Diabetes & Obesity
RESEARCH REVIEW™

Making Education Easy

Issue 139 – 2020

In this issue:

Abbreviations used in this issue
CV = cardiovascular
DKA = diabetic ketoacidosis
DPP = dipeptidyl peptidase
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
HF = heart failure
HR = hazard ratio
SGLT = sodium glucose cotransporter

Welcome to issue 139 of Diabetes and Obesity Research Review.

Antidiabetes drugs that reduce CV events and progression of kidney disease are the focus of a number of papers in this issue. We begin with a large matched cohort study reporting on major CV events with SGLT-2 inhibitors, but there is also a meta-analysis of two trials confirming the benefits of SGLT-2 inhibitors in patients with HF and reduced ejection fraction (with or without diabetes), a study reporting an increased risk of DKA with their use, and a safety assessment of their use in type 1 diabetes. We also report on an NZ audit comparing the proposed PHARMAC funding criteria for SGLT-1 inhibitor and GLP-1 receptor agonist eligibility with those used in the US and Europe.

We hope you enjoy the papers selected for this issue. Please keep sending us your comments and feedback.

Best regards,

Professor Jeremy Krebs
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Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events

Authors: Filion KB et al., on behalf of the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators

Summary: SGLT-2 inhibitors and DPP-4 inhibitors were compared for CV events in a retrospective real-world cohort of individuals with type 2 diabetes from multiple Canadian and UK databases. Compared with new users of DPP-4 inhibitors (n=209,867), matched new users of SGLT-2 inhibitors (n=209,867) had significantly lower incidences of major adverse CV events (11.4 vs. 16.5 per 1000 person-years; HR 0.76 [95% CI 0.69, 0.84]), myocardial infarction (5.1 vs. 6.4 per 1000 person-years; 0.82 [0.70, 0.96]), CV-related death (3.9 vs. 7.7 per 1000 person-years; 0.60 [0.54, 0.67]), HF (3.1 vs. 7.7 per 1000 person-years; 0.43 [0.37, 0.51]) and death from any cause (8.7 vs. 17.3 per 1000 person-years; 0.60 [0.54, 0.67]), and a nonsignificant trend for a lower incidence of ischaemic stroke (2.6 vs. 3.5 per 1000 person-years; 0.85 [0.72, 1.01]). The benefits in terms of major adverse CV events were similar for canagliflozin, dapagliflozin and empagliflozin (respective HRs 0.79 [95% CI 0.66, 0.94], 0.73 [0.63, 0.85] and 0.77 [0.68, 0.87]).

Comment: On the eve of funded access to SGLT-2 inhibitors in NZ, I have included a few papers in this issue that are relevant. We have seen a multitude of long-term CV randomised controlled outcome studies for SGLT-2 inhibitors reported over the last few years. There is a pretty consistent reduction in the risk of combined CV outcomes of about 12% for all of the agents compared with placebo. However, it is important to remember that these trials enrolled particular groups of patients and that the results do not always translate into real-world practice. This paper reported a comparison between SGLT-2 inhibitors and DPP-4 inhibitors when initiated in the real world. It is not a randomised trial, but a matched cohort study, which does raise the possibility of confounding; however, the number of participants was very large. What is striking is that even over a very short follow-up period (mean of just 0.9 years), the outcomes for SGLT-2 inhibitors were consistently better than for DPP-4 inhibitors. Furthermore, the effect size was very similar, if not greater, in this unselected population compared with the highly controlled clinical trials.

Reference: BMJ 2020;370:m3342
Abstract

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For more information, please go to www.medsafe.govt.nz

New Zealand may finally get funded access to diabetes drugs which reduce cardiovascular events and progression of kidney disease

Authors: Vitz M et al.

Summary: This retrospective audit compared the proposed PHARMAC criteria for SGLT-2 inhibitor and GLP-1 receptor agonist eligibility with those of the ADA (American Diabetes Association) and EASD (European Society for the Study of Diabetes) criteria for 1160 patients with type 2 diabetes registered at three general practices within the Wellington/Porirua region. The proposed PHARMAC criteria would see 34.4% of the patients eligible for funded access, compared with 27.2% and 48.2% according to the 2018 and revised 2020 ADA/EASD criteria, respectively. The differences in eligibility are due to HbA_{1c} level thresholds and inclusion of microalbuminuria for treatment.

Comment: This audit is the work of a group of students last summer, and was conceived to compare who would be eligible for funded access to either SGLT-2 inhibitors or GLP-1 agonists under the proposed PHARMAC criteria with those who would be recommended for these agents by the consensus ADA and EASD guideline. At the time the audit was being conducted, the ADA/EASD released a revised guideline on the back of new evidence. Therefore comparisons with both criteria were included. The main message is that 34% of patients with type 2 diabetes in NZ will be eligible for these agents. Most importantly those who are likely to benefit the most will have access, with a large proportion of Māori and Pacific patients. This is a major change for primary care, and what will be critical to promote equity will be the strategies put in place to roll these agents out.

Reference: N Z Med J 2020;133(1523):76–86
Abstract

Central fatness and risk of all cause mortality

Authors: Jayedi A et al.

Summary: This systematic review and meta-analysis aimed to determine the relationship of indices of central obesity with risk of all-cause mortality in the general population based on 72 prospective cohort studies (n=2,528,297). The all-cause mortality risk was increased by a 10cm increase in waist circumference (HR 1.11 [95% CI 1.08, 1.13]), a 0.1-unit increase in waist-to-hip ratio (1.20 [1.15, 1.25]), a 0.1-unit increase in waist-to-height ratio (1.24 [1.12, 1.36]), a 0.1-unit increase in waist-to-thigh ratio (1.21 [1.03, 1.39]), a 10% increase in body adiposity index (1.17 [1.00, 1.33]) and a 0.005-unit increase in A body shape index (1.15; [1.10, 1.20]); however, the all-cause mortality risk was decreased by a 10cm increase in hip circumference (0.90 [0.81, 0.99]) and a 5cm increase in thigh circumference (0.82 [0.75, 0.89]). There were J-shaped relationships of waist circumference and waist-to-height ratio with risk of all-cause mortality, a positive monotonic relationship for waist-to-hip ratio and A body shape index, and a U-shaped relationship for body adiposity index.

Comment: It is well known that obesity is associated with an increased risk of premature mortality. It is also known that if that excess weight is carried centrally, or more specifically in the visceral compartment, that this risk is even greater. There are many different ways to estimate visceral adiposity, and each has its proponents. This study attempts to compare the performance of these different tools in predicting risk for mortality using data from prospective cohort studies with a meta-analysis. All of the methods perform similarly, either showing increased or decreased risk, suggesting that any of them could be used. Furthermore, they add additional information over and above simple body mass index. Despite this knowledge, which isn't really new, any measure of central adiposity is seldom recorded clinically. Why is this? It really isn't any more invasive to measure waist circumference than it is to weigh a person, or check their blood pressure. Something stops us from doing it as part of routine care.

Reference: BMJ 2020;370:m3324
Abstract

SGLT2 inhibitors in patients with heart failure with reduced ejection fraction

Authors: Zannad F et al.

Summary: This meta-analysis of the EMPEROR-Reduced (investigating empagliflozin) and DAPA-HF (investigating dapagliflozin) trials examined the effect of SGLT-2 inhibition on fatal and nonfatal HF events and renal outcomes in a total of 8474 participants with HF and reduced ejection fraction with and without diabetes. The estimated treatment effects were significant reductions in all-cause mortality (HR 0.87 [95% CI 0.77, 0.98]), CV-related mortality (0.86 [0.76, 0.98]), the combined risk of CV-related death or first hospitalisation for HF (0.74 [0.68, 0.82]), a composite of recurrent hospitalisations for HF and CV-related deaths (0.75 [0.68, 0.84]) and a composite renal endpoint (0.62 [0.43, 0.90]).

Comment: Most of the early large trials of SGLT-2 inhibitors were conducted in patients with type 2 diabetes and either established CV disease or at higher risk of this. People with existing HF or significant renal disease were excluded. However, in the last couple of years we have been seeing the publication of the results of later trials that specifically enrolled patients with these more downstream complications. This paper reports a pooled patient level meta-analysis of two of the biggest trials using either dapagliflozin or empagliflozin in people with HF and reduced ejection fraction either with or without diabetes. Once again the CV and renal benefits of SGLT-2 inhibitors are seen widely across patient groups, and this now extends beyond only those with diabetes. Data such as these will add compelling evidence to PHARMAC that these agents perhaps should be made more widely available than the proposed special authority criteria will allow. This is of course a significant fiscal commitment, but nevertheless the cost savings of reduced admissions to hospital with HF and progression to renal dialysis surely offset such costs.

Reference: Lancet 2020;396:819–29
Abstract

Sodium-glucose cotransporter-2 inhibitors and the risk for diabetic ketoacidosis

Authors: Douros A et al., for the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators

Summary: SGLT-2 inhibitor versus DPP-4 inhibitor use was assessed for DKA risk in a time-conditional propensity score-matched analysis of population-based cohorts of Canadian and UK patients with type 2 diabetes who were new users of these classes of agents during 2013–2018 (n=208,757 for each class). Over 370,454 person-years, 521 patients were diagnosed with DKA, for an incidence rate of 1.40 per 1000 person-years. Compared with DPP-4 inhibitor use, SGLT-2 inhibitor use was associated with a greater incidence rate of DKA (2.03 vs. 0.75 per 1000 person-years; HR 2.85 [95% CI 1.99, 4.08]), with increased risks specifically for dapagliflozin, empagliflozin and canagliflozin (respective HRs 1.86 [1.11, 3.10], 2.52 [1.23, 5.14] and 3.58 [2.13, 6.03]). The relationship between SGLT-2 inhibitor use and DKA risk was not modified by age or sex, but prior insulin use appeared to lower the risk.

Comment: One of the main concerns hanging over the widespread use of SGLT-2 inhibitors is the reported increased risk of ketoacidosis, particularly because it occurs with relatively normal glucose levels. This paper is a second report from the real-world study comparing SGLT-2 inhibitors and DPP-4 inhibitors discussed previously in this issue. Here the focus is specifically on rates of DKA. Compared with DPP-4 inhibitors, SGLT-2 inhibitors had a 2.8-fold greater risk of DKA. However, the absolute rates of DKA were still low with an incidence rate of 1.4 per 1000 patient-years. This is pretty reassuring, and whilst it is important that we educate patients on when to be careful and when to consider withholding the drug, and ensure that after hours and emergency departments are familiar with the risk, for those with type 2 diabetes, the benefits appear to well outweigh this risk. That may not be the case for type 1 diabetes, as we see in another paper that I have included.

Reference: Ann Intern Med 2020;173:417–25
Abstract

Independent commentary by Professor Jeremy Krebs
MBChB, FRACP, MD

Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He is a Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established. **FOR FULL BIO CLICK HERE.**

Intrauterine exposure to diabetes and risk of cardiovascular disease in adolescence and early adulthood

Authors: Guillemette L et al.

Summary: The possibility that intrauterine exposure to maternal diabetes increases the risk of CV disease and related endpoints in adulthood was explored in a Canadian population-based birth cohort (n=293,546) followed until the age of 35 years (mean age at latest follow-up, 20.5 years). During 3,628,576 person-years of follow-up, 4.3% of the cohort were recorded as having a CV disease risk factor and 0.9% experienced a CV disease endpoint. A propensity-score matched analysis revealed that the risk of a CV endpoint was significantly increased for individuals exposed *in utero* to gestational diabetes (adjusted HR 1.42 [95% CI 1.12, 1.79]) but not type 2 diabetes (1.40 [0.98, 2.01]), while the likelihood of CV disease risk factors was significantly increased for intrauterine exposure to both gestational and type 2 diabetes (1.92 [1.75, 2.11] and 3.40 [3.00, 3.85], respectively).

Comment: The intergenerational risk for diabetes and CV disease is one of the contentious areas of research in obesity and gestational diabetes, the key questions being whether intrauterine exposure to maternal obesity and/or diabetes confers greater risk to the offspring of subsequent obesity, metabolic or CV disease. This large registry-based retrospective cohort study of the offspring followed up to a mean of 20 years showed a 40% greater rate of CV disease, and almost double the incidence of CV risk factors in those exposed to gestational diabetes and a >3-fold increase for those exposed to type 2 diabetes *in utero*. The important limitation of this study is that this is not adjusted for maternal or paternal factors such as obesity or other CV risk factors. Therefore, we cannot assume that the increased risk is truly due to the intrauterine environment alone. Nor do we know whether modifying the exposure by tight glycaemic control or weight management during pregnancy influences this subsequent risk.

Reference: CMAJ 2020;192:E1104–13
Abstract

Precision medicine in type 2 diabetes: using individualized prediction models to optimize selection of treatment

Author: Dennis JM

Summary: This was a review of the current evidence on differential drug responses with noninsulin treatments after metformin; it discussed how these differences could be used to inform the optimal treatment of type 2 diabetes. A novel framework that uses existing routine clinical and trial data is presented for the development and testing of precision medicine-based strategies for such optimal treatment. The author reported that application of this framework has demonstrated that 'subtype' approaches (patients classified into subgroups based on features reflecting their underlying pathophysiology) are likely to be less clinically useful than approaches that combine the same features as continuous measures in probabilistic 'individualised prediction' models.

Comment: When it comes to type 2 diabetes, all things are not created equal. For example, it is very apparent in clinical practice that the pathogenesis of the disease in a young person who is morbidly obese with a strong family history is quite different to the elderly lean person. Similarly, we see clear evidence of differential responses to therapy. As we have broadened access to a range of agents with different mechanisms of action, it will become increasingly important to try to optimise treatment strategies. The concept of precision medicine is not new, and indeed something we all do every day, even if subconsciously. What this paper reports and proposes is a more structured approach to this utilising data from clinical trials and responses to medications, related to readily available clinical data such as weight, HbA_{1c} level, renal function, duration of diabetes and the like. There are some interesting observations and it is well worth a read.

Reference: Diabetes 2020;69:2075–85
Abstract

An observational study of the equivalence of age and duration of diabetes to glycemic control relative to the risk of complications in the combined cohorts of the DCCT/EDIC study

Authors: Bebu I et al., on behalf of the DCCT/EDIC Research Group

Summary: This epidemiological analysis of pooled data from the DCCT/EDIC cohort equated the impact of a 1-percentage point increase in HbA_{1c} level with years of additional age or duration of type 1 diabetes on the risks of complications. Each percentage point increase in HbA_{1c} level equated to: i) 4.3 additional years of age and 5.6 additional years of type 1 diabetes duration in terms of any CV disease risk; ii) 12.1 and 18.0 additional years, respectively, in terms of the risk of estimated glomerular filtration rate falling below 60 mL/min/1.73m^2 and/or end-stage renal disease; iii) 6.4 additional years of type 1 diabetes duration in terms of proliferative diabetic retinopathy risk; and iv) 12.9 additional years of age in terms of mortality risk.

Comment: The risk of micro- and macrovascular complications of diabetes relate to total glycaemic burden. This is most commonly reflected by HbA_{1c}, and we are very familiar with the exponential relationship between HbA_{1c} level and microvascular complications. However, even with tight glycaemic control, many years of diabetes still expose an individual to significant glycaemic burden compared with a person with normal glucose levels. This paper used long-term follow-up data from the DCCT and EDIC datasets in people with type 1 diabetes to explore this concept. For example, a 1-percenage point (11 mmol/mol) increase in HbA_{1c} level is equivalent to an increased age of about a decade for risk of mortality. This may be a useful comparison in discussion with people with diabetes to highlight the importance of achieving the best glycaemic control they can.

Reference: Diabetes Care 2020;43:2478–84
Abstract

Evaluation of the safety of sodium-glucose co-transporter-2 inhibitors for treating patients with type 1 diabetes

Authors: Wang W et al.

Summary: These researchers analysed data from 22 studies with qualitative-based results, including eight randomised controlled trials with quantitative-based results, to assess the overall safety of SGLT-2 inhibitors when used to treat type 1 diabetes. Compared with controls, SGLT-2 inhibitors were associated with increased likelihoods of ketoacidosis (odds ratio 4.34 [95% CI 2.37, 7.96]), events leading to discontinuation (1.76 [1.34, 2.31]), genital infections (3.64 [2.82, 4.70]), volume depletion (2.10 [1.23, 3.59]) and diarrhoea (1.64 [1.14, 2.36]; the risk of diarrhoea was found to be dose-related). SGLT-2 inhibitor use was not associated with an increased incidence of urinary tract infections, CV events, renal events, liver injury or fractures.

Comment: With the accumulating evidence for CV renal protection with SGLT-2 inhibitors in type 2 diabetes and indeed in those with HF without diabetes (see other study in the review), it is not surprising that the question about the use of these agents in people with type 1 diabetes is raised. Anecdotally, I have had several patients who have found them to be very helpful in glycaemic management. However, the concern regarding ketoacidosis makes me wary about their use. This paper reports an analysis of published studies of SGLT-2 inhibitors in type 1 diabetes and confirms a more than 4-fold increased risk of DKA compared with control groups. Once again, because this can present with relatively normal glucose levels, there is a definite clinical risk of using SGLT-2 agents in people with type 1 diabetes that needs to be carefully discussed and managed.

Reference: Diabetes Obes Metab 2020;22:1767–76
Abstract

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Metformin in women with type 2 diabetes in pregnancy (MiTy)

Authors: Feig DS et al., on behalf of the MiTy Collaborative Group

Summary: The MiTy trial randomised women with type 2 diabetes during pregnancy at Australian and Canadian centres to receive metformin 1000mg (evaluable n=233) or placebo (evaluable n=240) twice daily added to insulin. There was no significant difference between the metformin and placebo groups for a primary composite of foetal and neonatal outcomes (40% vs. 40%; relative risk 1.02 [95% CI 0.83, 1.26]), but the metformin-treated mothers had significantly better glycaemic control, required significantly less insulin and underwent significantly fewer caesarean deliveries, and their offspring weighed significantly less, had reduced measures of adiposity and were more likely to be small for gestational age. There was no significant between-group difference for hypertensive disorders or cord C-peptide levels. Gastrointestinal adverse events were the most common type reported (38 in each group).

Comment: Metformin was previously contraindicated in pregnancy because of lack of safety data rather than any known risk. It is now commonly used after the NZ led MIG trial showed safety in gestational diabetes. This randomised controlled trial of the addition of metformin to insulin in women with known type 2 diabetes further adds to the literature. Here the primary outcome was a composite of foetal and neonatal outcomes. The use of metformin did not improve this measure over insulin use alone. However, it was associated with lower maternal weight gain, lower birthweight and better glycaemic control, all of which may lead to better outcomes for infant and adolescent weight and metabolic factors. A long-term outcome study of the children would be very useful.

Reference: Lancet Diabetes Endocrinol 2020;8:834–44
Abstract