great public health importance.

8 Research questions and objectives

The overall objective of the study is to evaluate whether and how the electronic patient information systems and national registers can be used to support evidence based decision making in health care.

The primary objectives are

- to identify the research permission processes for accessing patient level data
    - from electronic patient information systems from different health care organizations and
    - from the nation-wide health care registers,
- to evaluate how the key elements of the Current Care guideline are realized in practice in type 2 diabetes mellitus patients (study cohort including only incident cases), and
- to evaluate the equality of data in local and nationwide medication registers.

The secondary objectives are

- to evaluate the cost and use of resources and to explore the costs of different outcomes in the implementation of recommendations,
- to compare different areas in Finland in relation to realization of the Current Care guideline for type 2 diabetes (study cohort including only incident cases), and
- to investigate which factors explain successful implementation of treatment recommendations.

9 Research methods

9.1 Study Design

This is a retrospective database linkage study using patient information system data from selected primary and specialty health care organisations with linkage to nationwide registers.

9.2 Setting

Primary and specialty health care organisations with sufficient geographical coverage in Finland using different patient information systems are selected. These may include but are not limited to Helsinki/Uusimaa, Hämeenlinna, Rauma, Oulu, Keski-Pohjanmaa, Pohjois-Pohjanmaa, Kainuu, Pohjois-Karjala, Sipoo, Hanko, Porvoo).

These are called as ***study sites***. The chosen sites use patient information systems provided either by Tieto Oyj, CGI Oy (former Logica Oy) or Mediconsult Oy who jointly have over 95% of the market share in Finland. They all have Evidence-Based Medicine electronic Decision Support (EBMeDS) implemented in their products (http://www.ebmeds.org/web/guest/home?).

Study population:

Inclusion criteria:

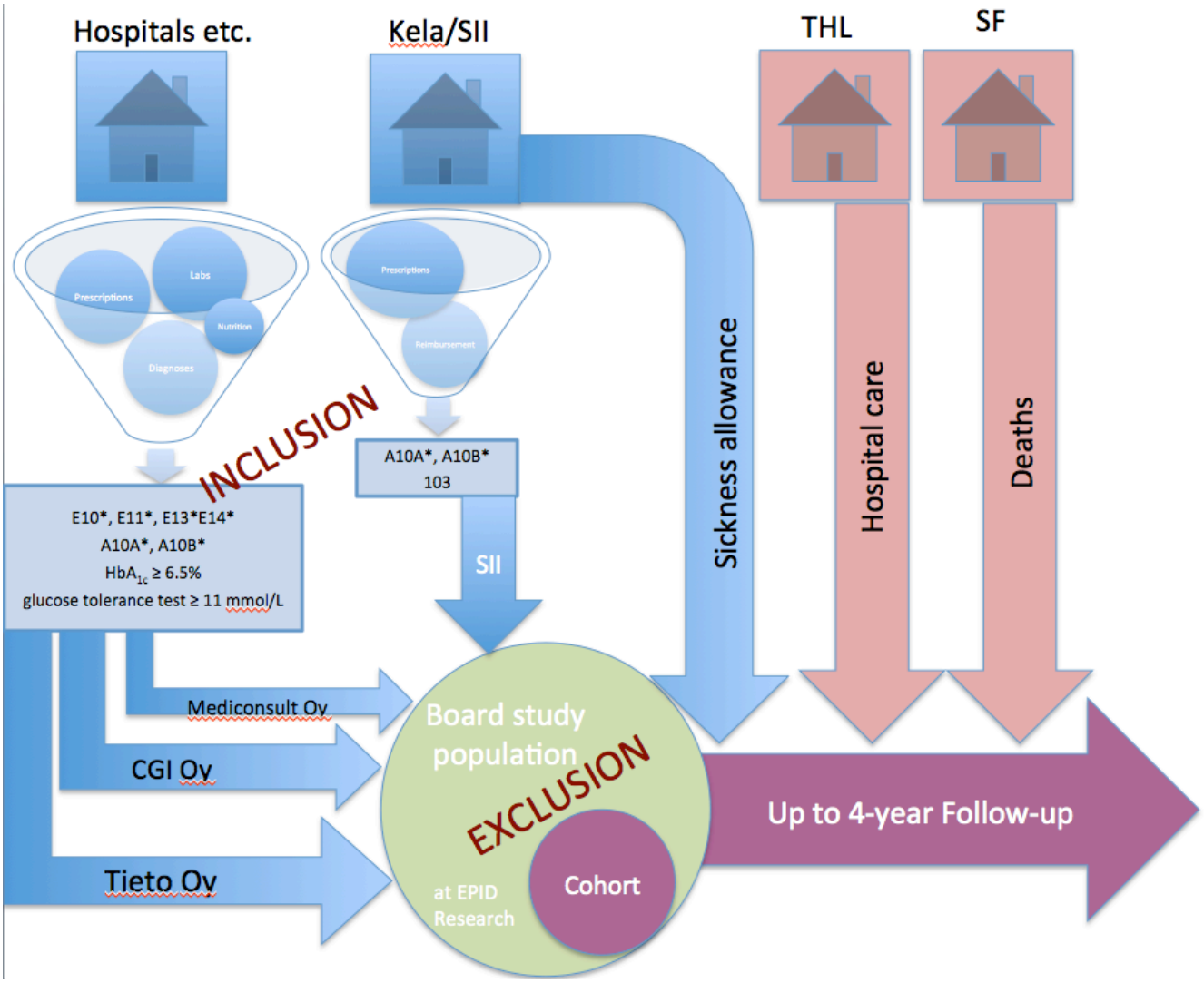
- The broad study population comprises all patients who have a diagnosis for diabetes (ICD-10 code E10*, E11*, E13* or E14*, or ICPC-2 code T89 or T90), a written prescription for diabetic medication (ATC code A10A* or A10B*), HbA_{1c} value ≥ 6.5%, glucose tolerance test ≥ 11 mmol/L or nutrition counselling related to diabetes in the electronic patient information systems within the selected study sites, or patients who have purchased prescriptions for diabetic medication (ATC code A10A* or A10B*) or who have special reimbursement for diabetes (refund code 103) in the Social Insurance Institution (SII) registers during 2009-2012.

For each patient the first date of such event mentioned above is called ***index date***. The following exclusion criteria are used to identify patients with an ***incident*** (first time) diagnosis for ***type 2 diabetes***.

Exclusion criteria:

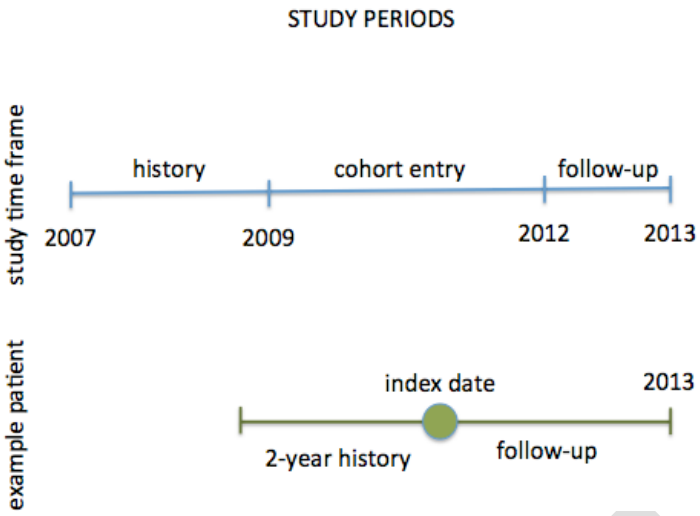
- Patients with a diagnosis for diabetes (ICD-10 code E10*, E11*, E13* or E14*, or ICPC-2 code T89 or T90) or a written prescription for diabetic medication (ATC code A10A* or A10B*) in the electronic patient information systems **within two years prior to index date**.
- Patients with a purchased prescription for diabetic medication (ATC code A10A* or A10B*) in the prescription register of the SII within two years prior to index date.
- Patients with special reimbursement decisions for diabetes (reimbursement category no 103) in the reimbursement register of the SII within two years prior to index date.
- Patients with abroad place of domicile within two years prior to index date.
- Patients with place of domicile not including in the study site areas at the end of any of the study years.

- Patients carrying **only** diagnosis for type 1 diabetes (ICD-10 code E10* or ICPC-2 code T89) in the electronic patient information systems (without codes E11*, E13*, E14* or T90 = clear type 1 diabetes mellitus patients).
- Patients with special reimbursement decision 103 for diagnosis E10* (type 1 diabetes) **only** in the reimbursement register of the SII (without codes E11*, E13* or E14* = clear type 1 diabetes mellitus patients).



Follow-up:

Follow-up of the patients starts on the index date, and ends on 31.12.2013, at time of death or at time of emigration whichever occurs first.



9.3 Study variables

9.3.1 Exposure variables

Continuous drug use periods are constructed according the principles presented by Nielsen *et al*. (Nielsen et al. 2008, 2009). Drug use periods create time-varying exposure to various treatments meaning that the exposure to any particular treatment group can change during the follow-up period. Based on the defined daily dose (DDD) information each prescription will be modified into a drug use period in prospective manner by defining the length of the prescription as the DDD plus an additional 50% treatment gap period (Nielsen *et al*. 2008, 2009). The purpose of the treatment gap period is to avoid unnecessary breaks between two prescriptions. The resulting consecutive drug use periods with possible gaps between them are used to define a time-dependent current exposure periods indicating in which treatment categories the patient is at any given time during the follow-up.

9.3.2 Baseline covariates

Baseline characteristics	
Variable	*Evaluation*
Age	Age (years) at index date (mean, min, max, Q1, median, Q3, standard deviation)
Gender	M/F (number of patients and percentage)
Smoking, BMI, dietary habits and physical exercise	Purpose to evaluate the availability and the quality of data. Smoking Yes/No, possible also the amount and information about

	previous smoking. BMI strait from the data or by weight and height: < 25 kg/m^2, 25–29,9 kg/m^2, 30–34,9 kg/m^2, 35–39,9 kg/m^2, ≥ 40 kg/m^2 *Note: Main purpose to study the availability.*
Concomitant diseases at baseline	Including but not limited to bronchial asthma, COPD, chronic hypertension hypertension, chronic renal insufficiency, chronic cardiac insufficiency, rheumatoid arthritis, atrial fibrillation, coronary artery disease, dyslipidemia, cancer (excluding *in situ* cancers), stroke and TIA, depression, obesity, peripheral arterial disease, and diabetic nephropathy, retinopathy and neuropathy * (number and percentage by disease category). The most common concomitant diseases listed (number and percentage by disease category). From Reimbursement decisions / Diagnoses *Note. Attempt to capture as broad information as possible on concomitant diseases*
Concomitant medications at baseline	Concomitant medications (number of patients and percentage by concomitant medication) From Written / Reimbursed prescriptions *Note. Attempt to capture as broad information as possible on concomitant medications*

* See Annex 3 for details.

9.3.3 Laboratory and blood pressure measurements as covariates (baseline and follow-up)

Variable	Evaluation
HbA_{1c}	Levels: < 6.5, 6.5-6.9, 7.0-7.9, and ≥ 8.0 %
S-CREA	Levels: < 130 mmol/L , 130-150 mmol/L , and > 150 mmol/L
Calculated GFR (Glomerular filtration rate)	Levels: ≤ 60 ml/min and > 60 ml/min
S-LDL	Levels: < 1.8mmol/L, 1.8-2.5mmol/L and > 2.5mmol/L
Blood pressure	Levels: < 130/80, not < 130/80 mmHg

9.3.4 Endpoints

Realization of the Current Care guideline: Diabetes medications and related measurements	
Variable	*Evaluation*
Initiation of metformin as 1st line treatment *	Not started at all or written or reimbursed prescription of metformin within 1/3/6/>6 months after index date (number of patients and percentage by category) Which diabetes treatment(s) started if not metformin (number of patients and percentage by treatment) Initiation of antidiabetic treatment(s) other than metformin between date of DM diagnosis and initiation of metformin (number of patients and percentage by treatment)
Dietary advice and exercise consultation provided	Dietary advice (SPAT codes 1139 and 1306) provided within 1 month of index date (Yes / No, number of patients and percentage) Exercise consultation (SPAT 1305) provided within 1 month of index date (Yes / No, number of patients and percentage) *Note. Information may not be available. Main purpose to study the availability. Text mining not used.*
Follow-up of HbA_{1c} **	At least one HbA_{1c} measurement taken within 6 months after index date (Yes / No, number of patients and percentage)
Treatment intensification during follow-up by adding 2nd or 3rd line treatment (i.e. sulphonylureas, glinides, gliptines, glitazones or insulin) *	If HbA_{1c} > 6.5% on follow-up after starting 1st line treatment, a written or reinbursed prescription of 2nd or 3rd line treatment: No intensification or within 1/3/6/>6 months after such measurement (number of patients and percentage by category) Distribution of time of filling 2nd or 3rd line treatment prescription after such measurement (mean, min, max, Q1, median, Q3, standard deviation)

* See Annex 4 for ATCs.

** See Annex 5 for ID numbers of laboratory measurements.

Realization of the Current Care guideline: Frequency of follow-up measurements - HbA_{1c} and S-LDL *	
Variable	*Evaluation*
Frequency of follow-up of HbA_{1c}	At least one HbA_{1c} measurement taken within 3/6/12/15/18/21/24/>24 months after index date (number of patients and percentage)

	Distribution of time between any two consecutive HbA_{1c} measurements during follow-up (mean, min, max, Q1, median, Q3, standard deviation)
HbA_{1c} on target	HbA_{1c} <6.5% (Yes / No, number of measurements and percentage) Distribution of all HbA_{1c} measurements (<6.5%, <7.0%, <8.0%, <9.0%, ≥9.0%) by time after index date (3/6/12/15/18/21/24/>24 months) (number of patients and percentage)
Follow-up of lipids (S-LDL)	At least one S-LDL measurement taken within 3/6/>6 months after index date (Yes / No, number of patients and percentage)
S-LDL on target	S-LDL < 2.5 mmol/L (Yes / No, number of patients and percentage) S-LDL < 1.8 mmol/L if prior diagnoses for coronary artery disease /stroke/TIA/periferal circulatory complication ** (Yes / No, number of patients and percentage) If elevated then control measurement taken within 3 months of such measurement (Yes / No, number of patients)

* See Annex 5 for ID numbers of laboratory measurements.

** ICD-10 and ICPC-2 codes mentioned in Annex 3.

Realization of the Current Care guideline: Follow-up measurements every 12 to 15 months	
Variable	*Evaluation*
At least one P/S-Crea * measurement taken within 12 to 15 months after index date	Yes / No, number of patients and percentage At least one S-Crea measurement taken within 1/12/15/24/36/>36 months after index date (number of patients and percentage)
At least one U-Alb * measurement taken within 12 to 15 months after index date	Yes / No, number of patients and percentage At least one U-Alb measurement taken within 1/12/15/24/36/>36 months after index date (number of patients and percentage)
At least one visit to foot therapist or similar health care professional within 12/15/>15 months after index date	Yes / No, number of patients and percentage Footrisk score available (Yes / No, number of patients and percentage) *Note. Data may not be available. Main purpose to study the availability.*
At least one visit to dentist within 12 months after index date	Yes / No, number of patients and percentage *To be checked in* National Institute for Health and Welfare registers*. Also SII reimbursement will be studied to cover private*

	sector dental visits.

* See Annex 5 for ID numbers of laboratory measurements.

Realization of the Current Care guideline: Follow-up measurements every 1-3 years	
Variable	*Evaluation*
At least one P-ALAT * measurement taken within 12 to 36 months after index date	Yes / No, number of patients and percentage. At least one P-ALAT measurement taken within 12/15/24/36/>36 months after index date (number of patients and percentage)
At least one S-LDL * measurement taken within 12 to 36 months after index date	Yes / No, number of patients and percentage. At least one S-LDL measurement taken within 12/15/24/36/>36 months after index date (number of patients and percentage)
S-LDL * on target	S-LDL < 2.5 mmol/L by 12/15/24/36/>36 months after index date (Yes / No, number of patients and percentage) S-LDL < 1.8 mmol/L by 12/15/24/36/>36 months after index date if prior diagnoses for coronary artery disease /stroke/TIA/periferal arterial disease ** (Yes / No, number of patients and percentage)
At least one fundus photography taken within 36 months after index date	Yes / No, number of patients and percentage. At least one fundus photography taken within 12/15/24/36/>36 months after index date (number of patients and percentage) *Note. Excluding patients who are under follow-up due to existing eye disease at index date.*

* See Annex 5 for ID numbers of laboratory measurements.

** ICD-10 codes mentioned in Annex 3

Realization of the Current Care guideline: Treatment decisions (other than diabetes treatment) based on follow-up measurements	
Variable	*Evaluation*
Blood pressure > 140 / 90 mmHg	Prescription of ACE/ARB * filled within 1/3/6 months of such measurement (Yes / No, number of patients and percentage) *Note. Data may not be available. To be included as comorbidity from special reimbursements, prescriptions, diagnoses.*
Renal insufficiency	GFR < 60, <45, <30 mL/min (Yes / No, number of patients and percentage) S-CREA ** >150 mmol/L (Yes / No, number of patients and

	percentage) Prescription of metformin filled within 1/3/6/>6 month of such measurement (Yes / No, number of patients and percentage) *Note. Calculation of GFR using CKD-EPI, and/or MDRD depending availability of patient's weight.*
Microalbuminuria	cU-Alb od nU-Alb ** <20 µg/min (Yes / No, number of patients and percentage) dU-Alb ** <30 mg/d (Yes / No, number of patients and percentage) U-AlbCrea or nU-AlbCrea** <2.5, <3.5 mg/mmol (Yes / No, number of patients and percentage) Prescription of ACE/ARB * filled within 1/3/6/>6 month of such measurement (Yes / No, number of patients and percentage)
S-LDL ** >2.5 mmol/L S-LDL ** >1.8 mmol/L with prior diagnoses for coronary artery disease/stroke/TIA/periferal arterial disease ***	Prescription of statins filled within 1/3/6/>6 month of such measurement (Yes / No, number of patients and percentage) *Note. Data may not be available because this would need reliable information on dose increases.*

* ATCs listed in Annex 6.

** See Annex 5 for ID numbers of laboratory measurements.

*** ICD-10 codes mentioned in Annex 3

Other endpoints and events for cost estimation	
Variable	*Evaluation*
Mortality	Time and cause of death
Health care resource use: visits, contacts and hospital/PHC inpatient admissions.	Total number of primary care contacts per patient overall and by type of contact. Cost weighting using appropriate patient grouping method and standard pricing. Total number of specialty care visits and hospitalizations per patient by type of visit/admission. Cost weighting using appropriate patient grouping method and standard pricing.
Amputations of the lower extremities	NCSP codes NFQ20, NGQ10, NGQ20, NHQ10, NHQ20, NHQ30, NHQ40 No / Yes, number of patients and percentage
Absence from work	Long absences over 10 days (No / Yes, number of patients and

	percentage) and duration (days)
Severe hypoglycemic events	Hospitalization and/or other health organization visit due to E11.00 (ICD-10) or T87 (ICPC-2) (No/Yes, number of patients and percentage)

9.3.5 Costs estimation

Hospitalizations and hospital outpatient visits due to any cause will be extracted from the Hospital Discharge Register based on the International Classification of Diseases 10th revision (ICD-10) codes, the Finnish version of the Nordic Classification of Surgical Procedures (NCSP) codes for diagnostic and treatment procedures, and the respective Nordic Diagnosis Related Groups (NordDRG) patient classifications. The unit costs for hospitalizations and outpatient visits are based on individual-level cost accounting data from one hospital district. Other unit cost estimates can be derived on the national price list for unit costs of health care services in Finland. The costs due to primary health care contact can be calculated using the Ambulatory and Primary Care Related Patient Groups (APR) patient classification for primary care outpatients, a grouping system equivalent to DRGs. The use of primary care grouping is based on diagnosis/cause for visit (ICD-10/ICPC-2), the type of contact (outpatient visit, phone call, e-mail) and the professional who is in charge of the contact (physician, nurse, physiotherapist, other). Large national samples from several Finnish primary health care centres will be used to calculate average unit cost for each contact category in APR.

9.4 Data sources

Register	Register Holder	Data Content
Prescription register	Social Insurance Institution	• Drug purchaces (ATC) • Date of purchase • DDD • Package code (Vnr) • Prescription text
Register for reimbursed medications	Social Insurance Institution	• Start/end date of special reimbursement (e.g. 103 for diabetes)
Health insurance	Social Insurance Institution	• Place of domicile (in study sites or abroad) • Reimbursement for dental care
Sickness allowance register	Social Insurance Institution	• Sickness allowance • ≥10 days sick leaves • Rehabilitation

Hospital care register (discharge register), Hospital benchmarking database	National Institute for Health and Welfare	• Organization code • Diagnoses (ICD-10) • Operations and other procedures (NCSP) • Bed-days • DRGs (NordDRG grouping) • Type of specialty • Type of service • Hospitalizations and visit/discharge dates • Inpatient days in PHC • Dental care
Primary care register	National Institute for Health and Welfare	• Diagnoses (ICD-10, ICPC-2) • Operations and other procedures (NCSP) • Dental care • Since 2011
Causes of death registry	Statistics Finland	• Causes of death (ICD-10) • Date and place of death
Effica (and other relevant)	Tieto Oy *	• Diagnoses (ICD-10, ICPC-2) • Medical procedures (NCSP) • Type of contact • Employee category • Prescriptions • Possible laboratory measurements • Glucose tolerance tests • Nutrition counselling
Pegasos (and other relevant)	CGI Oy (former Logica Oy) *	
Mediatri (and other relevant)	Mediconsult Oy *	

* The owner of the data is not the company mentioned here but the hospital district or other instance using the provided service.

Data permits will be requested separately from Social Insurance Institution, National Institute for Health and Welfare, and Statistics Finland. The National Institute for Health and Welfare study permission covers all patient information in Finland. However, data owners (e.g. hospital district or central hospital) will be informed about the study by referring to the National Institute for Health and Welfare permit. Non-nationwide patient data is collected via the information service providers. Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) will be requested to cover the nationwide study.

9.5 Study size

Type 2 diabetes patients from the selected primary and specialty health care organizations (i.e. study sites) from Finland. The size of the study population depends on the number and size of the selected study sites. The sites use patient information systems provided either by Tieto Oyj, CGI Oy (former Logica Oy) or Mediconsult Oy who jointly have over 95% of the market share in Finland. Thus it is anticipated that a large proportion of type 2 diabetes patients from the selected sites are captured in the study population.

9.6 Data management

R language (http://www.r-project.org) 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 modeling. 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" (http://www.r-project.org/doc/R-FDA.pdf). Full audit trail starting from raw data obtained from register holder(s), 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), steering committee, or by the competent authorities.

All study data and supporting documents will be retained for five (5) years after the end of the study and then destroyed. As the register holder of the study register EPID Research is in charge of archival and deletion 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 to identify 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 are handled by the steering committee and must be subjected to appropriate data permit processes.

9.7 Data analysis

A separate detailed analysis plan including templates for result tables and figures will be prepared. The main principles of the statistical analysis are presented below with an example table template.

The baseline characteristics will be presented as number of cases and percentages separately for each study site and for all sites combined. Appropriate statistical tests will be applied to statistically quantify any between site differences. Baseline characteristics include:

- Age
- Gender
- Smoking
- BMI
- Dietary habits
- Physical exercise
- Concomitant disease

- Concomitant medication
- Laboratory measurements

Realization of current care guidelines will be evaluated for each site separately and for all sites combined. The variables will be evaluated according to the tables in chapter 9.3. Appropriate statistical tests will be applied to statistically quantify between site differences.

A (multi) logistic regression model will be used to model the study end-points with respect to the baseline covariates and study sites. When possible a binomial endpoint will be used (i.e., never vs. ever start of metformin or under 1 month vs. over 1 month to start of metformin).

Here we present an example of tables to be used in the study.

Table X: Initiation of metformin as the 1st line treatment

		Site 1	Site 2	Site N	Total
Time from index date to start of metformin treatment	Under 1 month	N(%)			
	1-3 months				
	3-6 months				
	Over 6 months				
	Never				
Treatment, if no metformin *	Sulfophonylureas	N(%)			
	Biguanides				
	DDP-4 inhibitors				
	Alpha glucosidase inhibiators				
	Insulin				
	Others				
Treatment before start of metformin*	Sulfophonylureas	N(%)			
	Biguanides				
	DDP-4 inhibitors				
	Alpha glucosidase inhibiators				

	Insulin				
	Others				

* Alternative diabetes medication categories to be defined based on the data (most prevalent alternatives)

9.8 Quality control

The study will be conducted as specified in the protocol. All revisions to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to register holder(s) whenever amendment(s) to the data permissions are required.

The study protocol has been written by following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP 2011) that provides a set of rules and principles for post-authorization studies with regard to the best practices and transparency, thereby promoting scientific independence of such studies. The study protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices by International Society for Pharmacoepidemiology (ISPE 2007), and the recent draft Guidance for Industry and FDA Staff "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets" (FDA 2011).

The study protocol will be registered in the ENCePP E-register of Studies (http://www.encepp.eu/encepp_studies/indexRegister.shtml). Study results will also be published in ENCePP.

9.9 Limitations of the research methods

This study has two main purposes: 1) to survey the availability of patient data form the local electronic patient files and the equivalency of it compared to the nationwide databases, and 2) to study the realization of the clinical practice guidelines for type 2 diabetes with its consequences. The use of e.g. laboratory results, lifestyle parameters, imaging results and other data types not recorded nationwide has been scarce in pharmacoepidemiological research in Finland. In this study these types of data will be surveyed while describing the process of the data collection. Diabetes has been chosen for the pilot disease of interest because the treatment of it requires actions that lead to different types of data recording.

The electronic patient files used in this study are operated by three different vendors. This may affect the comparability of the data in different areas. Because the whole country is not covered there may be some cases that cannot be followed-up if they have moved to some other geographic area of e.g. from communal health care to occupational health care. The follow-up of the patients is then stressed with nationwide data.

In general Finland has a well-developed population register system with tens of years of longitudinal follow-up data. The persons are identified in the registers with a unique personal identification number enabling linkage between different registers. These data has not been collected for study purposes, which may affect the quality of the data. Only those citizens that have been living in Finland for two years prior to index date will be included in the study.

Coverage of the Prescription Register containing reimbursement information of all permanent residents of Finland is about 97%. Missing data includes relatively inexpensive packages that are not reimbursed. No exact prescribed dosing information is available in structured format but in this pilot study we survey also the written dosing text. Usually the dosing is assumed based on the information of purchases and package sizes with defined daily doses.

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 during the follow-up period will be taken into account.

Nationwide primary care register is available since 2011 only. The coverage of deaths is 100%.

10 Protection of human subjects

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

Register data from different sources will be linked in EPID Research. EPID Research will first receive data with real IDs but artificial study IDs (SIDs) will be formed outright e.g. by MD5 one-way hashing algorithm. The lists including both IDs and SIDs will be kept separately from the rest of the data and the EPID Research personnel analysing the data will be working with the data including SIDs only. For follow-up data requests both IDs and SIDs are given to register holders but the results will be asked to include SIDs only. This way patient level data can be linked while transferring the IDs as little as possible. 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 protocol will be subjected to Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) for review and approval. Register notification of the forming study registers will be sent to the Office of the Data Protection Ombudsman.

11 Management and reporting of adverse events/adverse reactions

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

12 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 steering committee. After study report the principal investigator and co-investigators with co-authors (members of the steering committee and possible other contributors) will prepare (a) scientific manuscript(s) for academic publication. The steering committee decides the publication forums.

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 of 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. The sponsor is entitled to view the final results without unjustifiably delaying the publication.

13 References

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UKPDS Group (1998) UK Prospective Diabetes Study 34. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type II diabetes. Lancet; 352:854-65.

Annex 1. Approvals

We have reviewed this study protocol (ER12-9451, Version 1.0, dated 30 April 2013) and agree to its terms by signing it.

			Date and signature
Principal investigator	Pasi Korhonen, Ph.D., adj. prof. biostatistics	EPID Research, Tekniikantie 12, FI-02150 Espoo	
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	Jarmo Hahl, M.Sc.	AT Medical Affairs Consulting, Tietäjäntie 3, FI-02130 Espoo	
	Fabian Hoti, Ph.D.	EPID Research, Tekniikantie 12, FI-02150 Espoo	
	Tuire Tirkkonen, Ph.D.	EPID Research, Tekniikantie 12, FI-02150 Espoo	

Annex 2. ENCePP checklist for study protocols

See separate document.

Annex 3. Concomitant Disease Variables

Concomitant Disease	ICD-10	Refund Catecory *	ICPC-2
asthma bronciale COPD chronic bronchitis	J41 J42 J44 J45	203	R79 R95 R96
chronic hypertension	I10–I13 I15	205	K86 K87
chronic renal insufficiency	I12 I13 E11.2 N17 N18 Z49	137	
chronic cardiac insufficiency	I11.0 I13 I50	201	K77
rheumatoid arthritis	M02 M05 M06 M45	202	L88
atrial fibrillation	I48	207	K78
coronary artery disease	I20 I21 I22 I24 I25	206	K74 K75 K76
dyslipidemia	E78		T93

cancer (excl. *in situ* cancers)	C00-C97	115 116 117 128 130	A79 B74 D74 D75 D76 D77 L71 N74 R84 R85 S77 T71 U75 U76 U77 W72 X75 X76 X77 Y77 Y78
stroke and TIA	I63 I64 G45		K89 K90
deppression	F32 F33 F34.1	112	P76
obesity	E66 E68		T82 T83
peripheral circulatory complications	I70 I70.2 in particular E11.5		K92
diabetic nephropathy	N08.3		
diabetic neuropathy	G63.2		
diabetic retinopathy	H36.0		

* to be used with ICD-10s. (There refund categories include also other diseases.)

Annex 4. ATCs of Antidiabetic Drugs

Antidiabetic drug	ATC
insulin (human)	A10AB01
insulin (beef)	A10AB02
insulin (pork)	A10AB03
insulin lispro	A10AB04
insulin aspart	A10AB05
insulin glulisine	A10AB06
combinations	A10AB30
insulin (human)	A10AC01
insulin (beef)	A10AC02
insulin (pork)	A10AC03
insulin lispro	A10AC04
combinations	A10AC30
insulin (human)	A10AD01
insulin (beef)	A10AD02
insulin (pork)	A10AD03
Insulin lispro	A10AD04
insulin aspart	A10AD05
combinations	A10AD30
insulin (human)	A10AE01
insulin (beef)	A10AE02
insulin (pork)	A10AE03
insulin glargine	A10AE04
insulin detemir	A10AE05
combinations	A10AE30
insulin (human)	A10AF01
phenformin	A10BA01
metformin	A10BA02
buformin	A10BA03
glibenclamide	A10BB01
chlorpropamide	A10BB02
tolbutamide	A10BB03
glibornuride	A10BB04
tolazamide	A10BB05
carbutamide	A10BB06
glipizide	A10BB07
gliquidone	A10BB08
gliclazide	A10BB09
metahexamide	A10BB10

glisoxepide	A10BB11
glimepiride	A10BB12
acetohexamide	A10BB31
glymidine	A10BC01
phenformin and sulfonamides	A10BD01
metformin and sulfonamides	A10BD02
metformin and rosiglitazone	A10BD03
glimepiride and rosiglitazone	A10BD04
metformin and pioglitazone	A10BD05
glimepiride and pioglitazone	A10BD06
metformin and sitagliptin	A10BD07
metformin and vildagliptin	A10BD08
pioglitazone and alogliptin	A10BD09
metformin and saxagliptin	A10BD10
metformin and linagliptin	A10BD11
pioglitazone and sitagliptin	A10BD12
metformin and alogliptin	A10BD13
acarbose	A10BF01
miglitol	A10BF02
voglibose	A10BF03
troglitazone	A10BG01
rosiglitazone	A10BG02
pioglitazone	A10BG03
sitagliptin	A10BH01
vildagliptin	A10BH02
saxagliptin	A10BH03
alogliptin	A10BH04
linagliptin	A10BH05
sitagliptin and simvastatin	A10BH51
guar gum	A10BX01
repaglinide	A10BX02
nateglinide	A10BX03
exenatide	A10BX04
pramlintide	A10BX05
benfluorex	A10BX06
liraglutide	A10BX07
mitiglinide	A10BX08
dapagliflozin	A10BX09

Annex 5. ID numbers of laboratory measurements

Test abbreviation	Lab test number *		Target/Limit	Unit
B-GHb-A_{1C}	1560		<6.5	%
B-GHbA_{1C}M	8514		<6.5	%
B-HbA_{1C} **	6128		<6.5 **	mmol/mol
B-HbA_{1C}VT **	14214		<6.5 **	mmol/mol
Pt-Gluk-R (Gluc.tolerance)	20271	0 h (atreria)	≥7 (for DM) *	mmol/L
		2 h (arteria)	≥11.1 (for DM) *	mmol/L
		0 h (capillary)	≥7 (for DM) *	mmol/L
		2 h (capillary)	≥12.2 (for DM) *	mmol/L
P-Crea S-Crea	4600 2143		<150	µmol/L
P-ALAT	1024	women (≥18-y)	10-45 *	U/L
		men (≥18-y)	10-70 *	U/L
fP-Chol-LDL	4599		<2.5	mmol/L
		with predisposing diseases	<1.8	mmol/L
cU-Alb	3557		<20	µg/min
nU-Alb	4836		<20	µg/min
dU-Alb	3134		<30 *	mg (/d)
U-AlbCrea	4511	women (>16-y)	<3.5	mg/mmol
		men (>16-y)	<2.5	mg/mmol
nU-AlbCrea	23572	women (>16-y)	<3.5	mg/mmol
		men (>16-y)	<2.5	mg/mmol

* http://huslab.fi/cgi-bin/ohjekirja/tt_show.exe?assay=2475&terms=pvk read 22 Mar 2013

** HbA_{1c} tests replacing GHb-A_{1c} tests since 03 Mar 2010. Formulas for transformation:

B-HbA_{1c} (mmol/mol) = 10,93 x B-GHb-A_{1c}(%) - 23,50

B-GHb-A_{1c}(%) = 0,0915 x B-HbA_{1c}(mmol/mol) + 2,15

See also http://huslab.fi/ohjekirjan_liitteet/hb_a1c_muuntotaulukko.pdf

Annex 6. ATCs for cardiovascular drugs

Group	Drug	ATC
ACE inhibitor	captopril	C09AA01
ACE inhibitor	enalapril	C09AA02
ACE inhibitor	lisinopril	C09AA03
ACE inhibitor	perindopril	C09AA04
ACE inhibitor	ramipril	C09AA05
ACE inhibitor	quinapril	C09AA06
ACE inhibitor	benazepril	C09AA07
ACE inhibitor	cilazapril	C09AA08
ACE inhibitor	fosinopril	C09AA09
ACE inhibitor	trandolapril	C09AA10
ACE inhibitor	spirapril	C09AA11
ACE inhibitor	delapril	C09AA12
ACE inhibitor	moexipril	C09AA13
ACE inhibitor	temocapril	C09AA14
ACE inhibitor	zofenopril	C09AA15
ACE inhibitor	imidapril	C09AA16
ACE inhibitor + diuretic	captopril and diuretics	C09BA01
ACE inhibitor + diuretic	enalapril and diuretics	C09BA02
ACE inhibitor + diuretic	lisinopril and diuretics	C09BA03
ACE inhibitor + diuretic	perindopril and diuretics	C09BA04
ACE inhibitor + diuretic	ramipril and diuretics	C09BA05
ACE inhibitor + diuretic	quinapril and diuretics	C09BA06
ACE inhibitor + diuretic	benazepril and diuretics	C09BA07
ACE inhibitor + diuretic	cilazapril and diuretics	C09BA08
ACE inhibitor + diuretic	fosinopril and diuretics	C09BA09
ACE inhibitor + diuretic	delapril and diuretics	C09BA12
ACE inhibitor + diuretic	moexipril and diuretics	C09BA13
ACE inhibitor + diuretic	zofenopril and diuretics	C09BA15
ACE inhibitor + calcium channel blocker	enalapril and lercanidipine	C09BB02
ACE inhibitor + calcium channel blocker	lisinopril and amlodipine	C09BB03
ACE inhibitor + calcium channel blocker	perindopril and amlodipine	C09BB04

ACE inhibitor + calcium channel blocker	ramipril and felodipine	C09BB05
ACE inhibitor + calcium channel blocker	enalapril and nitrendipine	C09BB06
ACE inhibitor + calcium channel blocker	ramipril and amlodipine	C09BB07
ACE inhibitor + calcium channel blocker	trandolapril and verapamil	C09BB10
ACE inhibitor + calcium channel blocker	delapril and manidipine	C09BB12
ACE inhibitor + statin + ASA	simvastatin, acetylsalicylic acid and ramipril	C10BX04
ARB	losartan	C09CA01
ARB	eprosartan	C09CA02
ARB	valsartan	C09CA03
ARB	irbesartan	C09CA04
ARB	tasosartan	C09CA05
ARB	candesartan	C09CA06
ARB	telmisartan	C09CA07
ARB	olmesartan medoxomil	C09CA08
ARB	azilsartan medoxomil	C09CA09
ARB + diuretic	losartan and diuretics	C09DA01
ARB + diuretic	eprosartan and diuretics	C09DA02
ARB + diuretic	valsartan and diuretics	C09DA03
ARB + diuretic	irbesartan and diuretics	C09DA04
ARB + diuretic	candesartan and diuretics	C09DA06
ARB + diuretic	telmisartan and diuretics	C09DA07
ARB + diuretic	olmesartan medoxomil and diuretics	C09DA08
ARB + calcium channel blocker	valsartan and amlodipine	C09DB01
ARB + calcium channel blocker	olmesartan medoxomil and amlodipine	C09DB02
ARB + calcium channel blocker	telmisartan and amlodipine	C09DB04
ARB + calcium channel blocker	irbesartan and amlodipine	C09DB05
ARB + calcium channel blocker	losartan and amlodipine	C09DB06
ARB + calcium channel blocker	valsartan, amlodipine and hydrochlorothiazide	C09DX01
ARB + renin inhibitor	valsartan and aliskiren	C09DX02
ARB + calcium channel blocker + diuretic	olmesartan medoxomil, amlodipine and hydrochlorothiazide	C09DX03