The Ohio State University
College of Pharmacy
Journal Club

Background and Overview	
Title	**FIGARO-DKD** • Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. doi: 10.1056 • The Impact Factor for the New England Journal of Medicine is 91.245 and this research is appropriate for this journal as it publishes a wide range of clinical research for new therapies and practices
Funding Source	• This trial was funded by Bayer HealthCare • The authors on this study receive consultant and speaking fees from Bayer HealthCare
Introduction/ Background	• Diabetic kidney disease (DKD) is a clinical syndrome in patients with diabetes characterized by albuminuria on at least 2 separate occasions separated by 3 months accompanied by hypertension, a progressive increase in proteinuria, and declining renal function • There is a strong correlation between cardiovascular disease (CVD) and increased mortality in patients with DKD with increased albuminuria and decreased glomerular filtration rate (GFR) **Guidelines and Therapeutics** • Kidney Disease Improving Global Outcomes (KDIGO) 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease • Treatment emphasizes risk reduction via lifestyle modifications including smoking cessation, diet and weight loss, glycemic control, and management of dyslipidemia and hypertension • The standard of care (SoC) is ACE inhibitors which have been shown to slow but not prevent the progression of DKD with a significant reduction in all-cause mortality/morbidity, overall survival benefit is **NOT** demonstrated with ARBs (RENAAL/IDNT) • Long-term use of ACE-i/ARBs result in incomplete suppression of aldosterone leading to an “aldosterone escape” phenomenon in which mineralocorticoid receptor antagonists (MRAs) have been shown to improve kidney outcomes such as proteinuria • No large, long-term studies have examined if MRAs can slow the progression of CKD or prevent cardiovascular (CV) events • Finerenone is a novel, non-steroidal selective antagonist of the mineralocorticoid receptor (MR) that blocks MR mediated sodium reabsorption and MR overactivation in both epithelial (e.g., kidney) and nonepithelial tissues (e.g., heart and blood vessels) • Shown to reduce cardiac and renal hypertrophy along with a greater reduction in serum BNP levels and proteinuria compared to eplerenone

Objective(s)	
Methods	

Study Design	• Prospective, Randomized, Superiority, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Event-driven Phase 3 Trial
	• Independent data and safety monitoring committee oversaw patient safety and conducted one planned efficacy interim analysis
	• **Outcomes**:
	  ○ **Primary**: composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure
	  ○ **Secondary**: composite of the first occurrence of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR for a period of at least 4 weeks, or death from renal causes
	  ○ Hospitalization for any cause, death from any cause, change in the urinary albumin-to creatinine ratio from baseline to month 4; and a kidney composite outcome
	• **Efficacy & Safety**
	  ○ **ARTS-DN trial**: finerenone doses ranging from 1.25-20 mg were investigated for safety and efficacy in patients with T2DM and a clinical diagnosis of CKD, all doses were found to be well-tolerated and resulted in statistically significant reductions in albuminuria compared to placebo
	• **Interventions**:
	  ○ 4-16 week run in period to optimize ACE-i/ARB therapy
	  ○ Wash out period starting at discontinuation of study drug at end of study visit and follow up post-treatment visit in 33 days
	  ○ Patients received either 10 or 20 mg finerenone oral tablets based on eGFR with titration to 20 mg if tolerated
	  ○ Ancillary treatments included ACEi/ARB (99%), SGLT-2 inhibitors (8.4%), and GLP-1 receptor agonists (7.5%)
	  ○ The mean adherence to finerenone and the placebo were 91.5% and 92.9% respectively
	• Median follow-up of 3.4 years
	• Intention-to-treat analysis

Study Population	• Subjects were identified based on inclusion/exclusion criteria at approximately 600 study centers worldwide • 1:1 randomization stratified by region, type of albuminuria, eGFR, and CVD history following the run-in period • **Inclusion Criteria**: ≥18 years old, DM II, CKD treated with maximum titrated dose of ACE/ARB, persistent high/very high albuminuria, and a serum potassium ≤4.8 mmol/L • **Exclusion Criteria**: serum K >4.8 mmol/L, non-diabetic kidney disease, UACR >5000 mg/g, A1c >12%, uncontrolled hypertension (SBP ≥170 mmHg, DBP ≥110 mmHg), hypotension (SBP <90 mmHg), clinical diagnosis of HFrEF and persistent symptoms, stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening HF in the past 30 days, receiving dialysis, Addison's disease, renal allograft in place or scheduled for a kidney transplant within 12 months, hepatic insufficiency classified as Child–Pugh C, known drug allergy to the study treatment, active malignancy, or pregnancy/breast-feeding

Statistical Analysis

- Time-to-event analysis stratified based on study region, eGFR at time of screening, albuminuria category at time of screening, and presence/absence of cardiovascular disease
- Cox proportional hazards models for primary subgroup analyses
- The secondary efficacy outcome of change in UACR from baseline to month 4 was tested using an ANCOVA model
- A mixed model repeated measures (MMRM) procedure was used as a sensitivity analysis to monitor changes from the baseline eGFR
    - Serial measurements of urine albumin and creatinine were conducted for the duration of the study, using MMRM is reasonable since data gathered can be properly analyzed as each measurement is not considered to be independent
- 90% power to detect a 20% lower risk of a primary outcome event
- P-value of 0.049674 adjusted from 0.05

Results

Results of Study

- Baseline characteristics of note: median age was 64.1 years old, median A1c of 7.7%, median systolic BP of ~136, 45% of patients with history of CVD, and mean eGFR of ~68 mL/min/1.73 m^2 with 2/3s of patients eGFR ≥60

Baseline medications — no. (%)	Finerenone	Placebo	Total
Renin–angiotensin system inhibitor	3681 (99.9)	3662 (99.9)	7343 (99.9)
Diuretic	1748 (47.4)	1748 (47.7)	3496 (47.6)
Statin	2552 (69.2)	2632 (71.8)	5184 (70.5)
Glucose-lowering therapy	3607 (97.9)	3589 (97.9)	7196 (97.9)
Insulin	2023 (54.9)	1970 (53.7)	3993 (54.3)
GLP-1 receptor agonist	308 (8.4)	242 (6.6)	550 (7.5)
SGLT2 inhibitor	314 (8.5)	304 (8.3)	618 (8.4)

Outcome	Finerenone (N=3686)	Placebo (N=3666)	
	no. of patients with event (%		Hazard Ratio (95% CI)
Primary composite outcome	458 (12.4)	519 (14.2)	0.87 (0.76–0.98)
Death from cardiovascular causes	194 (5.3)	214 (5.8)	0.90 (0.74–1.09)
Nonfatal myocardial infarction	103 (2.8)	102 (2.8)	0.99 (0.76–1.31)
Nonfatal stroke	108 (2.9)	111 (3.0)	0.97 (0.74–1.26)
Hospitalization for heart failure	117 (3.2)	163 (4.4)	0.71 (0.56–0.90)
Kidney composite outcome with ≥40% decrease in eGFR	350 (9.5)	395 (10.8)	0.87 (0.76–1.01)
Kidney failure	46 (1.2)	62 (1.7)	0.72 (0.49–1.05)
End-stage kidney disease	32 (0.9)	49 (1.3)	0.64 (0.41–0.995)
Sustained decrease in eGFR of <15 ml/min/1.73 m^2	28 (0.8)	38 (1.0)	0.71 (0.43–1.16)
Sustained ≥40% decrease in eGFR from baseline	338 (9.2)	385 (10.5)	0.87 (0.75–1.00)
Death from renal causes	0	2 (0.1)	—
Hospitalization for any cause	1573 (42.7)	1605 (43.8)	0.97 (0.90–1.04)
Death from any cause	333 (9.0)	370 (10.1)	0.89 (0.77–1.04)
Kidney composite outcome with ≥57% decrease in eGFR	108 (2.9)	139 (3.8)	0.77 (0.60–0.99)
Sustained ≥57% decrease in eGFR from baseline	90 (2.4)	116 (3.2)	0.76 (0.58–1.00)

Table 2. Safety Outcomes.*

Event	Finerenone (N=3683)	Placebo (N=3658)
Investigator-reported adverse events — no. (%)		
Any adverse event	3134 (85.1)	3129 (85.5)
Adverse event related to finerenone or placebo	560 (15.2)	413 (11.3)
Adverse event leading to discontinuation of trial regimen	207 (5.6)	183 (5.0)
Any serious adverse event	1158 (31.4)	1215 (33.2)
Serious adverse event related to finerenone or placebo	35 (1.0)	27 (0.7)
Serious adverse event leading to discontinuation of trial regimen	70 (1.9)	76 (2.1)
Adverse event with outcome of death	79 (2.1)	100 (2.7)
Hyperkalemia†	396 (10.8)	193 (5.3)
Hyperkalemia related to finerenone or placebo	240 (6.5)	114 (3.1)
Serious hyperkalemia	25 (0.7)	4 (0.1)
Hospitalization due to hyperkalemia	21 (0.6)	2 (0.1)
Permanent discontinuation of trial regimen due to hyperkalemia	46 (1.2)	13 (0.4)
Central laboratory assessments — no./total no. (%)		
Serum potassium level		
>5.5 mmol/liter	495/3677 (13.5)	233/3655 (6.4)
>6.0 mmol/liter	86/3677 (2.3)	43/3655 (1.2)

- Overall incidences of any serious adverse events were similar between both groups with hyperkalemia being twice as likely in the finerenone group, none of these adverse events led to death

Authors' Conclusion

- Patients in the finerenone group had a lower risk for the primary composite outcome driven mainly by a significant reduction in hospitalizations due to heart failure (3.2% vs 4.4%)
- Cardiovascular benefits were consistent across all study groups according to baseline urinary albumin-to-creatinine ratio (UACR) and eGFR
- Finerenone's cardiovascular benefits appear to be independent of the benefits seen with concomitant use of SGLT-2 inhibitors and GLP-1 receptor agonists
- Although symptomatic heart failure patients were excluded from this trial, reduction in heart failure hospitalizations was still a key driver of the primary outcome suggesting finerenone may be useful in the prevention and management of heart failure
- The effects of finerenone on the kidney composite outcome were similar to the findings from FIDELIO-DKD however significance was not achieved for this outcome in FIGARO-DKD
- Hyperkalemia was predictably the most common adverse event due to finerenone's mechanism of action, although incidences of hyperkalemia are still lower than with equivalent doses of spironolactone (4.5% vs 11.1%)

Student's Discussion and Conclusion

Strengths/ Limitations

- Potentially some sampling bias due poor representation of African Americans, Hispanics, and American Indians which have higher rates of CKD than the general population
- Study medications and dosages were appropriate, would like to see further efficacy studies with finerenone versus current MRAs on the market
- The study met power to detect significance of the primary composite outcome
- Internal & external validity

	○ **Patient recruitment**- external validity may be more limited due to homogenous patient population, less than 10% of patients were on either an SGLT-2 inhibitor or GLP-1 receptor agonist ○ **Study design**- patients could be titrated up or down on their dose of finerenone depending on changes in their eGFR or serum potassium, approximately 10% of patients receiving finerenone experienced hyperkalemia which would warrant a dose decrease skewing results towards being less significant • Compared to FIDELIO-DKD, the kidney composite outcome failed to be significant • Safety and efficacy were similar to previous findings in ARTS-DN and FIDELIO-DKD
Conclusion/ Recommendations for practice site	• Finerenone as an adjunctive therapy shows promise for preventing the progression of CKD with albuminuria in patients with T2DM for which no current therapies exist • In clinical practice, lower incidences of hyperkalemia and greater selectivity compared to current MRAs should increase patient compliance via reduction in adverse events and undesirable side effects • From a pathophysiology standpoint, long-term use should theoretical be effective for primary prevention of CV events and prevention of CKD in patients with albuminuria • A significant reduction in hospitalizations suggests finerenone may have a place in heart failure treatment • The number needed to treat (NNT) to prevent one primary outcome event was 47 • May see recommendations for finerenone's use be incorporated into the ADA and KDIGO guidelines • Finerenone should be added to formulary with restrictions being: ○ Only to be used as an adjunct treatment in patients with T2DM with mild-to-moderate albuminuria who are on maximally tolerated doses of an ACE/ARB
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