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ORIGINAL ARTICLE

Dapagliflozin and cardiovascular mortality and disease outcomes in a population with type 2 diabetes similar to that of the DECLARE-TIMI 58 trial: A nationwide observational study

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Aims: To investigate cardiovascular (CV) safety and event rates for dapagliflozin versus other glucose-lowering drugs (GLDs) in a real-world type 2 diabetes population after applying the main inclusion criteria and outcomes from the DECLARE-TIMI 58 study.

Methods: Patients with new initiation of dapagliflozin and/or other GLDs were identified in Swedish nationwide healthcare registries for the period 2013 to 2016. Patients were included if they met the main DECLARE-TIMI 58 inclusion criteria: age ≥40 years and established CV disease or presence of multiple-risk factors, e.g. men aged ≥55 years and women aged ≥60 years with hypertension or dyslipidaemia. Propensity scores for the likelihood of dapagliflozin initiation were calculated, then 1:3 matching was carried out. DECLARE-TIMI 58 outcomes were hospitalization for heart failure (HHF) or CV-specific mortality, and major adverse CV events (MACE; CV-specific mortality, myocardial infarction, or stroke). Cox survival models were used to estimate hazard ratios (HRs).

Results: After matching, a total of 28 408 new-users of dapagliflozin and/or other GLDs were identified, forming the population for the present study (henceforth referred to as the DECLARE-like cohort. The mean age of this cohort was 66 years, and 34% had established CV disease. Dapagliflozin was associated with 21% lower risk of HHF or CV mortality versus other GLDs (HR 0.79, 95% confidence interval [CI] 0.69-0.92) and had no significant association with MACE (HR 0.90, 95% CI 0.79-1.03). HHF and CV mortality risks, separately, were lower at HR 0.79 (95% CI 0.67-0.93) and HR 0.75 (95% CI 0.57-0.97), respectively. Non-significant associations were seen for myocardial infarction and stroke: HR 0.91 (95% CI 0.74-1.11) and HR 1.06 (95% CI 0.87-1.30), respectively.

Conclusion: In a real-world population similar to those included in the DECLARE-TIMI 58 study, dapagliflozin was safe with regard to CV outcomes and resulted in lower event rates of HHF and CV mortality versus other GLDs.

KEYWORDS

cardiovascular disease, cohort study, dapagliflozin, pharmaco-epidemiology, type 2 diabetes

1 | INRODUCTION

Despite modern preventive treatment for cardiovascular (CV) complications, patients with type 2 diabetes (T2D) are still at increased risk of CV disease, CV-specific mortality and heart failure.[1,2] CV outcome trials (CVOTs) of sodium-glucose-co-transporter-2 (SGLT2) inhibitor treatment of patients with T2D have previously shown paradigm-shifting reductions in risk of hospitalization for heart

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failure (HHF) and CV disease compared to placebo, which was given on top of other glucose-lowering drugs (GLDs).[3–6] However, several of these CVOTs were conducted mainly in patients with very high initial CV risk, resulting in the trial cohorts not being representative of the general T2D population in which baseline CV risk is lower.[3,4,7] The largest and most representative CVOT of an SGLT2 inhibitor is the DECLARE-TIMI 58 study on dapagliflozin, which included 17 160 patients with a broad range of CV risk, both those with established CV disease and those with multiple risk factors but without established CV disease.[5,7] DECLARE-TIMI 58 showed that dapagliflozin lowered risks of HHF and kidney disease in patients with T2D with a broad CV risk profile, as was also indicated by previous observational studies.[5,8–10] Dapagliflozin is currently the most commonly prescribed SGLT2 inhibitor drug worldwide,[10–12] and has been shown to be effective in lowering blood glucose in various clinical settings.[13–22]

One fundamental difference between CVOTs and observational studies is the use of strict CV inclusion criteria in the former, whereas a broader range of patients are included in the latter. The choice of CV inclusion criteria in CVOTs therefore predefines the trial-specific baseline CV risk, thereby impacting the representativeness of the trial population compared to a general T2D population.[7] This difference is important, as people with T2D who have, for example, a high CV risk may respond differently to the intervention compared with those with low CV risk, potentially challenging the external validity of results when comparing a trial population with a general T2D population.[23,24]

We present a novel way of evaluating the external validity of CVOT results (DECLARE-TIMI 58) in an observational setting, by both using similar main CV inclusion criteria to define a population (DECLARE-like-population), and by assessing identical trial- specific outcomes (HHF or CV mortality, and major adverse CV events [MACE]).[5] To our knowledge, no observational study assessing an SGLT2 inhibitor and its associations with CV risk has previously investigated the external validity of CVOT results by applying the same CV inclusion criteria to a general T2D population and assessing identical outcomes.

The aim of the present analysis was to study the CV safety and event rates of new use of dapagliflozin compared with new use of other GLDs in a DECLARE-like real-world T2D population after applying similar main inclusion criteria and identical outcomes to those of DECLARE-TIMI 58.[5]

2 | MATERIALS AND METHODS

2.1 | Data sources

This work is part of the D360 Nordic programme, a large-scale diabetes investigation to obtain full understanding of T2D and its drug treatment.[1,25] This programme uses the unique features of available mandatory healthcare registries and corresponding healthcare systems to identify all patients with T2D with filled GLD prescriptions (Supporting Information File S1).[26]

Sweden has a comprehensive, nationwide public healthcare system. All citizens have a unique personal identification number (person-ID), which is mandatory for all administrative purposes (including any contact with the healthcare system and filling of drug prescriptions), thus providing a complete full population medical history. The present study included data from the Swedish Prescribed Drug Register, the Cause of Death Register, and the National Patient Register, covering all hospitalizations with discharge diagnoses and all outpatient hospital visits (Supporting Information File S1). Individual patient-level data from the national registers were linked using the person-ID. The linked anonymized database was managed separately by Statisticon AB, Uppsala, Sweden. The study was approved by the Stockholm regional ethics committee (registration number 2013/2206-31).

2.2 | Study population

All patients with T2D aged >18 years with incident new-user events of filled prescriptions of either dapagliflozin or another GLD (any GLD class excluding SGLT2 inhibitors) during the years 2013 to 2016 were eligible. Patients with type 1 diabetes, gestational diabetes and polycystic ovarian syndrome were excluded (Supporting Information File S2).

To define our study population, henceforth referred to as the DECLARE-like cohort, the main CV inclusion criteria from DECLARE-TIMI 58 were applied to the general T2D population: age ≥40 years and established CV disease, or multiple risk factors (men aged ≥55 years and women aged ≥60 years with hypertension or dyslipidaemia [see Supporting Information Table S1 for how inclusion criteria in the trial were translated to fit with codes in the registry data]).[5]A new-user event date (index date) was defined as the date of the initial filled prescription for dapagliflozin or another GLD, preceded by a 12-month period without any filled prescription for the same drug class. This definition allowed several possible new-user dates for a patient within the observation period, both within drug class and between classes (Supporting Information File S3).

2.2.1 | Baseline data

Patient characteristics included age at the date of index drug, sex, index date and date of first registered dispensing of another GLD)[1,27,28]; detailed definitions are provided in Table S2. Comorbidities were searched for in all available data prior to and including the index date, with the exception of severe hypoglycaemia (up to 12 months prior to index date) and cancer (up to 5 years prior to index date); detailed definitions are provided in Table S3. Previous medications were defined as any drugs received within the 12 months preceding and including the index date; detailed definitions are provided in Table S4.

2.3 | Follow-up

Patients were observed from index date until 31 December 2016 or death, the period used for the intention-to-treat (ITT) analyses. An on-treatment (OT) approach was also used, whereby follow-up stopped at index drug treatment discontinuation, defined as the first gap of twice the length (6 months) of a reiteration period of 3-months after the last drug dispense.

2.4 | Definition of outcomes

Similar to DECLARE-TIMI 58,[5] dual primary outcomes were studied: HHF or CV mortality, and MACE, defined as a main diagnosis of myocardial infarction or ischaemic stroke or CV-specific mortality. In addition, secondary outcomes were HHF, all-cause mortality (defined as death from any cause), and atrial fibrillation and severe hypoglycaemia, both defined by in- or outpatient visits for these conditions. For detailed outcome definitions, see Table S3.[10]

2.5 | Statistical analysis

Baseline characteristics are presented as mean and SD values for continuous variables and absolute and relative frequencies for categorical variables. Standardized differences were calculated for all baseline variables and a standardized difference of >10% was used to detect non-negligible group imbalance.[29]

The propensity score for new-drug initiation of dapagliflozin was calculated for each event and 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 (Supporting Information File S3). For detailed information on variables included in the propensity score, see Tables S5A–C.

The propensity scores were then used to match each incident event of new use of dapagliflozin with incident episodes of new use of other GLDs (1:3 match, using a caliper of 0.2) using the "Match" function in the R package Matching.[30] Consequently, each patient might have contributed >1 event of new GLD initiation, for different drug classes (eg, dapagliflozin as well as various other classes of GLDs) and at different time points.[12]

The primary analysis was a survival analysis using a Cox proportional hazards model, with time since index date as underlying time scale, where a risk reduction in the dapagliflozin group was considered to be statistically significant where *P* values were <0.05 and the hazard ratio (HR) was <1.

The dependence between episodes within a patient was handled by using the robust variance estimator for clustered observations (in this case, a >1 drug initiation episode being potentially clustered within the same patient) to statistically adjust the CIs to take this into account.[31] Proportional assumptions were tested by examination of the scaled Schoenfeld residual over time. All-cause mortality event rates per 1000 patient-years and established CV disease percent was plotted for the comparator groups, both in the DECLARE-like cohort and in the three CVOTs to analyse the relationship descriptively. All analyses were conducted using R statistical software (R version 3.5.0).[32]

2.5.1 | Sensitivity analyses

For the sensitivity analyses, firstly, the HR for each outcome was estimated after additional adjustment for history of heart failure, age, sex, frailty, history of myocardial infarction, history of atrial fibrillation, duration of diabetes mellitus treatment, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, β-blocker or α-blocker use, calcium channel blocker use, loop diuretic use, and thiazide diuretic use.[33–35]

Secondly, ITT analyses were performed for all episodes of new use of dapagliflozin and other GLDs; for example, without applying main inclusion criteria from DECLARE-TIMI 58, calculating new propensity scores and re-matching using identical methods as for the primary cohort.

3 | RESULTS

3.1 | Unmatched patient characteristics and treatments

Overall, 287 180 new-user events for dapagliflozin or other GLDs were identified during the observation period years 2013 to 2016 (Figure 1). Before matching, patients in the dapagliflozin group were younger, were less frequently women, and had more microvascular disease and less CV burden, compared to patients in the other GLD group (Table S5). The dapagliflozin and other GLD groups were similar with respect to CV disease-preventive treatment, statins, antihypertensives and low-dose aspirin.

3.2 | Propensity-score-matched analyses

After matching, a total of 28 408 new-user events for either dapagliflozin (n = 7102) or other GLDs (n = 21 306) were identified (Figure 1). The groups were well balanced at baseline. The mean patient age was 66 years, 34% were women, 35% had established CV disease, 9% had prior heart failure, 38% had microvascular disease, and 100% had prescription fills of CV disease-preventive drugs (Table 1; for more detailed baseline data see Table S6). Compared with the participants in DECLARE-TIMI 58, the DECLARE-like cohort was 2 years older, had 6% less CV disease, 1% less heart failure, and similar metformin, insulin and CV disease-preventive drug treatment (Table 2). Dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1RAs were more frequently used in the DECLARE-like cohort, whereas sulphonylureas were less frequently used. The mean total follow-up time was 1.6 years, with a total of 45 434 patient-years.

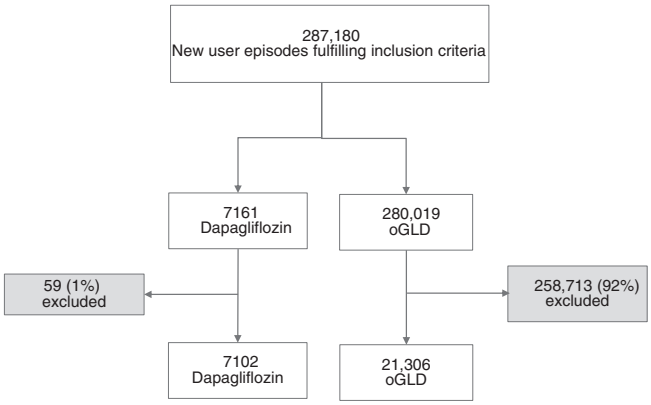

FIGURE 1 Flow charts for dapagliflozin versus other glucose-lowering drug (GLD) groups. Proportions not fulfilling propensity-matching 1:3 with 0.2 caliper were excluded and shown in grey boxes

TABLE 1 Baseline characteristics of new users of dapagliflozin versus other glucose-lowering drugs, propensity-score-matched 1:3

	Dapagliflozin N = 7102	Other GLDs N = 21 306	Standardized difference (%)[a]
Age, mean (SD) years	66.3 (7.5)	66.2 (8.1)	0.4
Sex: female, n (%)	2388 (33.6)	7200 (33.8)	0.3
Mean (SD) years since first GLD	7.4 (3.0)	7.5 (3.0)	3.5
CV disease, n (%)	2395 (33.7)	7419 (34.8)	1.9
Myocardial infarction	919 (12.9)	2763 (13.0)	0.1
Coronary revascularization	1133 (16.0)	3455 (16.2)	0.6
Coronary artery bypass grafting	333 (4.7)	1013 (4.8)	0.3
Percutaneous coronary intervention	903 (12.7)	2755 (12.9)	0.5
Unstable angina	480 (6.8)	1412 (6.6)	0.4
Angina pectoris	1131 (15.9)	3436 (16.1)	0.4
Heart failure	613 (8.6)	1865 (8.8)	0.4
Atrial fibrillation	731 (10.3)	2223 (10.4)	0.4
Stroke	520 (7.3)	1580 (7.4)	0.3
Ischaemic	451 (6.4)	1375 (6.5)	0.3
Haemorrhagic	87 (1.2)	266 (1.2)	0.2
Transitory ischaemic attack	244 (3.4)	714 (3.4)	0.4
Peripheral artery disease, n (%)	441 (6.2)	1334 (6.3)	0.2
Chronic kidney disease, n (%)	85 (1.2)	248 (1.2)	0.2
Microvascular complications, n (%)	2708 (38.1)	8188 (38.4)	0.5
Neuropathy	365 (5.1)	1014 (4.8)	1.4
Eye complications	1571 (22.1)	4623 (21.7)	0.8
Peripheral angiopathy	334 (4.7)	839 (3.9)	3.1
Kidney disease	237 (3.3)	691 (3.2)	0.4
Several−/unspecified complications	1665 (23.4)	5163 (24.2)	1.5
Severe hypoglycaemia, n (%)	38 (0.5)	126 (0.6)	0.6
Cancer, n (%)	574 (8.1)	1711 (8.0)	0.2
Lower limb amputations, n (%)	28 (0.4)	85 (0.4)	0.1
Glucose-lowering drugs, n (%)			
Metformin	5636 (79.4)	17 373 (81.5)	4.5
Sulphonylureas	1699 (23.9)	5221 (24.5)	1.1
DPP-4 inhibitors	1895 (26.7)	5748 (27.0)	0.5
GLP-1RAs	1372 (19.3)	3712 (17.4)	4.0
Metiglinides	361 (5.1)	1120 (5.3)	0.6
Thiazolidinediones	182 (2.6)	521 (2.4)	0.6
Acarbose	59 (0.8)	171 (0.8)	0.3
Insulin	3181 (44.8)	9570 (44.9)	0.2
Short-acting	1267 (17.8)	3746 (17.6)	0.6
Intermediate-acting	1403 (19.8)	4139 (19.4)	0.7
Premixed insulin	849 (12.0)	2625 (12.3)	0.9
Long-acting	1288 (18.1)	3864 (18.1)	0.0
CV risk treatment, n (%)	7102 (100.0)	21 306 (100.0)	n/a
Low dose aspirin	3104 (43.7)	9316 (43.7)	0.0
Statins	5467 (77.0)	16 438 (77.2)	0.3
Antihypertensives	6463 (91.0)	19 329 (90.7)	0.8
ACE inhibitors	2897 (40.8)	8799 (41.3)	0.8
ARB	3155 (44.4)	9331 (43.8)	1.0
Dihydropyridines	2810 (39.6)	8375 (39.3)	0.4
Thiazides	626 (8.8)	1874 (8.8)	0.1
β-Blockers	3717 (52.3)	11 142 (52.3)	0.1
Loop diuretics, n (%)	1279 (18.0)	3802 (17.8)	0.3

(Continues)

TABLE 1 (Continued)

	Dapagliflozin N = 7102	Other GLDs N = 21 306	Standardized difference (%)[a]
Aldosterone antagonists, n (%)	505 (7.1)	1544 (7.2)	0.4
Warfarin, n (%)	518 (7.3)	1601 (7.5)	0.7
Receptor P2Y12 antagonists, n (%)	484 (6.8)	1446 (6.8)	0.1

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GLD, glucose-lowering drug; CV, cardiovascular; DPP-4, dipeptidyl-peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist.
[a] Standardized difference of >10% was considered to represent a non-negligible group imbalance.

TABLE 2 Overview of trial and observational patient populations

	CV outcome trials			Present observational study
	EMPA-REG[4]	CANVAS[3]	DECLARE[5]	DECLARE-like
Follow-up	ITT	ITT	ITT	ITT
Intervention	Empagliflozin	Canagliflozin	Dapagliflozin	Dapagliflozin
Comparator	Placebo	Placebo	Placebo	Other GLDs
Main CV inclusion criteria	eCVD only	eCVD or ≥3 risk factors	eCVD or ≥2 risk factors	eCVD or ≥2 risk factors
Baseline CV disease	99%	66%	41%	35%
Age, years	63	63	64	66
Women, %	29	36	37	34
Heart failure, %	10	14	10	9
Metformin, %	74	77	79	80
Sulphonylureas, %	43	43	41	24
DPP-4 inhibitors, %	11	12	16	27
GLP-1RAs, %	3	4	4	18
Insulin, %	48	50	40	45
Statins, %	77	75	71	77
Antihypertensives, %	95	80	89	91
Number of patients	7020	10 142	17 160	28 408

Abbreviations: CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eCVD, established cardiovascular disease; GLD, glucose-lowering drug; GLP-1RA, glucagon-like peptide-1 receptor agonist.

In the other GLD group, the index drug insulin had the highest proportion of exposure time (44%), followed by DPP-4 inhibitors (17%), GLP-1RAs (12%), sulphonylureas (11%), metformin (10%) and other drugs (5%). Detailed exposure time data per separate index GLD in the other GLD group are specified in Figure S1.

3.3 | Baseline CV and population mortality rates

The all-cause mortality rates in the other-GLD group were plotted against the prevalence of established CV disease at baseline for the total DECLARE-like cohort (34%), and the groups without and with established CV disease (Figure 2). The association between baseline CV disease and all-cause mortality rates appears to be linear. A similar linearity was also observed when assessing the three CVOTs in the same way. In Figure 2, the 34% baseline CV disease mark indicates a 70% greater all-cause mortality rate for the DECLARE-like cohort compared to the CVOT populations.

3.4 | Cardiovascular outcomes

The dapagliflozin group was associated with 21% lower risk of HHF or CV mortality (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.69-0.92) and no significant associations with MACE (HR 0.90, 95% CI 0.79-1.03; Table 3 and Figure 3). HHF and CV mortality risks, separately, were lower: HR 0.79 (95% CI 0.67-0.93) and HR 0.75 (95% CI 0.57-0.97), respectively. Non-significant associations for myocardial infarction and stroke were observed: HR 0.91 (95% CI 0.74-1.11) and HR 1.06 (95% CI 0.87-1.30), respectively. The CV outcome point estimates were of similar range to those presented in DECLARE-TIMI 58 and the other CVOTs (Figure 3). The dapagliflozin group was associated with a lower risk of all-cause mortality compared with the other-GLD group: HR 0.63 (95% CI 0.54-0.74; Table 3). Non-significant associations for atrial fibrillation and severe hypoglycemia were also shown for the dapagliflozin group compared with the other-GLD group: HR 0.94 (P = 0.425) and HR 0.91 (P = 0.243), respectively.

3.5 | ITT vs OT analyses

When comparing OT with ITT analyses, the CIs overlapped the point estimates, but a consistent trend of more beneficial HRs for dapagliflozin vs other GLDs was observed (Figure 4). For MACE, the risk estimate was significant when comparing dapagliflozin vs other GLDs:

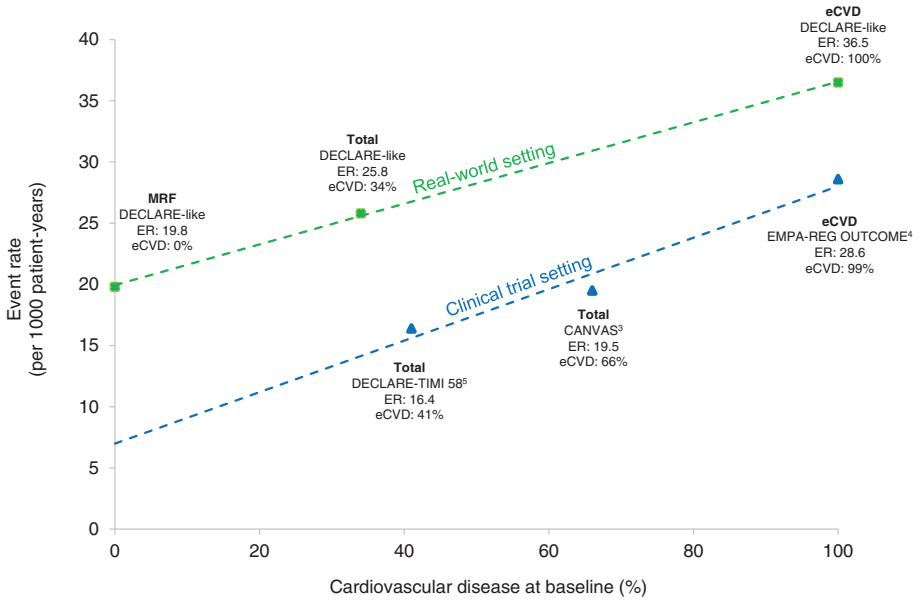

FIGURE 2 Correlation between baseline established cardiovascular disease (eCVD) and all-cause mortality rates in the comparator groups from populations with multiple risk factors (MRF) and eCVD in a real-world DECLARE-like vs clinical trial setting. References: Neal et al NEJM 2017[3]; Zinman et al NEJM 2015[4]; Wiviott et al NEJM 2018[5], ER, event rates, events per 1000 patient-years

TABLE 3 Intention-to-treat hazard ratios for new-user episodes for dapagliflozin versus new-user episodes for other glucose-lowering drugs, propensity-score-matched 1:3

	Dapagliflozin N = 7102		Other GLDs N = 21 306		N = 28 408		
	No. events	Events/1000 patient-years	No. events	Events/1000 patient-years	HR	95% CI	*P*
HHF or CV mortality	232	20.6	866	26.0	0.79	(0.69–0.92)	0.002
MACE	292	26.1	961	28.9	0.90	(0.79–1.03)	0.129
HHF	174	15.5	655	19.6	0.79	(0.67–0.93)	0.005
Myocardial infarction	116	10.3	381	11.3	0.91	(0.74–1.11)	0.347
Stroke	135	12.0	378	11.2	1.06	(0.87–1.30)	0.531
CV mortality	69	6.1	276	8.1	0.75	(0.57–0.97)	0.003
All-cause mortality	184	16.1	878	25.8	0.63	(0.54–0.74)	<0.001
Atrial fibrillation	198	17.7	626	18.8	0.94	(0.80–1.10)	0.425
Severe hypoglycemia	209	18.7	681	20.5	0.91	(0.78–1.06)	0.243

Abbreviations: CV, cardiovascular; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events (CV-specific mortality, non-fatal myocardial infarction and non-fatal stroke).

HR 0.78 (95% CI 0.66-0.92). Detailed data on the OT analyses are shown in Table S7.

3.6 | Sensitivity analyses

A multiple adjusted model for the ITT analyses showed similar results to the unadjusted ITT model (Table S8). When addressing all patients with new use of dapagliflozin and new use of another GLD (ie, without application of the DECLARE-TIMI-58 inclusion criteria), the number of patients increased by 49% to 42 292. Groups were well balanced, and the mean age and prevalence of CV disease were lower in this new cohort compared to the DECLARE-like cohort: 61.6 vs 66.2 years and 23% vs 34%, respectively (Table S9). Results remained numerically similar for all outcomes. The number of MACE increased by 20%, from 1253 to 1503 and the association was 0.85 (0.76-0.96; Table S10).

4 | DISCUSSION

In this nationwide observational study, a novel approach to studying the external validity of a randomized controlled trial was applied. The DECLARE-like cohort was defined by applying the main CV inclusion criteria from DECLARE-TIMI 58[5] to a general T2D population to study the CV safety and event rates comparing new treatment initiation of dapagliflozin vs other GLDs. The real-world study in the DECLARE-like cohort showed nearly identical outcome results for dapagliflozin to those observed in the randomized controlled trial DECLARE-TIMI 58.[5]

There are several major important findings from this work. First, despite the fact that after propensity-score matching, the DECLARE-like cohort was similar in baseline characteristics compared with the trial population in DECLARE-TIMI-58,[5] the real-world DECLARE-like cohort seemed to be substantially frailer, with higher all-cause

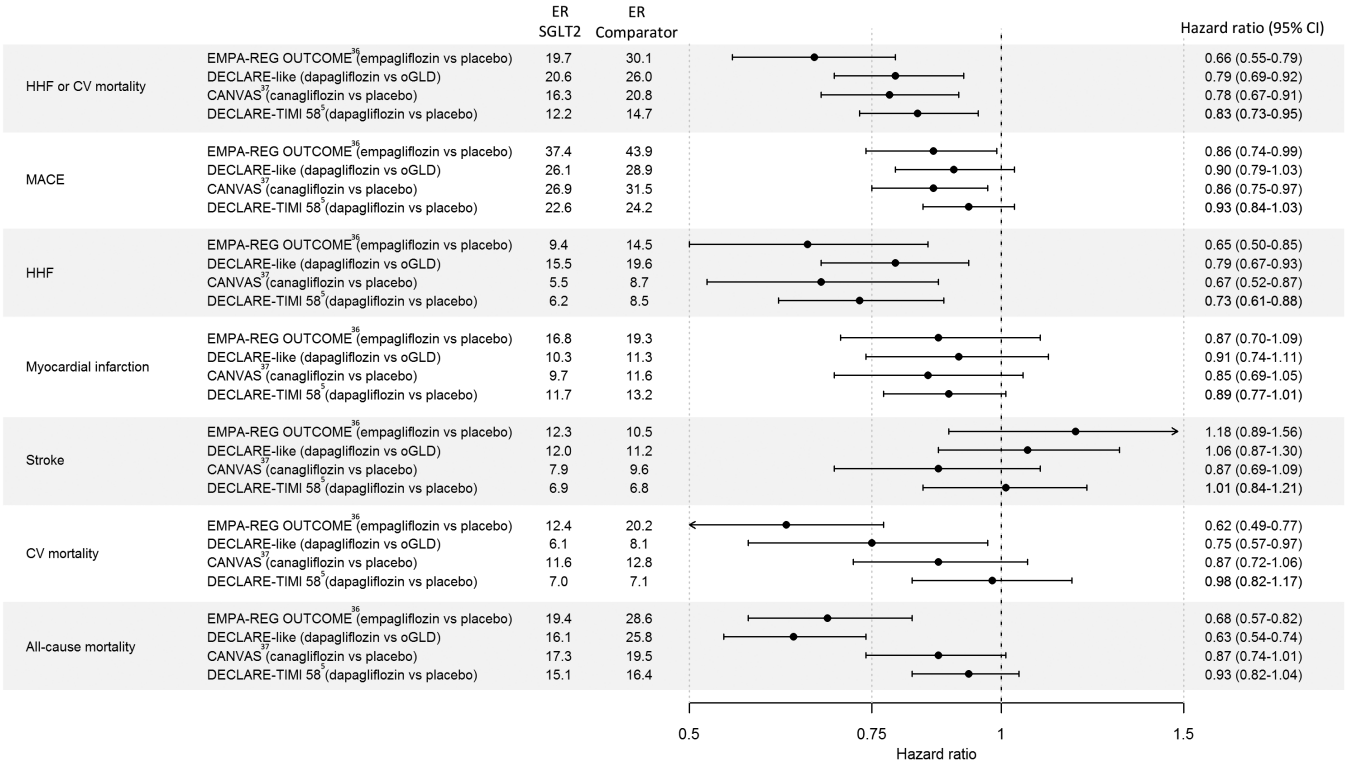

FIGURE 3 Forest plots comparing the real-world DECLARE-like results with those of other sodium-glucose co-transporter-2 inhibitor cardiovascular outcome trials. The studies are presented according to mortality event rates in the comparator group, that is, highest in EMPA-REG OUTCOME and lowest in DECLARE-TIMI 58. References: Fitchett et al Eur Heart J 2018[36]; Radholm et al Circulation 2018[37]; Wiviott et al NEJM 2018[5]. CV, cardiovascular; ER, event rate per 1000 patient-years; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events (CV-specific mortality, non-fatal myocardial infarction and non-fatal stroke)

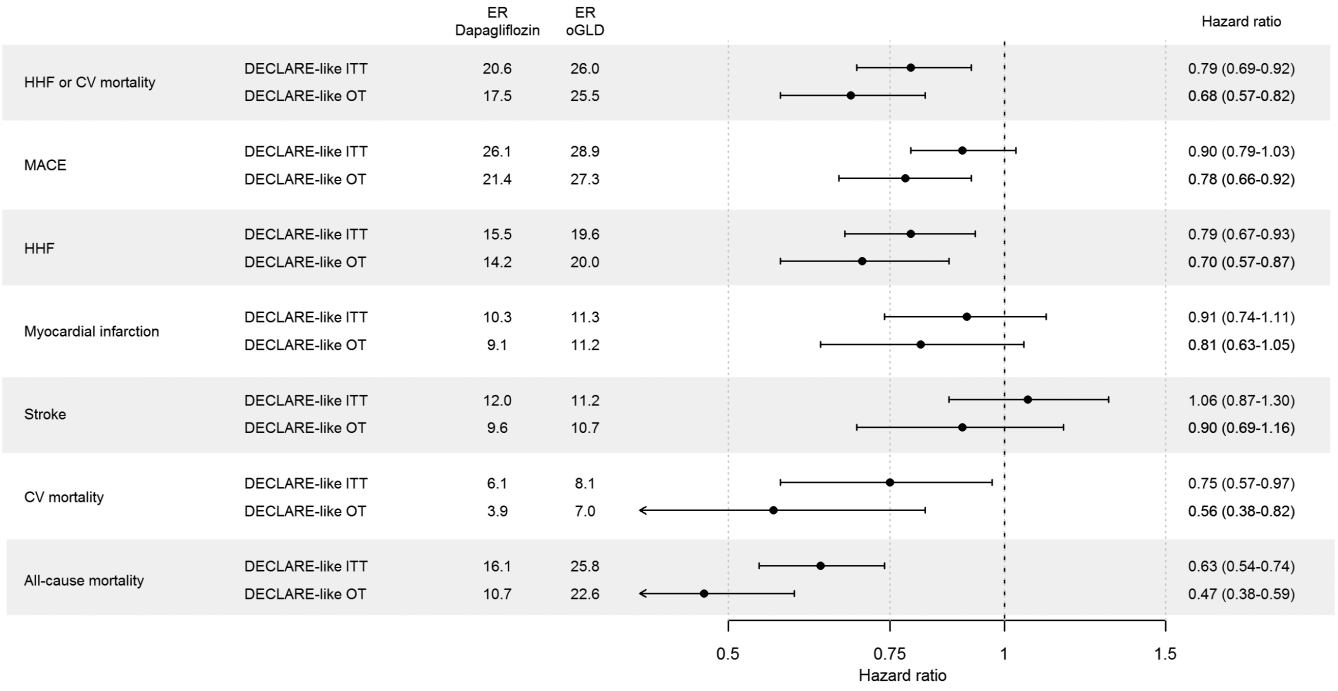

FIGURE 4 Forest plots comparing results from intention-to-treat (ITT) vs an on-treatment (OT) analysis. CV, cardiovascular; ER, event rate per 1000 patient-years; HHF, hospital event for heart failure; MACE, major adverse cardiovascular events (CV-specific mortality, non-fatal myocardial infarction and non-fatal stroke)

mortality rates. Very similar efficacy findings were observed in the DECLARE-like cohort to those found in the DECLARE-TIMI 58 cohort, with dapagliflozin being associated with reductions in HHF or CV mortality (21% vs 17%), HHF (21% vs 27%) and non-significant for MACE (10% vs 7%), while for myocardial infarction and stroke the associations were neutral in both studies.[5] In the DECLARE-like cohort, however, effects on CV-specific mortality and all-cause mortality were observed, in contrast to the results of the DECLARE-TIMI 58 study. This variability in results may be explained by the large difference in population frailty observed between the two studies. In fact, the DECLARE-like cohort was substantially more frail than that of DECLARE-TIMI 58, as suggested by the 1.7-fold higher mortality rate, which might have conferred a higher risk of dying for example, from an HHF event, than surviving. This is important as the likelihood of surviving an heart failure event is higher in a less frail population (that of the DECLARE-TIMI 58 study) than in both the present real-world DECLARE-like cohort and the populations of other CVOTs in which use of SGLT2 inhibitors vs other GLDs might have greater impact on heart failure-mediated CV mortality (Figure 3).[3–5].

Moreover, the size of treatment effect of SGLT2 inhibitors on CV mortality seems to be associated with population frailty, as shown clearly in Figure 3. It is therefore likely that, as a result of the lower population frailty in the DECLARE-TIMI 58 population, the beneficial effects of dapagliflozin on CV mortality risk are underestimated, both when compared with other CVOTs and compared with patient populations in a real-world setting.[5] This is also relevant as general T2D populations are even frailer, with all-cause mortality event rates as high as 36 per 1000 years,[1] compared with the DECLARE-like cohort, in which there were 25.6 events per 1000 patient-years, indicating a potentially greater dapagliflozin effect if its use were to be applied in a broader population. Additionally, there may be a greater impact on all-cause mortality in a real-world setting as the non-CV-specific mortality may be partly attributable to underlying CV disease, which is not as well captured by real-world clinical assessment and death certificate reports as it would be by the CVOT endpoint committee adjudication.

The second important finding is that MACE risk was similarly lower for dapagliflozin in the DECLARE-like cohort compared to the cohorts of the other CVOTs, but the difference was not statistically significant[3–5]; however, in a separate analysis in the present study, using all new use of dapagliflozin or other GLDs (removing application of inclusion criteria), statistical power increased (number of MACE events increased by 20%) and the result (HR 0.85 [95% CI 0.76-0.96]) was also similar to other CVOTs regarding significance level.[3–5]

To assess the effects of discontinuing the index drug, we compared results from the ITT approach with those of the OT approach by censoring at index drug discontinuation (Figure 4). In the OT analyses, the results showed a consistent trend towards stronger risk-reduction estimates with dapagliflozin for all CV-related outcomes. For all CV outcomes, the event rate decrease was greater with dapagliflozin compared with more stable rates for other GLDs when comparing ITT vs OT approach; suggesting that we rather observe a treatment effect of dapagliflozin than adverse effects with other GLDs, see Figure 4. The results for dapagliflozin are similar to those reported in the CVD-REAL Nordic studies, which shows the robustness of our methods and results.[9,10]

Strengths of the present study include its population-based, nationwide and real-world design, which provides high external validity and a large enough population to allow propensity-score-matched analyses. The results were consistent with DECLARE-TIMI 58 as well as several observational studies and subgroup analyses.[5,9,10] In addition, national registers with full coverage for hospitalizations, filled drug prescriptions and cause of death were used in the setting of an established and complete public healthcare system. Because diagnostic accuracy, such as identification of HHF in registries, can be challenging, it is reassuring that CV diagnoses in Sweden have high validity.[38] Anticipated neutral associations with atrial fibrillation and severe hypoglycaemia confirm the balanced baseline risk profile for the dapagliflozin group and other-GLD group.

The study is limited by confounding factors, for example, selection bias or lack of data, impacting the CV risk at baseline, which is a common concern in observational studies; however, in the present study, strikingly similar results were obtained with regard to a broad number of outcomes compared to the CVOTs, which is unlikely to be explained solely by random or confounding effects. In the other-GLD group, a significant proportion of patients had an index date for new initiation of insulin, which in observational studies has been shown to be associated with increased CV and mortality risks and to drive adverse effects when used as a comparator[28,39–41]; however, in the present DECLARE-like cohort, 45% of the patients were already on insulin at baseline, which may have diluted the potential effects of new insulin treatment initiation. Moreover, the greater event rate decrease with dapagliflozin compared with stable event rates in other GLD, comparing the ITT with the OT approach, suggest a CV effect with dapagliflozin rather than adverse effects in the other GLD group, see Figure 4. In the recently published CVD-REAL Nordic study by Persson et al,[9] comparing dapagliflozin with DPP-4 inhibitors, nearly identical results were found using the same methods and including data from several countries, support the notion of beneficial effects of dapagliflozin rather than adverse effects of other GLDs. In another CVD-REAL Nordic study by Birkeland et al,[10] comparing SGLT2 inhibitor use (94% dapagliflozin) with use of other GLDs, subgroup analyses with respect to treatment with insulin did not detect any interactions; thus, these large observational studies with similar outcomes and results showed no interactions with insulin treatment at baseline[10] or during follow-up.[9] The results of the present study design, based on propensity-score matching on a large number of clinically relevant variables (>90 variables), have been shown to be robust, and the differences in mortality risks are probably explained by different levels of population frailty, as also discussed by Wiviott et al.[5]

The results are only representative for patients who have initiated dapagliflozin treatment in a single country or have similar clinical characteristics and cannot be extended to all patients with T2D; however, in a recent publication, it is suggested that primary analyses should be performed in a single database and discussed in the context of cross-national comparisons.[42] Hence, we would encourage multinational studies, similar to the present DECLARE-like study, using the rich healthcare registry data available across the world.[11,12]

The present work has no information on laboratory measurements, lifestyle variables, primary healthcare data or socio-economic 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 for, but even propensity-score matching does not address all potential confounding, for example, residual confounding by indication. Furthermore, we had no information on 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. We had no information on emigration, which could result in loss to follow-up. No information on immigration was available, and some patients might have less comprehensive disease history in this patient group.

A novel aspect of the present study is the two-step approach for the complete translation of CVOT results from a selected trial population to a broad T2D population. First, the unique design of this observational study provides a translation of beneficial dapagliflozin efficacy results from DECLARE-TIMI 58 into a real-world DECLARE-like cohort by applying both main CV inclusion criteria to a general T2D population and using the same specific outcomes. Second, the results from this DECLARE-like study are consistent with previously reported observational dapagliflozin studies, thereby supporting the translation of effect from the present study to all available patients using dapagliflozin, for example, those in the CVD-REAL Nordic study.[9,10]

In summary, we showed significant and robust dapagliflozin effects in a DECLARE-like cohort similar to that of the DECLARE-TIMI 58 trial, suggesting that the CVOT results can be translated in to a real-world setting and vice versa. Moreover, we also showed that mortality results might be different in DECLARE-TIMI 58 because of its relatively low population frailty compared to other CVOTs and observational studies. Finally, we showed that assessment of drug treatments in a real-world setting could provide valuable additional insights if carried out correctly, and that results could be an important complement to randomized controlled trials.

In conclusion, in this DECLARE-like cohort consisting of patients with T2D with established CV disease or multiple risk factors, we showed that the beneficial CV effects of dapagliflozin were similar to those reported in the DECLARE-TIMI 58 trial, suggesting that the results can be translated into a real-world setting. Despite the similarities between results of this DECLARE-like study and several CVOTs, it is not unlikely that the effect of dapagliflozin on mortality in DECLARE-TIMI 58 might be different in a real-world setting were patients are significantly more frail.

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CONFLICT OF INTEREST

T.N. has received unrestricted grants from AstraZeneca and NovoNordisk, and is on the national board of NovoNordisk, Sanofi-Aventis, Eli Lilly and Boehringer Ingelheim. J.W.E. has received honoraria or research grants from AstraZeneca, NovoNordisk, Bayer, Sanofi and MSD. D.N. has received consultancy fees from Novo Nordisk, Astra Zeneca and Eli Lilly. M.T. is employed by an independent statistical consultant company, Statisticon AB, Uppsala, Sweden, of which AstraZeneca Nordic-Baltic is a client. A.N. has received honoraria from MSD, Astra Zeneca, Eli Lilly, Boehringer Ingelheim and Novo Nordisk. J.B. holds a full-time position at AstraZeneca as epidemiologist.

Author contributions

All authors participated in the research design. M.T. 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 responsibility for the decision to submit for publication.

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SUPPORTING INFORMATION

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

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