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Drug Class Update with New Drug Evaluation: Diuretics

Date of Review: June 2022

Date of Last Review: June 2020
Dates of Literature Search: 11/22/2019 – 03/31/2022
Brand Name (Manufacturer): Kerendia® (Bayer)
Dossier Received: Yes

Generic Name: finerenone

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:

- Evaluate new comparative evidence for the effectiveness and safety of diuretics for the prevention of mortality and cardiovascular disease (CVD) in patients with hypertension (HTN), heart failure (HF) and chronic kidney disease (CKD).
- Evaluate the data supporting the efficacy and safety of finerenone and determine its appropriate place in therapy.

Research Questions:

1. Is there any new comparative evidence for diuretics in reducing mortality or CV outcomes in patients treated for HTN, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), or CKD?
2. Is there any new comparative evidence for the safety of diuretics in patients treated for HTN, HFpEF, HFrEF, or CKD?
3. What are the comparative benefits and harms of finerenone in patients with CKD?

Conclusions:

- There is low quality evidence evaluating aldosterone antagonists on clinical outcomes in patients with CKD. There is very low-quality evidence of an uncertain effect on kidney failure (relative risk [RR] 3.00; 95% confidence interval [CI] 0.33 to 27.65) and moderate level evidence of an increased risk of hyperkalemia (RR 2.17; 95% CI 1.47 to 3.22; number needed to harm [NNH] 41).[1]
- There is moderate quality evidence of no significant effect on CV mortality with mineralocorticoid receptor antagonists (MRAs) compared to placebo or standard of care (RR 0.90; 95% CI 0.74 to 1.11; 3 studies) or all-cause mortality (RR 0.91; 95% CI 0.78 to 1.06; 5 studies) but a significant reduction in heart failure hospitalizations with MRAs (11% vs. 14%; RR 0.82; 95% CI 0.69 to 0.98; number needed to treat [NNT] 41).[2] There was high quality evidence based on six studies of an increased risk of hyperkalemia with MRAs compared to placebo or standard of care (16% vs. 8%; RR 2.11; 95% CI 1.77 to 2.51).[2]
- There is moderate quality evidence that finerenone reduces adverse renal outcomes compared to placebo in patients with CKD and type 2 diabetes (T2DM) (17.8% vs. 21.1%; hazard ratio [HR]0.82; 95% CI 0.73-0.93; NNT 29 over 3 years) on background therapy with an angiotensin converting enzyme inhibitor

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(ACEI) or angiotensin receptor blocker (ARB).[3] This was primarily driven by a reduction in sustained estimated glomerular filtration rate (eGFR) and renal failure.

- There is moderate quality evidence that finerenone increases the risk of hyperkalemia-related adverse events compared to placebo in patients with CKD and T2DM (18.3% vs. 9.0%, respectively), despite being a nonsteroidal aldosterone antagonist.[3]
- There is moderate quality evidence that finerenone modestly decreases a composite of time to CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or HF hospitalizations in patients with CKD and T2DM over a median duration of 3.4 years compared to placebo (12.4% vs. 14.2%; HR 0.87; 95% CI 0.76 to 0.98; p=0.03 NNT 56).[4] Results were primarily driven by a reduction in HF hospitalizations. There was no difference in MI or stroke between the groups.

Recommendations:

- No changes to the preferred drug list (PDL) were recommended based on clinical evidence.
- Maintain finerenone as non-preferred on the PDL and include prior authorization to limit use to patients with CKD and T2DM on background therapy with an ACE-I and ARB.
- After evaluation of comparative costs in executive session, no PDL changes were made.

Summary of Prior Reviews and Current Policy

- High quality evidence suggests thiazide-type diuretics should continue to be recommended as a first-line option for hypertension due to benefit at reducing mortality and stroke. High-dose diuretic regimens have been shown to reduce mortality and stroke (moderate quality evidence), while low-dose regimens have been found to reduce mortality, stroke, coronary heart disease, and total CV events (high quality evidence). Evidence for use of "low" dose thiazide-type diuretics is stronger than "high" dose thiazide-type diuretics.[5-10] Low doses are less than chlorthalidone (CTDN) 50 mg per day, indapamide (INDAP) 5 mg per day or hydrochlorothiazide (HCTZ) 50 mg per day.[5] High doses are CTDN 50 mg or more each day, INDAP 5 mg more each day, or HCTZ 50 mg or more each day.[5]
- Thiazide-like diuretics [e.g. CTDN and INDAP] are preferred over thiazide diuretics [e.g HCTZ] by certain high quality guidelines for the treatment of HTN,[7-9] while another guideline has no preference between the two agent types.[10] These recommendations were all based on the same body of literature. High quality randomized controlled trials (RCTs) of CTDN and INDAP show cardiovascular benefits as well as pharmacokinetic superiority in the form prolonged half-life compared to HCTZ, but there is insufficient evidence to *directly* compare these agents for efficacy and safety.[7-12]
- Loop diuretics are recommended for edema in HF but they have not been shown to reduce mortality, and there is insufficient evidence to differentiate between agents.[13-17] (low quality evidence)
- There is high quality evidence that aldosterone receptor antagonists (spironolactone or eplerenone), unless contraindicated, reduce morbidity and mortality when added to evidence-based HF therapy in patients with systolic HF and reduced LVEF. There is insufficient evidence comparing spironolactone with eplerenone.
- There is moderate quality evidence that adding spironolactone to patients with systolic HF and preserved LVEF reduces hospitalizations; however, spironolactone does not yield any additional morbidity or mortality benefit.

Background:
The diuretics class encompasses multiple sub-classes of agents which differ mechanistically.[18] The most familiar agents are loop diuretics, thiazide-type diuretics, and potassium-sparing diuretics.[18] Potassium sparing diuretics are divided into agents which directly block sodium channels without antagonism of mineralocorticoid receptor (e.g., amiloride) and agents which function with direct inhibition of the mineralocorticoid receptor (e.g., spironolactone).[18] Additionally, there are a number of miscellaneous medications such as carbonic anhydrase inhibitors, osmotic diuretics, or vasopressin antagonists which function with diuretic properties; however, their clinical use varies significantly from disease states commonly treated with loop, thiazide-type, and potassium sparing agents.[18] These miscellaneous agents were excluded for the purpose of this review.

Loop, thiazide-type, and potassium-sparing diuretics are most commonly used for hypertension and HF.[9,15] Elevated blood pressure increases risk of complications such as MI, stroke, HF, and kidney disease.[9] It was the leading cause of death and disability-adjusted life years worldwide in 2010.[9] Hypertension has been the cause of more CV deaths than any other modifiable risk factor.[9] Risk for developing HTN increases with age and is more common in African-Americans than other races.[9] Diuretics, with thiazide-type agents being used most commonly for HTN, work by causing a net excretion of water, resulting in decreased blood pressure.[18] Depending upon comorbidities and electrolyte levels, different diuretic sub-types can be combined[9], though combinations require close monitoring to avoid adverse effects such as electrolyte abnormalities, dehydration, and acute kidney injury.[18]

Heart failure is a clinical syndrome involving structural or functional impairment of ventricular filling or ejection of blood.[16] It primarily manifests with symptoms of dyspnea, fatigue, and fluid retention.[16] There is a 20% lifetime risk for development of HF in Americans 40 years of age and older, and risk increases with increasing age.[16] Diuretics, primarily loop agents, find utility in reducing symptoms of fluid overload in heart failure.[16] Potassium-sparing agents with mineralocorticoid inhibition have also been shown to improve outcomes,[16] likely due to a reduction of the adverse effects of excess aldosterone on the heart.[18]

Progression from CKD to kidney failure is rising due to increasing prevalence of diabetes and HTN worldwide. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are the standard of care to slow progression of CKD in patients with proteinuria.[19] More recently, sodium-glucose co-transporter-2 (SLGT2) inhibitors have shown to reduce the risk of development of microalbuminuria or progression to overt nephropathy.[20] Furthermore, aldosterone blockade may reduce the development of hypertensive kidney disease, vascular injury, myocardial fibrosis, and glomerulosclerosis in those with CKD.[21] However, many of the steroidal aldosterone antagonists are limited in use due to the risk of hyperkalemia and gynecomastia. Finerenone is a nonsteroidal mineralocorticoid receptor antagonist (MRA) that is highly selective for the mineralocorticoid receptor.[21] It was FDA approved in 2021 to reduce the risk of eGFR decline, end stage renal disease (ESRD), CV death, nonfatal MI, and hospitalization for HF in adults with CKD associated with T2DM.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 13 systematic reviews were excluded due to poor quality[22-29] (e.g., indirect network-meta analyses), wrong study design of included trials[30-32] (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied[33,34] (e.g., non-clinical). The additional four are summarized below.

Chronic Kidney Disease

- A Cochrane Collaboration systematic review evaluated the effects of aldosterone antagonists, including steroidal (spironolactone and eplerenone) and non-steroidal (finerenone), in combination with ACEI or ARB in adults with CKD and proteinuria on kidney failure, major CV events, death, and adverse events.[1] There were 44 studies (n=5745) identified that were included in the review with follow-up for generally 3 to 12 months.[1] Twenty-three studies included participants who had kidney disease due to diabetes. The majority used the non-selective aldosterone antagonist, spironolactone, and 3 studies used finerenone, the non-steroidal mineralocorticoid antagonist. Risk of bias was unclear or high in many studies due to unclear allocation concealment, unclear blinding of outcome assessors, incomplete outcome reporting, and inadequate random sequence generation. None of the studies were powered to detect differences in clinical outcomes including death, or major CV events. There was very low-quality evidence of uncertain effects on kidney failure (RR 3.0; 95% CI 0.33 to 27.65; 2 studies) with aldosterone antagonists plus ACEI/ARB compared to placebo or standard care.[1] There was moderate quality evidence that aldosterone antagonists increase risk of hyperkalemia (RR 2.17; 95% CI 1.47 to 3.22; 17 studies; NNH 41) compared to placebo or standard of care.[1] There was low quality evidence of an uncertain outcome on death, CV events, and proteinuria. There was low quality evidence that aldosterone antagonists may reduce mean eGFR by 3.0 ml/min (95% CI 5.51 to 0.49) compared to placebo or standard of care.[1] There was not enough evidence to make comparisons to other active treatments on clinical outcomes, including diuretics, calcium channel blockers, or ACEI.

- Another Cochrane Collaboration systematic review evaluated the benefits and harms of aldosterone antagonists in comparison to placebo or standard care in people with CKD requiring hemodialysis (HD).[35] A literature search for RCTs, cross-over trials, and quasi-RCTs in patients with end stage renal disease was completed. The primary outcomes were death, CV death, CV events, and hyperkalemia. A total of 16 studies were included (n=1446). Fourteen of these studies included spironolactone at doses of 12.5 to 50 mg/day and one study evaluated eplerenone 50 mg/day. [35] Most studies had an unclear or low risk of bias. However, six studies had a high risk of attrition bias. Overall, there was moderate quality evidence that compared to placebo or standard care aldosterone antagonists probably reduce the risk of all-cause death (RR 0.45; 95% CI 0.30 to 0.67; 9 RCTs; NNT 14), CV death (RR 0.37; 95% CI 0.22 to 0.64; 6 RCTs; NNT 16), and CV events (RR 0.38; 95% CI 0.18 to 0.76; 3 RCTs; NNT 12).[35] There was low quality evidence that in those with CKD requiring HD, aldosterone antagonists may not significantly increase the risk of hyperkalemia (RR 1.41; 95% CI 0.72 to 2.78; 9 studies; NNH 27). [35]

Chronic Heart Failure with Preserved Ejection Fraction

- A Cochrane Collaboration systematic review was done to determine if beta blockers, ACEIs, ARBs, and MRAs are beneficial in people with HFpEf. [2] For the purpose of this review, only evidence including MRAs will be summarized. A total of 13 studies evaluating aldosterone antagonists were included (n=4459). Eight studies included placebo as a comparator and five included standard of care. Ten of the studies evaluated spironolactone and the mean age of participants ranged from 54 to 80 years. Most studies had unclear (selection bias and reporting bias) or low risk of bias. There was moderate quality evidence of no significant effect on CV mortality with MRAs compared to placebo or standard of care (RR 0.90; 95% CI 0.74 to 1.11; 3 RCTs) or all-cause mortality (RR 0.91; 95% CI 0.78 to 1.06; 5 studies) but a significant reduction in HF hospitalizations with MRAs (11% vs. 14%; RR 0.82; 95% CI 0.69 to 0.98; NNT 41). There was high quality evidence based on six studies of an increased risk of hyperkalemia with MRAs compared to placebo or standard of care (16% vs. 8%; RR 2.11; 95% CI 1.77 to 2.51).

Hypertension

- A Cochrane Collaboration systematic review was conducted to determine if there are differences in clinical outcomes between initiating monotherapy for the treatment of HTN versus initiating combination therapy.[36] An initial 14 RCTs were identified. Subgroup data focusing on treatment initiation were requested from study authors and therefore only four studies were included in the meta-analysis. Overall risk of bias was low in all 4 studies. However, other bias was unknown since data came from subgroups of participants and the outcome of interest was not the primary outcome in any of the included trials. [36] The total number of participants (n=568) and events was very low, limiting ability to make conclusions about clinical outcomes. Therefore, despite low risk of bias, the overall certainty of the evidence was very low. There was very low-quality evidence of no difference in overall mortality (RR 1.35; 95% CI 0.08 to 21.72), CV mortality (RR not estimable), CV events (RR 0.98; 95% CI 0.22 to 4.41), serious adverse events (RR 0.77; 95% CI 0.31 to 1.92) or withdrawals due to adverse events (RR 0.85; 95% CI 0.53 to 1.35). [36] The authors concluded the quality of evidence is very low and no conclusions can be made about the relative efficacy of monotherapy versus combination therapy for the initial treatment of primary HTN. [36]

New Guidelines:
After review, 1 guideline was excluded due to limited applicability[37].

High Quality Guidelines:

Heart Failure

The European Society of Cardiology (ESC) updated guidelines for the treatment of acute and chronic HF in 2021, with a focus on diagnosis and treatment.[38] The guidelines continue to recommend an ACEI or angiotensin receptor-neprilysin inhibitor, beta-blocker, MRA and a sodium-glucose co-transporter 2 (SLGT2) inhibitor (dapagliflozin or empagliflozin) in all patients with HFrEF unless contraindicated or not tolerated to reduce the risk of HF hospitalization and death (Class I, Level A). The evidence-based drugs and doses included for an MRA include spironolactone target dose of 50 mg daily or eplerenone target dose of 50 mg daily. Caution should be used when MRAs are used in patients with impaired renal function and in those with serum potassium concentrations > 5.0 mmol/L. There is also a Class I recommendation based on Level C evidence that diuretics are recommended in patients with HFrEF to reduce HF symptoms, improve exercise capacity and reduce HF hospitalizations. The guidelines comment that the evidence for diuretics is poor and their effects on morbidity and mortality have not been studied in RCTs.

For those with HF and mildly reduced ejection fraction (HFmEF) (including those with ejection fraction of 41-49%), there is a Class IIb recommendation based on Level C evidence to consider an MRA to reduce the risk of HF hospitalization and death. This is based on a retrospective analysis of the TOPCAT trial demonstrating a reduction in hospitalizations and CV Death in those with HFmEF. Due to no treatment showing a reduction in mortality and morbidity with HFpEF, the guidelines give no specific recommendations for use of MRAs despite a possible decrease in hospitalizations.

Blood pressure in Chronic Kidney Disease

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the management of blood pressure in CKD was published in 2021.[19] The updated guidelines include a weak recommendation based on moderate quality evidence that adults with HTN and CKD be treated to a target systolic blood pressure (SBP) of < 120 mm Hg, when tolerated. The guidelines include a strong recommendation for starting an ACEI or ARB for those with HTN, CKD and severely increased albuminuria and a weak recommendation for moderately increased albuminuria. The following additional recommendations are included regarding diuretic therapy:

- MRAs are effective for management of refractory HTN but may cause hyperkalemia or a reversible decline in kidney function (Practice Point)

Hypertension

In 2022, National Institute for Health and Care Excellence (NICE) updated the 2019 guidelines for the diagnosis and management of hypertension in non-pregnant adults, including those with T2DM.[39] Treatment is recommended in stepwise fashion, and is based on various age, race, and comorbidity factors. For step 1 therapy, initiation of an ACEI or ARB is recommended for patients with T2DM or for non-African/African-Caribbean patients who are under 55 years of age. [39] See **Table 1** before for full details of step therapy. For those initiating or changing diuretic treatment, thiazide-like agents, such as indapamide, are preferred over conventional thiazide diuretics of hydrochlorothiazide. Patients who are well controlled on conventional thiazides should continue those agents.

Table 1: NICE Guidelines Step Therapy for Hypertension[39]

Patient Characteristics	**Step 1**	**Step 2**	**Step 3**	**Step 4**
Type 2 diabetes mellitus • Regardless of age or family origin	ACEI or ARB	CCB or thiazide-like diuretic	Combination of: (ACEI or ARB) AND CCB AND thiazide-like diuretic	If potassium 4.5 mEq/L or less consider: Low-dose spironolactone Monitor potassium and use caution in patients with reduced renal function. If potassium 4.5 mEq/L or higher consider: Alpha-blockers or beta-blockers
Age 55 or older • **NOT** African or African-Caribbean origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic		
Age 55 and older • African or African-Caribbean Origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic **Consider ARB in preference to ACEI*		
Age under 55 years • **NOT** African or African-Caribbean origin	ACEI or ARB	ACEI or ARB or thiazide-like diuretic		
Age under 55 years • African or African-Caribbean Origin	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic **Consider ARB in preference to ACEI*		
Clinical suspicion of heart failure	Consider thiazide-like diuretic, then follow chronic heart failure guidelines			

New Formulations:
In June, 2021 a new once daily formulation of torsemide (Soaanz®) was FDA approved for the treatment of edema associated with heart failure and renal disease.[40] It is dosed once daily and has a diuretic effect lasting about 6 to 8 hours.

Randomized Controlled Trials:
A total of 44 citations were manually reviewed from the initial literature search. After initial review, 19 RCTs were selected for more detailed evaluation for inclusion. After further review, 13 citations were excluded because of wrong study design (e.g., observational)[41-46], comparator[47-50] (e.g., no control or placebo-controlled), or outcome studied[51-53] (e.g., non-clinical). The primary approval study for finerenone is included in Table 4. The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Filipattos, et al.[54] DB, PC, PG, RCT	Finerenone vs. placebo	Adults with T2D and CKD (n=5734)	New onset atrial fibrillation	Finerenone: 82 (3.2%) Placebo: 117 (4.5%) HR 0.71; 95% CI 0.53-0.94 P=0.016	Secondary analysis of a pre-specified outcome of the FIEDLIO-DKD trial
Agarwal, et al.[55] Pooled analysis or 2 RCTs	Finerenone vs. placebo	Adults with T2D and CKD (n=13,026)	Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure	Finerenone: 825 (12.7%) Placebo: 939 (14.4%) HR 0.86; 95% CI 0.78 to 0.95 P=0.018	Pooled analysis of FIEDELIO-DKD and FIGARO-DKD studies
Filippattos, et al.[56] DB, PC, PG, RCT	Finerenone vs. placebo	Adults with T2D and CKD (n=7352)	New onset heart failure	Finerenone: 65 (1.9%) Placebo: 95 (2.8%) HR 0.68; 95% CI 0.50-0.93 P=0.0162	Secondary analysis of a pre-specified outcome of the FIGARO-DKD trial
Pitt, et al.[4] Phase III, DB, PC, MC, RCT	Finerenone vs. placebo Mean follow up of 3.4 years	Adults with T2D and CKD (n=7437)	Time to CV death non-fatal MI, non-fatal stroke, or hospitalization for heart failure	Finerenone: 458 (12.4%) Placebo: 519 (14.2%) HR 0.87; 95% CI 0.76 to 0.98 P=0.03	FIGARO-DKD trial Composite outcome results primarily driven by heart failure hospitalizations
Abbreviations: CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; DB: double-blind; HR: hazard ratio; MC: multicenter; PC: placebo controlled; PG: parallel group; RCT: randomized controlled trial; T2D: type 2 diabetes					

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Finerenone is a non-steroidal mineralocorticoid receptor antagonist (MRA) FDA approved to reduce the risk of sustained eGFR decline, end stage kidney disease (ESRD), CV death, non-fatal MI, and hospitalization for HF in adult patients with CKD associated with type 2 diabetes.[57] It was FDA approved based on one placebo-controlled, double-blind, RCT evaluating the efficacy and safety of finerenone (FIDELIO-DKD) (**Table 4**) in adults with type 2 diabetes and CKD on maximum dose of an ACE-I or ARB. [3] In this trial, CKD was defined as moderately elevated albuminuria (urinary albumin to creatinine ratio [UACR] 30-300 mg/g), eGFR of 25 to 60 ml/min and a history of diabetic retinopathy, or severely elevated albuminuria (UACR ≥ 300 mg/g) and eGFR 25-75 ml/min. The primary outcome was a time to event analysis of a composite of kidney failure (defined as end stage kidney disease or an eGFR of less than 15 ml/min), sustained decrease of at least 40% in eGFR from baseline, or death from renal causes.

The trial consisted of a 4–16-week run-in period to allow for optimization of standard of care (ACEI or ARB) and a 2-week screening period. Of the 13,911 patients initially enrolled, only 5,734 were randomized.[3] Over half (59%) patients were excluded during the run-in period mostly due to not meeting eligibility criteria. There was no further information on which eligible criteria were not met. Almost all (~98%) patients were on an ACEI or ARB at baseline. However only 22% of patients on an ACEI and 55% of an ARB were on maximum recommended doses. Very few patients (4.6%) were on background therapy with a SGLT-2 inhibitor and over half (56.6%) were on either a loop or thiazide diuretic. Most patients (87.5%) had significant albuminuria (UACR ≥ 300 mg/g) and the mean eGRF was 44.3 ml/min.[3] There were very few subjects with an eGFR < 25 ml/min (2.4%).

After a median follow up of 2.6 years, there was a reduction in the risk of the primary composite outcome with finerenone compared to placebo (17.8% vs. 21.1%; HR 0.825; 95% CI 0.732 to 0.928; p=0.0014).[3] This was largely driven by a reduction in sustained decrease in eGFR and kidney failure. There were very few renal deaths that occurred (<0.1%). This difference was seen starting around 12 months. This difference was less than the absolute benefit reported in clinical trials of SLGT2 inhibitors and there is insufficient evidence evaluating use of finerenone in addition to an SLGT2 inhibitor. There was also a very modest reduction in a composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF (13.0% vs. 14.8%; HR 0.86; 95% CI 0.75 to 0.99; p=0.04), with the largest effect seen in hospitalizations due to HF.

This trial had extensive inclusion and exclusion criteria and a run-in and screening period that excluded a significant number of patients. This decreases external validity and limits the study population to those most likely to benefit and most likely to tolerate the medication. Additionally, the trial was funded by the manufacturer who was significantly involved in the study design process. Lastly, there is unclear attrition bias due to high levels of attrition overall, but similar between the two groups (~29%).

A similarly designed trial (FIGARO-DKD) was published after FDA approval (**Table 2**) and found a modest benefit in a composite outcome of time to CV death, non-fatal MI, non-fatal stroke, or HF hospitalizations in patients with CKD and T2DM over a median duration of 3.4 years with finerenone compared to placebo (12.4% vs. 14.2%; p=0.03).[4] Patients in this trial had more moderate CKD (stage 2-4 with moderate albuminuria, or stage 1-2 with severe albuminuria) with a

mean eGFR of 69 ml/min compared to 44 ml/min in the previous trial. Results were primarily driven by a reduction in heart failure hospitalizations. There was no difference in MI or stroke between the groups.

Clinical Safety:

In the primary clinical study, serious adverse events occurred in 31.9% of patients on finerenone and 34.3% on placebo. More patients taking finerenone discontinued treatment due to adverse events than those in placebo (7.3% vs. 5.9%, respectively) and the most common reason for discontinuation was hyperkalemia. Finerenone is contraindicated with concomitant strong CYP3A4 inhibitors, due to a potential increase in area under the curve up to 531% seen in pharmacokinetic studies. FDA labeling also includes a warning for hyperkalemia and a contraindication in those with adrenal insufficiency. There was a higher rate of hyperkalemia related adverse effects with finerenone compared to placebo (18.3% vs. 9.0%), a higher rate of discontinuation due to hyperkalemia (2.3% vs. 0.9%), and more hospitalizations due to hyperkalemia (1.4% vs. 0.3%). It is not recommended to initiate therapy if serum potassium is greater than 5.0 mEq/L or if eGFR is < 25 ml/min. Other adverse reactions that occurred in more than 1% of patients on finerenone and more frequently than placebo include hypotension (4.8% vs. 3.4%) and hyponatremia (1.4% vs. 0.7%). Gynecomastia was uncommon in both arms (<0.5%). There are no data on the use of finerenone in pregnancy or lactation.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Cardiovascular death
2) End stage kidney disease
3) All-cause mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Time to first occurrence of the composite endpoint of onset of kidney failure, sustained decrease of eGFR ≥ 40% from baseline, or renal death

Table 3. Pharmacology and Pharmacokinetic Properties.[57]

Parameter	
Mechanism of Action	Blocks mineralocorticoid receptor mediated sodium reabsorption and overactivation in both epithelial and nonepithelial tissues. Mineralocorticoid receptor overactivation is thought to contribute to fibrosis and inflammation. Finerenone is nonsteroidal and has no affinity for androgen, progesterone, estrogen and glucocorticoid receptors.
Oral Bioavailability	44%
Distribution and Protein Binding	Volume of distribution: 52.6 L; Protein binding 92%
Elimination	80% in urine (<1% unchanged) and 20% in feces
Half-Life	23 hours
Metabolism	CYP3A4 (90%) and CYP2C8 (10%)

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
FIDELIO-DKD[3] Phase 3, DB, PC, MC, RCT	1. Finerenone 10-20 mg daily 2. Placebo Duration: 3 years On background ACEI or ARB	Demographics: Mean Age 66 y/o 70% male 63% white 19.8% Asian 3.5% Black ACEI 34.2% ARB 65.7% Key Inclusion Criteria: • ≥ 18 y/o • T2DM • CKD • On ACEI or ARB • K ≤ 4.8 mEq/L Key Exclusion Criteria: • Non-diabetic kidney disease • HgA1C > 12% • BP ≥ 160/100 • NYHA Class II-IV HF • Addison's disease • On potassium sparing diuretic • Strong CYP3A4 inducers or inhibitors • ACS or stroke in last 30 days • Child-Pugh C hepatic dysfunction	ITT: 2866 2868 FAS: 2833 2841 PP: 2011 2013 Attrition: 822; 29% 828, 29%	Primary Endpoint: Composite of kidney failure, a sustained decrease of ≥40% in eGFR, or death from renal causes 1. 504 (17.8%) 2. 600 (21.1%) HR 0.82; 95% CI 0.73-0.93 P = 0.001 Secondary Endpoints: Composite of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for heart failure 1. 367 (13%) 2. 420 (14.8%) HR 0.86; 95% CI 0.75-0.99 P = 0.04 All-cause mortality 1. 219 (7.7%) 2. 244 (8.6%) HR 0.90; 95% CI 0.75 to 1.01 P = 0.24	ARR 3.4% / NNT 29 ARR 1.8% / NNT 56 NS	Discontinuations due to adverse events: * 1. 207 (7.3%) 2. 168 (5.9%) RD 1.5% (95% CI 0.1% to 2.7%) Hyperkalemia related effects* 1. 18.3% 2. 9.0% *p-values not reported	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomization managed centrally using an interactive voice and web response system. Groups similar at baseline. Performance Bias: low; double-blinded, double dummy design. Detection Bias: low: clinical event committee who adjudicated outcome events was blinded to study treatment assignment. Attrition Bias: unclear; high overall rates of attrition, but similar between groupsand for similar reasons (adverse events, physician choice, death and withdrew). Efficacy analysis done on FAS with ~1% due to study violations. Reporting Bias: low; study protocol available and all outcomes reported on. Other Bias: high; study funded by Bayer, medical writing was funded by Bayer, and Bayer was involved in study design. Many of the authors had financial conflicts of interest disclosed. Extensive run-in and screening periods. **Applicability**: Patient: Run-in period and screening period and extensive exclusion criteria limits generalizability. Very few patients included on background therapy with a SGLT2 inhibitor. Intervention: NA Comparator: No active comparator. Outcomes: Composite outcome with outcomes of different levels of significance Setting: 1024 centers in 48 countries; 16.6% in North America and 41.6% in Europe

Abbreviations [alphabetical order]: ACEI = ace inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; ARR = absolute risk reduction; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; CV =cardiovascular; DB = double-blind; eGRF = estimated glomerular filtration rate; FAS = full analysis set; HG = heart failure; HG = hazard ratio; ITT = intention to treat; K = potassium; MC = multicenter; Mg = milligram; MI = myocardial infarction; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; NYHA = new York heart association; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus; y/o = years old

References:

1. Chung EY, Ruospo M, Natale P, et al. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. Oct 27 2020;10(10):Cd007004. doi:10.1002/14651858.CD007004.pub4
2. Martin N, Manoharan K, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. *Cochrane Database Syst Rev*. May 22 2021;5(5):Cd012721. doi:10.1002/14651858.CD012721.pub3
3. Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *The New England journal of medicine*. Dec 3 2020;383(23):2219-2229. doi:10.1056/NEJMoa2025845
4. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *The New England journal of medicine*. Dec 9 2021;385(24):2252-2263. doi:10.1056/NEJMoa2110956
5. Wright JM, Musini VM, Gill R. First-line drugs for hypertension. *Cochrane Database of Systematic Reviews*. 2018;(4)doi:10.1002/14651858.CD001841.pub3
6. Musini VM, Tejani AM, Bassett K, Puil L, Wright JM. Pharmacotherapy for hypertension in adults 60 years or older. *Cochrane Database Syst Rev*. Jun 5 2019;6:Cd000028. doi:10.1002/14651858.CD000028.pub3
7. National Institute for Health and Care Excellence (NICE). Hypertenstion in adults: diagnosis and management. 28 Aug 2019.
8. Department of Veterans Affairs and Department of Defense. VA/DoD clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. Version 3.0. Oct 2014.
9. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. Jun 2018;71(6):e13-e115. doi:10.1161/HYP.0000000000000065
10. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. Sep 1 2018;39(33):3021-3104. doi:10.1093/eurheartj/ehy339
11. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone: antihypertensive and metabolic effects. *Hypertension*. May 2015;65(5):1041-6. doi:10.1161/hypertensionaha.114.05021
12. Liang W, Ma H, Cao L, Yan W, Yang J. Comparison of thiazide-like diuretics versus thiazide-type diuretics: a meta-analysis. *J Cell Mol Med*. Nov 2017;21(11):2634-2642. doi:10.1111/jcmm.13205
13. Miles JA, Hanumanthu BK, Patel K, Chen M, Siegel RM, Kokkinidis DG. Torsemide versus furosemide and intermediate-term outcomes in patients with heart failure: an updated meta-analysis. *J Cardiovasc Med (Hagerstown)*. Jun 2019;20(6):379-388. doi:10.2459/jcm.0000000000000794
14. National Institute for helath and Care Excellence (NICE). Chronic heart failure in adults: diagnosis and management. 12 Sep 2018.
15. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. Aug 8 2017;136(6):e137-e161. doi:10.1161/cir.0000000000000509
16. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. *Journal of the American College of Cardiology*. 2013;62(16):1495-1539. doi:10.1016/j.jacc.2013.05.020

17. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. Jul 14 2016;37(27):2129-2200. doi:10.1093/eurheartj/ehw128
18. UpToDate [online database]. Mechanism of action of diuretics. https://www.uptodate.com/contents/mechanism-of-action-of-diuretics?search=diuretics&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 7 Feb 2020.
19. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int*. Mar 2021;99(3s):S1-s87. doi:10.1016/j.kint.2020.11.003
20. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol*. Sep 2018;6(9):691-704. doi:10.1016/s2213-8587(18)30141-4
21. Frampton JE. Finerenone: First Approval. *Drugs*. Oct 2021;81(15):1787-1794. doi:10.1007/s40265-021-01599-7
22. Katsi V, Michalakeas C, Soulaidopoulos S, et al. Evaluating the Safety and Tolerability of Azilsartan Medoxomil Alone or in Combination With Chlorthalidone in the Management of Hypertension: A Systematic Review. *Curr Hypertens Rev*. 2021;17(3):217-227. doi:10.2174/1573402117666210112144505
23. Lin M, Heizati M, Wang L, et al. A systematic review and meta-analysis of effects of spironolactone on blood pressure, glucose, lipids, renal function, fibrosis and inflammation in patients with hypertension and diabetes. *Blood Press*. Jun 2021;30(3):145-153. doi:10.1080/08037051.2021.1880881
24. Wierda E, Dickhoff C, Handoko ML, et al. Outpatient treatment of worsening heart failure with intravenous and subcutaneous diuretics: a systematic review of the literature. *ESC Heart Fail*. Jun 2020;7(3):892-902. doi:10.1002/ehf2.12677
25. Kuno T, Ueyama H, Fujisaki T, Briasouli A, Takagi H, Briasoulis A. Meta-Analysis Evaluating the Effects of Renin-Angiotensin-Aldosterone System Blockade on Outcomes of Heart Failure With Preserved Ejection Fraction. *The American journal of cardiology*. Apr 15 2020;125(8):1187-1193. doi:10.1016/j.amjcard.2020.01.009
26. Lunney M, Ruospo M, Natale P, et al. Pharmacological interventions for heart failure in people with chronic kidney disease. *Cochrane Database Syst Rev*. Feb 27 2020;2(2):Cd012466. doi:10.1002/14651858.CD012466.pub2
27. Tromp J, Ouwerkerk W, van Veldhuisen DJ, et al. A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail*. Feb 2022;10(2):73-84. doi:10.1016/j.jchf.2021.09.004
28. Fu Z, Geng X, Chi K, et al. Efficacy and safety of finerenone in patients with chronic kidney disease: a systematic review with meta-analysis and trial sequential analysis. *Ann Palliat Med*. Jul 2021;10(7):7428-7439. doi:10.21037/apm-21-763
29. Benmassaoud A, Freeman SC, Roccarina D, et al. Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database Syst Rev*. Jan 16 2020;1(1):Cd013123. doi:10.1002/14651858.CD013123.pub2
30. Kapelios CJ, Bonou M, Malliaras K, et al. Association of loop diuretics use and dose with outcomes in outpatients with heart failure: a systematic review and meta-analysis of observational studies involving 96,959 patients. *Heart Fail Rev*. Jan 2022;27(1):147-161. doi:10.1007/s10741-020-09995-z
31. Abraham B, Megaly M, Sous M, et al. Meta-Analysis Comparing Torsemide Versus Furosemide in Patients With Heart Failure. *The American journal of cardiology*. Jan 1 2020;125(1):92-99. doi:10.1016/j.amjcard.2019.09.039
32. Khan MS, Khan MS, Moustafa A, Anderson AS, Mehta R, Khan SS. Efficacy and Safety of Mineralocorticoid Receptor Antagonists in Patients With Heart Failure and Chronic Kidney Disease. *The American journal of cardiology*. Feb 15 2020;125(4):643-650. doi:10.1016/j.amjcard.2019.11.014

33. McNally RJ, Faconti L, Cecelja M, Farukh B, Floyd CN, Chowienczyk PJ. Effect of diuretics on plasma renin activity in primary hypertension: A systematic review and meta-analysis. *British journal of clinical pharmacology*. May 2021;87(5):2189-2198. doi:10.1111/bcp.14597
34. Filipova E, Dineva S, Uzunova K, Pavlova V, Kalinov K, Vekov T. Combining angiotensin receptor blockers with chlorthalidone or hydrochlorothiazide - which is the better alternative? A meta-analysis. *Syst Rev*. Aug 24 2020;9(1):195. doi:10.1186/s13643-020-01457-9
35. Hasegawa T, Nishiwaki H, Ota E, Levack WM, Noma H. Aldosterone antagonists for people with chronic kidney disease requiring dialysis. *Cochrane Database Syst Rev*. Feb 15 2021;2(2):Cd013109. doi:10.1002/14651858.CD013109.pub2
36. Garjón J, Saiz LC, Azparren A, Gaminde I, Ariz MJ, Erviti J. First-line combination therapy versus first-line monotherapy for primary hypertension. *Cochrane Database Syst Rev*. Feb 6 2020;2(2):Cd010316. doi:10.1002/14651858.CD010316.pub3
37. Hiremath S, Sapir-Pichhadze R, Nakhla M, et al. Hypertension Canada's 2020 Evidence Review and Guidelines for the Management of Resistant Hypertension. *Can J Cardiol*. May 2020;36(5):625-634. doi:10.1016/j.cjca.2020.02.083
38. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. Sep 21 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
39. National Institute for Health and Care Excellence (NICE). Hypertenstion in adults: diagnosis and management. 28 Aug 2019. Updated March 2022.
40. Torsemide (Soaanz®) Prescribing Information. 6/2021. Sarfez Pharmaceuticals, Inc. Vienna, Va. 22182.
41. Ferreira JP, Collier T, Clark AL, et al. Spironolactone effect on the blood pressure of patients at risk of developing heart failure: an analysis from the HOMAGE trial. *Eur Heart J Cardiovasc Pharmacother*. Feb 16 2022;8(2):149-156. doi:10.1093/ehjcvp/pvab031
42. Rossing P, Agarwal R, Anker SD, et al. Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP-1RA treatment: A subgroup analysis from the FIDELIO-DKD trial. *Diabetes, obesity & metabolism*. Jan 2022;24(1):125-134. doi:10.1111/dom.14558
43. Li Y, Li L, Guo Z, Zhang S. Comparative effectiveness of furosemide vs torasemide in symptomatic therapy in heart failure patients: A randomized controlled study protocol. *Medicine*. Feb 19 2021;100(7):e24661. doi:10.1097/md.0000000000024661
44. Edwards C, Hundemer GL, Petrcich W, et al. Comparison of Clinical Outcomes and Safety Associated With Chlorthalidone vs Hydrochlorothiazide in Older Adults With Varying Levels of Kidney Function. *JAMA Netw Open*. Sep 1 2021;4(9):e2123365. doi:10.1001/jamanetworkopen.2021.23365
45. Shen W, Alshehri M, Desale S, Wilcox C. The Effect of Amiloride on Proteinuria in Patients with Proteinuric Kidney Disease. *Am J Nephrol*. 2021;52(5):368-377. doi:10.1159/000515809
46. Hripcsak G, Suchard MA, Shea S, et al. Comparison of Cardiovascular and Safety Outcomes of Chlorthalidone vs Hydrochlorothiazide to Treat Hypertension. *JAMA internal medicine*. Apr 1 2020;180(4):542-551. doi:10.1001/jamainternmed.2019.7454
47. Asakura M, Ito S, Yamada T, et al. Efficacy and Safety of Early Initiation of Eplerenone Treatment in Patients with Acute Heart Failure (EARLIER trial): a multicentre, randomized, double-blind, placebo-controlled trial. *Eur Heart J Cardiovasc Pharmacother*. Feb 16 2022;8(2):108-117. doi:10.1093/ehjcvp/pvaa132
48. Agarwal R, Sinha AD, Cramer AE, et al. Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease. *The New England journal of medicine*. Dec 30 2021;385(27):2507-2519. doi:10.1056/NEJMoa2110730
49. Huang P, Yu Y, Wei F, et al. Association of long-term SBP with clinical outcomes and quality of life in heart failure with preserved ejection fraction: an analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. *J Hypertens*. Jul 1 2021;39(7):1378-1385. doi:10.1097/hjh.0000000000002807

50. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and Cardiovascular Effects of SGLT2 Inhibition in Combination With Loop Diuretics in Patients With Type 2 Diabetes and Chronic Heart Failure: The RECEDE-CHF Trial. *Circulation*. Nov 3 2020;142(18):1713-1724. doi:10.1161/circulationaha.120.048739
51. Vakil D, Zinonos S, Kostis JB, et al. Monotherapy treatment with chlorthalidone or amlodipine in the systolic blood pressure intervention trial (SPRINT). *J Clin Hypertens (Greenwich)*. Jul 2021;23(7):1335-1343. doi:10.1111/jch.14296
52. Sperry BW, Hanna M, Shah SJ, Jaber WA, Spertus JA. Spironolactone in Patients With an Echocardiographic HFpEF Phenotype Suggestive of Cardiac Amyloidosis: Results From TOPCAT. *JACC Heart Fail*. Nov 2021;9(11):795-802. doi:10.1016/j.jchf.2021.06.007
53. Edwards NC, Price AM, Mehta S, et al. Effects of Spironolactone and Chlorthalidone on Cardiovascular Structure and Function in Chronic Kidney Disease: A Randomized, Open-Label Trial. *Clin J Am Soc Nephrol*. Oct 2021;16(10):1491-1501. doi:10.2215/cjn.01930221
54. Filippatos G, Bakris GL, Pitt B, et al. Finerenone Reduces New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes. *J Am Coll Cardiol*. Jul 13 2021;78(2):142-152. doi:10.1016/j.jacc.2021.04.079
55. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J*. Feb 10 2022;43(6):474-484. doi:10.1093/eurheartj/ehab777
56. Filippatos G, Anker SD, Agarwal R, et al. Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial. *Circulation*. Feb 8 2022;145(6):437-447. doi:10.1161/circulationaha.121.057983
57. Finerenone (Kerendia) Prescribing Information. 7/2021. Bayer Pharmaceuticals Inc. Whippany, NJ 07981.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
amiloride HCl	AMILORIDE HCL	ORAL	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE HCL W/HCTZ	ORAL	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE-HYDROCHLOROTHIAZIDE	ORAL	TABLET	Y
bumetanide	BUMETANIDE	ORAL	TABLET	Y
chlorthalidone	CHLORTHALIDONE	ORAL	TABLET	Y
furosemide	FUROSEMIDE	ORAL	SOLUTION	Y
furosemide	FUROSEMIDE	ORAL	TABLET	Y
furosemide	LASIX	ORAL	TABLET	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	CAPSULE	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	SOLUTION	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	TABLET	Y
indapamide	INDAPAMIDE	ORAL	TABLET	Y
spironolact/hydrochlorothiazid	ALDACTAZIDE	ORAL	TABLET	Y
spironolact/hydrochlorothiazid	SPIRONOLACTONE-HCTZ	ORAL	TABLET	Y
spironolactone	ALDACTONE	ORAL	TABLET	Y
spironolactone	SPIRONOLACTONE	ORAL	TABLET	Y
torsemide	TORSEMIDE	ORAL	TABLET	Y
triamterene	TRIAMTERENE	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	MAXZIDE	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	MAXZIDE-25 MG	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	ORAL	TABLET	Y
chlorothiazide	DIURIL	ORAL	ORAL SUSP	N
chlorthalidone	THALITONE	ORAL	TABLET	N
eplerenone	EPLERENONE	ORAL	TABLET	N
eplerenone	INSPRA	ORAL	TABLET	N
ethacrynic acid	EDECRIN	ORAL	TABLET	N
ethacrynic acid	ETHACRYNIC ACID	ORAL	TABLET	N
finerenone	KERENDIA	ORAL	TABLET	N
furosemide	FUROSEMIDE	ORAL	SOLUTION	N
metolazone	METOLAZONE	ORAL	TABLET	N
spironolactone	CAROSPIR	ORAL	ORAL SUSP	N
hydroflumethiazide	SALURON	ORAL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

1. Filippatos G, Bakris G, Pitt B, et al. Finerenone Reduces New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes **J Am Coll Cardiol** 2021 Jul 13;78(2):142-152. doi: 10.1016/j.jacc.2021.04.079. Epub 2021 May 17.

Background: Patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) are at risk of atrial fibrillation or flutter (AFF) due to cardiac remodeling and kidney complications. Finerenone, a novel, selective, nonsteroidal mineralocorticoid receptor antagonist, inhibited cardiac remodeling in preclinical models.

Objectives: This work aims to examine the effect of finerenone on new-onset AFF and cardiorenal effects by history of AFF in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study.

Methods: Patients with CKD and T2D were randomized (1:1) to finerenone or placebo. Eligible patients had a urine albumin-to-creatinine ratio ≥30 to ≤5,000 mg/g, an estimated glomerular filtration rate (eGFR) ≥25 to <75 ml/min/1.73 m^2 and received optimized doses of renin-angiotensin system blockade. Effect on new-onset AFF was evaluated as a pre-specified outcome adjudicated by an independent cardiologist committee. The primary composite outcome (time to first onset of kidney failure, a sustained decrease of ≥40% in eGFR from baseline, or death from renal causes) and key secondary outcome (time to first onset of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) were analyzed by history of AFF.

Results: Of 5,674 patients, 461 (8.1%) had a history of AFF. New-onset AFF occurred in 82 (3.2%) patients on finerenone and 117 (4.5%) patients on placebo (hazard ratio: 0.71; 95% confidence interval: 0.53-0.94; p = 0.016). The effect of finerenone on primary and key secondary kidney and cardiovascular outcomes was not significantly impacted by baseline AFF (interaction p value: 0.16 and 0.85, respectively).

Conclusions: In patients with CKD and T2D, finerenone reduced the risk of new-onset AFF. The risk of kidney or cardiovascular events was reduced irrespective of history of AFF at baseline. (EudraCT 2015-000990-11 [A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease]; Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease [FIDELIO-DKD]; NCT02540993).

2. Agarwal R., Gilippatos G. Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. **Eur Heart J**. 2022 Feb 10;43(6):474-484.

Aims: The complementary studies FIDELIO-DKD and FIGARO-DKD in patients with type 2 diabetes and chronic kidney disease (CKD) examined cardiovascular and kidney outcomes in different, overlapping stages of CKD. The purpose of the FIDELITY analysis was to perform an individual patient-level prespecified pooled efficacy and safety analysis across a broad spectrum of CKD to provide more robust estimates of safety and efficacy of finerenone compared with placebo.

Methods and results: For this prespecified analysis, two phase III, multicentre, double-blind trials involving patients with CKD and type 2 diabetes, randomized 1:1 to finerenone or placebo, were combined. Main time-to-event efficacy outcomes were a composite of cardiovascular death, non-fatal myocardial infarction,

non-fatal stroke, or hospitalization for heart failure, and a composite of kidney failure, a sustained ≥57% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death. Among 13 026 patients with a median follow-up of 3.0 years (interquartile range 2.3-3.8 years), the composite cardiovascular outcome occurred in 825 (12.7%) patients receiving finerenone and 939 (14.4%) receiving placebo [hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.78-0.95; P = 0.0018]. The composite kidney outcome occurred in 360 (5.5%) patients receiving finerenone and 465 (7.1%) receiving placebo (HR, 0.77; 95% CI, 0.67-0.88; P = 0.0002). Overall safety outcomes were generally similar between treatment arms. Hyperkalaemia leading to permanent treatment discontinuation occurred more frequently in patients receiving finerenone (1.7%) than placebo (0.6%).

Conclusion: Finerenone reduced the risk of clinically important cardiovascular and kidney outcomes vs. placebo across the spectrum of CKD in patients with type 2 diabetes.

3. Pitt B. Filippatos G. Agarwal R. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med. 2021 Dec 9;385(24):2252-2263. doi: 10.1056/NEJMoa2110956. Epub 2021 Aug 28.

Background: Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has favorable effects on cardiorenal outcomes in patients with predominantly stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. The use of finerenone in patients with type 2 diabetes and a wider range of CKD is unclear.

Methods: In this double-blind trial, we randomly assigned patients with CKD and type 2 diabetes to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 30 to less than 300 and an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m^2 of body-surface area (stage 2 to 4 CKD) or a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of at least 60 ml per minute per 1.73 m^2 (stage 1 or 2 CKD). Patients were treated with renin-angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects. The primary outcome, assessed in a time-to-event analysis, was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The first secondary outcome was a composite of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR, or death from renal causes. Safety was assessed as investigator-reported adverse events.

Results: A total of 7437 patients underwent randomization. Among the patients included in the analysis, during a median follow-up of 3.4 years, a primary outcome event occurred in 458 of 3686 patients (12.4%) in the finerenone group and in 519 of 3666 (14.2%) in the placebo group (hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P = 0.03), with the benefit driven primarily by a lower incidence of hospitalization for heart failure (hazard ratio, 0.71; 95% CI, 0.56 to 0.90). The secondary composite outcome occurred in 350 patients (9.5%) in the finerenone group and in 395 (10.8%) in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 1.01). The overall frequency of adverse events did not differ substantially between groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (1.2%) than with placebo (0.4%).

Conclusions: Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared with placebo. (Funded by Bayer; FIGARO-DKD ClinicalTrials.gov number, NCT02545049.).

4. Filippatos G., Anker S., Agarwal R., et al. Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial. Circulation. 2022 Feb 8;145(6):437-447.

Background: Chronic kidney disease and type 2 diabetes are independently associated with heart failure (HF), a leading cause of morbidity and mortality. In the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trials, finerenone (a selective, nonsteroidal mineralocorticoid receptor antagonist) improved cardiovascular outcomes in patients with albuminuric chronic kidney disease and type 2 diabetes. These prespecified analyses from FIGARO-DKD assessed the effect of finerenone on clinically important HF outcomes.

Methods: Patients with type 2 diabetes and albuminuric chronic kidney disease (urine albumin-to-creatinine ratio ≥30 to <300 mg/g and estimated glomerular filtration rate ≥25 to ≤90 mL per min per 1.73 m2, or urine albumin-to-creatinine ratio ≥300 to ≤5000 mg/g and estimated glomerular filtration rate ≥60 mL per min per 1.73 m2), without symptomatic HF with reduced ejection fraction, were randomized to finerenone or placebo. Time-to-first-event outcomes included new-onset HF (first hospitalization for HF [HHF] in patients without a history of HF at baseline); cardiovascular death or first HHF; HF-related death or first HHF; first HHF; cardiovascular death or total (first or recurrent) HHF; HF-related death or total HHF; and total HHF. Outcomes were evaluated in the overall population and in prespecified subgroups categorized by baseline HF history (as reported by the investigators).

Results: Overall, 7352 patients were included in these analyses; 571 (7.8%) had a history of HF at baseline. New-onset HF was significantly reduced with finerenone versus placebo (1.9% versus 2.8%; hazard ratio [HR], 0.68 [95% CI, 0.50-0.93]; P=0.0162). In the overall population, the incidences of all HF outcomes analyzed were significantly lower with finerenone than placebo, including an 18% lower risk of cardiovascular death or first HHF (HR, 0.82 [95% CI, 0.70-0.95]; P=0.011), a 29% lower risk of first HHF (HR, 0.71 [95% CI, 0.56-0.90]; P=0.0043) and a 30% lower rate of total HHF (rate ratio, 0.70 [95% CI, 0.52-0.94]). The effects of finerenone on improving HF outcomes were not modified by a history of HF. The incidence of treatment-emergent adverse events was balanced between treatment groups.

Conclusions: The results from these FIGARO-DKD analyses demonstrate that finerenone reduces new-onset HF and improves other HF outcomes in patients with chronic kidney disease and type 2 diabetes, irrespective of a history of HF.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to April 01, 2022>

1 indapamide.mp. or Indapamide/ 1432
2 hydrochlorothiazide.mp. or Hydrochlorothiazide/ 9047
3 spironolactone.mp. or Spironolactone/ 9525
4 triamterene.mp. or Triamterene/ 1420
5 amiloride.mp. or Amiloride/ 12172
6 furosemide.mp. or Furosemide/ 17307
7 bumetanide.mp. or Bumetanide/ 3458
8 torsemide.mp. or Torsemide/ 448
9 chlorothiazide.mp. or Chlorothiazide/ 2549
10 Chlorthalidone/ or chlorthalidone.mp. 1928
11 metolazone.mp. or Metolazone/ 316
12 eplerenone.mp. or Eplerenone/ 1569
13 ethacrynic acid.mp. or Ethacrynic Acid/ 2871
14 finerenone.mp. 186
15 loop diuretics.mp. or Sodium Potassium Chloride Symporter Inhibitors/ 3142
16 Mineralocorticoid Receptor Antagonists/ 5458
17 Diuretics, Potassium Sparing/ or Diuretics/ 29112
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 76814
19 Heart Failure/dt [Drug Therapy] 26701
20 Hypertension/de, dt [Drug Effects, Drug Therapy] 66170
21 chronic kidney disease.mp. or Renal Insufficiency, Chronic/ 72158
22 19 or 20 or 21 161716
23 18 and 22 16616
24 limit 23 to (english language and humans and yr="2020 -Current" and (clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "systematic review")) 176
25 from 24 keep 1-2,4-6,8,19-20,22,26,34,41,44,46,48,51-52,59,62-64,67,69-70,75,85,88-89,96,100,105-106,108,115,125,129,146,150,157,162,166,168,171,174 44

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KERENDIA safely and effectively. See full prescribing information for KERENDIA.

KERENDIA (finerenone) tablets, for oral use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

Kerendia is a non-steroidal mineralocorticoid receptor antagonist (MRA) indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D). (1)

DOSAGE AND ADMINISTRATION

- The recommended starting dosage is 10 mg or 20 mg orally once daily based on estimated glomerular filtration rate (eGFR) and serum potassium thresholds. (2.1)
- Increase dosage after 4 weeks to the target dose of 20 mg once daily, based on eGFR and serum potassium thresholds. (2.3)
- Tablets may be taken with or without food (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg and 20 mg (3)

CONTRAINDICATIONS

- Concomitant use with strong CYP3A4 inhibitors. (4, 7.1)
- Patients with adrenal insufficiency. (4)

WARNINGS AND PRECAUTIONS

- Hyperkalemia. Patients with decreased kidney function and higher baseline potassium levels are at increased risk. Monitor serum potassium levels and adjust dose as needed. (2.1, 2.2, 2.3, 5.1)

ADVERSE REACTIONS

Adverse reactions occurring in ≥ 1% of patients on Kerendia and more frequently than placebo are hyperkalemia, hypotension, and hyponatremia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors: Use is contraindicated. (7.1)
- Grapefruit or Grapefruit Juice: Avoid concomitant use. (7.1)
- Moderate or weak CYP3A4 Inhibitors: Monitor serum potassium during drug initiation or dosage adjustment of either Kerendia or the moderate or weak CYP3A4 inhibitor, and adjust Kerendia dosage as appropriate (7.1)
- Strong or moderate CYP3A4 Inducers: Avoid concomitant use. (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2021

Appendix 5: Key Inclusion Criteria

Population	Adults and Pediatrics
Intervention	Diuretic therapy
Comparator	Active control or placebo
Outcomes	Mortality, composite cardiovascular outcome, hospitalizations, safety outcomes
Timing	N/A
Setting	Inpatient or outpatient

Finerenone

Goal(s):

- Promote use of finerenone that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:

- 12 months

Requires PA:

- Finerenone (Kerendia™)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code; go to #2	
2. Is the patient 18 years or older with a diagnosis of type 2 diabetes?	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Does the patient have a diagnosis of chronic kidney disease?	**Yes:** Go to #4	**No:** Pass to RPh; deny for medical appropriateness.
4. Does the patient have a documented estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) < 25 ml/min **OR** require hemodialysis?	**Yes:** Pass to RPh; deny for medical appropriateness. Request eGFR if not provided	**No:** Document eGFR and go to #5 Recent eGFR: _____ Date:

Approval Criteria		
5. Is the patient currently on a maximally tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), OR have a documented contraindication to both?	**Yes:** Go to #6	**No:** Pass to RPh; deny for medical appropriateness.
6. Is the patient's serum potassium ≤ 5.0 mEq/L?	**Yes:** Approve for up to 12 months Recent potassium: _____ Date: _____	**No:** Pass to RPh; deny for medical appropriateness.

P&T / DUR Review: *06/22 (MH)*
Implementation: *7/1/22*