



# Healthcare Resource Utilization and Costs for Empagliflozin Versus Glucagon-Like Peptide-1 Receptor Agonists in Routine Clinical Care in Denmark

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## ABSTRACT

**Introduction:** The sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin has shown reductions in major adverse cardiac events similar to glucagon-like peptide-1 receptor agonists (GLP-1RAs). However, evidence is limited about how these therapies compare regarding overall healthcare resource utilization and costs in routine clinical care.

**Methods:** We conducted a comparative cohort study based on linked prospective healthcare databases for the entire population of Denmark during 2015–2018. We included 13,747 new

users of empagliflozin and 13,249 new users of GLP-1RAs. Propensity scores were applied to balance potential confounders across the two treatment groups through inverse probability treatment weighting (IPTW). We assessed directly referable costs per person-year associated with healthcare resource utilization (inpatient, emergency room, and outpatient clinic hospital care, primary care health services, and prescription medication costs at pharmacies) among drug initiators while on-treatment.

**Results:** The two IPTW cohorts were well balanced at baseline (median age 61 years, 60% men, diabetes duration 6.7 years, 19% with pre-existing ischemic heart disease, 8% with pre-existing cerebrovascular disease), with similar healthcare costs in the previous year. During follow-up, average on-treatment costs per person-year were very similar among empagliflozin and GLP-1 RA initiators for the following services: inpatient hospitalizations (13,565 DKK versus 13,275 DKK), hospital outpatient clinic visits (12,007 DKK versus 12,152 DKK), emergency room visits (370 DKK versus 399 DKK), and primary care services (4108 DKK versus 4302 DKK). Total costs for any prescription drugs were clearly lower for empagliflozin initiators than for GLP-1 RA initiators (8946 DKK versus 14,029 DKK). In sum, overall healthcare costs on-treatment were lower for empagliflozin initiators (38,995 DKK per person-year) than for GLP-1RA initiators (44,157 DKK per person-year).

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**Conclusions:** In this nationwide population-based cohort study, average healthcare costs after drug initiation and while on treatment were lower for empagliflozin initiators than for GLP-1RAs initiators, driven by lower drug costs. **Registration:** The study protocol and analysis plan have been registered on the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) (<http://www.encepp.eu/encepp/viewResource.htm?id=37726>, first protocol registration 4 June 2019), and on [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT03993132) (<https://clinicaltrials.gov/ct2/show/NCT03993132>, first posted 20 June 2019).

**Keywords:** Type 2 diabetes; Comparative effectiveness; Real-world data; Economy; Health services; Cohort; Empagliflozin; GLP-1 receptor agonist

### Key Summary Points

#### *Why carry out this study?*

Clinical trial and routine clinical care observational evidence have shown that the SGLT2 inhibitor empagliflozin and GLP-1 receptor agonists reduce major adverse cardiac events to a similar degree.

However, evidence is limited on how these therapies compare regarding overall healthcare resource utilization and costs.

To examine this further, we conducted a comparative cohort study following 13,747 new users of empagliflozin and 13,249 new users of GLP-1 receptor agonists in routine clinical care. We applied propensity-score balancing and investigated directly referable healthcare costs per person-year after drug initiation.

#### *What was learned from the study?*

The average direct healthcare costs after drug initiation and while on treatment were lower for empagliflozin initiators than for GLP-1 receptor agonist initiators.

Hospital and primary care healthcare resource utilization was remarkably similar in the two groups, with cost differences entirely driven by lower costs of prescription drugs among empagliflozin users.

## INTRODUCTION

Patients with type 2 diabetes have recently experienced major reductions in risk of cardiovascular disease (CVD) and mortality compared with the general population [1]. Still, CVD remains the most frequent cause of mortality in patients with type 2 diabetes [2]. The advent of two new classes of glucose-lowering drugs (GLDs), the sodium-glucose cotransporter-2 inhibitors (SGLT2is) and the glucagon-like peptide-1 receptor agonists (GLP-1RAs), has led to a paradigm shift in type 2 diabetes treatment [3] since these drugs may reduce CVD risk and mortality effectively [4–6]. In 2015, the EMPA-REG OUTCOME trial [7] of empagliflozin in type 2 diabetes patients with established CVD was the first large cardiovascular outcome trial (CVOT) to show a significantly reduced risk of major adverse cardiac events (MACE) and all-cause death. This trial was followed by other large CVOTs with several other types of SGLT2is and GLP-1RAs, conducted in type 2 diabetes populations mostly at high CVD risk. These later trials demonstrated varying degrees of CVD risk reductions [4–6]. Accordingly, since 2018 European Association for the Study of Diabetes (EASD)/American Diabetes Association (ADA) and national guidelines [2, 4, 8] have recommended initiation of either a SGLT2i or a GLP-1RA with proven CVD benefit for patients with type 2 diabetes and clinical CVD or high risk of CVD.

No direct head-to-head randomized trials have yet been published whether the benefit of treatment on cardiovascular outcomes and mortality in type 2 diabetes is greater with SGLT2is or GLP-1RAs. However, trial data have suggested similar effectiveness on MACE and death, with evidence for reduction of heart

failure and kidney disease being strongest for SGLT2is [4–6]. Also, recent routine clinical care observational cohort studies have provided corroboration that initiators of SGLT2is (including empagliflozin) and initiators of GLP-1RAs may have comparable rates of CVD and mortality outcomes in routine clinical care, with possible advantages of SGLT2is over GLP-1RAs in reducing incident heart failure [9, 10]. This is reflected in updated guidelines [2, 8]. Given this background, it is important from a health economics perspective to compare these therapies in terms of overall healthcare resource utilization and associated costs. Pharmacy purchase prices of GLP-1RAs are higher than pharmacy purchase prices of SGLT2is in Denmark, but drug prices are just one aspect of the total costs of treatment. Thus, they should not be the only economic input used to assess drug costs [11]. Because direct comparisons of total healthcare costs between an SGLT2i and a GLP-1RA are very scarce [12], we undertook a comparative cohort study in a routine clinical care setting in Denmark. Our aim was to assess direct healthcare resource utilization, including all hospital care, primary care, and prescription medication costs associated with initiation of empagliflozin versus GLP-1RAs.

## METHODS

### Study Design

This nationwide population-based cohort study was based on linked prospective healthcare databases for the entire population of Denmark (current population 5.9 million) from January 1, 2015 to December 31, 2018. Denmark has a free tax supported health care system [13]. The overall study design and methods have been described in detail in a previous publication, which compared CVD outcomes in patients using empagliflozin vs. liraglutide [9]. In brief, we chose an active comparator new user design [14], as guidelines recommend use of empagliflozin and GLP-1RAs in type 2 diabetes patients in similar clinical situations [2, 8]. We addressed confounding by indication for choice of drug

and disease severity [15] by controlling for potential confounders through propensity-score (PS) inverse probability treatment weighting (IPTW) [16]. The study protocol and analysis plan have been registered on the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) (<http://www.encepp.eu/encepp/viewResource.htm?id=37726>, first protocol registration 4 June 2019), and on [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT03993132) (<https://clinicaltrials.gov/ct2/show/NCT03993132>, first posted 20 June 2019).

### Data Sources

We linked the following six population-based databases in our study: the Civil Registration System, which includes information on residence, migration, and vital status of all Danish residents since 1968 [17]; the Danish National Patient Registry, which includes data on all inpatient and outpatient hospital diagnoses and treatments beginning in 1977 [18]; the Danish Diagnosis-Related Group (DRG) and Danish Ambulatory Grouping System (DAGS) (<http://www.drg.dk>), which includes costs associated with diagnoses and procedures during all hospital contacts; the National Prescription Registry, which includes individual-level data on all medications purchased at any pharmacy in Denmark since 1995 [19]; the National Health Insurance Service Registry, which includes data on primary care services (e.g., services provided by general practitioners, medical specialists in private practice, psychologists, physiotherapists, chiropractors, dentists, etc.) since the early 1990s [20]; and the Register of Laboratory Results for Research, which includes individual-level data on all biochemical laboratory tests performed on patients receiving primary or secondary care [21]. Our observational registry-based study was approved by the Danish Data Protection Agency. The study complied with the General Data Protection Regulation and Danish law via the national Data Protection Act. According to Danish law further approval from an ethics review board was not required for this registry-based study.

## Study Population

The source population included all individuals in Denmark with type 2 diabetes, defined as persons who initiated non-insulin GLD or insulin between January 1, 1995 and December 31, 2018. Individuals who initiated insulin as monotherapy under the age of 30 were excluded, as they were likely to have type 1 diabetes. Within the type 2 diabetes source population, we identified our study cohort's population of patients aged 18 years or older with a first-time prescription for empagliflozin or a GLP-1RA (liraglutide, exenatide, or dulaglutide) 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 prior to initiating treatment. To counteract skewed cost results by few individuals with extremely expensive therapies, individuals were excluded if they had a recorded diagnosis of any cancer, HIV, or chronic hepatitis within 5 years before the index date (see study cohort flow chart in Supplementary Material, Supplementary Table S1).

## Drug Use and Covariates

Patients were included on the date of their first prescription for empagliflozin or an GLP-1RA (index date), 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 with empagliflozin or a GLP-1RA were not included in the analyses. In the GLP-1RA cohort, we excluded patients prescribed liraglutide 3.0 mg daily, as it was 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. (Please see covariate definitions provided in Supplementary Table S2).

## Healthcare Resource Utilization and Cost Outcomes

As outcomes, we estimated direct healthcare costs in the public healthcare system, i.e., costs associated with primary and secondary health care services that can be directly referred or traced to the individual patient through linked Danish healthcare databases [13]. Secondary care (hospital) outcomes included all types of patient encounters at somatic Danish hospitals, including inpatient hospitalizations, contacts with hospitals' emergency rooms (with or without subsequent inpatient hospitalization), and ambulatory visits at hospital specialty outpatient clinics (most medical specialists in Denmark work in a hospital-based outpatient clinic). Primary care outcomes included all health care services provided in primary care by general practitioners, medical specialists in private practice, psychologists, physiotherapists, chiropractors, dentists, etc.). Drug cost outcomes included any prescription drugs redeemed at community pharmacies (these pharmacies have the exclusive right in Denmark to sell prescription-only medicinal products to consumers). Finally, we calculated the total costs of all these outcomes.

Hospital costs were based on the total DRG and DAGS charges recorded for each person in the database, including rehabilitation costs, add-ons for long-term stays, etc. Individuals' total costs of primary care services were based on public fees for each service available in the Danish healthcare system. Costs for prescribed drugs were based on Danish pharmacy purchase prices (Danish: Apoteksindkøbspris), i.e., the price from the wholesaler without value added tax, pharmacies' retail margin, or handling fees. All costs for hospital and primary care were calculated in Danish kroner (DKK) in 2018 prices, using the price index available at Statistics Denmark, with no correction for inflation.

## PS Balancing

We applied PS balancing of potential confounders across the two treatment groups by using IPTW [9, 16], controlling for the wide

range of covariates shown in Table 1: age, sex, calendar year, diabetes-related characteristics at time of drug initiation, complete hospital contact history for comorbid conditions within 15 years before drug initiation, co-medications used within 1 year before drug initiation, social and frailty markers, as well as health care resource utilization within the last year (Table 1). In the PS analysis, we chose the IPTW-approach over PS-matching for three 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 non-representative sample; and (3) we wanted to counteract the risk of being unable to find a proper match for treated patients, since the number of patients in our two treatment groups were similar [22]. We applied weight trimming to reduce the importance of large weights, trimming them down to the value at the 99th percentile. Covariate balance was assessed by checking standardized differences (SDs) between the groups. A covariate was considered well balanced if the SD was below 0.1.

### Statistical Analysis

We used an on-treatment (OT) exposure definition in our main analysis. Treatment duration (days) was calculated as the number of drug packages  $\times$  volume + a 60-day grace period, where the volume was the duration of treatment covered by a single package. The volume was defined individually for each combination of Anatomical Therapeutic Chemical (ATC) code and item number. Participants were censored from further follow-up at treatment cessation of empagliflozin, treatment cessation of GLP-1RA, or initiation of a drug from the comparator study drug class (for example, a GLP-1RA among empagliflozin users). In an alternative intention-to-treat (ITT) analysis, 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 from the date of initiation of empagliflozin or GLP-1RA treatment until date of death, emigration, or end of the study on December 31,

2018 (or, in the OT analyses, until treatment cessation or change in drug as explained above). We first used descriptive statistics to examine the mean, median, and total follow-up time in the two cohorts, and the proportions of patients who experienced one or more hospital or primary care contacts of different types. This included the average number of contacts in the two cohorts overall and among patients who had at least one contact. Next, we calculated costs as they accumulated during follow-up since drug initiation for each type of healthcare resource use and displayed them graphically for each cohort. In an additional analysis, we calculated average monthly costs in both cohorts among participants who were still followed at the beginning of each month, to take possible differences in follow-up time into further account, finally, we calculated overall healthcare costs per person-year in the unweighted and weighted empagliflozin and GLP-1 RA cohorts.

All confidence intervals were constructed by bootstrapping. The standard deviation of the sampling distribution was estimated from 1000 bootstrap samples, and the confidence intervals were determined by normal approximation.

All statistical analyses were carried out using SAS version 9.4.

## RESULTS

Inverse probability treatment weighting resulted in two weighted cohorts of 13,442 empagliflozin and 13,192 GLP-1 RA initiators. The cohorts were well balanced at baseline (median age 61 years, 60% men, diabetes duration of 6.7 years, 19% with pre-existing ischemic heart disease, 8% with CVD). Median costs in the year before drug initiation were also well balanced (Table 1).

In the weighted cohorts, mean follow-up in OT analyses was 11 months for empagliflozin initiators vs. 12 months for GLP-1 RA initiators (Table 2), with longer mean follow-up as expected in the ITT analyses (18 months for empagliflozin initiators and 19 months for GLP-1RA initiators (Supplementary Table S3). In the OT analyses, very similar proportions of



**Table 1** Characteristics of new users of empagliflozin or GLP-1 RA, overall and after propensity-score balancing, Denmark, 2015–2018

	Unweighted cohort			Weighted cohort		
	GLP-1RA use, <i>n</i> (%)	Empagliflozin use, <i>n</i> (%)	SD	GLP-1RA use, <i>n</i> (%)	Empagliflozin use, <i>n</i> (%)	SD
Number of patients	13,249	13,747		13,192	13,442	
Age, median (Q1–Q3)	59.7 (50.6; 68.5)	62.3 (53.7; 70.3)	0.217	61.1 (52.3; 69.4)	61.2 (52.4; 69.6)	0.019
Male	7347 (55.5)	8818 (64.1)	0.178	7887 (59.8)	8083 (60.1)	0.007
Year of index date						
2015	3020 (22.8)	729 (5.3)	0.520	1843 (14.0)	1633 (12.1)	0.054
2016	3031 (22.9)	2619 (19.1)	0.094	2801 (21.2)	2906 (21.6)	0.009
2017	3166 (23.9)	4408 (32.1)	0.183	3687 (27.9)	3840 (28.6)	0.014
2018	4032 (30.4)	5991 (43.6)	0.275	4861 (36.8)	5063 (37.7)	0.017
Diabetes-related variables						
Diabetes duration, median (Q1–Q3)	6.6 (2.8; 11.4)	6.8 (3.1; 11.1)	0.003	6.7 (3.0; 11.2)	6.7 (3.0; 11.3)	0.005
Diabetes drugs used within the past 100 days, median (Q1–Q3)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	0.081	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	0.002
Metformin use	11,071 (83.6)	12,470 (90.7)	0.215	11,516 (87.3)	11,808 (87.8)	0.017
Insulin use	3821 (28.8)	2170 (15.8)	0.317	2968 (22.5)	2955 (22.0)	0.012
Hospital-diagnosed retinopathy	2333 (17.6)	2493 (18.1)	0.014	2328 (17.6)	2376 (17.7)	0.001
Hospital-diagnosed neuropathy	915 (6.9)	882 (6.4)	0.020	882 (6.7)	904 (6.7)	0.002
Hospital-diagnosed nephropathy	1152 (8.7)	674 (4.9)	0.151	905 (6.9)	886 (6.6)	0.011
eGFR measurement within the past 365 days						
eGFR < 45	841 (6.3)	277 (2.0)	0.218	555 (4.2)	533 (4.0)	0.012
eGFR 45–59	1090 (8.2)	918 (6.7)	0.059	1004 (7.6)	1030 (7.7)	0.002
eGFR 60–89	3919 (29.6)	5314 (38.7)	0.192	4463 (33.8)	4640 (34.5)	0.014
eGFR ≥ 90	6594 (49.8)	6947 (50.5)	0.015	6646 (50.4)	6815 (50.7)	0.006
No eGFR measurement available	805 (6.1)	291 (2.1)	0.201	524 (4.0)	423 (3.1)	0.044
Coexisting conditions (within prior 15 years)						
Ischemic heart disease	2409 (18.2)	2772 (20.2)	0.050	2535 (19.2)	2588 (19.3)	0.001
Cerebrovascular disease	986 (7.4)	1132 (8.2)	0.029	1051 (8.0)	1094 (8.1)	0.006
Heart failure	865 (6.5)	938 (6.8)	0.012	884 (6.7)	898 (6.7)	0.001
Rheumatological disease	475 (3.6)	401 (2.9)	0.038	430 (3.3)	432 (3.2)	0.003
Dementia	106 (0.8)	117 (0.9)	0.006	110 (0.8)	114 (0.9)	0.002
Osteoporosis/fractures	190 (1.4)	228 (1.7)	0.018	206 (1.6)	216 (1.6)	0.003

**Table 1** continued

	Unweighted cohort			Weighted cohort		
	GLP-1RA use, <i>n</i> (%)	Empagliflozin use, <i>n</i> (%)	SD	GLP-1RA use, <i>n</i> (%)	Empagliflozin use, <i>n</i> (%)	SD
Medical obesity	4033 (30.4)	2500 (18.2)	0.289	3211 (24.3)	3159 (23.5)	0.020
Chronic obstructive pulmonary disease	1437 (10.8)	1181 (8.6)	0.076	1266 (9.6)	1273 (9.5)	0.004
Cancer	563 (4.2)	625 (4.5)	0.014	564 (4.3)	582 (4.3)	0.003
Co-medications (prescription within past 365 days)						
ACE-I or ARBs	8575 (64.7)	8900 (64.7)	0.000	8580 (65.0)	8771 (65.3)	0.004
Other antihypertensive drugs	1253 (9.5)	1310 (9.5)	0.002	1246 (9.4)	1247 (9.3)	0.006
Statins	9107 (68.7)	9966 (72.5)	0.083	9312 (70.6)	9530 (70.9)	0.007
Antiplatelet drugs	4278 (32.3)	4764 (34.7)	0.050	4422 (33.5)	4527 (33.7)	0.003
Corticosteroids (systemic)	861 (6.5)	788 (5.7)	0.032	806 (6.1)	828 (6.2)	0.002
Inhalants/asthma medications	2078 (15.7)	1811 (13.2)	0.071	1887 (14.3)	1900 (14.1)	0.005
Social and frailty markers						
Married	7163 (54.1)	7832 (57.0)	0.059	7341 (55.6)	7509 (55.9)	0.004
Prescription to treat mental disorder within past 365 days	3362 (25.4)	2922 (21.3)	0.098	3079 (23.3)	3135 (23.3)	0.000
Alcoholism	140 (1.1)	150 (1.1)	0.003	146 (1.1)	144 (1.1)	0.004
Prior healthcare resource utilization (within past 365 days)						
Prior inpatient hospitalizations, mean (SD)	0.4 (1.1)	0.4 (0.9)	0.039	0.4 (1.0)	0.4 (0.9)	0.001
Prior hospital admission days, mean (SD)	1.8 (7.4)	1.7 (7.1)	0.014	1.7 (7.4)	1.8 (6.9)	0.001
Prior inpatient hospitalization costs, mean (SD)	14,462.5 (55,052.2)	14,960.7 (57,806.9)	0.009	14,645.3 (60,806.1)	14,704.2 (54,252.8)	0.001
Prior outpatient clinic visits, mean (SD)	4.3 (5.6)	3.6 (5.0)	0.129	3.9 (5.2)	3.9 (5.1)	0.010
Prior hospital outpatient visit costs, mean (SD)	10,818.9 (21,344.2)	9255.2 (17,575.8)	0.080	10,042.0 (19,611.6)	9904.9 (18,177.8)	0.007
Prior emergency room visits, mean (SD)	0.2 (0.6)	0.1 (0.5)	0.024	0.2 (0.6)	0.2 (0.5)	0.002
Prior emergency room visit costs, mean (SD)	284.7 (1961.8)	283.5 (1768.8)	0.001	283.9 (1972.0)	283.1 (1707.5)	0.000
Prior costs of primary care health services, mean (SD)	4503.7 (3967.6)	4213.9 (3606.1)	0.076	4365.0 (3801.6)	4368.5 (3767.2)	0.001

**Table 1** continued

	Unweighted cohort			Weighted cohort		
	GLP-1RA use, <i>n</i> (%)	Empagliflozin use, <i>n</i> (%)	SD	GLP-1RA use, <i>n</i> (%)	Empagliflozin use, <i>n</i> (%)	SD
Prior number of primary care health services, mean (SD)	42.2 (37.6)	38.5 (32.7)	0.105	40.4 (35.3)	40.4 (34.7)	0.002
Prior prescription medication costs, mean (SD)	4900.2 (5649.5)	3835.9 (4428.8)	0.210	4373.6 (5006.7)	4337.3 (5218.4)	0.007

*ACE-I* angiotensin-converting enzyme (ACE) inhibitors, *ARB* angiotensin receptor blockers, *eGFR* estimated glomerular filtration rate, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *SD* standard deviation

empagliflozin vs. GLP-1 RA initiators experienced at least one inpatient hospitalization (16.5 vs. 18.5% with one or more hospitalizations, mean annual days of hospitalization of 1.9 vs. 1.9 in the two cohorts), emergency room contacts (10.2 vs. 11.1% with one or more contacts), hospital outpatient clinic contacts (66.9 vs. 68.5% with one or more contacts, mean annual clinic contacts 5.0 vs. 4.9), and primary care services (95.7 vs. 96.5% with any service, mean 40.7 vs. 43.6 annual services) (Table 2). Findings were similar for ITT analyses (Supplementary Table S3).

Figure 1 shows the healthcare costs accumulating over the first year of follow-up after drug initiation, stratified by type of healthcare resource use. Inpatient and outpatient clinic hospital costs and primary healthcare services were similar for the weighted empagliflozin and GLP-1 RA cohorts, while costs were lower for prescription drugs in the empagliflozin cohort. Findings were similar in ITT analyses (Supplementary Figure S1).

Figure 2 shows mean healthcare costs for each month of follow-up among GLP-1RA and empagliflozin initiators alive at the beginning of each month. The most marked difference each month was for cost of prescription drugs, which was consistently higher for GLP-1RA users. Findings were similar in ITT analyses (Supplementary Figure S2). As shown in Supplementary Table S4, mean costs for the different types of healthcare services fluctuated

somewhat from month to month across the two weighted cohorts. In some months costs were slightly higher in the empagliflozin cohort and in other months slightly higher in the GLP-1RA cohort. However, the lower cost of prescription drugs in the empagliflozin cohort was the most persistent difference in all months.

Table 3 shows the resulting healthcare costs per person-year (in DKK) in the unweighted and weighted empagliflozin and GLP-1 RA cohorts, including pharmacy costs. Overall healthcare costs in the on-treatment analyses were lower among empagliflozin initiators (38,995 DKK per person-year) than among GLP-1RA initiators (44,157 DKK per person-year). This disparity was primarily driven by differences in total costs of prescription drugs, while costs were similar for inpatient and outpatient hospital costs, emergency room visits, and primary healthcare services. Figure 3 shows healthcare costs components in the unweighted and weighted empagliflozin and GLP-1 RA cohorts graphically. Corresponding results for intention-to-treat analyses are shown in Supplementary Table S5.

## DISCUSSION

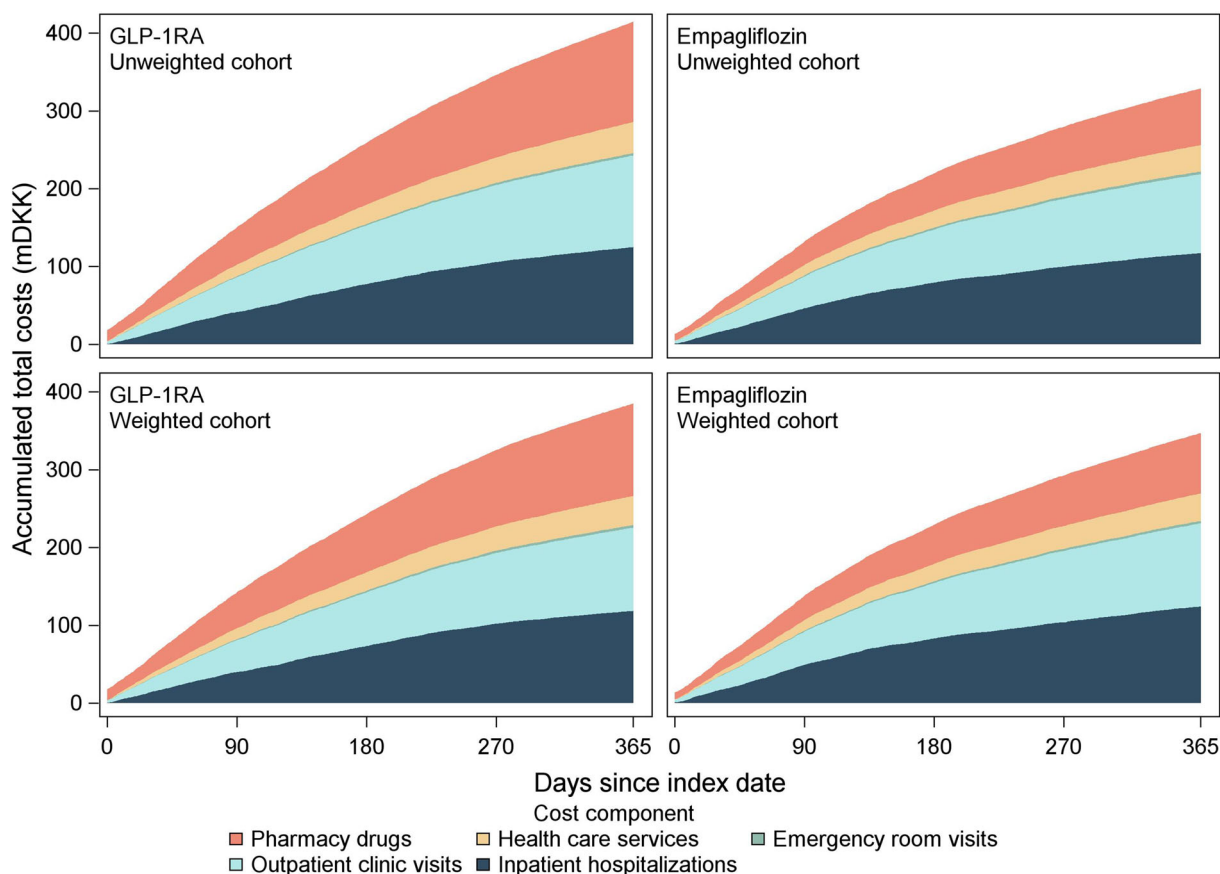
We found that empagliflozin and GLP-1RA initiators had comparable healthcare resource utilization after drug initiation, with the directly referable costs of healthcare being lower for



**Table 2** Descriptive data for healthcare utilization following initiation of empagliflozin or GLP-1 RA use, on-treatment analysis

	Unweighted cohort		Weighted cohort	
	GLP-1RA	Empagliflozin	GLP-1RA	Empagliflozin
On-treatment + 60 days of follow-up time, months, median (Q1–Q3)	9.5 (4.0; 20.7)	7.4 (3.2; 14.7)	8.5 (3.5; 18.3)	7.9 (3.4; 16.1)
On-treatment + 60 days of follow-up time, months, mean (SD)	13.7 (11.9)	10.3 (8.9)	12.3 (10.9)	11.3 (9.8)
Inpatient hospitalizations				
Patients with $\geq 1$ inpatient hospitalization, <i>n</i> (%)	2707 (20.4)	2038 (14.8)	2442 (18.5)	2214 (16.5)
Total number of events	5202	3597	4485	3998
Person-years	15,086	11,801	13,499	12,605
Event rate per year (95% CI)	0.3 (0.3; 0.4)	0.3 (0.3; 0.3)	0.3 (0.3; 0.3)	0.3 (0.3; 0.3)
Hospital days in patients hospitalized during follow-up, median (Q1–Q3)	4 (2; 10)	4 (2; 9)	4 (2; 9)	4 (2; 9)
Hospital days in patients hospitalized during follow-up, mean (SD)	9 (14)	8 (13)	8 (12)	9 (15)
Outpatient clinic visits				
Patients with $\geq 1$ outpatient clinic visits, <i>n</i> (%)	9616 (72.6)	8706 (63.3)	9036 (68.5)	8991 (66.9)
Total number of events	69,355	50,028	58,951	55,848
Person-years	15,149	11,848	13,554	12,657
Event rate per year (95% CI)	4.6 (4.5; 4.7)	4.2 (4.1; 4.3)	4.3 (4.2; 4.4)	4.4 (4.3; 4.5)
Emergency room contacts				
Patients with $\geq 1$ emergency room contact <sup>b</sup> , <i>n</i> (%)	1651 (12.5)	1274 (9.3)	1463 (11.1)	1371 (10.2)
Total number of events	2396	1683	2054	1837
Person-years	15,149	11,848	13,554	12,657
Event rate per year (95% CI)	0.2 (0.1; 0.2)	0.1 (0.1; 0.2)	0.2 (0.1; 0.2)	0.1 (0.1; 0.2)
Primary care services				
Patients with $\geq 1$ primary care service, <i>n</i> (%)	12,820 (96.8)	13,096 (95.3)	12,725 (96.5)	12,865 (95.7)
Total number of events	643,388	451,649	565,590	496,560
Person-years	15,149	11,848	13,554	12,657
Event rate per year (95% CI)	42.5 (41.7; 43.2)	38.1 (37.4; 38.8)	41.7 (41.1; 42.4)	39.2 (38.3; 40.2)

GLP-1 RA glucagon-like peptide-1 receptor agonist



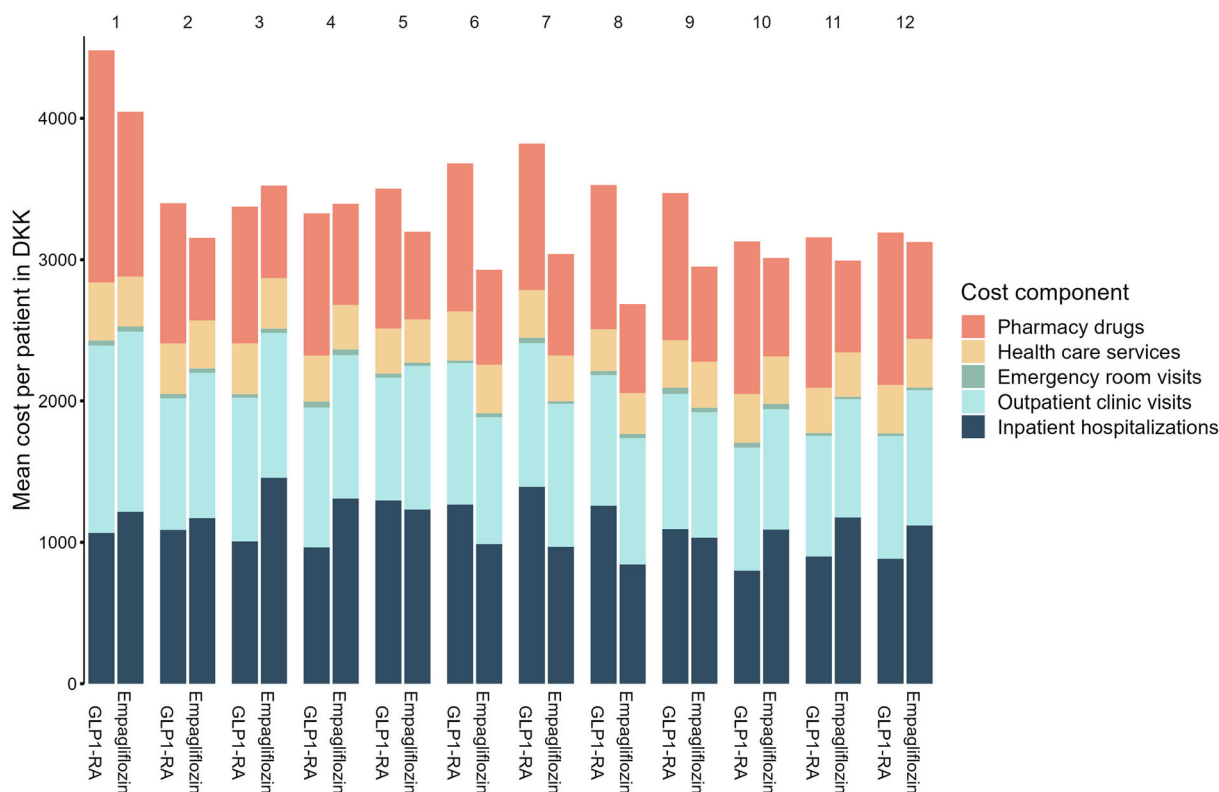
**Fig. 1** Cumulative health care costs during the first year of follow-up among GLP-1RA initiators (*left panels*) and among empagliflozin initiators (*right panels*), stratified by type of health care use. On-treatment analysis

empagliflozin users, driven by lower prescription drug costs.

### Comparison with Other Studies

Evidence from routine clinical care settings is sparse regarding overall healthcare resource utilization and costs for SGLT2i vs. GLP-1RA therapies. Few, if any, population-based studies have directly compared observed healthcare costs in new users of empagliflozin vs. new users of a GLP-1RA in a nationwide setting. A recent Danish simulation study used pooled data from clinical trials to evaluate the cost-effectiveness of subcutaneous semaglutide vs. empagliflozin among patients with type 2 diabetes treated with metformin who required treatment intensification [12]. The study found that the difference in costs between the two groups was

mainly driven by different prices of the GLP-1RA and the SGLT2i. The estimated cost difference of approximately DKK 23,000 in the first 5 years of treatment was remarkably similar to the cost difference of approximately DKK 5000 per person-year that we observed during our study's relatively short drug exposure time. In contrast, a cost-effectiveness analysis in the UK reported that once-weekly treatment with 1 mg subcutaneous semaglutide was cost-effective from a healthcare payer perspective, compared with 25 mg empagliflozin for patients with T2D for whom metformin monotherapy provided inadequate glycemic control [23]. The UK study was a projection of outcomes over patient lifetimes in a real-world setting based on short-term clinical trial data. As a projection, the study did not include cardiovascular outcomes, and it compared patients with T2D in different



**Fig. 2** Mean healthcare costs for each month of follow-up among GLP-1RA and empagliflozin initiators alive at the beginning of each month, by type of health care use. Weighted cohorts, on-treatment analysis

stages to high-risk patients with advanced disease from CVOTs. The UK study reported 10-year estimated costs, but no short-term costs [23]. The Danish [12] and UK [23] cost-effectiveness analyses were based on the same meta-analysis and indirect comparison of clinical trial data and both had a 50-year time horizon. The main difference was the duration of therapy for once-weekly subcutaneous semaglutide or empagliflozin [12]. In the Ehlers et al. analysis [12], patients continued the GLP-1RA or SGLT2i plus metformin along with basal insulin at time of treatment intensification with basal insulin. In the UK analysis [23], Capehorn et al. switched patients from a GLP-1RA or SGLT2i plus metformin to basal insulin alone and thus discontinued treatment with the GLP-1RA or SGLT2i at time of treatment intensification, which is not as recommended in updated treatment guidelines. Treatment intensification occurred in both analyses after 2 and 3 years, respectively, for the two comparators. Since the

yearly cost of once-weekly SC semaglutide is three times as high as the yearly cost of empagliflozin, inclusion or exclusion of the cost of the two drugs for up to 50 years had a significant impact on the cost-effectiveness results [12].

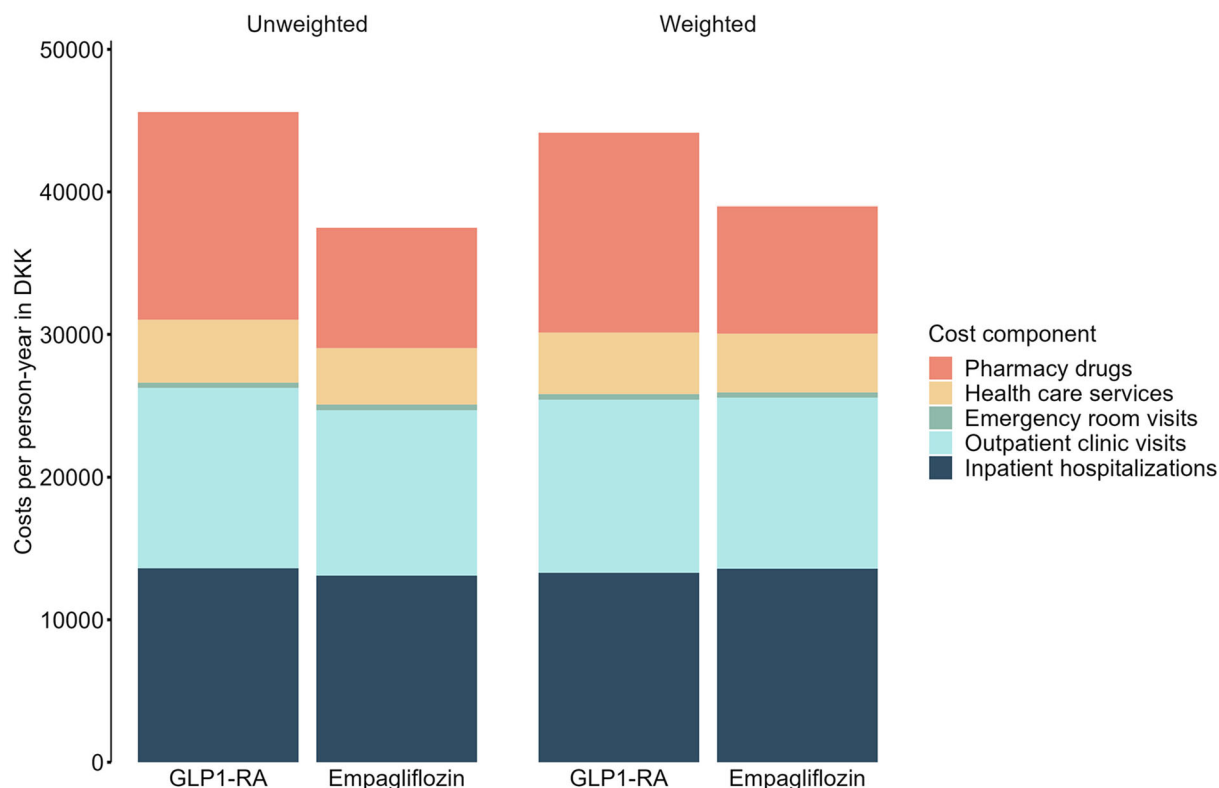
Our findings were corroborated by a recent study based on claims data of German sickness funds [24]. Using methods similar to ours, this German study matched patients with type 2 diabetes starting treatment with empagliflozin versus GLP-1RA and DPP-4 inhibitors, respectively. The study found lower direct healthcare costs (inpatient care, outpatient care, and drug costs together) for empagliflozin initiators, with the differences in total costs between empagliflozin and GLP-1RA users mainly attributed to the higher drug price of GLP-1RA [24].

In a previous real-world comparative effectiveness study, we observed that initiators of empagliflozin vs. liraglutide (the GLP-1RA used almost exclusively in Denmark during

**Table 3** Healthcare costs per person-year (in DKK) in the unweighted and weighted empagliflozin and GLP-1 RA cohorts, on-treatment analysis

	Unweighted cohorts		Weighted cohorts	
	GLP-1RA	Empagliflozin	GLP-1RA	Empagliflozin
<i>N</i> participants	13,249	13,747	13,192	13,442
Total follow-up time, years	15,149	11,848	13,554	12,657
Follow-up time, years, median (Q1; Q3)	0.8 (0.3; 1.7)	0.6 (0.3; 1.2)	0.7 (0.3; 1.5)	0.7 (0.3; 1.3)
Follow-up time, years, mean (SD)	1.1 (1.0)	0.9 (0.7)	1.0 (0.9)	0.9 (0.8)
Healthcare costs	Total costs (mDKK)	Costs per person-year (95% CI), DKK	Total costs (mDKK)	Costs per person-year (95% CI), DKK
Overall healthcare cost	691	45,614 (44,461; 46,766)	444	37,496 (36,256; 38,736)
Inpatient hospitalizations	206	13,603 (12,741; 14,465)	155	13,080 (12,126; 14,034)
Outpatient clinic visits	192	12,654 (12,140; 13,168)	138	11,605 (11,117; 12,094)
Emergency room visits	6	373 (335; 411)	5	405 (352; 458)
Primary health care services	67	4397 (4318; 4476)	47	3967 (3887; 4048)
Pharmacy drugs	221	14,586 (14,423; 14,750)	100	8438 (8326; 8549)
			Total costs (mDKK)	Costs per person-year (95% CI), DKK
			599	44,157 (43,058; 45,255)
			180	13,275 (12,410; 14,139)
			165	12,152 (11,683; 12,621)
			5	399 (353; 444)
			58	4302 (4235; 4370)
			190	14,029 (13,898; 14,161)
			494	38,995 (37,353; 40,638)
			172	13,565 (12,289; 14,841)
			152	12,007 (11,407; 12,607)
			5	370 (325; 414)
			52	4108 (4000; 4216)
			113	8946 (8785; 9106)

*DKK* Danish kroner, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *SD* standard deviation



**Fig. 3** Healthcare cost components per person-year during total follow-up time in the unweighted and weighted empagliflozin and GLP-1 RA cohorts

2015–2018) had remarkably similar rates of MACE and all-cause death during the first 1–1.5 years of follow-up [9]. Together, our studies indicate no notable short-term differences in clinical outcomes, but a small difference in costs. This could indicate that SGLT2is are cost-effective in the short-term. However, decision-makers should also look at long-term cost-effectiveness in prioritizing and decision-making [11]. Our study supports the short-term estimates from Ehlers 2022 [12], but cannot address long-term cost-effectiveness, which remains to be explored in further studies.

### Strengths and Weaknesses

Our routine clinical care study has both strengths and weaknesses. A major strength is its setting within the comprehensive Danish public healthcare system, allowing a population-based design with inclusion of all patients

initiating treatment with empagliflozin or a GLP-1RA in a well-defined geographical region. This largely eliminated patient selection biases affecting studies restricted to specific clinics, insurance programs, age groups, or gender. Accordingly, our data reflect actual population-based clinical practice in diabetes care.

A study limitation was the relatively short exposure time to the study drugs, i.e., approximately 1 year mean on-treatment duration. Thus, the long-term durability of the cost associations is inherently uncertain. Of note, we found similar results for costs when comparing empagliflozin and a GLP-1RA using an OT and an ITT approach, which underscores the robustness of our findings. We were able to counteract any confounding by indication (e.g., potentially more or less advanced diabetes stage or obesity) through balancing a wide range of factors related to both diabetes stage and body weight in empagliflozin and GLP-1RA initiators, including diabetes duration, presence of



complications, diabetes medication intensity, and diagnoses of obesity. We cannot exclude some unmeasured or residual confounding, as in any non-randomized study. We thus lacked detailed data on clinical and anthropometric measures (such as BMI, individual metabolic syndrome components, and beta-cell-function), lifestyle factors, and socioeconomic measures [25]. These factors all may be associated both with choice of empagliflozin vs. a GLP-1RA and the likelihood of experiencing given healthcare outcomes with their associated costs.

## CONCLUSIONS

In conclusion, we found that healthcare costs were lower for initiators of empagliflozin than for initiators of GLP-1RAs while on treatment. Healthcare resource utilization in hospital and primary care was remarkably similar in the two groups, with cost differences entirely driven by lower costs of prescription drugs among empagliflozin users.

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**Author Contributions.** RWT, LWBC, JK, JSK, AU, SS, PHH, LHE, and HTS conceptualized the study. LWBC performed calculations. RWT wrote the first draft. All authors participated in the interpretation of results and provided critical inputs to the paper.

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**Compliance with Ethics Guidelines.** 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 entirely registry-based and did not involve any contact with patients or interventions. Therefore, according to Danish legislation, ethics approval and informed consent were not required.

**Data Availability.** 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 must be sent to the Danish Health Data Authority by e-mail to forskerservice@sundhedsdata.dk.

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