Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

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Document Number:	**<document number>**
BI Study Number:	<Study Number>
BI Investigational Product(s):	Empagliflozin (Jardiance®) Empagliflozin + Linagliptin (Glyxambi®) Empagliflozin + Metformin (Synjardy®)
Title:	**Cardiovascular outcomes and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus liraglutide as second-line therapy: A Danish nationwide comparative effectiveness study**
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PASS:	No
EU PAS register number:	*If applicable: Registration number in the EU PAS register; indicate "Study not registered" if the study has not been registered in the EU PAS register*
Active substance:	A10BX12 Empagliflozin A10BK03 Empagliflozin A10BD19 Empagliflozin + Linagliptin A10BD20 Empagliflozin + Metformin A10BX07 Liraglutide A10BJ02 Liraglutide *A10AE56 Insulin degludec + Liraglutide*
Medicinal product:	Jardiance Glyxambi Synjardy Victoza Xultophy
Product reference:	Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study

Procedure number:	*If applicable, Agency or national procedure number(s), e.g. EMA/X/X/XXX*
Joint PASS:	No
Research question and objectives:	To compare, among patients with type 2 diabetes in Denmark, clinical outcomes among new users (initiators) of empagliflozin versus liraglutide.
Country(-ies) of study:	Denmark
Authors:	Jakob S. Knudsen, MD Reimar W. Thomsen, MD, PhD On behalf of the DCE Aarhus team
Marketing authorisation holder(s):	*Name, address and contact details of the marketing authorisation holder(s)*
MAH contact person:	*Contact person for this (PASS) protocol submission (if this a joint PASS, only one person should be mentioned)*
In case of PASS, add: **<EU-QPPV:>**	*In case of PASS, insert name and contact details of the EU-QPPV or his/her delegate*
In case of PASS, add: **<Signature of EU-QPPV:>**	*In case of PASS, insert the signature of the EU-QPPV or add <The signature of the EU-QPPV is provided electronically>as applicable.*
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2. LIST OF ABBREVIATIONS

AE	Adverse Event
AUC	Area under the Curve
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Subteam
OPU	Operative Unit
p.o.	per os (oral)
PCC	Protocol Challenge Committee
q.d.	quaque die (once a day)
SAE	Serious Adverse Event
s.c.	subcutaneous
SPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

<Adapt and complete as appropriate>

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: A10BX12 (Empagliflozin (Jardiance®)) A10BK03 (Empagliflozin (Jardiance®)) A10BD19 (Empagliflozin + Linagliptin (Glyxambi®)) A10BD20 (Empagliflozin + Metformin (Synjardy®)) A10BX07 (Liraglutide (Victoza®) A10BJ02 (Liraglutide (Victoza®) A10AE56 (Insulin degludec + Liraglutide (Xultophy®))			
Name of active ingredient: See above.			
Protocol date: 13JUL2018	**Study number:**	**Version/Revision:** 2	**Version/Revision date:** 16AUG2018
Title of study:	**Cardiovascular outcomes and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus liraglutide**		
Rationale and background:	Utilization of the newer glucose-lowering drugs GLP1 receptor agonists and SGLT2 inhibitors has increased substantially in people with type 2 diabetes worldwide. Trials have shown that the GLP1 receptor agonist liraglutide and the SGLT2 inhibitor empagliflozin caused (13% and 14%, respectively) reductions in major adverse cardiac events among T2D patients with high cardiovascular risk, with similar reductions in HbA1c of 0.4% and 0.3%, Little is known about how these therapies compare regarding clinical outcomes in routine clinical care. In Denmark, nationwide population-based databases holding individual-level patient data enable comparative effectiveness studies among non-selected patients with type 2 diabetes.		
Research question and objectives:	Our primary objective is to compare clinical outcomes (cardiovascular events, mortality) among empagliflozin initiators and liraglutide initiators in Denmark.		
Study design:	Non-interventional cohort study using existing data. The study will use a new user design and compare new users of empagliflozin with new users of liraglutide.		

Population:	The study population will include all eligible patients with type 2 diabetes initiating treatment with empagliflozin or with liraglutide in 2014-2017.
Variables:	*Exposure:* First-time prescription of empagliflozin or liraglutide. *Outcomes:* Hospital admission with heart failure / initiation of loop diuretics, stroke, myocardial infarction, unstable angina, coronary revascularization, all-cause acute hospital admission, all-cause death. *Confounders:* Age, gender, marital status, calendar time, diabetes duration, frailty markers, previous history of cardiovascular disease, other diabetes complications, smoking- and alcohol-related disorders, medical obesity, glucose-lowering co-therapy, cardiovascular drug use, psychiatric medications.
Data sources:	Danish population-based linked registries: The Civil Registration System, The Danish National Patient Register, The National Database of Reimbursed Prescriptions, The LABKA Database
Study size:	Source population: 270.000 patients with drug-treated or hospital-treated type 2 diabetes in Denmark. The study size will be driven by the uptake of empagliflozin following its approval and launch in Denmark, with expected rapid increase after 2015. In 2016 there were 13,362 users of SGLT2 inhibitors in Denmark, including approximately 6,000 users of empagliflozin. In 2016, there were 24,273 users of GLP-1 receptor agonists, including 23,420 users of liraglutide. Presciption data for 2017 are expected mid-2018. We expect at least 10,000 person-years of empagliflozin exposure and 20,000 person-years of liraglutide exposure by end of 2017, yielding a power of >80% to detect an outcome incidence rate ratio of 0.83 associated with empagliflozin use.
Data analysis:	Current use of the drugs under study will be defined from the date of first prescription of empagliflozin or liraglutide to the end of supply for that prescription plus a period of 30 days. Our main analysis will be an as-treated analysis, censoring patients at time of index drug exposure discontinuation. In a sensitivity analysis, we will apply an intention-to-treat analysis, following patients according to their initial drug exposure. We will start follow up all empagliflozin or liraglutide initiators from the first prescription date until first study outcome, drug discontinuation, emigration, or end of follow-up. Cumulative incidence function curves will be constructed to display the cumulative incidence over time of each of the outcomes under study, comparing empagliflozin and liraglutide initiators. Similarly, Kaplan-Meier curves will be used for mortality outcomes. Incidence rates of each of the outcomes among empagliflozin new users and liraglutide new users will be calculated per 1,000 person-years with 95% confidence intervals. We will use Cox regression analyses to compute crude and adjusted hazard ratios (HRs) with 95% CIs to examine the association between empagliflozin versus liraglutide initiation and study outcomes. If feasible in our data, we will apply propensity score (PS) balancing of potential confounders across the

	two treatment groups, through inverse probability treatment weighting (IPTW) and/or PS score matching. A number of different analyses will be performed. In one analysis, we will use a new augmenter design, comparing exclusively patients who initiate empagliflozin versus liraglutide as add-on therapy to glucose-lowering monotherapy (usually metformin). Moreover, a number of stratified and sensitivity analyses will be performed to assess effect measure modification and possible residual confounding.
Milestones:	Figure 1 Milestone 1 (December 2017): Project synopsis developed, research collaboration agreement finalized, project initiated. Figure 2 Milestone 2 (August 2018): Protocol finalized. Figure 3 Milestone 3 (October 2018): First data analysis prepared. Figure 4 Milestone 4 (April 2019): Publication submitted.

5. AMENDMENTS AND UPDATES

Write "None" or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below.
NONE: Data are routinely collected.

Number	Date	Section of study protocol	Amendment or update	Reason
<1>	DD Month YYYY	<Text>	<Text>	<Text>
<2>	DD Month YYYY	<Text>	<Text>	<Text>
<n>	DD Month YYYY	<Text>	<Text>	<Text>

6. MILESTONES

Planned dates for study milestones should be indicated in a table as indicated below. Milestones between <> are optional and should be included only if applicable. Start of data collection and End of data collection are defined in Module VIII of the GVP (where the study uses data from existing electronic databases such as claims, prescriptions or health care records, "secondary use of data" applies to these definitions). Other important timelines can be added.

Milestone	**Planned Date**
Start of data collection	01JAN1977
End of data collection	Ongoing
<Study progress report 1>	
<Study progress report 2>	
<Study progress report n>	
<Interim report 1>	
<Interim report 2>	
<Interim report n>	
<Registration in the EU PAS register>	
Final report of study results:	30APR2019

7. RATIONALE AND BACKGROUND

Utilization of the newer type 2 diabetes (T2D) medications GLP1 receptor agonists and SGLT2 inhibitors in Denmark has increased substantially, after clinical trials have provided evidence that these drugs reduce cardiovascular disease (CVD) risk beyond their glucose-lowering effect. For example, in the LEADER and EMPA-REG OUTCOME trials(6,7), the GLP1 receptor agonist liraglutide and the SGLT2 inhibitor empagliflozin caused (13% and 14%, respectively) reductions in major adverse cardiac events (MACE; i.e., CVD death, myocardial infarction, or stroke) among T2D patients, with reductions in HbA1c of 0.4% and 0.3%, respectively. Since GLP1 receptor agonists and SGLT2 inhibitors furthermore both are associated with weight loss and low risk of hypoglycemia, they have become a popular choice for second-line therapy, in particular as add-on therapy to metformin. In Denmark, liraglutide has been the overwhelmingly used GLP1 receptor agonist since 2010(8), while use of exenatide has remained low; use of lixisenatide and dulaglutide is still low as of 2016(9). Regarding SGLT2 inhibitors in Denmark, dapagliflozin has been the clearly most used SGLT2 inhibitor up to 2015(10), whereas from 2016 onwards the use of empagliflozin has increased substantially (use of canagliflozin has generally been low)(9).

Little is known about the differences in patient characteristics between users of liraglutide versus users of empagliflozin, and how these therapies compare regarding clinical outcomes in routine clinical care. In Denmark, nationwide population-based databases holding individual-level patient data enable drug utilization studies and comparative effectiveness studies in clinical practice among non-selected patients with type 2 diabetes (10,11). In an ongoing collaboration between Boehringer Ingelheim and the Department of Clinical Epidemiology in Aarhus, we investigate patient characteristics at the time of empagliflozin initiation, and compare the characteristics with those of initiators of other frequently used newer glucose-lowering drugs, namely: SGLT2 inhibitors other than empagliflozin, GLP-1 receptor agonists, and DPP-4 inhibitors. Our preliminary results suggest that initiators of empagliflozin and GLP-1 receptor agonists in Denmark are very similar regarding demographic and clinical variables and baseline glycemic control. We now propose to conduct a cohort study of cardiovascular outcomes and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus liraglutide.

8. RESEARCH QUESTION AND OBJECTIVES

The primary research question is to evaluate whether, among patients with type 2 diabetes, initiation of empagliflozin changes the adjusted incidence of outcomes compared with initiation of liraglutide.

The primary objectives of the study are to estimate, for new users (initiators) of empagliflozin compared with initiators of liraglutide, the adjusted hazard ratio of:

Co-Primary study outcomes:

- Acute inpatient hospital admission with a diagnosis of HF and/or initiation of community prescription drug therapy with loop diuretics
- Acute inpatient hospital admission with a diagnosis of HF and/or all-cause death
- "Expanded MACE": All-cause death, acute admission with non-fatal (within 30 days) stroke, acute admission with non-fatal (within 30 days) MI, acute admission with unstable angina, coronary revascularization, or acute admission with non-fatal HF

Secondary outcomes of interest:

- All-cause acute inpatient hospital admissions, or emergency room visits leading or not leading to inpatient hospital admission
- All-cause acute inpatient hospital admission
- Acute hospital admission with HF
- All-cause acute inpatient hospital admission or all-cause death.
- All-cause death

For the above study outcomes, "acute inpatient hospital admission" in the Danish registries covers all types of hospital entry, for example; admission via emergency room entrance, admission by ambulance, self-referral, referral from GP/primary health care provider.

If the number of empagliflozin initiators allows, we will compare the rates of the above outcomes for initiators of empagliflozin and liraglutide stratified by calendar periods before and after publication of major cardiovascular outcome trials (CVOTs) in 2015-2016.

9. RESEARCH METHODS

Description of the research methods, including:

9.1 STUDY DESIGN

Non-interventional cohort study using existing data.

The study will use a "new user" (also known as "incident users") design and will compare new users of empagliflozin to new users of liraglutide. To avoid the inclusion of prevalent users, patients starting empagliflozin or liraglutide will be required to be new users, defined as having no previous exposure to empagliflozin or other SGLT2 inhibitors, and no previous exposure to liraglutide or other GLP-1 receptor agonists, during the 12 months prior to the index date of a first drug prescription of empagliflozin or liraglutide.

Both empagliflozin and liraglutide are usually a second- or third-line treatment for type 2 diabetes; thus, it is expected that few patients initiating empagliflozin or liraglutide will be treatment naive. For the majority of patients, these study drugs will be added to an existing treatment (e.g., added to metformin), or patients will be switched to these drugs (e.g., from metformin plus an oral glucose-lowering drug other than the study drugs to metformin plus empagliflozin or metformin plus liraglutide) due to disease progression, treatment failure / insufficient glucose control, or side effects that may be related to study outcome. Therefore, in one of our analyses, we will use a new augmenter design, comparing exclusively patients who initiate empagliflozin versus liraglutide as add-on therapy to glucose-lowering monotherapy (usually metformin). In another analysis, we will compare people who switch from previous dual therapy that did not include the two study drugs to dual therapy including either empagliflozin or liraglutide. If the number of events is sufficient, additional analyses will be accomplished by comparing patients who start dual or even triple therapy at diabetes debut with empagliflozin versus liraglutide as part of the combination therapy, and by comparing patients who start e.g. third-line therapy with empagliflozin as an add-on or switch-to drug with patients starting third-line therapy with liraglutide as an add-on or switch-to drug.

A cohort design will allow direct estimation of the absolute rates, rate differences, and relative risk or hazard ratios of multiple outcomes of interest among new users of empagliflozin compared with new users of liraglutide. A cohort study design will also allow accurate chronologic confounder assessment and assessment of the outcomes at multiple time points. The covariate information will be assessed during the time preceding treatment initiation and will include all historical information available for each patient. Follow-up will start the day after treatment initiation.

Propensity scores will be estimated for each cohort member based on information prior to the index date. Propensity scores will incorporate measured potential predictors of the outcome as independent variables and exposure group status as the dependent variable. Propensity scores will be used to minimise confounding.

9.2 SETTING

Study population

The source population for our study consists of individuals with type 2 diabetes, who are are defined in our study as individuals who live in Denmark and have ever used oral antihyperglycemic drugs or insulin (ATC-codes A10A, A10B) between 2004-2017, defined as one or more prescriptions for: metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, insulin, alfa-glucosidase inhibitors, other oral antihyperglycemic drugs, or combination products, according to the Anatomical Therapeutic Chemical (ATC) classification system (12). Diabetic patients who under the age of 30 used insulin as mono-therapy and never used oral antihyperglycemic medications will be excluded as likely T1D patients(2,13). Within this source population, we will identify our study population of adult type 2 diabetes patients initiating empagliflozin or liraglutide between 2014-2017.

The use of hospital ICD codes recorded in the Danish National Patient Register to identify patients with diabetes excluding gestational diabetes can only identify diabetes patients who required hospital treatment and treatment by hospital-based specialist doctors. Uncomplicated type 2 diabetes is usually treated by general practitioners (i.e., ~80% of type 2 diabetes patients are followed mainly in primary care), and thus not completely registered in hospital registries(14). The sensitivity of the Danish National Patient Register in identifying patients with known diabetes through diabetes diagnosis codes has been estimated at 64% (as most people with diabetes have hospital contact at some point of time), while the PPV of a diabetes diagnosis in the same Register is 97%(15). In comparison, the sensitivity of the Danish National Prescription Registry in identifying patients with diabetes through one or more glucose-lowering drug prescriptions has been estimated at 72% (as not all diabetes is drug treated), while the PPV of one glucose-lowering drug prescription for presence of diabetes is 95% (15). In the case of the present study all patients redeeming a prescription for the drugs examined will be registered with the Danish National Prescription Registry(16). Empagliflozin and liraglutide are prescribed/started as initial drug both by general practitioners (GPs) and specialist physicians in Denmark, and most of the follow-up prescriptions (for chronic treatment) will be issued by GPs or primary care physicians. All these prescriptions, no matter which physician prescribed them, are dispensed and registered on the individual level at essentially monopolized community pharmacies in Denmark, and therefore, new user data for the drugs is complete on the national level.

Study period

The planned study period is 1JAN2014 to 31DEC2017. Empagliflozin was launched in Denmark August 2014.

Index prescription definition

The index prescription will be the first prescription for the study medication of interest that fulfils the definition of new user during the study period. Index prescriptions/dispensings of the study drugs include the single study drugs or fixed-dose combinations of the study drugs with other glucose-lowering drugs.

Index date

The index date will be defined as the date on which each identified new user receives the index prescription for empagliflozin or liraglutide.

Baseline and lookback period

To characterise the empagliflozin and liraglutide cohorts at the time of study drug initiation, all information available during the lookback (pre-index) time period will be collected. The lookback time period is defined as the time period ending on the index date. All cohort members are required to have at least 12 months of data history before the index date (baseline period), the lookback period will therefore include at least 365 days during which covariates can be evaluated. For most cohort members, more data on covariates is available beyond 365 days, and all available information will be considered for covariate classification related to diabetes, diabetes medications, and concomitant chronic conditions.

Inclusion criteria

All patients will be required to meet all of the following criteria:

- Be aged 18 or more years at the index date (date of initiation of empagliflozin or liraglutide).
- Have at least 12 months of residency in Denmar prior to the index date.
- Have type 2 diabetes ever before the index date

The empagliflozin-exposed population must also meet the following criteria:

- Have at least one prescription for empagliflozin or fixed-dose combination of empagliflozin with another drug, with or without treatment with another glucose-lowering drug.
- Have no prior prescription/dispensing of SGLT2 inhibitors (including empagliflozin) alone or in fixed-dose combination during the 12 months prior to the index date.
- Have no prior prescription/dispensing of a GLP-1 receptor agonist alone or in fixed-dose combination during the 12 months prior to the index date.

The population exposed to liraglutide must meet the following criteria:

- Have at least one prescription for liraglutide or a fixed-dose combination of liraglutide with another drug, with or without treatment with another glucose-lowering drug.
- Have no prior prescription/dispensing of a GLP-1 receptor agonist alone or in fixed-dose combination during the 12 months prior to the index date.
- Have no prior prescription/dispensing of SGLT2 inhibitors (including empagliflozin) alone or in fixed-dose combination during the 12 months prior to the index date.

Exclusion criteria

Patients with type 1 diabetes T1D before the index date will not be included in the study.

Exclusion criteria by outcome of interest: Different exclusion criteria will be applied to generate sets of cohorts for the analysis of the different outcomes of interest.

In one main analysis, we will assess co-primary and secondary outcomes among all patients, regardless of a history of previous outcome events being present or not. In other words, we will allow a previous history of CVD events. We will adjust for the history of these events in the regression model rather than excluding patients with previous events (e.g. assess outcome rates of myocardial infarction in empagliflozine and liraglutide initiators while adjusting for previous history of myocardial infarction, unstable angina, or coronary revascularization).

In another main analysis of outcomes, we will exclude patients who had a specific outcome previously.

For example in the analysis of the primary heart failure outcome (heart failure admission or loop-diuretics), patients will not be included if a diagnosis of heart failure is recorded any time before or at the index date, or if a prescription for loop-diuretics has been filled within 12 months before or at the index date.

For the secondary outcome of acute hospital admission with heart failure, we will include also patients with previous prescription for loop-diuretics, but exclude those with previous heart failure admission.

For analysis of stroke, patients will not be included if a diagnosis of stroke is recorded any time before or at the index date.

For analysis of myocardial infarction, unstable angina, or coronary revascularization, patients will not be included if any of these 3 major atherosclerotic cardiovascular events are recorded any time before or at the index date.

In additional analyses, other criteria will apply (*To be discussed, RWT*). Thus, an additional analysis will include also patients with previous outcome events, and adjust for the history of these events in the regression model rather than excluding them (e.g. assess outcome rates of myocardial infarction in empagliflozine and liraglutide initiators while adjusting for previous history of myocardial infarction, unstable angina, or coronary revascularization).

Follow-up of subjects

Follow-up will start the day after the index date, which will be the date of the first prescription for empagliflozin or liraglutide.

For the analysis of each outcome, follow-up time in a given cohort in a given exposure category for each patient will end at whichever of the following dates occurs first:

- The date of the outcome event; acute hospital admission with heart failure (or initiation of loop diuretics), stroke, myocardial infarction, unstable angina, or coronary revascularization, or all-cause acute hospital admission

- The date of death.

- The date of study end.

- The emigration date out of Denmark.

- Main as-treated analysis: The end date of the first continuous treatment of the index drug (empagliflozin or liraglutide) plus a defined grace period:

    - Main analysis: 30 days after the end of the last prescription's days' supply.

    - Sensitivity analysis: the earliest of 90 days after the end of the last prescription's days' supply or the date on which a new treatment episode starts with the same index drug.

- Intention-to-treat analysis: the continuous treatment end criteria will not be applied for this analysis.

- Within each exposure cohort, the date on which a new treatment episode with any of the other index drug or drug groups starts (e.g. prescription of empagliflozin or any other SGLT2 inhibitor, or GLP-1 receptor agonists other than liraglutide, in liraglutide initiators; and prescription of liraglutide or any other GLP-1 receptor agonist, or SGLT2 inhibitors other than empagliflozin, in empagliflozin initiators). This criterion will not be applied for the intention-to-treat sensitivity analysis.

Follow-up will not be censored if glucose-lowering drugs other than the index drugs are prescribed in addition to empagliflozin or liraglutide after the index date.

9.3 VARIABLES

Exposures

For this study, eligible patients will be identified from prescription/dispensing for the study medications of interest listed in the Danish prescription registries:

A10BX12 (Empagliflozin (Jardiance®))
A10BK03 (Empagliflozin (Jardiance®))
A10BD19 (Empagliflozin + Linagliptin (Glyxambi®))
A10BD20 (Empagliflozin + Metformin (Synjardy®))

A10BX07 (Liraglutide (Victoza®)
A10BJ02 (Liraglutide (Victoza®)
A10AE56 (Insulin degludec + Liraglutide (Xultophy®))

Exposure and time at risk

For this study, it will be assumed that the risk of clinical outcomes related to use of empagliflozin or liraglutide (the index drugs) increases at the beginning of therapy, is maintained at a specific level for the duration of treatment, and decreases gradually to the background risk once treatment is stopped.

Only use at the first continuous treatment will be considered in the main analyses. The risk/exposure window for current use starts on the date of the prescription and ends 30 days after end of supply. The main analysis is based on current use. This time at risk will be used for comparisons and estimation of incidence rate ratios in the study main analysis.

In Denmark, most oral glucose-lowering drugs are supplied for either 28 to 30 days or 90 to 100 days, based on pack sizes of either 28, 30 or 90, 98, or 100 tablets. SGLT2 prescriptions are generally supplied for 28 to 30, or 90 to 98 days, with empagliflozin coming in packages of 30 or 90 tablets with either 10 mg or 25 mg strength (DDD 17.5 mg). The patient's individually prescribed daily dose is not available in the Danish prescription data. Since empagliflozin is normally dosed 1 tablet daily, we will use the number of pills in the package to denote days of supply. The injectable liraglutide prescriptions currently contain drug supplies from 20 days (smallest package, highest dose) and up to 300 days (largest package, lowest dose) (there are 2 to 10 pens á 18mg in packages on the Danish market; daily dose 0.6 mg (start dose) to 1.2 mg (typical dose) or 1.8 mg (highest dose), DDD 1.2 mg). Since most patients use the liraglutide DDD of 1.2 mg daily, we will use the number of DDDs in the package to denote days of supply for liraglutide.

Duration of exposure will be based on the duration of current use. By adding a 30 day grace period to the end of the days' supply, we allow some time to account for non-adherence and extended use of the discontinued index drug, and a potential delayed increase in risk for outcomes after termination of the index drugs can be detected. In a sensitivity analysis, a 90 day grace period after the end of the last prescription's days' supply will be used.

The dose for an individual patient will be the dosage at the prescription date, estimated from the strength, number of tablets/units, and amount of drug prescribed in each single prescription, as explained above. Evaluation of different doses of empagliflozin will be

performed if variation in the dose used by the empagliflozin cohort is observed and an adequate number of events occur within the different daily dose categories.

Study outcomes

The primary outcomes of interest for this study are cardiovascular outcomes and mortality.

Co-Primary study outcomes:

- Acute inpatient hospital admission with a diagnosis of HF and/or initiation of community prescription drug therapy with loop diuretics

- Acute inpatient hospital admission with a diagnosis of HF and/or all-cause death

- "Expanded MACE": All-cause death, acute admission with non-fatal (within 30 days) stroke, acute admission with non-fatal (within 30 days) MI, acute admission with unstable angina, coronary revascularization, or acute admission with non-fatal HF

Secondary outcomes of interest:

- All-cause acute inpatient hospital admissions or emergency room visit not leading to inpatient hospital admission

- All-cause acute inpatient hospital admission

- Acute hospital admission with HF

- All-cause acute inpatient hospital admission or all-cause death.

- All-cause death

For the above study outcomes, "acute inpatient hospital admission" in the Danish registries covers all types of hospital entry that lead to inpatient admission, for example; admission via emergency room entrance, admission by ambulance, self-referral, and referral from GP/primary health care provider. Major cardiovascular outcomes such as myocardial infarction or acute heart failure almost always lead to inpatient admission in the Danish health care system and these discharge diagnoses have documentedly high validity. The validity of diagnoses of apparently major cardiovascular events that do not lead to subsequent inpatient admission (for example, myocardial infarction coded during emergency room contact without admitting the patient to hospital) have considerably lower validity.

Table A. Codes for study outcomes

Co-Primary study outcomes:	ICD-10	Data Source	Comment
• Hospital Admissions for HF and/or initiation of therapy with loop diuretics	Either admission for HF: I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 **OR** initiation of loop diuretic: ATC codes C03C	DNPR, prescription registry	Emergency room visits that do not lead to hospital inpatient admission are NOT included due to low positive predictive value
• Hospital Admission for HF and all-cause death	Either admission for HF: I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 **OR** All-cause death	DNPR, CRS	
• "Expanded MACE": All cause death, non-fatal stroke, non-fatal MI, hospital admission for unstable angina, coronary revascularization, hospital admission for HF	Either Admission for MI: I21 **OR** Admission for unstable angina: I200	DNPR, CRS	

	OR admission for HF: I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 **OR** procedure code CABG: KFNA-KFNE, KFNH20 **OR** Procedure code PCI: KFNG, KFNF **OR** All-cause death		

Secondary outcomes /other points of interest:			
• All-cause acute inpatient hospital admission or emergency room visit	Various diagnoses and procedures from all acute hospital contacts	DNPR	
Acute hospital admission with HF	Admission for HF: I500, I501, I502, I503, I508, I509, I110, I130,	DNPR	

	I132, I420, I426, I427, I428, I429		
• All-cause acute inpatient hospital admission or all-cause death	Various diagnoses and procedures from all inpatient hospital admissions **OR** All-cause death	DNPR, CPR	
• All-cause death	All-cause death	CPR	

Covariates

For all patients with a first initiation of empagliflozin or liraglutide, we will ascertain data on a range of variables potentially associated with the outcomes of interest, including the following:

Age, gender, marital status, calendar time, diabetes duration (years since first recorded diabetes diagnosis), frailty (assessed by total number of consecutive days of inpatient hospital admission during the year before drug initiation), previous history of any cardiovascular disease, micro- and macrovascular diabetes complications, smoking- and alcohol-related disorders, medical obesity, other antihyperglycemic therapy, cardiovascular drug use (including antihypertensive therapy, lipid-lowering therapy, and antithrombotic therapy), and psychiatric medications. In the Northern Denmark subcohort, we will additionally assess data on pre-treatment HbA1c, eGFR, lipid levels, and (if these data can be legally achieved) BMI(21).

Table B. Codes for all antihyperglycemic (glucose-lowering) drugs of interest

Drug	**ATC code in database**
SGLT2-inhibitor	MA10BX09,M A10BX11, MA10BX12 MA10BK, MA10BD15, MA10BD16, MA10BD21, MA10BD20, MA10BD19,

	MA10BK
GLP1 receptor agonists	MA10BX04, MA10BX07, A10BX10, MA10BX13, MA10BX14, A10BJ, MA10AE54, MA10AE56
DPP4 inhibitors	MA10BH, MA10BD07, MA10BD12, MA10BD08, MA10BD09, MA10BD10, MA10BD11, MA10BD13, MA10BD18, MA10BD19, MA10BD21,
biguanides	MA10BA, MA10BD01, MA10BD02, MA10BD03, MA10BD05, MA10BD07, MA10BD08, MA10BD10, MA10BD11, MA10BD13, MA10BD14, MA10BD15, MA10BD16, MA10BD17, MA10BD18, MA10BD20
sulfonylureas	A10BB, A10BD04, A10BD02, A10BD06, A10BD01, A10BC01
glitazones	A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12
alfa-glucosidase inhibitors	MA10BF, MA10BD17

Insulin and analogues	A10A
meglitinides	A10BX02, A10BX03, A10BX08, A10BD14

Table C. Codes for other covariates: comorbidities and diabetes complications

Variable	Database	Codes	Notes
HbA1c	LABKA		
Any macrovascular diabetes complication	DNPR Diagnosis codes + procedure codes	"DI21" "DI23" "DI24" "DT822A" "DT823" "KFNA" "KFNB" "KFNC" "KFND" "KFNE" "KFNF" "KFNG" "KFNH" "KFNW" "KFLF" "DG45" "DI20" "DI25" "DG45" "DI672" "DI678" "DI679" "DI691" "DI693" "DI694" "DI695" "DI696" "DI697" "DI698" "DI708" "DI61" "DI63" "DI64" "DI65" "DI66" "KAAL10" "KAAL11" "KPAE" "KPAF" "KPAH" "KPAN" "KPAP" "KPAQ" "KPAW99" "KPAU74" "KPBE" "KPBF" "KPBH" "KPBN" "KPBP" "KPBQ" "KPBW" "KPGH10" "KPCE" "KPCF" "KPCH" "KPCN" "KPCP" "KPCQ" "KPCW99" "KPCW20" "KPCU74" "KPCU82" "KPCU83" "KPCU84" "KPGE" "KPGF" "KPGH" "KPGN" "KPGP" "KPGQ" "KPGW99" "KPGW20" "KPEE" "KPEF" "KPEH" "KPEN" "KPEP" "KPEQ" "KPEW" "KPFE" "KPFH" "KPFN" "KPFP" "KPFQ" "KPFW" "KPGH20" "KPGH21" "KPGH22" "KPGH23" "KPGH30" "KPGH31" "KPGH40" "KPGH99" "KPDU74" "KPDU82" "KPDU83" "KPDU84" "KPEU74" "KPEU82" "KPEU83" "KPEU84" "KPFU74" "KPFU82" "KPFU83" "KPFU84" "KPGU74" "KPGU83" "KPGU84" "KPGU99" "KPGW" "KPWG" "DI702" "DI742" "DI743" "DI744" "DI745" "DI739A" "DI739C" "DE105" "DE115" "DE145" "DI700" "DI739" "DI748" "DI749" "DI709" "DI740" "DI741"	Ischemic Heart Disease, Cerebrovascular disease, Abdominal and peripheral vascular disease all data before index date (”ever before”)

Any microvascular diabetes complication			
Neurological complications		"DE104" "DE114" "DE144" "DG590" "DG632" "DG598" "DG603" "DG628" "DG629" "DG632" "DG638" "DG990"	all data before index date (”ever before”)
Eye complications	DNPR Diagnosis codes + procedure codes	"DE103" "DE113" "DE143" "DH340" "DH341" "DH342" "DH280" "DH334" "DH450" "DH360" "DH540" "DH541" "DH544" "DH25" "DH268" "DH269" "DH430" "DH431" "DH438C" "DH439" "DH334A" "DH330" "DH335" "DH470" "KCKC10" "KCKC15" "KCKD65"	all data before index date (”ever before”)
Renal complications	DNPR Diagnosis codes + procedure codes	"DE102" "DE112" "DE142" "DI120" "DN083" "DN06" "DN17" "DN18" "DN19" "DR809"'BJFD2'	all data before index date (”ever before”)
Microalbumin-uria	LAB KA		Micro-albuminuria defined as two positive tests on two different dates – all data before index date (”ever before”)

eGFR <= 60 ml/min/1.73 m^2	LAB KA		
Charlson Comorbidity Index[a] (excl. diabetes)			all data before index date (”ever before”)
Previous myocardial infarction	DNPR		S1 from Charlson
Cerebrovascular disease	DNPR		S4 from Charlson
Peripheral vascular disease	DNPR		S3 from Charlson
Chronic heart failure	DNPR	'DI50"DI110"DI130' 'DI132'	all data before index date (”ever before”)
Atrial fibrillation	DNPR	'DI48'	all data before index date (”ever before”)
Hypertension	DNPR	'DI10'-'DI15'	all data before index date (”ever before”)
Chronic obstructive pulmonary disease	DNPR	'DJ40'-'DJ48"DJ60'-'DJ68' 'DJ684"DJ701"DJ703' 'DJ961"DJ982"DJ983'	all data before index date (”ever before”)
Cancer	DNPR	'DC00'-'DC99'	all data before

			index date (”ever before”)
Renal disease	DNPR	'DI12"DI13"DN00"DN06' 'DN07"DN11"DN14' 'DN17"DN20"DQ61'	all data before index date (”ever before”)
Rheumatic disease	DNPR	'DM05"DM06"DM08"DM09' 'DM30"DM31"DM32"DM33' 'DM34"DM35"DD86'	all data before index date (”ever before”)
Osteoarthritis	DNPR	'DM15'-'DM20'	all data before index date (”ever before”)
Osteoporosis /fracture	DNPR	'DM80"DM83"DS72'-'DS722' 'DS724"DS526"DM485’	all data before index date (”ever before”)
History of infections requiring hospitalization	DNPR	DA00-DA09,DA15-DA44, DA46, DA48 - DA99, DB00-DB09, DB15-DB99, DE060, DE321, DG00-DG07, DH00, DH010, DH030, DH031, DH050, DH061, DH10, DH131, DH191, DH192, DH220, DH320, DH440, DH600, DH601, DH603, DH620, DH621, DH622, DH623, DH650, DH660-DH664, DH67, DH700, DH853, DI01, DI02, DI301, DI320, DI33, DI38, DI398, DI400, DJ00-DJ06, DJ10-D18, DJ20-22, DJ34, DJ36, DJ390, DJ391, DJ440, DJ851, DJ86,DK040, DK047, DK052, DK113, DK122, DK36, DK37, DK570, DK572, DK574, DK578, DK61, DK619, DK630, DK650, DK659, DK67, DK750, DK751, DK800, DK803, DK804, DK810, DK819, DK830, DK859,	all data before index date (”ever before”)

		DL00-DL08, DM00, DM01, DM86, DM 631, DM632, DN10, DN12, DN151, DN30, DN330, DN340, DN341, DN390, DN41, DN45, DN70-DN77, DO23, DO264, DO411, DO740, DO753, DO85, DO86, DO883, DO91, DO98, DT802, DT814, DT826, DT827, DT835, DT836, DT845-DT847, DT857, DT880, DT899	
Obesity	DNPR	'DE65'-'DE68'	all data before index date (”ever before”)
Alcoholism	DNPR	'DG312"DG621"DG721' 'DI426"DK292"DK860' 'DK70"DR780"DT51' 'DZ714"DZ721')	all data before index date (”ever before”)
Mental disorders	DNPR + prescr iption s	'DF00'-'DF99' or c_diag=:'DF99' + 'N05A' 'N05BA' 'N05CD' 'N05CF' 'N06A'	all data before index date (”ever before”)
Previous hypoglycaem ia		'DE160'-'DE162"DE15' 'DT383A'	all data before index date (”ever before”)
Any macroangiop athy	Diagn osis + proce dures	’DI20-DI25’'DT822A' 'DT823' 'DG45"DI61"DI63"DI64' 'DI678"DI679"DI691' 'DI693"DI694"DI695' 'DI696"DI697"DI698"DI702' 'DI742"DI743"DI744' 'DI745"DI739A"DI739B' 'DI739C"DE105"DE115"DI700' 'DI708"DI709"DI740' 'DI741"DI748"DI749"DN280' 'DI701"DK550"DK551' 'DK558"DK559'KFNA,KFNB,KFNC,KFND,	all data before index date (”ever before”)

		KFNE,KFNF, KFNG,KFNH,KFNW,KFLF,KPAE,KPAF,KPAH,KPAN,KPAP ,KPAQ,KPAW99,KPAU74, KPBE,KPBF,KPBH,KPBN,KPBP, KPBQ,KPBW,KPGH10,KPCE,KPCF,KPCH, KPCN,KPCP, KPCQ,KPCW99,KPCW20,KPCU74,KPCU82, KPCU83, KPCU84,KPGE,KPGF,KPGH,KPGN,KPGP,KPGQ,KPGW99, KPGW20,KPEE,KPEF,KPEH,KPEN,KPEP,KPEQ,KPEW,KPFE, KPFH,KPFN,KPFP,KPFQ,KPFW,KPGH20,KPGH21,KPGH22 ,KPGH23,KPGH30,KPGH31,KPGH40,KPGH99,KPDU74, KPDU82,KPDU83,KPDU84,KPEU74,KPEU82,KPEU83,KPEU84, KPFU74,KPFU82,KPFU83,KPFU84,KPGU74,KPGU83,KPGU84 ,KPGU99,KPGW,KPWG, KAAL10,KAAL11,"KNBQ" "KNCQ" "KNDQ" "KNEQ" "KNFQ" "KNGQ" "KNHQ"	
Trombocytaggregation prophylaxis	prescriptions	"B01AC06" "N02BA01" "B01AC30" "B01AC07" "B01AC22" "B01AC04" "B01AC24"	Prescriptions 1 year before index date
Statins	prescriptions	"C10AA" "C10BA" "C10BX"	Prescriptions 1 year before index date
Achieved cholesterol target	LABKA	Last LDL within 1 year of index data < 1,8mmol/L or <50% of previous high(20)	
CVD-drug use	prescriptions	C02, C03, C07, C08 C09, "C10AA" "C10BA" "C10BX" "B01AC06" "N02BA01" "B01AC30" "B01AC07" "B01AC22" "B01AC04" "B01AC24"	Prescriptions 1 year before index date
Any antihypertens	prescription	C02, C03, C07, C08 C09	Prescriptions 1

ive treatment	s		year before index date
ACE inhibitors	prescr iption s	"C09A" "C09B"	Prescript ions 1 year before index date
ATII antagonists	prescr iption s	"C09C" "C09D"	Prescript ions 1 year before index date
Oral steroids	prescr iption s	"H02AB"	Prescript ions 1 year before index date
Marital status	CPR		Current marital status, if no current status in CPR, last value carried forward.

9.4 DATA SOURCES

The Danish health care system provides universal coverage to all Danish residents (5.7 million inhabitants. Health care coverage includes visits to general practitioners and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health system.

The centralised Civil Registration System in Denmark allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registers containing civil registration numbers, such as the registers mentioned below.

Data collected in these registers are available for research purposes after following a standard application procedure to the relevant data board. The process requires collaboration with a local university or investigator affiliated with a research institute to access the data; Danish Data Protection Agency approval to handle data; data release by the Danish National Data Board; and, for accessing medical charts, approval of a Patient Safety Board. All applications have to be submitted in Danish.

Denmark's primary health care sector, which includes GPs, specialists, and dentists, generates about 96% of the prescription sales, most of which are reimbursable and are dispensed by community pharmacies. Each dispensing record contains information on the patient, drug, and prescriber. Dispensing records retain the patient's universal personal identifier, allowing for individual-level linkage to all Danish registers and medical databases.

The study will draw on the following Danish population-based registries:

The Civil Registration System: Holds records of central personal registry (CPR)-number, address, marital status, emigration and immigration status, and date of death (if any) of the entire population of Denmark since 1968. This system can be used to link all Danish registries containing CPR-numbers(1).

The Danish National Patient Register: The Danish National Patient Register (DNPR) includes information of all hospitalized patients since 1977 and on outpatient hospital contacts since 1995. The register contains information about the date of admission, discharge, diagnosis codes and surgical procedures. From 1977 to 1993 diagnosis codes were coded with reference to the ICD-8 classification and from 1994 onwards they have been coded according to ICD-10(2).

The National Database of Reimbursed Prescriptions: Contains complete information on all prescriptions dispensed at community pharmacies in the Danish regions since 2004. Records information about the drug user including civil registration number, age, gender, residence, ATC (Anatomical Therapeutic Chemical) code of the drug, package size, and date of dispensing(3).

The Aarhus University Prescription Database: Covers the Northern and Central Denmark Regions beginning in 1991 with complete coverage from 1998 onwards. It contains similar data than the national database(4).

The LABKA Database: Computerized clinical biochemistry data have been kept for all patients in a subpopulation of Danish drug users, i.e., inhabitants of the North and Central Denmark Regions (population, 1.3 million; approximately 23% of the Danish population), beginning in 1997 and complete from 2000. Data on e.g. HbA1c and blood glucose can be extracted from this registry(5).

9.5 STUDY SIZE

Approximately 233.230 patients have antihyperglycemic drug-treated diabetes in Denmark nationwide as of 2014 (more than 90% of these have type 2 diabetes)(17).

Detailed population-based laboratory data (e.g., HbA1c, blood glucose, eGFR)(12,18)are currently restricted to Northern Denmark (i.e., the North and Central Denmark regions, population in 2013 approx. 1.8 million, or 30% of Denmark's population). BMI is restricted to electronic patient records in the central Denmark Region (population, 1.3 million) and a special application to a Patient Safety Board is needed to access these data. Thus, the population is limited in regional analyses to individuals who have residence in Northern Denmark for at least 12 months prior to antihyperglycemic treatment start, to allow for complete baseline data collection. Estimated from the Danish National Diabetes Register(19), approx. 90,000 patients with diabetes live in the regional study area (North and Central Denmark regions) as of 2012, with an incidence of 9,000 new patients per year (more than 90% of these have type 2 diabetes).

In general, the study size will be driven by the uptake of empagliflozin following approval and launch of empagliflozin for the treatment of T2D to improve glycaemic control in adults in Denmark in 2014. In 2016, according to www.medstat.dk there were 13,362 users of SGLT2 inhibitors in Denmark, including 7,343 users of dapagliflozin, with the rest of users (approximately 6,000) mainly using empagliflozin (updated data for empgliflozin pending, www.medstat.dk). In 2015, there were approximately 1,500 empagliflozin users, of whom almost all started their use in 2015. If most of the 1500 empagliflozin initiators in 2014-2015 continued their use in 2016 and 2017, and most of the expected ~4,500 empagliflozin initiators in 2016 continued their use in 2017, with many new users during 2017 contributing considerable additional exposure time, we expect a minimum of 10,000 empagliflozin initiator exposure years by the end of 2017.

In 2016, there were 24,273 users of GLP-1 receptor agonists in Denmark, including 23,420 users of liraglutide(9). The number of liraglutide users in Denmark was approximately 20,000 individuals already in 2014, and the annual nationwide number of new liraglutide initiators in 2014 and 2015 was approximately 3,000 individuals per year (own unpublished data). This may yield an estimated at least 20,000 liraglutide initiator exposure years during 2014-2017 for comparison.

We thus estimate that at least 10,000 person-years of empagliflozin exposure and 20,000 person-years of liraglutide exposure can be included in our study up to the end of 2017.

Assuming an annual incidence rate of 3 per 100 person-years for experiencing the expanded MACE outcome of heart failure/any cardiovascular outcome or death (median patient age in empagliflozin and liuraglutide initiators ~60 years, median diabetes duration ~8 years (own unpublished data)), we will have >80% power to detect an incidence rate ratio of 0.83 (i.e., approximate annual incidence reduction from 3% to 2.5%) for MACE in empagliflozin versus liraglutide users (*To be discussed, RWT*).

9.6 DATA MANAGEMENT

The Department of Clinical Epidemiology at Aarhus University is a large academic department, with more than 15 years' experience conducting data management and epidemiologic research based on Danish registry data. This includes several successfully fulfilled calls from the EMA, specifically on utilization and safety of antidiabetic agents using Danish registry data. The department has a cadre of 25 statisticians at Master or PhD level, one of whom will be assigned to this project for its duration.
Standard security processes at Aarhus University will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.
All conversion of the original data to analysis variables will be performed using SAS software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina).

Identification of anti-diabetic drug users from the National Database of Reimbursed Prescriptions/Aarhus University Prescription Database, we will identify all patients with a recorded first prescription for any anti-diabetic drug during the period January 1, 2004 through December 31, 2017. Duration of a single prescription in days is calculated as the total amount of the drug received measured in DDDs (because the prescribed daily dose is not available in our data) and adding 20% to account for reduced compliance.
For each patient, exposure to empagliglozin and liraglutide will start on the date of first filling a prescription for the drug of interest (the new-user index date). We will use different analytic approaches to categorize exposure in our follow-up analyses, see Statistical analyses below.

For all patients with a first initiation of empagliflozin and liraglutide, we will ascertain data on: age, gender, marital status, calendar time, diabetes duration (years since first recorded diabetes diagnosis), frailty (assessed by total number of consecutive days of inpatient hospital admission during the year before drug initiation), previous history of any cardiovascular disease, micro- and macrovascular diabetes complications, smoking- and alcohol-related disorders, medical obesity (ICD-codes), other antihyperglycemic therapy, cardiovascular drug use (including antihypertensive therapy, lipid-lowering therapy, and antithrombotic therapy), and psychiatric medications(22). In the Northern Denmark subcohort, we will additionally assess data on pre-treatment HbA1c, eGFR, and lipid levels (21,23–25). Patients are characterized at drug initiation of either empagliflozin or liraglutide. For details se characteristic variable definitions.

9.7 DATA ANALYSIS

Current use of the drugs under study will be defined from the date of first prescription of empagliflozin or liraglutide to the end of supply for that prescription plus a period of 30 days, see Section 9.3 Variables, paragraph Exposure and time at risk.

Our main analysis will be an as-treated analysis, based on current users and censoring patients at time of index drug exposure discontinuation. In a sensitivity analysis (see below), we will apply an intention-to-treat analysis, following patients according to their initial drug exposure.

Decisions to begin a specific glucose-lowering drug are influenced by demographic, medical, and clinical factors, and those same factors might be associated with the outcomes of interest. For balanced comparison of the two treatment groups, we plan to conduct two cohort analyses: a traditional Cox regression analysis and a propensity score approach.

The propensity score is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates. Because a propensity score model predicts not the probability of experiencing the (relatively rare) outcome but the probability of the (frequent) exposure i.e. being treated with empagliflozin or liraglutide in this study, more of our potential confounding covariates may be used in the model than in our conventional Cox regression model. As recently discussed (Kahlert et al: Control of confounding in the analysis phase. Clin Epidemiol 2017), in the majority of studies that have used both multivariable analysis and propensity score methods, there were no important differences in the results. Propensity score methods may be more robust in situations with rare outcomes and common exposures than traditional multivariable analysis, as expected in our proposed study. However, just as with multivariable analysis, propensity score methods do not protect against unknown, unmeasured and residual confounding when comparing liraglutide and empagliflozine initiators. Moreover, propensity score methods estimate treatment effects not in the entire population of real-world treated individuals but in a trimmed subset of the data, limiting sample size and in some cases hampering the feasibility and interpretability of the results obtained by the propensity score method. Therefore, our approach will be to first examine and learn about the data available in our dataset, apply stratified analyses and investigate available confounders and sample size, and then seek to apply the two different methods. If inverse probability treatment weighting (IPTW), and/or propensity score matching, with all confounders deemed important is feasible in our dataset, a PS method may end up being the main analytic method.

We will start follow up all empagliflozin or liraglutide initiators from the first prescription date until first study outcome, drug discontinuation, emigration, or end of follow-up.

Crude and adjusted incidence rates of study outcomes among new users of empagliflozin and of liraglutide will be estimated and compared. Incidence rates will be reported as point estimates (in outcomes per 1,000 person-years) with 95% CIs. Ascertainment during follow-

up will allow estimation of the number of new incident events for each of the primary outcomes. Current use person-time for each patient will be allocated as the time between the date of the first prescription for either empagliflozin or liuraglutide and the end of current time at risk (see Section 9.3 for time at risk definitions). The total person-time of observation among individuals at risk will then be calculated.

Cumulative incidence function curves will be constructed to depict the cumulative incidence over time of each of the outcomes under study, comparing empagliflozin and liraglutide initiators. Kaplan-Meier curves will be used for mortality outcomes.

We will use Cox regression analyses to compute crude and adjusted hazard ratios (HRs) with 95% CIs to examine the association between empagliflozin versus liraglutide initiation and study outcomes. For each of the primary outcomes (primary objective) and secondary outcomes (secondary objective) of interest, estimation of adjusted current use HRs with 95% CIs will be considered the main analysis of interest.

The selection of variables to be included in the Cox regression model will be based on evidence from previous literature, covariate data availability, examination of exposure group differences in the distribution of each covariate, and the association of covariates with the outcomes of interest. The current list of potential confounders for the Cox regression model is included in section 9.3, and includes age, gender, calendar time, diabetes duration, previous history of any cardiovascular disease, micro- and macrovascular diabetes complications, smoking- and alcohol-related disorders, medical obesity, other antihyperglycemic therapy, cardiovascular drug use and psychiatric medications, marital status, and frailty markers. In the Northern Denmark subcohort, we will additionally assess data on pre-treatment HbA1c, eGFR, lipid levels, and (if data can be achieved) BMI(21).

Adjustment will also be implemented by propensity score methods, if possible in our data. For such methods, we will estimate propensity scores using multivariable logistic regression models with the preselected potential confounders as predictors. Propensity score distributions will be plotted by treatment group to observe the comparability of the empagliflozin and liraglutide initiators. Using the propensity score, we will create a matched population where empagliflozin initiators are weighted to have a similar propensity score distribution to and balanced covariates with the liraglutide initiators. The outcome rate ratio will then be re-estimated in the resulting weighted population, resulting in the average treatment effect in empagliflozine users. We plan to bootstrap 300 iterations of the model to estimate CIs.

Patients with previous cardiovascular disease

It may be of interest how the empagliflozin or liraglutide association with study outcomes interacts with presence or absence of previous CVD. empagliflozin or liraglutide. Our main analysis is in patients who did not previously have the outcome of interest. Additional analysis will include also patients with previous outcome events, and adjust for the history of these events in the regression model rather than excluding them (e.g. assess outcome rates of myocardial infarction in empagliflozine and liraglutide initiators while adjusting for previous history of myocardial infarction, unstable angina, or coronary revascularization).

Stratified analyses

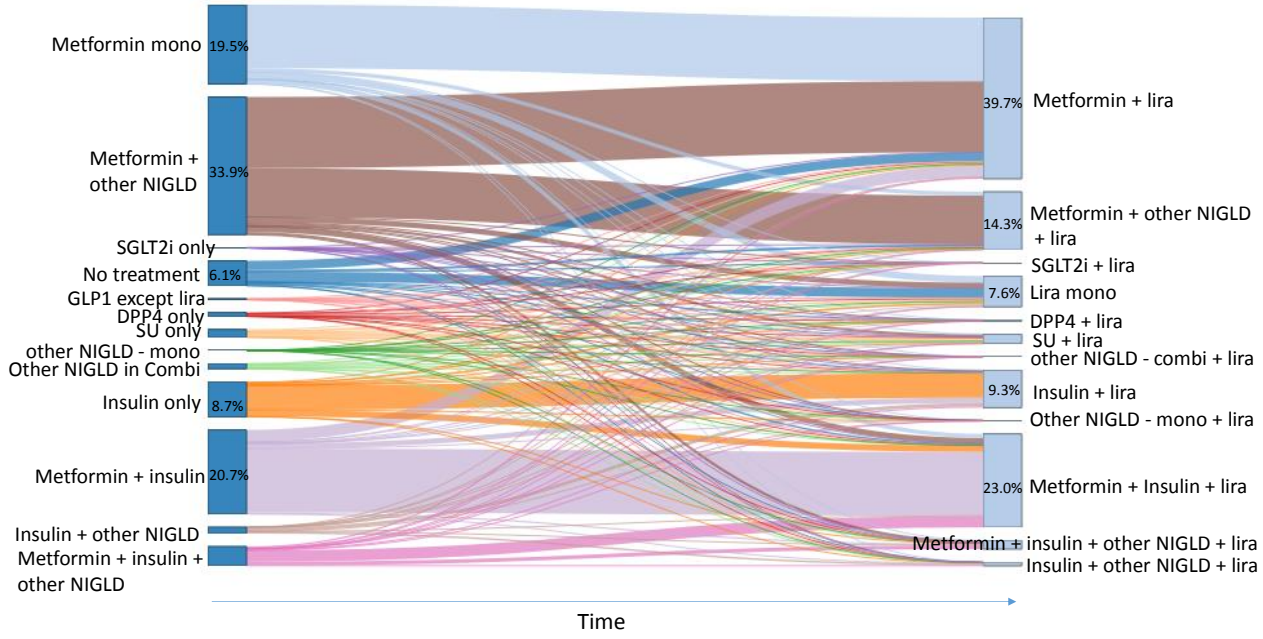
A number of stratified and sensitivity analyses will be performed to assess effect measure modification and possible residual confounding.

Adjusted incidence rates will be calculated, stratified by age, sex, level of comorbidity, presence of medically diagnosed obesity, nature of baseline glucose-lowering treatment including presence or absence of insulin use, baseline glucose control, and calendar period (before and after publication of the major study drug CVOTs in 2015-2016).

Line of therapy analysis

Immortal time bias and time-lag bias(26) is often seen in studies that compare first-, second-, and third-line therapies, caused by patients not being at the same stage of diabetes at these therapy events, and only survivors reaching a later time point of intensification therapy(27). In additional analyses, we will therefor categorize patients by line of therapy. Using the nationwide prescription data, we will first characterize patients at drug initiation according to treatment just prior to treatment initiation, and immediately following initiation of empagliflozin or liraglutide. We will then compare patients all using empagliflozin and liraglutide as add-on therapy to (continuing) antihyperglycemic monotherapy (most often with metformin). In additional analyses, we will compare patients all using empagliflozin and liraglutide as add-on therapy to (continuing) antihyperglycemic dual therapy.

The figure below shows a figure presented at the European Diabetes Epidemiology Group meeting 2018 (Knudsen et al, unpublished), characterizing liraglutide users based on their glucose lowering drug prescriptions redeemed 100 days prior (left hand side) to and 100 days after (right hand side) first liraglutide initiation.



Intention-to-treat analysis

In our main analysis, we will use an on-treatment approach, observing patients from the new-user index date (empagliflozin or liraglutide) until discontinuation of the index drug(10) (defined as number of days after last prescription covered by the amount of the drug received plus 30 days account for reduced compliance), or until reaching a study outcome, emigration, or end of study period. Second, we will do an intention-to-treat analyses, observing patients from the new-user index date (empagliflozin or liraglutide) as exposed to the index drug of interest and including the follow-up time after any index drug discontinuation(28).

Potential effect of unmeasured confounders

We will assess the potential effect of unmeasured confounders on the association between empagliflozin and liraglutide use and, for example, heart failure, by using methods described by Lash et al. These methods may be of special interest to evaluate BMI, blood pressure, and smoking, as data are not generally available in the Danish data.

9.8 QUALITY CONTROL

Quality control and management will follow the routines of Aarhus University Hospital.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Several clinical epidemiological studies involving linkage between the prescription and laboratory database and the other Danish population-based data sources have been published in major international peer reviewed journals, thus the quality of the data sources is well established within the epidemiologic field(5).

Selection bias: These studies will use unique population-based databases and include all patients with known medically treated type 2 diabetes in the regions. As there is virtually no loss to follow-up, the risk of selection bias in the cohort studies will be negligible.

Information bias: All studies are based on administrative coding and are thus dependent on validity and reliability of registry data. For diabetes, the National Diabetes Register has documented sensitivity and positive predictive value (PPV) above 85% when using prescription and hospital contact data (3). The PPVs for important comorbidities are also documented high in the patient registry. Filled prescriptions are only a marker of actual drug consumption and there is a possibility of non-compliance to treatment. This will bias the possible effects of the examined drugs and any differences in drug effects towards the null.

Confounding: By using stratified and regression analysis and propensity score matching, we will be able to reduce the confounding effect of a range of measurable variables as explained above. Unmeasured or unknown confounders may still affect our relative risk estimates in the outcome analyses, and misclassification of data on confounders may lead to some residual confounding. In particular, in this study there will be no access to journal data from primary care journals, thus vital clinical data for e.g. smoking habits, blood pressure and weight in most patients are missing. This might hamper effectiveness comparisons between different treatment regimens. We will do an assessment of the possible impact of unmeasured confounding as decribed above.
Considering drug exposure, our as-treated analysis (i.e., terminating drug exposure upon discontinuation) may be prone to bias if the discontinuation of a study drug (empagliflozin or liraglutide) predicts future cardiovascular outcomes or death (informative censoring)(27) We will therefore evaluate the temporal distribution of outcome occurrence shortly after drug discontinuation, to assess the presence of informative censoring. Our intention-to-treat approach (i.e., carrying forward the initial exposure status and disregarding changes in treatment status over time) is not affected by informative censoring bias in the same way, but may on the other hand be biased through exposure misclassification that increases with longer follow-up periods and is open to potential differential loss to follow-up(27). We will therefore consider results from both analyses carefully in evaluating the clinical effects of empagliflozin and liraglutide, in light of the strengths and limitations inherent in each approach.

9.10 PRELIMINARY BASELINE DATA ON STUDY SUBJECTS UNTIL 2015

TABLE 1: CLINICAL CHARACTERISTICS AMONG INCIDENT FIRST-TIME USERS OF SELECTED NEWER GLUCOSE LOWERING DRUGS IN DENMARK, 2012-2015

Nationwide	SGLT2		GLP1		DPP4		Empagliflozin		SGLT2 ex Empagliflozin	
	N = 9528	Percent (%)	N = 14822	Percent (%)	N= 31834	Percent (%)	N = 1537	Percent (%)	N = 7991	Percent (%)
Index year										
2012	19	0.2	5148	34.7	7354	23.1	0	0	19	0.2
2013	1917	20.1	3465	23.4	7794	24.5	0	0	1917	24.0
2014	2998	31.5	2821	19.0	8056	25.3	193	12.6	2805	35.1
2015	4594	48.2	3388	22.9	8630	27.1	1344	87.4	3250	40.7
Gender										
Female	3754	39.4	6301	42.5	12675	39.8	605	39.4	3149	39.4
Male	5774	60.6	8521	57.5	19159	60.2	932	60.6	4842	60.6
Age										
0-30	33	0.3	166	1.1	119	0.4	2	0.1	31	0.4
30-59	4489	47.1	7429	50.1	11323	35.6	645	42.0	3844	48.1
60-69	3226	33.9	4828	32.6	9784	30.7	557	36.2	2669	33.4
70+	1780	18.7	2399	16.2	10608	33.3	333	21.7	1447	18.1
Region of residence										
Hovedstaden	2817	29.6	4530	30.6	9580	30.1	659	42.9	2158	27.0
Midtjylland	2192	23.0	3024	20.4	6969	21.9	295	19.2	1897	23.7
Nordjylland	719	7.5	1338	9.0	3584	11.3	129	8.4	590	7.4
Sjælland	1976	20.7	2676	18.1	5000	15.7	187	12.2	1789	22.4
Syddanmark	1824	19.1	3254	22.0	6701	21.0	267	17.4	1557	19.5
Baseline HbA1c (=<1 year before index)										
.	6623	69.5	10463	70.6	21364	67.1	1113	72.4	5510	69.0
<6.5	68	0.7	200	1.3	635	2.0	8	0.5	60	0.8
6.5-<7	162	1.7	278	1.9	1236	3.9	19	1.2	143	1.8
7-<7-5	399	4.2	548	3.7	2176	6.8	49	3.2	350	4.4
7.5-<8	430	4.5	633	4.3	1701	5.3	70	4.6	360	4.5
8-<9	882	9.3	1173	7.9	2382	7.5	135	8.8	747	9.3
9-<10	514	5.4	764	5.2	1150	3.6	78	5.1	436	5.5
>=10	450	4.7	763	5.1	1190	3.7	65	4.2	385	4.8
Diabetes duration										
DM duration < 5 year	2368	24.9	5300	35.8	14881	46.7	355	23.1	2013	25.2
DM duration 5-10 year	3485	36.6	5283	35.6	10068	31.6	465	30.3	3020	37.8
DM duration >= 10 year	3675	38.6	4239	28.6	6885	21.6	717	46.6	2958	37.0
Any macro vascular complication	6668	70.0	10324	69.7	21773	68.4			5659	70.8

TABLE 1: CLINICAL CHARACTERISTICS AMONG INCIDENT FIRST-TIME USERS OF SELECTED NEWER GLUCOSE LOWERING DRUGS IN DENMARK, 2012-2015

Nationwide	SGLT2		GLP1		DPP4		Empagliflozin		SGLT2 ex Empagliflozin	
0							1009	65.6		
1	2860	30.0	4498	30.3	10061	31.6	528	34.4	2332	29.2
Ischaemic Heart Disease										
0	7442	78.1	11468	77.4	24551	77.1	1119	72.8	6323	79.1
1	2086	21.9	3354	22.6	7283	22.9	418	27.2	1668	20.9
Cerebrovascular disease										
0	8755	91.9	13567	91.5	28377	89.1	1398	91.0	7357	92.1
1	773	8.1	1255	8.5	3457	10.9	139	9.0	634	7.9
Abdominal and peripheral vascular disease										
0	8625	90.5	13400	90.4	28957	91.0	1393	90.6	7232	90.5
1	903	9.5	1422	9.6	2877	9.0	144	9.4	759	9.5
ANY Micro vascular complication (Neuro, Eye, Renal, Microalbuminuria, Nephropathy)										
0	5764	60.5	9369	63.2	20028	62.9	904	58.8	4860	60.8
1	3764	39.5	5453	36.8	11806	37.1	633	41.2	3131	39.2
Eye complications										
0	7371	77.4	11768	79.4	25154	79.0	1180	76.8	6191	77.5
1	2157	22.6	3054	20.6	6680	21.0	357	23.2	1800	22.5
Renal complications										
0	8883	93.2	13692	92.4	28953	90.9	1421	92.5	7462	93.4
1	645	6.8	1130	7.6	2881	9.1	116	7.5	529	6.6
Neurological complications										
0	8676	91.1	13558	91.5	29947	94.1	1394	90.7	7282	91.1
1	852	8.9	1264	8.5	1887	5.9	143	9.3	709	8.9
Microalbuminuria (min. 2 positive tests ever)										
0	8292	87.0	13119	88.5	28650	90.0	1333	86.7	6959	87.1
1	1236	13.0	1703	11.5	3184	10.0	204	13.3	1032	12.9
eGFR<60 ml/min (moderate or severe nephropathy)							1491	97.0		
0	9249	97.1	14257	96.2	29483	92.6			7758	97.1
1	279	2.9	565	3.8	2351	7.4	46	3.0	233	2.9
eGFR										
.	6307	66.2	9991	67.4	20430	64.2	1064	69.2	5243	65.6
>=60 ml/min	2942	30.9	4266	28.8	9053	28.4	427	27.8	2515	31.5
30 - 60 ml/min	274	2.9	538	3.6	2062	6.5	45	2.9	229	2.9

TABLE 1: CLINICAL CHARACTERISTICS AMONG INCIDENT FIRST-TIME USERS OF SELECTED NEWER GLUCOSE LOWERING DRUGS IN DENMARK, 2012-2015

Nationwide	SGLT2		GLP1		DPP4		Empagliflozin		SGLT2 ex Empagliflozin	
<30 ml/min	5	0.1	27	0.2	289	0.9	1	0.1	4	0.1
Comorbidity level										
CCI score = 0	5743	60.3	8763	59.1	17317	54.4	845	55.0	4898	61.3
CCI score = 1	1971	20.7	3104	20.9	6318	19.8	328	21.3	1643	20.6
CCI score = 2	1056	11.1	1703	11.5	4136	13.0	206	13.4	850	10.6
CCI score >= 3	758	8.0	1252	8.4	4063	12.8	158	10.3	600	7.5
Chronic heart failure										
.	9038	94.9	13872	93.6	29439	92.5	1430	93.0	7608	95.2
1	490	5.1	950	6.4	2395	7.5	107	7.0	383	4.8
Atrial fibrillation							1408	91.6		
.	8894	93.3	13786	93.0	28685	90.1			7486	93.7
1	634	6.7	1036	7.0	3149	9.9	129	8.4	505	6.3
Hypertension										
.	5645	59.2	8905	60.1	19937	62.6	847	55.1	4798	60.0
1	3883	40.8	5917	39.9	11897	37.4	690	44.9	3193	40.0
COPD										
.	8651	90.8	13247	89.4	28474	89.4	1375	89.5	7276	91.1
1	877	9.2	1575	10.6	3360	10.6	162	10.5	715	8.9
Cancer										
.	8751	91.8	13722	92.6	28359	89.1	1399	91.0	7352	92.0
1	777	8.2	1100	7.4	3475	10.9	138	9.0	639	8.0
Renal disease										
.	9353	98.2	14430	97.4	30206	94.9	1498	97.5	7855	98.3
1	175	1.8	392	2.6	1628	5.1	39	2.5	136	1.7
Rheumatic disease										
.	9248	97.1	14323	96.6	30669	96.3	1493	97.1	7755	97.0
1	280	2.9	499	3.4	1165	3.7	44	2.9	236	3.0
Osteoarthritis										
.	7831	82.2	12237	82.6	26403	82.9	1256	81.7	6575	82.3
1	1697	17.8	2585	17.4	5431	17.1	281	18.3	1416	17.7
Osteoporosis/fracture										
.	9257	97.2	14431	97.4	30393	95.5	1483	96.5	7774	97.3
1	271	2.8	391	2.6	1441	4.5	54	3.5	217	2.7
History of hospitalized infections										
.	5509	57.8	8289	55.9	18561	58.3	844	54.9	4665	58.4
1	4019	42.2	6533	44.1	13273	41.7	693	45.1	3326	41.6

TABLE 1: CLINICAL CHARACTERISTICS AMONG INCIDENT FIRST-TIME USERS OF SELECTED NEWER GLUCOSE LOWERING DRUGS IN DENMARK, 2012-2015

Nationwide	SGLT2		GLP1		DPP4		Empagliflozin		SGLT2 ex Empagliflozin	
Obesity										
.	6853	71.9	10410	70.2	26722	83.9	1108	72.1	5745	71.9
1	2675	28.1	4412	29.8	5112	16.1	429	27.9	2246	28.1
Alcoholism										
.	9400	98.7	14611	98.6	31324	98.4	1520	98.9	7880	98.6
1	128	1.3	211	1.4	510	1.6	17	1.1	111	1.4
Mental disorders										
.	5955	62.5	9010	60.8	20403	64.1	958	62.3	4997	62.5
1	3573	37.5	5812	39.2	11431	35.9	579	37.7	2994	37.5
Previous hypoglycaemia										
.	9388	98.5	14584	98.4	31249	98.2	1504	97.9	7884	98.7
1	140	1.5	238	1.6	585	1.8	33	2.1	107	1.3
Any macro angiopathy										
.	6745	70.8	10463	70.6	22005	69.1	1010	65.7	5735	71.8
1	2783	29.2	4359	29.4	9829	30.9	527	34.3	2256	28.2
Trombocytaggregation prophylaxis										
.	5798	60.9	8991	60.7	19653	61.7	881	57.3	4917	61.5
1	3730	39.1	5831	39.3	12181	38.3	656	42.7	3074	38.5
Statins										
.	2302	24.2	3844	25.9	9453	29.7	359	23.4	1943	24.3
1	7226	75.8	10978	74.1	22381	70.3	1178	76.6	6048	75.7
ACE inhibitors							965	62.8		
.	5750	60.3	8647	58.3	19578	61.5			4785	59.9
1	3778	39.7	6175	41.7	12256	38.5	572	37.2	3206	40.1
ATII antagonists										
.	6201	65.1	10161	68.6	22890	71.9	959	62.4	5242	65.6
1	3327	34.9	4661	31.4	8944	28.1	578	37.6	2749	34.4
Oral steroids										
.	9007	94.5	13929	94.0	29489	92.6	1450	94.3	7557	94.6
1	521	5.5	893	6.0	2345	7.4	87	5.7	434	5.4
Any antihypertensive treatment										
.	1914	20.1	3188	21.5	7741	24.3	287	18.7	1627	20.4
1	7614	79.9	11634	78.5	24093	75.7	1250	81.3	6364	79.6
Marital status							242	15.7		
Unmarried	1530	16.1	2435	16.4	4113	12.9			1288	16.1

TABLE 1: CLINICAL CHARACTERISTICS AMONG INCIDENT FIRST-TIME USERS OF SELECTED NEWER GLUCOSE LOWERING DRUGS IN DENMARK, 2012-2015

Nationwide	SGLT2		GLP1		DPP4		Empagliflozin		SGLT2 ex Empagliflozin	
Widowed	726	7.6	1143	7.7	4307	13.5	114	7.4	612	7.7
Divorced	1598	16.8	2432	16.4	4878	15.3	280	18.2	1318	16.5
Married	5610	58.9	8629	58.2	18138	57.0	896	58.3	4714	59.0
Unknown	64	0.7	183	1.2	394	1.2	5	0.3	59	0.7

The source population for Table 1 is all patients that have redeemed one or more prescriptions for any glucose lowering drugs in Denmark since 2004. Diabetic patients who were under the age of 30 y when using insulin as mono-therapy and never used oral antihyperglycemic medications were excluded as likely T1D patients. The study population in Table 1 consists of all new incident users of each drug in question during the period 2012 through 2015. Patients are included on the date of their first use of the drug, and prevalence of clinical characteristics are assessed on that date. For each drug, individuals who had used the drug previously, i.e. at any time before the period 2012 through 2015, were excluded. An individual may be included in several categories, for example as a new first-time DPP4 user in 2012 and as a new first-time SGLT2 user in 2014.

Laboratory data are only available for samples analysed at hospitals in North and Central Denmark Regions. Therefore, many patients have missing lab data in the nationwide study population. In Tables 2 and 3, laboratory values are shown restricted to the ~1/3 of patients residing within these regions.

The Charlson Comorbidity Index (CCI) includes 19 major disease categories, ascertained from each individual's complete hospital contact history before the date of first-time drug use. Diabetes was excluded from the CCI.

Abbreviations: COPD: Chronic Obstructive Pulmonary Disorder; IQR: 25th and 75th percentile; eGFR: estimated Glomerular Filtration Rate; ACE: Angiotensin-Converting-enzyme; ATII: Angiotensin II.

TABLE 2: MEDIAN VALUES FOR SELECTED CONTINUOUS MEASUREMENTS

Nationwide		SGLT2	GLP1	DPP4	Empagliflozin	SGLT2 ex empa
Age	Median	60.68	59.57	64.97	62.15	60.41
	Q1	52.86	50.75	55.53	53.54	52.65
	Q3	68.16	67.18	72.82	68.98	67.98
Baseline HbA_{1c} (measurement =<1 year before index)	Median	8.37	8.37	7.82	8.37	8.37
	Q1	7.64	7.55	7.18	7.64	7.64
	Q3	9.38	9.47	8.83	9.29	9.29
ALAT	Median	30.00	30.00	27.00	28.00	30.00
	Q1	21.00	22.00	19.00	21.00	21.00
	Q3	43.00	45.00	40.00	43.00	43.00
LDL	Median	2.00	2.10	2.10	2.10	2.00
	Q1	1.60	1.60	1.60	1.70	1.60
	Q3	2.60	2.60	2.70	2.80	2.60
Diabetes duration (years)	Median	8.54	7.07	5.47	9.44	8.40
	Q1	5.03	3.48	2.22	5.39	4.96
	Q3	11.66	10.64	9.43	12.59	11.46

Lab values restricted to only in North and Central Denmark Regions. HbA_{1c}: Glycated haemoglobin, ALAT: Alanine transaminase, LDL: low-density lipoprotein

TABLE 3: LABORATORY VALUE CATEGORIES RESTRICTED TO NORTHERN DENMARK

Northern and Central Regions of Denmark	SGLT2		GLP1		DPP4		Empagliflozin		SGLT2 ex Empagliflozin	
	N	Percent (%)	N	Percent (%)	N	Percent (%)	N	Percent (%)	N	Percent (%)
Baseline HbA1c (=<1 year before index)										
.	36	1.2	70	1.6	180	1.7	3	0.7	33	1.3
<6.5	66	2.3	187	4.3	620	6.0	8	1.9	58	2.3
6.5-<7	159	5.5	268	6.2	1209	11.6	19	4.5	140	5.7
7-<7-5	394	13.6	532	12.3	2135	20.5	49	11.6	345	14.0
7.5-<8	423	14.6	616	14.3	1674	16.1	70	16.6	353	14.3
8-<9	868	30.0	1146	26.6	2331	22.4	133	31.6	735	29.7
9-<10	505	17.5	750	17.4	1121	10.8	76	18.1	429	17.4
>=10	441	15.2	739	17.2	1141	11.0	63	15.0	378	15.3
Microalbuminuria (min. 2 positive tests ever)										
0	1469	59.4	2652	61.6	7299	70.1	224	53.2	1469	59.4
1	1002	40.6	1656	38.4	3112	29.9	197	46.8	1002	40.6
eGFR<60 / nephropathy										
0	2261	91.5	3783	87.8	8202	78.8	375	89.1	2261	91.5
1	210	8.5	525	12.2	2209	21.2	46	10.9	210	8.5
eGFR										
.	11	0.4	33	0.8	73	0.7	3	0.7	11	0.4
>=60 ml/min	2250	91.1	3750	87.0	8129	78.1	372	88.4	2250	91.1
30 - 60 ml/min	208	8.4	501	11.6	1938	18.6	45	10.7	208	8.4
<30 ml/min	2	0.1	24	0.6	271	2.6	1	0.2	2	0.1

HbA_{1c}: Glycated haemoglobin, eGFR: estimated Glomerular Filtration Rate.

10. PROTECTION OF HUMAN SUBJECTS

According to Danish law, individual informed consent, or permission from ethical committee, is not required for observational registry-based studies without patient contact. The project has been approved by the Danish Data Protection Agency (Record number 2014-54-0922 KEA-2015-4).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable. Study is performed on register data.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study milestones will be agreed with BI.

The Department of Clinical Epidemiology reserves the right to submit the results from any of the study analyses for publication and commits that at least the final results will be published. Any publications will follow guidelines, including those for authorship, established by the International Committee of Medical Journal Editors. When reporting results of this study, the appropriate STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist will be followed.

13. REFERENCES

PUBLISHED REFERENCES

1. Pedersen CB. The Danish Civil Registration System. Scand J Public Health [Internet]. 2011;39(7_suppl):22–5. Available from: http://journals.sagepub.com/doi/10.1177/1403494810387965
2. Leegaard A, Riis A, Kornum JB, Prahl JB, Thomsen V, Sørensen HT, et al. Diabetes, glycemic control, and risk of tuberculosis: A population-based case-control study. Diabetes Care. 2011;34(12):2530–5.
3. Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology: The Danish National database of reimbursed prescriptions. Clin Epidemiol. 2012;4(1):303–13.
4. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol. 2010;2(1):273–9.
5. Grann, Erichsen R, Nielsen, Frøslev, Thomsen R. Existing data sources for clinical epidemiology: The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. Clin Epidemiol. 2011;1(1):133–8.
6. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med [Internet]. 2016;375(4):311–22. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1603827
7. Thrasher J. Pharmacologic Management of Type 2 Diabetes Mellitus: Available Therapies. Am J Med [Internet]. 2017;130(6):S4–17. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0002934317304576
8. Pottegård A, Bjerregaard BK, Larsen MD, Larsen KS, Hallas J, Knop FK, et al. Use of exenatide and liraglutide in Denmark: A drug utilization study. Eur J Clin Pharmacol. 2014;70(2):205–14.
9. Sundhedsdatastyrelsen. "Medstat.dk."
10. Birkeland KI, Jørgensen ME, Carstensen B, Persson F, Gulseth HL, Thuresson M, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol. 2017;5(9):709–17.
11. Thomsen RW, Baggesen LM, Søgaard M, Pedersen L, Nørrelund H, Buhl ES, et al. Early glycaemic control in metformin users receiving their first add-on therapy: a population-based study of 4,734 people with type 2 diabetes. Diabetologia. 2015;58(10):2247–53.
12. Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sørensen HT, Thomsen RW. Impact of Glycemic Control on Risk of Infections in Patients with Type 2 Diabetes: A Population-Based Cohort Study. Am J Epidemiol. 2017;186(2):227–36.
13. Horsdal HT, Johnsen SP, Søndergaard F, Rungby J. Type of preadmission glucose-lowering treatment and prognosis among patients hospitalised with myocardial infarction: A nationwide follow-up study. Diabetologia. 2008;51(4):567–74.
14. M.a S, S.A.J.a S, J.L.b S, V.a E, L.a P, H.T.a S. The Danish National patient registry: A review of content, data quality, and research potential. Clin Epidemiol [Internet].

2015;7:449–90. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84947945481&partnerID=40&md5=b3064ef56eb42aeaddf3d6d3f466c733

15. Kristensen JK, B DT, Carstensen B, Marianne S-J, Green A. Validering af metoder til identifikation af erkendt diabetes på basis af administrative sundhedsregistre. Ugeskr læger. 2007;(April):1687–92.
16. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: The Danish national prescription registry. Int J Epidemiol. 2017;46(3):798–798f.
17. Christensen DH, Rungby J, Thomsen RW. Nationwide trends in glucose-lowering drug use, Denmark, 1999-2014. Clin Epidemiol. 2016;8:381–7.
18. Thomsen RW, Nicolaisen SK, Hasvold P, Sanchez RG, Pedersen L, Adelborg K, et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes—a Danish population-based cohort study. Nephrol Dial Transplant [Internet]. 2017;1(April):1–10. Available from: http://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfx312/4644812
19. Carstensen B, Kristensen JK, Ottosen P, Register ND. The Danish National Diabetes Register : trends in incidence , prevalence and mortality. 2008;2187–96.
20. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2013;34(39):3035–87.
21. Gribsholt SB, Pedersen L, Dekkers O, Thomsen W. Body Mass Index of 92 , 027 patients acutely admitted to general hospitals in Denmark : Associated clinical characteristics and 30-day mortality. PLoS One. 2018;1–16.
22. Svensson E, Baggesen LM, Johnsen SP, Pedersen L, Nørrelund H, Buhl ES, et al. Early Glycemic Control and Magnitude of HbA $_{1c}$ Reduction Predict Cardiovascular Events and Mortality: Population-Based Cohort Study of 24,752 Metformin Initiators. Diabetes Care [Internet]. 2017;40(June):dc162271. Available from: http://care.diabetesjournals.org/lookup/doi/10.2337/dc16-2271
23. Thomsen RW, L.M. B, E S, L. P, Nørrelund H, E.S.Buhl, et al. Early glycaemic control among patients with type 2 diabetes and initial glucose-lowering treatment: a 13-year population-based cohort study. Diabetes, Obes Metab. 2015;771–80.
24. Thomsen RW, Nicolaisen SK, Hasvold P, Sanchez RG, Pedersen L, Adelborg K, et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes—a Danish population-based cohort study. Nephrol Dial Transplant [Internet]. 2017;1(January):1–10. Available from: http://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfx312/4644812
25. Svensson E, Nielsen RB, Hasvold P, Aarskog P, Thomsen RW. Statin prescription patterns, adherence, and attainment of cholesterol treatment goals in routine clinical care: A Danish population-based study. Clin Epidemiol. 2015;7:213–23.
26. Suissa S. Lower Risk of Death With SGLT2 Inhibitors in Observational Studies: Real or Bias? Diabetes Care [Internet]. 2018;41(1):6–10. Available from: http://care.diabetesjournals.org/lookup/doi/10.2337/dc17-1223
27. Patorno E, Patrick AR, Garry EM, Schneeweiss S, Gillet VG, Bartels DB, et al. Observational studies of the association between glucose-lowering medications and cardiovascular outcomes: addressing methodological limitations. Diabetologia. 2014;57(11):2237–50.

28. Mor A, Petersen I, SØrensen HT, Thomsen RW. Metformin and other glucose-lowering drug initiation and rates of community-based antibiotic use and hospital-treated infections in patients with type 2 diabetes: A Danish nationwide population-based cohort study. BMJ Open. 2016;6(8).
29. Christiansen C, Johansen M, Christensen S, O'Brien JM, Tønnesen E, Sørensen H. Preadmission metformin use and mortality among intensive care patients with diabetes: a cohort study. Crit Care [Internet]. 2013;17(5):R192. Available from: http://ccforum.biomedcentral.com/articles/10.1186/cc12886

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Documents listed in Annex 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request. Write "None" if there is no document or list documents in a table as indicated below.

Number	**Document Reference Number**	**Date**	**Title**
<1>	<Number>	DD Month YYYY	<Text>
<2>	<Number>	DD Month YYYY	<Text>
<n>	<Number>	DD Month YYYY	<Text>

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

A copy of the ENCePP Checklist for Study protocols available at website: encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

"Study start" means "Start of data collection"
"Study progress" means "Progress report(s)"
"Study completion" means "End of data collection"
"Reporting" means "Final report of the study results"

ANNEX 3. ADDITIONAL INFORMATION

Additional annexes may be included if necessary.