# Effects of Finerenone’s Mechanism of Action

Subjects: Cardiac & Cardiovascular Systems

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Finerenone is a novel, selective, nonsteroidal MRA that is efficacious in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Steroidal MR antagonists (MRAs) are included in treatment paradigms for resistant hypertension and heart failure with reduced ejection fraction, while the nonsteroidal MRA finerenone was shown to reduce renal and cardiovascular outcomes in two large phase III trials (FIDELIO-DKD and FIGARO-DKD) in patients with chronic kidney disease and type 2 diabetes, respectively.

Keywords: finerenone ; hypertrophy ; inflammation ; kidney ; mineralocorticoid receptor ; oxidative stress

## 1. Introduction

The available evidence suggests that finerenone offers cardiorenal protection, as observed in patients with HF and mild-to-moderate CKD (phase II study MinerAlocorticoid Receptor antagonist Tolerability Study (ARTS)) and T2D and CKD (phase III studies FIDELIO/FIGARO; phase II study MinerAlocorticoid Receptor antagonist Tolerability Study in Diabetic Nephropathy (ARTS-DN)) via a combination of different mechanisms determined in preclinical studies. As an MRA, finerenone acts as a natriuretic [1] to prevent sodium and fluid retention in the body and, thus, the development of hypertension [2]. By blocking the MR, finerenone may also inhibit the generation of reactive oxygen species (ROS), which promote oxidative stress in cells of the kidney [3][4], cardiac, and vascular systems, leading to tissue injury. Finerenone also appears to prevent inflammation and fibrosis driven by the MR on inflammatory cells, which further contribute to tissue damage, as well as hypertrophy and tissue remodeling, in the cardiovascular system [5][6][7].

## 2. Sodium Retention

Under normal physiologic conditions in the distal nephron of the kidney, aldosterone promotes sodium reabsorption and water retention, as well as potassium and magnesium excretion via the MR to regulate extracellular volume and blood pressure [2]. MR activation in renal epithelial cells leads to the gene expression of subunits of epithelial sodium channels, the upregulation of serum- and glucocorticoid-regulated kinase 1 (Sgk1), and finally, increased sodium transport in epithelial tissues. In the cell membrane, the turnover of the sodium channels is mediated by the neural precursor cell-expressed developmentally down-regulated 4 ligase (Nedd4-2), a ubiquitin protein ligase. The phosphorylation of Nedd4-2 by Sgk1 prevents the binding of Nedd4-2 to channels, thereby promoting sodium influx [8].

Natriuresis is beneficial in patients with cardiovascular diseases because it can lower blood pressure and reduce the risk of myocardial infarction (MI) and stroke. MRAs are able to inhibit sodium retention, and finerenone has demonstrated dose-dependent natriuretic efficacy in healthy human volunteers [1][9]. Neurohumoral stimulation by the renin–angiotensin–aldosterone system, the sympathetic nervous system, and vasopressin contribute to permanent sodium retention and an associated extracellular volume load in the development of chronic HF and kidney failure, so MR antagonism should inhibit or delay this process [10][11][12]. Indeed, finerenone has been shown to repress increased Sgk1 levels in a murine model of CKD progression in T2D [13].

In addition to effects on volume distribution and pressure due to natriuresis, sodium retention in skin reservoirs is also hypothesized to be a trigger for inflammation [14]. Sodium ions can accumulate in skin reservoirs, a process that increases with age, in addition to the onset of inflammation [14]. The pro-inflammatory activity of immune cells is favored in an environment with readily available sodium while anti-inflammatory capacity is reduced [14]. This suggests that immunity is regulated by sodium availability and, consequently, that reducing local sodium, e.g., via the blockade of the MR, may be a possible remedy for autoimmune and cardiovascular diseases [14]. In support of this hypothesis, higher plasma interleukin (IL)-6 and high-sensitivity C-reactive protein levels were detected in patients undergoing peritoneal dialysis and hemodialysis, which correlated with increased muscle and skin sodium content [15].

## 3. Oxidative Stress—ROS Generation

MR overactivation in preclinical models increases oxidative stress in multiple cell types via increased levels of nicotinamide adenine dinucleotide phosphate oxidase (NOX) [16]. NOX controls the production of superoxide radicals in renal cells and plays a major role in ROS generation in cardiac and vascular tissue [17]. Oxidative stress also activates the nuclear factor kappa B pathway, leading to inflammation and fibrosis [18]. The further induction of MR signaling potentiates pro-inflammatory cytokine levels, resulting in the amplification of inflammation that directly increases fibrosis [19].

### 3.1. Kidney ROS

In the kidneys, MR overactivation increases the availability of ROS by upregulating NOX; superoxide radicals induce malfunction in the renal vasculature and tubules while hydrogen peroxide also causes preglomerular dysfunction [16][20][21]. Increased oxidant damage and reduced nitric oxide (NO) bioavailability are also associated with ischemia in renal ischemia–reperfusion (IR) injury leading to acute kidney injury (AKI) [22]. The genetic deletion of MR in SMCs or the pharmacologic use of finerenone reduces oxidative stress production [3], and the expression of markers of tubular injury in the kidney, kidney injury molecule 1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL), was found to be blocked by finerenone in mice [3] and rats [4] (**Table 1**). Finerenone was also shown to normalize pathophysiologic increases in the oxidative stress markers malondialdehyde and 8-hydroxyguanosine after renal IR injury [4].

**Table 1.** Renal biomarkers modulated by finerenone in preclinical studies and their clinical association.

| Marker | Effect of Finerenone in Preclinical Models | Function/Role | Evidence for Clinical Association |
|---|---|---|---|
| Kidney | | | |
| Fibronectin | ↓ Kidney mRNA expression and protein levels in model of CKD progression in T2D [13] | Glycoprotein in the glomerular mesangial ECM | CKD progression [23] |
| KIM-1 | ↓ Kidney expression in rat model of AKI [22] | Kidney injury molecule-1 (marker of tubule cell injury) | Acute kidney injury [24] |
| MCP-1 (CCL-2) | ↓ Kidney mRNA expression in DOCA-salt model of CKD [25] and in model of CKD progression in T2D [13] | Pro-inflammatory cytokine (regulating monocyte/macrophage recruitment) | CKD/CKD progression [26][27][28][29][30] |
| MMP-2 | ↓ Kidney mRNA expression in DOCA-salt model of CKD [25]<br>↓ Plasma activities in nondiabetic CKD model [31] | ECM homeostasis | CKD/CKD progression [30][32] |
| MMP-9 | ↓ Plasma activities in nondiabetic CKD model [31] | ECM homeostasis | CKD/CKD progression [32][33] |
| NGAL (LCN2) | ↓ Kidney mRNA expression [3][4] | Involved in innate immunity and in response<br>to tubular injury | CKD/CKD progression [34][35] |
| NKD2 | ↓ Kidney expression in mouse models of kidney fibrosis [36] | Pro-fibrotic cytokine | Kidney fibrosis [37] |

| Marker | Effect of Finerenone in Preclinical Models | Function/Role | Evidence for Clinical Association |
|---|---|---|---|
| Kidney | | | |
| OPN (=Spp1) | ↓ Kidney mRNA expression in DOCA-salt models of CKD [25][38] | Pro-inflammatory cytokine involved in chronic inflammation<br>Key cytokine-regulating tissue repair, promoting collagen organization and regulating ECM and myofibroblast interactions | CKD/CKD progression [39] |
| PAI-1 | ↓ Kidney mRNA expression in DOCA-salt model of CKD [25], two models of kidney fibrosis [36] and model of CKD progression in T2D [13] but ↑ mRNA expression in macrophages from kidney tissue in IR injury model [40] | Serine protease inhibitor, which limits fibrinolysis; marker of inflammation and remodeling | CKD progression [41], kidney fibrosis [30] |
| Sgk1 | ↓ Kidney mRNA expression and protein levels in model of CKD progression in T2D [13] | Promotes inflammation and fibrosis | - |
| TGF-β | ↓ Kidney mRNA expression in model of AKI-mediated CKD [4] | Pro-fibrotic cytokine | CKD/CKD progression [30] [42] |
| COL1A1 | ↓ Kidney mRNA expression in model of AKI-mediated CKD [4], a nondiabetic hypertensive cardiorenal disease model [43], and two models of kidney fibrosis [36] | ECM molecule | - |
| E-cadherin | ↑ Protein expression in model of AKI-mediated CKD [4] | Cell adhesion molecule | - |
| Nrf2 | ↑ mRNA expression in model of AKI-mediated CKD [4] | Regulator of antioxidant defense | CKD progression [44] |
| SOD-3 | ↑ Protein expression in model of AKI-mediated CKD [4] | Antioxidant enzyme | SOD-3 is depleted from human CKD kidneys [45] |
| Endothelin-B receptor | Prevents cysteine sulfenic acid modification of ET-B receptor in model of IR-induced AKI [4][22] | Regulator of vascular function | - |
| MDA | Kidney levels in model of IR-induced AKI [4] | Oxidative stress marker | - |

| Marker | Effect of Finerenone in Preclinical Models | Function/Role | Evidence for Clinical Association |
|---|---|---|---|
| Kidney | | | |
| 8-OHdG | Plasma levels in model of IR-induced AKI [4] | Oxidative stress marker | - |
| IL-6 | ↓ Kidney mRNA expression in IR injury model [40] | Pro-fibrotic and pro-inflammatory cytokine | CKD progression [46] |
| IL-1β | ↓ Kidney mRNA expression in IR injury model [40] | Pro-inflammatory cytokine and M1 macrophage marker | CKD progression [46] |
| TNF-α | ↓ Kidney mRNA expression in IR injury model [40] | Pro-inflammatory cytokine | CKD progression [26][46][47] |
| Mannose receptor | ↑ mRNA expression in macrophages from kidney tissue in IR injury model [40] | Anti-inflammatory marker | - |
| PPAR-γ | ↑ mRNA expression in macrophages from kidney tissue in IR injury model [40] | Anti-inflammatory marker | - |
| IL-10 | ↑ mRNA expression in macrophages from kidney tissue in IR injury model [40] | Anti-inflammatory cytokine | - |
| Arginase 1 | ↑ mRNA expression in macrophages from kidney tissue in IR injury model [40] | Anti-inflammatory marker | CKD progression |
| IL-34 | ↓ Kidney mRNA expression in DOCA-salt model of CKD [38] | Monocyte growth and survival | Worsening of CKD and severity of renal dysfunction [48] |

↑, increased; ↓, decreased; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; AKI, acute kidney injury; CCL-2, C-C motif chemokine ligand 2; CKD, chronic kidney disease; COL1A1, collagen type I α 1 chain; DOCA, deoxycorticosterone acetate; ECM, extracellular matrix; ET-B, endothelin-B receptor; IL, interleukin; IR, ischemia–reperfusion; KIM-1, kidney injury molecule 1; LCN2, lipocalin 2; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MMP, matrix metalloproteinase; mRNA, messenger RNA; NGAL, neutrophil gelatinase-associated lipocalin; NKD2, naked cuticle homolog 2; Nrf2, nuclear factor erythroid-2-related factor 2; OPN, osteopontin; PAI-1, plasminogen activator inhibitor-1; PPAR-γ, peroxisome proliferator-activated receptor-γ; Sgk1, serum- and glucocorticoid-regulated kinase 1; SOD-3, superoxide dismutase-3; Spp1, secreted phosphoprotein 1; T2D, type 2 diabetes; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

### 3.2. Cardiac ROS

Preclinical models have evaluated ROS in the heart together with the effect of MR antagonism [49][50]. In a mouse model of cardiac fibrosis induced by short-term isoproterenol injection, finerenone reduced cardiac NOx2 expression [49] (**Table**

**2**). Another model that assessed cardiac dysfunction related to the metabolic syndrome in rats (Zucker fa/fa) showed that short-term treatment with finerenone increased myocardial tissue perfusion, reduced the level of myocardial ROS, and increased NO bioavailability [50]. Long-term effects of finerenone in a metabolic syndrome model, including modifications in myocardial structure, were also apparent [50].

**Table 2.** Cardiac biomarkers modulated by finerenone in preclinical studies and their clinical association.

| Marker | Effect of Finerenone in Preclinical Models | Function/Role | Evidence for Clinical Association |
|---|---|---|---|
| Cardiac | | | |
| CTGF | ↓ Protein expression in cardiac fibroblasts [51] | Pro-fibrotic cytokine that induces collagen production and subsequent pro-fibrotic enzymes | Cardiac fibrosis and dysfunction [52] |
| Fibronectin | ↓ Protein expression in cardiac fibroblasts [51] | Glycoprotein in fibrotic cardiac tissue | - |
| Galectin 3 | ↓ Cardiac mRNA expression after isoproterenol treatment [49] | Implicated in cardiac and renal inflammation and fibrosis | CKD progression [53][54] |
| COL1A1 | ↓ Cardiac mRNA expression after isoproterenol treatment [49] | ECM molecule | Heart failure progression [55] |
| LOX | ↓ Protein expression in cardiac fibroblasts [51] | Downstream mediator of CTGF, important for collagen cross-linking | Cardiac fibrosis [56] |
| NGAL (LCN2) | ↓ Protein expression in human cardiac fibroblasts and ↓ cardiac NGAL expression in mice post-MI [57] | Involved in innate immunity and cardiovascular extracellular matrix remodeling after MR activation | Serum NGAL levels were associated with lower 6-month LV ejection fraction recovery in post-MI patients [57] |
| Nox2 | ↓ Cardiac mRNA expression after isoproterenol treatment [49] | ROS-generating enzyme | Adverse myocardial remodeling in end-stage DCM [58] |
| TGF-β | ↓ Cardiac expression [51] after isoproterenol treatment [49] | Pro-fibrotic cytokine | - |
| Tnnt2 | ↓ Cardiac mRNA expression [59] | Contractile protein | - |
| Tenascin-X | ↓ Cardiac mRNA expression after isoproterenol treatment [49] | Pro-fibrotic cytokine | - |

↓, decreased; CKD, chronic kidney disease; COL1A1, collagen type I α 1 chain; CTGF, connective tissue growth factor; DCM, dilated cardiomyopathy; ECM, extracellular matrix; LCN2, lipocalin 2; LOX, lysyl oxidase; LV, left ventricular; MI, myocardial infarction; MR, mineralocorticoid receptor; mRNA, messenger RNA; NGAL, neutrophil gelatinase-associated lipocalin; Nox2, nicotinamide adenine dinucleotide phosphate oxidase 2; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; Tnnt2, troponin T type 2.

### 3.3. Vascular ROS

MR-dependent ROS production impedes vascular homeostasis by interrupting the differentiation and migration of bone marrow-derived endothelial progenitor cells [60]. Endothelial dysfunction due to oxidative stress is one potential mechanism for the development of cardiorenal disease that was investigated in a rat model of CKD [61]. Finerenone treatment improved endothelial dysfunction in this albuminuric CKD model by increasing NO bioavailability and superoxide dismutase protein levels. A corresponding reduction in albuminuria was also observed [61]. In the same model, finerenone treatment also dampened plasma matrix metalloproteinase-2 (MMP-2) and MMP-9 activities, lowering arterial stiffness and oxidative stress [31] (**Table 1**).

## 4. Inflammation

MR activation in cells of the immune system has been shown to drive systemic and local inflammation, organ fibrosis, and vascular, cardiac, and renal damage [62]. Cardiac damage activates an inflammatory reaction, thus generating further pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), IL-1β, and IL-6. This transcriptional upregulation can also be triggered by increased ROS [63]. In a broad range of preclinical models, finerenone has been found to have a blocking effect on the transcriptional expression of several pro-inflammatory genes expressed in the kidney, heart, and other organs.

### 4.1. Renal Inflammation

MR signaling in myeloid cells was shown to contribute to the progression of renal injury in a murine knockout model of glomerulonephritis [64]. The knockout of the MR on myeloid cells appeared to protect from renal injury, predominantly resulting from a decrease in macrophage and neutrophil recruitment [64]. This reduction in leukocytes correlated with the downregulated gene expression of proinflammatory markers, including TNF-α, inducible NO synthase, chemokine (C-C motif) ligand 2, and MMP-12 [64]. After an ischemic episode in the kidney, macrophage recruitment plays an essential role during the injury and repair phases [65]. MR activation in monocytes polarizes macrophages toward an “inflammatory M1”-like phenotype [66]. MR inhibition through finerenone promotes increased IL-4 receptor expression in murine kidney IR models and activation in the kidney and in isolated macrophages, thereby facilitating macrophage polarization to an M2 phenotype, which supports the rationale behind using MRAs to block progression of AKI into CKD [40]. Finerenone was shown to decrease the macrophage messenger RNA (mRNA) expression of proinflammatory cytokine TNF-α and M1 macrophage marker IL-1β [40]. In finerenone-treated uninephrectomized deoxycorticosterone acetate (DOCA)-treated mice, kidney retinoid-related orphan receptor (ROR) gamma t-positive T-cells were downregulated, which was accompanied by a significant reduction in the urine albumin-to-creatinine ratio (UACR), demonstrating significant renal protection [67]. In humans, IL-6 expression is induced through an MR-dependent process promoted by angiotensin II, a proinflammatory effect that can be blocked by MR antagonism [68]. Inflammation is an important precursor to fibrosis and a player in the development of AKI-induced CKD [69]. The levels of the proinflammatory cytokines IL-6 and IL-1ß were found to have increased after the induction of IR injury in untreated mice. However, this inflammatory response was prevented by finerenone administration, suggesting that MR antagonism by finerenone can modify inflammation [40]. Finerenone has also been shown to reduce the expression of renal NGAL [3][4], which is released from neutrophils during systemic inflammation and from renal tubular cells in response to tubular injury [3][4], and the pro-inflammatory cytokine monocyte chemoattractant protein-1 (MCP-1) in the DOCA-salt model of cardiorenal end-organ damage [25]. Both NGAL and MCP-1 are implicated in CKD progression in humans [27][34]. Finerenone also reduced renal osteopontin (OPN) expression in a DOCA-salt rat CKD model [25]. During renal fibrogenesis, this cytokine is thought to modulate fibroblast proliferation, macrophage activation and infiltration, cytokine secretion, and the synthesis of ECM. A previous investigation demonstrated that OPN is implicated in CKD progression, and its plasma levels are elevated from the early stages of CKD [39]. In a murine model of CKD progression in T2D (uninephrectomized mice with T2D fed a high-salt diet), finerenone offered protection from podocyte injury by reducing the expression of fibronectin, as well as inflammatory markers including MCP-1 and plasminogen activator inhibitor-1 (PAI-1), in glomeruli [13].

### 4.2. Cardiac Inflammation

The role of the MR in cardiac inflammation was investigated in mice that were genetically modified to lack MR expression in cardiomyocytes. Here, a central role for the MR was established in the initiation and progression of cardiac tissue inflammation and remodeling following induction with DOCA-salt [70]. The early innate inflammatory response was lost and the full inflammatory response was blocked, as evidenced by a reduced number of monocytes and macrophages in cardiac tissue of mice that lacked the MR on cardiomyocytes [70]. MR-deleted macrophages have an M2-type profile [71] associated with anti-inflammatory and repair properties in cardiac tissues [72]. Cardiac macrophage infiltration was also

significantly blocked by finerenone in an isoproterenol-induced model of inflammation and fibrosis in mice [49]. Finerenone also reduced the cardiac mRNA expression of galectin-3 in this model [49], which is notable as it has been identified as a novel biomarker that may be associated with disease progression in patients with CKD [53]. Finally, the effect of finerenone on the previously identified inflammatory MR target NGAL (or lipocalin 2 (LCN2)) was investigated in vitro and in vivo [57]. Finerenone blunted the aldosterone-induced NGAL protein synthesis in human cardiac fibroblasts, as well as in cardiac tissue from post-MI mice. NGAL seems to play a key role in the development of cardiac dysfunction post-MI since an increase in serum NGAL levels during follow-up was significantly associated with lower 6-month left ventricular ejection fraction (LVEF) recovery in a cohort of 119 post-MI patients [57] (**Table 2**).

## 5. Fibrosis

Sustained and prolonged inflammation leads to fibrosis, an excessive accumulation of ECM and increased collagen synthesis in response to tissue injury [73][74]. This close association with prolonged inflammation generally leads to damage in a variety of organs, including the heart and the kidneys [74][75]. MR overactivation by aldosterone is thought to increase fibrosis by driving collagen expression, as well as by causing the upregulation of PAI-1, which inhibits the production of plasmin, enables the accumulation of ECM, and promotes fibrosis.

### 5.1. Renal Fibrosis

In the kidneys, the development of fibrosis contributes to CKD and renal failure via the disruption of the renal tubules and surrounding blood vessels. Research in patients with kidney disease has revealed that the pro-fibrotic cytokine transforming growth factor-β (TGF-β), MCP-1, and MMP-2 are potential biomarkers for the development of fibrosis and correlate with worsening renal function [30]. Plasma PAI-1 also had a moderate correlation with fibrosis on biopsy [30]. Several preclinical models have been used to evaluate the role of the MR in the development of fibrosis and the progression of CKD and to determine the efficacy of finerenone in reducing renal fibrosis. In the DOCA-salt model of CKD in rats, finerenone reduced renal mRNA expression of the pro-fibrotic marker PAI-1 as well as renal fibrosis determined by histopathology [25]. Finerenone also reduced renal fibrosis and the renal expression of pro-fibrotic collagen type I α 1 chain (COL1A1) in a hypertensive cardiorenal rat model [43]. Furthermore, in a mouse model of renal fibrosis, finerenone dose-dependently lowered pathologic myofibroblast accumulation and collagen deposition independently of systemic blood pressure or changes in inflammatory markers [36]. Corresponding decreases in the expression of the fibrotic markers PAI-1 and naked cuticle homolog 2 (NKD2) were also observed in the kidneys [36]. NKD2 was recently identified as a myofibroblast-specific marker in human renal fibrosis [37]. In a chronic CKD rat model with renal dysfunction, increased proteinuria, and extensive tubule-interstitial fibrosis, finerenone was found to limit renal collagen deposition and fibrosis, as scored by histopathology [4]. Finerenone administration prevented an increase in the renal expression of the pro-fibrotic cytokine TGF-β and collagen-I [4]. Similarly, in a mouse CKD model of unilateral, IR-induced tubulo-interstitial fibrosis, finerenone significantly reduced the severity of renal fibrosis [40] (**Table 1**).

### 5.2. Cardiac and Vascular Fibrosis

Pathophysiologic MR overactivation promotes cardiac and vascular fibrosis with and without concomitant oxidative damage and inflammation [6][51]. The effects of finerenone on cardiac and vascular fibrosis have been investigated in several preclinical models. Finerenone was shown to reduce cardiac fibrosis in a hypertensive cardiorenal rat model and the cardiac expression of pro-fibrotic PAI-1 in mouse models of renal fibrosis [36][43]. The treatment of a genetic mouse model of Duchenne muscular dystrophy (DMD) with finerenone also prevented significant reductions in myocardial strain rate, the earliest sign of human DMD cardiomyopathy, with a corresponding reduction in the accumulation of fibrotic tissue in the heart [76]. In a transgenic mouse model with the cardiac-specific overexpression of Rac1 (RacET), a model of left ventricular and left atrial fibrosis, 5 months of treatment with finerenone significantly reduced the cardiac mRNA expression of TGF-β; myocardial fibrosis was also reduced with finerenone [51]. In an isoproterenol-induced cardiac fibrosis mouse model, the examination of cardiac tissues revealed an increased cardiac collagen accumulation. Treatment with finerenone significantly reduced the isoproterenol-induced pro-fibrotic effect and ameliorated the isoproterenol-induced increase in tenascin-X, a protein involved in the regulation of collagen deposition and degradation [49]. Furthermore, the expression of classical fibrotic molecules (including TGF-β, COL1A1, and galectin-3) was increased through isoproterenol treatment, the effects of which were substantially reduced with finerenone treatment [49] (**Table 2**).

The role of the MR in the development of atrial fibrosis, a predisposing factor for the development of atrial fibrillation (AF) has also been studied. The left atrial myocardium of patients with AF exhibited an increased hydroxyproline content, a marker of fibrosis, compared with patients in sinus rhythm. MR antagonism by finerenone prevented the aldosterone-induced upregulation of connective tissue growth factor (CTGF) protein expression (a marker for structural remodeling)

and cardiac fibrotic remodeling, as well as lysyl oxidase (which is involved in collagen cross-linking) [51]. In a mouse model of post-MI-induced heart failure, treatment with finerenone for 2 months improved left ventricular compliance and elastance, as well as reducing interstitial fibrosis [77].

## 6. Hypertrophy/Remodeling

Cardiac hypertrophy occurs as a compensatory response to a sustained increased in stress enacted on the left ventricular wall [78]. Cardiac hypertrophy can become pathologic and contribute to the development of HF. MR blockade has been shown to suppress cardiac hypertrophy and remodeling in animal models of pressure overload [79] and the knockout of the MR, specifically in myeloid cells, attenuated cardiac hypertrophy following cardiac and vascular damage [71]. In a transverse aortic constriction model in mice, finerenone reduced the cardiac gene expression of troponin T type 2, leading to a significant reduction in left ventricular wall thickening [59]. Finerenone was also able to reduce cardiac hypertrophy and renal damage in DOCA-salt-treated rats [25]. Finerenone has also been shown to significantly reduce the apoptosis of ECs and simultaneously attenuate SMC proliferation, resulting in accelerated endothelial healing and the reduced neointima formation of injured vessels following electric injury of the murine carotid artery [80]. Thus, finerenone appears to provide favorable vascular effects through restoring vascular integrity and preventing adverse vascular remodeling [80].

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