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JOURNAL OF BIOMEDICAL SCIENCES

2013
Vol. 2 No. 1:4
doi: 10.3823/1015

Hypertension-a paradox-The challenges and newer perspectives of Treatment

Navin Gupta[1], Govind Rai Garg[2]

1 Assistant Professor, Department of Pharmacology, Faculty of Dentistry, Jamia Millia Islamia, New Delhi.

2 Assistant Professor, Department of Pharmacology, Maulana Azad Medical College, New Delhi.

Correspondence:
drgargmedico2002@yahoo.co.in

This article is available from:
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Abstract

Hypertension is a part of metabolic syndrome affecting millions of people across the globe. Though early detection and timely meditation decreases the chances of Coronary-Vascular-Disease (CVD) and angiopathies which increases the life expectancy, but the Resistant Hypertension is increasing which reduces the overall morbidity and mortality. Hence detecting newer targets and to supplement main-line therapy is essential to control the ever-increasing Hypertension.

Key words: Angiotensin-converting-enzyme (ACE), Angiotensin receptor blocker (ARB), Tetrahydrobiopterin (BH4), Vaccine- CYT006-AngQb, Rostafuroxin.

Untreated hypertension puts cardiovascular system and kidney at major risk and shortens life expectancy by approximately 5 years [1]. Researchers believe that keeping blood pressure in desired limits would reduce the overall morbidity and mortality. This demands a sustained control of blood pressure to goal levels [2]. Hypertension affects more than half of people aged between 60-69 years and almost three fourth of those aged above 70 years. Sustained control of blood pressure can be achieved only in less than a third of hypertensive patients with use of current therapeutic approaches. So nevertheless despite the enormous advances in antihypertensive-drug therapy, it is paradoxical that the number of people with uncontrolled hypertension has continued to rise. There is a urgent need to have additional drugs which can modify the malicious ill effects of hypertensive disease, can protect end target organs specially the vessel endothelium, should be safe add on therapy and may cater the need of individuals having resistant hypertension. Nevertheless only about a third of patients with hypertension in the USA are estimated to have their blood pressure under control [3]. In addition to inadequate diagnosis and prescription, low adherence to prescribed treatment is a major reason for the high proportion of patients with uncontrolled arterial hypertension [4]. Key factors affecting patients' adherence to treatment include the presence of side-effects and concerns over taking long-term medication in the absence of symptoms [5]. Resistant, or refractory, hypertension is defined by a blood pressure of at least 140/90 mm Hg or at least 130/80 mm Hg in patients with diabetes or renal disease (i.e., with a creatinine level of more than 1.5 mg per deciliter [133 µmol per liter] or urinary protein excretion of more than 300 mg over a 24-hour period), despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic [6]. Patients who have recently received a diagnosis of hypertension or who have not yet received treatment should not be considered to have resistant hypertension, regardless of their blood-pressure level. National Health and Nutrition Examination Survey (NHANES) data indicate that prevalence has increased among U.S. adults, from approximately 50 million in the period from 1988 through 1994 to 65 million in the period from 1999 through 2004 [7]. Prevalence worldwide is projected to increase from approximately 1.0 billion in 2000 to 1.5 billion by 2025 [1]. Being an increasing global burden and growing resistant pandemic it is pertinent to device novel strategies to combact or may reverse the pathological changes associated with this disease.

Drugs in clinical trial

1) Aliskiren-FDA approved MARCH 2007	**9)** Manidipine- Comp. ph 3
2) APN01 (Recombinant Human ACE2)- Completed Ph 1	**10)** Delapril - comp. ph3
3) ETA rec.anta.- Darusentan (Ph 3)	**12)** Alagebrium Comp ph2(sapphire, silver, diamond study)
4) Vasopeptidase inhibitors - Omapatrilat- comp.ph 3 -Ilepatril(AVE-7688) in phase IIb/III (completed Ph 2)	**13)** L arginine- comp ph3
5) DARA-PS433540 (completed Ph 2)	**14)** Tetrahydrobiopterin BH4- ompleted ph2
6) ROSTAFUROXIN(ouabain antagonist)- completed Ph 2	
7) Vaccine-CYT006-AngQb(completed ph 2)	
8) Moxonidine-Comp.ph 3	

Direct Renin Inhibitors-Aliskiren

They block the rate-limiting step i.e. the conversion of angiotensinogen to angiotensin I by renin, thus reducing plasma renin activity that is upregulated by ACEIs, ARBs and diuretics. It is hypothesized that achieving more complete renin-angiotensin system inhibition, should exert cytoprotective effects in target tissues. Aliskiren is the first oral direct renin inhibitor that received FDA approval in 6th March 2007. It is an attractive new option as add-on therapy. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide [8]. Addition of aliskiren to an ARB has recently been shown to cause an additional fall in blood pressure [9]. These findings differentiates from ACE inhibitors as combined ACE inhibitor/ARB therapy does not yield a greater fall in blood pressure than a maximal dose of either drug alone. There is still no evidence base to justify replacing an ACE Inhibitor or ARB with aliskiren for end-organ protection in patients with heart failure, chronic kidney disease, or diabetes. There are some potential limitations of aliskiren. As monotherapy aliskiren appears to be equally effective as an ACE Inhibitor or ARB in lowering blood pressure, but not more effective [10]. There is capping of maximum daily dose at 300mg since higher doses can produce diarrhea, as 98% of the drug is not absorbed from the gut. Absorption is further reduced if aliskiren is taken with a fatty meal. When aliskiren is co-administered with furosemide, the peak furosemide blood concentration is reduced by as much as 50% [11]. Also enzymatic block by the direct renin inhibitor is not 100% but closer to 75% with a reactive rise in renin secretion greater than with an ACE Inhibitor or ARBs [12]. And if aliskiren is combined with HCTZ or an ARB, the reactive rise in renin secretion is dramatic [10] Furthermore, high circulating levels of renin—and its precursor (Pro)renin—may activate fibrotic signaling pathways by novel receptor-mediated mechanisms that are completely independent of angiotensin II production and angiotensin II type 1 receptor stimulation [13] (Pro)renin receptors are present in the heart, kidneys, and presumably other target organs. (Pro) renin circulates at levels that are 10–100 times higher than renin. However good news is recent study suggesting that high concentrations of renin and prorenin evoke feedback suppression of prorenin receptor expression [14] Aliskiren is taken in a dose of 150 to 300 mg per day. It is very well tolerated, have placebo-like side-effect profile. Aliskiren has high affinity binding of renin for kidney, so it concentrates in the kidney, a unique property that holds particular promise for renal protection. This explains the long half-life of > 24 hours and the slow recovery of blood pressure after the drug has been discontinued.

Angiotensin converting enzyme 2(ACE2)

ACE2 is a 805 amino monocarboxypeptidase enzyme found in plasma membranes of virtually all organs as an ectopeptide. It converts Ang I to Ang(1-9) and Ang II to Ang(1-7). Ang II has more affinity for ACE2. Ang(1-7) acts on Mas receptors (GPCR) which is said to have vasoprotective effects.

Ace 2 is also involved in metabolising Apelin-13, neurotensin 1-8, dynorphin-A 1-13, (des-Arg9)-bradykinin & (Lys-des-Arg9)-bradykinin. Role of ACE2-Ang(1-7)-Mas axis in hypertension has been studied in animal studies. Rentzsch et.al. (2007) have reported that overexpression of ACE2 in the vasculature reduces blood pressure and improves endothelial function in hypertensive rats. In adult animals, Ferreira & Raizada (2008) overexpressed ACE2 in the heart using gene transfer techniches. They found to protect heart against Ang II induced infusion ischemia or damages elicited by high BP in SHR.

In addition, cardiac fibroblasts in culture infected with ACE2 lentivirus showed a decrease in collagen production induced by acute hypoxic exposure. They reasonably concluded that ACE2 plays a protective role in the organs that are directly influenced by hypertension and cardiovascular-associated diseases by balancing the ACE-Ang II-AT1 receptor axis [15] They also stated that specific ACE2 inhibitor MLN-4760 showed exacerbation of renal damages induced by diabetes.

Three strategies show initial promise: targeted viral delivery of ACE2 cDNA, direct administration of recombinant ACE2 protein, and structure-based design and lastly development of ACE2 activator small molecules. Involvement of ACE2 in baroreflexes function has been stated recently. Angiotensin II type 1 receptor–mediated ACE2 inhibition impairs baroreflex function in brain and support a critical role for ACE2 in the central regulation of BP and the development of hypertension [16] Currently APN01-(Recombinant Human ACE2) drug has completed phase 1.

Endothelin system

Endothelin-1 ET-1, which acts through ETA and ET2B receptors increase vascular smooth muscle tone and growth. Also as the blood pressure increases, endothelial damage may increase the expression of ET-1 in the blood vessels and the heart. Therefore, blocking the ET system (as shown in the figure) may provide a new therapeutic approach by improving the prognosis beyond blood pressure lowering in hypertension.

Darusentan is orally available, propanoic-acid class, selective ETA antagonist. It promotes vasodilatation and prevents several proliferative and inflammatory processes and is coming up as a potential therapy in cases of resistant hypertension.Its long half life (16–18 hrs) and sustained 24-hour blood pressure lowering effect make it suitable for once daily dosing regimen. Completed Phase II-b for the treatment of resistant systolic hypertension.

DORADO (DAR-311) study assessed safety, efficacy and tolerability of darusentan. A total of 379 patients were randomised to receive once-daily doses of placebo (n=132) or darusentan 50mg (n=81), 100 mg (n=81), 300 mg (n=85) .Reductions in mean trough sitting SBP from baseline were 8.6 mmHg, 16.5 mmHg, 18.1 mmHg and 18.1 mmHg respectively, after 14 weeks of treatment .The most common treatment-emergent adverse event was peripheral edema/ fluid retention, which was reported in 17, 32, 36 and 29 percent of the randomised patients give above respectively. Most cases were mild to moderate in severity. Darusentan has completed Phase 3 studies.

First-In-Class dual-acting angiotensin and endothelin receptor antagonist (DARA)-

PS433540 is being developed as a potential treatment for hypertension and diabetic nephropathy. Results from the initial Phase 1 trial of PS433540, a single ascending dose (SAD) study, indicated that the compound was well tolerated at all six doses administered ranging from 20 mg to 1,000 mg and that the compound has a half-life that is consistent with once daily administration . At 12 weeks, PS433540 in a dose of 200 mg, 400 mg and 800 mg reduced systolic BP and diastolic BP statistically significant greater than placebo. The 800 mg daily dose of PS433540 produced a statistically significant reduction in systolic and diastolic blood pressure as compared to irbesartan. It is usually well tolerated and there is no serious adverse events. Headache was most frequent in the placebo group (17%), while edema was most frequent on the 800 mg PS433540 dose (11%). PS433540 has completed phase 2 studies.

Dual NEP/ACE inhibitors or Vasopeptidase inhibitors

Neutral endopeptidase (NEP) degrades natriuretic peptides which are Atrial Natiuretic Peptide(ANP), Brain Natiuretic Peptide(BNP), and C-type Natiuretic Peptide(CNP). Vasopeptidase inhibitors inhibits both NEP and ACE. There major advantage is to lower blood pressure in all models of hypertension irrespective of the degree of activity of the renin-angiotensin system.

Vasopeptidase inhibitors include Fasidoprilat, Sampatrilat, Omapatrilat, and Ilepatril (AVE-7688 in phase IIb/III). Omapatrilat is the most clinically advanced of a new class of drugs, vasopeptidase inhibitors, which are being studied for the treatment of patients with cardiovascular disease [17] Omapatrilat has completed phase 3 in 2002. Recommended dose is 10-80mg/day, and graded increase is required. The drug does not affect the activity of cytochrome P450 enzymes in the liver, and has no effect on other drugs such as warfarin, digoxin, and furosemide. Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) study revealed 3.8 mmHg greater falls in blood pressure than enalapril. The incidence of angioneurotic oedema was also higher with omapatrilat (2.17%) than with enalapril (.8%). Use in black-skinned patients and smokers was offered special caution because of increased risk of this adverse effect. It usually occurs within 1 week after the start of therapy, can occur as late as 3 years or longer after.

Rostafuroxin, a new antihypertensive ouabain antagonist

Rostafuroxin is an ouabain antagonist that corrects renal and vascular Na-K-ATPase Iterations in ouabain and adducin-dependent hypertension. Staessen JA et. al. 2005 [18] showed that approximately one-third of essential hypertensive patients show increased circulating levels of Endogenous Ouabain (EO). EO and adducin protein polymorphisms play a pathogenetic role in hypertension and related organ complications. These effects occur through complex interaction between genetic-molecular mechanisms. errandi M. et. al.

1996 [19] ocumented the polymorphism of the cytoskeletal protein-adducin invivo studies on Milan Hypertensive (MHS) rats. Ferrari P and Bianchi G. 1995 [20] howed the increased circulating levels of endogenous ouabain (EO) in rat models made hypertensive by chronic infusion of low doses of ouabain.

Bianchi G et. al. (005 [21]) recently reviewed the role of hypertension of the human -adducin (ADD1) Trp allele. Both lead to increased activity and expression of the renal Na+-K+ pump, the driving force for tubular Na transport. The vascular effect involves inhibition of the $\alpha 2$ Na^+-K^+ pump that, by reducing the Na^+ concentration gradient across the plasma membrane, promotes both Na^+/Ca^{2+} exchanger-mediated Ca^{2+} entry into the myocytes and contraction [22]. Recent data indicate that EO also acts at the vascular level and is responsible for an increase in myogenic tone of small resistance arteries, thus contributing to a sustained increase of blood pressure through the enhancement of total peripheral resistance [21]. Acute oral toxicity of rostafuroxin in rats yields LD50 2,000 mg/kg^2 [23]. One-and three-month chronic toxicological studies, performed in rats and monkeys, indicate that the compound does not induce mortality or any toxicological alterations at doses up to 100 mg/kg p.o. for rats and 180 mg/kg p.o. for monkeys [22]. In rats, the ratio between the effective antihypertensive and the toxic dose appears to be higher than 1 to 25,000, considering an ED50 of 4 g/kg^2po [22]. Rostafuroxin corrects the altered renal Na-K-ATPase defect so only corrects body hydrosaline set point and is devoid of any natriuretic and diuretic effects in comparison to diuretics inhibits physiological sodium transporters). It does not cause the typical diuretic's side effects such as activation of the renin-angiotensin-aldosterone system, hypokalemia, alterations of lipidic and glucidic profiles [24]. Phase I studies revealed complete tolerability either after single or repeated oral administrations up to a dose of 10 mg/day, and there was no significant differences in side effect patterns compared with placebo. In two small exploratory studies in patients with mild uncomplicated hypertension, rostafuroxin has been demonstrated to be effective in lowering blood pressure in a statistically significant way at oral doses from 0.1 to 1 mg/day [25]. The new antihypertensive agent rostafuroxin (completed phase 2), described here, may represent a novel therapeutic approach tailored to the individual patients carrying these specific pathogenetic mechanisms.

Moxonidine: Selective imidazoline receptor agonis

It has complete phase 3 clinical trials. It is given administered orally, once daily with selective agonistic activity at imidazoline 1 receptors and only minor activity at $\alpha 2$-adrenoceptor. (clonidine binds to both receptors with equal affinity). Moxonidine acts centrally to reduce peripheral sympathetic activity, thus decreasing peripheral vascular resistance without causing the dry mouth and sedation as caused by clonidine. Moxonidine did not affect driving performance and it suppressed critical blood pressure peaks in stress situations and stabilised blood pressure [26]. Analysis of data from 9295 patients revealed that the dry mouth occurs in 2.7 %, dizziness in 1.5 %, faintness in 1.3 %, fatigue in 1.3 %, sleep disorders in 0.2 %, while depression and impotence were not reported [27-28]. It can be used in mild to moderate hypertension, as monotherapy as a so called first line drug. It has found to improve the metabolic profile in patients with hypertension and diabetes mellitus or impaired glucose tolerance. It is well tolerated an has a low potential for drug interactions and may be administered once daily in most patients. Doses of 200–400 µg are usual (once or two divided doses). Maximum daily dose is 600 µg. There is no evidence that moxonidine has any teratogenic, mutagenic or carcinogenic potential.

Manidipine

Manidipine is a dihydropyridine calcium antagonist, which causes systemic vasodilation by inhibiting the voltage-dependent calcium inward currents in smooth muscle cells. It has completed phase 3b and is available in Germany, Greece, France, Austria, Spain, Italy, Brazil. Japan, Philippines and Thailand. It is given 10 to 40mg once daily. The decline in BP was maintained over 24 hours (trough to peak BP ratios were >50%) without disturbing the circadian BP pattern [29] in patients with mild to moderate essential hypertension. It is usually well tolerated and appears to have less potential for pedal oedema than amlodipine.

Delapril

It has completed phase 3 clinical trials.In mild to moderate hypertension, at 30 milligrams per day once daily. The most common side effects reported include headache, edema and persistent cough. Spain, Brazil and Austria have approved the use of delapril in the treatment of hypertension. Delapril/manidipine combination offers several potential benefits in hypertensive patients with type 2 DM [30]. In clinical trials (DEMAND Study), the combination was as effective as ramipril/hydrochlorothiazide (HCTZ), valsartan/HCTZ, olmesartan/HCTZ, and irbesartan/HCTZ.

Delapril/manidipine is associated with a low incidence of ankle edema and does not appear to have an orthostatic hypotensive effect. The combination has renoprotective benefits, reducing microalbuminuria and stabilizing serum creatinine levels. In addition, there is evidence that the combination

increases insulin sensitivity, improves coagulation (via an increase in TP), and reduces left ventricular mass in diabeti hypertensive patients.

Alagebrium - (formerly known as ALT-711)

Alagebrium is the first drug to be clinically tested for the purpose of breaking the crosslinks caused by advanced glycation endproducts (A.G.E.s), thereby reversing one of the main mechanisms of aging. Importantly, alagebrium does not disrupt the natural carbohydrate modification to proteins, intramolecular crosslinking or peptide bonds that are responsible for maintaining the normal integrity of the collagen chain. Alagebrium enhances peripheral artery endothelial function and improves overall impedance matching. To date approximately 1,000 patients have received alagebrium treatment and the drug continues to exhibit a clean safety profile. In preclinical studies, alagebrium consistently demonstrates the ability to reverse the upregulation of genes for proteins and growth factors known to be associated with the pathological hypertrophy of tissues. Alagebrium has completed a series of single- and multiple-dose Phase 1 studies in humans and has demonstrated efficacy in heart failure in several open-label Phase 2 trials such as SPECTRA (Systolic Pressure Efficacy and Safety Trial of Alagebrium).

Vaccine- CYT006-AngQb- against Angiotensin II

Vaccine- CYT006-AngQb is virus like particle coupled with an angiotensin II peptide to provoke an immune response against angiotensin II. The vaccine produces a long-lived antibody response against angiotensin II with a half life of about 4 months after 3rd subcutaneous injection. Currently the limitation is that the blood-pressure reducing effect of AngQb is comparable with that of low doses of renin inhibitor [31]. In phase 2 trials [32], subcutaneous injections were given of either 100 µg CYT006-AngQb (n=24), 300 µg CYT006-AngQb (n=24), placebo (n=24), at weeks 0, 4, and 12. It is safe, well tolerated and effective except mild, transient influenza-like symptoms were seen in three patients in the 100 µg group, seven in the 300 µg group, and none in the placebo group. Immune response against angiotensin II was seen even after one dose of the vaccin.

Daytime systolic and diastolic blood pressure of 100 µg CYT006-AngQb group at week 14 was decreased by 9 and 4 mm Hg compared with placebo group (p=0·015 for systolic and 0·064 for diastolic). The 300 µg dose reduced the early morning blood-pressure surge compared with placebo (change at 0800 h for systolic/diastolic was a fall of 25/13 mm Hg; p<0·0001 for systolic; p=0·0035 for diastolic). The advantage of vaccine seen in contrast to conventional drugs is that the drop in BP is especially pronounced in the early morning, when the renin-angiotensin-aldosterone system is most active and when most cardiovascular events occur [33]. By contrast, small-molecule inhibitors of the renin-angiotensin-aldosterone system, while lowering blood pressure over 24 h, do not affect the surge in early-morning blood pressure [34]. The level of anti-angiotensin II antibodies increases comparatively slowly over days without much fluctuation. A low reactive rise in renin could indeed be advantageous, since renin and prorenin are proposed to increase cardiovascular risk factors directly through binding to the renin/prorenin receptor [35] Currently, the blood-pressure reducing effect of AngQb is comparable with that of low doses of renin inhibitor [34].

L-arginine (2-amino-5-guanidinovaleric acid)

L-arginine is a common natural amino acids.First isolated from a lupin seedling extract in 1886 by the Swiss chemist Ernst. Most of the time it can be manufactured by the human body, and does not need to be obtained directly through the die Infants are unable to meet their requirements and thus arginine is nutritionally essential for infants.

Boger RH (2004) said that action of L-arginine may involve nitric oxide synthase substrate provision, especially in patients with elevated levels of the endogenous NO synthase inhibitor asymmetric dimethylarginine (ADMA). ADMA competes with arginine for binding with eNOS, subsequently down-regulating activity of this vital enzyme. Increased plasma ADMA has been shown to be an independent risk factor for cardiovascular disease because of its inhibitory activity on eNOS. Oral arginine supplementation overrides the inhibitory effect of ADMA on eNOS, and improves vascular function in those with high ADMA levels [36, 37, 38].

Inhibition of NO synthase by L-arginine analogues such as N-nitro-L-arginine methyl ester (L-NAME) in spontaneously hypertensive rats (SHR) is associated with malignant hypertension and enhanced expression of the endothelin-1 gene in some blood vessel.

Supplemental dosage of arginine is 2g to 8 g per day. Some people may experience bothersome side effects due to taking L-arginine orally, such as abdominal (stomach) pain, bloating, and diarrha , and rarely gout. Deficiency of arginine could result delay in sexual maturity, impairment of the production of insulin, glucose tolerance, and liver lipid metabolism. Acute and chronic administration of L-arginine has been shown to improve endothelial function in animal models of hypercholesterolemia and atherosclerosis. Chronic oral administration of L-arginine or intermittent infusion therapy with L-arginine can improve clinical symptoms of cardiovascular disease in

man [39] In a small, controlled trial, hypertensive patients refractory to enalapril and hydrochlorothiazide responded favorably to the addition of oral arginine (2 g three times daily). Small, preliminary trials have found oral (Siani A et. al. 2000) and IV (Maccario M et. al. 1997) arginine significantly lowers blood pressure in healthy volunteers. Role of L– arginine in pregnancy has also been explored and discussed. Endothelial dysfunction appears to be involved in the pathogenesis of preeclampsia (Roberts JM et. al. 1999). In an animal model of experimental preeclampsia, IV administration of arginine (0.16 g/kg body weight/day) from gestational day 10 until term reversed hypertension, intrauterine growth retardation, proteinuria, and renal injury (Helmbrecht GD et. al. 1996). Intravenous infusion of arginine (30 g) in preeclamptic women has reportedly increased systemic NO production and reduced blood pressure (Facchinetti F et. al. 1999).

Tetrahydrobiopterin (BH4)

BH4 is an essential cofactor for the normal enzymatic function of endothelial NO synthase (eNOS) to produce NO, because it is involved in the catalytic process of L-arginine oxidation. Insufficient BH4 availability impairs this process, and the free radical superoxide anion (O2-) is released rather than NO, a condition termed "eNOS uncoupling". Evidence exists that eNOS uncoupling contributes to endothelial dysfunction in atherosclerosis and hypertension. In summary, by BH4 depletion using GTP cyclohydrolase-1 blockade, Ceylan-Isik et al [40] clearly demonstrate that BH4 deficiency and subsequent eNOS uncoupling disrupt cardiac structure and function, which is linked to mitochondrial dysfunction, indicating a crosstalk between uncoupled NO synthase and the mitochondria.

References

1. Franco, OH., Peeters, A., Bonneux, L., de Laet, C. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women. Hypertension 2005; 46: 280-6.
2. Lewington, S., Clarke, R., Qizilbash, N., Peto, R., Collins, R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13.
3. Elliott, WJ. The economic impact of hypertension. J Clin Hypertens (Greenwich) 2003; 5: 3-13.
4. Burnier, M. Long-term compliance with antihypertensive therapy: another facet of chronotherapeutics in hypertension. Blood Press Monit 2000; 5 (suppl. 1): S31-34.
5. Osterberg, L., Blaschke, T. Adherence to medication. N Engl J Med 2005; 353: 487-97.
6. Chobanian, AV., Bakris, GL., Black, HR. et al. The Seventh Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-72.
7. Cutler, JA., Sorlie, PD., Wolz, M., Thom, T., Fields, LE., Roccella, EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. Hypertension 2008; 52: 818-27.
8. Villamil, A., Chrysant, SG., Calhoun, D. et al. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. J Hypertens. 2007; 25 (1): 217-226.
9. Oparil, S., Yarows, SA., Patel, S., Fang, H., Zhang, J., Satlin, A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet. 2007; 370 (9583): 221-229.
10. Oh, BH., Mitchell, J., Herron, JR., Chung, J., Khan, M., Keefe, DL. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. J Am Coll Cardiol. 2007; 49 (11): 1157-63.
11. Novartis Pharmaceuticals Corporation. Tekturna (aliskiren) Prescribing Information. 2007.
12. Sealey, JE., Laragh, JH. Aliskiren, the first renin inhibitor for treating hypertension: reactive renin secretion may limit its effectiveness. Am J Hypertens. 2007; 20 (5): 587-597.
13. Ichihara, A., Kaneshiro, Y., Takemitsu, T. et al. Nonproteolytic activation of prorenin contributes to development of cardiac fibrosis in genetic hypertension. Hypertension 2006; 47 (5): 894-900.
14. Schefe, JH., Menk, M., Reinemund, J. et al. A novel signal transduction cascade involving direct physical interaction of the renin/prorenin receptor with the transcription factor promyelocytic zinc finger protein. Circ Res. 2006; 99 (12): 1355-66.
15. Ferreira, A. J., Raizada, M. K. Are we poised to target ACE2 for the next generation of antihypertensives? J Mol Med. 2008; 86: 685-90.
16. Huijing, X., Yumei, F., Teresa, D., Obr. P., Hickman, J., Lazartigues, E. Angiotensin II Type 1 Receptor–Mediated Reduction of Angiotensin-Converting Enzyme 2 Activity in the Brain Impairs Baroreflex Function in Hypertensive Mice. Hypertension 2009; 53: 210-16.
17. Nawarskas, JJ., Anderson, JR. Omapatrilat: a unique new agent for the treatment of cardiovascular disease. Heart Dis. 2000; 2 (3): 266-74.
18. Staessen, JA., Kuznetsova, T., Acceto, R., Bacchieri, A., Brand, E., Burnier, M., Celis, H. et al. Ouabain and adducin for specific intervention on sodium in hypertension (OASIS-HT): design of a pharmacogenomic dose-finding study. Pharmacogenomics 2005; 6: 755-775.
19. Ferrandi, M., Tripodi, G., Salardi, S., Florio, M., Modica, R., Barassi, P., Parenti, P., Shainskaya, A. et al. Renal Na-K ATPase in genetic hypertension. Hypertension 1996; 28: 1018-25.
20. Ferrari, P., Bianchi, G. Lessons from experimental genetic hypertension. Hypertension: Pathophysiology, Diagnosis and Management.edited by Laragh JH and Brenner BM. New York: Raven. 1995. p. 126.
21. Bianchi, G. The Starling Lecture. Genetic variations of tubular sodium reabsorption leading to "primary" hypertension: from gene polymorphism to clinical symptoms. Am J Physiol Regul Integr Comp Physiol. 2005; 289: R1536-R1549.
22. Iwamoto, T., Kita, S., Zhang, J., Blaustein, MP., Arai, Y., Yoshida, S., Wakimoto, K. et al. Salt-sensitive hypertension is triggered by Ca^{2+}entry via Na^{+}/Ca^{2+} exchanger type-1 in vascular smooth muscle. Nat Med. 2004; 10: 1193-99.
23. Ferrari, P., Ferrandi, M., Torielli, L., Tripodi, MG., Melloni, P., Bianchi, G. PST 2238: a new antihypertensive compound that modulates Na^{+}-K^{+} ATPase and antagonizes the pressor effect of OLF. Cardiovasc Drug Rev. 1999; 17: 39-57.
24. Ferrandi, M., Barassi, P., Minotti, E., Duzzi, L., Molinari, I., Bianchi, G., Ferrari, P. PST 2238: a new antihypertesive compound that modulates renal Na-K pump function without diuretic activity in Milan hypertensive rats. J Cardiovasc Pharmacol 2002; 40: 881-889.
25. Ferrandi, M., Manunta, P., Ferrari, P., Bianchi, G. The endogenous ouabain: molecular basis of its role in hypertension and cardiovascular complications. Front Biosci 2005; 10: 2472-77.
26. Schmidt, U., Frerick, H., Kraft, K., Schrenk, N., Löw-Kröger, A. Hypertension: a possible risk in road traffic. J Cardiovasc Pharmacol 1992; 20 (suppl. 4): S50-S56.
27. Van Zwieten, PA., Peters, LM. Central I1-imidazoline receptors as a target of centrally acting antihypertensive drugs. Clinical pharmacology of moxonidine and rilmenidine. Ann N Y Acad Sci. 1999; 881: 420-9.
28. Busquet, P., Feldman, J. Drugs acting on imidazoline receptors. A review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. Drugs 1999; 58: 799-812.
29. Cheer, S. M., McClellan, K. Manidipine: A review of its use in Hypertension. Drugs 2001; 61 (Iss. 12): 1777-1799.
30. Fogari, R. Diabetic Hypertensive Patient: A New Treatment Approach. Clinical Therapeutics 2007; 29 (supp. 2): S54-S63.
31. Stanton, A., Jensen, C., Nussberger, J., O'Brien, E. Blood pressure lowering in essential hypertension with an oral renin inhibitor, Aliskiren. Hypertension 2003; 42: 1137-43.
32. Alain, C., Tissot, P. M., Nussberger, J., Sabat, R., Pfister, T., Ignatenko, S. et al. Effect of immunisation against angiotensin II with CYT006-AngQb on ambulatory blood pressure: a double-blind, randomised, placebo controlled phase IIa study. Lancet 2008; 371: 821-27.
33. Peixoto, AJ., White, WB. Circadian blood pressure: clinical implications based on the pathophysiology of its variability. Kidney Int. 2007; 71: 855-60.
34. White, WB., Lacourciere, Y., Davidai, G. Effects of the angiotensin II receptor blockers telmisartan versus valsartan on the circadian variation of blood pressure: impact on the early morning period. Am J Hypertens 2004; 17: 347-53.

35. Nguyen, G., Delarue, F., Burckle, C., Bouzhir, L., Giller, T., Sraer, JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. J Clin Invest 2002; 109: 1417-27.
36. Boger, RH. Asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, explains the "L-arginine paradox" and acts as a novel cardiovascular risk factor. J Nutr. 2004; 134: 2842S-2847S.
37. Boger, RH., Vallance, P., Cooke, JR. Asymmetric dimethylarginine (ADMA): a key regulator of nitric oxide synthase. Atherosclerosis 2003; 4 (suppl.): 1-3.
38. Böger, RH., Ron, ES. L-Arginine improves vascular function by overcoming deleterious effects of ADMA, a novel cardiovascular risk factor. Altern Med Rev. 2005; 10: 14-23.
39. Böger, RH., Bode-Böger, S.M. The clinical pharmacology of arginine. Annual Review of Pharmacology and Toxicology April 2001; 41: 79-99.
40. Ceylan-Isik, AF., Guo, KK., Carlson, EC., Privratsky, JR., Liao, S-J., Cai, L., Chen, AF., Ren, J. Metallothionein abrogates GTP cyclohydrolase I inhibition–induced cardiac contractile and morphological defects: the role of mitochondrial biogenesis. Hypertension 2009; 53: 1023-1031.