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Current and Future Therapeutic Perspective in Chronic Heart Failure

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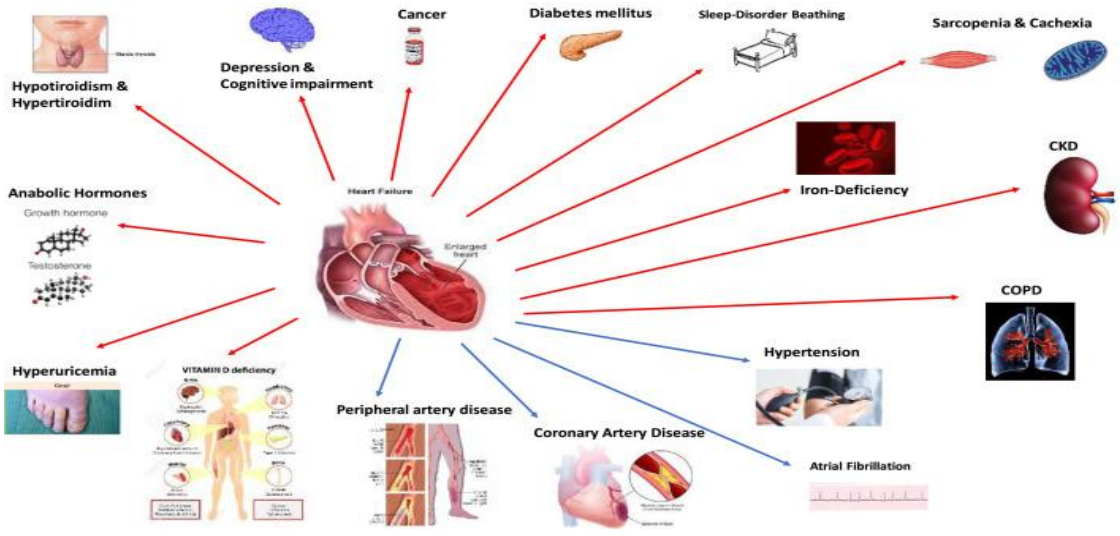
ABSTRACT

The incidence of heart failure is primarily flat or declining for a presumably reflecting better management of cardiovascular diseases, but that of heart failure with preserved ejection fraction (HFpEF) is probably increasing for the lack of an established effective treatment. Moreover, there is no specific pharmacological treatment for patients with heart failure with mildly reduced ejection fraction (HFmrEF) since no substantial prospective randomized clinical trial has been performed exclusively in such population. According to the recent 2021 European Society of Cardiology (ESC) guidelines, the triad composed of an Angiotensin Converting Enzyme inhibitor or Angiotensin Receptor-Neprilysin Inhibitor (ARNI), a beta-blocker, and a Mineralcorticoid Receptor Antagonist is the cornerstone therapy for all patients with heart failure with reduced ejection fraction (HFrEF) but a substantial gap exists for patients with HFpEF/HFmrEF. Despite the important role of the Renin- Angiotensin-Aldosterone System (RAAS) in heart failure pathophysiology, RAAS blockers were found ineffective for HFpEF patients. Indeed, even the new drug class of ARNI was found effective only in HFrEF patients. In this regard, a therapeutic alternative may be represented by drug stimulating the non-classic RAAS (ACE2 and A1–7) as well as other emerging drug classes (such as SGLT2 inhibitors). Reflecting on this global health burden and the gap in treatments among heart failure phenotypes, we summarize the leading players of heart failure pathophysiology, the available pharmacological treatments for each heart failure phenotype, and that in future development.

GRAPHICAL ABSTRACT



KEYWORDS: Chronic heart failure, Renin-angiotensin-aldosterone systemTreatment**,** Heart failure with preserved ejection fraction, Therapeutic perspective.

INTRODUCTION

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels that represents the leading cause of global deaths. As estimated by the World Health Organization, 17.9 million people died for CVDs in 2019, representing 32% of all global deaths. [1] CVDs include a significant number of conditions such as coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, heart failure, and congenital heart disease. Among them, many efforts have been made to treat better and manage heart failure. According to the recent 2021 European Society of Cardiology (ESC) guidelines [2], heart failure is a clinical syndrome characterized by a structural/functional abnormality of the heart that results in elevated intracardiac pressures and inadequate cardiac output at rest or during exercise. Fundamental for the heart failure diagnosis and treatment is the identification of the underlying cardiac dysfunction. Most commonly, heart failure can be caused by a systolic or diastolic dysfunction, or both. However, in some cases, the presence of pathology of the valves, pericardium, and endocardium, or heart rhythm abnormalities can also contribute to the onset of heart failure. Today, heart failure is classified into three phenotypes based on the measurement of left ventricular ejection fraction (LVEF), which can be: reduced, with a value of ≤ 40% (heart failure with reduced ejection fraction, HFrEF); mildly reduced, with a value ranging between 41% and 49% (heart failure with mildly reduced ejection fraction, HFmrEF); preserved, with a value of ≥ 50% (heart failure with preserved ejection fraction, HFpEF) [2]

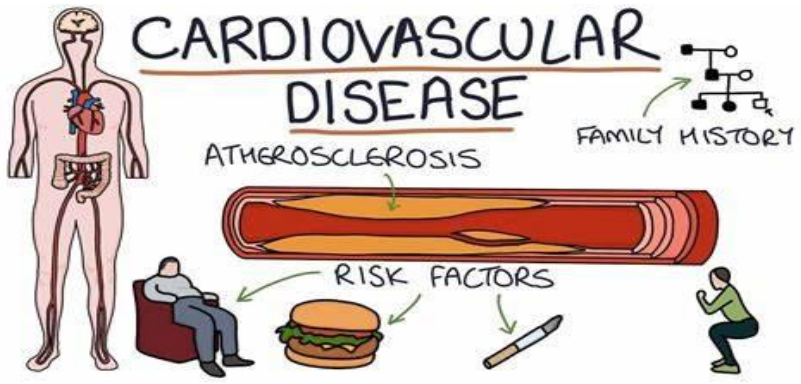


FIG: RISK OF CARDIOVASCULAR DISEASE

Neurohormonal systems in heart failure

Neuro-hormonal systems, including the Sympathetic Nervous System (SNS), the Renin-Angiotensin-Aldosterone System (RAAS), and the Natriuretic Peptides (NPs) system, participate in heart failure pathophysiology. These systems are activated at the early phase to increase the myocardial contractility, the ventricular filling, and the peripheral vasoconstriction, which have the final goal of maintaining the perfusion of vital organs. However, prolonged activation of these systems is also responsible for heart failure progression and unfavorable prognosis. Indeed, SNS and RAAS can cause cardiac damage mediated by an increase in the left ventricular afterload and preload, an increase in heart rate, myocardial hypertrophy, fibrosis, and apoptosis [3].

Specifically, the hyperactivation of the SNS results in cardiac dysfunction [4] through the activation of β1 and β2 adrenergic receptors. These receptors are involved, with opposite mechanisms, in the pathophysiology of heart failure; there is evidence that receptor β1 is involved in apoptotic signaling, while receptor β2 appears to stimulate both autophagic and antiapoptotic responses . Moreover, the stimulation of the renal juxtaglomerular adrenergic receptor β1 contributes to the activation of the RAAS system, which determines cardiac remodeling and apoptosis. The main mediator of the RAAS system is the angiotensin II (AII) [5], which synthesis is shown in Fig. 2.

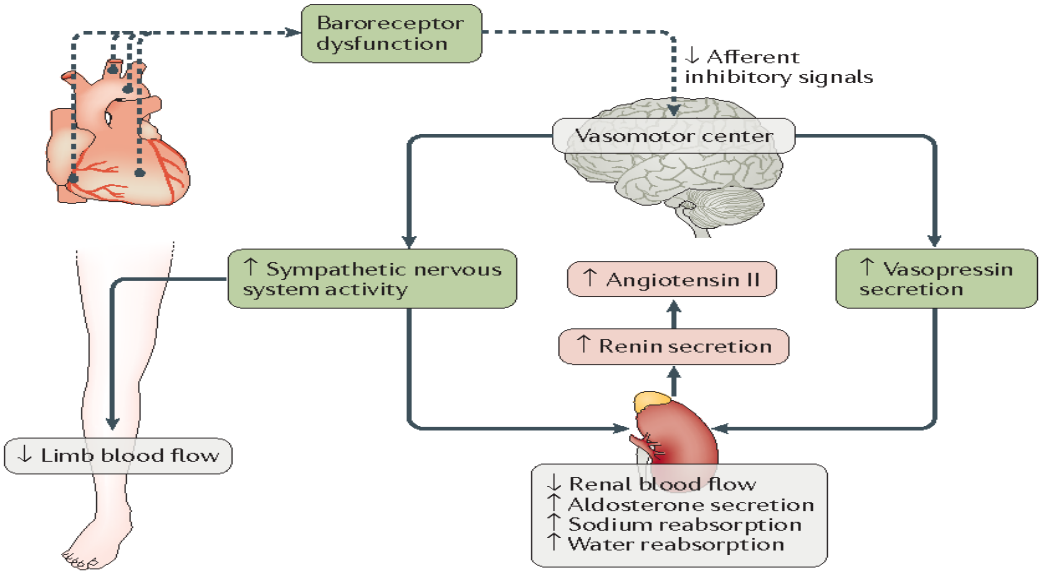


FIG: 2Neurohormonal systems in heart failure

The NPs system also plays a vital role in maintaining cardiovascular homeostasis in patients with chronic heart failure [6]. It is an endocrine, autocrine and paracrine system composed of the atrial natriuretic peptide (ANP), the natriuretic peptide type B or "brain natriuretic peptide" (BNP), and the natriuretic peptide type C (CNP) . NPs exert their biological activity through the receptors NPR-A, NPR-B, and NPR-C. While NPR-A and NPR-B receptors are guanylate cyclase receptors, NPR-C receptors act as "clearance receptors" and remove NPs from the systemic circulation [7]. Moreover, the clearance of NPs is mediated by different enzymes . The most important is neprilysin (NEP), which also metabolizes other peptides, such as substance P, bradykinin, endothelin-1 (ET-1), and AII [8] and converts AI into A1–7. The main biological effects of natriuretic peptides are diuresis and natriuresis, inhibition of secretion and production of neurohormonal factors (aldosterone, AII, endothelin, renin, vasopressin), decrease in blood pressure, and inhibition of cardiac and vascular remodeling. Considering the positive effects determined by NPs, they probably are a compensatory mechanism to attenuate the deleterious RAAS-induced impact [9]. However, the increased levels of NPs are insufficient to balance the RAAS and SNS hyperactivation, probably for establishing several resistance mechanisms [10].

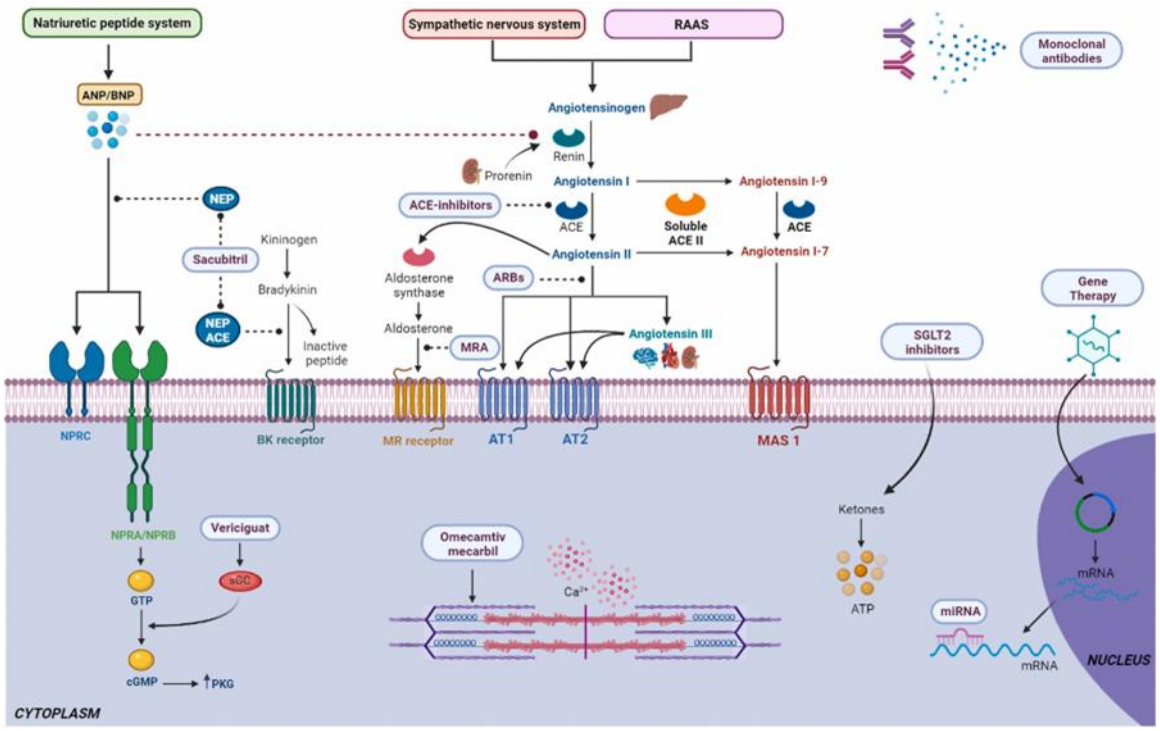


FIG: 3 Neurohumoral pathways and pharmacological targets in heart failure. NEP = neprilysin, BK = bradykinin, MR = mineralcorticoid receptor, GTP = guanosine triphosphate, cGMP = guanosine monophosphate cyclic, sGC = soluble guanylate cyclase, ATP = adenosine triphosphate, NPR = natriuretic peptide receptor, PKG = protein kinase G, ANP/BNP = atrial/brain natriuretic peptide, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, MRA = mineralcorticoid receptor antagonist, RAAS = renin-angiotensin-aldosterone system, SGLT2 = sodium-glucose cotransporter 2.

PHARMACOLOGICAL TREATMENTS

Pharmacotherapy is the cornerstone of the treatment of heart failure, and it can be divided based on the phenotype of heart failure. A schematic representation of the main mechanisms of action of drugs used/ investigated for heart failure is shown in fig 4.

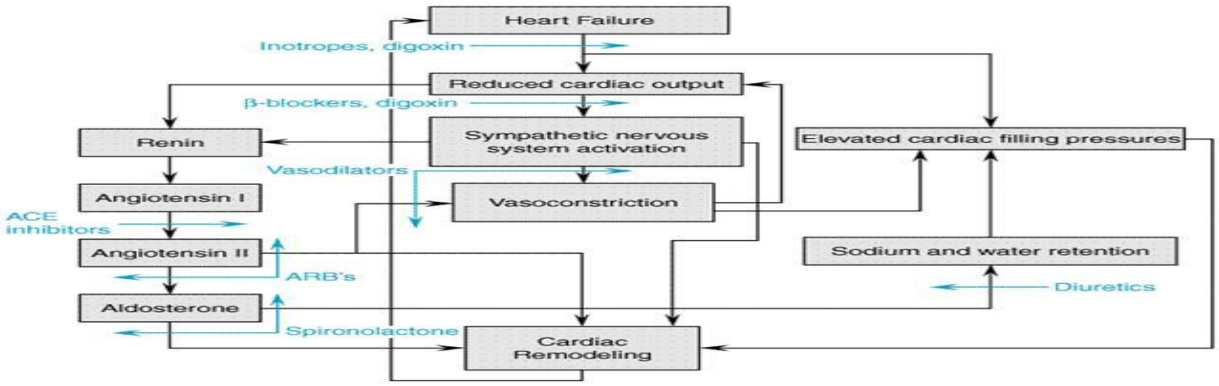


FIG: 4 PHARMACOLOGICAL TREATMENT OF HEART FAILURE

TABLE: 1 Characteristics of main therapeutic classes used/investigated in patients with heart failure.

Therapeutic class	Drugs	Main mechanism of action	Main adverse events	Main Drug-drug interactions
ACE-inhibitors	Captopril Enalapril Lisinopril Ramipril Trandolapril	Inhibition of AII synthesis by blocking the ACE	Cough, hypotension, dyspnea, dizziness, headache, gastrointestinal symptoms	Trimethoprim/sulfamethoxazole, mTOR inhibitors, other RAAS-inhibitors, other antihypertensive drugs, NSAIDs, lithium
β-blockers	Bisoprolol Carvedilol Metoprolol Nebivolol	B adrenergic receptor antagonists	Bradycardia, hypo/hypertension, hypervolemia, gastrointestinal symptoms, edema, respiratory and urinary tract infections, hyperglycemia and asthma	Digoxin, cyclosporine, CYP2D6 and 2C9 inducers, amiodarone, fluoxetine, paroxetine, clonidine, diltiazem
MRAs	Eplerenone Spironolactone Potassium canrenoate	Aldosterone receptor antagonists	Hypokalaemia, hypercholesterolemia, insomnia, dizziness, syncope, headache, left ventricular failure, atrial fibrillation, hypotension, cough, gastrointestinal symptoms, cutaneous reactions, muscle spasms, renal damage	Potassium-sparing diuretics, ACE-inhibitors, lithium, ciclosporin, tacrolimus, NSAIDs, trimethoprim, α1-blockers, tricyclic antidepressants, neuroleptics, glucocorticoids
ARNI	Sacubitril/ valsartan	Neprilysin inhibitor (sacubitril) and angiotensin receptor blocker (valsartan)	Cough, dizziness, hyperkalaemia, hypoglycemic, swelling, kidney failure (renal failure), anemia, headache, gastrointestinal symptoms, fatigue	RAAS-inhibitors, potassium, NSAIDs, lithium, metformin, PDE5-inhibitors
Gliflozines	Dapagliflozin Empagliflozin	SGLT2-inhibitors	Urinary tract infections, dizziness, cutaneous reactions, dysuria and polyuria, increased creatinine, decreased weight	Diuretics, mefenamic acid, rifampicin
Positive inotropic agents	Omecamtiv mecarbil	Activation of cardiac myosin and increase in the rate of ATP hydrolysis	Dyspnea, ventricular extrasystoles, hypertension, photopsia, rhinitis	–
Soluble guanylate cyclase receptor stimulator	Vericiguat	Increases of intracellular cGMP levels	Hypotension, dizziness, anemia, headache, gastrointestinal symptoms	PDE5-inhibitors
Gene therapy	AAV/SERCA2a Ad5.hAC6	Myocardial restoration of gene expression	Safety profile of gene therapies is currently under investigation	–
Biological drugs	Canakinumab Rituximab Infliximab Etanercept	Inhibition of specific inflammatory targets	Immunogenicity, infections, injection site reactions, anaphylactic reactions, leukopenia and neutropenia	–

PHARMACOTHERAPY OF HFREF

As reported in the 2021 ESC guidelines, the foundation of pharmacotherapy of HFrEF includes drugs able to modulate the RAAS, the SNS, or the natriuretic peptide system, such as ACE inhibitors, angiotensin receptor-NEP inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRAs). These drugs have all been demonstrated to reduce mortality and the risk of hospitalizations or symptoms [11]. ACE inhibitors (e.g., captopril, enalapril, lisinopril, ramipril, trandolapril) other than blocking the conversion of AI into AII, can facilitate the AI conversion into A1–7 that can further contribute to the cardiovascular benefit [12,]. However, there is no data on the difference in A1–7 levels obtained by comparing other RAAS blockers. MRAs (eplerenone, potassium canrenoate, and spironolactone) are aldosterone antagonists also recognized to produce cardiovascular benefits in treating HFrEF when added to an ACE-inhibitor a beta-blocker . Many novel compounds with a non-steroidal structure (such as finerenone) are under investigation to obtain an MRA that exerts cardiovascular benefits without determining renal adverse events . In this regard, the first results showed that finerenone was well tolerated and induced a 30% or greater reduction in NT-proBNP levels in a similar proportion of patients treated with eplerenone [13].

- Most patients with HFrEF should be routinely treated with guideline-directed medical therapy (GDMT) that includes an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), or angiotensin II blocker/Neprilysin inhibitor and an evidence-based β-blocker.

- Preference is given to the use of pharmacotherapy in the majority of patients with HFrEF across the spectrum of symptoms. There is limited clinical trial data to inform decision-making surrounding the use of MRA as part of GDMT in those without symptoms of HF or high-risk features.

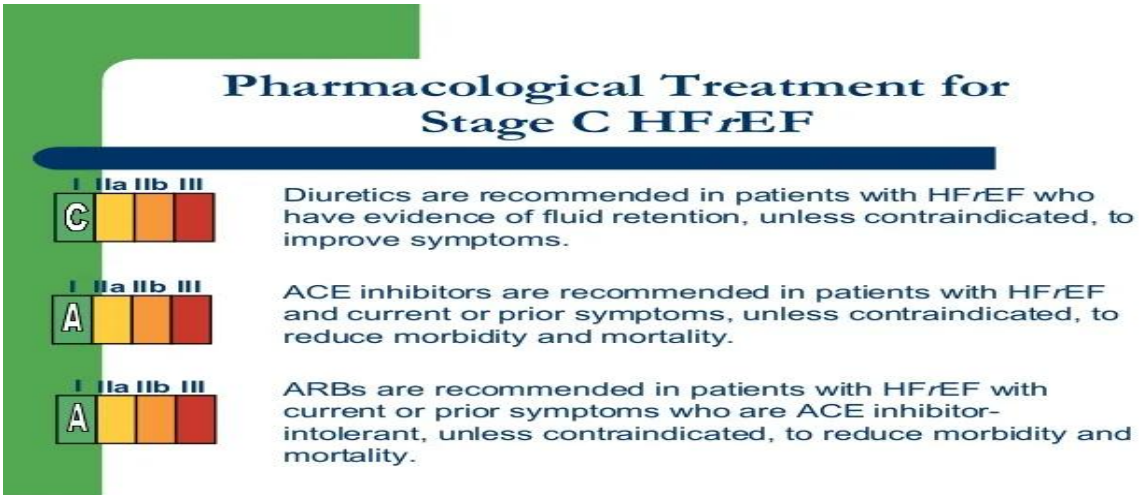


FIG: 5 Pharmacological Treatment For STRAES C HFREF

Pharmacotherapy of HFmrEF

There is no specific pharmacological treatment for patients with HFmrEF since no substantial prospective randomized clinical trial has been performed exclusively in such a population. However, some data can be extracted from a subgroup analysis of trials conducted in patients with HFpEF, which do not have met their primary endpoints. Nonetheless, clinical evidence suggested that patients with EF in the 40–50% range may benefit from therapy recommended for HFrEF. At this regard, the 2021 ESC guidelines on heart failure stated that "although no strong recommendations for this heart failure phenotypes can be made, some drugs such as ACE inhibitors, ARB, MRA, beta-blockers, and ARNI can be considered to reduce the risk of death and heart failure hospitalization" [14].

Pharmacotherapy of HFpEF

Currently, there is a gap in the treatment of HFpEF, and most approved drugs for HFrEF are ineffective for HFpEF. This has suggested the presence of significant differences in the fundamental pathophysiology and therapeutic targets of HFpEF compared to HFrEF. The HFpEF is a heterogeneous clinical syndrome in which coexist different comorbidities such as obesity, diabetes, hypertension, atrial fibrillation, kidney dysfunction, and metabolic syndrome and systemic inflammation plays a major role [15].

Nevertheless, it should be considered that the diagnosis of HFpEF is still challenging, although several diagnostic criteria have been proposed over the years. In this regard, the 2021 ESC guideline recommends a simplified approach for diagnosing HFpEF, which considers the common major elements of diagnosis and emphasizes the most frequently used variables from clinicians such as the left atrium size, mitral E-wave velocity, and septal e' velocity [16].

Clinical trials on perindopril (PEP-CHF) , candesartan (CHARM-Preserved) , irbesartan (I-PRESERVE) , spironolactone (TOPCAT), digoxin (DIG-Preserved) [17], and sacubitril-valsartan (PARAGON-HF) failed to convincingly reduce morbidity and mortality in such patients. In particular, the PARAGON-HF trial, investigating the innovative association sacubitril-valsartan, showed no difference in the primary endpoint (hospitalizations for heart failure and cardiovascular deaths) compared to valsartan alone (rate ratio, 0.87; 95% CI, 0.75–1.01; P = 0.06) [18].

Another study investigating sacubitril–valsartan among patients with HFmEF or HFpEF is the PARALLAX clinical trial that showed a reduction in NT-proBNP but not an improvement in 6-minute walk distance when sacubitril/valsartan was compared to individualized medical therapy [19].

Finally, the PARAGLIDE-HF clinical trial is still ongoing to investigate the effect of sacubitril–valsartan on changes in NT-proBNP, outcomes, and safety in patients with HFpEF (ClinicalTrials.gov Identifier: NCT03988634). Moreover, another therapeutic class for treating patients with HFpEF is that of MRAs (spironolactone and eplerenone).

However, as highlighted in a review, additional data are necessary to define better the risk-benefit profile of MRAs in HFpEF patients [20].

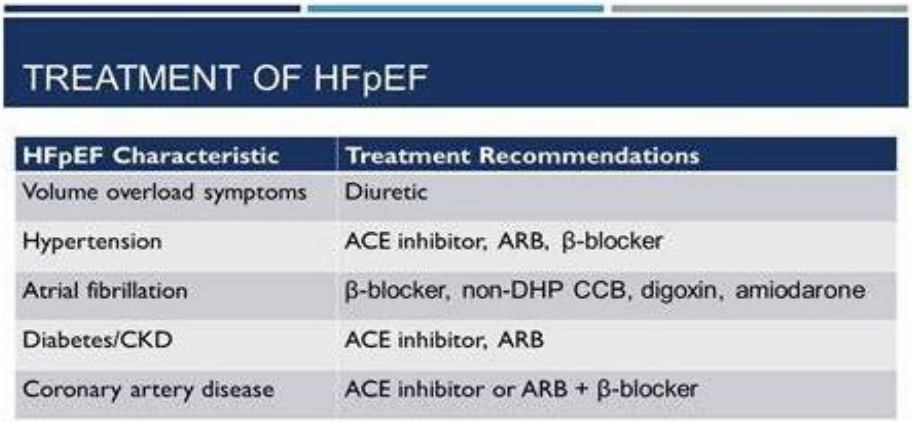


FIG: 6 TREATMENT OF HFpEF

What is in the future?

miRNA

A role in the pathophysiology of cardiac diseases is recovered by microRNAs (miRNAs). MiRNAs are conserved noncoding RNA molecules (approximately 22 nucleotides long, single-stranded) that can regulate gene expression through imperfect base-pairing with complementary sequences of mRNA, leading to translational repression or transcript degradation [21].

Over the years, many miRNAs have been investigated and found to be upregulated or downregulated in several cardiac pathogenic conditions such as myocardial infarction, cardiac hypertrophy, arrhythmias, contractility defects, and chronic heart failure[22].

MiRNAs are emerging as vital post-transcriptional regulators involved in almost all cardiac biological processes and multiple physiological functions. It is known that various miRNAs regulate

each cardiac pathophysiological event and that a single miRNA can have multiple mRNA targets. By this mechanism of gene expression regulation, miRNAs are an exciting and novel therapeutic target for modulating networks involved in the maladaptive remodeling of heart failure.

The miRNA-1, miRNA-133, miRNA-378, miRNA-185, and miRNA-155 are particularly interesting, showing anti-hypertrophic cardiac effects, while the miRNA-208 family miRNA-212/132, miRNA-23, and miRNA-199 have been shown to promote cardiomyocyte hypertrophy. Moreover, the miRNA-133, miRNA-21, miRNA-30 family, miRNA-138, miRNA-499, and miRNA-181c have been shown to induce myocardial cell apoptosis, while the miRNA-28 to have an antiapoptotic effect in cardiomyocytes[23].

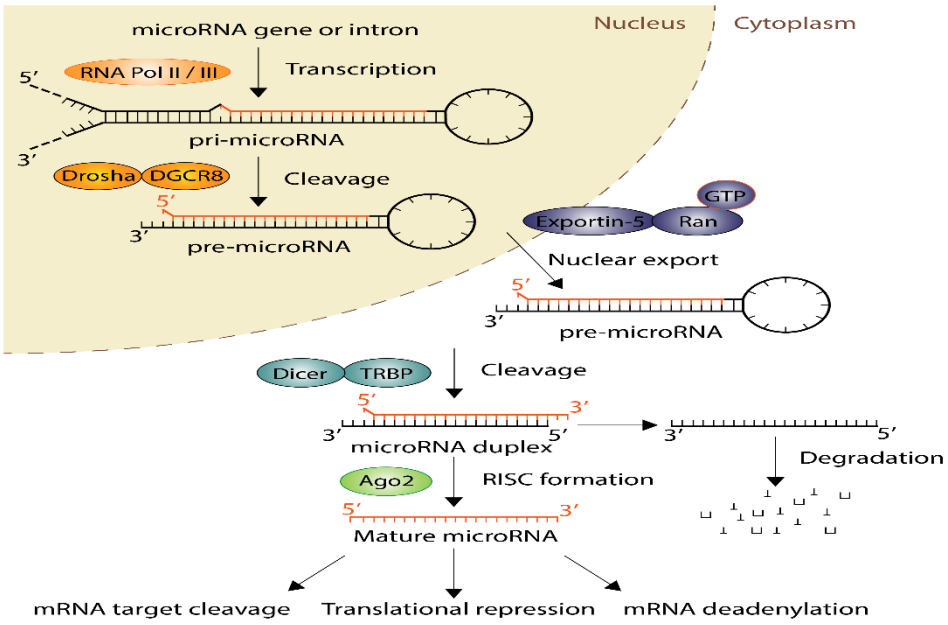


FIG: 7 MIRNA Mechanism

GENE THERAPY

Many attempts have been made to develop effective gene therapy for heart failure. Among them, indeed of interest, was the upregulation of the sarcoplasmic reticulum calcium ATPase (SERCA2a) that plays a significant role in regulating calcium levels in cardiomyocytes and improving myocardial contraction. SERCA2a gene therapy was investigated in heart failure patients and delivered through an adeno- associated virus (AAV). First results from the phase 1/2 CUPID trial have shown the safety and the potential efficacy of AAV/SERCA2a in advanced heart failure patients [24]. Later, two clinical trials (CUPID2b and AGENT-HF trials) failed to demonstrate an improvement of the clinical outcome and ventricular remodeling, respectively , but it should be highlighted that the AGENT-HF trial was not powered enough due to its premature conclusion based on the results of the CUPID2b trial [25]. Another clinical trial (SERCA-LVAD) that aimed to investigate the efficacy and safety of AAV/SERCA2a was prematurely interrupted due to the results of CUPID2b trial (ClinicalTrials.gov Identifier: NCT00534703). The main hypothesis justifying the CUPID2 trial results is the difficulty to develop an accurate delivery system that allows to achieve high doses of gene in the heart. Indeed, it has become clear that novel vectors that will escape innate immunity and have higher cardiac tropism are

needed. Hopefully, the therapeutic benefits of gene therapy will be coming in the next years with the development of new gene delivery methodologies [26].

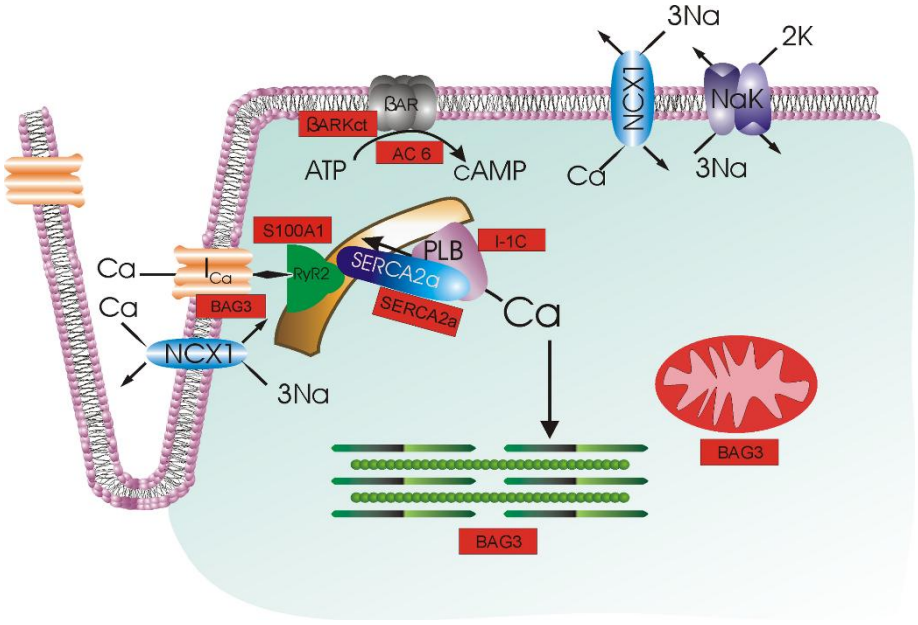


FIG: 8 GENE THERAPY OF HF

Conclusions

The RAAS activity is increased in patients with heart failure, and when this mechanism turns maladaptive, targeting the components of RAAS produces significant benefits. ACE inhibitors remain the first-line therapy for all patients with HFrEF but a substantial gap exists for patients with HFpEF/HFmrEF. Even the new drug class of ARNI was found effective only in HFrEF patients. In this regard, stimulating the non- classic RAAS (ACE2 and A1–7) might be a novel strategy for heart failure, including phenotypes with preserved and mildly-reduced ejection fraction. Thus, more basic, translational and clinical research is needed to delineate the benefits of targeting non-classic RAAS. At the same time, the most promising strategy arising for HFpEF are the SGLT2 inhibitors that have recently been shown to reduce worsening heart failure and cardiovascular death in patients with HFrEF, reaching quickly the prominent position in HF guidelines. On the contrary, although inflammation undisputedly contributes to the onset and progression of chronic heart failure, anti-inflammatory and immunomodulating strategies are yet to be translated into clinically effective approach. Finally, miRNAs, gene and epigenetic therapies that carry the potential to modulate neurohormonal and immune activation are still far from clinical arena.

REFERENCES

1. World Health Organization, Cardiovascular Diseases (CVDs), 2021. Published online 11 June. 〈https://www.who.int/news-room/fact-sh eets/detail/cardiovascular-diseases-(cvds)〉. (Accessed 2 September 2021).
2. G. Filippatos, S.D. Anker, M. Bohm, M. Gheorghiade, L. ¨ Køber, H. Krum, A. P. Maggioni, P. Ponikowski, A.A. Voors, F. Zannad, S.Y. Kim, C. Nowack,G. Palombo, P. Kolkhof, N. Kimmeskamp-Kirschbaum, A. Pieper, B. Pitt,A randomized controlled study of

finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease, Eur. Heart J. 37 (2016), 2105–14.

3. G. Karayannis, G. Kitsios, H. Kotidis, F. Triposkiadis, Left atrial remodellingcontributes to the progression of asymptomatic left ventricular systolicdysfunction to chronic symptomatic heart failure, Heart Fail. Rev. 13 (2008)
   91–98
4. F. Rossi, A. Mascolo, V. Mollace, The pathophysiological role of natriureticpeptide-RAAS cross talk in heart failure, Int. J. Cardiol. 226 (2017) 121–125.
5. G. Olivetti, R. Abbi, F. Quaini, J. Kajstura, W. Cheng, J.A. Nitahara, E. Quaini,C. Di Loreto, C.A. Beltrami, S. Krajewski, J.C. Reed, P. Anversa, Apoptosis in the failing human heart, N. Engl. J. Med. 336 (1997), 1131–41.
6. S. Sridharan, R.M. Kini, A.M. Richards, Venom natriuretic peptides guide the design of heart failure therapeutics, Pharmacol. Res. 155 (2020), 104687
7. T. Maack, M. Suzuki, F.A. Almeida, D. Nussenzveig, R.M. Scarborough, G. A. McEnroe, J.A. Lewicki, Physiological role of silent receptors of atrialnatriuretic factor, Science 238 (1987) 675–678.
8. T.G. von Lueder, D. Atar, H. Krum, Current role of neprilysin inhibitors inhypertension and heart failure, Pharmacol. Ther. 144 (2014) 41–49.
9. A.M. Richards, G. Tonolo, M. Tree, J.I. Robertson, P. Montorsi, B.J. Leckie, J. Polonia, Atrial natriuretic peptides and renin release, Am. J. Med. 84 (1988) 112–118.
10. F. Rossi, A. Mascolo, V. Mollace, The pathophysiological role of natriureticpeptide-RAAS cross talk in heart failure, Int. J. Cardiol. 226 (2017) 121–125.
11. G. Filippatos, S.D. Anker, M. Bohm, M. Gheorghiade, L. ¨ Køber, H. Krum, A. P. Maggioni, P. Ponikowski, A.A. Voors, F. Zannad, S.Y. Kim, C. Nowack,G. Palombo, P. Kolkhof, N. Kimmeskamp-Kirschbaum, A. Pieper, B. Pitt,A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease, Eur. Heart J. 37 (2016), 2105–14.
12. G. Filippatos, S.D. Anker, M. Bohm, M. Gheorghiade, L. ¨ Køber, H. Krum, A. P. Maggioni, P. Ponikowski, A.A. Voors, F. Zannad, S.Y. Kim, C. Nowack,G. Palombo, P. Kolkhof, N. Kimmeskamp-Kirschbaum, A. Pieper, B. Pitt,A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease, Eur. Heart J. 37 (2016), 2105–14.
13. G. Filippatos, S.D. Anker, M. Bohm, M. Gheorghiade, L. ¨ Køber, H. Krum, A. P. Maggioni, P. Ponikowski, A.A. Voors, F. Zannad, S.Y. Kim, C. Nowack,G. Palombo, P. Kolkhof, N. Kimmeskamp-Kirschbaum, A. Pieper, B. Pitt,A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease, Eur. Heart J. 37 (2016), 2105–14.
14. G. Filippatos, S.D. Anker, M. Bohm, M. Gheorghiade, L. ¨ Køber, H. Krum, A. P. Maggioni, P. Ponikowski, A.A. Voors, F. Zannad, S.Y. Kim, C. Nowack,G. Palombo, P. Kolkhof, N. Kimmeskamp-Kirschbaum, A. Pieper, B. Pitt,A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease, Eur. Heart J. 37 (2016), 2105–14.

15. J. Wintrich, I. Kindermann, C. Ukena, et al., Therapeutic approaches in heartfailure with preserved ejection fraction: past, present, and future, Clin. Res. Cardiol. 109 (2020) 1079–1098.
16. G. Filippatos, S.D. Anker, M. Bohm, M. Gheorghiade, L. ¨ Køber, H. Krum, A. P. Maggioni, P. Ponikowski, A.A. Voors, F. Zannad, S.Y. Kim, C. Nowack,G. Palombo, P. Kolkhof, N. Kimmeskamp-Kirschbaum, A. Pieper, B. Pitt,A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease, Eur. Heart J. 37 (2016), 2105–14.
17. A. Ahmed, M.W. Rich, J.L. Fleg, M.R. Zile, J.B. Young, D.W. Kitzman, T.E. Love, W.S. Aronow, Jr Adams KF, M. Gheorghiade, Effects of digoxin on morbidity andmortality in diastolic heart failure: the ancillary digitalis investigation group trial,Circulation 114 (2006) 397–403.
18. S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D. , J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S. A. Boytsov, J. Comin-Colet, J. Cleland, H.D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A. R. Rizkala, J. Gong, V.C. Shi, M.P. Lefkowitz, C. PARAGON-HF Investigators, Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction, angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction, N. Engl. J. Med. 381 (2019) 1609–1620, https://doi.org/10.1056/NEJMoa1908655.
19. A.A. Bavry, Angiotensin Receptor Neprilysin Inhibition Compared With Individualized Medical Therapy for Comorbidities in Patients With Heart Failure and Preserved Ejection Fraction, American College of Cardiology, 2020. Published online 30 August. 〈https://www.acc.org/latest-in-cardiology/clinical -trials/2020/08/28/17/06/parallax〉. (Accessed 7 September 2021).
20. A. Capuano, C. Scavone, C. Vitale, L. Sportiello, F. Rossi, G.M. Rosano, A.J. Coats,Mineralocorticoid receptor antagonists in heart failure with preserved ejectionfraction (HFpEF), Int. J. Cardiol. 200 (2015) 15–19.
21. V. Ambros, The functions of animal microRNAs, Nature 431 (2004) 350–355, 4317006.
22. R.M.W. Colpaert, M. Calore, MicroRNAs in cardiac diseases, Cells 8 (2019) 737, 8:737.
23. H. Wang, J. Cai, The role of microRNAs in heart failure, Biochim. Biophys. ActaMol. Basis Dis. 1863 (2017) 2019–2030.
24. M. Jessup, B. Greenberg, D. Mancini, T. Cappola, D.F. Pauly, B. Jaski,A. Yaroshinsky, K.M. Zsebo, H. Dittrich, R.J. Hajjar, I. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID), Calcium upregulation by percutaneous administration of gene therapy in cardiacdisease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure, Circulation 124 (2011) 304–313.
25. B. Greenberg, J. Butler, G.M. Felker, P. Ponikowski, A.A. Voors, A.S. Desai, D. Barnard, A. Bouchard, B. Jaski, A.R. Lyon, J.M. Pogoda, J.J. Rudy, K.M. Zsebo, Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind,placebo-controlled, phase 2b trial, Lancet 387 (2016) 1178–1186.
26. J.S. Hulot, K. Ishikawa, R.J. Hajjar, Gene therapy for the treatment of heart failure: promise postponed, Eur. Heart J. 37 (2016) 1651–1658.