NEW APPROACHES AND PERSPECTIVES FOR THE PHARMACOLOGICAL TREATMENT OF ARTERIAL HYPERTENSION

CAMELIA CRISTINA DIACONU^{1#}, CRISTINA MANUELA DRĂGOI^{2#*}, OVIDIU GABRIEL BRATU^{3#}, TIBERIU PAUL NEAGU^{1#}, ANCA PANTEA STOIAN^{4#}, PAVEL CĂLIN COBELSCHI^{5#}, ALINA CRENGUȚA NICOLAE^{2#}, MIHAELA ADELA IANCU^{6#}, RĂZVAN HAINĂROȘIE^{7#}, ANA MARIA ALEXANDRA STĂNESCU^{8#}, BOGDAN SOCEA^{9#}

¹"Carol Davila" University of Medicine and Pharmacy, Clinical Emergency Hospital of Bucharest, Romania

²"Carol Davila" University of Medicine and Pharmacy, Faculty of Pharmacy, Bucharest, Romania

³"Carol Davila" University of Medicine and Pharmacy, Emergency Central Military Hospital, Bucharest, Romania

⁴"Carol Davila" University of Medicine and Pharmacy, "N. C. Paulescu" Institute, Bucharest, Romania

⁵Transilvania University, Faculty of Medicine, Brașov, Romania

⁶"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

⁷"Carol Davila" University of Medicine and Pharmacy, "Prof. Dr. Dorin Hociotă" Institute of Phonoaudiology and Functional ENT Surgery, Bucharest, Romania

⁸"Carol Davila" University of Medicine and Pharmacy, Elias Hospital, Bucharest, Romania

⁹"Carol Davila" University of Medicine and Pharmacy, Clinical Emergency Hospital "Sf. Pantelimon", Bucharest, Romania

*corresponding author: cristina.dragoi@umfcd.ro

#All authors have equal contribution.

Manuscript received: February 2018

Abstract

Arterial hypertension is one of the most common cardiovascular diseases worldwide. Despite the availability of various antihypertensive drug classes, a high percentage of hypertensive population have uncontrolled blood pressure values. Due to the very high prevalence of the disease, there is a major interest for developing more effective antihypertensive drugs, with a better safety profile and impact on the short and long-term cardiovascular outcomes of hypertensive patients. During the last years, new drugs have been developed to control the high blood pressure: a novel mineralocorticoid receptor antagonist, inhibitors of vasopeptidases, aldosterone synthase and soluble epoxide hydrolase, agonists of natriuretic peptide A and vasoactive intestinal peptide receptor 2, inhibitors of aminopeptidase A, dopamine beta-hydroxylase inhibitors, intestinal Na⁺/H⁺ exchanger 3 inhibitors, agonists of components of the angiotensin-converting enzyme 2/angiotensin(1-7)/Mas receptor axis, vaccines against angiotensin II and its type 1 receptor. These new drug classes address different pathophysiological mechanisms involved in the appearance of arterial hypertension. This review focuses on new drug development for the treatment of arterial hypertension.

Rezumat

Hipertensiunea arterială este una dintre cele mai frecvente boli cardiovasculare la nivel mondial. În ciuda existenței diferitelor clase de medicamente antihipertensive, un procent ridicat al populației hipertensive are valori necontrolate ale tensiunii arteriale. Din cauza prevalenței foarte ridicate a bolii, există un interes major pentru dezvoltarea de medicamente antihipertensive mai eficiente, cu un profil de siguranță mai bun și cu impact asupra prognosticului cardiovascular pe termen scurt și lung al pacienților hipertensivi. În ultimii ani s-au dezvoltat noi medicamente pentru a controla valorile tensionale arteriale crescute: un antagonist al receptorilor mineralocorticoizi, inhibitori ai vasopeptidazelor, aldosteronsintetazei și hidrolazei epoxidice solubile, agoniști ai peptidului natriuretic A și receptorului peptidic intestinal vasoactiv 2, inhibitori ai aminopeptidazei A, inhibitori ai dopamin beta-hidroxilazei, inhibitori ai pompei intestinale Na⁺/H⁺ (*Na⁺/H⁺ exchanger* 3), agoniști ai componentelor axei receptorului angiotensinei II/angiotensinei (1-7)/Mas, vaccinuri împotriva angiotensinei II și a receptorului său de tip 1. Aceste clase noi de medicamente abordează diferite mecanisme fiziopatologice implicate în apariția hipertensiunii arteriale, acest *review* concentrându-se pe detalierea noilor abordări terapeutice ale acestei patologii.

Keywords: arterial hypertension, vasopeptidase inhibitors, aldosterone synthase inhibitors, inhibitors of aminopeptidase A

Introduction

Arterial hypertension is one of the most common cardiovascular diseases worldwide, associated with cardiovascular events (myocardial infarction, stroke,

peripheral artery disease, chronic heart failure, sudden death) and renal complications [47, 50]. The prevalence of arterial hypertension in the general population is about 30 - 45%, with a higher incidence and prevalence in older population [1, 51]. Hypertensive patients

have a high total cardiovascular risk, because they usually associate additional cardiovascular risk factors, such as obesity, dyslipidaemia, physical inactivity, family history, metabolic syndrome etc. [30, 32, 35, 43]. According to the 2013 ESH/ESC Guidelines for the management of arterial hypertension, hypertension is defined as a systolic blood pressure value ≥ 140 mmHg and/or diastolic value ≥ 90 mmHg [1]. However, at the end of 2017, the new guidelines of the American College of Cardiology/American Heart Association have been published. These guidelines have brought a new definition of the high blood pressure, with different cut-off values. According to the American guidelines, stage 1 arterial hypertension is defined as a systolic blood pressure of 130 - 139 mmHg or diastolic blood pressure of 80-89 mmHg, and stage 2 as a systolic blood pressure ≥ 140 mmHg or diastolic

blood pressure ≥ 90 mmHg [2]. This new definition of high blood pressure had an impact on the treatment strategies, due to the decrease of the blood pressure threshold imposed in order to initiate treatment.

Perspectives on the pharmacological approaches of arterial hypertension

The objectives of the antihypertensive treatment are: on short term – to reduce the blood pressure values and on long term – to reduce mortality due to hypertension-induced diseases, target organ damage, stroke, congestive heart failure, coronary artery disease, nephropathy, retinopathy. The current antihypertensive drugs used in clinical practice have different mechanisms of action (Table I).

Table I

Antihypertensive drugs and their mechanisms of action

Class of antihypertensive drugs	Mechanisms of action
Beta blockers	decrease the force and rate of cardiac contraction, the blood volume and the sympathetic outflow
Angiotensin inhibitors	decrease the blood volume and relax the vascular smooth muscle
Diuretics	decrease the blood volume
Calcium channel blockers	relax the vascular smooth muscle
Direct vasodilators	induce relaxation of the vascular smooth muscle
Peripherally acting sympatholytics	decrease the force and rate of cardiac contraction and relax the vascular smooth muscle
Centrally acting sympatholytics	decrease the sympathetic outflow

Despite the availability of various antihypertensive drug classes, a high percentage of the hypertensive population faces uncontrolled blood pressure values, mainly because of nonadherence to the treatment or intolerance to current antihypertensive drugs. Moreover, the blood pressure is uncontrolled in a large percentage of hypertensive population, despite the use of two or more antihypertensive drugs [37, 45]. Due to the very high prevalence of the disease, there is a major interest for developing more effective antihypertensive drugs, with a better safety profile and impact on the short and long-term cardiovascular outcomes of hypertensive patients. During the last years, new drugs have been developed: a novel mineralocorticoid receptor antagonist, inhibitors of vasopeptidases, aldosterone synthase and soluble epoxide hydrolase, agonists of natriuretic peptide A and vasoactive intestinal peptide receptor 2, inhibitors of aminopeptidase A, dopamine beta-hydroxylase inhibitor, intestinal Na^+/H^+ exchanger 3, agonists of components of the angiotensin-converting enzyme 2/angiotensin(1-7)/Mas receptor axis, vaccines against angiotensin II and its type 1 receptor. These new drug classes address different pathophysiological mechanisms involved in the occurrence of arterial hypertension.

Mineralocorticoid receptor antagonists have been used in the treatment of arterial hypertension for over 50 years. Spironolactone was the first drug in this

class, particularly efficient in patients with resistant hypertension. Because of its lack of selectivity, spironolactone has antiandrogenic effects, with some important side effects in both men and women. Eplerenone is a more selective mineralocorticoid receptor antagonist, with fewer side effects, but with a modest antihypertensive effect. Finerenone (BAY-94-8862), the newest mineralocorticoid receptor antagonist, nonsteroidal, offers a better cardiovascular and renal protection in hypertensive patients. Unlike currently marketed antimineralocorticoids, finerenone is not a steroid but a dihydropyridine derivative. It was studied in the mineralocorticoid receptor antagonist tolerability study (ARTS), a multicentre, randomized, double-blind trial, on patients with heart failure with reduced ejection fraction and chronic kidney disease [3]. These patients were divided in 2 groups: the first group (patients with heart failure with reduced ejection fraction and mild chronic kidney disease) received either 2.5, 5 or 10 mg finerenone once daily; the second group (patients with heart failure with reduced ejection fraction and moderate chronic kidney disease) were treated with doses of 2.5, 5 or 10 mg finerenone daily or *placebo* or spironolactone (25 - 50 mg daily) [3]. The results obtained in patients taking finerenone have been encouraging, these patients having lower values of heart failure biomarkers (BNP and NT-proBNP), indicating a better hemodynamic profile obtained

with finerenone. Also, they had lower incidence of albuminuria and hyperkalemia and a better safety profile than spironolactone [3].

Selective aldosterone synthase inhibitors represent a new class of anti-aldosteronic drugs developed for patients with arterial hypertension and heart failure. The first aldosterone synthase inhibitor was LCI699, an oral drug that decreases the aldosterone levels in serum and urine, with protective effects for target organs in hypertensive patients [4]. In a clinical study, LCI699, administered in doses of 0.5 - 1 mg twice a day in patients with primary hyperaldosteronism, led to a decrease by 70 - 80% of serum and urinary aldosterone, a dose-dependent effect [4]. Another study, in patients with primary hypertension stage 1 or 2, who received 1 mg of LCI699 orally daily, has demonstrated an anti-hypertensive effect comparable to eplerenone 50 mg twice a day. [5]. LCI699 was associated with a partial inhibition of the glucocorticoid axis, which was dose-related, but the clinical safety was similar to *placebo* or eplerenone [5]. This effect limits the use of higher doses in patients with hypertension, but the drug may be used in patients with Cushing syndrome.

Activators of the Angiotensin-Converting Enzyme 2/Angiotensin (1-7)/MAS Receptor Axis

The renin-angiotensin system (RAS) plays a central role in the pathophysiology of hypertension, the most frequently used antihypertensive drugs targeting this system being the angiotensin-converting enzyme inhibitors (ACEI) and the angiotensin receptor blockers (ARBs). The ARBs blood pressure lowering effect is at least comparable with other drug classes, having in addition, fewer side effects and a more discrete harmful profile than ACE inhibitors (ACE-I), β -blockers, calcium channel blockers and diuretics. Irbesartan, an angiotensin receptor blocker, has demonstrated its high efficacy in lowering blood pressure, which is at least comparable with ACEIs and superior to other pharmacologic agents from the same drugs class such as losartan and valsartan. This fact is translated into a better cost-effectiveness, irbesartan having shown to be effective, also, in both early and late stage diabetic nephropathy [30, 32, 42].

Angiotensin (Ang)-(1-7) is a product of the RAS cascade, with a regulatory role, by counter-acting the actions of angiotensin II on AT receptors. Ang-(1-7) acts *via* Mas receptor and has anti-inflammatory and anti-cellular growth effects [6]. However, Ang-(1-7) has a short half-life *in vivo*. Ang-(1-9) is a newer molecule, with antihypertensive effects in animal models, without activating the Mas receptor.

AVE0991 and CGEN-856S, other specific agonists of the Mas receptor, have been studied in animal models,

demonstrating a blood pressure lowering effect [7]. These molecules are being studied nowadays for a correct assessment of their therapeutic potential.

The inhibitors of aminopeptidase A

Aminopeptidase A (APA) and aminopeptidase N are metalloproteases involved in the metabolism of brain Ang II and III. They activate the sympathetic nervous system and stimulate the release of arginine vasopressin in circulation. Studies of inhibitors of aminopeptidase A and aminopeptidase N inhibitors showed that brain Ang III has an important role in the control of blood pressure in animal models and concluded that APA may be a target for the anti-hypertensive drugs [8-10]. EC33, a new APA inhibitor, has an *in vitro* inhibiting effect in humans and mice. Because EC33 does not cross the blood-brain barrier, an orally active prodrug has been obtained [11]. In deoxycorticosterone acetate (DOCA)-salt hypertensive rats, administration of QGC001 blocks the synthesis of brain Ang III, decreasing plasma vasopressin and blood pressure [12]. The first APA inhibitor, QGC001, has already been included in the clinical trials, being administered orally in a single dose of 1250 mg that proved to be safe, without significant alterations of serum or urine aldosterone or cortisol levels [12].

Vasopeptidase inhibitors

A new class of drugs represented by vasopeptidase inhibitors has emerged recently, simultaneously inhibiting the activity of ACE and neutral endopeptidase, an endothelial cell surface zinc metallopeptidase. This major enzymatic pathway results in the degradation of natriuretic peptides, and also constitutes a secondary enzymatic pathway for the degradation of kinins [16].

Neprilysin, a zinc metalloprotease, has an important role in the degradation of bioactive peptides. Neprilysin inhibitors have been evaluated for the treatment of heart failure and hypertension, in monotherapy or associated with inhibitors of the renin-angiotensin-aldosterone system. The first neprilysin inhibitor was LCZ696, a molecule composed of sacubitril (neprilysin inhibitor prodrug) and valsartan. LCZ696 was introduced on the market following the results of the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial. In this study, patients who received LCZ696 200 mg twice daily registered reduced mortality and hospitalization rates for heart failure compared with patients who received enalapril 10 mg twice daily [13]. Neprilysin intervenes in the synthesis and degradation of bioactive peptides, chronic neprilysin inhibition having potential benefits but also potential side effects, such as angioedema, cancer, bronchoconstriction, and development of Alzheimer disease. Neprilysin

inhibitors have been studied also for their antihypertensive effects; it was demonstrated that acute neprilysin inhibition leads to a reduction of the blood pressure in DOCA (deoxycorticosterone acetate)-salt hypertensive rats, but not in spontaneously hypertensive rats [14]. The effects seem to be similar in human studies. In some studies, neprilysin inhibition decreased the blood pressure values in patients with primary hypertension, whereas in other studies it had limited or no effect [15, 16]. In PARAMOUNT trial (Prospective comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction), the effects of LCZ696 have been compared to those of valsartan in 301 patients with heart failure with preserved ejection fraction [17]. Patients who received LCZ696 had a more consistent reduction of the systolic blood pressure (9 mmHg *versus* 3 mmHg) and of the biomarkers of heart failure (NT-proBNP) [17]. In a multi-country trial, PARAMETER, LCZ696 has been studied for its effect of reducing the arterial stiffness in older patients [18]. The effects of LCZ696 on aortic stiffness and aortic haemodynamics, in patients older than 60 years, have been compared to olmesartan. The authors concluded that LCZ696 is more efficient than an angiotensin receptor blocker in reducing central blood pressure and pulse pressure [18].

Dual-acting endothelin converting enzyme-neprilysin inhibitors

Dagliutril is an oral dual inhibitor of neprilysin and endothelin-converting enzyme, first-in-class, that is metabolized to an active metabolite, KC-12615. This inhibitor has been studied on animals (rat models with diabetes and hypertension), in whom it showed antihypertensive effects, reducing also proteinuria. In a crossover study, on patients with type 2 diabetes and nephropathy, daglutril 300 mg/day improved the blood pressure control in diabetic hypertensive patients with nephropathy, having an acceptable safety profile [19]. Studies on patients with heart failure have demonstrated that daglutril decreased the pulmonary and right atrial pressures, but not the systemic arterial pressure [20].

Agonists of natriuretic peptide A

Atrial natriuretic peptide (ANP) is a vasodilatory molecule, modulating water, sodium and potassium homeostasis, which mediates its actions *via* three receptor types: two guanylyl cyclase receptors known as NPR1 and NPR2 and a natriuretic peptide clearance receptor (NPR3/NPRC) [23].

These agonists inhibit the degradation of endogenous natriuretic peptides and have been studied for the treatment of resistant arterial hypertension and also for the treatment of heart failure. PL-3994, (Hept-

cyclo(Cys-His-Phe-d-Ala-Gly-Arg-d-Nle-Asp-Arg-Ile-Ser-Cys)-Tyr-[Arg mimetic]-NH₂), is a novel natriuretic peptide receptor-A (NPR-A) agonist. It is resistant to neprilysin, that has been studied in healthy volunteers, in a phase I trial, administered subcutaneously, demonstrating natriuretic and diuretic effects, with decreased systemic blood pressure. Also, plasma cGMP level increased after administration of PL-3994 in a dose-dependent manner, having a high affinity for recombinant human, dog, or rat NPR-As [21, 41]. The safety profile of the drug was good, without severe side effects. A phase II trial in hypertensive patients receiving at least one anti-hypertensive drug showed the reduction of blood pressure as compared to *placebo* [22]. In this trial, PL-3994 had similar effects to ACE inhibitors, suggesting that it can be used for the treatment of patients with resistant hypertension or heart failure [22]. C-atrial natriuretic peptide (ANP)4-23 is a ring deleted analog of ANP, that reduces the enhanced expression of G α proteins involved in the pathophysiology of arterial hypertension. One study investigated the effects of C-ANP 4-23 in hypertensive rats, who received intraperitoneal injections with C-ANP 4-23. C-ANP 4-23 decreased the values of blood pressure and heart rate, suggesting that this drug may be used as a therapeutic agent in arterial hypertension [23].

Vasoactive intestinal peptide receptor agonist (VIP)

VIP is a neuropeptide hormone, a therapeutic target for hypertension, due to its involvement in different cardiopulmonary diseases, mediated by the G-protein-coupled receptors VPAC1 and VPAC2.

Vasomera[®] (PB1046) is a novel long-acting biopolymer-based selective VPAC2-receptor agonist, which may overpass the limitations of classical VIP agonists. Vasomera[®] is a more stable form of VIP, displaying less gastrointestinal side effects, usually associated with activation of VPAC1. Vasomera[®] has antihypertensive effects, and also inotropic effects, in animals with hypertension and heart failure [24]. This drug is currently studied for the treatment of arterial pulmonary hypertension.

Soluble epoxide hydrolase inhibitors

Inhibitors of soluble epoxide hydrolase (s-EH) have been studied in animal models for their antihypertensive and anti-inflammatory effects. They showed promising results in animal models of cardiac hypertrophy [25], being currently evaluated in clinical trials as oral drugs for the treatment of arterial hypertension.

Intestinal Na^+/H^+ exchanger 3 inhibitor

Sodium plays an important role in the pathophysiology of arterial hypertension. The intestinal absorption of salt and water is regulated by the sodium proton exchanger subtype 3 (NHE3). In rat models, inhibition of intestinal NHE3 decreases sodium and water absorption, with antihypertensive effects [26]. Tenapanor is the first-in-class NHE3 inhibitor, that decreases the blood pressure and albuminuria in nephrectomized rats with sodium-dependent hypertension [26]. A randomized, double-blind study was conducted on tenapanor orally administered in healthy adults, in multiple increasing doses and has shown that the drug was well tolerated. It demonstrated reduced intestinal sodium absorption and increased stool sodium excretion, suggesting the potential benefits of the drugs for patients who need intervention on the gastrointestinal sodium balance [27].

Dopamine beta-hydroxylase (D β H) inhibitor

D β H is an enzyme involved in the hydroxylation of dopamine to noradrenaline in the sympathetic nervous system. This enzyme may be a potential therapeutic target in hypertensive patients with sympathetic stimulation. Etamicastat, a novel D β H inhibitor, has been studied in young healthy male subjects, in order to assess the safety, tolerability and pharmacokinetics [28]. In this study, etamicastat was administered once-daily in increasing doses and has demonstrated a good tolerance and a decreased urinary excretion of norepinephrine [28].

Vaccines against angiotensin II and its type 1 receptor

The first vaccine targeting renin for the treatment of arterial hypertension has been developed in 1951 by Goldblatt [29]. In animal models, the renin vaccine demonstrated a successful reduction of the blood pressure, but with a major side effect: the occurrence of a kidney autoimmune disease. In late 1980's, newer immunological tools, more pure, have been used for immunization against renin, with the same side effect [31]. The safety concerns led to the interruption of further studies on renin immunization.

In 1970, Johnston *et al* tried the first immunization against angiotensin-II on animals, without effects on established hypertension, despite the reduced response to exogenous angiotensin II [33]. The combined immunization against angiotensin I and angiotensin II was studied in rats, the sustained angiotensin I and or angiotensin II immunity not influencing the blood pressure [34].

Due to the fact that immunization against angiotensin II did not alter the blood pressure, immunizations

against angiotensin I have been assessed, without favourable effects regarding the blood pressure levels [36, 38].

A virus-like particle (VLP)-based antihypertensive vaccine, ATR12181, has been developed in China and studied in many preclinical trials, with reduction of the blood pressure values, but still not to the target values [39]. A multicentre, double-blind, randomized phase II trial, on 72 patients with mild-to-moderate hypertension who received AngQb (a modified AngII peptide linked to the VLP Qb), showed promising results, with a reduction of the mean blood pressure values and of the morning levels, without significant side effects [40]. This study was the first to show that immunization may be used in arterial hypertension in humans, against a vasoactive endogenous peptide.

A recent experimental study published promising data on an angiotensin II type 1 receptor-pneumococcal surface protein A (AT1R-PspA) vaccine, consisting of a cationic nanometer-sized hydrogel incorporating AT1R partial peptide conjugated with PspA and cyclic diguanylate monophosphate adjuvant [44].

This vaccine was developed for intranasal administration and was tested on spontaneously hypertensive rats. Immune responses and the antihypertensive effects of the vaccine were assessed, the *in vitro* and *in vivo* studies revealing that responses to angiotensin II were suppressed in vaccinated rats. Intranasal immunization with AT1R-PspA vaccine has the potential to simultaneously attenuate the development of hypertension and protect from lethal pneumococcal infection [44].

However, further studies are needed in order to establish the most appropriate doses and schedule of immunization.

New horizons of pharmaceutical formulations for an optimal control of arterial hypertension

Considering the fact that the utmost majority of hypertensive patients need at least two antihypertensive drugs to lower their blood pressure effectively, new approaches need to be explored in order to optimize the pathology management and increase the patients' compliance. Consequently, several active agents combined in single pharmaceutical formulations, under the name of fixed-dose formulations, appear to be a novel and efficient strategy in overcoming the cardiovascular burden. Fixed-dose combinations proved many benefits compared with single drug and separate agents in terms of effects, convenience, compliance, and costs [48, 51].

Fixed-dose formulations give patients some surprising effects comparing with taking only one of the ingredients of the combinations, and sometimes may provide a synergistic effect in a perfect ratio, besides the usual addictive effect. Since drugs in

formulations from different classes exert their effects based on individual mechanisms of action, target tissue and action time, fixed-dose combinations in hypertension have a great potential. In addition, combining two antihypertensive agents from different classes in a formulation may decrease the adverse effects based on the lower doses used and their counteracting ability. Currently, there are fixed-dose combinations that usually contain two active drugs: thiazide diuretics + ACEI/ARB, thiazide diuretics + β -blockers, β -blockers + calcium channel blockers, β -blockers + ACEI/ARB, calcium channel blockers + ACEI/ARB or even three combined medicines. The three-in-one fixed-dose combination of reserpine, apresoline and hydrochlorothiazide was the first marketed triple fixed-dose formulation, exhibiting great advantages. Other triple fixed-dose combinations consist of amlodipine, olmesartan medoxomil and hydrochlorothiazide, or amlodipine + valsartan/aliskiren + hydrochlorothiazide, displaying tremendous market prospect in future [49, 52].

Other drug design engineered formulations imply using cyclodextrins as host molecules, or nanoparticulate systems as they improve certain properties of the drugs, such as solubility, stability, and bioavailability. These are suitable drug delivery systems because of their ability to optimize physicochemical properties and biological properties of the molecules, hereby reducing the frequency of dosing in addition to minimizing toxicity associated with high doses of the drugs [30, 46].

Conclusions

Every day, new molecules are studied in order to be included in the pharmacological *armamentarium* of antihypertensive medicines. Research in this domain is an effervescent one, some studies of new molecules showing promising results, other having disappointing outcomes. For some drugs, new evidence is expected in order to be marketed.

Despite tremendous efforts, it remains a great need to develop novel agents and approaches to anti-hypertensive therapy that facilitate the attainment of optimal blood pressure levels and nevertheless depict a favourable balance between the therapeutic effects and the safety profile.

References

- Mancia G, Fagard R, Narkiewicz K, *et al.*, ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.*, 2013; 34(28): 2159-2219.
- Whelton PK, Carey RM, Aronow WS, *et al.*, ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.*, 2017; 23976.
- Filippatos G, Anker SD, Bohm M, A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J.*, 2016; 37: 2105-2114.
- Amar L, Azizi M, Menard J, Aldosterone synthase inhibition with LCI699: A proof-of-concept study in patients with primary aldosteronism. *Hypertension*, 2010; 56: 831-838.
- Calhoun DA, White WB, Krum H, Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomized, double-blind, placebo- and active- controlled phase 2 trial. *Circulation*, 2011; 124: 1945-1955.
- Simoes e Silva AC, Silveira KD, Ferreira AJ, Teixeira MM, ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *British J Pharmacology*, 2013; 169: 477-492.
- Savergnini SQ, Ianzer D, Carvalho M, The novel Mas agonist, CGEN-856S, attenuates isoproterenol-induced cardiac remodeling and myocardial infarction injury in rats. *PLoS One*, 2013; 8(3): e57757.
- Iturriz X, Rozenfeld R, Michaud A, Study of asparagine 353 in aminopeptidase A: characterization of a novel motif (GXMEN) implicated in exopeptidase specificity of monozinc aminopeptidases. *Biochemistry*, 2001; 40: 14440-14448.
- Luciani N, Marie-Claire C, Ruffet E, Characterization of Glu350 as a critical residue involved in the N-terminal amine binding site of aminopeptidase N (EC 3.4.11.2): insights into its mechanism of action. *Biochemistry*, 1998; 37: 686-692.
- Fournie-Zaluski MC, Fassot C, Valentin B, Brain renin-angiotensin system blockade by systemically active aminopeptidase A inhibitors: a potential treatment of salt-dependent hypertension. *Proc Natl Acad Sci. USA*, 2004; 101: 7775-7780.
- Zini S, Masdehors P, Lenkei Z, Aminopeptidase A: Distribution in rat brain nuclei and increased activity in spontaneously hypertensive rats. *Neuroscience*, 1997; 78: 1187-1193.
- Bodineau L, Frugiere A, Marc Y, Orally active aminopeptidase A inhibitors reduce blood pressure: A new strategy for treating hypertension. *Hypertension*, 2008; 51: 1318-1325.
- Hubers SA, Brown NJ. Combined angiotensin receptor antagonism and neprilysin inhibition. *Circulation*, 2016; 133: 1115-1124.
- Monopoli A, Ongini E, Cigola E, Olivetti G, The neutral endopeptidase inhibitor, SCH 34826, reduces left ventricular hypertrophy in spontaneously hypertensive rats. *J Cardiovasc Pharmacol.*, 1992; 20: 496-504.
- Richards AM, Crozier IG, Espiner EA, Acute inhibition of endopeptidase 24.11 in essential hypertension: SCH 34826 enhances atrial natriuretic peptide and natriuresis without lowering blood pressure. *J Cardiovasc Pharmacol.*, 1992; 20: 735-741.
- Richards AM, Crozier IG, Kosoglou T, Endopeptidase 24.11 inhibition by SCH 42495 in essential hypertension. *Hypertension*, 1993; 22: 119-126.

17. Scott S, Michael Z, Pieske B, The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *The Lancet*, 2012; 380 (9851): 1387-1395.
18. Williams B, Cockcroft JR, Kario K, Principal results of the prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin receptor blocker measuring arterial stiffness in the elderly (PARAMETER) study. European Society of Cardiology 2015 Congress; August 31, 2015; London, UK. Abstract 4143.
19. Parvanova A, van der Meer I, Iliev I, Effect on blood pressure of combined inhibition of endothelin-converting enzyme and neutral endopeptidase with daglutril in patients with type 2 diabetes who have albuminuria: a randomised, crossover, double-blind, placebo-controlled trial. *Lancet Diab Endocrin.*, 2013; 1(1): 19-27.
20. Seed A, Kuc RE, Maguire JJ, The dual endothelin converting enzyme/neutral endopeptidase inhibitor SLV-306 (daglutril) inhibits systemic conversion of big endothelin-1 in humans. *Life Sciences*, 2012; 91(13-14):743-748.
21. Jordan R, Stark J, Huskey S, Phase I study of the novel A-type natriuretic receptor antagonist, PL-3994, in healthy volunteers. Presented at the 12th Scientific Meeting of the Heart Failure Society of America, September 21-24, 2008, Toronto, Ontario, Canada.
22. Sica D, Jordan R, Fischkoff SA. Phase IIa study of the NPR-agonist, PL-3994, in healthy volunteers with controlled hypertension. Presented at the 13th Scientific Meeting of the Heart Failure Society of America, Sep. 13-16, 2009, Boston, Massachusetts, USA.
23. Li Y, Sarkar O, Brochu M, Natriuretic peptide receptor-C attenuates hypertension in spontaneously hypertensive rats. *Hypertension*, 2014; 63: 846-855.
24. Del Rio CL, George R, Kloepper P, VasomeraTM, a novel VPAC2-selective vasoactive intestinal peptide agonist, enhances contractility and decreases myocardial demand in dogs with both normal hearts and with pacing-induced dilated cardiomyopathy. *J Am Coll Cardiol.*, 2013; 61: 1-10.
25. Harris TR, Li N, Chiamvimonvat N, The potential of soluble epoxide hydrolase inhibition in the treatment of cardiac hypertrophy. *Congest Heart Fail*, 2008; 14(4): 219-224.
26. Spencer AG, Labonte ED, Rosenbaum DP, Intestinal inhibition of the Na⁺/H⁺ exchanger 3 prevents cardiorenal damage in rats and inhibits Na⁺ uptake in humans. *Sci Transl Med.*, 2014; 6: 227ra36.
27. Rosenbaum DP, Yan A, Jacobs JW, Pharmacodynamics, safety, and tolerability of the NHE3 inhibitor tenapanor: two trials in healthy volunteers. *Clin Drug Investig.*, 2018; 38(4): 341-351.
28. Nunes T, Rocha JF, Vaz-da-Silva M, Safety, tolerability, and pharmacokinetics of etamicastat, a novel dopamine-beta-hydroxylase inhibitor, in a rising multiple-dose study in young healthy subjects. *Drugs in R&D*, 2010; 10(4): 225-242.
29. Goldblatt H, Haas E, Lamfrom H, Antirenin in man and animals. *Trans Assoc Am Physicians*, 1951; 64: 122-125.
30. Drăgoi CM, Nicolae AC, Grigore C, Dinu-Pîrvu CE, Arsene AL, Characteristics of glucose homeostasis and lipidic profile in a hamster metabolic syndrome model, after the co-administration of melatonin and irbesartan in a multiparticulate pharmaceutical formulation. The 2nd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications, INTERDIAB 2016, 3-5 March, Bucharest, Romania, Diabetes Mellitus as Cardiovascular Disease, Ed. Niculescu, București, 221-229.
31. Michel JB, Guettier C, Philippe M, Active immunization against renin in normotensive marmoset. *Proc Natl Acad Sci. USA*, 1987; 84: 4346-4350.
32. Mohamad Abdulwahabe M, Mitrea N, Nicolae AC, Constantinescu MZ, Drăgoi CM, Arsene AL, Barbu CG, The dynamics of adiponectin and leptin on metabolic syndrome patients and age matched healthy subjects. *Farmacia*, 2014; 62(3): 532-545.
33. Johnston CI, Hutchinson JS, Mendelsohn FA. Biological significance of renin-angiotensin immunization. *Circ Res.*, 1970; 26(Suppl. II): 215-222.
34. Oates HF, Stokes GS, Storey BG, Renal hypertension in rats immunized against angiotensin I and angiotensin II. *J Exp Med.*, 1974; 139: 239-248.
35. Neguț C, Pintilie L, Tănase C, Udeanu DI, Drăghici C, Munteanu C, Moroșan E, Oleic acid amides with potential pharmacological effects in the overweight treatment. *Rev Chim (Bucharest)*, 2018; 69(5): 790-794.
36. Smits J, Auton T, Sharp J, Antihypertensive properties of angiotensin immunotherapeutic in spontaneous hypertension in rats. *FASEB J.*, 1999; 13: A48.
37. Prodan Pura G, Leucuța DC, Marc G, Simu H, Nastasă C, Oniga O, The impact of urapidil use in hypertension prehospital emergency intervention. *Farmacia*, 2017; 65(6): 896-899.
38. Gardiner SM, Auton TR, Downham MR, Active immunization with angiotensin I peptide analogue vaccines selectively reduces the pressor effects of exogenous angiotensin I in conscious rats. *Br J Pharmacol.*, 2000; 129: 1178-1182.
39. Zhu F, Liao YH, Li LD, Target organ protection from a novel angiotensin II receptor (AT1) vaccine ATR 12181 in spontaneously hypertensive rats. *Cell Mol Immunol.*, 2006; 3: 107-114.
40. Tissot AC, Maurer P, Nussberger J, Effect of immunizations against angiotensin II with CYT006-AngQb on ambulatory blood pressure: a double-blind, randomized, placebo-controlled phase IIa study. *Lancet*, 2008; 371(9615): 821-827.
41. Otelea MR, Rascu A, Genomics and proteomics technique in nanoparticles studies new approach in environmental research. *Environmental Engineering and Management J.*, 2015; 14(10): 2283-2291.
42. Bramlage P, Durand-Zaleski I, Desai N, Pirk O, Hacker C, The value of irbesartan in the management of hypertension. *Exp Opin Pharmacotherapy*, 2009; 10(11): 1817-1831.
43. Cioates Negut C, Stefan-van Staden RI, Ungureanu EM, Udeanu DI, Stochastic sensors designed for

- assessment of biomarkers specific to obesity. *J Pharmac Biomed Analysis*, 2016; 128: 280-285.
44. Azegami T, Yuki Y, Hayashi K, Hishikawa A, Sawada SI, Ishige K, Akiyoshi K, Kiyono H, Itoh H, Intranasal vaccination against angiotensin II type I receptor and pneumococcal surface protein A attenuates hypertension and pneumococcal infection in rodents. *J Hypertens.*, 2018; 36(2): 387-394.
 45. Diaconu CC, Dediu GN, Iancu MA, Drug-induced arterial hypertension, a frequently ignored cause of secondary hypertension: a review. *Acta Cardiologica*, 2018, *in press*.
 46. de Burgos M de Azevedo M, Tasic L, Fattori J, Rodrigues FHS, Cantos FC, Ribeiro LP, de Paula V, Ianzer D, Santos RA, New formulation of an old drug in hypertension treatment: the sustained release of captopril from cyclodextrin nanoparticles. *Int J Nanomedicine*, 2011; 6: 1005-1016.
 47. Diaconu C, Comorbidities of hypertensive patients: are there differences between men and women?. *Arch Balk Med Union.*, 2016; 51(3): 307-310.
 48. Xinhuan Wan, Panqin Ma, Xiangrong Zhang, A promising choice in hypertension treatment: Fixed-dose combinations. *As J Pharmac Sci.*, 2014; 9(1): 1-7.
 49. Epstein BJ, Shah NK, Borja-Hart NL, Management of hypertension with fixed-dose triple-combination treatments. *Ther Adv Cardiovasc Dis.*, 2013; 7: 246-259.
 50. Diaconu CC, Manea M, Iancu MA, Stanescu AMA, Socea B, Spinu DA, Marcu D, Bratu OG, Hyponatremia in patients with heart failure: a prognostic marker. *Rev Chim (Bucharest)*, 2018; 69(5): 1071-1074.
 51. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J, Global burden of hypertension: Analysis of worldwide data. *Lancet*, 2005; 365(9455): 217-223.
 52. Panjabi S, Lacey M, Bancroft T, Treatment adherence, clinical outcomes, and economics of triple-drug therapy in hypertensive patients. *J Am Soc Hypertens.*, 2013; 7(1): 46-60.