Biological Actions and Metabolism of Currently Used Pharmacological Agents for the Treatment of Congestive Heart Failure

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Abstract: Congestive heart failure (CHF), a complex clinical syndrome with impaired cardiac pump function, occurs as a consequence of mechanical deformities (pressure and volume overload), myocardial abnormalities (neurohormonal disorders, myocarditis, cardiomyopathies, inflammation and loss of cardiomyocytes) and rhythmic defects (conduction disturbances, fibrillation and tachycardia). Several studies have demonstrated that chronic activation of sympathetic and renin-angiotensin systems, alteration in myocardial substrate utilization, increase in intracellular Ca^{2+} concentration, development of oxidative stress, release of pro-inflammatory cytokines and increased production of endothelin are responsible for the maladaptive cardiac and subcellular remodeling depending upon the type and stage of heart failure. A variety of pharmacological agents have been used to prevent the development and progression of CHF under different experimental and clinical settings. Although these drugs belong to specific classes, depending on their mechanism of action, individual drug biotransformation into different metabolites makes them distinct chemical moieties. Thorough understanding of biological effects of these pharmacological agents and metabolism is necessary to establish the basis for their preeminent use in clinical settings. The purpose of this review is to present a mechanistic understanding for the biological activities of different drugs used to treat CHF and to provide an insight of different metabolites formed after biotransformation of these chemical entities. Since development of CHF is a multifactorial and heterogeneous process, induction of combination regimens and improvement in patient compliance are the major challenges for future drug development.

Keywords: Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, aldosterone antagonists, diuretics, digoxin, vasodilators.

1. INTRODUCTION

It is now well known that congestive heart failure (CHF), an end stage of a cardiac disease, occurs as a consequence of hypertension, ischemic heart disease, genetic and idiopathic cardiomyopathy, diabetes, septal defects, hypercholesterolemia and valvular defects [1]. It has become a major challenge for the health care system; 5,300,000 Americans ≥20 years of age are currently suffering from CHF and another 660,000 develop this condition each year [National Health and Nutrition Examination Survey: NHANES (1999-2004)] [2]. The incidence and prevalence of CHF correlates directly with age as the annual rate per 1000 population of new CHF events in white men vs. women are 15.2, 8.2 for 65-74 years, 31.7, 19.8 for 75-84 years and 65.2, 45.6 for ≥ 85 years of age [2]. Similarly, in the same age groups of black men vs. women the rates are 16.9, 14.2; 25.5, 25.5 and 50.6, 44.0, respectively [2]. According to the 44 year follow-up of the National Heart, Lung and Blood Institute (NHLBI) Framingham Heart Study (FHS) cohort and 20 year follow-up of the offspring cohort, 80% of men and 70% of women (less than 65 years of age) are currently suffering from this condition and will die within next 8 years [3]. It is pointed out that the incidence of sudden cardiac death in CHF patients is 6-9 times higher than the general population with 1 year mortality rate of 20% [2]. With the advent of different pharmacological and surgical interventions hospital discharge for CHF patients have increased from 400,000 to 1,084,000 (1979-2005). However, the number of total deaths due to CHF remains as high in 2004 (284,365) as in 1994 (284,087) [2]. In addition, the number of visits to hospitals and physicians were 3.4 million in the US for the period of 1 year (1999-2000) and estimated direct and indirect costs to treat CHF was $34.8 billion for 2008 [2, 4]. Therefore, it seems likely that CHF has become a major social and economic burden and it is absolutely essential to understand the pathophysiologic basis of this condition with a focus on the different targets for current and future drug development.

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Accordingly, in this review we have discussed in detail the biological actions of different drugs acting at a number of targets to better decipher this complex pathological condition. Since these drugs are biochemically modified into active or inactive metabolites through specialized enzyme systems present in the body which determines the duration and intensity of their action, a comprehensive overview of different biotransformation mechanisms has also been provided. Although in recent years various surgical interventions such as biventricular pacers, ventricular assist devices, cardiac transplantation, and stem cell transplantation are emerging to treat end stages of heart failure (HF) [5-8], this review will only focus on the available and future targets for drug development under experimental and clinical settings.

2. RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) AS A TARGET FOR PHARMACOTHERAPY OF CHF

Epidemiological and experimental studies have demonstrated that activation of RAAS is one of the key events during the development of heart failure [9, 10]. Increased production of renin due to decreased cardiac output and as a result of reduced blood flow causes the conversion of angiotensinogen to angiotensin I (Ang I), which is subsequently converted to angiotensin II (Ang II) by the action of angiotensin-converting enzyme (ACE) (dipeptidyl carboxypeptidase I) [10] . Ang II is the major effector hormone which exhibits its multiple deleterious effects through the action on Ang II type 1 (AT_1) receptors [11, 12]. It causes an increase in blood pressure via vasoconstriction of efferent arterioles and enhances epinephrine release from the adrenal medulla [9, 10, 13]. In addition, Ang II promotes the synthesis and release of aldosterone from adrenal cortex leading to sodium and water retention [14]. Ang II also enhances the release of vasopressin from the pituitary [13]. Ang II has been implicated in cardiac remodeling, which occurs as an adaptive response to alter shape and size of the heart and contribute to worsening of CHF condition in the compromised myocardium [9, 12]. Ang II and aldosterone increases intracellular Ca^{2+}, which is known to be a second messenger in increasing fibroblast collagen turnover leading to myocardial fibrosis [15]. Different components

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of RAAS pathway and the target for drug therapy are summarized in Fig. (**1**).

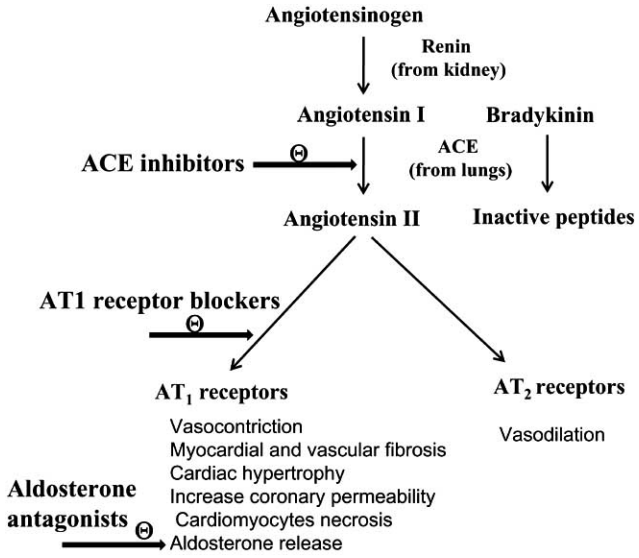

Fig. (1). Schematic representation of renin-angiotensin-aldosterone system (RAAS) indicating the targets for different pharmacological agents. ACE: angiotensin converting enzyme.

2.1. Angiotensin Converting Enzyme (ACE) Inhibitors

Depending upon the molecular structure, ACE inhibitors have been classified into sulfhydryl containing agents (captopril and zofenopril), dicarboxylate containing agents (enalapril, ramipril, lisinopril, quinapril, perindopril and benazepril) and phosphonate containing agents (fosinopril) [16]. The structures of prototype agents are given in Fig. (**2**). Several clinical trials [17-21] have shown that ACE inhibitors are the drugs of choice for the treatment of patients at different stages of heart failure as shown in Table **1**. Although significant reduction in all cause mortality and decreased frequency of hospitalization were observed in CHF patients (with impaired left ventricular ejection fraction) after treatment with ACE inhibitors [22, 23], differential effects of ACE inhibitors were observed in CHF patients while conducting a direct comparison. In this context, Fosinopril Heart Failure Study Investigators indicated that fosinopril (5-20 mg/day) was more effective in improving the event-free survival time and total rate of hospitalizations as compared to enalapril (5-20 mg/day) in CHF patients with ejection fraction (EF) <40% [24]. On the other hand, no significant differences were observed between long acting ACE inhibitor lisinopril (5-20 mg once daily) and captopril (12.5-50 mg b.i.d) [25] as well as lisinopril (5-20 mg once daily) with enalapril (5-20 mg once daily) in patients with mild-to moderate CHF [26]. In addition, no significant difference in the mortality was observed between enalapril, ramipril, quinapril, captopril, lisinopril, benzapril, perindopril and cilazapril [27]. Therefore, it seems likely that evidence-based choice of a particular ACE inhibitor is the option for the treatment of CHF. Ramipril has been selected as drug of choice in patients in which β-blockers are contraindicated and have a greater risk of fatal or non fatal arrhythmias [28]. Oral administration of ramipril in patients with transient or overt CHF resulted in a significant reduction in premature death [28]. Since 50-65% patients of CHF have myocardial infarction (MI) as an underlying cause [29], the beneficial effects of ACE inhibitors have also been established in MI-induced CHF under these clinical and experimental settings [9]. It is important to point out that ACE inhibitors show maximum benefit in terms of decreasing the risk of premature death and development of CHF in patients with acute MI (within 24 hours of heart attack) [30].

Captopril, lisonopril, ramipril, quinapril, fosinopril and enalapril have been approved for the treatment of CHF by the United States Food and Drug Administration (FDA) [31]. Captopril, enalapril and quinapril have an absolute bioavailability of 70%, 60% and 50%, respectively after oral administration [32]. Captopril differs from enalapril and quinapril as it is mainly metabolized in the plasma [33]. On the other hand, enalapril and quinapril are de-esterified in the liver to their active metabolites enalaprilat and

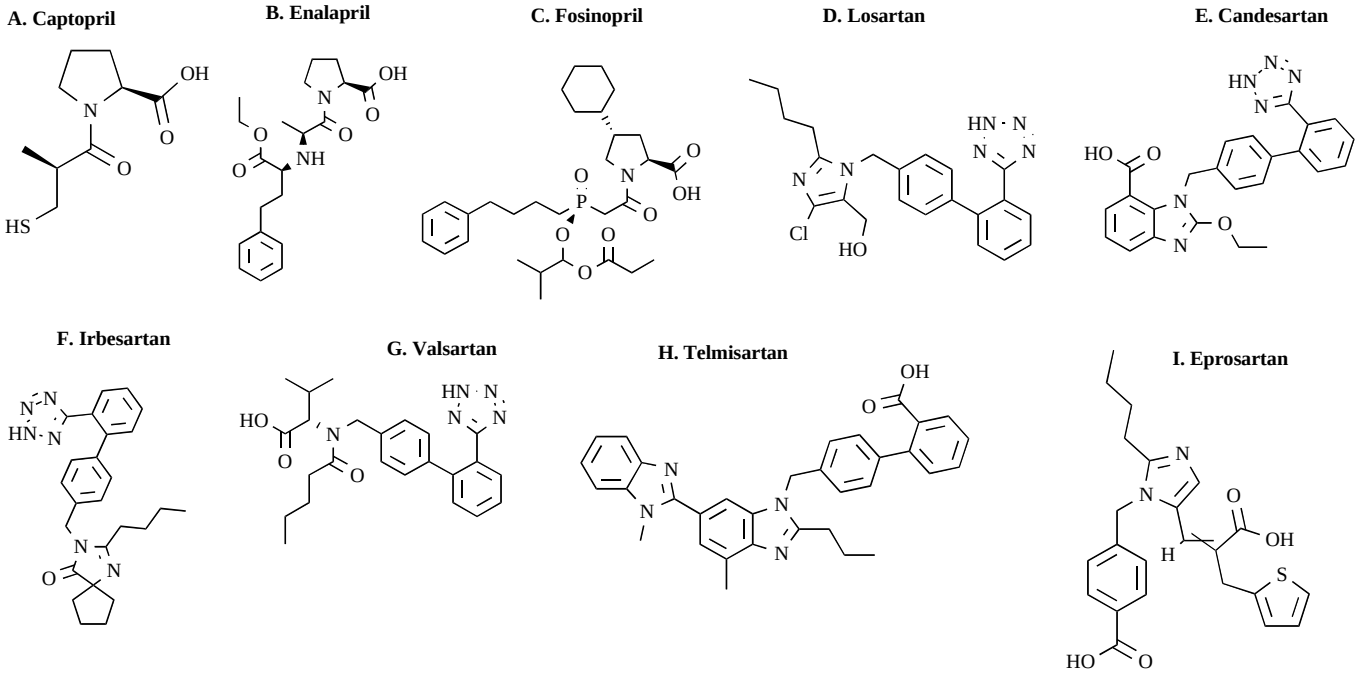

Fig. (2). Chemical structures of different angiotensin converting enzyme (ACE) inhibitors captopril (A), enalapril (B) and fosinopril (C) and AT_1 receptor blockers (ARBs) losartan (D), candesartan (E), irbesartan (F), valsartan (G), telmisartan (H) and eprosartan (I).

Table 1. Major Clinical Trials of Various ACE Inhibitors for the Treatment of CHF

Drug and dosage	NYHA classif ication	Clinical trial	End effect	Reference
Enalapril (2.5-40 mg/day)	Class IV	CONSENSUS (enalapril with conventional CHF therapy vs. placebo)	50% reduction in total mortality without any difference in sudden cardiac death as compared to placebo	17
Enalapril (2.5-20 mg/day)	Class II and III with EF≤ 35%	SOLVD-T (enalapril with conventional CHF therapy vs. placebo)	Significant reduction in mortality (209 vs. 251 placebo) and hospitalization (613 vs. 736 placebo)	18
Enalapril (2.5-20 mg/day)	Asymptomatic Class I with EF≤ 35%	SOLVD-P (enalapril vs. placebo)	Reduction in total no. of deaths and cases of CHF (630 vs. 818 placebo) and hospitalization (434 vs. 518 placebo)	19
Lisinopril (low dose 2.5-5 mg/day) and high dose (32.5-35 mg/day)	Class II-IV with EF≤ 30%	ATLAS (lisinopril low dose vs. high dose)	24% decrease in hospitalization and 4% reduction in end point mortality in high dose group vs. low dose group without any difference in side-effect profile	20
Fosinopril (10-40 mg/day)	Class II and III with EF=26.5 ± 6.9%	FEST (fosinopril with diuretic therapy and optional digoxin treatment vs. placebo)	62% increase in exercise tolerance time, reduction in frequency of clinical events (89% vs. 75% placebo) and hospitalization (3% vs. 12 % placebo)	21

NYHA: New York Heart Association; CONSENSUS: Cooperative North Scandinavian Enalapril Survival Study; SOLVD-T: Studies of Left Ventricular Dysfunction-Treatment; SOLVD-P: Studies of Left Ventricular Dysfunction-Prevention; ATLAS: Assessment of Treatment with Lisinopril and Survival and EFST: Fosinopril Efficacy/Safety Trial. Conventional therapy includes the treatment with vasodilators, digitalis and diuretics for the treatment of CHF.

quinaprilat, respectively [34]. In addition, benazepril, cilazapril, fosinopril, perinopril, ramipril and trandolapril are designed as pro-drugs and are hydrolyzed to their active metabolites benezeprilat, cilazaprilat, fodinoprilat, perinoprilat, ramiprilat and trandolaprilat, respectively, in the liver to improve their bioavailability [32, 34]. Hepatic dysfunction slows down the conversion of quinapril to its active metabolite [35]. Plasma concentration of quinapril increases with a decrease in quinaprilat in patients with liver cirrhosis suggesting that patients with primary liver disease should not be treated with quinapril [33]. A study by Ohnishi *et al.* [36] showed impairment in biotransformation of enalapril to enalaprilat in patients with hepatic dysfunction due to liver cirrhosis. Incontrast, a study by Baba *et al*. [37] revealed no alteration in the conversion of enalapril to its active metabolite in hepatic dysfunction due to compensated liver cirrhosis. However, it was noted by Ohnishi *et al.* [36] that the pharmacodynamic effects of enalapril were unaffected in patients with liver cirrhosis. Due to these discrepancies in enalapril metabolism, intravenous enalaprilat, which is devoid of hepatic activation, has been suggested as the preferred ACE inhibitor for hospitalized patients with liver dysfunction [16]. Some new ACE inhibitors such as moexipril, spirapril, temocapril and imidapril have also been designed as pro-drugs and are converted to their active metabolites moexiprilat, spiraprilat, temocaprilat and imidiprilat, respectively, by hydrolysis in the liver [38-41]. Unlike enalapril, ramipril and lisinopril, food intake decreases the bioavailability of captopril [35]. A dosage reduction of 25-50% has been suggested in patients with renal impairment as most of the ACE inhibitors are excreted through the kidneys [42]. Fosinopril is the only drug which is recommended in CHF patients with reduced renal function as it is mainly eliminated by the hepatobiliary pathway under these conditions [42]. In healthy subjects 46% of fosinopril is eliminated via hepatic metabolism and 44% via kidney secretion [43]; however in patients with renal insufficiency, the hepatic clearance of fosinopril increases significantly as a compensatory response due to reduced kidney function [44, 45]. The major side effects of ACE inhibitors are dry cough, symptomatic hypotension and renal dysfunction mainly due to ACE inhibitor mediated accumulation of bradykinin [46]. In 0.1-0.2% patients, a rare but potentially life-threatening side effect of ACE inhibitors is angioedema characterized by localized swelling of the face, lips, tongue, and glottis [47, 48]. Brown *et al.* [49] have suggested that the risk of developing angioedema is more common in black Americans in contrast to white subjects. Therapy with any ACE inhibitor should be interrupted promptly after immediate recognition of the warning signs of angioedema and an alternative class of medication is preferred under such conditions [50]. ACE inhibitors are also contraindicated in patients taking high doses of K^+-sparing diuretics (spironolactone) and NSAIDS (aspirin) [51]. Therefore alternative therapies are needed in patients intolerant to ACE inhibitors.

2.2. AT_1 Receptor Blockers (ARBs)

Since ACE inhibitors reduce the potential beneficial effects of Ang II through AT_2 receptors [52], it is important to selectively block AT_1 receptors. Long term treatment with ACE inhibitors have been shown to cause reversal of Ang II levels or increase its level from pretreatment values [53]. The existence of alternative local pathways of Ang II production through chymase, which is not blocked by ACE inhibitors, is the major reason for such an increase [54, 55]. Therefore, the blockage of AT_1 receptors is considered as a rationale therapy for the treatment of CHF.

ARBs can be divided into different groups on the basis of their chemical structure related to a prototype antagonist CV-2961 [56]. Losartan, candesartan and irbesartan have biphenyl and tetrazole substituted imidazole groups whereas valsartan has biphenyl groups [57]. Telmisartan is a substituted benzimidazole derivative and eprosartan is non-biphenyl non-tetrazole substituted imidazole derivative [57] (Fig. **2**). A number of studies have examined the effect of AT_1 receptor blockers alone (ELITE, ELITE I and CHARM-alternative) or in combination with an ACE inhibitor (CHARM-added) (Table **2**) [58-63]. A subpopulation of the CHARM-alternative trial, not taking ACE inhibitors, demonstrated that ARB's are the choice of drug in ACE intolerant patients [62]. The results of the Val-HeFT trial demonstrated the beneficial effects of valsartan in reducing clinical signs and symptoms of CHF in ACE inhibitor intolerant patients [60]. Recently, the FDA approved valsartan for the treatment of patients who are unable to take ACE inhibitors. However, in patients with asymptomatic heart failure with preserved LV function ACE inhibitors are preferred over ARBs [64]. Similarly, in CHF patients with LV dysfunction early after MI, a non-significant difference in mortality in favor of captopril as compared to losartan was observed (OPTIMAL: Optimum Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan) [65]. The authors concluded that ACE inhibitors should remain the first-choice of drug in complicated acute MI patients [65]. On the other hand, the results of VALIANT (Valsartan in Acute Myocardial Infarction Trial) have demonstrated that valsartan was as effective as captopril in reducing the cardiovascular events after MI [66]. It still remains questionable whether the combination therapy of ACE inhibitors and ARB is more beneficial than monotherapy. The VALIANT trial results have shown that the combination therapy of valsartan and captopril increased the risk

Table 2. Major Clinical Trials of Various ARBs for the Treatment of CHF

Drug and dosage	NYHA classification	Clinical trial	End effect	Ref.
Losartan (50 mg/day) or captopril (50 t.i.d)	Class II-IV with EF≤ 40% age ≥65 yr	ELITE (losartan vs. captopril)	Decrease in all cause mortality with losartan (4.8% vs. 8.7% with captopril) with fewer adverse effects	58
Losartan (50 mg/day) or captopril (50 t.i.d)	Class II-IV EF≤ 40% age ≥60 yr	ELITE II (losartan vs. captopril)	Losartan was well tolerated without any difference in all-cause mortality, sudden death or resuscitated arrests as compared to captopril	59
Valsartan (160 mg b.i.d)	Class II-IV	Val-HeFT (valsartan with conventional CHF therapy vs. placebo))	Reduction in mortality and morbidity as well as improve clinical signs and symptoms of CHF. Combination with ACE inhibitor and β-blocker causes adverse effects	60
Candesartan (32 mg/day)	Class II-IV with EF≥ 40% with preserved LV function	CHARM-preserved (candesartan with conventional CHF therapy vs. placebo)	Reduced hospitalization without any difference in cardiovascular deaths	61
Candesartan (32 mg/day)	Class II-IV with EF≤ 40% intolerant to ACE inhibitors	CHARM-alternative (candesartan vs. placebo)	Well tolerated with decreased cardiovascular mortality and morbidity as compared to placebo	62
Candesartan (32 mg/day)	Class II-IV with EF≤ 40%	CHARM-added candesartan with ACE inhibitors and conventional CHF therapy vs. placebo)	Reduced hospitalization and cardiovascular events.	63

NYHA: New York Heart Association; ELITE: Evaluation of Losartan in the Elderly Study; Val-HeFT: Valsartan Heart Failure Trial; CHARM: Candesartan in Heart Failure-Assessment of Reduction in Morbidity and Mortality.

for adverse events without any improvement in survival [66]. Even with monotherapy, hypotension and renal dysfunction were common with valsartan treated patients and dry cough, rash and taste disturbance were more common side effects in captopril treated patients. In contrast, the RESOLVD (Randomized Evaluation of Strategies for Left ventricle Dysfunction) Pilot Study showed that candesartan alone was as safe, effective and tolerable as enalapril and combination of candesartan and enalapril was more efficacious than candesartan or enalapril monotherapy for preventing ventricular remodeling in CHF patients [67]. Differences in the dose and type of ARB as well as differences in the patient populations may be the reason for these inconsistent effects. It should be noted that the VALIANT trial employed high doses of captopril (50 mg t.i.d) and valsartan (160 mg b.i.d) in combination whereas RESOLVD used relatively low doses of candesartan (4 or 8 mg daily) plus enalapril (10 mg b. i. d.) [66, 67]. In addition, the VALIANT trial looked at the use of ACE inhibitors and ARBs after an acute MI, complicated by CHF, left ventricular dysfunction, or both.

Losartan is different from other ARBs as it is metabolized *in vivo* by oxidation in the liver through cytochrome P450 (CYP)2C9 to form its active metabolite EXP 3174 [68-70]. Isolated human liver microsomal studies have shown that *in vitro* losartan is metabolized to EXP 3174 via two CYP isoforms: CYP2C9 and CYP3A4 [71]. Losartan is not considered as a classic pro-drug as it is only 10-fold less active than its metabolite and only 14% of the drug is converted to EXP 3174 [69]. Candesartan cilexetil is a pro-drug and is hydrolyzed to candesartan and its inactive metabolite CV-15959 in the small intestinal wall [57]. Irbesartan is mainly metabolized through CYP2C9 to its inactive metabolite and is eliminated through the bile. All other ARBs are mainly eliminated through the kidneys; therefore dosage adjustment is needed in patients with renal impairment [57]. However, dosage adjustment for losartan is needed in patients with hepatic impairment. An approximate 50% reduction in losartan dose is recommended in patients with mild to moderate liver cirrhosis [35, 72]. The oral bioavailability of these agents is not affected by food, therefore these drugs can be taken with or without meals [57].

ARBs vary in their ability to bind to Ang II type 1 receptors. Studies in isolated rabbit aorta have shown that Ang II-induced contractions are inhibited competitively by losartan indicating that losartan is a competitive antagonist, whereas candesartan blocked the contractions in an insurmountable manner [56, 73]. EXP 3174, valsartan and irbesartan have intermediate receptor antagonism properties as they block the Ang-II induced aortic contractions in a manner intermediate between competitive and insurmountable antagonism [56]. Candesartan cilexetil, has the highest affinity for AT_1 receptors [74]. Binding studies in the rabbit aorta have shown that candesartan had 80 and 10 times higher affinity for AT_1 receptors than losartan and EXP 3174, respectively [74]. In addition, candesartan has a half life of 9 hr as compared to losartan (2 hr) and EXP 3147 (4-6 hours) [75]. Valsartan has a 80-100 times greater AT_1 receptor affinity as compared to losartan [76]. However, the clinical significance of these differences in the mechanism of action of these agents needs further investigation.

2.3. Aldosterone Receptor Antagonists

Aldosterone is not only released by high levels of Ang II in CHF patients, other stimulants such as increased K^+ levels, reduced Na^+ levels, low fluid levels and blood volume, high plasma corticotrophin as well as circulating catecholamines, endothelins, arginine and vasopressin play an important role in its excretion [77]. Long term treatment with ACE inhibitors and AngII receptor blockers may not suppress the production of aldosterone [78, 79]. In severe hypertensive patients, treatment with the ACE inhibitor captopril caused an initial decrease in plasma concentration of aldosterone (74 to 21 pg/ml) [80]. However, after one year of treatment with captopril a significant increase in plasma concentration of aldosterone (163 pg/ml) was observed [80]. Similarly, *aldosterone escape* of RAAS blockade was observed in patients with acute MI [81]. In addition, in 40% of heart failure patients > 144 pg/ml plasma aldosterone concentration was observed after long term treatment with ACE inhibitors [54]. Reduced hepatic perfusion in CHF patients with attenuated clearance of aldosterone from hepatic venous plasma seemed to be the major reason for such an increase [82].

Increased levels of aldosterone have been known to cause Na^+ and water retention as well as K^+ excretion and this results in an increase in blood pressure and kidney perfusion in hypo-perfused kidneys [83]. However, in CHF patients where the myocardium is already compromised, the heart has to pump against a stronger afterload and preload which can aggregate the damage on the ailing myocardium [83]. Increased levels of aldosterone in patients with CHF have been shown to promote magnesium loss, endothelial dysfunction, peripheral and interstitial fibrosis as well as blunting the baroreflex response [78]. In addition, aldosterone decreases the

uptake of norepineprine from neurons and hence accelerates the probability of cardiac arrhythmias in CHF patients [78].

The various clinical trials [84, 85] showing cardioprotective effects of aldosterone receptor blockers (spironolactone and eplerenone) are provided in Table **3** and their structures are shown in Fig. (**3**). The data from RALES (Randomised Aldactone Evaluation Study) indicated that the reduction in mortality by spironolactone was linked with the reduction of fibrosis, in addition to its diuresis effects [84]. In addition, reduction in reentry arrthymias was the reason for attenuated percentage of sudden cardiac death in the spironolactone treated group [84]. In a sub-study of RALES, spironolactone has been shown to reduce the serum markers of extracellular matrix turnover, PIIINP (procollagen type III amino terminal peptide) [86]. Although significant reduction in mortality was observed in CHF patients with sprinolactone, which is a competitive inhibitor of mineralocorticoid receptors, the nonspecific anti-androgenic and progestrogenic effects blunted its long term use in CHF patients. In this context, 10% of men in the spironolactone group (RALES trial) suffered from gynaecomastia or breast pain [84]. These endocrine side effects of spironolactone lead to high rate of discontinuation of treatment in the spironolactone group as compared to placebo [84]. A newer selective antagonist of the aldosterone receptor, eplerenone, has not shown these endocrine adverse effects as it has a 500-fold lower affinity for androgenic and progesterone receptors [87]. The presence of 9, 11-epoxy in the lactone ring and 7α–ester substitution is mainly responsible for the selectivity of eplerenone for mineralocorticoid receptors [88]. Eplrenone has been approved by the FDA for the treatment of CHF patients following an acute MI [83].

Spironolactone is metabolized quickly in the liver without any unchanged drug in the urine [89]. The concomitant intake of food increases its bioavailability by improving the drugs dissolution and absorption as well as decreasing the first pass metabolism [90-92]. Pharmacokinetic studies demonstrated that the dethioacetylated derivative, canrenone, is the major metabolite of spironolactone [89]. However, 7α-thiomethylspironolactone (7α-TMS) is mainly responsible for the pharmacodynamic action of spironolactone [90]. 7α-TMS is also responsible for the endocrine side effects of spironolactone [88]. Eplerenone is mainly metabolized by CYP 3A4 with an elimination $t_{1/2}$ of 4-6 hrs [93]. Eplerenone has no active metabolite; however two inactive metabolites 6-β hydroxy eplerenone and an open lactone ring form of eplerenone have been observed in human mineralocorticoid studies [94]. 6-β hydroxy eplerenone, 6-β 21-hydroxy eplerenone, 21-hydroxy eplerenone and 2β, 3β, 21-hydroxy eplerenone have been observed in urine and feaces after oral eplerenone treatment [95].

One major problem with aldosterone receptor antagonists is the risk of hyperkalemia (increased serum K^+ levels), which is more common with eplerenone as observed in the EPHESUS trial [85] as compared to spironolactone in CHF patients [84]. Hypokalemia and hyperkalemia occur in succession during the development of CHF. Hypokalemia occurs in the early stages of HF development when renal function is intact, whereas hyperkalemia occurs in the later decompensated stages with progressive loss of renal function [96]. ACE inhibitors and Ang II receptor blockers affect the renal clearance of K^+ [97, 98]. Therefore, serum K^+ levels should be monitored when adding aldosterone receptor antagonists to ACE inhibitors or Ang II receptor blockers depending upon the stage of HF.

3. β-BLOCKERS FOR THE TREATMENT OF CHF

Binding of catecholamines to β-adrenoceptors (β-AR) triggers the activation of G_s protein-adenylyl cyclase-cAMP-protein kinase pathway leading to an increase in cardiac contractile force [99]. Varying degrees of defects in the β-AR signal transduction pathway comprising downregulation of β_1-ARs, decreased adenylyl cyclase activity, uncoupling of β_2-ARs, increase in inhibitory $G_{i\alpha}$-proteins and upregulation of G-protein coupled receptor kinases (GRK2) seem to be responsible for the depression in contractile function due to reduction in inotropic response to adrenergic stimulation in different types and stages of HF [100, 101]. β-Blockers were once contraindicated for the treatment of CHF based on the theoretical rationale that inhibition of sympathetic stimulation, a vital component of circulatory function, may further depress the cardiac contractility and aggravate the signs of CHF [102]. It is now recognized that activation of the sympathetic nervous system during the early stages of HF development is important to maintain the heart function. However, with the progression of the disease increased sympathetic drive causes cardiotoxic effects via cardiac and subcellular remodeling with LV dysfunction, cardiomyocyte death, defects in Ca^{2+}-cycling proteins and attenuated contractility [103, 104]. This *adrenergic hypothesis* leads to the use of β-blockers in the treatment of CHF under experimental and clinical settings.

β-blockers can be classified on the basis of their selectivity for β_1- and β_2-ARs. The first generation β-AR blockers (propranolol as a prototype) are non-selective for β_1- and β_2-ARs and have similar affinity for β_1- and β_2. The second generation agents are selective β_1-AR blockers with higher affinity for β_1-AR ($\beta_1 >> \beta_2$) (metoprolol, and bisoprolol) whereas third generation β-blockers have mixed α_1 and β_1 β_2 antagonist effect ($\beta_1 = \beta_2$) (carvedilol and bucindolol) [105]. The structures of these agents are shown in Fig. (**3**). The first generation agents are contraindicated for the treatment of CHF as they increase systemic vascular resistance and reduce cardiac index (ratio of cardiac output to body surface area) with an initial negative inotropic effect [106]. Clinical trials [107-110] have shown that β-AR blockers (long acting metoprolol, bisoprolol and carvedilol) decrease the all cause mortality in CHF patients (Table **4**). It is noted that β-AR blocker therapy should be started as a low dose with stepping slowly towards the target dose to avoid serious pulmonary and peripheral side effects with signs of decompensation in CHF patients [111]. Although the specific mechanism of action of different β-blockers is not completely understood, reduction of sympathetic activity with decrease in heart rate, increase in myocardial diastolic filling with effective coronary perfusion, reduction in energy expenditure of the compromised myocardium by reducing after-load and wall stress as well as improvement of EF seems to be responsible for the cardioprotection [51, 111]. In addition, β-blockers have anti-ischemic effects and they attenuate the degree of cardiac remodeling [104] and the frequency of supraventricular and ventricular arrhythmias [112]. β-blockers have also been shown to act synergistically with ACE inhibitors as they prevent the conversion of prorenin to renin [113] and thus suppress the RAAS system in CHF patients [114]. Ancillary properties (vasodilation, antioxidant, anti-proliferative effects) of some β-AR blockers (e.g. carvedilol) in addition to its anti-adrenergic effect, have an additional benefit in CHF patients [115]. Cardvedilol seemed to be superior to metoprolol tartarate as observed in COMET (Carvedilol or Metoprolol European Trial) [116]. This trial compared the effects of carvedilol (target dose 50 mg/day) with metoprolol tartarate (target dose 100 mg/day) in CHF patients (NYHA: New York Heart Association Class II-IV, EF<35%) already taking ACE inhibitors and diuretics. All cause mortality: carvedilol 33.9% vs. metoprolol 39.5% group, annual mortality rate: carvedilol 8.35% vs. metoprolol 10% and the degree of sudden cardiac death carvedilol 14% vs. metoprolol 17% were observed in all CHF groups [116]. Recently a newer third generation selective β_1 blocker, nebivolol, with vasodilating effect through the L-arginine/nitric oxide pathway, showed a potential benefit in older patients with CHF [117]. The results of SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) showed that nebivolol (target dose 10 mg/day) caused a 38% decrease in overall cause of mortality with a significant reduction in hospitalization [118]. The cardioprotective effects of β-AR blockers are not consistent throughout the class. In this context, bucindolol, a third generation agent, did not show a significant reduction in mortality in NYHA class III or IV patients in the β-blocker Evaluation

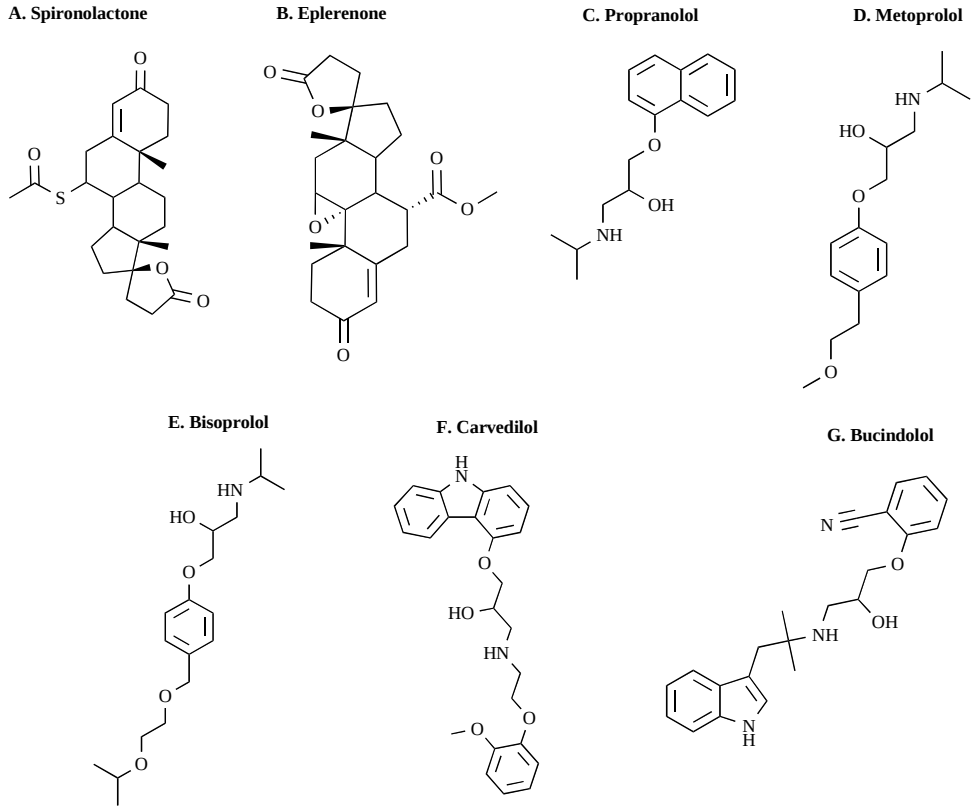

Fig. (3). Chemical structures of different aldosterone receptor antagonists spironolactone (A) and eplerenone (B) and β-blockers propranolol (C), metoprolol (D), bisoprolol (E), carvedilol (F) and bucindolol (G).

Table 3 Major Clinical Trials of Various Aldosterone Receptor Antagonists for the Treatment of CHF

Drug and dosage	NYHA classification	Clinical trial	End effect	Ref.
Spironolactone (25 mg/day)	Class II-IV with EF≤ 35%	RALES (spironolactone with loop diuretic, ACE inhibitor (if tolerated) and β-blocker vs. placebo)	30% reduction in all cause mortality and 32% lower risk of sudden cardiac death with spironolactone	84
Eplerenone (50 mg/day)	-Class II-IV EF≤ 40% -Acute phase of MI	EPHESUS (elperenone with ACE inhibitor or AT_1 receptor blocker or β-blocker vs. placebo)	13% reduction in all cause mortality and 17% reduction in sudden cardiac death with reduced hospitalization	85

NYHA: New York Heart Association ; RALES: Randomized Aldactone Evaluation Study Investigators; EPHESUS: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators

Table 4. Major Clinical Trials of Various β-Adrenoceptor Blockers for the Treatment of CHF

Drug and dosage	NYHA classification	Clinical trial	End effect	Ref.
Metoprolol (starting dose 12.5 or 25 mg/day with target dose 200 mg/day). Dose titration period 1-8 weeks	Class II-IV with EF≤ 40%	MERIT-HF (metoprolol with ACE inhibitor, diuretic and digoxin (optional) vs. placebo)	38% reduction in all cause mortality, 41% decrease in sudden cardiac death and 49% reduction in death due to worsening heart failure)	107
Bisoprolol (starting dose 1.25 mg/day with target dose 10 mg/day). Dose titration period 1-15 weeks	Class III-IV EF≤ 35%	CIBIS-II (bisoprolol with ACE inhibitor, diuretic and digoxin (optional) vs. placebo)	34% reduction in all cause mortality, all cause hospital admission (440 vs. 513 placebo), 44% reduction in sudden cardiac death and 26% reduction in death due to worsening heart failure	108
Carvedilol (6.25 mg/b.i.d with target dose 25-50 mg/b.i.d). Dose titration period	Class II and III EF≤ 35%	U.S. Carvedilol HF Study Group (carvedilol with ACE inhibitor, diuretic and digoxin (optional) vs. placebo)	65% reduction in all cause mortality 27% reduction in rate of hospitalization for cardiovascular reasons and 38% reduction of combined risk of hospitalization or death	109
Carvedilol (target dose 25 mg b.i.d)	Class II and III EF≤ 25%	COPERNICUS (carvedilol with ACE inhibitor, diuretic and digoxin (optional) vs. placebo)	35% reduction in all cause mortality	110

NYHA: New York Heart Association; MERIT-HF: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; CIBIS-II: The Cardiac Insufficiency Bisoprolol Study II ; COPERNICUS: The Carvedilol Prospective Randomized Cumulative Survival.

of Survival Trial (BEST) [119]. Heterogeneity in patient populations and the presence of intrinsic sympathomimetic activity (ISA) of bucindolol, which is known to increase cAMP with damaging effects on the myocardium, seemed to be responsible for the detrimental effect [119]. Similarly, xamoterol, a β_1-selective partial agonist with β_1-AR antagonistic effect at high sympathetic tone and a 45% ISA, was reported to be associated with increased sudden cardiac and overall mortality in CHF patients (NYHA class III-IV) (The Xamoterol in Severe Heart Failure Study Group) [120]. It should be noted that β-AR blocker therapy is contraindicated in patients with symptomatic bradycardia or hypotension, acute pulmonary edema, severe pulmonary congestion and severe generalized edema [121].

All β-blockers used in major clinical trials such as metoprolol (lipophilic), bisoprolol (moderately lipophilic) and carvedilol (lipophilic) are administered as racemic mixtures containing R(+)- and S(-) enantiomers. S-bisoprolol has a 30-80 times higher β_1-blockade activity than R-bisoprolol [122]. Horikiri *et al.* [123] demonstrated that the plasma concentration of S-enantiomer was higher that the R-enantiomer and was dependent upon the *in vivo* metabolism by CYP2D6. *In vitro* metabolic studies using recombinant human CYP450 isoforms have indicated that CYP2D6 causes a steroselective metabolism of bisoproprol, whereas CYP3A4 mediated metabolism is not stereospecific [124]. Bisoprolol has a long elimination $t_{1/2}$ (9-12 hrs) and [±] 4-{[2-hydroxy-3-(isopropylamino)-propoxy] benzyloxy)}ethanol is the major metabolite of bisoprolol after *O*-deisopropylation [125].

The S-enantiomer of metoprolol is 30 times more potent than the R- enantiomer for its β_1-blockade properties [125]. Metoprolol has been shown to be metabolized by α-hydroxylation and *O*-dealkylation to α-hydroxymetoprolol, *O*-demethymetoprolol, N-dealklyl metoprolol and metoprolol acid [126]. The metabolism of metoprolol is highly affected by CYP2D6 polymorphism with carriers of CYP2D6 variants encoding for poor metabolizes (PM), ultrafast metabolizers (UM) and extensive metabolizers (EM) [127, 128]. PMs have a 5-fold lower drug clearance than UMs and UMs have a 2-fold higher drug clearance than EMs. PMs seem to have higher risk of development of adverse effects [128, 129]. Significant pharmacokinetic and pharmacodynamic differences exist between immediate release metoprolol tartarate (duration of action 6-12 hr b.i.d or t.i.d) and extended release metoprolol succinate (once daily with 24 hr duration of action) [125].

The S- enantiomer of carvedilol has both α_1- and β-AR blockade properties with a similar affinity to α_1-AR like R- enantiomer but a 100-fold higher affinity for β-ARs than the R- enantiomer [130]. It is mainly metabolized by oxidation and glucuronidation into several active metabolites such as desmethyl carvedilol (M2), 4′-hydroxyphenyl-carvedilol (M4), 5′-hydroxyphenyl-carvedilol (M5), 1-hydroxycarbazolyl-carvedilol (M14) and 8-hydroxycarbazolyl-carvedilol (M16) [131]. It has sterospecific first pass metabolism with a 3-fold higher plasma concentration of R-carvedilol than S-carvedilol in healthy human volunteers [132]. Oral administration of carvedilol (6.25, 12.5, 25 and 50 mg) in CHF patients (NYHA class III-IV) caused a dose-proportional increase in steady state plasma concentration and its active metabolites [131]. Zhou and Wood showed that sterospecific metabolism of carvedilol in humans was highly dependent upon the phenotype of CYP2D6 [133]. In poor and extensive metabolizers of debrisoquin, an adrenergic neuron blocker exclusively metabolized by CYP2D6, the plasma concentration of R-carvedilol was higher than S- carvedilol indicating that clearance of R-carvedilol was significantly lower than S-carvedilol. In poor metabolizers a further decrease in clearance for R-carvedilol and metabolites of carvedilol (M4 and M5) was observed. On the other hand, clearance of S-carvedilol was not different between poor and extensive metabolizers [133]. Therefore, the determination of CYP2D6 phenotype is an important measure during the administration of β-blockers for the treatment for CHF to avoid serious side effects.

4. DIURETICS FOR THE TREATMENT OF CHF

In CHF patients, decreased cardiac output has been shown to cause the activation of sympathetic nervous system, RAAS and non-osmotic release of arginine vasopressin, which leads to decrease in renal flow and Na^+ secretion as a compensatory response [134]. The resulting retention of Na^+ and water results in an expansion of extracellular fluid volume and consequently pulmonary congestion and peripheral edema [135]. The therapeutic goal of diuretic therapy in CHF is to reduce and eventually eliminate the symptoms of fluid retention and hence prevent the progression of disease [136, 137]. In addition, diuretics also cause decrease in pulmonary wedge pressure, preload and arterial resistance [138]. According to American Heart Association (AHA) Task Force and European Society of Cardiology guidelines, diuretics should always be administered in conjunction with ACE inhibitors and β-blockers for symptomatic treatment of CHF [139, 140].

Depending upon their site of action, diuretics can be classified into 5 categories: carbonic anhydrase inhibitors (acetazomide), osmotic diuretics (mannitol), loop diuretics (furosemide, bumetanide, torsemide and ethacrynic acid), thiazide diuretics (hydroclorthiazide and metazole) and K^+-sparing diuretics (spironolactone) [141]. The structures of prototype agents are shown in Fig. (**4**). The phamacodynamic and pharmacokinetic properties of spironolactone have been previously discussed in the section of aldosterone receptor antagonists. Acetazolamide inhibits carbonic anhydrase and blocks the formation of H^+ and HCO_3^- from CO_2 and H_2O which results in $NaHCO_3$ excretion into the urine [141]. Indirectly, it also blocks the Na^+-H^+ exchanger in the renal proximal convulated tubule by decreasing the conversion of intracellular CO_2 and H_2O into bicarbonate and H^+ which is needed for the Na^+-H^+ exchanger to reabsorb sodium and H_2O back from the tubule lumen [141, 142]. Mannitol exerts an osmotic effect and impairs the ability of proximal tubule and thick ascending limb to reabsorb Na^+ and H_2O [141, 142]. The most commonly used diuretics used for the treatment of CHF are loop diuretics which act on the ascending limb of loop of Henle and inhibit Na^+-K^+-$2Cl^-$ symporter [143]. This portion of loop of Henle is responsible for 25% of Na^+-reabsorption and thus inhibiting the transport at this site results in greater degree of diuresis [144]. Loop diuretics act on the luminal surface of the epithelial cells and they reach there via urine through active secretion [141]. In CHF patients with renal impairment, a reduction of secretion of loop diuretics has been observed. Accumulation of organic anions, which compete with loop diuretics at their site of action and prevent the reabsorption of Na^+, Cl^- and K^+, seem to be the major reason for such an effect in CHF patients [145]. Furosemide, a short acting loop diuretic, causes natriuresis as long as it can block the Na^+-K^+-$2Cl^-$ symporter; however, it gets metabolized quickly from the body and *post-diuretic salt retention* occurs during the diuretic free period [146]. High concentrations of furosemide are needed to overcome this competitive inhibition in CHF patients with renal insufficiency. Nevertheless, higher doses can increase the chances of serious side effects such as ototoxicity and hypokalemia with furosemide [147]. In addition, chronic administration of loop diuretics causes *diuretic resistance*, which results in reduced natriuresis [145]. High concentrations of loop diuretics expose the cells of distal convoluted tubule (DCT) to increased levels of Na^+ by inhibiting the reabsorption of Na^+ at the ascending limb of the loop of Henle, which causes adaptative changes (increased hypertrophy and hyperplasia) in DCT epithelial cells. This results in increased reabsorption of Na^+ from DCT and thus blunts the natriuretic effect of loop diuretics [148, 149]. Combination of thiazide diuretics with low doses of loop diuretics have been shown to be effective in preventing *diuretic resistance* in patients with severe CHF [150]. Some caution must be exercised in CHF patients when giving combina-

tions of diuretics as they can cause severe loss of K^+ and Mg^{2+}. Frequent monitoring of electrolyte levels as well as adding a K^+-sparing diuretic (spironolactone) to the drug regime may be required.

Although loop diuretics are used interchangeably in different treatment regimens, a significant difference exists in their pharmacokinetic properties. Up to 80% of bumetanide is excreted unchanged in the urine and rest undergoes hydroxylation and glucuronization [151]. Similarly, 20% of furosemide undergoes phase II metabolism via glucuronidation and the rest is excreted unchanged in the urine [151]. Furosemide acyl glucuronide is responsible for the diuretic action of furosemide [152]. Pharmacokinetics of furosemide rely more on kidney function unlike torsemide and bumetanide, which rely more on hepatic clearance [153]. Torsemide has 80% bioavailability (approximately double than that of furosemide 26-65%) with minimal first pass effect [153] and undergoes extensive hepatic metabolism to different metabolites such as M1, M3 and M5 [154]. M1 and M3 are formed by hydroxylation of methyl groups of phenyl ring and phenyl ring of torsemide, respectively. M5, a carboxylic acid derivative, is formed after metabolism of M1 [154]. Experimental studies have demonstrated that M3 is equipotent to parent molecule, whereas M1 is 10% active and M5 is inactive; 20% of torsemide is eliminated unchanged in the urine [155]. Vormfelde *et al*. have shown that *in vivo* biotransformation of torsemide and its metabolites M1 and M3 is dependent on CYP2C9*3 polymorphism [156]. On the other hand, the carboxylation metabolite (M5) clearance was independent of any variation in the CYP2C*3 allele [157].

5. CARDIAC GLYCOSIDES FOR THE TREATMENT OF CHF

Cardiac glycosides are divided on the basis of their sources: digitalis from the leaves of *Digitalis purpurea*, digitoxin, and digoxin from the leaves of *Digitalis lanata*, strophanthin-K from the seeds of *Strophanthus kombe* and strophanthin-G (ouabain) is obtained from the seeds of *Strophanthus gratus* [158]. Digitalis is applied as a collective term and is defined as a prototype for cardiac glycosides. Digitalis in the form of digoxin is the most commonly used cardiac glycoside for the treatment of CHF specifically in patients with atrial fibrillation [159]. The structure of digoxin is provided in Fig. (**4**). Digoxin is known as a positive inotropic agent which inhibits Na^+-K^+ ATPase and increases cardiac contractility via activation of Na^+-Ca^{2+} exchanger with subsequent accumulation of intracellular Ca^{2+} [160]. However, the beneficial effect of digoxin in CHF is mainly mediated by neurohormonal modulation at low doses of digoxin (<0.25 mg/day) in contrast to inotropic effect at high doses (>0.25 mg/day) [161]. Digoxin increases the vagotonic response by inhibiting Na^+-K^+ ATPase in the vagal afferent fibers and causes a reduction in sympathetic activity [162]. In addition, digoxin suppresses the release of renin from the kidneys and decreases tubular reabsorption of Na^+ [163]. The combination of carvedilol (a mixed α_1 and β_1 β_2 antagonist) and digoxin seems more advantageous than either carvedilol or digoxin alone for the treatment of atrial fibrillation in CHF patients (mean EF<40%) [164]. Two major short-term randomized clinical trials, the Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) [165] and the Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme (RADIANCE) [166] trials, assessed the effect of digoxin withdrawal in mild to moderate (NYHA II-III) HF patients in sinus rhythm. PROVED compared HF patients treated with digoxin and diuretics vs. diuretics alone and RADIANCE compared the effect of digoxin, diuretics and ACE inhibitors vs. diuretics and ACE inhibitors alone. These trials demonstrated that digoxin withdrawal from the standard therapy resulted in higher risk of worsening of HF with a deterioration of functional capacity of the myocardium [165, 166]. The long-term benefit of digoxin (in combination with diuretics and ACE inhibitors) in CHF patients (NYHA class III-IV) was observed in the Digitalis Investigation Group (DIG) trial [167].

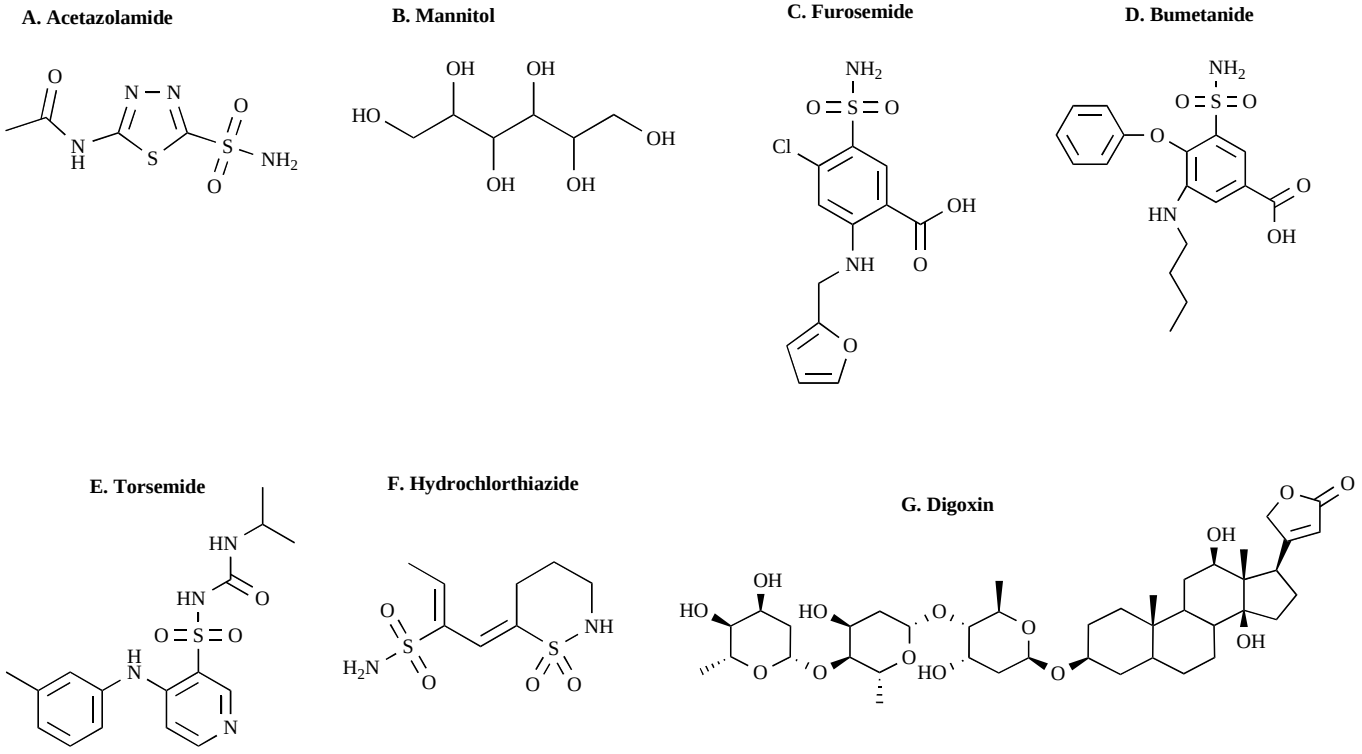

Fig. (4). Chemical structures of different classes of diuretics acetazolamide (A), mannitol (B), furosemide (C), bumetanide (D), torsemide (E) and hydrochlorthiazide (F) and digitalis glycosides (digoxin) (G).

Although digoxin addition to conventional therapy did not reduce overall mortality, a significant reduction in the rate of hospitalization and less worsening of HF was observed [167]. In the DIG trial the average dose of digoxin was 0.25 mg/day and digoxin toxicity (11.9% vs. 7.9%) was observed in treated groups [167]. On the other hand, in PROVED and RADIANCE, relatively high doses of digoxin (0.375 mg/day and 0.370mg/day, respectively) were used and only one episode of digoxin toxicity was observed in RADIANCE with no significant toxicity in PROVED [165, 166]. The long term vs. short term duration of therapy in these trials seem to be the major reason for such discrepancies.

CHF patients are at higher risk of developing digoxin toxicity which is shown to be associated with ventricular tachycardia or fibrillation, second-or-third degree atrioventricular block as well as supraventricular arrhythmias [167, 168]. Diuretic-induced hypokaelemia increases the sensitivity of Na^+-K^+ ATPase to digoxin and may lead to toxicity in CHF patients [169]. A post-hoc subgroup analysis of the DIG trial showed sex based differences in the effects of digoxin and revealed that digoxin treatment was associated with a higher rate of death in women as compared to men [170]. It was suggested that digitalis toxicity was the major reason for the higher rate of death in women in the DIG trial [171]. Serum digoxin concentrations (SDC) from 0.5-1.5 ng/ml are recommended in HF patients without any toxicity [172]. Although little relationship has been observed between SDC and its therapeutic effects in different clinical trials [169], routine measurement of SDC during HF therapy is an important aspect to consider. Young *et al.* [173] have suggested that *"triple therapy"* with digoxin, diuretics and ACE inhibitors should be considered as the first choice for the initial management of patients with symptomatic heart failure due to systolic dysfunction. However, Dhaliwal *et al*. [174] have shown that addition of digoxin to concomitant ACE inhibitors and β-blocker therapy did not decrease the hospitalization rates and mortality in CHF patients with systolic dysfunction and atrial fibrillation. Nevertheless, the ACC/AHA 2005 guidelines recommended that digoxin should be used as a first line drug in CHF patients with atrial fibrillation and as a second line drug after diuretics, ACE inhibitors and β-blockers in CHF patients with in sinus rhythm [139, 159].

Digoxin is mainly metabolized in the liver into several metabolites via hydrolysis, oxidation, epimerization and conjugation. The mono-digitoxoside and bis-digitoxoside and metabolites are considered to be cardioactive, whereas 3-keto and 3-α (epi) digoxigenin are considered to be less cardioactive than digoxin [175]. In approximately 10% of patients taking digoxin other cardioinactive metabolites known as digoxin reduction products (DRPs) such as dihydrodigoxin and dihydrodigoxigenin result from the metabolism of digoxin by gastrointestinal bacteria [176]. Digoxin is primarily eliminated via the kidney (70%) and the rest via bile with an elimination $t_{1/2}$ of 36 to 48 hrs and 3.5 to 5 days in patients with impaired renal function. Therefore determination of creatinine clearance in CHF patients with renal dysfunction is mandatory [171]. P-glycoprotein, a xenobiotic transport protein localized in liver, pancreas, kidney, colon and jejunum, plays an important role in the pharmacokinetics of digoxin [177]. Digoxin is actively transported via P-glycoproteins and agents that inhibit the activity of P-glycoproteins (e.g. antiarrhythmic drugs like amiodarone) increase the SDC [178]. Therefore, some caution must be exercised while using P-glycoprotein inhibitors in combination with digoxin to avoid the risk of digoxin toxicity.

6. STATUS OF OTHER PHARMACOLOGICAL AGENTS IN THE TREATMENT OF CHF

Other agents such as nitro vasodilators (combination of isosorbide dinitrate and hydralazine) have shown some beneficial effects on survival of CHF patients [Vasodilator-Heart failure Trial I (V-HeFT I)] [179], this combination was not superior to the treatment of an ACE inhibitor ([Vasodilator-Heart failure Trial I (V-HeFT I)] [180]. Similarly, the results of Outcomes of a Prospective Trial of Intavenous Milrinone for exacerbations of Chronic Heart Failure (OPTIME-CHF) have reported an increase in the incidence of sustained hypotension and mortality with milrinone, a phosphodiesterase III inhibitor with vasodilator and positive inotropic properties [181]. A new class of positive inotropic agents, the Ca^{2+}-sensitizers (levosimendan and pimobendan), have shown some hemodynamic and symptomatic improvement in CHF patients [182, 183]; however their effect on long-term mortality in CHF is controversial and may even increase the incidences of atrial fibrillation [182]. Other pharmacological agents such as endothelin receptor antagonists, cytokine antagonists and vasopeptidase inhibitors have shown beneficial effects on altering cardiac remodeling and symptomatic improvement during the development of HF in experimental studies [184, 185]. Large scale trials with clinical endpoints are needed to establish their status for the treatment of CHF.

7. CONCLUSIONS AND FUTURE DIRECTIONS

On the basis of current available clinical data, ACE inhibitors, AT_1 receptor antagonists, β-blockers, diuretics and digoxin form the basis of therapeutic recommendations of CHF patients at different stages of development of the disease [139, 140]. Since the changes in myocardial structure and function can occur silently after the initial acute insult before the development of CHF [11], the time frame of drug administration which can lead to attenuation of the disease process stays questionable. In fact, mortality due to CHF is quite high with impaired quality of life [2]. Identification of the stage and the underlying reason of HF, genetic polymorphism and the rate of drug metabolism, which determines the individual responsiveness to a particular drug regimen, must be taken into consideration when recommending a particular therapy. Careful titration of drug dose and a rational analysis of biotransformation of a particular drug are needed to optimize the CHF therapy with minimal adverse drug effects.

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