Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2024**; 25(3): 93
https://doi.org/10.31083/j.rcm2503093

Review

Hypertensive Heart Disease: Mechanisms, Diagnosis and Treatment

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Academic Editor: Vincent Figueredo
Submitted: 30 September 2023 Revised: 19 November 2023 Accepted: 22 November 2023 Published: 6 March 2024

Abstract

Hypertensive heart disease (HHD) presents a substantial global health burden, spanning a spectrum from subtle cardiac functional alterations to overt heart failure. In this comprehensive review, we delved into the intricate pathophysiological mechanisms governing the onset and progression of HHD. We emphasized the significant role of neurohormonal activation, inflammation, and metabolic remodeling in HHD pathogenesis, offering insights into promising therapeutic avenues. Additionally, this review provided an overview of contemporary imaging diagnostic tools for precise HHD severity assessment. We discussed in detail the current potential treatments for HHD, including pharmacologic, lifestyle, and intervention devices. This review aimed to underscore the global importance of HHD and foster a deeper understanding of its pathophysiology, ultimately contributing to improved public health outcomes.

Keywords: hypertensive heart disease; mechanisms; diagnosis; treatment

1. Introduction

Despite notable advancements in blood pressure management, hypertension remains a prevalent health condition, particularly in developing countries, with low control rates [1,2]. Sustained elevated arterial blood pressure imposes an increased cardiac load, triggering a cascade of structural and functional changes in the heart known as hypertensive heart disease (HHD) [3]. The disease burden caused by HHD has risen steadily in recent years, and HHD was the main cause of 1.16 million deaths in 2019 worldwide [4]. A common manifestation of HHD is left ventricular hypertrophy (LVH) [5]. Findings from large-scale population studies based on echocardiograms indicate that the prevalence of LVH among individuals with hypertension exceeds 20% [6] and is significantly higher in Asians and Africans [7,8]. However, in addition to race, the detection rate of LVH also greatly depends on factors such as age, sex, and the diagnostic methods employed [9,10]. Patients with HHD face a significant risk of progressing to heart failure (HF) [11–13]. Thus, HHD is a spectrum, ranging from asymptomatic left ventricular diastolic dysfunction to clinical heart failure [14]. Additionally, HHD has been linked to numerous adverse cardiovascular outcomes, including myocardial infarction, stroke, and even sudden cardiac death (SCD) [10,15,16].

In recent decades, the comprehension of HHD has transformed. Initially, viewed as a cardiomyocyte response to increased load, it is now recognized as a complex and dynamic phenomenon encompassing structural and functional changes in the heart [17]. These changes arise from various factors, such as neurohormones, myocardial metabolic remodeling, interstitial fibrosis, immunity, inflammation and mechanosensation [18,19]. Advancements in treatment strategies have significantly impacted the prognosis of individuals, with new protocols for blood pressure management, particularly intensive antihypertensive approaches, yielding promising results [20,21]. A notable breakthrough in combating heart failure is the utilization of sodium-glucose cotransporter-2 (SGLT2) inhibitors, which have proven effective in reducing left ventricular mass in participants with LVH and type-2 diabetes [22]. Furthermore, novel potentially therapeutic tools based on an improved understanding of the mechanisms underlying HHD have been proposed, offering potential avenues for intervention [23,24]. This article summarizes the mechanisms associated with HHD, delves into the dynamic progression of the disease across different stages, and reviews past and future therapeutic tools.

2. Mechanisms Contributing to Hypertensive Heart Disease

When hypertension leads to increased cardiac load, the ventricular wall thickens initially to reduce stress and maintain contraction efficiency, following Laplace's law [25]. Cardiomyocytes cannot proliferate, so ventricular wall thickening occurs through a parallel increase in sarcomeres. Pathological ventricular hypertrophy due to hypertension differs from physiological hypertrophy [18]. However, in the initial stage of HHD, these changes are also compensatory and often present as concentric thickening. Although the ejection fraction remains in the normal range at this stage, a reduction in overall cardiac con-

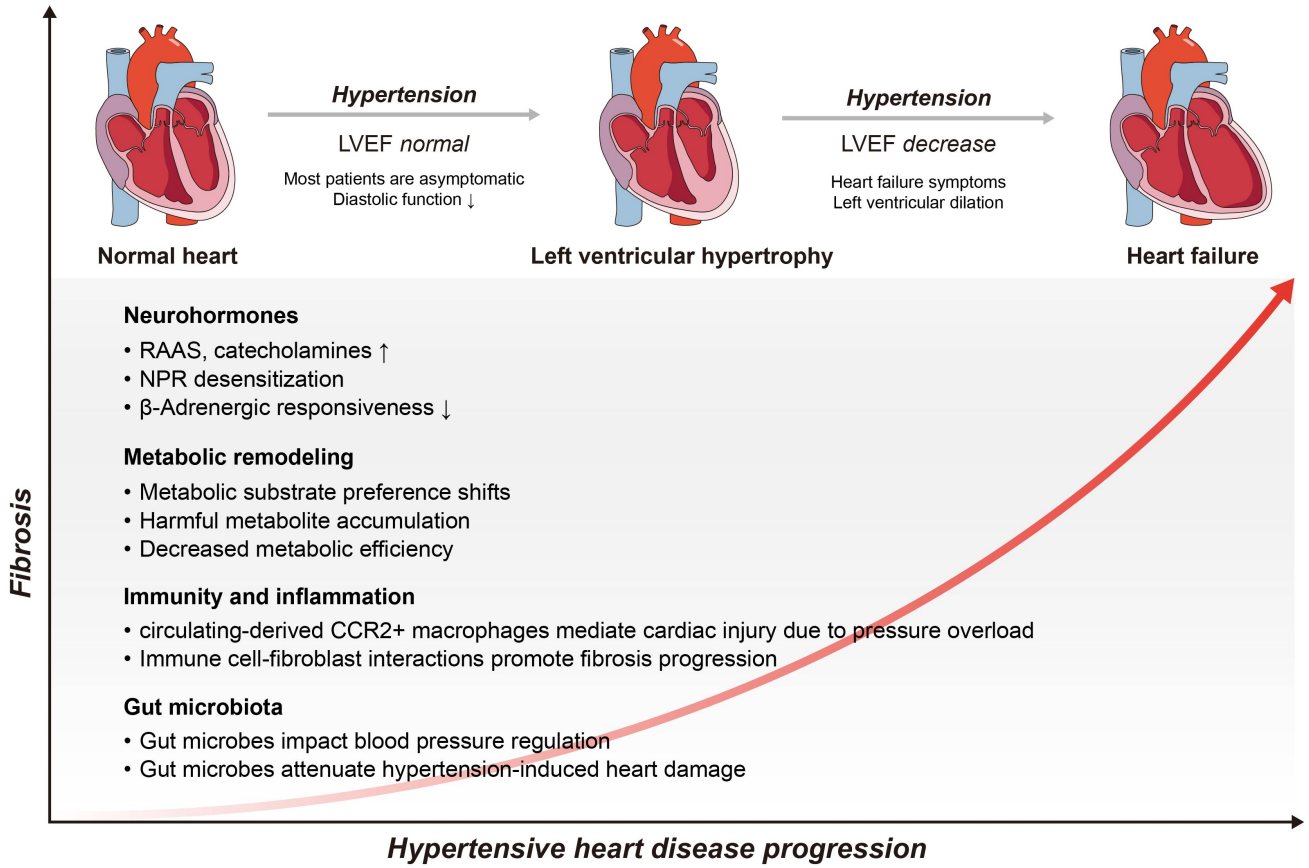

Fig. 1. Complex mechanisms of hypertensive heart disease (HHD). As HHD progresses, the level of cardiac fibrosis increases, while the heart has different macroscopic manifestations. Multiple factors, including neurohormones, metabolic remodeling, inflammation, and gut microbiota, among others, contribute to this progression. LVEF, left ventricular ejection fraction; NPR, natriuretic peptide receptors; RAAS, renin-angiotensin aldosterone system.

tractile reserve and global longitudinal strain has occurred [26]. As the afterload pressure continues, the deterioration of cardiac function persists and eventually leads to heart failure [17]. A number of factors, such as neurohormones, metabolism, immunity, and gut microbiota, play important roles in this process. Furthermore, fibrosis emerges as a pivotal consequence of cardiac injury in hypertension. Cardiac fibrosis significantly fuels the progression of HHD and contributes to adverse outcomes [5]. Thus, we also provide an overview of the mechanisms underpinning cardiac dysfunction in HHD (Fig. 1). In addition, we briefly describe the role of the left atrium and right heart in the development of HHD.

2.1 Neurohormones

Hypertension disrupts the neuroendocrine system. Neuroendocrine factors have long been considered the main contributors to the development of HHD [25]. Among them, the renin-angiotensin-aldosterone system (RAAS) and catecholamines play a crucial role in the progression of HHD.

The activation of the RAAS is a crucial component of the pathological changes caused by hypertension. Angiotensin II (Ang II) is an important driver of a series of changes in the heart during HHD [18]. Ang II, which binds to angiotensin II type I receptor (AT1R) on the surface of cardiac myocytes, activates the $G\alpha_q$ protein and phospholipase C (PLC), leading to the production of diacylglycerol and inositol 1,4,5-trisphosphate (IP_3). IP_3 increases intracellular calcium levels, increasing myocardial contractility through the calcium-calmodulin kinase II pathway [18,27]. Initially, Ang II stimulation enables the heart to cope with higher afterloads. However, chronic stimulation of Ang II through sustained $G\alpha q$ activation leads to myocardial hypertrophy [28]. Moreover, overexpression of $G\alpha q$ can induce apoptosis in cardiac myocytes, which may be associated with increased endonuclease activity due to elevated intracellular calcium levels [29]. Inhibitors of $G\alpha_q$ overexpression block the development of pressure overload-induced cardiac hypertrophy [30]. Another study also demonstrated that negative regulation of G protein-coupled receptor-mediated signaling pathways attenuates Ang II-induced cardiomyocyte hypertrophy and cardiac re-

modeling due to pressure overload [31,32]. Ang II can also generate reactive oxygen species (ROS) through coupling with $G\alpha_q$, which may further promote HHD [33,34]. Apart from its direct effects on cardiac myocytes, Ang II can stimulate cardiac fibroblasts to release various cytokines, such as transforming growth factor-beta 1 (TGF-β1) and interleukin-6, promoting local production of Ang II and AT1R expression [35,36]. Furthermore, the activation of the RAAS also promotes cardiac fibrosis progression. However, current research does not show beneficial effects of RAAS inhibitor treatment in heart failure with preserved ejection fraction (HFpEF) patients [37]. This suggests that RAAS activation may not be the main mechanism underlying the progression to HFpEF in HHD patients [38].

Increased blood pressure activates the sympathetic nervous system, leading to the release of catecholamines. Catecholamines bind to β-adrenergic receptors in cardiac cells [39]. The heart primarily expresses two types of β-adrenergic receptors (βAR), β1AR and β2AR, with β1AR being the most abundant on the surface of myocardial cells and β2AR accounting for 20% of myocardial adrenergic receptors in normal physiological conditions [40]. Current research suggests that excessive activation of β1AR leads to myocardial cell apoptosis and other adverse effects, while β2AR mediates cardiac protection [41,42]. β1AR activation stimulates adenylate cyclase via $G\alpha_s$, leading to increased cyclic adenosine monophosphate (cAMP) levels, subsequent activation of protein kinase A, and ultimately, upregulation of contractile proteins and calcium ion levels in myocardial cells [40]. However, cAMP also activates exchange proteins activated by cAMP (EPAC) [43]. EPAC1 contributes to the pathological growth of myocardial cells and may promote the transition from myocardial hypertrophy to heart failure, while EPAC2 may be involved in the occurrence of arrhythmias [18].

However, prolonged exposure to elevated blood pressure results in desensitization of adrenergic receptors due to sustained catecholamine stimulation [40]. β-adrenergic receptor desensitization leads to reduced downstream signaling and impaired cardiac functional reserve. This change serves as an important mechanism underlying the development of heart failure. β-adrenergic receptor desensitization is primarily mediated by GPCR kinases (GRKs) [44]. GRKs belong to the serine/threonine kinase family and consist of seven members, with GRK2 and GRK5 being the main regulators of β-adrenergic receptor desensitization in the heart. Inhibition of GRK2 with paroxetine improves hypertension-induced cardiac hypertrophy, dysfunction, and fibrosis in mice [45]. Additionally, in hypertensive patients with depression, those treated with paroxetine exhibited less cardiac remodeling than patients receiving other antidepressant medications [45]. Furthermore, β-arrestins are also involved in β-adrenergic receptor desensitization [46].

Natriuretic peptides (NPs) constitute a class of peptide hormones with blood pressure-regulating functions categorized into three types: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [47]. ANP and BNP are produced and secreted by the heart, while CNP is synthesized by vascular cells [48]. It has been demonstrated that NPs are closely associated with the development of LVH and HF resulting from hypertension [23]. Upon binding of ANP and BNP to natriuretic peptide receptor (NPR), the activation of guanylate cyclase ensues, leading to increased levels of cyclic guanosine monophosphate (cGMP) [47]. This activation initiates downstream processes, including the activation of protein kinase G (PKG) and cGMP-gated ion channels, ultimately reducing intracellular calcium ion levels [47]. This cascade also suppresses signals linked to cardiac hypertrophy. This series of events is thought to be a critical mechanism through which natriuretic peptides exert their anti-cardiac hypertrophy effects [49]. Furthermore, NPs have been found to mitigate the progression of cardiac fibrosis. Knockout mice lacking NPR exhibit a notable increase in myocardial fibrosis, which does not correlate with blood pressure levels [50]. Additionally, NPs can inhibit the proliferation of cardiac fibroblasts induced by Ang II. Current research suggests that the antifibrotic effects of NPs are also mediated through the cGMP-PKG pathway. ANP is susceptible to degradation by neprilysin. Recent studies indicate that inhibiting neprilysin can impede the activation and proliferation of cardiac fibroblasts, which is attributed to the restoration of PKG signaling within fibroblasts [51]. Furthermore, ANP has been shown to stimulate mitochondrial autophagy, enhance mitochondrial function, and lower intracellular oxidative stress levels [52]. Patients with hypertension exhibit elevated levels of NPs [47]. However, prolonged exposure to high levels of NPs can lead to desensitization of NPR [23]. This desensitization weakens the cardioprotective effects of NPs, thereby promoting the occurrence and development of HHD [53].

2.2 Metabolic Remodeling

The heart's unique function demands a substantial amount of energy. Physiologically, 95% of the heart's adenosine triphosphate (ATP) is produced through oxidative phosphorylation in the mitochondria, while the remaining ATP is primarily derived from glycolysis [54]. Most (>60%) ATP is generated using fatty acids as metabolic substrates, with the rest coming from glucose, lactate, ketone bodies, and other sources [55,56]. Cardiac contraction is powered by approximately 60% to 70% of the generated ATP [54]. Due to limited ATP reserves in cardiomyocytes, which can be depleted within seconds, any disruption in the energy production process significantly impacts cardiac function [54]. To cope with this characteristic, the myocardium is highly adaptable in its choice and shift of metabolic substrates, despite fatty acids being the pri-

mary substrates [57]. Studies indicate that cardiomyocytes rapidly shift to glucose metabolism when the workload increases [58].

Traditionally, it was believed that myocardial substrate preference would shift toward glucose during ventricular hypertrophy and heart failure [59]. However, recent research suggests that cardiac metabolism maintains a great deal of flexibility even in severe heart failure, allowing it to adjust substrate use to accommodate changes in arterial supply and workload [60]. Consequently, myocardial fatty acid uptake may remain unaffected [18]. However, fatty acid oxidation (FAO) is reduced in pathological ventricular myocardial hypertrophy [57]. The imbalance between fatty acid uptake and utilization leads to the accumulation of lipids such as triglycerides, ceramides, and diacylglycerols, which are synthesized from excess fatty acids within cardiomyocytes. While triglycerides are considered harmless, the lipotoxicity of ceramides and diacylglycerols can result in mitochondrial dysfunction and apoptosis [57,61,62]. Furthermore, an excess of intracellular fatty acids can promote the development of myocardial insulin resistance [63,64].

Acetyl coenzyme A carboxylase is the rate-limiting enzyme for fatty acid synthesis, and animal studies have shown that knocking down the acetyl coenzyme A carboxylase 2 gene in cardiac tissues increases fatty acid oxidation, reduces glucose oxidation, and prevents ventricular hypertrophy caused by increased load [65,66]. Similarly, overexpression of medium-chain acyl-coenzyme A dehydrogenase has been shown to reduce left ventricular hypertrophy caused by increased load [67]. Additionally, increasing dietary fatty acid intake in the context of heart failure reduces glucose oxidation and improves cardiac function [68].

During HHD, early increased glucose utilization can compensate for the energy deficit caused by decreased fatty acid metabolism efficiency. However, as the pathology progresses, the overall metabolic efficiency decreases [18]. Recent studies indicate that myocardial glucose uptake capacity varies at different stages of progression. The glucose uptake rate rises in hearts with mild diastolic and systolic dysfunction but declines significantly in severe cardiac dysfunction [69]. Cardiomyocytes facilitate glucose entry through glucose transporter proteins (GLUT1 and GLUT4), with GLUT4 being the main isoform in adults and GLUT1 in fetuses [70]. Glucose transport via the GLUT1 pathway increases during the development of cardiac hypertrophy [71]. Overexpression of GLUT1 has been found to prevent heart failure due to increased load and attenuate mitochondrial dysfunction [72]. However, it can aggravate cardiac hypertrophy. Conversely, knocking down GLUT4 leads to more severe cardiac hypertrophy and contractile dysfunction [73]. Therefore, increased glucose levels in cardiomyocytes may attenuate cardiac hypertrophy development. Similar to fatty acids, despite increased glucose uptake and glycolysis, the oxidation rate remains unchanged [18]. This results in the accumulation of metabolic intermediates, including glucose-6-phosphate. The buildup of intermediates, in turn, may promote cell growth and protein synthesis, ultimately contributing to the progression of ventricular hypertrophy. This occurs through activating the mammalian target of rapamycin protein complex 1, enhancing the pentose phosphate pathway, and stimulating the hexosamine biosynthesis pathway [74–76].

Under physiological conditions, ketone bodies provide approximately 10% of the energy source for the myocardium [77]. In contrast, ketone body metabolism is elevated in patients with heart failure cachexia [57]. It has been shown that specific knockdown of succinyl coenzyme A:3 ketoacyl coenzyme A transferase in mouse cardiomyocytes promotes cardiac hypertrophy [78]. Thus, increased ketone body metabolism may be a metabolic adaptation to HHD.

Branched-chain amino acids provide less than 5% of the energy source for the myocardium under physiologic conditions [77]. In contrast, the levels of branched-chain amino acids are similarly increased in patients with HF. Excessive levels of branched-chain amino acids have been shown to inhibit α-ketoglutarate and pyruvate dehydrogenase activity and promote contractile dysfunction [79,80]. The mechanism by which they are elevated during pathological remodeling is unclear. However, branched-chain amino acids and their metabolites have been shown to activate mammalian rapamycin target proteins, which may lead to alterations in cardiomyocyte anabolism, proliferation, autophagy, and other processes [77].

2.3 Immunity and Inflammation

Inflammation and immunity also play important roles in HHD [18,81,82]. Previous clinical trials targeting inflammation in LVH and HF drugs have yielded disappointing results [83]. However, the results of the CANTOS trial demonstrated that interleukin (IL)-1β monoclonal antibody can reduce heart failure-related hospitalization and mortality in patients with previous myocardial infarction, demonstrating the potential of inflammation in HF treatment [84]. While the role of inflammation and immunity in HHD and heart failure has long been recognized, the understanding of this process has been limited by the knowledge of the immune environment in the heart and the available research methods. Recent advancements in fate mapping and single-cell analysis techniques have provided valuable opportunities for advancing cardiac immunology [85]. These tools have revealed the heterogeneity of the cardiac immune system, offering new insights into the roles of immunity and inflammation in HHD.

Macrophages, the most abundant immune cells in the heart, constitute 5–10% of the total cardiac cells [85,86]. The heterogeneity of cardiac macrophages is being unveiled, with human heart macrophages categorized into at least three types based on transcriptomic and functional

differences: self-renewing cardiac resident macrophages ($TIMD4^+LYVE1^+FOLR2^+CCR2^-$ macrophages, $TIMD4^-LYVE1^-FOLR2^-CCR2^-$ macrophages) and $TIMD4^-LYVE1^-FOLR2^-CCR2^+$ macrophages derived from circulating monocytes [87,88]. Current research supports the notion that $CCR2^-$ cardiac resident macrophages are involved in tissue repair and maintaining cardiac homeostasis [89,90]. Under normal physiological conditions, these cells are the primary macrophage source in the adult mammalian heart. Conversely, $CCR2^+$ macrophages derived from circulating monocytes increase in number in the postinjury heart and contribute to the inflammatory response during cardiac injury [89,90].

Macrophages have been identified as key contributors to the development and progression of HHD [91]. Earlier animal experiments utilized the nonselective depletion of macrophages through clodronate liposome injection to investigate their role in HHD. One study demonstrated a deterioration in left ventricular ejection function in hypertensive rats following macrophage removal [92]. Conversely, another study found that macrophage depletion attenuated hypertension-induced left ventricular hypertrophy while improving cardiac fibrosis [93]. These studies suggest a potential heterogeneous role of macrophages in HHD. To further elucidate the distinctions among different macrophage sources, Liao *et al.* [94] employed a $CCR2^+$ antagonist-based approach to specifically block circulating-derived monocyte infiltration in mouse hearts. The results revealed an initial increase in macrophage numbers in the heart after transverse aortic constriction (TAC), returning to baseline levels at 2 weeks, and a mild increase again in the late phase (4 weeks). These changes in macrophage numbers corresponded to alterations in cardiac function, with the heart exhibiting compensatory hypertrophy early after TAC, followed by progressive cardiac dysfunction and heart failure at 2–4 weeks. The increase in macrophages resulted from the proliferation of cardiac resident macrophages, which facilitated the initial adaptive changes in response to pressure overload, potentially by promoting vascular generation [94]. A recent study of a genetic fate-mapping approach and single-cell transcriptome analysis demonstrated the cardioprotective role of cardiac resident macrophages in HHD [95]. This study also identified insulin-like growth factor-1 (IGF-1) as a potentially significant pathway for resident macrophage-mediated cardioprotection. The subsequent increase in late cardiac macrophages originated from the infiltration of circulating monocytes. However, circulating-derived $CCR2^+$ macrophages mediate inflammatory injury and contribute to the deterioration of cardiac function, while reducing their infiltration helps maintain cardiac function. These findings are supported by additional studies, highlighting the potential of targeting $CCR2^+$ macrophages as an important intervention strategy in HHD [96].

The activation of macrophages during HHD involves various mechanisms. Recent studies have shown that Ang II can directly promote macrophage activation through a pathway independent of AT1R [97]. This process is facilitated by the pattern recognition receptor dectin-1 on the macrophage surface, and the knockdown of dectin-1 significantly reduces Ang II-mediated cardiac injury. Although direct studies in HHD are lacking, mechanical stress can directly activate macrophages. A study utilizing a mouse model of dilated cardiomyopathy demonstrated that tissue-resident macrophages can sense mechanical stretch via transient receptor potential vanilloid 4 (TRPV4), leading to increased macrophage production of IGF-1, which plays a critical role in cardiac vascular neogenesis [98]. Furthermore, other studies have indicated that mechanosensory ion channels on the macrophage surface, such as PIEZO1, can respond to changes in mechanical stress and initiate downstream proinflammatory pathways [99].

Lymphocytes likewise play an important role in the pathologic process of HHD. Studies have shown that $CD4^+$ T cells promote the development of cardiac fibrosis due to pressure load [100]. In a mouse model of pressure overload, the development of cardiac fibrosis coincided with the infiltration of $CD4^+$ T cells into the myocardium [101,102]. The interaction between cardiac fibroblasts and T cells plays an important role in this process. A recent study demonstrated that cardiac fibroblasts induced by interferon-gamma (IFN-γ) can express major histocompatibility complex II (MHCII) and present antigens to $CD4^+$ T cells [103]. At the same time, T cells can promote the transformation of fibroblasts to myofibroblasts, thereby facilitating the progression of fibrosis [101]. Meanwhile, the use of T cells expressing chimeric antigen receptor targeting fibroblast activation proteins significantly reduced cardiac fibrosis in the Ang II-induced hypertensive mouse model [104]. Other immune cells, such as dendritic cells, are also involved in the development of HHD [105].

2.4 Gut Microbiota

The gut microbiota is crucial in maintaining host health, impacting various physiological functions, including blood pressure regulation [106]. Bacterial metabolites are instrumental in mediating this effect [107]. Moreover, the gut microbiota has emerged as a significant factor influencing hypertension-induced target-organ damage. A recent study demonstrated that germ-free mice exhibit more severe cardiac and renal injury following Ang II-induced hypertension than colonized mice [108]. This highlights the protective role of gut microbes in mitigating hypertension-induced organ damage. Dietary habits significantly influence physiological factors in the host, with the gut microbiota serving as a vital intermediary. Different dietary patterns impact gut microbial metabolites, which are crucial for their physiological functions [109]. For instance, the fermentation of dietary fiber by gut microbes produces

short-chain fatty acids, known to lower blood pressure and reduce cardiac hypertrophy and fibrosis [110]. The gut microbiota also influences other host metabolites associated with hypertension and immune system modulation [106].

2.5 Fibrosis

Elevated blood pressure can trigger the development of cardiac fibrosis, characterized by excessive collagen buildup in the spaces between cells and blood vessels [17]. In HHD, the distribution of fibrosis can vary at different stages of progression. In the early stages, fibrosis may be localized to the subendocardium or around blood vessels. As HHD advances, fibrosis can extend outward toward the subepicardium, leading to a more diffuse pattern [16,111]. Fibrosis reduces the flexibility of the ventricles and serves as the underlying mechanism for hypertension-related HFpEF. The presence of higher levels of fibrosis may explain why pathological LVH is resistant to treatment, unlike physiological hypertrophy [23]. Recent studies have shed light on several factors contributing to cardiac fibrosis in hypertension, including the activation of the RAAS [112,113], inflammation and immunity [114,115], and mechanical strain [116].

The production and maintenance of the cardiac collagen matrix primarily involve cardiac fibroblasts, which constitute 10–25% of all cardiac cells [86,117]. These fibroblasts originate from both the endocardium and the epicardium [118]. When activated, fibroblasts can transform into myofibroblasts, which have an increased capacity to produce collagen and are key contributors to tissue fibrosis following cardiac injury [119]. The current studies support the significant role of proinflammatory cytokines and changes in the extracellular matrix composition in converting fibroblasts into myofibroblasts [116,120,121]. It should be noted that the role of fibroblasts from different origins in the development of cardiac fibrosis may not be consistent. Recent investigations indicate that endocardial-origin fibroblasts exhibit a preference for responding to cardiac injury caused by pressure overload compared to epicardial-origin fibroblasts [122]. The Wnt signaling pathway promotes the activation of endocardial-origin fibroblasts. Targeted removal of endocardial-origin fibroblasts attenuated pressure overload-induced cardiac fibrosis and improved cardiac function in one study. However, an earlier study suggested that fibroblasts from different origins play similar roles in cardiac hypertrophy resulting from TAC [123]. The reason for this discrepancy may be advances in genetic tracing techniques.

Myofibroblasts express α-smooth muscle actin, which grants them contractile capabilities [124]. Therefore, during the early stages of the disease, myofibroblast production helps maintain cardiac function to some extent. However, these cells exhibit an enhanced ability to synthesize and secrete collagen, and the collagen produced is fortified through cross-linking, making them more resistant to degradation by matrix metalloproteinases [125]. Consequently, collagen production increases while degradation decreases, leading to collagen matrix accumulation and fibrosis formation. Furthermore, once formed, myofibroblasts can secrete TGF-β, triggering the activation of additional myofibroblasts and further fueling the progression of fibrosis [119].

2.6 Left Atrial and Right Heart Involvement in HHD

The heart is an integrated system where various components, apart from the left ventricle (LV), play significant roles in the progression of HHD.

Enlargement of the left atrium (LA) is a recognized hallmark of HHD, and LA dysfunction is pivotal in facilitating the transition to HF while serving as a key marker for cardiovascular conditions, such as atrial fibrillation [126–129]. The mechanisms behind LA involvement in HHD are multifaceted. Hypertension itself can induce atrial myocardial dysfunction and fibrosis. Indications of LA dilation and fibrosis markers are observed in spontaneously hypertensive rats at seven months of age [130]. Similar to the LV, aberrant activation of the RAAS and the adrenergic system in hypertension is instrumental in LA remodeling and fibrosis [131,132]. The electrophysiologic function of the left atrium is similarly affected, with hypertension-induced changes in atrial myocytes potentially contributing to the development of atrial fibrillation due to alterations in calcium homeostasis [130,133]. Meanwhile, unfavorable LV characteristics, including increased LV mass and impaired diastolic function, are associated with diminished LA function in HHD patients, potentially exacerbated by higher afterload [134]. In a mouse model with partial stenosis of the ascending aorta, the left atrium exhibited fibrosis, increased susceptibility to atrial fibrillation, and conduction abnormalities, among other changes [135]. Importantly, the neurohumoral functions related to the LA can also have a significant impact on HHD, as evidenced by a clinical trial demonstrating that left atrial appendage closure significantly reduced RAAS activity and lowered systemic blood pressure [136].

Systemic hypertension also impacts the right ventricle (RV), resulting in concentric RV remodeling and impaired RV diastolic function [137,138]. Numerous clinical studies have linked adverse RV remodeling to an unfavorable prognosis [139–141]. Right heart involvement may be attributed to pulmonary hypertension secondary to left heart conditions [142]. Similar to the LV, the right heart undergoes a transition from compensation to decompensation as pulmonary artery pressure rises [143]. Right ventricle-pulmonary artery decoupling occurs when right ventricular contractility no longer matches the increased afterload. The precise mechanism by which left heart alterations lead to pulmonary hypertension remains unclear, with possible contributors including endothelial injury and neuroendocrine hormone metabolic disorders [142,144].

3. Classification of HHD and Assessment

HHD encompasses a spectrum of diseases ranging from asymptomatic functional impairment to heart failure, even SCD [16,145]. Traditionally, HHD is classified into four stages based on clinical symptoms and echocardiographic findings [146]. In stage one, patients are asymptomatic with echocardiographic evidence of left ventricular diastolic dysfunction but no LVH. Stage two involves asymptomatic or mildly symptomatic patients with LVH observed on echocardiography. In stage three, patients present with heart failure with preserved ejection fraction. Stage four is characterized by heart failure with reduced ejection fraction (HFrEF) and left ventricular dilation.

However, clinical observations and animal study evidence suggest that this classification may be arbitrary [3]. Disease progression does not necessarily follow a linear sequence. For example, although left ventricular hypertrophy is considered a significant manifestation of HHD, it is not a mandatory feature. Cardiac hypertrophy is not always the obligatory compensatory response to increased mechanical load [147]. Complications and patient-specific characteristics, such as age, body mass index (BMI), and complications, can also influence the specific manifestations of HHD in the heart [148,149].

A more rational approach to identifying HHD involves a comprehensive assessment of left ventricular cardiac morphological changes, diastolic function, mechanics, and interstitial fibrosis [150]. Evaluating these indicators relies on advances in assessment techniques.

Detection of morphological changes to assess LV remodeling in the heart is the traditional diagnostic modality for HHD [146]. As the primary assessment tool, echocardiography allows simultaneous monitoring of left ventricular shape, systolic and diastolic function, and mechanical indices [151]. Nevertheless, the main limitation of echocardiography lies in its dependence on skilled and experienced technicians for image quality. Moreover, the diagnostic thresholds for HHD through imaging remain a contentious area [152]. For example, the left ventricular mass index is calculated by adjusting left ventricular mass to the body surface area, but some studies also support using height$^{2.7}$ for correction [151,153]. The current American echocardiography guidelines recommend thresholds of $>$115 g/m^2 for males and $>$95 g/m^2 for females to diagnose left ventricular hypertrophy [154]. However, this diagnostic threshold may differ among people of different races [155,156]. Hence, further research is needed to establish reference standards for diagnosing left ventricular hypertrophy via cardiac imaging that are suitable for diverse ethnic groups.

Cardiac magnetic resonance (CMR) currently serves as the gold standard for evaluating cardiac structure and function in clinical practice [10]. CMR can also provide information about tissue characteristics, enabling clinicians to assess the level of cardiac fibrosis, a crucial factor influencing HHD progression [150]. However, the cost of CMR and practical constraints, such as patients with metallic implants, hinder its widespread use. Computed tomography (CT) also holds value in assessing cardiac structure, but functional evaluation remains challenging with CT [157].

One of the most classical indicators for assessing cardiac systolic function is the left ventricular ejection fraction (LVEF). However, this indicator may not decrease in patients with HHD until they progress to decompensated heart failure [3]. Global longitudinal strain (GLS) and other cardiac mechanics parameters may offer greater sensitivity [158]. While there is currently no gold standard for *in vivo* myocardial strain measurement, speckle-tracking echocardiography has been validated and widely utilized compared to other methods [159]. GLS is impaired in various forms of hypertension, and it indicates changes in cardiac systolic function before alterations in LVEF [158,160–163]. Nevertheless, standardization issues exist with myocardial strain indices, influenced by factors such as measurement devices, operator skills, and timing [159]. Therefore, current guidelines do not establish a normal reference range for myocardial strain but emphasize the heterogeneity of measurement results [154]. Another crucial consideration is that, despite the relative insensitivity of myocardial strain indices to changes in afterload compared to LVEF, alterations in afterload can still significantly affect measurement results [3]. This suggests that changes in the measurement indices may originate from variations in blood pressure. The pressure-strain loop (PSL) is an innovative analytical approach that combines speckle-tracking strain imaging with estimated left ventricular pressure, reducing the impact of afterload on measurement results and providing a more accurate assessment of cardiac function [164]. PSL quantifies myocardial work, including four components: the Global Work Index (GWI), the Global Wasted Work (GWW), the Global Constructive Work (GCW), and the Global Work Efficiency (GWE). These indices reflect the total work during left ventricular systole, work not directly contributing to left ventricular ejection, work essentially contributing to ejection, and the ratio of work essentially contributing to ejection-to-total work. Therefore, in addition to assessing systolic function, a comprehensive analysis of these indices offers insights into cardiac mechanical efficiency.

Changes in cardiac mechanical efficiency are crucial alterations associated with the progression of HHD. The core of mechanical efficiency lies in the ratio between systolic work and total energy expenditure, and these changes have been linked to adverse cardiovascular events [165–167]. Although invasive cardiac catheterization provides the most precise estimation of cardiac work, it remains challenging for widespread clinical application [168]. Currently, there are various methods for estimating cardiac mechanical efficiency, such as the calculation of the GWE via PSL analysis and the ratio of estimated stroke work (represented as the product of systolic blood pressure and stroke volume) to cardiac oxygen consumption (represented as the

product of systolic blood pressure and heart rate) [164,166]. In pressure-strain loop-based analyses, research indicates that hypertensive patients exhibit increased GWI, GCW, and GWW. However, the most significant increase is observed in GWW, leading to a decrease in GWE, suggesting a reduced cardiac mechanical efficiency in HHD [169,170]. Moreover, several clinical trials have indicated that antihypertensive therapy can improve mechanical efficiency [171,172].

Since diastolic dysfunction tends to manifest earlier and more commonly in HHD than systolic dysfunction, the assessment of diastolic function holds particular importance in evaluating HHD. Currently, two-dimensional echocardiography and tissue Doppler measurements of E/A and E/e' ratios serve as the primary methods for diastolic function assessment and have found widespread clinical application [3,173]. However, recent research indicates that after antihypertensive treatment, the improvement in GLS is greater than that of E/e', suggesting that GLS may be a more suitable monitoring parameter for antihypertensive therapy in hypertensive patients [174].

Other imaging techniques also contribute to HHD assessment. Recently, positron emission tomography (PET) has shown promise in predicting the risk of hypertension patients developing heart failure. Physiological indicators derived from PET results, which reflect myocardial perfusion adequacy, can effectively identify subclinical HHD [175].

Biopsy and pathological examination are valuable tools for accurately assessing cardiac abnormalities [176]. In patients who have experienced sudden cardiac death due to HHD, pathological examination reveals myocardial cell hypertrophy and cardiac fibrosis [16]. However, it is important to acknowledge the limitations of using pathological examination for the widespread evaluation of HHD due to the restrictive nature of clinical cardiac biopsies. Another significant constraint is the heterogeneity of HHD lesions throughout different regions of the heart [16]. Limited biopsy samples from specific areas may make it challenging to accurately assess the overall extent of HHD pathology [177].

4. Potential Treatments for HHD

Currently, the treatment of HHD involves blood pressure control and cardiac remodeling reversal [178]. Lifestyle management is the basis of blood pressure control. Drug therapy is the main strategy for the treatment of HHD. The current first-line antihypertensive drugs mainly include angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs), thiazide diuretics, calcium channel blockers, and beta blockers [179]. Due to the advantage of ACEIs/ARBs in reversing ventricular remodeling by combating RAAS, it is recommended to be used to treat HHD over other first-line antihypertensive drugs [180]. Here, we summarized a randomized controlled study and meta-analysis on the drug treatment of left ventricular hypertrophy (LVH) or cardiac remodeling from 2013–2023 (Table 1, Ref. [22,181–213]). However, even with medical treatment, patients with HHD still face the risk of progressing to heart failure (HFpEF or HFrEF) and SCD, and the use of antihypertensive drugs is ineffective in reducing the risk of sudden death in hypertensive patients (relative risk (RR): 0.96, 95% confidence interval (95% CI): 0.81–1.15) [16,214,215]. Heart failure is the final stage of HHD, necessitating the selection of appropriate drug treatments based on the specific type of heart failure. Furthermore, interventional devices are also effective treatments for heart failure.

4.1 RAAS Inhibitors for HHD Treatment

ACEIs/ARBs are the most commonly used class of drugs for the treatment of HHD, with the effects of lowering blood pressure, reversing cardiac remodeling, and relieving myocardial fibrosis [216,217]. ACEIs are more recommended than ARBs for the treatment of hypertension [179,218]. However, in a recent network meta-analysis of randomized controlled trials comparing the effects of different antihypertensive drugs on reversing LVH, ARBs not only have a better effect on reversing LVH than β-blockers and calcium channel blockers but also have a better effect on reversing LVH than ACEIs. Similar advantages of ARBs have been observed in animal studies [219]. This may be because ARBs reduce oxidative stress and better inhibit collagen synthesis [220]. In addition, ARBs reduce cardiac damage by raising plasma Ang II levels and activating the ACE2-angiotensin (1-7) [Ang (1-7)]-Mas pathway [221].

The ACE2-angiotensin (1-7) [Ang (1-7)]-Mas pathway can antagonize the systematic biological effects of the RAAS and become a possible target for the treatment of myocardial fibrosis. An animal study revealed that pirfenidone inhibited the AT1R/p38 MAPK/RAS axis and activated the ACE2-angiotensin (1-7) [Ang (1-7)]-Mas pathway by activating liver X receptor alpha (LXR-α), thereby improving the imbalance of the ACE/ACE2 ratio in rats with myocardial infarction and inhibiting myocardial remodeling and fibrosis [222]. A phase II clinical trial assessing the treatment of HFpEF patients with pirfenidone has shown effective reductions in myocardial fibrosis, but further trials are needed to verify this [223].

Angiotensin receptor/neprilysin inhibitors (ARNIs, such as sacubitril/valsartan) can antagonize both the natriuretic peptide system and RAAS, and they are recommended to be used to treat heart failure in preference to ACEIs/ARBs [224,225]. Sacubitril/valsartan also effectively reduces blood pressure in hypertensive patients and has a high safety profile [226,227]. The PARAMETER study revealed that ARNIs are more effective than ACEIs/ARBs in reducing dynamic central aortic and brachial artery pressures in elderly patients with high systolic blood pressure [228]. This suggested that ARNIs are superior to ACEIs/ARBs in controlling and preventing the

Table 1. Summary of randomized controlled study and meta-analysis on the drug treatment of left ventricular hypertrophy (LVH) or cardiac remodeling.

Study	Country	Study population	Comparison	Length of follow-up	Main finding
Meta-analysis					
Jian-Shu Chen *et al.*, 2020 [181]	China	5402 from 49 studies	/	1992–2020	The use of ARB, in antihypertensive therapy could achieve better efficacy then ACEI, beta-blockers and CCB reversing LVH in hypertensive.
Yao Wang *et al.*, 2023 [182]	China	984 from 11 studies	/	2019–2022	SGLT-2i have the beneficial effects on reversal of left ventricular remodeling (LVM: SMD –0.23, 95% CI –0.44 to –0.02; LVMI: SMD –0.25, 95% CI –0.38 to –0.12).
Yiwen Wang *et al.*, 2019 [183]	China	10,175 from 20 studies	/	2010–2019	ARNI can improve functional capacity and CRR in patients with HFrEF(LVMI: MD –3.25 g/m^2, 95% CI –3.78, –2.72).
Quênia Janaína Tomaz de Castro *et al.*, 2020 [184]	Brazil	1738 from 5 studies	/	By April 2020	The antihypertensive therapy combined with physical exercise practice can reduce LVM (95% CI –21.63 to –1.81) and HR.
Ye Liu *et al.*, 2022 [185]	The United States	209 from 5 studies	/	By June 2020	ARB treatment is not associated with reduced LVM nor remarkable LVEF change among patients with hypertrophic cardiomyopathy.
George C Roush *et al.*, 2018 [186]	The United States	2299 patients from 27 articles	/	1992–2009	CHIP diuretics surpass HCTZ for reducing LVM and CHIP diuretics reduce LVM 2-fold more than HCTZ among hypertensive patients.
Dimitrios Patoulias *et al.*, 2020 [187]	Greece	212 patients	/	By July 2020	SGLT-2i treatment in patients with T2D has a favorable effect on LVM.
Li-Ya Yang *et al.*, 2013 [188]	China	207 from 6 studies	/	By November 2010	ARBs are associated with a greater reduction in LVH in patients on dialysis. however, the combination of ARBs with ACEIs did not show additional benefit to LVH in patients on hemodialysis.
RenJie Lu *et al.*, 2016 [189]	China	4935 CKD patients from 12 studies	/	By December 2015	MRA benefits CKD patients in terms of LVMI, MRA treatment versus non-MRA treatment resulted in a significant change of 0.93 SMD in LVM.
FuWei Xing *et al.*, 2017 [190]	China	2566 patients with HT and LVH from 41studies	/	By December 2016	FS-β-B showed greater efficacy when compared with diuretic (MD, 13.04; 95% CI, 3.38, 22.59) or CCB (MD, 10.90; 95% CI, 1.98, 19.49). FS-β-B have the beneficial effects on HT and LVH patients.
Yue Yang *et al.*, 2016 [191]	China	357 patients from 8 clinical trials	/	By December 2015	The comparison between ACEI/ARB and controls (other antihypertensive drugs or placebo) showed that the former type of drug causes a greater reduction in LVMI with hemodialysis patients.
Elisa Giannetta *et al.*, 2014 [192]	Italy	1622 patients from 24 studies	/	2012–2013	PDE5i have an anti-remodeling effect by reducing cardiac mass (–12.21 g/m^2, 95% CI: –18.85 to –5.57) in patients with LVH.
Randomized Controlled Trial					
Alexander J M Brown *et al.*, 2020 [22]	United Kingdom	66 people with T2D, LVH, and controlled blood pressure	dapagliflozin 10 mg once daily *vs.* placebo	12 months	Dapagliflozin treatment significantly reduced LVM in people with T2D and LVH (mean change –2.92 g; 95% CI: –5.45 to –0.38, $p = 0.025$).
Amil M Shah *et al.*, 2022 [193]	The United States	457 PARADISE-MI participants	sacubitril/valsartan twice daily *vs.* ramipril 5 mg twice daily	8 months	Treatment with sacubitril/valsartan compared with ramipril after AMI did not result in changes in LVEF or LAV at 8 months.

Table 1. Continued.

Study	Country	Study population	Comparison	Length of follow-up	Main finding
			Meta-analysis		
Balwant Lal *et al*., 2018 [194]	Pakistan	76 patients with LVH	allopurinol *vs*. febuxostat	6 months	Allopurinol was found to be more effective than febuxostatin reducing the LVM and LVH independent of blood pressure.
Valentina Mercurio *et al*., 2020 [195]	Italy	158 patients with MS and LVH	Nutraceutical combination (berberine 500 mg, red yeast rice 200 mg and policosanol 10 mg) once daily *vs*. placebo	24 weeks	Treatment with AP is associated with a significant reduction in LVM in subjects with MS and LVH.
Alvin Chandra *et al*., 2022 [196]	The United States	1025 patients	vitamin D3 (2000 IU/d) and n-3 fatty acids (1 g/d) *vs*. placebo	2 years	Among adults aged $\geq$50 years, neither vitamin D3 nor n-3 fatty acids supplementation had significant effects on cardiac structure and function after 2 years.
Phillip D Levy *et al*., 2023 [197]	The United States	113 patients with hypertension (systolic blood pressure [BP] $>$160 mm Hg), increased LVMI, and vitamin D deficiency ($<$20 ng/mL)	50,000 IU vitamin D3 *vs*. placebo	1 year	The study not find an association between vitamin D supplementation and differential regression of LVMI or reduction in systolic BP.
Mohapradeep Mohan *et al*., 2019 [198]	United Kingdom	68 patients without diabetes who have CAD with IR and/or pre-diabetes	metformin XL (2000 mg daily dose) *vs*. placebo	1 year	Metformin treatment significantly reduced LVMI (95% CI: –2.63 to –0.12, $p = 0.033$) and LVM ($p = 0.032$).
Luigi Gnudi *et al*., 2023 [199]	United Kingdom	45 patients with T2D and CKD	0.5 mcg calcitriol once daily *vs*. placebo	48 weeks	The study did not provide evidence that treatment with calcitriol as compared to placebo might improve LVMI in patients with T2D, mild left ventricular hypertrophy and stable CKD.
Christopher R Gingles *et al*., 2019 [200]	United Kingdom	362 patients with essential hypertension and LVH	allopurinol (600 mg/day) *vs*. placebo	12 months	Treatment with high-dose allopurinol in normouricemic controlled hypertensive patients and LVH is detrimental (LVM: –0.37 $\pm$ 6.08 *versus* –3.75 $\pm$ 3.89 g; $p = 0.012$).
Mads Ersbøll *et al*., 2022 [201]	Denmark	91 patients with high-risk T2D	empagliflozin (25 mg/day) *vs*. placebo	13 weeks	13 weeks empagliflozin treatment in patients with type-2 diabetes at high CV risk significantly reduced LVM, improved LV geometry and improved diastolic function compared to placebo.
Roland E Schmieder *et al*., 2017 [202]	Germany	114 patients with essential hypertension	sacubitril/valsartan *vs*. olmesartan	52 weeks	LVMI decreased to a greater extent in the sacubitril/valsartan group compared to the olmesartan group from baseline to 12 weeks (–6.36 *vs*. –2.32 g/m^2; $p = 0.039$) and from baseline to 52 weeks (–6.83 *vs*. –3.55 g/m^2; $p = 0.029$).
Greicy Mara Mengue Feniman-De-Stefano *et al*., 2015 [203]	Brazil	17 hemodialysis patients	25 mg of spironolactone *vs*. placebo	6 months	The group receiving spironolactone had a LVMI reduction from 77 $\pm$ 14.6 g/m$^{2.7}$ to 69 $\pm$ 10.5 g/m$^{2.7}$, $p < 0.04$, whereas in placebo group there was an increase from 71 $\pm$ 14.2 g/m$^{2.7}$ to 74 $\pm$ 17.4 g/m$^{2.7}$. Spironolactone treatment in hemodialysis patients was secure and effective in regression of left ventricular hypertrophy.

Table 1. Continued.

Study	Country	Study population	Comparison	Length of follow-up	Main finding
			Meta-analysis		
Benjamin R Szwejkowski *et al*., 2013 [204]	United Kingdom	66 T2D patients	Allopurinol, 600 mg/day *vs*. placebo	9 months	Allopurinol causes regression of LVM in patients with T2D and LVH (LVM –2.65 ± 5.91 g *vs*. placebo group +1.21 ± 5.10 g, $p = 0.012$ and LVMI to body surface area –1.32 ± 2.84 g/m^2 *vs*. placebo group +0.65 ± 3.07 g/m^2, $p = 0.017$).
Hirohiko Motoki *et al*., 2014 [205]	Japan	32 hypertensive patients	5 mg of amlodipine/day *vs*. 16 mg of azelnidipine/day	12 months	Azelnidipine has beneficial effects on LVM regression, transmitral flow, tissue Doppler, and LV longitudinal strain that are comparable to those of amlodipine on the same parameters.
Han Li *et al*., 2013 [206]	China	64 PD patients with hypertension	nitrate group *vs*. non-nitrate group	24 weeks	It was concluded that organic nitrates favor regression of LVH in hypertensive patients on chronic peritoneal dialysis (LVMI reduction:nitrate group: 14.6 ± 4.9 g/m^2 *vs*. non-nitrate group: 10.6 ± 6.7 g/m^2).
Uğur Abbas Bal *et al*., 2015 [207]	Turkey	22 postmenopausal osteoporotic women	raloxifene 60 mg/day *vs*. control group	6 months	Raloxifene therapy does not affect myocardial hypertrophy in postmenopausal women after 6 months of treatment.
C Moroni *et al*., 2017 [208]	Italy	56 sex-, age- and therapy-matched subjects with essential hypertension and LVH	losartan (100 mg/die) on-top treatment *vs*. control group	3 years	Losartan induced both a significant reduction of LVH and an improvement of LV diastolic function with a subsequent expected beneficial shift on the prognosis.
Giuseppe Derosa *et al*., 2015 [209]	Italy	145 patients in hypertensive, T2D with LVH	lercanidipine, 20 mg/day and losartan, 100 mg/day *vs*. barnidipine, 20 mg/day and losartan, 100 mg/day	6 months	Barnidipine + losartan provided a greater improvement of echocardiographic parameters compared to lercanidipine + losartan. (such as LVMI and so on).
Huan Zheng *et al*., 2016 [210]	China	50 borderline and mildly hypertensive patients	exercise group received a 4 months' exercise program *vs*. control group	4 months	Four-month exercise training in borderline and mildly hypertensive patients not only decreased their blood pressure levels, but also induced an improvement of exercise capability, left ventricular remodeling and heart rate recovery.
Sushma Rekhraj *et al*., 2013 [211]	United Kingdom	66 patients with IHD and LVH	600 mg/day allopurinol *vs*. placebo	9 months	High-dose allopurinol regresses LVH, reduces LV end-systolic volume, LVM (allopurinol –5.2 ± 5.8 g *vs*. placebo –1.3 ± 4.48 g; $p = 0.007$) and LVMI (allopurinol –2.2 ± 2.78 g/m^2 *vs*. placebo –0.53 ± 2.5 g/m^2; $p = 0.023$).
Yasuhiko Ito *et al*., 2014 [212]	Japan	158 patients under treatment with ACEI or ARB and undergoing peritoneal dialysis	The 25-mg once-daily dose of spironolactone *vs*. control group	2 years	In this trial, spironolactone prevented cardiac hypertrophy and decreases in left ventricular ejection fraction in patients undergoing peritoneal dialysis, without significant adverse effects.
Takafumi Okura *et al*., 2013 [213]	Japan	53 patients with hypertension	50 mg/day of losartan and 12.5 mg/day of HCTZ *vs*. a standard dose of ARB and CCB	48 weeks	These results suggest that combination therapy of an ARB and diuretic has greater potential to cause regression compared with an ARB and CCB.

ARB, angiotensin receptor blockers; ACEI, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; LVM, left ventricular mass; LVMI, left ventricular mass index; SMD, standardized mean difference; 95% CI, 95% confidence interval; ARNI, angiotensin receptor-neprilysin inhibitors; CRR, cardiac reverse remodeling; HFrEF, heart failure with reduced ejection fraction; MD, mean difference; HR, heart rate; LVEF, left ventricular ejection fraction; T2D, type-2 diabetes; CHIP diuretics, chlorthalidone, indapamide, and potassium-sparing diuretic/hydrochlorothiazide; HCTZ, hydrochlorothiazide; MRA, mineralocorticoid-receptor antagonists; LVH, left ventricular hypertrophy; CKD, chronic kidney disease; HT, hypertension; FS-β-B, fat-soluble and selective β1-receptor blockers; PDE5i, phosphodiesterase type 5 inhibitors; AMI, acute myocardial infarction; LAV, left atrial volume; AP, armolipid plus; MS, metabolic syndrome; BP, blood pressure; CAD, coronary artery disease; IR, insulin resistance; CV, cardiovascular; LV, left ventricular; PD, peritoneal dialysis; IHD, ischemic heart disease.

progression of HHD. However, whether ARNIs can reverse hypertensive LVH is still being investigated (NCT03553810). Therefore, more research is needed to determine whether patients with HHD can use angiotensin receptor-neprilysin inhibitors (ARNIs) as an early alternative to ACEIs/ARBs. In HFrEF, sacubitril/valsartan outperformed ACEIs/ARBs in reducing the risk of cardiovascular death and improving LVH [229]. In HFpEF, a recent meta-analysis showed no significant difference in all-cause and cardiovascular mortality with RAAS antagonists in HFpEF patients, but ARNIs demonstrated superiority over ARB (odds ratio (OR): 0.80, 95% CI: 0.71–0.91) in reducing HFpEF-related hospitalizations [230]. Therefore, when patients with HHD progress to heart failure, ARNIs may be more effective than ACEIs/ARBs.

Mineralocorticoid receptor antagonists (MRAs) are a class of drugs that act on mineralocorticoid receptors by antagonizing aldosterone, which is used to treat heart failure and relieve cardiac remodeling and myocardial fibrosis [231]. In a randomized controlled study of 140 patients with type-2 diabetes, the eplerenone-treated group had a 3.7 g/m^2 reduction in indexed left ventricular mass from baseline (95% CI: –6.7 to –0.7; p = 0.017) [232]. Compared with the control group, the concentration of plasma N terminal pro B type natriuretic peptide (NT-proBNP) and pro-collagen type I N-terminal propeptide decreased significantly, which suggested that it could reverse cardiac remodeling and prevent heart failure [232]. For HFrEF, MRA is often used in combination with other drugs, which are thought to reduce the risk of death better and reverse cardiac remodeling [233,234]. For HFpEF, MRA does not reduce the risk of death [235,236]. Therefore, the use of MRA is more beneficial when HHD progresses to HFrEF compared to when it progresses to HFpEF. The use of steroidal MRA (spironolactone, eplerenone) has been limited due to adverse effects (hyperkalemia, renal insufficiency, etc.) [237]. As a nonsteroidal MRA, finerenone is considered safer and can be used for treating diabetic nephropathy and heart failure [237,238]. At natriuretic doses, finerenone was more effective than eplerenone in reducing cardiac hypertrophy and BNP and improving left ventricular systolic and diastolic function [239]. Finerenone may be an alternative to traditional MRA in the treatment of HHD.

In addition to drug therapy, RAAS antagonism has become the goal of many hypertension vaccines [240–243]. In animal models, angiotensin I and II vaccines reduced blood pressure in hypertensive rats [240,241]. However, in clinical trials, angiotensin I, while increasing angiotensin-1 antibody titers, did not reduce blood pressure in patients [242]. A randomized controlled trial evaluating the angiotensin-2 vaccine AGMG0201 revealed that AGMG0201 improved angiotensin-2 antibody titers and had a good safety profile but did not assess the effect of the vaccine on blood pressure in patients [243]. Another recent clinical trial found that zilebesiran, as a small interfering RNA (siRNA) drug, inhibits angiotensinogen synthesis in liver cells, and a single subcutaneous injection can reduce serum angiotensinogen and blood pressure levels and can be maintained for up to 24 weeks [244]. A new clinical trial of zilebesiran as an add-on treatment for patients with inadequately controlled hypertension is also underway (NCT05103332). Due to the lack of long-term antihypertensive drugs, compliance in patients with hypertension and HHD is often low. This often leads to unsatisfactory curative effects for HHD patients. Hypertension vaccines and siRNA drugs are expected to become effective long-term therapies to reduce blood pressure and compensate for the gap in hypertension treatment.

4.2 Beta-Blockers for HHD Treatment

The ESC/ESH (European Society of Cardiology/European Society of Hypertension) guidelines for hypertension include beta-blockers as first-line antihypertensive agents, while the ACC/AHA (American College of Cardiology/American Heart Association) guidelines do not [179,218]. Beta-blockers should be preferred for heart rate control in patients with myocardial infarction [245]. There is a lack of recommendations for the use of beta-blockers in hypertensive LVH without coronary heart disease, possibly due to the limited effect in reversing LVH [246,247]. However, beta-blockers are superior to other antihypertensive medications in alleviating myocardial ischemia and preventing tachyarrhythmia in hypertensive LVH [246,247]. Thus, beta-blockers possibly offer irreplaceable advantages in the treatment of HHD. In hypertensive heart failure, beta-blockers can effectively improve patients' ejection fraction [248]. Moreover, a meta-analysis revealed that beta-blockers may reduce the risk of cardiovascular death in HFpEF patients, but the evidence is limited [235]. Therefore, trials of beta-blockers in the treatment of each stage of HHD are insufficient.

4.3 Inhibitors of Sodium-Glucose Cotransporter 2 for HHD Treatment

Cardiometabolic abnormalities are an important risk factor for hypertension and cardiovascular diseases, and patients with metabolic syndrome have a higher risk of HHD [249]. Improving metabolic abnormalities in HHD patients is a new therapeutic target. SGLT2 may be an important target for the treatment of cardiovascular diseases by improving metabolism. In a randomized controlled clinical trial, 124 hypertension patients with type-2 diabetes were randomly given 25 mg empagliflozin quaque die (QD) or a placebo for 12 weeks. The 24 h mean ambulatory blood pressure decreased significantly in patients treated with empagliflozin [250]. Another meta-analysis also demonstrated that SGLT2 inhibitors reduced ambulatory blood pressure but also revealed that the antihypertensive effect of SGLT2 inhibitors was more pronounced during the day than at night and was independent of the dose used [251]. SGLT2 in-

hibitors are beneficial in patients with LVH. In a randomized controlled trial, a group with type-2 diabetes and LVH using dapagliflozin had a significant decrease in left ventricular mass compared with a control group (95% CI: –5.13 to –0.51 g; $p = 0.018$), effectively reversing left ventricular remodeling [22]. Another randomized controlled trial of the effects of empagliflozin on left ventricular mass in patients with type-2 diabetes and coronary artery disease reported similar results [252]. In hypertensive heart failure rats, empagliflozin can modify cardiac relaxation and contraction functions and alleviate myocardial fibrosis [253]. In other clinical studies, SGLT2 inhibitors have benefits for both HFrEF and HFpEF, mainly reducing the risk of cardiovascular death and hospitalization for heart failure and improving the quality of life of patients with heart failure [254–256]. More clinical trials of SGLT2 inhibitors in patients with heart failure are also being conducted (NCT05737186). However, there is still a lack of clinical studies on the therapeutic effects of SGLT-2 inhibitors in patients limited to hypertensive heart failure.

4.4 Improving Gut Microbiota for HHD Treatment

Probiotics and prebiotics have beneficial effects on patients with HHD through multiple channels. Treatment with Bifidobacterium breve can reduce blood pressure and damage to related target organs in deoxycorticosterone acetate-salt rats [257]. By feeding Lactobacillus fermentum to male Wistar rats on a high-fat diet, systolic blood pressure (SBP) can be effectively reduced, and cardiometabolic abnormalities associated with hypersympathetic function can be inhibited [258]. The role of probiotics and prebiotics in treating hypertension has been further confirmed in clinical trials. In a meta-analysis of 14 studies involving 846 people with high blood pressure, the use of probiotics reduced SBP by 2.05 mmHg (95% CI: 3.87–0.24; $p = 0.03$) and diastolic blood pressure (DBP) by 1.26 mmHg (95% CI: 2.51–0.004; $p = 0.047$) [259]. The intake of multiple probiotics and probiotic intake for more than 11 weeks may have a greater antihypertensive effect [260]. A meta-analysis that explored the effect of prebiotics on blood pressure came to a similar conclusion that the intake of prebiotic beta-glucan fiber was effective in reducing blood pressure [261]. In addition to blood pressure control, probiotics and prebiotics can improve myocardial lesions. The probiotic Lactobacillus rhamnosus GR-1 reduced left ventricular hypertrophy and improved the ejection fraction in rats after myocardial infarction [262]. A high-fiber diet improves gut microbiota and supplements with acetate to lower blood pressure and improve LVH due to myocardial fibrosis and hypertension [263]. In addition, probiotics and prebiotics are also associated with benefits in lipid regulation and obesity treatment [264,265]. Trials are underway to explore more different combinations of probiotics to treat hypertension [266]. As an important method to improve intestinal flora disorders, fecal microbial transplantation is being explored for more indications [267]. Trials of fecal microbiota transplantation for the treatment of hypertension are also in progress (NCT04406129, NCT05608447) [268].

4.5 Lifestyle Modification for HHD Treatment

Lifestyle management is essential for the treatment of hypertension and HHD. The lifestyle benefits for HHD patients mainly include reasonable diet control, moderate physical exercise, prevention of obesity, and moderate alcohol consumption or abstinence [179,218].

Reasonable diet control is beneficial to patients with hypertension and heart disease. First, sodium intake is considered to have a causal relationship with hypertension, and reasonable sodium intake can effectively prevent and control hypertension [269,270]. In addition, an appropriate increase in potassium-containing foods can also help control blood pressure [271]. The Dietary Approaches to Stop Hypertension (DASH) diet is considered a dietary strategy for hypertension independent of sodium intake [272]. A meta-analysis of 30 randomized controlled studies (5545 participants) found that the DASH diet reduced SBP by 3.2 mmHg (95% CI: –4.2 to –2.3; $p < 0.001$) and DBP by 2.5 mmHg (95% CI: –3.5 to –1.5; $p < 0.001$), regardless of whether participants had high blood pressure [273]. In addition, the Mediterranean diet can also reduce blood pressure and the risk of heart failure, but there is still insufficient research evidence [274,275]. Long-term adherence to other dietary strategies, such as the Paleolithic diet (PD) or a Nordic Nutrition Recommendation (NNR) diet, is thought to improve left ventricular remodeling and may also benefit HHD [276].

Proper aerobic exercise can also be beneficial for people with high blood pressure. In a randomized controlled study on the effects of aerobic exercise on patients with refractory hypertension, 24-hour ambulatory blood pressure and office systolic blood pressure in patients with refractory hypertension who engaged in aerobic exercise decreased significantly compared with the control group [277]. Another meta-analysis highlighted that aerobic exercise reduced ambulatory blood pressure only in hypertensive patients taking antihypertensive medications [278]. Exercise is also beneficial for left ventricular hypertrophy in HHD patients. An animal experiment found that the metalloproteinase 2 of rats with losartan combined with physical exercise decreased significantly compared with that of sedentary spontaneously hypertensive rats using losartan. The reduction in cardiomyocyte diameter was observed only in rats with high doses of losartan (10 mg/kg) combined with physical exercise [279]. Another meta-analysis showed that physical exercise combined with antihypertensive medication significantly reduced left ventricular mass (95% CI: –21.63 to –1.81 g), and although there was a downward trend in left ventricular mass index and an upward trend in ejection fraction, the difference was not statistically significant [184].

4.6 MicroRNAs for HHD Treatment

MicroRNAs (miRNAs) are a class of endogenous noncoding small RNAs that mainly play a regulatory role in mRNA translation and degradation [280]. Many miRNAs participate in hypertension and HHD development [281–283]. The method of using microRNA to treat diseases is introducing miRNA-mimic or anti-miRNA oligonucleotide inhibitors [283]. A study has shown that recombinant adeno-associated virus delivery of endogenous and exogenous miRNA-21 into spontaneous hypertensive rats can reduce blood pressure and reverse cardiac hypertrophy. This is related to miRNA-21's ability to promote mitochondrial translation to produce mitochondrial DNA (mtDNA)-encoded cytochrome b [284]. Another study effectively improved cardiac remodeling and cardiac function in rats with hypertension-induced heart failure by subcutaneous delivery of microRNA-208A inhibitors [285]. However, there is currently a lack of clinical trials on miRNAs for hypertension and HHD, so the efficacy and safety of miRNA therapy remain uncertain.

4.7 Interventional Devices for HHD Treatment

When HHD advances to severe heart failure, medication therapy alone is insufficient. Cardiac resynchronization therapy (CRT) is an effective surgical treatment to improve the prognosis and quality of life of patients with heart failure [286–288]. In recent years, cardiac contractility modulation (CCM) has emerged as a new surgical modality for the treatment of heart failure and has become a significant option for individuals who are ineligible for or do not respond well to CRT. A prospective study identified the safety and efficacy of CCM for HFpEF [289]. This discovery could offer new hope for HHD patients progressing to HFpEF, as they lack effective therapeutic drugs. In addition, patients with HHD usually have a higher risk of ventricular arrhythmia, especially in the presence of LVH and heart failure [290]. Implantable cardioverter defibrillators (ICDs) can effectively treat ventricular arrhythmias and significantly reduce the risk of death in heart failure patients [291,292]. Therefore, for hypertensive heart failure patients who meet the indications, ICD therapy is necessary.

5. Perspectives

The incidence of HHD has been continuously increasing in recent years, with a total of 18.6 million people suffering from HHD worldwide in 2019 and more than one million people dying from HHD each year [4]. The worldwide prevalence of hypertension is still high, and a large proportion of patients with diagnosed hypertension have unsatisfactory blood pressure control, indicating that they are potentially at high risk for HHD [293–295]. First, due to the symptoms of early hypertension being covert, many hypertension patients have no obvious symptoms, even though some of them have structural changes in the heart [296]. Obvious symptoms typically do not occur until symptoms associated with severe cardiac impairment are present. Second, the heart is one of the most common target organs for hypertension damage [179,297]. In addition, hypertension is a necessary condition for HHD, and the risk factors for hypertension also promote the development of HHD. However, there are increasing factors that promote and exacerbate hypertension (such as obesity and alcoholism) with changes in nutrition and lifestyle [249,298–300].

At present, early diagnosis and treatment of hypertension and control of blood pressure within the normal range are important measures to reduce the occurrence and development of HHD, which mainly includes regular use of appropriate antihypertensive drugs and improvement of lifestyle. In addition to drug therapy and lifestyle improvement, surgery may be used for patients with HHD progressing to HF. However, there is a lack of specific drug therapy for the progression of heart damage in the intermediate process from hypertension to HF. Currently, most patients only control damage in the heart by controlling blood pressure, which is far from sufficient for the treatment of HHD.

6. Conclusions

In summary, future studies are needed to determine the mechanism of HHD progression and design drugs specifically to improve hypertension-induced heart damage. In addition, in treating patients with hypertension and HHD, the importance of controlling multiple hypertension risk factors in combination with anti-HHD drugs should be emphasized to improve myocardial remodeling in HHD treatment.

Author Contributions

XH and LH drafted the manuscript, collected data and literatures. ZL and XW collected and analyzed data, edited manuscript and provided valuable suggestions to the revision. JC and JW conceived the idea, edited manuscript for important intellectual content, and supervised the study. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This work was supported by the Science and Technology Innovation Program of Hunan Province 2022RC3073 (J. C), Hunan Key Research and Development Project 2022SK2030 (J. C).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nature Reviews. Nephrology. 2020; 16: 223–237.

[2] Chen MM, Zhang X, Liu YM, Chen Z, Li H, Lei F, *et al*. Heavy Disease Burden of High Systolic Blood Pressure During 1990-2019: Highlighting Regional, Sex, and Age Specific Strategies in Blood Pressure Control. Frontiers in Cardiovascular Medicine. 2021; 8: 754778.

[3] Tadic M, Cuspidi C, Marwick TH. Phenotyping the hypertensive heart. European Heart Journal. 2022; 43: 3794–3810.

[4] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al*. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update from the GBD 2019 Study. Journal of the American College of Cardiology. 2020; 76: 2982–3021.

[5] Drazner MH. The progression of hypertensive heart disease. Circulation. 2011; 123: 327–334.

[6] Tingleff J, Munch M, Jakobsen TJ, Torp-Pedersen C, Olsen ME, Jensen KH, *et al*. Prevalence of left ventricular hypertrophy in a hypertensive population. European Heart Journal. 1996; 17: 143–149.

[7] Drazner MH, Dries DL, Peshock RM, Cooper RS, Klassen C, Kazi F, *et al*. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. Hypertension (Dallas, Tex.: 1979). 2005; 46: 124–129.

[8] Wang SX, Xue H, Zou YB, Sun K, Fu CY, Wang H, *et al*. Prevalence and risk factors for left ventricular hypertrophy and left ventricular geometric abnormality in the patients with hypertension among Han Chinese. Chinese Medical Journal. 2012; 125: 21–26.

[9] Pewsner D, Jüni P, Egger M, Battaglia M, Sundström J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. BMJ (Clinical Research Ed.). 2007; 335: 711.

[10] Gjesdal O, Bluemke DA, Lima JA. Cardiac remodeling at the population level–risk factors, screening, and outcomes. Nature Reviews. Cardiology. 2011; 8: 673–685.

[11] Suthahar N, Lau ES, Blaha MJ, Paniagua SM, Larson MG, Psaty BM, *et al*. Sex-Specific Associations of Cardiovascular Risk Factors and Biomarkers with Incident Heart Failure. Journal of the American College of Cardiology. 2020; 76: 1455–1465.

[12] Shah AM, Cikes M, Prasad N, Li G, Getchevski S, Claggett B, *et al*. Echocardiographic Features of Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction. Journal of the American College of Cardiology. 2019; 74: 2858–2873.

[13] de Simone G, Gottdiener JS, Chinali M, Maurer MS. Left ventricular mass predicts heart failure not related to previous myocardial infarction: the Cardiovascular Health Study. European Heart Journal. 2008; 29: 741–747.

[14] Messerli FH, Rimoldi SF, Bangalore S. The Transition from Hypertension to Heart Failure: Contemporary Update. JACC. Heart Failure. 2017; 5: 543–551.

[15] Kawel-Boehm N, Kronmal R, Eng J, Folsom A, Burke G, Carr JJ, *et al*. Left Ventricular Mass at MRI and Long-term Risk of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis (MESA). Radiology. 2019; 293: 107–114.

[16] Westaby JD, Miles C, Chis Ster I, Cooper STE, Antonios TF, Meijles D, *et al*. Characterisation of hypertensive heart disease: pathological insights from a sudden cardiac death cohort to inform clinical practice. Journal of Human Hypertension. 2022; 36: 246–253.

[17] González A, Ravassa S, López B, Moreno MU, Beaumont J, San José G, *et al*. Myocardial Remodeling in Hypertension. Hypertension (Dallas, Tex.: 1979). 2018; 72: 549–558.

[18] Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. Nature Reviews. Cardiology. 2018; 15: 387–407.

[19] Xu M, Liu PP, Li H. Innate Immune Signaling and Its Role in Metabolic and Cardiovascular Diseases. Physiological Reviews. 2019; 99: 893–948.

[20] Soliman EZ, Ambrosius WT, Cushman WC, Zhang ZM, Bates JT, Neyra JA, *et al*. Effect of Intensive Blood Pressure Lowering on Left Ventricular Hypertrophy in Patients with Hypertension: SPRINT (Systolic Blood Pressure Intervention Trial). Circulation. 2017; 136: 440–450.

[21] Deng Y, Liu W, Yang X, Guo Z, Zhang J, Huang R, *et al*. Intensive Blood Pressure Lowering Improves Left Ventricular Hypertrophy in Older Patients with Hypertension: The STEP Trial. Hypertension (Dallas, Tex.: 1979). 2023; 80: 1834–1842.

[22] Brown AJM, Gandy S, McCrimmon R, Houston JG, Struthers AD, Lang CC. A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: the DAPA-LVH trial. European Heart Journal. 2020; 41: 3421–3432.

[23] Martin TG, Juarros MA, Leinwand LA. Regression of cardiac hypertrophy in health and disease: mechanisms and therapeutic potential. Nature Reviews. Cardiology. 2023; 20: 347–363.

[24] Deng KQ, Zhao GN, Wang Z, Fang J, Jiang Z, Gong J, *et al*. Targeting Transmembrane BAX Inhibitor Motif Containing 1 Alleviates Pathological Cardiac Hypertrophy. Circulation. 2018; 137: 1486–1504.

[25] Frohlich ED, Apstein C, Chobanian AV, Devereux RB, Dustan HP, Dzau V, *et al*. The heart in hypertension. The New England Journal of Medicine. 1992; 327: 998–1008.

[26] Fung MJ, Thomas L, Leung DY. Left ventricular function and contractile reserve in patients with hypertension. European Heart Journal. Cardiovascular Imaging. 2018; 19: 1253–1259.

[27] Ljubojevic-Holzer S, Herren AW, Djalinac N, Voglhuber J, Morotti S, Holzer M, *et al*. CaMKIIδC Drives Early Adaptive Ca^{2+} Change and Late Eccentric Cardiac Hypertrophy. Circulation Research. 2020; 127: 1159–1178.

[28] Billet S, Bardin S, Verp S, Baudrie V, Michaud A, Conchon S, *et al*. Gain-of-function mutant of angiotensin II receptor, type 1A, causes hypertension and cardiovascular fibrosis in mice. The Journal of Clinical Investigation. 2007; 117: 1914–1925.

[29] Cigola E, Kajstura J, Li B, Meggs LG, Anversa P. Angiotensin II activates programmed myocyte cell death *in vitro*. Experimental Cell Research. 1997; 231: 363–371.

[30] Salazar NC, Chen J, Rockman HA. Cardiac GPCRs: GPCR signaling in healthy and failing hearts. Biochimica et Biophysica Acta. 2007; 1768: 1006–1018.

[31] Miao R, Lu Y, Xing X, Li Y, Huang Z, Zhong H, *et al*. Regulator of G-Protein Signaling 10 Negatively Regulates Cardiac Remodeling by Blocking Mitogen-Activated Protein Kinase-Extracellular Signal-Regulated Protein Kinase 1/2 Signaling. Hypertension (Dallas, Tex.: 1979). 2016; 67: 86–98.

[32] Huang J, Chen L, Yao Y, Tang C, Ding J, Fu C, *et al*. Pivotal Role of Regulator of G-protein Signaling 12 in Pathological Cardiac Hypertrophy. Hypertension (Dallas, Tex.: 1979). 2016; 67: 1228–1236.

[33] Dai DF, Johnson SC, Villarin JJ, Chin MT, Nieves-Cintrón M, Chen T, *et al*. Mitochondrial oxidative stress mediates angiotensin II-induced cardiac hypertrophy and Galphaq overexpression-induced heart failure. Circulation Research. 2011; 108: 837–846.

[34] Liu J, Li W, Deng KQ, Tian S, Liu H, Shi H, *et al*. The E3 Ligase TRIM16 Is a Key Suppressor of Pathological Cardiac Hypertrophy. Circulation Research. 2022; 130: 1586–1600.

[35] Fredj S, Bescond J, Louault C, Delwail A, Lecron JC, Potreau D. Role of interleukin-6 in cardiomyocyte/cardiac fibroblast interactions during myocyte hypertrophy and fibroblast proliferation. Journal of Cellular Physiology. 2005; 204: 428–436.
[36] Sano M, Fukuda K, Kodama H, Pan J, Saito M, Matsuzaki J, *et al*. Interleukin-6 family of cytokines mediate angiotensin II-induced cardiac hypertrophy in rodent cardiomyocytes. The Journal of Biological Chemistry. 2000; 275: 29717–29723.
[37] Wintrich J, Kindermann I, Ukena C, Selejan S, Werner C, Maack C, *et al*. Therapeutic approaches in heart failure with preserved ejection fraction: past, present, and future. Clinical Research in Cardiology: Official Journal of the German Cardiac Society. 2020; 109: 1079–1098.
[38] Mishra S, Kass DA. Cellular and molecular pathobiology of heart failure with preserved ejection fraction. Nature Reviews. Cardiology. 2021; 18: 400–423.
[39] Lymperopoulos A, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. Circulation Research. 2013; 113: 739–753.
[40] Wang J, Gareri C, Rockman HA. G-Protein-Coupled Receptors in Heart Disease. Circulation Research. 2018; 123: 716–735.
[41] Zhu WZ, Wang SQ, Chakir K, Yang D, Zhang T, Brown JH, *et al*. Linkage of beta1-adrenergic stimulation to apoptotic heart cell death through protein kinase A-independent activation of Ca2+/calmodulin kinase II. The Journal of Clinical Investigation. 2003; 111: 617–625.
[42] Zhu WZ, Zheng M, Koch WJ, Lefkowitz RJ, Kobilka BK, Xiao RP. Dual modulation of cell survival and cell death by beta(2)-adrenergic signaling in adult mouse cardiac myocytes. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98: 1607–1612.
[43] Métrich M, Lucas A, Gastineau M, Samuel JL, Heymes C, Morel E, *et al*. Epac mediates beta-adrenergic receptor-induced cardiomyocyte hypertrophy. Circulation Research. 2008; 102: 959–965.
[44] Pfleger J, Gresham K, Koch WJ. G protein-coupled receptor kinases as therapeutic targets in the heart. Nature Reviews. Cardiology. 2019; 16: 612–622.
[45] Sun X, Zhou M, Wen G, Huang Y, Wu J, Peng L, *et al*. Paroxetine Attenuates Cardiac Hypertrophy Via Blocking GRK2 and ADRB1 Interaction in Hypertension. Journal of the American Heart Association. 2021; 10: e016364.
[46] Rajagopal S, Shenoy SK. GPCR desensitization: Acute and prolonged phases. Cellular Signalling. 2018; 41: 9–16.
[47] Goetze JP, Bruneau BG, Ramos HR, Ogawa T, de Bold MK, de Bold AJ. Cardiac natriuretic peptides. Nature Reviews. Cardiology. 2020; 17: 698–717.
[48] Sarzani R, Allevi M, Di Pentima C, Schiavi P, Spannella F, Giulietti F. Role of Cardiac Natriuretic Peptides in Heart Structure and Function. International Journal of Molecular Sciences. 2022; 23: 14415.
[49] Rainer PP, Kass DA. Old dog, new tricks: novel cardiac targets and stress regulation by protein kinase G. Cardiovascular Research. 2016; 111: 154–162.
[50] Ellmers LJ, Knowles JW, Kim HS, Smithies O, Maeda N, Cameron VA. Ventricular expression of natriuretic peptides in Npr1(-/-) mice with cardiac hypertrophy and fibrosis. American Journal of Physiology. Heart and Circulatory Physiology. 2002; 283: H707–H714.
[51] Burke RM, Lighthouse JK, Mickelsen DM, Small EM. Sacubitril/Valsartan Decreases Cardiac Fibrosis in Left Ventricle Pressure Overload by Restoring PKG Signaling in Cardiac Fibroblasts. Circulation. Heart Failure. 2019; 12: e005565.
[52] Raffa S, Forte M, Gallo G, Ranieri D, Marchitti S, Magrì D, *et al*. Atrial natriuretic peptide stimulates autophagy/mitophagy and improves mitochondrial function in chronic heart failure. Cellular and Molecular Life Sciences: CMLS. 2023; 80: 134.
[53] Vinnakota S, Chen HH. The Importance of Natriuretic Peptides in Cardiometabolic Diseases. Journal of the Endocrine Society. 2020; 4: bvaa052.
[54] Doenst T, Nguyen TD, Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. Circulation Research. 2013; 113: 709–724.
[55] Ng ACT, Delgado V, Borlaug BA, Bax JJ. Diabesity: the combined burden of obesity and diabetes on heart disease and the role of imaging. Nature Reviews. Cardiology. 2021; 18: 291–304.
[56] Chen Z, Jin ZX, Cai J, Li R, Deng KQ, Ji YX, *et al*. Energy substrate metabolism and oxidative stress in metabolic cardiomyopathy. Journal of Molecular Medicine (Berlin, Germany). 2022; 100: 1721–1739.
[57] Bertero E, Maack C. Metabolic remodelling in heart failure. Nature Reviews. Cardiology. 2018; 15: 457–470.
[58] Goldberg IJ, Trent CM, Schulze PC. Lipid metabolism and toxicity in the heart. Cell Metabolism. 2012; 15: 805–812.
[59] Heusch G, Libby P, Gersh B, Yellon D, Böhm M, Lopaschuk G, *et al*. Cardiovascular remodelling in coronary artery disease and heart failure. Lancet (London, England). 2014; 383: 1933–1943.
[60] Watson WD, Green PG, Lewis AJM, Arvidsson P, De Maria GL, Arheden H, *et al*. Retained Metabolic Flexibility of the Failing Human Heart. Circulation. 2023; 148: 109–123.
[61] Liu L, Shi X, Bharadwaj KG, Ikeda S, Yamashita H, Yagyu H, *et al*. DGAT1 expression increases heart triglyceride content but ameliorates lipotoxicity. The Journal of Biological Chemistry. 2009; 284: 36312–36323.
[62] Listenberger LL, Han X, Lewis SE, Cases S, Farese RV, Jr, Ory DS, *et al*. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. Proceedings of the National Academy of Sciences of the United States of America. 2003; 100: 3077–3082.
[63] Kim JK, Fillmore JJ, Sunshine MJ, Albrecht B, Higashimori T, Kim DW, *et al*. PKC-theta knockout mice are protected from fat-induced insulin resistance. The Journal of Clinical Investigation. 2004; 114: 823–827.
[64] Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, *et al*. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. Science (New York, N.Y.). 2001; 293: 1673–1677.
[65] Choi YS, de Mattos ABM, Shao D, Li T, Nabben M, Kim M, *et al*. Preservation of myocardial fatty acid oxidation prevents diastolic dysfunction in mice subjected to angiotensin II infusion. Journal of Molecular and Cellular Cardiology. 2016; 100: 64–71.
[66] Kolwicz SC, Jr, Olson DP, Marney LC, Garcia-Menendez L, Synovec RE, Tian R. Cardiac-specific deletion of acetyl CoA carboxylase 2 prevents metabolic remodeling during pressure-overload hypertrophy. Circulation Research. 2012; 111: 728–738.
[67] Bernardo BC, Weeks KL, Pongsukwechkul T, Gao X, Kiriazis H, Cemerlang N, *et al*. Gene delivery of medium chain acyl-coenzyme A dehydrogenase induces physiological cardiac hypertrophy and protects against pathological remodelling. Clinical Science (London, England: 1979). 2018; 132: 381–397.
[68] Christopher BA, Huang HM, Berthiaume JM, McElfresh TA, Chen X, Croniger CM, *et al*. Myocardial insulin resistance induced by high fat feeding in heart failure is associated with preserved contractile function. American Journal of Physiology. Heart and Circulatory Physiology. 2010; 299: H1917–27.
[69] Li J, Minczuk K, Huang Q, Kemp BA, Howell NL, Chordia MD, *et al*. Progressive Cardiac Metabolic Defects Accompany Diastolic and Severe Systolic Dysfunction in Spontaneously Hypertensive Rat Hearts. Journal of the American Heart Association. 2023; 12: e026950.

[70] Abel ED. Glucose transport in the heart. Frontiers in Bioscience: a Journal and Virtual Library. 2004; 9: 201–215.
[71] Liao R, Jain M, Cui L, D'Agostino J, Aiello F, Luptak I, *et al*. Cardiac-specific overexpression of GLUT1 prevents the development of heart failure attributable to pressure overload in mice. Circulation. 2002; 106: 2125–2131.
[72] Pereira RO, Wende AR, Olsen C, Soto J, Rawlings T, Zhu Y, *et al*. Inducible overexpression of GLUT1 prevents mitochondrial dysfunction and attenuates structural remodeling in pressure overload but does not prevent left ventricular dysfunction. Journal of the American Heart Association. 2013; 2: e000301.
[73] Wende AR, Kim J, Holland WL, Wayment BE, O'Neill BT, Tuinei J, *et al*. Glucose transporter 4-deficient hearts develop maladaptive hypertrophy in response to physiological or pathological stresses. American Journal of Physiology. Heart and Circulatory Physiology. 2017; 313: H1098–H1108.
[74] Sen S, Kundu BK, Wu HCJ, Hashmi SS, Guthrie P, Locke LW, *et al*. Glucose regulation of load-induced mTOR signaling and ER stress in mammalian heart. Journal of the American Heart Association. 2013; 2: e004796.
[75] Sharma S, Guthrie PH, Chan SS, Haq S, Taegtmeyer H. Glucose phosphorylation is required for insulin-dependent mTOR signalling in the heart. Cardiovascular Research. 2007; 76: 71–80.
[76] Ritterhoff J, Tian R. Metabolism in cardiomyopathy: every substrate matters. Cardiovascular Research. 2017; 113: 411–421.
[77] Gibb AA, Hill BG. Metabolic Coordination of Physiological and Pathological Cardiac Remodeling. Circulation Research. 2018; 123: 107–128.
[78] Schugar RC, Moll AR, André d'Avignon D, Weinheimer CJ, Kovacs A, Crawford PA. Cardiomyocyte-specific deficiency of ketone body metabolism promotes accelerated pathological remodeling. Molecular Metabolism. 2014; 3: 754–769.
[79] Sun H, Olson KC, Gao C, Prosdocimo DA, Zhou M, Wang Z, *et al*. Catabolic Defect of Branched-Chain Amino Acids Promotes Heart Failure. Circulation. 2016; 133: 2038–2049.
[80] Li T, Zhang Z, Kolwicz SC, Jr, Abell L, Roe ND, Kim M, *et al*. Defective Branched-Chain Amino Acid Catabolism Disrupts Glucose Metabolism and Sensitizes the Heart to Ischemia-Reperfusion Injury. Cell Metabolism. 2017; 25: 374–385.
[81] Zhang Y, Huang Z, Li H. Insights into innate immune signalling in controlling cardiac remodelling. Cardiovascular Research. 2017; 113: 1538–1550.
[82] Jiang DS, Li L, Huang L, Gong J, Xia H, Liu X, *et al*. Interferon regulatory factor 1 is required for cardiac remodeling in response to pressure overload. Hypertension (Dallas, Tex.: 1979). 2014; 64: 77–86.
[83] Adamo L, Rocha-Resende C, Prabhu SD, Mann DL. Reappraising the role of inflammation in heart failure. Nature Reviews. Cardiology. 2020; 17: 269–285.
[84] Everett BM, Cornel JH, Lainscak M, Anker SD, Abbate A, Thuren T, *et al*. Anti-Inflammatory Therapy with Canakinumab for the Prevention of Hospitalization for Heart Failure. Circulation. 2019; 139: 1289–1299.
[85] Wong A, Hamidzada H, Epelman S. A cardioimmunologist's toolkit: genetic tools to dissect immune cells in cardiac disease. Nature Reviews. Cardiology. 2022; 19: 395–413.
[86] Litviňuková M, Talavera-López C, Maatz H, Reichart D, Worth CL, Lindberg EL, *et al*. Cells of the adult human heart. Nature. 2020; 588: 466–472.
[87] Dick SA, Macklin JA, Nejat S, Momen A, Clemente-Casares X, Althagafi MG, *et al*. Self-renewing resident cardiac macrophages limit adverse remodeling following myocardial infarction. Nature Immunology. 2019; 20: 29–39.
[88] Dick SA, Wong A, Hamidzada H, Nejat S, Nechanitzky R, Vohra S, *et al*. Three tissue resident macrophage subsets coexist across organs with conserved origins and life cycles. Science Immunology. 2022; 7: eabf7777.
[89] Bajpai G, Bredemeyer A, Li W, Zaitsev K, Koenig AL, Lokshina I, *et al*. Tissue Resident CCR2- and CCR2+ Cardiac Macrophages Differentially Orchestrate Monocyte Recruitment and Fate Specification Following Myocardial Injury. Circulation Research. 2019; 124: 263–278.
[90] Bajpai G, Schneider C, Wong N, Bredemeyer A, Hulsmans M, Nahrendorf M, *et al*. The human heart contains distinct macrophage subsets with divergent origins and functions. Nature Medicine. 2018; 24: 1234–1245.
[91] Wang L, Zhang YL, Lin QY, Liu Y, Guan XM, Ma XL, *et al*. CXCL1-CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte infiltration. European Heart Journal. 2018; 39: 1818–1831.
[92] Zandbergen HR, Sharma UC, Gupta S, Verjans JWH, van den Borne S, Pokharel S, *et al*. Macrophage depletion in hypertensive rats accelerates development of cardiomyopathy. Journal of Cardiovascular Pharmacology and Therapeutics. 2009; 14: 68–75.
[93] Kain D, Amit U, Yagil C, Landa N, Naftali-Shani N, Molotski N, *et al*. Macrophages dictate the progression and manifestation of hypertensive heart disease. International Journal of Cardiology. 2016; 203: 381–395.
[94] Liao X, Shen Y, Zhang R, Sugi K, Vasudevan NT, Alaiti MA, *et al*. Distinct roles of resident and nonresident macrophages in nonischemic cardiomyopathy. Proceedings of the National Academy of Sciences of the United States of America. 2018; 115: E4661–E4669.
[95] Zaman R, Hamidzada H, Kantores C, Wong A, Dick SA, Wang Y, *et al*. Selective loss of resident macrophage-derived insulin-like growth factor-1 abolishes adaptive cardiac growth to stress. Immunity. 2021; 54: 2057–2071.e6.
[96] Patel B, Bansal SS, Ismahil MA, Hamid T, Rokosh G, Mack M, *et al*. CCR2^{+} Monocyte-Derived Infiltrating Macrophages Are Required for Adverse Cardiac Remodeling During Pressure Overload. JACC. Basic to Translational Science. 2018; 3: 230–244.
[97] Ye S, Huang H, Han X, Luo W, Wu L, Ye Y, *et al*. Dectin-1 Acts as a Non-Classical Receptor of Ang II to Induce Cardiac Remodeling. Circulation Research. 2023; 132: 707–722.
[98] Wong NR, Mohan J, Kopecky BJ, Guo S, Du L, Leid J, *et al*. Resident cardiac macrophages mediate adaptive myocardial remodeling. Immunity. 2021; 54: 2072–2088.e7.
[99] Solis AG, Bielecki P, Steach HR, Sharma L, Harman CCD, Yun S, *et al*. Mechanosensation of cyclical force by PIEZO1 is essential for innate immunity. Nature. 2019; 573: 69–74.
[100] Yang D, Liu HQ, Liu FY, Tang N, Guo Z, Ma SQ, *et al*. The Roles of Noncardiomyocytes in Cardiac Remodeling. International Journal of Biological Sciences. 2020; 16: 2414–2429.
[101] Nevers T, Salvador AM, Grodecki-Pena A, Knapp A, Velázquez F, Aronovitz M, *et al*. Left Ventricular T-Cell Recruitment Contributes to the Pathogenesis of Heart Failure. Circulation. Heart Failure. 2015; 8: 776–787.
[102] Laroumanie F, Douin-Echinard V, Pozzo J, Lairez O, Tortosa F, Vinel C, *et al*. CD4+ T cells promote the transition from hypertrophy to heart failure during chronic pressure overload. Circulation. 2014; 129: 2111–2124.
[103] Ngwenyama N, Kaur K, Bugg D, Theall B, Aronovitz M, Berland R, *et al*. Antigen presentation by cardiac fibroblasts promotes cardiac dysfunction. Nature Cardiovascular Research. 2022; 1: 761–774.
[104] Aghajanian H, Kimura T, Rurik JG, Hancock AS, Leibowitz MS, Li L, *et al*. Targeting cardiac fibrosis with engineered T cells. Nature. 2019; 573: 430–433.
[105] Wang H, Kwak D, Fassett J, Liu X, Yao W, Weng X, *et al*.

Role of bone marrow-derived CD11c$^+$ dendritic cells in systolic overload-induced left ventricular inflammation, fibrosis and hypertrophy. Basic Research in Cardiology. 2017; 112: 25.
[106] O'Donnell JA, Zheng T, Meric G, Marques FZ. The gut microbiome and hypertension. Nature Reviews. Nephrology. 2023; 19: 153–167.
[107] Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, *et al*. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106: 3698–3703.
[108] Avery EG, Bartolomaeus H, Rauch A, Chen CY, N'Diaye G, Löber U, *et al*. Quantifying the impact of gut microbiota on inflammation and hypertensive organ damage. Cardiovascular Research. 2023; 119: 1441–1452.
[109] Koponen KK, Salosensaari A, Ruuskanen MO, Havulinna AS, Männistö S, Jousilahti P, *et al*. Associations of healthy food choices with gut microbiota profiles. The American Journal of Clinical Nutrition. 2021; 114: 605–616.
[110] Xu C, Marques FZ. How Dietary Fibre, Acting via the Gut Microbiome, Lowers Blood Pressure. Current Hypertension Reports. 2022; 24: 509–521.
[111] Cooper STE, Westaby JD, Haines ZHR, Malone GO, Sheppard MN, Meijles DN. Of Mouse and Man: Cross-Species Characterization of Hypertensive Cardiac Remodeling. International Journal of Molecular Sciences. 2022; 23: 7709.
[112] Sharp TE, 3rd, Polhemus DJ, Li Z, Spaletra P, Jenkins JS, Reilly JP, *et al*. Renal Denervation Prevents Heart Failure Progression Via Inhibition of the Renin-Angiotensin System. Journal of the American College of Cardiology. 2018; 72: 2609–2621.
[113] AlQudah M, Hale TM, Czubryt MP. Targeting the renin-angiotensin-aldosterone system in fibrosis. Matrix Biology: Journal of the International Society for Matrix Biology. 2020; 91-92: 92–108.
[114] Hulsmans M, Sager HB, Roh JD, Valero-Muñoz M, Houstis NE, Iwamoto Y, *et al*. Cardiac macrophages promote diastolic dysfunction. The Journal of Experimental Medicine. 2018; 215: 423–440.
[115] Rurik JG, Aghajanian H, Epstein JA. Immune Cells and Immunotherapy for Cardiac Injury and Repair. Circulation Research. 2021; 128: 1766–1779.
[116] Pesce M, Duda GN, Forte G, Girao H, Raya A, Roca-Cusachs P, *et al*. Cardiac fibroblasts and mechanosensation in heart development, health and disease. Nature Reviews. Cardiology. 2023; 20: 309–324.
[117] Pinto AR, Ilinykh A, Ivey MJ, Kuwabara JT, D'Antoni ML, Debuque R, *et al*. Revisiting Cardiac Cellular Composition. Circulation Research. 2016; 118: 400–409.
[118] Tallquist MD. Developmental Pathways of Cardiac Fibroblasts. Cold Spring Harbor Perspectives in Biology. 2020; 12: a037184.
[119] Hall C, Gehmlich K, Denning C, Pavlovic D. Complex Relationship Between Cardiac Fibroblasts and Cardiomyocytes in Health and Disease. Journal of the American Heart Association. 2021; 10: e019338.
[120] Vistnes M, Erusappan PM, Sasi A, Nordén ES, Bergo KK, Romaine A, *et al*. Inhibition of the extracellular enzyme A disintegrin and metalloprotease with thrombospondin motif 4 prevents cardiac fibrosis and dysfunction. Cardiovascular Research. 2023; 119: 1915–1927.
[121] Ma F, Li Y, Jia L, Han Y, Cheng J, Li H, *et al*. Macrophage-stimulated cardiac fibroblast production of IL-6 is essential for TGF β/Smad activation and cardiac fibrosis induced by angiotensin II. PLoS ONE. 2012; 7: e35144.
[122] Han M, Liu Z, Liu L, Huang X, Wang H, Pu W, *et al*. Dual genetic tracing reveals a unique fibroblast subpopulation modulating cardiac fibrosis. Nature Genetics. 2023; 55: 665–678.
[123] Ali SR, Ranjbarvaziri S, Talkhabi M, Zhao P, Subat A, Hojjat A, *et al*. Developmental heterogeneity of cardiac fibroblasts does not predict pathological proliferation and activation. Circulation Research. 2014; 115: 625–635.
[124] Liu M, López de Juan Abad B, Cheng K. Cardiac fibrosis: Myofibroblast-mediated pathological regulation and drug delivery strategies. Advanced Drug Delivery Reviews. 2021; 173: 504–519.
[125] González A, López B, Ravassa S, San José G, Díez J. The complex dynamics of myocardial interstitial fibrosis in heart failure. Focus on collagen cross-linking. Biochimica et Biophysica Acta. Molecular Cell Research. 2019; 1866: 1421–1432.
[126] Olsen FJ, Møgelvang R, Jensen GB, Jensen JS, Biering-Sørensen T. Relationship Between Left Atrial Functional Measures and Incident Atrial Fibrillation in the General Population: The Copenhagen City Heart Study. JACC. Cardiovascular Imaging. 2019; 12: 981–989.
[127] Cameli M, Mandoli GE, Mondillo S. Left atrium: the last bulwark before overt heart failure. Heart Failure Reviews. 2017; 22: 123–131.
[128] Gupta S, Matulevicius SA, Ayers CR, Berry JD, Patel PC, Markham DW, *et al*. Left atrial structure and function and clinical outcomes in the general population. European Heart Journal. 2013; 34: 278–285.
[129] Miller JT, O'Rourke RA, Crawford MH. Left atrial enlargement: an early sign of hypertensive heart disease. American Heart Journal. 1988; 116: 1048–1051.
[130] Pluteanu F, Heß J, Plackic J, Nikonova Y, Preisenberger J, Bukowska A, *et al*. Early subcellular Ca2+ remodelling and increased propensity for Ca2+ alternans in left atrial myocytes from hypertensive rats. Cardiovascular Research. 2015; 106: 87–97.
[131] Kockskämper J, Pluteanu F. Left Atrial Myocardium in Arterial Hypertension. Cells. 2022; 11: 3157.
[132] Selejan SR, Linz D, Mauz M, Hohl M, Huynh AKD, Speer T, *et al*. Renal denervation reduces atrial remodeling in hypertensive rats with metabolic syndrome. Basic Research in Cardiology. 2022; 117: 36.
[133] Zhang H, Cannell MB, Kim SJ, Watson JJ, Norman R, Calaghan SC, *et al*. Cellular Hypertrophy and Increased Susceptibility to Spontaneous Calcium-Release of Rat Left Atrial Myocytes Due to Elevated Afterload. PLoS ONE. 2015; 10: e0144309.
[134] Soullier C, Niamkey JT, Ricci JE, Messner-Pellenc P, Brunet X, Schuster I. Hypertensive patients with left ventricular hypertrophy have global left atrial dysfunction and impaired atrioventricular coupling. Journal of Hypertension. 2016; 34: 1615–1620.
[135] Kim SJ, Choisy SCM, Barman P, Zhang H, Hancox JC, Jones SA, *et al*. Atrial remodeling and the substrate for atrial fibrillation in rat hearts with elevated afterload. Circulation. Arrhythmia and Electrophysiology. 2011; 4: 761–769.
[136] Lakkireddy D, Turagam M, Afzal MR, Rajasingh J, Atkins D, Dawn B, *et al*. Left Atrial Appendage Closure and Systemic Homeostasis: The LAA HOMEOSTASIS Study. Journal of the American College of Cardiology. 2018; 71: 135–144.
[137] Todiere G, Neglia D, Ghione S, Fommei E, Capozza P, Guarini G, *et al*. Right ventricular remodelling in systemic hypertension: a cardiac MRI study. Heart (British Cardiac Society). 2011; 97: 1257–1261.
[138] Cuspidi C, Sala C, Muiesan ML, De Luca N, Schillaci G, Working Group on Heart, Hypertension of the Italian Society of Hypertension. Right ventricular hypertrophy in systemic hypertension: an updated review of clinical studies. Journal of Hypertension. 2013; 31: 858–865.
[139] Ghio S, Temporelli PL, Klersy C, Simioniuc A, Girardi B,

Scelsi L, *et al*. Prognostic relevance of a non-invasive evaluation of right ventricular function and pulmonary artery pressure in patients with chronic heart failure. European Journal of Heart Failure. 2013; 15: 408–414.

[140] Bosch L, Lam CSP, Gong L, Chan SP, Sim D, Yeo D, *et al*. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. European Journal of Heart Failure. 2017; 19: 1664–1671.

[141] Proplesch M, Merz AA, Claggett BL, Lewis EF, Dwyer KH, Crousillat DR, *et al*. Right atrial structure and function in patients with hypertension and with chronic heart failure. Echocardiography (Mount Kisco, N.Y.). 2018; 35: 905–914.

[142] Huston JH, Shah SJ. Understanding the Pathobiology of Pulmonary Hypertension Due to Left Heart Disease. Circulation Research. 2022; 130: 1382–1403.

[143] Rako ZA, Kremer N, Yogeswaran A, Richter MJ, Tello K. Adaptive versus maladaptive right ventricular remodelling. ESC Heart Failure. 2023; 10: 762–775.

[144] Ventetuolo CE, Lima JAC, Barr RG, Bristow MR, Bagiella E, Chahal H, *et al*. The renin-angiotensin system and right ventricular structure and function: The MESA-Right Ventricle Study. Pulmonary Circulation. 2012; 2: 379–386.

[145] Nwabuo CC, Vasan RS. Pathophysiology of Hypertensive Heart Disease: Beyond Left Ventricular Hypertrophy. Current Hypertension Reports. 2020; 22: 11.

[146] Iriarte M, Murga N, Sagastagoitia D, Morillas M, Boveda J, Molinero E, *et al*. Classification of hypertensive cardiomyopathy. European Heart Journal. 1993; 14 Suppl J: 95–101.

[147] Samuel JL, Swynghedauw B. Is cardiac hypertrophy a required compensatory mechanism in pressure-overloaded heart? Journal of Hypertension. 2008; 26: 857–858.

[148] Fuchs A, Mejdahl MR, Kühl JT, Stisen ZR, Nilsson EJP, Køber LV, *et al*. Normal values of left ventricular mass and cardiac chamber volumes assessed by 320-detector computed tomography angiography in the Copenhagen General Population Study. European Heart Journal. Cardiovascular Imaging. 2016; 17: 1009–1017.

[149] Chen Z, Liu J, Zhou F, Li H, Zhang XJ, She ZG, *et al*. Nonalcoholic Fatty Liver Disease: An Emerging Driver of Cardiac Arrhythmia. Circulation Research. 2021; 128: 1747–1765.

[150] Tadic M, Cuspidi C, Plein S, Milivojevic IG, Wang DW, Grassi G, *et al*. Comprehensive assessment of hypertensive heart disease: cardiac magnetic resonance in focus. Heart Failure Reviews. 2021; 26: 1383–1390.

[151] Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, *et al*. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE)†. European Heart Journal. Cardiovascular Imaging. 2015; 16: 577–605.

[152] Taylor HCM, Chaturvedi N, Davey Smith G, Ferreira DLS, Fraser A, Howe LD, *et al*. Is Height$^{2.7}$ Appropriate for Indexation of Left Ventricular Mass in Healthy Adolescents? The Importance of Sex Differences. Hypertension (Dallas, Tex.: 1979). 2023; 80: 2033–2042.

[153] de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, *et al*. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. Journal of the American College of Cardiology. 1992; 20: 1251–1260.

[154] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal. Cardiovascular Imaging. 2015; 16: 233–270.

[155] Sheng Y, Li M, Xu M, Zhang Y, Xu J, Huang Y, *et al*. Left ventricular and atrial remodelling in hypertensive patients using thresholds from international guidelines and EMINCA data. European Heart Journal. Cardiovascular Imaging. 2022; 23: 166–174.

[156] Asch FM, Miyoshi T, Addetia K, Citro R, Daimon M, Desale S, *et al*. Similarities and Differences in Left Ventricular Size and Function among Races and Nationalities: Results of the World Alliance Societies of Echocardiography Normal Values Study. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2019; 32: 1396–1406.e2.

[157] Ko SM, Kim TH, Chun EJ, Kim JY, Hwang SH. Assessment of Left Ventricular Myocardial Diseases with Cardiac Computed Tomography. Korean Journal of Radiology. 2019; 20: 333–351.

[158] Salas-Pacheco JL, Lomelí-Sánchez O, Baltazar-González O, Soto ME. Longitudinal systolic dysfunction in hypertensive cardiomyopathy with normal ejection fraction. Echocardiography (Mount Kisco, N.Y.). 2022; 39: 46–53.

[159] Collier P, Phelan D, Klein A. A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. Journal of the American College of Cardiology. 2017; 69: 1043–1056.

[160] Tadic M, Majstorovic A, Pencic B, Ivanovic B, Neskovic A, Badano L, *et al*. The impact of high-normal blood pressure on left ventricular mechanics: a three-dimensional and speckle tracking echocardiography study. The International Journal of Cardiovascular Imaging. 2014; 30: 699–711.

[161] Tadic M, Cuspidi C, Ivanovic B, Ilic I, Celic V, Kocijancic V. Influence of White-Coat Hypertension on Left Ventricular Deformation 2- and 3-Dimensional Speckle Tracking Study. Hypertension (Dallas, Tex.: 1979). 2016; 67: 592–596.

[162] Tadic M, Cuspidi C, Pencic-Popovic B, Celic V, Mancia G. The influence of night-time hypertension on left ventricular mechanics. International Journal of Cardiology. 2017; 243: 443–448.

[163] Tadic M, Cuspidi C, Majstorovic A, Pencic B, Mancia G, Bombelli M, *et al*. The association between 24-h blood pressure patterns and left ventricular mechanics. Journal of Hypertension. 2020; 38: 282–288.

[164] Moya A, Buytaert D, Penicka M, Bartunek J, Vanderheyden M. State-of-the-Art: Noninvasive Assessment of Left Ventricular Function Through Myocardial Work. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2023; 36: 1027–1042.

[165] Juszczyk A, Jankowska K, Zawiślak B, Surdacki A, Chyrchel B. Depressed Cardiac Mechanical Energetic Efficiency: A Contributor to Cardiovascular Risk in Common Metabolic Diseases-From Mechanisms to Clinical Applications. Journal of Clinical Medicine. 2020; 9: 2681.

[166] de Simone G, Chinali M, Galderisi M, Benincasa M, Girfoglio D, Botta I, *et al*. Myocardial mechano-energetic efficiency in hypertensive adults. Journal of Hypertension. 2009; 27: 650–655.

[167] de Simone G, Izzo R, Losi MA, Stabile E, Rozza F, Canciello G, *et al*. Depressed myocardial energetic efficiency is associated with increased cardiovascular risk in hypertensive left ventricular hypertrophy. Journal of Hypertension. 2016; 34: 1846–1853.

[168] Suga H. Total mechanical energy of a ventricle model and cardiac oxygen consumption. The American Journal of Physiology. 1979; 236: H498–H505.

[169] Sahiti F, Morbach C, Cejka V, Tiffe T, Wagner M, Eichner FA, *et al*. Impact of cardiovascular risk factors on myocardial work-insights from the STAAB cohort study. Journal of Human Hypertension. 2022; 36: 235–245.

[170] Li X, Liu Q, Bao W, Li M, Zhang Y, Wan X, *et al*. Impact of blood pressure changes on myocardial work indices in hyperten-

sive patients in a day. Journal of Clinical Hypertension (Greenwich, Conn.). 2022; 24: 3–14.
[171] Osranek M, Eisenach JH, Khandheria BK, Chandrasekaran K, Seward JB, Belohlavek M. Arterioventricular coupling and ventricular efficiency after antihypertensive therapy: a noninvasive prospective study. Hypertension (Dallas, Tex.: 1979). 2008; 51: 275–281.
[172] Lam CSP, Shah AM, Borlaug BA, Cheng S, Verma A, Izzo J, *et al*. Effect of antihypertensive therapy on ventricular-arterial mechanics, coupling, and efficiency. European Heart Journal. 2013; 34: 676–683.
[173] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, *et al*. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2016; 29: 277–314.
[174] Wu T, Zheng L, Zhang S, Duan L, Ma J, Zha L, *et al*. Left ventricular long-axis ultrasound strain (GLS) is an ideal indicator for patients with anti-hypertension treatment. Clinical and Experimental Hypertension (New York, N.Y.: 1993). 2022; 44: 20–25.
[175] Brown JM, Zhou W, Weber B, Divakaran S, Barrett L, Bibbo CF, *et al*. Low coronary flow relative to myocardial mass predicts heart failure in symptomatic hypertensive patients with no obstructive coronary artery disease. European Heart Journal. 2022; 43: 3323–3331.
[176] Cooper LT, Jr. Role of left ventricular biopsy in the management of heart disease. Circulation. 2013; 128: 1492–1494.
[177] Seferović PM, Tsutsui H, McNamara DM, Ristić AD, Basso C, Bozkurt B, *et al*. Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society Position statement on endomyocardial biopsy. European Journal of Heart Failure. 2021; 23: 854–871.
[178] Georgiopoulou VV, Kalogeropoulos AP, Raggi P, Butler J. Prevention, diagnosis, and treatment of hypertensive heart disease. Cardiology Clinics. 2010; 28: 675–691.
[179] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018; 39: 3021–3104.
[180] Whelton PK, Carey RM, Aronow WS, Casey DE, Jr, Collins KJ, Dennison Himmelfarb C, *et al*. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension (Dallas, Tex.: 1979). 2018; 71: e13–e115.
[181] Chen JS, Pei Y, Li CE, Li YN, Wang QY, Yu J. Comparative efficacy of different types of antihypertensive drugs in reversing left ventricular hypertrophy as determined with echocardiography in hypertensive patients: A network meta-analysis of randomized controlled trials. Journal of Clinical Hypertension (Greenwich, Conn.). 2020; 22: 2175–2183.
[182] Wang Y, Zhong Y, Zhang Z, Yang S, Zhang Q, Chu B, *et al*. Effect of sodium-glucose cotransporter protein-2 inhibitors on left ventricular hypertrophy in patients with type 2 diabetes: A systematic review and meta-analysis. Frontiers in Endocrinology. 2023; 13: 1088820.
[183] Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. Journal of the American Heart Association. 2019; 8: e012272.
[184] de Castro QJT, Tomaz FSC, Watai PY, Grabe-Guimarães A. Physical Exercise Combined with Antihypertensive Drug Therapy on Left Ventricular Hypertrophy: Systematic Review and Meta-Analysis. High Blood Pressure & Cardiovascular Prevention: the Official Journal of the Italian Society of Hypertension. 2020; 27: 493–503.
[185] Liu Y, Teramoto K, Wing VK, Supasiri T, Yin K. Effects of Angiotensin II Receptor Blockers on Ventricular Hypertrophy in Hypertrophic Cardiomyopathy: A Meta-Analysis of Randomized Controlled Trials. Cardiovascular Drugs and Therapy. 2022; 36: 371–378.
[186] Roush GC, Abdelfattah R, Song S, Ernst ME, Sica DA, Kostis JB. Hydrochlorothiazide vs chlorthalidone, indapamide, and potassium-sparing/hydrochlorothiazide diuretics for reducing left ventricular hypertrophy: A systematic review and meta-analysis. Journal of Clinical Hypertension (Greenwich, Conn.). 2018; 20: 1507–1515.
[187] Patoulias D, Papadopoulos C, Katsimardou A, Kalogirou MS, Doumas M. Meta-analysis Assessing the Effect of Sodium-Glucose Co-transporter-2 Inhibitors on Left Ventricular Mass in Patients with Type 2 Diabetes Mellitus. The American Journal of Cardiology. 2020; 134: 149–152.
[188] Yang LY, Ge X, Wang YL, Ma KL, Liu H, Zhang XL, *et al*. Angiotensin receptor blockers reduce left ventricular hypertrophy in dialysis patients: a meta-analysis. The American Journal of the Medical Sciences. 2013; 345: 1–9.
[189] Lu R, Zhang Y, Zhu X, Fan Z, Zhu S, Cui M, *et al*. Effects of mineralocorticoid receptor antagonists on left ventricular mass in chronic kidney disease patients: a systematic review and meta-analysis. International Urology and Nephrology. 2016; 48: 1499–1509.
[190] Xing F, Chen J, Zhao B, Jiang J, Tang A, Chen Y. Real role of β-blockers in regression of left ventricular mass in hypertension patients: Bayesian network meta-analysis. Medicine. 2017; 96: e6290.
[191] Yang Y, Wang R, Li MX, Xing Y, Li WG. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on left ventricular mass index and ejection fraction in hemodialysis patients: A meta-analysis with trial sequential analysis of randomized controlled trials. International Journal of Cardiology. 2016; 219: 350–357.
[192] Giannetta E, Feola T, Gianfrilli D, Pofi R, Dall'Armi V, Badagliacca R, *et al*. Is chronic inhibition of phosphodiesterase type 5 cardioprotective and safe? A meta-analysis of randomized controlled trials. BMC Medicine. 2014; 12: 185.
[193] Shah AM, Claggett B, Prasad N, Li G, Volquez M, Jering K, *et al*. Impact of Sacubitril/Valsartan Compared with Ramipril on Cardiac Structure and Function After Acute Myocardial Infarction: The PARADISE-MI Echocardiographic Substudy. Circulation. 2022; 146: 1067–1081.
[194] Lal B, Iqbal A, Butt NF, Randhawa FA, Rathore R, Waseem T. Efficacy of high dose Allopurinol in reducing left ventricular mass in patients with left ventricular hypertrophy by comparing its efficacy with Febuxostat - a randomized controlled trial. JPMA. the Journal of the Pakistan Medical Association. 2018; 68: 1446–1450.
[195] Mercurio V, Pucci G, Bosso G, Fazio V, Battista F, Iannuzzi A, *et al*. A nutraceutical combination reduces left ventricular mass in subjects with metabolic syndrome and left ventricular hypertrophy: A multicenter, randomized, double-blind, placebo-controlled trial. Clinical Nutrition (Edinburgh, Scotland). 2020; 39: 1379–1384.
[196] Chandra A, Picard MH, Huang S, Gupta DK, Agusala K, Buring JE, *et al*. Impact of Vitamin D3 Versus Placebo on Cardiac Structure and Function: A Randomized Clinical Trial. Journal of the American Heart Association. 2022; 11: e025008.
[197] Levy PD, Twiner MJ, Brody AM, Dawood R, Reed B, Mango

L, *et al*. Does Vitamin D Provide Added Benefit to Antihypertensive Therapy in Reducing Left Ventricular Hypertrophy Determined by Cardiac Magnetic Resonance? American Journal of Hypertension. 2023; 36: 50–62.

[198] Mohan M, Al-Talabany S, McKinnie A, Mordi IR, Singh JSS, Gandy SJ, *et al*. A randomized controlled trial of metformin on left ventricular hypertrophy in patients with coronary artery disease without diabetes: the MET-REMODEL trial. European Heart Journal. 2019; 40: 3409–3417.

[199] Gnudi L, Fountoulakis N, Panagiotou A, Corcillo A, Maltese G, Rife MF, *et al*. Effect of active vitamin-D on left ventricular mass index: Results of a randomized controlled trial in type 2 diabetes and chronic kidney disease. American Heart Journal. 2023; 261: 1–9.

[200] Gingles CR, Symon R, Gandy SJ, Struthers AD, Houston G, MacDonald TM, *et al*. Allopurinol treatment adversely impacts left ventricular mass regression in patients with well-controlled hypertension. Journal of Hypertension. 2019; 37: 2481–2489.

[201] Ersbøll M, Jürgens M, Hasbak P, Kjær A, Wolsk E, Zerahn B, *et al*. Effect of empagliflozin on myocardial structure and function in patients with type 2 diabetes at high cardiovascular risk: the SIMPLE randomized clinical trial. The International Journal of Cardiovascular Imaging. 2022; 38: 579–587.

[202] Schmieder RE, Wagner F, Mayr M, Delles C, Ott C, Keicher C, *et al*. The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodelling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study. European Heart Journal. 2017; 38: 3308–3317.

[203] Feniman-De-Stefano GMM, Zanati-Basan SG, De Stefano LM, Xavier PS, Castro AD, Caramori JCT, *et al*. Spironolactone is secure and reduces left ventricular hypertrophy in hemodialysis patients. Therapeutic Advances in Cardiovascular Disease. 2015; 9: 158–167.

[204] Szwejkowski BR, Gandy SJ, Rekhraj S, Houston JG, Lang CC, Morris AD, *et al*. Allopurinol reduces left ventricular mass in patients with type 2 diabetes and left ventricular hypertrophy. Journal of the American College of Cardiology. 2013; 62: 2284–2293.

[205] Motoki H, Koyama J, Izawa A, Tomita T, Miyashita Y, Takahashi M, *et al*. Impact of azelnidipine and amlodipine on left ventricular mass and longitudinal function in hypertensive patients with left ventricular hypertrophy. Echocardiography (Mount Kisco, N.Y.). 2014; 31: 1230–1238.

[206] Li H, Wang S. Organic nitrates favor regression of left ventricular hypertrophy in hypertensive patients on chronic peritoneal dialysis. International Journal of Molecular Sciences. 2013; 14: 1069–1079.

[207] Bal UA, Atar İ, Öktem M, Zeyneloğlu HB, Yıldırır A, Kuşcu E, *et al*. The effect of raloxifene on left ventricular hypertrophy in postmenopausal women: A prospective, randomized, and controlled study. Anatolian Journal of Cardiology. 2015; 15: 480–484.

[208] Moroni C, Tolone S, Lopreiato F, Scrofani AR, Bossini A, Affricano C, *et al*. Effects of losartan on left ventricular mass: a three-year follow-up in elderly hypertensives with myocardial hypertrophy despite successful conventional antihypertensive treatment. European Review for Medical and Pharmacological Sciences. 2017; 21: 1323–1328.

[209] Derosa G, Mugellini A, Querci F, Franzetti I, Pesce RM, D'Angelo A, *et al*. Barnidipine or Lercanidipine on Echocardiographic Parameters in Hypertensive, Type 2 Diabetics with Left Ventricular Hypertrophy: A Randomized Clinical Trial. Scientific Reports. 2015; 5: 12603.

[210] Zheng H, Xie N, Xu H, Huang J, Xie X, Luo M. Effects of 4 month exercise on left ventricular remodeling and autonomic nervous system in hypertensive patients. Panminerva Medica. 2016; 58: 1–7.

[211] Rekhraj S, Gandy SJ, Szwejkowski BR, Nadir MA, Noman A, Houston JG, *et al*. High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. Journal of the American College of Cardiology. 2013; 61: 926–932.

[212] Ito Y, Mizuno M, Suzuki Y, Tamai H, Hiramatsu T, Ohashi H, *et al*. Long-term effects of spironolactone in peritoneal dialysis patients. Journal of the American Society of Nephrology: JASN. 2014; 25: 1094–1102.

[213] Okura T, Miyoshi KI, Irita J, Enomoto D, Jotoku M, Nagao T, *et al*. Comparison of the effect of combination therapy with an angiotensin II receptor blocker and either a low-dose diuretic or calcium channel blocker on cardiac hypertrophy in patients with hypertension. Clinical and Experimental Hypertension (New York, N.Y.: 1993). 2013; 35: 563–569.

[214] Slivnick J, Lampert BC. Hypertension and Heart Failure. Heart Failure Clinics. 2019; 15: 531–541.

[215] Taverny G, Mimouni Y, LeDigarcher A, Chevalier P, Thijs L, Wright JM, *et al*. Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals. The Cochrane Database of Systematic Reviews. 2016; 3: CD011745.

[216] Ma TKW, Kam KKH, Yan BP, Lam YY. Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status. British Journal of Pharmacology. 2010; 160: 1273–1292.

[217] Di Palo KE, Barone NJ. Hypertension and Heart Failure: Prevention, Targets, and Treatment. Heart Failure Clinics. 2020; 16: 99–106.

[218] Whelton PK, Carey RM, Aronow WS, Casey DE, Jr, Collins KJ, Dennison Himmelfarb C, *et al*. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2018; 71: e127–e248.

[219] Tamura T, Said S, Harris J, Lu W, Gerdes AM. Reverse remodeling of cardiac myocyte hypertrophy in hypertension and failure by targeting of the renin-angiotensin system. Circulation. 2000; 102: 253–259.

[220] Murphy A, LeVatte T, Boudreau C, Midgen C, Gratzer P, Marshall J, *et al*. Angiotensin II Type I Receptor Blockade Is Associated with Decreased Cutaneous Scar Formation in a Rat Model. Plastic and Reconstructive Surgery. 2019; 144: 803e–813e.

[221] Serfozo P, Wysocki J, Gulua G, Schulze A, Ye M, Liu P, *et al*. Ang II (Angiotensin II) Conversion to Angiotensin-(1-7) in the Circulation Is POP (Prolyloligopeptidase)-Dependent and ACE2 (Angiotensin-Converting Enzyme 2)-Independent. Hypertension (Dallas, Tex.: 1979). 2020; 75: 173–182.

[222] Li C, Han R, Kang L, Wang J, Gao Y, Li Y, *et al*. Pirfenidone controls the feedback loop of the AT1R/p38 MAPK/renin-angiotensin system axis by regulating liver X receptor-α in myocardial infarction-induced cardiac fibrosis. Scientific Reports. 2017; 7: 40523.

[223] Lewis GA, Dodd S, Clayton D, Bedson E, Eccleson H, Schelbert EB, *et al*. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. Nature Medicine. 2021; 27: 1477–1482.

[224] Kuchulakanti PK. ARNI in cardiovascular disease: current evidence and future perspectives. Future Cardiology. 2020; 16: 505–515.

[225] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021; 42: 3599–3726.

[226] Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong

J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet (London, England). 2010; 375: 1255–1266.

[227] Kario K, Sun N, Chiang FT, Supasyndh O, Baek SH, Inubushi-Molessa A, *et al*. Efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Asian patients with hypertension: a randomized, double-blind, placebo-controlled study. Hypertension (Dallas, Tex.: 1979). 2014; 63: 698–705.

[228] Williams B, Cockcroft JR, Kario K, Zappe DH, Brunel PC, Wang Q, *et al*. Effects of Sacubitril/Valsartan Versus Olmesartan on Central Hemodynamics in the Elderly with Systolic Hypertension: The PARAMETER Study. Hypertension (Dallas, Tex.: 1979). 2017; 69: 411–420.

[229] McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al*. Angiotensin-neprilysin inhibition versus enalapril in heart failure. The New England Journal of Medicine. 2014; 371: 993–1004.

[230] Kuno T, Ueyama H, Fujisaki T, Briasouli A, Takagi H, Briasoulis A. Meta-Analysis Evaluating the Effects of Renin-Angiotensin-Aldosterone System Blockade on Outcomes of Heart Failure with Preserved Ejection Fraction. The American Journal of Cardiology. 2020; 125: 1187–1193.

[231] Rico-Mesa JS, White A, Ahmadian-Tehrani A, Anderson AS. Mineralocorticoid Receptor Antagonists: a Comprehensive Review of Finerenone. Current Cardiology Reports. 2020; 22: 140.

[232] Brandt-Jacobsen NH, Lav Madsen P, Johansen ML, Rasmussen JJ, Forman JL, Holm MR, *et al*. Mineralocorticoid Receptor Antagonist Improves Cardiac Structure in Type 2 Diabetes: Data from the MIRAD Trial. JACC. Heart Failure. 2021; 9: 550–558.

[233] De Marzo V, Savarese G, Tricarico L, Hassan S, Iacoviello M, Porto I, *et al*. Network meta-analysis of medical therapy efficacy in more than 90,000 patients with heart failure and reduced ejection fraction. Journal of Internal Medicine. 2022; 292: 333–349.

[234] Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P, *et al*. A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure with Reduced Ejection Fraction. JACC: Heart Failure. 2022; 10: 73–84.

[235] Martin N, Manoharan K, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. The Cochrane Database of Systematic Reviews. 2021; 5: CD012721.

[236] Mares A, Rodriguez T, Deoker A, Lehker A, Mukherjee D. Effect of Mineralocorticoid Receptor Antagonists in Heart Failure with Preserved Ejection Fraction and with Reduced Ejection Fraction - A Narrative Review. Current Vascular Pharmacology. 2022; 20: 46–51.

[237] Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, *et al*. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. European Heart Journal. 2021; 42: 152–161.

[238] Frampton JE. Finerenone: First Approval. Drugs. 2021; 81: 1787–1794.

[239] Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Bärfacker L, *et al*. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. Journal of Cardiovascular Pharmacology. 2014; 64: 69–78.

[240] Chen X, Qiu Z, Yang S, Ding D, Chen F, Zhou Y, *et al*. Effectiveness and safety of a therapeutic vaccine against angiotensin II receptor type 1 in hypertensive animals. Hypertension (Dallas, Tex.: 1979). 2013; 61: 408–416.

[241] Azegami T, Sasamura H, Hayashi K, Itoh H. Vaccination against the angiotensin type 1 receptor for the prevention of L-NAME-induced nephropathy. Hypertension Research: Official Journal of the Japanese Society of Hypertension. 2012; 35: 492–499.

[242] Brown MJ, Coltart J, Gunewardena K, Ritter JM, Auton TR, Glover JF. Randomized double-blind placebo-controlled study of an angiotensin immunotherapeutic vaccine (PMD3117) in hypertensive subjects. Clinical Science (London, England: 1979). 2004; 107: 167–173.

[243] Nakagami H, Ishihama T, Daikyoji Y, Sasakura C, Yamada E, Morishita R. Brief report on a phase I/IIa study to assess the safety, tolerability, and immune response of AGMG0201 in patients with essential hypertension. Hypertension Research: Official Journal of the Japanese Society of Hypertension. 2022; 45: 61–65.

[244] Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, *et al*. Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension. The New England Journal of Medicine. 2023; 389: 228–238.

[245] Wernhart S, Papathanasiou M, Rassaf T, Luedike P. The controversial role of beta-blockers in heart failure with preserved ejection fraction. Pharmacology & Therapeutics. 2023; 243: 108356.

[246] Koracevic G, Mićić S, Stojanovic M, Bozinovic N, Simic D, Lović D, *et al*. Significance of Beta-Blocker in Patients with Hypertensive Left Ventricular Hypertrophy and Myocardial Ischemia. Current Vascular Pharmacology. 2023; 21: 81–90.

[247] Koracevic G, Stojanovic M, Lovic D, Zdravkovic M, Sakac D. Certain beta blockers (e.g., bisoprolol) may be reevaluated in hypertension guidelines for patients with left ventricular hypertrophy to diminish the ventricular arrhythmic risk. Journal of Human Hypertension. 2021; 35: 564–576.

[248] Marazzi G, Volterrani M, Caminiti G, Iaia L, Massaro R, Vitale C, *et al*. Comparative long term effects of nebivolol and carvedilol in hypertensive heart failure patients. Journal of Cardiac Failure. 2011; 17: 703–709.

[249] Litwin M, Kułaga Z. Obesity, metabolic syndrome, and primary hypertension. Pediatric Nephrology (Berlin, Germany). 2021; 36: 825–837.

[250] Cheng L, Fu Q, Zhou L, Fan Y, Liu F, Fan Y, *et al*. Effect of SGLT-2 inhibitor, empagliflozin, on blood pressure reduction in Chinese elderly hypertension patients with type 2 diabetes and its possible mechanisms. Scientific Reports. 2022; 12: 3525.

[251] Georgianos PI, Agarwal R. Ambulatory Blood Pressure Reduction with SGLT-2 Inhibitors: Dose-Response Meta-analysis and Comparative Evaluation with Low-Dose Hydrochlorothiazide. Diabetes Care. 2019; 42: 693–700.

[252] Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, *et al*. Effect of Empagliflozin on Left Ventricular Mass in Patients with Type 2 Diabetes Mellitus and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. Circulation. 2019; 140: 1693–1702.

[253] Lee HC, Shiou YL, Jhuo SJ, Chang CY, Liu PL, Jhuang WJ, *et al*. The sodium-glucose co-transporter 2 inhibitor empagliflozin attenuates cardiac fibrosis and improves ventricular hemodynamics in hypertensive heart failure rats. Cardiovascular Diabetology. 2019; 18: 45.

[254] Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, *et al*. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. The New England Journal of Medicine. 2021; 385: 1451–1461.

[255] Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, *et al*. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients with Heart Failure and Reduced Ejection Fraction: Results from the DAPA-HF Trial. Circula-

tion. 2020; 141: 90–99.
[256] Bhatt AS, Kosiborod MN, Vaduganathan M, Claggett BL, Miao ZM, Kulac IJ, *et al*. Effect of dapagliflozin on health status and quality of life across the spectrum of ejection fraction: Participant-level pooled analysis from the DAPA-HF and DELIVER trials. European Journal of Heart Failure. 2023; 25: 981–988.
[257] Robles-Vera I, de la Visitación N, Toral M, Sánchez M, Romero M, Gómez-Guzmán M, *et al*. Probiotic Bifidobacterium breve prevents DOCA-salt hypertension. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2020; 34: 13626–13640.
[258] Cavalcante RGS, de Albuquerque TMR, de Luna Freire MO, Ferreira GAH, Carneiro Dos Santos LA, Magnani M, *et al*. The probiotic Lactobacillus fermentum 296 attenuates cardiometabolic disorders in high fat diet-treated rats. Nutrition, Metabolism, and Cardiovascular Diseases: NMCD. 2019; 29: 1408–1417.
[259] Chi C, Li C, Wu D, Buys N, Wang W, Fan H, *et al*. Effects of Probiotics on Patients with Hypertension: a Systematic Review and Meta-Analysis. Current Hypertension Reports. 2020; 22: 34.
[260] Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. Hypertension (Dallas, Tex.: 1979). 2014; 64: 897–903.
[261] Evans CEL, Greenwood DC, Threapleton DE, Cleghorn CL, Nykjaer C, Woodhead CE, *et al*. Effects of dietary fibre type on blood pressure: a systematic review and meta-analysis of randomized controlled trials of healthy individuals. Journal of Hypertension. 2015; 33: 897–911.
[262] Gan XT, Ettinger G, Huang CX, Burton JP, Haist JV, Rajapurohitam V, *et al*. Probiotic administration attenuates myocardial hypertrophy and heart failure after myocardial infarction in the rat. Circulation. Heart Failure. 2014; 7: 491–499.
[263] Marques FZ, Nelson E, Chu PY, Horlock D, Fiedler A, Ziemann M, *et al*. High-Fiber Diet and Acetate Supplementation Change the Gut Microbiota and Prevent the Development of Hypertension and Heart Failure in Hypertensive Mice. Circulation. 2017; 135: 964–977.
[264] Lew LC, Choi SB, Khoo BY, Sreenivasan S, Ong KL, Liong MT. *Lactobacillus plantarum* DR7 Reduces Cholesterol via Phosphorylation of AMPK That Down-regulated the mRNA Expression of HMG-CoA Reductase. Korean Journal for Food Science of Animal Resources. 2018; 38: 350–361.
[265] Korcz E, Kerényi Z, Varga L. Dietary fibers, prebiotics, and exopolysaccharides produced by lactic acid bacteria: potential health benefits with special regard to cholesterol-lowering effects. Food & Function. 2018; 9: 3057–3068.
[266] Mähler A, Wilck N, Rauch G, Dechend R, Müller DN. Effect of a probiotic on blood pressure in grade 1 hypertension (HYPRO): protocol of a randomized controlled study. Trials. 2020; 21: 1032.
[267] Allegretti JR, Mullish BH, Kelly C, Fischer M. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. Lancet (London, England). 2019; 394: 420–431.
[268] Fan L, Ren J, Chen Y, Wang Y, Guo Z, Bu P, *et al*. Effect of fecal microbiota transplantation on primary hypertension and the underlying mechanism of gut microbiome restoration: protocol of a randomized, blinded, placebo-controlled study. Trials. 2022; 23: 178.
[269] He FJ, Campbell NRC, Woodward M, MacGregor GA. Salt reduction to prevent hypertension: the reasons of the controversy. European Heart Journal. 2021; 42: 2501–2505.
[270] He FJ, MacGregor GA. Role of salt intake in prevention of cardiovascular disease: controversies and challenges. Nature Reviews. Cardiology. 2018; 15: 371–377.
[271] Stone MS, Martyn L, Weaver CM. Potassium Intake, Bioavailability, Hypertension, and Glucose Control. Nutrients. 2016; 8: 444.
[272] Rifai L, Pisano C, Hayden J, Sulo S, Silver MA. Impact of the DASH diet on endothelial function, exercise capacity, and quality of life in patients with heart failure. Proceedings (Baylor University. Medical Center). 2015; 28: 151–156.
[273] Filippou CD, Tsioufis CP, Thomopoulos CG, Mihas CC, Dimitriadis KS, Sotiropoulou LI, *et al*. Dietary Approaches to Stop Hypertension (DASH) Diet and Blood Pressure Reduction in Adults with and without Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Advances in Nutrition (Bethesda, Md.). 2020; 11: 1150–1160.
[274] De Pergola G, D'Alessandro A. Influence of Mediterranean Diet on Blood Pressure. Nutrients. 2018; 10: 1700.
[275] Sanches Machado d'Almeida K, Ronchi Spillere S, Zuchinali P, Corrêa Souza G. Mediterranean Diet and Other Dietary Patterns in Primary Prevention of Heart Failure and Changes in Cardiac Function Markers: A Systematic Review. Nutrients. 2018; 10: 58.
[276] Andersson J, Mellberg C, Otten J, Ryberg M, Rinnström D, Larsson C, *et al*. Left ventricular remodelling changes without concomitant loss of myocardial fat after long-term dietary intervention. International Journal of Cardiology. 2016; 216: 92–96.
[277] Lopes S, Mesquita-Bastos J, Garcia C, Bertoquini S, Ribau V, Teixeira M, *et al*. Effect of Exercise Training on Ambulatory Blood Pressure Among Patients with Resistant Hypertension: A Randomized Clinical Trial. JAMA Cardiology. 2021; 6: 1317–1323.
[278] Saco-Ledo G, Valenzuela PL, Ruiz-Hurtado G, Ruilope LM, Lucia A. Exercise Reduces Ambulatory Blood Pressure in Patients with Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of the American Heart Association. 2020; 9: e018487.
[279] Tomaz de Castro QJ, Araujo CM, Watai PY, de Castro E Silva SS, de Lima WG, Becker LK, *et al*. Effects of physical exercise combined with captopril or losartan on left ventricular hypertrophy of hypertensive rats. Clinical and Experimental Hypertension (New York, N.Y.: 1993). 2021; 43: 536–549.
[280] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004; 116: 281–297.
[281] Nosalski R, Siedlinski M, Denby L, McGinnigle E, Nowak M, Cat AND, *et al*. T-Cell-Derived miRNA-214 Mediates Perivascular Fibrosis in Hypertension. Circulation Research. 2020; 126: 988–1003.
[282] Li X, Wei Y, Wang Z. microRNA-21 and hypertension. Hypertension Research: Official Journal of the Japanese Society of Hypertension. 2018; 41: 649–661.
[283] Jusic A, Devaux Y, EU-CardioRNA COST Action (CA17129). Noncoding RNAs in Hypertension. Hypertension (Dallas, Tex.: 1979). 2019; 74: 477–492.
[284] Li H, Zhang X, Wang F, Zhou L, Yin Z, Fan J, *et al*. MicroRNA-21 Lowers Blood Pressure in Spontaneous Hypertensive Rats by Upregulating Mitochondrial Translation. Circulation. 2016; 134: 734–751.
[285] Montgomery RL, Hullinger TG, Semus HM, Dickinson BA, Seto AG, Lynch JM, *et al*. Therapeutic inhibition of miR-208a improves cardiac function and survival during heart failure. Circulation. 2011; 124: 1537–1547.
[286] Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, *et al*. Cardiac resynchronization in chronic heart failure. The New England Journal of Medicine. 2002; 346: 1845–1853.
[287] Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, *et al*. Effects of multisite biventricular pacing in patients with

heart failure and intraventricular conduction delay. The New England Journal of Medicine. 2001; 344: 873–880.

[288] Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al*. The effect of cardiac resynchronization on morbidity and mortality in heart failure. The New England Journal of Medicine. 2005; 352: 1539–1549.

[289] Linde C, Grabowski M, Ponikowski P, Rao I, Stagg A, Tschöpe C. Cardiac contractility modulation therapy improves health status in patients with heart failure with preserved ejection fraction: a pilot study (CCM-HFpEF). European Journal of Heart Failure. 2022; 24: 2275–2284.

[290] Lip GYH, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH, *et al*. Hypertension and cardiac arrhythmias: executive summary of a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). European Heart Journal. Cardiovascular Pharmacotherapy. 2017; 3: 235–250.

[291] Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, *et al*. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. The New England Journal of Medicine. 2005; 352: 225–237.

[292] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Journal of Heart Failure. 2016; 18: 891–975.

[293] Wang JG, Zhang W, Li Y, Liu L. Hypertension in China: epidemiology and treatment initiatives. Nature Reviews. Cardiology. 2023; 20: 531–545.

[294] Hisamatsu T, Segawa H, Kadota A, Ohkubo T, Arima H, Miura K. Epidemiology of hypertension in Japan: beyond the new 2019 Japanese guidelines. Hypertension Research: Official Journal of the Japanese Society of Hypertension. 2020; 43: 1344–1351.

[295] Ostchega Y, Fryar CD, Nwankwo T, Nguyen DT. Hypertension Prevalence Among Adults Aged 18 and Over: United States, 2017-2018. NCHS Data Brief. 2020; 1–8.

[296] Prisant LM. Hypertensive heart disease. Journal of Clinical Hypertension (Greenwich, Conn.). 2005; 7: 231–238.

[297] Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet (London, England). 2007; 370: 591–603.

[298] Jaacks LM, Vandevijvere S, Pan A, McGowan CJ, Wallace C, Imamura F, *et al*. The obesity transition: stages of the global epidemic. The Lancet. Diabetes & Endocrinology. 2019; 7: 231–240.

[299] Carvalho AF, Heilig M, Perez A, Probst C, Rehm J. Alcohol use disorders. Lancet (London, England). 2019; 394: 781–792.

[300] Benenson I, Waldron FA, Jadotte YT, Dreker MP, Holly C. Risk factors for hypertensive crisis in adult patients: a systematic review. JBI Evidence Synthesis. 2021; 19: 1292–1327.