






ORIGINAL ARTICLE

Lower cardiorenal risk with sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes without cardiovascular and renal diseases: A large multinational observational study

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Abstract

Aims: We compared the new use of sodium-glucose cotransporter-2 inhibitor (SGLT2i) versus dipeptidyl peptidase-4 inhibitor (DPP4i) and the risk of cardiorenal disease, heart failure (HF) or chronic kidney disease (CKD), in patients with type 2 diabetes without a history of prevalent cardiovascular and renal disease, defined as cardiovascular and renal disease (CVRD) free, managed in routine clinical practice.

Materials and methods: In this observational cohort study, patients were identified from electronic health records from England, Germany, Japan, Norway, South Korea and Sweden, during 2012-2018. In total, 1 006 577 CVRD-free new users of SGLT2i or DPP4i were propensity score matched 1:1. Unadjusted Cox regression was used

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to estimate hazard ratios (HRs) for outcomes: cardiorenal disease, HF, CKD, stroke, myocardial infarction (MI), cardiovascular and all-cause mortality.

Results: Baseline characteristics were well balanced between the treatment groups (n = 105 130 in each group) with total follow-up of 187 955 patient years. Patients had a mean age of 56 years, 43% were women and they were indexed between 2013 and 2018. The most commonly used agents were dapagliflozin (91.7% of exposure time) and sitagliptin/linagliptin (55.0%), in the SGLT2i and DPP4i, groups, respectively. SGLT2i was associated with lower risk of cardiorenal disease, HF, CKD, all-cause and cardiovascular mortality; HR (95% confidence interval), 0.56 (0.42-0.74), 0.71 (0.59-0.86), 0.44 (0.28-0.69), 0.67 (0.59-0.77), and 0.61 (0.44-0.85), respectively. No differences were observed for stroke [0.87 (0.69-1.09)] and MI [0.94 (0.80-1.11)].

Conclusion: In this multinational observational study, SGLT2i was associated with a lower risk of HF and CKD versus DPP4i in patients with type 2 diabetes otherwise free from both cardiovascular and renal disease.

KEYWORDS

dapagliflozin, diabetic nephropathy, DPP-IV inhibitor, heart failure, observational study, SGLT2 inhibitor

1 | INTRODUCTION

Heart failure (HF) and chronic kidney disease (CKD) have been shown to be reaching epidemic proportions,¹⁻³ particularly in patients with type 2 diabetes, with negative consequences on quality of life, concomitant disease risks and health care utilization.^{1,3-6} The combination of high prevalence of type 2 diabetes, 425 million patients world-wide⁷ and associated elevated risks of HF and CKD puts these patients in a particularly vulnerable group.⁸

Despite successful treatment strategies addressing prevention of atherosclerotic cardiovascular disease,⁹ significant residual risks of HF and CKD in type 2 diabetes have been reported from several studies.¹⁰⁻¹³ One study reported that optimal management of cardiovascular risk factors in type 2 diabetes might neutralize the excess risk of myocardial infarction (MI) and stroke, but not the risk for HF, which remained high when compared with patients without type 2 diabetes.¹³ Other reports have shown that CKD prevalence and mortality risk in clinical practice remain high despite widely used renin-angiotensin inhibition.^{10,11} In addition, a large multinational study including both European and Asian countries, reported that HF and CKD are the most frequent first manifestations of cardiovascular and renal diseases (CVRD) in patients without prevalent cardiovascular or renal diseases (defined as CVRD-free).⁸ Findings from this study also demonstrated that these complications were associated with high risk of subsequent mortality, highlighting the prevalence and impact of cardiorenal diseases in the type 2 diabetes population.⁸ Therefore, there is an unmet clinical need and urgent requirement for more effective cardiorenal risk prevention strategies for HF and CKD in type 2 diabetes.¹⁴ DECLARE-TIMI 58 and CANVAS are cardiovascular outcome trials (CVOTs) with sodium-

glucose transporter-2 inhibitors (SGLT2i), which demonstrated preventive effects on cardiorenal disease in patients with type 2 diabetes with both atherosclerotic cardiovascular disease and cardiovascular risk factors, HF or overt CKD.¹⁵⁻¹⁸ Recent trials have extended preventive effects to treatment effects to patients with HF with reduced ejection fraction and potentially in patients with CKD.^{19,20}

Little is known about how the primary preventative effects of SGLT2i on cardiorenal disease shown in randomized controlled trials translate into a broad real-world population from a clinical practice setting and, further, how these effects may compare with other commonly used novel oral antihyperglycaemic agents.^{15,17,21} Dipeptidyl peptidase 4 inhibitor (DPP4i) belongs to a class of widely used glucose-lowering drugs (GLDs), which have been shown to be associated with cardiovascular and renal safety in several large clinical trials.²²⁻²⁴ Both SGLT2i and DPP4i are oral drugs of comparative costs being recommended for use after metformin in patients with CVRD-free type 2 diabetes, hence well suited to be compared as common treatment options in a real-world clinical setting.²⁵

In this multinational and contemporary cohort study from Europe and Asia we evaluated cardiorenal disease risk with new initiation of SGLT2i compared with those with new initiation of DPP4i in propensity score matched patients with type 2 diabetes without prevalent CVRD.

2 | MATERIALS AND METHODS

This study utilizes available linked electronic health care records across six countries: England, Germany, Japan, Norway, South Korea

and Sweden. Additional details of the individual datasets can be found in Supporting Information (pp. 3-5).

2.1 | Study population

All patients with type 2 diabetes, defined by use of GLDs and/or diagnosis codes (Supporting Information, p. 6),⁸ without any recorded pre-index history of cardiovascular or renal disease, defined as stroke, MI, angina pectoris (including the use of nitrates), unstable angina pectoris, atrial fibrillation, HF, coronary revascularization, peripheral artery disease, peripheral artery revascularization and CKD (chronic/acute/unspecified kidney disease, hypertensive kidney failure and diabetic nephropathy), were eligible, hereinafter referred to as CVRD-free type 2 diabetes patients (Table S1).⁸ Diseases and treatments were searched in prescribed drug and hospital records in all countries except in England where additional general practice records were searched.

A new-user event date (index date) was defined as the date of the initial filled prescription for an SGLT2i or a DPP4i preceded by a 12-month period without any filled prescription for the same drug classes.²⁶ For the sensitivity analysis comparing SGLT2i with new use of any other GLD (oGLD), the index date for any initiation of oGLD was defined by all filled prescriptions of a new GLD class other than SGLT2i.²⁷ This oGLD definition allowed for several possible new-user dates for a patient within the observation period, both within drug class and between classes.

2.2 | Baseline

Patient characteristics were described at index, including age, sex, index date, drug treatment and comorbidities (see Table S2 for detailed definitions). Comorbidities were searched for in all available data before and including the index date, with the exception of severe hypoglycaemia (up to 12 months before the index date) and cancer (up to 5 years before the index date) (see Table S1 for detailed definitions).⁸ Previous medications were defined as any drugs received within the 12 months preceding and including the index date (see Table S2 for detailed definitions).

2.3 | Outcomes

First event of recorded hospital diagnoses of cardiorenal disease (diagnosis of HF or CKD), HF (including hypertensive HF), CKD (including diabetic nephropathy, acute kidney failure, unspecified kidney disease, hypertensive kidney failure and dialysis), stroke (including ischaemic and haemorrhagic stroke), MI, and all-cause and cardiovascular mortality were analysed as outcomes (Table S3).

2.4 | Statistical analysis

Baseline characteristics were described using standard statistical measures such as mean and standard deviations for numerical variables,

and frequencies and percentages for categorical variables. An imbalance in baseline characteristics was considered if a >10% standardized difference occurred between the two groups. The CVRD-free populations are described separately by country and the overall summary is weighted according to the number of patients from each country. The proportion of exposure time contributed by individual agents was summarized both overall and by country.

To avoid immortal time bias, only the first incident episode during the inclusion period of either SGLT2i or DPP4i treatment was eligible for inclusion.²⁸ One year of not using/filling prescriptions of both SGLT2i and DPP4i was required prior to index. Patients initiated on an SGLT2i and a DPP4i on the same date were excluded.

A propensity score for initiating SGLT2i was developed (separately within each country) for each episode of new treatment initiation using an extensive number of variables (Supporting Information, pp. 6-7). Based on propensity scores, patients initiating SGLT2i were matched 1:1 with patients initiating DPP4i. The adequacy of matching was assessed by evaluating post-match standardized differences in patient characteristics (Table 1).

The time to first event was compared between groups using Cox proportional hazards models, presented as hazard ratios [HR; 95% confidence interval (CI)] for each outcome separately by country. Patients were observed from the index date until discontinuation of the index drug (where 6 months grace time after the last filled prescription was allowed), death or end of study. To explore the effects of off-treatment time, patients were followed from the start of index treatment until either occurrence of the first outcome event, or the censoring date (whichever came first), regardless of whether index treatment was discontinued. When calculating the off-treatment time, the added effects of grace time were not possible to assess.

The HRs for each endpoint from each individual country were then pooled for an overall weighted summary,²⁹ with random-effects models with inverse variance weighting for each country implemented.³⁰ Forest plots displaying country-specific HRs and pooled overall HR were produced. Analyses were also repeated in the same cohort regardless of whether index treatment was discontinued. In addition, to test the robustness of our results, an analysis that removed the data from one country at a time was performed. Subgroup analyses were multiple adjusted and tested for interactions. Multiple adjustments were performed using the following variables: age, gender, frailty (at least one hospitalization of three consecutive days within 1 year before index), duration of diabetes (if available), use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β -blockers, Ca^{2+} -channel blockers and aldosterone antagonists.

In a few of the countries (England, Japan, Norway and Sweden), where estimated glomerulus filtration rate (eGFR, mL/min/1.73 m²) measurements were available for a subset of patients, the validity of the CKD definition was tested using a simplistic method where all patients with type 2 diabetes were classified as CKD yes/no based on all available data (one diagnosis), and the latest available eGFR measurement was used. The predictive probabilities of eGFR for CKD diagnosis were tested using receiver operating characteristic curves

TABLE 1 Baseline characteristics of patients with type 2 diabetes free from cardiovascular and renal disease

	SGLT2i	DPP4i	Standardized difference (%) ^a
Number of patients	105 130	105 130	n/a
Age, years (mean ± SD)	55.7 ± 11.9	55.4 ± 12.6	2.5
Females, n (%)	45 254 (43.0)	45 095 (42.9)	0.3
Microvascular complications, n (%)	25 830 (24.6)	24 870 (23.7)	2.1
Frailty, n (%)	11 146 (10.6)	10 980 (10.4)	0.5
CVD prevention, n (%)			
Statins	56 688 (53.9)	56 318 (53.6)	0.7
Antihypertensives	59 559 (56.7)	58 776 (55.9)	1.5
ACE inhibitors	17 358 (16.5)	17 111 (16.3)	0.6
ARBs	35 705 (34.0)	35 398 (33.7)	0.6
Beta blockers	15 478 (14.7)	15 248 (14.5)	0.6
Loop diuretics	4490 (4.3)	4343 (4.1)	0.7
Aldosterone antagonists	1400 (1.3)	1339 (1.3)	0.5
Glucose-lowering drugs, n (%)			
Metformin	81 010 (77.1)	81 435 (77.5)	1.0
Sulphonylurea	31 804 (30.3)	31 068 (29.6)	1.5
GLP1-RA	4747 (4.5)	3955 (3.8)	3.8
Thiazolidinediones	7507 (7.1)	7105 (6.8)	1.5
Insulin	18 012 (17.1)	17 395 (16.5)	1.6
Index year			
2013	1657 (2.6)	1593 (2.5)	0.6
2014	11 231 (10.7)	10 839 (10.3)	1.2
2015	24 681 (23.5)	24 715 (23.5)	0.1
2016	33 295 (31.7)	33 102 (31.5)	0.4
2017	16 178 (25.5)	16 300 (25.7)	0.4
2018	18 081 (28.5)	18 578 (29.3)	1.7

Note: All numbers in parenthesis are percentages if not stated otherwise. Frailty, three or more consecutive days in hospital within the year before the index.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CVD, cardiovascular disease; DPP4i, dipeptidyl-peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

^aAn imbalance in baseline characteristics was considered when standardized difference >10%.

(ROC), including area under the curve of the receiver operating characteristic curve. In addition, the optimal cut-off was estimated using the Youden index. The validity of CKD diagnoses only set in primary care and outpatient hospital visits were tested separately.

3 | RESULTS

Before matching, the majority of variables between the SGLT2i and DPP4i group were similar, standardized difference <10%, but with differences in age, GLP1-RA, metformin and insulin treatment (Figure S1). After matching (Figure 1), baseline characteristics were well balanced between the SGLT2i and DPP4i groups (n = 105 130 in each group) with mean follow-up of 1.5 years (311 992 patient-years) (Table 1 and Figure S1). The mean patient age was 56 years, 43% were women, and there was moderate use of statins (54%) and

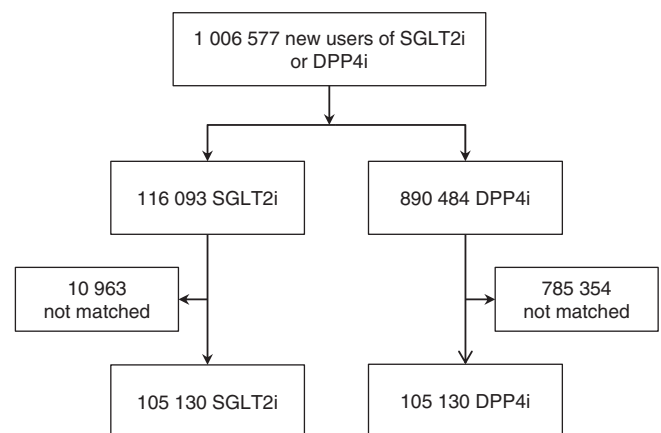


FIGURE 1 Patient flow-chart of patients with type 2 diabetes without cardiovascular or renal disease. DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor

antihypertensives (57%). Similar findings were found when comparing SGLT2i versus oGLD (Table S4).

Figure 2 shows the distribution of follow-up time for SGLT2i and DPP4i types (details in Table S5). The SGLT2i group was dominated by dapagliflozin (91.7%), whereas the DPP4i group mainly consisted of sitagliptin (29%), linagliptin (26%), gemigliptin (14%), vildagliptin (11%) and alogliptin (8%). Event rates of cardiorenal disease in the SGLT2i and DPP4i groups were 6.4 and 11.5 events per 100 patient-years, respectively (Figure 3). SGLT2i, compared with DPP4i, was associated with a lower incidence of cardiorenal disease; HR (95% CI) 0.56 (0.42-0.74) (Figure 3).

Event rates of HF, CKD, all-cause and cardiovascular death for SGLT2i/DPP4i were 2.9/4.1, 3.7/7.9, 4.3/6.3 and 1.5/2.4, respectively (Figure 3). Significant beneficial associations for SGLT2i were also observed for the individual components of HF [0.71 (0.59-0.86)] and CKD [0.44 (0.28-0.69)] and with the mortality outcomes of all-cause death and cardiovascular death, 0.67 (0.59-0.77) and 0.61 (0.44-0.85), respectively (Figure 3). Neutral associations were observed for stroke and MI, 0.87 (0.69-1.09) and 0.94 (0.80-1.11), respectively.

3.1 | Sensitivity analyses

When working stepwise and excluding one single country at a time, risk estimates remained similar and significant (Figure S3), indicating that the overall conclusion was not caused by one separate country. The multiple adjusted model showed near identical and significant results compared with the unadjusted model (Figure S4). When comparing SGLT2i versus oGLD, similar risk-lowering effects were observed for cardiorenal disease, HF, CKD, all-cause and cardiovascular death, HR (95% CI) 0.56 (0.50-0.63), 0.69 (0.60-0.80), 0.48 (0.38-0.61), 0.54 (0.45-0.64), 0.65 (0.52-0.82), respectively (Figure S5). Subgroup analyses for cardiorenal disease were all in favour of SGLT2i

and there were no significant interactions (Figure 4). For all the other endpoints, no interaction was observed except for age for the risk of HF (Figure S6).

When including the follow-up time after discontinuation of index treatment, an added 'off-treatment' follow-up time by 66% was observed, similar in both the SGLT2i and DPP4i groups (Figure S7). Here, similar and significant results were observed for cardiorenal disease, HF, CKD, all-cause and cardiovascular death, HR (95% CI) 0.68 (0.55-0.84), 0.88 (0.79-0.98), 0.56 (0.40-0.78), 0.74 (0.67-0.82) and 0.72 (0.56-0.94), respectively (Figure S8).

Validation of the CKD definition using available eGFR data showed robust sensitivity and specificity results across multiple countries (Figure S9a). Detailed validation of CKD diagnosis registered in outpatient clinic and primary care visits, showed similar results (Figures S9b and S9c).

4 | DISCUSSION

In this multinational study of 210 060 patients with CVRD-free type 2 diabetes across six countries in Asia and Europe, we have shown a new use for SGLT2i associated with significant primary preventive effects of cardiorenal disease compared with a new use for DPP4i. Significant beneficial associations were also observed for the individual components of HF and CKD and with the mortality outcomes of all-cause and CV mortality. The associations were consistent across all countries and subgroups. No association with MI and stroke risk was observed. When compared with new use of any other GLDs and multiple sensitivity tests, the results remained similar.

Whereas many CVOTs have shown beneficial SGLT2i effects on HF and kidney function in high-risk populations (patients with type 2 diabetes with atherosclerotic cardiovascular disease),^{15-17,31} a small number of trials have also reported on cardiorenal effects in low-risk

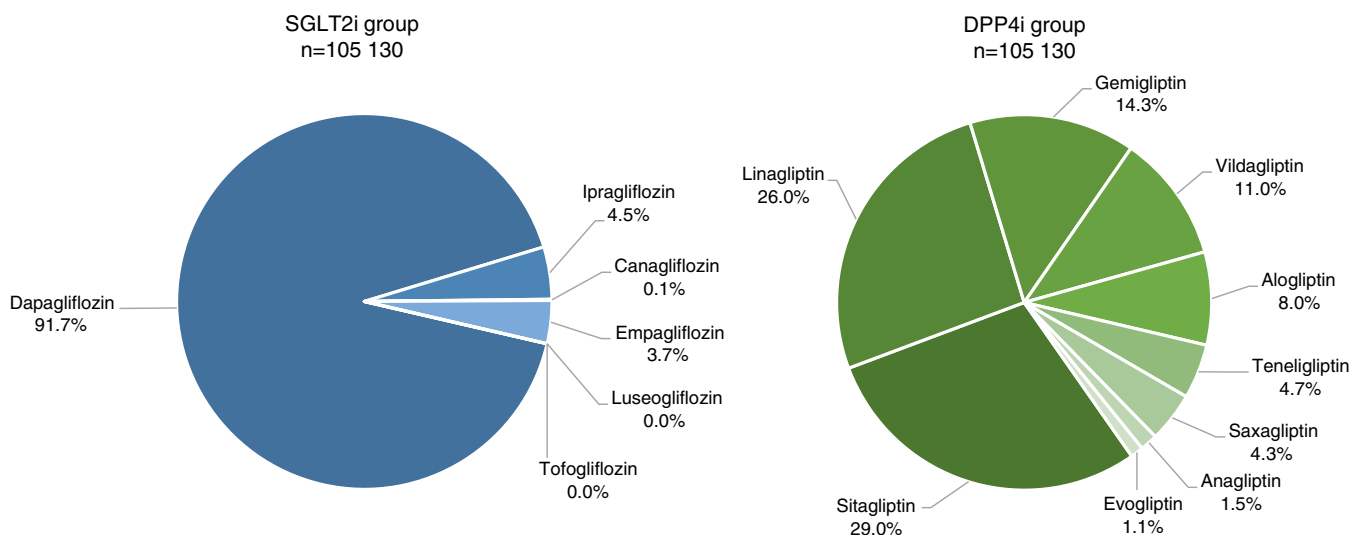


FIGURE 2 Distribution of follow-up time for the different SGLT2i and DPP4i types. DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor

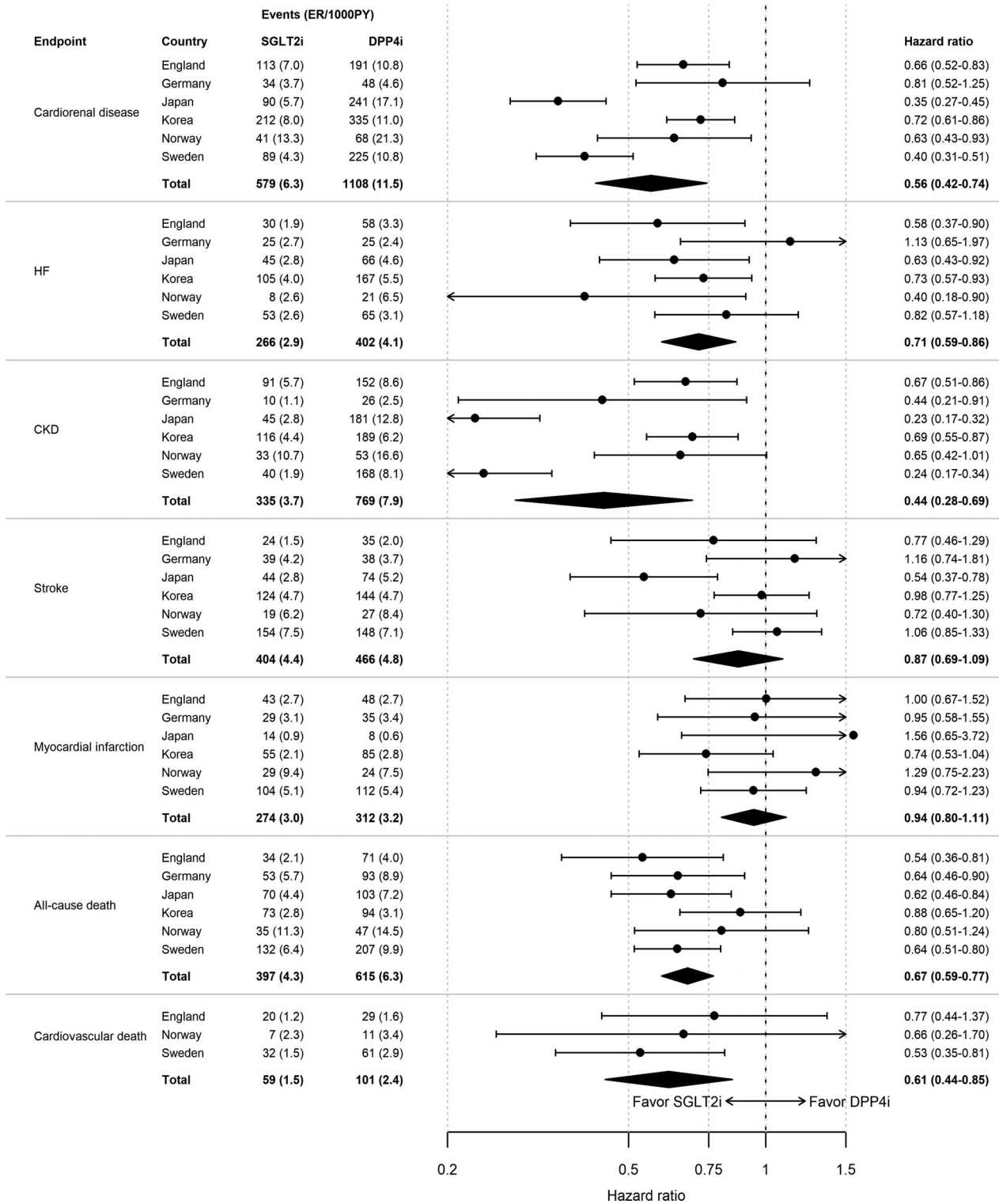


FIGURE 3 Risks of cardiorenal disease, cardiovascular disease and death in patients with type 2 diabetes free from cardiovascular and renal disease. ER, event rates; PY, patient-years; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; HF, heart failure; SGLT2i, sodium-glucose cotransporter-2 inhibitor

populations.^{15,17} The DECLARE-TIMI 58 trial included 17 160 patients with type 2 diabetes, of which 59% had no atherosclerotic cardiovascular disease, but multiple risk factors (defined as ≥ 2 cardiovascular risk factors).^{1,17} One of the inclusion criteria for this CVOT was an eGFR >60 mL/min \times 1.73 m², resulting in a patient population

with predominantly preserved renal function (92.1% had eGFR >60 mL/min \times 1.73 m²) compared with other SGLT2i CVOTs.^{16,31,32} In the multi-risk factor group, dapagliflozin showed significant risk reduction of incident cardiorenal disease, 36% [HR 0.64 (0.46-0.88)] and 49% [HR 0.51 (0.37-0.69)] for HF and CKD, respectively.^{15,17} Our

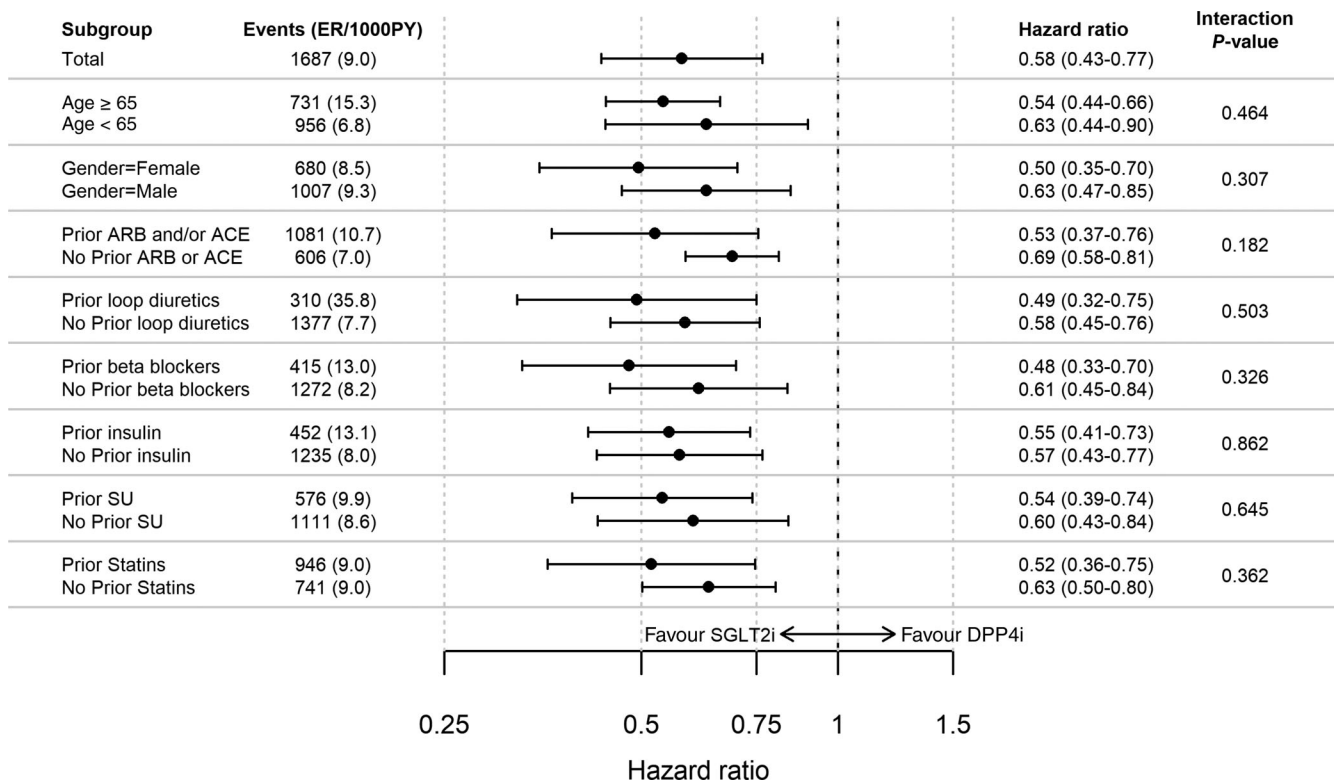


FIGURE 4 Subgroup analyses of cardiorenal disease in patients with type 2 diabetes free from cardiovascular and renal disease. ER, event rates; PY, patient-years; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; DPP4i, dipeptidyl peptidase-4 inhibitor; loop diuretics, high ceiling diuretics; RAASi, renin angiotensin aldosterone system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor

results show that the beneficial cardiorenal disease prevention with SGLT2i seen in patients with multiple risk factors indeed translates into a real-world setting of comparable CVRD-free patients managed in routine clinical practice.^{15,17} To the best of our knowledge, the present study including younger patients (mean age 55 years) and patients with CVRD-free type 2 diabetes is the first to validate cardiorenal prevention in a real-world setting shown in SGLT2i CVOTs when compared with DPP4i.^{15,17}

Large observational studies and CVOTs have consistently shown SGLT2i to reduce the risk of hospitalization for HF, with similar results to the present study,^{16,17,26,31,33-39} of which some have compared SGLT2i with DPP4i but in patients with type 2 diabetes both with and without CVRD.^{26,39} Two of the observational studies have shown beneficial HF risk reductions specifically with SGLT2i in both general- and CVOT-like type 2 diabetes populations with similar results compared with SGLT2i CVOTs.^{26,36} However, none of these studies have studied the prevention of cardiorenal disease with SGLT2i versus DPP4i in CVRD-free patients. The findings in our study are directionally aligned with these reports and, hence, extend the SGLT2i effects to a real-world primary cardiorenal prevention setting when compared with the commonly used DPP4i.

In many CVOTs, SGLT2i have been shown to prevent or delay worsening of renal function also in patients without CKD.^{15,18} In general, strong beneficial SGLT2i risk reducing effects of approximately 50% on various renal function outcomes have been reported from

both clinical trials and large observational studies.^{15,18,32,40} Our results show similar beneficial SGLT2i effects on primary renal protection, translating the effects of the early treatment demonstrated in CVOTs into a real-world clinical setting.

Cardiovascular death event rates were lower in the SGLT2i group compared with the DPP4i group [HR 0.61 (0.44-0.81)], and these results were directionally similar with overlapping CIs when compared with the SGLT2i CVOT meta-analysis by Zelniker et al. [0.84 (0.75-0.94)], and consistent with multiple large observational studies.^{18,33,36,41} However, results from the same meta-analysis of patients without atherosclerotic cardiovascular disease were less convincing for cardiovascular death. However, real-world populations are in general more frail compared with CVOT populations because of unselected inclusion and having less structured follow-up,⁴² which might be associated with a lower likelihood of surviving preventable events such as HF.^{36,43} This is also seen when comparing CVOTs; the cardiovascular mortality SGLT2i effects seem greater in more frail populations^{31,41,44,45} compared with less frail populations.^{16,17,36,43} Hence, the SGLT2i mortality results in a real-world setting might be different compared with a CVOT setting, including less frail patient populations and having a more structured follow-up.^{36,43} Moreover, the SGLT2i effect on HF [0.71 (0.59-0.86)] and CKD [0.44 (0.28-0.69)] and neutral effects on MI [0.94 (0.80-1.11)] and stroke [0.87 (0.69-1.09)] in the present study are similar to multiple CVOTs [0.69 (0.61-0.79), 0.55 (0.48-0.64), 0.89 (0.80-0.98) and 0.97 (0.86-1.10),

respectively] and observational studies, making confounding less likely.^{16–18,26,31,33,34,36} Consequently, these findings support that the observed significant risk-reducing effects with SGLT2i on cardiovascular and all-cause mortality are reasonable in a real-world setting where patients are probably frailer.

In the present study, DPP4i is a relevant comparator frequently used for early glucose treatment, having similar costs to SGLT2i in many countries and both being recommended options for treatment of patients with CVRD-free type 2 diabetes.²⁵ DPP4i, in contrast to SGLT2i, has no cardiovascular and cardiorenal protective effects.^{22,46} To the best of our knowledge, there are no trials assessing the relative effectiveness of cardiorenal risk reduction with SGLT2i and DPP-4i in a primary preventative setting, thus our results represent the first and most comprehensive assessment of this comparison to date.

The primary^{15–18} and secondary^{20,47} preventive effects on HF and CKD seem to appear very early after initiating treatment with an SGLT2i, and are not explained by the drug's effect on known risk factors such as glycated haemoglobin, blood pressure and body weight. A plethora of mechanistic hypotheses that may mediate these effects have been raised; some of the most interesting may be the natriuretic/diuretic effects and improved renal haemodynamics, a reduction in ventricular mass and improved diastolic function and myocardial energy metabolism.^{48–55} Nevertheless, the explanation of the beneficial cardiorenal effects of SGLT2is is unclear and further translational research is needed.⁵⁰

In summary, recent results have shown that cardiorenal disease is a very common and serious complication in, initially, patients with CVRD-free type 2 diabetes and that it can be prevented with SGLT2i both in CVOTs and in a real-world clinical setting.^{8,15–18} These data further support increased clinical focus on identifying and implementing early cardiorenal prevention strategies in the treatment of patients with type 2 diabetes at risk for cardiorenal events.

The strength of this study is that, to the best of our knowledge, this is the first analyses of the primary prevention of cardiorenal disease with SGLT2i versus DPP4i in patients with CVRD-free type 2 diabetes. The current analyses include populations across numerous well-established health care registries in countries and regions covering several ethnicities, resulting in a large, widely representative data set yielding a large number of events.⁸ Robust propensity score matching using multiple variables, and well-established methods to minimize risks of immortal time bias were used.^{26,27,33–36,43,56} The large study size of >200 000 patients resulted in a substantial number of outcome events, for example 1683 cardiovascular disease events during follow-up for up to 6 years (mean 1.5 years), warranting robust statistical power to assess risk differences. Following several sensitivity tests with multiple adjustments, step-wise removal of countries, subgroup analyses and including time after treatment discontinuation, the results remained similar and significant. Similar treatment persistence during follow-up was shown in both groups (Figure S7). Validation of the study CKD definition showed high sensitivity and specificity.⁸

This study does have some limitations. Despite the large size of the study, observational comparative effectiveness studies can never

replace randomized clinical trials and our results should be interpreted with several potential limitations in mind. The results are only representative of patients who have initiated treatment with SGLT2i or DPP4i with similar characteristics (e.g. treatments and comorbidities), and cannot be extended to all patients with type 2 diabetes. This study provides no information on laboratory measurements (e.g. blood pressure, serum cholesterol, body weight), lifestyle parameters, or socio-economic data, and consequently there could be residual confounding factors. The close matching on many essential variables ensures that some confounding factors are controlled, but even propensity score matching does not remedy all confounding; for example, residual confounding by indication, to the extent that prescribers will probably use more information about their patients than we have available. Measurements of eGFR albuminuria were not provided in the registries. However, a recent comparative effectiveness study by Heerspink et al.,⁴⁰ including eGFR in the propensity score, showed similar risk reducing effects on renal outcomes with SGLT2i between 51% and 67% [0.49 (0.35–0.67) and 0.33 (0.16–0.68)], compared with the 56% [0.44 (0.28–0.69)] in the present study, suggesting that renal function in part could be reflected by the extensive number of variables included in the propensity score calculations, for example age, gender, disease history (e.g. microvascular complications) and use of drugs (e.g. renin-angiotensin-aldosterone system inhibitor, sulphonylurea, metformin, insulin). Furthermore, there is no information available about the duration of diabetes in these patients. However, a robust proxy for diabetes duration is the inclusion of variables associated with diabetes duration in the propensity score, such as index date and the date of first-line initiation (i.e. diabetes treatment duration), GLD use, and cardiovascular and microvascular disease burden. Moreover, recent studies indicate that HF and CKD reduction of SGLT2i is present regardless of diabetes duration.⁵⁷ Duration of hypertension was not available. However, based on similar disease progression concerning glucometabolic (similar use of GLDs), hypertensive (similar use of antihypertensive drugs) and CVRD (CVRD-free patients) risk in both groups, it is probable that the hypertensive duration is similar in both groups. We did not examine safety. Another important limitation is that dapagliflozin was much more widely used than other SGLT2i drugs in our study population; thus, potential differences between different SGLT2i could not be assessed.

5 | CONCLUSION

In this large multinational observational study of patients with type 2 diabetes free from cardiovascular and renal disease, we have shown that the cardiorenal disease risk-lowering effects of SGLT2i reported in clinical trials translate to a multinational real-world setting.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors participated in the research design. Marcus Thuresson performed the data management and statistical analyses for all countries

after discussion with all authors. Statistical analyses were performed in Japan, Norway and Sweden by Marcus Thuresson, Germany by Nils Kossack, England by Ruiqi Zhang and South Korea by Kyoung Hwa Ha. 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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DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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