New Therapeutic Perspectives in Hypertension Treatment

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Despite the many therapeutic options available today for the treatment of hypertension, a large number of patients remain uncontrolled. The classic antihypertensive therapies including β-blockers, diuretics, calcium channel blockers and the wide class of renin–angiotensin–aldosterone system blockers (converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor blockers), are variably successful in achieving the target blood pressure values in hypertensive patients. Although these numerous, safe and effective pharmacologic therapies are available to treat hypertension, novel therapeutic approaches are warranted to improve the management and prognosis of patients with this condition. Several lines of research suggest promising results based on novel pharmacologic and device-based approaches that may treat effectively resistant hypertension and target organ damage in the future. A large number of the new therapeutic strategies are related to renin angiotensin aldosterone system (RAAS). Modulation of the RAAS provides the rationale for current new antihypertensive drugs already used in clinical practice, including eplerenone and aliskiren. The combined angiotensin-converting-enzyme and neutral endopeptidase blockade decreases blood pressure, aldosterone synthase inhibitors improve tolerability in aldosterone antagonism, prorenin-receptor blockers could prevent the angiotensin-independent actions of renin. In the past few years new minimally invasive surgical procedures like carotid baroreceptor activation and renal symphatetic denervation were developed and could be a therapeutic option for patients with uncontrolled hypertension.

Keywords: direct renin inhibitors, vasopeptidase inhibitors, pro-renin receptors, aldosteron receptor antagonists, endothelin, carotid baroreceptor activation, renal symphatetic denervation

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Introduction

Hypertension is one of the most common worldwide diseases and because of the cardiovascular complications and mortality, an important public health challenge. Hypertension is the most important modifiable risk factor for coronary artery disease, stroke, heart failure, end-stage renal disease and peripheral vascular disease. Meta-analyses have demonstrated linear relationship between the blood pressure values and risk for cardiovascular events [1]. Suboptimal blood pressure control is, consequently, the most common modifiable risk factor for death worldwide, being responsible for 61% of cerebrovascular disease and 48% of coronary artery disease, producing estimated over 7 million deaths a year [2]. Several large hypertension trials also demonstrate a failure to achieve blood pressure goals in spite of protocol-defined treatment regimens. In these trials, 25% to 30% of participants could not achieve blood pressure control despite receiving >3 antihypertensive medications [3,4].

The classical antihypertensive treatment with diuretics, β-blockers, calcium channel blockers, converting enzyme inhibitors, angiotensin receptor blockers and aldosteron antagonists are variably successful in the target blood pressure values achievement in hypertensive patients [5,6]. Difficult to treat or resistant hypertension is a commonly observed problem worldwide. Therefore, a large number of drugs and device-based strategies are considered to be used as novel therapies for hypertension. A new antihypertensive therapy is generally judged based on its capability to effectively reduce blood pressure values, its effectiveness in the treatment of resistant hypertension and in reduction of cardiovascular risk. In this review article some new means for modulation of the renin-angiotensin-aldosterone and endothelin system will be discussed, some new developed antihypertensive drugs and two novel device-based antihypertensive strategies will be presented.

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Current RAAS therapies and novel concepts in RAAS modulation

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are the current gold standard in the treatment of cardiovascular diseases due to their well-documented cardioprotective effects. The beneficial effects of ACEI and receptor blockers are attributed to inhibition of the AT_1R with vasodilatative, anti-hypertensive, anti-inflammatory and antiproliferative effect. A large number of clinical trials have demonstrated the beneficial effects of these drugs in hypertension, coronary artery disease, heart failure, atherosclerosis, as well as their nephroprotective effects (HOPE [7], EUROPA [8], HYVET [9], ONTARGET [10], VALUE [11], ACCESS [12], CHARM [13]. Both ACEI and ARBs reduce the onset of new diabetes mellitus and some ARBs (e.g. telmisartan) have perisome proliferators-activated receptor γ activating properties [14].

Renin inhibitors

Direct renin inhibitors (DRIs) are a relatively new group of antihypertensives that block the RAS at its point of

origin, the renin-angiotensinogen interaction, preventing the conversion of angiotensinogen to angiotensin I, interrupting by this step the RAAS cascade. Aliskiren was the first drug in the DRI class to be approved for clinical use in hypertension, and it has been shown to modulate vascular diseases such as hypertension [15], experimental atherosclerosis and diabetic nephropathy [16]. Renin inhibition by aliskiren increases the concentration of renin; it also attenuates the negative feedback effect of angiotensin II on renin synthesis, although plasma renin activity (PRA) is significantly reduced. This effect was considered relevant after the discovery of a specific trans-membrane renin/prorenin receptor (PRR). Prorenin binds PRR three times more efficiently than renin. After the prorenin binding to the receptor this cleaves angiotensin with kinetics similar of active renin [17]. Although aliskiren increases renin production, the renin produced has a reduced capacity to form angiotensin I from angiotensinogen [18]. ACEIs [18], ARBs [19], and thiazide-type diuretics [20] all increase plasma renin concentration and PRA, producing angiotensin I, in contrary aliskiren reduces PRA [21].

Data from clinical trials demonstrated that aliskiren produced blood pressure reduction comparable with diuretics, ACEI, ARBs, and calcium channel blockers [18, 19,20,22,23]. These clinical trials were also demonstrated a favorable side effect profile similar in the aliskiren treatment arms comparing to ACEIs, ARBs. Aliskiren no inhibits the breakdown of bradykinin (as seen with ACEI treatment), therefore there is no subsequent increase in serum bradykinin levels and this reduces the incidence of cough.

A large of number trials with cardiovascular and renal primary endpoints was performed with aliskiren. The Aliskiren Observation of Heart Failure Treatment (ALOFT) trial pointed out that the addition of aliskiren to an ACEI or ARB and a beta-blocker leads to favorable effects on neurohormonal actions in patients with congestive heart failure [24]. The AVOID trial (Aliskiren in the Evaluation of Proteinuria in Diabetes) trial demonstrated that the addition for 6 months of aliskiren to therapy with losartan in patients with hypertension and type 2 diabetes and nephropathy produced a 20% reduction in mean urinary albumin-to-creatinine ratio, when compared with losartan alone [25]. Data from the secondary prevention ALTITUDE trial (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) demonstrated that direct renin inhibition with aliskiren reduces cardiovascular and renal morbidity and mortality in patients with type 2 diabetes [27]. The ASPIRE trial (Aliskiren Study in Post-MI Patients to Reduce Remodeling) evaluated the role of aliskiren on left ventricular remodeling when added to standard therapy with an ACEI or an ARB in high-risk post-myocardial infarction patients with left ventricular systolic dysfunction [27].

The determination of the impact of DRI aliskiren on clinical end points is essential to establish the most appropriate use of this drug in clinical practice. Results from trials designed to answer these questions were published this year [28,29] and are expected in the near future [30].

Vasopeptidase inhibitors

Vasopeptidase inhibitors are a new class of agents that inhibit the ACE and neutral endopeptidase (NEP). Vasopeptidase inhibitors have been in clinical development for the management of hypertension and chronic heart failure for the past several years. Vasopeptidase inhibitors inhibit the action of the zinc-containing ACE and NEP, action which prevents the angiotensin II-mediated vasoconstriction. NEP inhibition facilitates the actions of kinins and vasodilatory natriuretic peptides. Blocking the production of angiotensin II and the secretion of the aldosterone produce an increase in the cardiac output and reduce sodium and water retention, vascular and myocardial hypertrophy with subsequent reduction of the peripheral vascular resistance, reduction in production of reactive oxygen species, with important role in vasoconstriction and damage the endothelial wall [31].

Blocking the action of NEP increases the half-life of atrial natriuretic peptide, bradykinin and brain natriuretic peptide (BNP). Bradykinin stimulates the angiotensin-converting enzyme-bradykinin type 2 receptors and mediates cardioprotective effects. Both atrial natriuretic peptide and BNP increase sodium and water excretion by the kidney, relax vascular smooth muscle (except renal glomerular arteries), increase vascular permeability, and inhibit the release aldosterone, angiotensin II, arginine vasopressin and endohelin-1 (ET-1) [32,33].

One of the most studied vasopeptidase inhibitors, omapatrilat, reduced blood pressure in several models of experimental hypertension [34] as well as in hypertensive subjects, similarly to sampatrilat [35]. The OVERTURE trial demonstrated the benefit of ACE/NEP dual inhibition in hypertension and heart failure, but they reported a higher incidence of angioedema in this group [36]. Omapatrilat is the first NEP inhibitor developed for both hypertension and heart failure, with a novel dual vasodilatory action, inhibiting ACE and NEP. The OVERTURE trial (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) has primary endpoint all-cause mortality and congestive heart failure hospitalizations. The trial showed a 6% reduction with omapatrilat on primary end-point versus enalapril, but this did not reach statistical significance. Adverse effects showed a lower rate of heart failure and renal function impairment with omapatrilat, but a higher incidence of dizziness and hypotension. Angioedema was slightly increased in the omapatrilat group in this study [36].

The explanation these properties are the convergence of this two vasopeptidase (ACE and NEP) on bradykinin degradation [32,33]. The the dual AT1R /NEP antago-

nism (angiotensin receptor neprilysin inhibitors, ARNI) shows a more favourable profile of tolerance [38].

Prorenin receptor (PRR) antagonists

The prorenin receptor (PRR), a new component the renin-angiotensin system, was cloned in the last few years. The PRR specifically binds renin and prorenin with two major consequences: prorenin, the inactive proenzyme form of renin, becomes enzymatically active and PRR activation triggers intracellular signaling pathways [38]. The binding of prorenin to PRR triggers intracellular signaling and the activation of the MAP (mitogen-activated protein) kinases ERK1/2. The result of this activation is an upregulation of tumor growth factor beta-1 (TGFβ1), plasminogen activator inhibitor- (PAI1), cyclooxygenase-2 (COX2), fibronectin, collagens [40]. Simultaneously, binding of renin to the PRR increases its angiotensin I-generating activity, and the binding of prorenin allows the inactive renin precursor to become enzymatically active. Therefore, the prorenin receptor system has two functions: an angiotensin-independent function related to PRR-induced intracellular signalling with downstream effects and an angiotensin-dependent function represented by an increased catalytic activity of prorenin bind to PRR [33].

DRIs (aliskiren) does not inhibit the activation of the PRR by prorenin consequently the specific blockade of PRR could not only reduce the enzymatic activity but also prevent some angiotensin independent actions of renin [41].

A peptide, called handle region peptide (HRP), inhibits prorenin binding to PRR and nonproteolytic activation, initially generated much interest because it suggested there was a PRR antagonist with preventing properties against diabetic nephropathy, cardiac fibrosis and ocular neovascularization [42]. HRP treatment suppressed the development of proteinuria and glomerulosclerosis without modification of renal angiotensin II levels. The development of a non-peptide PRR antagonist (a renin/prorenin receptor blocker, RERB) could elucidate the role of PRR in the development of cardiovascular damage and on the potential of its therapeutic inhibition [43,33].

Aldosteron antagonists

Aldosterone exerts a key role in the pathogenesis of hypertension and target organ damage,including mediation of increased extracellular fluid volume and vasoconstriction, promoting endothelial dysfunction, myocardial and vascular fibrosis [44]. Aldosterone acts on mineralocorticoid receptors (MRs) in epithelial cells in the distal tubule and collecting duct and promotes sodium reabsorption and potassium excretion. Aldosterone represents an important risk factor for cardiovascular disease, therefore, the use of MR antagonists, in addition to thiazides, ACEIs and ARBs could provide additional benefit in the prevention of hypertensive target organ damage [45]. Thiazides reduce extracellular fluid volume therefore increase aldosterone levels; thus, the combination of thiazides and aldosterone antagonists is recommended. During long-term treatment with ACE inhibitors and ARBs there is evidence that some patients may present aldosterone escape, in which aldosterone levels are initially suppressed but gradually return to baseline levels, therefore the combination treatment with MR antagonists (MRAs) has a rational basis [45]. The use of MRAs in the treatment resistant hypertension has stepped up in the past few years with an increasing appreciation for the role of aldosteron in this disease state [33,46].

Spironolactone, a nonselective MRA, has been in clinical practice for decades and a selective MRA (eplerenone) has also been developed in the last few years and it is now in clinical use. Spironolactone is indicated in treatment of hypertension particularly effective when given with a thiazide-type diuretic and it is effective treatment in most patients with low-renin forms of hypertension, particularly in the elderly, and many diabetics. Spironolactone is proven to be effective specific hypertensive subgroups with metabolic syndrome (hypertension, obesity, dyslipidemia, insulin resistance) [44]. Eplerenone the selective MRA lowered effectively the blood pressure values in patients with stage 1 and 2 hypertension and comorbidities as left ventricular hypertrophy or diabetes mellitus, and used alone or in combination with other antihypertensive drugs was well tolerated [48]. Data from recent clinical studies indicate that aldosterone blockade with spironolactone or eplerenone provides significant reduction in blood pressure values when added to treatment regimens of patients with resistant hypertension [46]. Spironolactone's reduced selectivity for MR results in progesterone and testosterone-dependent adverse effects, such as gynaecomastia, loss of libido or menstrual disturbances. Eplerenone is less frequently associated with these adverse effects and might serve as an alternative substitute for spironolactone in patients with gynaecomastia. Hyperkalaemia occurs with all MRAs and should always be anticipated [48].

A large number of clinical studies demonstrated the activation of the RAAS in heart failure. The recommendation to use aldosterone antagonists in patients with moderately severe to severe heart failure is based on the RALES (Randomized Aldactone Evaluation Study) [49]. The primary endpoint of this study was to evaluate all-cause mortality in patients with severe class IV heart failure. After 24 months the trial was interrupted due to a 30% reduction in death in patients treated with spironolactone. There was also a significant 35% decrease in hospitalizations due to worsening heart failure in spironolactone treated group. The EPHESUS trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy Survival Study) [50] compared eplerenone to placebo in over 6000 patients after acute myocardial infarction complicated by left ventricular dysfunction, and signs or symptoms of heart failure with the majority on standard therapy for this indication. Treatment with eplerenone significantly decreases the primary endpoints of death from any cause and death from car-

diovascular causes (eplerenone 26% vs. placebo 30%). The EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) enrolled over 2000 patients with NYHA class II heart failure and on standard therapy for heart failure at optimal doses. After 21 months the trial was early stopped due to a significant reduction in the primary outcome of composite cardiovascular death or first heart failure hospitalization. The treatment with eplerenone decreased the risk of the primary endpoint by 37% compared to placebo [51].

Endothelin system and endothelin receptor antagonists

From the endothelin polypeptide family endothelin-1 (ET-1) is the biologically and clinically most pertinent isoform and binds to ETA receptors. The result of this binding is vasoconstriction, cell proliferation, neurophysiological functions such as pain signaling, cardiovascular homeostasis, cancer cell growth, endocrine function, inflammation, bronchoconstriction [52].

Endothelins via activation of ETA receptors in the vascular system have a basal vasoconstricting role and contributes to the development of vascular disease as hypertension and atherosclerosis [53]. Endothelins play important role in myocardial contractility, chronotropy and arrhythmogenesis, myocardial remodelling following post-infarct congestive heart failure, and in water and sodium excretion and acid-base balance [54].

Darusentan the ETA/ETB receptor antagonist have been studied in resistant hypertension being the one most extensively evaluated substance in the endothelin system antagonists [55]. In patients with resistant hypertension, darusentan reduced systolic and diastolic blood pressure values in the DAR-311 (DORADO) trial [56] Endothelin antagonists have been approved only for use in pulmonary artery hypertension and their perspectives for the treatment of hypertension are not particularly promising [57]. The side-effects of endothelin receptor antagonists are: salt and water retention and peripheral edema, and teratogenicity. The results from trials in heart failure, cerebral vasospasm, chronic kidney disease and erectile dysfunction were not encouraging [33,58].

Novel device based approaches in treatment of hypertension

Baroreceptor activation therapy (BAT)

Resistant hypertension, as mentioned above, is defined as failure to achieve goal blood pressure (BP) (<140/90 mm Hg for most patients, <130/80 mm Hg for patients with diabetes or chronic kidney disease) under treatment with 3 antihypertensive drugs in maximally tolerated doses, including a diuretic. The prevalence of resistant hypertension is expected to increase due to the aging of the population and an increased prevalence of cardiovascular disease, obesity or cardiometabolic syndrome [59].

The carotid baroreflex represents a significant element of blood pressure physiology and in the pathophysiology hypertension. Carotid baroreceptors percepts the intra-arterial blood pressures changes and modulate the sympathetic balance. Compensatory changes in sympathetic nervous system function are an important component of primary hypertension. Decreased parasympathetic and increased sympathetic tone enhance the peripheral vascular resistance, increase the sodium and water retention, reduce renal blood flow, impair the glucose metabolism contributing to adverse cardiac and vascular remodeling [60].

Recent experimental and clinical data suggest the ability of the carotid baroreflex having long-term effects on blood pressure and therefore the activation of the carotid baroreflex has revived for the management of resistant hypertension [61]. A new surgically implantable device for the treatment of resistant hypertension (Rheos System, CVRx, Inc. Minnesota) has been developed to administer baroreflex activation therapy (BAT) using electrical stimulation of the carotid baroreceptors [62]. A pulse generator is implanted in the infraclavicular space and connects to two electrode leads placed in the perivascular space of the carotid sinuses. The generator communicates with computer software that is capable to program the baroreceptor activation in a non-invasive way. This BAT modulates the sympathic and vagal balance and acutely reduces muscle sympathetic nerve activity and increase parasympathetic activity [62].

Studies in humans have confirmed the efficacy of this interventional approach in treatment of resistant hypertension [63]. The device based therapy of hypertension (DEBuT-HT) trial in 45 patients with resistant hypertension revealed a significant reduction in systolic and diastolic blood pressure, from the beginning of the study and with prolonged effect [64]. The Rheos Pivotal Trial is the first randomized, double-blind, parallel-design clinical trial designed to assess the efficacy and safety of the Rheos System in patients with resistant hypertension using the surgically implantable device [64]. The mean reductions in systolic blood pressure of up to 35 mm Hg were observed after 12 months in all subjects participating in the trial. The observation that during of the first 6 month of the trial, the subjects receiving BAT experienced a 40% reduction in serious adverse events for hypertensive urgency highlights. Chronic stimulation of the carotid baroreceptors does not cause stenosis, remodelling or injuries of the carotid artery wall. Available data also suggests that carotid baroreceptor activation does not decrease the renal function in patients with resistant hypertension [64,65].

Available experimental and clinical data demonstrates the efficacy with acceptable safety of this BAT device. Although some concerns have been raised lately and therefore, further studies are needed to define the place and role of carotid baroreceptor activation in the treatment of patients with resistant hypertension [33].

Renal symphatetic denervation

Selective renal sympathetic denervation (RSD) is the latest and a very interesting approach used recently to interrupt the influence of the sympathetic nervous system on the kidney and consequently to systemic hemodynamics [66]. The sympathetic innervation of the kidney is represented by a dense network of postganglionic neurons. Renal preganglionic nerves run along the renal artery and enter in the renal hilus. Renal sympathetic nerve activation increases the noradrenalin production for nerve endings, while interruption of renal sympathetic innervation results in a marked decrease of noradrenalin secretion. The renal sympathetic nerves activation produce an enhanced renin secretion via beta-1 adrenergic receptors and renal vasoconstriction, decrease in renal blood flow, increased sodium and fluid reabsorption via alfa-1 receptor activation. The sympathetic innervation of the kidney has an important role in the pathogenesis of hypertension through renin secretion, enhanced plasma renin activity, sodium and water retention, and reduction of renal blood flow [66].

RSD presents a major improvement with general advantages compared to radical sympathectomy that was performed five decades ago [69]. It is a minimally invasive, localized procedure, without important systemic side effects. The technique was pioneered by Krum, Sobotka and collaborators [69,70,71]. In patients with resistant hypertension, RSD was achieved using a radiofrequency ablation catheter which was inserted through the femoral artery and selectively engaging the renal artery bilaterally (Symplicity, Ardian Inc., USA). Renal sympathetic ablation resulted in significant reduction on blood pressure values that were maintained during the 12-month follow-up period. This studies opens new avenues in the treatment of resistant hypertension and provided evidence that catheter-based ablation of renal sympathetic fibers is safe and effective. Only two adverse effects were described: a renal artery dissection and a femoral artery pseudoaneurysm, but both complications were related to the percutaneous technique and not to radiofrequency ablation.

Recently a catheter-based RSD study (Simplicity HTN-2) [71] study was published. In this randomized, multicentre, prospective trial, patients with a baseline systolic blood pressure of 160 mmHg or more were randomly assigned to renal denervation with previous treatment for hypertension or to maintaining previous treatment (control group). After 6 months 84% patients who underwent renal denervation presented a 10mmHg reduction in systolic blood pressure, compared with 35% of controls.

Results of these studies, performed in patients with resistant hypertension and catheter-based RSD, opens new perspectives for the treatment of patients with resistant or difficult-to-control hypertension. Future research is necessary to investigate the role of RSD in other forms of hypertension, in noncompliant patients and in patients with several other conditions, such as hypertension with left ventricular hypertrophy, congestive heart failure, and chronic kidney disease.

Summary

Despite the considerable advances in the treatment of arterial hypertension that have occurred over the past decades, hypertension remains one of the major epidemics in worldwide. Thus, efforts are ongoing to develop new therapeutic methods to combat this disease. Novel therapeutic approaches in the management of hypertension can be classified in two major categories: those that improve blood pressure lowering efficacy using new therapeutic strategies in addition to standard pharmacological approaches and novel novel device based therapeutic strategies. Other novel therapeutic approaches in hypertension treatment in clinical evaluation stages are: aldosteron synthase inhibitors, the renalase system, gene and vaccine based therapies. The result of these studies and trial will be presented in 2012 and beyond. Implementation of these new strategies must continue to be on a background of lifestyle management involving weight loss, dietary sodium-intake reduction, alcohol restriction, and exercise as well as individualized choice of drug therapy. The next few years will determine which of these approaches meets with the greatest success and enters the clinic.

Abbreviations

RAAS – renin angiotensin aldosterone system
ACEI – angiotensin converting enzyme inhibitors
AT1R – angiotensin 1 receptor
ARBs – angiotensin receptor blockers
DRIs – direct renin inhibitors
PRA – plasma renin activity
PRR – renin/prorenin receptor
NEP – neutral endopeptidase
BNP – brain natriuretic peptide
ET-1 – endohelin-1
ETA – endothelin receptor type A
ARNI – angiotensin receptor neprilysin inhibitors
MAP – mitogen-activated protein
TGFβ1– tumor growth factor beta-1
PAI-1 – plasminogen activator inhibitor
COX-2 – cyclooxygenase-2
HRP – handle region peptide
RERB – renin/prorenin receptor blocker
MRs – mineralocorticoid receptors
MRAs – mineralocorticoid receptors antagonists
BAT – baroreceptor activation therapy
RSD – renal sympathetic denervation

References

1. Farsang C, Naditch-Brule L, Perlini S et al. Inter-regional comparisons of the prevalence of cardiometabolic risk factors in patients with hypertension in Europe: the GOOD survey. J Hum Hypertens 2009;23(5):316-324.
2. Grassi G, Cifkova R, Erdine S et al. Blood pressure control and cardiovascular risk profile of hypertensive patients in Central and East European countries: results of the BP-CARE study J Hypertens 2009; 27 Suppl 4:S24
3. Kearney PM, Whelton M, Reynolds K et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365(9455):217-223.

4. Wolf-Maier K, Cooper RS, Kramer H et al. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension. 2004;43(1):10-17.
5. Mancia, De Backer G, Dominiczak A et al. 2007 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 J Hyperten. 2007;25(6):1105-1187.
6. Mancia et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;11:232-236.
7. Yusuf S, Sleight P, Pogue J et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342:145-153.
8. The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362:782-788.
9. Beckett NS, Peters R, Fletcher AE et al. Treatment of Hypertension in Patients 80 Years of Age Older N Engl J Med. 2008;358:1887-98.
10. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Eng J Med. 2008;358:1547-1557.
11. Julius S, Kjeldsen SE, Weber M, et al. VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. Lancet. 2004;363:2022-2031.
12. Schrader J et al. On behalf of the ACCESS Study Group: The ACESS Study. Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke. 2003;34:16699-1703.
13. Pfeffer MA, Swedberg K, Granger CB et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362:759-766.
14. Kappert K, Tsuprykov O, Kaufmann J et al. Chronic treatment with losartan results in sufficient serum levels of the metabolite EXP3179 for PPARgamma activation. Hypertension. 2009;54:738-743.
15. Gradman AH, Schmieder RE, Lins RL et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. Circulation. 2005;111:1012-1018.
16. Verdecchia P, Calvo C, Mockel V etal - Safety and efficacy of the oral direct renin inhibitor aliskiren in elderly patients with hypertension. Blood Press. 2007;16:381-391.
17. Staessen JA, Li Y, Richart T. Oral renin inhibitors. Lancet. 2006;368: 1449-1456.
18. Strasser RH, Puig JG, Farsang C et al. A comparison of the tolerability of the direct renin inhibitor aliskiren and lisinopril in patients with severe hypertension. J Hum Hypertens. 2007;21:780-787.
19. Oparil S, Yarows SA, Patel S et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet. 2007;370:221-229.
20. 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;25:217-226.
21. Andersen K, Weinberger MH, Egan B et al. Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. J Hypertens. 2008;26:589-599.
22. Schmieder RE, Philipp T, Guerediaga J, et al. Long-term antihypertensive efficacy and safety of the oral direct renin inhibitor aliskiren: a 12-month randomized, double-blind comparator trial with hydrochlorothiazide. Circulation. 2009;119:417-425.
23. Brown MJ, McInnes GT, Papst CC et al. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet. 2011;377:312-320.
24. McMurray JJ, Pitt B, Latini R et al, Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators - Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. Circ Heart Fail. 2008;1:17-24.
25. Parving HH et al for the AVOID Study Investigators: Aliskiren combined with losartan type 2 diabetes and nephropathy. N Engl J Med. 2008;358:2433-2466.
26. Parving HH, Brenner BM, McMurray JJ et al. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. Nephrol Dial Transplant. 2009;24:1663-1671;
27. Solomon SD, Hee SS, Shah A et al. Effect of the direct renin inhibitor aliskiren on left ventricular remodelling following myocardial infarction with systolic dysfunction. Eur Heart J. 2011;119:530-537. (ASPIRE)
28. Krum H, Massie B, Abraham WT et al. Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) study. Eur J Heart Fail. 2011;13:107-114.
29. Gheorghiade M, Albaghdadi M, Zannad F et al. Rationale and design of the multicentre, randomized, double-blind, placebo-controlled Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT). Eur J Heart Fail. 2011;13:100-106.
30. Lee HY, Oh BH. Cardio-renal protection with aliskiren, a direct renin inhibitor, in the ASPIRE HIGHER program. Expert Rev Cardiovasc Ther. 2009;7:251-257.
31. Dive V, Chang CF, Yiotakis A, Sturrock ED. Inhibition of zinc metallopeptidases in cardiovascular disease—from unity to trinity, or duality? Curr Pharm Des. 2009;15:3606-3621.
32. Campbell DJ. Vasopeptidase inhibition: a double-edged sword? Hypertension. 2003;41:383-389.
33. Unger T, Paulis L, Sica DA. Therapeutic perspectives in hypertension: novel means for renin-angiotensin-aldosterone system modulation and emerging device-based approaches. Eur Heart J. 2011;32(22):2739-47.
34. Intengan HD, Schiffrin EL. Vasopeptidase inhibition has potent effects on blood pressure and resistance arteries in stroke-prone spontaneously hypertensive rats. Hypertension. 2000;35:1221-1225.
35. Norton GR, Woodiwiss AJ, Hartford C et al. Sustained antihypertensive actions of a dual angiotensin-converting enzyme neutral endopeptidase inhibitor, sampatrilat, in black hypertensive subjects. Am J Hypertens. 1999;12:563-571.
36. Packer M, Califf RM, Konstam MA. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat vs. Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2009;106:920-926.
37. Ruilope LM, Dukat A, Bohm M et al. Bloodpressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375:1255-1266.
38. Bader M. The second life of the (pro)renin receptor. J Renin Angiotensin Aldosterone Syst. 2007;8:205-208.
39. Batenburg WW, Krop M, Garrelds IM et al. Prorenin is the endogenous agonist of the (pro)renin receptor. Binding kinetics of renin and prorenin in rat vascular smooth muscle cells overexpressing the human (pro)renin receptor. J Hypertens. 2007;25:2441-2453.
40. Ichihara A, Sakoda M, Kurauchi-Mito A et al. Possible roles of human (pro)renin receptor suggested by recent clinical and experimental findings. Hypertens Res. 2010;33:177-180.
41. Feldt S, Batenburg WW, Mazak I et al. Prorenin and renin-induced extracellular signal-regulated kinase 1/2 activation in monocytes is not blocked by aliskiren or the handle-region peptide. Hypertension. 2008;51:682-688.
42. Feldt S, Maschke U, Dechend R, Luft FC, Muller DN. The putative (pro) rennin receptor blocker HRP fails to prevent (pro)renin signaling. J Am Soc Nephrol. 2008;19:743-748.
43. Funke-Kaiser H, Zollmann FS, Schefe JH, Unger T; Signal transduction of the pro)renin receptor as a novel therapeutic target for preventing end-organ damage. Hypertens Res. 2010;33:98-104.
44. Sica DA, Flack J. Treatment considerations with aldosterone receptor antagonists. J Clin Hypertens. 2011;13:65-69.
45. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol. 2009;20:2641-2650.
46. Gaddam K, Pimenta E, Thomas SJ et al. Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. J Hum Hypertens. 2010;24:532-537.
47. Chapman N, Dobson J, Wilson S et al. Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in patients with resistant hypertension. Hypertension. 2007;49:839-845.
48. White WB, Carr AA, Krause S et al. Assessment of the novel selective aldosterone blocker eplerenone using ambulatory and clinical blood pressure in patients with systemic hypertension. Am J Cardiol. 2003; 92:38-42.
49. Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Eng J Med. 1999;341:709-717.
50. Pitt B, Remme W, Zannad F et al. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker,

in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309-1321.
51. Zannad F, McMurray JJV, Krum H et al. Eplerenone in patients with systolic heart failure and mild symptoms. New Eng J Med. 2010;6,364:11-21.
52. Kirkby NS, Hadoke PWF, Bagnall AJ, Webb DJ. The endothelin system as a therapeutic target in cardiovascular disease: great expectations or bleak house? Br J Pharmacol. 2008;153:1105-1119.
53. Dhaun N, Pollock DM, Goddard J, Webb DJ. Selective and mixed endothelin receptor antagonism in cardiovascular disease. Trends Pharmacol Sci. 2007;28:573-579.
54. Feldstein C, Romero C. Role of endothelins in hypertension. Am J Ther 2007;4:147-153.
55. Weber MA, Black H, Bakris G et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double blind, placebo-controlled trial. Lancet. 2009;374:1423-1431.
56. Webb DJ. DORADO: opportunity postponed: lessons from studies of endothelin receptor antagonists in treatment-resistant hypertension. Hypertension. 2010;56:806-807.
57. Bakris GL, Lindholm LH, Black HR et al. Divergent results using clinic and ambulatory blood pressures: report of a darusentan-resistant hypertension trial. Hypertension. 2010;56:824-830.
58. Sica DA. Endothelin receptor antagonism: what does the future hold? Hypertension. 2008;52:460-461.
59. Acelajado MC, Calhoun DA. Resistant hypertension, secondary hypertension, and hypertensive crises: diagnostic evaluation and treatment Cardiol Clin. 2010;28:639-54.
60. Heusser K, Tank J, Engeli S et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. Hypertension. 2010;55:619-26.
61. Grassi G. Sympathetic neural activity in hypertension and related diseases Am J Hypertens. 2010;23:1052-60.
62. Scheffers IJM, Kroon AA, Schmidli J, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study J Am Coll Cardiol. 2010;56:1254-8.
63. Wustmann K, Kucera JP, Scheffers I, et al. Effects of chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant arterial hypertension Hypertension. 2009;54:530-6.
64. Scheffers I, Schmidli J, Kroon AA et al. Sustained blood pressure reduction by baroreflex hypertension therapy with a chronically implanted system: 2-year data from the Rheos DEBUT-HT study in patients with resistant hypertension. J Hyperten. 2008;26(1):S19.
65. Bisognano JD, Bakris G, Nadim MK et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos Pivotal Trial. J Am Coll Cardiol. 2011;58(7):765-773.
66. Bakris G, Bisgnano J, Nadim M, et al. Achievement of blood pressure goal in patients with resistant hypertension treated with Baroreflex Activation Therapy J Hypertens. 2010;26(E-Suppl A):282.
67. Schlaich MP, Sobotka PA, Krum H et al. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. Hypertension. 2009;54:1195-1201.
68. Dibona GF, Esler MD. Translational medicine: the antihypertensive effect of renal denervation. Am J Physiol Regul Integr Comp Physiol. 2010;298:R245-R253.
69. Krum H, Sobotka P, Mahfoud F et al. Device-based antihypertensive therapy: therapeutic modulation of the autonomic nervous system. Circulation. 2011;123:209–215.
70. H Krum, M Schlaich, R Whitbourn et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;9671:1275-1281.
71. MD Esler, H Krum, PA Sobotka et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376:1903-1909.