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ORIGINAL RESEARCH

Cardiovascular Events, Acute Hospitalizations, and Mortality in Patients With Type 2 Diabetes Mellitus Who Initiate Empagliflozin Versus Liraglutide: A Comparative Effectiveness Study

Reimar W. Thomsen, MD, PhD; Jakob S. Knudsen, MD, PhD; Johnny Kahlert, MSc, PhD; Lisbeth M. Baggesen, MSc, PhD; Maria Lajer, MSc, PhD; Pia H. Holmgaard, BSc; Ola Vedin, MD, PhD; Anastasia Ustyugova, MD, PhD; Henrik T. Sørensen, MD, PhD, DMSc

BACKGROUND: In cardiovascular outcome trials, the sodium glucose cotransporter 2 inhibitor empagliflozin and glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide caused similar reductions in major adverse cardiac events (MACE). We compared clinical outcomes in routine clinical care.

METHODS AND RESULTS: EMPLACE (Cardiovascular and Renal Outcomes, and Mortality in Danish Patients with Type 2 Diabetes Who Initiate Empagliflozin Versus GLP-1RA: A Danish Nationwide Comparative Effectiveness Study) is an ongoing nationwide population-based comparative effectiveness cohort study in Denmark. For the present study, we included 14 498 new users of empagliflozin and 12 706 new users of liraglutide, 2015 to 2018. Co-primary outcomes were expanded major adverse cardiac events (stroke, myocardial infarction, unstable angina, coronary revascularization, hospitalization for heart failure [HHF], or all-cause death); HHF or all-cause death; and first HHF or first initiation of loop-diuretic therapy. Secondary outcomes included all-cause hospitalization or death. We applied propensity score balancing and Cox regression to compute adjusted hazard ratios (aHRs) in on-treatment (OT) and intention-to-treat (ITT) analyses. Cohorts were well balanced at baseline (median age 61 years, 59% men, diabetes mellitus duration 6.6 years, 30% with preexisting cardiovascular disease). During mean follow-up of 1.1 years in OT and 1.5 years in ITT analyses, empagliflozin versus liraglutide was associated with a similar rate of expanded major adverse cardiac events (OT aHR, 1.02; 95% CI, 0.91–1.14; ITT aHR, 1.06; 95% CI, 0.96–1.17), and HHF or all-cause death (OT aHR, 0.97; 95% CI, 0.85–1.11; ITT aHR, 1.02; 95% CI, 0.91–1.14); and a decreased rate of a first incident HHF or loop-diuretic initiation (OT aHR, 0.80; 95% CI, 0.68–0.94; ITT aHR, 0.87; 95% CI, 0.76–1.00), and of all-cause hospitalization or death (OT aHR, 0.93; 95% CI, 0.89–0.98; ITT aHR, 0.93; 95% CI, 0.90–0.97).

CONCLUSIONS: Empagliflozin and liraglutide initiators had comparable rates of expanded major adverse cardiac events, and HHF or all-cause death, whereas empagliflozin initiators had a lower rate of a first HHF or loop-diuretic initiation.

Key Words: cardiovascular outcome trials ■ comparative effectiveness ■ EMPLACE study ■ macrovascular complications ■ mortality ■ real-world data ■ type 2 diabetes mellitus

Correspondence to: Reimar W. Thomsen, MD, PhD, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. E-mail: rwt@clin.au.dk

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CLINICAL PERSPECTIVE

What Is New?

- There is limited evidence for and no large head-to-head trials demonstrating whether treatment benefit on cardiovascular outcomes and mortality is greatest with sodium-glucose cotransporter-2 inhibitor or glucagon-like peptide-1 receptor agonist.
- This nationwide population-based comparative effectiveness cohort study showed that empagliflozin and liraglutide initiators in routine clinical care have comparable rates of expanded major adverse cardiovascular events, heart failure hospitalization, and all-cause death.
- The rate of first heart failure hospitalization or loop-diuretic initiation in individuals with no previous heart failure hospitalization or loop-diuretic use was lower in empagliflozin initiators.

What Are the Clinical Implications?

- In broader unselected groups of real-world patients who are at different levels of baseline risk, empagliflozin and liraglutide initiators have comparable rates of expanded major adverse cardiovascular events, heart failure hospitalization, and all-cause death.
- Rate of first heart failure hospitalization or loop-diuretic initiation among heart failure-naïve individuals was in favor of empagliflozin, consistent with clinical trial findings.

Nonstandard Abbreviations and Acronyms

CVOT	cardiovascular outcome trial
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial
EMPLACE	Cardiovascular and Renal Outcomes, and Mortality in Danish Patients with Type 2 Diabetes Who Initiate Empagliflozin Versus GLP-1RA: A Danish Nationwide Comparative Effectiveness Study
GLD	glucose-lowering drugs
GLP-1RA	glucagon-like peptide-1 receptor agonist
HHF	hospitalized heart failure
IPTW	inverse probability treatment weighting
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial
MACE	major adverse cardiac events
OT	on-treatment
PS	propensity score
SGLT2i	sodium-glucose cotransporter-2 inhibitor

Cardiovascular disease remains the most frequent cause of mortality in patients with type 2 diabetes mellitus.[1] The advent of 2 new classes of glucose-lowering drugs (GLD), the sodium-glucose cotransporter-2 inhibitors (SGLT2i) and GLP-1RA (glucagon-like peptide-1 receptor agonists), has led to a recent paradigm shift in type 2 diabetes mellitus treatment.[2,3] In 2015, the EMPA-REG OUTCOME trial[4] (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial) of empagliflozin in patients with type 2 diabetes mellitus with established cardiovascular disease was the first to show a 14% reduced risk (44 versus 37 events per 1000 person-years) of major adverse cardiac events (MACE), and a 32% relative risk reduction of death from any cause (29 versus 19 events per 1000 person-years). One year later, the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial of liraglutide in patients with type 2 diabetes mellitus with high cardiovascular risk showed a 13% reduced risk (39 versus 34 events per 1000 person-years) of MACE and a 15% relative risk reduction of death from any cause (25 versus 21 events per 1000 person-year).[5] These 2 landmark trials paved the way toward a shift in how clinicians conceptualize type 2 diabetes mellitus treatment,[3] increasing focus on cardiovascular risk management in addition to glycemic control. These trials have since been followed by other large cardiovascular outcome trials (CVOTs) with several other SGLT2i and GLP-1RA, conducted in populations with type 2 diabetes mellitus mostly at high cardiovascular risk and demonstrating varying degrees of cardiovascular risk reductions.[5–9]

Accordingly, in recent updates of the European Association for the Study of Diabetes/American Diabetes Association and national guidelines from 2018 and onwards,[1,10,11] initiation of either a SGLT2i or a GLP-1RA with proven cardiovascular benefit is recommended for patients with type 2 diabetes mellitus

and clinical cardiovascular disease.[12] Currently, however, there are no head-to-head randomized controlled trials that could guide clinicians on the comparative effectiveness of empagliflozin versus liraglutide, or other SGLT2i versus GLP-1RA, on hard clinical outcomes. A few network meta-analyses of randomized trials of SGLT2i and GLP-1RA have been conducted,[13–15] with mixed results and conflicting conclusions. Consequently, whether treatment benefit on cardiovascular and mortality risk is greatest with SGLT2i or GLP-1RA is unclear, in particular in broader unselected groups of patients who are likely to have different levels of risk at baseline.[16]

High-quality population-based healthcare databases provide a unique opportunity to investigate a range of cardiovascular outcomes associated with newer GLD use in real-world settings[17,18] including observational studies of comparative treatment effectiveness.[19] In the present first substudy of EMPLACE (Cardiovascular and Renal Outcomes, and Mortality in Danish Patients with Type 2 Diabetes Who Initiate Empagliflozin Versus GLP-1RA: A Danish Nationwide Comparative Effectiveness Study) 2015 to 2018, we compared clinical outcomes (cardiovascular events, acute hospitalizations, and mortality) among empagliflozin initiators and liraglutide initiators among people with type 2 diabetes mellitus in routine clinical care in Denmark.

METHODS

Data and Code Availability

Danish law does not allow researchers to share raw data from the registries with third parties. To protect patient privacy, the combined set of data as used in this study can be made available only through a trusted third party, the national Danish Health Data Authority. This state organization holds the data used for this study. University-based Danish scientific organizations can be authorized to work with data within the Danish Health Data Authority. Requests for data may be sent to the Danish Health Data Authority: https://sundhedsdatastyrelsen.dk/da/forskerservice, by e-mail to: forskerservice@sundhedsdata.dk. For information on programming code, the Department of Clinical Epidemiology can be contacted, see: https://kea.au.dk.

The study was approved by the Danish Data Protection Agency (record number 2014-54-0922) through registration at Aarhus University (record number KEA-2015-4). Data were linked and analyzed in pseudonymized form in a safe and protected data environment on a secure server at the Danish Health Data Authority, Copenhagen. The study was purely registry-based and did not involve any contact with patients or interventions; therefore, according to Danish legislation, ethics approval and informed consent are not required. Because of the sensitive nature of the data collected for this study, requests to access the databases used in this study from researchers at authorized institutions may be sent to the Danish Health Data Authority by e-mail to forskerservice@sundhedsdata.dk.

Study Design

We did a nationwide population-based comparative effectiveness cohort study based on linked prospective healthcare databases for the entire population in Denmark (current population 5.8 million) during January 1, 2015, to December 31, 2018, to assess the effectiveness on clinical outcomes (cardiovascular events, all-cause hospitalizations, and mortality) associated with initiation of empagliflozin versus liraglutide in patients with type 2 diabetes mellitus. We used an active comparator, new user design,[20] as empagliflozin and liraglutide are used in similar clinical situations in patients with type 2 diabetes mellitus according to guidelines.[1,11] We considered confounding by indication and disease severity,[21] as we controlled for potential confounders through propensity score (PS) inverse probability treatment weighting (IPTW).[22] The study protocol and analysis plan was registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance website (http://www.encepp.eu/encepp/viewResource.htm?id=37726, first protocol registration June 4, 2019), and on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT03993132, first posted June 20, 2019).

Data Sources

We linked the following databases for our study: The Civil Registration System, including information on residence, migration, and vital status of all Danish residents since 1968[23]; The Danish National Patient Registry, including data on all in- and outpatient hospital diagnoses and treatments beginning in 1977[24]; and The Danish National Prescription Registry, including individual-level data on all medications bought at any pharmacy in Denmark since 1995.[25]

Study Population

The source population included all individuals in Denmark with type 2 diabetes mellitus, defined as people who initiated noninsulin GLD or insulin between January 1, 1995 and December 31, 2018 while excluding individuals, who under the age of 30 initiated insulin as monotherapy as likely patients with type 1 diabetes mellitus. Within this source population with type 2 diabetes mellitus, we identified our

cohort study population of patients aged 18 years or older with a first-time prescription for empagliflozin or liraglutide from January 1, 2015, to December 31, 2018. To ensure proper covariate assessment, cohort members were required to have resided in Denmark for at least 12 months before initiating treatment (see flow chart in Figure S1).

Drug Exposure and Covariates

Patients were included on the index date of their first prescription for empagliflozin or liraglutide, respectively (either as monotherapy or fixed-dose combination with another drug), with or without treatment with other GLD. Patients with previous use of any SGLT2i or GLP-1RA at any time before treatment initiation with empagliflozin or liraglutide were excluded. We disregarded patients prescribed liraglutide 3.0 mg daily, approved as a treatment for obesity in 2015. Information on demographic characteristics, social and frailty markers, medical history, and prescription drug use were obtained from the nationwide databases (covariate definitions shown in Table S1).

Outcomes

The 3 prespecified co-primary outcomes in our study were (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.[26] Prespecified secondary outcomes were composite of all-cause hospitalization or death, all-cause hospitalization, all-cause death, and HHF. All outcomes were preselected based on their important clinical and public health implications, focusing not only on atherosclerotic cardiovascular disease but also on heart failure as an increasingly acknowledged complication of type 2 diabetes mellitus,[26,27] on all-cause hospitalizations, and on all-cause death; and based on observations that the drugs under study may substantially reduce all of these end points (eg, expanded MACE,[4,5] all-cause death),[4,5] HHF (significant reduction in,[4] nonsignificant reduction in[5]), and all-cause hospitalization.[28] Hospitalization was 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 a general practitioner, outpatient clinic, or other healthcare provider. Outcome definitions are shown in Table S1. Both primary and secondary discharge diagnoses were included. Identification of cardiovascular hospitalization outcomes through patient registers have been validated in Denmark, with reported positive predictive values of 98% to 100% for myocardial infarction, 81% to 97% for stroke, 79% to 88% for heart failure, and 98% for coronary revascularization.[26]

PS Balancing

We applied PS balancing of potential confounders across the 2 treatment groups through IPTW,[22] controlling for the following covariates (Table): age, sex, year of inclusion, diabetes mellitus duration, number of diabetes mellitus drugs used, metformin use, insulin use, diagnoses of retinopathy, neuropathy, or nephropathy, estimated glomerular filtration rate (handled as categorical covariate, patients with missing estimated glomerular filtration rate data [≈2% of individuals] as separate category), 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 or angiotensin II receptor blockers, other antihypertensives, statins, antiplatelet drugs, social and frailty markers, marital status, prescriptions for mental disorders, alcoholism, and number of prior hospital admission days. In the PS analysis, we chose the IPTW approach over PS matching for 3 reasons: (1) we aimed to measure the average treatment effect at the population level; (2) we wanted to avoid excluding patients, to reduce the risk of a nonrepresentative sample; and (3) because the number of patients in our 2 treatment groups differed little (ratio 1–1.1), we wanted to counteract not being able to find a proper match to treated patients.[29] We applied weight trimming to reduce the importance of large weights; thus, these weights were trimmed down to the value at the 99th percentile. Covariate balance was assessed by checking standardized differences between the groups; a covariate was considered well balanced if the standardized difference was below 0.1.

Statistical Analysis

We used 2 alternative pharmacoepidemiological approaches in our study: an on-treatment (OT) exposure definition and an intention-to-treat (ITT) exposure definition.

For the OT analyses, treatment duration was 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 was added. In the OT analysis, participants were 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 were defined as exposed from the start of treatment throughout follow-up, analogous to an ITT design in a clinical trial.

In both analyses, participants were followed up from the date of initiation of empagliflozin or liraglutide treatment until outcome event, date of death, emigration, or end of study at December 31, 2018 (or, in the OT analyses, also until treatment cessation or drug changes as explained previously). In the analyses of the composite outcomes, patients were censored at the first occurrence of any outcome-defining event. For individual outcomes, patients were censored at the first occurrence of the outcome analyzed, independent of other outcomes. We constructed adjusted cumulative incidence curves for the different outcomes, taking competing risk of death into account when examining nonfatal outcomes. We computed incidence rates of outcomes per 1000 person-years in the PS balanced treatment groups. We used Cox proportional hazards regression with time since treatment initiation as the underlying timescale to compute adjusted hazard ratios (aHRs) with 95% CIs. The proportional-hazards assumption was assessed by visual inspection of the logarithmic cumulative hazard plots.

We repeated all outcome analyses among empagliflozin versus liraglutide initiators stratified by different baseline characteristics, that is, by applying PS balancing of potential confounders across the 2 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 2 major CVOTs (January 2015–June 2016, July 2016–December 2018).

All statistical analyses were carried out with SAS version 9.4.

RESULTS

Descriptive Characteristics

Between 1994 and 2018, we identified a total of 23 335 patients with a first-time prescription for empagliflozin and 43 687 patients with a first-time prescription for liraglutide in our Danish databases (Figure S1). After exclusion criteria were applied, 14 498 incident empagliflozin users and 12 706 incident liraglutide users who initiated treatment between January 1, 2015 and December 31, 2018 remained. Baseline characteristics and standardized differences for the cohorts before matching are shown in Table. Before IPTW, empagliflozin initiators were older than liraglutide initiators (median age 62.7 versus 59.3 years) and more likely male (64% versus 54%) whereas diabetes mellitus duration (6.8 versus 6.1 years) and atherosclerotic cardiovascular disease history (31% versus 28%) were largely comparable. After IPTW, comparability was substantially increased between groups. IPWT reduced covariate standardized differences from 0.01 to 0.78 before PS balancing to <0.1 for all covariates (Table, Figure S2). Thus the treatment groups were regarded as well balanced on all measured covariates.

Outcomes

For the 3 primary outcomes of expanded MACE, HHF or all-cause death, and first incident HHF or loop-diuretic initiation in patients with HF who were loop-diuretic naïve, the total follow-up time in person-years after IPWT among empagliflozin initiators was 21 176, 21 543, and 18 239 years in the ITT analyses. Among liraglutide initiators, corresponding figures were 20 117, 20 430, and 16 319 years. As expected, follow-up was shorter in the OT analyses, that is, 15 762, 15 985, and 13 682 years for empagliflozin and 14 917, 15 085, and 12 024 years for liraglutide, respectively.

Figure 1A through 1G show the cumulative incidences of the primary and secondary outcomes in the 2 IPTW groups. The absolute risk differences at 3 years are shown in Table S2. As seen from Figure 2 (entire population), the incidence rates of expanded MACE per 1000 person-years were comparable in OT analyses at 39.0 (n=614) among empagliflozin versus 38.1 (n=568) among liraglutide initiators; and in ITT analyses at 39.7 (n=840) among empagliflozin versus 37.4 (n=753) among liraglutide initiators. The corresponding rates of HF hospitalization or all-cause death were also similar at 24.7 (n=394) versus 25.4 (n=383) in OT and 25.3 (n=545) versus 24.8 (n=507) in ITT analyses. Finally, rates of first incident HHF or initiation of loop-diuretic tended to be lower with empagliflozin at 15.6 (n=214) versus 19.6 (n=235) in OT and 17.3 (n=315) versus 20.0 (n=326) in ITT analyses, respectively. Rates of secondary outcomes are shown in Figure S3.

The use of empagliflozin was associated with a similar rate of expanded MACE compared with use of liraglutide (aHR in OT, 1.02; 95% CI, 0.91–1.14; aHR in ITT, 1.06; 95% CI, 0.96–1.17) (Figure 2). The rate of HHF or all-cause death was also similar among empagliflozin and liraglutide users (aHR in OT, 0.97; 0.85–1.11; aHR in ITT, 1.02; 0.91–1.14). However, the rate of first incident HHF or loop-diuretic initiation among patients with HF who were loop-diuretic naïve was lower among empagliflozin users (OT aHR, 0.80; 95% CI, 0.68–0.94; ITT aHR, 0.87; 95% CI, 0.76–1.00). The aHRs for all-cause hospitalization or death associated with empagliflozin were 0.93 (95% CI, 0.89–0.98) in OT and 0.93

Table. Characteristics of New Users of Empagliflozin or Liraglutide, Overall and After Propensity Score Balancing of Potential Confounders

	Overall Cohort			Propensity Score-Weighted Cohort		
	Liraglutide Use, N (%)	Empagliflozin Use, N (%)	SD	Liraglutide Use, N (%)	Empagliflozin use, N (%)	SD
Number of patients	12 706	14 498		12 628	14 148	
Age, y, median (Q1–Q3)	59.3 (50.2–68.2)	62.7 (54.0–70.6)	0.39	61.2 (52.3–69.5)	61.6 (52.7–69.8)	0.06
Male	6820 (53.7)	9264 (63.9)	0.30	7465 (59.1)	8455 (59.8)	0.02
2015	3085 (24.3)	770 (5.3)	0.78	1809 (14.3)	1822 (12.9)	0.06
2016	3013 (23.7)	2755 (19.0)	0.16	2746 (21.7)	3125 (22.1)	0.01
2017	3016 (23.7)	4649 (32.1)	0.26	3585 (28.4)	4077 (28.8)	0.01
2018	3592 (28.3)	6324 (43.6)	0.46	4488 (35.5)	5124 (36.2)	0.02
Diabetes mellitus-related variables						
Diabetes mellitus duration, median (Q1–Q3)	6.1 (2.2–10.9)	6.8 (3.1–11.1)	0.12	6.6 (2.8–11.0)	6.7 (3.0–11.1)	0.03
Diabetes mellitus drugs used, median (Q1–Q3)	1 (1–2)	1 (1–2)	0.19	2 (1–2)	1 (1–2)	0.03
Metformin use	10 163 (80.0)	13 402 (92.4)	0.52	10 945 (86.7)	12 394 (87.6)	0.04
Insulin use	3536 (27.8)	2344 (16.2)	0.40	2805 (22.2)	3113 (22.0)	0.01
Hospital-diagnosed retinopathy	2125 (16.7)	2642 (18.2)	0.06	2181 (17.3)	2498 (17.7)	0.01
Hospital-diagnosed neuropathy	793 (6.2)	919 (6.3)	0.006	795 (6.3)	903 (6.4)	0.001
Hospital-diagnosed nephropathy	1002 (7.9)	689 (4.8)	0.18	800 (6.3)	871 (6.2)	0.01
eGFR <45	748 (5.9)	301 (2.1)	0.28	501 (4.0)	559 (4.0)	0.005
eGFR 45–59	1020 (8.0)	1019 (7.0)	0.05	979 (7.8)	1121 (7.9)	0.01
eGFR 60–89	3826 (30.1)	5710 (39.4)	0.28	4350 (34.5)	5015 (35.5)	0.03
eGFR ≥90	6202 (48.8)	7193 (49.6)	0.02	6258 (49.6)	7002 (49.5)	0.002
No eGFR measurement available	910 (7.2)	275 (1.9)	0.36	540 (4.3)	451 (3.2)	0.08
Coexisting conditions (within prior 15 y)						
Ischemic heart disease	2255 (17.8)	2928 (20.2)	0.09	2431 (19.3)	2747 (19.4)	0.01
Cerebrovascular disease	891 (7.0)	1214 (8.4)	0.07	981 (7.8)	1144 (8.1)	0.02
Peripheral vascular disease	976 (7.7)	1045 (7.2)	0.03	956 (7.6)	1076 (7.6)	0.002
New primary diagnosis heart failure ≤6 mo	37 (0.3)	90 (0.6)	0.07	54 (0.4)	67 (0.5)	0.01
New secondary diagnosis heart failure ≤6 mo	18 (0.1)	33 (0.2)	0.03	25 (0.2)	26 (0.2)	0.005
Primary heart failure diagnosis >6 mo	493 (3.9)	622 (4.3)	0.03	536 (4.3)	601 (4.3)	0.0001
Secondary heart failure diagnosis >6 mo	218 (1.7)	210 (1.5)	0.03	199 (1.6)	228 (1.6)	0.003
Medical obesity	3940 (31.0)	2629 (18.1)	0.43	3075 (24.4)	3314 (23.4)	0.03
Chronic obstructive pulmonary disease	1388 (10.9)	1259 (8.7)	0.11	1223 (9.7)	1365 (9.7)	0.002
Cancer	1075 (8.5)	1327 (9.2)	0.03	1100 (8.7)	1247 (8.8)	0.005
Co-medication (prescription within 365 d)						
Angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers	8086 (63.6)	9624 (66.4)	0.08	8315 (65.8)	9397 (66.4)	0.02
Other antihypertensive drugs	9276 (73.0)	10 996 (75.8)	0.09	9470 (75.0)	10 701 (75.6)	0.02
Statins	8583 (67.6)	10 957 (75.6)	0.25	9092 (72.0)	10 329 (73.0)	0.03
Antiplatelet drugs	4012 (31.6)	5173 (35.7)	0.12	4295 (34.0)	4903 (34.7)	0.02
Social and frailty markers						
Married	6970 (54.9)	8295 (57.2)	0.07	7104 (56.3)	7996 (56.5)	0.01
Prescription for mental disorder	6761 (53.2)	6912 (47.7)	0.16	6329 (50.1)	7086 (50.1)	0.001
Alcoholism	129 (1.0)	158 (1.1)	0·01	144 (1.1)	155 (1.1)	0.01
Prior hospital admission d, median (Q1–Q3)	24 (10–50)	20 (7–42)	0.06	22 (9–46)	22 (8–46)	0.001

eGFR indicates estimated glomerular filtration rate; Q1, lower quartile; Q3, upper quartile; and SD, standardized difference.

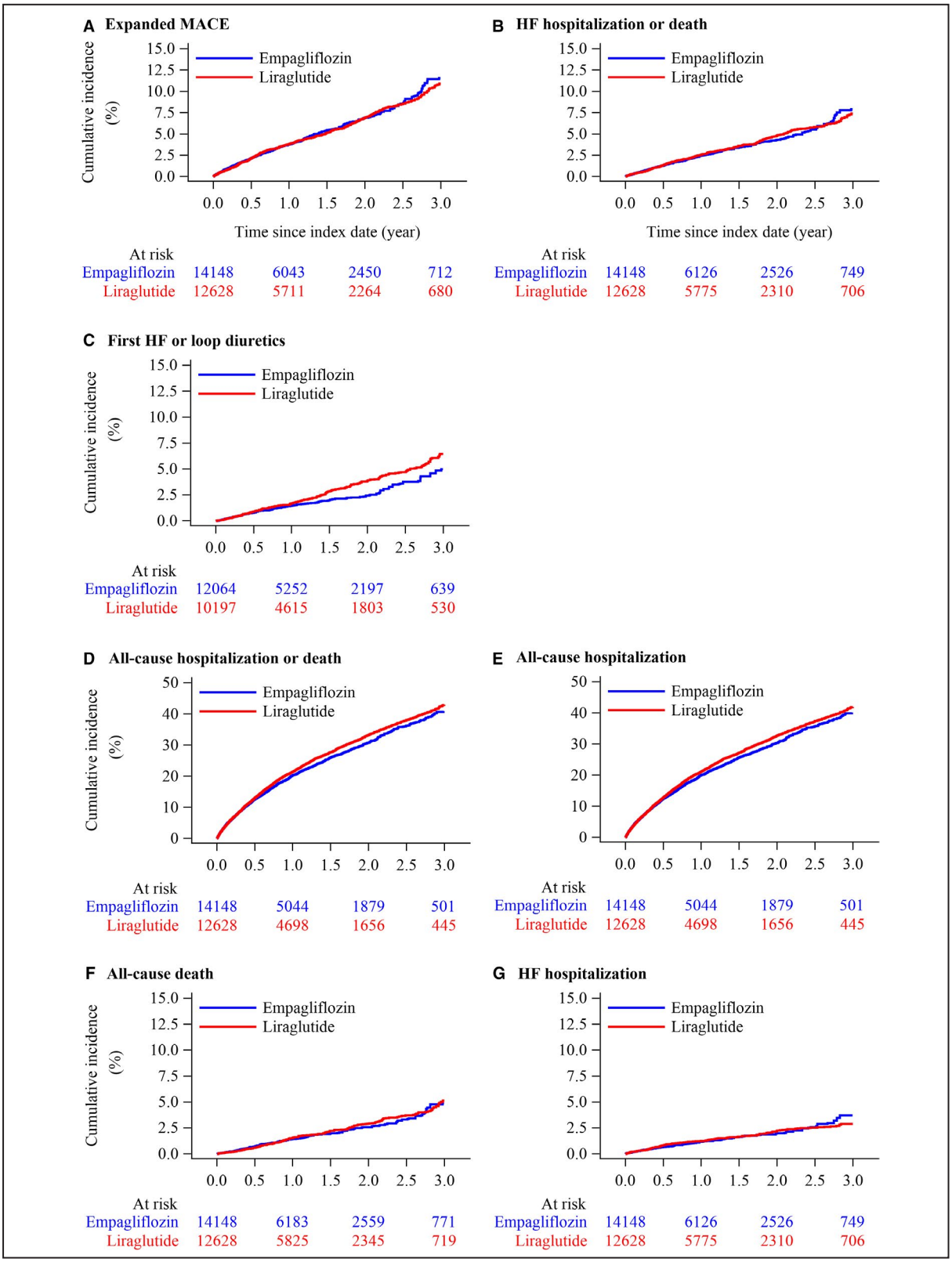


Figure 1. Risk of outcome events associated with use of empagliflozin compared with use of liraglutide in PS balanced populations.

Part 1, (**A** through **F**): on-treatment (OT) analyses; Part 2: (**A** through **F**): intention-to-treat (ITT) analyses. **A**, Expanded major adverse cardiac events (MACE) (stroke, myocardial infarction, unstable angina, coronary revascularization, hospitalization for heart failure, or all-cause death). **B**, Heart failure (HF) hospitalization or all-cause death. **C**, First hospitalization for heart failure (HF) or first initiation of loop-diuretic therapy. **D**, All-cause hospitalization or all-cause death. **E**, All-cause hospitalization. **F**, All-cause death. **G**, Heart failure (HF) hospitalization. PS indicates propensity score.

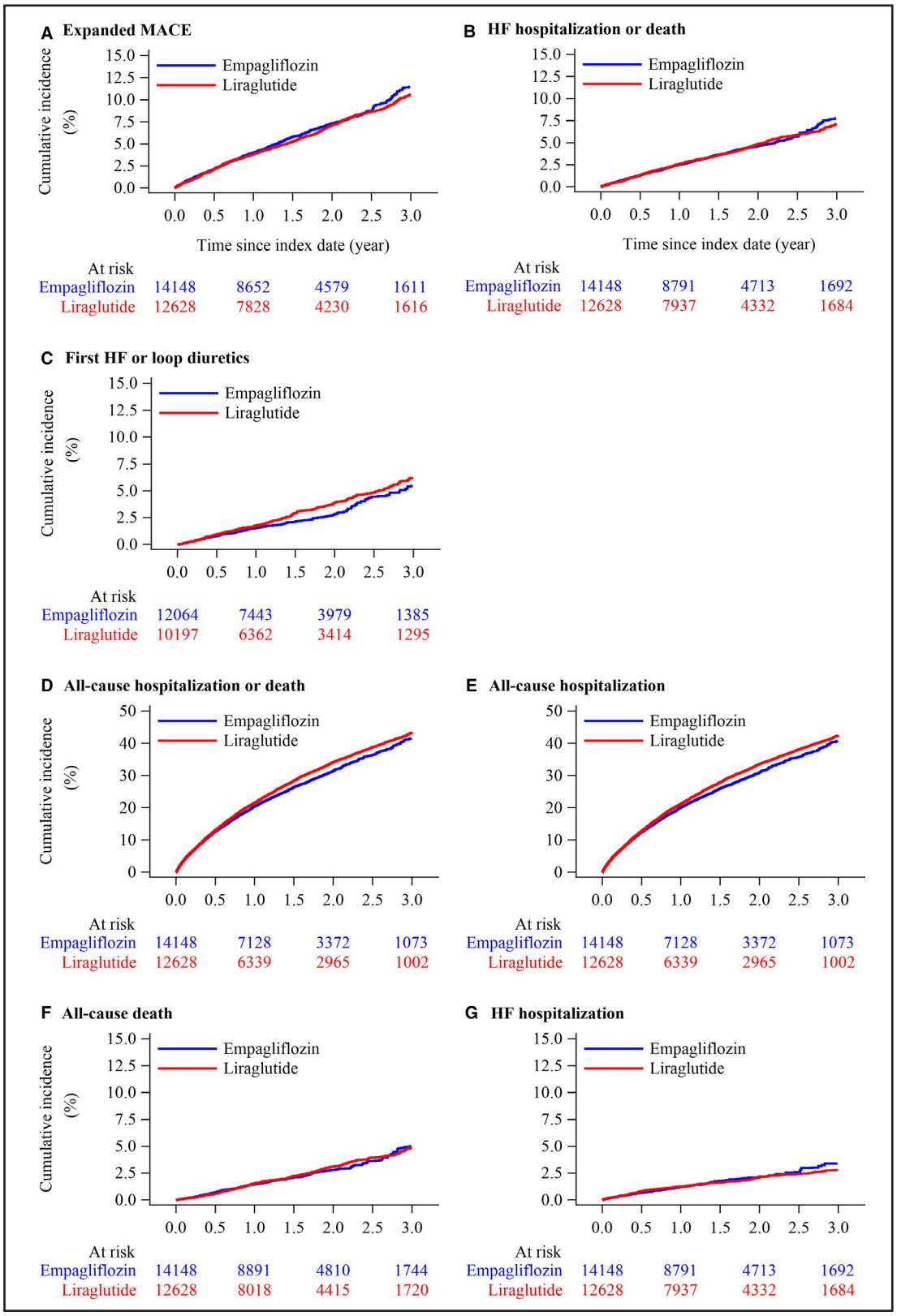
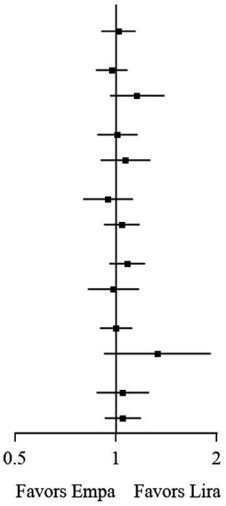


Figure 1. Continued

(95% CI, 0.90–0.97) in ITT analyses, consistent with a reduced rate of all-cause hospitalization (aHRs of 0.94; 95% CI, 0.89–0.98; and 0.93, 95% CI, 0.90–0.98; and aHRs for all-cause death of 0.95, 95% CI, 0.81–1.11; and 0.96; 95% CI, 0.84–1.10). Tables S3 and S4 show the most common primary

A Expanded MACE

Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
Entire population	**14,148 (52.8)**	**614**	**39.0**	**12,628 (47.2)**	**568**	**38.1**	**1.02 (0.91-1.14)**
Men	9,091 (57.3)	468	45.3	6,761 (42.7)	368	46.6	0.97 (0.87-1.08)
Women	5,022 (46.1)	157	29.1	5,865 (53.9)	176	25.0	1.16 (0.96-1.39)
Age>=65 years	6,114 (59.1)	388	59.2	4,231 (40.9)	292	57.9	1.01 (0.88-1.16)
Age<65 years	8,002 (48.8)	236	25.9	8,404 (51.2)	239	24.2	1.07 (0.90-1.27)
January 2015 to June 2016	2,008 (30.2)	126	33.3	4,635 (69.8)	325	35.0	0.95 (0.80-1.12)
July 2016 to December 2018	12,193 (60.2)	425	41.9	8,058 (39.8)	309	39.5	1.04 (0.92-1.18)
History of CVD	4,428 (55.5)	417	89.3	3,552 (44.5)	336	81.9	1.08 (0.96-1.22)
No history of CVD	9,719 (51.7)	211	19.0	9,075 (48.3)	209	19.4	0.98 (0.82-1.17)
Metformin use at baseline	13,165 (56.6)	548	36.7	10,079 (43.4)	445	36.6	1.00 (0.89-1.12)
No metformin use at baseline	968 (27.5)	57	61.6	2,555 (72.5)	115	45.7	1.33 (0.92-1.92)
Insulin use at baseline	2,254 (39.0)	141	55.7	3,522 (61.0)	233	52.6	1.05 (0.87-1.25)
No insulin use at baseline	11,811 (56.3)	462	35.1	9,169 (43.7)	354	33.4	1.05 (0.93-1.19)



Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
Entire population	**14,148 (52.8)**	**840**	**39.7**	**12,628 (47.2)**	**753**	**37.4**	**1.06 (0.96-1.17)**
Men	9,091 (57.3)	624	46.5	6,761 (42.7)	486	45.4	1.02 (0.93-1.13)
Women	5,022 (46.1)	233	30.6	5,865 (53.9)	236	25.1	1.22 (1.04-1.45)
Age>=65 years	6,114 (59.1)	537	61.0	4,231 (40.9)	392	60.8	1.00 (0.89-1.12)
Age<65 years	8,002 (48.8)	322	26.3	8,404 (51.2)	316	23.0	1.15 (0.99-1.33)
January 2015 to June 2016	2,008 (30.2)	199	35.5	4,635 (69.8)	500	35.3	1.01 (0.88-1.16)
July 2016 to December 2018	12,193 (60.2)	529	42.5	8,058 (39.8)	381	39.3	1.07 (0.95-1.20)
History of CVD	4,428 (55.5)	552	87.6	3,552 (44.5)	425	77.4	1.13 (1.01-1.26)
No history of CVD	9,719 (51.7)	309	20.8	9,075 (48.3)	302	20.7	1.01 (0.88-1.16)
Metformin use at baseline	13,165 (56.6)	739	37.1	10,079 (43.4)	591	36.1	1.03 (0.93-1.14)
No metformin use at baseline	968 (27.5)	87	66.2	2,555 (72.5)	153	44.3	1.48 (1.10-2.01)
Insulin use at baseline	2,254 (39.0)	192	54.5	3,522 (61.0)	305	51.3	1.05 (0.90-1.24)
No insulin use at baseline	11,811 (56.3)	631	36.1	9,169 (43.7)	473	33.0	1.09 (0.98-1.21)

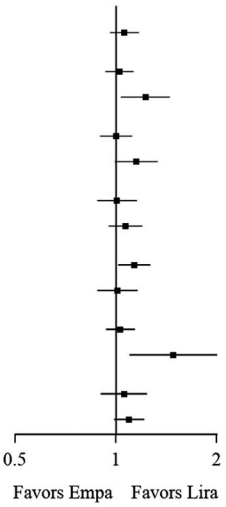


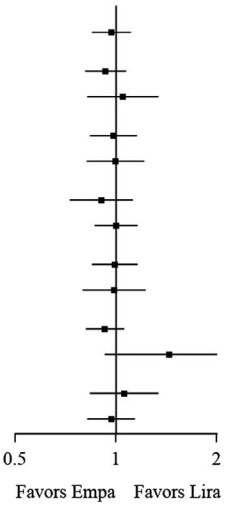
Figure 2. Rate of primary end points associated with new use of empagliflozin compared with new use of liraglutide: (A) expanded MACE, (B) HF hospitalization or all-cause death, (C) first HF hospitalization or initiation of loop diuretics.
Upper panels: on-treatment (OT) analyses, lower panels: intention-to-treat (ITT) analyses. CVD indicates cardiovascular disease; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; LD, loop diuretics; and MACE, major adverse cardiac events.

diagnosis codes associated with the all-cause hospitalization end point. As expected, a variety of different diagnosis codes known to be frequent in middle-aged and elderly hospitalized individuals were observed, including observation for suspected disease, abdominal/chest/musculoskeletal pain, infections, cardiopulmonary diseases, dyspnea, syncope, etc, with similar ranking of *International Classification of Diseases, Tenth Revision* (*ICD-10*) chapters and diagnoses observed in both cohorts. The aHRs for any HHF associated with empagliflozin were 0.98 (95% CI, 0.80–1.19) in OT and 1.09 (95% CI, 0.92–1.30) in ITT analyses.

The aHRs for empagliflozin versus liraglutide users across different subgroups are shown in Figure 2 for the 3 primary outcomes (secondary outcomes are shown in Figure S3). For most subgroups, results did not differ substantially from the

B HF hospitalization or death

Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
Entire population	**14,148 (52.8)**	**394**	**24.7**	**12,628 (47.2)**	**383**	**25.4**	**0.97 (0.85-1.11)**
Men	9,091 (57.3)	302	28.7	6,761 (42.7)	246	30.8	0.93 (0.81-1.07)
Women	5,022 (46.1)	98	17.9	5,865 (53.9)	120	17.0	1.05 (0.82-1.34)
Age>=65 years	6,114 (59.1)	281	42.2	4,231 (40.9)	219	42.8	0.98 (0.83-1.16)
Age<65 years	8,002 (48.8)	123	13.3	8,404 (51.2)	133	13.4	1.00 (0.82-1.22)
January 2015 to June 2016	2,008 (30.2)	80	20.8	4,635 (69.8)	219	23.2	0.90 (0.73-1.12)
July 2016 to December 2018	12,193 (60.2)	273	26.6	8,058 (39.8)	207	26.3	1.00 (0.86-1.16)
History of CVD	4,428 (55.5)	265	54.7	3,552 (44.5)	230	54.8	0.99 (0.85-1.16)
No history of CVD	9,719 (51.7)	138	12.3	9,075 (48.3)	136	12.5	0.99 (0.79-1.23)
Metformin use at baseline	13,165 (56.6)	341	22.5	10,079 (43.4)	299	24.3	0.93 (0.81-1.06)
No metformin use at baseline	968 (27.5)	43	46.4	2,555 (72.5)	82	31.9	1.44 (0.93-2.24)
Insulin use at baseline	2,254 (39.0)	96	36.9	3,522 (61.0)	155	34.5	1.06 (0.84-1.34)
No insulin use at baseline	11,811 (56.3)	288	21.6	9,169 (43.7)	239	22.3	0.97 (0.82-1.14)



Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
Entire population	**14,148 (52.8)**	**545**	**25.3**	**12,628 (47.2)**	**507**	**24.8**	**1.02 (0.91-1.14)**
Men	9,091 (57.3)	410	29.9	6,761 (42.7)	323	29.6	1.01 (0.90-1.15)
Women	5,022 (46.1)	144	18.6	5,865 (53.9)	164	17.3	1.07 (0.86-1.33)
Age>=65 years	6,114 (59.1)	390	43.5	4,231 (40.9)	297	45.1	0.96 (0.84-1.10)
Age<65 years	8,002 (48.8)	172	13.8	8,404 (51.2)	171	12.3	1.12 (0.93-1.35)
January 2015 to June 2016	2,008 (30.2)	131	22.9	4,635 (69.8)	332	22.9	1.00 (0.85-1.18)
July 2016 to December 2018	12,193 (60.2)	342	27.1	8,058 (39.8)	259	26.4	1.02 (0.88-1.17)
History of CVD	4,428 (55.5)	355	54.1	3,552 (44.5)	287	50.7	1.07 (0.93-1.22)
No history of CVD	9,719 (51.7)	201	13.4	9,075 (48.3)	202	13.7	0.98 (0.83-1.16)
Metformin use at baseline	13,165 (56.6)	460	22.7	10,079 (43.4)	394	23.7	0.96 (0.85-1.07)
No metformin use at baseline	968 (27.5)	69	51.5	2,555 (72.5)	110	31.2	1.65 (1.15-2.35)
Insulin use at baseline	2,254 (39.0)	132	36.5	3,522 (61.0)	207	34.0	1.07 (0.86-1.32)
No insulin use at baseline	11,811 (56.3)	397	22.4	9,169 (43.7)	318	21.9	1.02 (0.88-1.18)

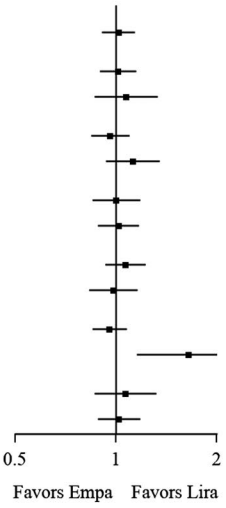


Figure 2. Continued

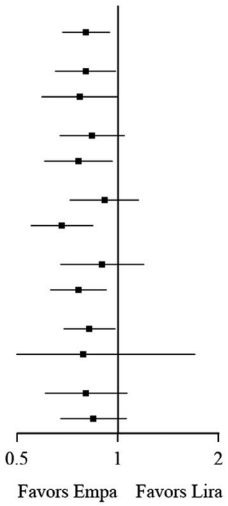
main analysis, when considering the limited statistical precision. Outcome aHRs tended to favor liraglutide in the small subgroup not using metformin at initiation, yet statistical precision was poor. Outcome aHRs tended to be slightly more in favor for empagliflozin when using an OT exposure definition, compared with the ITT analysis.

Post Hoc Sensitivity Analyses

Because loop diuretics may sometimes be used for severe hypertension, we repeated our analysis of the co-primary end point of first incident HHF or first loop-diuretic therapy restricted to patients with HF who were loop-diuretic naïve and had no previous hypertension diagnosis or antihypertensive therapy. In this IPWT weighted population, the aHRs of first incident HHF or loop-diuretic initiation associated with empagliflozin versus liraglutide were 0.77 (95% CI, 0.49–1.20) in OT and 0.76 (95% CI, 0.51–1.14) in ITT analyses. When restricting the any HHF outcome analyses to patients with HF who were loop-diuretic naïve (ie, the same denominator as for the first

C First HF or loop-diuretic

Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
No previous HHF or LD	**12,064 (54.2)**	**214**	**15.6**	**10,197 (45.8)**	**235**	**19.6**	**0.80 (0.68-0.94)**
Men	7,761 (59.0)	153	17.1	5,387 (41.0)	136	21.4	0.80 (0.65-0.99)
Women	4,269 (47.0)	60	12.8	4,805 (53.0)	95	16.8	0.77 (0.59-1.00)
Age>=65 years	4,805 (62.8)	122	23.1	2,850 (37.2)	95	27.7	0.84 (0.67-1.05)
Age<65 years	7,255 (49.7)	95	11.3	7,351 (50.3)	128	14.9	0.76 (0.60-0.96)
January 2015 to June 2016	1,730 (31.6)	63	19.0	3,746 (68.4)	159	21.2	0.91 (0.72-1.15)
July 2016 to December 2018	10,389 (61.5)	115	13.1	6,491 (38.5)	120	19.1	0.68 (0.55-0.84)
History of CVD	3,006 (58.5)	95	28.3	2,135 (41.5)	81	32.1	0.90 (0.67-1.20)
No history of CVD	9,052 (52.9)	121	11.7	8,062 (47.1)	147	15.4	0.76 (0.63-0.93)
Metformin use at baseline	11,345 (58.0)	200	15.3	8,202 (42.0)	185	18.7	0.82 (0.69-0.98)
No metformin use at baseline	703 (26.0)	13	18.5	1,999 (74.0)	46	23.9	0.79 (0.36-1.70)
Insulin use at baseline	1,720 (40.6)	50	25.2	2,512 (59.4)	101	31.9	0.80 (0.60-1.07)
No insulin use at baseline	10,264 (57.0)	158	13.7	7,736 (43.0)	144	16.1	0.84 (0.67-1.06)



Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
No previous HHF or LD	**12,064 (54.2)**	**315**	**17.3**	**10,197 (45.8)**	**326**	**20.0**	**0.87 (0.76-1.00)**
Men	7,761 (59.0)	219	18.9	5,387 (41.0)	194	22.4	0.86 (0.72-1.02)
Women	4,269 (47.0)	100	15.3	4,805 (53.0)	123	16.1	0.96 (0.76-1.21)
Age>=65 years	4,805 (62.8)	196	28.1	2,850 (37.2)	136	31.0	0.91 (0.76-1.09)
Age<65 years	7,255 (49.7)	128	11.4	7,351 (50.3)	170	14.2	0.81 (0.65-1.02)
January 2015 to June 2016	1,730 (31.6)	99	20.2	3,746 (68.4)	241	20.8	0.96 (0.80-1.17)
July 2016 to December 2018	10,389 (61.5)	153	14.3	6,491 (38.5)	160	20.4	0.70 (0.58-0.84)
History of CVD	3,006 (58.5)	133	29.7	2,135 (41.5)	106	30.9	0.98 (0.76-1.25)
No history of CVD	9,052 (52.9)	186	13.5	8,062 (47.1)	211	16.4	0.83 (0.70-0.98)
Metformin use at baseline	11,345 (58.0)	291	16.9	8,202 (42.0)	261	19.5	0.88 (0.76-1.01)
No metformin use at baseline	703 (26.0)	20	20.1	1,999 (74.0)	56	20.9	0.96 (0.53-1.74)
Insulin use at baseline	1,720 (40.6)	68	24.7	2,512 (59.4)	131	30.3	0.82 (0.64-1.05)
No insulin use at baseline	10,264 (57.0)	243	15.8	7,736 (43.0)	209	17.3	0.92 (0.77-1.11)

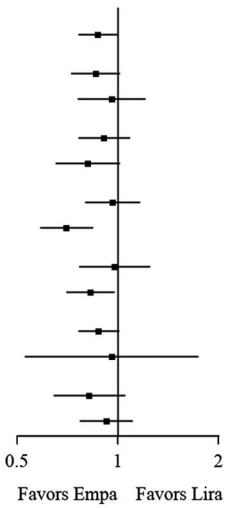


Figure 2. Continued

incident HHF or loop-diuretic composite end point), the aHRs for a first HHF associated with empagliflozin were 1.10 (95% CI, 0.73–1.66) in OT and 1.10 (95% CI, 0.78–1.54) in ITT analyses.

DISCUSSION

This population-based study shows that empagliflozin and liraglutide initiators in routine clinical care have comparable rates of expanded MACE outcomes and of HHF or all-cause death. Rates of a first HHF or loop-diuretic initiation in those with no previous HHF or loop-diuretic use were in favor of empagliflozin, as were rates of all-cause acute hospitalization.

Our real-life observational study has both strengths and weaknesses. A major strength is its setting within the comprehensive Danish public healthcare system, permitting a population-based design with inclusion of all patients with empagliflozin or liraglutide initiation in a well-defined geographical region. This largely eliminated patient selection problems affecting studies based on

given clinics, insurance programs, age groups, or sex. Accordingly, our data reflect actual population-based clinical practice in diabetes mellitus care.

A limitation in our study was the relatively short exposure time to the study drugs, that is, ≈1 to 1.5 years, with inherent uncertainty as to the long-term durability of the associations observed until longer-term follow-up study results become available. The overall accuracy of our results depends on the validity of diagnoses and prescriptions in the registries we used. Our algorithm for identifying diabetes mellitus through prescriptions has a positive predictive value of 95%.[30] Positive predictive values for important comorbidities including cardiovascular diseases are high in the Danish National Patient Registry.[31] Although initiation of oral loop-diuretic therapy is regarded as a reasonable and practical marker of incident HF in the outpatient setting,[26] the exact positive predictive value for HF is unknown. Moreover, prescription redemption is only a marker of actual drug consumption. We considered results arising from both OT and ITT analyses; an approach that has been recommended when evaluating the clinical effects of GLD, in light of the strengths and limitations inherited in each approach.[21] Although an OT analysis, which terminates exposure to a medication upon discontinuation, is often the approach of choice in observational studies of drug effects, it may be prone to bias from informative censoring if the discontinuation predicts future outcomes. An ITT approach, which carries forward the initial drug exposure status and disregards changes in treatment status over time, is not affected by informative censoring bias in the same way but might be biased through exposure misclassification that increases with longer follow-up periods.[21] Of note, we found rather similar aHRs for most outcomes when comparing empagliflozin and liraglutide with an OT and ITT approach, underscoring the robustness of our findings.

We were able to assess the role of a wide range of confounding factors. As in any observational study, we cannot exclude unmeasured or residual confounding. In particular, we lacked clinical data for detailed clinical and anthropometric measures including body mass index, other components of the metabolic syndrome, beta cell function, lifestyle factors, and exact socioeconomic measures. These factors may all be associated both with choice of empagliflozin versus liraglutide and likelihood of experiencing a clinical outcome. We adjusted by PS IPWT for numerous conditions that may have indicated or contraindicated drug use, including advanced age, cardiovascular, liver, and renal disease including estimated glomerular filtration rate, psychiatric morbidity, and markers of smoking and alcohol overuse, but we may have been unable to adjust for impact of less severe conditions treated by general practitioners. Ultimately, a high-quality active comparator randomized trial would be needed to draw firm conclusions about empagliflozin versus liraglutide effects on clinical outcomes in patients with type 2 diabetes mellitus.

Few, if any, comparable population-based studies have directly compared clinical outcomes in new users of empagliflozin versus liraglutide. Two network meta-analyses of randomized trials showed mixed results. Lorenzi et al evaluated 16 randomized controlled trials and concluded that liraglutide was generally associated with larger reductions in hemoglobin A1c than were SGLT2i, whereas weight reductions were comparable.[13] In contrast, Zaccardi et al suggested comparable hemoglobin A1c reductions with SGLT2i and GLP-1RA and slightly greater weight reduction for SGLT2i.[14] Finally, in 2 recent meta-analyses of CVOTs, GLP-1RA, and SGLT2i reduced MACE to a similar degree compared with placebo,[15,32] whereas SGLT2i had a larger effect than GLP-1RA on preventing HF[15,32] and renal outcomes.[15] In general, reductions in HF risk in individual trials have been larger for SGLT2i than for GLP-1RA, with an HHF relative risk with empagliflozin versus placebo of 0.65 (95% CI, 0.50–0.85) in EMPA-REG OUTCOME[4] compared with an HHF relative risk with liraglutide versus placebo of 0.87 (95% CI, 0.73–1.05) in LEADER.[5] Although the overall association with HHF in this study did not significantly differ between empagliflozin and liraglutide, the trial findings are in good accordance with our observation of a reduction of first incident HHF or loop-diuretic initiation, as a surrogate for HF, associated with empagliflozin use. As this end point excluded patients with prior HF or loop-diuretic use, it emphasizes the possible preventive benefits of treatment and the need for early consideration of cardioprotective therapies in patients with type 2 diabetes mellitus. Finally, slightly lower rates of all-cause hospitalizations with empagliflozin use were also observed in the EMPA-REG-OUTCOME trial.[4] All-cause hospitalization by definition reflects a broad set of clinical outcomes requiring inpatient care, especially in elderly individuals. Nonetheless, it is a relevant and important measure for healthcare providers and patients at risk for multiple comorbidities, as compared with disease-specific outcomes.

Differences exist in the proportion with cardiovascular disease and other comorbidities between patient populations in CVOTs and the broad patient population represented in real-world settings.[16,33] Our findings suggest that the outcome results from the CVOTs EMPA-REG OUTCOME and LEADER translate into similar results in a much broader population in terms of underlying cardiovascular risk. The present results also support the equal position of the 2 drugs in recent updated treatment guidelines for type 2 diabetes mellitus.[1,10,11] Future real-world studies may further improve our understanding of the potential adverse effects associated with use of empagliflozin and liraglutide in

everyday clinical practice. At the same time, our data do not replace the need for high-quality, randomized, active comparator trials addressing clinically relevant questions on how and when to use these 2 drugs.

CONCLUSIONS

In conclusion, this population-based study provides evidence that empagliflozin and liraglutide initiators in routine clinical care have comparable rates of expanded MACE, HF hospitalization, and all-cause death. Rates of first HF hospitalization or loop-diuretic initiation among individuals who are HF naïve appear lower in empagliflozin initiators, coherent with clinical trials findings. Rates of all-cause hospitalizations were slightly lower in empagliflozin versus liraglutide initiators, and future studies should shed light on the exact reasons behind this finding.

ARTICLE INFORMATION

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Affiliations

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark (R.W.T., J.S.K., J.K., L.M.B., H.T.S.); Boehringer Ingelheim A/S, Copenhagen, Denmark (M.L., P.H.H.); Boehringer Ingelheim AB, Stockholm, Sweden (O.V.); and Boehringer Ingelheim International GmbH, Ingelheim, Germany (A.U.).

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Disclosures

Dr Lajer, Mrs Holmgaard, Dr Vedin, and Dr Ustyugova are employees of Boehringer Ingelheim. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S4
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Codes used in study

Anatomical Therapeutic Chemical (ATC) codes for diabetes drugs	
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

DNPR=Danish National Patient Registry. CRS=Civil Registration System.

International Classification of Diseases version 10 (ICD-10) codes for primary 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	DNPR	Various diagnoses and procedures	
Hospital admission with HF	DNPR	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, CRS	Various diagnoses and procedures **OR** All-cause death	
All-cause death	CRS	All-cause death	

International Classification of Diseases version 10 (ICD-10) 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, 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	Atherosclerotic peripheral vascular 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 + procedure codes	E102, E112, DE142, I120, N083, N06, N17, N18, N19, R809 BJFD2	
Creatinine (eGFR)	Laboratory databases	NPU18016, NPU01807, NPU04998, NPU09101, 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, 1807, 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	Prescription registry	N05A, N05BA, N05CD, N05CF, N06A	
Antiplatelet drugs	Prescription registry	B01AC06, N02BA01, B01AC30, B01AC07, B01AC22, B01AC04, B01AC24, B01AC25	
Statins	Prescription registry	C10AA, C10BA, C10BX, A10BH51	
Any antihypertensive drugs	Prescription registry	C02, C03A, C03B, C03X, C07, C08, C09	
ACE inhibitors	Prescription registry	C09A, C09B	
ARB	Prescription registry	C09C, C09D	
Marital status	CRS		Current marital status (if no current status in CRS, last value carried forward)

Table S2. Absolute risk differences at three years of outcome events associated with use of empagliflozin compared with use of liraglutide in PS balanced populations. On-treatment (OT) analyses and intention-to-treat (ITT) analyses.

		Empagliflozin use	Liraglutide use	Empagliflozin vs Liraglutide
Outcome	**OT or ITT analysis**	**3-year outcome risk, %**	**3-year outcome risk, %**	**Absolute risk difference, % (95% CI)**
Expanded MACE	**OT**	11.6	10.9	0.6 (-1.1- 2.4)
	ITT	11.5	10.6	0.9 (-0.4- 2.1)
HHF or death	**OT**	7.9	7.4	0.5 (-1.0- 2.0)
	ITT	7.8	7.1	0.7 (-0.4- 1.7)
First HHF or loop-diuretic	**OT**	5.0	6.5	-1.4 (-3.0- 0.1)
	ITT	5.5	6.2	-0.7 (-1.8- -0.4)
All-cause hospitalization or death	**OT**	41.0	43.0	-2.0 (-4.6- 0.5)
	ITT	41.6	43.3	-1.7 (-3.6- 0.2)
All-cause hospitalization	**OT**	40.2	42.0	-1.8 (-4.3- -0.7)
	ITT	40.8	42.5	-1.7 (-3.6- 0.2)
All-cause death	**OT**	4.9	5.1	-0.2 (-1.5- 1.1)
	ITT	5.0	4.9	0.1 (-0.7- 1.0)
HHF	**OT**	3.7	2.9	0.8 (-0.1- 1.8)
	ITT	3.4	2.8	0.6 (-0.0- 1.3)

Table S3. The most common primary discharge diagnosis categories associated with all-cause hospitalization endpoint, ranked after frequency by International Classification of Diseases version 10 (ICD-10) chapter.

Empagliflozin use (N=12,631 patients, n=2,788 all-cause hospitalizations)			Liraglutide use (N=14,130 patients, n=2,816 all-cause hospitalizations)		
ICD-10 chapter	**n of hospitalizations within each ICD-10 chapter**	**% of hospitalizations within each ICD-10 chapter**	**ICD-10 chapter**	**n of hospitalizations within each ICD-10 chapter**	**% of hospitalizations within each ICD-10 chapter**
IX: Diseases of the circulatory system	505	16.26	XVIII: Symptoms, signs and abnormal clinical and laboratory findings	672	17.03
XVIII: Symptoms, signs and abnormal clinical and laboratory findings	469	15.10	IX: Diseases of the circulatory system	476	12.06
XXI: Factors influencing health status and contact with health services	412	13.26	XXI: Factors influencing health status and contact with health services	446	11.30
XIII: Diseases of the musculoskeletal system and connective tissue	263	8.47	IV: Endocrine, nutritional and metabolic disorders	355	8.99
IV: Endocrine, nutritional and metabolic disorders	224	7.21	XIII: Diseases of the musculoskeletal system and connective tissue	342	8.66
XI: Diseases of the digestive system	202	6.50	X: Diseases of the respiratory system	270	6.84
XIX: Injury and poisoning	192	6.18	XI: Diseases of the digestive system	260	6.59
X: Diseases of the respiratory system	185	5.96	XIV: Diseases of the genitourinary system	237	6.00
XIV: Diseases of the genitourinary system	180	5.80	XIX: Injury and poisoning	208	5.27
II: Neoplasms	151	4.86	II: Neoplasms	181	4.59
I: Certain infectious and parasitic diseases	122	3.93	I: Certain infectious and parasitic diseases	179	4.54
VI: Diseases of the nervous system	88	2.83	VI: Diseases of the nervous system	106	2.69
XII: Diseases of the skin and subcutaneous tissue	45	1.45	XII: Diseases of the skin and subcutaneous tissue	96	2.43
VII: Diseases of the eye and adnexa	29	0.93	XV: Pregnancy, childbirth and the puerperium	34	0.86

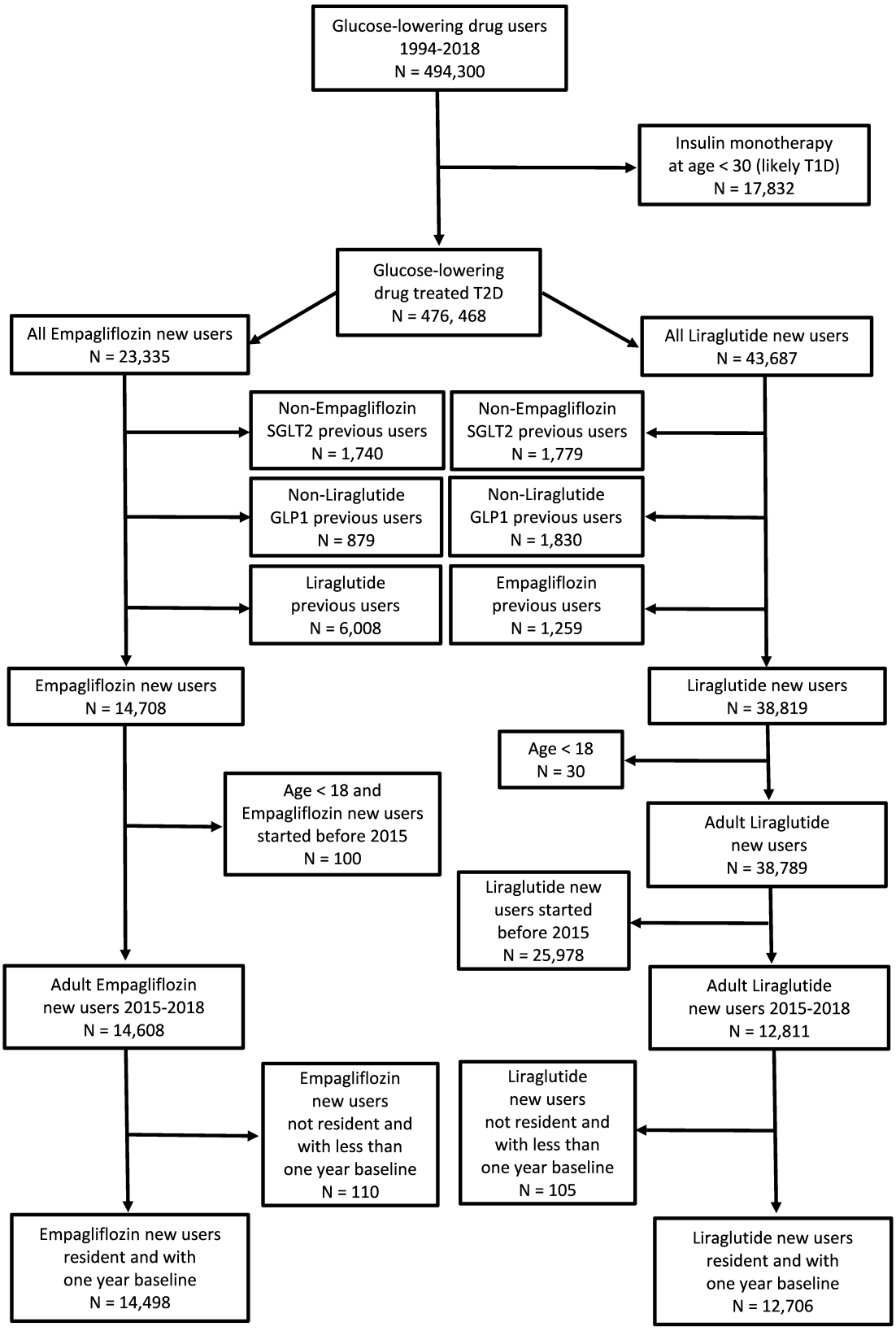
V: Mental and behavioral disorders	19	0.61	VII: Diseases of the eye and adnexa	28	0.71
III: Hematological diseases	11	0.35	III: Hematological diseases	27	0.68
VIII: Diseases of the ear and mastoid process	6	0.19	VIII: Diseases of the ear and mastoid process	15	0.38
XV: Pregnancy, childbirth and the puerperium	<5	-	V: Mental and behavioral disorders	13	0.33

Table S4. The 25 most common International Classification of Diseases version 10 (ICD-10) primary discharge diagnoses at the three-digit level associated with all-cause hospitalization endpoint, ranked after frequency.

Empagliflozin use (N=12,631 patients, n=2,788 all-cause hospitalizations)			Liraglutide use (N=14,130 patients, n=2,816 all-cause hospitalizations)		
Primary diagnosis (ICD-10 code)	**n of hospitalizations with each primary diagnosis**	**% of all hospitalizations**	**Primary diagnosis (ICD-10 code)**	**n of hospitalizations with each primary diagnosis**	**% of all hospitalizations**
Medical observation and evaluation for suspected diseases and conditions, ruled out (Z03)	332	10.69	Medical observation and evaluation for suspected diseases and conditions, ruled out (Z03)	333	8.44
Type 2 diabetes mellitus (E11)	110	3.54	Abdominal and pelvic pain (R10)	142	3.60
Abdominal and pelvic pain (R10)	106	3.41	Obesity (E66)	126	3.19
Atrial fibrillation and flutter (I48)	84	2.70	Type 2 diabetes mellitus (E11)	95	2.41
Angina pectoris (I20)	68	2.19	Pneumonia, organism unspecified (J18)	85	2.15
Gonarthrosis [arthrosis of knee] (M17)	67	2.16	Pain in throat and chest (R07)	83	2.10
Pain in throat and chest (R07)	67	2.16	Atrial fibrillation and flutter (I48)	77	1.95
Pneumonia, organism unspecified (J18)	61	1.96	Gonarthrosis [arthrosis of knee] (M17)	69	1.75
Acute myocardial infarction (I21)	50	1.61	Angina pectoris (I20)	59	1.49
Chronic ischaemic heart disease (I25)	50	1.61	Dyspnoea (R06)	57	1.44
Coxarthrosis [arthrosis of hip] (M16)	46	1.48	Syncope and collapse (R55)	56	1.42
Cerebral infarction (I63)	42	1.35	Acute myocardial infarction (I21)	50	1.27
Heart failure (I50)	40	1.29	Cerebral infarction (I63)	47	1.19
Other sepsis (A41)	33	1.06	Cutaneous abscess, furuncle and carbuncle (L02)	47	1.19
Erysipelas (A46)	33	1.06	Other sepsis (A41)	46	1.17
Other chronic obstructive pulmonary disease (J44)	32	1.03	Erysipelas (A46)	43	1.09
Syncope and collapse (R55)	32	1.03	Calculus of kidney and ureter (N20)	43	1.09
Transient cerebral ischaemic attacks and	29	0.93	Chronic ischaemic heart disease (I25)	41	1.04

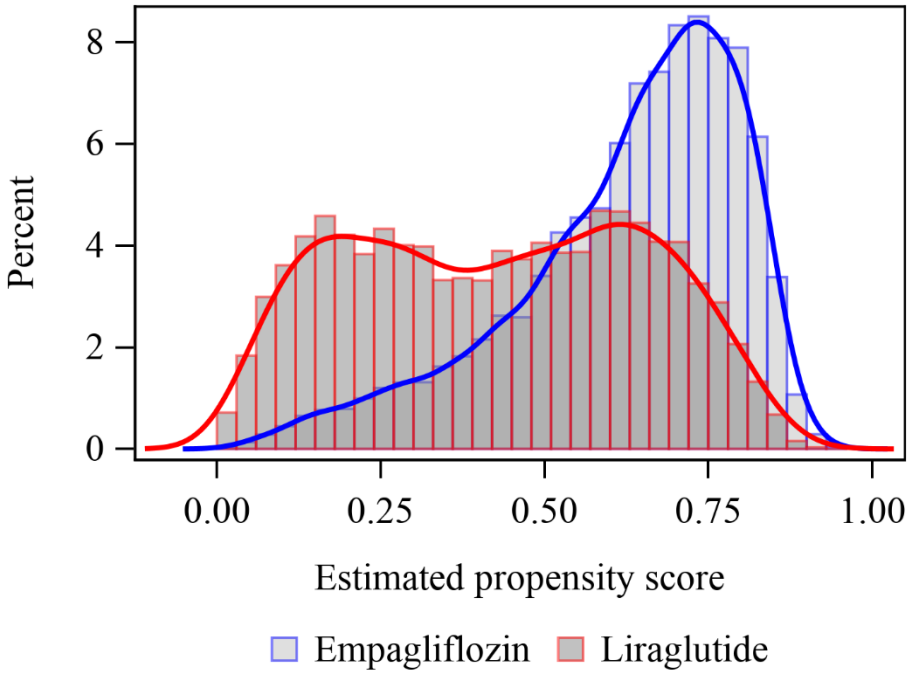
related syndromes (G45)					
Calculus of kidney and ureter (N20)	29	0.93	Coxarthrosis [arthrosis of hip] (M16)	40	1.01
Urinary tract infection, site not specified (N39)	29	0.93	Other chronic obstructive pulmonary disease (J44)	39	0.99
Dyspnoea (R06)	29	0.93	Respiratory failure, not elsewhere classified (J96)	38	0.96
Malaise and fatigue (R53)	29	0.93	Urinary tract infection, site not specified (N39)	38	0.96
Cutaneous abscess, furuncle and carbuncle (L02)	28	0.90	Heart failure (I50)	37	0.94
Other disorders of fluid, electrolyte and acid-base balance (E87)	27	0.87	Other gastroenteritis and colitis of infectious and unspecified origin (A09)	36	0.91
Elevated blood glucose level (R73)	25	0.80	Cholelithiasis (K80)	34	0.86

Figure S1. Flow chart of the study population



The two exclusion categories of empagliflozin users aged less than 18 years and empagliflozin users starting therapy before 2015 were merged in in one box, due to Danish data privacy protection regulations (numbers too small to be legally displayed for one of the categories). T1D=type 1 diabetes. T2D=type 2 diabetes.

Figure S2. Propensity score distributions before and after weighting.



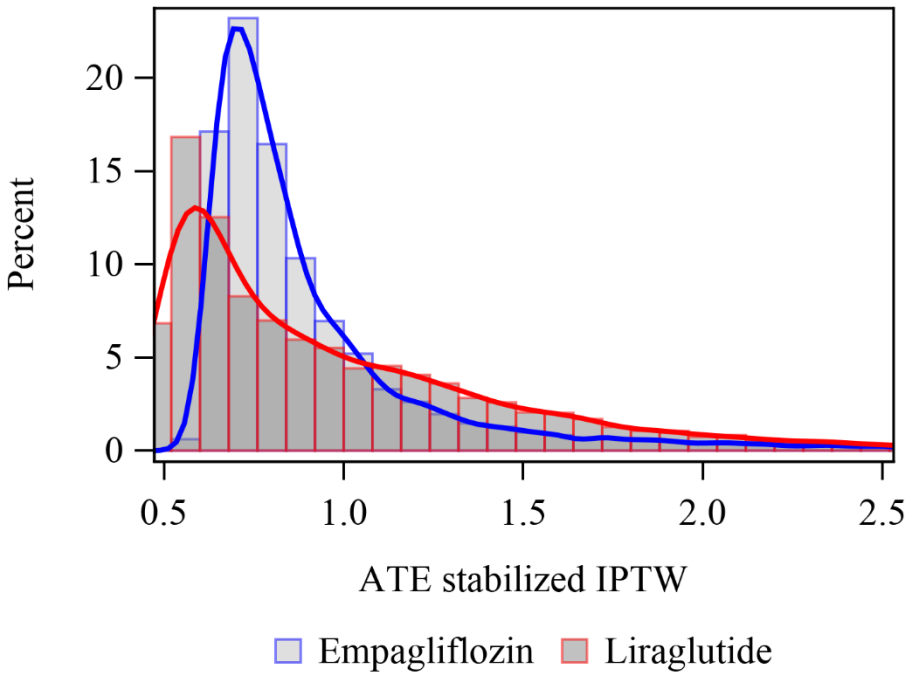


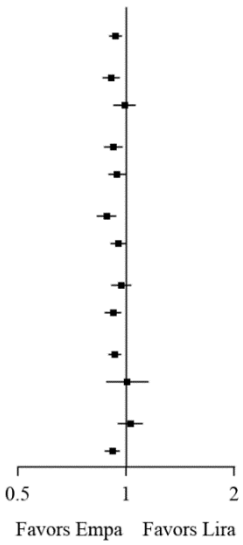
Figure S3. Subgroup analyses for secondary study outcomes.

Upper panels: on-treatment (OT) analyses, lower panels: intention-to-treat (ITT) analyses.

A All-cause hospitalization or death

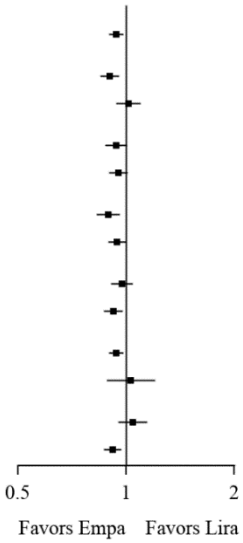
Subgroups	Empagliflozin			Liraglutide			HR (95% CI)
	Patients (%)	Events	Events per 1000 py	Patients (%)	Events	Events per 1000 py	
Entire population	**14,148 (52.8)**	**2875**	**210.7**	**12,628 (47.2)**	**2845**	**225.0**	**0.93 (0.89-0.98)**
Men	9,091 (57.3)	1859	206.9	6,761 (42.7)	1560	232.8	0.89 (0.84-0.95)
Women	5,022 (46.1)	1015	218.4	5,865 (53.9)	1265	212.1	1.01 (0.94-1.10)
Age>=65 years	6,114 (59.1)	1490	268.5	4,231 (40.9)	1181	284.6	0.93 (0.87-1.00)
Age<65 years	8,002 (48.8)	1415	177.0	8,404 (51.2)	1593	186.9	0.95 (0.89-1.01)
January 2015 to June 2016	2,008 (30.2)	587	185.4	4,635 (69.8)	1560	208.9	0.88 (0.82-0.95)
July 2016 to December 2018	12,193 (60.2)	2038	225.4	8,058 (39.8)	1596	233.7	0.94 (0.89-1.00)
History of CVD	4,428 (55.5)	1299	341.0	3,552 (44.5)	1146	348.3	0.97 (0.90-1.04)
No history of CVD	9,719 (51.7)	1604	163.6	9,075 (48.3)	1669	177.9	0.92 (0.87-0.98)
Metformin use at baseline	13,165 (56.6)	2617	202.1	10,079 (43.4)	2241	216.2	0.93 (0.89-0.98)
No metformin use at baseline	968 (27.5)	244	313.7	2,555 (72.5)	625	301.8	1.04 (0.89-1.21)
Insulin use at baseline	2,254 (39.0)	604	288.4	3,522 (61.0)	990	271.3	1.04 (0.95-1.14)
No insulin use at baseline	11,811 (56.3)	2210	192.1	9,169 (43.7)	1913	210.7	0.91 (0.86-0.97)

Subgroups	Empagliflozin			Liraglutide			HR (95% CI)
	Patients (%)	Events	Events per 1000 py	Patients (%)	Events	Events per 1000 py	
Entire population	**14,148 (52.8)**	**3563**	**202.0**	**12,628 (47.2)**	**3514**	**215.6**	**0.93 (0.90-0.97)**
Men	9,091 (57.3)	2274	200.6	6,761 (42.7)	1919	219.7	0.91 (0.86-0.96)
Women	5,022 (46.1)	1282	206.5	5,865 (53.9)	1571	207.8	0.99 (0.92-1.06)
Age>=65 years	6,114 (59.1)	1828	257.3	4,231 (40.9)	1416	279.0	0.92 (0.87-0.98)
Age<65 years	8,002 (48.8)	1766	169.8	8,404 (51.2)	2026	179.0	0.94 (0.89-1.00)
January 2015 to June 2016	2,008 (30.2)	793	177.2	4,635 (69.8)	2125	198.3	0.88 (0.83-0.94)
July 2016 to December 2018	12,193 (60.2)	2392	221.4	8,058 (39.8)	1876	227.1	0.95 (0.90-1.00)
History of CVD	4,428 (55.5)	1572	322.2	3,552 (44.5)	1376	330.8	0.97 (0.91-1.03)
No history of CVD	9,719 (51.7)	2025	159.2	9,075 (48.3)	2103	172.7	0.92 (0.87-0.97)
Metformin use at baseline	13,165 (56.6)	3227	193.8	10,079 (43.4)	2771	207.4	0.93 (0.89-0.97)
No metformin use at baseline	968 (27.5)	298	287.7	2,555 (72.5)	760	287.7	1.01 (0.88-1.15)
Insulin use at baseline	2,254 (39.0)	741	266.4	3,522 (61.0)	1198	256.3	1.03 (0.95-1.11)
No insulin use at baseline	11,811 (56.3)	2751	186.3	9,169 (43.7)	2383	203.3	0.91 (0.87-0.96)

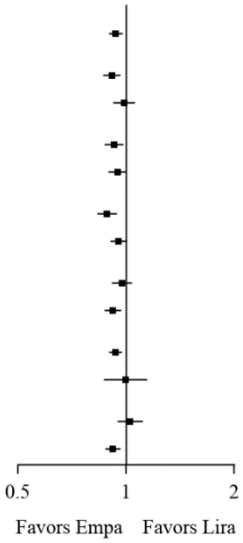


B All-cause hospitalization

Subgroups	Empagliflozin			Liraglutide			HR (95% CI)
	Patients (%)	Events	Events per 1000 py	Patients (%)	Events	Events per 1000 py	
Entire population	**14,148 (52.8)**	**2832**	**207.6**	**12,628 (47.2)**	**2793**	**220.9**	**0.94 (0.89-0.98)**
Men	9,091 (57.3)	1833	203.9	6,761 (42.7)	1529	228.1	0.90 (0.85-0.95)
Women	5,022 (46.1)	1000	215.0	5,865 (53.9)	1246	209.0	1.01 (0.94-1.10)
Age>=65 years	6,114 (59.1)	1460	263.2	4,231 (40.9)	1152	277.5	0.94 (0.88-1.00)
Age<65 years	8,002 (48.8)	1401	175.2	8,404 (51.2)	1573	184.7	0.95 (0.89-1.01)
January 2015 to June 2016	2,008 (30.2)	582	184.0	4,635 (69.8)	1535	205.5	0.89 (0.83-0.96)
July 2016 to December 2018	12,193 (60.2)	2003	221.5	8,058 (39.8)	1565	229.1	0.94 (0.89-1.00)
History of CVD	4,428 (55.5)	1283	336.9	3,552 (44.5)	1125	341.8	0.97 (0.91-1.04)
No history of CVD	9,719 (51.7)	1577	160.8	9,075 (48.3)	1639	174.7	0.92 (0.87-0.98)
Metformin use at baseline	13,165 (56.6)	2580	199.2	10,079 (43.4)	2198	212.1	0.94 (0.89-0.98)
No metformin use at baseline	968 (27.5)	238	307.1	2,555 (72.5)	616	297.5	1.03 (0.88-1.20)
Insulin use at baseline	2,254 (39.0)	592	282.9	3,522 (61.0)	970	265.6	1.04 (0.95-1.14)
No insulin use at baseline	11,811 (56.3)	2180	189.5	9,169 (43.7)	1881	207.2	0.92 (0.87-0.97)

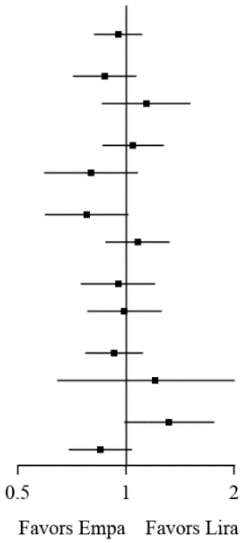


Subgroups	Empagliflozin			Liraglutide			HR (95% CI)
	Patients (%)	Events	Events per 1000 py	Patients (%)	Events	Events per 1000 py	
Entire population	**14,148 (52.8)**	**3506**	**198.8**	**12,628 (47.2)**	**3452**	**211.8**	**0.94 (0.90-0.98)**
Men	9,091 (57.3)	2242	197.8	6,761 (42.7)	1883	215.5	0.91 (0.86-0.97)
Women	5,022 (46.1)	1258	202.6	5,865 (53.9)	1547	204.7	0.99 (0.92-1.06)
Age>=65 years	6,114 (59.1)	1790	251.9	4,231 (40.9)	1382	272.2	0.93 (0.87-0.98)
Age<65 years	8,002 (48.8)	1746	167.9	8,404 (51.2)	2002	176.9	0.94 (0.89-1.00)
January 2015 to June 2016	2,008 (30.2)	782	174.7	4,635 (69.8)	2087	194.7	0.88 (0.83-0.94)
July 2016 to December 2018	12,193 (60.2)	2349	217.5	8,058 (39.8)	1845	223.3	0.95 (0.90-1.00)
History of CVD	4,428 (55.5)	1550	317.6	3,552 (44.5)	1351	324.8	0.97 (0.91-1.04)
No history of CVD	9,719 (51.7)	1989	156.4	9,075 (48.3)	2067	169.8	0.92 (0.87-0.97)
Metformin use at baseline	13,165 (56.6)	3181	191.0	10,079 (43.4)	2723	203.8	0.93 (0.89-0.97)
No metformin use at baseline	968 (27.5)	289	278.9	2,555 (72.5)	745	282.0	0.99 (0.87-1.14)
Insulin use at baseline	2,254 (39.0)	726	260.9	3,522 (61.0)	1175	251.5	1.02 (0.94-1.11)
No insulin use at baseline	11,811 (56.3)	2711	183.6	9,169 (43.7)	2343	199.9	0.92 (0.87-0.96)

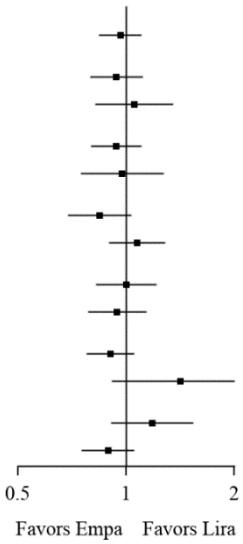


C All-cause death

Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
Entire population	**14,148 (52.8)**	**234**	**14.5**	**12,628 (47.2)**	**234**	**15.4**	**0.95 (0.81-1.11)**
Men	9,091 (57.3)	163	15.4	6,761 (42.7)	143	17.7	0.87 (0.71-1.07)
Women	5,022 (46.1)	72	13.1	5,865 (53.9)	83	11.6	1.14 (0.86-1.51)
Age>=65 years	6,114 (59.1)	195	29.0	4,231 (40.9)	144	27.8	1.04 (0.86-1.27)
Age<65 years	8,002 (48.8)	51	5.5	8,404 (51.2)	70	7.0	0.80 (0.59-1.08)
January 2015 to June 2016	2,008 (30.2)	43	11.1	4,635 (69.8)	143	15.0	0.78 (0.59-1.01)
July 2016 to December 2018	12,193 (60.2)	171	16.6	8,058 (39.8)	124	15.5	1.08 (0.88-1.32)
History of CVD	4,428 (55.5)	127	25.8	3,552 (44.5)	117	27.2	0.95 (0.75-1.20)
No history of CVD	9,719 (51.7)	110	9.8	9,075 (48.3)	109	10.0	0.99 (0.78-1.25)
Metformin use at baseline	13,165 (56.6)	209	13.7	10,079 (43.4)	185	14.9	0.92 (0.77-1.11)
No metformin use at baseline	968 (27.5)	22	22.6	2,555 (72.5)	48	18.7	1.20 (0.64-2.25)
Insulin use at baseline	2,254 (39.0)	56	21.5	3,522 (61.0)	75	16.5	1.31 (0.98-1.75)
No insulin use at baseline	11,811 (56.3)	170	12.7	9,169 (43.7)	162	15.0	0.85 (0.69-1.04)

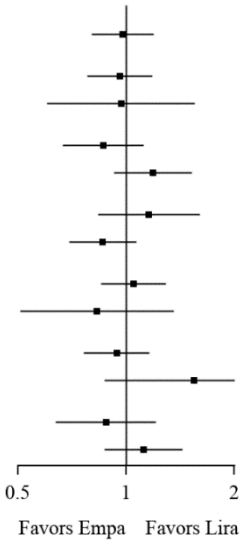


Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
Entire population	**14,148 (52.8)**	**334**	**15.3**	**12,628 (47.2)**	**332**	**16.1**	**0.96 (0.84-1.10)**
Men	9,091 (57.3)	233	16.7	6,761 (42.7)	201	18.1	0.94 (0.79-1.11)
Women	5,022 (46.1)	103	13.2	5,865 (53.9)	120	12.6	1.05 (0.82-1.35)
Age>=65 years	6,114 (59.1)	267	29.2	4,231 (40.9)	210	31.4	0.94 (0.80-1.10)
Age<65 years	8,002 (48.8)	81	6.5	8,404 (51.2)	94	6.7	0.97 (0.75-1.27)
January 2015 to June 2016	2,008 (30.2)	76	13.1	4,635 (69.8)	239	16.3	0.84 (0.69-1.03)
July 2016 to December 2018	12,193 (60.2)	217	17.1	8,058 (39.8)	159	16.1	1.07 (0.90-1.29)
History of CVD	4,428 (55.5)	177	26.2	3,552 (44.5)	156	26.7	1.00 (0.82-1.22)
No history of CVD	9,719 (51.7)	161	10.7	9,075 (48.3)	168	11.3	0.94 (0.78-1.14)
Metformin use at baseline	13,165 (56.6)	285	13.9	10,079 (43.4)	260	15.5	0.90 (0.78-1.05)
No metformin use at baseline	968 (27.5)	39	28.6	2,555 (72.5)	73	20.4	1.41 (0.91-2.19)
Insulin use at baseline	2,254 (39.0)	80	21.9	3,522 (61.0)	117	18.8	1.18 (0.91-1.54)
No insulin use at baseline	11,811 (56.3)	242	13.5	9,169 (43.7)	223	15.2	0.89 (0.75-1.05)



D HF hospitalization

Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
Entire population	**14,148 (52.8)**	**186**	**11.6**	**12,628 (47.2)**	**177**	**11.8**	**0.98 (0.80-1.19)**
Men	9,091 (57.3)	160	15.3	6,761 (42.7)	126	15.8	0.96 (0.78-1.18)
Women	5,022 (46.1)	31	5.6	5,865 (53.9)	40	5.7	0.97 (0.60-1.55)
Age>=65 years	6,114 (59.1)	103	15.4	4,231 (40.9)	90	17.6	0.86 (0.66-1.12)
Age<65 years	8,002 (48.8)	82	8.9	8,404 (51.2)	74	7.4	1.19 (0.92-1.53)
January 2015 to June 2016	2,008 (30.2)	45	11.6	4,635 (69.8)	92	9.7	1.16 (0.83-1.60)
July 2016 to December 2018	12,193 (60.2)	117	11.4	8,058 (39.8)	101	12.8	0.86 (0.69-1.07)
History of CVD	4,428 (55.5)	160	33.2	3,552 (44.5)	131	31.2	1.05 (0.85-1.29)
No history of CVD	9,719 (51.7)	31	2.7	9,075 (48.3)	36	3.3	0.83 (0.51-1.36)
Metformin use at baseline	13,165 (56.6)	156	10.3	10,079 (43.4)	133	10.8	0.94 (0.76-1.16)
No metformin use at baseline	968 (27.5)	24	25.5	2,555 (72.5)	42	16.3	1.54 (0.87-2.72)
Insulin use at baseline	2,254 (39.0)	49	18.8	3,522 (61.0)	94	20.9	0.88 (0.64-1.21)
No insulin use at baseline	11,811 (56.3)	131	9.8	9,169 (43.7)	93	8.7	1.12 (0.87-1.43)



Subgroups	Empagliflozin Patients (%)	Empagliflozin Events	Empagliflozin Events per 1000 py	Liraglutide Patients (%)	Liraglutide Events	Liraglutide Events per 1000 py	HR (95% CI)
Entire population	**14,148 (52.8)**	**251**	**11.7**	**12,628 (47.2)**	**216**	**10.6**	**1.09 (0.92-1.30)**
Men	9,091 (57.3)	207	15.1	6,761 (42.7)	153	14.0	1.07 (0.88-1.29)
Women	5,022 (46.1)	52	6.8	5,865 (53.9)	50	5.3	1.26 (0.85-1.87)
Age>=65 years	6,114 (59.1)	147	16.4	4,231 (40.9)	112	17.0	0.95 (0.76-1.19)
Age<65 years	8,002 (48.8)	107	8.6	8,404 (51.2)	87	6.3	1.36 (1.08-1.71)
January 2015 to June 2016	2,008 (30.2)	69	12.0	4,635 (69.8)	120	8.3	1.37 (1.06-1.76)
July 2016 to December 2018	12,193 (60.2)	145	11.5	8,058 (39.8)	122	12.5	0.89 (0.73-1.09)
History of CVD	4,428 (55.5)	211	32.2	3,552 (44.5)	157	27.7	1.14 (0.94-1.38)
No history of CVD	9,719 (51.7)	48	3.2	9,075 (48.3)	47	3.2	1.00 (0.68-1.47)
Metformin use at baseline	13,165 (56.6)	210	10.4	10,079 (43.4)	164	9.8	1.04 (0.87-1.26)
No metformin use at baseline	968 (27.5)	34	25.1	2,555 (72.5)	49	14.0	1.77 (1.09-2.87)
Insulin use at baseline	2,254 (39.0)	65	18.0	3,522 (61.0)	112	18.5	0.95 (0.71-1.28)
No insulin use at baseline	11,811 (56.3)	178	10.0	9,169 (43.7)	116	8.0	1.24 (0.99-1.56)