# Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study

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## Summary

**Background** Cardiovascular and kidney outcome trials have shown that sodium-glucose co-transporter-2 (SGLT2) inhibitors slow progression of chronic kidney disease in patients with type 2 diabetes with or without chronic kidney disease. The aim of this study was to assess whether these benefits extend to patients with type 2 diabetes treated in routine clinical practice.

**Methods** CVD-REAL 3 was a multinational observational cohort study in which new users of SGLT2 inhibitors and other glucose-lowering drugs with measurements of estimated glomerular filtration rate (eGFR) before and after (within 180 days) initiation were identified via claims, medical records, and national registries in Israel, Italy, Japan, Taiwan, and the UK. Propensity scores for SGLT2 inhibitor initiation were developed in each country, with 1:1 matching with initiators of other glucose-lowering drugs. Propensity score included (in addition to other clinical and demographic variables) baseline eGFR and eGFR slope before SGLT2 inhibitor or other glucose-lowering drug initiation. The main outcome measure was rate of eGFR decline (slope) calculated with a linear mixed regression model. Differences in eGFR slope between SGLT2 inhibitors and other glucose-lowering drugs were calculated and pooled. We also assessed a composite outcome of 50% eGFR decline or end-stage kidney disease.

**Findings** After propensity matching, there were 35 561 episodes of treatment initiation in each group, from 65 231 individual patients. Dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin accounted for 57·9%, 34·1%, 5·7%, 1·4%, 0·5%, and 0·4% of SGLT2 inhibitor initiation episodes, respectively. At baseline, 29 363 (41·3%) of 71 122 initiations were in women, mean age was 61·3 years, mean $HbA_{1c}$ was 72 mmol/mol (8·71%), and mean eGFR was 90·7 mL/min per 1·73 m². During follow-up, SGLT2 inhibitor initiation was associated with reduced eGFR decline (difference in slope for SGLT2 inhibitors *vs* other glucose-lowering drugs 1·53 mL/min per 1·73 m² per year, 95% CI 1·34–1·72, p<0·0001). During a mean follow-up of 14·9 months, 351 composite kidney outcomes occurred: 114 (3·0 events per 10 000 patient-years) among initiators of SGLT2 inhibitors and 237 (6·3 events per 10 000 patient-years) among initiators of other glucose-lowering drugs (hazard ratio 0·49, 95% CI 0·35–0·67; p<0·0001). These findings were consistent across countries ($p_{heterogeneity}$ 0·10) and prespecified subgroups.

**Interpretation** In this large, international, real-world study of patients with type 2 diabetes, initiation of SGLT2 inhibitor therapy was associated with a slower rate of kidney function decline and lower risk of major kidney events compared with initiation of other glucose-lowering drugs. These data suggest that the benefits of SGLT2 inhibitors on kidney function identified in clinical trials seem to be largely generalisable to clinical practice.

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## Introduction

Since the introduction of the regulatory requirement to test the cardiovascular safety of new glucose-lowering drugs for marketing authorisation, many large clinical trials in patients with type 2 diabetes have been completed. These trials showed that sodium-glucose co-transporter-2 (SGLT2) inhibitors substantially reduced the risk of hospital admission for heart failure and slowed the progression of kidney function decline in patients with type 2 diabetes with or without chronic kidney disease.[1–4]

Assessing whether the results of these clinical trials are applicable to the broader range of patient populations treated in clinical practice is of importance to determine the magnitude of effectiveness of SGLT2 inhibitor use. The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors) study showed that the benefits of SGLT2 inhibitors in reducing the risk of cardiovascular events and heart failure extend to a large, broad patient population with type 2 diabetes treated in clinical practice, with findings consistent in various parts of the world.[5–7] However,

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## Research in context

### Evidence before this study

We searched PubMed for all English-language publications from Jan 1, 2000, to Sept 1, 2019, using the search terms "SGLT2", "SGLT2 inhibitor", "chronic kidney disease", "nephropathy", and "real world evidence". Secondary analyses from cardiovascular outcome trials and a dedicated kidney outcome trial have shown that sodium-glucose co-transporter-2 (SGLT2) inhibitors slow the progression of kidney disease and reduce major kidney outcomes in patients with type 2 diabetes. The benefits of SGLT2 inhibitors to reduce the risk of cardiovascular events and heart failure in a broad population of patients with type 2 diabetes treated in clinical practice were previously reported in the CVD-REAL study. However, whether kidney benefits as observed in clinical trials extend to a broader range of patients treated in clinical practice was unknown.

### Added value of this study

To our knowledge, the CVD-REAL 3 study is the first to assess the association between SGLT2 inhibition and preservation of kidney function compared with other glucose-lowering drugs in real-world clinical practice databases of patients with type 2 diabetes. The results show that SGLT2 inhibition was associated with a significantly slower annual rate of eGFR change compared with treatment with other glucose-lower drugs. Additionally, initiation of SGLT2 inhibitors compared with initiation of other glucose-lowering drugs was associated with a 51% lower risk of a composite outcome of a 50% decline in estimated glomerular filtration rate or end-stage kidney disease. This effect was consistent across countries and prespecified subgroups.

### Implications of all the available evidence

The available evidence suggests that the kidney protective effects of SGLT2 inhibitors as reported in clinical trials extend to the broader patient population treated in clinical practice.

whether kidney benefits of SGLT2 inhibitors identified in clinical trials also translate to clinical practice in different regions of the world is not known.

Large clinical practice data sources have recently become available that routinely record a broad range of clinical data, including diagnoses, medication use, and biochemical measures such as estimated glomerular filtration rate (eGFR) and major kidney outcomes. These databases allow assessment of the association between SGLT2 inhibitor use and kidney function in a real-world practice setting. In CVD-REAL 3, using these well-established data sources, we assessed and compared the association between the initiation of SGLT2 inhibitor treatment versus treatment with other glucose-lowering drugs and the rate of eGFR decline and kidney outcomes in patients with type 2 diabetes across five countries from different geographical regions.

## Methods

### Data sources and study population

The CVD-REAL protocol and the statistical analysis plan for the current analyses can be found in the appendix (pp 20, 67, respectively). Anonymised health records from five countries (Israel, Italy, Japan, Taiwan, and the UK) were analysed. Data collection for CVD-REAL 3 occurred between 2013 and 2018 (appendix p 3). Because of the deidentified nature of patient records, informed consent was not obtained. Analyses of deidentified data were done in accordance with local laws and regulations, and received approvals from respective scientific, ethics, or data protection committees. A description of each participating cohort is provided in the appendix (p 1).

See Online for appendix

Patients with type 2 diabetes who initiated an SGLT2 inhibitor or another glucose-lowering drug were identified from each country starting from the date of first prescription of an SGLT2 inhibitor (range February 2013 [UK] to May 2016 [Taiwan]). Episodes of treatment initiation were defined as prescription or filling of a prescription, as either initial or add-on therapy, for any SGLT2 inhibitor (dapagliflozin and empagliflozin in all countries; additionally, canagliflozin in Italy, Japan, and the UK, and ipragliflozin, tofogliflozin, and luseogliflozin in Japan) or other glucose-lowering drug, including fixed-dose combinations, with no issued prescriptions for that medicine class during the preceding year. Additional inclusion criteria were age 18 years or older at index date, and more than 1 year of continuous enrolment history in the database before the index date. Inclusion criteria with respect to kidney function were at least two eGFR measurements before the index date, with at least one eGFR measurement within 180 days of the index date. We additionally specified that there should be at least 180 days between first and last eGFR measurement before the index date to more reliably estimate the eGFR change before the index date. Patients with known type 1 diabetes were excluded. Patients were followed up from the index date until end of the index treatment (on-treatment analysis only), migration or leaving of the practice or database, death, or last date of data collection.

## Outcomes

The main outcome for this study was the rate of change in eGFR from the initiation of the SGLT2 inhibitor or other glucose-lowering drug treatment. eGFR was estimated by use of the Modification of Diet in Renal Disease equation, except in Italy and the UK, where the Chronic Kidney Disease Epidemiology Collaboration equation was used. An additional outcome for this study was a composite

endpoint of a sustained reduction in eGFR of 50% or more (confirmed by a second measurement) or end-stage kidney disease (ESKD), which was defined as an eGFR of less than 15 mL/min per 1·73 m² (confirmed at a subsequent measurement), dialysis for 30 days or more, or kidney transplantation. Other kidney outcomes assessed were ESKD alone and a sustained 40%, 50%, and 57% eGFR decline (confirmed by a subsequent measurement). These eGFR-based endpoints were assessed because they have been recommended as alternative endpoints in trials of chronic kidney disease progression.[8] Non-kidney outcomes assessed were hospital admission for heart failure (data available from all countries except Italy and the UK) and all-cause mortality (data available from all countries except Italy).

### Statistical analysis

Baseline characteristics were analysed with descriptive statistics. Mean (SD) was used to describe continuous variables, and frequencies and percentages were used to describe categorical variables. For continuous variables, the overall mean across countries was a weighted estimate according to the number of patients in each country. The percentage of individual drugs and their respective contributions to the SGLT2 inhibitor exposure time and the percentage of individual index drug classes to the other glucose-lowering drug exposure time were summarised by country and overall.

A non-parsimonious propensity score for initiating an SGLT2 inhibitor was developed (separately within each country) for each individual episode of a new treatment initiation. Variables that could potentially affect treatment assignment or outcomes were selected (appendix p 4). Propensity matching was assessed by evaluating standardised differences of patient characteristics post match. An imbalance was considered non-negligible if a standardised difference of more than 10% was present between the two groups after propensity matching.

Two definitions of follow-up time were used. The intention-to-treat (ITT) follow-up time was defined as the time from index date to either migration, leaving the practice or database, or date of last data collection or death, whichever occurred first. The on-treatment follow-up time was defined as the time from index date to end of index treatment (a gap of twice the length of the most recent prescription); initiation of a new other glucose-lowering drug or SGLT2 inhibitor; migration or leaving the practice or database; or date of last data collection or death, whichever occurred first. The on-treatment follow-up was the primary timescale for the eGFR change analysis because it was likely to be a more conservative approach and consistent with previous studies.[1,2] The ITT follow-up was used for time-to-event analyses.

The difference in eGFR slope after index date between SGLT2 inhibitors and other glucose-lowering drugs was assessed using a linear mixed regression model, where treatment group (SGLT2 inhibitors or other glucose-lowering drugs), time (linear), and the interaction between treatment group and time were included as fixed factors and episode was included as a random factor. Analyses were done both unadjusted (within the matched cohort) and adjusted for selected baseline covariates (pre-index slope, pre-index intercept, age, sex, previous cardiovascular disease, and baseline cardiovascular drugs). Further adjustment was done because the entire matched cohort could not be used for the eGFR slope analysis. The analysis used the on-treatment follow-up definition (as used in other eGFR slope studies) and the ITT follow-up definition. The eGFR trajectory from pre-index to post-index date was displayed graphically over time at prespecified timepoints. Each timepoint was represented with the eGFR value closest to the timepoint of interest, within a defined interval. The exception was time zero, which was representative of the estimated intercept of the pre-index slopes. Analyses for eGFR slope were repeated across multiple patient subgroups to examine the consistency of the findings. Prespecified subgroups included those by baseline $HbA_{1c}$, eGFR, established atherosclerotic cardiovascular disease, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and use of diuretics.

To be included in the eGFR slope analyses at least two post-baseline assessments were required, where the first measurement was less than 120 days after index and the last was more than 180 days after the first post-baseline measurement. Thus, the number of patients included in these analyses is lower than the total number of matched patients. There was no maximum specified for the observation time.

Incidence rate for the outcomes based on the development of ESKD or sustained reduction in eGFR were assessed by

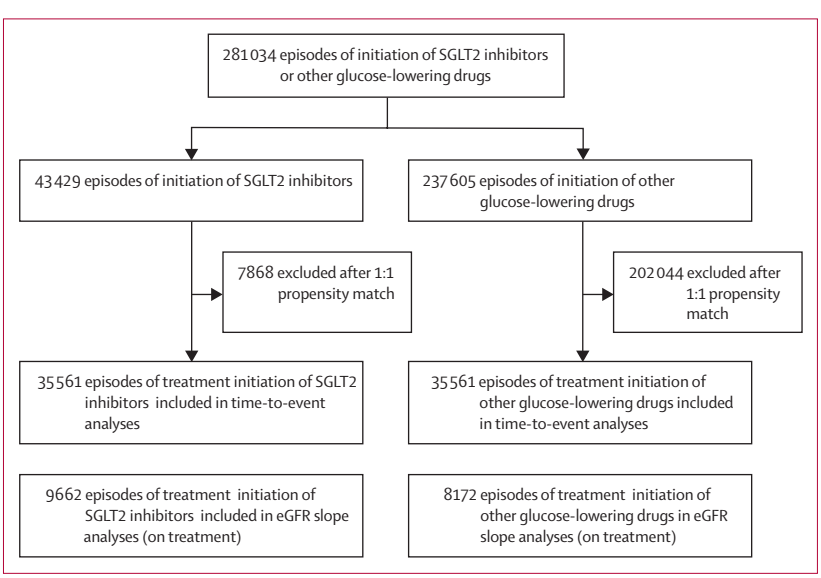


***Figure 1:*** **Flowchart for all countries combined**
eGFR=estimated glomerular filtration rate. SGLT2=sodium-glucose co-transporter-2.

| | SGLT2 inhibitors (n=35 561) | Other glucose-lowering drugs (n=35 561) | Standardised difference* |
|---|---|---|---|
| Age (years) | 61·2 (10·2) | 61·4 (11·0) | 1·1% |
| Sex | | | |
| Women | 14 589 (41·0%) | 14 774 (41·5%) | 1·1% |
| Men | 20 972 (59·0%) | 20 787 (58·5%) | 1·1% |
| $HbA_{1c}$ (%) | 8·67% (1·50) | 8·75% (1·65) | 4·7% |
| $HbA_{1c}$ (mmol/mol) | 71 (16·4) | 72 (18·0) | 4·7% |
| eGFR (mL/min per 1·73 m²) | 90·6 (21·5) | 90·9 (23·1) | 1·1% |
| eGFR >90 | 18 150 (51·0%) | 19 151 (53·9%) | 5·6% |
| eGFR >60–90 | 13 864 (39·0%) | 13 256 (37·3%) | 3·5% |
| eGFR ≤60 | 2747 (7·7%) | 3154 (8·9%) | 4·2% |
| Rate of eGFR change before index (mL/min per 1·73 m² per year) | −0·73 (7·29%) | −0·75 (11·89%) | 0·2% |
| Microvascular disease† | 12 562 (35·3%) | 12 571 (35·4%) | 0·1% |
| History of cardiovascular disease | 6354 (22·8%) | 6226 (22·3%) | 1·1% |
| Myocardial infarction | 2587 (7·3%) | 2613 (7·3%) | 0·3% |
| Unstable angina | 2158 (6·1%) | 2177 (6·1%) | 0·2% |
| Heart failure | 1229 (3·5%) | 1247 (3·5%) | 0·3% |
| Diabetes drugs | | | |
| Metformin | 30 717 (86·4%) | 30 862 (86·8%) | 1·2% |
| DPP-4 inhibitor | 15 411 (43·3%) | 15 377 (43·2%) | 0·2% |
| Sulfonylurea | 12 783 (35·9%) | 12 828 (36·1%) | 0·3% |
| Insulin | 6017 (21·6%) | 5736 (20·6%) | 2·5% |
| GLP-1 receptor agonist | 4379 (12·3%) | 4083 (11·5%) | 2·6% |
| Thiazolidinedione | 2112 (5·9%) | 2036 (5·7%) | 0·9% |
| Blood pressure drugs | 21 185 (75·9%) | 21 027 (75·4%) | 1·3% |
| ACE inhibitors | 13 374 (37·6%) | 13 592 (38·2%) | 1·3% |
| ARBs | 11 273 (31·7%) | 10 860 (30·5%) | 2·5% |
| Loop diuretics | 4820 (13·6%) | 4818 (13·5%) | 0·0% |
| Thiazide diuretics | 2918 (10·5%) | 2901 (10·4%) | 0·2% |
| Statins | 26 158 (73·6%) | 26 163 (73·6%) | 0·0% |
| β blockers | 11 180 (31·4%) | 11 113 (31·3%) | 0·4% |
| Aldosterone antagonists | 999 (3·6%) | 995 (3·6%) | 0·1% |

Data are mean (SD) or n (%). SGLT2=sodium-glucose co-transporter-2. eGFR=estimated glomerular filtration rate. DPP-4=dipeptidyl peptidase-4. GLP-1=glucagon-like peptide-1. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. *Standardised difference of more than 10% is considered a non-negligible difference. †Microvascular disease was defined as diabetic mononeuropathy or polyneuropathy, diabetic eye complications, diabetic foot or peripheral angiopathy, or diabetic kidney disease.

***Table:*** **Baseline characteristics after propensity score matching**

treatment. Only the first occurrence of each outcome was used for analysis and the crude incidence rate in each group was calculated as the number of incident events divided by the overall number of person-years at risk. Time-to-first event for SGLT2 inhibitors and other glucose-lowering drugs were compared by use of Cox proportional-hazard models and presented as the hazard ratio (HR) and 95% CI for each outcome separately by country. If an episode of SGLT2 inhibitor initiation occurred followed by a later episode of other glucose-lowering drug initiation for the same patient (or vice versa), any outcome event occurring after the second initiation would be accounted for in both groups. To account for within-subject dependence for multiple episodes of treatment initiation within a study period, we used a robust variance estimator in the Cox models, which is used for clustered observations (in this case, more than one drug-initiation episode being potentially clustered within the same patient). This approach was used previously,[7] and is a way of statistically adjusting the CIs to account for the potential clustering. This approach was considered optimal because many patients might have started both an SGLT2 inhibitor and another glucose-lowering drug during the study period. The ITT population was used for time-to-event analyses in which patients were followed up from the initiation of an index treatment until the occurrence of the outcome of interest or censoring date, whichever occurred first, irrespective of whether index treatment was discontinued. The obtained HRs (95% CIs) for each of the endpoints from each individual country were subsequently pooled with inverse variance weighting for each country. Forest plots were created displaying the country-specific HRs (95% CI) and the overall pooled HR (95% CI). Statistical analysis was done using R software.

### Role of the funding source

The funder of the study was involved in study design, data interpretation, data collection, data analysis, and writing of the report. Statistical analyses were done by an independent source (Statisticon, Uppsala, Sweden), sponsored by the study funder, to support the unbiased review of all data. All authors had access to all the data and had final responsibility for the decision to submit for publication.

## Results

In the overall cohort, from 214 366 individuals with type 2 diabetes, 43 429 new episodes of SGLT2 inhibitor initiation and 237 605 new episodes of other glucose-lowering drug initiation were identified (figure 1). Before propensity matching, patients initiated on an SGLT2 inhibitor were younger, had a higher $HbA_{1c}$ and eGFR, and were more likely to have microvascular complications (appendix p 6). Prevalence of cardiovascular disease was similar between groups. Patients initiated on an SGLT2 inhibitor were more frequently using additional glucose-lowering drugs. Statins and ARBs were also more frequently prescribed to SGLT2 inhibitor initiators, whereas diuretics were less frequently prescribed.

After propensity matching, there were 35 561 episodes of treatment initiation in each group, from 65 231 individual patients. All baseline characteristics were well matched, with standardised differences for all variables of 4·7% or less. Mean age at initiation of the SGLT2 inhibitor or other glucose-lowering drug was 61·3 years; 29 363 (41·3%) of 71 122 initiations were in women; mean $HbA_{1c}$ was 72 mmol/mol (8·71%); mean eGFR was 90·7 mL/min per 1·73 m²; eGFR of 60 mL/min per 1·73 m² or less was apparent in 5901 (8·3%) initiations and 25 133 (35·3%) initiations were in patients with a history of microvascular disease. Of the 71 122 treatment initiations, 61 579 (86·6%) were in patients treated with metformin and 49 099 (69·0%) were

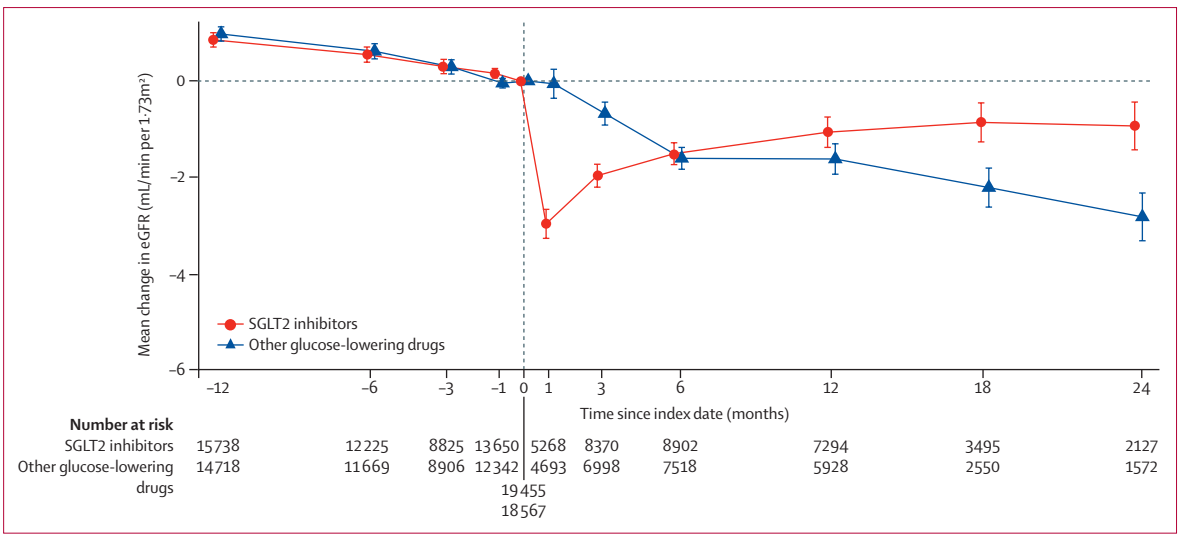


***Figure 2:*** **Change in eGFR over time before and after initiation of SGLT2 inhibitors or other glucose-lowering drugs (on treatment)**
Error bars show 95% CI. Numbers below the graph refer to the number of patients at each timepoint. The eGFR slope calculation was calculated from baseline, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. As a result of the acute decrease in eGFR followed by a small increase in eGFR during the remainder of the follow-up, the overall eGFR slope was positive despite the change from baseline at the end of follow-up being negative. eGFR=estimated glomerular filtration rate. SGLT2=sodium-glucose co-transporter-2.

in patients treated with ACE inhibitors or ARBs at baseline (table).

The distribution of specific SGLT2 inhibitors in the overall cohort and in the individual countries, and the classes of index medications in the initiators of other glucose-lowering drugs are shown in the appendix (pp 7–8). Dapagliflozin (57·9%; 22 662 years of exposure) and empagliflozin (34·1%; 13 364 years of exposure) were the most frequently initiated SGLT2 inhibitors, followed by canagliflozin (5·7%), ipragliflozin (1·4%), tofogliflozin (0·5%), and luseogliflozin (0·4%; appendix pp 7–8). Dipeptidyl peptidase-4 inhibitors (23·1%; 9577 years of exposure) and insulin (18·4%; 7629 years of exposure) were the most frequently initiated other glucose-lowering drugs. The mean follow-up time was 14·9 months for both SGLT2 inhibitors and other glucose-lowering drugs (appendix p 9).

During follow-up, the median number of eGFR measurements in the SGLT2 inhibitor group and the other glucose-lowering drugs group, respectively, were 3 (IQR 2–5) and 3 (2–4) in both Israel and Italy, 4 (3–5) and 3 (2–6) in the UK, 4 (2–5) and 4 (2–5) in Taiwan, and 9 (6–14) and 10 (7–15) in Japan. Detailed numbers for eGFR measurements for individual countries are shown in the appendix (p 10).

Before initiation of index treatment, the mean annual rates of eGFR change were –0·73 mL/min per 1·73 m² (SD 7·3) and –0·75 mL/min per 1·73 m² (11·9) in the SGLT2 inhibitor and other glucose-lowering drugs groups, respectively (table). After initiation of SGLT2 inhibitors and other glucose-lowering drugs, the mean annual rates of eGFR change were 0·46 mL/min per 1·73 m² per year (95% CI 0·34 to 0·58) and –1·21 (–1·35 to –1·06), respectively (figures 2 and 3). The between-group difference in the rate of eGFR decline was 1·53 mL/min per 1·73 m² per year (1·34 to 1·72), favouring SGLT2 inhibitors (p<0·0001; figure 3). This finding was similar across $HbA_{1c}$ and eGFR subgroups and was consistent irrespective of the presence or absence of cardiovascular disease or concomitant treatment with diuretics or ACE inhibitors or ARBs (figure 3). Similar results were obtained when the effect of SGLT2 inhibitors versus other glucose-lowering drugs was assessed in the ITT population or in models not adjusted for selected baseline covariates (appendix pp 12–13). Additionally, subgroup analysis in the ITT analysis revealed similar results (appendix p 14). Finally, because there were frequent eGFR measurements in the Japanese database, we adjusted the linear mixed model for the number of eGFR measurements to ensure that the results were not affected by more frequent eGFR assessments in the SGLT2 inhibitor group; the adjustment did not alter our findings (appendix p 11).

During follow-up, 351 outcome events for the composite of a 50% eGFR decline or ESKD occurred: 114 in SGLT2 inhibitor initiators and 237 in other glucose-lowering drug initiators (rates of 3·0 and 6·3 per 10 000 patient-years, respectively). Initiation of SGLT2 inhibitors was associated with a 51% lower relative risk of this composite outcome (HR 0·49, 95% CI 0·35 to 0·67; p<0·0001); this finding was consistent across countries ($p_{heterogeneity}$ 0·10; figure 4). Similar results were observed in the on-treatment analyses (appendix p 17). Initiation of SGLT2 inhibitors versus other glucose-lowering drugs was also associated with a lower risk for ESKD alone (HR 0·33, 95% CI 0·16 to 0·68; p=0·0024; $p_{heterogeneity}$

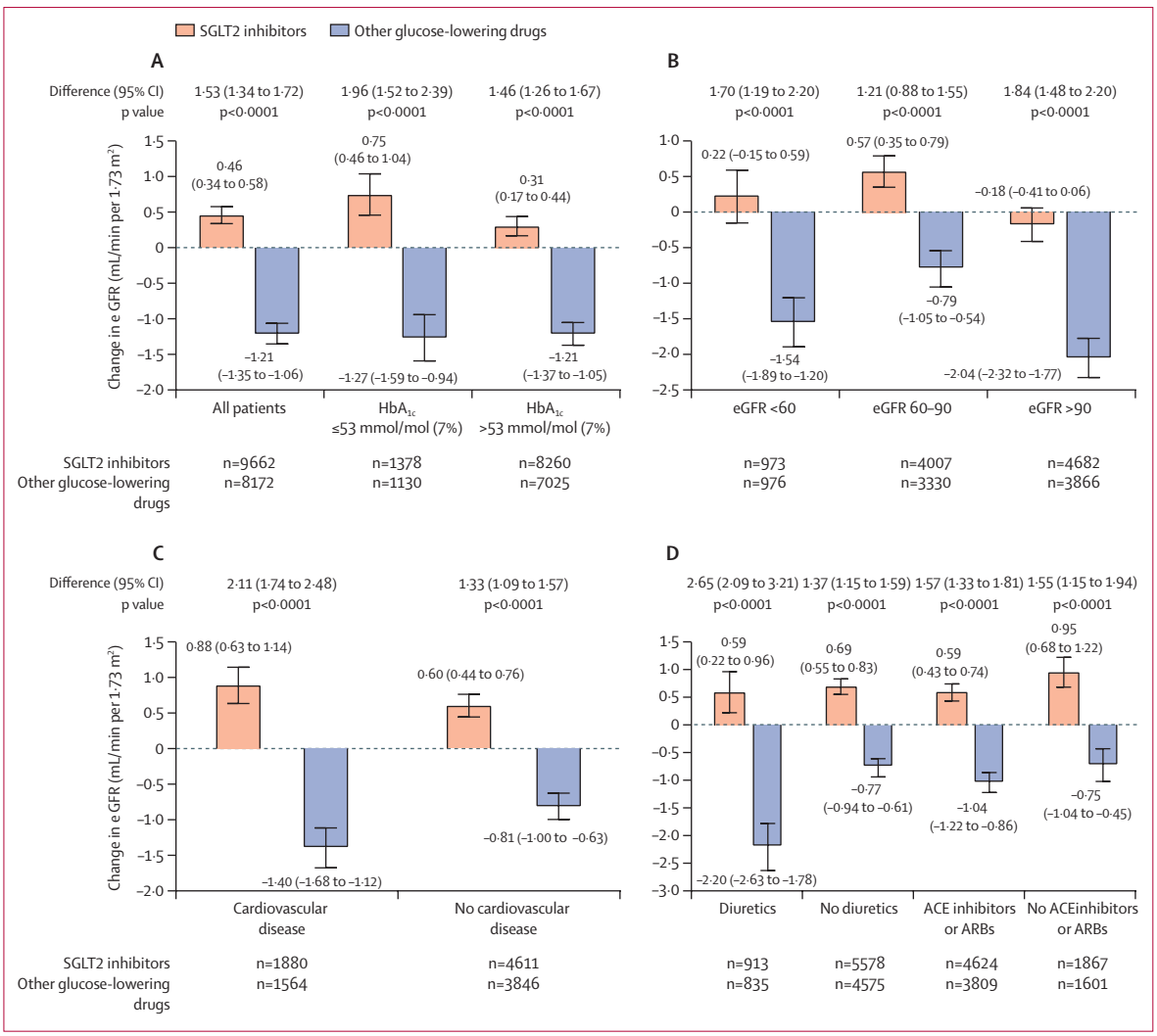


***Figure 3:*** **Annual rate of eGFR change in the total population and in various subgroups (on-treatment, adjusted)**
(A) All patients and by $HbA_{1c}$ subgroup. (B) By eGFR subgroup. (C) By presence or absence of cardiovascular disease. (D) By diuretic use and use of ACE inhibitors or ARBs. Diuretics include thiazide and loop diuretics. The numbers below the graph do not add up to the total numbers as eGFR slope data were not available in all patients and data for baseline characteristics were missing in some patients. eGFR change was calculated from the post-index eGFR measurements and adjusted for pre-index slope, pre-index intercept, age, sex, previous cardiovascular disease, and baseline cardiovascular drugs. Error bars are 95% CIs. SGLT2=sodium-glucose co-transporter-2. eGFR=estimated glomerular filtration rate. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker.

0·048; figure 4), with similar results in the on-treatment analyses (appendix p 17). Results were consistent across prespecified subgroups, including concomitant use of ACE inhibitors or ARBs and use of diuretics (ITT adjusted analysis; appendix p 18).

During follow-up, there were 185, 299, and 548 outcome events of a confirmed 57%, 50%, and 40% eGFR decline, respectively. Initiation of SGLT2 inhibitors versus other glucose-lowering drugs was consistently associated with a lower risk for each of these endpoints (figure 5). SGLT2 inhibitor initiation was also associated with a lower risk of hospital admission for heart failure (0·60, 0·47–0·76, p<0·0001) and all-cause mortality (0·55, 0·48–0·64, p<0·0001) compared with initiation of other glucose-lowering drugs.

## Discussion

In this global study involving well established data sources from real-world clinical practice and more than 65 000 patients with type 2 diabetes, initiation of SGLT2 inhibitors versus other glucose-lowering drugs was associated with a significantly lower rate of eGFR decline and lower risk of a clinically important composite endpoint of 50% eGFR decline or ESKD. Results were consistent across countries, baseline eGFR, and other prespecified patient subgroups. These findings highlight the potential value of SGLT2 inhibitor in slowing the progression of chronic kidney disease in a contemporary population of patients with type 2 diabetes and suggest that results reported in clinical trials extend to daily clinical practice.

Our findings complement results from randomised controlled trials of SGLT2 inhibitors. Three cardiovascular outcome trials have shown the beneficial effects of SGLT2 inhibitors in slowing the rate of eGFR decline.[1–3] These trials predominantly enrolled patients with preserved kidney function (eGFR of about 80 mL/min per 1·73 m²). Consequently, the majority of kidney endpoints were based on measurements of serum creatinine. Few clinically relevant ESKD events occurred, leaving some uncertainty about the effects of SGLT2 inhibitors on hard kidney endpoints. The CREDENCE study with canagliflozin was the first kidney outcome trial with an SGLT2 inhibitor and showed that, in patients with type 2 diabetes and chronic kidney disease, canagliflozin safely reduced the risk of major kidney and cardiovascular outcomes.[4] Our results extend these findings to a population that more closely mirrors the use of SGLT2 inhibitors in clinical practice, where this class is still predominantly prescribed to patients with preserved kidney function. Although the kidney events were not rigorously adjudicated (given the real-world nature of our analyses), the number of ESKD outcomes was three times higher than in the three SGTL2 inhibitor cardiovascular outcome trials, and provided adequate power to assess the association of SGLT2 inhibitor use with clinically relevant kidney outcomes.

SGLT2 inhibitors are currently not recommended for use in patients with diabetic kidney disease and eGFR of less than 45 mL/min per 1·73 m² in most countries because of their reduced glucose-lowering efficacy in these patients. The small number of patients with chronic kidney disease in our study reflects this restriction. Our results cannot be generalised to patients with moderately to severely impaired kidney function. However, the CREDENCE trial showed that the benefit of canagliflozin in slowing chronic kidney disease progression was consistent irrespective of baseline eGFR, and extended to patients with eGFR 30–45 mL/min per 1·73 m².[4] Based on these results, eGFR thresholds for initiating canagliflozin have been updated to include patients with moderately to severely impaired kidney function.

Various mechanisms have been postulated to explain the protective effects of SGLT2 inhibitors on kidney function. Correction of glomerular hyperfiltration is probably the most widely cited mechanism.[9,10] Reducing hyperfiltration is reflected by an acute reduction in eGFR followed by its stabilisation during long-term treatment, observed in all SGLT2 inhibitor outcome trials and confirmed in our study. eGFR increased after the initial reduction in our study. This finding has also been observed in clinical trials.[11] The responsible mechanisms are largely unknown, but it is possible that compensatory upregulation of SGLT1 results in increased sodium-glucose co-transport, leading to afferent arteriolar redilatation and an increase in renal perfusion and eGFR.[12] However, we cannot rule out the possibility that some patients discontinued SGLT2 inhibitor treatment during the initial weeks of treatment, resulting in an increase in eGFR, although the effect of such discontinuations on our results is expected to be small.

Several large real-world studies have compared SGLT2 inhibitors with other glucose-lowering drugs.[7,13–14] To our

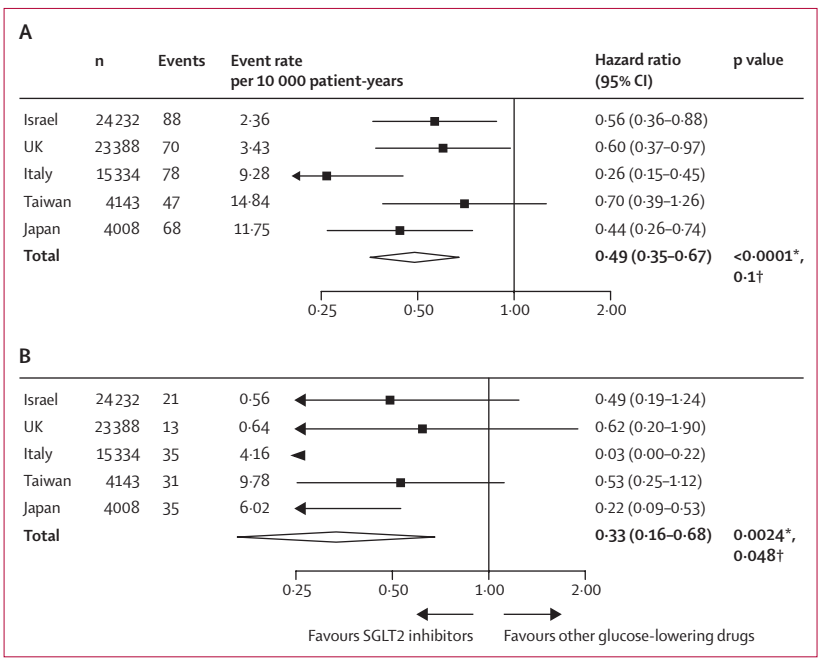


***Figure 4:*** **Forest plots for the composite kidney outcome and ESKD (intention to treat)**
(A) Composite of 50% decline in estimated glomerular filtration rate or ESKD. (B) ESKD alone. ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. *p value for SGLT2 inhibitors compared with other glucose-lowering drugs. †$p_{heterogeneity}$.

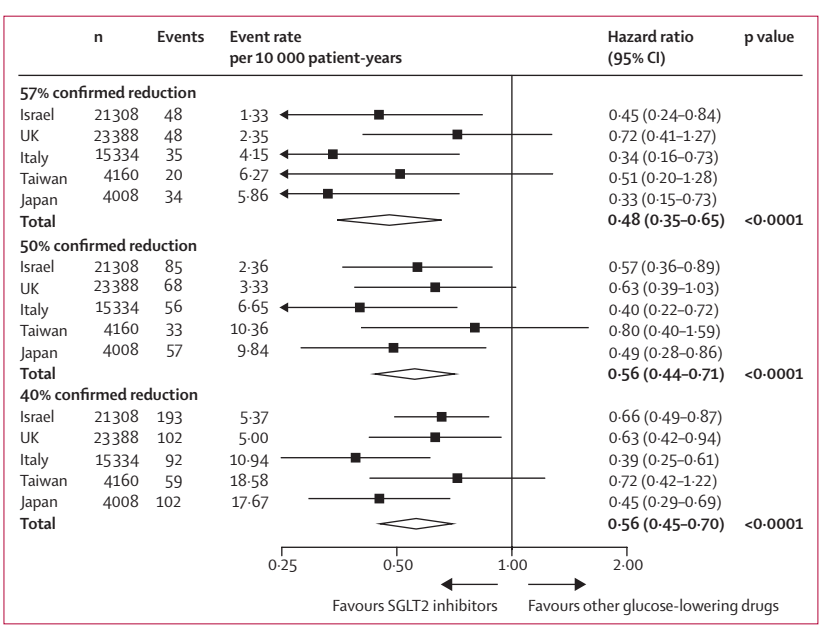


***Figure 5:*** **Forest plots for the 57%, 50%, and 40% eGFR decline (intention to treat)**
p value is for SGLT2 inhibitors compared with other glucose-lowering drugs. eGFR=estimated glomerular filtration rate. SGLT2=sodium–glucose co-transporter-2.

knowledge, only one of these previous studies included laboratory measurements of kidney function.[14–15] Data from CVD-REAL 3 are unique because of the availability of multiple eGFR measurements before and after initiation of SGLT2 inhibitor or other glucose-lowering drug therapy. These data enabled us to determine changes in eGFR trajectories within individual patients and allowed us to match patients based on their rate of kidney function decline before initiation of an SGLT2 inhibitor or another glucose-lowering drug. By matching patients on the rate of kidney function decline we ensured equal distribution of risk of chronic kidney disease—something that has not been done before in observational studies or randomised trials. In comparing the change in rate of pre-index eGFR decline, we found no differences between SGLT2 inhibitor initiators and initiators of other glucose-lowering drugs, whereas the rate of eGFR decline after SGLT2 inhibitor initiation was significantly attenuated.

Previous studies from CVD-REAL showed that initiation of SGLT2 inhibitor treatment was associated with a significantly lower risk of cardiovascular events, hospital admission for heart failure, and death.[6,16] Laboratory measurements were not available in all countries that participated in CVD-REAL, and, therefore, these data sources were not included in CVD-REAL 3. The heart failure and mortality data from the registries included in this study showed that SGLT2 inhibitor initiation was associated with a lower risk of these outcomes compared with initiation of other glucose-lowering drugs, which is consistent with previous CVD-REAL results. In keeping with previous CVD-REAL studies, event rates for clinical outcomes varied among countries. However, SGLT2 inhibitor initiation was consistently associated with a lower risk of major kidney outcomes.

Clinical trials enrol highly selected patient populations, usually to enrich the population for risk of a primary outcome event and to reduce the signal-to-noise ratio; therefore, the results might not directly reflect the effectiveness of the intervention in real-world practice. Indeed, a recent analysis that assessed the representativeness of participants in SGLT2 inhibitor cardiovascular outcome trials showed that most patients with type 2 diabetes seen in clinical practice would not have qualified for any of these trials.[17,18] Relaxing inclusion and exclusion criteria for clinical trials or implementing pragmatic clinical trials that enrol a broader patient population might overcome this limitation to some extent, but still would not offer complete resolution. A potential solution is to combine clinical trial results with data collection from well-established registries, because each can be used to address a different question (drug efficacy *vs* drug effectiveness).[19]

Our results should be interpreted with several potential limitations in mind. First, although we matched patients on multiple patient characteristics (including baseline eGFR and eGFR slopes before initiation of SGLT2 inhibitors or other glucose lowering drugs) using robust statistical techniques and did multiple sensitivity analyses, we cannot rule out the possibility of residual unmeasured confounding. Specifically, data on socioeconomic status such as education or income were not available in all countries and could affect the exposure–outcome association. Selection bias because of matching or exclusion of patients also cannot be ruled out. Additionally, bias might result from creatinine measurements being made in clinical practice because of incident ill health as well as regular more routine follow-up. However, this situation reflects real-world clinical practice and is the only way to assess eGFR change over time. Although immortal time bias by excluding or misclassifying some of the follow-up time has previously been raised as a limitation of large epidemiological studies such as ours,[20] the methods we employed in this study (including matching all new treatment initiation episodes of glucose-lowering drugs) were specifically designed to exclude this type of bias. Second, our analyses focused on efficacy and did not include safety data. Specifically, previous case reports from clinical practice suggest that SGLT2 inhibitors are associated with an increased risk of acute kidney injury.[21] However, a meta-analysis of clinical trials, as well as matched case-control studies in real-world practice registries, suggests that SGLT2 inhibitors might actually protect patients with type 2 diabetes from acute kidney injury.[22,23] Further prospective studies with rigorous definitions for acute kidney injury are warranted to address this issue. Third, we analysed eGFR slope with a linear model consistent with previous cardiovascular outcome trials, although a linear model might not be optimal to capture the acute and chronic eGFR trajectory during SGLT2 inhibitor therapy. Finally, data on albuminuria was available in only a small proportion of patients and could therefore not be analysed.

In conclusion, in this large, international, real-world cohort of patients with type 2 diabetes treated in routine clinical practice, use of SGLT2 inhibitors was associated with a slower rate of kidney function decline and lower risk of clinically meaningful kidney events compared with use of other glucose-lowering drugs. These data complement findings from randomised trials and suggest that the benefits of SGLT2 inhibitors on kidney function as observed in clinical trials seem to translate to clinical practice.

#### Contributors

HJLH, MK, PF, and MT contributed to the development of the study concept and design, data collection and analysis, interpretation of the data, and writing of the Article. KK, JPHW, LAGR, SK, AK, F-JL, C-YW, and EW contributed to the interpretation of the data and critical review and revision of the Article. CM-C, GC, LC-S, AN, and GL contributed to the data collection and analysis, interpretation of the data, data report finalisation, and critical review and revision of the Article.

#### Declaration of interests

HJLH reports grants and other from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen; and consultancy fees from CSL Pharma, Gilead, Merck, MundiPharm, Mitsubishi Tanabe, and Retrophin. AK reports grants and consulting fees from AstraZeneca, Novo Nordisk, Merck, and Boheringer Ingelheim. MT is an employee at Statisticon, for which

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