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Recent advancement over traditional drug in the treatment of hypertension

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ABSTRACT

Hypertension is the most serious health problems and associated with many cardiovascular risks. Many combination therapies are prescribed for the management of hypertension. This prudent approach resulted in the overburden of medications associated with adverse effects and patient non-compliance. Exploration of the new potential targets led to the brain renin-angiotensin system (RAS) and vasopeptidase. Brain RAS inhibitor decreases arginine-vasopressin and decreasing sympathetic tone. Vasopeptidase inhibitors are the dual blockers of angiotensin-converting enzyme and prohibit the degradation of natriuretic peptidase by enzyme neuronal endopeptidase. Overall, this review gives a glimpse of new targets with recognizable clinical implications in lowering blood pressure.

Keywords— *Hypertension, Vasopeptidase inhibitors, Brain RAS inhibitors, Combination drugs*

1. INTRODUCTION

Hypertension (HT) is one of the most common non-communicable cardio vascular diseases responsible for the death and morbidity of a large number of the population worldwide. In common term, it is also known as High Blood Pressure. It may affect any group of people of any age of either sex, i.e. male or female. It may cause damage to a major organ of the body such as the heart, brain, kidneys, blood vessels and eyes.[1] There are various types of cardiovascular diseases which occur due to hypertension such as ischemia, cardiac arrest, atherosclerosis, Congestive Heart Failure (CHF). According to Global Health Observatory (GHO) data 2015, 1.13 billion people are affected by hypertension. In India, 25.8 % of people are affected by it which means 1 in every 3 people.[2] About 80 % of all Cardiovascular Death (CVD) occurs due to heart attack and stroke.[3] The researcher has found that there is a high dominance of hypertension in developing and African countries than those in developed countries like UK, USA, Canada and Korea.[4] According to data 2015, there are 597 million men and 527 million women being affected by hypertension. Out of total hypertension population, 200 million people are found in India. Croatia, Latvia, Lithuania, Hungry and Slovenia are the top 5 countries ranking with blood pressure while South Korea, USA, Canada, Peru and Singapore are least affected by the Hypertension[5]. With the development and advancement in science and technology, a large category of drugs is being introduced for the treatment and prevention of hypertension disease. Single-dose formulations are available for the treatment of hypertension and widely prescribed under different brand names[7-8] (Table 1). These types of drugs are generally used for the treatment and management of a normal raised blood pressure patient. Their mechanism of action is generally the inhibition of a single pathway for decreasing the raised blood pressure. Besides, fixed-dose combinations of drugs are also available in the market with differences in strength and composition. The fixed-dose combination drugs are used to increase the effectiveness of hypertension drugs through a different mechanism of action. The patients who become resistance with single dose administration of a particular category are allowed to take with a combination dose therapy. Combination therapy is a therapeutic treatment in which more than one drug is administered at the same time. Combination therapy drugs can simultaneously inhibit more than one pathway and become convenient for the patients. Because of the need and management for hypertension, there have been a large number of fixed-dose double and triple mixture drugs approved by US FDA.[9]

Table 1. List of antihypertensive drugs of various categories with their brand name

S. no.	Category	Name of a drug approved	Brand name
1	Aldosterone antagonists	(a) Eplerenone (b) Spironolactone	(a) Inspra (b) Aldactone
2	Alpha-adrenergic blockers	(a) Doxazosin (b) Prazosin (c) Terazosin	(a) Candura (b) Minipress (c) Hytin
3	ACE inhibitors	(a) Benazepril (b) Captopril (c) Enalapril	(a) Lotensin (b) Capoten (c) Vasoten

		(d) fosinopril (e) isinopril (f) moexipril, (g) perindopril (h) quinapril (i) ramipril (j) trandolapril	(d) Monopril (e) Prinivil (f) Univsac (g) Aceon (h) Accupril (i) Altace (j) Mavik
4	Angiotensin II receptor blockers	(a) Candesartan (b) Irbesartan (c) Losartan (d) Olmesartan (e) Telmesartan (f) Valsartan (g) Eprosartan	(a) Atacand (b) Avapro (c) Cozaar (d) Benicar (e) Micardis (f) Diovan (g) Tevetan
5	Autonomic ganglionic vasodilators	Mecamylamine	Inversine
6	Arteriolar vasodilators	(a) Hydralazine (b) Minoxidil	(a) Apresoline, Dralzine (b) Loniten
7	Beta-adrenergic blockers	(a) Acebutolol (b) Atenolol (c) Bisoprolol (d) Carvedilol, (e) Labetolol, (f) Metoprolol, (g) Nadolol, (h) Penbutolol (i) Pindolol, (j) Propranolol, (k) Timolol	(a) Spectral (b) Tenormin (c) Zebeta (d) Coreg,coreg CR (e) Trandate (f) Lopressor,Toprol XL (g) Corgard (h) Levatol (i) Visken (j) Inderal LA (k) Blocadren
8	Catecholamine-depleting sympatholytic	(a) Guanadrel (b) Reserpine	(a) Hylorel (b) Serpas
9	Central-alpha-2 adrenergic agonists	(a) Clonidine (b) Guanabenz (c) Guanfacine (d) Methyldopa	(a) Catapress, (b) Catapress TTS (c) Wytensin (d) Aldomet
10	Non-Dihydropyridine calcium channel blockers	Verapamil	Calan
11	Dihydropyridine calcium channel blocker	(a) Amlodipine (b) Felodipine (c) Isradipine (d) Nicardipine (e) Nifedipine (f) Nisoldipine	(a) Norvasc (b) Plendil (c) DynaCirc (d) Cardene SR (e) Nifidiac (f) Sular
12	Loop diuretics	(a) Bumetanide (b) Ethacrynic-acid (c) Furosemide (d) Torsemide	(a) Burnex (b) Edecrin (c) Lasix (d) Demadex
13	Renin inhibitors	Aliskiren	Tektrna
14	Thiazide-like diuretics	(a) Chlorthalidone (b) Indapamide (c) Metolazone	(a) Hygroton (b) Lozol (c) Mykrox

2. RECENT ADVANCEMENT ON HYPERTENSION

Advancement in molecular biology helps to identify new molecular targets that play important role in controlling the BP in better ways. Table 2 displays some of the new molecules that have been approved by USFDA for the management of hypertension. However, some are under the clinical trials.

2.1 Vasopeptidase inhibitors (VIP)

These are the recent class of drugs having a dual mechanism of action responsible for the treatment of hypertension. They inhibit two enzymes i.e. Angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP). More precisely, ACE prevents the production of Angiotensin II (Ang II) and also prevents the destruction of natriuretic peptidase. The combination of these two enzymes inhibitor is responsible not only for the treatment of hypertension but also for treatment and prevention of various cardiovascular diseases such as congestive heart failure (CHF), ischemic heart disease (IHD) and renal failure. Sampatrilat, fasidotril, gemopatrilat, omapatrilat and lleptril are some of the examples of vasopeptidase inhibitors.[10-11]

ANP, BNP and CNP are the three natriuretic peptidase hormones which are found in the human system. ANP is found in cardiac atria responsible for showing volume expansion due to atrial stretch while BNP is produced and secreted from ventricles in the

reflex to raised ventricular pressure and volume. This peptidase possesses diuretic, sodium excretion and vasodilatory properties. CNP is produced in stimulus to shear stress, secreted from vascular endothelial and thus having weak vasodilatory properties. The two modes of action is responsible for the inactivation of Natriuretic peptidase: by cell surface clearance receptor and neutral endopeptidase (NEP), a membrane-bound metalloproteinase enzyme. Thus, drugs designed for inhibiting both ACE and NEP (Figure 1), significantly reduce the BP and are mostly preferred during the emergency cases when there is a high raised in the blood pressure.[12-13]

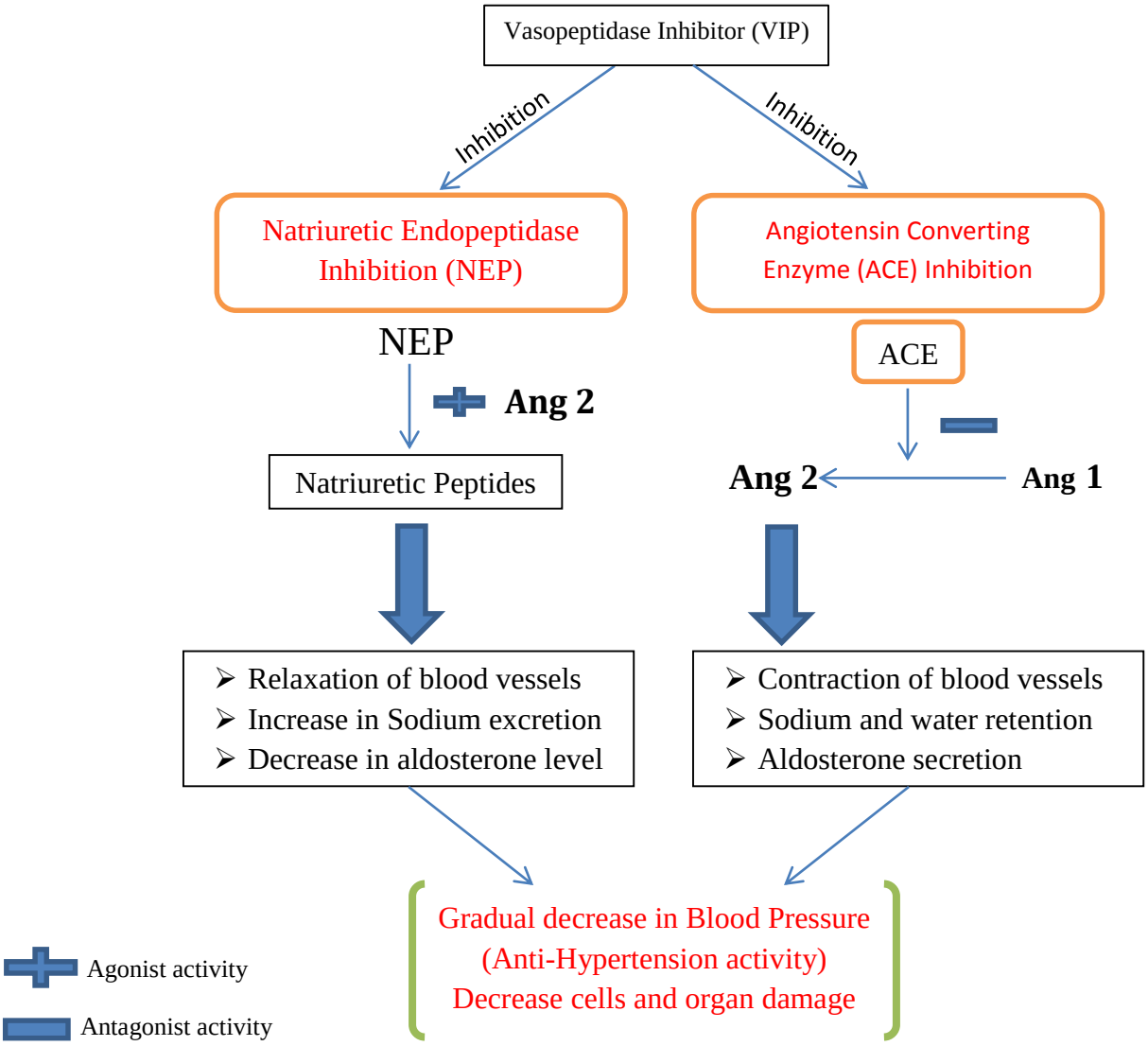

Fig. 1: Role of vasopeptidase inhibitor in hypertension

2.2 Anti-Aldosterone

The anti-aldosterone class of drugs are responsible for blocking the action of aldosterone which is responsible for reducing the sodium reuptake by blocking sodium channel and decreasing the water reabsorption. Finally, the reduction in the blood pressure and fluid around the cardiac muscle takes place. This decreases the hypertension activity in hypertensive patients[14-15]. Eplerenone, a better-tolerated mineralocorticoid aldosterone antagonist is mostly used for the therapy of myocardial infarction and heart failure.

2.3 LCZ696 (Sacubutril/valsartan)

It is first in class Angiotensin 2 AT 1 receptor neprilysin inhibitor comprising of two moieties in a molar ratio of 1:1. The Food and Drug Administration (FDA) has approved LCZ696 in July 2015 for the therapy of heart failure with declined ejection fraction. It prevents the inhibition of angiotensin converting enzyme and amino peptidase P and finally reduces the risk of angioedema. The research is also been going on to find that whether it is beneficial for the treatment of patients with HFpEF.[16]

Table 2: Names of new drugs designed for new targets

S. No.	Name of drug	Category	Approval	References
1	Sampatrilat	Vasopeptidase inhibitors	Phase 2 and discontinued	17
2	Fasidotril	Vasopeptidase inhibitors	Phase 3 trail	18
4	Gemopatrilat	Vasopeptidase inhibitors	Phase 2 trial and discontinued	19
5	Omapatrilat	Vasopeptidase inhibitors	Phase 3 trial	20
6	Ilepatril	Vasopeptidase inhibitors	Phase 2 trail	21
7	LCZ696 (Valsartan-Sacubitril)	Vasopeptidase inhibitors	2015	22
8	Daglutril	Vasopeptidase inhibitors	Phase 2	23
9	QGC001(RB-150)	Brain RAAS	Phase 2	24
10	Eplerenone	Anti-Aldosterone	2002	25

3. CONCLUSIONS

Overall, the current review summarizes some of the new molecular targets which have been found to have a better therapeutic effect in achieving the target blood pressure. However, potential risk is always associated with long term medications that need to be assessed through feedback from physicians and pharmacovigilance programs

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APPENDIX

Abbreviations and Acronym

HT	: Hypertension
CHF	: Congestive Heart Failure
GHO	: Global Health Organization
CVD	: Cardiovascular disease
FDCs	: Fixed Dose Combinations
USFDA	: United State Food and Drug Association
VPI	: Vasopeptidase Inhibitor
NEP	: Neutral Endopeptidase
ACE	: Angiotensin Converting Enzyme
IHD	: Ischemic Heart Disease
ANP	: Atrial Natriuretic peptide
BNP	: Beta Natriuretic peptide
CNP	: C- type Natriuretic peptide

