REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Heart Failure: Review on Pathophysiology and Pharmacological Therapy

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Abstract

Heart failure is an important cardiovascular disease because of its increasing prevalence, significant morbidity, high mortality, and rapidly expanding healthcare cost. Heart failure is caused by structural and/or functional cardiac defects resulting in decreased cardiac production, characterized by distinct symptoms and signs. Ischemic heart disorders, hypertension and diabetes mellitus are among the most common causes of heart failure. Heart failure patients typically experience dyspnea, fluid retention and intolerance to exercise. To counteract deleterious effects of heart failure, compensatory mechanisms are established. These compensatory mechanisms include frank-starling mechanism, increasing ventricular wall thickness and neurohormonal activation. Initially, these compensatory mechanisms improve heart failure condition but with time these compensatory mechanisms lead to deterioration of heart failure. Drugs used in management of heart failure include Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, Angiotensin receptor neprilysin inhibitor, beta blockers, mineralocorticoid receptor antagonists, diuretics, digoxin, ivabradine and sodium glucose cotransporter 2 inhibitors.

Keywords: Heart Failure; Natriuretic peptides; Sacubitril/valsartan; Sodium glucose cotransporter 2 inhibitors; Renin–angiotensin–aldosterone system**.**

1. Introduction

Heart failure (HF) is a syndrome characterized by a decline in heart muscle efficiency to pump a sufficient amount of blood to meet body metabolic needs. HF affects about 26 million people worldwide **(Ponikowski et al., 2014)**. HF health care expenses are huge. Although there are great advances in HF therapies, mortality and morbidity are still high worldwide **(Savarese & Lund, 2017)**. Symptoms of HF include shortness of breath, fatigue and edema **(Inamdar & Inamdar, 2016)**. Patient clinical history, physical examination, electrocardiogram, echocardiography and natriuretic peptides levels are used in assessment of HF **(Ponikowski et al., 2016)**. Reduction in cardiac output which characterize HF leads to activation of compensatory mechanisms to counteract harmful effects of HF but with

time these compensatory mechanisms become ineffective and worsen the condition **(Jackson et al., 2000)**. Treatment of HF is focused on improving contractility, suppressing action of harmful neurohormones and optimizing fluid status of the patient **(Kemp & Conte, 2012)**.

2. Pathophysiology

2.1. Left ventricular dysfunction

Left ventricular dysfunction can be presented as either inability of left ventricle to pump a sufficient amount of blood to meet body needs (systolic dysfunction) so ejection fraction is reduced or impaired filling of left ventricle (diastolic dysfunction) and in this case ejection fraction will be preserved. Systolic dysfunction represents about 70 % of cases while diastolic dysfunction represents about 30% of cases **(Lilly, 2012)**. Causes of ventricular dysfunction include ischemic heart diseases, hypertension, and valvular heart diseases. Systolic dysfunction leads to accumulation of blood in left ventricle which in turn increases end diastolic volume. Elevated end diastolic pressure causes an increase in left atrial pressure which in turn causes pooling of blood in pulmonary veins which leads to pulmonary congestion which is responsible for dyspnea associated with HF **(Kemp & Conte, 2012)**.

2.2. Compensatory mechanisms

Reduced cardiac output (CO) in HF causes a reduction in the tissue perfusion which leads to development of compensatory mechanisms to counteract this deleterious effect. These compensatory mechanisms include Frank–Starling mechanism, neurohormonal activation and cardiac hypertrophy and remodelling. Initially, these compensatory mechanisms ameliorate symptoms and general condition of the disease but with time these compensatory mechanisms lead to worsening of heart failure as shown in Figure 1 **(Kemp & Conte, 2012)**.

2.2.1. Frank-Starling mechanism

Because the CO is reduced, the body redistributes the blood to the most critical organs which are the brain and the heart. Due to reduced perfusion to the kidney and the peripheral tissues, the renin-angiotensin-aldosterone system (RAAS) is activated where angiotensin II stimulates production of aldosterone which causes sodium and water retention aiming to rise intravascular volume and consequently preload. The Frank-Starling mechanism correlates end diastolic volume and stroke volume where the increase in the ventricular diastolic volume will increase the stretch of myocardial fibers which will in turn increase the

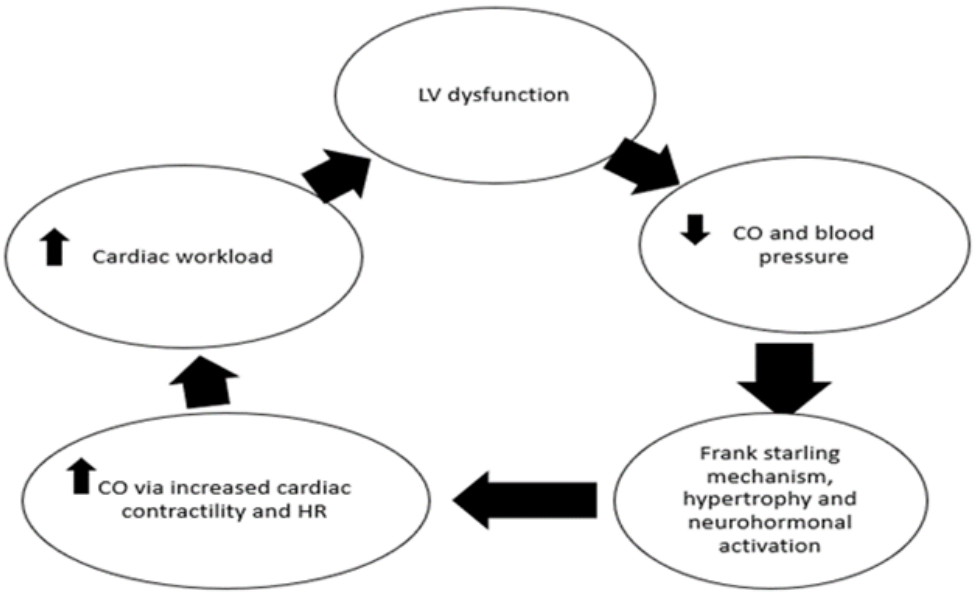

Figure 1. Cardiac compensatory mechanism cycle in heart failure **(Kemp & Conte, 2012)**

myocardial force of contraction. This mechanism compensates the reduction in the CO associated with the HF trying to maintain enough perfusion to the body organs. Unfortunately, this mechanism is limited, meaning that beyond certain limit Frank-Starling mechanism benefits become ineffective in maintaining the cardiac contractility **(Delicce et al., 2017)**.

2.2.2. Cardiac remodeling and hypertrophy

Cardiac remodeling is a group of molecular, cellular and interstitial changes that are expressed clinically as changes in size, mass, geometry and function of the heart **(Azevedo et al., 2016)**. Cardiac remodeling can be classified in 2 types **(Mihl et al., 2008)**:

1) Physiological remodeling as seen in pregnant women and athletes.

2) Pathological remodeling as result of myocardial infarction (MI), hypertension and valvular heart diseases.

Ventricular hypertrophy is an increase in the muscle thickness as an adaptive response to hemodynamic stress to ameliorate ventricular contractility **(Bornstein et al., 2021)**.

Physiological hypertrophy is regulated by growth factors such as insulin-like growth factor-1 (IGF-1) and transforming growth factor beta (TGF-β), which act on tyrosine kinase-coupled receptors (RTKs) while pathological hypertrophy is regulated by catecholamines, angiotensin II, and endothellin-1 which activate G-protein-coupled receptors (GPCR) as shown **Figure 2 (Samak et al., 2016)**.

Cardiac remodeling is a progressive process which leads eventually to the impairment of contractility of the heart muscle due to increased cardiac wall tension and fibrosis **(Azevedo et al., 2016)**.

2.2.3. Neurohormonal activation

Reduced CO in HF results in the activation of neurohormonal pathways. These pathways include RAAS, the sympathetic nervous system (SNS), endothelin, vasopressin and pro-inflammatory cytokines which produce unfavorable effects while natriuretic peptide system and nitric oxide might have favorable effects **(Hartupee & Mann, 2017)**.

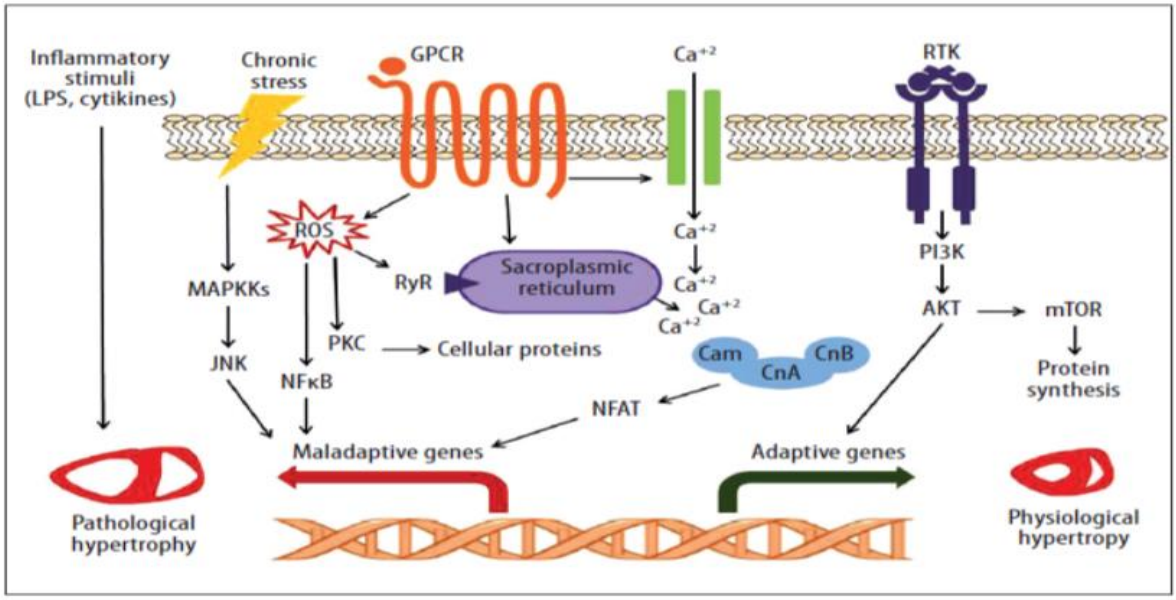

Figure 2. Intracellular signaling pathways regulating cardiac hypertrophy **(Samak et al., 2016)**. GPCR = G-protein-coupled receptor, RTK = Receptor tyrosine kinase, MAPKKs = Mitogen activated protein kinase kinases, ROS = Reactive oxygen species, RyR = Ryanodine receptor, PI3K = Phosphoinositide-3 kinase, JNK = c-Jun N-terminal kinase, NFkB = Nuclear factor kappa B, PKC = Protein kinase C, Cam = Calmodulin, CnA = Calcineurin A, CnB = Calcineurin B, NFAT = Nuclear factor of activated T-cell, Akt = Protein kinase B (PKB), mTOR = Mammalian target of rapamycin, LPS = Lipopolysaccharide.

2.2.3.1. Renin–angiotensin–aldosterone system

In HF, reduced renal blood flow and sympathetic activation result in activation of RAAS. Kidney secretes renin which converts angiotensinogen to angiotensin I, Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II causes systemic vasoconstriction which increases afterload and blood pressure. Angiotensin II causes release of aldosterone which causes sodium and water retention in attempt to enhance CO. This compensatory mechanism increases already elevated ventricular filling pressure and causes electrolyte imbalance as aldosterone causes hypokalemia **(Fountain & Lappin, 2021)**. It was found that aldosterone increases collagen deposition which has a role in cardiac fibrosis and hypertrophy **(Jessup & Brozena, 2003)**.

2.2.3.2. Sympathetic nervous system

Sympathetic nervous system is activated via baroreceptor and reduced mean arterial pressure (MAP). Catecholamines (Epinephrine and Norepinephrine) are released in response to activation of sympathetic nervous system **(Gordan et al., 2015)**.

Catecholamines increase heart rate, cardiac contractility and produce vasoconstriction to maintain perfusion to different body organs but prolonged action of catecholamines has detrimental effects. Increased concentration of catecholamines increases workload of the heart, risk of ischemia and accelerates cardiac myocyte apoptosis **(Jackson et al., 2000)**. Sustained sympathetic nervous system stimulation causes downregulation and desensitization of adrenergic receptors which further causes release of norepinephrine. Activation of SNS also activates RAAS to increase mean arterial pressure through sodium and water retention **(Fountain & Lappin, 2021)**.

2.2.3.3. Endothelin

Vascular endothelial cells secrete endothelin. Endothelin 1 is a potent vasoconstrictor which has a role in cardiac pathophysiology **(Kowalczyk et al., 2015)**.

2.2.3.4. Vasopressin

Reduced MAP in heart failure causes release of vasopressin (Antidiuretic hormone). Vasopressin causes vasoconstriction and water retention through its action on vasopressin type 1a (V1a) and vasopressin type 2 (V2) receptors respectively **(Schrier & Abraham, 1999)**.

2.2.3.5. Natriuretic peptide system

Natriuretic peptide system consists of three types of natriuretic peptides (NPs), they are atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) **(Potter et al., 2009)**.

Atrial natriuretic peptides are generated and stored in atrial granules. Cardiac stretch due to volume overload causes release of ANP from atrial granules to produce natriuretic and vasodilator effect **(Volpe et al., 2016)**. Cardiac wall stress transcriptionally regulates Ventricular BNP synthesis which reduces volume overload **(Grépin et al., 1994)**. C-type natriuretic peptides have limited effects on natriuresis and vasodilatation, and they are found mainly in vascular epithelium and central nervous system.

Three types of natriuretic peptide receptor are shown in **Figure 3**.

1) NPR-A: determines biological effects of NP

2) NPR-B: determines biological effects of NP

3) NPR-C: does not possess any known intrinsic enzymatic activity.

Natriuretic peptides produce their physiological actions through NPR-A binding and the activation of guanylate cyclase and the production of cyclic guanosine monophosphate (cGMP) **(Ashman et al., 1963)**.

Kidney, lung, aortic tissues express a high content of NPR-A **(Chang et al., 1989)**. NPR-B is highly expressed in fibroblasts **(Abbey & Potter, 2002)**. NPR-C is located in lung, atrial, kidney and aortic endothelial cells **(Porter et al., 1990)**.

Atrial natriuretic peptides adjust blood pressure by their natriuretic and inhibitory effect on RAAS. They improve glomerular filtration rate (GFR) by raising intra-glomerular pressure by dilating afferent arteriole and causing efferent arteriolar constriction **(Marin-Grez et al., 1986)**.

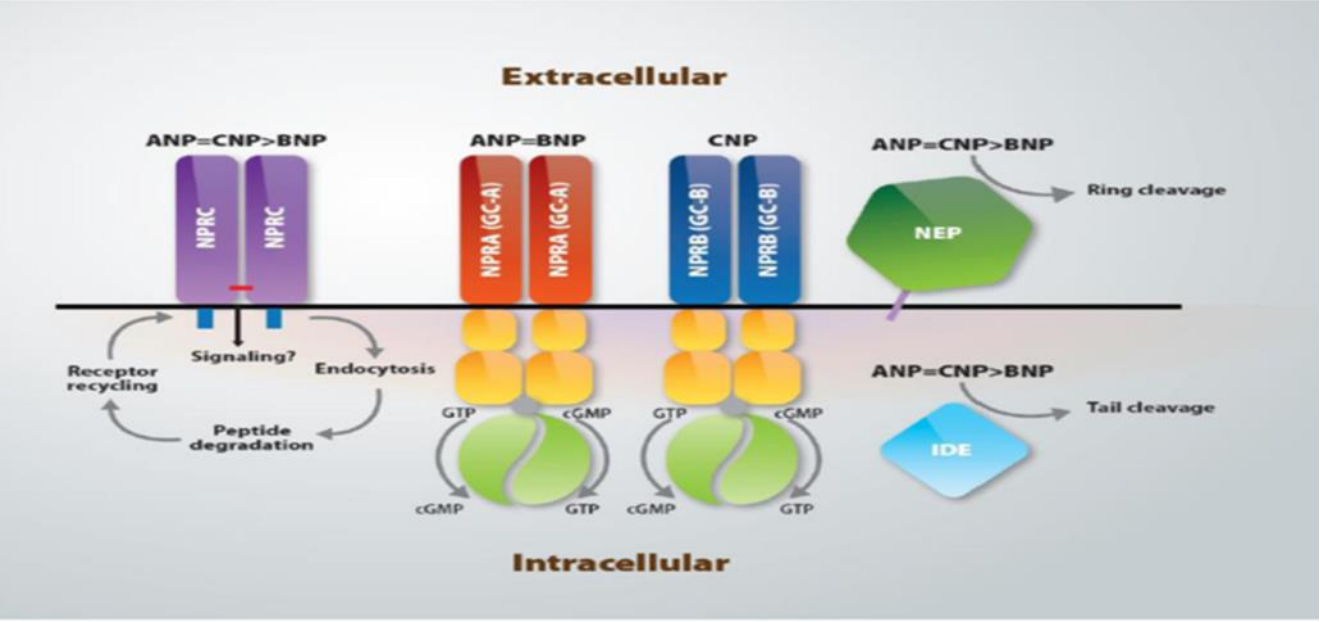

Figure 3. Natriuretic peptide-binding receptors, intracellular signalling and degradation processes **(Abbey & Potter, 2002)**. GC-A: guanylate cyclase type A; GC-B: guanylate cyclase type B.

Atrial natriuretic peptide diminishes SNS effects and improves vagal tone. Angiotensin II and endothelin-1 hypertrophic effect on heart is inhibited by ANP **(Hayashi et al., 2004)**.

Brain natriuretic peptide has similar actions to ANP. BNP reduces preload and afterload by inducing natriuresis and diuresis. BNP antagonizes hypertrophic effect of angiotensin II. RAAS, catecholamines and vasopressin are inhibited by BNP. BNP enhances vagal reflexes and inhibits sympathetic tone **(Woods, 2004)**.

Actions of ANP and BNP are summarized in **Figure 4**.

In congestive heart failure (CHF), reduced cardiac output stimulates sodium and water retention which increases intravascular volume. NPs mainly BNP and ANP are released as result of cardiac wall stretch to alleviate volume overload through their natriuretic and diuretic effects but vasoconstrictive and anti-natriuretic actions of RAAS and SNS counteracts effects of NPs. Renal response to NPs in patients with CHF is attenuated and this could be due to downregulation of NPs receptors **(Volpe et al., 2016)**.

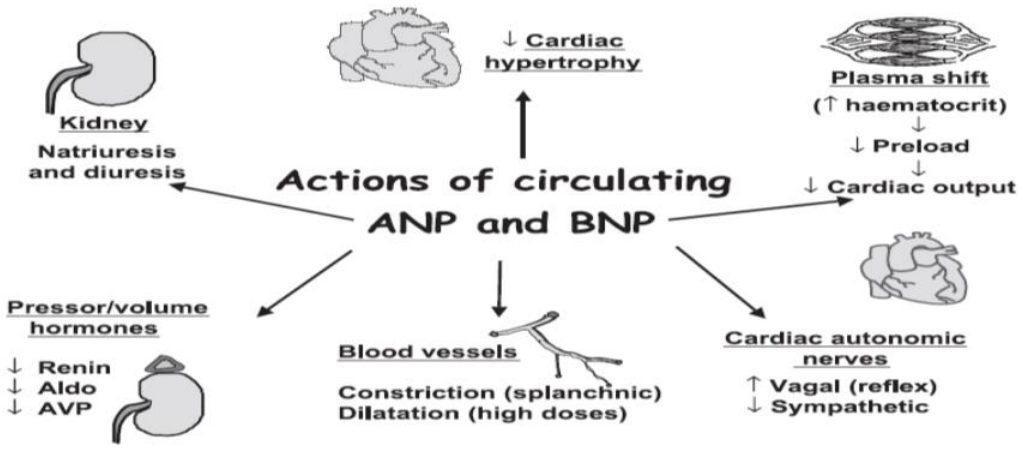

Figure 4. cardio-protective actions of circulating atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) **(Woods, 2004)**.

2.2.3.6. Bradykinin

Heart failure is characterized by elevated levels of bradykinins to counteract vasoconstriction **(Mann, 2002)**.

2.2.3.7. Nitric oxide

Levels of Nitric oxide is elevated in HF which provide vasodilation and counteract endothelin effects **(Mann, 2002)**.

2.2.3.8. Proinflammatory Cytokines

Some proinflammatory cytokines are highly expressed in HF such as tumor necrosis factor [TNF]-α, interferon-γ and interleukin 1 and 6. Myocardial cell apoptosis and negative inotropic effect are stimulated by TNF-α **(Hedayat et al., 2010)**.

3. Management

3.1. Angiotensin-converting enzyme inhibitors

Angiotensin converting enzyme inhibitors are the mainline of treatment in HF with reduced ejection fraction (HFrEF). ACE inhibitors inhibit angiotensin II which induces vasoconstriction and cardiac remodeling. Regardless the presence of symptoms, patients with left ventricular dysfunction should receive ACE inhibitors unless contraindicated **(Herman et al., 2021)**.

Angiotensin converting enzyme inhibitors reduce hospitalization, mortality. Improvements in symptoms and exercise tolerance in patients with HF is associated with ACE inhibitors use. It was found that early use of ACE inhibitors after Myocardial infarction prevents development of HF due to their inhibitory effect on angiotensin II which induce cardiac remodeling **(Herman et al., 2021)**.

Close monitoring is required in case of hyperkalemia, cough, renal impairment, unilateral renal stenosis and hypotension **(Goyal et al., 2021)**.

Angiotensin converting enzyme inhibitors use may be associated with elevation in serum creatinine. Maximum acceptable rise in serum creatinine after initiation of ACE inhibitors is 30% of the baseline serum creatinine.**(Shah et al., 2017)**

Due to inhibitory effect of ACE inhibitors on aldosterone release, their use may be associated with hyperkalaemia. Accumulation of bradykinins is associated with ACE inhibitors use as they prevent their degradation, so this accumulation may result in dry cough which is different from productive cough that is caused by pulmonary congestion. If the patient cannot tolerate cough, he can switch to angiotensin receptor blockers **(Hill & Vaidya, 2021)**.

3.2. Angiotensin II type I receptor blockers

Angiotensin II receptor blockers (ARBs) are used in patients who are intolerant to ACE inhibitors as an alternative. ARBs selectively block action of angiotensin II on angiotensin type 1 receptor which mediates vasoconstriction, aldosterone release and cardiac remodelling **(Hill & Vaidya, 2021)**.

The most commonly used ARBs in case of heart failure are valsartan, candesartan and losartan **(Dézsi, 2016)**.

Angiotensin II receptor blockers are less likely to produce cough as they don't cause accumulation of bradykinins **(Hill & Vaidya, 2021)**.

3.3. Beta Blockers

Use of beta blockers in patients with HFrEF reduces mortality and hospitalization **(Yancy et al., 2013)**. SNS are inhibited by beta blockers. Negative effects of catecholamines on cardiac muscle which include cardiac remodelling and increased apoptosis are inhibited by beta blockers **(Lymperopoulos et al., 2013)**.

Beta blockers are used in conjugation with ACE inhibitors in patients with HFrEF who are clinically stable and with normal volume status **(McDonagh et al., 2021)**. Most used beta blockers in management of HFrEF are metoprolol succinate, bisoprolol and carvedilol **(Klapholz, 2009)**.

Patient clinical status affects the choice of beta blocker, where hypertensive patients with HFrEF can gain benefit from the use of carvedilol due its β1and α1 receptor blocking activity while patients who are at increased risk of developing hypotension can use metoprolol succinate due to its selectivity in blocking β1 receptors. Selective β1 receptors blockers as metoprolol succinate are preferred in case of active pulmonary disease and in case of peripheral vascular diseases but still used with caution **(Whelton et al., 2018)**.

3.4. Mineralocorticoid/aldosterone receptor antagonists (MRAs)

Mineralocorticoid/aldosterone receptor antagonists are used as an add on therapy in symptomatic patient with HFrEF and with left ventricular ejection fraction ≤35% despite treatment with ACE inhibitors and beta blockers **(Yancy et al., 2013)**.

Mineralocorticoid/aldosterone receptor antagonists include spironolactone and eplerenone. MRAs block binding of aldosterone to mineralocorticoid receptors with different degree of affinity. MRAs play an important role in management of patient with HFrEF, in addition to their diuretic and anti-hypertensive effects they block harmful effects of aldosterone on the heart, kidney and vascular tissue **(Sica, 2015)**

In heart, aldosterone induces cardiac hypertrophy and fibrosis **(Lijnen & Petrov, 2000)**. Elevated serum levels of collagen synthesis markers as procollagen type III amino-terminal peptide and procollagen type I amino-terminal peptide are associated with increased hospitalization and mortality rates, spironolactone reduces these markers which improves survival rates, reduces left ventricular remodeling and reduces markers of myocardial remodeling such as ANP and BNP **(Tsutamoto et al., 2001)**.

Eplerenone reduces collagen synthesis markers **(Rossignol et al., 2009)** and reduces incidence of atrial fibrillation **(Fudim et al., 2018)**.

Stimulation of mineralocorticoid receptors in coronary artery and aortic smooth muscle increases the risk of coronary artery events and strokes **(Milliez et al., 2005)**.

Hyperkalemia is a major side effect of MRAs, so serum potassium and serum creatinine should be assessed before and within one week of the treatment **(Shah et al., 2017).**

Mineralocorticoid/aldosterone receptor antagonists cannot be started in patients with potassium levels above 5 mEq/L and creatinine clearance less than 30 mL/min. Spironolactone has endocrine side effects such as breast enlargement in men and menstrual irregularities in women, this is less common with eplerenone due to its selectivity to mineralocorticoid receptors **(Struthers et al., 2008)**.

3.5. Diuretics

Volume status is managed by diuretics in HF. Pulmonary congestion, peripheral edema, and elevated jugular venous pressure are the most common indicators of hypervolemia in patients with HF **(Miller, 2016)**.

Diuretics do not reduce mortality in HF, they are only used to adjust volume status of HF patients **(Shah et al., 2017).**

Managing volume overload in HF is commonly done by loop diuretics. Loop diuretics include Furosemide, torsemide and bumetanide. Efficacy of loop diuretics are preserved in case of renal hypoperfusion which give them an advantage over thiazide diuretics. Presence of intestinal mucosal edema and quickness of desired action determines choice of loop diuretic used and route of administration. Average bioavailability of oral furosemide is about 50 % while torsemide and bumetanide have almost complete bioavailability **(Huxel et al., 2021)**.

Prostaglandin synthesis is enhanced by loop diuretics so concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces their diuretic effect (**Raftery, 1994)**.

Thiazide diuretics include hydrochlorothiazide, chlorthalidone, chlorothiazide and metolazone. Thiazide diuretics can be combined with loop diuretics in case of resistant edema. Renal insufficiency limits the use of thiazide diuretics except for metolazone which retains its efficacy in case of renal insufficiency **(Bond et al., 2021)**.

Spironolactone and eplerenone are potassium sparing diuretics, they have a weak diuretic effect as they work on collecting duct where only 3 % of sodium is reabsorbed. They can be used in combination with other types of diuretics to help in maintaining a normal potassium level **(Casu & Merella, 2015)**.

3.6. Angiotensin receptor neprilysin inhibitor

The first drug in class of Angiotensin receptor neprilysin inhibitor is LCZ696 which combines valsartan and sacubitril in one molecule.

Valsartan is angiotensin II Receptor Blocker. Sacubitril is a prodrug that is metabolized to LBQ657 which inhibits neprilysin. **(Nicolas et al., 2021)**.

Neprilysin is responsible for breakdown of natriuretic peptides, bradykinins, angiotensin II, vasopressin and endothelin, so inhibition of neprilysin by LBQ657 which is the active metabolite of sacubitril leads to elevated levels of natriuretic peptides, bradykinins and angiotensin II **(Hubers & Brown, 2016)**. Combination of valsartan with sacubitril is to counteract elevated levels of angiotensin II caused by neprilysin inhibition **(Shah et al., 2017)**.

Benefits of sacubitril/valsartan in patients with HFrEF include reduction of cardiovascular mortality and hospitalization when compared with enalapril **(McMurray et al., 2014)**. In individuals with HFrEF, sacubitril/valsartan is indicated as a substitute for an ACE-I to lower the risk of HF hospitalization and death **(McMurray et al., 2014)**. In patient with HFpEF (EF ≤ 45 %) sacubitril/valsartan did not significantly reduce cardiovascular mortality and hospitalization when compared with valsartan **(Solomon et al., 2019)**.

It was found that patients hospitalized for acute decompensated HF can initiate therapy with sacubitril/valsartan after hemodynamic stabilization as it reduces NT-proBNP levels more significantly than enalapril **(Velazquez et al., 2019)**. sacubitril/valsartan combination reduces HbA1c in diabetic patients with HFrEF more efficiently than enalapril **(Seferovic et al., 2017)**. sacubitril/valsartan combination reduces the rate of decline of glomerular filtration rate in patients with HFrEF than enalapril **(Damman et al., 2018)**. Patients with HFrEF treated with sacubitril/valsartan and MRA are less likely to develop hyperkalemia than patients treated with enalapril and MRA **(Desai et al., 2017)**. ARNI reduces mitral regurgitation than did valsartan **(Kang et al., 2019)**.

3.7. Ivabradine

Ivabradine slows sinus node firing by inhibiting If channel in the sinus node so it is used only in patients with sinus rhythm. It was found that use of ivabradine in HF symptomatic patients with LVEF ≤35% and with a heart rate ≥70 beats per minute reduces mortality and hospitalization **(Swedberg et al., 2010)**.

3.8. Digoxin

The inhibition of the Na-K-ATPase pump by digoxin causes accumulation of sodium intracellularly and increases the calcium level in the myocardium. Increased level of calcium in the myocardium improves contractile force of the heart muscle. Increased contractile force of the heart muscle causes an increase in the ejection fraction of the left ventricle. In addition to digoxin positive inotropic effect, it is thought that digoxin has a neurohumoral blockade effects that improve cardiac function in patients with HF **(Ren et al., 2020).**

Neurohormonal blockade effects of digoxin are manifested by reduction in sympathetic tone and improvement in the parasympathetic effects. Digoxin reduces sympathetic tone by improving activity of the carotid baroreceptors **(DiPiro et al., 2014)**. Increased level of norepinephrine which characterize HF is reduced after administration of digoxin **(Krum et al., 1995)**.

Digoxin can be prescribed to symptomatic patients with sinus rhythm who are on ACE inhibitor, beta blockers and MRA to reduce risk of hospitalization **(Group, 1997)**. Digoxin may be prescribed to patient with HF and atrial fibrillation to control ventricular rate **(David & Shetty, 2021)**.

3.9. Sodium glucose cotransporter 2 (SGLT2) inhibitors

Dapagliflozin is the first drug in the class SGLT2 inhibitors to be approved by FDA for treatment of patients of HFrEF with left ventricular ejection fraction ≤ 40% with or without type 2 diabetes (T2D) **(Blair, 2021)**.

Patients with HFrEF can take either dapagliflozin or empagliflozin to reduce the risk of HF hospitalization and death **(McDonagh et al., 2021)**.

4. Conclusions

Heart failure is still a major burden on health systems. Due to high morbidity and mortality rates of HF, research is still ongoing to find new treatments to alleviate burden of the disease. In the last decade there is an enormous breakthrough in the field of HF. Many treatments have improved prognosis and quality of life in patients with HF as sacubitril/valsartan, SGLT2 inhibitors and

vericiguat. Although pharmacological management plays a limited role in advanced cases of HF, novel therapeutic agents, such as regenerative and gene therapy, are at the stage of development and need further refinement prior to their approval for HF therapy.

References:

Abbey, S. E., & Potter, L. R. (2002). Vasopressin-dependent inhibition of the C-type natriuretic peptide receptor, NPR-B/GC-B, requires elevated intracellular calcium concentrations. Journal of Biological Chemistry, 277(45), 42423–42430.

Ashman, D., Lipton, R., Melicow, M. M., & Price, T. (1963). Isolation of adenosine 3′, 5′-monophosphate and guanosine 3′, 5′-monophosphate from rat urine. Biochemical and Biophysical Research Communications, 11(4), 330‑334.

Azevedo, P. S., Polegato, B. F., Minicucci, M. F., Paiva, S. A. R., Zornoff, L. A. M., Azevedo, P. S., Polegato, B. F., Minicucci, M. F., Paiva, S. A. R., & Zornoff, L. A. M. (2016). Cardiac Remodeling: Concepts, Clinical Impact, Pathophysiological Mechanisms and Pharmacologic Treatment. Arquivos Brasileiros de Cardiologia, 106(1), 62–69.

Blair, H. A. (2021). Dapagliflozin: A Review in Symptomatic Heart Failure with Reduced Ejection Fraction. American Journal of Cardiovascular Drugs,21(6),701–710.

Bond, G., Adnan, G., Dua, A., Singh, K., & Crew, C. M. (2021). Metolazone. In StatPearls. StatPearls Publishing.

Bornstein, A. B., Rao, S. S., & Marwaha, K. (2021). Left Ventricular Hypertrophy. In StatPearls. StatPearls Publishing.

Casu, G., & Merella, P. (2015). Diuretic Therapy in Heart Failure–Current Approaches. European Cardiology Review, 10(1), 42.

Chang, M., Lowe, D. G., Lewis, M., Hellmiss, R., Chen, E., & Goeddel, D. V. (1989). Differential activation by atrial and brain natriuretic peptides of two different receptor guanylate cyclases. Nature, 341(6237), 68–72.

Damman, K., Gori, M., Claggett, B., Jhund, P. S., Senni, M., Lefkowitz, M. P., Prescott, M. F., Shi, V. C., Rouleau, J. L., & Swedberg, K. (2018). Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. JACC: Heart Failure, 6(6), 489–498.

David, M. N. V., & Shetty, M. (2021). Digoxin. In StatPearls. StatPearls Publishing.

Delicce, A. V., Basit, H., & Makaryus, A. N. (2017). Physiology, frank starling law.

Desai, A. S., Vardeny, O., Claggett, B., McMurray, J. J., Packer, M., Swedberg, K., Rouleau, J. L., Zile, M. R., Lefkowitz, M., & Shi, V. (2017). Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: A secondary analysis of the PARADIGM-HF trial. JAMA Cardiology, 2(1), 79–85.

Dézsi, C. A. (2016). The Different Therapeutic Choices with ARBs. Which One to Give? When? Why? American Journal of Cardiovascular Drugs, 16, 255–266.

DiPiro, J. T., Talbert, R. L., Yee, G. C., Matzke, G. R., Wells, B. G., & Posey, L. M. (2014). Pharmacotherapy: A Pathophysiologic Approach, ed. McGraw-Hill Medical, New York.

Fielitz, J., Dendorfer, A., Pregla, R., Ehler, E., Zurbrügg, H. R., Bartunek, J., Hetzer, R., & Regitz-Zagrosek, V. (2002). Neutral endopeptidase is activated in cardiomyocytes in human aortic valve stenosis and heart failure. Circulation, 105(3), 286–289.

Fountain, J. H., & Lappin, S. L. (2021). Physiology, Renin Angiotensin System. In StatPearls. StatPearls Publishing.

Fudim, M., Liu, P. R., Shrader, P., Blanco, R. G., Allen, L. A., Fonarow, G. C., Gersh, B. J., Kowey, P. R., Mahaffey, K. W., & Hylek, E. (2018). Mineralocorticoid Receptor Antagonism in Patients With Atrial Fibrillation: Findings From the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) Registry. Journal of the American Heart Association, 7(8), e007987.

Gordan, R., Gwathmey, J. K., & Xie, L.-H. (2015). Autonomic and endocrine control of cardiovascular function. World Journal of Cardiology, 7(4), 204–214.

Goyal, A., Cusick, A. S., & Thielemier, B. (2021). ACE Inhibitors. In StatPearls. StatPearls Publishing.

Grépin, C., Dagnino, L., Robitaille, L., Haberstroh, L., Antakly, T., & Nemer, M. (1994). A hormone-encoding gene identifies a pathway for cardiac but not skeletal muscle gene transcription. Molecular and Cellular Biology, 14(5), 3115–3129.

Group, D. I. (1997). The effect of digoxin on mortality and morbidity in patients with heart failure. New England Journal of Medicine, 336(8), 525–533.

Hartupee, J., & Mann, D. L. (2017). Neurohormonal activation in heart failure with reduced ejection fraction. Nature Reviews. Cardiology, 14(1), 30–38.

Hayashi, D., Kudoh, S., Shiojima, I., Zou, Y., Harada, K., Shimoyama, M., Imai, Y., Monzen, K., Yamazaki, T., & Yazaki, Y. (2004). Atrial natriuretic peptide inhibits cardiomyocyte hypertrophy through mitogen-activated protein kinase phosphatase-1. Biochemical and Biophysical Research Communications, 322(1), 310–319.

Hedayat, M., Mahmoudi, M. J., Rose, N. R., & Rezaei, N. (2010). Proinflammatory cytokines in heart failure: Double-edged swords. Heart Failure Reviews, 15(6), 543–562.

Herman, L. L., Padala, S. A., Ahmed, I., & Bashir, K. (2021). Angiotensin Converting Enzyme Inhibitors (ACEI). In StatPearls. StatPearls Publishing.

Hill, R. D., & Vaidya, P. N. (2021). Angiotensin II Receptor Blockers (ARB). In StatPearls. StatPearls Publishing.

Hubers, S. A., & Brown, N. J. (2016). Combined angiotensin receptor antagonism and neprilysin inhibition. Circulation, 133(11), 1115–1124.

Huxel, C., Raja, A., & Ollivierre-Lawrence, M. D. (2021). Loop Diuretics. In StatPearls. StatPearls Publishing.

Inamdar, A. A., & Inamdar, A. C. (2016). Heart Failure: Diagnosis, Management and Utilization. Journal of Clinical Medicine, 5(7), 62.

Jackson, G., Gibbs, C. R., Davies, M. K., & Lip, G. Y. H. (2000). Pathophysiology. BMJ: British Medical Journal, 320(7228), 167–170.

Jessup, M., & Brozena, S. (2003). Heart Failure. New England Journal of Medicine, 348(20), 2007–2018.

Kang, D.-H., Park, S.-J., Shin, S.-H., Hong, G.-R., Lee, S., Kim, M.-S., Yun, S.-C., Song, J.-M., Park, S.-W., & Kim, J.-J. (2019). Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation: PRIME study. Circulation, 139(11), 1354–1365.

Kemp, C. D., & Conte, J. V. (2012). The pathophysiology of heart failure. Cardiovascular Pathology, 21(5), 365–371.

Klapholz, M. (2009). β-Blocker Use for the Stages of Heart Failure. Mayo Clinic Proceedings, 84(8), 718–729.

Kowalczyk, A., Kleniewska, P., Kolodziejczyk, M., Skibska, B., & Goraca, A. (2015). The Role of Endothelin-1 and Endothelin Receptor Antagonists in Inflammatory Response and Sepsis. Archivum Immunologiae et Therapiae Experimentalis, 63(1), 41–52.

Krum, H., Bigger, T., Goldsmith, R. L., & Packer, M. (1995). Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. Journal of the American College of Cardiology, 25(2), 289–294.

Lijnen, P., & Petrov, V. (2000). Induction of cardiac fibrosis by aldosterone. Journal of Molecular and Cellular Cardiology, 32(6), 865–879.

Lilly, L. S. (2012). Pathophysiology of Heart Disease: A Collaborative Project of Medical Students and Faculty. Lippincott Williams & Wilkins.

Lymperopoulos, A., Rengo, G., & Koch, W. J. (2013). The Adrenergic Nervous System in Heart Failure: Pathophysiology and Therapy. Circulation Research, 113(6), 739-753.

Mangiafico, S., Costello-Boerrigter, L. C., Andersen, I. A., Cataliotti, A., & Burnett Jr, J. C. (2013). Neutral endopeptidase inhibition and the natriuretic peptide system: An evolving strategy in cardiovascular therapeutics. European Heart Journal, 34(12), 886–893.

Mann, D. L. (2002). Inflammatory mediators and the failing heart: Past, present, and the foreseeable future. Circulation Research, 91(11), 988–998.

Marin-Grez, M., Fleming, J., & Steinhausen, M. (1986). Atrial natriuretic peptide causes pre-glomerular vasodilatation and post-glomerular vasoconstriction in rat kidney. Nature, 324(6096), 473–476.

McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., Burri, H., Butler, J., Čelutkienė, J., Chioncel, O., Cleland, J. G. F., Coats, A. J. S., Crespo-Leiro, M. G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A. W., Jaarsma, T., Jankowska, E. A., Lainscak, M., Lam, C. S. P., Lyon, A. R., McMurray, J. J. V., Mebazaa, A., Mindham, R., Muneretto, C., Francesco Piepoli, M., Price, S., Rosano, G. M. C., Ruschitzka, F., Kathrine Skibelund, A., & ESC Scientific Document Group. (2021). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal, 42(36), 3599–3726.

McMurray, J. J., Packer, M., Desai, A. S., Gong, J., Lefkowitz, M. P., Rizkala, A. R., Rouleau, J. L., Shi, V. C., Solomon, S. D., & Swedberg, K. (2014). Angiotensin–neprilysin inhibition versus enalapril in heart failure. New England Journal of Medicine, 371, 993–1004.

Mihl, C., Dassen, W. R. M., & Kuipers, H. (2008). Cardiac remodelling: Concentric versus eccentric hypertrophy in strength and endurance athletes. Netherlands Heart Journal, 16(4), 129–133.

Miller, W. L. (2016). Fluid Volume Overload and Congestion in Heart Failure. Circulation: Heart Failure, 9(8), e002922.

Milliez, P., Girerd, X., Plouin, P.-F., Blacher, J., Safar, M. E., & Mourad, J.-J. (2005). Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. Journal of the American College of Cardiology, 45(8), 1243–1248.

Nicolas, D., Kerndt, C. C., & Reed, M. (2021). Sacubitril/Valsartan. In StatPearls. StatPearls Publishing.

Ponikowski, P., Anker, S. D., AlHabib, K. F., Cowie, M. R., Force, T. L., Hu, S., Jaarsma, T., Krum, H., Rastogi, V., Rohde, L. E., Samal, U. C., Shimokawa, H., Siswanto, B. B., Sliwa, K., & Filippatos, G. (2014). Heart failure: Preventing disease and death worldwide. ESC Heart Failure, 1(1), 4–25.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., Falk, V., González-Juanatey, J. R., Harjola, V.-P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M. C., Ruilope, L. M., Ruschitzka, F., Rutten, F. H., & van der Meer, P. (2016). 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 Heart Journal, 37(27), 2129–2200.

Porter, J. G., Arfsten, A., Fuller, F., Miller, J. A., Gregory, L. C., & Lewicki, J. A. (1990). Isolation and functional expression of the human atrial natriuretic peptide clearance receptor cDNA. Biochemical and Biophysical Research Communications, 171(2), 796–803.

Potter, L. R., Yoder, A. R., Flora, D. R., Antos, L. K., & Dickey, D. M. (2009). Natriuretic Peptides: Their Structures, Receptors, Physiologic Functions and Therapeutic Applications. Handbook of Experimental Pharmacology, 191, 341–366.

Raftery, E. (1994). Haemodynamic effects of diuretics in heart failure. British Heart Journal, 72(2 Suppl), S44.

Ren, Y., Ribas, H. T., Heath, K., Wu, S., Ren, J., Shriwas, P., Chen, X., Johnson, M. E., Cheng, X., Burdette, J. E., & Kinghorn, A. D. (2020). Na+/K+-ATPase-Targeted Cytotoxicity of (+)-Digoxin and Several Semisynthetic Derivatives. Journal of Natural Products, 83(3), 638–648.

Rossignol, P., Iraqi, W., Angioi, M., Fay, R., Nuée, J., Ketelslegers, J.-M., Vincent, J., Pitt, B., & Zannad, F. (2009). H016 Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: Insights from the ephesus study. Archives of Cardiovascular Diseases, 102, S77.

Samak, M., Fatullayev, J., Sabashnikov, A., Zeriouh, M., Schmack, B., Farag, M., Popov, A.-F., Dohmen, P. M., Choi, Y.-H., Wahlers, T., & Weymann, A. (2016). Cardiac Hypertrophy: An Introduction to Molecular and Cellular Basis. Medical Science Monitor Basic Research, 22, 75–79.

Savarese, G., & Lund, L. H. (2017). Global Public Health Burden of Heart Failure. Cardiac Failure Review, 3(1), 7–11.

Schrier, R. W., & Abraham, W. T. (1999). Hormones and Hemodynamics in Heart Failure. New England Journal of Medicine, 341(8), 577–585.

Seferovic, J. P., Claggett, B., Seidelmann, S. B., Seely, E. W., Packer, M., Zile, M. R., Rouleau, J. L., Swedberg, K., Lefkowitz, M., & Shi, V. C. (2017). Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: A post-hoc analysis from the PARADIGM-HF trial. The Lancet Diabetes & Endocrinology, 5(5), 333–340.

Shah, A., Gandhi, D., Srivastava, S., Shah, K. J., & Mansukhani, R. (2017). Heart Failure: A Class Review of Pharmacotherapy. Pharmacy and Therapeutics, 42(7), 464–472.

Sica, D. A. (2015). Mineralocorticoid Receptor Antagonists for Treatment of Hypertension and Heart Failure. Methodist DeBakey Cardiovascular Journal,11(4), 235–239.

Solomon, S. D., McMurray, J. J. V., Anand, I. S., Ge, J., Lam, C. S. P., Maggioni, A. P., Martinez, F., Packer, M., Pfeffer, M. A., Pieske, B., Redfield, M. M., Rouleau, J. L., van Veldhuisen, D. J., Zannad, F., Zile, M. R., Desai, A. S., Claggett, B., Jhund, P. S., Boytsov, S. A., Comin-Colet, J., Cleland, J., Düngen, H. D., Goncalvesova, E., Katova, T., Kerr Saraiva, J. F., Lelonek, M., Merkely, B., Senni, M., Shah, S. J., Zhou, J., Rizkala, A. R., Gong, J., Shi, V. C., Lefkowitz, M.P., & PARAGON-HF Investigators and Committees. (2019). Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. New England Journal of Medicine, 381(17), 1609–1620.

Struthers, A., Krum, H., & Williams, G. H. (2008). A comparison of the aldosterone-blocking agents eplerenone and spironolactone. Clinical Cardiology: An International Indexed and Peer-Reviewed Journal for Advances in the Treatment of Cardiovascular Disease, 31(4), 153–158.

Swedberg, K., Komajda, M., Böhm, M., Borer, J. S., Ford, I., Dubost-Brama, A., Lerebours, G., Tavazzi, L., & investigators, S. (2010). Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. The Lancet, 376(9744), 875–885.

Tsutamoto, T., Wada, A., Maeda, K., Mabuchi, N., Hayashi, M., Tsutsui, T., Ohnishi, M., Sawaki, M., Fujii, M., & Matsumoto, T. (2001). Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. Journal of the American College of Cardiology, 37(5), 1228–1233.

Velazquez, E. J., Morrow, D. A., DeVore, A. D., Duffy, C. I., Ambrosy, A. P., McCague, K., Rocha, R., & Braunwald, E. (2019). Angiotensin–neprilysin inhibition in acute decompensated heart failure. New England Journal of Medicine, 380(6), 539–548.

Volpe, M., Carnovali, M., & Mastromarino, V. (2016). The natriuretic peptides system in the pathophysiology of heart failure: From molecular basis to treatment. Clinical Science, 130(2), 57–77.

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Dennison Himmelfarb, C., DePalma, S. M., Gidding, S., Jamerson, K. A., Jones, D. W., MacLaughlin, E. J., Muntner, P., Ovbiagele, B., Smith, S. C., Spencer, C. C., Stafford, R. S., Taler, S. J., Thomas, R. J., Williams, K. A., Williamson, J. D., & Wright, J. T. (2018). 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, 71(6), e13–e115.

Woods, R. L. (2004). Cardioprotective functions of atrial natriuretic peptide and B-type natriuretic peptide: A brief review. Clinical and Experimental Pharmacology and Physiology, 31(11), 791–794.

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., Fonarow, G. C., Geraci, S. A., Horwich, T., Januzzi, J. L., Johnson, M. R., Kasper, E. K., Levy, W. C., Masoudi, F. A., McBride, P. E., McMurray, J. J. V., Mitchell, J. E., Peterson, P. N., Riegel, B., Sam, F., Stevenson, L. W., Tang, W. H., Tsai, E. J., Wilkoff, B. L; American College of Cardiology Foundation; & American Heart Association Task Force on Practice Guidelines. (2013). 2013 ACCF/AHA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology, 62(16), e147–e239.