

Dapagliflozin Compared to DPP-4 inhibitors is Associated with Lower Risk of Cardiovascular Events and All-cause Mortality in Type 2 Diabetes Patients (CVD-REAL Nordic): a multinational observational study

Short running title: Dapagliflozin vs DPP-4i and cardiovascular disease in T2D

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Abstract

Aims: To compare the sodium glucose-cotransporter-2-inhibitor (SGLT-2i) dapagliflozin versus dipeptidyl peptidase-4 inhibitors (DPP-4i) regarding risk associations of MACE (nonfatal myocardial infarction, nonfatal stroke or cardiovascular [CV] mortality), hospital

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events for heart failure (HHF), atrial fibrillation, and severe hypoglycemia for type 2 diabetes (T2D) patients in a real-world setting.

Methods: All T2D patients dispensed with glucose lowering drugs (GLDs) during 2012—2015 were identified in nationwide registries in Denmark, Norway and Sweden. Patients were divided in two groups; new users of dapagliflozin and new users of DPP-4i, matched 1:3 by propensity score, calculated by patient characteristics, co-morbidities and drug treatment. Cox survival models estimated hazard ratio per country separately; a weighted average was calculated.

Results: After matching, a total of 40,908 T2D patients were identified as new users of dapagliflozin (n=10,227) or DPP-4i (n=30,681). The groups were well balanced at baseline; mean-age was 61 years and 23% had CV disease. Mean follow-up time was 0.95 years, with a total of 38,760 patient-years. Dapagliflozin was associated with lower risk of MACE, HHF and all-cause mortality compared to DPP-4i; hazard ratios (HRs): 0.79 (95% CI 0.67-0.94), 0.62 (0.50-0.77), and 0.44 (0.33-0.60), respectively. Numerically lower, but non-significant HRs were observed for myocardial infarction (0.91 [0.72-1.16]), stroke (0.79 [0.61-1.03]) and CV mortality (0.76 [0.53-1.08]) Atrial fibrillation and severe hypoglycemia showed neutral associations.

Conclusions: Dapagliflozin was associated with lower risks of cardiovascular events and all-cause mortality compared to DPP-4i in a in a real-world clinical setting and broad T2D population.

1 Introduction

Despite modern preventive treatment for cardiovascular (CV) complications, patients with type 2 diabetes (T2D) have increased risk of mortality, heart failure and CV disease.(1, 2) The sodium glucose-cotransporter-2-inhibitors (SGLT-2i) empagliflozin and canagliflozin recently showed reduced risk of CV disease and hospitalization for heart failure, and empagliflozin also for all-cause mortality, compared to placebo and on top of other glucose lowering drugs (GLD) in T2D patients with high CV disease risk profile.(3, 4) As part of the CVD-REAL study program designed to study SGLT-2i and CV outcome in a real-world setting(5, 6), the CVD-REAL Nordic Study, a large multinational observational study of >90,000 T2D patients, has suggested SGLT-2i class effects by showing lower risk of CV mortality, major CV adverse events (MACE, nonfatal myocardial infarction, nonfatal stroke or CV mortality) and hospitalization event for heart failure (HHF) compared to other GLDs.(7) However, the comparator group of other GLDs in this study(7), consisted of almost 50% insulin or sulphonylurea treated T2D patients, that in previous reports have shown to have increased associated CV risks compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) in other observational studies.(8-15) Also, it is not fully clear to what extent this could have influenced the risk estimates. Moreover, the comparator group other GLDs do not reflect any particular GLD class but rather the real-world use of glucose lowering drugs in T2D patients comparable to new use of SGLT-2i. It is therefore of high importance to assess CV risks by comparing SGLT-2i with a specific and clinical relevant treatment strategy, e.g. DPP-4i. This has to the best of our knowledge not been reported before and there are no ongoing CV outcome trials comparing SGLT-2i with a DPP-4i.

DPP4i belong to a class of widely used GLDs, which have been proven CV safe in several large clinical trials although concerns on increased heart failure risk have been raised.(16-18) Being a widely used modern oral treatment for T2D, as is SGLT-2is, DPP-4i is a well-suited

comparator for examining the effectiveness of another GLD. Moreover, for second- or higher line therapy for patients with T2D, both SGLT-2i and DPP4-i are recommended treatment strategies. (19)

The primary aim was to investigate if dapagliflozin, the most frequently used SGLT2-i in the Nordic countries,(7) was associated with risks of MACE, HHF and all-cause mortality compared to DPP-4i in a broad unselected type 2 diabetes populations using nationwide data from Denmark, Norway and Sweden. Secondary aims were to study unstable angina, atrial fibrillation and severe hypoglycemia.

2 Material and methods

2.1 Data Sources

The three Nordic countries Denmark, Norway and Sweden have comprehensive, nationwide public health care systems. All citizens have a unique personal identification number (person-ID), which is mandatory for all administrative purposes (including any contact with the health care system and drug purchases) thus providing a complete full population medical history. This work used data from Prescribed Drug Registers, the Cause of Death Registers, and the National Patient Registers covering all hospitalisations with discharge diagnoses and all out-patient hospital visits. Individual patient-level data from the national registers were linked using the person-ID. The linked databases were managed separately by Steno Diabetes Center Copenhagen, Gentofte, Denmark (Danish database) and Statisticon AB, Uppsala, Sweden (Swedish and Norwegian databases). Anonymized data were used and analyses were performed within each separate country database (detailed country specific database information, Supplemental Appendix section 1). The separate studies were approved accordingly by the Danish Data Protection Agency (Datatilsynet, registration number 2015-41-4148), the Norwegian Data Protection Agency (registration number 16/00005-2/GRA) and Regional Committee for Medical and Health Research Ethics South East (registration number 2015/1337/REK), and the Stockholm regional ethics committee (registration number 2013/2206-31).

2.2 Study Population

All T2D patients aged 18 years and above who were new drug users of either dapagliflozin or DPP-4i during the years 2012 to 2015, when dapagliflozin were available in all three countries, could be included (Supplemental Table 1a). Patients with type 1 diabetes, gestational diabetes and polycystic ovarian syndrome were excluded; Supplementary Appendix section 2. A new user date was defined as the date of a dispense of the drug class

of interest, preceded with a 12-month period without any dispense of the same drug class. This definition allowed for several possible new user dates for a patient within the observation period, both within drug class and between classes. In case multiple new user dates were found, the definition of an index date followed a hierarchical structure starting with the dapagliflozin new user date if present.

Baseline data

Patient characteristics included age at the date of index drug, sex, index date, date of first registered GLD dispense, and a description of patient frailty (defined as at least one hospitalization of three or more consecutive days during the year prior to index date).(1, 13, 14); detailed definitions Supplemental Table 1b. Comorbidities were searched for in all available data prior to and including the index date, with an exception for severe hypoglycaemia (within 12 months prior to index date) and cancer (within 5 years prior to index date); detailed definitions Supplemental Table 1c. Prior medications were defined as any dispense 12 months prior to and including index date. Detailed definitions, Supplemental Table 1d.

2.3 Follow-up

The primary analyses utilized an on-treatment approach. Patients were observed from index date until index drug discontinuation (defined as the first gap of six months between filled prescriptions), death, or 31st of December 2015. In addition, intention to treat analyses were performed also including the follow-up time after index treatment discontinuation.

2.4 Definition of outcomes

Outcomes were: MACE, defined by main diagnosis of myocardial infarction or ischemic/haemorrhagic stroke or CV mortality. HHF, defined by in- or outpatient visits with a main diagnosis of heart failure. All-cause mortality, defined as death from any cause. MACE+, MACE or unstable angina. MACE++, MACE+ or HHF. Other predefined

outcomes were unstable angina, atrial fibrillation and severe hypoglycaemia. For detailed outcome definitions, see Supplemental Table 1c.

2.5 *Propensity score matching*

Propensity scores were used to match each patient who initiated dapagliflozin with patients who initiated a DPP-4i (1:3 match, using a caliper of 0.2). The probability of having a new drug initiation of dapagliflozin was estimated using a logistic regression model with patient characteristics, age, time since first GLD initiation, comorbidity, coronary revascularization, frailty, all separate classes of GLDs, CV disease preventive drugs, drugs associated with treatment of heart failure, and date of both index drug and first line initiation as independent variables. Detailed information about variables included in the propensity score, see Supplementary Tables 2a-c, Tables 3a-c and Appendix section 3. The matching was performed using the Match function in the R package Matching.(20)

2.6 *Statistical analysis*

Standardized differences of >10% was used to detect significant group imbalance between baseline variables.(21) The primary analysis was a survival analysis using a Cox proportional hazards model with time since index date as underlying time scale and a risk reduction in the dapagliflozin group is considered to be significant when p-value <0.05 and hazard ratio (HR) <1. Proportional assumptions were tested. Pooled Kaplan-Meier plots from all three countries were used for descriptive purposes only.(22) The primary model only used index drug as covariate (dapagliflozin vs. DPP-4i). All analyses were conducted using R statistical software (R version 3.2.3).(23)

3 Results

3.1 *Unmatched patient characteristics and treatments*

During the observation period years 2012 to 2015, 94,064 T2D patients initiated new therapy with dapagliflozin or DPP-4i (Figure 1). Before matching, patients in the dapagliflozin group were younger, less frequently women, had more microvascular disease and lower CV burden, compared to patients in the DPP-4i group (Supplementary Table 2). The dapagliflozin and DPP-4i group were similar with respect to CV preventive treatment, statins, antihypertensives and low dose aspirin.

3.2 *Propensity score matched analyses*

Following matching, a total of 40,908 T2D patients could be included as new users of either dapagliflozin (n=10,227) or DPP-4i (n=30,681). The groups were well balanced at baseline; mean-age was 61 years, 40% were women, 23% had CV disease, 15% microvascular disease and 84% had dispensed CV preventive drugs (Table 1). Mean follow-up time was 0.95 years (dapagliflozin 0.91 years and DPP-4i 0.96 years), with a total of 38,760 patient-years.

3.3 *Cardiovascular disease*

The dapagliflozin group was associated with lower risk of MACE and HHF compared to the DPP-4i group: hazard ratios 0.79 (95% CI 0.67-0.94) and 0.62 (0.50-0.77), respectively (Table 2). Risk of nonfatal myocardial infarction, nonfatal stroke and CV mortality was non-significantly lower in the dapagliflozin group, hazard ratios 0.91 (0.72-1.16), 0.79 (0.61-1.03), and 0.76 (0.53-1.08), respectively. Lower HRs for MACE+ and MACE++ in the dapagliflozin group were observed, hazard ratio 0.81 (0.69-0.94) and 0.75 (0.66-0.86) respectively. No associations were observed with unstable angina.

3.4 *Other outcomes*

All-cause mortality in the dapagliflozin group showed lower hazard ratio compared to the DPP-4i group, 0.44 (95% CI 0.33-0.60). The dapagliflozin group showed neutral associations

for atrial fibrillation and severe hypoglycemia compared to DPP-4i, hazard ratio 0.92 (0.76-1.12) and 0.94 (0.74-1.19), respectively.

3.5 Sensitivity analyses

When including time after treatment discontinuation (e.g. intention-to-treat), the analysis showed similar risk associations between the dapagliflozin group and the DPP-4i group, see Supplementary Table 4. Risk estimation for heart failure registered in-hospital only (e.g. excluding outpatient events) remained unchanged compared to HHF, including both in- and outpatient events, see Supplementary Table 4.

4 Discussion

In this large type 2 diabetes population of more than 40,000 patients from three countries covering approximately 20 million inhabitants, new use of dapagliflozin was associated with 21% lower risks of MACE and 38% lower risk of HHF compared to new use of DPP-4i. In addition, a 54% lower all-cause mortality risk was observed. The MACE components, myocardial infarction, stroke and CV mortality, did separately show lower, but non-significant differences. Extended outcome combinations of MACE; adding unstable angina and HHF respectively did not change the lower risk associations with dapagliflozin compared to DPP-4i. Neutral associations were found with severe hypoglycemia and atrial fibrillation.

Similar to our reported 21% (0.79 [0.67-0.94]) associated lower risk for MACE, a recent meta-analysis of dapagliflozin treatment in patients with 30% established CV disease at baseline showed a numerically 23% (0.77 [0.54-1.10]) lower risk of MACE compared with placebo.(24) Furthermore, the numerical risk reductions for MACE+ reported by the same meta-analysis also showed similarities with our results, 0.79 (0.58-1.07) and 0.81 (0.69-0.94) respectively.(24) Despite not being significant, these meta-analyses on MACE outcomes, indirectly provide clinical trial data support to our real-world results.

The EMPA-REG OUTCOMEE trial showed that empagliflozin reduced the risk of MACE, hospitalization for heart failure, and all-cause mortality compared to placebo by 14%, 35%, and 32%, respectively, also similar to canagliflozin in the CANVAS trial.(3, 4) This is comparable to our findings of respectively 21%, 38% and 56%, but an important difference is the substantially lower CV risk profile at baseline where our population had 23% established CV disease compared to the 99% and 72% reported in the EMPA-REG OUTCOME and CANVAS trial respectively. This may indicate that the risk lowering effects reported for empagliflozin and canagliflozin also extend to dapagliflozin, and to a T2D patient population with a substantially lower CV risk profile at baseline.

Heart failure is a both common and frequently underdiagnosed complication in T2D, (25, 26) increasing mortality and cardiovascular risks (27) and thus emphasizing the importance of its prevention and treatment. We show that dapagliflozin treatment, compared to DPP-4i, is associated with significantly lower risks of HHF in patients with a broader CV risk profile compared to clinical trials. As evidence-based treatment of heart failure in T2D is currently lacking,(28) these new findings might be of particular clinical importance while waiting for results from ongoing randomized mechanistic and outcome trials of dapagliflozin.(Clinicaltrials.gov: NCT03030235, NCT02653482 and NCT03036124)

Interestingly, both atrial fibrillation and severe hypoglycemia showed no associations between the two treatment groups in the present work. The risk of atrial fibrillation has not, to our knowledge, been reported to show associations with either SGLT-2is or DPP-4i, and should thus be expected to be neutral. In addition, it is known that both dapagliflozin and DPP-4i show low and similar risks of hypoglycemia.(29) Hence, these expected neutral associations support that the treatment groups were well balanced at baseline regarding disease burden, including also unknown confounders.

In contrast to the EMPA-REG OUTCOME trial, reporting non-significant higher stroke risk (1.24 [0.92—1.67]), we report a lower risk association for stroke (0.79 [0.61-1.03]) with dapagliflozin compared to DPP-4i. This finding is of particular interest since it is more in line with the CANVAS trial results (0.90 [0.711-1.15]) and considers benefit in stroke rates that could be expected by a mild reduction in blood pressure. The seemingly disparity finding between our results and the EMPA-REG OUTCOME trial could be due by chance and/or presence of a potential unknown confounding at baseline. However, the virtually identical baseline, similar risk estimates for other outcomes compared to the EMPA-REG OUTCOME and CANVAS trial,(3, 4) and absent atrial fibrillation and hypoglycemia associations all are in support of our results.

Previous observational multi-country studies have recently shown that parts of the EMPA-REG OUTCOME and CANVAS trial results do translate to the SGLT-2i class as such, and into a real world setting with T2D patients having broader CV risk profiles.(3, 4, 6, 7, 30) However, by using a wider range of outcomes, the present paper further adds to this knowledge base by showing that a specific SGLT-2i, dapagliflozin, is associated with lower CV risk in a real-world setting compared to a widely-used glucose lowering drug class, DPP-4i. Observational effectiveness studies cannot replace randomized clinical trials, but might prove an important complement translating results to a broader and more generalized patient population in a real-world setting.(31) While awaiting more complete evidence, observational comparative effectiveness studies may increase the understanding of the SGLT-2i treatment outcome effects. However, confounding, particularly confounding by indication, cannot be fully ruled out in observational studies, and the large ongoing prospective trial DECLARE-TIMI 58 (clinicaltrials.gov, NCT01730534), including more than 17,000 patients with both low and high CV risk, will further elucidate dapagliflozin specific findings.

Strengths

The present work has a population-based, nationwide and unselected real-world design, which provides a high external validity and large enough population allowing for country-wise propensity score matched analyses. The results were consistent across all three countries and across several subgroup analyses. In addition, national registers with full coverage for hospitalizations, filled drug prescriptions and cause of death were used in three countries with established and complete public healthcare systems. Since diagnostic accuracy can be challenging for e.g. HHF in registries, it is reassuring that CV diagnoses in Denmark, Norway and Sweden have high validity.(32-36) Anticipated neutral associations with atrial fibrillation and severe hypoglycemia confirms balanced risk profile at baseline for the dapagliflozin and DPP-4i group.

Limitations

The results are only representative for patients that have been initiated on SGLT-2i treatment or are similar on available clinical variables and cannot be extended to all T2D patients. The present work has no information on laboratory measurements, lifestyle parameters, primary healthcare data, or socioeconomic data, and consequently there may be remaining confounding factors. The close matching on a large number of essential variables ensures that some confounding factors are controlled, but even propensity score matching does not remedy all confounding, e.g. residual confounding by indication. Further, there is no information of diabetes duration. However, we used a proxy for time since diagnosis by matching for age at index date, time since first registered GLD treatment and classes of GLDs at baseline. Since dapagliflozin have been on the market since year 2012 the mean follow-up was short, circa one year. However, in EMPA-REG OUTCOME early effects were seen similarly to our report supporting that the mean one year follow-up time might be sufficient. We did not examine safety, but recent reports have not identified any new safety signals with dapagliflozin.(37, 38) For Norway and Sweden, we had no information on emigration, which could result in loss to follow-up. No information of immigration was available and some patients might have less comprehensive disease history. However, the on-treatment analyses used should minimize the effects of patients emigrating because they would be classified as discontinuing treatment. Furthermore, the results were consistent with Denmark where migration information was included.

5 Conclusion

Dapagliflozin, when compared to DPP-4i, was associated with lower risk of major cardiovascular events, heart failure and all-cause mortality in a real-world type 2 diabetes population, where 23% had a previously established cardiovascular disease. A large ongoing prospective dapagliflozin trial will further elucidate these findings.

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Author contributions

All authors participated in the research design. MT and BC performed the data management and statistical analyses after discussion with all authors. All authors participated in data interpretation and in writing the manuscript. All authors took final responsibility in the decision to submit for publication.

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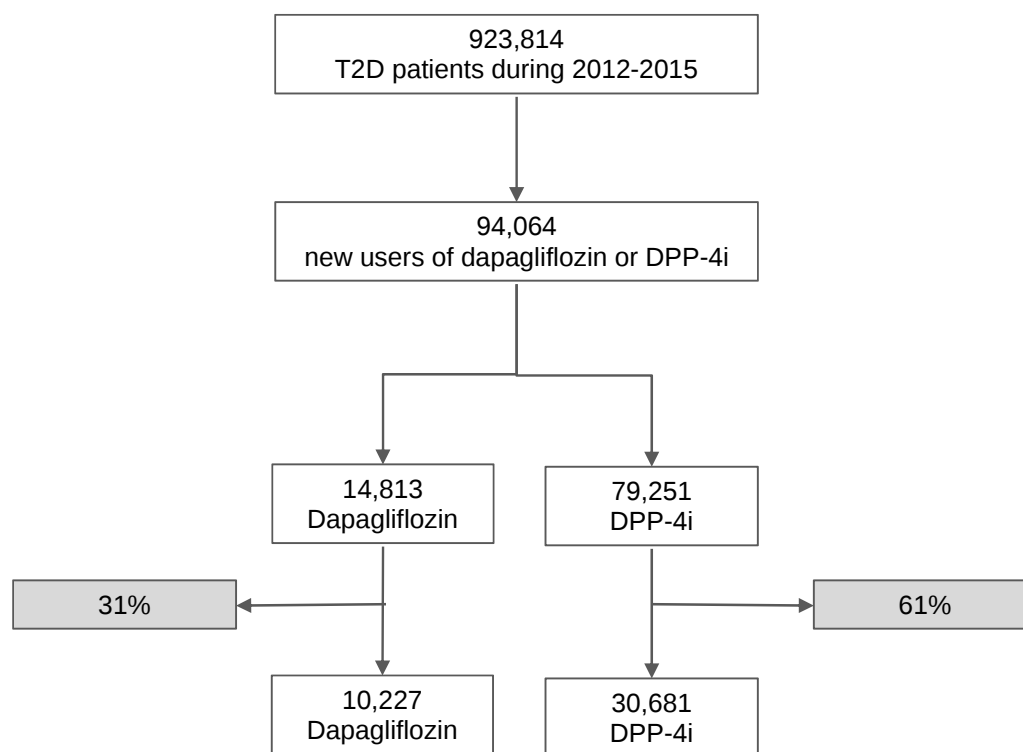


Figure 1 — Patient flow-charts for dapagliflozin versus DPP-4i groups. Patients proportion not fulfilling propensity matching 1:3 with 0.2 caliper were excluded and shown in grey boxes

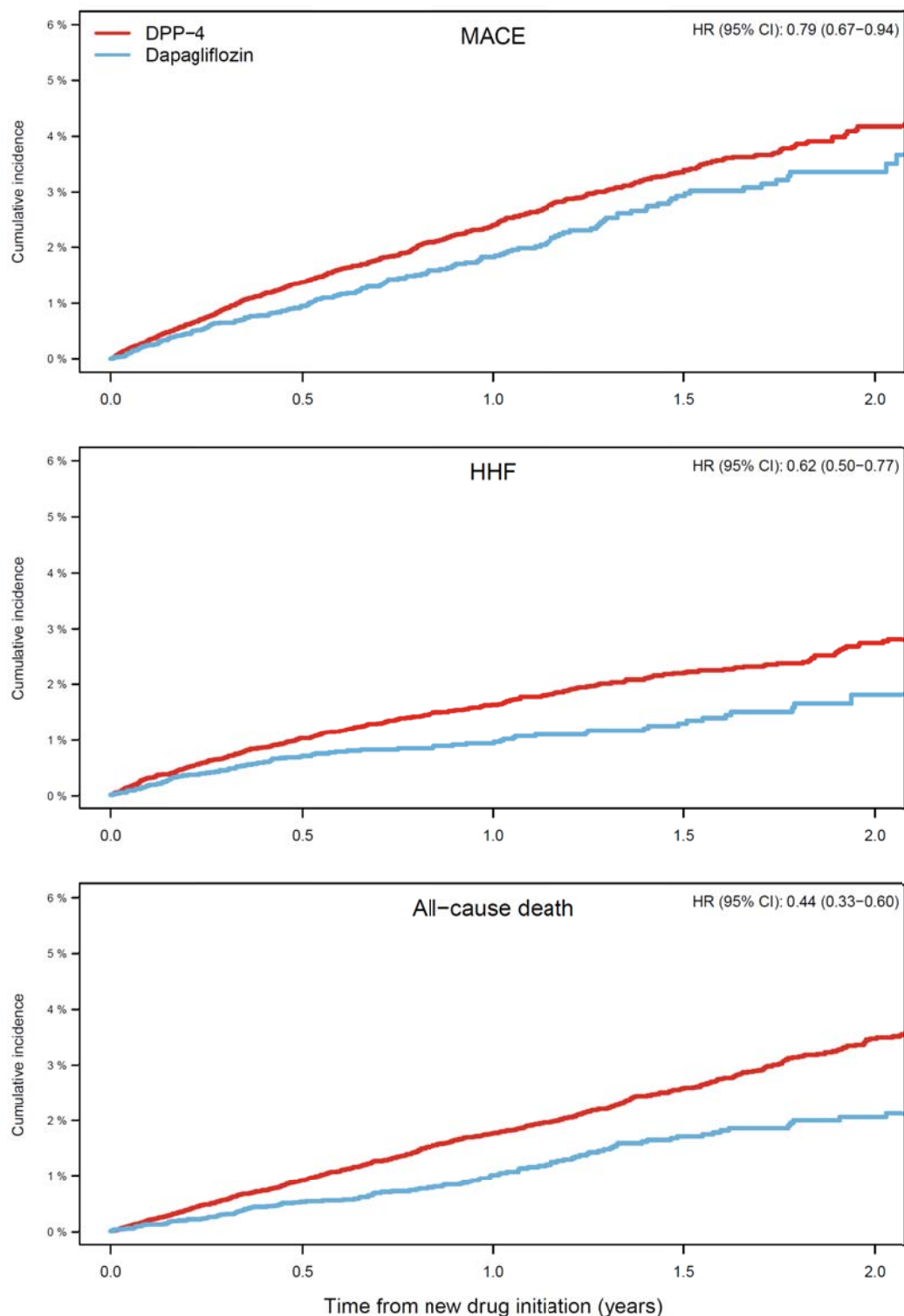


Figure 2 — Pooled Kaplan-Meier curves from all three countries and hazard ratios (HR) comparing propensity score matched 1:3 groups of new users of dapagliflozin versus dipeptidyl peptidase 4 inhibitor (DPP-4i) for major adverse cardiovascular event (MACE), hospital events for heart failure (HHF) and all-cause mortality.

Table 1 — Baseline patient characteristics of propensity matched 1:3 type 2 diabetes patients being new users of dapagliflozin versus dipeptidyl peptidase-4 inhibitor (DPP-4i).

	Dapagliflozin N=10,227	DPP-4i N=30,681	Standardized Difference*
Age, years (SD)	61 (11.1)	60.8 (12.4)	0.017
Sex (Female)	4,196 (41.0)	12,391 (40.4)	0.011
First GLD, Years (SD)	6.5 (4.1)	6.5 (4.1)	0.009
CV disease	2,356 (23.0)	6,970 (22.7)	0.006
Myocardial infarction	730 (7.1)	2,183 (7.1)	0.001
Stroke	566 (5.5)	1,699 (5.5)	0.000
Unstable angina	286 (2.8)	900 (2.9)	0.007
Heart failure	485 (4.7)	1,440 (4.7)	0.002
Atrial fibrillation	879 (8.6)	2,549 (8.3)	0.008
Chronic kidney disease	219 (2.1)	626 (2.0)	0.006
Microvascular complications	1,497 (14.6)	4,449 (14.5)	0.003
Cancer	850 (8.3)	2,624 (8.6)	0.007
Metformin	8,522 (83.3)	25,705 (83.8)	0.010
Sulphonylurea	2,668 (26.1)	7,920 (25.8)	0.005
GLP-1RA	798 (7.8)	2,309 (7.5)	0.008
Thiazolidinediones	148 (1.4)	416 (1.4)	0.006
Insulin	3,105 (30.4)	8,920 (29.1)	0.023
<i>Short-acting</i>	1,124 (11.0)	3,307 (10.8)	0.006
<i>Intermediate-acting</i>	1,504 (14.7)	4,358 (14.2)	0.012
<i>Premixed insulin</i>	813 (7.9)	2,350 (7.7)	0.009
<i>Long-acting</i>	1,044 (10.2)	3,062 (10.0)	0.006
CV preventive drugs	8,702 (85.1)	26,041 (84.9)	0.005
Low dose aspirin	3,497 (34.2)	10,434 (34.0)	0.003
Statins	6,457 (63.1)	19,405 (63.2)	0.002
Antihypertensives	7,483 (73.2)	22,255 (72.5)	0.012
Loop diuretics	1,364 (13.3)	4,036 (13.2)	0.004
Aldosterone antagonists	441 (4.3)	1,303 (4.2)	0.003
Warfarin	527 (5.2)	1,530 (5.0)	0.006
Receptor P2Y12 antagonists	471 (4.6)	1,351 (4.4)	0.008

SD. Standard deviation. All numbers in parenthesis are percentage if not stated otherwise.

*Standardized difference of >10% (>0.1) is considered to represent a statistical difference

CV. cardiovascular; DPP-4i. dipeptidyl-peptidase-4 inhibitors; SGLT-2i. Sodium-glucose-cotransporter-2-inhibitors; GLP-1RA. glucagon-like peptide-1 receptor agonists

Table 2 — Weighted means of hazard ratios (HRs) in Denmark, Norway and Sweden for new users of dapagliflozin versus new users of dipeptidyl-peptidase-4 inhibitors (DPP-4i). The groups were matched 1:3 using propensity scores based on age, sex, frailty (three or more days in hospital within one year prior to index) comorbidity and treatment.

	Dapagliflozin N=10,227		DPP-4i N=30,681		Weighted average estimates N=40,908		
	No. events	Events/100 PYR	No. events	Events/100 PYR	Hazard ratio	95% CI	p-value
MACE	177	1.86	695	2.34	0.79	(0.67-0.94)	0.006
Nonfatal myocardial infarction	87	0.91	304	1.02	0.91	(0.72-1.16)	0.445
Nonfatal stroke	69	0.72	270	0.90	0.79	(0.61-1.03)	0.086
Cardiovascular mortality	38	0.40	160	0.53	0.76	(0.53-1.08)	0.122
HHF	95	0.99	467	1.57	0.62	(0.50-0.77)	<0.001
MACE +	202	2.12	779	2.63	0.81	(0.69-0.94)	0.007
Unstable angina	37	0.39	107	0.36	1.09	(0.75-1.59)	0.655
MACE ++	285	3.01	1164	3.96	0.75	(0.66-0.86)	<0.001
All-cause mortality	120	1.03	644	1.75	0.44	(0.33-0.60)	<0.001
Atrial fibrillation	140	1.47	469	1.58	0.92	(0.76-1.12)	0.414
Severe hypoglycemia	91	0.95	300	1.01	0.94	(0.74-1.19)	0.618

HHF, hospital event for heart failure

MACE, major adverse cardiovascular event defined by cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke.

MACE+, addition of unstable angina

MACE++, addition of unstable angina and HHF