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STUDY REVIEW

Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes

Making Education Easy 2022

About the Expert

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Ryan Paul is an endocrinologist and diabetologist at the Waikato DHB and in private practice in Hamilton. Ryan is active in research in his roles as a Senior Lecturer at the University of Waikato and as an Honorary Lecturer at the University of Auckland. He has key roles in teaching Primary Care and Diabetes Nurse Prescribers in New Zealand and is a member of the RACP New Zealand Adult Medicine Committee. Ryan is the immediate Past President of the New Zealand Society of Endocrinology (NZSE) and is a current Executive Member of the NZSSD. In 2019, he was awarded Clinical Educator of the Year by the New Zealand Medical Council.

Abbreviations used in this review
ACS = acute coronary syndrome
CVD = cardiovascular disease
HF = heart failure
MACCE = major adverse cardiac and cerebrovascular event
MI = myocardial infarction
OR = odds ratio
TIA = transient ischaemic attack

The objective of this real-world study was to assess associations between current use of SGLT-2 inhibitors and GLP-1 receptor agonists on the risk of MACCE and HF in adults with T2D and without known CVD. This is important because previous studies have largely focussed on the benefits of these medicines in "high-risk" patients and have not been designed to detect primary prevention benefits. Interestingly, the investigators also assessed the potential benefits of using SGLT-2 inhibitors and GLP-1 receptor agonists in combination.This review is sponsored by Boehringer Ingelheim and Eli Lilly.

The full text of the study is available here: Wright, A.K. et al. Diabetes Care 2022; 45(4):909-918 *Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes.*

The study design was a nested case-control series derived from primary care databases from England (CPRD-Gold and CPRD) and Wales (SAIL) linked to hospital and mortality records. The primary composite endpoint was the first record of MACCE after cohort entry defined as MI/ACS, stroke/TIA (including intracerebral and subarachnoid haemorrhage), and/or CV death. The secondary endpoint was the first record of HF after cohort entry. Each patient who experienced a MACCE or HF was linked to up to 20 control patients and cases without eligible controls were excluded. Patients were identified if they had their first ever prescription of a non-insulin glucose-lowering therapy between January 1998 and July 2018 and had started at least one new class of glucose-lowering therapy between November 2012 (when SGLT-2 inhibitors became available in the UK) and July 2018. Patients were only included for the primary end point if they were without prior CVD (non-fatal MI, ACS, stroke, TIA, unstable angina, HF and revascularisation) and patients were only included for the secondary end point if they had no prior admission for HF.

Patients were grouped according to their prior exposure to different glucose-lowering therapies:

- Combination SGLT-2 inhibitor and GLP-1 receptor agonist regimens
- GLP-1 receptor agonist regimens without SGLT-2 inhibitors
- SGLT-2 inhibitors without GLP-1 receptor agonists
- Other combination regimens not including SGLT-2 inhibitors or GLP-1 receptor agonists
- Other monotherapy regimens
- No current exposure

The study identified 440,089 people with T2D treated with non-insulin glucose-lowering therapies, 336,334 of whom did not have known CVD. The number of T2D patients without CVD who experienced a MACCE was 18,490 (5.5%) giving an unadjusted incidence rate of CVD of 18.1 per 1,000 person-years. From the cohort of MACCE cases, 3.2% were taking a SGLT-2 inhibitor regimen, 2.5% were taking a GLP-1 receptor agonist regimen, 0.3% were taking a SGLT-2 inhibitor/GLP-1 receptor agonist combination, 26.5% were using other combination regimens, 43.1% were taking monotherapy (mainly metformin) and 24.4% were not currently taking any glucose-lowering therapies when the MACCE occurred.

There were 411,206 people with T2D without HF and of these, 17,428 (4.2%) subsequently developed HF giving an unadjusted incidence rate of HF of 13.9 per 1,000 person-years. From the cohort of HF cases, 1.7% were taking a SGLT-2 inhibitor regimen, 2.8% were taking a GLP-1 receptor agonist regimen, 0.2% were taking a SGLT-2 inhibitor/GLP-1 receptor agonist combination, and 25% were taking other treatment combinations.

In people with T2D and without prior CVD, SGLT-2 inhibitor regimens were associated with an 18% (OR 0.82; 95% CI 0.73-0.92) lower risk of MACCE, compared to other combination regimens (**Figure 1**). In the same group, GLP-1 receptor agonist regimens were not associated with a significantly lower risk of MACCE, compared to other combination regimens. The combined SGLT-2 inhibitor and GLP-1 receptor agonist regimen was associated with a 30% (OR 0.70; 95% CI 0.50-0.98) lower risk of MACCE, compared with other combination regimens.

Treatment with a SGLT-2 inhibitor or GLP-1 receptor agonist regimen in people with T2D and without prior HF was associated with a 51% (OR 0.49; 95% CI 0.42-0.58) and 18% (OR 0.82; 95% CI 0.71-0.95) lower odds of HF respectively, compared to other glucose-lowering therapy combinations (**Figure 2**). Combination SGLT-2 inhibitor and GLP-1 receptor agonist regimens were associated with a 57% (OR 0.43;95% CI 0.28-0.64) reduction in HF risk, compared to other combination regimens.

This real-world study found that SGLT-2 inhibitor regimens and combinations of SGLT-2 inhibitors and GLP-1 receptor agonists may provide primary prevention of MACCE, in comparison to other combinations of glucose-lowering therapies. SGLT-2 inhibitor and GLP-1 receptor agonist regimens may provide primary prevention against HF, in comparison to other treatment combinations. Combining a SGLT-2 inhibitor and a GLP-1 receptor agonist may provide further benefits in terms of primary prevention of MACCE than regimens with either medicine alone. This comparison did not, however, achieve statistical significance, possibly due to the relatively small number of patients taking the two medicines in combination. Further studies are required to determine if SGLT-2 inhibitors and GLP-1 receptor agonists in combination provide additive primary prevention benefits.

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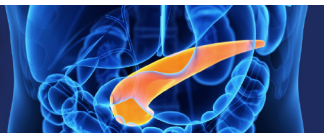

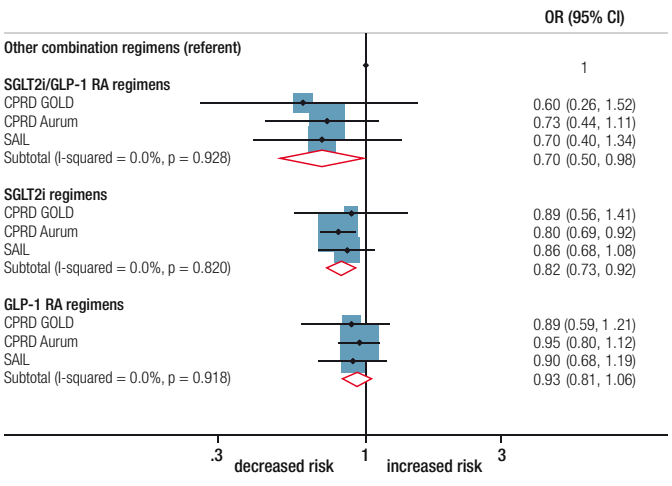

Figure 1: Association between current use of SGLT-2 inhibitor and GLP-1 receptor agonist regimens and the risk of MAACE versus other combination regimens adjusted for case-control matching factors. Adapted from Wright *et al* (2022).

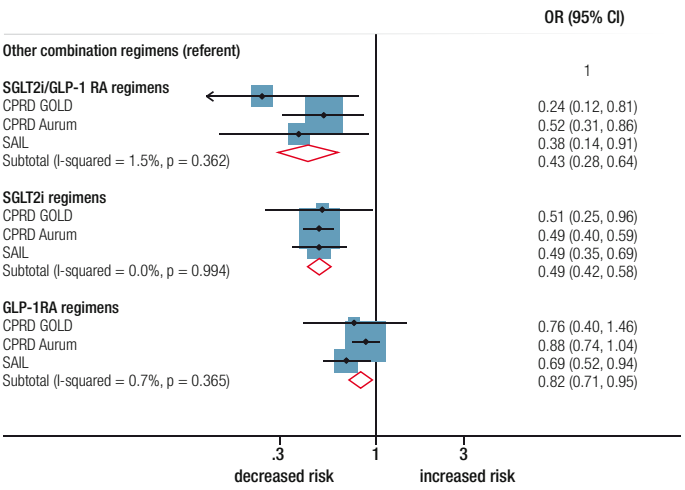

Figure 2: Association between current use of SGLT-2 inhibitor and GLP-1 receptor agonist regimens and risk of heart failure versus other combination regimens adjusted for case-control matching factors. Adapted from Wright *et al* (2022).

EXPERT COMMENTARY

Whilst the benefits of SGLT2 inhibitors and GLP1 receptor agonists in reducing CV events in those with T2D and existing CVD are well-established, their roles in preventing CVD (i.e. primary prevention) are not clear. This is because previous studies that have demonstrated the CV benefit of these agents have been primarily designed to assess CV safety predominantly in those with existing CVD or a very high CV risk. Indeed, those studies that did include people without CVD were not adequately powered to demonstrate primary prevention, and we continue to wait for prospectively designed studies to definitively answer this question. In the interim, Wright and colleagues have tried to determine any benefit of SGLT2 inhibitors and/or GLP1 receptor agonists in primary prevention of CVD by performing a large, real-world retrospective analysis of primary care data in the United Kingdom. Interestingly, they found that SGLT2 inhibitors appear to prevent CVD and HF to a similar degree in the secondary prevention setting. Conversely, GLP1 receptor agonists prevented HF and not CV events, which is surprising given GLP1 receptor agonists appear to do the opposite by preventing CV events but not HF in those with known CVD. However, all retrospective analyses have significant limitations and no definitive conclusions can be determined from these results, particularly due to the differences in this study population to those in the majority of randomised control trials of SGLT2 inhibitors and GLP1 receptor agonists.

It is important to note that these findings are not necessarily directly applicable to Aotearoa New Zealand for many reasons, especially the differences in populations and access to different agents in the SGLT2 inhibitor and GLP1 receptor agonist families. In particular, the 'class effect' of SGLT2 inhibitors in secondary prevention of CVD appears to be stronger than the class effect of GLP1 receptor agonists. Although direct comparisons cannot be made between studies, the reductions in CVD with dulaglutide appear to be stronger than the earlier GLP1 receptor agonists, which is relevant given the latter were likely the most frequent GLP1 receptor agents used in this study since dulaglutide was not available in the UK until 2015.

This also highlights that PHARMAC have done well in selecting dulaglutide and empagliflozin as the agent from each class given their 'CV prowess' over other family members. However, this study is now one of many that highlights PHARMAC's shortfall in only providing funded access to either dulaglutide or empagliflozin, and not both in those with or at risk of CVD, given the likely additive benefits they have together in preventing CV events and death. These additive benefits of SGLT2 inhibitors and GLP1 receptor agonists are yet to be proven in either primary or secondary prevention of renal disease, which was not investigated in this study.

Nevertheless, the findings that SGLT2 inhibitors may prevent CVD in T2D is welcome news given most patients with T2D die from CVD, particularly Māori and Pacific peoples with T2D. Although the limitations of this study prevent any definitive changes in guidelines, the findings highlight the potential role of empagliflozin or dulaglutide as a second line agent after lifestyle management and metformin in patients without CVD or HF. Especially those patients who have a high lifetime risk of CVD and/or when weight loss is beneficial. Many of these patients already qualify for funded empagliflozin under the Māori/Pacific peoples and/or developing diabetes at a young age Special Authority criteria. For those that do not meet the criteria, particularly those at a high lifetime risk of CVD, it is now likely more pertinent than ever to discuss the role of self-funding empagliflozin if their HbA1c is above target despite lifestyle management and metformin +/- vildagliptin. This can be a difficult discussion with empagliflozin costing $85 per month, but many patients and their whānau will opt for this cost over the cost of dulaglutide and/or any potential adverse effects of pioglitazone, sulfonylureas and insulin. Moreover, it is always important to ensure the use of empagliflozin is appropriate and adequate education is provided to prevent adverse effects as per the New Zealand Society for the Study of Diabetes (NZSSD)/Ministry of Health national guidance on the management of T2D.

Lastly, we all hope that future studies reveal that SGLT2 inhibitors and/or GLP1 receptor agonists definitively prevent CVD so we can further reduce the burden of T2D and decrease inequities for Māori and Pacific peoples with T2D.