Finerenone and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Type 2 diabetes

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- ## Background
  - Patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) are at an increased risk for developing cardiovascular disease (CVD).These patients have a 3-fold higher risk of cardiovascular death than those with only type 2 diabetes. Assessing albuminuria and reduced estimated glomerular filtration rate (eGFR) can help predict mortality in these patients. There are several risk factors that predisposes patients such as hypertension, history of cardiovascular events, endothelial dysfunction, and others. In addition, overactivation of the mineralocorticoid receptor (MR) causes inflammation and fibrosis which leads to damage in the kidney, heart, and peripheral vasculature leading to an elevated cardiovascular risk.
  - Finerenone also known as Kerendia is a novel, nonsteroidal, selective MR antagonist (MRA) that has been studied in patients with type 2 diabetes and/or CKD who also had worsening chronic heart failure with reduced ejection fraction in comparison with the steroidal MRA eplerenone. Since finerenone has been studied in reducing kidney failure and disease progression, this study aimed to look at the effects of finerenone on cardiovascular and kidney failure outcomes in patients with CKD and T2D.

- ## What they did
  - Evaluated the effects of finerenone in patients with and without a history of cardiovascular disease
  - Randomized, double blinded, placebo-controlled trial performed in 48 countries and territories in African, Asia, Australia, Europe, Latin America, and North America.
  - Patients were randomized to either receive oral finerenone (10-20mg daily based on estimated glomerular filtration rate (eGFR) at the screening visit of 25-60 ml/min/1.73m^2 or greater than 60 ml/min/1.73m^2, respectively) or matching placebo.

- ## Inclusion
  - 18 years of age or older
  - Clinical diagnosis of type 2 diabetes
  - Moderately elevated albuminuria (urine albumin-to-creatinine ratio of 30-300mg/g)
  - Severely elevated albuminuria (urine albumin-to-creatinine ratio of 300-5000 mg/g)
  - eGFR of 25-75 ml/min/1.73m^2

- A history of diabetic retinopathy
- Patients were required to have a stable treatment with a maximum tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at least 4 weeks before screening visit
- Serum potassium levels must be less than 4.8 meq/L

Exclusion

- Known nondiabetic kidney disease
- Chronic symptomatic heart failure with reduced ejection fraction (New York Heart Association Class II-IV)
- Recent history of dialysis for acute kidney failure
- A kidney transplant
- Uncontrolled hypertension
- Patients receiving concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued ≥4 weeks prior to the screening visit
- Pregnancy

Outcomes

- **The composite cardiovascular outcomes**
  - Time to first onset of cardiovascular death
  - Nonfatal MI
  - Nonfatal stroke
  - Hospitalization for heart failure
- **The composite kidney outcome**
  - Time to first onset of kidney failure
    - Chronic dialysis for greater than 90 days
    - Kidney transplantation
    - eGFR < 15 ml/min/1.73m^2
  - A sustained greater than 40% decrease in eGFR from baseline over at least 4 weeks
  - Renal death

Results

- **Patients**
  - 5734 patients were randomized
    - 60 were excluded due to Good Clinical Practice violations
    - 5674 were included in the full analysis set
  - The median follow up was 2.6 years
- **Cardiovascular Outcomes**
  - **The incidence of the composite cardiovascular outcome were lower in the finerenone group than in the placebo group**
    - 13.0% vs 14.8% (HR 0.86 [95% CI 0.75-0.99] P=0.034)

        - **Death with cardiovascular causes**
            - 4.5% vs 5.3% (HR 0.86 [95% CI 0.69-1.08])
        - **Nonfatal MI**
            - 2.5% vs 3.1% (HR 0.80 [95% CI 0.58-1.09])
        - **Nonfatal stroke**
            - 3.2% vs 3.1% (HR 1.03 [95% CI 0.76-1.38])
        - **Hospitalization for heart failure**
            - 4.9% vs 5.7% (HR 0.86 [95% CI 0.68-1.08])
        - **Incidence of composite cardiovascular outcomes in patients with a history of CVD**
            - With CVD (17.7% vs. 20.2% (HR 0.85 [95% CI 0.71-1.01] P=0.85)
            - Without CVD (8.9% vs. 10.2% (HR 0.86 [95% CI 0.68-1.08] P =0.85)
    - **Kidney Outcomes**
        - **The composite kidney outcome was lower with finerenone versus placebo**
            - With CVD (15.3% vs 20.5% (HR 0.70 [95% CI 0.58-0.84]) P = 0.016)
            - Without CVD (19.9% vs 21.6% (HR 0.94 [95% CI 0.81-1.10] P=0.016)
        - **Time to first onset of kidney failure**
            - With CVD (HR 0.64 [95% CI 0.49-0.83] P = 0.07)
            - Without CVD (HR 0.87 [95% CI 0.70-1.07] P = 0.07)
    - **Safety Outcomes**
        - **Serious adverse events**
            - With CVD (33.9% vs 38.5%)
            - Without CVD (30.2% vs 30.7%)
        - **Treatment emergent hyperkalemia**
            - With CVD (18.3% vs 8.5%)
            - Without CVD (18.2% vs 9.5%)
        - **Hospitalization caused by hyperkalemia**
            - With CVD (1.5% vs 0.2%)
            - Without CVD (1.4% vs 0.3%)
        - **Discontinuation because of hyperkalemia**
            - With CVD (2.3% vs 0.8%)
            - Without CVD (2.2% vs 1.0%)

● Strengths

- Randomized, double-blind, placebo controlled study
- Large sample size that included patients in 48 countries
- This study stemmed from a larger trial called FIDELIO-DKD which investigated the effects of finerenone on heart and kidney outcomes in a broad population.

- **Limitation**
  - This study did not look at patients with uncontrolled blood pressures and chronic heart failure with reduced ejection fraction so finerenone may not be beneficial in these patients.
  - History of CVD was determined by review of medical records and not assessed at baseline
  - The patient population was not evenly distributed and did not use a larger sample size of other populations that may be at a higher risk for developing chronic kidney disease and type 2 diabetes such as African American and Hispanics in America.
  - The study looked at cardiac death, MI, stroke, and hospitalization due to heart failure as a composite outcome. However, on their own they were not statistically significant. Hospitalization due to heart failure could be a separate outcome since it may not be as severe as cardiac death, MI, or stroke. In addition, each outcome by itself was not statistically significant, and so it is difficult to say that the composite outcome was really statistically significant.
- **Discussion**
  - Finerenone reduced the incidence of cardiovascular composite outcomes which showed to have a beneficial effect on overall risk for a composite of cardiovascular events. This was seen consistently in patients with or without a history of CVD. Finerenone was also beneficial in preserving kidney function and reducing the risk of the composite kidney outcomes. Overall these findings indicated that finerenone can be used in patients with CKD and T2D as primary and secondary prevention for CVD.

- **Author's conclusion**
  - "Finerenone reduced the risk of cardiovascular and kidney failure outcomes in patients both with and without a history of CVD. The results suggest that finerenone may represent an important treatment advance to reduce cardiovascular morbidity and mortality in patients with CKD and T2D"

- **Clinical take home point**
  - Would we change our practice based on this study? This study demonstrated the benefits of using finerenone in T2D and CVD patients for prevention of cardiovascular events with patients optimizing angiotensin-converting enzyme inhibitor or angiotensin receptor blocker medications. Finerenone was also well tolerated by most patients with few having to discontinue from the study. However, based on the patient population, it is difficult to say that this study will be beneficial in other patients given that 5% of patients were African Americans/Black, 0% were Hispanics, and 70% were White. I would not apply this to my population until I see a better representation of other races having benefit using finerenone. In addition, when the cardiovascular outcomes were

measured as a whole they were statistically significant, but by themselves they were not, and so it is difficult to be confident that their results were really statistically significant. Lastly, since finerenone is in the same class as spironolactone and eplerenone, more studies should be conducted to see if there is a benefit to using one of these over the other to lower cardiovascular events in T2D and CVD patients.

- **References**
  - Filippatos, G, et al. “Finerenone and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Type 2 Diabetes.” *Circulation.* 2021. 143: 540-552.