University of South Wales Prifysgol De Cymru

SCIENTIFIC POSTER PRESENTATION FOR AN ACADEMIC REVIEW OF MAJOR RANDOMISED CONTROLLED TRIALS: THE EFFECT OF SODIUM-GLUCOSE CO TRANSPORTER 2 INHIBITORS (SGLT2) ON THE CARDIOVASCULAR OUTCOME AND THE RENAL OUTCOME IN TYPE 2 DIABETES MELLITUS PATIENTS

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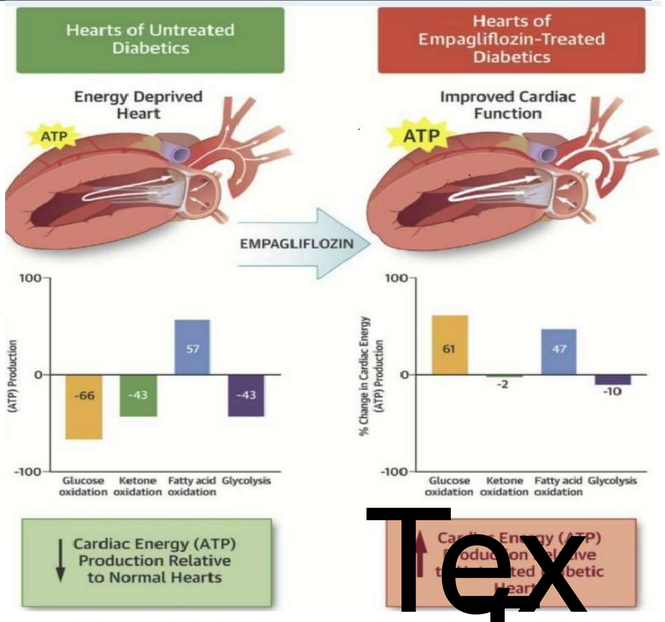
Abstract

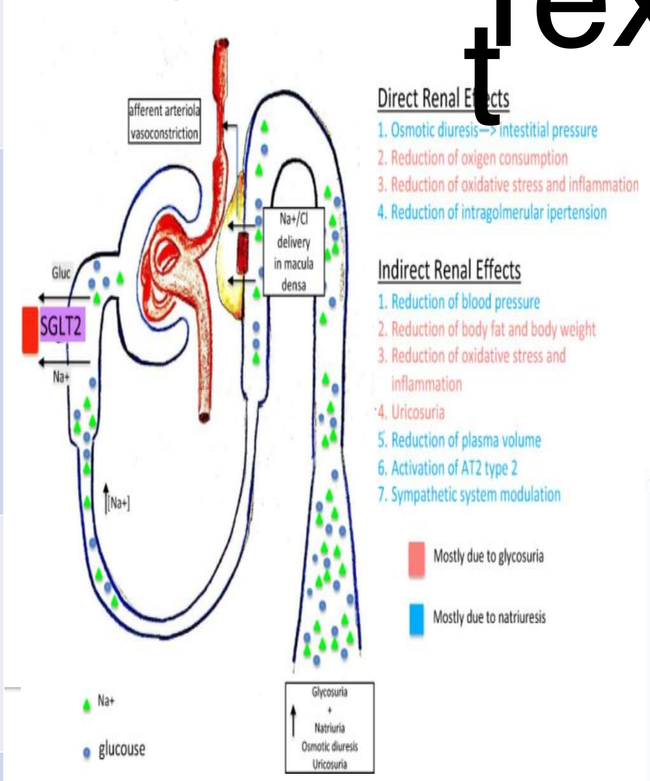
The most common causes of mortality and morbidity in patients with type 2 DM are CVD and renal diseases, taking into consideration that, globally the focusing was changed not only to provide glycaemic control but also to produce cardiovascular and renal protection, many published studies and trial evaluated that some antihyperglycemic medications shown evidence of cardiovascular benefits and one of those medications are Sodium-glucose co-transporter type 2 inhibitors (SGLT2i), many powered trials were published reviewing the cardiovascular effect and the renal outcome of SGLT2 inhibitors in patients with type 2 Diabetes Mellitus namely canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), sotagliflozin and ertugliflozin (Steglatro), we reviewed the multicentric trials and the clinical studies published after 2015 where the participants involved had type 2 diabetes mellitus with different baseline characteristics as in age, sex, duration of the disease (type 2 DM), history of renal disease, history of established atherosclerotic cardiovascular disease, glomerular filtration rate, and presence of albuminuria, etc. despite their varies, SGLT2 inhibitors were found to be significantly effective in decreasing the risk of, death from cardiovascular disease hospitalization of heart failure and all-causes of mortality, showed especially with empagliflozin, dapagliflozin, sotagliflozin and canagliflozin, More useful and beneficial clinical studies and data are needed with a long follow up duration to emphasise this issue which is the cardiovascular and renal benefits of SGLT2 inhibitors. (Rehman and Rahman, 2020)

THE CARDIOVASCULAR OUTCOMES

Name of Trial	Intervention	Endpoint	No. of Patients	Duration of follow up (yrs)	Year of Project Completion
Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)	Empagliflozin 10 or 25 mg daily	Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), nonfatal MI, and nonfatal stroke	7000	5	2015
Canagliflozin cardiovascular Assessment Study (CANVAS)	Canagliflozin 100 or 300 mg daily	Major adverse cardiovascular events, including CV death, nonfatal MI, and nonfatal stroke	4330	≥ 4	2017
Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetes type2 and kidney disease (CREDENCE)	Canagliflozin 100 mg daily	Time to the first occurrence of an event in the primary composite endpoint: ESRD, heart failure, doubling of serum creatinine, renal or CV death	4200	Median 2.62 years	2019
Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58)	Dapagliflozin 10 mg daily	Time to the first event included in the composite outcome of CV death, MI or ischemic stroke	17150	6	2019
VERTIS CV study Cardiovascular Outcomes Following Treatment with Ertugliflozin in Participants with Type 2 Diabetes Mellitus and Established Vascular Disease.	Ertugliflozin 5 or 15 mg daily	The primary outcome, major adverse cardiovascular events(CV death, nonfatal MI, or nonfatal stroke) the secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure	8246	3.5 years	2020
SOLOIST-WHF trial The effect of Sotagliflozin in DM Patients and Recent Worsening Heart Failure	Sotagliflozin 200mg daily before or 3 days after discharge from the hospital	Cardiovascular death and risk of hospitalization for heart failure	1222	9months	2020
DAPA-HF Dapagliflozin in Patients with Heart Failure regardless of the presence or absence of diabetes	Dapagliflozin 10mg once daily or placebo	Worsening of heart failure and death from cardiovascular causes also the unplanned hospitalization for heart failure	4744	18.2 months	2019



(Lopaschuk and Verma, 2020)



(Margonato et al., 2021)

THE CONCLUSION

Patients with type 2 DM who already established cardiovascular (CV) diseases or at risk to major CV events; SGLT2 especially empagliflozin, canagliflozin, and dapagliflozin are showed a significant lowering in MACE, heart failure hospitalization and other CV mortalities, also, the study showed that we can argue to use those drugs as the first line due to their CV benefits and the favourable outcomes.
Education is very important and effective to implement any changes.
It could be provided through multiple methods such as clinical trials pr studies to ensure a regular update and new management for the health care providers, as the prevention can't stop the occurrence of Diabetes. the health care services need to maintain good quality care for those patients with diabetes by improving the skill of the physicians and implementing up to date trials, guidelines and other medical supplies when planning the treatment for each patient.
In the end, the physicians must weigh the benefits and risks of any drugs before prescribing them and doing that is suitable for each patient.

THE RENAL OUTCOMES

Name of Trial	Intervention	Renal outcomes	Estimated GFR mL/min/1.73 m2	UACR	History of CKD
Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)	Empagliflozin 10 or 25 mg daily	Worsening nephropathy (defined as progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy or death from renal causes)	Mean of 74.1	mean18mg/g 59.4 % normoalbuminuric 29% micro 11% macro	Not required
(EMPA-KIDNEY) The Study of Heart and Kidney Protection with Empagliflozin	Empagliflozin daily with or without food	Time to the first occurrence of kidney disease and the progression, renal death and cardiovascular death	eGFR ≥20 to <45 mL/min/1.73m² eGFR ≥45 to <90 mL/min/1.73m² with urinary albumin: creatinine ratio ≥200 mg/g	ratio ≥200 mg/g	with a history of chronic renal disease
CANVAS and CANVAS RENAL	Canagliflozin 100 or 300 mg daily	the progression of albuminuria, the reduction in eGFR, the progression to the end stage and the death from renal causes.			
CREDENCE trial Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation.	Canagliflozin 100 mg daily	composite of end-stage renal disease or the progression to dialysis for around 30 days or, death from renal or cardiovascular causes and the increasing of creatinine level	30 to <90	ratio of albumin [mg] to creatinine [g]) of >300–5,000 mg/g	patients with chronic kidney disease with the standard dose of renal protective treatment
VERTIS CV study Cardiovascular Outcomes Following Treatment with Ertugliflozin in Participants With Type 2 Diabetes Mellitus and Established Vascular Disease.	Ertugliflozin 5 or 15 mg daily	The primary outcome, major adverse cardiovascular events(CV death, nonfatal MI, or nonfatal stroke) the secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure	estimated glomerular filtration rate above 30 ml per minute per 1.73 m2 of body-surface area.	NA	with type 2 DM and a high risk of atherosclerotic CV disease
(DAPA-CKD) Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease	Dapagliflozin 10 mg daily	progression of CKD without relation to the presence of Diabetes	25-75	ratio of albumin [mg] to creatinine [g]) of >200–5,000 mg/g	with a history of chronic renal disease
DIAMOND Trial	Dapagliflozin 10 mg daily	in reduction of major chronic kidney outcomes in those with chronic kidney disease	At least 25	24 hr urinary protein excretion between 500mg to 3500 mg, not more	patient with chronic kidney disease and not related to being mediated by the presence of diabetes or not

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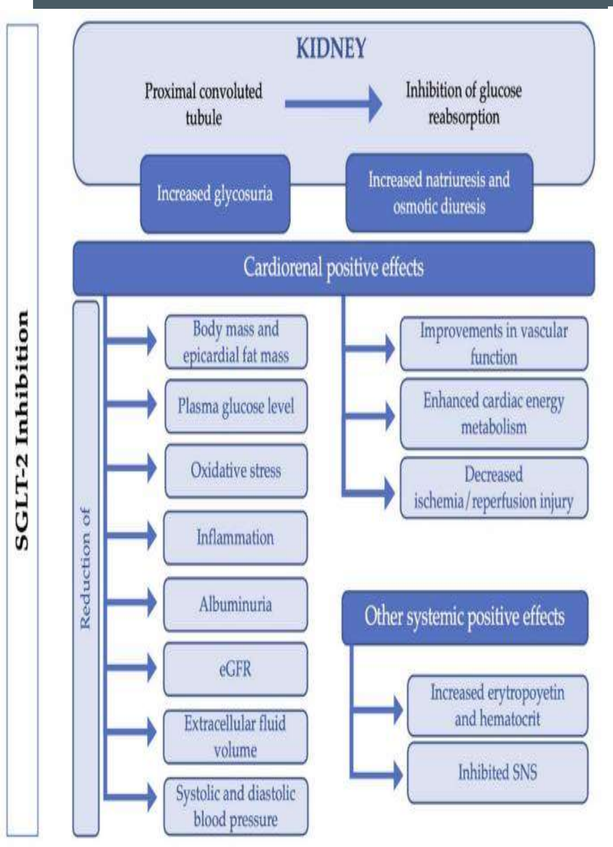
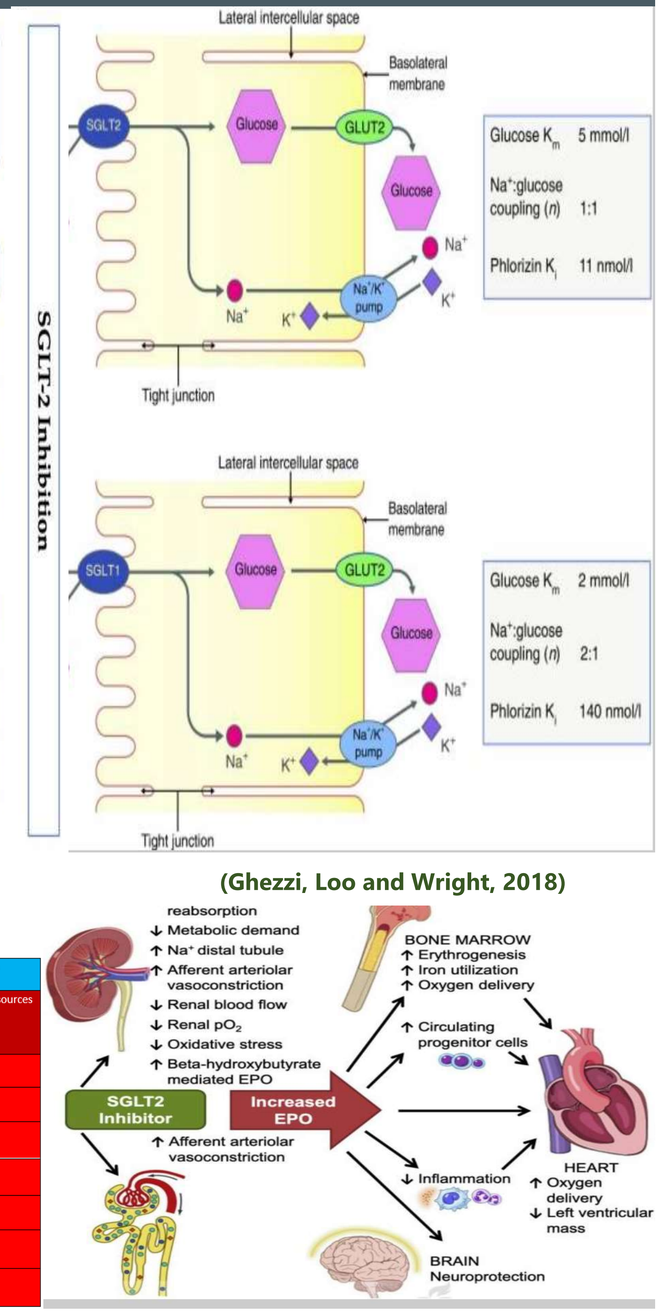


(Martínez-Vizcaíno et al., 2021)

The risk of bias for each individual trial was already independently evaluated and assessed using Cochrane Collaboration's tool for assessing the risk of bias.

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Others
Study/Trial	Random sequence generation	Allocation concealment	Blinding (participants and personnel)	Blinding outcome assessment)	Incomplete outcome data	Selective reporting	Other sources of bias
EMPA-REG OUTCOME							
CANVAS							
VERTIS CV							
DECLARE-TIMI 58							
DAPA-HF							
SOLOIST-WHF							
CREDENCE							

High risk of bias (red colour) Low risk of bias (green colour) Unclear risk of bias (grey colour).



(Ghezzi, Loo and Wright, 2018)

(Lopaschuk and Verma, 2020)

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