EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 9
263-270
Year: 2021

A REVIEW ARTICLE ON CONVENTIONAL AND NOVEL DRUGS USED IN TREATMENT OF HYPERTENSION

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Article Received on 04/07/2021 **Article Revised on 25/07/2021** **Article Accepted on 15/08/2021**

ABSTRACT

Most patients who develop primary hypertension are treated with medications despite lifestyle changes. For providers, determining when to start medications can be confusing as guidelines frequently change and determining which medication to start can also be challenging. In general, medication is initiated after assessing a patient's risk for developing atherosclerotic cardiovascular disease using risk calculators as well as their medical comorbidities. Target blood pressure, time for follow-up, and initial medication(s) vary among patients. First-line agents include thiazide diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Second-line agents include beta-blockers, diuretics, alpha-1 antagonists, alpha-2 agonists, and direct-acting vasodilators. It is important to note that not all classes of blood pressure-lowering medications are considered equal and each patient's unique medical comorbidities should always be taken into account before initiating treatment. These medications have their own respective side effects and contraindications that providers should be aware of so that they can monitor for adverse reactions as well as council their patients. Over the years it has been observed that some patient are not getting treated with the conventional drugs used for cure. So with the advancement in medical research some new methods/combinations or new individual drugs have been developed and some are being developed to treat the patient. This new types of drugs/methods includes:- New Aldosterone Antagonist, polypill, Mictario, Fimsartan Combinations etc. These have been discussed further.

KEYWORDS: Atherosclerotic, Co- morbidities, Predisposition, Accentuates, Hyponatremia, Mineralocorticoid, Natriuresis, Neprilysin, Urodilatin, Orthostatic, Ambulatory.

1. INTRODUCTION

Hypertension is a hemodynamic disorder, associated with a rise in peripheral vascular resistance that can, in turn, lead to myocardial infarction, renal failure, strokes and death, if not identified early and treated correctly. It is the most common condition seen in South Africa, estimated to have caused 46 888 deaths and 390 860 disability-adjusted life years in 2000. Most patients with hypertension do not attain the blood pressure (BP) goal of < 140/90 mmHg. A reduction in BP is considered to be the primary determinant of a reduction in cardiovascular risk. Factors found to be associated with high BP are the result of a complex relationship between genetic and environmental elements, which can lead to activation or inhibition of one or more of the processes involved in the normal control of BP.

Dietary factors and physical inactivity contribute to the genetic predisposition, while environmental factors include smoking, drinking, obesity and alcohol, thus making hypertension a preventable cause of morbidity and mortality. The advantages of populations with hypertension leading a healthy lifestyle cannot be stressed enough, and this includes a controlled diet and regular exercise. The primary goal of treatment is to abolish the risks factors associated with hypertension, without reducing the patient's quality of life.

The renin-angiotensin-aldosterone system (RAAS), as well as the sympathetic nervous system, is involved in regulating arterial BP. Hypertension is usually viewed as a multifactorial condition, which interferes with different pressor mechanisms and acts on several physiological systems. The three main factors that determine BP are renal sodium excretion (and the resultant impact on plasma and total body volume), vascular tone and cardiac performance. Each of these factors controls the vital determinants of BP, such as cardiac output, intravascular volume and systemic vascular resistance. The RAAS plays a central role in elevating BP through these mechanisms. This system regulates the secretion of renin, with feedback systems from sodium balance,

arterial BP levels and angiotensin II. The direct vasoconstrictor effect of angiotensin II, resulting from the secretion of renin, can increase systemic vascular resistance, and salt and water retention can lead to an increase in the extracellular blood volume. The rationale for combining drugs from different classes lies in reaching the BP target more rapidly, as each drug will work on a separate site, blocking different effector pathway Hypertension is a growing global problem that is associated with numerous underlying pathophysiological conditions.

These include ventricular hypertrophy, endothelial dysfunction, metabolic syndrome, a procoagulant state, oxidative stress, inflammation and a genetic predisposition to cardiovascular events. The high prevalence of hypertension is a particular concern in developing countries as it contributes to the present and anticipated pandemic of cardiovascular disease (CVD). CVD was previously ranked as the second highest cause-of-death category in South Africa, resulting in major cost implications for developing countries. The control of hypertension and trying to curb the risk factors, such as cigarette smoking, dyslipidemia and diabetes mellitus, is a major challenge. This indicates that there is a great need for antihypertensive agents that achieve more than the mere lowering of BP, and which provide advantage in prevention and management of CVD.

2. CLASSIFICATION OF HYPERTENSION

According to the JNC 7 guidelines and the South African hypertension guidelines, the seven categories of BP defined in the JNC 6 were simplified and reduced to four. BP should be recorded with an approved device in a patient who has been seated for at least five minutes prior to taking the measurement. The patient should not have smoked, or taken any caffeinated drink or food in the preceding 30 minutes. To document postural hypotension in patients aged 60 years and older, and those with other co-morbid conditions, e.g. diabetes mellitus, BP should also be recorded after the patient has been standing upright for at least one minute. The cuff size appropriate to the size of the patient's arm is an important parameter, and both the SBP and DBP should be recorded.

- The following are the new optimal BP levels in patients 60 years of age or older, with or without co-morbidities, according to the JNC 8:
- The BP goal is < 150/90 mmHg in patients aged 60 years or older, and who do not have diabetes or chronic kidney disease.
- The new BP goal is < 140/90 mmHg in patients aged 60 years and older who have diabetes, chronic kidney disease or both.
- Optimal BP is < 140/90 mmHg in patients aged 18-59 years of age, without any co-morbidities.

2.1. TYPES OF TREATMENT

NON PHARMACOLOGICAL TREATMENT

A) LIFESTYLE MODIFICATION

A healthy lifestyle remains the foundation of managing hypertension, regardless of BP level. In addition to decreasing BP, it enhances antihypertensive drug efficaciousness and decreases total CV risk.

Thus, the following measures assist the patient to ensure a better, healthier life:

- Achieving and maintaining an ideal body weight*:* The ideal body weight is a body mass index of 18.5-24.9 kg/m2.
- Limiting total sodium intake*:* Sodium intake should be limited to < 2 400 mg/day or < 1 teaspoon of salt.
- Limiting alcohol intake: Alcohol should be limited to two standard drinks per day for men, and one standard drink per day for women and men of a lesser stature.
- Avoiding the use of all tobacco products: All tobacco products should be avoided, including snuff.

PHARMACOLOGICAL TREATMENT

Patients of African descent without chronic kidney disease should use calcium-channel blockers and thiazides alone or in combination, instead of ACE inhibitors, when initiating therapy. It was indicated in a single large trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), that a thiazide-type diuretic was shown to be more effective in improving cerebrovascular heart failure and combined cardiovascular outcomes, than an ACE inhibitor. A calcium-channel blocker was also tested and the outcome was no different to that of a thiazide diuretic. In addition, a significant 51% increase in the risk of a stroke was seen in patients who used an ACE inhibitor as initial therapy, compared to a calcium-channel blocker.

The following factors should be considered when selecting an antihypertensive drug:

- The cost of the drug class.
- Patient-related factors, such as the presence of major risk factors, conditions flavouring use and contraindications.
- Associated clinical conditions and target organ damage.

1. **First-line and later-line treatment should be limited to four classes of medicine**

- Thiazide-type diuretics
- Calcium-channel blockers
- ACE inhibitors
- ARBs.

2. **Second and third-line alternatives include higher dosages or a Combination of**

- Thiazide-type diuretics
- Calcium-channel blockers
- ACE inhibitors

- ARBs.

3. Numerous medications are now selected as later-line alternatives, such as

- B-receptor blockers
- Loop diuretics
- α-receptor blockers
- Direct vasodilators
- Aldosterone antagonists
- α-1 blockers and β blockers
- Vasodilating β blockers
- Central α2-adrenergic receptor agonists

2.2 CLASIFICATION OF ANTI – HYPERTENSIVE DRUGS

1] Diuretics

Thiazides*:* Hydrochlorothiazide, Chlorthalidone, Indapamide

High ceiling: Furosemide, Bumetanide etc.

K+ Sparing*:* Spironolactone, Amiloride

2] ACE inhibitors: Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril

3] Angiotensin (AT_1 receptor) blockers*:* Losartan, Candesartan, Irbesartan, Valmesartaan

4] Direct renin inhibitor: Aliskiren

5] Calcium channel blockers*:* Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.

6] Beta Adrenergic blockers*:* Propranolol, Metoprolol, Atenolol, etc.

7] Beta + Alpha Adrenergic blockers: Labetalol, Carvedilol

8] Alpha Adrenergic blockers*:* Prazosin, Terazosin, Doxazosin Phentolamine, Phenoxybenzamine.

9] Central sympatholytic: Clonidine, Methyldopa

10] Vasodilators:

Arteriolar: Hydralazine, Minoxidil, Diazoxide

Arteriolar + venous: Sodium nitroprusside

2.3 DIURETICS

2.3.1 Thiazide Diuretics

Thiazides are the most commonly used diuretics and are typically a first-line agent for treating hypertension. These diuretics work by inhibiting the sodium chloride transporter in the distal convoluted tubule of the nephron, thus resulting in inhibition of sodium reabsorption and promoting water excretion.

Side effects are predominantly electrolyte disturbances, which include hyponatremia, hypomagnesemia, hypokalemia, hyperuricemia, hyperglycemia, hypercalcemia, and metabolic alkalosis. Side effects are typically dose dependent.

2.3.2 LOOP DIURETICS

Loop diuretics work by inhibiting the Na-K-2Cl transporter in the thick ascending loop of Henle. They can lead to the excretion of up to 20–25% of filtered sodium and thus decrease BP.[38] Loop diuretics are preferred in patients with moderate-to-severe CKD (GFR < 30 mL/min) over thiazide diuretics and are used in patients with symptomatic heart failure. Side effects include hypokalemia, metabolic alkalosis, hyperuricemia, and hyponatremia.

2.3.3 POTASSIUM - SPARRING DIURETICS

Potassium-sparing diuretics act in the collecting tubule by blocking sodium channels, thereby decreasing the reabsorption of sodium and thus decreasing the excretion of potassium. These agents are minimally effective at lowering blood pressure; however, they can be used in patients with hypokalemia on thiazide monotherapy. Side effects include hyperkalemia and metabolic acidosis and should be avoided in patients with GFR < 45 ml/min.

1. ALDOSTERONE ANTAGONIST

Aldosterone antagonists include eplerenone and spironolactone. These medications act by directly inhibiting the mineralocorticoid receptor, thus limiting the effects of aldosterone. This leads to a decrease in sodium reabsorption and potassium excretion in the collecting tubule. Eplerenone has a higher affinity for the mineralocorticoid receptor than spironolactone, therefore causing fewer endocrine side effects. These are primary agents when treating hyperaldosteronism and are also useful add-on therapies when treating resistant hypertension. It has been proven that these agents reduce mortality in patients with HFrEF and an ejection fraction of <35%. Side effects include hyperkalemia, gynecomastia, menstrual abnormalities, impotence, and decreased libido.

2.4 ANGIOTENSIN CONVERTING ENZYME INHIBITOR / ANGIOTENSIN RECEPTOR BLOCKER

Angiotensin is a peptide hormone important in regulating vasoconstriction. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) both work effectively in the same way on the angiotensin system. Both of these medications limit the systemic effects of angiotensin II; ACE inhibitors decrease the amount of angiotensin II, and ARBs block the binding of angiotensin II to its respected receptors, thereby decreasing vasoconstriction. Perkalemia is the most common side effect. Dry cough, which usually begins 1–2 weeks after starting therapy, however, can develop up to 6 months after starting treatment and is much more common in ACE inhibitors than in ARBs. Angioedema is rare but potentially fatal complication that is associated with ACE inhibitors and is less likely to develop with ARBs.

2.5 DIRECT RENIN INHIBITOR

Aliskiren

It directly inhibits renin and thus act earlier in the renin-angiotensin-aldosterone system than ACE inhibitors or ARBs. Aliskiren, (2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoyl-2-methyl-propyl)-4-hydroxy-7-{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-8-methyl-2-propan-2-yl-nonanamide (Tekturna), is the first renin

inhibitor introduced into the U. S. market. It was approved by the FDA in 2007 for the management of hypertension. The trade name for aliskiren in the United Kingdom is Rasilez.

2.6 CALCIUM CHANNEL BLOCKER

Calcium channel blockers (CCBs) reduce calcium flux into cells by binding to voltage-gated calcium channels located in vascular smooth muscle cells and cardiac myocytes, including the sinoatrial (SA) and atrioventricular (AV) nodes. In cardiac tissue (including the SA and AV nodes), these channels play an important role in cardiac inotropy and chronotropy. These medications are offered in two different classes: Dihydropyridine CCBs and non-dihydropyridine CCBs. Dihydropyridine CCBs usually exhibit more vasodilation, causing a decrease in systemic vascular resistance (SVR) and are useful in decreasing blood pressure. Non-dihydropyridine CCBs work primarily by reducing chronotropy and inotropy in the SA/AV nodes and are useful in the management of supraventricular tachycardia. Side effects include peripheral edema, flushing, headache, and constipation.

2.7 BETA ADRENERGIC BLOCKER

Beta-blockers include a large class of medications that have variable affinities for beta and alpha receptors throughout the body, thus giving them diverse roles in treating different conditions. Depending on their target beta-receptor (β-1 or β-2), certain beta-blockers have a significant role in metabolic activity and smooth muscle relaxation. Beta-blockers are rarely used as initial therapy for hypertension list, a patient has a history of prior MI, coronary artery disease (CAD), or heart failure (HF). In the case of CAD or HF, cardioselective beta-blockers are first-line agents in treating hypertension as they block the β-1 receptors in cardiomyocytes, leading to decreased chronotropy/inotropy and therefore cardiac oxygen demand. Non-cardioselective beta-blockers should be avoided in patients with reactive airway disease.

2.8 ALPHA ADRENERGIC BLOCKER

Alpha-1 blockers

These medications work by inhibiting the activation of alpha-1 receptors (located on the peripheral vasculature) by norepinephrine, thus leading to a decrease in BP. They are often used in patients with benign prostate hypertrophy (BPH) and are typically considered second-line BP agents, often used in combination with other agents. They are associated with orthostatic hypotension and should be used with caution in the elderly.

Alpha-2 agonists

These agents work by stimulating alpha-2 receptors in the central nervous system (CNS), which reduces sympathetic outflow and causes a decrease in peripheral resistance, heart rate, and blood pressure. These agents are generally used as last line efforts to control blood pressure. Abrupt cessations of drugs like clonidine can lead to rebound hypertension and should, therefore, be tapered. Additional adverse reactions include sedation orthostatic hypotension, dry mouth, and sedation.

2.9 CENTAL SYMPATHOLYTICS

CLONIDINE:- It acts centrally as an alpha 2 agonist to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure.

Methyldopa Hydrochloride, USP. Methyldopate hydrochloride, L-3-(3,4-dihydroxyphenyl)-2-methylalanine ethyl ester hydrochloride (Aldomet ester hydrochloride),-methyldopa, lowers blood pressure by inhibiting the outflow of sympathetic vasoconstrictor impulses from the brain. Early studies had suggested that the hypotensive action of -methyldopa was a result of the peripheral properties of the drug as a decarboxylase inhibitor or a false transmitter.

The current hypothesis concerning the hypotensive activity of methyldopa involves the CNS as the site of action. Methyldopa, on conversion to -methyl norepinephrine acts on 2-adrenergic receptors to inhibit the release of norepinephrine, resulting in decreased sympathetic outflow from the CNS and activation of parasympathetic outflow.

2.10 VASODILATORS

These agents include hydralazine, minoxidil, and nitrates. work by relaxing the peripheral smooth muscles, causing vasodilation and a decrease in blood pressure. They are typically used in patients with angina to help control symptoms and blood pressure. The combination of hydralazine and long-acting nitrates has been shown to decrease mortality in patients with HFrEF and can be considered if patients cannot tolerate ACE inhibitor/ARB therapy. Hydralazine hydrochloride is useful in the treatment of moderate-to-severe hypertension. It is often used in conjunction with less potent antihypertensive agents, because side effects occur frequently when it is used alone in adequate doses. In combinations, it can be used in lower and safer doses. Its action appears to be centered on the smooth muscle of the vascular walls, with a decrease in peripheral resistance to blood flow. This results in increased blood flow through the peripheral blood vessels.

2.11 NEW APPROACHES / NOVEL METHODS IN TREATMENT OF HYPERTENSION

2.11.1 Anti-Aldosterone Agents

Aldosterone is a mineralocorticoid that regulates electrolyte and volume homeostasis in normal subjects and, when elevated, can contribute to the development of hypertension and a variety of related pathologies, including myocardial hypertrophy and fibrosis and HF. The principal effector of aldosterone action is the mineralocorticoid receptor (MR), a nuclear transcription factor that is expressed at high levels in the cortical

collecting duct of the kidney. Activated MRs stimulate expression of sodium channels, resulting in increased sodium and water reabsorption and potassium loss, leading eventually to a volume expanded form of hypertension. Activation of MRs in extra adrenal tissues, particularly the heart and blood vessels, also promotes the development of hypertension and CVD by upregulating NADPH oxidase and increasing production of reactive oxygen species. This reduces the bioavailability of nitric oxide and leads to endothelial dysfunction and vascular disease. Aldosterone is synthesized from 11-deoxycorticosterone in the zona glomerulosa of the adrenal cortex via the action of a mitochondrial cytochrome P450 enzyme, aldosterone synthase, which is encoded by the CYP11B2 gene11 Aldosterone synthase catalyzes the final 3 rate-limiting steps of aldosterone synthesis.

2.11.2 Mineralocorticoid Receptor Antagonist

MRs have been therapeutic targets in hypertension treatment for over half a century: the first MR antagonist (MRA), spironolactone, appeared in the early 1960s. Although spironolactone monotherapy has modest BP lowering efficacy, it has had a recent resurgence as add-on therapy in patients with resistant hypertension and in the treatment of HF. Spironolactone use has been limited by its lack of selectivity for the MR, particularly at higher (>25 mg) doses. Because of its structural similarity to progesterone, spironolactone has significant progestogenic and ant androgenic activity, leading to troublesome adverse effects in both men and women. The more selective MRA eplerenone lacks the antiandrogenic effects of spironolactone, but is less potent and has a shorter (3–4 h) half-life, leading to reduced antihypertensive efficacy and a requirement for twice daily dosing. The search for newer nonsteroidal MRAs that have superior selectivity and affinity for the MR began with the observation that some dihydropyridine calcium channel blockers compete with aldosterone for binding to the ligand binding domain of the MR and decrease aldosterone-mediated recruitment of transcriptional coactivators that are necessary for MR-directed DNA transcription.

2.11.3 Activators of the Angiotensin-Converting Enzyme2/Angiotensin(1–7)/MAS Receptor Axis.

The classical renin–angiotensin system (RAS) has been studied extensively for decades and has yielded numerous effective therapies for hypertension and its complications. More recently, components of the RAS that play counter regulatory roles have been identified, characterized and put forward as therapeutic targets for hypertension and other forms of CVD46–50. The carboxypeptidase angiotensin-converting enzyme 2 (ACE2) converts 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 studied intensively and shown to activate the G-protein-coupled Mas receptor, triggering a signaling cascade that results in vasodilation, reduction in oxidative stress, and ant hypertrophic and ant fibrotic effects. ACE2 also mediates degradation of Ang II, likely contributing to the antihypertensive/vasoprotective effects of the counter regulatory RAS pathway.

2.11.4 Centrally Acting Aminopeptidase Inhibitors

Activation of the brain RAS plays an important role in the pathogenesis of hypertension in animal models. Two membrane-bound zinc metalloproteases, aminopeptidase A (APA) and aminopeptidase N, are involved in the metabolism of brain Ang II and III. APA cleaves the N-terminal Asp from Ang II to form Ang III, and aminopeptidase N cleaves the N-terminal Ang from Ang III to form Ang IV. Ang II and Ang III have similar affinities for Ang II receptors and both peptides stimulate pressor responses by activating sympathetic nervous system activity, inhibiting the baroreflex at the level of the nucleus tractus solitarius and increasing release of arginine vasopressin into the circulation. Orally administered RB150, a dimer of EC33, has been shown to enter the brain of SHR and DOCA (deoxy corticosterone acetate)-salt rats to inhibit brain APA activity and block the formation of Ang III and to normalize BP for several hours. The RB150-induced depressor response was related to inhibition of arginine vasopressin release, resulting in a diuresis and reduction in volume, and a decrease in sympathetic tone, resulting in reduced vascular resistance.

2.11.5 Vasopeptidase Inhibitor

The zinc metalloprotease neprilysin (neutral endopeptidase 24.11) is a therapeutic target for hypertension and other forms of CVD because it degrades the natriuretic peptides atrial natriuretic peptide (ANP), BNP, and urodilatin, and the increase in circulating natriuretic peptide levels that results from neprilysin inhibition leads to natriuresis, vasodilation, renin– angiotensin–aldosterone system inhibition, reduced sympathetic drive, and ant proliferative and ant hypertrophic effects on the heart and vasculature. However, neprilysin inhibitors are ineffective in lowering BP, likely because nepriysin also degrades vasoconstrictor peptides, for example, Ang II and endothelin-Thus, combining a neprilysin inhibitor with an RAS blocker or an endothelin-converting enzyme inhibitor offers the theoretical advantage of enhancing the favorable vasodilator/natriuretic effects of ANP and BNP and reducing the deleterious vasoconstrictor effects of Ang II or endothelin-1 on BP and target organ damage.

2.11.6 Dual L-Type Calcium Channel Blocker/Endothelin A/B2 Receptor Antagonist

Entry of calcium into vascular smooth muscle cells via L-type calcium channels is a major determinant of vascular tone and BP. Blockade of the L-type calcium channel with calcium channel blockers effectively lowers BP in hypertensive subjects. Endothelin-1 (ET-1) is a potent vasoconstrictor and mediator of inflammation when activating its type A and type B2 receptors. In

contrast, ET-1 has vasodilator and anti-inflammatory effects mediated by its B1 receptor. Recently, a dual L-type calcium channel blocker/ET A/B2 antagonist, sargachromenol-D, was isolated from Sargassum siliquastrum, a marine brown alga. Sargachromenol-D was shown to reduce ET-1 and K+ depolarization-induced vasoconstriction in basilar arteries of rabbits and to reduce BP in rodent models of hypertension.

2.11.7 Ouabain Inhibitors

Ouabain binds to and activates Na+/K+ ATPase, initiating a signaling cascade that leads to inhibition of Na+ and K+ flux and activation of the cytoplasmic tyrosine kinase (cSRC), resulting in inflammation and reactive oxygen species formation in the vasculature. Activation of cSRC over time can cause hypertension and HF, and ouabain has been shown to increase vascular resistance, leading to hypertension in rodent models. Thus, ouabain inhibitors have been considered as potential therapies for hypertension and CVD. Rostafuroxin, which was developed to antagonize the action of ouabain on Na+/K+ ATPase, has been shown to lower SBP, facilitate endothelium-mediated vascular relaxation, increase nitric oxide production, and reduce oxidative stress in resistance arteries from DOCA-salt hypertensive rats.

2.12 COMBINATION THERAPY & NOVEL DRUGS

2.12.1 Tripliam / Triplixam

Tripliam contains the angiotensin converting enzyme (ACE) inhibitor perindopril, the dihydropyridine CCB amlodipine, and the idolize diuretic indapamide. Multiple phase III clinical trials of Tripliam have been completed, and it is currently in a phase IV study. The Perindopril-Indapamide plus Amlodipine in high risk hypertensive patients (PIANIST) trial evaluated the BP lowering effect of the perindopril- amlodipine-indapamide combination in 4731 patients with difficult to treat hypertension who were high-risk for CVD and were uncontrolled on their current regimen, which included a wide range of antihypertensive. The three-drug combination reduced office BP significantly from a baseline mean of 160/93 mmHg to a treatment mean of 132/80 mmHg and also significantly reduced ambulatory BP (ABP).

2.12.2 Micatrio

Micatrio contains the angiotensin II receptor blocker (ARB) telmisartan, the dihydropyridine CCB amlodipine, and the thiazide diuretic hydrochlorothiazide. One of the earliest studies to examine this three-drug combination in 2009 showed that the fixed-dose combination resulted in mean reductions in SBP and diastolic BP (DBP) of 38.5 mmHg and 16 mmHg greater than telmisartan monotherapy. Subsequent studies found that Micatrio is more effective at lowering SBP and DBP compared to telmisartan and amlodipine combined. The Telmisartan/Amlodipine+ Hydrochlorothiazide Versus Telmisartan/Amlodipine Combination Therapy for Essential Hypertension Uncontrolled With Telmisartan/Amlodipine (TAHYTI) trial was a randomized controlled trial of 310 patients that showed that addition of hydrochlorothiazide to telmisartan and amlodipine resulted in a clinically significant 12.3/ 8.4 mmHg reduction in office BP compared to telmisartan/ amlodipine.

2.12.3 Fimasartan Combinations

Fimasartan is an ARB that was approved for the treatment of hypertension in South Korea under the name Kanarb after studies found it to produce DBP reductions greater than losartan and comparable to candesartan after 12 weeks. Fimasartan was combined with amlodipine and approved in South Korea under the name Dukarb after clinical studies revealed greater reduction in sitting DBP for the fixed-dose combination of fimasartan and amlodipine over placebo or either agent as monotherapy. A phase I clinical trial of a fixed-dose combination pill containing fimasratan, amlodipine, and hydrochlorothiazide is currently underway, and a fixed-dose combination of fimasartan, amlodipine, and rosuvastatin, a HMG-CoA reductase inhibitor, is currently in phase III clinical trials. The combination of fimasartan and rosuvastatin has been found to be efficacious in lowering both BP and LDL cholesterol and to be as safe as either agent administered alone.

2.12.4 Entresto

Entresto, a fixed-dose combination of sacubitril, a neprilysin inhibitor, and the ARB valsartan was approved by the FDA in 2014 for the treatment of heart failure (HF) and has also been evaluated as a potential treatment for hypertension. Neprilysin is a neutral endopeptidase that degrades endogenous vasodilator peptides such as bradykinin and natriuretic peptides, leading to increased BP and target organ damage. The Prospective Comparison of ARNI With an ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial is a randomized double-blind study of 8442 patients with HF with reduced left ventricular ejection fraction (HFrEF) that demonstrated a reduction in the composite outcome of death from CV causes or hospitalization for recurrent HF for Entresto compared to enalapril.

The Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Measuring Arterial Stiffness in the Elderly (PARAMETER) study is a randomized, double-blind trial that compared the effects of Entresto to olmesartan on central hemodynamics by measuring overall reduction in mean central aortic systolic pressure (CASP) in elderly patients with systolic hypertension.

2.12.5 Polypill

Polypill is a general term used to describe a fixed-dose combination pill (FDCP) with multiple therapeutic targets. The polypill was first proposed for the primary prevention of CVD in 2003 by Wald and Law as a

combination of a statin, thiazide diuretic, beta blocker, ACE inhibitor, folic acid, and aspirin. Since that time, various polypills have been evaluated in multiple clinical trials for safety, efficacy, adherence, and cost and is now approved for use in over 30 countries. Polypills have been shown to increase patient adherence by reducing a patient's pill burden, thus improving BP control. Most polypill formulations are comprised of a statin and one or two antihypertensive with or without aspirin, though other formulations, such as atorvastatin, aspirin, and clopidogrel, have been proposed for chronic heart disease. (HOPE-3) trial showed an overall benefit of a multi-target FDCP consisting of rosuvastatin, candesartan, and hydrochlorothiazide compared to placebo in primary prevention for those at intermediate risk of CVD.

2.12.6 Finerenone

Finerenone, the newest MRA, is being evaluated in clinical trials for the treatment of hypertension, HF, and diabetic nephropathy. Finerenone has less structural similarity to steroid hormones than the other MRAs and thus does not produce the adverse effects seen with spironolactone. The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) was the first to evaluate the effect of finerenone in humans with CVD. ARTS compared finerenone to placebo and spironolactone in patients with HFrEF and CKD. Finerenone use resulted in significantly lower serum potassium concentrations and preserved glomerular filtration rates compared with spironolactone. However, finerenone did not lower SBP (a secondary outcome) when compared to placebo. The ARTS results redirected the developmental profile of finerenone toward the treatment of some well-known complications of hypertension, HF, and CKD, rather than hypertension.

3. CONCLUSION

Hypertension has been identified by WHO as one of the most significant risk factors for morbidity and mortality worldwide, and despite strong evidence for treatment, studies suggest that many people remain sub-optimally controlled. New approaches, including new technologies, are therefore needed to improve screening, detection and control of raised blood pressure in the community. Breaking away from traditional cuff-based measurement of blood pressure, the widespread accessibility of smartphones and mobile health applications offers new prospects for ubiquitous monitoring of parameters such as blood pressure, but evidence of both accuracy and efficacy is currently lacking. Current market penetration of smartphones into the elderly is not sufficient for widespread implementation of technology such as smartphone apps in this age group, but M-health has definite potential to aid screening and diagnosis in younger adults, pregnant women, children and adolescents as well as older populations as the technology becomes more commonplace. A key issue with both apps and novel non-invasive devices are the lack of a universally agreed standard for the validation of this technology, and current protocols simply do not include them. There is thus limited incorporation of this technology into clinical practice at present, and this must be addressed as a matter of urgency by European, UK, and American regulators.

Recent evidence for the beneficial effects of targeting lower BP goals in hypertensive patients has created a paradigm shift in CVD treatment development. Prior to these recent revelations in hypertension management, development of antihypertensive medications had reached a low point over the last decades. But now, FDCPs, polypills, and novel therapeutic agents offer promising solutions as treatments for hypertension. Although few hypertensive treatments have been approved for clinical use in recent years, the drugs and vaccines discussed in this review remain viable options for treatments in the near future and represent a means to close the gap between new stricter BP goals and the current suboptimal rates of goal BP achievement.

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