Review Article

A Class Review on Ace Inhibitors/Arbs and Beta Blockers and Effectiveness in HFrEF

Rakhi K R[a], Dr. C. Dhandapani*[b], Dr. M.Mohan[c]

a. Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamil Nadu, India (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University).

b. Associate Professor, KMCH College of Pharmacy, Coimbatore, Tamil Nadu, India (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University).

c. Consultant Interventional Cardiologist, Kovai Medical Center Hospital, Coimbatore, Tamil Nadu, India.

***Corresponding author's E-mail:** rakhikr25@gmail.com

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ABSTRACT

Heart failure is a serious, progressive, and common illness with a significant morbidity and mortality burden. For patients with HF with reduced ejection fraction (HFrEF), defined by ejection fraction ≤40%, morbidity and mortality is reduced with target doses of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and β-blockers. Large trials have demonstrated improved outcomes with pharmacotherapy targeting the neurohormonal disturbances of heart failure, especially in patients with impaired left ventricular function. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and β blockers, are of proven benefit and are used commonly for management of patients with heart failure and reduced ejection fraction. As a result, recommendations for prescription of angiotensin converting enzyme inhibitors or angiotensin II receptor blocker and beta-blockers are incorporated into leading clinical guidelines. Guideline directed use of ACE inhibitors, ARBs and BBs in patients with HF reduces mortality and morbidity in contemporary clinical practice.

Keywords: Heart failure, Angiotensin converting enzyme inhibitor, Angiotensin receptor blocker, Beta blocker, HFrEF.

INTRODUCTION

Heart failure (HF) is considered as a global pandemic affecting at least 26 million people worldwide and is increasing in prevalence yearly. Heart failure is a progressive clinical syndrome affecting the pumping ability of heart or fill with blood. Considering the physiological point of view, Heart Failure can be defined as the inadequate cardiac output to meet metabolic demands of body or adequate cardiac output secondary to compensatory neurohormonal activation. Heart Failure has also been classified into three subtypes apart from the symptomatic classification, namely Heart Failure with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) and Heart Failure mid-range ejection fraction (HFmrEF), according to the ejection fraction, natriuretic peptide levels and the presence of structural heart disease and diastolic dysfunction.[1]

Inhibition of the renin-angiotensin system by angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) and blocking Adrenergic beta receptor forms the foundation of the evidence-based therapy for patients with HF and reduced ejection fractions. National HF guidelines vary in their recommendations regarding whether ACE inhibitors, ARBs and beta blockers should be used as the drugs of first choice. The efficacy of ACE inhibitors and ARBs has been compared in randomized clinical trials of patients with HF and reduced ejection fractions and those with post–myocardial infarction and left ventricular systolic dysfunction.[2]

Heart failure with reduced ejection fraction is mainly develops as a consequence of long existing cardiovascular disease, Hypertension, coronary artery disease etc. Apart from the usual pathophysiology of heart failure, the pathophysiology of HFrEF seems to be multifactorial. The chronic positive neurohormonal compensative mechanism that involving angiotensin II, norepinephrine, aldosterone, natriuretic peptides being maladaptive and ultimately leads to the clinical deterioration. The most severe case of HFrEF may lead to the formation of edema in the pulmonary system that causes the backward pressure in the congested capillaries which compromises the gas exchange and creates in a life threatening situation.[3]

Pharmacotherapy

The goals of therapy of HF are to improve their clinical status, functional capacity and quality of life, prevent hospital admission and reduce mortality. Neurohormonal antagonists like ACEIs, ARBs, and Beta blockers are found to have improvements in the survival rate of patients with HFrEF. ARBs are recommended only in patients who are tolerated to ACEI. Beta blockers are found to be effective in patients with HFrEF in reducing the morbidity and mortality.[4]

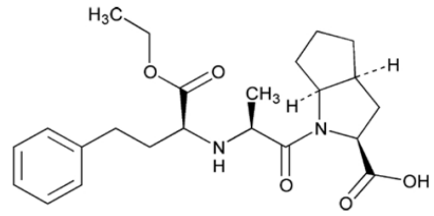
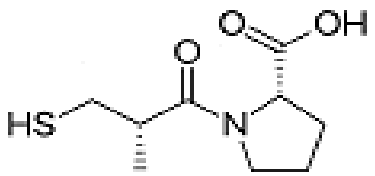
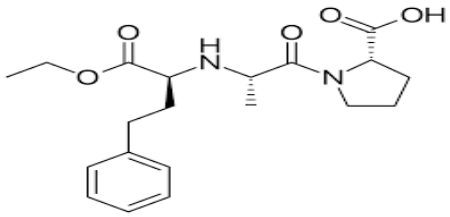
Ace Inhibitors

The mechanism of action of ACEIs is mainly the RAAS inhibition. That is ACEIs inhibit the conversion of angiotensin I to angiotensin II which results in the lower secretion of aldosterone. Inhibition of ACE leads to

decreased systemic arteriolar resistance and mean diastolic and systolic blood pressure. In patients with CHF, inhibition of ACE results in decreased afterload and heart rate as well as increased cardiac output, stroke volume and stroke work.ACE inhibition in patients with symptoms of heart failure with or without coronary artery disease has shown benefits during the established randomized clinical trials. The treatment with ACEIs should be started with a lower dose and titrated to a dose that reduces the risk of cardiac events.[5]

Table 1 shows the drug profile of ACEIs.

Table 1: Drug profile of ACEIs

Drug	Structure	MOL. Formula	MOL. Weight
Ramipril		$C_{23}H_{32}N_2O_5$	416.5g/mol
Captopril		$C_9H_{15}NO_3S$	217.29 g/mol
Enalapril		$C_{20}H_{28}N_2O_5$	376.4g/mol

The angiotensin converting-enzyme inhibitors available so far are active-site directed inhibitors. They utilize all the critical binding interactions of the substrate and convert the catalytic interaction with the zinc atom into an effective binding interaction[6].

Dosage

In patients with HF with reduced ejection fraction, compared with lower doses, higher doses of ACEI significantly improved the all-cause mortality or HF hospitalization without significantly increasing the chances of discontinuation [7].

The dosing of ACEIs are shown below.

Ramipril: IN HFrEF, 2.5 mg twice-daily; titrate to 5 mg twice daily as tolerated, maximum upto 10 mg.

Captopril: 6.25-12.5 mg three times a day with goal of 50 mg three times a day for HFrEF.

Enalapril: HFrEF/HTN: 2.5-5 mg once or twice daily, increased up to 40 mg/day every 1-2 weeks in 2.5 mg intervals [8].

Adverse Drug Reactions

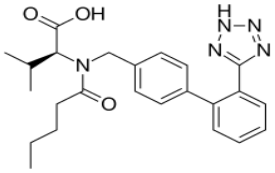
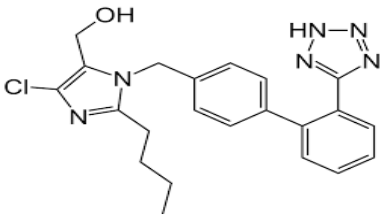
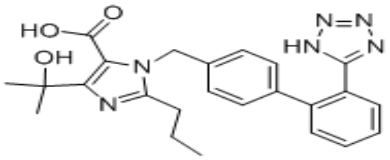
The side effects that do occur are related directly or indirectly to reduced angiotensin II formation. These include hypotension, acute renal failure, hyperkalemia.There are other complications like cough, angioedema, and anaphylactic reactions that are thought to be related to increased kinins since ACE is also a kininase[9].

Angiotensin Receptor Blockers

Angiotensin II receptor blockers provide more successful blockade of the renin-angiotensin system than ACE inhibitors and have been shown to decrease morbidity and mortality to a degree similar, but not superior, to that of ACE inhibitors. ARBs have less side effects than ACE inhibitors and, in some cases, may be of benefit when combined with ACE inhibitors as part of standard with ARBs with considerable caution as studies have reported increased morbidity and mortality, and no significant all-cause mortality benefit, particularly among patients also receiving an aldosterone antagonist. ARBs are a reasonable alternative for patients who are unable to tolerate ACE inhibitor therapy[3].

Table 2 shows the drug profile of ARBs like losartan, valsartan and olmesartan.

Table 2: Drug profile of ARBs[6]

Drug	Structure	Molecular formula	Molecular weight
Valsartan		$C_{24}H_{29}N_5O_3$	435.5g/mol
Losartan		$C_{22}H_{23}ClN_6O$	422.91 g/mol
Olmesartan		$C_{29}H_{30}N_6O_6$	558.6 g/mol

Dosage

Initial and maximal dosages of ARBs in HFrEF are Losartan: 25 to 150 mg daily

Valsartan: 20 to 160 mg two times daily, Olmesartan: 20-80mg two times daily[8].

Adverse Drug Reactions

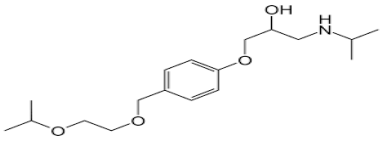
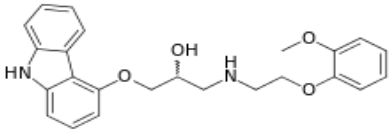
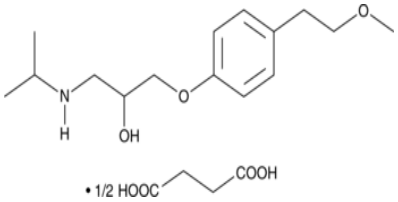
Common side effects include dizziness, headache, drowsiness, Elevated potassium levels. ARBs cause cough less frequently than ACE inhibitors. Therefore, they are often substituted for ACE inhibitors when patients complain of cough with ACE inhibitors. Like other antihypertensive, ARBs are associated with sexual dysfunction. Serious, butrare, side effects include kidney failure, liver failure, allergic reactions, low white blood cells, and swelling of tissues.

Beta-Blockers

Beta-blockers are a class of drugs used to control symptoms of heart failure that are worsened by certain hormones called catecholamines. The body releases catecholamines as a part of its response to heart failure. Because of this reasons, beta-blockers have been shown to be effective for treating most people who have heart failure. Beta-blockers possess variety of effects throughout the body. They are utilized to treat heart disease that causes chest pain, high blood pressure, heart attacks, and cardiomyopathy and irregular, rapid heartbeats[10].

Table 3 shows the drug profile of Beta blockers

Table.3

Drug	Structure	Mol. Formula	Mol. Weight
Bisoprolol		$C_{18}H_{31}NO_4$	325.4 g/mol
Carvedilol		$C_{24}H_{27}ClN_2O_4$	442.9 g/mol
Metoprolol		$C_{34}H_{56}N_2O_{10}$	652.8 g/mol

β-blockers are sympatholytic drugs. Some *β-blockers* partially activate the receptor while preventing catecholamines from binding to the receptor, making them partial agonists. They provide a background of sympathetic *activity*, while preventing normal and enhanced sympathetic *activity*[6].

Dosage

Initial and maximal dosages for commonly used Beta blockers in HFrEF are:

• Bisoprolol: 1.25 to 10 mg daily

• Carvedilol: 3.125 to 50 mg twice daily

• Metoprolol succinate : 12.5 to 200 mg daily[8].

Beta blockers should be started at low doses and titrated slowly to target doses if tolerable.

Adverse Drug Reactions

As an addition of their beneficial effect, they slow heart rate and reduce blood pressure, but they may cause adverse effects such as heart failure or heart block in patients with heart problems.

Beta blockers should not be withdrawn suddenly because sudden withdrawal may worsen angina and cause heart attacks, serious arrhythmia, or sudden death[8].

ACEIs and HFrEF

Early institution of maximal therapy with ACE inhibitors saves lives. Numerous studies have shown that treatment with ACE inhibitors slows development of HF and can improve quality of life and long-term prognosis. The biggest limitation of this class of agents is that many patients are not receiving maximal beneficial dosages. Such under treatment events anticipated therapeutic benefits. ACE inhibitors should strongly be considered in all patients with reduced ejection fraction to help prevent symptomatic HF, as well as in those with HF*r*EF unless contraindicated[8].

The usual dosing strategy for ACE inhibitors is to start at a low dose and double the dose every one to two weeks, if tolerated, up to the prespecified target dose.

The advantage of ACE inhibitors, such as enalapril and lisinopril, to reduce mortality when taken along with other HF*r*EF medications has made this class of medications the mainstay for treatment of HF*r*EF in patients free from any contraindications to their use. The efficacy of ACE inhibitors has been proven over several decades.

The CONSENSUS trial, which compared enalapril with placebo, proved that enalapril reduced overall mortality risk by 27% and significantly decreased the number of patients with HF*r*EF development.

The SOLVD trial showed that, compared with placebo, therapy with enalapril over the three years prevented 50 premature deaths and 350 hospitalizations per 1,000 patients.

Together, these trials suggest that ACE inhibitors, when taken along with other HF*r*EF medications, provide significant reductions in morbidity and mortality. These benefits have been proven to remain clinically significant throughout long courses of treatment[11].

ARBs and HFrEF

Angiotensin receptor blockers inhibit the renin–angiotensin–aldosterone system (by preventing the binding of angiotensin II to its receptor, which in turn leads to vasoconstriction and inhibits the release of aldosterone. Although their mechanism of action is same as that of ACE inhibitors, ARBs do not cause blockade of kininase, which decrease the incidence of cough in comparison with ACE inhibitors.

The 2016 ACCF/AHA/HFSA guidelines suggests that ARBs are used to decrease morbidity and mortality in patients who are intolerant of ACE inhibitors because of cough or angioedema or in patients who are tolerating ARBs for other indication. In addition, the 2016 guidelines suggests that ARBs be used with caution in patients with a past history of angioedema with ACE inhibitors because of the risk of cross-reaction.

Placebo-controlled trials have demonstrated that the use of ARBs decreases hospitalization and mortality. The 2003 Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM Alternative) study analysed that whether candesartan could increase cardiovascular outcomes compared with placebo, including the composite endpoint of cardiovascular death or hospital admission in patients with symptomatic HF with an EF of 40% or less who were intolerant of ACE inhibitors.

It is important to monitor patients on ARB therapy and increase the dose as tolerated. A study with losartan dosing, shows the value of up titrating ARB dosing for maximal benefit. When starting ARB therapy, start with a low dose and titrate up as tolerated by doubling the dose to the target dose[11].

Beta Blockers and HFrEF

The benefit of beta blocker in HF*r*EF has been documented for more than 40 years.22 Since 1975, data have shown that the use of bisoprolol, carvedilol, or sustained release metoprolol succinate decreases morbidity and mortality in patients with HF*r*EF. Bisoprolol, carvedilol and metoprolol are the only beta blockers tested in large clinical trials to show a mortality benefit, which led to their inclusion in the HF guidelines as first-line agents in all patients with HF*r*EF to reduce morbidity and mortality unless contraindicated. These three agents follows a common pathway: They all block the β1-adrenergic receptor in the heart. HF*r*EF stimulates the RAAS and sympathetic system to compensate for the reduced EF. However, this activation may speed up ventricular remodeling. By blocking β1 receptors, beta blockers inhibit ventricular remodeling promoted by the stimulated RAAS and sympathetic system. While metoprolol and bisoprolol are selective for the β1

receptor, carvedilol also blocks both β2 and α1 receptors, leading to vasodilatation.

Adverse events include fluid retention and worsening HF*r*EF, bradycardia or heart block, and hypotension. The fluid retention associated with beta blockers do not generally necessitate the permanent withdrawal of treatment[11].

CONCLUSION

In this review we demonstrated that ACE inhibitors/ARBs and Beta blockers have been proven to reduce morbidity and mortality in a wide range of HF*r*EF patients. The neurohormonal activity of these drugs have been utilized for the treatment of HFrEf. Increased achieved doses of ACE inhibitors or ARBs and β blockers were associated with improved outcomes. Although smaller doses of ACE inhibitors or ARBs and β blockers conferred some benefit, guideline-recommended doses led to maximum benefit. These proven benefits warrant the use of these agents in all patients with HF.

REFERENCES

1. Teng T H K, Tromp J, Tay W T, Anand I, Ouwerkerk W, Chopra V, Wander G S, Yap J L, MacDonald M R, Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study, *Lancet Glob Health*, 6, 2018, 1008–18.
2. Zhang Y, Fonarow G C, Sanders P.W, Farahmand F, Allman R M, Aban I B, Love T E, Levesque R, A Propensity-Matched Study of the Comparative Effectiveness of Angiotensin Receptor Blockers versus Angiotensin-Converting Enzyme Inhibitors in Heart Failure Patients Age >65 Years, Am J Cardiol, 108, 2011,1443–1448.
3. Greenfield R H, Heart Failure, Integrative medicine, 2, 2017, 242-252.
4. Banarjee A K, Evaluation and Management of Heart Failure in Patients with Reduced Ejection Fraction,indian heart journal,2011,153-158.
5. www.rXmed.com; available from the URL;https://www.rxmed.com/b.main/b2.
6. Spharmaceutical/b2.1.monographs/cps-_monographs/CPS-_(General_Monographs-_A)/ACE_INHIBITORS.html: cited on 25/8/19.
7. www.pubchem.ncbi.nlm.nih.gov,available from the URL, https://pubchem.ncbi.nlm.nih.gov› compound› ACE inhibitors>ARBS>Beta Blockers.
8. Khan M S, Fonarrow G C, Ahmed A, Greene S J, Vaduganathan M, Khan H, Marti C Dose of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers and Outcomes in Heart Failure; A Meta-Analysis. American Heart Association journals.2017.1-8.
9. Dalpoas, Stacy E, and Lipika Samal,ACE Inhibitors, *Johns Hopkins Diabetes Guide*, 2017.
10. Townsend R R, Bakris G L, Forman J P, Major side effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, *Uptodate.*2018.
11. www.medicinenet.com,available from the URL;https://www.medicinenet.com/angiotensin_ii_receptor_blockers/article.htm#what_are_the_uses_for_arbs:cited on 25/8/19.
12. Shah A, Gandhi D, Srivastava S, Shah K J, Mansukhani R. Heart failure: A class review of pharmacotherapy, *P&T*, 42,7, 2017, 464-472.

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