Study Protocol

Title:	Prevalence of cardiovascular disease in Swedish patients with type 2 diabetes and in patients initiating on Empagliflozin (ATC code A10BK03)
Study code	F_07_2018
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List of abbreviations

Term	Definition / description
BMI	Body mass index
CDR	Cause-of-Death register
CI	Confidence interval
eGFR	Estimated glomerular filtration rate
HbA1c	Glycated haemoglobin A1c
HDL	High Density Lipoprotein
ICD-10	International classification of diseases
MI	Myocardial infarction
NDR	National diabetes register
NPR	National patient register
PH	Proportional hazards
PS	Propensity score
RR	Relative risk
SPDR	Swedish prescribed drug register
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Introduction

The Swedish National Diabetes Register (NDR) was launched in 1996 for the purpose of promoting evidence-based development of diabetes care. The NDR has been online since April 2002 (www.ndr.nu), allowing individual clinics to quickly monitor their activities on a regular basis. The register offers a unique opportunity to monitor the quality of care in terms of risk factors and the potential complications of diabetes. The results generated by the register have been presented at many international meetings and conferences. To our knowledge, the NDR is the largest diabetes register in the world.

Patients with Type 2 diabetes mellitus (T2DM) are at high risk for developing cardiovascular disease (CVD) complications.

The EMPA-REG OUTCOME (ERO) trial demonstrated a reduction in cardiovascular death, hospitalization from heart failure and all-cause mortality. Empagliflozin also reduces the risk for new onset or worsening of nephropathy, progression to macroalbuminuria and doubling of serum creatinine accompanied by eGFR of ≤45 ml/min/1,73 m^2. Empagliflozin is also associated with weight loss. (1)

In the ERO patients had a history of CV disease. (Appendix 1). It is not known how many of patients in clinical practice have a history of CV disease according to the ERO definition. In a publication by Norhammar et al patients with CVD was approximately 34 %. (2)However those data also included patients with atrial fibrillation and excluded patients with peripheral artery disease.

According to newly published Swedish guidelines by both the National board of Health and Welfare and the Medical Products Agency patients with type 2 diabetes and cardiovascular disease start treatment with Empagliflozin. (3) It is not known how many patients with T2DM and cardiovascular disease receive empagliflozin today.

Research question and objectives

Research questions

1. Describe the prevalence of T2DM patients with established CVD according to ERO study definition in a Swedish population. (Appendix 1).
2. Describe the prevalence of established CVD according to ERO study definition in patients with T2DM who initiates treatment with empagliflozin.

Objectives

Primary objectives

1. To estimate the point prevalence of cardiovascular disease among persons with T2DM at 2017-12-31.
2. To estimate the prevalence of cardiovascular disease among persons with T2DM who initiates treatment with empagliflozin between 2015-01-01 and 2017-12-31

Secondary objectives

1. Describe the T2DM patients with established CVD according to ERO study definition with respect to demographics and disease characteristics.
2. Describe the patients initiating with empagliflozin with respect to demographics and disease characteristics.

Subject sets analyzed

Source population in the study

The broad study population will include patients with T2DM and at least one registration in the NDR (at any time from start of registry until 2017) and who are alive on 2015-01-01. Based on this population, the following two sub-populations will be identified, corresponding to each of the two research questions:

Table 1 Populations

Population	**Definition**	**Details**	**Data source**
Broad population	Patients with T2DM and at least one registration in the NDR (at any time from start of registry until 2017) and alive on 2015-01-01		NDR
Population 1	Among the broader study population, those who are alive also on 2017-12-31 will be included.		NDR
Population 2	Among the broader study population, those	SPDR used to	NDR

	who initiate on empagliflozin (ATC code A10BK03) between 2015-01-01 and 2017-12-31 will be included	determine population

Index date

The index date for question 1 will be 2017-12-31. For question 2, the index date will be the date corresponding to the first collection of empagliflozin.

Baseline and look back period

To characterize the study population, all information available during the look-back (pre-index) time period will be collected.

The look-back time period is defined as the time period ending on the day before the index date (Table 2).

Table 2 Data sources with look-back periods and total data collection periods

Data source	Data holder	Look-back period	Total data collection period
National diabetes register (NDR)	Centre of Registers, Region Västra Götaland	1 year	1996-2017
Swedish prescribed drug register (SPDR)	National Board of Health and Welfare		2015.01.01-2017.12.31
National patient register (NPR), both inpatient[3] and outpatient[4] registers	National Board of Health and Welfare	1997-index date (i.e. as long as data allows)	1997-2017
Cause of death register (CDR)	National board of health and welfare	Will be used to establish the broader population and population 2 (i.e to establish that patients are alive)	2017

Established CVD

Table 3 Established CVD

Variable	Definition	Details	Data source
Established CVD	Presence of at least one of the ICD10 codes as defined in appendix 1	NPR introduced ICD10-codes in 1997, i.e. data from that year and later will be used	NPR inpatient and outpatient

Initiation on Empagliflozin

Table 4 Initiation of empagliflozin

Variable	Definition	Details	Data source
Date for initiation of empagliflozin	The date for first collection of Empagliflozin (ATC code A10BK03)	Index date for Question 2	SPDR

Other variables

Demographics and clinical baseline variables

Table 5 Demographics and other baseline variables

Variable	Definition	Details	Data source
Age at index	Patient age at index. **Evaluated at the index date.**	Continuous	NDR
Sex	Patient sex. **Evaluated at index date.**	Categorical: Female Male	NDR
BMI	Patient BMI value at index date. **Evaluated at index date.**	Continuous	NDR
Smoking status	Patient smoking status at index date. **Evaluated at the index date.**	Categorical: Yes	NDR

		No	
HbA1c value (in mmol/mol)	Patient HbA1c measurement value at index date in mmol/mol. **Evaluated at the index date.**	Continuous	NDR
Duration of diabetes at index date	Time difference between [index date] and [first type 2 diabetes diagnosis date]. **Evaluated at the index date.**	Continuous	NDR
Systolic blood pressure	Patient systolic blood pressure measurement value in mm Hg at then index date. **Evaluated at the index date.**	Continuous	NDR
Diastolic blood pressure	Patient diastolic blood pressure measurement value in mm Hg. **Evaluated at the index date.**	Continuous	NDR
Total cholesterol	Patient Total cholesterol measurement **Evaluated at the index date.**	Continuous	NDR
LDL	Patient LDL measurement value in mmol/L. **Evaluated at the index date.**	Continuous	NDR
HDL	Patient HDL measurement value in mmol/L. **Evaluated at the index date.**	Continuous	NDR
Triglyceride	Patient Triglyceride measurement value at index date in mmol/L. **Evaluated at the index date.**	Continuous	NDR
Creatinine	Patient Creatinine measurement **Evaluated at the index date.**	Continuos	NDR
Estimated glomerular filtration rate (eGFR)	Patient eGFR at index date estimate derived from serum creatinine measurement using the CKD-Epi equation: eGFR (mL/min/1.73 m^2) = 141 x $\min(S_{cr}/K,1)^a$ x $\max(S_{cr}/K,1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female]. a = -0.329 (females) or -0.411 (males). **Evaluated at the index date.**	Continuous	NDR
Micro albuminurea	**Evaluated at the index date.**	Categorical: Yes	NDR

		No	
Macro albuminurea	**Evaluated at the index date.**	Categorical: Yes No	NDR
Retinopathy	**Evaluated at the index date.**		NDR
Lipid lowering drugs	**Evaluated at the index date.**		NDR
Blood pressure lowering drugs	**Evaluated at the index date.**		NDR
Diabetes drugs	**Evaluated at the index date.**		NDR

Planned analysis

Summary of study populations identification

The identification process used to identify the study populations and subgroups will be summarized using population flowcharts including the following information:

- The total number of patients in the broad population (i.e. patients with T2DM and with at least one registration in the NDR and who are alive on 2015-01-01).
- The number of patients who are also alive on 2017-12-31 (the population for Question 1).
- The number of patients collecting Empagliflozin between 2015-01-01 and 2017-12-31 but who are not part of the broad population
- The number of patients in the broad population initiating Empagliflozin between 2015-01-01 and 2017-12-31 (the population for question 2)

Main analysis

All analyses will be descriptive and no testing of hypotheses will be performed. The number and percentage of subjects with established CVD will be calculated and reported for both questions.

Variables in Table 5 will be descriptively reported for patients with established CVD within population 1 as well as for all patients in population 2.

Relating to question 2, the sub-group of patients initiating Empagliflozin during 2017 will be described with respect to prevalence of established CVD as well as the demographic and disease characteristics of Table 5.

Data management

Statistical software

The analysis and data management will be performed using SAS 9.4® or R 3.4.0.

R language is described in more details 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 21 December 2016).

Quality control

Programs used in the data management and statistical analysis will be validated though independent review of the programming code, analysis data and output based on a risk assessment.

References

1. Zinman et al. *Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes.* N Engl J Med 2015; 373:2117-2128

2. Norhammar et al. *Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006–2013.* Diabetologia (2016) 59:1692–1701

3. Socialstyrelsen. 2017. *Nationella riktlinjer för diabetesvård.* Retrieved from http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/20633/2017-5-31.pdf