Journal of Advanced Zoology
ISSN: 0253-7214
Volume 45 Issue 2 Year 2024 Page 1341-1349

Complete Review On Recent Advancement And Development For The Treatment Of Hypertension

Dhruvisha Dobariya[1*], Adarsh S Bhadoria[2], Dr. Pragnesh Patani[3]

[1]*Student, Khyati College of Pharmacy, Palodia, Ahmedabad
[2]Assistant Professor, Khyati College of Pharmacy, Palodia, Ahmedabad
[3]Principal, Khyati College of Pharmacy, Palodia, Ahmedabad

***Corresponding Author:** Dhruvisha Dobariya
*Student, Khyati College of Pharmacy, Palodia, Ahmedabad

ABBREVIATION

WHO – World Health Organization, BP - Blood Pressure, HTN – Hypertension, CVD- Cardiovascular Disease, ACE inhibitors- Angiotensin-converting enzyme, ACE_2 – Angiotensin converting enzyme 2, Ang-I –Angiotensin 1, Ang-II – Angiotensin 2, AT_1R -Angiotensin type 1 receptor, AT_2R- Angiotensin type 2 receptor, NHBPEP- National High Blood Pressure Education Program, SNS- Sympathetic Nervous System, RAAS- Renin-Angiotensin-Aldosterone-System, OTC- Over The Counter, NO- Nitric Oxide, B-blocker- Beta Blocker, C-21 – compound 21, ETA- Endothelia-A, ETB- Endothelial-B, PAI-1- Plasminogen Activator inhibitor-1, NEP- Neutral Endopeptidase, ECE- Endothelin-converting enzyme, ARNI- Angiotensin Receptor-Neprilysin inhibitor, MAS- metabolic angiotensin, ARB_s – Angiotensin receptor blockers, DIZE- diminazene aceturate, $rhACE_2$ – recombinant human angiotensin converting enzyme 2, SHR – spontaneously hypertensive rat, $_cGMp$ - Guano sine 3',5'-cyclic monophosphate, NHE_3 - Na^+/H^+ exchanger 3, NKA – Na^+/K^+ ATPase, ATP - adenosine-5'-triphosphate, TNF-α – tumour necrosis factor- α, IL-6 – interleukin-6, TGF-β_1- transforming growth factor β_1, JNC – joint national committee, AHA – American heart association, ACC – American college of cardiology.

Article History

Received: 6 Jan 2024
Revised: 29 Jan 2024
Accepted: 5 Feb 2024

Abstract

Hypertension affect daily life of individuals also it is a long-lasting condition with the primary underlying cause of mortality and morbidity worldwide and a significant risk factor foe heart disease, kidney disease, and cerebrovascular illness. It also has an adverse effect on life quality, as per the claim by WHO that the hypertension is a leading cause of death in high-income nations, where it is still mainly underdiagnosed and undertreated, hypertension is having an increasing impact right now, especially in low-income nations. Tentatively 24% men's and 23% women's in between the 20 to 70 years adult old population had hypertension, which is estimated on the basis of reading more than or equal to 140/90 mm Hg patients are currently taking anti-hypertension drug either in combination of as single during the period of condition. Studies on genetics and pharmacogenomics of primary hypertension during the past 20 years have produced interesting results that suggest the importance of genetics, but no specific information that can be used to tailor treatment. ACE inhibitors, calcium channel blockers, beta blockers, and renin inhibitors are just some of the traditional medications that are available to treat hypertension. There are several researches available and also still going on hypertension medication. A new medication might significantly improve on currently used treatments for

hypertension but they cannot cure hypertension completely .all we can do is reduce the risk factor by changing dietary and lifestyle habits. The current review focuses on how new technological and dedicational advancements might help in the diagnosis and treatment of hypertension.

Keywords: Hypertension, Inhibitors, Self-medication, Self-treatment

INTRODUCTION

Many pharmacology and non-pharmacology method are used to treat hypertension.[1] non-pharmacological care of pre-hypertension may prevent the development of hypertension, but early and strong management of hypertension with anti-hypertensive medications lower both short-and-long-term cardiovascular risk.[2] The National High Blood Pressure Education Program (NHBPEP) has worked for more than twenty years working with the public and medical professionals to improve the identification, assessment, and management of high blood pressure in the general population as well as in subgroups of people who experience an increased risk of hypertension-related cardiovascular disease.[3] There is many classics available for hypertension medication for example beta blockers, calcium channel blockers, vasodilators, ACE inhibitors, renin inhibitors, vasodilators. All this drug are react with the two system of body that is sympathetic nervous system (SNS) and renin-angiotensin-system (RAAS) and modulate hypertension. A main goal of all this therapies is to reduce/manage/control the hypertension.[1] in UK, National Institute of Health and Care Excellence authentic, High blood pressure (BP), commonly referred to as hypertension, is defined as a clinic reading of 140/90 mmHg or above, which is then validated by a later ambulatory blood pressure monitoring daytime average (or personal blood pressure monitoring average) reading of 135/85 mmHg or higher.[4] since there are no vaccines to prevent the developing of hypertension, it is not completely preventable, but its occurrence can be decreased by lowering the risk factors of it, such as obesity, a high sodium and fat intake from food, a low potassium intake, physical inactivity, smoking, and binge drinking and genetic factors.[5] patients with long-term conditions, such hypertension, are much more likely to self-medicate. Studies on individuals with cardiovascular problems have shown that OTC medications and complementary and ssssalternative medicines are frequently used with cardiovascular problems have shown that OTC medications and complementary and alternative medicines are frequently used.[6]

SR. NO	NAME OF DRUG	BRAND NAME	CLASS OF DRUG	ACTIVITY OF DRUG
1	Nebivolol	NEBISTAR-SA$_{Tab}$	Beta-blocker	Nebivolol is a third-age, β-adrenergic-impeding specialist with vasodilator properties.[1] Nebivolol is cardio selective, exhibiting exceptionally high liking for the β1 Receptor and a 50-overlap lower partiality for β2 Receptors.[8] The medication is a racemic combination of two enantiomers, d-and l-nebivolol.[9] The β1 impeding movement of the specialist lives in d-nebivolol, which shows a more than 100-overlap more noteworthy partiality for β1 Receptors contrasted with l-nebivolol. obviously nebivolol remarkable vasodilatory properties of the specialist that are not interceded by barricade of α-adrenergic or excitement of B2-adrenergic receptors.[10] The property that recognizes nebivolol from other β-impeding specialists (with the conceivable exemption of carvedilol) is its capacity to impact vasodilation in the two veins Furthermore, veins by means of the l-arginine/nitric oxide (NO) pathway.[11] In people, nebivolol has been displayed to create Endothelial-reliant, NO-intervened vasodilation in Both normotensive and hypertensive subjects.[12]
2	Aliskiren	Rasilez-HCT - Novartis India	renin inhibitors	Aliskiren is the main in another class of orally compelling, no peptide, low-sub-atomic weight renin inhibitors, and Is at present being produced for the treatment of hypertension. Aliskiren is an incredibly powerful and exceptionally Explicit inhibitor of human renin. The physiochemical properties of aliskiren, including high water dissolvability and low lipophilicity, render it to some extent impervious to biodegradation by peptidases in the digestive system, blood, Also, liver. Thus, aliskiren shows worked on oral bioavailability contrasted with prior renin inhibitors.[13,14] this is a critical property, as prior specialists needed adequate oral bioavailability to turn into clinically helpful antihypertensive medications.[15]
3	clevidipine	CLEVIPREX	Calcium channel blockers	Clevidipine is a vascular specific dihydropyridine calcium Channel blocker that is basically connected with felodipine.[16] It is presently a work in progress as an intravenous specialist for

				Use in controlling BP in the perioperative setting. The novel pharmacokinetic properties of this specialist incorporate exceptionally fast freedom and a super short pharmacodynamics term Of activity.[17]
4	Darusentan	-	Endothelia-receptor antagonist	Darusentan is a new endothelia-receptor antagonist That produces selective blockade of the endothelia-A (ET_A) receptor.[18] Endothelin-1 is a naturally dynamic peptide that applies different consequences for the vasculature Through excitement of estimated time of arrival and ET_B receptors. Acting at the estimated time of arrival receptor, endothelia is a powerful vasoconstrictor that, similar to angiotensin II and norepinephrine, advances Vascular smooth muscle cell development and hypertrophy. Conversely, actuation of the ETB receptor brings about vasodilation and the arrival of NO.[19] The original of endothelia-receptor adversaries, of which bosentan is the model, produces vague barricade of both Estimated time of arrival ET_A and ET_B receptors.[20]
5	Carvedilol	cardivas tab	Non selective beta-blockers	Carvedilol, a nonselective b-blocker, gives hemodynamic, hostile to ischemic, anti-proliferative, against arrhythmic, and cell reinforcement benefits, which make the drug helpful in the treatment of hypertension, Coronary illness, and congestive cardiovascular breakdown. [21,22] Carvedilol, due to its vasodilating impact, could be beneficial in treating hypertensive patients with Insulin obstruction or type 2 diabetes.[23] Be that as it may, not at all like nebivolol, it doesn't usefully affect the prothrombic state (fibrinogen, homocysteine, and PAI-1).[24]
6	Celiprolol	Edsivo	Cardio selective beta-blockers	Celiprolol, a cardio selective b-blocker with an energizer impact on b-2 receptors, is as powerful an antihypertensive specialist as other b-blockers. In light of its vasodilating impact, it could likewise be favourable for hypertensive patients with insulin opposition or type 2 diabetes or then again in patients with constant glomerulonephritis and blood vessel hypertension.[25] Celiprolol might be utilized in the treatment of hypertensive patients with Aviation route brokenness.[26] Celiprolol additionally fundamentally influences prothrombic boundaries (plasma levels of fibrinogen and homocysteine and serum levels of PAI-1) yet less significantly than nebivolol.[27] Celiprolol isn't reasonable in that frame of mind with heart disappointment, however it might utilized in patients with hypertension Furthermore, angina or modified heart capability.[28]

DEVELOPMENT IN THE TREATEMENT OF HYPERTENSION

- **Vasopeptidases inhibitors :-**

Alongside Pro there are other metallopeptidases that convert vasoactive substances, like ACE2, NEP, or endothelin-changing over catalyst (ECE-1). Late discoveries show an extraordinary potential for consolidated Pro/ECE inhibitors, [29] however most exploration was committed to the job of NEP and the restorative capability of its hindrance. Nonpartisan endopeptidase substrates have a place with vasodilators too as vasoconstrictors and the impact of NEP hindrance on BP is in this way exceptionally unassuming and variable Then again, the impact of decreased corruption of vasodilative substances after NEP hindrance could win in conditions, when the development or activity of the vasoconstrictors is as of now impeded. Moreover, the plan of molecules hindering both Pro and NEP is truly achievable. One of the most contemplated vasopeptidase inhibitors, omapatrilat, diminished BP in a few models of exploratory hypertension[30] as well as in hypertensive subjects[31] comparatively to sampatrilat. The preliminaries OCTAVE and Suggestion upheld the advantage of ACE/NEP hindrance in hypertension and cardiovascular breakdown, however they detailed a higher frequency of angioedema in patients on double restraint.[32] The most probable clarification is the combination of both vasopeptidases on bradykinin corruption Subsequently the double AT_1R/NEP threat (angiotensin receptor and neprilysin inhibitors, ARNI) could show a better resilience profile. To be sure, LCZ696, a first-in-class ARNI, decreased BP moreover with the impact of valsartan, without being related with event of angioedema in a Stage II concentrate in gentle to direct hypertensive patients[33] Furthermore, ARNIs cause expanded natriuretic peptide fixations. In primates, natriuretic peptides lead to lipolysis, a reality that may be restoratively taken advantage of however that likewise calls for cautious portrayal of these impact.

- **Modulating the renin-angiotensin aldosterone pathway: innovative pathway**

Renin-angiotensin-aldosterone framework (RAAS) plays a significant job in human body.[34] but it's also create a as well as on the pathogenesis of cardiovascular infections, including hypertension also, cardiovascular

breakdown. The complexity of the RAAS is perpetually extending with the quickly advancinsg exploration on angiotensin peptides, their extra receptors and crosstalk with old style angiotensin II receptors, and the initiation of the cerebrum renin-angiotensin framework (RAS). Subsequently, cross-controlled flagging organizations might have a large number of impacts regulating the sanctioned pathway. Likewise, such organizations actuating the vasoprotective hub might aid the quest for novel medications for the administration of cardiovascular issues. Old style antihypertensive medications incorporate renin inhibitor, Pro inhibitors, angiotensin II receptor blockers(blocking the movement of Ang1-7/Mas and Ang II-Ang type 1 receptor (AT1R)/Ang type 2 receptor (AT2R)), β-adrenoreceptor blockers (impeding the emission of renin), aldosterone-related blocker (obstructing the movement of the blend of aldosterone and receptor).[34]

- **Activators of the Angiotensin-Changing over Enzyme2/Angiotensin (1-7)/MAS Receptor Axis**

The traditional renin-angiotensin framework (RAS) has been read up widely for a really long time[35] furthermore, has yielded various effective treatments for hypertension and its intricacies. All the more as of late, parts of the RAS that play counter regulatory jobs have been recognized, portrayed and set forward as remedial focuses for hypertension and different types of CVD The carboxypeptidase angiotensin-changing over compound 2 (ACE2) changes over the decapeptide angiotensin I (Ang I) to the Ang (1-9) Nona peptide and the octapeptide Ang II to the Ang (1-7) heptapeptide. Ang (1-7) has been contemplated seriously and displayed to enact the G-protein-coupled Mas receptor, setting off a flagging outpouring that outcomes in vasodilation, decrease in oxidative pressure, and ant hypertrophic and ant fibrotic impacts.

ACE2 likewise intercedes corruption of Ang II, possible adding to the antihypertensive/vasoprotective impacts of the counter regulatory RAS pathway. Intensification of ACE2/Ang (1-7)/Mas flagging goes against the impacts of the old style RAS and brings down BP and forestalls or switches related target organ harm in hypertensive creature models. Strangely, inhibitors of the old style RAS, including Pro inhibitors and angiotensin receptor blockers (ARBs), increment flowing Ang(1-7) levels, and the Mas bad guy A-779 constricts the impacts of the Pro inhibitors and ARBs, demonstrating that the 2 RAS Axis associate, what's more, give further proof for the helpful capability of the ACE2/Ang(1-7)/ Mas Axis in hypertension.

The more as of late depicted Ang (1-9) has been displayed to lower BP and switch/enhance cardiovascular injury in animal models of hypertension by a component that includes activation of the angiotensin type 2 receptor.[36] In contrast to Ang (1-7), Ang (1-9) doesn't actuate the Mas receptor. The remedial capability of angiotensin type 2 receptor enactment is being investigated in preclinical examinations. A specific non peptide angiotensin type 2 receptor agonist, compound 21(C21), has been found to have calming, ant fibrotic and ant apoptotic properties, yet not to bring down BP. These discoveries recommend that C21 might be valuable in forestalling hypertension-prompted target organ harm. interest in ACE2 as a restorative objective has prompted the union of little particle ACE2 activators, including XNT[37] and DIZE,[38]which lower BP, work on myocardial capability, also, switch myocardial and perivascular fibrosis in the immediately hypertensive rodent . Initiation of ACE2 likewise diminishes monocrotaline-instigated pneumonic hypertension by an instrument that includes Mas enactment.[39] As an option to pharmacological ACE2 enactment, recombinant human ACE2 (rhACE2) has been displayed to bring down BP in SHR, to have calming impacts in a model of lipopolysaccharide-prompted lung injury,[40] and to slow the movement of diabetic nephropathy in creature models.

A stage I concentrate on in solid workers exhibited supported (>24 h) concealment of coursing Ang II levels after a solitary intravenous infusion of rhACE2 with no impact on BP and no major unfriendly effects.[41]Ang(1-7) has been regulated in stage I/II examinations as a putative ant proliferative and antiangiogenic specialist to patients with cutting edge malignant growths hard-headed to standard treatment and as a hematopoietic specialist to patients with multiline age cytopenias following chemotherapy.[42]These examinations were restricted in degree, and local Ang(1-7) has not been grown further in view of its contracted half-life in vivo. A cyclic Ang(1-7) simple holding back a together span that makes it impervious to enzymatic processing and a hydroxypropyl-β-cyclodextrin integrated Ang(1-7) definition (HP-β-Cd/Ang1-7) have been blended and demonstrated to be cardio protective in creature models of myocardial dead tissue and insulin obstruction/type 2 diabetes.[43,44]

As an option in contrast to Ang (1-7), nonpeptide agonists of the Mas receptor, for instance, the imidazole compound AVE0991,[45]and novel G-protein-coupled receptor enacting peptides, for instance, CGEN-856S that have high particularity for the Mas receptor, have been displayed to bring down BP and protect the vasculature and kidneys in creature models of hypertension and CVD (Table). The overall benefits of Mas receptor actuation versus ACE2 excitement are being discussed, yet all at once all concur that randomized controlled preliminaries in people with hypertension and related CVDs are expected to evaluate the remedial capability of enacting the ACE2/Ang (1-7)/Mas receptor axis. A clever individual from the Ang peptide

family, Ala1 -Ang (1-7) (almandine), has been disconnected from human plasma and rodent heart. Almandine is a result of decarboxylation of the N-terminal Asp build-up of Ang II to frame Ala, which has been shown in heart, trailed by hydrolysis of Ala1 -Ang II by ACE2. Almandine is comparable in design to Ang (1-7) with the exception of substitution of the N-terminal Asp build-up by Ala. It has antihypertensive, ant fibrotic, and focal cardiovascular impacts like those detailed for Ang(1-7), yet acts through an alternate receptor, the Mas-related G-protein coupled receptor, part D. Almandine integrated into a β-cyclodextrin incorporation complex (almandine/HPβCD) has been demonstrated to be orally dynamic and to lessen BP in SHR and restrain heart fibrosis in isoproterenol-treated rats. The oral bioavailability of almandine/HPβCD has resuscitated possibilities for investigating the helpful capability of Ang(1-7)- related peptides.[45]

- **AngII-AT1R/ AT2R axis**

Ang II predominantly works by initiating AT1Rs and AT2Rs. AT1Rs intercede vascular smooth muscle compression, aldosterone emission, dipsogenic reactions, renal sodium reabsorption and pressor and tachycardia reactions.[46] Alternately, AT2Rs by and large initiate the contrary impacts, including vasodilation, natriuretic, cell separation and development hindrance.[47] Hence, AT2R agonists could act as a likely remedial medication for the treatment of hypertension. Compound 21 (C-21) is a profoundly specific nonpeptide AT2R agonist which is the first detailed AT2R agonist.[48] C-21-prompted AT2R enactment evoked a bradykinin-nitric oxide (NO)- cyclic guano sine 3,5-monophosphate (cGMP) flagging fountain that animated the downstream flagging arbiters Src kinase and extracellular sign related kinase, prompting the assimilation/inactivation of the major renal proximal tubule (RPT) Na^+ carriers Na^+/H^+ exchanger 3 (NHE3) and Na^+/K^+ ATPase (NKA) and bringing about natriuresis.[49]Earlier examinations found that Ang II can increment sodium maintenance and BP in rodents, nonetheless, the infusion of C-21 forestalled Ang II-interceded sodium maintenance and BP rise. The enactment of constant AT2R starts and supports receptor movement to RPT apical plasma films. It additionally advances the assimilation/inactivation of NHE3 and NKA and forestalls Na+ maintenance, which brings about a negative combined Na^+ equilibrium and brings down BP in models of exploratory Ang II-actuated hypertension. The outcomes demonstrated that C-21 is a potential medication contender for the treatment of hypertension and Na+ holding states in people. Likewise, in the cut kidneys of two-kidney, one-cut hypertensive rodents model, C-21 altogether diminished TNF-α, IL-6 and TGF-β1 levels and expanded nitric oxide (NO) and cGMP) levels in the kidneys.[50]These outcomes recommend that AT2R is another objective for the treatment of hypertension and AT2R agonists might go about as original enemy of hypertensive medications in the future.

- **Combination therapies: synergizing treatment approaches**

Since hypertension is a multifactorial illness, basically obstructing one of its pathophysiologic components by monotherapy is generally deficient to control it. Treatment with a solitary antihypertensive specialist will for the most part control BP in under portion of the patients, also, over 60% of the patients require mix treatment with at least two medications of various classes to accomplish target BP, as has been seen in various huge clinical preliminaries.[51] Dark and old hypertensive patients require at least 2 medications to control their BP.[52] As indicated by the JNC7, people with BP more than 20/10 mm Hg above objective ought to be begun on blend drug treatment, including patients with BP more prominent than 160/100 mm Hg and diabetics with BP over the objective (,130/80 mmHg). In diabetic patients with nephropathy, tight BP control is expected to forestall decay of end organ harm, which is hard to accomplish and generally requires the utilization of 3 to 5 unique classes of antihypertensive agents.[53]New clinical preliminaries are expected to decide ideal medication blends that will likewise present objective organ security notwithstanding furthermore, autonomous of their BP bringing down impacts. In this respect, a huge preliminary, achieve, is in the works that is looking at the blends Pro inhibitor (benazepril)/CCB (amlodipine) and Expert inhibitor (benazepril)/diuretic. Organization of an Expert inhibitor alongside an ARB has been found to be more viable than the singular medications in treating hypertensive patients with diabetic nephropathy or on the other hand those with extreme hypertension.[54]Fixed drug blends are much of the time valuable in upgrading the treatment of hypertension. Such mixes (endorsed in the US) are normally with a diuretic (for the most part hydrochlorothiazide) and an Expert inhibitor (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, or quinapril), an ARB (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, or valsartan) or a b-blocker (bisoprolol, propranolol, metprolol, or timolol). Different diuretics have been joined with some b-blockers (atenolol + chlorthalidone and nadolol + bendroflumethiazide). A few different mixes incorporate clonidine +chlorthalidone, benazepril + amlodipine, trandolapril + verapamil, and prazosin + polythiazide. Diuretics with various systems of activity have additionally been joined in certain arrangements (hydrochlorothiazide with amiloride, spironolactone, or triamterene). As of late, a decent blend of an

antihypertensive specialist with a statin (amlodipine/atorvastatin) has shown to be preferable over the antihypertensive medication alone in treating hypertensive patients.[55] this could be on the grounds that statins alone lower BP, particularly in salt sensitive patients such mixes additionally decrease the Framingham cardiovascular gamble score in hypertensive patients with dyslipidaemia.[56]

- **Healthy habits to lower blood pressure**

By way of life/changing on a surface level (heftiness, high dietary admission of fat and sodium, actual latency, smoking, unreassonable liquor admission, low dietary potassium consumption) to control BP and furthermore to work on the viability of pharmacologic treatment of high BP. To accomplish most extreme advantages, plans for diet, work out, and other required changes ought to be started in the essential consideration setting, and talked about with the patient, and proper objectives ought to be laid out, which ought to be sensible.e Self-drug is a typical type of taking care of oneself and is characterized as the utilization of items [including over-the-counter (OTC) prescriptions, home grown drugs, dietary enhancements and vitamins] to treat self-perceived wellbeing grievances or diseases. It permits patients to assume a sense of ownership with dealing with their wellbeing, causing an identity strengthening. Not with standing, self-medicine practices can prompt medication collaborations because of the simultaneous utilization of unprescribed items with recommended drug[57] or can cause incidental effects. People are concentrated to changing their lifestyles and that's help to maintain and control the blood pressure.

- **Better diet for healthier heart**

Concerning HTN counteraction and support, late dietary suggestions have zeroed in on exact proof analysing food varieties devoured in mixes, or the general dietary example, and its connection among food and BP. All things considered, bigger accentuation on dietary examples have been embraced by the Dietary Rules for Americans, and the AHA/ACC/The Weight Society,[58] as they offer the chance to portray the generally speaking wholesome thickness, and subsequently, dietary nature of something else 'reasonable' eating ways of behaving in a populace. Among dietary examples contemplated, the Dietary Ways to deal with Stop Hypertension (Run) diet has been reliably supported by wellbeing associations (for example Public Heart, Lung, and Blood Organization, AHA, Dietary Rules for Americans, US (US) rules for treatment of high BP) as a successful diet for controlling BP. Its advancement was affected by early observational investigations featuring the connection between low pervasiveness paces of HTN what's more, CVD in those with eating ways of behaving that stay away from eating creature items, are low in soaked fat, high in polyunsaturated fat, and low in cholesterol.[59] Sodium is most important factor for the increasing blood pressure. We can control the blood pressure by low intake of sodium in diets. The typical American's eating routine comprises of generally 3400 mg of sodium each day, far surpassing the upper, safe constraint of the clinical dietary suggestions of 2400 mg/day.

- **Vaccine**

The advantages anticipated from gene-based strategies may be comparable to those offered by an immunological strategy. Two vaccines against hypertension were recently developed: Cyt006 against Ang II and PMD3117 against Ang I. Even though there was some excitement, the outcomes were not very good. Despite the fact that Cyt006 reduced SHR BP, it achieved a lower reduction (9/4 mmHg)[60] than conventional antihypertensive. In additional examinations Cyt006 neglected to duplicate this BP decrease, in spite of more limited dosing spans and higher antibody titres, and PMD3117 didn't diminish BP, notwithstanding some level of RAAS blockade. Additionally, in order to increase patient compliance, the suggested vaccination schedules of Weeks 0, 4, 12, or 0, 2, 4, 6, and 10 may not be sufficiently appealing. However, despite the fact that previous anti-renin vaccinations were linked to severe kidney disease, Cyt006 and PMD3117 were well tolerated in the Phase I study, and Cyt006 also slowed the rise in blood pressure in the early morning.

CONCLUSION

In conclusion, late progressions in the treatment of hypertension have essentially worked on our way to deal with this medical issue. New methodologies, like medicines and therapies have been examined in this article. A new medication for hypertension may enhance existing treatments in a number of ways. It has the potential to lower blood pressure through a novel pharmacologic strategy that offers the possibility of further developed end-point reduction when administered either by itself or in combination with other specialists. Examples of this kind of leap forward include the presentation of Expert inhibitors and beta-blockers. All the

headway and improvement in a medication and treatments of hypertension assists with decreasing blood pressure. However, since hypertension is a disease of daily living, we cannot completely treat it; all we can do is alter our lifestyle and diet.

REFERENCES

1. Grad man AH, Vivas Y. "New drugs for hypertension: what do they offer?" *Current hypertension reports*. **2006** Sep; 8(5):425-32.
2. Cohen JD. "Managing hypertension: state of the science." *The Journal of Clinical Hypertension.* **2006** Oct; 8:5-11.
3. Hyman BN, Moser M. "Hypertension update." *Survey of ophthalmology*. **1996** Jul 1; 41(1):79-89.
4. Grad man AH, Vivas Y. "New drugs for hypertension: what do they offer?" *Current hypertension reports*. **2006** Sep; 8(5):425-32.
5. Kitt J, Fox R, Tucker KL, McManus RJ. "New approaches in hypertension management: a review of current and developing technologies and their potential impact on hypertension care." *Current hypertension reports*. **2019** Jun; 21:1-8.
6. Israili ZH, Hernández-Hernández R, Valasco M. "The future of antihypertensive treatment." *American journal of therapeutics.* **2007** Mar 1; 14(2):121-34.
7. Rahmawati R, Bajorek BV. "Self-medication among people living with hypertension: a review." *Family practice.* **2017** Apr 1; 34(2):147-53.
8. Van de Water A, Janssen's W, Van Neuten J, et al.: "Pharmacological and hemodynamic profile of nebivolol, a chemically novel, potent, and selective beta 1-adresnergic antagonist." *J Cardiovascular Pharmacol* **1988**, 11:552–563.
9. Janssen's WJ: "Pharmacology of nebivolol." *J Pharm Beg* **1992**, 47:323–327.
10. Rozec B, Quang TT, and Noireaud J, et al.: "Mixed beta (3) - adrenoceptor agonist and alpha (1)-adrenoceptor antagonist properties of nebivolol in rat thoracic aorta." *Br J Pharmacol* **2006**, 147:699–706.
11. Dessy C, Saliez J, and Ghisdal P, et al.: "Endothelial 3-adrenoreceptors mediate nitric oxide–dependent vasorelaxation of coronary micro vessels in response to the third generation beta-blocker nebivolol." *Circulation* **2005**, 112:1198–1205.
12. McEniery CM, Schmitt M, and Qasem A, et al.: "Nebivolol increases arterial distensibility in vivo." *Hypertension* **2004**, 44:305–310.
13. Dawes M, Chowienczyk PJ, Ritter JM: "Effects of inhibition of the L-arginine/nitric oxide pathway on vasodilation caused by beta-adrenergic agonists in human forearm." *Circulation* **1997**, 95:2293–2297.
14. Mason P, Kalinowski L, and Jacob R, et al.: "Nebivolol reduces nitroxidative stress and restores nitric oxide bioavailability in endothelium of black Americans." *Circulation* **2005**, 112:3795–3801.
15. Stanton a, Jensen C, Nussberger J, et al.: "Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren." *Hypertension* **2003**, 42:1137–1143.
16. Ericsson H, Tholander B, and Bjorkman JA, et al.: "Pharmacokinetics of new calcium channel antagonist clevidipine in the rat, rabbit, and dog and pharmacokinetic / pharmacodynamics relationship in anesthetized dogs". *Drug me tab Dispose* **1999**, 27:558–564.
17. Schwieler JH, Ericsson H, Lofdahl P, et al.: "Circulatory effects and pharmacology of clevidipine, a novel ultra-short acting and vascular selective calcium antagonist, in hypertensive humans." *J Cardiovascular Pharmacol* **1999**, 34:268–274.
18. Kirchengast M, Witte K, Stolpe K, et al.: "Effects of chronic Endothelin ET (A) receptor blockade on blood pressure and vascular formation of cyclic guanosine3', 5'-monophosphate in spontaneously hypertensive rats." *Arzneimittelforschung* **2005**, 55:498–504.
19. Strachan F, Spratt JC, and Wilkinson IB, et al.: "Systemic blockade of the Endothelin-B receptor increases peripheral vascular resistance in healthy men." *Hypertension* **1999**, 33:581–585.
20. Nakov R, Pharr E, and Eberle S, et al.: "Darusentan: an effective Endothelin-A receptor antagonist for treatment of hypertension HEAT Investigators." *Am J Hypertension* **2002**, 15:583– 589.
21. Palazzuoli A, Calabria P, Verzuri MS, et al. "Carvedilol: something else than a simple beta-blocker?" *Eur Rev Medical Pharmacol Sci.* **2002**; 6:115–126.
22. Bakris GL, Bell DS, Fonseca V, et al. "The rationale and design of the glycaemic effects in diabetes mellitus: Carvedilol-Metoprolol Comparison in Hypertensive (GEMINI) trial." *J Diabetes Complications.* **2005**; 19:74–79.

23. Jacob S, Balletshofer B, Henriksen EJ, et al. “Beta-blocking agents in patients with insulin resistance: effects of vasodilating beta-blockers [Review].” *Blood Press*. **1999**; 8: 261–268.
24. Vyssoulis GP, Marinakis AG, Aznaouridis KA, et al. “The impact of third-generation beta-blocker antihypertensive treatment on endothelial function and the prothrombotic state: effects of smoking.” *Am J hypertension*. **2004**; 17:582– 589.
25. Fogari R, Zoppi A, Corradi L, et al. “Beta-blocker effects on plasma lipids during prolonged treatment of hypertensive patients with hypercholesterolemia.” *J Cardiovascular Pharmacol*. **1999**; 33:534–539.
26. Cazzola M, Noschese P, D’Amato G, et al. “The pharmacologic treatment of uncomplicated arterial hypertension in patients with airway dysfunction.” *Chest.* **2002**; 121:230–241.
27. Vyssoulis GP, Marinakis AG, Aznaouridis KA, et al. “The impact of third-generation beta-blocker antihypertensive treatment on endothelial function and the prothrombotic state: effects of smoking.” *Am J hypertension.* **2004**; 17:582– 589.
28. Witchitz S, Cohen-Solal A, Dartois N, et al. “Treatment of heart failure with celiprolol, a cardio selective beta blocker with beta-2 agonist vasodilatory properties.” The CELICARD Group. *Am J Cordial.* **2000**; 85:1467– 1471.
29. Dive V, Chang CF, Yiotakis A, Sturrock ED. “Inhibition of zinc metallopeptidases in cardiovascular disease—from unity to trinity, or duality?” *Curr Pharm Des* **2009**; 15:3606–3621.
30. Intengan HD, Schiffrin EL. “Vasopeptidases inhibition has potent effects on blood pressure and resistance arteries in stroke-prone spontaneously hypertensive rats.” *Hypertension* **2000**; 35:1221–1225.
31. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. “Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial.” *Am J hypertension* **2004**; 17:103-111.
32. Tabrizchi R. Omapatrilat. Bristol-Myers Squibb. “Current opinion in investigational drugs (London, England: 2000).” **2001** Oct 1; 2(10):1414-22.
33. Ruilope LM, Dukat A, Bo¨hm M, Lacourcie`re Y, Gong J, Lefkowitz MP. “Blood pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and Neprilysin: a randomised, double-blind, placebo-controlled, active comparator study.” *Lancet* **2010**; 375:1255–1266.
34. Gao Q, Xu L, and Cai J. “New drug targets for hypertension: A literature review.” *Biochemical ET Biophysical Act: Molecular Basis of Disease*. **2021**; 1867(3):166037-166037.
35. Oparil S, Haber E. “The renin-angiotensin system (second of two parts).” *N Engl J Med.* **1974**; 291:446–457.
36. Ocaranza MP, Moya J, Barrientos V, et al. “Angiotensin-(1-9) reverses experimental hypertension and cardiovascular damage by inhibition of the angiotensin converting enzyme/Ang II axis.” *J hypertension.* **2014**; 32:771– 783.
37. Ferreira AJ, Shenoy V, Qi Y, Fraga-Silva RA, Santos RA, Katovich MJ, Raizada MK. “Angiotensin-converting enzyme 2 activation protects against hypertension-induced cardiac fibrosis involving extracellular signal-regulated kinases.” *Exp Physiol.* **2011**; 96:287–294.
38. Kulemina LV, Ostrov DA. “Prediction of off-target effects on angiotensin-converting enzyme 2.” *J Biomol Screen.* **2011**; 16:878–885.
39. Ferreira AJ, Shenoy V, Yamazato Y, Sriramula S, Francis J, Yuan L, Castellanos RK, Ostrov DA, Oh SP, Katovich MJ, Raizada MK. “Evidence for angiotensin-converting enzyme 2 as a therapeutic target for the prevention of pulmonary hypertension.” *Am J Respire Crit Care Med.* **2009**; 179:1048–1054.
40. Treml B, Neu N, Kleinsasser A, Gritsch C, Finsterwalder T, Geiger R, Schuster M, Janzek E, Loibner H, Penninger J, Loeckinger A. “Recombinant angiotensin-converting enzyme 2 improves pulmonary blood flow and oxygenation in lipopolysaccharide-induced lung injury in piglets.” *Crit Care Med.* **2010**; 38:596–601.
41. Haschke M, Schuster M, Poglitsch M, Loibner H, Salzburg M, Bruggisser M, Penninger J, Krähenbühl S. “Pharmacokinetics and pharmacodynamics of recombinant human angiotensin-converting enzyme 2 in healthy human subjects.” *Clin Pharmacokinetic.* **2013**; 52:783–792.
42. Petty WJ, Miller AA, McCoy TP, Gallagher PE, Tallant EA, Torti FM. “Phase I and pharmacokinetic study of angiotensin-(1-7), an endogenous antiangiogenic hormone.” *Clin Cancer Res.* **2009**; 15:7398–7404.
43. Kluskens LD, Nelemans SA, Rink R, de Vries L, Meter-Arkema A, Wang Y, Walther T, Kuipers A, Moll GN, Haas M. “Angiotensin-(1-7) with together bridge: an angiotensin-converting enzyme-resistant, potent angiotensin-(1-7) analogy.” *J Pharmacol Exp Ther.* **2009**; 328:849–854.
44. Santos SH, Andrade JM. Angiotensin 1-7: “a peptide for preventing and treating metabolic syndrome. Peptides.” **2014**; 59:34–41.

45. Singh Y, Singh K, Sharma PL. "Effect of combination of renin inhibitor and Mas-receptor agonist in DOCA-salt-induced hypertension in rats." *Mol Cell Biochem.* **2013**; 373:189–194.
46. R.M. Carey, H.M. Siragy," Newly recognized components of the renin-angiotensin system: potential roles in cardiovascular and renal regulation, Endocr." Rev.**2003**; 261–271.
47. B.A. Kemp, N.L. Howell, S.R. Keller, J.J. Gildea, S.H. Padia, R.M. Carey, "AT2 receptor activation prevents sodium retention and reduces blood pressure in angiotensin II-dependent hypertension." *Circ. Res.* 119:**2016**; 532–543.
48. Y. Wan, C. Wallinder, B. Plouffe, H. Beaudry, A.K. Maralinga, X. Wu, et al., "Design, synthesis, and biological evaluation of the first selective non peptide AT2 receptor agonist." *J. Med. Chem.* 47:**2004**; 5995–6008.
49. B.A. Kemp, N.L. Howell, J.J. Gildea, S.R. Keller, S.H. Padia, R.M. Carey, "AT2 receptor activation induces natriuretic and lowers blood pressure." *Circ. Res.* 115:**2014**; 388–399.
50. L.C. Matavelli, J. Huang, H.M. Siragy, "Angiotensin AT2 receptor stimulation inhibits early renal inflammation in Reno vascular hypertension." *Hypertension* 57:**2011**; 308–313.
51. Segura J, Praga M, Campo C, et al. "Combination is better than monotherapy with ACE inhibitor or angiotensin receptor antagonist at recommended doses." *J Renin Angiotensin Aldosterone Syst.* **2003**; 4:43–47.
52. Bakris GL, Smith DH, Giles TD, et al. "Comparative antihypertensive efficacy of angiotensin receptor blocker-based treatment in African-American and white patients." *J Clin hypertension (Greenwich).* **2005**; 7:587–595.
53. Schwenger V, Ritz E. "Audit of antihypertensive treatment in patients with renal failure." *Nephron Dial Transplant*. **1998**; 13:3091–309.
54. Tanemoto M, Abe T, Obara N, et al. "Successful treatment of severe hypertension with the combination of angiotensin converting enzyme inhibitor and angiotensin II receptor blocker." *Hypertension,* Res. **2003**; 26:863–868.
55. Sica DA. "Fixed-dose combination therapy: is it time for this approach to hypertension and dyslipidaemia management?" *J Clin hypertension (Greenwich).* **2004**; 6:164– 167.
56. Preston RA, Harvey P, Herfert O, et al. "Reduction in Framingham Cardiovascular Risk with concomitant treatment of hypertension/dyslipidaemia with amlodipine/atorvastatin [Abstract]." *Am J hypertension.* **2005**; 18: 226A.
57. Qato DM, Alexander GC, Conti RM, et al. "Use of prescription and over the-counter medications and dietary supplements among older adults in the United States." *JAMA* **2008**; 300: 2867–78.
58. Jensen MD, Ryan DH, Apovian CM, et al. 2013 "AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society." *J Am Coll Cardiol* **2014**; 63(25 Pt. B):2985–3023.
59. Sacks FM, Rosner B, Kass EH. "Blood pressure in vegetarians." *Am J Epidemiology* **1974**; 100:390–398
60. Brown MJ, Coltart J, Gunewardena K, Ritter JM, Auton TR, Glover JF. "Randomized double-blind placebo-controlled study of an angiotensin immunotherapeutic vaccine (PMD3117) in hypertensive subjects." *Clin Sci (Lond)* **2004**; 107: 167–173.