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Review Article

Finerenone May Be Added as Standard Care for Patients with Heart Failure and Mildly Reduced or Preserved Ejection Fraction

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Abstract

The non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone was shown in 2 trials (FIDELIO-DKD and FIAGARO-DKD) to significantly decrease cardiovascular (CV) events and slow progression of kidney function in patients with type 2 diabetes and chronic kidney diseases (CKD). The only medications recommended as first line therapy for patients with heart failure and mildly reduced ejection fraction and preserved ejection fraction (HFmrEF/HFpEF) are the sodium-glucose co-transporters type 2 inhibitors (SGLT-2i). Recently, finerenone was evaluated in patients with HFmr/HFpEF in a trial called the FINEARTS-HF. The latter was a randomized, double-blind, placebo-controlled international trial with the primary composite outcome consisting of first and recurrent (i.e. total) worsening heart failure (HF) events and death from CV causes. Patients included were 40 years or older with left ventricular ejection fraction (LVEF) ≥40%, New York Heart Association (NYHA) functional status, mostly II and III, elevated natriuretic peptides, and evidence of structural heart disease. After a median follow-up of 32 months, 14.9 and 17.7 primary outcome events per 100 patient-year occurred in the finerenone and placebo group, respectively, rate ratio (RR) 0.84 (95% CI, 0.74 to 0.95; P 0.007). The significant reduction in the primary outcome was mainly driven by the reduction in total worsening HF events (RR 0.82; 95% CI 0.71 to 0.94), whereas reduction in CV death did not reach statistical significance RR 0.93 (95% CI, 0.78 to 1.11). Results of secondary outcomes of the FINEART-HF trial showed a trend towards reduction in all-cause death [hazard ratio (HR) 0.93, 95% CI, 0.83 to 1.06)] and worsening of kidney composite outcome HR 1.33 (95% CI, 0.94 to 1.89). There was no heterogeneity in results in different patient subgroups classified by diabetes status, baseline EF, and use of sodium-glucose co-transporters type 2 inhibitors (SGLT-2is). The most common adverse effects of finerenone were hyperkalemia (serum potassium > 5.5 mmol/L) occurring in 14.3% and 6.9% of patients in the finerenone and placebo, groups, respectively. In summary, finerenone is a useful agent for treatment of HFmr/HFpEF that can be added to SGLT2i. Its main limitations are hyperkalemia and possibly worsening kidney function in patients with (HFmr/HFpEF). Long-term studies are required to evaluate the safety of finerenone in patients with (HFmr/HFpEF).

Kew Words: finerenone; heart failure; cardiovascular events; kidney; finearts-hf; hyperkalemia

Introduction

Finerenone (Kerendia) is a non-steroidal MRA approved in patients with type 2 diabetes and CKD to decrease risk of CV events and progression of kidney disease [1]. This approval was based on results of 2 complementary randomized trials, the FIDELIO-DKD and FIGARO-DKD [2,3]. Pooled analysis of the latter 2 trials showed that finerenone significantly decreased the composite CV outcome (time to CV death, non-fatal myocardial infarction and stroke or heart failure hospitalization) by 14% compared with placebo [HR 0.86 (95% CI, 0.78-0.95; P=0.0018)] and the composite kidney outcome (time to kidney failure, sustained ≥57% decrease in eGFR from baseline, and renal death by 23% [HR 0.77 (95% CI, 0.67 to 0.88)] [4]. More recently, finerenone was evaluated for treatment of patients with HFmrEF/HFpEF irrespective of presence of diabetes [5]. In fact, apart from SGLT2is, there are no available drugs that reduce CV events in subjects with HFmrEF/HFpEF [6]. The FINEARTS-HF study was designed to study the efficacy of finerenone on decreasing CV events in patients with HFmrEF/HFpEF defined as having EF > 40% [5]. The main purpose of this review is to provide an appraisal of finerenone as new therapy for HFmrEF/HFpEF.

Study population of FINEARTS-HF

Patients recruited in the FINEARTS-HF trial (n=6,001, mean age 72 years, 45% women) had symptomatic HF with LVEF ≥ 40% (mean 52%), elevated levels of natriuretic peptides, and evidence of structural heart disease [5,7]. Majority of subjects (69%) had NYHA functional class II and 30% had class II [5]. Patients were randomized in a 1:1 ratio to finerenone at maximum dose of 20 mg po once daily if estimated glomerular filtration rate (eGFR) is ≤60 ml/min/1.73 m^2 or 40 mg once daily if eGFR is > 60 ml/min/1.73 m^2 versus matching placebo [5]. Participants were enrolled at different times

from the diagnosis of HF. Thus, 20.3% were enrolled during or within 7 days, 33.8% were enrolled between 7 days and 3 months, and the remaining 30.3% were enrolled more than 3 months from a worsening HF event [8].

Results of the Finearts-Hf Trial

Primary outcome

The primary outcome of the FINEARTS-HF trial was a composite of total (i.e first and recurrent) worsening HF events (defined as HF requiring admissionto the hospital or urgent care) and death from CV causes. After a median follow-up of 32 months, the number of events per 100 patient-year was 14.9 and 17.7 in the finerenone and placebo groups, respectively RR 0.84 (95% CI, 074 to 0.95; P=0.007) [5]. When analyzed individually, RR for total worsening HF was 0.82 (95% 071 to 0.94; P=0.006), but reduction in death from CV causes did not reach statistical significance with a HR of 0.93 (95% 0.78 to 1.11) [5]. Amelioration in the primary outcome occurred rapidly with the first statistical difference from placebo was observed after 28 days (RR 0.62, 95% CI, 0.40 to 0.97; P=0.037) (9). Interestingly, Desai et al [8] found that risk reductions for the primary outcome tended to be greater among the group of patients enrolled during or within 7 days of worsening HF events (risk ratio 0.74, 95% CI, 0.57to 0.95), then decreased slightly in patients enrolled from 7 days to 3 months from the worsening HF event (risk ratio 0.79; 95% CI, 0.64 to 0.97) to finally disappear in patents enrolled more than 3 months from the worsening HF event (risk ratio 0.99, 95% CI, 0.81 to 1.21) [8].

Secondary outcomes

Finerenone had variable effects on secondary outcomes in the FINEARTS-HF trial. There was mild but significant effect in HF symptoms as evaluated by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score, difference from placebo being 1.6 (95% CI, 0.8 to 1.15, P<0.001) [5]. Meanwhile, finerenone had no effect on the NYHA functional class. Reduction in frequency of death from any cause with finerenone, similar to CV death, did not reach statistical significance (HR 0.93, 95% CI, 0.83 to 1.89) [5]. Effects of finerenone on the secondary outcome of kidney outcomes are discussed below.

Effects of finerenone on kidney outcomes in patients with HFmrEF/HFpEF

In the FINEARTS-HF trial, one secondary outcome was a kidney composite of a sustained decrease in the eGFR of ≥50%, a sustained decline in the eGFR to < 15 ml/min/1.73 m^2, or the initiation of long-term dialysis or kidney transplantation [5]. The latter outcome occurred in 2.5% (n=75) and 1.8% (n=55) of patients receiving finerenone and placebo, respectively, HR 1.33 (95% CI, 0.94 to 1.89) [5]. This finding seems paradoxical given the clear kidney benefits previously documented with finerenone in patients with type 2 diabetes and CKD in the FIDELIO-DKD and FIGARO-DKD mentioned earlier [2,3]. There are several possibilities to explain this paradox. First, patients enrolled in the FINEARTS-HF trial had low risk of progression of kidney disease and therefore the number of kidney events was limited and results were prone for the play of chance. Second, the duration of follow-up was relatively short and kidney function might improve with finerenone after longer time. In fact, in the FIDELIO-CKD trial (mean baseline eGFR 44 ml/min/1.73 m^2), patients randomized to finerenone had decreased eGFR compared with placebo up to 20 months of follow-up but the decline in eGFR values in the finerenone group was slower than placebo thereafter [2]. Third, it is possible that there may be a true deleterious effect of finerenone on kidney function as reflected by reduction in eGFR in patients with HFmrEF/HFpEF [10]. Indeed, this finding was also shown with the 2 steroidal MRAs, spironolactone and eplerenone, in a recent meta-analysis [11]. Despite worsening the eGFR slope, finerenone use was associated with 30% reduction (95% CI, 25% to 34%) in urinary albumin excretion cpmpared with placebo [10]. Interestingly, in a separate analysis of the FINEARTS-HF data, the composite kidney outcome was in favor of finerenone in the subgroup of patients with EF ≥ 60% (HR 0.37 (0.15 to 0.87), whereas patients with EF of <50% or 50 to <60% had worse kidney outcome with finerenone. [12]. The latter observation suggests that possible kidney worsening effects of finerenone start to be evident at lower levels of EF.

Efficacy of finerenone in patient subgroups

The primary outcome results of the FINEARTS-HF were similar in different patient subgroups classified by age, gender, baseline LVEF and kidney function and diabetes status [5]. Approximately 40% of patients in FINEARTS-HF had type 2 diabetes and reduction in the primary outcome was very close in patients with and without type 2 diabetes RR 0.83 and 0.85, respectively [5].

SGLT2 inhibitors

The 2 SGLT2i (empagliflozin and dapagliflozin) are recommended as first line treatment for HF irrespective of ejection fraction based on strong data showing reduction in risk of composite HF hospitalization or CV death [13]. In the FINEARTS-HF trial, 13.6 % (n=817) of patients were treated with a SGLT2i at baseline, mainly dapagliflozin (48.7%, n=406) and empagliflozin (47.2%, n=394) [5,14]. In addition, during follow-up, 980 participants (17.7% and 20.1% in the finerenone and placebo arm, respectively) initiated a SGLT2i [14]. The treatment benefits of finerenone were similar irrespective of concomitant use of SGLT2is. These findings suggest that the combined administration of finerenone and SGLT2i may have additive protective effects against CV events. These observations are also in agreement with a metanalysis by Banerjee et al [15] showing that concomitant use of MRA did not influence the reduction in incidence of the composite of HF hospitalization and CV death. Safety profile of finerenone was not altered with adjunctive therapy with SGLT2 inhibitor [14]. Specifically, although one meta-analysis suggested that SGLT2 inhibitors could attenuate MRA-induced mild hyperkalemia, in FINEARTS-HF trial, the increase in serum potassium levels was 0.19 mmol/L whether patients were receiving or not SGLT2i [14,15].

Pooled analysis of kidney and cardiac trials of finerenone

In a pre-specified analysis called FINE-HEART, Vaduganathan et al [16] pooled results of the three major randomized trials of finerenone in patients with type 2 diabetes and CKD (The FIGARO-DKD and FIDALIO-DKD) and in those with HF-mp/pRF (FINEARTS-HF). The 3 trials included 18,991 patients (mean age 67 years-old, 35% women). The primary outcome of the pooled trials was CV death. After a median follow-up of 2.9 years, CV deaths occurred in 4.4% and 5.0% with finerenone and placebo, respectively. This reduction in CV death did not reach statistical significance; HR 0.89 (95% 0.78 to 1.01; P=0.076) [16]. However, finerenone significantly decreased the risk of CV death when "undetermined" death was added to CV death which occurred in 6.6% and 7.4% with finerenone and placebo, respectively; HR 0.88 (95% CI, 0.79 to 0.98; P=0.025) [16]. Finerenone significantly decreased risk of several important secondary outcomes such as death from any cause (HR 0.91; 95% CI, 0.84 to 0.99; P=0.027), HF hospitalization (HR 0.83, 95% CI, 0.75 to 0.92; P <0.001), atrial fibrillation HR 0.83; 95% CI, 0.71 to 0.97; P=0.019) and kidney composite outcome (HR 0.80, 95% CI 0.72 to 0.90; P<0.001) [16]. Yet, this reduction in kidney composite was driven by data from the 2 kidney trials, whereas in the FINEARTS-HF trial, as mentioned earlier, there was a trend towards worsening the kidney composite with finerenone (HR 1.30 95% CI, 0.92 to 1.84) [16]. Taken together, results of this pooled analysis suggests that finerenone may decrease CV events and mortality in a wide spectrum of patient disease including type 2 diabetes with CKD and HFmrEF/HFpEF with or without diabetes.

Safety of finerenone in patients with HFpEF

Hyperkalemia with serum potassium (k) > 6 mmol/L occurred in 3.0% and 1.4% in patients randomized to finerenone and placebo, respectively [5]. Proportions of patients with serum K > 5.5 mmol/L were 14.6% and 7.1% with finerenone and placebo, respectively [5]. Conversely, hypokalemia with serum K < 3.5 mmol/L occurred in 5% in patients receiving finerenone versus 10.3% among patients receiving placebo [5]. Elevation of serum

creatinine ≥3.0 mg/dl was reported in 2.6% and 1.5% with finerenone and placebo, respectively [5]. Frequency of acute kidney injury was slighter higher with finerenone 3.7% versus placebo 2.1% in the whole study population but was more than double in the subgroup of patients with baseline eGFR < 45 ml/min/1.73 m^2, being 8.4% and 3.7% with finerenone and placebo, respectively [10]. Being an aldosterone antagonist, finerenore lowered systolic blood pressure (SBP) by -3.4 mmHg (95% CI, -2.6 to -4.2) versus placebo at 6 months [5]. Thus, reduction in SBP < 100 mmHg was more common with finerenone and recorded in 19% of patients versus 12.7% with placebo [5].

Limitations of finerenone as treatment for HF-mrEF/pEF

While the FINEARTS-HF was multinational, generalizability of its results may be limited since less than 2% were Blacks and proportion of Hispanics in the study was not mentioned [5]. Hyperkalemia was the main safety issue associated with finerenone use with approximately 2-fold higher rates of hyperkalemia when compared to placebo [5]. In real life, incidence of finerenone-induced hyperkalemia is likely to be even higher because patients with serum K > 5 mol/L and eGFR < 25 ml/min/1.73 m^2 were excluded from the FINEARTS-HF trial [5]. In addition, as stated above, the trend towards worsening kidney outcomes with finerenone in patients with HFmEF/HFrEF is concerning and requires further studies. Excessive reduction in SBP was more common with finerenone than placebo despite the exclusion of subjects with SBP < 90 mmHg from the trial. Finally, finerenone is a pricy drug. The cost of monthly supply of 10 mg/d in the USA ranges between $ 648 and $ 695 [17].

Clinical implications of the FINEARTS-HF trial

Results of the FINEARTS-HF imply that finerenone should be considered as first line therapy to patients with HFmr/pEF like SGLT2 inhibitors. Available data suggest that clinical benefits of finerenone in patients HF-mr/pEF are not attenuated in presence of concomitant SGLT2 inhibitors. Therefore, until further data become available, finerenone may be added to SGLT2 inhibitors. Regarding the timing of its use, finerenone should be started as early as possible up 3 months from worsening HF to get the maximum clinical benefit as suggested by the analysis of Desai et al [8].

Conclusions and future needs

No doubt, finerenone is a useful addition to the management of HFmrEF/HFpEF. In such patients, finerenone significantly decreased total worsening HF events by 16%, whereas the 7% reduction in death from CV causes and death from any cause did not reach statistical significance. Results were similar in subgroups of patients classified by age, gender, diabetes status, baseline EF, and SGLT2 inhibitors use. There was a clear tendency towards greater clinical benefit if finerenone was started within 3 months from the worsening heart failure event. Meanwhile, there was a trend toward worsening kidney function with finerenone. Hyperkalemia was the most common adverse effect of finerenone. Further trials are needed to study the long-term kidney effects of finerenone in subjects with HFmrEF/HFpEF. In addition, to confirm the potential additive beneficial CV effects of finerenone with SGLT2i, randomized trials are required to compare SGLT2i + finerenone with SGLT2i + placebo.

Conflict of interest

The author has no conflict of interest to declare.

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