Protocol for non-interventional studies based on existing data

Document Number:	**<document number>**
BI Study Number:	<Study Number>
BI Investigational Product(s):	Empagliflozin (Jardiance®) Empagliflozin + Linagliptin (Glyxambi®) Empagliflozin + Metformin (Synjardy®)
Title:	**Cardiovascular and renal outcomes, and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus GLP1-RA: A Danish nationwide comparative effectiveness study**
Protocol version identifier:	2.0
Date of last version of protocol:	22OCT2020
PASS:	No
EU PAS register number:	Not applicable
Active substance:	A10BX12 Empagliflozin A10BK03 Empagliflozin A10BD19 Empagliflozin + Linagliptin A10BD20 Empagliflozin + Metformin A10BX07 Liraglutide A10BJ GLP1-RA class *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:	*Not applicable*
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 GLP1-RA.
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:>**	not applicable
In case of PASS, add: **<Signature of EU-QPPV:>**	not applicable
Date:	22OCT2020

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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
LABKA	The clinical laboratory information system (LABKA) research database at Aarhus University, Denmark
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**l**
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:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
13JUL2018		2.0	13JUL2020

Title of study:	**Cardiovascular and renal outcomes, and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus GLP1-RA: A Danish nationwide comparative effectiveness study**
Rationale and background:	Utilization of the 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 GLP1-RA 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 and renal events, mortality) among empagliflozin initiators and GLP1-RA 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 GLP1-RA.

Population:	The study population will include all eligible patients with type 2 diabetes initiating treatment with empagliflozin or with GLP1-RA in 2015-2020.
Variables:	*Exposure:* Patients will be included on the index date of their first prescription for empagliflozin or GLP1-RA, respectively (either as monotherapy or fixed-dose combination with another drug), with or without treatment with other GLDs. Patients with previous use of any SGLT2i or GLP-1RA at any time before treatment initiation will be excluded. We will also exclude patients prescribed liraglutide with the brand-name Saxenda® (liraglutide 3.0 mg daily, approved as a treatment for obesity in 2015). *Outcomes:* The co-primary outcomes in our study will be (1) a composite of hospitalization due to stroke, myocardial infarction, unstable angina, coronary revascularization, hospitalized heart failure (HHF), or all-cause death (expanded MACE); (2) a composite of HHF or all-cause death; and (3) a composite of first incident HHF or first initiation of loop diuretic therapy in patients with no previous HHF or loop-diuretic use. Secondary outcomes will be: composite of all-cause hospitalization or death; all-cause hospitalization; all-cause death; and HHF. Hospitalization will be defined as any inpatient hospital admission at any Danish hospital, independent of admissions being through emergency room contact, by ambulance, self-referral, or via referral from GP, outpatient clinic, or other health care provider. *Confounders:* Age, gender, year of inclusion, diabetes duration, number of diabetes drugs used, metformin use, insulin use, diagnoses of retinopathy, neuropathy, or nephropathy, estimated glomerular filtration rate (eGFR), history of ischemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure (further divided by duration and primary/secondary diagnosis), medical obesity, chronic obstructive pulmonary disease, cancer, use of angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), other antihypertensives, statins, antiplatelet drugs, social and frailty markers, marital status, prescriptions for mental disorders, alcoholism, and number of prior hospital admission days.
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: Approx. 0.5 mill. patients with drug-treated type 2 diabetes in Denmark, during the period 1994-2020. The study size will be driven by the uptake of empagliflozin following its approval and launch in Denmark, with 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 GLP1-RA.

Data analysis:	We will provide two approaches in our study across the two exposure groups: an on-treatment (OT) exposure definition, and an intention-to-treat (ITT) exposure definition (see section 9.1 for details). For balanced comparison of the two treatment groups, we plan to conduct propensity score (PS) balancing of potential confounders (see section 9.3, covariates) across the two treatment groups. Covariate balance will be assessed by checking standardized differences (SD) between the groups; a covariate being considered well balanced if the SD is below 0.1. We will use Cox regression analyses to compute crude and adjusted hazard ratios (HRs) with 95% CIs to examine the association between empagliflozin versus GLP1-RA initiation and study outcomes. For each of the primary outcomes (primary objective) and secondary outcomes (secondary objective) of interest, estimation of adjusted use HRs with 95% CIs will be considered the main analysis of interest.	
Milestones:	Figure 1	Protocol development
	Figure 2	First interim analysis 2017 data
	Figure 3	Second interim analysis 2018 data
	Figure 4	Protocol amendment (October 2020)
	Figure 5	3rd interim analysis (year 2019 data)
	Figure 6	Final analysis (year 2020 data)

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>	13 July 2020	<all sections>	<update>	<alignment of protocol with publication>
<2>	DD Month YYYY	<Text>	<Text>	<Text>
<n>	DD Month YYYY	<Text>	<Text>	<Text>

6. MILESTONES

Milestone	**Planned Date**
Start of data collection	01JAN2015
End of data collection	Ongoing
<Study progress report 1>	19 September 2017
<Study progress report 2>	
<Study progress report n>	
<Interim report 1>	Prior to IPTW, empagliflozin initiators were older than liraglutide initiators (median age 62.4 vs 59.5 years) and more likely male (64% vs 56%). Diabetes duration (6.9 vs 6.4 years) and CV disease history (29.9% vs 28.0%) were comparable. IPTW substantially increased comparability between groups, reducing covariate standardized differences from 0.02-1.39 before propensity score balancing to <0.05 for all covariates. **Expanded MACE:** empagliflozin (n =284) Incidence rate per 1000 person years: 34.9; liraglutide: (n =723), Incidence rate per 1000 person years: 32.4 adjusted hazard ratio (95% CI) 0.98 (0.79-1.22). **HF hospitalization or all-cause death:** empagliflozin (n =187) Incidence rate per 1000 person years: 22.8; liraglutide: (n =512), Incidence rate per 1000 person years: 22.6 adjusted hazard ratio (95% CI) 0.87 (0.67-1.12). **All-cause acute hospitalization or all-cause death:** empagliflozin (n =1515) Incidence rate per 1000 person years: 213.4; liraglutide: (n =3904), Incidence rate per 1000 person years: 223 adjusted hazard ratio (95% CI) 0.88 (0.79-0.98).
<Interim report 2>	
<Interim report n>	

<Registration in the EU PAS register>	
Final report of study results:	TBD, planned for 2021

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 GLP1-RA 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 GLP1-RA.

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 GLP1-RA.

For the above study outcomes, "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.

9. RESEARCH METHODS

Description of the research methods, including:

9.1 STUDY DESIGN

Non-interventional cohort study using existing data.

We will use two alternative analytic approaches in our study: an on-treatment (OT) exposure definition, and an intention-to-treat (ITT) exposure definition.
For the OT analyses, treatment duration will be based on the estimated number of days covered by each filled prescription, calculated as the number of packages * the numerical volume of a package. A grace period of 180 days will be added. In the OT analysis, participants are censored from further follow-up at either treatment cessation, initiation of an alternative drug in the study drug class (for example, dapagliflozin among empagliflozin users), and initiation of a drug from the comparator study drug class (for example, liraglutide or another GLP-1RA among empagliflozin users).

For the ITT analyses, participants are defined as exposed from the start of treatment throughout follow-up, analogous to an ITT design in a clinical trial.

In both analyses, participants will be followed from the date of initiation of empagliflozin or GLP1-RA treatment until outcome event, date of death, emigration, or end of study at December 31, 2020 or last data availability (or, in the OT analyses, also until treatment cessation or drug changes as explained above). In the analyses of the composite outcomes, patients are censored at the first occurrence of any outcome-defining event. For individual outcomes, patients are censored at the first occurrence of the outcome analyzed, independent of other outcomes. We will construct adjusted cumulative incidence curves for the different outcomes, taking competing risk of death into account when examining non-fatal outcomes. We will use Cox proportional hazards regression with time since treatment initiation as the underlying timescale to compute adjusted hazard ratios (aHRs) with 95% CIs.

We will repeat all outcome analyses among empagliflozin vs. GLP1-RA initiators stratified by different baseline characteristics, i.e. by applying propensity score balancing of potential confounders across the two treatment groups within strata of sex, age (<65, >=65 years), presence or absence of cardiovascular disease at baseline (ischemic heart disease, HF, cerebrovascular disease, or peripheral vascular disease), current insulin use, current metformin use, and calendar periods before and after publication of the two major CVOTs (current analysis Jan 2015 – June 2016, July 2016 – Dec 2018).

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 1994-2020, 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 GLP1-RA between 2015-2020.

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 GLP1-RA 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 1JAN2015 to 31DEC2020. 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 GLP1-RA.

Baseline and lookback period

To characterize the empagliflozin and GLP1-RA 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. Thus, the look-back period for co-medication will be 365 days and up to 15 years for co-diagnoses.

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 GLP1-RA).
- Have at least 12 months of residency in Denmark 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 prescription/dispensing of SGLT2 inhibitors (including empagliflozin) alone or in fixed-dose combination prior to the index date.
- Have no prescription/dispensing of a GLP-1 receptor agonist alone or in fixed-dose combination prior to the index date.

The population exposed to GLP1-RA must meet the following criteria:

- Have at least one prescription for GLP1-RA or a fixed-dose combination of GLP1-RA with another drug, with or without treatment with another glucose-lowering drug.
- Have no prescription/dispensing of a GLP-1 receptor agonist alone or in fixed-dose combination prior to the index date.
- Have no prescription/dispensing of SGLT2 inhibitors (including empagliflozin) alone or in fixed-dose combination 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:

In general, analysis will include patients with previous outcome events, and adjustment for the history of these events will be carried out in the regression models rather than excluding them (e.g. assess outcome rates of myocardial infarction in empagliflozine and GLP1-RA *initiators while adjusting for previous history of myocardial infarction, unstable angina, or coronary revascularization). However, an analysis of a composite of first incident HHF or first initiation of loop diuretic therapy will be restricted to patients with no previous HHF or loop-diuretic use*.

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 GLP1-RA.

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.

For the OT analyses, treatment duration will be based on the estimated number of days covered by each filled prescription, calculated as the number of packages * the numerical volume of a package. A grace period of 180 days will be added. In the OT analysis, participants are censored from further follow-up at either treatment cessation, initiation of an alternative drug in the study drug class (for example, dapagliflozin among empagliflozin users), and initiation of a drug from the comparator study drug class (for example, liraglutide or another GLP-1RA among empagliflozin users).

For the ITT analyses, participants are defined as exposed from the start of treatment throughout follow-up, analogous to an ITT design in a clinical trial.

Follow-up will not be censored if glucose-lowering drugs other than the index drugs are prescribed in addition to empagliflozin or GLP1-RA 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®)
A10BJ GLP1-RAs
A10AE56 (Insulin degludec + Liraglutide (Xultophy®))

Study outcomes

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

Primary study outcome:

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

Secondary outcomes of interest:

- Inpatient hospital admission with a diagnosis of HF and/or initiation of community prescription drug therapy with loop diuretics
- Inpatient hospital admission with a diagnosis of HF and/or all-cause death
- composite of all-cause hospitalization or death
- all-cause hospitalization
- all-cause death
- Hospitalization for HF.

For the above study outcomes, "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 documented 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

Variable	Database	Codes
Hospital Admissions for HF and/or initiation of therapy with loop diuretics	DNPR, prescription registry	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, C03EB
Hospital Admission for HF and all-cause death	DNPR, CRS	Either admission for HF: I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 **OR** All-cause death
"Expanded MACE": All cause death, non-fatal stroke, non-fatal MI, hospital admission for unstable angina, coronary revascularization, hospital admission for HF	DNPR, CRS	Either Admission for MI: I21 **OR** Admission for unstable angina: I200 **OR** nonfatal stroke: I61, I63, I64, **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

ICD-10 codes for secondary outcomes

Variable	Database	Codes	Notes
All-cause inpatient hospital admission or emergency room visit	DNPR	Various diagnoses and procedures from all acute hospital contacts	
Hospital admission with HF	DNPR	Admission for HF:	

		I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429	
All-cause inpatient hospital admission or all-cause death	DNPR, CPR	Various diagnoses and procedures from all inpatient hospital admissions **OR** All-cause death	
All-cause death	CPR	All-cause death	

Covariates

For all patients with a first initiation of empagliflozin or GLP1-RA, we will ascertain data on a range of variables potentially associated with the outcomes of interest, including the following:

Included in current analysis as potential confounders:
Age, gender, year of inclusion, diabetes duration, number of diabetes drugs used, metformin use, insulin use, diagnoses of retinopathy, neuropathy, or nephropathy, estimated glomerular filtration rate (eGFR), history of ischemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure (further divided by duration and primary/secondary diagnosis), medical obesity, chronic obstructive pulmonary disease, cancer, use of angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), other antihypertensives, statins, antiplatelet drugs, social and frailty markers, marital status, prescriptions for mental disorders, alcoholism, and number of prior hospital admission days.

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

Variable	Database	Codes	Notes
Ischemic heart disease	DNPR	I20-I25, T822A, T823, KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF	Ischemic heart disease diagnosis incl angina or coronary OP
Cerebrovascular disease	DNPR	G45, I61, I63-I66, I672, I678-I679, I691, I693-I698, G45, KAAL10, KAAL11	Atherosclerotic cerebrovascular disease incl thrombolysis/thrombectomy, TCI, intracerebral hemorrhage
Peripheral vascular disease	DNPR	I702, I742-I745, I739A, I739B, I739C, E105, E115, E125, E135, E145, KPBE+F+H+N+P+Q,	Atherosclerotic peripheral vascular

		KPBW, KPGH10, KPDE+F+H+N+P+Q, KPDW99, KPDW20, KPEE+F+H+N+P+Q+W, KPFE+H+N+P+Q+W, KPGH20+21+22+23+30+31+40+99, KPDU74+82+83+84, KPEU74+82+83+84, KPFU74+82+83+84, KNBQ, KNCQ, KNDQ, KNEQ, KNFQ, KNGQ, KNHQ	disease incl vascular OP or amputation
Neuropathy		E104,E114, E144, G590, G632, G598, G603, G628, G629, G632, G638, G990	
Retinopathy	DNPR Diagnosis codes + procedure codes	E103, E113, E143, H340, H341, H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335, H470 KCKC10, KCKC15, KCKD65	
Nephropathy	DNPR Diagnosis codes +	E102, E112, DE142, I120, N083, N06, N17, N18, N19, R809 BJFD2	
Creatinine (eGFR)	LABKA	NPU18016, NPU01807, NPU04998, NPU17559, ASS00354, ASS00355, ASS00356 or analysis codes: 110266, 111016, 1311235, 1411235, 1511235, 1511236, 1511237, 1610154, 1610296, 1611807, 1710552, 1710301, 1711807, 1811807, 1817156, 1817428, 18016, 1155, 38927, 4998, 716, 1807, 5224, 38926, 38928	
Chronic pulmonary disease	DNPR	J40-J48, J60-J68, J684, J701, J703, DJ961, J982, J983	
Cancer	DNPR	C00-C99	

Medical obesity	DNPR	E65-E68	
Alcoholism	DNPR	G312, G621, G721, I426, K292, K860, K70, R780, T51, Z714, Z721	
Mental disorders	prescriptions	N05A, N05BA, N05CD, N05CF, N06A	
Antiplatelet drugs	prescriptions	B01AC06, N02BA01, B01AC30, B01AC07, B01AC22, B01AC04, B01AC24, B01AC25	
Statins	prescriptions	C10AA, C10BA, C10BX, A10BH51	
Any antihypertensive drugs	prescriptions	C02, C03A, C03B, C03X, C07, C08, C09	
ACE inhibitors	prescriptions	C09A, C09B	
ARB	prescriptions	C09C, C09D	
Marital status	CRS		Current marital status (if no current status in CPR, last value carried forward)

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

Diabetes drugs	**ATC codes in database**
Empagliflozin	A10BX12, A10BK03, A10BD19, A10BD20
Liraglutide	A10BX07, A10BJ02, A10AE56
SGLT2-inhibitor	A10BX09, A10BX11, A10BX12, A10BK, A10BD15, A10BD16, A10BD21, A10BD20, A10BD19, A10BD23, A10BD24, A10BD25
GLP1 receptor agonists	A10BX04, A10BX07, A10BX10, A10BX13, A10BX14, A10BJ, A10AE54, A10AE56
DPP4 inhibitors	A10BH, A10BD07, A10BD12, A10BD08, A10BD09, A10BD10, A10BD11, A10BD13, A10BD18, A10BD19, A10BD21, A10BD22, A10BD24, A10BD25

biguanides	A10BA, A10BD01, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25
sulfonylureas	A10BB, A10BD04, A10BD02, A10BD06, A10BD01, A10BC01
glitazones	A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12
alfa-glucosidase inhibitors	A10BF, A10BD17
Insulin and analogues	A10A
meglitinides	A10BX02, A10BX03, A10BX08, A10BD14

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 centralized 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 1994. 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 National Laboratory Database: Data from samples which involve laboratory analysis (e.g. blood samples) are compiled in this database. Danish regions were affiliated with the database from 2013. In addition, historical data from some regions have been incorporated.
Data on e.g. creatinine 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).

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 2019, according to www.medstat.dk there were 23,350 users of empagliflozin in Denmark.

In 2019, there were 41,715 users of GLP-1 receptor agonists in Denmark (9). This may yield an estimated at least 50,000 GLP-1 RA users during 2014-2020 for comparison making statistical power a minor concern when including 2020 data in the final analysis.

We thus estimate that at least 40,000 person-years of empagliflozin exposure and 60,000 person-years of liraglutide exposure can be included in our study up to the end of 2020.

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 9.4 (SAS Institute, Inc., Cary, North Carolina).

9.7 DATA ANALYSIS

We will provide two approaches in our study across the two exposure groups: an on-treatment (OT) exposure definition, and an intention-to-treat (ITT) exposure definition (see section 9.1 for details).

Decisions to start 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 propensity score (PS) balancing of potential confounders (see section 9.3, covariates) across the two treatment groups. Covariate balance will be assessed by checking standardized differences (SD) between the groups; a covariate being considered well balanced if the SD is below 0.1.

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 GLP1-RA in this study, more of our potential confounding covariates may be used in the model than in a conventional multivariable 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 GLP1-RA and empagliflozin initiators. Moreover, propensity score methods may not in some settings estimate treatment effects 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 methods. Given that 1) We aim to measure the average treatment effect at the population level; 2) We wanted to avoid excluding patients, to reduce the risk of a non-representative sample; and 3) The number of patients in our two treatment groups will likely differ little, the Inverse Probability Treatment Weighting approach (IPTW) may be a feasible approach

Cumulative incidence function curves will be constructed to depict the cumulative incidence over time of each of the outcomes under study, comparing empagliflozin and GLP1-RA initiators.

We will use Cox regression analyses to compute crude and adjusted hazard ratios (HRs) with 95% CIs to examine the association between empagliflozin versus GLP1-RA initiation and study outcomes. For each of the primary outcomes (primary objective) and secondary outcomes (secondary objective) of interest, estimation of adjusted 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.

Stratified analyses

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

Relative estimates will be calculated, stratified by strata of sex, age (<65, >=65 years), presence or absence of cardiovascular disease at baseline (ischemic heart disease, HF, cerebrovascular disease, or peripheral vascular disease), current insulin use, current metformin use, GLD treatment lines and calendar periods before and after publication of the two major CVOTs (Jan 2015 – June 2016, July 2016 – Dec 2018).

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 controlling for confounding during the analysis phase and by undertaking stratified analysis , 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 described above.

Considering drug exposure, our on-treatment (i.e., terminating drug exposure upon discontinuation) may be prone to bias if the discontinuation of a study drug (empagliflozin or GLP1-RA) 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 GLP1-RA, in light of the strengths and limitations inherent in each approach.

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 analyzed 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: 25^{th} and 75^{th} percentile; eGFR: estimated Glomerular Filtration Rate; ACE: Angiotensin-Converting-enzyme; ATII: Angiotensin II.

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).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable. Study is performed on register data.

11. 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.

12. 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. Anon. 2020. Documentation of The National Laboratory Database. https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/doedsaarsager-og-biologisk-materiale/laboratoriedatabasen. In Danish
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 CHECKLIST 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.