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Should sodium glucose co-transporter 2 inhibitors be considered as first line oral therapy for people with type 2 diabetes?

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Type 2 diabetes mellitus (T2DM) is a chronic condition associated with long-term microvascular and macrovascular complications. Evidence-based guidelines recommend the individualisation of therapies to manage hyperglycaemia in order to reduce risk of complications. Therapies that target hyperglycaemia but do not correct the underlying pathophysiological mechanisms are unlikely to lead to long-term sustained reductions in glycaemic control.

Globally, in almost all type 2 diabetes guidelines, metformin is considered the first-line recommendation for management of hyperglycaemia, mainly based on the findings from the UKPDS Study[(1)]. Metformin has been used for over 60 years and there is increased understanding now of its mechanism of action of overall directly or indirectly reducing hepatic glucose production, increase glucose utilisation, via several mechanisms including altering microbiome, increasing GLP1, acting via both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms and lowering cyclic-AMP. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are the latest addition to the oral glucose-lowering agents recommended for use as second or third line agents after metformin therapy[(2)]. They address a number of pathophysiological mechanisms. As well as reducing renal glucose reabsorption, they have effects on the liver, pancreas, adipose tissue, skeletal muscle and the gut. Additionally, they have a number beneficial effects on metabolic risk factors such as reductions in blood pressure, reduction in albumin excretion, reductions in uric acid, improvements in endothelial function, weight loss and reduced visceral fat[(2)]. There has also been great interest recently on the mechanisms of SGLT-2 inhibition for the cardio-renal protection. In terms of glycaemic control, most studies demonstrate that despite treatment, glycaemic control deteriorates with most currently-used therapies. The UKPDS analyses using homeostatic model assessment (HOMA) of insulin sensitivity and ² –cell function demonstrated an annual steady decline in ² –cell function of 4%.[(3)]

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Overall 50-60% of people with type 2 diabetes will die of cardiovascular disease and it is estimated that chronic kidney disease affects 50% of people with type 2 diabetes globally[4]. Despite huge improvements in survival from cardiovascular disease, patients with type 2 diabetes remain at increased risk of cardiovascular mortality compared to matched population controls[5]. There has also been great interest recently in improving outcomes with people with heart failure in view of the findings of the recent cardiovascular outcome trials[4]. There has therefore been intense interest in the use of SGLT-2 inhibitors due to the observed benefits in the cardiovascular outcome trials including reducing cardiovascular mortality, improvements in progression of renal disease and hospitalisation for heart failure[4].

The main indication for the use of metformin has been based on the UKPDS trial[6] with only 753 participants of whom 342 participants were randomised to metformin versus the conventional care group. The UKPDS was conducted prior to the introduction of cardiovascular protective therapies such as ACE inhibitors, anti-hypertensive therapies or statins and the newer glucose lowering therapies[6]. In 2008, US Food and Drug Administration industry guidance called for evaluation cardiovascular safety of new glucose-lowering therapies to assess cardiovascular safety[4]. The recent cardiovascular outcome trials Empagliflozin Cardiovascular Out Come Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and the Canagliflozin and cardiovascular and renal events in Type 2 diabetes (CANVAS) program included large numbers of patients the majority of whom were on at least one glucose lowering therapy (over 70% on metformin), over 90% were on antihypertensive therapies, around 80% were on ACE inhibitors and three-quarters of the participants were on statins[7; 8]. In addition these were event-driven trials with the EMPA-REG OUTCOME trial having 672 events[8], CANVAS Program having over a thousand events compared to the UKPDS which had 112 myocardial infarction events[7]. Additionally the UKPDS assessed the outcomes after ten years[6] compared to the EMPA-REG study which had a median follow up of three years and the

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CANVAS Program which had median follow up of 2.4 years[7; 8]. There were significant reductions in death from any cause and myocardial infarctions in the UKPDS[6] significant reductions in deaths from any caused with the EMPA-REG OUTCOME trial but the CANVAS Program, just failed to meet significance[4]. The results of these efficacy trials were translated in the real-world setting of the CVD-REAL Study showing benefits of SGLT-2 inhibitors on death from any cause[9]. Although UKPDS did not assess hospitalisation for heart failure[3] the EMPA-REG OUTCOME study, CANVAS Program and CVD-REAL all demonstrated significantly consistent reductions in this important outcome (Table 1)[7-9]. Glucagon-like peptide 1 (GLP-1) receptor agonists have also demonstrated significant reductions in cardiovascular outcomes and mortality.[10] However, in view of GLP-1 receptor agonists being an injectable therapy, it is unlikely to be initiated as first line therapy.

The EMPA-REG OUTCOME trial and the CANVAS Program included patients with cardiovascular disease or at a high cardiovascular risk, the UKPDS excluded patients if they had myocardial infarction in the previous year, had current angina or heart failure or severe vascular disease and people with chronic kidney disease[3]. Both the CANVAS Programme and the CVD-REAL Study have suggested improved cardiovascular outcomes with no statistical evidence of heterogeneity of the treatment effect across primary and secondary prevention groups[4]. The EMPA-REG OUTCOME trial also conducted sub-group analysis of people with and without metformin and again showed consistent benefits without heterogeneity[4].

Although the recommendations for major guidelines include metformin as the first-line therapy, these findings have not been consistent in other metformin cardiovascular or microvascular outcome trials. Meta-analysis of 13 randomised control trials showed no beneficial effect of metformin on all-cause mortality, cardiovascular mortality or microvascular complications[11].

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SGLT-2 inhibitors have been shown to be well tolerated and relatively safe except for small increase in increased genital infections which are self-managed. There have been reports of diabetic ketoacidosis, however these were not emergent in the cardiovascular outcome trials. The CANVAS Program did show an increase in bone fractures and limb amputations but the mechanistic reasons for this is still not understood. There has been no signal for these outcomes with Empagliflozin or Dapagliflozin from randomised controlled trials, however, the European Medical Agency stated that data are limited with dapagliflozin and empagliflozin and the risk may apply to these SGLT2 inbitors as well.[12] Metformin has also been shown to have increased risk of lactic acidosis. SGLT-2 inhibitors have also been shown to be safe in the elderly and are well tolerated. In view of the extraordinary results from the SGLT-2 inhibitor cardiovascular outcome trials, many diabetes and cardiovascular guidelines have endorsed SGLT-2 inhibitors in people with type 2 diabetes and cardiovascular disease.

In summary, there is paucity of evidence of the benefits of metformin for prevention of microvascular or macrovascular complications except for the findings in UKPDS. SGLT-2 inhibitors target some of the pathophysiological defects of type 2 diabetes. SGLT-2 inhibitor cardiovascular outcome trials and real-world evidence have shown significant cardio-renal benefits. Both randomised control trials and real-world evidence have reported benefits that may also be applicable to a broader population in the real-world setting without prevalent cardiovascular disease. Overall, SGLT-2 inhibitors are safe and should be considered first line at the very least, in people with type 2 diabetes and cardiovascular disease.

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Duality of Interest

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme.

SS has acted as consultant, advisory board member and speaker for Novo Nordisk, Amgen, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, NAPP and Novartis. He has received research grants Jansen.

MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and Investigator-initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly

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Table 1

Baseline characteristics and outcomes of participants in UKPDS, EMPA-REG Trial, CANVAS Program and CVD-REAL study

	UKPDS [1]	EMPA-REG Trial	CANVAS Programme	CVD-REAL Study
BASELINE CHARACTERISTICS				
Number of patients	**753**	**7020**	**10 142**	**309 056**
Age, years	53	63.1	63.3	57.0
Female, %	44	28.6	35.8	44.5
Current s moker %	25	13.2	17.8	NR
History of cardiovascular disease, %	**3**	**99.2**	**65.6**	**13.1**
History of heart failure, %	0	10.1	14.4	3.1
Baseline therapies, %				
Metformin	0	74	77	79
Sulphonylurea	0	44	43	38
DPP-4 inhibitor	0	11	12.4	33
Insulin	0	48	50	29
GLP-1RA	0	3	4	18 to 20
Antihypertensive therapies %	36	94	95	80
ACE inhibitors or ARB %	0	81	80	75
Statins %	0	77	75	67
OUTCOMES				
MACE	NR	0.86 (0.74-0.99)	0.86 (0.75-0.97)	NR

a) Estimated

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Death from any cause	0.64 (0.45-0.9)	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.49 (0.41-0.57)
Hospitalization for heart failure	NR	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.61 (0.51-0.73)
Death from cardiovascular causes or hospitalization for heart failure	NR	0.66 (0.55-0.79)	0.78 (0.67-0.91)	0.54 (0.48-0.60)
Myocardial Infarction	0.61 (0.41-0.86)	0.87 (0.70, 1.09)	0.87 (0.70-1.09)	NR

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