

# Aliskiren – an alternative to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the therapy of arterial hypertension

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## Abstract

There has been enormous progress in antihypertensive therapy over the last few decades. However, the management of arterial hypertension is still insufficient and more efforts are needed to improve both non-pharmacological and pharmacological treatment of this widely prevalent disease. Renin-angiotensin-aldosterone system (RAAS) inhibition is crucial both for blood pressure (BP) control and for prevention of organ damage or its development in patients with hypertension. Angiotensin-converting enzyme inhibitors and/or sartans block RAAS incompletely. Aliskiren is one of the novel drugs that has been introduced to antihypertensive therapy recently. Up to now no trial has confirmed that aliskiren is efficacious in reducing cardiovascular events. Double RAAS blockade with aliskiren was not always safe. This review article presents the current view on the place of aliskiren in the therapy of arterial hypertension.

**Key words:** antihypertensive therapy, renin-angiotensin-aldosterone system, renin inhibitor.

## Introduction

Essential hypertension (EH) is a major risk factor for cardiovascular diseases and related disorders and the most frequent cause of death worldwide. The WHO data show that EH was the cause of 7.1 million deaths (13% of all deaths), 62% of all strokes and 49% of all myocardial infarctions (MI) [1]. In 2004, 65.2 million Americans (31.3% of the adult population) had EH [2]; 44.2% of people aged 35–75 were diagnosed with EH in analysis conducted in 6 European countries [3]. Essential hypertension is the second most frequently detected cardiovascular risk factor in the Polish population. According to the NATPOL 2011 study, 32% of adults under 80 years were diagnosed with EH [4].

According to WHO, 27% of the population were diagnosed with EH but not treated, while 28% of men and 37% of women were undertreated. Essential hypertension control was proper in 9% of males and 14% of females [5]. Antihypertensive therapy is expected to meet target blood pressure (BP) and reduce cardiovascular endpoints, i.e. stroke, myocardial infarction and heart failure. Monotherapy achieves this goal in 26–33% of patients, while 45% and 22% of hypertensives require 2 or  $\geq 3$  agents, respectively [6]. High-

risk patients with hypertension (coexisting coronary artery disease, heart failure, diabetes mellitus, chronic hypertensive cardiovascular disease, stroke) should be carefully selected for both specific drug(s) use and BP targets due to potential adverse effects and the J-curve phenomenon [7].

Depending on a patient's age, in this group, BP should be reduced below 140/90 mm Hg (< 80 years), and to 140–145 mm Hg (systolic, if tolerated among patients > 80 years) [8]. Blood pressure decreased below 110–115/70–75 brings a risk of increased incidence of cardiovascular events [7]. For resistant hypertension, non-pharmacological methods were also introduced – an implantable device which stimulates the carotid baroreceptors or catheter-based radiofrequency ablation of the renal sympathetic nerves – but their safety and long-term efficacy are subject to debate [6]. This situation gives rise to the need for optimization of treatment and research on new antihypertensive drugs. Studies into the nature of drugs exerting an impact on the renin-angiotensin-aldosterone system (RAAS) became a milestone in EH pharmacotherapy. Renin-angiotensin-aldosterone system inhibition improves both the clinical condition and the prognosis for EH patients, because it lowers BP and prevents organ damage or its development [9].

### Renin-angiotensin-aldosterone system

Renin-angiotensin-aldosterone system, a group of proteins in the circulatory system, undergoes cascade reactions, which result in the formation of angiotensin II (AngII) and aldosterone. Two independent RAASs, intravascular and endocrine, play a role in the BP, water-electrolyte balance, and in the local tissue auto- and paracrine system – crucial for physiological processes (brain development, learning, memory boost and tissue growth), and for inflammation, small and large vessel hypertrophy and remodeling and obesity [10]. The RAAS may be pharmacologically influenced on the following levels [11–14]:

1. inhibition of renin release from the renal juxtaglomerular apparatus ( $\beta$ -blockers use);
2. renin inhibition (angiotensinogen analogs = renin inhibitors use);
3. competitive inhibition of the ACE enzyme and decreased AngII formation (angiotensin-converting enzyme inhibitors – ACEI);
4. block of renin binding to the angiotensin type 1 receptor ( $AT_1R$ ), no angiotensin type 2 receptor ( $AT_2R$ ) stimulation prevention (AngII antagonists, angiotensin receptor blockers – ARBs);
5. block of the mineralocorticoid receptor (MR) (aldosterone antagonists use).

### Renin

Renin, an aspartate protease, highly specific towards its only substrate, angiotensinogen, is the

key, first rate-limiting step enzyme of the biochemical RAA cascade, an important BP regulator. High serum renin activity (SRA) *per se* might be a risk factor for cardiovascular diseases. Alderman *et al.* found that the SRA value, before the antihypertensive treatment of 2902 hypertensives, was directly correlated with the risk of myocardial infarction (MI), despite optimal BP control [15]. A link between high SRA and kidney dysfunction and left ventricle hypertrophy was demonstrated [16, 17]. The RAAS blockade is not full and long-term when an ACEI is used: the reactive serum renin rise results in increased AngI formation, which boosts AngII synthesis through the ACE dependent and independent pathways (i.e., tissue chymases) [18]. The degree of compensatory renin release is proportional to the decrease of AngII, generated or bound to the  $AT_1R$  in the renal juxtaglomerular apparatus.

### The history of renin inhibitors' development

In 1957 Seggs *et al.* stated: “...the production of hypertensin I from renin substrate might be prevented by the inhibition of renin. Since renin is the initial and rate-limiting substance in the renin-angiotensin system, it seems that this last approach would be the most likely to succeed. This view is reinforced by the observation that immunization with heterologous renin has been used successfully in the treatment of dogs with experimental renal hypertension” [19].

In the last 30 years many renin inhibitors have been synthesized and studied (enalkiren, remikiren, terlakiren, zankiren), but they did not become clinically useful because of their low efficacy, low bioavailability, short duration of action after oral use and high costs of synthesis [20, 21]. Further research on renin inhibitors' molecular modifications were focused on solving the problem of bioavailability of the drugs. X-ray crystallography and computer-aided molecular design methods (for the reconstruction of enzyme active center structure) were used in the Hoffmann-La Roche laboratory to synthesize piperidine renin inhibitors, which have only gone through pre-clinical trials [22]. A non-peptide, orally active compound, aliskiren (CGP 60536 B) was discovered in Ciba-Geigy (now Novartis) by using the same methods of preparation [23]. Aliskiren synthesis was not suitable for mass production since it was multilevel and costly. In 1999 Speedel AG took over the license for aliskiren production and developed a cost-effective method of its synthesis [24]. In 2001 Hoffmann-La Roche discovered a new subclass of renin inhibitors, SPP600 series, and in 2005 Speedel AG synthesized another series of compounds with analogous effects, SSP800 [25].

## Aliskiren

Aliskiren (SPP100), an octanamide, is the first representative of the new class, non-peptidic, low molecular weight, specific, orally active renin inhibitors which made it through to the third phase of clinical trials [26]. The drug is hydrophilic, refractory to intestine, serum and hepatic peptidases biodegradation, and its inhibitory concentration of 50% (IC50) is measured in the low nanomolar range [27]. Studies in healthy volunteers [27] showed that with aliskiren doses from 40 to 640 mg daily there was a dose-related increase of its serum level, with maximum concentration within 3–6 h after the drug administration. Plasma steady-state concentrations were achieved within 5–8 days during the drug use and oral bioavailability of aliskiren in the single dose of 75 mg was 2.6%. Aliskiren may be administered once a day (half life = 20–45 h ( $\pm 23.7$ )) [27], does not influence cytochrome P450 isoenzymes, underwent hepatic metabolism to a minimal extent, and is moderately bound by the serum proteins; thus no pharmacokinetic interactions between aliskiren and co-administered drugs (e.g., warfarin) were observed [28]. After oral administration, aliskiren is eliminated unchanged, mainly with bile (less than 1% excreted with urine) [27]. Patients in all age groups tolerate aliskiren well. Vaidyanathan *et al.* reported that no dose adjustment of aliskiren is needed for patients aged 65–74 and older [29]. Ethnicity seems to have no influence on pharmacokinetic and pharmacodynamic properties of aliskiren, as they are similar in Caucasian and Japanese populations [29].

### Selected data concerning aliskiren

Aliskiren caused prolonged, dose-dependent inhibition of RAAS in healthy volunteers [27]. Azizi *et al.* [30] compared the influence of monotherapy with aliskiren (300 mg daily) or valsartan (160 mg daily), or of both drugs co-administered in half doses on serum renin, angiotensins, aldosterone levels and SRA, which were initially high. A single aldosterone dose, after 1 h, caused total inhibition of SRA, which lasted for 48 h. Valsartan administration caused SRA increase within 4 h, followed by higher than after placebo use SRA increase for 48 h. Combination therapy lowered SRA 1 h after the drugs administration to a level lower than in the placebo group. Aliskiren increased renin serum concentrations far more than valsartan: 15-fold and 10-fold, respectively. When compared with valsartan, aliskiren inhibited urine aldosterone excretion for a longer time (8 h and 48 h, respectively). Combination therapy had similar hypotensive efficacy as monotherapy with aliskiren, and more positive results than the sole use of 160 mg of valsartan. Thus, co-administration of inhibitor (150 mg of ali-

skiren) and AngII inhibitor (80 mg of valsartan) in small doses acts synergistically on RAAS [30]. Stanton *et al.* examined 226 hypertensives (mild-to-moderate EH), treated with 300 mg of aliskiren daily. The BP decrease was comparable to that obtained with higher than recommended losartan doses [31]. The investigation by Gradman *et al.* revealed that 2-week treatments of patients with mild-to-moderate EH, with different aliskiren single daily doses (150 mg, 300 mg, 600 mg), were effective and safe similarly to a single daily dose of 150 mg of irbesartan [32]. Selected clinical trials concerning aliskiren use in mild-to-moderate EH are presented in Table I.

### Aliskiren – hypotensive effects

The Musini *et al.* meta-analysis of studies assessing aliskiren, used for 4–8 weeks in daily doses of 75–600 mg, in 3694 adult patients with EH, confirmed significant, dose-dependent, hypotensive effects of aliskiren, as compared with placebo, which was comparable with the antihypertensive efficacy of ACEIs and ARBs. During 4–8 weeks of observation, cessation of treatment because of drug adverse reactions was equally frequent in groups treated with aliskiren and placebo [34]. The meta-analysis of 10 clinical trials prepared by Gao *et al.*, including 3732 hypertensives, confirmed similar antihypertensive efficacy and safety of aliskiren and AT<sub>2</sub>R blockers, namely losartan, valsartan and irbesartan [35]. Comparable hypotensive effects of aliskiren in both sexes (2064 males and 1527 females) were found in Gradman's meta-analysis of 2010. Occurrence of aliskiren adverse effects in females and in the placebo group was similar, but more frequent in comparison with the males given aliskiren [36]. Stanton *et al.* (meta-analysis of data from 8 clinical trials) found that aliskiren monotherapy does not cause paradoxical, sudden increase of BP more often than monotherapies with other antihypertensive drugs, such as ACEIs (ramipril), sartans (losartan, irbesartan, valsartan), or diuretics (hydrochlorothiazide) [37].

### Aliskiren – metabolic syndrome

Aliskiren increased insulin sensitivity both in humans [38] and in animals on a high-fructose diet [39], due to decreased AngII formation. Chou *et al.* [39] demonstrated hypertension, hyperinsulinaemia, insulin resistance, hyperglycemia, hypercholesterolemia and hypertriglyceridaemia induced by persistent high-fructose diet in male Sprague-Dawley rats. All those metabolic disturbances were prevented or reversed by aliskiren in the dose of 100 mg/kg/daily s.c. for 4–8 weeks [39]. Stucchi *et al.* demonstrated reduction of plasma leptin levels and decreased insulin resistance fol-

**Table 1.** Selected clinical trials concerning aliskiren therapy among patients with mild and moderate EH (own work on the basis of Table II in [33])

Clinical trial	Population	Period of observation	Comparison (successive numbers stand for successive groups compared in the trial)	Results
O'Brien E, <i>et al.</i> Hypertension 2007; 49: 276-84	67 patients with mild and moderate EH	6 weeks	1. Aliskiren → aliskiren + HCTZ 2. Ramipril → ramipril + aliskiren 3. Irbesartan → irbesartan + aliskiren	Monotherapy < combination therapy <sup>1</sup>
Pool JL, <i>et al.</i> Am J Hypertens 2007; 20: 11-20	1123 patients with mild and moderate EH	8 weeks	1. Placebo 2-4. Aliskiren (75-300 mg) 5-7. Valsartan (80-20 mg) 8-10. Aliskiren + valsartan (75-300/80-320 mg) 11. Valsartan + HCTZ (160/12.5 mg)	Placebo < aliskiren = valsartan < aliskiren + valsartan = valsartan + HCTZ <sup>2</sup>
Oparil S, <i>et al.</i> Lancet 2007; 370: 221-9	1797 patients with mild and moderate EH	8 weeks	1. Placebo 2. Aliskiren (150 → 300 mg) 3. Valsartan (160 → 320 mg) 4. Aliskiren + valsartan (150/160 → 300/320 mg)	Placebo < aliskiren = valsartan < aliskiren + valsartan <sup>1</sup>
Villamil A, <i>et al.</i> J Hypertens 2007; 25: 217-26	2776 patients with mild and moderate EH	8 weeks	1. Placebo 2-4. Aliskiren (75-300 mg) 5-7. HCTZ (6.25-25 mg) 8-15. Aliskiren + HCTZ (75-300 mg/6.25-25 mg)	Placebo < aliskiren = HCTZ < aliskiren + HCTZ <sup>2</sup>
Andersen K, <i>et al.</i> J Hypertens 2008; 26: 589-99	842 patients with mild and moderate EH	26 weeks	1. Ramipril (5 → 10 mg) ± HCTZ 2. Aliskiren (150 → 300 mg) ± HCTZ	Ramipril ± HCTZ < aliskiren ± HCTZ
Schmieder RE, <i>et al.</i> J Hypertens 2009; 27: 1493-501	1124 patients with mild and moderate EH	52 weeks <sup>3</sup>	1. HCTZ (12.5 → 25 mg) ± amlodipine (5-10 mg) 2. Aliskiren (150 → 300 mg) ± amlodipine (5-10 mg)	HCTZ ± amlodipine < aliskiren ± amlodipine

HCTZ – hydrochlorothiazide, ABPM – ambulatory blood pressure monitoring, <sup>1</sup>average 24 h BP with ABPM, <sup>2</sup>variations in results depending on drug dosage, <sup>3</sup>main end point included hypotensive effect after 26 weeks of observation

lowing aliskiren administration in obese mice on a high-fat diet [40].

### Aliskiren – cardio- and nephroprotective effects

Studies assessing cardio- and nephroprotective effects of aliskiren, both in mono- and combination therapy with other RAAS blockers, have been conducted. ALLAY (Aliskiren in Left-Ventricular Hypertrophy Study), which included 465 obese patients with EH and left ventricular hypertrophy, concluded that aliskiren and losartan have a comparable effect on left ventricular hypertrophy regression and similar hypotensive efficacy and safety of use [41]. ALOFT (Aliskiren Observation of Heart Failure Treatment) compared the effects of aliskiren and placebo on the brain natriuretic peptide (BNP) serum concentration in patients with heart failure. Three-month aliskiren therapy, as compared with placebo, statistically significantly decreased the concentration of BNP, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), aldosterone and SRA [42]. In the AVOID program (Aliskiren in the Evaluation of Proteinuria In Diabetes Trial) aliskiren or placebo was combined with losartan, to assess the urine albumin-to-creatinine ratio of 599 hypertensives with type 2 diabetes mellitus and diabetic nephropathy. After 24 weeks of observation, in the group given aliskiren the urine albumin-to-creatinine ratio decreased (–18% vs. +2% – change of 20%), which proves additional significant nephroprotective properties [43]. In the AVOID2 program, aliskiren's influence on renal blood flow and glomerular filtration rate (GFR) in diabetic patients with EH, having estimated GFR (eGFR) over 40 ml/min/1.73 m<sup>2</sup>, was tested. After 2-month therapy, a decrease in urinary albumin excretion by 48%, as compared with placebo, was noted. It has been shown that combining aliskiren and irbesartan (300 mg and 60 mg daily, respectively) decreased albuminuria by 71%, more efficiently than monotherapy [44]. The beneficial effects of aliskiren and its good tolerance in combination with sartans (valsartan, losartan) or a diuretic were confirmed in White's meta-analysis of July 2011, including over 12 000 patients with EH. Incidents of angioedema or hyperkalemia were noted equally frequently in groups treated with double RAAS blockade, as well as groups with sartan or diuretic monotherapy [45]. According to the statement of the European Medicines Agency of 17 February 2012, aliskiren co-administered with ACEIs or ARBs is not recommended in patients with diabetes (type 1 or 2) and moderate-to-advanced renal failure. The agency added a warning that a double RAAS blockade is not recommended in other patients, due to potential adverse effects: hypotension, fainting, stroke, hyperkalemia, and renal failure, including acute one. The opinion issued by the European Medicines

Agency is based on an analysis of data concerning safety of combining aliskiren with ACEIs or ARBs, prepared after early termination of the ALTITUDE study in December 2011 [46]. Moist's meta-analysis of January 2012, including studies conducted with the use of aliskiren, ACEIs and ARBs, concludes that combination therapy based on aliskiren and another drug blocking the RAAS far more often than monotherapy with any of these drugs leads to moderate (potassium concentration within the 5.5–5.9 mmol/l range) hyperkalemia. No statistically significant differences in the occurrence of acute hyperkalemia ( $\geq 6.0$  mmol/l) or acute renal failure episodes were noted [47]. Significantly more frequent occurrence of hyperkalemia when using aliskiren in combination with ACEI or a ARB, as well as the necessity to carefully monitor serum potassium level among these patients, was confirmed by the meta-analysis of 10 clinical trials, including 4814 patients with EH, published also in January 2012 by Harel *et al.* In this analysis the risk of acute renal failure showed no statistically significant differences between the group given double RAAS blockade and the group with monotherapy (1.14, 0.68 to 1.89) [48]. Most recent analyses concerning renin inhibitors in nephroprotection emphasize that double blockade of the RAAS can be considered in cases of chronic nephropathy with albuminuria among patients who, despite treatment with an optimal dose of ACEI or sartan, do not achieve full and permanent albuminuria remission. The necessity to strictly monitor kalemia and renal function among these patients is stressed [49]. Because of the lack of suitable trials, aliskiren is still not included in ESH/ASH/ACC/ESC guidelines as a recommended therapy for HT treatment. So far no long-term data proving aliskiren to reduce cardiovascular events have been gathered. Thus, at present, not aliskiren, but ACEIs or ARBs are the drugs of choice in prevention of cardiovascular events in patients with EH.

### Summary

Essential hypertension-induced cardiovascular diseases are a common cause of death among the worldwide population. Blockade of RAAS, which plays a major role in developing EH, is suboptimal when using ACEI and/or ARB. The key, rate-limiting step reaction of the RAAS cascade can be inhibited pharmacologically by using aliskiren, which successfully decreases BP and has a positive effect on organ damage caused by EH. There are groups of patients for whom complex therapy with ACEI or ARB and aliskiren is not recommended. Further long-term studies on large groups of patients are required to precisely determine the place of aliskiren in antihypertensive therapy.

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