

A SELECTION OF TEN READINGS ON "CONTEMPORARY TYPE 2 DIABETES MANAGEMENT – WHAT'S NEW?"

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Some available as free full text and some requiring payment

Selection of readings made by A/Prof Goh Lee Gan

READING 1 - COST-EFFECTIVENESS OF SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS IN TYPE 2 DIABETES MELLITUS

McEwan P, Bennett H, Khunti K, et al. Assessing the cost-effectiveness of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus: A comprehensive economic evaluation using clinical trial and real-world evidence. *Diabetes Obes Metab.* 2020 Aug 3.

URL: PMID 31579904. doi: 10.1111/dom.14162[Payment required].

ABSTRACT

AIMS: The economic burden of diabetes is driven by the management of vascular complications. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated reductions in cardiovascular and renal complications, including hospitalisation for heart failure (HHF) and renal disease progression, in randomised clinical trials. The objective of this study was to evaluate the cost-effectiveness of the SGLT2i class versus standard of care in type 2 diabetes mellitus (T2DM), using evidence from both clinical trial and real-world studies.

METHODS: An established T2DM model was adapted to use contemporary outcomes evidence from real-world studies and randomised controlled trial evaluations of SGLT2i, and extrapolated over a lifetime for HHF, myocardial infarction, stroke, end-stage renal disease and all-cause mortality. The economic analysis considered adults with T2DM, with and without established cardiovascular disease, and was conducted over a lifetime from the perspective of the health care payer in the United Kingdom, United States and China, discounted at country-specific rates.

RESULTS: SGLT2i were consistently associated with increased treatment costs, reduced complication costs and gains in quality-adjusted life years driven by differences in projected life expectancy, cardiovascular and microvascular morbidity and weight loss. SGLT2i were estimated to be cost-saving or cost-effective at relevant thresholds for the overall population in the United Kingdom, United States and China, with cost-effectiveness being the greatest in higher risk subgroups.

CONCLUSIONS: The findings highlight the need to take into account cost savings from reducing common, morbid and preventable T2DM complications when considering the cost of diabetes medications.

READING 2 - EFFICACY AND SAFETY OF EMPAGLIFOZIN IN OLDER PATIENTS

Monteiro P, Bergenstal RM, Tournal E, et al. Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME® trial. *Age Ageing.* 2019; 48(6):859-866. PMID: 31579904.

URL: DOI: 10.1093/ageing/afz096 [Payment required].

ABSTRACT

OBJECTIVE: The risks of cardio-renal complications of diabetes increase with age. In the EMPA-REG OUTCOME® trial, empagliflozin reduced cardiovascular (CV) mortality by 38 percent in patients with type 2 diabetes (T2DM) and CV disease. Here we compare outcomes with empagliflozin in older patients in EMPA-REG OUTCOME.

METHODS: Patients with T2DM and CV disease were randomised to empagliflozin 10 or 25 mg, or placebo plus standard of care. In post hoc analyses, risks of 3-point major adverse CV events (3P-MACE: composite of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke), CV death, hospitalisation for heart failure, all-cause mortality, all-cause hospitalisation and incident/worsening nephropathy were evaluated for empagliflozin versus placebo by baseline age (<65, 65 to <75, ≥75 years). Adverse events (AEs) were analysed descriptively.

RESULTS: Effect of empagliflozin on all outcomes was consistent across age categories ($P \geq 0.05$ for interactions) except 3P-MACE. The 3P-MACE hazard ratios (HRs) were 1.04 (95 percent confidence interval [CI] 0.84, 1.29), 0.74 (0.58, 0.93) and 0.68 (0.46, 1.00) in patients aged <65 , 65 to <75 , and ≥ 75 years, respectively ($P = 0.047$ for treatment-by-age group interaction). Corresponding CV death HRs were 0.72 (95 percent CI 0.52, 1.01), 0.54 (0.37, 0.79) and 0.55 (0.32, 0.94), respectively ($P = 0.484$ for treatment-by-age group interaction). Across age categories, empagliflozin AEs reflected its known safety profile. Rates of bone fractures, renal AEs, and diabetic ketoacidosis were similar between empagliflozin and placebo across age categories.

CONCLUSIONS: In the EMPA-REG OUTCOME trial, empagliflozin reduced risks of CV mortality, heart failure, and renal outcomes, supporting its cardio-renal benefits in older patients.

READING 3 - PLACE OF SULPHONYLUREAS TODAY

Webb DR, Davies MJ, Jarvis J, Seidu S, Khunti K. The right place for Sulphonylureas today. *Diabetes Res Clin Pract.* 2019 Nov; 157:107836. PMID: 31479704.

URL: PMID: 31479704. doi: 10.1016/j.diabres.2019.107836 [Payment required].

ABSTRACT

The place of Sulphonylurea based insulin secretagogues in the management of Type 2 diabetes appears as controversial today as it was fifty years ago.

Newer therapies are associated with less hypoglycaemia and weight gain than Sulphonylurea but currently cost more and lack assurances which come with long-term exposure.

Emergence of recent CVOT data for SGLT-2 inhibitors and GLP-1 receptor agonists is likely to influence therapeutic choices and guidance is now supportive of their earlier use in cases at high risk of cardiovascular disease.

Meta-analyses of Sulphonylurea trials have failed to indicate a consistent effect (positive or negative) on cardiovascular disease or mortality, although are limited by the relative scarcity of studies directly reporting these outcomes.

The CAROLINA trial is reassuring in demonstrating cardiovascular safety for the Sulphonylurea Glimepiride when compared directly with the DPP-4 inhibitor Lina gliptin, suggesting either of these agents would be relatively safe second line options after Metformin in the majority of patients.

This review provides a balanced assessment of available Sulphonylurea treatments in the context of current cardiovascular outcome trial data (CVOT) data and hopefully assists informed decision making about the place of these drugs in contemporary glucose lowering practice.

READING 4 - CARDIOVASCULAR SAFETY OF NEW DRUGS FOR DIABETES MANAGEMENT

Bailey CJ, Day C. The future of new drugs for diabetes management. *Diabetes Res Clin Pract.* 2019 Sep; 155:107785. PMID: 31326453.

URL: PMID 31326453. doi: 10.1016/j.diabres.2019.107785 [Payment required].

ABSTRACT

The future of the newer classes of glucose-lowering drugs, namely dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium/glucose co-transporter-2 (SGLT-2) inhibitors, is being redefined by the large prospective cardiovascular outcome trials (CVOTs).

These trials have more than confirmed cardiovascular (CV) safety: indeed, various cardio-renal parameters have improved during some of the trials with GLP-1RAs and SGLT-2 inhibitors in type 2 diabetes. Benefits have included reductions in major adverse cardiovascular events such as fatal and non-fatal myocardial infarction and stroke, decreased hospitalisation for heart failure, a slower decline in glomerular filtration rate and reduced onset and progression of albuminuria.

In consequence, the CVOTs have raised expectations that newer glucose-lowering agents should offer advantages that extend beyond glycaemic control and weight management to address complications and comorbidities of type 2 diabetes, particularly cardio-renal diseases.

Although large prospective outcome trials incur a high cost which may prompt reconsideration of their design, these trials are generating evidence to enable more exacting and more effective management of type 2 diabetes and its accompanying cardio-renal diseases.

READING 5 - SGLT2 INHIBITORS OR GLP-1 ANTAGONISTS HAVE THE MOST BENEFICIAL EFFECTS, ESPECIALLY IN T2DM PATIENTS WITH PREVIOUS CV DISEASES

Grenet G, Ribault S, Nguyen GB, et al. GLUCose Control Safety & Efficacy in type 2 Diabetes, a systematic review and NETwork meta-analysis. *PLoS One* 2019 Jun 25; 14(6):e0217701. PMID: 31237921.

URL: PMID: 31237921. doi: 10.1371/journal.pone.0217701 [Free full text].

ABSTRACT

BACKGROUND: The last international consensus on the management of type 2 diabetes (T2DM) recommends SGLT-2 inhibitors or GLP-1 agonists for patients with clinical cardiovascular (CV) disease; metformin remains the first-line glucose lowering medication. Last studies suggested beneficial effects of SGLT-2 inhibitors or GLP-1 agonists compared to DPP-4 inhibitors, in secondary CV prevention. Recently, a potential benefit of SGLT-2 inhibitors in primary CV prevention also has been suggested. However, no comparison of all the new and the old hypoglycaemic drugs is available on CV outcomes. We aimed to compare the effects of old and new hypoglycaemic drugs in T2DM, on major adverse cardiovascular events (MACE) and mortality.

METHODS AND FINDINGS: We conducted a systematic review and network meta-analysis of clinical trials. Randomised trials, blinded or not, assessing contemporary hypoglycaemic drugs on mortality or MACE in patients with T2DM, were searched for in Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. References screening and data extraction were done by multiple observers. Each drug was analysed according to its therapeutic class. A random Bayesian network meta-analysis model was used. The primary outcomes were overall mortality, cardiovascular mortality, and MACE. Severe adverse events and severe hypoglycaemia were also recorded. A total of 175,966 patients in 34 trials from 1970 to 2018 were included.

No trials evaluating glinides or alpha glucosidase inhibitors were found. A total of 17 trials included a majority of patients with previous cardiovascular history, 16 trials a majority of patients without.

Compared to control, SGLT-2 inhibitors were associated with a decreased risk of overall mortality (OR = 0.84 [95 percent CrI: 0.74; 0.95]), SGLT-2 inhibitors and GLP-1 agonists with a decreased risk of MACE (OR = 0.89 [95 percent CrI: 0.81; 0.98] and OR = 0.88 [95 percent CrI: 0.81; 0.95], respectively).

Compared to DPP-4 inhibitors, SGLT-2 inhibitors were associated with a decreased risk of overall mortality (OR = 0.82 [95 percent CrI: 0.69; 0.98]), GLP-1 agonists with a decreased risk of MACE (OR = 0.88 [95 percent CrI: 0.79; 0.99]).

Insulin was also associated with an increased risk of MACE compared to GLP-1 agonists (OR = 1.19 [95 percent CrI: 1.01; 1.42]). Insulin and sulfonylureas were associated with an increased risk of severe hypoglycaemia.

In the trials including a majority of patients without previous CV history, the comparisons of SGLT-2 inhibitors, metformin and control did not show significant differences on primary outcomes. We limited our analysis at the therapeutic class level.

CONCLUSIONS: SGLT-2 inhibitors and GLP-1 agonists have the most beneficial effects, especially in T2DM patients with previous CV diseases. Direct comparisons of SGLT-2 inhibitors, GLP-1 agonists and metformin are needed, notably in primary CV prevention.

READING 6 - SGLT2S AND GLP-1 HAVE BENEFICIAL EFFECTS ESPECIALLY IN T2DM PATIENTS WITH PREVIOUS CARDIOVASCULAR DISEASES

Connelly KA, Bhatt DL, Verma S. Can We DECLARE a Victory against Cardio-Renal Disease in Diabetes? *Cell Metab.* 2018 Dec 4;28(6):813-815. PMID: 30517896.

URL: PMID: 30517896. doi: 10.1016/j.cmet.2018.11.010 [Free full text].

ABSTRACT

Heart failure and renal disease remain significant complications in people with type 2 diabetes (T2DM). Recent outcome studies with sodium-glucose cotransporter-2 (SGLT2) inhibitors have provided increasing insights, with the latest reporting trial DECLARE-TIMI 58 (Wiviott et al., 2018), pointing toward a role for these agents in the primary prevention of cardio-renal complications in T2DM.

READING 7 - RAPID REDUCTION OF HF OUTCOMES WITH EMPAGLIFLOZIN IS OBSERVED ACROSS THE SPECTRUM OF CVD AND HF RISK

Fitchett DH. Empagliflozin and Cardio-renal Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease - Implications for Clinical Practice. *Eur Endocrinol.* 2018; 14(2):40-49. PMID: 30349593.

URL: PMID: doi:10.17925/EE.2018.14.2.40 [Free full text].

ABSTRACT

In patients with type 2 diabetes (T2DM), the excretion of glucose by the kidney with sodium-glucose cotransporter 2 (SGLT2) inhibitors lowers glycosylated haemoglobin (HbA1c) levels, decreases body weight and visceral adiposity, as well as improving cardio-renal haemodynamic.

Currently, four SGLT2 inhibitors are approved in the US and Europe to improve glycaemic control - empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin. Recently, the SGLT2 inhibitor empagliflozin was approved by the Food and Drug Administration (FDA) for the reduction of cardiovascular (CV) death in adults with T2DM and CV disease (CVD).

This approval was based on the findings of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study, which was the first study to show a significant reduction of a primary CV endpoint with a glucose-lowering agent. In this study, the primary outcome (CV mortality, non-fatal myocardial infarction [MI] and non-fatal stroke) was reduced by empagliflozin (10.5 percent; 490/4,687) compared with placebo (12.1 percent; 282/2,333); hazard ratio (HR), 0.86 (95 percent confidence interval [CI]: 0.74, 0.99).

The primary outcome was driven by a large reduction of CV mortality (relative risk reduction [RRR], 38 percent). Empagliflozin also reduced all-cause mortality (RRR, 32 percent).

Furthermore, empagliflozin reduced the adjudicated outcome of heart failure (HF) hospitalisation by 35 percent (HR, 0.65; 95 percent CI: 0.50, 0.85). Other non-adjudicated measures of HF outcomes were similarly reduced including investigator reported HF, the introduction of loop diuretics and death from HF.

In the analysis of renal outcomes, incident or worsening nephropathy was reduced for empagliflozin (12.7 percent) compared with placebo (18.8 percent); HR, 0.61 (95 percent CI: 0.53, 0.70). Empagliflozin significantly reduced the risk of progression to macroalbuminuria (38 percent) and doubling of creatinine (44 percent), as well as the need of starting renal-replacement therapy (55 percent).

The benefits of empagliflozin for the reduction of CV death, all-cause death and hospitalisation for HF were observed across a range of baseline subgroups such as HbA1c level and renal function (down to estimated glomerular filtration rate [eGFR] 30 ml/min/1.73 m²).

The rapid reduction of HF outcomes with empagliflozin is observed across the spectrum of CVD and HF risk and represents a therapeutic advance in the prevention and perhaps also in the treatment of HF, an often poorly recognised complication of T2DM. This review discusses the EMPA-REG OUTCOME study and the implications for treating patients with T2DM and CVD.

READING 8 - CARDIOVASCULAR SAFETY OF SODIUM-GLUCOSE CO-TRANSPORTER-2 (SGLT-2) INHIBITORS (GLIFLOZINS), GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISTS AND DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS (GLIPTINS)

Manolis AA, Manolis TA, Manolis AS. Cardiovascular Safety of Antihyperglycemic Agents: “Do Good or Do No Harm”. *Drugs*. 2018 Oct; 78(15):1567-1592. PMID: 30251174.

URL: PMID: 30251174. doi: 10.1007/s40265-018-0985-4 [Payment required].

ABSTRACT

Results from recent cardiovascular outcome trials have ushered in a new era in the management of type 2 diabetes mellitus, moving from a focus on glycaemic control to the cardiovascular safety of antihyperglycemic agents.

Several new antihyperglycemic drugs have been shown to exert either neutral or cardio protective effects in patients with diabetes. Among them, the sodium-glucose co-transporter-2 (SGLT-2) inhibitors (gliflozins) and selected agents from the incretin mimetics or enhancers, such as the glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins), appear to confer cardiovascular safety and/or protection in patients with underlying, or at high risk for, cardiovascular disease.

Metformin remains the standard first-line drug treatment for patients with diabetes because of its established effectiveness and cardiovascular safety. However, this initial drug therapy may not prove adequate as this disease appears to be progressive with a decline in function of the pancreatic beta cells, necessitating the addition of other agents to better control rising glucose levels.

With the advent of several new classes of antihyperglycemic drugs and the completion of their respective cardiovascular outcome trials, the therapeutic armamentarium against this disease pandemic appears to be greatly expanding and moving closer to the direction of the Hippocratic aphorism “Do Good or Do No Harm”. In this review, we discuss all these issues and summarise the contemporary literature on cardiovascular safety and outcomes of the available glucose-lowering agents.

READING 9 - CARDIO-RENAL-METABOLIC (CaReMe) CONDITIONS IN ADULT T2DM

Arnold SV, Kosiborod M, Wang J, Fenici P, Gannedahl G, LoCasale RJ. Burden of cardio-renal-metabolic conditions in adults with type 2 diabetes within the Diabetes Collaborative Registry. *Diabetes Obes Metab*. 2018 Aug; 20(8):2000-2003. PMID: 29577540.

URL: PMID: 29577540. doi: 10.1111/dom.13303 [Payment required].

ABSTRACT

We examined the prevalence of cardio-renal-metabolic (CaReMe) conditions and their combinations among 530,747 adults with type 2 diabetes in a USA-based outpatient registry of 271 primary care, cardiology and endocrinology offices.

We evaluated the following CaReMe conditions: hypertension, hyperlipidaemia, coronary artery disease (CAD), chronic kidney disease (CKD), cerebrovascular disease, peripheral artery disease, atrial fibrillation, heart failure, and gout or hyperuricaemia; prevalence estimates were adjusted based on the distribution of diabetes by age in the US population in 2015.

We found that it was uncommon for patients to have isolated type 2 diabetes without other CaReMe conditions, with only 6.4 percent having no other CaReMe conditions and 51 percent having ≥ 3 other CaReMe conditions.

The most prevalent individual conditions were hypertension (83 percent), hyperlipidaemia (81 percent), CAD (32 percent) and CKD (20 percent), and the most common combinations included various groupings of hypertension, hyperlipidaemia, atherosclerotic cardiovascular disease and CKD.

Older age, male sex and tobacco use were each associated with increased numbers of CaReMe conditions. These findings highlight the clinical need for novel treatment strategies for diabetes that address both glycaemia and coexisting disease states.

READING 10 - MANAGEMENT OF DIABETES DURING AIR TRAVEL

Pavela J, Suresh R, Blue RS, Mathers CH, Belalcazar LM. Management of diabetes during air travel: a systematic literature review of current recommendations and their supporting evidence. *Endocr Pract.* 2018 Feb; 24(2):205-219.

URL: PMID: 29466062. doi: 10.4158/EPI171954.RA [Payment required].

ABSTRACT

OBJECTIVE: Individuals with diabetes are increasingly seeking pretravel advice, but updated professional recommendations remain scant. We performed a systematic review on diabetes management during air travel to summarise current recommendations, assess supporting evidence, and identify areas of future research.

METHODS: A systematic review of the English literature on diabetes management during air travel was undertaken utilising PubMed and MEDLINE. Publications regarding general travel advice; adjustment of insulin and non-insulin therapies; and the use of insulin pumps, glucometers and subcutaneous glucose sensors at altitude were included. Gathered information was used to create an updated summary of glucose-lowering medication adjustment during air travel.

RESULTS: Sixty-one publications were identified, most providing expert opinion and few offering primary data (47 expert opinion, two observational studies, two case reports, and ten device studies). General travel advice was uniform, with increasing attention to pre-flight security. Indications for oral antihyperglycemic therapy adjustments varied. There were few recommendations on contemporary agents and on non-hypoglycaemic adverse events. There was little consensus on insulin adjustment protocols, many antedating current insulin formulations. Most publications advocated adjusting insulin pump time settings after arrival; however, there was disagreement on timing and rate adjustments. Glucometers and subcutaneous glucose sensors were reported to be less accurate at altitude, but not to an extent that would preclude their clinical use.

CONCLUSION: Recommendations for diabetes management during air travel vary significantly and are mostly based on expert opinion. Data from systematic investigation on glucose-lowering medication adjustment protocols may support the development of a future consensus statement.

ABBREVIATIONS: CSII = continuous subcutaneous insulin infusion (device) DPP-4 = dipeptidyl peptidase 4 EGA = error grid analysis GDH = glucose dehydrogenase GOX = glucose oxidase GLP1 = glucagon-like peptide-1 NPH = neutral protamine Hagedorn SGLT2 = sodium-glucose cotransporter-2.