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REVIEW

Research Progress in Finerenone in Cardiovascular Diseases

Sun Xue[1], Dong Yanghong[1], Gu Jiaxin[1], Liu Wenxiu[2] and Liu Yue[2]

[1]*Harbin Medical University, Harbin 150001, Heilongjiang, China*
[2]*Department of Cardiology, First Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang, China*

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Abstract

Mineralocorticoid receptor antagonists (MRA) have significant therapeutic effects on heart failure, hypertension, chronic kidney disease and primary aldosteronism. However, steroid MRA can cause hyperkalemia, deterioration of renal insufficiency, menstrual disorder and male breast development, and consequently has found limited clinical applications. In recent years, basic and clinical studies have confirmed that finerenone is a new non-steroidal MRA with high receptor affinity and selectivity, which can decrease adverse effects such as hyperkalemia and exert powerful cardioprotective effects. Herein, the structure, function, pharmacological mechanism and adverse effects of finerenone are summarized, and its cardiovascular protective effects and clinical applications are described in detail, to aid in understanding of the roles of finerenone in treating cardiovascular diseases and to explore future directions.

Keywords: finerenone; non-steroidal MRA; cardiovascular disease; cardioprotection

Introduction

With the aging of population and the acceleration of urbanization, lifestyles have changed dramatically: unhealthful lifestyles have become increasingly prominent, the effects of cardiovascular risk factors on public health have become more pronounced, and the incidence of cardiovascular disease (CVD) continues to increase. Moreover, CVD is the leading cause of death due to illness worldwide [1, 2] and is the primary cause of death due to illness among urban and rural residents in China (44.26% and 46.74%, respectively) [3]. Consequently, the burden of CVD on residents and social economy has become a major public health problem.

The mineralocorticoid receptor (MR) is a steroid hormone receptor that is expressed in a variety of tissues and organs, including the heart, and has physiological functions such as maintaining water balance and ion balance in the body. Excessive activation of MR can lead to myocardial fibrosis, myocardial hypertrophy, vascular smooth muscle cell proliferation, inflammatory responses, increased oxidative stress, and ultimately ventricular remodeling, heart failure (HF) and malignant arrhythmias [4]. MR antagonists (MRAs) are drugs increasingly being demonstrated to have benefits in CVD, such as by decreasing morbidity and mortality in patients with HF with decreased ejection fraction

Correspondence: **Liu Wenxiu and Liu Yue**, Department of Cardiology, First Affiliated Hospital of Harbin Medical University, No. 23 Youzheng Street, Nangang District, Harbin 150001, China, Tel.: +86045185555723, Fax: +86 451 86620586, E-mail: hitlqn@126.com; liuyue198002@163.com

(HFrEF) and treating refractory hypertension [5]. Steroidal MRAs are commonly used in clinical practice, but their applications are limited by their adverse effects [5, 6]. In recent years, non-steroidal MRAs (such as finerenone) have received increasing attention because of their high receptor affinity and selectivity, thus avoiding adverse effects such as hyperkalemia while exerting potent cardioprotective effects. This article reviews the structure, function and pharmacological mechanisms of non-steroidal MRAs; discusses their cardiovascular protective effects and clinical applications in detail; and describes potential future research directions.

Mineralocorticoid Receptor and its Antagonists

The MR, whose cDNA was first cloned in 1987 [7], is a steroid hormone receptor expressed in many cardiac cells, including cardiomyocytes, vascular smooth muscle cells and fibroblasts [8]. Physiologically, blood pressure is controlled by regulation of sodium secretion through kidneys, and blood potassium is controlled by regulation of potassium excretion and permeability after MR activation. Under pathological conditions, MR hyperactivity modulation is involved in cell proliferation, fibrosis, vascular injury and tissue inflammation [6].

MRAs include steroid MRAs (e.g., spironolactone and eplerenone) and non-steroid MRAs (e.g., finerenone). Spironolactone was the first MRA used clinically as a potassium-sparing diuretic to treat edema, essential hypertension and primary aldosteronism, in 1960 [9]. The RALES study has indicated that spironolactone decreases mortality among patients with severe HF [10]. However, the steroid structure of spironolactone allows it to bind androgen and progesterone receptors in a non-selective manner, thus resulting in many adverse effects associated with hormone imbalance, such as male breast development and impotence, and female menstrual disorder and breast tenderness [6, 11], and limiting its clinical applications. In 1987, eplerenone appeared as a second generation steroid MRA with higher MR selectivity than spironolactone; this drug is used for the treatment of essential hypertension and HF [9]. However, eplerenone binds MR with only 1/40 the affinity of spironolactone [12] and poses a high risk of hyperkalemia [5]. Therefore, non-steroidal MRAs have become a new clinical and basic research hotspot, because of their high selectivity and affinity. We searched and summarized the relevant characteristics of current non-steroidal MRAs (Table 1) [13–15]. Among them,

Table 1 Comparison of Four Non-Steroidal MRAs.

	Finerenone	Esaxerenone	Apararenone	Ocedurenone
Drug code	BAY 94-8862	CS-3150	MT-3995	KBP-5074
Half-life time	2–3 h	20–30 h	275–285 h (Parent drug) 1126–1250 h (Active metabolite 1118174)	–60 h
Affinity (IC_{50} values, nM)				
MR IC_{50}	18	3.7	280	2.7
GR IC_{50}	>10,000	>5000	-	2410
AR IC_{50}	>10,000	>5000	-	No activity
PR IC_{50}	>10,000	>5000	-	122
Clinical application				
Blood pressure	Modest	Effective	No date	Effective
Cardiovascular disease	Effective	Effective	No date	Effective
Kidney disease	Effective	Effective	Effective	Effective
Side effects				
Renal-related	Not often	Not often	Not often	Often
SSHR-related	None	None	No date	No date

finerenone (BAY 94-8862), the first non-steroidal MRA identified by high-throughput screening, in 2012 [16], has higher MR selectivity and affinity than steroidal MRAs [17]. Finerenone has cardiorenal protective effects [18, 19] and has been used in patients with type 2 diabetes mellitus (T2DM) with chronic kidney disease (CKD) [20].

MRAs: mineralocorticoid receptor antagonists, MR: mineralocorticoid receptor, GR: glucocorticoid receptor, AR: androgen receptor, PR: progesterone receptor, SSHR: sex steroid hormone receptor, IC50: semi-inhibitory concentration (the lower the IC50 value of MR, the stronger the inhibitory effect of the MRA on MR; the higher the IC50 value of AR/GR/PR, the weaker the affinity of the MRA for AR/GR/PR, thus reflecting the stronger the selectivity of the MRA for MR).

Pharmacological Mechanism and Adverse Effects of Finerenone

Pharmacological Mechanism of Finerenone

MR is distributed primarily in the cytoplasm; after ligand binding, ligand-specific conformational changes occur, and FKBP51 of the MR multi-partner complex HSP90-FKBP51 is replaced by FKBP52, which in turn mediates nuclear translocation of the MR complex [21]. After entering the nucleus, the MR complex dissociates, and monomers dimerize at the hormone response element [22] and recruit co-regulators that promote gene expression [23].

Finerenone is completely absorbed in the gastrointestinal tract after oral administration and has a short half-life of only 2–3 hours. It is metabolized primarily into inactive metabolites by the cytochrome P450 oxidase family (CYP3A4); 80% is excreted in urine and the remainder is excreted in feces [24].

Finerenone has a high affinity for MR, and little cross-reactivity with other steroid and non-steroid receptors and ion channels [24]. It has higher selectivity than spironolactone and greater efficacy than eplerenone [17]. Unlike steroid MRAs, which directly bind the ligand domain of MR and competitively inhibit MR, the finerenone side chain binds the helical 12 domain of MR with the assistance of cofactors, thus resulting in conformational changes inhibiting the translocation of receptors to the nucleus and downstream signal transduction [25]. Finerenone is evenly distributed in the heart and kidneys, in marked contrast to steroid MRAs, which are distributed primarily in the kidneys [26]; consequently, finerenone may provide greater cardiovascular protection at relatively lower doses, and have less of an influence on sodium and potassium balance. Compared with steroid MRAs, non-steroid MRAs aid in decreasing hyperkalemia and aldosterone escape. Aldosterone escape occurs primarily because of the increase in blood potassium concentration [4]; however, finerenone has little effect on sodium and potassium channels, thus resulting in a low incidence of hyperkalemia and consequently decreasing aldosterone escape [26].

Finerenone not only directly inhibits the MR signaling cascade but also prevents the recruitment of transcription cofactors involved in downstream hypertrophy, pro-inflammatory and pro-fibrosis effects [5] – including at least 22 cofactors associated with MR, such as the cofactor SRC1, activation signal cointegration factor 2 and peroxisome proliferator-activated receptor γ cofactor 1-α (PGC-1α) – thus decreasing the expression of pro-inflammatory and pro-fibrosis genes [4]. Finerenone and steroid MRA have opposite activation effects on cofactor recruitment, and can passively antagonize gene expression without aldosterone [4], in an important mechanism of anti-fibrosis and anti-ventricular remodeling.

Adverse Effects of Finerenone

Although finerenone has fewer adverse effects than steroidal MRAs, it is associated with hyperkalemia, hyponatremia, hypotension, pruritus, decreased glomerular filtration rate and decreased hemoglobin. In patients with renal insufficiency, dose adjustment of finerenone is required: the recommended dosages are 20 mg once daily when the estimated glomerular filtration rate (eGFR) is ≥60 mL/min/1.73 m^2 and 10 mg once daily when the eGFR is 25–60 mL/min/1.73 m^2, whereas finerenone is not recommended when the eGFR is <25 mL/min/1.73 m^2. In addition, patients taking finerenone require continuous monitoring of renal function, and treatment should be discontinued if they progress to end-stage renal disease (eGFR <15 mL/min/1.73 m^2). In patients with liver

cirrhosis, exposure to finerenone is not affected by mild hepatic impairment (Child Pugh A): whereas the AUC increases by 38%, the Cmax is not affected by moderate hepatic impairment (Child Pugh B); however, no data are available for severe hepatic impairment (Child Pugh C), because finerenone is not recommended in this scenario [27].

Cardiovascular Protective Effects and Mechanisms of Finerenone

Overactivation of the MR increases inflammation and fibrosis in the kidneys in T2D [28, 29], thus leading to CKD progression (decreased glomerular filtration rate and increased albuminuria) [30–33]. MR blockade decreases albuminuria and enhances the preservation of renal function at the renal level [31, 34–36]. Finerenone blocks the recruitment of transcriptional coactivators involved in the expression of pro-inflammatory and profibrotic mediators by selectively binding MR [37–39]. Finerenone has been found to decrease renal failure and disease progression in diabetic nephropathy [18, 40] and is currently approved for the treatment of CKD (stages 3 and 4 with albuminuria) associated with T2D. The benefits of finerenone are not limited to slowing the progression of kidney disease: finerenone has also been shown to prevent cardiovascular complications in this population. The known relevant effects and mechanisms are summarized below.

Improving Left Ventricular Function

In a rat model of chronic HF caused by hypertension and acute myocardial infarction (MI), finerenone has been found to be more effective than eplerenone in improving left ventricular systolic and diastolic function, and decreasing plasma pro-BNP [26]. Bonnard and others have shown that finerenone prevents cardiac systolic and diastolic dysfunction caused by CKD in mice [41]. Similarly, finerenone ameliorates the left ventricular diastolic dysfunction caused by ovariectomy in mice, without affecting the ejection fraction, and effectively delays HF progression [42]. Simultaneously, finerenone plays a protective role against HF caused by MI, through maintaining the coronary artery reserve, and improving coronary endothelial function and left ventricular dysfunction after MI [43].

Inhibiting Fibrosis

In MI mice, finerenone has been found to decrease left ventricular fibrosis and improve myocardial contractility and compliance by inhibiting neutrophil gelatinase-associated lipocalin (NGAL), thus increasing stroke output. Further studies have found that these effects are associated with inactivation of the NF-κB signaling pathway by finerenone through inhibition of NGAL and collagen I production [44]. Simultaneously, another study on MI in mice has suggested that finerenone effectively prevents cardiac fibrosis in MI mice and improves the corresponding parameters such as global longitudinal peak strain of Speckle tracking echocardiography; moreover, the effects of finerenone may be associated with the inhibition of tenascin-X gene expression mediated by MR cofactor binding [42]. In addition, studies by Kolkhof et al. and others have shown that finerenone decreases the expression of osteopontin, a marker of pro-inflammatory and pro-fibrosis, in a dose-dependent manner [26].

Decreasing Blood Pressure

Many basic experimental studies have shown that finerenone regulates blood pressure [26, 45, 46]. Kolkhof et al. have found that the antihypertensive effect of finerenone is dose-dependent. Finerenone decreases systolic blood pressure (SBP) at 10 mg/kg, but has no effect at 1 mg/kg [26]. In rats without diabetes mellitus (DM) with organ damage induced by hypertension, the mean SBP is significantly decreased by a single treatment with finerenone (1 mg/kg and 3 mg/kg) or a combination of low-dose finerenone and empagliflozin [46], which was associated with the different experimental models. Pieronne-Deperrois and others have found that finerenone decreases blood pressure in ovariectomized mice by improving endothelial dysfunction [45].

Decreasing Myocardial Hypertrophy

Cardiac hypertrophy is a common cardiac complication of hypertension. In a mouse model of myocardial hypertrophy induced by pressure loading, treatment with finerenone, compared with placebo and eplerenone, has been found to result in echocardiography findings indicating significant decreases in left ventricular wall thickening and the

left ventricular mass increase (finerenone: 28.4 ± 3.7 mg; eplerenone: 38.4 ± 4.3 mg; placebo: 39.3 ± 3.1 mg; $P < 0.05$); these findings may be associated with finerenone's ability to induce different cardiac gene expression profiles [47].

Clinical Studies and Guideline Recommendations in CVD

The RALES study, EPHESUS study and EPHESUS-HF study have provided strong evidence of the application of the first-generation steroid MRA spironolactone and the second-generation steroid MRA eplerenone in patients with HFrEF [10, 48, 49]. Domestic and foreign guidelines for HF treatment all include a class I recommendation of MRA for the treatment of patients with New York Heart Association (NYHA) II–IV HFrEF [50, 51].

The mineralocorticoid receptor antagonistic tolerance study (ARTS, a phase II clinical study), the ARTS-HF study (a phase IIb clinical study) and several meta-analyses have shown that the cardiovascular benefits of finerenone are not less than those of steroid MRAs [17, 52], and that finerenone significantly decreases adverse reactions. Simultaneously, these two clinical studies and related analyses have demonstrated the benefit of finerenone in chronic HFrEF and acute HF exacerbation. The phase III clinical studies FIDELIO-DKD and FIGARO-DKD, examining the decrease in renal failure and disease progression in patients with DM with nephropathy treated with finerenone, have shown that finerenone decreases complex cardiovascular outcomes in patients with T2DM and different degrees of CKD [18, 19]. On this basis, the first non-steroidal MRA approved by the US Food and Drug Administration in 2021 is used primarily to improve the renal and cardiovascular outcomes of patients with T2DM and CKD [20].

ARTS

The ARTS phase II clinical study, the first randomized controlled study of finerenone, compared the efficacy and adverse effects of spironolactone and finerenone on HF in patients with mild to moderate CKD and chronic HFrEF (NYHA II–III, LVEF ≤40%). The results have indicated that finerenone not only has the same effect as spironolactone in decreasing ventricular remodeling (25 or 50 mg Qd) at a low dose (5 and 10 mg Qd), but also is associated with lower risk of hyperkalemia and renal function deterioration [52]. Thus, finerenone aids in improving cardiovascular prognosis and safety in patients with HFrEF with CKD. Moreover, a meta-analysis by Pei et al., comparing finerenone with spironolactone/eplerenone in 1520 patients with chronic heart failure (HFrEF), has found that finerenone dose-dependently decreases the levels of biochemical markers such as NT-pro-BNP and the urinary albumin/creatinine ratio [53].

ARTS-HF

To explore the efficacy of finerenone and eplerenone in the treatment of patients with HFrEF with T2DM and/or CKD, 1066 cases of patients with worsening HFrEF requiring hospitalization and receiving intravenous diuretics, as well as T2DM and/or CKD, were included in the ARTS-HF phase IIb clinical study, and were followed up for 9 months. Compared with eplerenone, except in the low-dose finerenone group (2.5–5 mg), the incidence of the compound clinical endpoint in patients treated with finerenone was low, and the compound outcome of patients in the 10–20 mg finerenone group showed the largest decline. The proportion of NT-proBNP in patients decreased by more than 30% with respect to baseline (30.9%–38.8%, depending on finerenone dose) [17]. However, further experiments are needed to evaluate the cardiovascular benefits of finerenone without complications.

FIDELIO-DKD

In a phase III clinical study of finerenone in decreasing kidney failure and disease progression in diabetic kidney disease (FIDELIO-DKD), patients with CKD and T2DM complicated with high renal risk were followed up for 2.6 years. Compared with the placebo, finerenone significantly decreased the incidence of the complex cardiovascular outcome, cardiovascular-associated deaths, and the hospitalization rate for HF and non-fatal MI [18]. This study provided the first demonstration that non-steroidal MRA treatment and ACEI/ARB dual renin-angiotensin-aldosterone system blockade is beneficial for complex cardiovascular outcomes, and research

on MRA supplementation in the non-HF population is insufficient [54]. Moreover, regardless of the baseline control of DM, use of other hypoglycemic drugs in combination and history of CVD, finerenone has shown benefits in compound cardiovascular outcomes [54–58] and therefore can be used for primary and secondary prevention of CVD.

The FIDELIO-DKD study has indicated that finerenone has antihypertensive effects [18], which are significant for clinical patients with SBP >148 mmHg at baseline [59]. The second phase analysis of the data from the FIDELIO-DKD study has indicated that, compared with placebo, finerenone significantly decreases the risk of new atrial fibrillation (AF) or atrial flutter (Af), regardless of baseline AF or Af history [60]. The results of a recent meta-analysis also support the benefits of finerenone on the incidence of new AF or Af [61]. However, Yang's recent meta-analysis has yielded different findings: no significant difference was observed in the risk of new AF between patients in the finerenone group and the placebo group (RR: 0.62; 95%CI: 0.19–2.00; P = 0.42) [62]. This difference may be partly due to the different follow-up periods and patient groups in the randomized controlled studies [18, 19, 63, 64].

FIGARO-DKD

The phase III clinical study on finerenone in decreasing cardiovascular mortality and mortality in diabetic kidney disease (FIGARO-DKD) included a subgroup of patients with T2DM with CKD with a high risk of central blood vessels. In that study, compared with the placebo, finerenone significantly decreased the complex cardiovascular outcome incidence (death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization due to HF) [19]. According to the post-analysis results of Filippatos, significantly lower incidence of new HF and of all HF outcomes was observed in the finerenone group than the placebo group; the risk of cardiovascular death or hospitalization caused by the first HF decreased by 18%, the risk of hospitalization caused by the first HF decreased by 29%, and the total hospitalization risk caused by HF decreased by 30%. Similarly, the findings were not affected by the presence or absence of HF history [65]. This study provided the first confirmation that finerenone delays HF progression in patients with T2DM with CKD.

The FIGARO-DKD study also indicated that the SBP in the finerenone group and placebo group decreased by 3.5 mmHg in the 4th month and 2.6 mmHg at the 24th month with respect to baseline [19]; however, the mechanism through which finerenone regulates blood pressure is unknown.

FIDELITY Analysis

Because FIDELIO-DKD and FIGARO-DKD had similar population inclusion, study design and evaluation of results, Agarwal et al. conducted a combined FIDELIO-DKD and FIGARO-DKD study scheme analysis (FIDELITY) [41]. Finerenone was found to be effective and safe in patients with T2DM with CKD, and to have protective effects on the heart and kidneys [66] regardless of baseline conditions such as history of coronary atherosclerotic CVD [67]; use of drugs such as GLP-1RA [68] and SGLT2i [66]; and previous blood glucose levels [69].

FIDELITY also showed that after 4 months of treatment, the SBP of patients in the finerenone group decreased by 3.2 mmHg [65]. Moreover, finerenone decreased the risk of new hypertension [62]. ARTS-DN has indicated that 10 mg and 20 mg doses of finerenone significantly decrease the risk of occult hypertension and nocturnal hypertension [70].

Guideline Recommendations

The U.K. National Institute for Health and Care Excellence recommends finerenone as an option for the treatment of stage 3 and 4 CKD (with proteinuria) with T2DM. The addition of finerenone is recommended for patients who have been taking the maximum tolerated doses of ACEIs/ARBs and SGLT2i and have an eGFR ≥25 mL/min/1.73 m^2 [71].

The 2022 version of the Heart Failure Management Guidelines jointly issued by the American Heart Association, the American College of Cardiology and the American Heart Failure Society recommends MRA with ARNI/ACEI/ARB, β-blockers, and SGLT2i as class IA treatments for patients with HFrEF, to aid in decreasing the risk of cardiovascular death and rehospitalization for HF [51]. However, the antihypertensive effect of spironolactone limits the use of steroidal MRAs in patients with HFrEF without hypertension; the mild regulation of blood

pressure by non-steroidal MRAs also helps solve this problem.

Although no clear guidelines are currently available regarding the use of finerenone for hypertension, a combination of low-dose finerenone and empagliflozin has shown the greatest survival benefit (93%) in a rat model of hypertension-induced organ damage [45]. Therefore, the benefits of combining finerenone with other types of drugs to lower blood pressure in patients with hypertension who must take two, three, or more drugs are worthy of exploration. Moreover, the anti-hypertrophic effect of finerenone [47] suggests that this drug has great potential prospects for decreasing the risk of long-term outcomes, such as progression to hypertensive heart disease in patients with hypertension.

Prospectives

This article summarized the pharmacological effects, protective effects and mechanisms of finerenone in CVD (Figure 1), and the current clinical studies and guideline recommendations. A large-scale phase III clinical study of finerenone has been conducted in patients with T2DM with CKD, and many preclinical studies have suggested that finerenone has great clinical application potential in the diagnosis and treatment of HF with preserved EF, AF, MI, hypertension and hypertensive heart disease, and combined treatment applications, which may be the focus of future research. The FINEARTS-HF study (NCT04435626) is currently being conducted to explore whether finerenone decreases the risk of HF-associated outcomes and new AF in patients with HF with mid-range EF and HF with preserved EF [72], and is expected to provide strong clinical evidence of the application of finerenone in large-scale HF and atrial fibrillation. The ongoing confidence phase II study (NCT05254002) is studying whether a combination of non-steroidal MRA finerenone and SGLT2i empagliflozin might yield stronger cardiorenal protection than the use of either drug alone

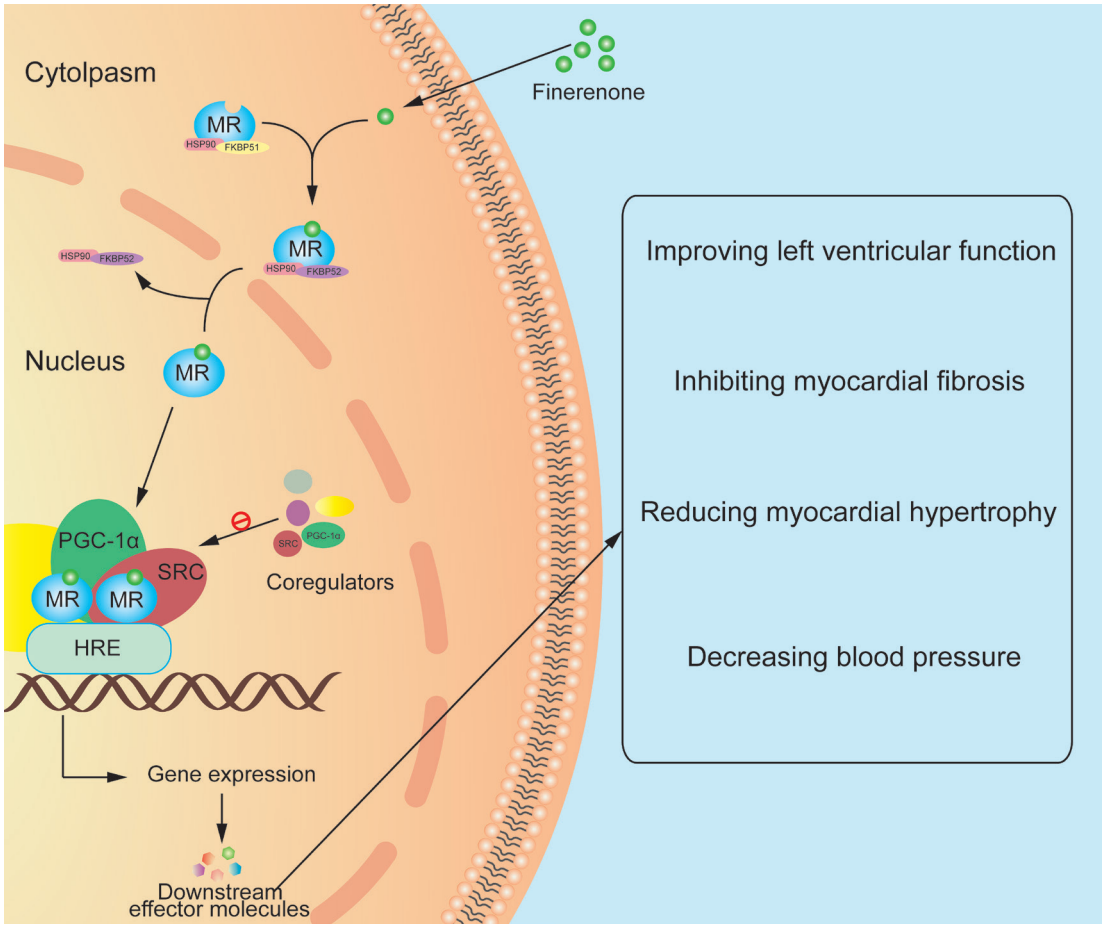

Figure 1 Pharmacological Mechanisms and Effects of Finerenone.

[73]. Simultaneously, the benefits of finerenone on CVD in a wider population, such as patients without CKD and/or DM, are worthy of exploration.

Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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