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NOVEL TREATMENTS FOR HYPERTENSION (T UNGER, SECTION EDITOR)

Novel Medical Treatments for Hypertension and Related Comorbidities

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Abstract

Purpose of Review The purpose of this review is to summarize the most recent data available on advances in development of novel medical treatments for hypertension and related comorbidities.

Recent Findings Approximately half of all hypertensive patients have not achieved goal blood pressure with current available antihypertensive medications. Recent landmark studies and new hypertension guidelines have called for stricter blood pressure control, creating a need for better strategies for lowering blood pressure. This has led to a shift in focus, in recent years, to the development of combination pills as a means of achieving improved blood pressure control by increasing adherence to prescribed medications along with further research and development of promising novel drugs based on discovery of new molecular targets such as the counter-regulatory renin-angiotensin system.

Summary Fixed-dose combination pills and novel treatments based on recently discovered pathogenic mechanisms of hypertension that have demonstrated promising results as treatments for hypertension and related comorbidities will be discussed in this review.

Keywords Hypertension · Blood pressure · Novel treatments · Medications

Introduction

Following the death of President Franklin D. Roosevelt in 1945 from a cerebral hemorrhage secondary to longstanding uncontrolled hypertension, the problem of high blood pressure (BP) gained national attention as a health crisis for the first time [1]. Healthcare providers and researchers began to turn their attention to the detection and treatment of hypertension and the development of antihypertensive medications. The earliest medications to be approved by the United States Food and Drug Administration (FDA) for hypertension treatment were the alpha adrenergic receptor antagonist phenoxybenzamine and the vasodilator hydralazine in 1953 (Table 1). Since then over 130 agents, many of which are available in single-pill combinations, have been approved by the FDA for the treatment of hypertension. Each of these agents uses one or more of the 17 mechanisms of action to lower BP [2]. Antihypertensive drug development and approval began in the early 1950s, peaked in the 1980s and 1990s, and decreased in the twenty-first century. Since 2011, only four antihypertensive drugs and drug combinations have been approved by the FDA, including azilsartan (Edarbi, Arbor Pharmaceuticals), azilsartan/chlorthalidone (Edarbiclor, Arbor Pharmaceuticals), perindopril/amlodipine (Prestalia, Marina Biotech), and most recently nebivolol/valsartan (Byvalson, Allergan) in 2016 [2]. In this review, we discuss new drugs and drug combinations that have undergone preclinical or clinical testing for the treatment of hypertension and its comorbidities since our previous review of the topic in 2015 [3••].

Based on the evidence from the landmark SPRINT trial (Systolic Blood Pressure Intervention Trial) that lowering systolic BP (SBP) to < 120 mmHg produced significant reductions in cardiovascular events and all-cause mortality compared to treating to the standard SBP target of < 140 mmHg and from a number of recent meta-analyses and observational studies that demonstrated similar benefits of aggressive BP reduction, the 2017 AHA/ACC Hypertension Guidelines

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Table 1 Current approved treatments for hypertension

Trade name	Generic name	MOA	Route	Year approved
Dibenzyline	Phenoxybenzamine	Alpha receptor antagonist	PO	1953
Apresoline	Hydralazine	Vasodilator	PO/IV	1953
Serpalan	Reserpine	Indole alkaloid	PO	1955
Inversine	Mecamylamine	Nicotinic receptor antagonist	PO	1956
Harmonyl	Deserpidine	DHP CCB	PO	1957
Esidrix	HCTZ	Thiazide	PO	1959
Naturetin	Bendroflumethiazide	Thiazide	PO	1959
Saluron	Hydroflumethiazide	Thiazide	PO	1959
Renese	Polythiazide	Thiazide	PO	1961
Enduronyl	Deserpidine/methyclothiazide	DHP CCB/thiazide	PO	1961
Diuril	Chlorthiazide	Thiazide	PO/IV	1961
Aldomet	Methyldopa	Alpha 2 receptor agonist	PO	1962
Aldoril	Methyldopa/HCTZ	Alpha 2 receptor agonist/thiazide	PO	1962
Renese-R	Polythiazide/reserpine	Thiazide/indole alkaloid	PO	1963
Midamor	Amiloride	ENAC inhibitor	PO	1967
Edecrin	ethacrynic acid	Loop diuretic	PO	1967
Inderal	Propranolol	Beta blocker	PO	1967
Lasix	Furosemide	Loop diuretic	PO	1968
Zaroxolyn	Metolazone	Thiazide-like diuretic	PO	1973
Catapres	Clonidine	Central acting alpha agonist	PO	1974
Minipress	Prazosin	Alpha blocker	PO	1976
Aquatensen	Methyclothiazide	Thiazide	PO	1977
Lopressor	Metoprolol tartrate	Beta blocker	PO	1978
Loniten	Minoxidil	Vasodilator	PO	1979
Inderide	Propranolol/HCTZ	Beta blocker/thiazide	PO	1979
Minizide	Polythiazide/prazosin	Thiazide/alpha blocker	PO	1980
Moduretic	Amiloride/HCTZ	ENAC inhibitor/thiazide	PO	1981
Procardia	Nifedipine	DHP-CCB	PO	1981
Blocadren	Timolol	Beta blocker	PO	1981
Timolide	Timolol/HCTZ	Beta blocker/thiazide	PO	1981
Oreticyl	Deserpidine/HCTZ	DHP CCB/thiazide	PO	<1982
Serpasil-Apresoline	Reserpine/hydralaine	Indole alkaloid/vasodilator	PO	<1982
Apresoline-Esidrix	Hydralazine/HCTZ	Vasodilator/thiazide	PO	<1982
Nitrostat	Nitroglycerin	Vasodilator	PO/IV	<1982
Thalitone	Chlorthalidone	Thiazide	PO	1982
Aldactazide	Spironolactone/HCTZ	MRA/thiazide	PO	1982
Wytensin	Guanabenz	Alpha 2 receptor agonist	PO	1982
Visken	Pindolol	Beta blocker	PO	1982
Bumex	Bumetanide	Loop diuretic	PO	1983
Corzide	Bendroflumethiazide/Nadolol	Thiazide/beta blocker	PO	1983
Aldactone	Spironolactone	MRA	PO	1983
Sectral	Acebutolol	Beta blocker	PO	1984
Catapress-TTS-1	Clonidine	Central acting alpha agonist	Transdermal	1984
Maxzide	Triamterene/HCTZ	MRA/thiazide	PO	1984
Lopressor HCT	Metoprolol tartrate/HCTZ	Beta blocker/thiazide	PO	1984
Tenoretic	Atenolol/chlorthalidone	Beta blocker/thiazide	PO	1984
Normodyne	Labetolol	Beta blocker	IV	1984
Capoten	Captopril	ACE I	PO	1985
Corgard	Nadalol	Beta blocker	PO	1986

Table 1 (continued)

Trade name	Generic name	MOA	Route	Year approved
Tenex	Guanfacine	Alpha 2 receptor agonist	PO	1986
Trandate	Labetalol/HCTZ	Beta blocker/thiazide	PO	1987
Inderal LA	Propranolol	Beta blocker	PO	1987
Prinivil	Lisinopril	ACE I	PO	1987
Norvasc	Amlodipine	DHP CCB	PO	1987
Normodyne	Labetalol	Beta blocker	PO	1987
Hytrin	Terazosin	Alpha blocker	PO	1987
Clorpres	Chlorthalidone/clonidine	Thiazide/central alpha agonist	PO	1987
Vasotec	Enalapril	ACEI	PO	1988
Cardene	Nicardipine	DHP-CCB	PO/IV	1988
Cartrol	Carteolol	Beta blocker	PO	1988
Kerlone	Betaxolol	Beta blocker	PO	1989
Hydro-Ride	Amiloride/HCTZ	ENAC inhibitor/thiazide	PO	1990
Cardura	Doxazosin	Alpha blocker	PO	1990
Tenormin	Atenolol	Beta blocker	PO	1990
Verelan	Verapamil	Non-DHP CCB	PO	1990
Monopril	Fosinopril	ACE I	PO	1991
Lotensin	Benazepril	ACE I	PO	1991
Altace	Ramipril	ACE I	PO	1991
Accupril	Quinapril	ACE I	PO	1991
Lotensin HCT	Benazepril/HCTZ	ACE I/thiazide	PO	1992
Zebeta	Bisoprolol	Beta blocker	PO	1992
Ziac	Bisoprolol/HCTZ	Beta blocker/thiazide	PO	1993
Aceon	Perindopril	ACE I	PO	1993
Lozol	Indapamide	Thiazide-like	PO	1993
Demadex	Torsemide	Loop diuretic	PO	1993
Zestoretic	Lisinopril/HCTZ	ACE I/thiazide	PO	1993
Monopril HCT	Fosinopril/HCTZ	ACEI/thiazide	PO	1994
Plendil	Felodipine	DHP-CCB	PO	1994
Cozaar	Losartan	ARB	PO	1995
Hyzaar	Losartan/HCTZ	ARB/thiazide	PO	1995
Lotrel	Amlodipine/benazepril	DHP-CCB/ACE I	PO	1995
Vaseretic	Enalapril/HCTZ	ACE I/thiazide	PO	1995
Toprol-XL	Metoprolol succinate	Beta blocker	PO	1995
Univasc	Moexipril	ACE I	PO	1995
Tiazac	Diltiazem	Non-DHP CCB	PO	1996
Teczem	Enalapril/diltiazem	ACEI/Non-DHP CCB	PO	1996
Mavik	Trandolapril	ACEI	PO	1996
Covera-HS	Verapamil	Non-DHP CCB	PO	1996
Tarka	Trandolapril/verapamil	ACE I/non-DHP CCB	PO	1996
Coreg	Carvedilol	Beta blocker	PO	1997
Avaprol	Irbasartan	ARB	PO	1997
Teveten	Eprosartan	ARB	PO	1997
Posicor	Mibefradil	CCB	PO	1997
Microzide	HCTZ	Thiazide	PO	1997
Lexxel	Enalapril/felodipine	ACEI/DHP-CCB	PO	1997
DynaCirc CR	Isradipine	DHP-CCB	PO	1997
Diovan	Valsartan	ARB	PO	1997
Corlopam	Fenoldopam	D1-recptor agonist	IV	1997

Table 1 (continued)

Trade name	Generic name	MOA	Route	Year approved
Uniretic	Moexipril/HCTZ	ACE I/thiazide	PO	1997
Avalide	Irbesartan/HCTZ	ARB/thiazide	PO	1997
Capozide	Captopril/HCTZ	ACEI/thiazide	PO	1997
Micardis	Telmisartan	ARB	PO	1998
Diovan HCT	Valsartan/HCTZ	ARB/thiazide	PO	1998
Accuretic	Quinapril/HCTZ	ACE I/thiazide	PO	1999
Micardis HCT	Telmisartan/HCTZ	ARB/thiazide	PO	2000
Cardizem	Diltiazem HCl	Non-DHP CCB	PO	2000
Atacand	Candesartan	ARB	PO	2000
Atacand HCT	Candesartan/HCTZ	ARB/thiazide	PO	2000
Teveten HCT	Eprosartan/HCTZ	ARB/thiazide	PO	2001
Inspra	Eplerenone	MRA	PO	2002
Benicar	Olmesartan	ARB	PO	2002
Brevibloc	Esmolol	Beta blocker	IV	2003
Caduet	Amlodipine/atorvastatin	DHP-CCB/HMG-CoA red	PO	2004
Dutoprol	Metoprolol succinate/HCTZ	Beta blocker/thiazide	PO	2006
Exforge	Amlodipine/valsartan	DHP-CCB/ARB	PO	2007
Bystolic	Nebivolol	Beta blocker	PO	2007
Tekturna	Aliskrien	Direct renin inhibitor	PO	2007
Azor	Amlodipine/olmesartan	DHP-CCB/ARB	PO	2007
Tekturna HCT	Aliskiren/HCTZ	DRI/thiazide	PO	2008
Cleviprex	Clevidipine	DHP CCB	IV	2008
Sular	Nisoldipine	DHP-CCB	PO	2008
Valturna	Aliskiren/valsartan	DRI/ARB	PO	2009
Exforge HCT	Amlodipine/valsartan/HCTZ	DHP-CCB/ARB/thiazide	PO	2009
Twynsta	Telmisartan/amlodipine	ARB/DHP-CCB	PO	2009
Amturnide	Aliskiren/amlodipine/HCTZ	DRI/DHP-CCB/thiazide	PO	2010
Tekamlo	Aliskiren/amlodipine	DRI/DHP-CCB	PO	2010
Tribenzor	Olmesartan/amlodipine/HCTZ	ARB/DHP-CCB/thiazide	PO	2010
Edarbi	Azilsartan	ARB	PO	2011
Edarbyclor	Azilsartan/chlorthalidone	ARB/thiazide	PO	2011
Prestalia	Perindopril/amlodipine	ACEI/DHP-CCB	PO	2015
Byvalson	Nebivolol/valsartan	Beta Blocker/ARB	PO	2016

DHP CCB dihydropyridine calcium channel blocker, *ENAC* epithelial sodium channel, *MRA* mineralocorticoid receptor antagonist, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin type 1 receptor blocker, *DRI* direct renin inhibitor

recommended a target BP < 130/80 mmHg for most hypertensive patients [4••, 5••]. Similarly, other major guideline writing committees in Canada, Australia, and Europe have concluded that the SBP target for antihypertensive drug treatment in adults with hypertension and high cardiovascular disease (CVD) risk should be lower than previously recommended [6–8]. Achieving these aggressive treatment goals will likely be a daunting task since approximately 50% of hypertensive patients are now uncontrolled to the traditional target of < 140/90 mmHg.

Failure to achieve BP control is often due to non-adherence to prescribed medication regimens [9]. Of all patients treated for hypertension, 40% stopped their regimen within 2 years of initiation and 61% stopped by 10 years [10]. In 2017, the Center for Disease Control (CDC) reported that one in five prescriptions is never filled and 50% that are filled are not taken properly [11]. Based on these data, it is apparent that a large gap exists between current treatment guidelines and long-term, successful BP control in the majority of patients. For these reasons, much of the ongoing research and development in hypertension treatment is dedicated to developing fixed-dose combination drugs, allowing for better BP control by improving adherence to medications. Recent research has been

directed toward improving adherence by combining two or more antihypertensive agents and combining antihypertensive medications with medicines that treat comorbidities such as hyperlipidemia [12]. Currently, 16 fixed-dose combination medications are in ongoing clinical trials for the treatment of hypertension and related comorbidities [12] (Table 2). Each of these contains at least one FDA-approved antihypertensive medication and four combinations contain three or more agents. The majority of these are combinations of an ACE inhibitor or an ARB with a calcium channel blocker (CCB) and/or thiazide diuretic.

Combination Therapy

Tripliam/Triplixam

Tripliam contains the angiotensin converting enzyme (ACE) inhibitor perindopril, the dihydropyridine CCB amlodipine, and the indoline 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-

Table 2 Antihypertensive drugs in current trials

Drug	Mechanism of action	Status
Finerenone	Mineralocorticoid receptor antagonist	Phases II & III
CS-3150 (Esaxerenone)	Mineralocorticoid receptor antagonist	Phase III
C21	AT2 receptor agonist	Preclinical
rhACE2	ACE2 activator	Phase II
HP-β-CD/angiotensin(1-7)	Ang 1-7 & Ang 1-7 Analog	Phase I
AVE0991	Non-peptide agonist of MAS	Preclinical
CGEN-856S	Peptide agonist of MAS	Preclinical
Alamandine/HP-β-CD	MAS-related G protein coupled receptor, member D agonist	Preclinical
QGC001	Aminopeptidase A inhibitor	Phase II (NEW-HOPE)
PB1046 (Vasomera)	Vasoactive Intestinal Peptide Receptor (VPAC 2) Agonist	Phase II
AZD1722 (Tenapanor)	Intestinal Na^+/H^+ Exchanger 3 Inhibitor	Phase III
Sargachromenol-D	L-type CCB & Endothelin A/B_2 Receptor Antagonist	Preclinical
Fimasartan	ARB	Phase III
Rostafuroxin	Ouabain Antagonist	Phase II
Allisartan	ARB	Phase IV
Dual acting drugs		
Sacubitril/valsartan (Entresto)	ARB-neprilysin inhibitor	Phase III
Candesartan/amlodipine (HL-068)	ARB/CCB	Phase IV
HL-040XC	ARB/HMG-CoA reductase inhibitor	Phase III
Perindopril/indapamide/amlodipine (tripliam)	ACE Inhibitor/indoline diuretic/CCB	Phase III
Telmisartan/amlodipine/HCTZ (Micatrio)	ARB/CCB/thiazide	Phase III
Valsartan/lercanidipine (Levacalm)	ARB/CCB	Phase III
Atorvastatin/amlodipine/losartan/HCTZ (Polypill)	HMG-CoA reductase Inhibitor/CCB/ARB/thiazide	Phase II
Fimasartan/amlodipine	ARB/CCB	Phase IV
Losartan/indapamide	ARB/indoline diuretic	Phase III
Olmesartan/chlorthalidone	ARB/thiazide	Phase III
Fimasartan/atorvastatin	ARB/HMG-CoA reductase Inhibitor	Phase III
Fimasartan/amlodipine/rosuvastatin	ARB/HMG-CoA red/CCB	Phase III
Duowell (telmisartan/rosuvastatin)	ARB/HMG-CoA reductase inhibitor	Phase IV
YHP1701	Antihypertensive/antihyperlipidemic	Phase III
Viena II	Antihypertensive/antihyperlipidemic	Phase II

Ang indicated angiotensin, *AT2* angiotensin type 2, *ACE2* angiotensin converting enzyme 2, *ARB* angiotensin type 1 receptor blocker, *ACE* angiotensin converting enzyme, *CCB* calcium channel blocker

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 antihypertensives [13]. 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). In another study, similar reductions in 24 h ABP, daytime and nighttime BP, and pulse pressure were shown with the fixed-dose triple combination compared to the same three individual "free" anti-hypertensive medications after 1 month of treatment [14]. The Once-daily Fixed combiNation vErsus freE-drug cOmbination of Three aNtihypertensive Agents in arteriaL hYpertension (ONE & ONLY) trial randomized 305 patients to receive either a fixed-dose combination of perindopril-indapamide-amlodipine-atorvastatin or a free-drug combination of perindopril, indapamide, and amlodipine with atorvastatin [15]. The study demonstrated that Tripliam significantly increased adherence and reduced SBP without increasing costs compared to the free-drug group. No significant difference in LDL lowering was found between the groups, though the fixed-dose combination group experienced greater CVD risk reduction overall.

Micatrio

Micatrio contains the angiotensin II receptor blocker (ARB) telmisartan, the dihydropyridine CCB amlodipine, and the thiazide diuretic hydrocholorothiazide. 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 [16]. 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 [17]. Another study revealed that the three-drug combination produced a significantly greater reduction in SBP (− 5.3 mmHg difference) when adjusted for baseline BP compared to telmisartan-amlodipine [18]. Micatrio is approved for the treatment of hypertension in Japan.

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 [19, 20]. 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 [21]. 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 [22]. Initial studies of the triple agent fixed-dose combination are expected to be completed in 2019.

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 (Fig. 1) [3••]. 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 [23•]. Since its approval for the treatment of HF in 2014, Entresto has been evaluated in multiple clinical trials as a treatment for hypertension and its comorbidities, including chronic kidney disease (CKD), HF, diabetes, and obesity [24–27].

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 [28•]. Entresto produced greater reduction in CASP and central aortic pulse pressure at 12 weeks that was not sustained at 52 weeks. However, the olmesartan group required more add-on therapy with either amlodipine or hydrochlorothiazide to achieve the same BP reduction. The Efficacy and Safety of Crystalline Valsartan/Sacubitril (LCZ696) Compared With Placebo and Combinations of Free Valsartan and Sacubitril in Patients With Systolic Hypertension (RATIO) study

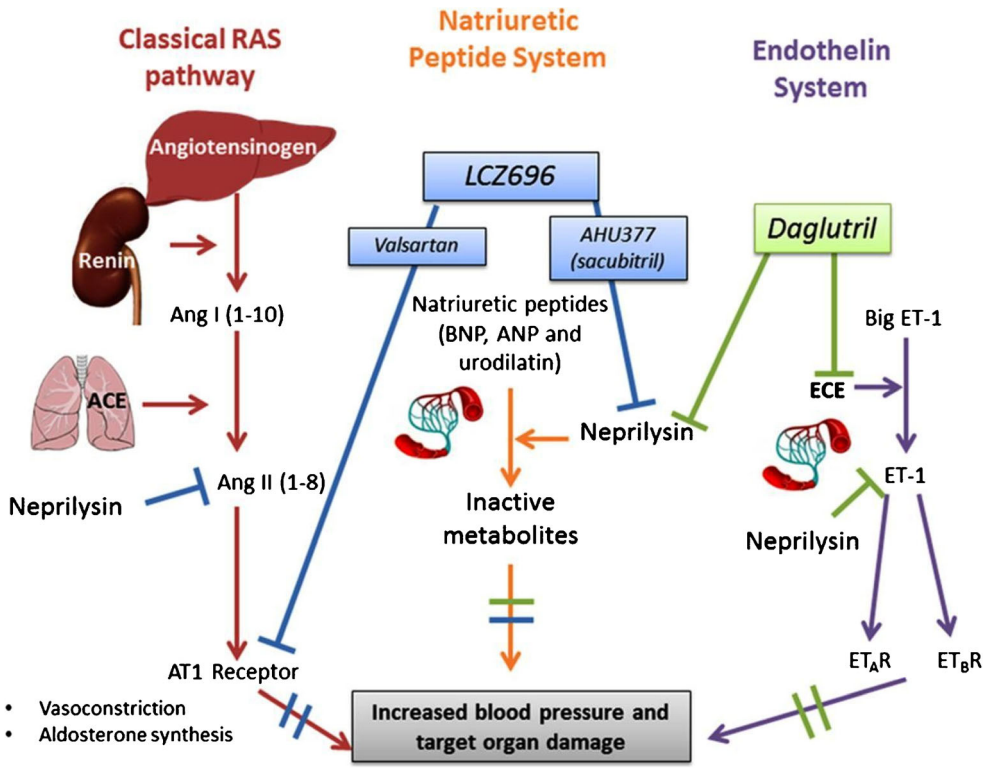

Fig. 1 Mechanism of Entresto (LCZ696). The ARB-neprilysin inhibitor, Entresto (LCZ696), is a single molecule comprising the ARB valsartan and the neprilysin inhibitor, sacubitril. Entresto has been shown to lower BP, and to prevent death from cardiovascular events and hospitalizations for HF in patients with HF with a reduced EF. (Reprinted with permission from Circulation Research 116:6, 2015)

examined the effectiveness of Entresto in reducing clinic sitting SBP compared to sacubitril and valsartan monotherapy [29]. Entresto produced significantly greater reductions in office BP, pulse pressure, and all secondary end-points (24 h mean BP, pulse pressure, mean daytime and nighttime ABP).

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 [30]. 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 [31, 32, 33••, 34, 35]. Polypills have been shown to increase patient adherence by reducing a patient's pill burden, thus improving BP control [31]. Most polypill formulations are comprised of a statin and one or two antihypertensives with or without aspirin, though other formulations, such as atorvastatin, aspirin, and clopidogrel, have been proposed for chronic heart disease [36]. Globally, the prevention and treatment of CVD have advanced to the forefront of healthcare policy in recent years, thereby creating a new push for use of polypills [37]. Recently, the Heart Outcomes Prevention Evaluation-3 (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 [38]. This FDCP has also been suggested as a primary and secondary prevention strategy for cerebrovascular disease [39]. Multiple studies have assessed the potential cost-effectiveness of polypills and have found them to be more cost-effective than the simultaneous use of each individual agent [32, 40]. There are many ongoing clinical trials of polypills worldwide, indicating continued interest and acknowledgement of their potential for improved public health globally. However, to date, polypills have struggled to gain widespread use because of low pharmaceutical interest, clinician concern, and a lack of advocacy for multi-target FDCPs [41•, 42].

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptors (MR) are expressed in high concentrations in the renal cortex where they line the collecting ducts and are activated by aldosterone, promoting sodium and water reabsorption and causing an increase in intravascular volume (Fig. 2). These changes over time can lead to hypertension. Further, extrarenal MRs in cardiac and vascular tissue stimulate NADPH oxidase, leading to endothelial damage through release of oxidative stressors [43]. MRs, starting with spironolactone, have long been a target for antihypertensive and vasoprotective therapy. Spironolactone is used in the treatment of HF and resistant hypertension, where it is considered the fourth drug of choice, after thiazide diuretics, CCBs, and RAS blockers [44, 45•]. Spironolactone is structurally similar

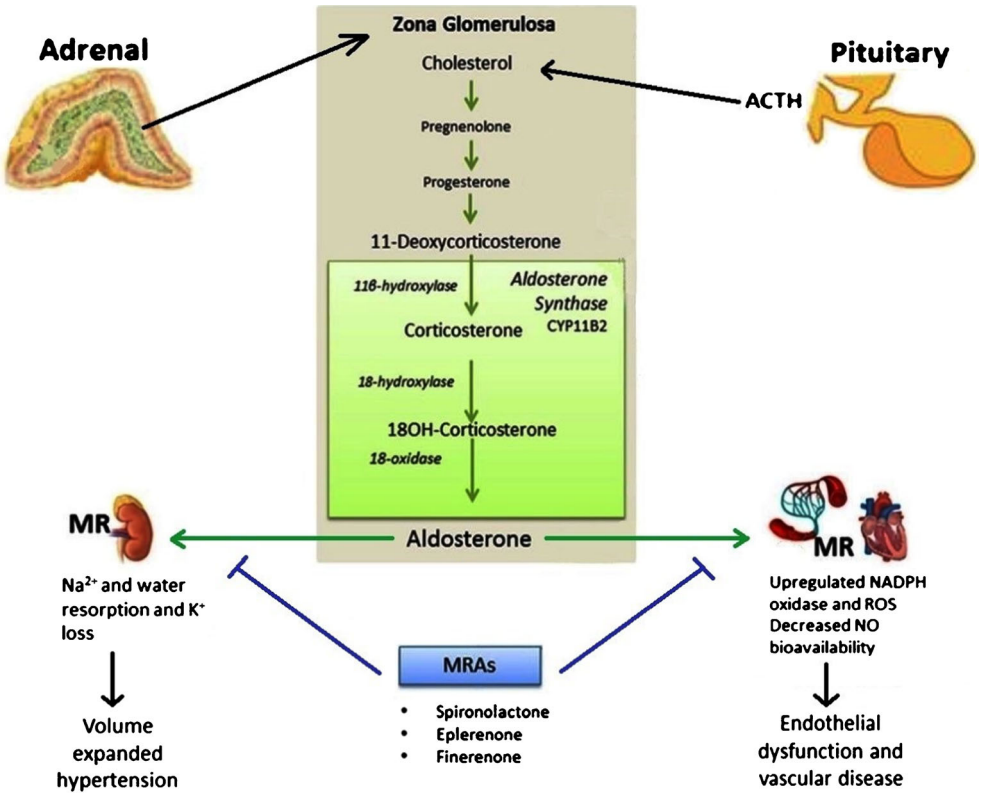

Fig. 2 Mechanism of aldosterone synthesis and the action of MRAs. MRAs, such as finerenone, compete for the binding sites of aldosterone and effectively decrease BP and aldosterone-mediated gene transcription. (Reprinted with permission from Circulation Research 116:6, 2015)

to progesterone and binds non-selectively to MRs and sex hormone receptors such as progesterone and estrogen receptors, causing adverse effects such as gynecomastia and erectile dysfunction in men and irregular menses in women. This unfavorable risk profile led to the development of eplerenone, a more selective MR antagonist (MRA) that causes fewer sex hormone-related adverse effects than spironolactone. However, eplerenone requires twice daily dosing and has less antihypertensive efficacy than spironolactone [46].

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 [47]. The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) was the first to evaluate the effect of finerenone in humans with CVD [48]. 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 per se.

The Mineralocorticoid Receptor Antagonist Study—Heart Failure (ARTS-HF) was a randomized, double-blind, multicenter study of 1286 patients that compared finerenone to eplerenone in patients with worsening HF and diabetes and/or CKD [49•]. ARTS-HF found that all-cause mortality, hospitalizations for CVD, and emergency department presentations for HF were significantly lower in the finerenone group compared to eplerenone.

A recent preclinical study demonstrated the efficacy of finerenone in prerenal acute kidney injury (AKI) and its progression to CKD in a rodent model [50]. Normotensive Wistar rats were randomized to either AKI or chronic kidney injury groups. The AKI group was further randomized to receive sham surgery or 25 min of bilateral renal ischemia with or without finerenone dosed at 48, 24, and 1 h prior to induction of ischemia. The chronic kidney injury groups were randomized to the same treatments but received 45 min of bilateral renal ischemia and were followed for 4 months following reperfusion. In the AKI group, finerenone treatment attenuated renal tubular injury and preserved normal renal function after 24 h of reperfusion. Expression of markers of tubular injury, including kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin-2 (NGAL-2) was reduced in finerenone-treated rats. In the chronic kidney injury group, untreated rats developed CKD characterized by increased proteinuria and renal vascular resistance, tubular

dilation, extensive tubule-interstitial fibrosis, and an increase in kidney transforming growth factor-ß and collagen-I mRNA after 4 months of follow-up. The transition from acute kidney injury to CKD was fully prevented by finerenone.

The Mineralocorticoid Receptor Antagonist Study—Diabetic Nephropathy (ARTS-DN) compared finerenone to placebo as add-on therapy in patients with diabetic kidney disease and a high level of albuminuria already treated with an ACE inhibitor or an ARB [51•]. Compared with placebo, finerenone treatment was associated with reduction (up to 38% at the highest dose) in urine albumin/creatine ratio, a surrogate marker for progression of diabetic nephropathy, and did not cause a significant decrease in GFR. Together, these studies have not shown robust evidence that finerenone lowers BP but have shown that finerenone may be an effective treatment for diabetic and non-diabetic CKD and HF, common comorbidities of hypertension. Two phase III clinical trials examining the effects of finerenone in patients with diabetic kidney disease, FIGARO-DKD and FIDELIO-DKD, are ongoing and expected to be completed by 2020 [12].

Classical RAS and Counter-Regulatory RAS Pathways

Classical RAS Pathway Inhibitors

The classical RAS pathway and its effect on BP have been well studied over the past several decades, and the ACE inhibitors and ARBs have become pivotal treatments for hypertension and its complications [52••, 53••] (Figs. 1 and 3). Two new ARBs, fimasartan and allisartan, have recently been approved for the treatment of hypertension in South Korea and China, respectively. Fimasartan has been shown to have a superior trough-to-peak ratio and a larger reduction in sitting SBP and DBP compared to valsartan, and a larger in-office BP reduction compared to losartan [19, 54, 55]. Allisartan has been studied in multiple clinical trials in China. A randomized, double-blind, placebo controlled trial in 2015 showed that allisartan was more effective than placebo in reducing BP in patients with essential hypertension [56].

Counter-Regulatory RAS Pathway Activators

The discovery of the counter-regulatory RAS pathway has provided researchers with novel targets for the development of new treatments for hypertension [57] (fig. 3). Emphasis has been placed on development of medications with the ability to upregulate and activate multiple mediators in the counter-regulatory RAS pathway. Several activators are under preclinical and clinical investigation as novel treatments for hypertension. While the classical RAS pathway works through a cascade of mediators to cause vasoconstriction, oxidative stress, and volume expansion, resulting in increased BP and target organ damage, the counter-regulatory RAS pathway blocks this cascade at several major points, causing vasodilation, decreased oxidative stress, and diuresis, thus reducing BP (Fig. 3). The counter-regulatory RAS system has thus become a target for development of treatments designed to lower BP and prevent related target organ damage [3••, 58]. None of these novel treatments has reached FDA approval, but many have advanced in clinical trials since 2015.

A major component of the counter-regulatory pathway is the ACE2/Ang (1-7)/MAS receptor axis (Fig. 3). ACE 2 is a carboxypeptidase that cleaves the C-terminal phenylalanine of Ang II to form the Ang (1-7) heptapeptide [59••]. ACE2 also cleaves the C-terminal leucine of Ang I to form the Ang (1-9) nonapeptide, but the affinity of ACE2 for Ang II is 400-fold stronger than for Ang I, making Ang (1-7) the major product of ACE2 activity. Ang (1–7) then activates the G protein coupled Mas receptor, which is found in mammalian testis, brain, and, most importantly for BP control, in the kidney and heart. Activation of the Mas receptor by Ang (1-7) antagonizes the actions of Ang II on the AT_1 receptor and promotes activation of NO synthase, triggering release of NO to cause vasodilation and decreased oxidative stress. This leads to decreased BP and reductions in vascular endothelial injury and target organ damage.

Recombinant Human ACE 2

Recombinant human ACE2 (rhACE2) was developed as a method of upregulating the generation of Ang (1-7) from Ang II, taking advantage of the antihypertensive and vasoprotective counter-regulatory RAS pathway. An initial study administered intravenous rhACE2 to 27 healthy human subjects in a dose escalating randomized, placebo controlled, double blind fashion [60]. Administration of rhACE2 resulted in significant reduction in serum levels of Ang II and elevation in Ang (1-7) compared to placebo. The terminal half-life of rhACE2 was 10 h. However, no effect on BP was seen with elevations of Ang (1-7). Therefore, further studies of rhACE2 have focused on its potential as treatment for a variety of other conditions that are associated with Ang II-induced vasoconstriction, fibrosis, and inflammation, including acute respiratory distress syndrome (ARDS) and HF.

A phase II clinical trial of rhACE2 administered at intervals to 46 patients with ARDS admitted to an Intensive Care Unit demonstrated increases in Ang (1-7) and decreases in Ang II levels in serum following rhACE2 administration [61]. However, rhACE2 did not improve lung mechanics and may have worsened lung compliance. The authors suggested that a better understanding of RAS effects in ARDS and of rhACE2 effects in pulmonary mechanics is needed if rhACE2 is to be further developed for this indication. Given the promising

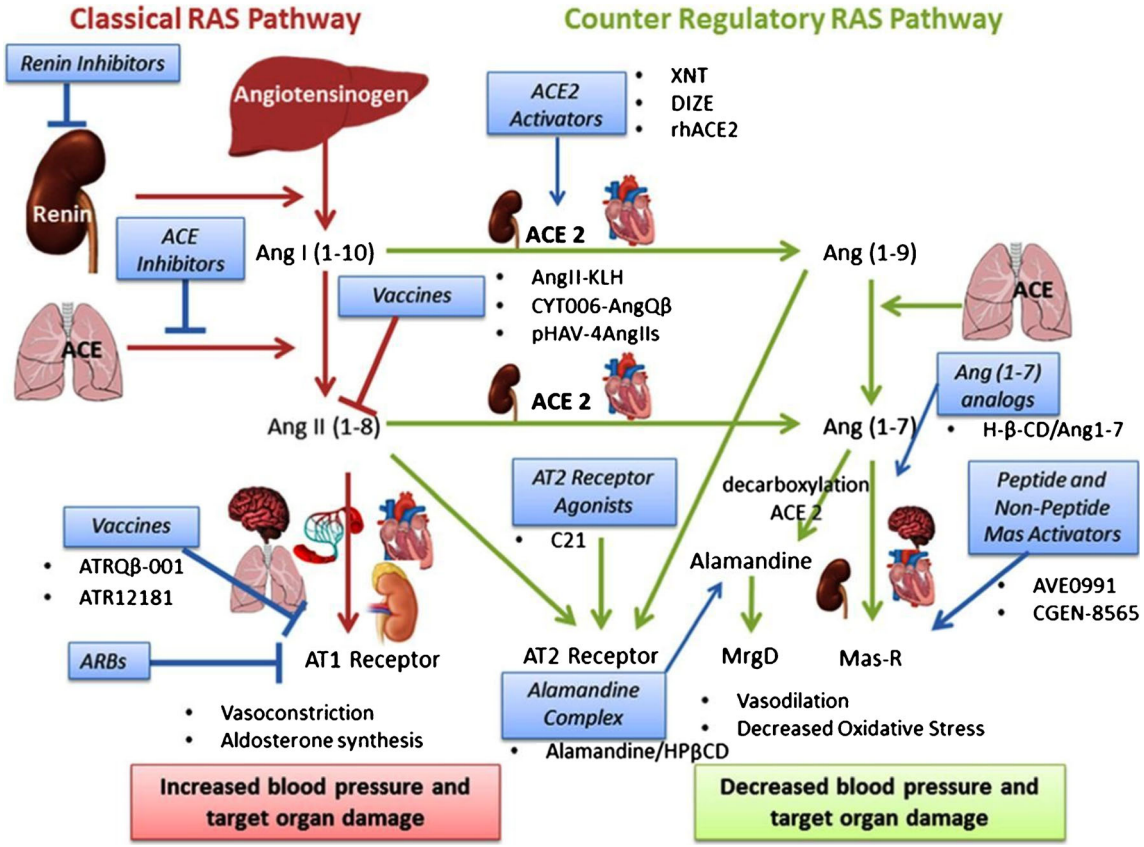

Fig. 3 Classical and counter-regulatory RAS pathways and drug targets. Activation of the classical RAS pathway increases BP and target organ damage, and this pathway is the target for many currently available antihypertensive drugs, including ACE inhibitors and ARBS. Novel approaches to RAS inhibition, including vaccines targeting Ang II and the AT1 receptor, are being evaluated in preclinical and clinical trials. In contrast, activation of the more recently described counter-regulatory RAS pathway decreases BP and target organ damage, and drugs that activate this pathway are being developed as antihypertensive agents. (Reprinted with permission from Circulation Research 116:6, 2015)

results from preclinical studies, it has been suggested that rhACE2 may be a reasonable candidate for the future treatment of HF due to its ability to decrease Ang II levels and protect against cardiac hypertrophy, remodeling, and fibrosis [62]. While multiple studies have demonstrated that ACE2 and rhACE2 reduce circulating Ang II levels, further studies are needed to test whether the reduction in Ang II results in the desired outcomes of improved hypertension control, treatment of ARDS, and/or cardiac protection in HF.

Angiotensin (1-7) Analogs

Ang (1-7) has been the subject of intense interest in hypertension research because of its dominant role in the counter-regulatory RAS pathway. Early studies in animal models revealed favorable effects on BP in hypertensive subjects and on components of the metabolic syndrome such as glycemic control and lipid profiles by increasing insulin sensitivity and decreasing oxidative stress [63, 64•]. Later studies suggested a beneficial effect of Ang (1-7) in rodent models of hypertension, cardiac remodeling, HF, and kidney disease via inhibition of oxidative stress, inflammation, and fibrosis/pathologic remodeling [65–69]. Ang (1-7) has especially promising effects in preventing progression of HF, a highly prevalent complication of hypertension [67, 70–72]. Due to the short half-life in vivo, conducting clinical studies with Ang (1-7) has been difficult. Only recently have multiple phase I clinical trials begun to evaluate the effects of Ang (1-7) on BP, the metabolic syndrome, and other CV parameters. Completion of these studies is expected by 2018 year-end [12].

Ang (1-7) Mimetics/Mas Receptor Agonists

With the success of Ang (1-7) in reducing BP in animal models, Ang (1-7) mimetics, including AVE 0991 and CGEN 856S, have been studied as potential targets for future treatment of hypertension [73–75]. These compounds are selective Mas receptor agonists and elicit similar BP lowering and cardioprotective effects as Ang (1-7). AVE 0991 has been shown to decrease BP in DOCA-salt hypertensive rats and potentiate the effect of aliskiren in combination therapy [75]. A more recent study demonstrated the cardioprotective effects

of AVE 0991 in C57BL/6J mice that were subjected to pressure overload. The AVE 0991-treated mice had decreased left ventricular (LV) weight, LV end diastolic diameter, and increased ejection fraction (EF) compared to controls [76]. Neither of these novel Mas receptor agonists has been tested in humans.

Alamandine

Alamandine is nearly identical in structure to Ang (1-7) with the exception of decarboxylation of the N-terminal aspartate radical to form alanine [77]. Alamandine is a selective agonist of the Mas-related G protein coupled receptor, member D (MrgD) that lowers BP and provides cardiovascular protection similar to that seen with Ang (1-7)-induced Mas receptor activation. Studies in hypertensive rat models suggest that alamandine decreases BP [77–79].

AT2 Receptor Agonists

Activation of the AT2 receptor in the counter-regulatory RAS pathway causes vasodilation and inhibition of arterial and myocardial hypertrophy/hyperplasia and fibrosis (Fig. 3). According to the hypothesis that activation of the AT_2R would lower BP, compound 21 (C21) was developed as the first nonpeptide AT_2R agonist. Although studies of C21 in hypertensive rat models have failed to produce conclusive evidence of a BP lowering effect, C21 has been shown to have beneficial effects on hypertension-induced target organ damage, including reducing vascular stiffness and myocardial fibrosis in hypertensive rats [80–82, 83•, 84]. Most recently, C21 has been found to be effective in preventing progression of CKD in type 1 and type 2 diabetic animal models [85].

Centrally Acting Aminopeptidase Inhibitors

The classical RAS pathway is expressed in brain tissue, where it plays an important role in hypertension development. Aminopeptidase A (APA) converts Ang II to Ang III in brain by removing the N-terminal aspartic acid residue. Ang III in brain increases sympathetic nervous system activity and causes release of arginine vasopressin, thereby raising BP. Thus, APA has gained interest as a potential target for antihypertensive therapy. The APA dimer RB150 has been developed as an orally active APA inhibitor that crosses the blood brain barrier to inhibit APA in hypertensive rats. RB150 given orally to spontaneously hypertensive rats (SHR) has been shown to inhibit formation of Ang III in brain and lower BP in a dose dependent fashion by decreasing sympathetic tone and vascular resistance [86, 87]. RB150 was found to work synergistically with enalapril to reduce BP in that study. Chronic treatment with RB150 has also been shown to reduce BP and plasma arginine vasopressin levels in DOCA-salt hypertensive rats [88]. RB150 was patented by Quantum Genomics and was renamed QGC001. QGC001 was well tolerated in phase I studies evaluating its efficacy and tolerability as a potential hypertension treatment [89]. The QUID-HF study is an ongoing multinational phase II trial comparing QGC001 to placebo in patients with NYHA class II-III HF. The primary outcomes are changes in NT-proBNP and BP, and results are expected later this year. QGC001 has recently been renamed FIRIBASTAT and is currently being investigated as a treatment for hypertension in a larger phase IIa trial, NEW-HOPE [12].

Vasoactive Intestinal Peptide Receptor Agonists

Vasoactive intestinal peptide (VIP) activates two G protein coupled receptors (VPAC 1 and VPAC 2) to produce positive inotropic, chronotropic, and vasodilator effects [90]. These properties have stimulated interest in VIP as a potential treatment for systemic and pulmonary hypertension and HF. PB1046 (Vasomera) is a synthetic analogue of VIP that is selective for VPAC 2 receptors and thus has minimal intestinal side effects. PB1046 also has a longer half-life than native VIP, making it more optimal for therapy. PB1046 was studied in a rodent model of diastolic dysfunction induced by renoprival hypertension (hypertension induced by bilateral nephrectomy) and was found to improve arterial elastance and inotropy and reduce filling pressures [91]. Two phase I randomized, double-blind, placebo controlled studies of PB1046 to evaluate its safety and tolerability in patients with essential hypertension (NCT 01873885, NCT 01523067) have been completed, but the results have not been published. A phase IIa randomized, double-blind, placebo controlled study of PB1046 in patients with stable HFrEF and patients with cardiac dysfunction due to Duchenne muscular dystrophy has recently completed enrollment, but results are not yet published (NCT 02808585) [12]. Most recently, a phase I trial to assess safety and tolerability of PB1046 in patients with pulmonary arterial hypertension (PAH) has begun. PhaseBio, the patent holders of Vasomera, plan to begin a phase II trial for PAH treatment in 2018.

Intestinal Na^+/H^+ Exchanger 3 Inhibitor

The intestinal Na^+/H^+ Exchanger 3 (NHE3) expressed on enterocytes throughout the intestinal lumen plays a major role in intestinal sodium absorption [92]. NHE3 controls

the majority of sodium absorption, and since sodium balance plays an important role in volume status and hypertension, inhibiting NHE3 has been seen as a potential target for the control of hypertension and its complications [93, 94]. Tenapanor is a NHE3 inhibitor that is effective in inhibiting sodium absorption from the gut when administered orally but is not, itself, absorbed from the gut [95]. Tenapanor has been shown to lower BP, reduce albuminuria, and prevent LV hypertrophy in salt-fed 5/6th nephrectomized rat models and to have an additional BP lowering effect when combined with enalapril [94]. Further studies have focused on the ability of tenapanor to reduce phosphorous absorption and protect against vascular calcification in CKD patients [96]. A phase II randomized, double-blind, placebo controlled efficacy and safety trial of tenapanor in the treatment of constipation-predominant irritable bowel syndrome is ongoing [97].

Dual L-Type Calcium Channel Blocker/Endothelin A/B_2 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 B_2 receptors. In contrast, ET-1 has vasodilator and anti-inflammatory effects mediated by its B_1 receptor. Recently, a dual L-type calcium channel blocker/ET A/B_2 antagonist, sargachromenol-D, was isolated from *Sargassum siliquastrum*, a marine brown alga [98]. 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. Further studies are needed to assess the potential role of sargachromenol-D in the treatment of human hypertension.

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 [99]. 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 [100]. 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 [101]. Further investigation is needed to explore the role of rostafuroxin as a potential treatment for hypertension in humans.

Antihypertensive Vaccines

Over the last three decades, attempts have been made to develop vaccines for the treatment of hypertension, with mixed results [102•, 103]. Most recently, two vaccines, ATRQß-001 and ATR12181, have revived the possibility of vaccine treatments for hypertension. Both contain peptides isolated from the AT_1R attached to a virus-like particle in order to stimulate production of antibodies to the AT_1R [104, 105]. Both vaccines reduced BP and resulted in favorable vascular remodeling and regression of CV complications when compared to controls in rodent models of hypertension [104]. ATRQß-001 also lowered BP and prevented streptozotocin-induced diabetic nephropathy in a rodent model [106]. These newer antihypertensive vaccines have yet to be evaluated in clinical trials, but offer the potential advantage of not requiring daily dosing to effectively lower BP in hypertensive patients, thus improving treatment adherence and BP control rates in the population.

Conclusion

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.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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