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Comparative Pharmacological Effects of LCZ696 and Captopril in Hypertension

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Abstract. Hypertension, a global health concern, necessitates effective pharmacological interventions. This study compares the pharmacological profiles of LCZ696, a dual angiotensin receptor-neprilysin inhibitor (ARNi), as well as captopril (an ACE inhibitor) in hypertension management. LCZ696 combines valsartan with AHU377, demonstrating better blood pressure reduction than valsartan monotherapy, attributed to RAAS blockade and natriuretic peptide enhancement. Captopril, via ACE inhibition, reduces angiotensin II but is limited by adverse effects like cough and hyperkalemia. While LCZ696 offers broader hemodynamic benefits, captopril remains cost-effective for specific populations. This work highlights the importance of personalized therapy, balancing efficacy and safety, and underscore LCZ696's potential as a next-generation antihypertensive agent.

Keywords: Hypertension, LCZ696, captopril, RAASs

1. Introduction

1.1. The definition of hypertension

Hypertension is both a distinct disease and a significant risk factor for other conditions. The international guidelines for management hypertension primarily adopt two approaches to define hypertension: either basing on the blood pressure (BP) threshold requiring treatment initiation, or determined by blood pressure cut-off level associated with elevated cardiovascular risk events. Current guidelines determine hypertension criteria based on blood pressure thresholds where the proven benefits of antihypertensive treatment surpass the treatment risks in interventional clinical trials. The threshold for defining hypertension based on this approach is 140/90 mmHg, consistent with standard clinical measurement methods [1]. Guidelines also emphasize ranges of hypertension severity by stratifying blood pressure level exceeding these thresholds into some tiers. Based on it, hypertension is defined into three stages, ranging from stage 1 to stage 3 hypertension (Table 1) [2,3].

Epidemiological studies demonstrate that the occurrence of cardiovascular incidents—including heart attack, stroke, heart failure, etc.—rises progressively with increasing blood pressure. This association follows an exponential trend and is more pronounced for systolic than diastolic pressure.

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Table 1. Classification and diagnostic criteria for hypertension

Stage	Systolic blood pressures(SBP) (mmHg)	Diastolic blood pressures(DBP) (mmHg)	Degree of Target Organ Damage
Normal blood pressure	<120	<80	/
Elevated blood pressure	120~139	80~89	/
Stage 1 hypertension	140~159	90~99	No organ damage
Stage 2 hypertension	160~179	100~109	Compensated organ injury
Stage 3 hypertension	≥180	≥110	Decompensated dysfunction of the injured organ

1.2. Global epidemiology

According to an analysis of 135 population-based studies encompassing 0.9 million adults, the worldwide age-standardized prevalence of hypertension in 2010 was approximated at 31.1% (95% confidence interval 30.0-32.2%). The finding showed a modestly higher rate among males (about 32%) compared to females (about 30%) [4]. When analyzed by national income levels, HICs exhibited a lower prevalence than LMICs (Table 2) [4]. Current evidence indicates that racial disparities in hypertension risk cannot be explained by genetic factors. Environmental exposures, sociodemographic characteristics, and behavioral patterns are more probable responsible for ethnic variations in mean blood pressure and hypertension prevalence [5]. Furthermore, multiple factors like obesity, high sodium intake, physical inactivity, and unhealthy dietary patterns—demonstrate consistent associations with elevated hypertension risk.

Table 2. General prevalence of hypertension in High-income countries (HICs) and Low and middle-income countries (LMICs) in 2010

Population	Men (Age-standardized prevalence %) (95% CIs)	Women (Age-standardized prevalence %) (95% CIs)
Global	31.9 (30.3–33.5)	30.1 (28.5–31.6)
HICs	31.6 (29.6–33.6)	25.3 (23.9–26.7)
LMICs	31.7 (29.7–33.6)	31.2 (29.3–33.1)

Hypertension is strongly linked to increased global incidence of cardiovascular disease. Data from 2015 demonstrated that SBP ≥115 mmHg contributed to about 10.7 million deaths from all causes accounting for 19.2% of all deaths. About 7.8 million deaths for 14.0% of all deaths were associated with SBP ≥140 mmHg. The most kinds of deaths that were related to SBP ≥115 mmHg, were included ischemic heart disease and hemorrhagic stroke and so on. When using the higher threshold (SBP≥140 mmHg), the corresponding mortality figures were 3.6 million and 1.4 million. Consistent with hypertension prevalence trends, there was a notable rise in blood pressure-related cardiovascular mortality between 1990 and 2015, particularly pronounced in LMICs [6].

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Randomized clinical trials showed that conventional antihypertensive regimens (including angiotensin receptor blockers, diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and calcium channel blockers) effectively reduce cardiovascular disease mortality. Meta-analyses show a positive correlation between the extent of BP reduction and the reduction of relative risk for both cardiovascular outcomes and all-cause death [7].

Scaling up coverage of blood pressure-lowering interventions to reduce associated incidence rate and mortality rate should constitute a worldwide public health priority.

1.3. Principles of antihypertensive agent therapy

The primary approach to managing hypertension involves pharmacological therapy combined with dietary sodium restriction. The primary goal of antihypertensive medication is to maintain blood pressure within a safe range, thereby preventing complications and reducing mortality risk. In clinical practice, most hypertensive patients requiring pharmacotherapy present with comorbidities such as hypercholesterolemia, obesity, or diabetes. For these individuals, treatment objectives extend beyond achieving blood pressure levels below 140/90 mmHg to include targeted management of concurrent conditions. Given the diverse mechanisms of action and patient-specific indications among antihypertensive drugs, individualized therapeutic regimens are essential.

• Targeted treatment principle: Due to variations in patients' age, underlying diseases, and tolerance levels, the selection of medications should consider complications and blood pressure values.

• Minimizing side effects principle: There are numerous medications available for the treatment of hypertension, each with distinct adverse reactions. Typically, hypertensive patients are treated with a combination of two or more drugs; however, the increased number of medications in combination therapy raises the risk of adverse reactions [8]. Therefore, patients should be instructed to promptly inform their physicians of any discomfort, and physicians—guided by pharmacists—should adjust the treatment regimen to minimize adverse drug effects.

1.4. The mechanism of primary hypertension

The fundamental factors determining arterial blood pressure (ABP) consist of two components: Cardiac output and vascular resistance. Cardiac output is primarily influenced by cardiac function, venous return, and blood volume, while peripheral resistance is associated with the constriction of arterioles. The regulation of arterial blood pressure occurs mainly through two mechanisms: neural regulation mediated by the sympathetic nervous system, and humoral regulation via the renin-angiotensin-aldosterone system (RAAS).

1.4.1. RAAS dysregulation

Current research consensus indicates that a significant proportion of hypertension cases result from dysfunction of the RAAS. To address this pathophysiological mechanism, regulating water-sodium metabolism serves as a crucial therapeutic target. Maintaining optimal water-sodium balance prevents relative hypervolemia, thereby contributing to blood pressure control. This principle forms a fundamental basis for clinical hypertension management [9].

Hepatic production of angiotensinogen, encoded by the AGT gene, initiates the RAAS [10]. Under renin's catalytic action, angiotensinogen is cleaved into angiotensin I (Ang I), which is later converted by angiotensin-converting enzyme (ACE) to angiotensin II (Ang II). Ang II binds to AT

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receptors, inducing vasoconstriction of arteriolar smooth muscle and elevating microcirculatory resistance, thereby increasing blood pressure (Figure 1). Besides, angiotensin II encourages aldosterone secretion from the adrenal cortex's zona glomerulosa, promoting renal sodium and water retention while enhancing potassium excretion—mechanisms that further exacerbate hypertension [11].Therefore, water-sodium retention is the direct causative factor of hypertension, while angiotensin II plays a crucial mediating role.

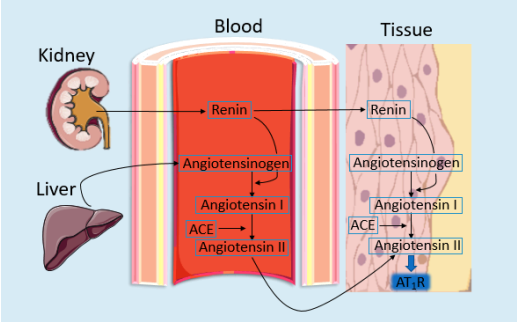

Figure 1. Mechanism of the renin-angiotensin-aldosterone system (RAAS)

1.4.2. Sympathetic nerve activity(SNA) contributions

The sympathetic nervous system regulates (ABP) through functional modulation of the vascular system, kidneys, and heart. Dysfunction in sympathetic activity is both a causative factor and a pathophysiological component in various cardiovascular diseases, including hypertension [12]. Manifestations of sympathetic overactivity in human hypertension include increased norepinephrine spillover, and an exaggerated blood pressure-lowering response following acute ganglionic blockade [13].

The pathogenesis of hypertension is predominantly linked to increased SNA. The regulation of SNA involves multiple brain nuclei, including the paraventricular nucleus (PVN), organum vasculosum of the lamina terminalis (OVLT), caudal ventrolateral medulla (CVLM), arcuate nucleus (Arc), subfornical organ (SFO), rostral ventrolateral medulla (RVLM), nucleus of the solitary tract (NTS), median preoptic nucleus (MnPO), and orexin neurons [14-16]. These nuclei constitute central sympathetic neural circuits via synaptic connections, collectively modulating blood pressure regulation and feedback control. The SFO and OVLT can sense angiotensin II, aldosterone, plasma osmolality, and certain cytokines, thereby activating the PVN-RVLM-SPGN pathway, which enhances SNA and increases blood pressure [17]. Elevated levels of insulin and leptin can be detected by the arcuate nucleus (Arc), leading to the activation of the PVN-RVLM-SPGN pathway [18]. The ARC can also directly activate the RVLM or SPGN, thereby enhancing SNA activity [19]. Carotid baroreceptors may activate the NTS, which in turn activates the CVLM. Once stimulated by upstream signals, the CVLM exerts inhibitory effects on the RVLM, leading to blood pressure reduction [20]. These sympathetic-related nuclei form intricate interactions, and dysfunction at any node within this feedback regulatory neural circuit may shift the homeostatic set point of blood pressure control—a potential mechanism underlying hypertension pathogenesis (Figure 2).

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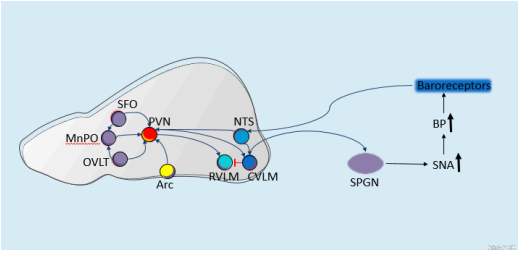

Figure 2. Mechanism of the sympathetic nerve activity (SNA)

1.5. Drugs used to treat the hypertension

Hypertension is commonly managed using various categories of antihypertensive drugs. Diuretics (e.g. thiazides like hydrochlorothiazide) reduce blood volume by promoting natriuresis. ACEIs (e.g. Enalapril) and angiotensin II receptor blockers (ARBs; e.g. losartan) modulate RAAS to induce vasodilation. Calcium channel blockers (CCBs; e.g. Nifedipine) inhibit vascular smooth muscle contraction, reducing peripheral resistance. Beta-blockers (e.g. Propranolol) decrease cardiac output via β-adrenergic receptor antagonism. This paper will conduct a comprehensive investigation into two representative antihypertensive drugs.

2. Entresto (LCZ696)

2.1. Chemical structure

Entresto (LCZ696) is an inhibitor targeting both angiotensin II receptor and neprilysin. This complex unimolecular compound consists of valsartan and AHU377 molecular moieties in a 1:1 stoichiometric ratio. With a molecular weight of 843.99 and molecular formula of $C_{48}H_{55}N_6O_8$, the structural configuration is depicted in Figure 3.

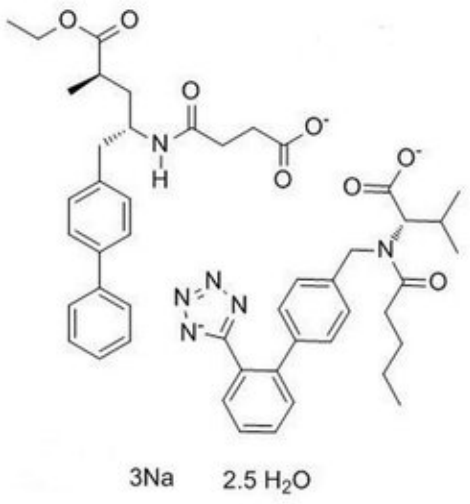

Figure 3. Structure of LCZ696

2.2. Pharmacology of LCZ696

As one of the primary active components of LCZ696, Angiotensin Receptor Blockers (ARBs) are currently recognized internationally as first-line antihypertensive medications. Sodium-water

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retention and activation of the RAAS are considered central factors in the pathogenesis of hypertension, with the latter being closely associated with both hypertension development and target organ damage. When the RAAS system is activated due to various causes, angiotensin II exerts multiple pathophysiological effects through binding to AT1 receptors, including promoting vascular smooth muscle contraction, stimulating aldosterone synthesis and exacerbating sodium-water retention, as well as inducing myocardial remodeling.

A trial was conducted to evaluate the effectiveness and safety of LCZ696 in Asian patients with hypertension. 364 Asian patients with hypertension randomly receive 100 mg, 200 mg, or 400 mg of LCZ696 or placebo for 8 weeks. Compared with the placebo group, patients receiving LCZ696 demonstrated significant reductions in diastolic blood pressure (7.84 mmHg, 7.29 mmHg, and 8.76 mmHg, respectively; $P < 0.0001$). Similarly, pulse pressure decreased by 4.01 mmHg, 5.4 mmHg, and 6.73 mmHg ($P < 0.001$). These findings indicate that one of the antihypertensive mechanisms of LCZ696 may involve the attenuation of sodium retention [21].

One of the active ingredients in LCZ696 is the angiotensin receptor antagonist valsartan. By inhibiting the AT_1 receptor, it blocks the harmful effects of Ang II mediated through AT_1 binding, thereby slowing the advancement of heart failure caused by activation of the RAAS. Additionally, due to the blockade of AT_1 receptors, the concentration of Ang II increases. The elevated Ang II binds to the AT_2 receptor, producing effects opposite to those of AT_1 activation, such as inhibiting cardiomyocyte growth, promoting cardiomyocyte differentiation, and enhancing nitric oxide synthesis [22]. In the randomized controlled trial, the antihypertensive efficacy of LCZ696 was comparison with valsartan monotherapy. The study enrolled about one thousand subjects ranging in age from 18 to 75 years with mild hypertension to moderate hypertension, who were designated to receive 100 mg, 200 mg, or 400 mg of LCZ696; 80 mg, 160 mg, or 320 mg of valsartan; 200 mg of AHU377; or placebo. Among them, 1,215 participants completed the trial. Results demonstrated that patients receiving LCZ696 exhibited substantially greater reduction in mean seated DBP in comparison to those receiving equivalent doses of valsartan. Notably, the blood pressure-lowering difference was more pronounced between LCZ696 compared to valsartan (Table 3). This trial confirmed that LCZ696 provides superior antihypertensive efficacy compared to equivalent doses of valsartan [23].

Table 3. Comparison of antihypertensive efficacy between LCZ696 and valsartan monotherapy

Dose (mg)	Additional reduction with LCZ696 (mmHg)	95% CI	p-value
Overall LCZ696 vs Valsartan	-2.17	-3.28 to -1.06	p<0.0001
200 mg LCZ696 vs 160 mg Valsartan	-2.97	-4.88 to -1.07	p=0.0023
400 mg LCZ696 vs 320 mg Valsartan	-2.70	-4.61 to -0.80	p=0.0055

3. Captopril

3.1. Chemical structure

Captopril, an ACEI, is a small-molecule compound whose chemical name is (2S)-1-[(2S)-2-methyl-3-sulfanyl-1-oxopropyl]-L-proline. It has a molecular weight of 217.29 and a molecular formula of $C_9H_{15}NO_3S$. The key structural features of captopril include a sulfhydryl (-SH) functional group, a proline-derived scaffold, and a stereogenic center (S-configuration). Its structural configuration is depicted in Figure 4.

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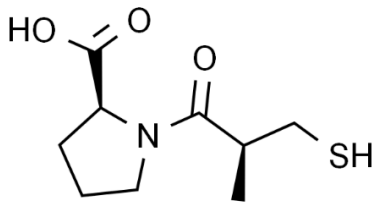

Figure 4. Structure of Captopril

3.2. Pharmacology of Captopril

Captopril is one of the earliest and most well-established ACEIs. Captopril exerts its antihypertensive effects primarily through inhibition of the RAAS [24]. As an ACEI, it competitively blocks the enzymatic conversion of Ang I to Ang II. This suppression results in reduced plasma angiotensin II levels, as well as vasodilation and decreased aldosterone secretion. Consequently, captopril reduces peripheral arterial resistance. Within the cardiovascular system, ACEIs diminish cardiac preload through vasodilation and natriuresis, while reducing afterload via inhibition of angiotensin II production, thereby improving cardiac output and lowering blood pressure [25]. Additionally, since ACE also catalyzes the degradation of bradykinin — a potent vasodilator — ACE inhibitors prolong bradykinin activity, which contributes to both therapeutic vasodilation and the characteristic bradykinin-mediated cough. Notably, among ACE inhibitors, only captopril and lisinopril are pharmacologically active without requiring metabolic activation, whereas other agents in this class necessitate biotransformation to achieve therapeutic efficacy.

Captopril is effectively absorbed when orally taken and reaches peak plasma levels about one hour after administration. Food intake significantly reduces its bioavailability, thus administration 1 hour before meals is advised. The drug has a distribution volume of 0.8 L/kg and demonstrates approximately 25%–30% plasma protein binding. It easily crosses the blood-brain barrier and undergoes metabolic conversion to captopril dimer disulfide and cysteine-captopril disulfide in vivo [26]. The primary excretion pathway is renal elimination, with an elimination half-life of about 2 hours.

Captopril, while typically well-tolerated, exhibits several potential adverse effects.

• Renal failure, urinary frequency nephrotic syndrome: Frequently observed with renal artery stenosis or nephrosclerosis dilatation of the efferent arterioles occurs, reduced renal perfusion pressure, and impaired renal function. These effects are often reversible upon discontinuation [27].

• Sulfhydryl group-related effects: May induce neutropenia/agranulocytosis with bone marrow depression and dysgeusia (reversible and typically self-limiting).

• Angioedema: Rare but serious; associated with bradykinin and its metabolites though definitive evidence remains lacking. May occur in any region, but epiglottis or larynx may cause respiratory obstruction. Immediate intubation is required if airway compromise occurs until edema resolves.

• Dry cough: A common adverse reaction and major reason for discontinuation, potentially due to pulmonary bradykinin accumulation.

• First-dose hypotension.

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• Hyperkalemia risk: ACE inhibitors may elevate serum potassium, particularly in renal impairment or diabetes with concomitant potassium-sparing diuretics. Fatal arrhythmias from hyperkalemia (e.g., cases combining ACE inhibitors with trimethoprim) have been reported [25].

4. Conclusion

The pharmacological profiles of LCZ696 and captopril demonstrate distinct mechanisms and clinical efficacies in hypertension management. LCZ696, as a ARNi, exhibits superior antihypertensive effects compared to valsartan monotherapy, attributed to synergistic RAAS inhibition and natriuretic peptide potentiation. This advantage is attributed to its synergistic RAAS inhibition and natriuretic peptides potentiation. In contrast, captopril, a classic ACE inhibitor, primarily targets angiotensin II suppression and bradykinin accumulation, though with a narrower therapeutic window and higher incidence of adverse effects (e.g., cough, hyperkalemia). While both drugs modulate RAAS, LCZ696's dual-target action offers enhanced hemodynamic benefits, particularly in reducing peripheral resistance and sodium retention. However, captopril remains relevant for its rapid onset and cost-effectiveness in specific populations. Ultimately, the choice of therapy should balance efficacy, safety, and patient-specific factors. Looking ahead, individualized treatment strategies and the development of next-generation agents may further improve hypertension management and outcomes.

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