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Review / Special Report format

Title:

When to use either spironolactone, eplerenone or finerenone in the spectrum of cardiorenal diseases

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1 **Abstract**

2 Kidney disease frequently coexists with cardiovascular diseases, and this dual
3 presence significantly amplifies the risk of adverse clinical outcomes. Shared
4 pathophysiological mechanisms and common cardiovascular risk factors contribute to the
5 increased expression of mineralocorticoid receptors, which in turn can drive the progression
6 of chronic cardiovascular-kidney disorder. The steroidal mineralocorticoid receptor
7 antagonists (MRAs) spironolactone and eplerenone have demonstrated the efficacy in
8 improving patient outcomes in cases of heart failure with reduced ejection fraction or those
9 after a myocardial infarction, but have limited value in patients with chronic kidney disease.
10 The non-steroidal MRA finerenone has now established itself as a foundational guideline-
11 recommended therapy in patients with diabetic kidney disease.

12 To date, these pharmacological agents have been developed in distinct patient
13 populations. The consequences of their distinct pharmacological profiles necessitate further
14 consideration. They have not undergone testing across the entire spectrum of cardiorenal
15 scenarios, and the evidence base is currently being complemented with ongoing trials.

16 In this review, we aim to synthesize the existing body of evidence and chart the future
17 trajectory for the use of spironolactone, eplerenone and finerenone in improving clinical
18 outcomes across the diverse spectrum of cardiorenal diseases. By consolidating the current
19 state of knowledge, we seek to provide valuable insights for informed decision-making in the
20 management of patients with these complex and interconnected conditions.

21

22 **Keywords**

23 kidney disease, heart failure, diabetes mellitus, mineralocorticoid receptor antagonist,
24 aldosterone

1 **Introduction**

2 Chronic kidney disease (CKD) often coexists with cardiovascular (CV) and metabolic
3 disorders such as hypertension, diabetes, myocardial infarction (MI) and heart failure (HF)(1).
4 CV disease (CVD) and CKD share common risk factors and pathophysiological mechanisms.
5 Both conditions may be consubstantial with “two sides of the same coin”, and part of a single
6 entity, a “*Chronic cardiovascular-kidney disorder*”(CCV-KD)(2), as the result of the
7 confluence of cardiovascular-kidney-metabolic risk(3). CVD is responsible for over 50% of
8 mortality in CKD, and simultaneous presence of CKD and CVD leads to a worse prognosis
9 than each condition separately(3). The cumulative risk resulting from two conditions is
10 substantial, possibly making CCV-KD the leading cause of mortality worldwide(4).

11 Shared risk factors and pathophysiology, and disease mechanistic pathways of
12 inflammation and oxidative stress-induced endothelial dysfunction, promoting fibrosis within
13 cardiac and renal tissues, contribute to the progression of CCV-KD, and may be mitigated by
14 renin angiotensin system inhibitors (RASis), sodium-glucose co-transporter-2 inhibitors
15 (SGLT2is) and mineralocorticoid receptor antagonists (MRAs)(1,5).

16 MRAs are a fundamental evidence-based therapy for patients with HF and reduced
17 ejection fraction (HFrEF)(6,7), those with left ventricular dysfunction after MI(8), and those
18 with resistant hypertension(9). Their impact on patients with heart failure and preserved
19 ejection fraction (HFpEF) presents a challenge due to the intricate interpretation of the
20 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
21 (TOPCAT) trial(10,11). In addition, finerenone, a non-steroidal MRA, has been shown to
22 decrease the risk of cardiorenal outcomes in patients with CKD and type 2 diabetes
23 (T2D)(12,13).

1 In this article, our objective is to offer an overview of the present status and
2 prospective advancements of spironolactone, eplerenone, and finerenone in patients with
3 CCV-KD.

4

5 **I/ Chronic Kidney Disease in Cardiovascular Disease and its impact on MRA use**

6 Kidney disease significantly elevates the risk of developing CVD. Once CVD
7 develops, the adverse outcomes in patients with CKD likely stem from the bidirectional
8 relationship between the kidney and heart(1). A progressively renal function decline may
9 increase the risk of cardiovascular mortality and progression of CVD. For instance, in acute or
10 chronic HF, risk of HF-related events increases as renal function declines. Hypertensive
11 patients with more advanced CKD often face more challenging blood pressure (BP) control.
12 Conversely, CVD progression, such as recurrent HF exacerbations in HF patients, recurrent
13 ischemic attacks in individuals with MI, and uncontrolled BP in hypertensive patients, can
14 gradually deteriorate renal function. According to the concept as a single CCV-KD entity,
15 depending on various combinations of risk factors and precipitants, patients with CCV-KD
16 may present initially with CVD or with hallmarks of CKD, but have already both organs
17 being altered. When screened for CKD, most patients with CVD will be found to have a
18 decline in estimated glomerular filtration rate (eGFR) and/or albuminuria. When screened for
19 CVD, reciprocally, most patients with CKD will be found to have elevated natriuretic peptide
20 levels and/or echocardiographic hallmarks of progressing HF.

21 Increased serum creatinine levels after the initiation of MRAs are caused by renal
22 hemodynamic effects, and may not adversely impact prognosis(14). However, patients with
23 advanced CKD are more prone to "pseudo-worsening renal function (WRF)," potentially
24 hindering the maintenance of MRA therapy. A U.S.-based HF registry, which encompassed
25 157,439 patients with HF and a left ventricular ejection fraction (LVEF)<40%, revealed that

1 over 60% of these patients also had CKD. There was obvious decrease in prescription rates of
2 MRAs with lower eGFR categories: 45%, 40%, 35%, 26%, 14%, and 5% for eGFR \geq 90, 60 to
3 89, 45 to 59, 30 to 44, $<30\text{ml}/\text{min}/1.73\text{m}^2$ and dialysis, respectively(15). In the Swedish HF
4 Registry, about half of patients with HFrEF had concurrent CKD. Patients with lower eGFR
5 were less likely to be initiated or continue MRAs: 41%, 39%, 31% and 20% of patients for
6 eGFR \geq 60, 45 to 59, 30 to 44, and $<30\text{ml}/\text{min}/1.73\text{m}^2$, respectively. Furthermore, among
7 patients who stopped MRAs, those with lower eGFR were less likely to be restarted(16). In
8 another report from the Swedish HF Registry, low creatinine clearance (<30 or 30 to 60 vs.
9 $\geq 60\text{ml}/\text{min}$) was a major reason for MRA non-use, independent of clinical confounders (*i.e.*,
10 the use of RASi and baseline potassium level)(17).

11

12 **II/ Aldosterone and MR Activation in Cardiorenal Diseases**

13 Aldosterone is an important contributor to the pathophysiology of HF, which was
14 initially thought to originate solely from the adrenal cortex and activate the mineralocorticoid
15 receptor (MR) in the distal nephron of the kidney. Actually, kidney, heart, visceral adipocytes
16 and many other tissues have also been shown to produce aldosterone outside of the adrenals.
17 MR is expressed in the kidney (podocytes, endothelial cells and mesangial cells), the heart
18 (cardiomyocyte and fibroblasts), and multiple other tissues, regulating a large variety of
19 functions(18). Elevated aldosterone levels or MR activation, often seen in aging, diabetes,
20 hypertension, and obesity, may contribute to an increased risk of CCV-KD progression, by
21 initiating a series of mechanisms including inflammation- and oxidative stress-induced
22 endothelial dysfunction. A study with 3,680 CKD patients showed that higher serum
23 aldosterone was associated with lower initial kidney function. Doubling of serum aldosterone
24 was linked to an 11% increased risk of CKD progression (*i.e.*, 50% decline in eGFR, chronic

1 dialysis or kidney transplant) independent of baseline kidney function and 24-hour urine
2 protein during a median follow-up of 9.6 years(19).

3 Circulating aldosterone levels are also associated with adverse myocardial
4 remodeling, and with increased risk of clinical events in hospitalized or ambulatory patients
5 with HF(20,21) or those with post-MI(22). In patients with worsening HF, higher serum
6 aldosterone on admission was associated with a higher risk of post-discharge rehospitalization
7 or cardiovascular death(20).

8

9 **III/ Comparative Pharmacology of Spironolactone, Eplerenone and Finerenone**

10 **Steroidal MRAs: Spironolactone and Eplerenone**

11 Historically, spironolactone was the first MRA to be used for therapeutic purposes.
12 Spironolactone is the least specific MRA, as it also binds to progesterone and androgen
13 receptors, leading to hormonal adverse effects such as gynecomastia and impotence in men,
14 and menstrual irregularities and breast tenderness in women. Spironolactone is a pro-drug,
15 and is converted mainly to canrenone as several other biologically active metabolites, which
16 have a longer half-life of >20 hours and can accumulate over time(23). After discontinuing
17 spironolactone, up to 3 weeks, the urinary levels of its metabolites were reported to be
18 detectable in 36% of patients with moderate CKD(24). In contrast, eplerenone is more
19 specific to MR receptors and has a much shorter half-life of 4-6 hours. These intrinsic
20 differences impact the drug tolerability but also adequacy to disease treatment (the stability of
21 spironolactone may benefit the long-term treatment of hypertension, while the rapid action of
22 eplerenone may be preferable in acute conditions such as decompensated HF(25))(Table 1).

23 **The non-steroidal MRAs**

24 **Finerenone, compared to Spironolactone and Eplerenone**

1 Finerenone has different pharmacological characteristics (*i.e.*, tissue distribution,
2 half-life, affinity, and specificity), with no steroidal-related adverse effects(*Table 1*). Of note,
3 in an experimental model with radio-labeled rats, finerenone was equally distributed between
4 the kidney and heart, while spironolactone and eplerenone prominently stayed in the
5 kidney(26). Finerenone may have a lower risk of hyperkalemia, as it has a milder impact on
6 kidney electrolyte transport. The relatively weak anti-hypertensive effect of finerenone may
7 be explained by its very short half-life (~2.5 hours) and low lipophilic properties, which
8 support that finerenone may not cross blood-brain barrier and activate the hypothalamic MR
9 in the brain, as a crucial role in MR-related BP control(27). Furthermore, finerenone has
10 different co-factor recruitment after MR binding compared with steroidal MRAs, potentially
11 impacting gene expression and leading to diverse anti-inflammatory and anti-fibrotic effects.
12 In pre-clinical study, finerenone outperformed eplerenone, reducing kidney hypertrophy,
13 proteinuria, renal pro-inflammatory and fibrotic associated gene expression despite equivalent
14 natriuretic doses(26).

15

16 **IV/ Potential Mechanism of Benefits of MRAs**

17 **Spironolactone and Eplerenone**

18 Briefly, the mechanisms underlying the cardiovascular benefits from spironolactone
19 or eplerenone has been underpinned by their anti-inflammatory and anti-fibrotic effects. In a
20 sub-study of the Randomized Aldactone Evaluation Study (RALES) trial including 151
21 patients with HFrEF, spironolactone lowered serum marker of type III myocardial fibrosis
22 over 6 months, and the efficacy of spironolactone was more marked among patients with high
23 levels of the fibrotic marker(28). In the Heart OMics in Aging (HOMAGE) trial including 527
24 patients at risk of HF, spironolactone vs. control lowered serum marker of type I myocardial
25 fibrosis, as well as improved ventricular remodeling over 9 months(29). In the Aldosterone

1 Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) trial including 422 patients with
2 HFpEF and mild HF symptoms, spironolactone vs. placebo improved diastolic dysfunction,
3 decreased left ventricular mass, and natriuretic peptide levels(30).

4 **Finerenone Compared to Spironolactone or Eplerenone**

5 Cardiorenal effects of finerenone compared with spironolactone or eplerenone have
6 been explored in the Phase II Mineralocorticoid Receptor Antagonist Tolerability Study
7 (ARTS) program. In the ARTS trial including 392 patients with HFrEF and moderate CKD,
8 finerenone was associated with significantly smaller mean increases in serum potassium and
9 less decline in eGFR than spironolactone, regardless of the doses of finerenone(31). In the
10 ARTS-HF trial including 1,066 patients with HFrEF who had either CKD or T2D, over 90
11 days, finerenone lowered natriuretic peptide levels comparably to eplerenone(32). In the
12 ARTS-DN trial of 823 patients with T2D and CKD randomized to receive either finerenone
13 or placebo, finerenone 7.5-20 mg/day reduced urine albumin creatinine ratio (UACR) in a
14 dose-dependent manner compared with placebo(33). Furthermore, in a post-hoc analysis of
15 ARTS-DN trial, despite its short half-life, finerenone persistently reduced BP throughout the
16 entire 24-hour period when administered once daily in the morning(34).

17 Aside from few comparisons between MRAs, based on clinical outcomes, there has
18 been a lack of direct biological comparisons, such as utilizing biological methods to assess
19 fibrosis and protein pathways, within clinical studies.

20

21 **V/ Major MRAs Cardio-Kidney Outcome Trials**

22 **Spironolactone and Eplerenone in Cardiovascular Trials**

23 **Hypertension**

1 The PATHWAY-2 trial demonstrated that, over a 12-week duration, spironolactone
2 25-50mg/day decreased systolic BP by approximately 15 mmHg among patients with resistant
3 hypertension and an eGFR above 45mL/min/1.73m². Notably, spironolactone exhibited a
4 greater BP-lowering effect compared to bisoprolol (5-10mg/day) and doxazosin modified
5 release (4-8mg/day)(9). The effect was more pronounced in patients with lower plasma renin,
6 which was explained by salt-retaining and hyper-aldosterone state.

7 In patients with essential hypertension, over 9-month period, eplerenone 200mg/day
8 was associated with a significant decline in BP, and regression of left ventricular mass,
9 comparable to enalapril 40mg/day. Notably, when eplerenone and enalapril were combined,
10 their anti-hypertensive and anti-remodeling effects were enhanced(35).

11 **Heart Failure**

12 In the RALES trial where 1,663 patients with HFrEF and severe HF symptoms were
13 included, spironolactone vs. placebo reduced the risk of all-cause death by 30% (*Table 2*).
14 However, rates of breast pain and gynecomastia in men were increased with
15 spironolactone(6). The subsequent large trial of eplerenone was conducted for HFrEF with
16 mild HF symptoms in the Eplerenone in Mild Patients Hospitalization and Survival Study in
17 Heart Failure (EMPHASIS-HF, N=2737) trial, showing consistent cardiovascular benefits
18 from eplerenone in patients with HFrEF(7)(*Table 2*).

19 In the TOPCAT trial involving 3,455 patients with symptomatic HFpEF,
20 spironolactone did not reduce the primary cardiovascular outcome, but lowered HF
21 hospitalization rates(10). Subsequent analysis revealed geographic variations, with Russia and
22 Georgia not representing an authentic HFpEF population. Among the remaining patients from
23 the United States, Canada, Brazil, and Argentina, spironolactone reduced the risk of primary
24 outcome(11). Nevertheless, given the complexity in interpreting the trial results, the ongoing
25 Spironolactone In The Treatment of Heart Failure (SPIRIT-HF, NCT04727073) and the

1 Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With
2 Preserved Ejection Fraction (SPIRRIT, NCT02901184) trials hold the promise of furnishing
3 more conclusive and definitive evidence.

4 **Post Myocardial Infarction**

5 In 6,642 patients with a LVEF <40% following MI in the Eplerenone Post-Acute
6 Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial,
7 eplerenone vs. placebo reduced the risk of primary cardiovascular outcome(8)(Table 2).
8 Subsequently, eplerenone was studied in patients with acute ST-elevation MI without HF in
9 the Impact Of Eplerenone On Cardiovascular Outcomes In Patients Post Myocardial
10 Infarction (REMINDER, N=1,012) trial. Eplerenone vs. placebo significantly reduced the rate
11 of the primary cardiovascular outcome, primarily due to reduced natriuretic peptide
12 levels(36). Finally, in the Aldosterone Lethal effects Blocked in Acute MI Treated with or
13 without Reperfusion to improve Outcome and Survival at Six months follow-up
14 (ALBATROS) trial involving 1,603 patients with acute MI, an MRA regimen (*i.e.*, a
15 potassium canrenoate iv plus spironolactone) vs. control had neutral associations with the
16 primary outcome(Table 2). However, mortality risk decreased in patients with ST-elevated MI
17 who received the MRA regimen, compared with standard therapy only (P-for-
18 interaction=0.01)(37).

19 **Spironolactone and Eplerenone and Outcomes in CKD patients**

20 Generally, cardioprotective effects of spironolactone or eplerenone appear
21 maintained even among those who decline renal function shortly after initiation of MRA
22 therapy. In a post-hoc analysis of the RALES trial, patients randomized to spironolactone
23 experienced more frequently WRF (>30% decline in eGFR) by week 12. However, their all-
24 cause mortality risk was not higher, whereas WRF in the placebo group increased a risk of all-
25 cause mortality (P-for-interaction=0.009)(38). Comparable findings were reported in pot-hoc

1 analyses of the EPHEBUS, EMPHASIS-HF and TOPCAT trials, and cardioprotective effects
2 of MRA therapy persisted irrespective of any definitions of WRF(39-41). In EMPHASIS-HF,
3 modifying the eplerenone dose based on renal function showed a consistent treatment effect
4 across different the severity of renal function, suggesting the potential benefit from tailoring
5 the eplerenone doses according to renal function(42).

6 The rate of change in eGFR (*i.e.*, GFR slope) as a viable alternative outcome for
7 CKD progression was assessed in the EPHEBUS, EMPHASIS-HF and TOPCAT
8 trials(39,43). Spironolactone or eplerenone did not show reno-protective effects in chronic
9 phase, in contrast with the results observed in trials for finerenone. It should be noticed that
10 patients in the placebo group of HF trials had minimal annual eGFR decline
11 ($<1\text{ml}/\text{min}/1.73\text{m}^2/\text{year}$), similar to the general population, and far less than those observed in
12 in T2D/CKD trials ($\sim 4\text{ml}/\text{min}/1.73\text{m}^2/\text{year}$)(12,13). Although baseline renal function and the
13 study period in T2D/CKD trials were numerically similar to those in HF trials, a lower rate of
14 renal function declines in patients with HF may explain why steroidal MRAs did not show
15 significant reno-protective effects on chronic slope.

16 Renal function declined early with steroidal MRAs, even in patients without HF. A
17 post-hoc analysis of the HOMAGE trial shed light on the mechanism of WRF following
18 spironolactone initiation(44). Their results showed that the initial eGFR decrease with
19 spironolactone correlated with decreased natriuretic peptide levels, kidney injury markers, and
20 BP, indicating no renal harm subsequent to the initial eGFR drop due to initiation of MRA
21 therapy.

22 Even though the presence and magnitude of albuminuria exhibit robust associations
23 with tubular injury, HF severity and risk of cardiorenal outcomes irrespective of the severity
24 of eGFR, among patients with HFpEF in the TOPCAT trial, spironolactone reduced placebo-

1 corrected UACR levels by 39% in the overall population, and by 76% among those with
2 macroalbuminuria, defined as UACR>300mg/day(45).

3

4 **Finerenone in Cardio-Kidney Outcome Trials**

5 **Finerenone in Kidney Trials**

6 Finerenone was investigated in two large CKD and T2D trials: (i) the Finerenone in
7 Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-
8 DKD); and (ii) the Finerenone in Reducing Cardiovascular Mortality and Morbidity in
9 Diabetic Kidney Disease (FIGARO-DKD)(12,13). In the FIDELIO-DKD trial for advanced
10 CKD and T2D, finerenone vs. placebo significantly reduced the risk of the primary kidney
11 outcome, and the secondary CV outcomes (*Table 2 & Figure 1*)(12). Complementarily, the
12 FIGARO-DKD trial was designed in CKD and T2D with a wider eGFR range (up to
13 90ml/min/1.73m²) and moderate UACR to provide a greater kidney failure-free interval
14 (*Table 2 & Figure 1*). Similarly, finerenone vs. placebo significantly reduced the risk of the
15 primary CV outcomes, and tended to decrease the risk of the secondary kidney outcome(13).

16 To further focus on specific cardiorenal outcomes with expanded number of sample
17 and events, FIDELITY program is a prespecified, individual patient data pooled analysis of
18 the FIDELIO-DKD and FIGARO-DKD trials. Among 13,026 patients enrolled in FIDELITY,
19 finerenone vs. placebo reduced a risk of a composite kidney outcome (*i.e.*, kidney failure,
20 $\geq 57\%$ decline in eGFR, or kidney death) by 23%, a sustained $\geq 57\%$ decline in eGFR by 30%
21 and end-stage kidney disease (*i.e.*, chronic dialysis and kidney transplantation) by 20%(46). In
22 general, the effects of finerenone on these renal outcomes were consistent across eGFR and/or
23 UACR categories.

24 **Finerenone in Cardiovascular Trials**

1 **Heart Failure**

2 Finerenone is undergoing several trials in HF. FINEARTS-HF (NCT04435626) trial
3 was designed to investigate the effects of finerenone on HF-related events in patients with
4 HFpEF and across a broad range of renal function (eGFR ≥ 25 ml/min/1.73m²).
5 CONFIRMATION-HF (NCT06024746) trial is investigating efficacy and safety profiles of
6 early combinations of finerenone and SGLT2i, in patients hospitalized with HF independent
7 of LVEF. REDEFINE-HF (NCT06008197) trial investigates the efficacy and safety profiles
8 of finerenone vs. placebo when initiated early in patients hospitalized with HF or recently
9 discharged with a LVEF of $\geq 40\%$, and FINALITY-HF (NCT06033950) examines the
10 efficacy and safety profiles of finerenone vs. placebo in patients with symptomatic HFrEF
11 intolerant of or not eligible for steroidal MRAs.

12

13 **VI/ Barriers in MRA Use and Practical Clinical Considerations**

14 The use of steroidal MRAs in patients with HF is hampered by a likely excessive
15 concern about hyperkalemia-associated risk. When MRA is discontinued, more than 75% of
16 patients are not re-started on MRAs during the subsequent year(47). The concern about
17 hyperkalemia-associated rhythm disturbance is obviously inflated. Although discontinuing
18 MRAs after an episode of hyperkalemia lowered the risk of recurrent hyperkalemia, it
19 significantly increased the incidence of subsequent cardiovascular events(48). Base on
20 practical algorithms guiding the pharmacologic management of HF, adjusting diuretic doses
21 and treating extra-cardiac causes of WRF may help maintain MRA therapy after an episode of
22 WRF(14).

23 Potassium binder such as patiomer may mitigate the risk of hyperkalemia and assist
24 in maintaining MRA therapy in patients with recurrent hyperkalemia and HF or hypertension,

1 as shown in the DIAMOND or AMBER trials(24,49). When indirectly comparing the rates of
2 hyperkalemia between finerenone and steroidal MRA in different trial populations, a lower
3 incidence of hyperkalemia might be expected with finerenone(50). However, there is
4 insufficient data from head-to-head comparisons. In the ARTS trial, finerenone produced less
5 hyperkalemia than the highest dose of spironolactone, which was superior to the 25mg routine
6 target dose(31), and in the ARTS-HF trial, the rise of serum potassium with eplerenone was
7 higher than with finerenone, but the number of hyperkalemia events was not high enough to
8 discriminate between the two agents(32). Notably, in these trials, finerenone was prescribed at
9 doses equal or below 20mg/day. Ongoing trials, such as FINEARTS-HF trial are using doses
10 up to 40mg/day. Awaiting real world data, and the results of ongoing trials, it is recommended
11 that in patients treated with finerenone, serum potassium is routinely monitored and advice
12 about prevention of hyperkalemia are given.

13

14 **VII/ Unmet Needs and Future Directions of MRA Clinical Trials for Cardiorenal** 15 **Diseases**

16 Patients with an eGFR $\leq 30\text{mL}/\text{min}/1.73\text{ m}^2$ were typically excluded from clinical
17 trials studying steroidal MRAs. However, these patients often exhibit an excess of aldosterone
18 and a heightened vulnerability to cardiovascular events, and face an increased risk of MRA-
19 related adverse events(15). Notably, meta-analysis of the RALES, EMPHASIS-HF, and
20 TOPCAT Americas trials revealed that only 2.6% of the participants had an eGFR
21 $\leq 30\text{ml}/\text{min}/1.73\text{m}^2$ (51). Steroidal MRAs had a neutral effect on composite cardiovascular
22 outcomes in patients with an eGFR $\leq 30\text{ml}/\text{min}/1.73\text{m}^2$, differing significantly from other
23 eGFR categories (P-for-trend=0.03). As eGFR decreased, the risk of hyperkalemia by MRAs
24 rose (P-for-trend=0.002). Thus, the use of steroidal MRAs in this context lacks strong
25 evidence.

1 In contrast, an exploratory analysis conducted within the FIDELITY program
2 (N=13,023) managed to encompass a substantial cohort of patients with an
3 eGFR<30ml/min/1.73m², numbering 890 individuals. Notably, finerenone showed similar
4 efficacy in both eGFR <30ml/min/1.73m² and eGFR >30ml/min/1.73m² groups (P-for-
5 interaction=0.67). The incidence of hyperkalemia leading to drug discontinuation remained
6 minimal in these patients (≤3%)(52). Although the interpretation of these results should be
7 cautious due to lack of adequate sample size or limited population, these data suggest that
8 finerenone can represent a sound therapeutic option with cardiorenal benefits in the context of
9 stage 4 CKD.

10 Currently, MRA therapy is not recommended for dialysis patients. The
11 ALCHEMIST trial (NCT01848639) failed to show a benefit of spironolactone in 644 patients
12 undergoing hemodialysis, on a composite CV outcome of nonfatal MI, acute coronary
13 syndrome, HF hospitalization, nonfatal stroke or CV mortality. The ongoing larger Phase III
14 placebo-controlled trials, ACHIEVE (NCT03020303) is underway and will determine the
15 efficacy and safety of spironolactone in dialysis patients, aiming to provide more clarity in
16 this regard. Furthermore, in the ongoing FINEARTS-HF trial, among the secondary
17 endpoints, an essential consideration is the composite renal outcome, defined as a persistent
18 reduction in eGFR by ≥50% compared to baseline, or an enduring decline in eGFR to
19 <15ml/min/1.73m², initiation of dialysis, or undertaking renal transplantation.

20 Sacubutril/Valsartan provides additional benefit in MRAs users with HFrEF in the
21 PARADIGM-HF trial, with less hyperkalemia events(53). SGLT2i has been proven to further
22 improve patient outcomes in patients with CCV-KD as well as decrease the risk of
23 hyperkalemia events in MRA users(54). In addition, SGLT2is have the potential to slow renal
24 function decline, which further promotes maintaining MRA therapy(55). Nonetheless, given
25 that the development of SGLT2is/MRAs has occurred in relatively contemporary timeframes,

1 the potential synergistic impact of these medications has not undergone adequate evaluation.
2 It will be the subject of future trials (*i.e.*, CONFIDENCE(56) and CONFIRMATION-HF).

3 While, more costly compared to spironolactone and eplerenone, finerenone has shown to
4 mitigate the progression of CCV-KD in patients with T2D and CKD. The benefit from finerenone
5 was supported by a significant reduction in costs, particularly HF incidences, chronic dialysis, and
6 kidney transplantation, which constitute major contributors to health care expenses associated with
7 CKD(12,13). Furthermore, the necessary integration of other strategies (*i.e.* SGLT2is and potassium
8 binders) may influence the cost-effectiveness of MRA therapy. Nonetheless, much remains to be
9 uncovered regarding the cost-effectiveness of MRAs in preventing CCV-KD progression.

10

11 **Conclusions**

12 Spironolactone, eplerenone, and finerenone show promise across diverse phenotypes of CCV-
13 KD, with eplerenone and spironolactone benefiting CVD and finerenone benefiting both CVD
14 and CKD. Ongoing trials have the potential of broadening the range of patients who might
15 benefit from MRA therapy. Compelling evidence from randomized trials, with consistent
16 benefits and lower hyperkalemia risks (potentially further mitigated through the concurrent
17 use of potassium binders and/or SGLT2i and/or Sacubutril/Valsartan), could encourage wider
18 use of these drugs in patients with CCV-KD.

19

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Table 1. Pharmacologic Differences among Spironolactone, Eplerenone and Finerenone

MR, mineralocorticoid receptor; CNS, central nervous system; BP, blood pressure.

***Based on animal model studies.**

Table 2. Major Trials of Cardiorenal Outcomes with Various MRAs

HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; HFpEF, heart failure with preserved ejection fraction; STEMI, ST-elevation myocardial infarction; NSTEMI, Non-ST-elevation myocardial infarction; CKD, chronic kidney disease; T2D, type 2 diabetes; K+, serum potassium; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BB, beta-blocker; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio; CCr, creatinine clearance; NNT, number needed to treat; CV, cardiovascular; HF, heart failure; BNP, b-type natriuretic peptide; NT-proBNP, N-terminal-pro-b-type natriuretic peptide; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter-defibrillator; ESKD, end-stage kidney disease.

Table 1. Pharmacologic Differences among Spironolactone, Eplerenone and Finerenone

	Spironolactone	Eplerenone	Finerenone
Structural properties	steroidal	steroidal	nonsteroidal
Absorption	100% bioavailable	69% bioavailable	44% bioavailable
MR affinity, nmol/L	24.2 (High)	990 (Low)	17.8 (High)
MR selectivity	Low	Medium	High
Tissue distribution	Kidney>>heart > 6-fold	Kidney>heart ≈ 3-fold	Equivalent (1:1)
Metabolites	Hepatic, active metabolites	No active	No active
Half-life, hours	>20	3-6	2-4
Hyperkalemia	High	Moderate	Low
BP lowering effect	Strong	Weak	Weak
Anti-fibrotic effect	Moderate	Moderate	High*

1 **Table 2. Major Trials of Cardiorenal Outcomes with Various MRAs**

Trials	Population	Drug (vs. placebo)	Inclusion criteria	mean eGFR, ml/min/1.73m ²	Median UACR, mg/g	Mean LVEF, %	Placebo mortality (Per 100py)	NNT	Follow up period, months	Primary outcome	Secondary outcome
										HR (95%CI) for TTx	HR (95%CI) for TTx
RALES	1663 patients with HFrEF and severe symptom	Spironolactone, -25 mg/day	Creatinine ≤2.5mg/dl; K+ ≤5.0mmol/L; ACE-inhibitor and a loop diuretic; LVEF ≤35%; NYHA ≥III	65	NA	26	27.3	9	24	All-cause death	CV death
										HR= 0.70 (0.60 to 0.82)	HR= 0.69 (0.58 to 0.82)
EPHESUS	6642 patients with HFrEF after MI	Eplerenone, -50 mg/day	Creatinine≤2.5mg/dl; K+≤5.0mmol/L; ACE-inhibitor, ARB or both and BB	70	NA	33	13.6	50	16	CV death, nonfatal MI, stroke and HF hospitalization	CV death
										HR= 0.87 (0.79 to 0.95)	HR= 0.83 (0.72 to 0.94)
EMPHASIS-HF	2737 patients with HFrEF and mild symptom	Eplerenone, -50 mg/day	eGFR ≥30mL/min/1.73m ² ; K+ ≤5mmol/L; ACE-inhibitor, ARB or both and BB; LVEF <30% (or, if >30 to 35%, a QRS >130msec); NYHA II	71	NA	26	7.1	51	21	CV death or HF hospitalization	All-cause death or HF hospitalization
										HR= 0.63 (0.54 to 0.74)	HR= 0.65 (0.55 to 0.76)
TOPCAT Americas	1767 patients with symptomatic HfpEF	Spironolactone, 15–45 mg/day	eGFR≥30mL/min/1.73m ² ; K+≤5mmol/L; LVEF ≥ 45%; SBP ≤140mmHg or ≤160mmHg if patient was taking ≥3drugs	61	27	58	4.6	83	40	CV death or HF hospitalization	CV death
										HR= 0.89 (0.77 to 1.04)	HR= 0.74 (0.57 to 0.97)
REMINDER	1012 patients with STEMI	Eplerenone, 25-50 mg/day	eGFR≥30mL/min/1.73m ² ; Creatinine<220μmol/L; Need for potassium-sparing diuretics; LVEF < 40%; Prior history of HF	86	NA	NA	NA	NA	10.5	CV death, HF hospitalization, VT/VF, LVEF≤40%, or BNP>200pg/mL or NT-proBNP>450pg/mL (in patients aged <50years), >900pg/mL (age 50–75 years), or 1800 pg/mL (patients aged >75 years) after 1 month	CV death
										HR= 0.58 (0.45 to 0.75)	HR= 0.99 (0.14 to 7.04)
ALBATROSS	1603 patients with STEMI or NSTEMI	MRA regimen (a single 200mg potassium canrenoate IVbolus plus spironolactone 25mg/day for 6 months)	Creatinine≤220μmol/L; K+≤5.5mmol/L	CCr, 101ml/min	NA	50	NA	NA	6	All-cause death, VT/VF, ICD indication or HF hospitalization	All-cause death
										HR= 0.97 (0.73 to 1.28)	HR= 0.65 (0.30 to 1.38)

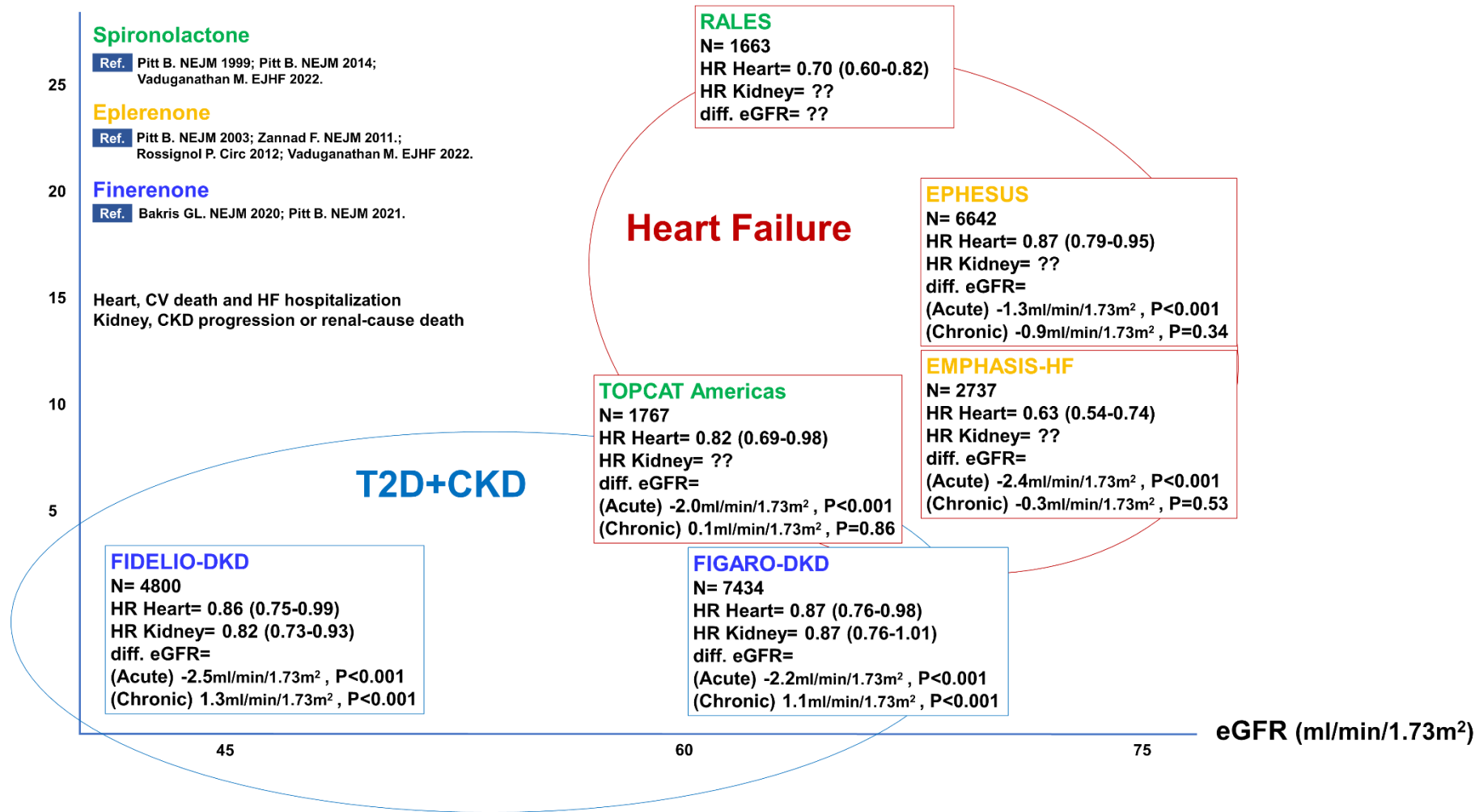
FIDELIO-DKD	4800 patients with CKD and T2D	Finerenone, 10–20 mg/day	UACR 30-300 mg/g and eGFR 25-60 ml/min/1.73m ² or UACR 300-5000 mg/g and eGFR 25-75 ml/min/1.73m ² ; serum K ⁺ <4.8mmol/L; ACE-inhibitor or ARB at the maximum dose	44	852	NA	3.2	111	31	ESKD (i.e., chronic dialysis or kidney transplantation), an eGFR of <15ml/min/1.73m ² or >40% decline in eGFR within 4 weeks or renal-cause death	CV death or nonfatal MI, stroke and HF hospitalization
										HR= 0.82 (0.75 to 0.93)	HR= 0.86 (0.75 to 0.99)
FIGARO-DKD	7434 patients with CKD and T2D	Finerenone, 10–20 mg/day	UACR 30-300mg/g and eGFR 25-90 ml/min/1.73m ² or UACR 300-5000 mg/g and eGFR >60 ml/min/1.73m ² ; serum K ⁺ <4.8mmol/L; ACE-inhibitor or ARB at the maximum dose	68	308	NA	3.0	91	41	CV death or nonfatal MI, stroke and HF hospitalization	ESKD (i.e., chronic dialysis or kidney transplantation), an eGFR of <15ml/min/1.73m ² or >40% decline in eGFR within 4 weeks or renal-cause death
										HR= 0.87 (0.76 to 0.98)	HR= 0.87 (0.76 to 1.01)

Figure 1. The Effects of Spironolactone, Eplerenone and Finerenone on Cardio-Kidney Outcomes in Major Clinical Trials

The efficacy of spironolactone and eplerenone has predominantly been investigated in heart failure trials, whereas finerenone efficacy has been studied in the context of diabetes and chronic kidney disease. These investigations encompassed populations with varying levels of mortality risk or renal function.

1 **Figure 1. The Effects of Spironolactone, Eplerenone and Finerenone on Cardio-Kidney Outcomes in Major Clinical Trials**

**Mortality risk
(per 100 patient-year)**



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3