Official Study Title:

Impact of Sodium-Glucose Co-transporter 2 inhibitors on Cardiovascular System and Anemia in Non-diabetic Chronic Kidney Disease Patients. A Randomized-Controlled Clinical Trial

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Mansoura Urology and Nephrology Center, Mansoura University, Egypt

Principal Investigator:

Dr. Mostafa Gamal, MD, PhD

Introduction

Chronic kidney disease (CKD) affects approximately 10% of the adult population worldwide **(1)**. The most common causes of CKD are diabetes, hypertension, and chronic glomerulonephritis **(2)**. Treatment for CKD includes angiotensin converting enzyme inhibitor (ACE-I) / angiotensin II receptor blockers (ARBs), lipid and blood pressure (BP) control **(3)**.

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a newly approved class of oral anti-diabetic agents that increase the urinary excretion of glucose, thereby lower blood glucose levels, weight, and blood pressure (**4**).

There is growing evidence indicating that SGLT2 inhibition is reno-protective. This effect is thought to be achieved partly by mechanisms independent of lowering blood glucose levels **(5)**, such as reduced intra-glomerular pressure through an enhanced tubule-glomerular feedback mechanism **(6-7)**, reduced glucose and sodium transport over the proximal tubular cells **(8)**, increased natriuresis **(9)** and reduced systemic BP **(10-11)**.

A recent clinical trial (**DAPA-CKD)** showed that SGLT2i treatment reduced the risk of worsening kidney function or death from cardiovascular or kidney disease in patients with chronic kidney disease with and without type 2 diabetes **(12).**

Also, there are data suggesting SGLT2i acts by inhibiting hepcidin, which will increase iron bioavailability and red blood cell production **(13). Another mechanism is suggested via inducing medullary hypoxia which by turn increases the level of hypoxia inducible factor (HIF) and increase erythropoietin production (14)**. These effects on erythropoiesis suggest that the use of SGLT2i reduces the occurrence of anemia. The post-hoc analysis of the CREDENCE trial found that the risk of anemia or the risk of starting anemia treatment in the anemia group of patients with type 2 diabetes and chronic kidney disease was significantly lower than that of the placebo group **(15)**. According to the exploratory analysis of EMPA-REG test data, anemia improvement during SGLT2i treatment was closely related to beneficial cardiovascular outcomes **(16)**.

Dapagliflozin, as a member of SGLT2i family, showed a beneficial effect on cardiovascular outcome **(17, 18)**. As shown in many other trials, Other SGLT2 inhibitors have shown favorable cardiovascular effects, including a reduction in the risk

of hospitalization for heart failure, predominantly in patients with type 2 diabetes and established cardiovascular disease **(19-21)**.

SGLT2 inhibition affects visceral adiposity, glycemic control, hyperinsulinemia, blood pressure, arterial stiffness, and albuminuria **(22)**. Two mechanisms have been proposed as major drivers for beneficial cardiovascular outcome: the diuretic effect associated with SGLT2 inhibition with subsequent hemodynamic unloading of the left ventricle **(23)** and a shift in cardiac metabolism secondary to increased ketogenesis **(24, 25)**.

Aim of the work

This study aims to:

1. Assess SGT2i role in delaying the progression of ongoing chronic kidney disease.
2. Investigate SGLT2i impact on anemia improvement among non-diabetic CKD patients.
3. Study the impact of SGLT2i on cardiovascular system in these patients.

Research questions

The main research question is: Does use of SGLT2i will show superiority over conventional lines of treatment of chronic kidney disease as regard to efficacy and safety?

Does the use of SGLT2i carry beneficial effect on anemia improvement among these patients?

Does the use of SGLT2i improve cardiac outcome in non-diabetic CKD patients?

Rationale and justification

Dapagliflozin which was originally developed to control blood glucose level in patients with diabetes has recently been shown to have beneficial effects on both the heart and kidney.

Importantly, a large clinical trial has shown dapagliflozin reduced kidney problems. From the way we think the pills work, there is good reason to believe this new medication could benefit people who have kidney disease even they are not diabetic.

To date, there hasn't been a trial that studied the effect of dapagliflozin in terms of anemia improvement only on non-diabetic CKD.

Objectives

The main objective of this study is to:

- Compare use of SGLT2i versus placebo and standard care in regression of chronic kidney disease in non-diabetic CKD patients.
- Study the effect of SGLT2i in decreasing the risk of anemia and improving anemia in non-diabetic CKD patients.
- Study the impact of SGLT2i regarding cardiovascular system.

Hypothesis

Additional therapies to slow kidney function decline are highly desired. The DAPA-CKD trial demonstrated that the sodium glucose co-transporter 2 inhibitor dapagliflozin significantly reduced the risk of kidney failure and prolonged survival in participants with chronic kidney disease with and without type 2 diabetes.

Patients and methods

Study sitting: Urology and Nephrology Center, Mansoura University.

Study design and sample size:

- **Sample size:** was calculated based on previous research by (DAPA-CKD) by **(Heerspink et al., 2020)** using G. power program with α error 0.05 and power 80% and it was equal to approximately 98 patients.

Type of the study: Randomized controlled trial.

Patients' enrollment: 100 patients with non-diabetic CKD with an estimated glomerular filtration rate (eGFR) of 20-75 ml/min/1.73m^2 will be randomized into 2 equal groups:

- **Study group:** 50 patients will receive SGLT2i as add on drug, Dapagliflozin 10 mg will be used once daily with or without food.

- **Control group:** 50 patients will receive placebo beside the conventional medications.

All patients will be followed-up for 12 months and their results will be interpreted.

Inclusion criteria:

1. Non-diabetic CKD patients aged more than 18 years.
2. Patient with eGFR > 20 ml/min/1.73m2 by 2021 CKD-EPI creatinine equation

Exclusion criteria:

1. eGFR < 20 ml/min per 1.73 m^2.
2. Medical history of chronic disease (diabetes mellitus, chronic liver disease, bladder cancer, severe respiratory distress).
3. Evidence of urinary obstruction of difficulty in voiding at screening.
4. Receiving high dose diuretics or combined ACEI and ARB.
5. History of recurrent urinary tract infection.

6. Active infection including TB and HIV.
7. Current or previous organ transplantation or expected to get a kidney transplant within 12 months.
8. Patients who are on SGLT2i for more than the preceding 3 months.

Study design:

Study Protocol:

- Patients included in the study will be treated with dapagliflozin initiated at a single daily morning dosage of 10 mg/day.

Methods:

The following data will be collected and evaluated for all patients:

I-Baseline investigations:

- Patients of both groups will be subjected to full history taking including duration of CKD and drug history and routine clinical examination.
- Ankle/brachial pressure index (ABPI) to assess peripheral vascular disease.

Laboratory investigations:

1) Serum creatinine, Creatinine clearance.
2) Urine analysis.
3) 24-hour urine protein and/or spot urine protein/creatinine ratio.
4) Random blood glucose.
5) Lipid profile
6) Iron profile tests:

- Hemoglobin
- Mean corpuscular volume (MCV) and Hematocrit (Hct).
- Serum ferritin
- Transferrin saturation (TSAT)
- Serum hepcidin level
- Serum erythropoietin level.

7) B-type natriuretic peptide (BNP) level.

- **Cardiovascular investigatory tools:**
  - Electrocardiography (ECG).
  - Echocardiography to assess myocardial function.
- **Radiological investigations:**
  - Agatston score using CT scan: for assessment of coronary calcification.

1. II-Post-intervention investigations:

<u>All patients will be evaluated every visit (every 3 months) regarding:</u>

- Regular measurement of blood pressure each visit.
- Ankle/brachial pressure index.
- Laboratory investigations:

1) Serum creatinine, creatinine clearance.
2) Urine analysis.
3) 24-hour urine protein and/or spot urine protein/creatinine ratio.
4) Fasting blood glucose.
5) Lipid profile.

6) Iron profile (Hemoglobin, MCV, hematocrit, ferritin, TSAT,)

<u>All patients will be evaluated at 12 months regarding:</u>

- Ankle/brachial pressure index.
- **Laboratory investigations:**

  1) Serum creatinine, Creatinine clearance.

  2) 24-hour urine protein and/or spot urine protein/creatinine ratio.

  3) Urine analysis.

  4) Fasting blood glucose.

  5) Lipid profile.

  6) Iron profile tests:

  - Hemoglobin
  - Mean corpuscular volume (MCV) and Hematocrit (Hct).
  - Serum ferritin
  - Transferrin saturation (TSAT)
  - Serum hepcidin level
  - Serum erythropoietin level.

- **Cardiovascular investigatory tools:**

  - Electrocardiography (ECG).
  - Echocardiography to assess myocardial function.

- **Radiological investigations:**

  - Agatston score using CT scan: for assessment of coronary calcification.

Outcomes:

Primary outcome measures:

- Time to the first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR, reaching end-stage kidney disease. [Time Frame: 12 months]

Secondary outcome measures:

- Effect of Dapagliflozin on eGFR.
- Effect of Dapagliflozin on anemia & erythropoietin level.
- Effect of Dapagliflozin on myocardial function and coronary calcifications.
- Safety of Dapagliflozin regarding the number of hypoglycemia episodes between groups and serious adverse events.

Statistical Analysis:

Qualitative data will be displayed in cross tabulations, and quantitative data will be described in terms of arithmetic mean ± SD. Bivariate techniques will be used for initial evaluation of contrasts. Thus, the chi-square and Fisher's exact tests will be used for comparisons of frequencies of qualitative variables; the Mann-Whitney test and the unpaired t-test will be used for comparisons of means of two quantitative variables. A p-value ≤ 0.05 is considered significant. Patient survival rates will be assessed using the Kaplan-Meier method. All analyses will be carried out using the computer package SPSS for windows, release 21 SPSS Inc. Chicago, III, USA.

Administrative design

All the patients provided written informed consent before study entry and the approval was obtained from institutional review board (MS.22.04.1973) in Faculty of Medicine, Mansoura University. There is no funding.

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