The latest development of antihypertensive medication

S Nasution¹, I Rey² and R Effendi-YS²

¹Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik General Hospital, Medan, Indonesia
²Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik General Hospital, Medan, Indonesia
*Corresponding author email: snasution988@gmail.com, imelda.rey@usu.ac.id

Abstract. Hypertension is the most common risk factor for cardiovascular disease, stroke, renal failure, and death. Recent drug monitoring studies found non-adherence to BP lowering therapy in 25% to 65% of patients with apparent treatment-resistant hypertension (TRH). This review focuses on the latest development of antihypertensive medication, such as vasopeptidase inhibitors, aldosterone synthase inhibitors, Soluble Epoxide Hydrolase Inhibitors, agonists of natriuretic peptide receptor, Vasoactive Intestinal Peptide Receptor Agonist, a novel mineralocorticoid receptor antagonist, inhibitors of aminopeptidase A, dopamine β-hydroxylase inhibitor, intestinal Na+/H+ exchanger 3 inhibitor and other agents.

1. Introduction
Hypertension is a problem health in the world that can cause damage to the kidney, heart, and brain, cause 7.5 million deaths. It accounts for 57 million of disability-adjusted life years. Around 25% of adults in the United States of America had hypertension in 2011-2012. Prevalence between male and female is similar but the prevalence increases with age.[1-4] In this review, we will discuss the latest development of antihypertensive medication.

2. New Drug Classes

2.1. Anti-Aldosterone
The principal effector of aldosterone action is the mineralocorticoid receptor (MRs), it could stimulate expression of Na channels, increases Na and H2O reabsorption, K loss, that cause volume expanded form of hypertension. Activation of MRs in extra-adrenal tissues can promote hypertension and CVD by upregulating NADPH oxidase and increasing production of reactive oxygen species (ROS), that reduces the bioavailability of nitric oxide, lead to endothelial dysfunction and vascular disease. Anti-Aldosterone Agents will inhibit this pathway as antihypertensive hypertension strategy.[5,6]

2.2. Mineralocorticoid Receptor Antagonists (MRAs)
Due to lack of selectivity for the MR, the use of Spironolactone has been limited. Spironolactone has significant progestogenic and antiandrogenic activity, that have adverse effects. Eplerenone, more selective MRAs, is less potent and, that reduce the efficacy and need twice daily dosing.[7,8]
Finerenone, a nonsteroidal MRA is more selective than spironolactone, and has a greater affinity than eplerenone, and does not have an effect on L-type Calcium channel.[9]

2.3. Aldosterone Synthase Inhibitors (ASIs)
The first orally active aldosterone synthase inhibitor to be developed for human use, LCI699 has a similar structure with FAD286, the dextroenantiomer of the nonsteroidal aromatase inhibitor fadrozole. It decreases plasma and urine aldosterone concentrations, increases plasma renin activity, and prevents target organ damage in animal models of hypertension and HF dose-dependently.[10,11]

2.4. Activators of the Angiotensin-Converting Enzyme2/Angiotensin(1–7)/Mas Receptor Axis
The carboxypeptidase ACE2 converts the decapeptide angiotensin I (Ang I) to the Ang(1–9) nonapeptide and the octapeptide Ang II to the Ang(1–7) heptapeptide. Amplification of ACE2/Ang(1–7)/Mas signaling opposes the effects of the classical RAS and lowers BP and prevents or reverses related target organ damage.

Novel approaches to RAS inhibition, are being evaluated in trials. Activation of the more recently described counter regulatory RAS pathway decreases blood pressure (BP) and target organ damage, and drugs that activate this pathway include ACE2 activators, Ang (1–7) analogs, AT2 receptor agonists, peptide and nonpeptide activators of the Mas receptor, and alamandine complexed with cyclodextrin.[12,13]

2.5. Aminopeptidase Inhibitors
Aminopeptidase A (APA) and aminopeptidase N, are involved in brain Ang II and III metabolism, and 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. Studies using selective APA (EC33) and aminopeptidase N (PC18) inhibitors have demonstrated that brain Ang III (not Ang II, as in the periphery) have a role in BP control, make APA a potential hypertension therapeutic target.[14,15]

2.6. Angiotensin Receptor–Nepriysin Inhibitors
The first-in-class angiotensin receptor–nepriysin inhibitor LCZ696 is a novel single molecule composed of the nepriysin inhibitor prodrug AHU377 (sacubitril) and the ARB valsartan in a 1:1 ratio.[16]

2.7. Natriuretic Peptide Receptor Agonists (NPR-A)
NPR-A inhibit degradation of endogenous natriuretic peptides for the treatment of HF and refractory or resistant hypertension. The NPR-A PL-3994 is a synthetic molecule that contains an amino acid mimetic and has reduced affinity for the natriuretic peptide clearance receptor (NPR-C), increased resistance to nepriysin, has prolonged half-life after subcutaneous administration. A phase I trial of a single subcutaneous dose of PL-3994 showed increased natriuresis and diuresis, elevation in plasma cyclic guanosine monophosphate levels, and reduction in systemic BP compared with placebo. A phase II trial in volunteers with hypertension that had ≥1 antihypertensive drugs showed a reduction in systemic BP. PL-3994 act synergistically with ACE inhibitors.[17,18]

2.8. Vasopeptidase Inhibitors
The zinc metalloprotease nepriysin degrades the natriuretic peptides atrial natriuretic peptide (ANP), BNP, and uroditatin. Nepriysin inhibition increased the levels of circulating natriuretic peptide, that promoted natriuresis, vasodilation, RAAS inhibition, reduced sympathetic drive, and antiproliferative and antihypertrophic effects on the heart and vasculature.[19,20]

2.9. Soluble Epoxide Hydrolase Inhibitors (s-EH)
Soluble epoxide hydrolase (s-EH) catalyzes the conversion of multiple lipid epoxides to the corresponding dihydroxy lipids. Substrates of s-EH include members of the arachidonic acid family, and the effects of s-EH inhibitors have been attributed to increased epoxyeicosatrienoic acid levels. Inhibitors of s-EH can cause lower BP, prevent and reverse pressure overload-induced cardiac hypertrophy, attenuate ischemic and ischemia-reperfusion injury of the brain and heart, prevent atherosclerosis and aneurysm formation, and attenuate insulin resistance in animal models.[21,22]

2.10. Vasoactive Intestinal Peptide (VIP) Receptor Agonist
VIP is a neuropeptide with vasodilator and positive inotropic/chronotropic effect. It is mediated by the G-protein-coupled receptors VPAC1 and VPAC 2. Deficiency in VIP and alterations in properties of VPAC1 and 2 were described in various forms of cardiopulmonary disease, and VIP is a therapeutic target for hypertension. Vasomera is a stable form of VIP, selective for VPAC2. It has been developed by fusing an analog of VIP with the elastin-like polypeptide.[23,24]

2.11. Intestinal Na+/H+ Exchanger 3 Inhibitor
Electroneutral Na+/H+exchangers, such as NHE2, NHE3, and NHE8, transport sodium from the intestinal lumen into enterocytes. NHE3 (SLC9A3) is inhibited selectively by tenapanor, which does not cross the intestinal barrier. Tenapanor decreases urinary sodium excretion and increases stool sodium in humans. A study in rat showed that Tenapanor reversed extracellular volume expansion, lowers BP, and reduces albuminuria and cardiac and renal injury.[25,26]

2.12. Dopamine β-hydroxylase Inhibitor
Dopamine β-hydroxylase (DβH), is the enzyme that catalyzes the dopamine hydroxylation to form noradrenaline. It becomes a therapeutic target for hypertension and cardiovascular disorders with sympathetic activation. Inhibition of DβH have a gradual sympathetic slowdown and increases dopamine availability, thus causing renal vasodilation, natriuresis, and diuresis.[27,28]

3. Anti-hypertension in liver disease
The prevalence of essential hypertension in with cirrhosis patients was around 15%.[29,30] Arterial hypertension is not frequently found in liver disease [31], but alcoholic liver disease (ALD) patients often have high blood pressure and need antihypertensive treatment.[31,32]

The plasma concentrations of antihypertensive drugs metabolized in the liver may increase in patients with advanced liver cirrhosis, therefore the reduction of the dose and prolongation of administration intervals is necessary at initial use. Drug-induced Liver disease agent such as labetalol and methyldopa must not be given in liver dysfunction.[33]

Ehnert et al found that antihypertensives may both positively and negatively influence chronic liver disease progression. They investigated amlodipine, captopril, furosemide, metoprolol, propranolol, and spironolactone on alcohol-induced damage to human hepatocytes (hHeps). They found that antihypertensives could influence the progression of liver fibrosis by modulating HO-1 activity in liver cells. The effect of amlodipine and propranolol was only observed at high concentrations close to the LC50. Meanwhile, captopril, metoprolol, or spironolactone, at low concentrations already have protecting effect. Furosemide-induced profibrogenic TGF-β1 signaling, that facilitated liver fibrosis in vivo.[32] Therefore, the choice of antihypertensive used is important in patients with ALD as they could both promote or reduce liver fibrosis, which needs further investigation.

4. Conclusion
There were several studies of antihypertensive medication that have a specific target therapy for the development of new drugs. Further studies are needed for the use in clinical practice.

References
[1] Nwankwo T, Yoon S S, Burt V and Gu Q 2013 Hypertension among adults in the United States:
national health and nutrition examination survey 2011-2012 NCHS Data Brief 133 1-8

[2] Balitbang Kemenkes RI 2013 Riset kesehatan dasar (Jakarta: RISKESDAS)

[3] Jarari N, Rao N, Peela J R, et al. 2016 A review on prescribing patterns of antihypertensive drugs Clin. Hypertens. 22 7

[4] Ruijope L M 2008 Aldosterone, hypertension, and cardiovascular disease: an endless story J. Hypertens. 52 207–8

[5] Oparil S and Schmieder R E 2015 New approaches in the treatment of hypertension AHA J. 116 1074-95

[6] Corvol P, Michaud A, Menard J, Freifeld M and Mahoudeau J 1975 Antiandrogenic effect of spironolactones: mechanism of action Endocrinology 97 52–8

[7] Colussi G, Catena C and Sechi L A 2013 Spironolactone, eplerenone and the new aldosterone blockers in endothrine and primary hypertension J. Hypertens. 31 3–15

[8] Kolkhof P and Borden S A 2012 Molecular pharmacology of the mineralocorticoid receptor: prospects for novel therapeutics Mol. Cell. Endocrinol. 350 310–7

[9] Ménard J and Pascoe L 2006 Can the dextroenantiomer of the aromatase inhibitor fadrozole be useful for clinical investigation of aldosterone synthase inhibition? J. Hypertens. 24 993–7

[10] Ménard J, Gonzalez M F, Guyene T T, and Bissery A 2006 Investigation of aldosterone-synthase inhibition in rats J. Hypertens. 24 1147–55

[11] Ferreira A J, Murça T M, Fraga-Silva R A, Castro C H, Raizada M K and Santos R A 2012 New cardiovascular and pulmonary therapeutic strategies based on the Angiotensin-converting enzyme 2/angiotensin-(1-7)/mas receptor axis Int. J. Hypertens. 147825

[12] Jiang F, Yang J, Zhang Y, Wang M, Zhang Q, Liu F F, Zhang K and Zhang C 2014 Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets Nat. Rev. Cardiol. 11 413–26

[13] Gao J, Marc Y, Iturrio X, Leroux V, Balavoine F and Llorens-Cortes C 2014 A new strategy for treating hypertension by blocking the activity of the brain renin-angiotensin system with aminopeptidase A inhibitors Clin. Sci. (Lond). 127 135–48

[14] Réaux A, de Mota N, Zini S, Cadel S, Fournié-Zaluski M C, Roques B P, Corvol P and Llorens-Cortés C 1999 PC18, a specific aminopeptidase N inhibitor, induces vasopressin release by increasing the half-life of brain angiotensin III Neuroendocrinology 69 370–6

[15] Gu J, Noe A, Chandra P, Al-Fayoumi S, et al. 2010 Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin-receptor-neprilysin inhibitor (ARNi) J. Clin. Pharmacol. 50 401–14

[16] Edelson J D, Makhлина M, Silvester K R, et al. 2013 In vitro and in-vivo pharmacological profile of PL-3994, a novel cyclic peptide (Hept-cyclo(Cys-His-Phe-d-Ala-Phe-Arg-d-Val-Asp-Arg-Ile-Ser-Cys)-Tyr-[Arg mimetic]-NH(2)) natriuretic peptide receptor-A agonist that is resistant to neutral endopeptidase and acts as a bronchodilator Pulm. Pharmacol. Ther. 26 229–38

[17] Li Y, Sarkar O, Brochu M and Srivastava M B 2014 Natriuretic peptide receptor-C attenuates hypertension in spontaneously hypertensive rats: role of nitroxide stress and Gi proteins J. Hypertens. 63 846–55

[18] Corti R, Burnett J C Jr, Rouleau J L, Ruschitzka F and Lüscher T F 2001 Vasopeptidase inhibitors: a new therapeutic concept in cardiovascular disease? Circulation 104 1856–62

[19] Bevan E G, Connell J M, Doyle J, Carmichael H A, Davies D L, Lorimer A R and McInnes G T 1992 Candoxatril, a neutral endopeptidase inhibitor: efficacy and tolerability in essential hypertension J. Hypertens. 10 607–13

[20] Morisseau C and Hammock B D 2005 Epoxide hydrolases: mechanisms, inhibitor designs, and biological roles Ann. Rev. Pharmacol. Toxicol. 45 311–33
Neckář J, Kopkan L, Husková Z, Kolář F, Papoušek F, Kramer H J, Hwang S H, Hammock B D, Imig J D, Malý J, et al. 2012 Inhibition of soluble epoxide hydrolase by cis-4-[4-(3-adamantan-1-ylureido)cyclohexyl-oxy] benzoic acid exhibits antihypertensive and cardioprotective actions in transgenic rats with angiotensin II-dependent hypertension Clin. Sci. (Lond). 122 513–25

Couvineau A and Laburthe M 2012 VPAC receptors: structure, molecular pharmacology, and interaction with accessory proteins Br. J. Pharmacol. 166 42–50

Henning R J and Sawmiller D R 2001 Vasoactive intestinal peptide: cardiovascular effects J. Cardiovasc. Res. 49 27–37

Linz D, Wirth K, Linz W, Heuer H O, et al. 2012 Antihypertensive and laxative effects by pharmacological inhibition of sodium-proton-exchanger subtype 3-mediated sodium absorption in the gut J. Hypertens. 60 1560–7

Spencer A G, Labonte E D, Rosenbaum D P, et al. 2014 Intestinal inhibition of the Na+/H+ exchanger 3 prevents cardiorenal damage in rats and inhibits Na+ uptake in humans J. Sci. Transl. Med. 6 227

Beliaev A, Learmonth D A and Soares-da-Silva P 2006 Synthesis and biological evaluation of novel, peripherally selective chromanyl imidazothione-based inhibitors of dopamine beta-hydroxylase J. Med. Chem. 49 1191–7

Almeida L, Nunes T, Costa R, et al. 2013 a novel dopamine β-hydroxylase inhibitor: tolerability, pharmacokinetics, and pharmacodynamics in patients with hypertension J. Clin. Ther. 35 1983–96

Krousel-Wood M A, Muntnier P, He J and Whelton P K 2004 Primary prevention of essential hypertension Med. Clin. North Am. 88 223–38

Andersen U O, Henriksen J H and Jensen G 2002 Sources of measurement variation in blood pressure in large-scale epidemiological surveys with follow-up Blood Press 11 357-65

Jens H H and Soren M 2006 Liver cirrhosis and arterial hypertension World J. Gastroenterol. 12(5) 678-85

Ehnert S, Lukoschek T, Bachmann A, Sánchez J J M , Damm G, Nussler N C, Pscherer S, Stöckle U, Dooley S, Mueller S, et al. 2013 The right choice of antihypertensives protects primary human hepatocytes from ethanol- and recombinant human TGF-β1-induced cellular damage Hepatic Med. Evid. Res. 5 31–41

JSH 2009 Chapter 7: Hypertension complicated by other diseases Hypertens. Res. 32, 51–6 doi:10.1038/hr.2008.11