Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis

Kåre I Birkeland, Marit E Jørgensen, Bendix Carstensen, Frederik Persson, Hanne L Gulseth, Marcus Thuresson, Peter Fenici, David Nathanson, Thomas Nyström, Jan W Eriksson, Johan Bodegård, Anna Norhammar

Summary

Background In patients with type 2 diabetes and a high cardiovascular risk profile, the sodium-glucose co-transporter-2 (SGLT2) inhibitors empagliflozin and canagliflozin have been shown to lower cardiovascular morbidity and mortality. Using real-world data from clinical practice, we aimed to compare cardiovascular mortality and morbidity in new users of SGLT2 inhibitors versus new users of other glucose-lowering drugs, in a population with a broad cardiovascular risk profile.

Methods CVD-REAL Nordic was an observational analysis of individual patient-level data from the Prescribed Drug Registers, Cause of Death Registers, and National Patient Registers in Denmark, Norway, and Sweden. All patients who filled a prescription for glucose-lowering drugs between 2012 and 2015 were included and followed up until Dec 31, 2015. Patients were divided into new users of SGLT2 inhibitors and new users of other glucose-lowering drugs. Each SGLT2 inhibitor user was matched with three users of other glucose-lowering drugs by use of propensity scores. Hazard ratios (HRs) were estimated by country (Cox survival model) and weighted averages were calculated. Cardiovascular outcomes investigated were cardiovascular mortality, major adverse cardiovascular events (cardiovascular mortality, myocardial infarction, and ischaemic or haemorrhagic stroke), hospital events for heart failure (inpatient or outpatient visit with a primary diagnosis of heart failure), non-fatal myocardial infarction, non-fatal stroke, and atrial fibrillation. We also assessed incidence of severe hypoglycaemia.

Findings Matched SGLT2 inhibitor (n=22 830) and other glucose-lowering drug (n=68 490) groups were well balanced at baseline, with a mean follow-up of 0·9 (SD 4·1) years (80 669 patient-years) and mean age of 61 (12·0) years; 40% (36 362 of 91 320) were women and prevalence of cardiovascular disease was 25% (22 686 of 91 320). 94% of the total SGLT2 inhibitor exposure time was for use of dapagliflozin, with 5% for empagliflozin, and 1% for canagliflozin. Compared with other glucose-lowering drugs, use of SGLT2 inhibitors was associated with decreased risk of cardiovascular mortality (HR 0·53 [95% CI 0·40–0·71]), major adverse cardiovascular events (0·78 [0·69–0·87]), and hospital events for heart failure (0·70 [0·61–0·81]; p<0·0001 for all). We did not identify significant differences between use of SGLT2 inhibitors and use of other glucose-lowering drugs for non-fatal myocardial infarction, non-fatal stroke, or atrial fibrillation. Compared with other glucose-lowering drugs, use of SGLT2 inhibitors was associated with a decreased risk of severe hypoglycaemia (HR 0·76 [0·65–0·90]; p=0·001). For cardiovascular mortality, the differences were similar for the 25% of individuals with cardiovascular disease at baseline and those without (HR 0·60 [0·42–0·85] *vs* 0·55 [0·34–0·90]), while for major adverse cardiovascular events the HR in the group with cardiovascular disease at baseline was 0·70 (0·59–0·83) versus 0·90 (0·76–1·07) in the group without.

Interpretation In a population of patients with type 2 diabetes and a broad cardiovascular risk profile, SGLT2 inhibitor use was associated with reduced cardiovascular disease and cardiovascular mortality compared with use of other glucose-lowering drugs—a finding consistent with the results of clinical trials in patients at high cardiovascular risk.

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Institute of Clinical Medicine, University of Oslo, Oslo, Norway (Prof K I Birkeland MD); **Department of Transplantation Medicine** (Prof K I Birkeland) **and Department of Endocrinology, Morbid Obesity and Preventive Medicine** (H L Gulseth MD), **Oslo University Hospital, Oslo, Norway; Steno Diabetes Center Copenhagen, Gentofte, Denmark** (Prof M E Jørgensen MD, B Carstensen MSc, F Persson MD); **National Institute of Public Health, Southern Denmark University, Copenhagen, Denmark** (Prof M E Jørgensen); **Statisticon AB, Uppsala, Sweden** (M Thuresson PhD); **AstraZeneca, Cambridge, UK** (P Fenici MD); **Department of Clinical Science and Education** (D Nathanson MD, T Nyström MD) **and Department of Medicine, Södersjukhuset,** (A Norhammar MD), **Karolinska Institutet, Stockholm, Sweden; Department of Medical Sciences, Uppsala University, Uppsala, Sweden** (Prof J W Eriksson MD); **Medical Department, AstraZeneca Nordic-Baltic, Oslo, Norway** (J Bodegård MD); **and Capio St Görans Hospital, Stockholm, Sweden** (A Norhammar)

Correspondence to: Dr Johan Bodegård, AstraZeneca Nordic-Baltic, Oslo 92 0601, Norway **johan.bodegard@astrazeneca.com**

Introduction

Patients with type 2 diabetes are at increased risk of mortality and cardiovascular disease.[1] Improved glucose control alone has not been convincingly shown to reduce the cardiovascular risk, pointing to a clinically unmet need.[2–4] Results from the EMPA-REG OUTCOME randomised controlled trial, which compared the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin with placebo in patients with type 2 diabetes and high cardiovascular risk, the SGLT2 inhibitor showed a convincing cardiovascular risk reduction (probably independent of the drug's glucose-

Research in context

Evidence before this study

In the EMPA-REG OUTCOME trial, the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin lowered cardiovascular morbidity and mortality in patients with type 2 diabetes and high cardiovascular risk; a similar effect was seen with the SGLT2 inhibitor canagliflozin in the CANVAS trial programme. To review observational studies reporting on the association between use of SGLT2 inhibitors and cardiovascular mortality and cardiovascular events, we searched PubMed for articles published after the introduction of this drug class, from Jan 1, 2013, to June 5, 2017, using the MeSH terms "SGLT2-inhibitor", "cardiovascular", "heart failure", "mortality", "empagliflozin", "dapagliflozin", and "canagliflozin". We identified one observational study reporting all-cause mortality, one reporting hospital admission (ie, inpatient admission) for heart failure and all-cause mortality, and one reporting cardiovascular disease and mortality for a combined intervention of dipeptidyl peptidase-4 inhibitors and SGLT2 inhibitors. None of these studies presented data for major adverse cardiovascular events, cardiovascular mortality, atrial fibrillation, or severe hypoglycaemia following new use of SGLT2 inhibitors in clinical practice in non-selected patients with type 2 diabetes. We also identified one meta-analysis, using data from placebo-controlled clinical trials, reporting that SGLT2 inhibitors protect against cardiovascular outcomes and death, and another reporting no increased risk of major adverse cardiovascular events with dapagliflozin.

Added value of this study

In this observational study, which includes all patients with type 2 diabetes who started a new glucose-lowering drug after the introduction of SGLT2 inhibitors until Dec 31, 2015, in Denmark, Norway, and Sweden, new use of an SLGT2 inhibitor was associated with a substantially decreased risk of cardiovascular mortality, major adverse cardiovascular events, and hospital events (inpatient and outpatient visits) for heart failure compared with new use of any other glucose-lowering drug. The magnitudes of these associations in a type 2 diabetes population in which 25% of patients had established cardiovascular disease were similar to the results of the EMPA-REG OUTCOME and CANVAS trials, which were done in patients at high risk of cardiovascular disease. The present data extend the results of these studies to the SGLT2 inhibitor drug class and to a real-world clinical setting in an unselected type 2 diabetes population with a broad cardiovascular risk profile.

Implications of all the available evidence

Health-care providers treating patients with type 2 diabetes should be aware of the potential beneficial cardiovascular outcomes associated with the use of SGLT2 inhibitors when added to existing diabetes therapy.

lowering effect), especially for cardiovascular mortality, cardiovascular disease, and heart failure outcomes.[5] Similar effects were seen in the CANVAS trial of the SGLT2 inhibitor canagliflozin.[6] These results have important implications regarding treatment strategies for type 2 diabetes, but it remains to be shown whether these effects will be seen for all SGLT2 inhibitors and whether these findings can be translated into real-world clinical settings in patients with a broader risk profile than that of the trial participants.

Findings from meta-analyses have supported a class effect of SGLT2 inhibitors on cardiovascular outcomes,[7,8] and data from the large observational CVD-REAL study have shown that the SGLT2 inhibitor drug class was associated with decreased risks of hospital events for heart failure and all-cause mortality in patients with or without established cardiovascular disease.[9,10] The CVD-REAL results extend part of the findings of the EMPA-REG OUTCOME and CANVAS trials into a broader cardiovascular risk population of patients with type 2 diabetes across six countries (Denmark, Germany, Norway, Sweden, UK, and USA). However, since only Denmark, Norway, and Sweden have complete population-level registries with full records of disease history and mortality causes, these countries represent a unique opportunity to further assess other important outcomes such as causes of death and other cardiovascular-related outcomes.[9] Analysis of these high-quality data sources to investigate a broad range of cardiovascular outcomes in real-world settings will complement results of cardiovascular outcome trials such as EMPA-REG OUTCOME[5] and CANVAS[6] (and ongoing trials such as DECLARE-TIMI 58 [dapagliflozin; NCT01730534] and VERTIS [ertugliflozin; NCT01986881]) to enhance our understanding of the cardiovascular effects of SGLT2 inhibitor drugs.

The aim of the CVD-REAL Nordic study was to investigate whether new use of SGLT2 inhibitors, compared with new use of other glucose-lowering drugs, was associated with changes in cardiovascular mortality and disease risk, including major adverse cardiovascular events and hospital events for heart failure.

Methods

Data sources and study population

This observational analysis was based on national registry data from Denmark, Norway, and Sweden—countries with comprehensive public health-care systems covering the entire population. Individual patient-level data from the Prescribed Drug Registers covering all filled prescriptions, and the Cause of Death Registers and National Patient Registers covering all hospital admissions with discharge diagnoses and all outpatient hospital visits, were linked by use of personal

identification numbers (which are mandatory for all administrative purposes, including health-care contacts and drug dispensing). Data linkage was done by the Swedish National Board of Health and Welfare, the Norwegian Institute of Public Health, and Statistics Denmark. The linked databases were managed separately by Statisticon AB (Uppsala, Sweden; Swedish and Norwegian databases) and by the Steno Diabetes Center Copenhagen (Gentofte, Denmark; Danish database). Detailed information on data linkage is provided in the appendix (pp 1, 2).

All patients who were new users of the glucose-lowering drug class of interest from the timepoint when SGLT2 inhibitor treatment became available in their respective countries were eligible for inclusion (Denmark: December, 2012; Norway: November, 2013; Sweden: January, 2013). Patients were followed up until Dec 31, 2015. Patients with type 1 diabetes, gestational diabetes, and polycystic ovarian syndrome were excluded (appendix). The index date was defined as the date of dispensing of a drug class of interest after a 12-month period without any dispensing of the drug class. For insulin, short-acting, intermediate-acting (ie, isophane), long-acting, and premixed (intermediate-acting and short-acting) insulins were considered to be different drug classes. This definition resulted in several possible new-user dates for the same patient within the observation period, both within and between drug classes. In cases where multiple new-user dates were identified, the index date definition followed a hierarchical structure, starting with the new user date for an SGLT2 inhibitor, if present. For patients starting on other glucose-lowering drugs at multiple new-user dates, the index date was randomly chosen from among the available dates (a detailed definition of the index drugs is included in the appendix p 5).

Baseline data and follow-up

Baseline patient characteristics included age, sex, index date, date of first registered glucose-lowering drug dispensed, and frailty (defined as at least one hospital admission of ≥3 consecutive days during the year before the index date; see appendix p 6).[1,11,12] Comorbidities were searched for in all available data up to and including the index date, with an exception for severe hypoglycaemia (within 1 year before the index date) and cancer (within 5 years before the index date; see appendix pp 6, 7). Previous medication was defined as any drug dispensed in the 1 year up to and including the index date (appendix pp 8, 9).

An on-treatment approach was used for the main analyses of follow-up data. Patients were observed from the index date until discontinuation of the index drug (defined as 6 months after the last filled prescription), death, or end of study (Dec 31, 2015). Additionally, intention-to-treat analyses were done, which included the follow-up time after index treatment discontinuation.

Outcomes

Cardiovascular outcomes investigated were cardiovascular mortality (any cardiovascular diagnosis listed as the main cause of death), major adverse cardiovascular events (cardiovascular mortality, main diagnosis of myocardial infarction, and main diagnosis of ischaemic or haemorrhagic stroke), hospital event for heart failure (defined as an inpatient or outpatient visit with a primary diagnosis of heart failure), non-fatal myocardial infarction, and non-fatal stroke. Other predefined outcomes were all-cause mortality, atrial fibrillation, and severe hypoglycaemia. Descriptions of diagnoses to define the outcomes are provided in the appendix (pp 6, 7).

See Online for appendix

Propensity score matching

Propensity scores were used to match each patient who initiated an SGLT2 inhibitor with patients who initiated other glucose-lowering drugs (in a 1:3 ratio) with a caliper of 0·2. The probability of initiation of an SGLT2 inhibitor (as opposed to other glucose-lowering drugs) was estimated by use of a logistic regression model, with all available patient variables at the date of the first filled prescription of the index drug considered as independent variables (appendix). Matching was done with the Match function in the R package Matching (R version 3.2.3).[13]

Statistical analysis

After matching, a standardised difference of more than 10% was used to detect significant group imbalance between baseline variables.[14] Analyses were done within each separate country database. The primary analysis was a survival analysis with a Cox proportional hazards model, with time since index date as the underlying timescale. The primary model used only index drug as a covariate (SGLT2 inhibitor *vs* other glucose-lowering drug), whereas the subgroup analyses

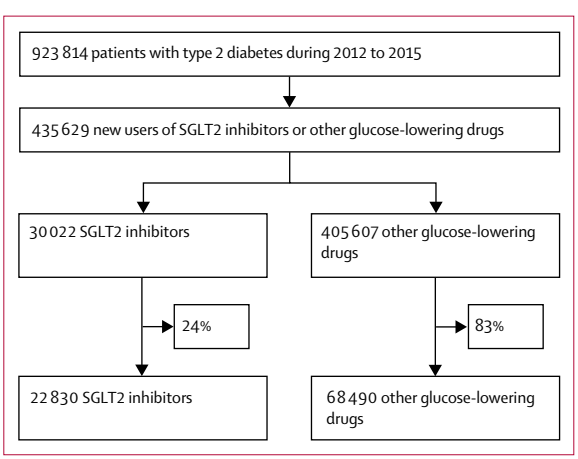

***Figure 1*: Flowcharts for new users of SGLT2 inhibitors and new users of other glucose-lowering drugs**

Patients not fulfilling 1:3 propensity score matching with a caliper of 0·2 were excluded (24% [7192 of 30 022] in the SGLT2 inhibitors group, 83% [337 117 of 405 607] in the other glucose-lowering drugs group). SGLT2=sodium-glucose co-transporter-2.

	SGLT2 inhibitors (n=22 830)	Other glucose-lowering drugs (n=68 490)	Standardised difference*
Age, years	61·2 (10·9)	61·2 (12·4)	0·001
Women	9278 (40·6%)	27 084 (39·5%)	0·018
Men	13 552 (59·4%)	41 406 (60·5%)	0·018
Time since first glucose-lowering drug, years	7·3 (4·1)	7·6 (4·1)	0·073
Cardiovascular disease	5681 (24·9%)	17 005 (24·8%)	0·001
Myocardial infarction	1725 (7·6%)	5299 (7·7%)	0·006
Stroke	1520 (6·7%)	4548 (6·6%)	0·001
Unstable angina	876 (3·8%)	2620 (3·8%)	0·000
Heart failure	1152 (5·0%)	3394 (5·0%)	0·003
Atrial fibrillation	1599 (7·0%)	4734 (6·9%)	0·003
Chronic kidney disease	269 (1·2%)	743 (1·1%)	0·007
Microvascular complications	5648 (24·7%)	16 722 (24·4%)	0·006
Cancer	1479 (6·5%)	4274 (6·2%)	0·008
Metformin	16 935 (74·2%)	53 006 (77·4%)	0·061
Sulfonylureas	6044 (26·5%)	18 623 (27·2%)	0·013
DPP4 inhibitors	4398 (19·3%)	12 566 (18·3%)	0·019
GLP-1 receptor agonists	3888 (17·0%)	10 105 (14·8%)	0·050
Thiazolidinediones	343 (1·5%)	948 (1·4%)	0·008
Insulin	6822 (29·9%)	20 634 (30·1%)	0·004
Short-acting	2452 (10·7%)	7257 (10·6%)	0·004
Intermediate-acting	3143 (13·8%)	9345 (13·6%)	0·003
Premixed	1630 (7·1%)	4809 (7·0%)	0·004
Long-acting	2585 (11·3%)	7650 (11·2%)	0·004
Low-dose aspirin	8244 (36·1%)	24 848 (36·3%)	0·003
Statins	15 384 (67·4%)	46 809 (68·3%)	0·017
Antihypertensive drugs	17 342 (76·0%)	51 847 (75·7%)	0·005
High-ceiling diuretics	3187 (14·0%)	9302 (13·6%)	0·009
Aldosterone antagonists	1087 (4·8%)	3203 (4·7%)	0·003
Warfarin	1172 (5·1%)	3474 (5·1%)	0·002
P2Y12 receptor antagonists	1139 (5·0%)	3402 (5·0%)	0·001

Data are n (%) or mean (SD), unless otherwise stated. Patients were matched 1:3 by propensity scores. SGLT2=sodium-glucose co-transporter-2. DPP4=dipeptidyl peptidase-4. GLP-1=glucagon-like peptide-1. *Standardised difference of more than 0·1 (10%) is considered to represent a statistically significant difference.

***Table 1*: Baseline characteristics of new users of SGLT2 inhibitors versus propensity-matched new users of other glucose-lowering drugs**

were done with further adjustment for multiple baseline covariates as the matched baseline balance might be violated within subgroups.[9] Proportionality assumptions were tested. Kaplan-Meier curves were plotted with pooled data from all three countries and used to show cardiovascular mortality and major adverse cardiovascular events for descriptive purposes only. Competing risks were not possible to take into account when pooling plots and would have inflated probabilities only slightly in this context.[15] Subgroup analyses were done to explore risk associations; formal interaction testing was not done because of the exploratory nature of the study. To explore potential effects of the type of hospital visit, separate analyses were done with inpatient visits for the hospital events for heart failure outcome, for Norway and Sweden only (it was possible to ascertain the type of visit by length of stay in Norway, and by inpatient or outpatient visit codes in Sweden, but these data were not available in Denmark). All analyses were done with R statistical software (version 3.2.3).[16]

Role of the funding source

The funder of the study, AstraZeneca, was involved in study design, data interpretation, data collection, data analysis, and writing of the report. All authors had access to relevant data and had final responsibility for the decision to submit for publication.

Results

During the observation period, 435 629 patients initiated new therapy with SGLT2 inhibitors or any other glucose-lowering drugs (figure 1; appendix p 18). Baseline characteristics, comorbidities, and information on drug treatment are provided in the appendix (pp 9–14).

Before matching, patients in the SGLT2 inhibitor group were younger, were more frequently men, had more microvascular disease, and had lower cardiovascular disease burden than those in the other glucose-lowering drugs group (appendix pp 9, 10). The SGLT2 inhibitor group received statins and antihypertensive treatment more frequently than did patients in the other glucose-lowering drugs group (appendix p 11).

Following 1:3 propensity score matching, 91 320 patients were included in either the SGLT2 inhibitor group (n=22 830) or the other glucose-lowering drugs group (n=68 490; figure 1). The matched groups were well balanced at baseline (table 1) with standardised differences for most variables of less than 10%. Mean age was 61 (SD 12·0) years, time since first glucose-lowering drug treatment was about 7–8 years, and baseline prevalence of both cardiovascular and microvascular comorbidity was 25% (table 1). Mean follow-up time was 0·9 (SD 4·1) years, with a total of 80 669 patient-years. Exposure time was about 18 000 years (94%) for dapagliflozin, 1000 years (5%) for empagliflozin, and 250 years (1%) for canagliflozin in the SGLT2 inhibitor group (appendix, p 20). Detailed information about exposure time per separate index glucose-lowering drug in the other glucose-lowering drugs group is reported in the appendix (p 21). New users of insulin had the highest proportion of exposure time (36%), followed by new users of dipeptidyl-peptidase 4 inhibitors (25%), sulfonylureas (13%), glucagon-like peptide-1 receptor agonists (12%), metformin (12%), and other drugs (2%).

The hazard ratios (HRs) for cardiovascular mortality and major adverse cardiovascular events showed that new users of SGLT2 inhibitors were at reduced risk compared with new users of other glucose-lowering drugs (table 2, figure 2). The HR estimates were below

	SGLT2 inhibitors		Other glucose-lowering drugs		Weighted means of hazard ratios (HR [95% CI; p value])	p value for heterogeneity between countries
	Events (n)	Events per 100 patient-years	Events (n)	Events per 100 patient-years		
Cardiovascular mortality	56	0·27	340	0·53	0·53 (0·40–0·71; p<0·0001)	0·076
Major adverse cardiovascular event*	339	1·64	1349	2·12	0·78 (0·69–0·87; p<0·0001)	0·099
Non-fatal myocardial infarction	161	0·78	574	0·90	0·87 (0·73–1·03; p=0·112)	0·105
Non-fatal stroke (ischaemic or haemorrhagic)	144	0·70	514	0·80	0·86 (0·72–1·04; p=0·113)	0·965
Hospital event for heart failure†	224	0·98	984	1·40	0·70 (0·61–0·81; p<0·0001)	0·428
All-cause mortality	289	1·05	1768	2·09	0·51 (0·45–0·58; p<0·0001)	0·002
Atrial fibrillation	328	1·44	1063	1·51	0·95 (0·84–1·08; p=0·456)	0·274
Severe hypoglycaemia	181	0·79	736	1·05	0·76 (0·65–0·90; p=0·001)	0·056

Groups were matched 1:3 by use of propensity scores based on age, sex, frailty (3 or more days in hospital within 1 year before index date), comorbidity, and treatment. SGLT2=sodium-glucose co-transporter-2. *Defined as cardiovascular mortality, myocardial infarction, or stroke. †Defined as an inpatient or outpatient visit with a primary diagnosis of heart failure.

***Table 2*: Weighted means of hazard ratios for cardiovascular, mortality, and other outcomes in Denmark, Norway, and Sweden for new users of SGLT2 inhibitors versus new users of other glucose-lowering drugs**

one in all three countries, with some numerical variations, and the risk difference was proportional during follow-up for both outcomes (figure 3). Hospital events for heart failure were also reduced among new users of SGL2 inhibitors compared with new users of other glucose-lowering drugs (table 2). Non-fatal myocardial infarction and stroke did not differ significantly between the two groups (table 2). Compared with new users of other glucose-lowering drugs, the SGLT2 inhibitor group showed reduced all-cause mortality, no difference in atrial fibrillation, and reduced severe hypoglycaemia (table 2). Absolute risk reductions in event rates are reported in the appendix (p 15). Table 2 shows p values for heterogeneity between countries for all outcomes. Country-wise HR estimates for all outcomes are presented in the appendix (p 17). Only all-cause mortality showed significant heterogeneity in the size of the effect estimate between countries.

Subgroup analyses for cardiovascular mortality and major adverse cardiovascular events showed some variability, but were mostly in favour of SGLT2 inhibitors (figure 4). In patients with and without cardiovascular disease at baseline, SGLT2 inhibitors were associated with reduced risk of cardiovascular mortality. However, for major adverse cardiovascular events the reduced associated risk was only present in patients with cardiovascular disease at baseline. Interestingly, neutral risk associations were found for both cardiovascular mortality and major adverse cardiovascular events in patients younger than 65 years. Intention-to-treat analyses showed similar risk associations between the SGLT2 inhibitor group and the other glucose-lowering drugs group (appendix p 16). When the analysis was done for main hospital events for heart failure only registered in patients admitted to hospital (eg, excluding outpatient events), the results remained unchanged (appendix, p 16). Country-specific results for on-treatment and intention-to-treat analyses are shown in the appendix (p 17).

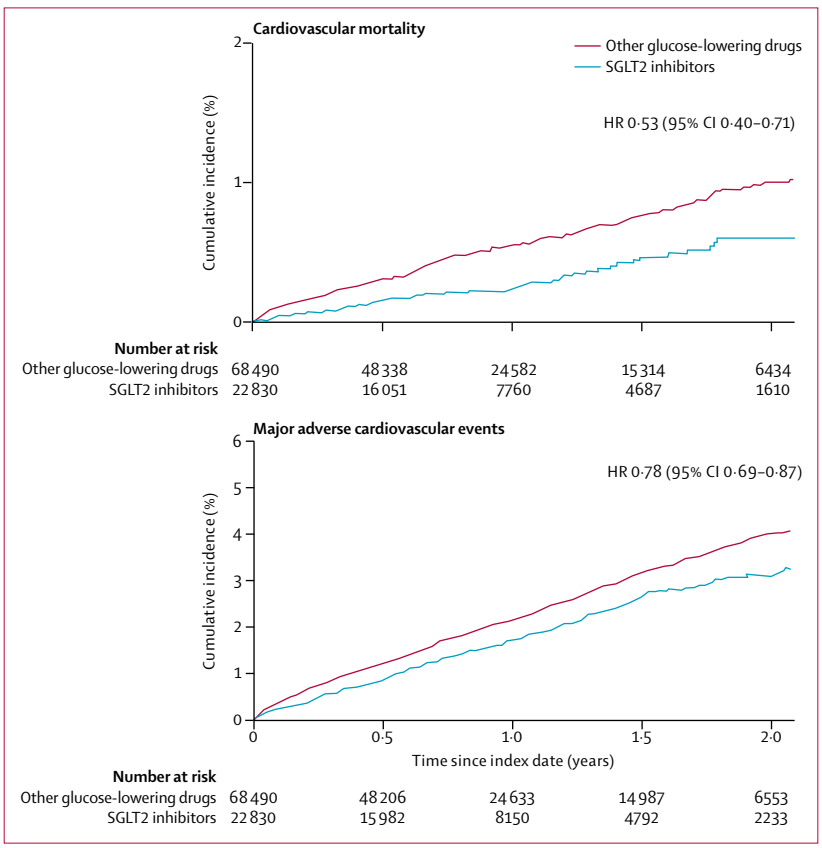

***Figure 2*: Pooled Kaplan-Meier curves and hazard ratios comparing new users of SGLT2 inhibitors and new users of other glucose-lowering drugs for cardiovascular mortality and major adverse cardiovascular events**
Groups were matched 1:3 by propensity score. SGLT2=sodium-glucose co-transporter-2. HR=hazard ratio.

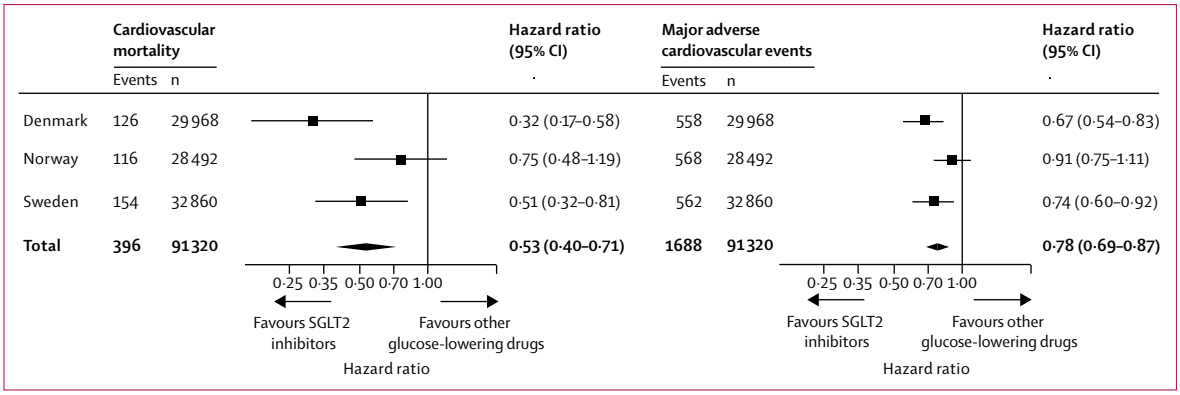

***Figure 3*: Forest plots comparing new users of SGLT2 inhibitors and new users of other glucose-lowering drugs for cardiovascular mortality and major adverse cardiovascular events**

Groups were matched 1:3 by propensity score. x-axis is on a log scale. SGLT2=sodium-glucose co-transporter-2.

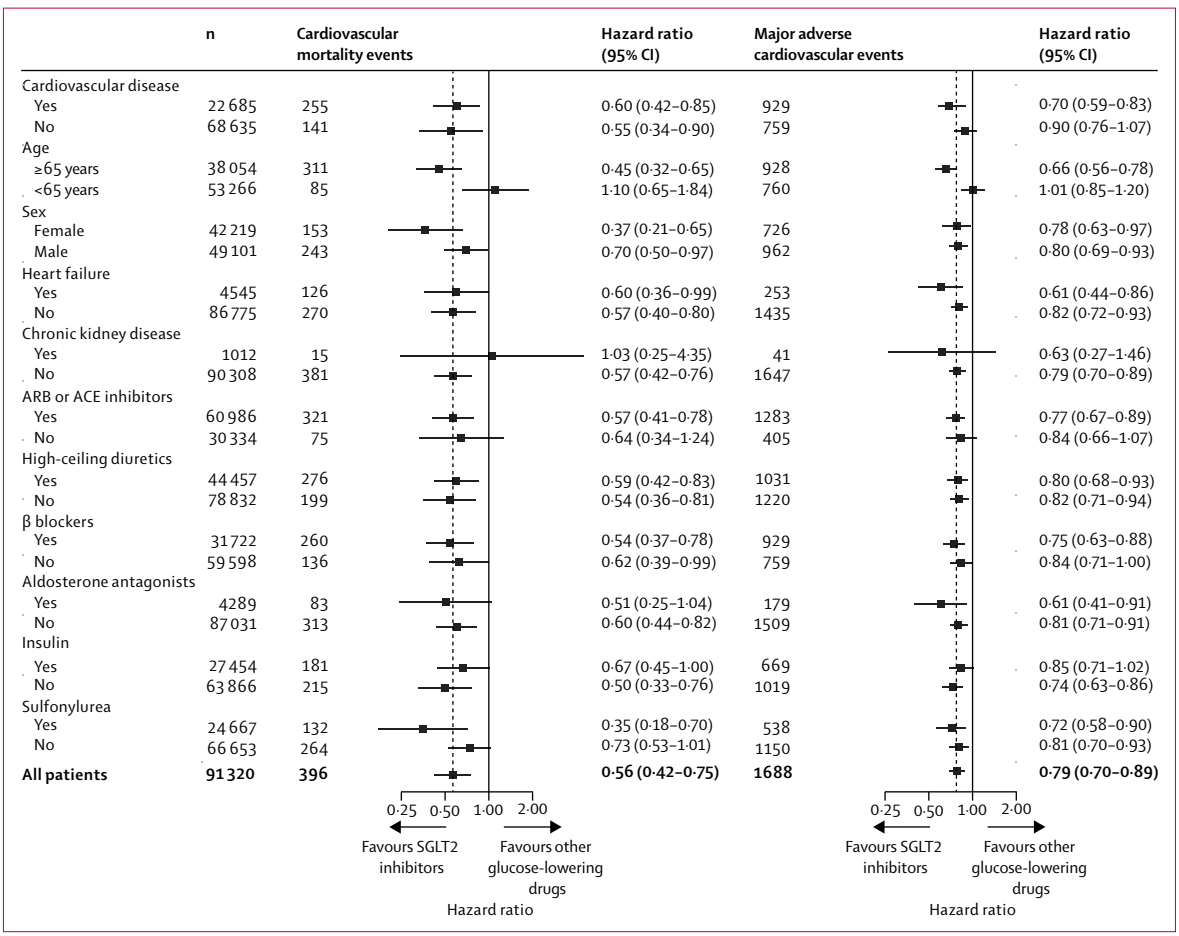

***Figure 4*: Subgroup analyses for new users of SGLT2 inhibitors versus new users of other glucose-lowering drugs for cardiovascular mortality and major adverse cardiovascular events**

ARB=angiotensin receptor blocker. ACE=angiotensin-converting enzyme. SGLT2=sodium-glucose co-transporter-2.

Discussion

In this observational analysis of almost 100 000 patients with type 2 diabetes, extracted from full-population health-care registries in three countries, we have shown that initiation of SGLT2 inhibitors was associated with substantially lower cardiovascular mortality and lower incidence of major adverse cardiovascular events than was initiation of other glucose-lowering drugs. The frequencies

of other important outcomes—hospital events for heart failure, all-cause mortality, and severe hypoglycaemia—were also lower with SGLT2 inhibitors than with other glucose-lowering drugs. For non-fatal events of myocardial infarction, stroke, or atrial fibrillation, we did not identify any significant differences between new users of SGLT2 inhibitors and new users of other glucose-lowering drugs.

In EMPA-REG OUTCOME, empagliflozin reduced the risk of cardiovascular mortality by 38%, major adverse cardiovascular events by 14%, hospital admissions for heart failure by 35%, and all-cause mortality by 32%, compared with placebo.[5] The results of the CANVAS trial programme showed similar risk-lowering effects with canagliflozin.[6] Our findings of reductions of 47% for cardiovascular mortality, 22% for major adverse cardiovascular events, 30% for hospital admissions for heart failure, and 49% for all-cause mortality are broadly similar to these trial results, despite the substantially lower cardiovascular burden at baseline in our study population. The neutral results for non-fatal myocardial infarction and stroke were also similar to the findings in the EMPA-REG OUTCOME and CANVAS trials.[5,6] Despite the methodological differences between observational and clinical intervention studies, our findings suggest that the risk-lowering effects of SGLT2 inhibitors might apply to a much broader population of patients with type 2 diabetes than were included in EMPA-REG OUTCOME and CANVAS, with less established cardiovascular disease at baseline and lower event rates, as is being investigated in the DECLARE-TIMI 58 trial of dapagliflozin. A meta-analysis[7] of randomised controlled trials has shown dapagliflozin to be associated with a reduced risk of major adverse cardiovascular events compared with placebo (HR 0·77 [95% CI 0·54–1·10]), which is in line with our HR estimate of 0·78 (0·69–0·87). Overall, the findings of this meta-analysis support our results, which might be considered particularly relevant since dapagliflozin was the predominantly used SGLT2 inhibitor in our study population.

Notably, in our subgroup analysis, the associations were of similar magnitude in patients with and without established cardiovascular disease at baseline—a finding supported by the results of another analysis from the CVD-REAL study[10] with individual patient-level data partly overlapping with those of this study. This finding might become clinically important if it is confirmed in the ongoing DECLARE-TIMI 58 trial.

Similar to the EMPA-REG OUTCOME and CANVAS trials, we noted numerically larger effect sizes of SGLT2 inhibitors on hospital events for heart failure than for the combined outcome of major adverse cardiovascular events and no significant effect on non-fatal myocardial infarction or non-fatal stroke.

Severe hypoglycaemia was reduced by 24% (95% CI 10–35) in the SGLT2 inhibitor group compared with the other glucose-lowering drugs group in our study, similar to the reduction seen in the EMPA-REG OUTCOME trial (13%).[5] Compared with the comparator group in our analysis, where almost half the patients were new users of insulin or sulfonylureas, the EMPA-REG OUTCOME trial also showed increased use of the same glucose-lowering drugs in the placebo group during follow-up, which could partly explain the differences in hypoglycaemia risk.[5] The differences in frequency of severe hypoglycaemia could help to account for some of the cardiovascular risk differences seen in both our analysis and EMPA-REG OUTCOME.[5,11,12,17,18] However, in our study, propensity scores included previous episodes of severe hypoglycaemia, and subgroup analyses for insulin and sulfonylurea use did show favourable trends, supporting the view that the decreased cardiovascular risk is driven by positive effects of SGLT2 inhibitors rather than an unfavourable effect of other specific glucose-lowering drugs.

Initiation and use of an SGLT2 inhibitor was significantly associated with reduced risk of hospital events for heart failure, which in turn is a key contributor to cardiovascular mortality. Heart failure in type 2 diabetes is an increasingly common complication,[19] often undiagnosed,[20] and, if present, sharply increases mortality risk.[3,21,22] Our findings are therefore of particular clinical interest, in view of the scarcity of evidence on which to base treatment of heart failure in patients with type 2 diabetes.[23]

Our results show frequencies of hospital events for heart failure that are similar to those reported in EMPA-REG OUTCOME, despite differences in the proportion of patients with heart failure at baseline (5% in this study *vs* 10% in EMPA-REG OUTCOME).[5] The main explanation for this difference might be that our heart failure outcome includes main diagnoses set at both inpatient and outpatient visits, whereas in EMPA-REG OUTCOME only inpatient diagnoses were used. This explanation is supported by the observation that event rates were nearly halved in our analyses when heart failure diagnoses only from inpatient care were used.[5] Another contributing factor could be that the methods used for registration of heart failure at baseline were substantially different. We captured patients with heart failure in need of hospital care before the index date, whereas in EMPA-REG OUTCOME the presence of heart failure was determined by the investigator (ranging from New York Heart Association class I to IV).[22] This difference might have led to an underestimation of heart failure prevalence in our study compared with EMPA-REG OUTCOME, and the prevalence at baseline might indeed have been higher, contributing to higher than expected event rates in our analysis.[5]

Since more than 90% of the SGLT2 inhibitor exposure time in our study was exposure to dapagliflozin, our findings lend support for a possible class effect of SGLT2 inhibitors on cardiovascular outcomes, complementing what has previously been shown in cardiovascular outcome trials of empagliflozin and canagliflozin and in observational studies and meta-analyses of trial data.[5–8,17]

The effects were seen in patients with a broader cardiovascular risk profile than that of the high-risk patients in EMPA-REG OUTCOME and CANVAS, with a lower proportion of established baseline cardiovascular disease and lower event rates.

Strengths of this study are the population-based, nationwide, and unselected real-world design, which provides high external validity and a large sample size, allowing for country-wise propensity score-matched analyses. The results were consistent across all three countries and several subgroups. Additionally, the registers used have full coverage for hospital admissions, outpatient care visits, filled drug prescriptions, and cause of death, with established and fully public health-care systems, and few patients lost to follow-up. Cardiovascular diagnoses in these registries have been reported to have high validity.[24–28] We have also shown that risk estimates for combined inpatient and outpatient visits for hospital events for heart failure are similar to those for inpatient visits only. Finally, because there are no reports or mechanistic reasons to suggest that glucose-lowering drugs would affect the risk of atrial fibrillation, the neutral risk association of atrial fibrillation seen for SGLT2 inhibitors compared with other glucose-lowering drugs is encouraging, since this expected finding is indicative of a balanced risk profile at baseline.

This study also had some limitations. The results are only representative of patients who have initiated SGLT2 inhibitor treatment or are similar on available clinical variables, such as patient characteristics, treatments, and comorbidities, and cannot be extended to all patients with type 2 diabetes. This study provides no information on laboratory measurements, lifestyle parameters, primary health-care data, or socioeconomic data, and consequently there could be residual confounding factors, particularly confounding by indication. The close matching on many essential variables ensures that some confounding factors are controlled, but even propensity score matching does not remedy all confounding—eg, residual confounding by indication, to the extent that prescribers are likely to use more information about their patients than we have available. Furthermore, there is no information available about diabetes duration 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 (ie, diabetes treatment duration), glucose-lowering drug use, and cardiovascular and microvascular disease burden.

Another important limitation is that dapagliflozin was much more widely used than other SGLT2 inhibitor drugs in our study population; thus, potential differences between different SGLT2 inhibitors could not be assessed. For Norway and Sweden, we had no information about emigration, which could result in loss to follow-up. Additionally, no information about immigration was available for Norway and Sweden, and some patients might have had less comprehensive disease history than others. However, the on-treatment analyses used should minimise the effects of emigration because these patients would be classified as discontinuing treatment. Furthermore, the results were consistent with those for Denmark, where information on migration was available.

In conclusion, in patients with type 2 diabetes in a real-world clinical setting, new use of an SGLT2 inhibitor was associated with decreased risk of cardiovascular disease and cardiovascular mortality compared with new use of other glucose-lowering drugs—a finding consistent with results of cardiovascular outcome trials of drugs in this class. Our results were obtained in a population with a broader cardiovascular risk profile than the high-risk populations included in these trials, which could have important clinical implications in terms of preventive treatment strategies. Ongoing randomised trials will further elucidate these findings.

Contributors

All authors contributed to the design of the study. MT and BC were responsible for data management and statistical analyses after discussion with all authors. All authors participated in data interpretation and in writing of the report.

Declaration of interests

KIB reports grants to his institution from AstraZeneca for this study and for lectures; and consulting fees from Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, and Merck Sharp & Dohme (MSD). JWE has received honoraria or research grants from AstraZeneca, Novo Nordisk, Bristol-Myers Squibb, Sanofi, and MSD. BC is a shareholder of Novo Nordisk. MEJ holds shares in Novo Nordisk and has received grants and lecture fees from AstraZeneca. JB holds a paid, full-time position at AstraZeneca as an epidemiologist. DN has received consultancy fees from Novo Nordisk, AstraZeneca, and Eli Lilly. MT is employed by an independent statistical consultant company, Statisticon AB (Uppsala, Sweden), for which AstraZeneca Nordic-Baltic is a client. FP reports research grants from AstraZeneca and Novartis; lecture fees from Novartis, Eli Lilly, MSD, AstraZeneca, and Boehringer Ingelheim; and has served as a consultant for AstraZeneca, Amgen, Novo Nordisk, and MSD. HLG reports honoraria from Sanofi, Novo Nordisk, Eli Lilly, AstraZeneca, and MSD, and Boehringer Ingelheim. TN has received unrestricted grants from AstraZeneca and Novo Nordisk, and is on the national boards of Novo Nordisk, Sanofi-Aventis, Eli Lilly, and Boehringer Ingelheim. AN has received honoraria from MSD, AstraZeneca, Eli Lilly, Boehringer Ingelheim, and Novo Nordisk. PF is a paid full-time employee of AstraZeneca.

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