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Rates of myocardial infarction and stroke in patients initiated on SGLT2-inhibitors versus other glucose-lowering agents in real-world clinical practice: results from the CVD-REAL study

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Abstract (206/180 words)

The multinational, observational CVD-REAL study recently showed that initiation of sodium-glucose co-transporter-2 inhibitors (SGLT-2i) was associated with significantly lower rates of death and heart failure vs. other glucose-lowering drugs (oGLDs). This sub-analysis of CVD-REAL sought to determine the association between initiation of SGLT-2i vs. oGLDs and rates of myocardial infarction (MI) and stroke. Medical records, claims and national registers from the US, Sweden, Norway and Denmark were used to identify patients with T2D newly initiated on SGLT-2i (canagliflozin, dapagliflozin or empagliflozin) or oGLDs. A non-parsimonious propensity score was developed within each country to predict initiation of SGLT-2i, and patients were matched 1:1 in the treatment groups. Pooled hazard ratios (HR) and 95% CI were generated using Cox regression models. Overall, 205,160 patients were included. In the intent-to treat analysis, over 188,551 and 188,678 person-years follow-up (MI and stroke, respectively), there were 1077 MI and 968 stroke events. Initiation of SGLT-2i vs. oGLD was associated with a modestly lower risk of MI and stroke (MI: HR 0.85, 95%CI 0.72–1.00; P=0.05; Stroke: HR 0.83, 95%CI 0.71–0.97; P=0.02). These findings complement the results of the cardiovascular outcomes trials, and offer additional reassurance in regards to the cardiovascular effects of SGLT-2i, specifically as it relates to ischaemic events.

Keywords (max 6, selected from a list): Cardiovascular disease; SGLT2 inhibitor; Type 2 diabetes; Observational study

Introduction

Despite advances in prevention, cardiovascular disease remains the leading cause of mortality and morbidity in patients with type 2 diabetes (T2D). Two large randomised controlled trials (RCTs) of sodium-glucose co-transporter-2 inhibitors (SGLT-2i; empagliflozin and canagliflozin) have shown significant reductions in major adverse cardiac events, as well as hospitalisations for heart failure.[1, 2] The rates of non-fatal myocardial infarction (MI) were numerically lower with both empagliflozin and canagliflozin vs. placebo; the point estimates for non-fatal stroke numerically favoured placebo vs. empagliflozin in EMPA-REG OUTCOME trial, and canagliflozin vs. placebo in the CANVAS Program, although none of these differences were statistically significant.[1, 2]

Recently, the CVD-REAL study, a multinational, observational study of over 300,000 patients, found that initiation of SGLT-2i was associated with a significant reduction in death and heart failure when compared to other glucose-lowering drugs (oGLDs).[3] Observational data from Nordic countries (CVD-REAL Nordic) has shown non-significant point estimates in favour of SGLT-2i for MI and stroke using somewhat different statistical methods, and with dapagliflozin dominating the SGLT-2i group.[4, 5] However, the effects of SGLT-2i on atherothrombotic events in the larger CVD-REAL cohort, including patients from the US, with a broader representation of SGLT-2i compounds, have not been previously explored. Accordingly, in this analysis of the global CVD-REAL data, we sought to determine the association between initiation of SGLT-2i vs. oGLD and MI and stroke events.

Methods

The CVD-REAL study design has been previously described.[3] For this analysis, adult patients with T2D who were newly initiated on SGLT-2i (canagliflozin, dapagliflozin or empagliflozin) or oGLD were identified from medical records, claims and national registers collected from four countries (US, Sweden, Norway and Denmark). Due to small numbers of patients and events in Germany and United Kingdom we elected not to include data from these countries in this analysis. A non-parsimonious propensity score was developed separately within each country to predict the likelihood of being prescribed an SGLT-2i, and patients were matched 1:1 in the two treatment groups. In the main, on-treatment analysis, patients were followed from the index date (initiation of the SGLT-2i or oGLD) until completion of treatment, occurrence of an outcome event, death or censoring. The endpoints of interest were time to MI and stroke. Pooled hazard ratios (HR) and 95% confidence interval (CI) for each endpoint were generated using Cox regression models, with inverse variance weighting for each country. In a sensitivity analysis, an intent-to-treat (ITT) approach was used, in which patients were followed after discontinuation of index treatment. Analyses of de-identified data were conducted in accordance with local laws and regulations, and received approvals from respective Scientific/Ethics/Data Protection Committees.

Results

After propensity-score matching, 205,160 patients were included in the analysis (102,580 in each group), and baseline characteristics were well balanced between the two groups. Mean age was 57 years, 43% were female, 14% had documented cardiovascular disease before SGLT-2i or oGLD initiation.

In the SGLT-2i group, of the total exposure time, 49% of patients received dapagliflozin, 44% canagliflozin and 7% empagliflozin. There was significant geographical variation with regards to the specific SGLT-2i used, with canagliflozin used predominately (75%) in the US, and dapagliflozin used predominately (90%) in Europe. In patients initiating oGLDs, the most commonly used classes were insulin (34%), dipeptidyl peptidase-4 (DPP-4) inhibitors (18%), sulfonylureas (17%), glucagon-like peptide-1 receptor agonists (14%) and metformin (12%).

For the on-treatment analysis, the mean follow-up time was 254 days in SGLT-2i and 232 days in oGLD groups. Over 136,524 and 136,626 person-years follow-up (MI and stroke, respectively), there were 779 MIs and 674 strokes (event rate [ER] 0.57 and 0.49/100 person-years, respectively). Initiation of SGLT-2i vs. oGLD was associated with a lower risk of MI and stroke (MI: ER 0.49/100 person-years for SGLT-2i vs. 0.66/100 person-years for oGLD; HR 0.78, 95% CI 0.65–0.95; P=0.01; **Figure 1A**; Stroke: ER 0.42/100 person-years for SGLT-2i vs. 0.58/100 person-years for oGLD; HR 0.80, 95%CI 0.66–0.97; P=0.02; **Figure 1B**); with no evidence of heterogeneity by country.

In the ITT analysis, the mean follow-up time was 339 days in SGLT-2i and 332 days in oGLD groups. Over 188,551 and 188,678 person-years follow-up (MI and stroke, respectively), there were 1077 MIs and 968 strokes (ER 0.57 and 0.51/100 person-years, respectively). Initiation of SGLT-2i vs. oGLD was associated with a lower risk of MI and stroke (MI: ER 0.52/100 person-years for SGLT-2i vs. 0.62/100 person-years for oGLD; HR 0.85, 95% CI 0.72–1.00; P=0.05; **Figure 1C**; Stroke: ER 0.45/100 person-years for SGLT-2i vs. 0.57/100 person-years for oGLD; HR 0.83, 95%CI 0.71–0.97; P=0.02; **Figure 1D**); with no evidence of heterogeneity by country.

Conclusions

In summary, in this multinational study of over 200,000 patients seen in real-world clinical practice, with a very large number of ischaemic events, initiation of SGLT-2i vs. oGLD was associated with modestly lower rates of MI and stroke. Although our patient population differed from the EMPA-REG OUTCOME trial and CANVAS Program (with lower prevalence of cardiovascular disease, and thus lower event rates), for MI our results were directionally and numerically consistent with both studies;[1, 2] with difference in width of the confidence intervals likely related to greater absolute number of events in our study. For stroke, our data were also directionally and numerically consistent with the CANVAS Program.[1] Our study offers important incremental information in regards to the association between SGLT-2i use and atherothrombotic events, including MI and stroke, in a broad population of patients with T2D from routine clinical practice. Although prior observational data from Nordic countries (CVD-REAL Nordic) examined these relationships, and showed numerically lower, non-significant point estimates for MI and stroke favouring SGLT-2i vs. oGLDs (as well as vs. DPP-4 inhibitors), those investigations evaluated smaller patient samples and numbers of events, used somewhat different statistical approaches, and dapagliflozin dominated the SGLT-2i group.[4, 5] Our report substantially expands these findings in the much larger CVD-REAL cohort, with a greater number of events, included patients from the US, and had a broader representation of SGLT-2i compounds. Collectively, our findings complement the results of the completed cardiovascular outcomes trials of SGLT-2i, and prior observational analyses, and offer additional reassurance in regards to the cardiovascular effects of SGLT-

2i, specifically as it relates to ischaemic events (and especially stroke, for which some concerns had previously been raised based on a small numerical excess of stroke events with empagliflozin vs. placebo, which was not statistically significant).[2]

The results of our study should be considered in the context of several potential limitations. First, given the observational nature of the analyses, and despite robust statistical techniques, including 1:1 propensity matching, a possibility of residual, unmeasured confounding cannot be definitively excluded. Second, despite a large number of accrued patient-years of follow up, the average duration of follow up was relatively limited as SGLT-2i use in real-world practice is still recent; longer-term follow up will be needed to evaluate if effects are sustained over time. Finally, given that CVD-REAL is a large, multinational pharmaco-epidemiologic comparative effectiveness study, it was not designed to examine the potential mechanisms linking the use of SGLT-2i and associated cardiovascular benefits. However, it is highly unlikely that glucose lowering *per se* is behind the lower risk of cardiovascular events. As an example, prior analyses from the EMPA-REG OUTCOME trial have demonstrated little mediation effect of HbA1c on cardiovascular benefits of empagliflozin.[6] Potential mechanisms may involve reductions in oxidative stress, improvement in endothelial function, neuro-hormonal modulation and anti-inflammatory effects, among others.[7-11] A metabolic hypothesis suggesting that a shift in myocardial metabolism from glucose and free fatty acids to ketones may contribute to cardiovascular benefits of SGLT-2i has also been proposed.[12] Importantly, this knowledge gap is being examined by mechanistic investigations across the SGLT-2i class, with more information forthcoming in the near future.

Author contributions

MK, NH and PF were involved in the study design, the protocol was finialised with contributions from all authors. NH, and MT were involved in the data collection, all authors were involved in the analysis and interpretation of the data. MK wrote the manuscript and all authors reviewed and critically revised the draft. All authors provided final approval for submission.

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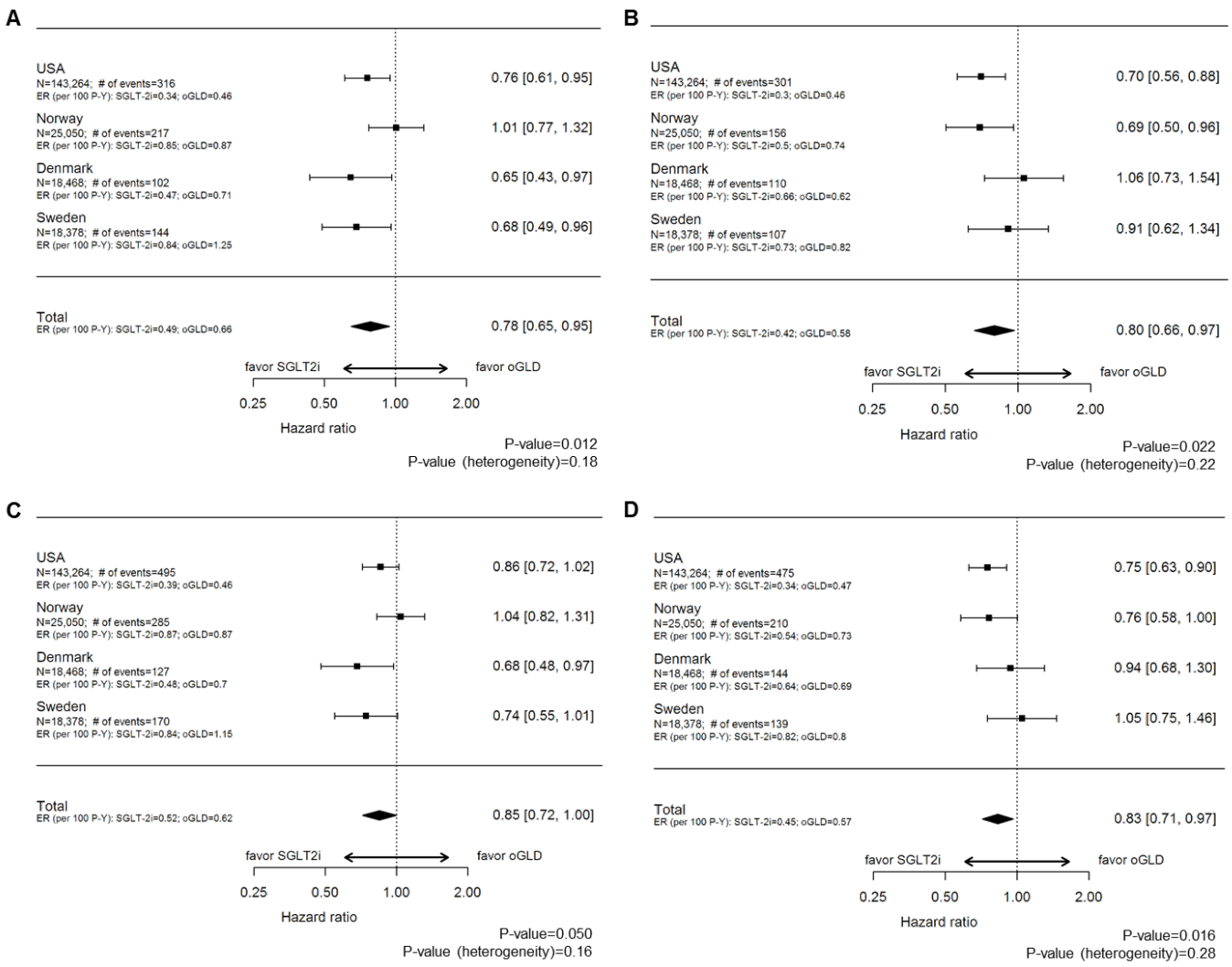
Figure 1. Event rates, unadjusted hazard ratios and 95% CI for acute myocardial infarction (A) and stroke (B) in the on-treatment population, and acute myocardial infarction (C) and stroke (D) in the ITT population



ER, event rate; oGLD, other glucose-lowering drug; P-Y, person-years; SGLT-2i, sodium-glucose transporter-2 inhibitors