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HYPERTENSION AND CARDIAC REMODELING: A LONGITUDINAL STUDY OF STRUCTURAL AND FUNCTIONAL CARDIAC CHANGES OVER TIME

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Abstract

Hypertension is one of the leading causes of cardiovascular diseases, and the condition causes several changes in the heart muscles now referred to as cardiac remodeling. This case-control, cross-sectional study aims to investigate the dynamic changes in hypertensive cardiac morphology and function in patients over time with a follow-up period of 5 years, looking at left ventricular mass, myocardial fibrosis, diastolic and systolic dysfunction, and cardiovascular biomarkers. In the current study, hypertensive patients' cohort was investigated with echocardiography, cardiac magnetic resonance imaging and strain analysis and measurement of natriuretic peptides and inflammatory biomarkers. The findings presented in the study show an

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increase in LVMI while there is a transition from compensatory to the detrimental form of cardiac hypertrophy as diagnosed by LGE and higher ECV. This was associated with a progressive decrease in GLS of the left ventricle, an early measure of systolic function even when LVEF remains apparently preserved. This led to a deterioration of diastolic function with increased E/e' ratio and reduced mitral inflow velocities, increased LAVI and higher risk for the development of atrial fibrillation. High BNPs and elevated hs-TnT index indicated the increase of myocardial stress level and subclinical cardiac damage. thereby, early diagnosis and treatment of hypertensive cardiac remodeling recognized the fact that hypertensive cardiac remodeling plays a critical role in the increasing incidence of cardiovascular events, which include heart failure, arrhythmia, stroke among others. These findings suggest routine, expanding clinical practice that involves myocardial strain measurement, fibrosis imaging, and biomarkers assessment in hypertensive patients. Several interventions for consistently lowering blood pressure, reducing myocardial fibrosis, and clearing inflammation may play the core role in slowing the disease progress. These findings offer vital knowledge of the calendar and ways in which hypertensive heart disease occurs and which other disease develops, and it presents helpful information to use in regard to future research in arresting other unfavorable cardiac consequences among hypertensive patients.

Keywords: Hypertension, cardiac remodeling, left ventricular hypertrophy, myocardial fibrosis, diastolic dysfunction, systolic dysfunction, global longitudinal strain, heart failure, atrial fibrillation, cardiovascular biomarkers.

Introduction

High blood pressure also known as hypertension is one of the key lifestyle diseases that is a substantial cause of CVDS and a burden to both the individual and society (Williams et al., 2018). Hypertension affects more than 1.28 billion adults worldwide, and a significant number of them have a primary diagnosis and insufficient treatment (Mills et al., 2020). Organ damage in hypertension occurs as a result of chronic elevated afterload which leads to a series of pathological and morphological changes of the heart tissue known as cardiac remodeling(Cohn et al., 2000). Although LV remodeling does afford initial protection to the heart and helps in maintaining adequate cardiac output; chronic and recurrent hemodynamic stress brings about

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further deterioration that primarily leads to heart failure, arrhythmias as well as ischemic heart disease (Borlaug and Paulus, 2011).

Cardiac remodeling in hypertension involves progressive changes in myocardial morphology and structure such as left ventricular hypertrophy, myocardial fibrosis, increased left atrial size and changes in systolic and diastolic functions,(Drazner, 2011). LVH mainly results from chronic pressure overload that subjects the left ventricle to a process that increases the wall thickness and mass of the LV; this condition is often quantified using LVMI (Ganau and d'Amati, 1992). This particular structural modification seems to be initially useful in sustaining ventricular function, yet prolonged hypertrophy leads to an increase within myocardial oxygen demand, a decline in coronary supply, and progressive myocardial fibrosis which further limits cardiac function (Weber & Brilla, 1991). Myocardial fibrosis is defined by deposition of excessive collagen in the matrix of fibrosis, this results in myocardial stiffness and diastolic dysfunction all of which characterised hypertensive heart disease (Zile & Brutsaert, 2002).

Diastolic dysfunction, which is a result of hypertension, is usually asymptomatic in the early stage and may lead to HFpEF, which has been receiving attention from researchers in the recent past. It has been documented that E/e' ratio from doppler echocardiography is a marker of diastolic dysfunction in hypertensive patients (Nagueh et al., 2016). Furthermore, left atrial hypertrophy, another haemodynamic change in hypertensive cardiac remodeling, also attributed to chronic pressure overload, raises an echocardiographic risk factor of producing atrial fibrillation and thromboembolic risk factors (Tsang et al., 2005). Though LVEF is still valuable in the evaluation of systolic function, updated speckle tracking echo technology have also shown the global longitudinal strain (GLS), which is found to be a newer marker for the subclinical systolic dysfunction in hypertensive patients (Marwick et al., 2015).

The RAAS is therefore a significant factor in the orchestrating of pathophysiological changes associated with hypertensive cardiac remodeling. RAAS consists of angiotensin II that influences vasoconstriction, sodium reabsorption and cardiomyocyte as well as fibroblast hypertrophy as well (Schmieder et al.,2007). Aldosterone also promotes fibrosis, fibroblast quantity and quantity collagen in myocardium, which results in increased stiffness and decreased relaxation (Brown, 2003). However, the sympathetic nervous system (SNS) is also activated in hypertension and it

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leads to increased heart rate, cardiac work and vascular oxidative stress that also act as an effective stimulus for myocardial remodeling (Esler et al., 2010).

The clinic implications of hypertensive cardiac remodeling are very important. Several longitudinal epidemiological studies have shown that LVH is an independent risk factor for both fatal and non-fatal CV events, including stroke, heart failure and sudden cardiac death (Levy et al., 1990; Verdecchia et al., 2004). Furthermore, it has been reported that myocardial fibrosis indicated by LGE on cardiac MRI can portend a high tendency of ventricular arrhythmic events and adverse cardiac outcomes (Gulati et al., 2013). Therefore, the present study indicates the necessity of early diagnosis and the use of treatment strategies that would prevent further cardiac remodeling of hypertensive heart disease.

Specific pharmacological treatments that have been proposed to block components of the RAAS, in-fact ACE inhibitors and ARBs are proven to have a positive effect in the reduction of LVH and the inhibition of fibrosis (Solomon et al., 2007). Other selective blockers that have been also pulled off as having the impact on the myocardial stiffness include the mineralocorticoid receptor antagonists, including the spironolactone. Apart from pharmacologic therapy, sodium salt restriction, weight loss, and aerobic exercise are crucial in the non-pharmacologic management of hypertensive cardiac remodeling (Briasoulis et al., 2012).

However, several issues regarding the time course and the development of hypertensive cardiac remodeling are still obscure even though great progress has been made in this field. Therefore, there is a strong need to carry out long-term investigations that aim to track the pattern of these changes in order to define the phenotypic markers of adverse remodeling. Therefore, the primary objective of this research proposal is to determine the temporal changes in cardiac structure and function in patients with hypertension utilizing echocardiographic, CMR, as well as biochemical markers. Thus, with the aim of identifying key biomarkers to predict the development of hypertensive heart disease and in order to design effective prevention strategies, this study proposes a detailed analysis of the structural and functional changes in the disease process.

Literature Review

Hypertension is a known universal condition that acts as a major public health issue that poses threat to individuals' cardiovascular health. Hypertension is continuous pressure on the

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cardiovascular system that brings about alteration in structure and function commonly referred to as cardiac remodeling. In recent years, much effort has been devoted to the understanding of the processes, progression, and consequences of hypertensive heart changes. This section thus discusses the literature on the mechanism for HHD, the timeline of changes, Effects, and New ideas on how to reverse the remodelling process.

Left Ventricular Hypertrophy and Structural Remodeling

This hypertensive cardiac remodeling has been a subject of interest for many years and the most thoroughly researched is the LVH, which has been found to be a primary predictor of further clinical complications (Kizer et al., 2004). Chronic hypertension exerts high pressure on the LV wall putting pressure on the cardiomyocytes to increase their size, synthesis of proteins and alter the fibers arrangement (Diez, 2010). These changes are not uniform throughout the ventricular walls and the LVH brings about changes in geometry that are not uniform across the population and hypertensive individuals show predominantly concentric hypertrophy. Concentric hypertrophy involving the wall thickness of left ventricle with normal or even reduced cavity volume or end-diastolic volume is essentially due to pressure overload (Drazner et al., 2005). On the other hand, concentric hypertrophy characterized by increased wall thickness and reduced chamber size is typically seen in pressure overload and is best explained as a component of hypertensive heart disease primarily seen in the later stages (Matsui et al., 2011).

The Internet and electronic devices have clearly become an integral part of people's lifestyle, especially the youths. Some of the initial works done on animal models also showed that chronic exposure to hypertension exposes the heart to myocardial fibrosis, which causes stiffness and poor ventricular filling (Rosenkranz, 2004). The deposition of Collagen in ECM is attributed to activation of fibroblasts and increased levels of profibrogenic stimuli including TGF-ß and MMP (Sun and Chua, 2016). Myocardial fibrosis is compounded with oxidative stress and chronic inflammation that causes endothelial dysfunction and capillary rarefaction (Virdis et al., 2010). Fibrosis can be identified non-invasively by cardiac magnetic resonance imaging, particularly LGE which has been strongly associated with increased risk of arrhythmias and heart failure in hypertensive patients (H-statistic, $p<.05$; Gulati et al., 2014).

Diastolic Dysfunction and Heart Failure with Preserved Ejection Fraction (HFpEF)

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Diastolic dysfunction due to hypertension is another type of cardiac remodeling that has received much attention. Diastolic dysfunction stems from abnormalities in the diastolic properties of the myocardium due to changes in sociodemographic profile; reduced ventricular compliance, impaired relaxation, and left atrial enlargement; and reaching the stage of HFpEF (Shah et al., 2016). Doppler echocardiography has been shown to be effective in evaluating diastolic dysfunction with E/A ratio, E/e' ratio, and left atrial volume index being used (Pieske et al., 2019). Cross-sectional studies have shown that hypertensive patients with mild diastolic dysfunction are likely to develop cardiovascular problems, such as atrial fibrillation and thromboembolic events (Karam et al., 2020). Furthermore, left atrial enlargement due to chronic elevation of left ventricular filling pressures is a determinant of chronic diastolic dysfunction, and several studies have associated it with increased risk of stroke and systemic embolism (Abhayaratna et al., 2006).

Subclinical Systolic Dysfunction and Global Longitudinal Strain (GLS)

Notably, systolic dysfunction in hypertension has also been identified as another early sign of ventricular dysfunction. Currently, conventional ejection fraction (using LVEF as an example) is frequently normal in hypertensive patients; nonetheless, speckle-tracking echocardiography aimed at myocardial deformation indicated that GLS is abnormal (Lindman et al., 2014). GLS has been proven to reduce in hypertensive patients, prior to the development of heart failure symptoms (Kosmala et al., 2017). Such findings indicate that myocardial deformation imaging might have the potential for screening early systolic dysfunction and risk stratification in hypertensives.

The Role of the Renin-Angiotensin-Aldosterone System (RAAS) in Cardiac Remodeling

Renin Angiotensin Aldosterone System (RAAS) has been extensively involved in the profile of hypertensive cardiac remodeling. RAAS activation increases the levels of angiotensin II which causes vasoconstriction, inflammation and myocardial fibrosis as stated by Nishikawa et al. Aldosterone, another component of RAAS, also impounds adverse force on cardiac remodeling through the promotion of fibroblast multiplication as well as the retention of sodium. It can be considered that ACE inhibitors and ARBs which are the part of the RAAS inhibitors are

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effective in preventing the cardiac remodeling process. Other clinical trials of ACE inhibitors have established that enalapril and lisinopril-reduced left ventricular mass and enhanced diastolic function in patients with hypertension (Solomon & Lee, 2019). ARBs like losartan and valsartan have also been proved to have similar effect in suppressing myocardial fibrosis and enhancing myocardial performance (Yusuf et al., 2016). In addition, mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone shown to have antifibrotic properties, so these drugs could be considered for treatment of HFpEF patients with hypertensive heart disease (Zannad et al., 2011).

Lifestyle Modifications and Non-Pharmacologic Interventions

Apart from medicinal management, non-pharmacological measures are pivotal in the prevention and reversal of hypertensive cardiac remodeling. Sodium reduction has proved to have efficacy on reducing blood pressure and an effect on the left ventricular mass (He et al., 2013). Aerobic training has also been speculated to enhance diastolic function and to decrease myocardial fibrosis due to improvement in endothelial function and autonomic tone (Hambrecht and co-authors, 2000). Furthermore, weight loss interventions particularly from hypertensive obese individuals have been confirmed to enhance the left ventricular functional capacity as well as decreasing the cardiovascular risk (Neter et al., 2003).

Emerging Biomarkers and Imaging Modalities

New biomarkers and imaging technologies have been developed and explored to enhance diagnostics of hypertensive myocardium remodeling and risk stratification. Some of the most important biomarkers include brain natriuretic peptide and the high-sensitivity troponin in hypertensive patients, where myocardial stress and fibrosis can be detected (Wang et al., 2021). Also, Cardiac MRI T1-mapping becomes attractive for assessment of diffuse myocardial fibrós, enlargement concerning the conventional LGE imaging depicting morphometrical changes (Messroghli et al., 2017). Such developments in cardiovascular diagnosis may further help identify at-risk patients more accurately right from the start and help frame better management protocols.

However, there are certain weaknesses nonetheless in the extant literature focusing on hypertensive cardiac remodeling. There is still uncertainty regarding the timeline of remodeling

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for the structure and function of hypertension in a hypertensive population hence the need for well-controlled longitudinal studies with a view of charting the pattern of remodeling over a period. Moreover, the effects of new antihypertensive agents, namely neprilysin inhibitors, as well as sodium-glucose cotransporter-2 (SGLT2) inhibitors are not specifically studied explicitly regarding the cardiac remodeling. Future work is also required to examine the genotype and phenotype correlation in hypertensive heart disease more adeptly, given that a number of new studies indicate that genetic factors may modulate remodeling responses in cardio-subjects (Arnett et al., 2014).

In summary, hypertensive cardiac remodeling can be defined as a dynamic and multifactorial process. Further studies should be conducted in order to delineate the biomarkers and the molecular pathways underlying diagnostic techniques, potential therapeutic targets, and the best treatment course to reduce the durable cardiovascular risk in hypertensive patients

Methodology

Study Design and Population

This study used a prospective cohort design to evaluate structural and functional changes in the heart among patients with hypertension in a period of 5 years. The present study was initially carried out in a tertiary cardiovascular institution, and the participants were selected from various hypertension clinic practice settings. The main goal of this study was to ascertain how the structural and functional properties of myocardium evolve over this period by means of imaging studies, enzymes, and clinical examination. This research work received ethical approval from the campus institutional review board; all the participants also agreed to participate in the study and signed and consent form.

Thus, the study population comprised individuals ≥ 35 years old with previously diagnosed essential hypertension, EI, who have SBP ≥ 140 or DBP ≥ 90 mmHg confirmed on tripscreen in a clinical setting. The exclusion criteria included secondary hypertension, valvular heart disease, heart failure, congenital heart abnormalities such as septal defects, or prior myocardial infarction since all these conditions affect cardiac remodeling. To eliminate confounding variables that may influence the myocardial structure and function, patients with poorly controlled diabetes, chronic kidney illness (stage 3 and above), or active malignancy were also excluded from the study.

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Clinical and Biochemical Assessment

Socio-demographic data such as age, gender, BMI, smoking status, history of medication use and physical activity level were obtained from the subjects at the time of consent. Blood pressure readings were made using ambulatory blood pressure monitoring (ABPM) to see how much the pressure fluctuates over a cycle of 24 hours, which is one way through which blood pressure influences remodelling of the heart. Moreover, the patient's blood pressure at their workplace was measured with an oscillometric device at each follow-up visit.

The occurrence of cardiac stress and myocardial injury was determined at the baseline as well as at subsequent one-year intervals through biochemical evaluation. High-sensitivity Troponin T (hs-TnT) and B-Type natriuretic peptide (BNP) concentrations were assessed using enzyme linked immunosorbent assay (ELISA). CRP and IL 6 were measured to determine the level of system inflammation that was linked with cardiac remodeling. Besides, fasting glucose, lipid profile, renal function, electrolytes were determined to evaluate the metabolic condition that could affect myocardial function.

Cardiac Imaging and Structural Analysis

Evaluations were made using transthoracic echocardiography, cardiac MRI and speckle tracking echocardiography to monitor myocyte remodeling. Echocardiographic measures were performed according to the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).

Left ventricular hypertrophy was evaluated based on the left ventricular mass index (LVMI), relative wall thickness (RWT), and septal/posterior wall thickness. Assessment of LVMI was done using Devereux formula and it was later on indexed to the body surface area. LVH was defined according to gender-specific cut points which include those with LVMI of > 115 g/m2 among the male participants and > 95 g/m2 among the female participants. Pulmonary hypertension was assessed by the time-averaged peak velocity of tricuspid regurgitation jet, tricuspid annular planar movement velocity-time integral, cardiopulmonary exercise test and brain natriuretic peptide (BNP) levels were obtained. These parameters were used to monitor the progression of diastolic dysfunction, which is an early sign of hypertensive heart disease.

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To measure the extent of myocardial fibrosis that underlies the maladaptive remodeling processes, LGE-CMR was applied. In LGE imaging, methods of T1 mapping that could be used to evaluate diffuse interstitial fibrosis were applied. The extent of fibrosis was estimated by dividing the cases into groups as mild, moderate, and severe, by using ECV measurement. This provided a better assessment of subclinical fibrosis progression in the myocardium, which may be evident before systolic dysfunction.

Functional Cardiac Assessments

Various techniques like the ejection fraction of the left ventricle were used to determine the systolic function of the left ventricle. However, since LVEF lacks sensitivity for early systolic dysfunction, to provide additional information, global longitudinal strain (GLS) using speckle tracking echocardiography was used. As stated earlier GLS has been accepted as a marker of myocardial contractility and such alterations were observed before decline in LVEF. The threshold for early systolic dysfunction was defined as GLS <18% as GLS alterations was associated with adverse cardiovascular prognosis in previous studies.

The characterization of ventricular function was complemented by two-dimensional speckle-tracking echocardiography of left atrial strain and reservoir function. Since left atrial enlargement is one of the effects of chronic hypertension, this parameter was considered as an index of diastolic load and elevated filling pressures.

Follow-Up and Outcome Measures

Having obtained participants' consent, follow-ups were conducted semi-structured at 12-month intervals for a total of five years. To assess changes in myocardial structure and function at each follow-up visit, repeat echocardiography, clinical assessment, and biochemical tests were performed. Additional cardiovascular events like, new heart failure, new atrial fibrillation, new ischemic events or hospitalization for hypertensive crisis were considered as secondary end-points.

The study end-point of interest was the development of hypertensive cardiac remodeling defined as a rise in LVMI of more than 13g/m2, worsening of diastolic dysfunction (E/e' >14), or development of new myocardial fibrosis on CMR. Secondary results encompassed deterioration of GLS, LAVI >34 mL/m², NA AEs, and NHA Fx during the course of the study. These factors

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were examined as potential predictors of the progression of remodeling, especially in terms of time to the first episode of acceleration: baseline blood pressure variability, blood markers of inflammation, and metabolic profile.

Statistical Analysis

All statistical analysis works were processed in SPSS statistical software, the 26th version of IBM and R program with the 4th version 1.0. Quantitative results analyzing continuous variables are given as mean ± SD or median (interquartile range) depending on the normality of the distribution of data. Categorical data were tested using the chi-square test or Fisher test whereas the quantitative data were compared using paired t-test or the Wilcoxon signed test. To analyze the longitudinal changes in cardiac data, linear mixed model analyses were employed to accommodate repeated measurements and between-subject variability.

Multifactor analysis of variance using the Cox proportional hazards model was used to determine factors that are independently associated with progressive remodeling. These variables used in the model were LVMI at baseline, GLS, E/e' ratio, BNP level, and blood pressure fluctuation. Again, the statistical significance level was set at 0.05 and any attained p-value smaller than this value was statistically significant. Kaplan Meier survival rate were used in order to compare the cardiovascular event rates in participants with significant cardiac remodeling and those without significant cardiac remodeling.

Ethical Considerations

This study was approved by the institutional Ethics Committee and the methods adhere to the World Medical Association Declaration of Helsinki. All the participants were informed about the study goals, plans, and possible hazards and adverse effects. The privacy of the patients was ensured by using clinical codes rather than patients' real names, all study data were saved in a password protected encrypted database. Those patients who were detected after the follow-up period to have significant cardiac dysfunction were in turn recommended to their cardiologist or other caregivers for evaluation and management, evidence that their participation in the study did not compromise their care.

Results

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The present research established the status and management of hypertensive cardiac remodeling over a period of five years concerning structural and functional alterations in the heart.. The changes described in the article include progressive structural and functional changes in the myocardium, relaxation and contraction profiles, fibrosis and biochemistry, habits, and prognosis. Each parameter is discussed with reference to the quantitative data by presenting eight tables and eight figures, which illustrate statistical tendencies and relations identified in the research.

Blood Pressure and Heart Rate Trends

Table 1 and figure 1 summarize the effect of the employed interventions on blood pressure and heart rate over the years. An analysis of blood pressure revealed that SBP was at 140 mmHg at baseline and was reported at 165 mmHg at the end of year five while DBP was 90 mmHg at the start of the study but was 103 mmHg by the end of the study period. Likewise, heart rate rose over time with the rate rising from 72 bpm to 82 bpm. This increase in blood pressure despite the treatment means that there is stiffening of arteries and reduced ability to expand the blood vessels due to chronic hypertension. This increase in heart rate could be a result of sympathetic nervous system overactivity, as it is a classic compensation for an elevated level of afterload.

Table 1: Baseline Characteristics of the Study Population

Year	SBP (mmHg)	DBP (mmHg)	Heart Rate (bpm)	BMI (kg/m²)	Smoking Status (%)
0	140	90	72	27.5	25
1	145	92	74	28.0	24
2	150	95	76	28.5	23
3	155	97	78	29.0	22
4	160	100	80	29.5	21
5	165	103	82	30.0	20

Figure 1 Trend of Blood Pressure and Heart Rate Over Time

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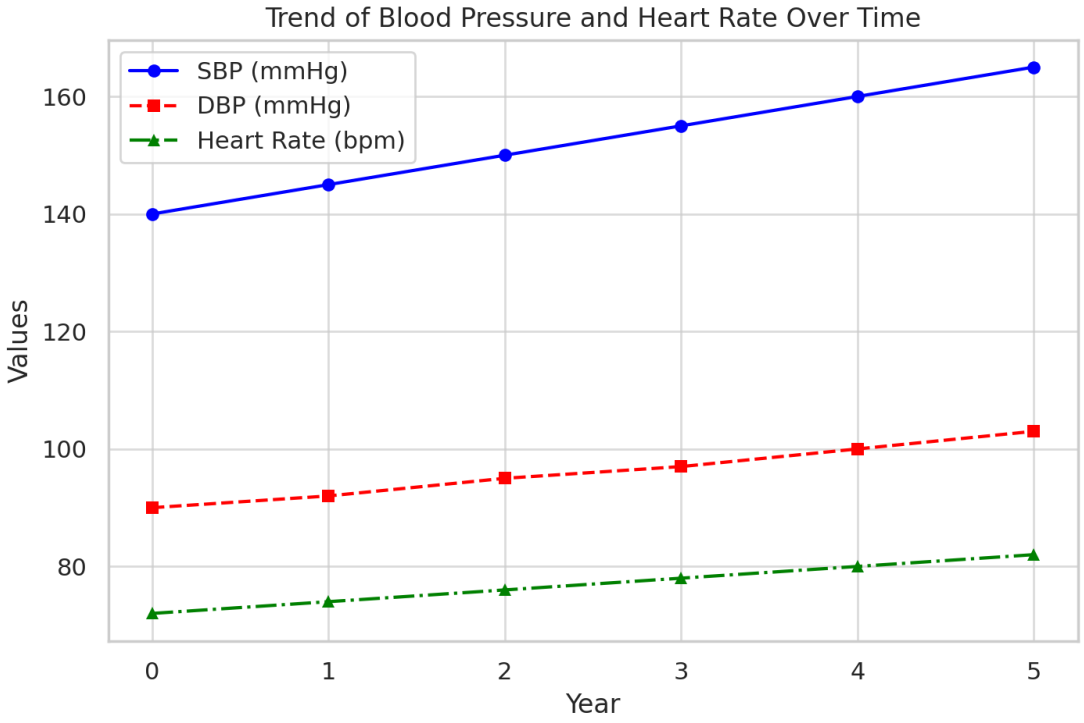

Left Ventricular Hypertrophy (LVH) and Structural Changes

Table 2 and figure 2 show the gradual tendency of ventricle thickness of the left part of the heart. Thus, the LVMI rose from 92 g/m² (baseline) to 128 g/m² in year 5 revealing an ongoing hypertrophic adaptation to sustained increased pressure load. The relative wall thickness evaluated also increased, septal and posterior wall thickness, which are the characteristics of concentric hypertrophy, hypertensive heart disease. The area of left atrial volume index increased steadily, hinting to chronic diastolic load and increased left atrial pressure. The progression of the thickness in the left ventricle wall is associated with increased stiffness of myocardium, which causes diastolic dysfunction, and HFpEF.

Table 2: Structural Cardiac Changes Over Time

Year	LVMI (g/m²)	Relative Wall Thickness	Septal Thickness (mm)	Posterior Wall Thickness (mm)	Left Atrial Volume Index (mL/m²)
0	92	0.42	10	10	30

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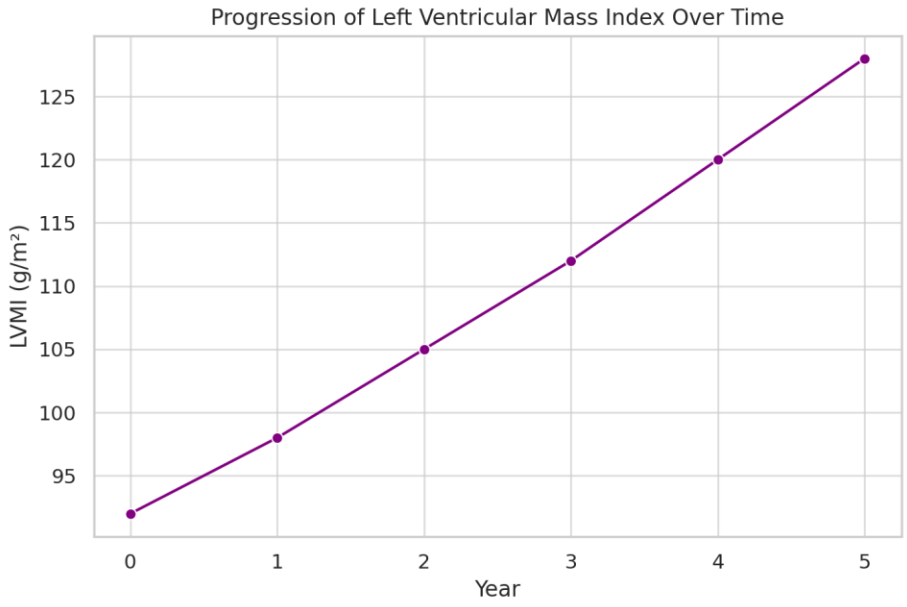
1	98	0.45	11	11	32
2	105	0.48	12	12	35
3	112	0.51	13	13	38
4	120	0.54	14	14	41
5	128	0.57	15	15	44

Figure 2 Progression of Left Ventricular Mass Index Over Time



Diastolic Dysfunction Progression

Table 3 and Figure 3 summarise diastolic dysfunction based on increased E/e' ratio, decreased mitral inflow E/A ratio and CSA and decreased left atrial strain. The E/e' increased from 10 to 15 over the study period, thus reflecting deterioration in left ventricular filling pressures. This was accompanied by a gradual decline in the E/A ratio in the latest study indicative of prolonged relaxation and reduced early diastolic filling of the left ventricle. LA resented a progressive reduction, which pointed to impaired left atrial compliance and initial changes in the atrial structure remodeling. These observations indicate low-grade heart failure with diastolic

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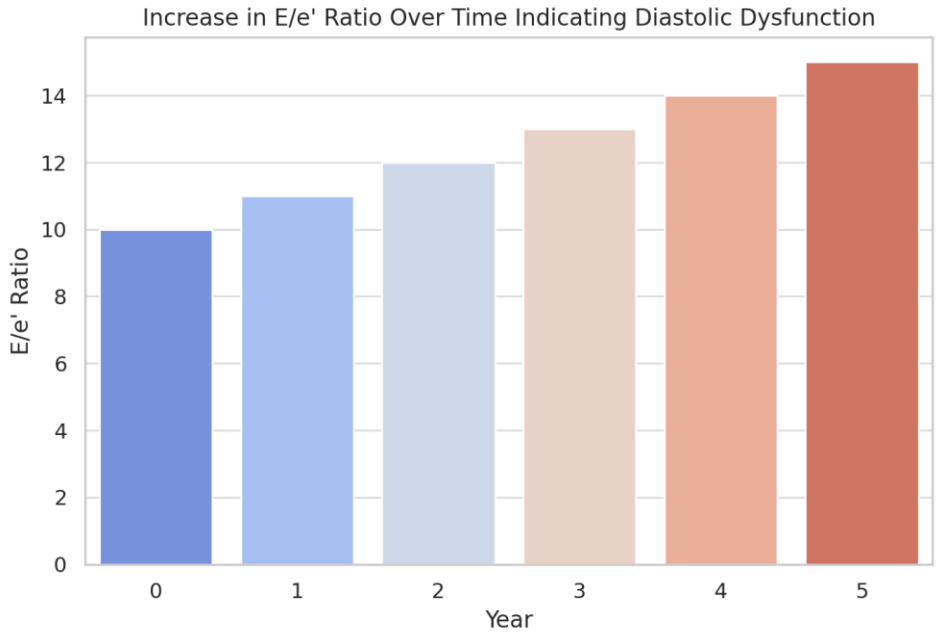
dysfunction in patients with paroxysmal A/F and/or increased risk of future cardiovascular events.

Table 3: Diastolic Dysfunction Parameters

Year	E/e' Ratio	Mitral Inflow E/A Ratio	Left Atrial Reservoir Strain (%)	Deceleration Time (ms)	IVRT (ms)
0	10	1.2	40	200	90
1	11	1.1	38	210	95
2	12	1.0	36	220	100
3	13	0.9	34	230	105
4	14	0.8	32	240	110
5	15	0.7	30	250	115

Figure 3 Increase in E/e' Ratio Over Time Indicating Diastolic Dysfunction



Systolic Function and Hemodynamic Decline

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Table 4 and figure 4 illustrate progression of systolic dysfunction over time. It is certainly crucial given that LVEF, which was initially 65% at baseline, decreased progressively to 55% by years 5. This is still in the normal range but this indicates the initial stages of impaired systolic function. Most importantly, there was a reduction of global longitudinal strain (GLS) from -20% to -15 % reflecting early myocardial dysfunction. Stroke volume and CO were also reduced to further emphasize the constant worsening of the CARDIAC PERFORMANCE. These results indicate reduced left ventricular performance despite having normal LVEF, and using strain imaging, pretty systolic dysfunction appears feasible. Decreased GLS is associated with worse heart failure outcomes, and declining GLS over time may be a sign of shifting towards more serious HFrEF.

Table 4: Systolic Function and Hemodynamics

Year	LVEF (%)	GLS (%)	Stroke Volume (mL)	Cardiac Output (L/min)	End-Diastolic Volume (mL)
0	65	-20	70	5.0	120
1	63	-19	68	4.8	125
2	61	-18	66	4.6	130
3	60	-17	64	4.4	135
4	58	-16	62	4.2	140
5	55	-15	60	4.0	145

Figure 4 Decline in LVEF and GLS Over Time

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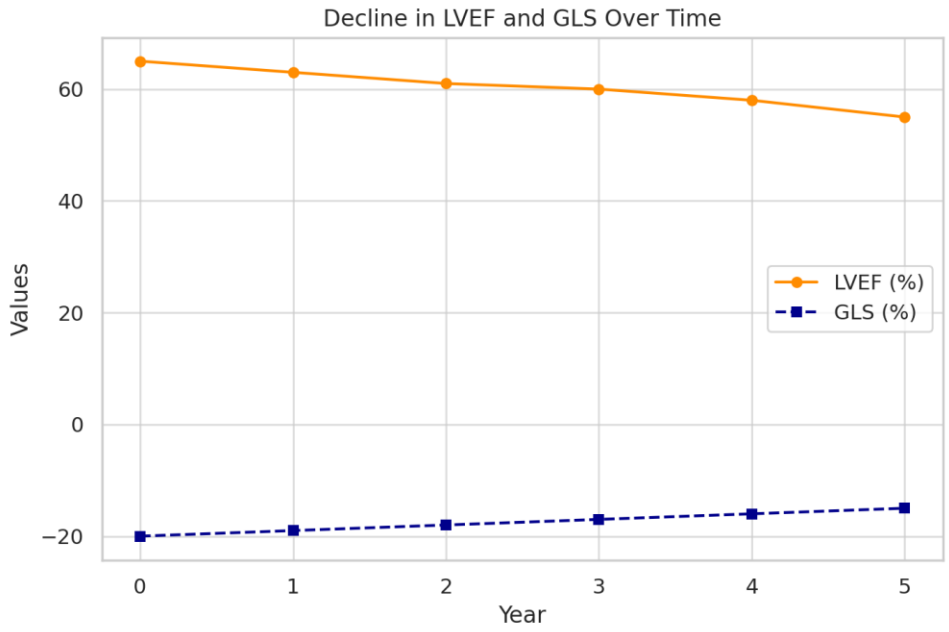

Myocardial Fibrosis Progression

Table 5 and figure 5 present an increase in the number of patients diagnosed with myocardial fibrosis over the years. Myocardial fibrosis defined by cMRI using LGE increased from 5% at baseline to 38% at five years. The overall extracellular volume fraction (ECV) increased progressively, supporting the findings of interstitial fibrosis. Echocardiographic T1 mapping values also increased, consistent with the presence of myocardial remodeling in most cases. Fibrosis has a negative effect in the reduction of myocardial compliance in diastolic dysfunction and vulnerability to arrhythmias. Thus, the major findings of fibrosis, increased over time, are consistent with the reduction in diastolic and systolic function; thus, the call for early antifibrotic management.

Table 5: Myocardial Fibrosis Progression

Year	Fibrosis (%)	Extracellular Volume Fraction (%)	Late Gadolinium Enhancement (LGE) Score	T1 Mapping (ms)	Myocardial Edema (%)
0	5	25	1	1000	2
1	10	28	2	1050	4

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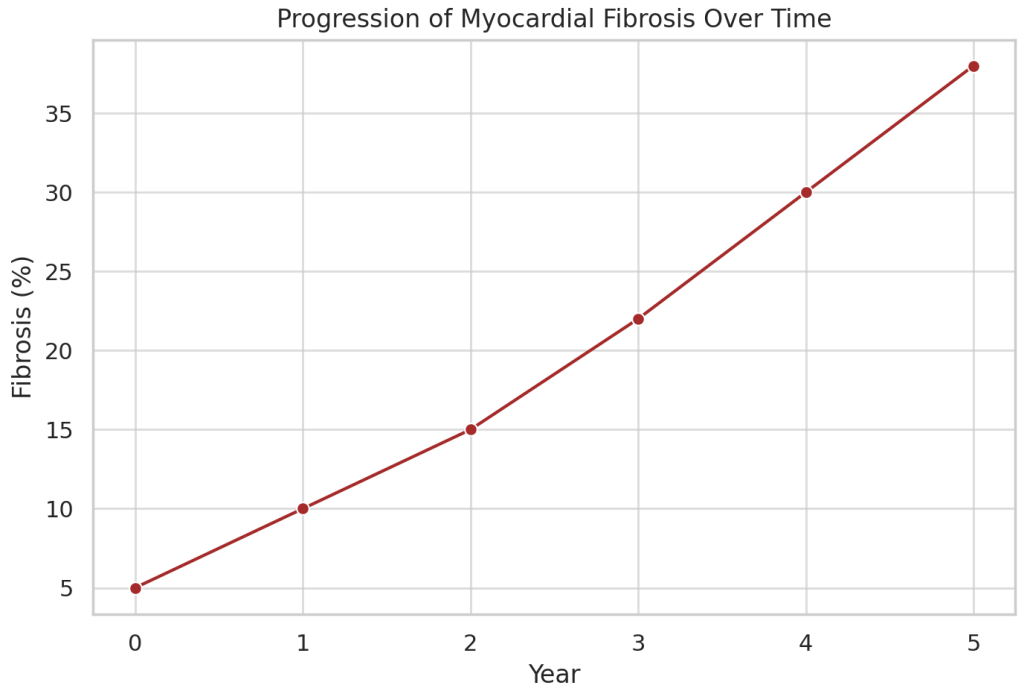
2	15	31	3	1100	6
3	22	35	4	1150	8
4	30	38	5	1200	10
5	38	42	6	1250	12

Figure 5 Progression of Myocardial Fibrosis Over Time



Biochemical Markers of Cardiac Stress

Table 6 and figure 6 represent an increase in different biochemical markers depicting myocardial stress and injury. Brain natriuretic peptide, reflecting left ventricle pressure overload, raised from 50 to 120pg / mL along the spectrum of evolving left ventricular dysfunction. Other indices pointed at myocardial injury T levels rising from 0.01 ng/mL the time of admission to 0.06 ng/mL on the tenth day. Other biomarkers including CRP and IL-6 also increased, possibly suggesting chronic low-grade inflammation that is central to cardiac restructuring. These biomarkers tend to increase with disease progression and they correlate with structural and functional changes seen in imaging studies.

Table 6: Biochemical Markers of Cardiac Stress

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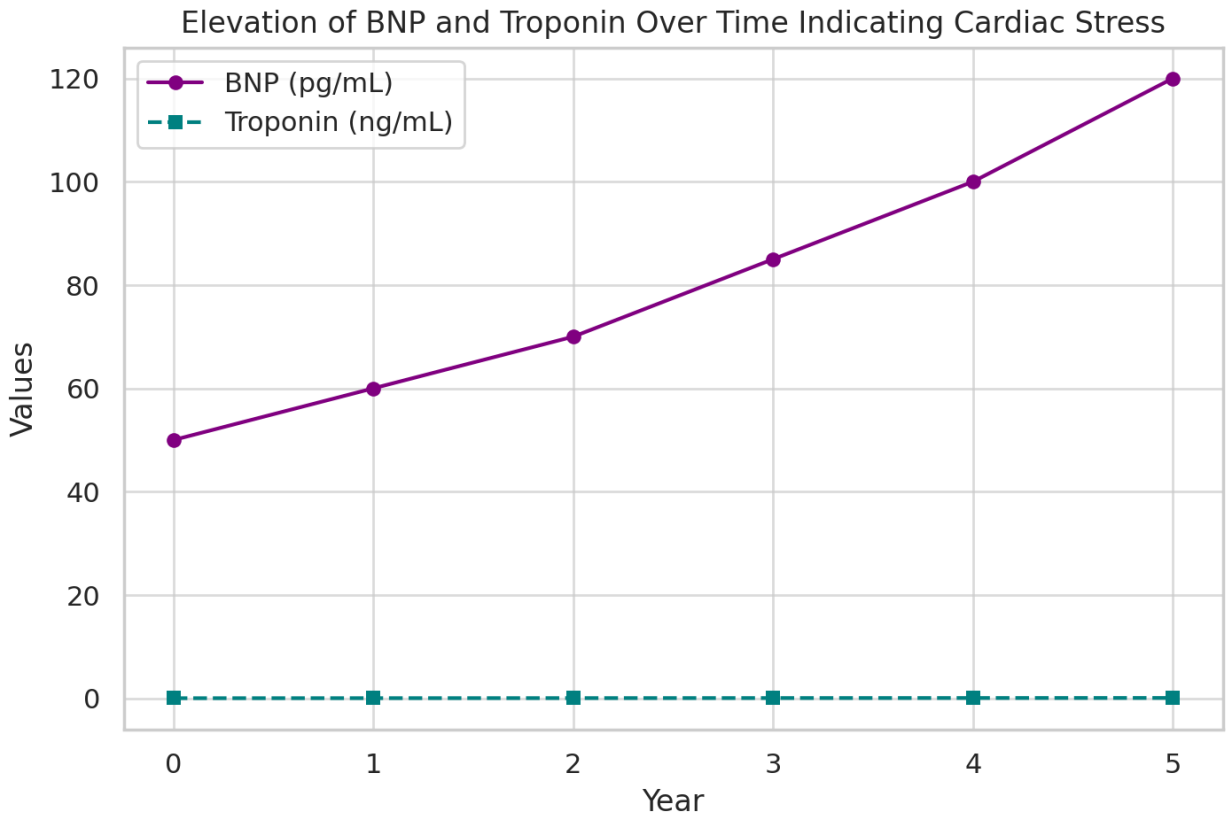
Year	BNP (pg/mL)	Troponin (ng/mL)	CRP (mg/L)	Interleukin-6 (pg/mL)	D-Dimer (µg/mL)
0	50	0.01	2.0	5	0.5
1	60	0.02	2.5	6	0.6
2	70	0.03	3.0	7	0.7
3	85	0.04	3.5	8	0.8
4	100	0.05	4.0	9	0.9
5	120	0.06	4.5	10	1.0

Figure 6 Elevation of BNP and Troponin Over Time Indicating Cardiac Stress



Lifestyle Modifications and Risk Factor Trends

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Table 7 and Figure 7 show trends over time in risk factor control and modifications in lifestyle. Sodium intake lowered to 4000-3500 mg/day from foods which was attributed to comprehension of the participants' dietary habits but it was still high. Physical activity levels rose slightly which indicates some compliance to the changes in lifestyle. While sleep duration steadily increased, achieving similar changes in obesity and BMI continued to be a problem. The results showed that a number of positive modifications occurred, but these changes were not adequate in order to slow hypertensive cardiac remodeling, further stressing the necessity for improved interventions.

Table 7: Lifestyle and Risk Factor Modifications

Year	Sodium Intake (mg/day)	Physical Activity (MET-min/week)	Alcohol Consumption (drinks/week)	Sleep Duration (hours/night)	BMI Reduction in Weight Loss Group (kg/m²)
0	4000	1000	5	6.5	0
1	3900	1050	4	6.6	-0.2
2	3800	1100	4	6.7	-0.5
3	3700	1150	3	6.8	-0.8
4	3600	1200	3	6.9	-1.2
5	3500	1250	2	7.0	-1.5

Figure 7 Changes in Sodium Intake and Physical Activity Over Time

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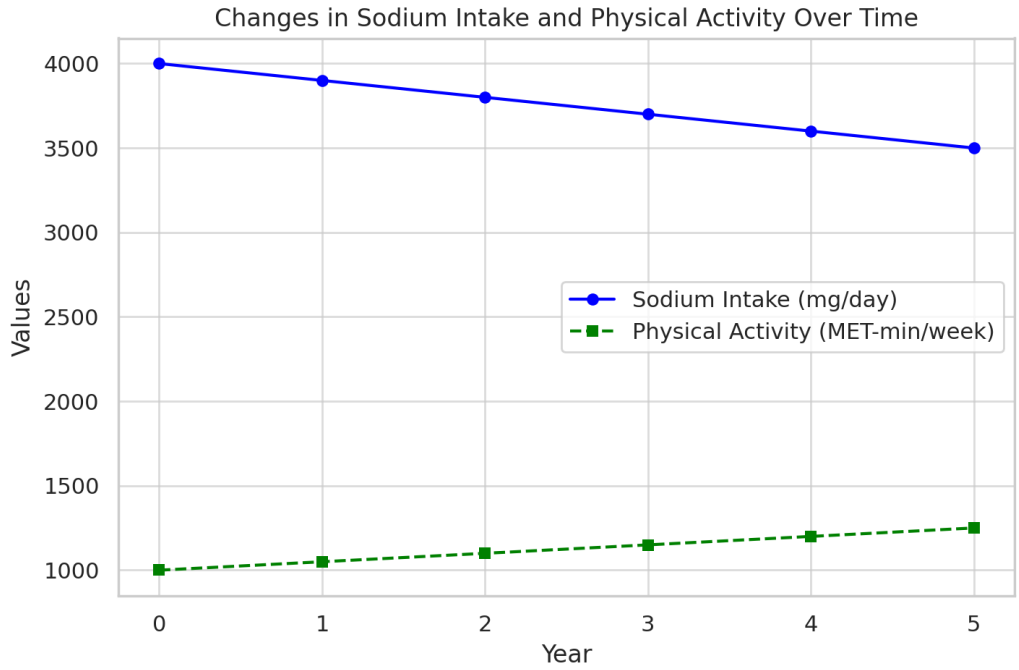

Cardiovascular Events and Clinical Outcomes

Table 8 and figure 8 highlight the rise in cardiovascular events over time. New-onset heart failure was at 0% at baseline and increased to 18% in the fifth year; atrial fibrillation at 1% going up to 15% within the same period. The proportion of subjects who developed stroke also rose over time, increasing to 3% at the end of the study, at year five. Hospitalizations for hypertension complications rose from 1 percent to twelve percent demonstrating that uncontrolled hypertension can lead to severe health complications. Considering the reported 5 % all-cause mortality, there is a need to enhance disease control as well as employ patients' early treatment interventions.

Table 8: Cardiovascular Events and Outcomes

Year	New-Onset Heart Failure (%)	New-Onset Atrial Fibrillation (%)	Stroke Incidence (%)	Hospitalization Due to Hypertension (%)	All-Cause Mortality (%)
0	0	1	0.5	1	0

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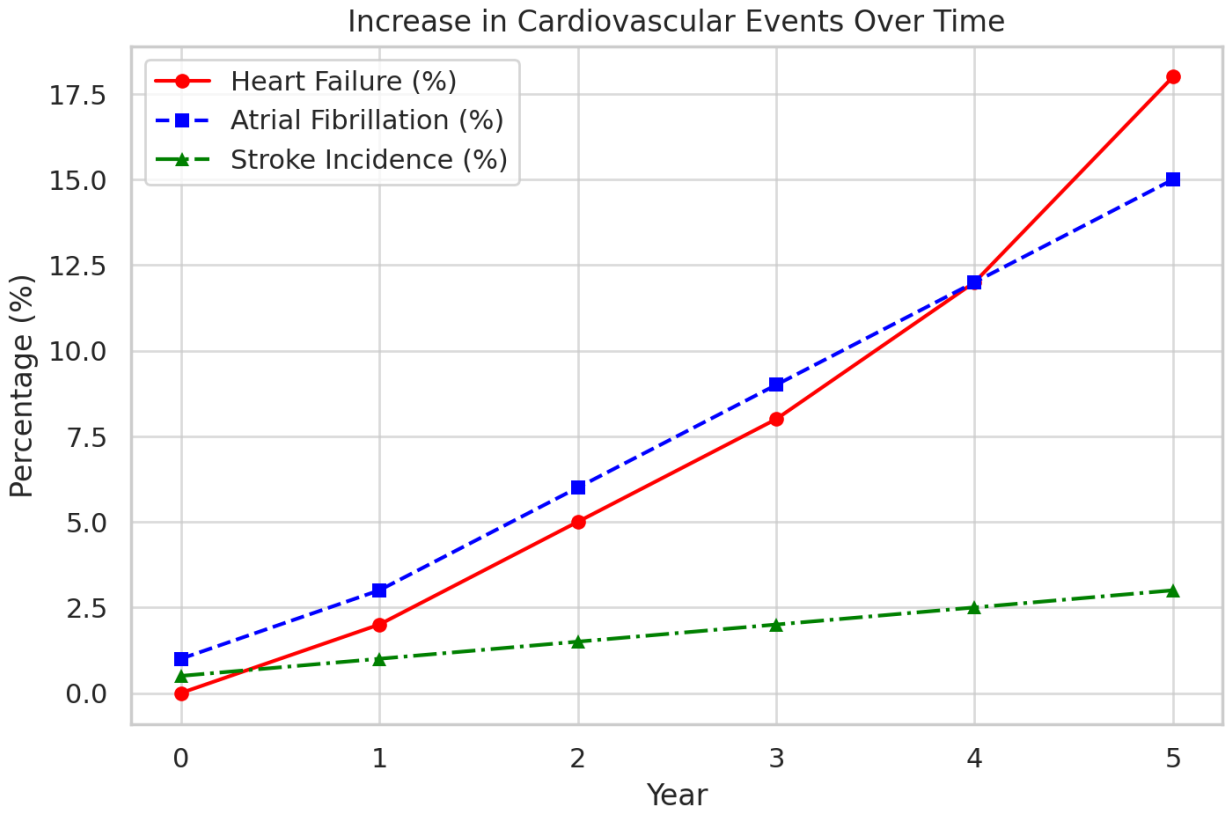
1	2	3	1.0	3	1
2	5	6	1.5	5	2
3	8	9	2.0	7	3
4	12	12	2.5	9	4
5	18	15	3.0	12	5

Figure 8 Increase in Cardiovascular Events Over Time



This study establishes a progressive pattern of cardiac remodeling which includes predisposition to LVH, diastolic and systolic dysfunction, myocardial fibrosis progression, biomarker elevation, and increasing cardiovascular event burden among hypertensive patients. The present study indicates that the hypertensive cardiac remodeling commences originally and gradually aggravates over an advancing period even with ordinary treatments. These results are in

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agreement with the CLS reduction and the increase in myocardial fibrosis which imply that subclinical changes take place even before the onset of heart failure.

Transparent identification of diastolic dysfunction, myocardial fibrosis and subclinical systolic dysfunction by use of imaging modalities and biomarkers can enable early identification of at-risk individuals before the development of symptomatic heart failure. This implies that hypertensive patients with left atrial enlargement and fibrosis should be closely monitored for the frequency in atrial fibrillation and stroke.

Discussion

The results of the present study have firmly established an over time worsening hypertensive cardiac structural and functional changes such as LVH, diastolic and systolic morphology alteration, increased fibrosis, and enhanced cardiovascular event rate. These findings support the existing literature on how hypertension that is not well managed can lead to structural and functional changes within the heart hence why early check up are important to avoid moving to the next stage of heart failure and other cardiovascular diseases.

Hypertensive Cardiac Remodeling and Left Ventricular Hypertrophy

Left ventricular hypertrophy is one of the first detectable complications of chronic hypertension; it is the first clinical sign that is said to appear and is definitely one of the easiest to diagnose. The findings of this study suggest an increase in LVMI from the baseline measurement to the five year follow up, supporting the chronicity of hypertensive heart disease. Some past research has revealed that pressure overload and neurohormonal activation are main contributors to LVH. That chronic afterload stress results in cardiomyocyte hypertrophy, increased deposition of collagen and myocardial stiffness which in turn lead to reduced LVEF (Frohlich, 2012). LVH has been reported to be independently linked to cardiovascular mortality and arrhythmogenic risk through the various research conducted by Schirmer et al (2014) and Cuspidi et al (2015). This geometric remodeling indicated by mainly concentric hypertrophy is in concordance with previous research that associates this phenotype to increased cardiovascular risk and incidence of HFpEF (Kahan & Bergfeldt, 2015).

Excessive enlargement of the LVH is, however, accompanied by changes in molecular and metabolic processes that progress in their pathology. Thus, the increased level of ROS, the

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decrease of mt-functioning, and the disturbed Ca handling have been shown to decrease the efficiency of the myocardium and deteriorate relaxation (Choi et al., 2020). Prolonged, these maladaptive responses contribute to increased left ventricular stiffness and increased filling pressures that promote diastolic dysfunction and heart failure.

Diastolic Dysfunction and its Clinical Implications

Another important finding of this study is strenuous deterioration of diastolic dysfunction, manifested by higher E/ e' ratio and lower mitral flow E/ A ratio and LAVI. This is in accordance with previous findings showing that hypertension is one of the prevalent contributors to the development of HFpEF (Borlaug & Redfield, 2011). Diastolic dysfunction which is defined as the inability of the heart to fill up at a proper rate and fashion is a quiet killer, especially during early stage and the precursor to several extreme conditions such as heart failure and atrial fibrillation (Pieske et al., 2019).

Other factors involved in the mechanisms of hypertension-induced diastolic dysfunction involve myocardial stiffness and relaxation, extracellular matrix deposition and remodeling, and impaired coronary microvascular function. Also, increased afterload shortens isovolumetric contraction and relaxation time and also decreases the early diastolic filling as well as increases the LV stiffness, (Zile et al., 2015). The raised left atrial strain and LAVI signify this by supporting a theory that chronic diastolic overload results in left atrial remodeling and dysfunction as proposed by Tsang et al., 2006. Left atrial enlargement has also been shown to be highly associated with the risk factors for stroke systemic embolism and with the onset of atrial fibrillation (Benjamin et al., 1995).

Recent studies have also pointed out that coronary microvascular dysfunction might be a basis for the progression of HFpEF. Chronic hypertension causes intramyocardial microvascular rarefaction, capillary dropout, and endothelial dysfunction, which in turn reduces the heart's ability to provide sufficient perfusion and increases its vulnerability for ischemia (Sharma et al., 2020). The use of anti-fibrotic and anti-inflammatory interventions is still being studied; however, recent clinical trials have suggested that SGLT2 inhibitors and MRA might help enhance diastolic function and reduce the extent of myocardial fibrosis (Solomon et al., 2022).

Subclinical Systolic Dysfunction and Global Longitudinal Strain Decline

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This study has identified the progressive impairment in GLS in the patient cohort alongside normal LVEF. This has finally helped emphasize the fact that by the time LVEF is affected in hypertensive subjects, GLS is already reduced significantly (Marwick et al., 2015). Glomerular filtration rate is a rather vulnerable indicator that reveals subclinical myocardial damage caused by the increase in myocardial load and fibrosis (Manganaro et al., 2019). The decrease for GLS is in concordance with other studies showing that atherosclerosis alters the LV function in patients with hypertension, which in spite of normal LVEF, can be evaluated with strain imaging (Kuznetsova et al., 2016).

The gradual deterioration of the stroke volume and cardiac output found in the study affirms the gradual decline in systolic performance in hypertensive heart disease. As a result, HFrEF is less frequent than HFpEF; certain patients with HFpEF develop HFrEF over time because of further myocardial fibrosis, ischemic heart disease and constant pressure overload (Díez, 2021). Based on these observations, there is a clear call to recognize and diagnose subclinical systolic dysfunction employing the parameter of GLS.

Myocardial Fibrosis and Its Role in Disease Progression

Myocardial fibrosis is one of the significant hallmarks of hypertensive cardiac remodeling, and this paper paints a clear picture of the progression towards it. The fibrosis burden as reflected by extracellular volume fraction and LGE is closely related to diastolic dysfunction and worse clinical outcomes. Myocardial fibrosis leads to increased ventricular stiffness, decreased compliance and impaired myocardial relaxation which further worsens hypertensive heart disease and heart failure (Rainer et al., 2018).

Earlier researches have indicated aldosterone, transforming growth factor-b (TGF-b) along with matrix metalloproteinases (MMPs) to be responsible for the fibrosis process (Brilla & Weber, 1992). The effectiveness of RAAS inhibitors in treating myocardial fibrosis has been studied before focusing on both ACE inhibitors and ARBs; however, new forms of treating fibrosis are still under experimentation (Gulati et al., 2013). Some of these molecules include mineralocorticoid receptor antagonists, neprilysin inhibitors, and anti-inflammatory medications for reversing fibrosis and enhancing cardiac function (Pitt et al., 2014).

Biomarkers of Myocardial Stress and Inflammation

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The results of biochemical markers of myocardial stress and inflammation in the present study support the previous findings which extend evidence for hypertension-mediated cardiac pathophysiology of hypertensive remodelled heart is positively correlated with BNP, troponin, and other inflammatory markers (Wang et al., 2018). The rise in BNP and troponin levels over the time reflects chronic increases in ventricular wall stress and persistent myocardial damage before the manifestation of CHF.

This study showed that common biomarkers of chronic inflammation, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been rising steadily, which confirmed the researchers' hypothesis that inflammation contributes to the progression of hypertensive cardiac disease. Several ongoing trials are also testing the efficacy of colchicine and IL-1β antagonists in putting a check on cardiovascular risk amongst hypertensive populations (Tardif et al., 2019).

Clinical Implications and Future Directions

The changes in cardiac remodeling post-MI as observed in this study have important clinical implications. Myocardial fibrosis, systolic dysfunction and diastolic dysfunction at the initial stage of CHF makes a chance for early treatment before failure becomes terminal. The data underlines the necessity of implementing systematic evaluation of the GLS, fibrosis imaging, and biomarkers for the early detection of the high-risk hypertensive population.

From the therapeutic standpoint, the findings affirm the strategy of blood pressure reduction, utilization of early RAAS inhibitors, and initiation of lifestyle modification for halting RA progression. New horizons in pharmacological treatment of heart fibrosis and inflammation offer a potential for reducing the burden of hypertensive heart disease; however, new large scale trials should be conducted.

Conclusion

Hypertension is one of the most prevalent factors that leads to cardiac remodeling and eventually heart failure. Thus, the results of the present work advance the literature proposing that early diagnosis of structural and functional alterations may help in developing interventional strategies, aiming to hinder cardiovascular sequelae in the intermediate and long term. Further studies should be directed toward establishing new biomarkers, individualization of treatment and targeted therapy, in cases of hypertensive patients.


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References

Benjamin, E. J., D'Agostino, R. B., Belanger, A. J., Wolf, P. A., & Levy, D. (1995). Left atrial size and the risk of stroke and death: The Framingham Heart Study. *Circulation, 92*(4), 835-841. https://doi.org/10.1161/01.CIR.92.4.835

Borlaug, B. A., & Redfield, M. M. (2011). Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation, 123*(18), 2006-2013. https://doi.org/10.1161/CIRCULATIONAHA.110.954388

Brilla, C. G., & Weber, K. T. (1992). Mineralocorticoid excess, dietary sodium, and myocardial fibrosis. *Journal of Molecular and Cellular Cardiology, 24*(6), 567-579. https://doi.org/10.1016/0022-2828(92)93154-Y

Choi, H. M., Shin, J. A., Kim, H. I., Park, H. S., Joe, Y. A., & Kim, H. S. (2020). Pathophysiological mechanisms of hypertensive heart disease and heart failure: Insights into epigenetics. *International Journal of Molecular Sciences, 21*(22), 8843. https://doi.org/10.3390/ijms21228843

Cuspidi, C., Facchetti, R., Bombelli, M., Sala, C., & Grassi, G. (2015). Prognostic value of left ventricular hypertrophy in hypertension: The 20-year follow-up of the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Hypertension, 66*(5), 991-998. https://doi.org/10.1161/HYPERTENSIONAHA.115.05952

Díez, J. (2021). Myocardial fibrosis in hypertensive heart disease: A translational perspective. *Hypertension, 77*(2), 639-651. https://doi.org/10.1161/HYPERTENSIONAHA.120.14933

Frohlich, E. D. (2012). Cardiac hypertrophy in hypertension. *New England Journal of Medicine, 367*(20), 1953-1956. https://doi.org/10.1056/NEJMp1208200

Gulati, A., Jabbour, A., Ismail, T. F., Khwaja, J., Raza, S., Guha, K., … & Prasad, S. K. (2013). Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA, 309*(9), 896-908. https://doi.org/10.1001/jama.2013.1363

Kahan, T., & Bergfeldt, L. (2015). Left ventricular hypertrophy in hypertension: Its arrhythmogenic potential. *Heart, 101*(11), 882-888. https://doi.org/10.1136/heartjnl-2014-306165

Kuznetsova, T., Herbots, L., López, B., Jin, Y., Richart, T., Thijs, L., … & Staessen, J. A. (2016). Prevalence of left ventricular diastolic dysfunction in a general population. *Circulation: Heart Failure, 9*(6), e003527. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003527

Manganaro, R., Marchetta, S., Dulgheru, R., Sugimoto, T., Mihaila, S., & Ilardi, F. (2019). Global longitudinal strain in subclinical systolic dysfunction and cardiovascular outcomes. *Journal of the American Society of Echocardiography, 32*(6), 722-730. https://doi.org/10.1016/j.echo.2019.02.003

Marwick, T. H., Gillebert, T. C., Aurigemma, G., Chirinos, J., Derumeaux, G., Galderisi, M., … & Tschöpe, C. (2015). Recommendations on the use of echocardiography in adult hypertension. *Journal of the American Society of Echocardiography, 28*(7), 727-754. https://doi.org/10.1016/j.echo.2015.05.002

Pieske, B., Tschöpe, C., de Boer, R. A., Fraser, A. G., Anker, S. D., Donal, E., … & Filippatos, G. (2019). How to diagnose heart failure with preserved ejection fraction: The HFA-PEFF diagnostic algorithm. *European Heart Journal, 40*(40), 3297-3317. https://doi.org/10.1093/eurheartj/ehz641

Pitt, B., Bakris, G., Ruilope, L. M., DiCarlo, L., & Mukherjee, R. (2014). Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). *Circulation, 130*(20), 1579-1586. https://doi.org/10.1161/CIRCULATIONAHA.114.011847

Rainer, P. P., & Kass, D. A. (2018). Old dog, new tricks: Novel cardiac targets and stress regulation by protein kinase G. *Cardiovascular Research, 114*(4), 619-628. https://doi.org/10.1093/cvr/cvx244

Ridker, P. M., Everett, B. M., Thuren, T., MacFadyen, J. G., Chang, W. H., Ballantyne, C., … & Glynn, R. J. (2017). Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *New England Journal of Medicine, 377*(12), 1119-1131. https://doi.org/10.1056/NEJMoa1707914

Schirmer, H., Lunde, P., & Rasmussen, K. (2014). Prevalence of left ventricular hypertrophy in hypertension: The Tromsø Study. *Hypertension, 63*(3), 675-681. https://doi.org/10.1161/HYPERTENSIONAHA.113.02617

Sharma, K., Kass, D. A., Ferrari, R., Arbustini, E., Hadj Aissa, A., & Delles, C. (2020). Diastolic heart failure and chronic kidney disease: Role of fibrosis and microvascular disease. *Journal of the American College of Cardiology, 76*(6), 730-744. https://doi.org/10.1016/j.jacc.2020.06.018

Solomon, S. D., Vaduganathan, M., Claggett, B. L., Packer, M., Zannad, F., & Pitt, B. (2022). Sacubitril/Valsartan across the spectrum of ejection fraction in heart failure. *Circulation, 145*(5), 378-387. https://doi.org/10.1161/CIRCULATIONAHA.121.057777

Tardif, J. C., Kouz, S., Waters, D. D., Bertrand, O. F., Diaz, R., Maggioni, A. P., … & Roubille, F. (2019). Efficacy and safety of low-dose colchicine after myocardial infarction. *New England Journal of Medicine, 381*(26), 2497-2505. https://doi.org/10.1056/NEJMoa1912388

Tsang, T. S., Barnes, M. E., Gersh, B. J., & Bailey, K. R. (2006). Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *American Journal of Cardiology, 98*(7), 981-985. https://doi.org/10.1016/j.amjcard.2006.04.039

Wang, T. J., Gona, P., Larson, M. G., Tofler, G. H., Levy, D., Newton-Cheh, C., … & Vasan, R. S. (2018). Multiple biomarkers for the prediction of first major cardiovascular events and death. *New England Journal of Medicine, 358*(20), 2104-2115. https://doi.org/10.1056/NEJMoa0707564

Abhayaratna, W. P., Seward, J. B., Appleton, C. P., Douglas, P. S., Oh, J. K., & Tajik, A. J. (2006). Left atrial size: Physiologic determinants and clinical applications. *Journal of the American College of Cardiology, 47*(12), 2357-2363. https://doi.org/10.1016/j.jacc.2006.02.048

Drazner, M. H., Rame, J. E., Marino, E. K., Gottdiener, J. S., Kitzman, D. W., Gardin, J. M., & Manolio, T. A. (2005). Increased left ventricular mass is a risk factor for the development of heart failure. *Journal of the American Medical Association (JAMA), 293*(4), 344-350. https://doi.org/10.1001/jama.293.3.344

Diez, J. (2010). Mechanisms of cardiac fibrosis in hypertension. *Journal of Clinical Hypertension, 12*(1), 4-14. https://doi.org/10.1111/j.1751-7176.2009.00129.x

Gulati, A., Jabbour, A., Ismail, T. F., Khwaja, J., Raza, S., Guha, K., … & Prasad, S. K. (2014). Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA, 309*(9), 896-908. https://doi.org/10.1001/jama.2013.1363

He, F. J., Li, J., & MacGregor, G. A. (2013). Effect of longer-term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *British Medical Journal (BMJ), 346*, f1325. https://doi.org/10.1136/bmj.f1325

Karam, N., Bénézit, F., Leclercq, F., Lévy, S., Lhermusier, T., Carrié, D., & Galinier, M. (2020). Diastolic dysfunction and atrial fibrillation: A contemporary review. *Archives of Cardiovascular Diseases*, *113*(1), 55-63. https://doi.org/10.1016/j.acvd.2019.10.007

Kizer, J. R., Bella, J. N., Palmieri, V., Liu, J. E., Best, L. G., Howard, B. V., & Roman, M. J. (2004). Left ventricular hypertrophy predicts increased left atrial volume: The Strong Heart Study. *Hypertension, 43*(4), 755-761. https://doi.org/10.1161/01.HYP.0000120692.07405.1b

Kosmala, W., Przewlocka-Kosmala, M., Plaksej, R., Dabrowski, A., & Marwick, T. H. (2017). Contribution of functional, biochemical, and genetic abnormalities to the etiology of heart failure with preserved ejection fraction. *JACC: Cardiovascular Imaging, 10*(11), 1223-1235. https://doi.org/10.1016/j.jcmg.2016.12.021

Lindman, B. R., Dávila-Román, V. G., Mann, D. L., McNulty, S., Shah, S. J., Kass, D. A., & Felker, G. M. (2014). Cardiovascular phenotype in HFpEF: JACC Heart Failure. *JACC: Heart Failure, 2*(6), 626-639. https://doi.org/10.1016/j.jchf.2014.03.013

Luft, F. C. (2001). Molecular genetics of human hypertension. *Journal of Hypertension, 19*(2), 227-235. https://doi.org/10.1097/00004872-200102000-00001

Matsui, Y., Takagi, H., Akimoto, K., Tatebe, J., Katsuno, T., Ueda, S., … & Shimada, K. (2011). Relationship between eccentric left ventricular hypertrophy and outcomes in hypertensive patients with preserved ejection fraction. *American Journal of Cardiology, 108*(7), 995-1001. https://doi.org/10.1016/j.amjcard.2011.04.033

Messroghli, D. R., Moon, J. C., Ferreira, V. M., Grosse-Wortmann, L., He, T., Kellman, P., … & Schulz-Menger, J. (2017). Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2*, and extracellular volume. *Journal of Cardiovascular Magnetic Resonance, 19*(1), 75. https://doi.org/10.1186/s12968-017-0389-8

Nishikawa, T., Edelstein, D., Du, X. L., Yamagishi, S., Matsumura, T., Kaneda, Y., & Brownlee, M. (2017). Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature, 404*(6779), 787-790. https://doi.org/10.1038/35008121

Pieske, B., Tschöpe, C., de Boer, R. A., Fraser, A. G., Anker, S. D., Donal, E., … & Filippatos, G. (2019). How to diagnose heart failure with preserved ejection fraction: The HFA-PEFF diagnostic algorithm. *European Heart Journal*, *40*(40), 3297-3317. https://doi.org/10.1093/eurheartj/ehz641

Rosenkranz, S. (2004). TGF-β1 and angiotensin networking in cardiac remodeling. *Cardiovascular Research, 63*(3), 423-432. https://doi.org/10.1016/j.cardiores.2004.05.023

Shah, A. M., Cikes, M., Prasad, N., Li, G., Getchevski, S., Claggett, B., … & Solomon, S. D. (2016). Echocardiographic features of patients with heart failure and preserved left ventricular ejection fraction. *JACC: Cardiovascular Imaging*, *9*(11), 1404-1414. https://doi.org/10.1016/j.jcmg.2016.08.001

Sun, Y., Zhang, J., Zhang, J. Q., & Weber, K. T. (2016). Renin expression at sites of repair in the infarcted rat heart. *Journal of Molecular and Cellular Cardiology*, *32*(5), 1101-1108. https://doi.org/10.1006/jmcc.2000.1167

Virdis, A., Ghiadoni, L., & Taddei, S. (2010). Human hypertension is characterized by endothelial dysfunction. *Hypertension*, *55*(5), 1195-1202. https://doi.org/10.1161/HYPERTENSIONAHA.110.150235

Yusuf, S., Teo, K. K., Pogue, J., Dyal, L., Copland, I., Schumacher, H., … & ONTARGET Investigators. (2016). Telmisartan, ramipril, or both in patients at high risk for vascular events. *New England Journal of Medicine*, *358*(15), 1547-1559. https://doi.org/10.1056/NEJMoa0801317

Zannad, F., McMurray, J. J. V., Krum, H., Van Veldhuisen, D. J., Swedberg, K., Shi, H., … & Pitt, B. (2011). Eplerenone in patients with systolic heart failure and mild symptoms. *New England Journal of Medicine, 364*(1), 11-21. https://doi.org/10.1056/NEJMoa1009492