JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Review

Aliskiren as a novel therapeutic agent for hypertension and cardio-renal diseases

Azhar Rashikh, Shibli Jameel Ahmad, Krishna Kolappa Pillai and Abul Kalam Najmi

Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi, India

Keywords
aliskiren; hypertension; plasma renin activity; renin angiotensin aldosterone system

Correspondence
Abul Kalam Najmi, Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi-110062, India.
E-mail: aknajmi@jamiahamdard.ac.in; aknajmi@hotmail.com

Received March 4, 2011
Accepted October 24, 2011

doi: 10.1111/j.2042-7158.2011.01414.x

Abstract

Objectives High blood pressure (BP) is a major risk factor for cardiovascular and renal complications. A majority of treated hypertensive patients still complain of high BP. The renin-angiotensin aldosterone system (RAAS) has been a centre-stage target for all the cardiovascular and cardio-renal complications. Aliskiren, is the first direct renin inhibitor (DRI) to be approved by the US FDA. Renin controls the rate-limiting step in the RAAS cascade and hence is the most favorable target for RAAS suppression.

Key findings This review article strives to summarize the pharmacokinetic, pre-clinical and clinical studies done so far pertaining to the efficacy of aliskiren. Further, the pharmacology of aliskiren has been comprehensively dealt with to enhance understanding so as to further research in this unfathomed area in the multitude of cardiovascular disorders and renal diseases.

Summary Aliskiren has been shown to have comparable BP-lowering effects to other RAAS inhibitors. Recent clinical trials have indicated that it might contribute significantly in combination with other agents for the protection of end-organ diseases.

Introduction

Hypertension is the foremost risk factor for cardiovascular diseases, affecting more than one billion people worldwide.[1] Evidence suggests that the renin-angiotensin-aldosterone system (RAAS) plays a vital role in the development of hypertension, cardiac hypertrophy, reperfusion injury and end-organ damage.[2] The juxtaglomerular cells in the afferent renal arterioles secrete renin in response to low plasma volume, reduced renal perfusion or increased sympathetic nervous system activity.[3] Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I, which is then converted by angiotensin-converting enzyme (ACE) to the active octapeptide angiotensin II, that interacts with type-1 angiotensin receptors (AT_1). This leads to vasoconstriction and raised blood pressure, promoting adrenal aldosterone secretion, renal sodium reabsorption and release of catecholamines from the adrenal medulla and prejunctional nerve endings.[4]

The role of renin is as a rate-limiting step in the conversion of angiotensinogen to angiotensin I and hence preventing the formation of angiotensin II in the RAAS cascade. Renin is, therefore, the primary determinant of RAAS activity,[5] and RAAS control is an imperative target of prevention of end-organ damage. ACE-inhibitors check the systemic effect of angiotensin II by inhibiting ACE, while angiotensin receptor blockers (ARBs) directly inhibit the binding of angiotensin II to the receptor. However, both ACE-inhibitors and ARBs lead to increase in plasma renin activity by blocking feedback inhibition of renin release. β-blockers restrain the β-adrenergic receptor-mediated release of renin from the kidney, which only partially reduces plasma renin activity and the generation of angiotensin II.[6]

The interest in absolute blockade of RAAS at its origin by inhibiting renin has existed for at least five decades. The first synthetic renin inhibitor was pepstatin, which required parenteral administration. Oral agents that were subsequently developed, such as enalkiren, remikiren and zankiren, had limited clinical use because they exhibited poor bioavailability, short half-lives and weak antihypertensive activity.[7] Of late, aliskiren, has been found to be the first orally effective direct renin inhibitor for the treatment of hypertension. The goal of this review article is to discuss the experimental and clinical studies of aliskiren and its potential use in the management of hypertension and other cardiovascular disorders and related target-organ damage.

Relevant experimental and clinical studies were identified by searching MEDLINE (from 1992 to Feb 24, 2011) using the

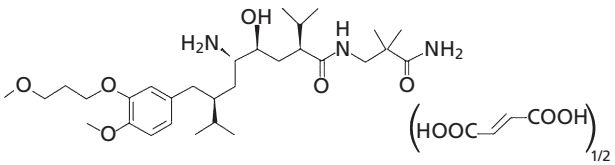

Figure 1 Chemical structure of aliskiren hemifumarate.

primary search terms aliskiren, plasma renin activity, renin-angiotensin-aldosterone system, hypertension, safety study and end organ protection.

Aliskiren

Aliskiren is the first of a new class of orally active, non-peptide, low-molecular-weight direct renin inhibitors, and has been approved by the US FDA as an antihypertensive drug. Aliskiren has the chemical structure 2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-(4-methoxy-3-[3-methoxypropoxyl]-phenyl)-octanamide and a molecular weight 551.8 g/mol.[8] The active form of aliskiren is the hemifumarate salt[9,10] (Figure 1). It has good water solubility (>350 mg/ml at pH 7.4), high hydrophilicity (log Poct/water = 2.45 at pH 7.4) and is resistant to biodegradation by peptidases found in the intestine, blood and liver.[8,10,11]

Mechanism of Action

Aliskiren is a potent competitive inhibitor of renin (Figure 2), but very poorly inhibits related aspartic peptidases.[10,12] Aliskiren is reported to have half of the inhibitory concentration (IC50) of 0.6 nmol/l for both purified human renin and human plasma renin.[8] In healthy human subjects, doses of 40–640 mg have exerted a dose-dependent reduction in plasma renin activity, angiotensin I and angiotensin II levels.[13,14] Few studies have suggested that in lower doses, renin inhibitors and ARBs might exert synergistic effects on the RAAS.[12]

Potential Advantages of Aliskiren over Current Existing RAAS Blockers

- Aliskiren is a highly selective inhibitor of renin and has shown lesser side effects.[15]
- Aliskiren prevents the formation of both angiotensin I and angiotensin II and may offer a therapeutic profile distinct from both ACE inhibitors and ARBs.[16]
- Aliskiren does not obstruct the metabolism of bradykinin and substance P into the inactive peptide kinin, therefore side effects such as cough or angioedema that occur with ACE inhibitors are not likely to occur with aliskiren treatment.[15]
- ARBs increase the level of angiotensin II and indirectly stimulates angiotensin II subtype 2 receptor (AT_2) that contribute to cardiac fibrosis, an effect that does not occur with renin inhibitors.[16]
- Aliskiren produces effective blockade of RAAS without the compensatory increase in plasma renin activity, while ACE-inhibitors and ARBs inhibit negative feedback mechanisms. This inhibition results in a reactive increase in plasma renin activity (capacity of renin to convert angiotensinogen to angiotensin I) that may lead to increased generation of angiotensin II.[17]
- After discontinuation of therapy no rebound hypertension is reported with aliskiren.[18]
- Aliskiren has a long half-life (23–45 h) and very high affinity for renin, therefore provides sustained control of blood pressure over 24 h.
- ACE-escape: ACE inhibition causes an increase in angiotensin I, which is then available for conversion to angiotensin II by ACE-independent pathways (chymase, chymotrypsin and cathepsin G), not blocked by ACE inhibitors. This is called ACE-escape.[19] With aliskiren, such a phenomenon is not observed.[20,21]
- Aliskiren is well tolerated in patients with hepatic impairment.[22]
- Renin receptors in the kidneys and vasculature are exposed to interface with rennin, leading to direct activation of the signalling pathway of pathogenic mitogen-activated protein kinase (MAPK), which may start profibrotic consequences.[23] Therefore, it can be speculated that aliskiren might provide additional protection over that provided by other RAAS inhibitors.

Pharmacokinetics

Pharmacokinetic studies have been performed in marmosets,[12] rats[24] and humans[25,26] with single daily oral doses of aliskiren. Aliskiren has been shown to have low oral bioavailability—2.4% in rats, 16% in marmosets and about 2.5% in humans. When aliskiren is administered with food, mean Cmax and AUC are reduced by approximately 81% and 62%, respectively, when compared with the fasting state.[27] However, this does not affect the inhibition of plasma renin activity. The apparent volume of distribution is reported to be 135 l in healthy volunteers, indicating extensive tissue uptake of the drug.[9] Approximately 47–51% of aliskiren is bound by plasma proteins in humans, independent of the concentration.[9,25] Aliskiren concentrations are greater in the kidney than in plasma and the drug is detectable in the kidney up to three weeks after discontinuation of therapy, whereas plasma levels of aliskiren are undetectable at this time point.[18,28] After oral administration, peak plasma concentrations of aliskiren

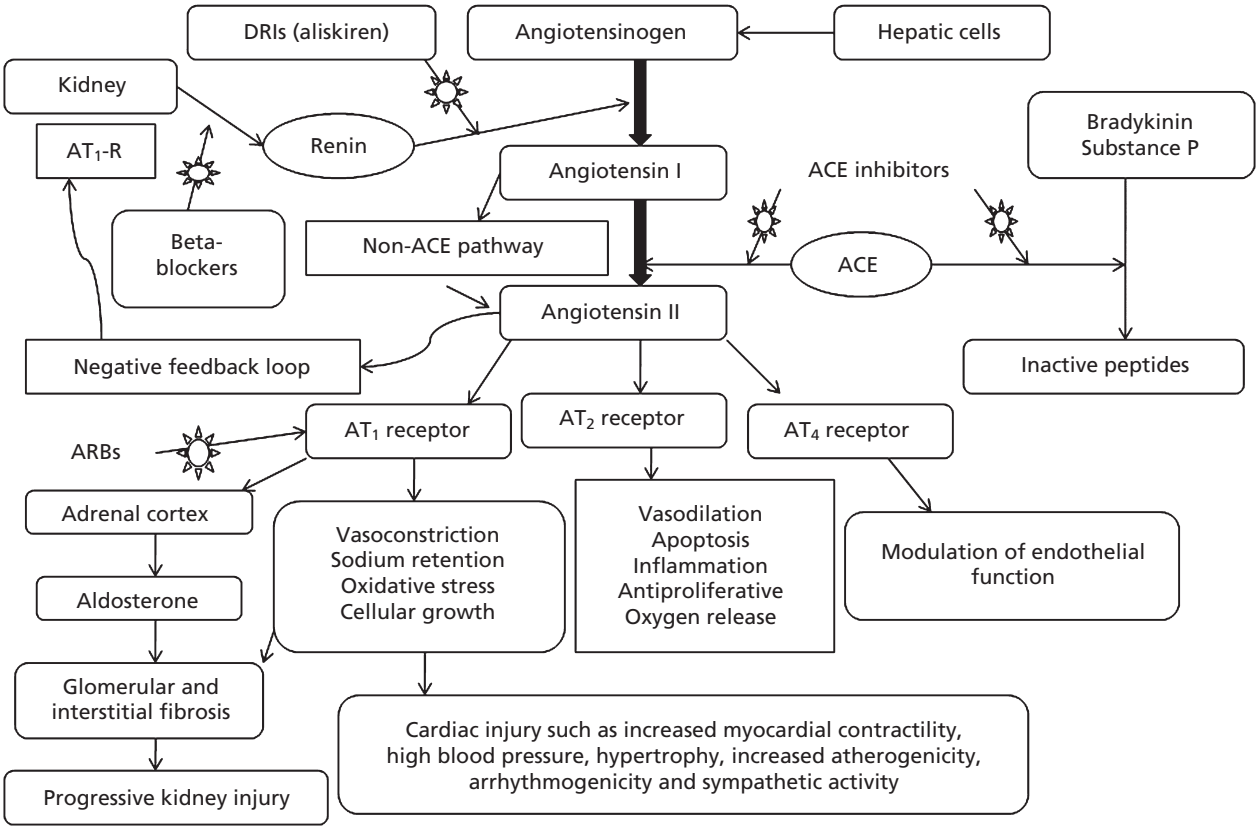

Figure 2 The renin-angiotensin aldosterone system (RAAS) pathway and different sites of blockade. DRIs, direct renin inhibitors; ACE, angiotensin converting enzyme; ARBs, angiotensin receptorblockers; AT, angiotensin.

are reached within 1–3 h[14,29] and steady-state blood levels are reached in about 7–8 days with once-daily administration.[25] The plasma half-life of aliskiren in rats, marmosets and humans shows a slow terminal elimination at 23, 26 and 23–40 h, respectively.[8,26,30] The variation in human terminal half-life is likely associated with differences in the duration of the post-dose sampling period.[14,22] The trough-to-peak (T : P) ratio is commonly used as an index of the duration of action of antihypertensive agents. For the treatment of hypertension, a drug with a T : P ratio of >0.5 is recommended.[31] The high T : P ratio of aliskiren in hypertensive patients was found consistent after oral administration of the drug as compared with healthy subjects.[16,32]

Aliskiren is slightly metabolized in humans (about 20%) and is approximately 50% metabolized in rodents. In in-vitro studies, the major enzyme responsible for aliskiren metabolism appears to be CYP3A4.[25,26] Aliskiren does not inhibit CYP450 isoenzymes at concentrations up to 100 times maximum concentrations measured in clinical trials.[9] The primary elimination route of aliskiren is via biliary excretion (91%) as unmetabolized drug.

Pharmacodynamics

Experimental and clinical studies are shown in Tables 1 and 2 respectively, describing potential therapeutic use, tolerability and safety of aliskiren.

Therapeutic Potential of Aliskiren

Aliskiren is available in the market for treatment of hypertension as a monotherapy. However, many experimental and clinical studies have suggested that it may have potential to treat other cardiac and renal disorders either alone or in combination with other RAAS blockers.

Suggested clinical uses of aliskiren are as follows:

- Component of combination therapy for hypertension, with diuretic, ACE-inhibitors and ARBs.[7,67]
- Alternative to ACE-inhibitors or ARBs in the management of hypertension and organ damage[14]
- Component of combination therapy for diabetic nephropathy, with ARBs[72]
- In patients with hypertension and left ventricular hypertrophy[74]

Table 1 Experimental studies

Treatment	Results	Animal used	References	Year
Aliskiren 3 mg, s.c. Losartan 10 mg orally	Aliskiren reduced albuminuria and complement expression more significantly than losartan	dTGRs	Shagdarsuren *et al*.[33]	2005
Aliskiren 50 mg, s.c., by osmopump	Aliskiren improved left ventricular dysfunction after myocardial infarction	C57J/bl6 mice	Westermann *et al*.[34]	2008
Aliskiren 25 mg, s.c. losartan 30/120 mg, p.o.	RAAS blockade was used to treat multiple sclerosis	*C57BL/6* mice	Stegbauer *et al*.[35]	2009
Aliskiren 2.5, 25 and 50 mg to normal diet	Inhibited mouse renin and reduced atherosclerosis	Mice	Lu *et al*.[36]	2008
Aliskiren 30 mg, s.c., implanted by osmotic Alzet	Antihypertensive and renoprotective effects in experimental diabetic nephropathy	Diabetic TG(mRen-2)27 rats	Feldman *et al*.[37]	2008
Aliskiren 30 mg, p.o., candesartan 1 mg, ip, benazepril 10 mg, p.o.	Angiotensin II synthesis, superoxide production and cardiac fibrosis were blocked by aliskiren	Sprague Dawley rats	Singh *et al*.[38]	2008
Aliskiren 50 mg, s.c., irbesartan 100 mg, atenolol 120 mg and amlodipine 6 mg	Aliskiren and irbesartan significantly prevented atherosclerosis progression	Mice	Nussberger *et al*.[39]	2008
Aliskiren 3 mg, s.c., cilazapril 10 mg, p.o.	Aliskiren and cilazapril blockade did not influence appetite or body weight in transgenic rats	Transgenic rats (TGR)	Gratze *et al*.[40]	2009
Aliskiren 40 mg Valsartan 5 mg Aliskiren 40 mg plus valsartan 5 mg, p.o.	Aliskiren in combination with valsartan showed additive protective effects on endothelial function and atherosclerosis	WHHL rabbits	Imanishi *et al*.[41]	2008
Aliskiren 3 or 10 mg, p.o.	Aliskiren 3 mg, lowered blood pressure by 10 mmHg and aliskiren 10 mg, lowered blood pressure by 16 mmHg	Marmosets	Wood *et al*.[10]	2003
Aliskiren 10–100 mg, s.c., benazeprilat 3 and valsartan 3 mg, p.o.	When combined with valsartan or benazeprilat, aliskiren provided additional blood pressure reduction over monotherapy	Spontaneously hypertensive rats (SHR)	Wood *et al*.[24]	2005
Aliskiren 0.3 and 3 mg, s.c.	Systolic blood pressure was reduced to 115 mmHg	dTGRs	Pilz *et al*.[42]	2005
Aliskiren 25 mg Valsartan 8 mg Aliskiren 12.5 mg plus valsartan 4 mg via osmotic pump	Combination of aliskiren and valsartan exerted greater organ-protective effects than monotherapy with a submaximum dose of either agent	eNOS-deficient mice	Yamamoto *et al*.[43]	2009
Aliskiren 3, 6, 12 and 25 mg Hydralazine 80 mg	Aliskiren (25 mg) attenuated the decreased insulin and prevented pancreatic islet fibrosis and reduced glucose intolerance	db/dbmice	Dong *et al*.[44]	2009
Aliskiren 3 mg, s.c.	Aliskiren ameliorated the type 2 diabetic nephropathy	db/dbmice	Dong *et al*.[45]	2010
Aliskiren 3 mg by osmotic minipump Omacor 25 mg in diet	n-3 PUFA ethyl-esters (Omacor) and aliskiren improved remodeling, arrhythmia induction, and connexin 43 expression	dTGRs	Fischer *et al*.[46]	2008
Aliskiren 10 μM Handle region decoy peptide (HRP) 1 μM	Aliskiren, but not treatment with the HRP protected against AngII-induced renal damage in dTGRs	Cell culture of dTGRs	Feldt *et al*.[47]	2008
Aliskiren 0.03 mg and 3 mg, s.c. by minipump	High-dose regimens provided complete protection against cardio-renal damage	dTGRs	Dechend *et al*.[48]	2007
Aliskiren 50 mg/kg, intraperitoneal (i.p.)	Systolic pressure, albuminuria, and ultrastructural podocyte foot-process effacement were attenuated	Transgenic Ren2 rat	Whaley-Connell *et al*.[49]	2010
Aliskiren 10 μmol/l	Aliskiren-binding increased the half life of renin and prorenin in rat aortic vascular smooth muscle	Cell culture of transgenic rats	Batenburg *et al*.[50]	2008
Aliskiren 50 mg, i.p. injection	Aliskiren attenuated insulin resistance, oxidative stress, and pancreatic remodeling	Transgenic Ren2 rats	Habibi *et al*.[51]	2008
Aliskiren 10 mg, s.c. losartan 5 mg, p.o.	Aliskiren treatment caused higher reduction in MAP and renal ET-1 and angiotensin II levels than losartan	TGRs(mRen2)27	Vanourkova *et al*.[52]	2010
Aliskiren 50 mg, s.c., by osmotic minipumps	Aliskiren improved insulin resistance by increasing insulin sensitivity	KK-A mice	Iwai *et al*.[53]	2010
Aliskiren 1 or 10 mg via i.v. injection for 1 week	Aliskiren protected against chlorhexidine digluconate-induced PF in rats by decreasing TGF-beta1 production	Sprague-Dawley rats	Ke *et al*.[54]	2010
Aliskiren 10 mg via osmotic minipumps, Losartan 5 mg orally	Antihypertensive effect of aliskiren was persistent even after the 12-day washout period	TGRs	Rakusan *et al*.[55]	2010
Aliskiren 20 mg, valsartan 30 mg alone and in combination	Aliskiren 10 mg with valsartan 15 mg showed higher renal protection than either monotherapy	UUO model of rats	Wu *et al*.[56]	2010
Aliskiren (3, 10, 25, 50 mg), via an osmotic pump	Aliskiren intensely reduced leucocyte recruitment in perivascular cuff injury	C57BL/6 mice	Ino *et al*.[57]	2009
Aliskiren 50 and 100 mg, p.o.	Aliskiren attenuated the doxorubicin-induced cardiotoxicity	Wistar albino rats	Rashikh *et al*.[58]	2011

dTGRs, double-transgenic rats; eNOS, endothelial NO synthase; ET-1, endothelin-1; LDL, low density lipoprotein; MAP, mean arterial pressure; p.o., per oral; PF, peritoneal fibrosis; PP, pulse pressure; PRA, plasma renin activity; PRC, plasma renin concentration; PUFAs, n-3 polyunsaturated fatty acids; TGF, transforming growth factor; UUO, unilateral ureteral obstruction; WHHL, Watanabe heritable hyperlipidamic.

Table 2 Clinical studies

Treatment	Results	No. of volunteers	Reference	Year
Aliskiren 160, 320 and 640 mg	Higher doses of aliskiren reduced angiotensin II levels by 89% and 75% respectively, compared with placebo	18	Nussberger *et al*.[32]	2002
Aliskiren 75 and 150 mg	Systolic blood pressure at baseline was 155 ± 11 mmHg and was lowered to 148 ± 14 mmHg after 4 weeks with aliskiren, 75 mg and treatment with aliskiren, 150 mg, resulted in reduction to 144 ± 18 mmHg	8	Wood *et al*.[10]	2003
Aliskiren 300 mg Valsartan 160 mg	Aliskiren completely inhibited PRA and this persisted for 48 h. Conversely, PRA increased within 4 h of valsartan administration and was still elevated 24–48 h after dosing	12	Azizi *et al*.[14]	2004
Aliskiren 150 mg Warfarin 25 mg	Aliskiren did not alter pharmacokinetics or pharmacodynamics effect of a single dose of warfarin assessed by PT, INR and aPTT	15	Dieterle *et al*.[59]	2004
Aliskiren 150 mg	Aliskiren did not show pharmacokinetic interactions with lovastatin, atenolol or cimetidine	57	Dieterle *et al*.[60]	2005
Aliskiren 150 or 300	Aliskiren lowered blood pressure significantly compared with placebo	776	Gradman and Kad[61]	2008
Aliskiren 150–600 mg	Aliskiren 300 mg, lowered diastolic but not systolic blood pressure and aliskiren 600 mg was not effective in further reducing blood pressure than the 300-mg	652	Gradman *et al*.[16]	2005
Aliskiren (37.5–300 mg)	Dose-dependent reduction in systolic blood pressure	226	Stanton *et al*.[11]	2003
Aliskiren 300 mg	Aliskiren showed a similar pharmacokinetic and pharmacodynamic profile in patients with type 2 diabetes as compared with healthy volunteers	60	Zhao *et al*.[62]	2006
Aliskiren 300 mg	Aliskiren demonstrated similar pharmacokinetic and pharmacodynamic properties in Japanese and Caucasian subjects	38	Vaidyanathan *et al*.[29]	2006
Aliskiren 300-mg oral dose	Aliskiren was well tolerated, with no adverse events reported in Caucasians	4	Waldmeier *et al*.[9]	2007
Aliskiren 75–300	All treatment groups showed lowered mean seated systolic and diastolic blood pressure compared with baseline	355	Verdecchia *et al*.[63]	2007
Aliskiren 150–300 Ramipril 5–10	Aliskiren monotherapy was superior to ramipril monotherapy in reducing systolic blood pressure and noninferior in reducing diastolic blood pressure	837	Uresin *et al*.[64]	2007
Aliskiren 150–300,aliskiren/valsartan	Combination of aliskiren and valsartan (150/160–300/320) was more effective in reducing both systolic and diastolic blood pressure than either of the monotherapies alone	1797	Oparil *et al*.[13]	2007
Aliskiren 300 HCTZ 25	Aliskiren was found to be effective in obese patients with hypertension who failed to achieve blood pressure control with thiazide diuretics	489 obese patients	Jordan *et al*.[65]	2007
Aliskiren 75–300,aliskiren/valsartan	Combination therapy was more effective than either monotherapy in reduction of systolic and diastolic blood pressure	1123	Pool *et al*.[7]	2007
Aliskiren 150–600 Placebo	Aliskiren 150, 300, and 600 mg significantly reduced mean blood pressure by 13.0/10.3, 14.7/11.1, and 15.8/12.5 mmHg, respectively, versus 3.8/4.9 mmHg with placebo	672	Oh *et al*.[66]	2007
Aliskiren 75–300 Aliskiren/hydrochlorothiazide	Aliskiren in combination with hydrochlorothiazide produced greater blood pressure reduction than aliskiren alone in eight week at all aliskiren doses	2779	Villamil *et al*.[67]	2007
Aliskiren 300 Aliskiren 150 plus valsartan 160 mg	This study demonstrated a more effective blockade of the renin-angiotensin system through aliskiren, alone or in combination, than that obtained with 320 mg of valsartan alone	12	Azizi *et al*.[68]	2007
Aliskiren/hydrochlorothiazide 300/25 mg	Combination of aliskiren with diuretics was useful in patients who did not respond to aliskiren monotherapy	900	Nickenig *et al*.[69]	2008

Table 2 (*Continued*)

Treatment	Results	No. of volunteers	Reference	Year
Aliskiren 75 to 600 mg	PRA and angiotensin levels were reduced and induction of renal vasodilation was dose-related	20	Fisher *et al*.[46]	2008
Aliskiren 150 Atenolol 50 mg, Aliskiren 150 plus atenolol 50	Aliskiren in combination with atenolol provided significant additional reductions in systolic blood pressure compared with either drug alone, and greater diastolic blood pressure reduction than aliskiren alone	694	Dietz *et al*.[70]	2008
Aliskiren 150–300 mg Ramipril 5–10	Aliskiren provided significantly better systolic and diastolic blood pressure reduction and higher rates of blood pressure control than ramipril-based therapy	842	Andersen *et al*.[71]	2008
Aliskiren 150–300 mg Losartan 100 mg	Aliskiren with ARB treatment reduced the mean UACR by 20%, with a reduction of 50% or more in 24.7% of the patients	599	Parving *et al*.[72]	2008
Aliskiren 150 mg Placebo	Aliskiren showed improvement in neurohormonal profiles, including reductions in PRA, BNP and N-terminal prohormone BNP levels	302	McMurray *et al*.[73]	2008
Aliskiren 300 Losartan 100 mg aliskiren/losartan	Aliskiren was noninferior to losartan in reducing left ventricular hypertrophy, but the combination was not superior to losartan alone	460	Solomon *et al*.[74]	2009
Aliskiren 300 HCTZ 25 mg	Aliskiren provided greater reductions in systolic and diastolic blood pressure among elderly and very elderly patients than diuretics	1124	Schmieder *et al*.[75]	2009
Aliskiren Valsartan	Combination treatment was more effective than monotherapy in systolic blood pressure lowering	1797	Yarows *et al*.[76]	2008
Aliskiren-HCTZ Ramipril-HCTZ	Aliskiren-based therapy was superior to ramipril-based therapy at 12 weeks and non-inferior at 36 weeks in msSBP lowering	901	Duprez *et al*.[77]	2008
Aliskiren 300 Irbesartan 300	Combination of aliskiren and irbesartan was more antiproteinuric in type 2 diabetic patients with albuminuria than either monotherapy	26	Persson *et al*.[78]	2009
Aliskiren 300	Aliskiren exerted a renal vasodilatory effect, suggesting that blockade of the RAAS may improve uncomplicated type 1 diabetes	10	Cherney *et al*.[79]	2010
Aliskiren 75, 150, 300 mg and placebo	Aliskiren produced dose-dependent reductions in mean systolic blood pressure (–8.57, –8.72, and –14.09 mm Hg) and DBP (–7.22, –7.75 and, –10.72 mm Hg)	455	Kushiro *et al*.[80]	2006
Aliskiren + hydrochlorothiazide/ Ramipril/Irbesartan	Aliskiren 150 with hydrochlorothiazide 25 significantly reduced day time but not nighttime systolic/diastolic blood pressure, with ramipril 5 mg lowered both daytime and nighttimesystolic/diastolic blood pressure and with irbesartan 150 mg lower nighttime but not daytime systolic/diastolic blood pressure	23	O'Brien *et al*.[81]	2007
Aliskiren 300	Aliskiren was well tolerated by all age groups (18–75 years)	57	Vaidyanathan *et al*.[22]	2007
Aliskiren 150, 300 and 600 and irbesartan 150	Aliskiren reduced SBP and PRA and increased PRC dose-dependently. In contrast, irbesartan reduced SBP but increased both PRC and PRA	569	Nussberger *et al*.[82]	2007
Aliskiren 300 allopurinol celecoxib 200 bid, cimetidine	Aliskiren did not show pharmacokinetic interactions when co-administered with allopurinol, celecoxib or cimetidine in healthy subjects	22	Ayalasomayajula *et al*.[83]	2008
Aliskiren 300, Furosemide 20 mg	Aliskiren coadministration reduced furosemide AUC by 28% and Cmax by 49% compared with furosemide alone	22	Vaidyanathan *et al*.[84]	2008
Aliskiren 300 mg	Aliskiren was found to be a substrate for but not an inhibitor of P-glycoprotein and CYP3A4	22	Vaidyanathan *et al*.[85]	2008a
Aliskiren 150 mg	Aliskiren reduced 24 h systolic blood pressure, and this was associated with a reduction in albuminuria in type 2 diabetes	15	Persson *et al*.[86]	2008
Aliskiren 75–600 mg	All doses of aliskiren were well tolerated	32	Limoges *et al*.[87]	2008
Aliskiren 150 mg	This study demonstrated a novel direct relation between aldosterone status and insulin resistance in heart failure	302	Freel *et al*.[88]	2009

Table 2 (*Continued*)

Treatment	Results	No. of volunteers	Reference	Year
Aliskiren 150, 300 mg	Aliskiren 300 mg provided a sustained blood pressure-lowering effect beyond the 24-h dosing interval	654	Palatini *et al*.[89]	2010
Aliskiren 300 Valsartan 320 mg	There was no evidence for a benefit of early initiation of inhibition of RAAS with valsartan, aliskiren, and their combination	1101	Scirica *et al*.[90]	2010
Aliskiren 150 mg Rifampicin 600 mg	Rifampicin reduced the plasma concentrations and the renin-inhibiting effect of aliskiren by decreasing its oral bioavailability	12	Tapaninen *et al*.[91]	2010
Aliskiren ARB	Dual blockade of the RAAS with ARB plus aliskiren therapy demonstrated an additive effect to decrease severe proteinuria and blood pressure	16	López *et al*.[92]	2010
Aliskiren 150 mg, 300 mg or 600 mg	Aliskiren 150, 300 and 600 mg reduced UAER significantly by 36%, 48% and 52% respectively compared with placebo	26	Persson *et al*.[93]	2010
Aliskiren 300 Losartan 100 mg	Aliskiren improved the fibrinolytic balance while losartan worsened the fibrinolytic balance		Fogari *et al*.[94]	2010
Aliskiren 150 and 300 mg	Aliskiren has favourable neurohormonal and haemodynamic profile that may benefit patients hospitalized with worsening heart failure	1782	Gheorghiade *et al*.[95]	2011
Aliskiren 300 Verapamil 240	No dose adjustment was necessary when aliskiren was administered with verapamil	18	Rebello *et al*.[96]	2011
Aliskiren 20 nM	Aliskiren mitigated the profibrotic and apoptotic effects of high glucose in cultured podocytes	In culture	Phillips *et al*.[97]	2011
Candesartan 32 + Hydrochlorothiazide 25, Aliskiren 300 + Hydrochlorothiazide 25, and Aliskiren 300 + Hydrochlorothiazide 25 + Amlodipine 5	Candesartan + Hydrochlorothiazide reduced systolic/diastolic blood pressure by 18.9/12.2 mmHg, Aliskiren + Hydrochlorothiazide further reduced to 2.8/3.1 mmHg between week 4 and week 8. In 61 patients not controlled after week 8, amlodipine 5 mg was added and triple therapy decreased systolic/diastolic blood pressure by a further 9.2/5.9 mmHg	186	Schweizer *et al*.[98]	2011

ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; msSBP, mean steady systolic blood pressure; PRA, plasma renin activity; UACR, urinary albumin to creatinine ratio; UAER, urinary albumin excretion rate.

- In patients with uncomplicated type 1 diabetes[79]
- In patients with symptomatic heart failure[73]
- In patients with type 2 diabetes, hypertension and albuminuria[78]

Adverse Effects

Aliskiren has been shown to have a good tolerability profile in several clinical studies when given in single and multiple oral doses.[99] Aliskiren-based therapy was well tolerated and produced sustained blood pressure reductions in patients with hypertension during 6 months, greater than those with ramipril-based therapy. The incidence of adverse effects during aliskiren treatment was relatively low and similar to results obtained in patients treated with placebo. The most common adverse effects reported with aliskiren were headache, nasopharyngitis, dizziness, fatigue, diarrhoea, hypotension and gastrointestinal disorders. All of these occurred in less than 5% of patients and were comparable with the placebo-treated group.[24,71,100]

Contraindications

Aliskiren is contraindicated in pregnancy and in patients with hypersensitivity or allergic reactions to previous exposure. Aliskiren belongs to Pregnancy Category C for first trimester exposure and Pregnancy Category D for second and third trimester exposure. Aliskiren therapy should be promptly discontinued when pregnancy is detected.[63,101] Similar to ACE inhibitors and ARBs, it should not be used in patients with bilateral renal artery stenosis or severe renal disease. It should be used cautiously in patients with biliary cirrhosis since it undergoes hepatobiliary excretion.[102]

Safety Studies

The combination of aliskiren with other drugs that act on the RAAS (ARBs, thiazides, calcium-channel blockers and ACE-inhibitors) has been evaluated and found to be safe, except that higher rates of increased serum potassium were observed with the combination of aliskiren and an ACE-inhibitor in

diabetic patients.[103] Aliskiren does not aggravate ACE-inhibitor-related cough and may even reduce it. There was also a tendency to decrease peripheral oedema when combining aliskiren with a calcium-channel blocker. The aim of the ALOFT (ALiskiren Observation of heart Failure Treatment) trial was to evaluate safety and tolerability of aliskiren when added to standard therapy. Findings from the trial study showed there was no significant excess of hypotension or renal dysfunction.[73] There were no dose-dependent adverse effects and no significant abnormalities in laboratory parameters were observed with aliskiren doses up to 300 mg.[11] Aliskiren is well tolerated in patients with hepatic impairment.[22]

Target Organ Protection

Elevated plasma renin activity has been associated with target organ damage including renal dysfunction and left ventricular hypertrophy.[104] A direct renin inhibitor may have potential, alone or in combination with ACE-inhibitors or ARBs to suppress renin activity and prevent end-organ damage. The study by Pilz and colleagues[42] tested the hypothesis that aliskiren provides target organ protection in double transgenic rats (dTGRs). Pilz observed that aliskiren has protective effect with doses (3 and 0.3 mg/kg) against increased albuminuria in dTGRs. In addition, markers of renal inflammation, such as macrophage infiltration, were reduced with aliskiren doses (3 and 0.3 mg/kg) and with valsartan, 10 mg/kg/day to the same level as observed in nontransgenic Sprague–Dawley rats. Echocardiograms taken during the study demonstrated that aliskiren reduced cardiac hypertrophy with the higher dose of 3 mg/kg/day.[42] On the whole these results indicate that aliskiren provides cardio-renal protection superior or at least comparable to ARBs in dTGR.

Future Perspectives

Drugs that have direct effects on the RAAS, which include ACE inhibitors, ARBs and aldosterone antagonists, have been found to not only effectively lower blood pressure but also improve mortality and morbidity in patients with heart failure, history of myocardial infarction, and nephropathy.[105,106] Aliskiren offers an advantage over ACE inhibitors and ARBs by inhibiting the rate-limiting step of angiotensin II formation and producing more effective and complete inhibition of angiotensin II. Whether these advantages of aliskiren provides a better protection from heart attack, stroke, myocardial infarction and diabetic nephropathy is still to be explored. In addition, it is not known whether patients who cannot tolerate ACE-inhibitors or ARBs can be safely switched to aliskiren. Therefore, further research through experimental studies and clinical trials is required to establish a place for aliskiren in prevention or regression of various forms of target-organ damage in humans.

The aim of one of the trials, ALTITUDE (Aliskiren Trial In Type 2 diabetes Using cardio-renal Disease End-point), is to randomize 8600 patients with type 2 diabetes who are at high risk because of proteinuria, microalbuminuria or a history of cardiovascular disease with reduced renal function and to determine whether adding aliskiren to conventional therapy reduces cardiovascular and renal morbidity and mortality in high-risk patients with type 2 diabetes.[107] Enlistment began in October 2007 and the study is likely to terminate in 2012. Another trial, Safety and Efficacy of Aliskiren in Post Myocardial Infarction Patients (ASPIRE), aims to observe the efficacy and safety of aliskiren in the prevention of left ventricular remodelling in post-acute myocardial infarction patients.

The ATMOSPHERE (Aliskiren Trial to Mediate Outcome Prevention in Heart FailuRE) trial deals with heart-failure patients similar to those included in ALOFT. Cardiovascular death and re-hospitalization for heart failure is the component of the primary end-point. The APOLLO (Aliskiren in Prevention Of Later Life Outcomes) trial will tackle elderly subjects with normal blood pressure (<140/90 mmHg), and a high cardiovascular risk profile, to test the efficacy of the drug in reducing the risk of major cardiovascular end-points. Results of these clinical trials will determine the role of this novel class of antihypertensive medication in the therapeutic armamentarium. Aliskiren possesses the potential to become the first orally active direct renin inhibitor that provides an alternative to other existing RAAS blockers (ACE-inhibitors, ARBs, diuretics and β-blockers) in the therapy of hypertension and other cardio-renal diseases.

Conclusions

Aliskiren is an orally active, direct renin inhibitor that demonstrates antihypertensive efficacy in animals superior to earlier renin inhibitors and at least equivalent to ACE-inhibitors and AT_1-receptor blockers. Aliskiren may therefore be a better approach to the management of hypertension and associated disorders, alone or in combination with other antihypertensive agents. Aliskiren exhibits a good safety and tolerability profile in special populations, including those with diabetes or hepatic disorders, or obese or elderly patients. Prolonged inhibition of plasma renin activity and steady blood pressure reduction are observed after aliskiren withdrawal. Adding aliskiren with different antihypertensive agents results in greater antihypertensive efficacy without serious adverse drug interactions. The ongoing ALTITUDE, ASPIRE and other clinical trials series, evaluating the effects of aliskiren on cardiovascular morbidity and mortality, will further identify the role of direct renin inhibition as an alternative treatment for hypertension and other cardio-renal diseases.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1. Rosamond W *et al*. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007; 115: e69–e171.
2. Baker KM *et al*. Cardiac actions of angiotensin II: role of an intracardiac renin-angiotensin system. *Annu Rev Physiol* 1992; 54: 227–241.
3. Jandeleit-Dahm K, Cooper ME. Hypertension and diabetes: role of the renin–angiotensin system. *Endocrinol Metab Clin North Am* 2006; 35: 469–490.
4. Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. *Pharmacol Rev* 2000; 52: 11–34.
5. Dzau VJ. Tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. *Hypertension* 2001; 37: 1047–1052.
6. Buhler FR *et al*. Antihypertensive action of propranolol: specific antirenin responses in high and normal renin forms of essential, renal, renovascular and malignant hypertension. *Am J Cardiol* 1973; 32: 511–522.
7. Pool JL *et al*. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. *Am J Hypertens* 2007; 20: 11–20.
8. Campbell DJ. Interpretation of plasma renin concentration in patients receiving aliskiren therapy. *Hypertension* 2008; 51: e27–e28.
9. Waldmeier F *et al*. Absorption, distribution, metabolism, and elimination of the direct renin inhibitor aliskiren in healthy volunteers. *Drug Metab Dispos* 2007; 35: 1418–1428.
10. Wood JM *et al*. Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun* 2003; 308: 698–705.
11. Stanton A. Therapeutic potential of renin inhibitors in the management of cardiovascular disorders. *Am J Cardiovasc Drugs* 2003; 3: 389–394.
12. Staessen JA *et al*. Oral renin inhibitors. *Lancet* 2006; 368: 1449– 1456.
13. Oparil S *et al*. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomized double-blind trial. *Lancet* 2007; 370: 221–229.
14. Azizi M *et al*. Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II-renin feedback interruption. *J Am Soc Nephrol* 2004; 15: 3126–3133.
15. Karlberg BE. Cough and inhibition of the renin-angiotensin system. *J Hypertens Suppl* 1993; 11: S49–S52.
16. Gradman AH *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.
17. Fisher ND, Hollenberg NK. Renin inhibition: what are the therapeutic opportunities? *J Am Soc Nephrol* 2005; 16: 592–599.
18. Herron J *et al*. The novel renin inhibitor aliskiren is not associated with rebound effects on blood pressure or plasma renin activity following treatment withdrawal. *J Clin Hypertens* 2006; 8: A86.
19. Hollenberg NK *et al*. Pathways for angiotensin II generation in intact human tissue: evidence from comparative pharmacological interruption of the renin system. *Hypertension* 1998; 32: 387–392.
20. Veniant M *et al*. Vascular damage without hypertension in transgenic rats expressing prorenin exclusively in the liver. *J Clin Invest* 1996; 98: 1966–1970.
21. Smithies O. A mouse view of hypertension. *Hypertension* 1997; 30: 1318–1324.
22. Vaidyanathan S *et al*. Pharmacokinetics, safety, and tolerability of the oral renin inhibitor aliskiren in patients with hepatic impairment. *J Clin Pharmacol* 2007; 47: 192–200.
23. Nguyen G *et al*. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 2002; 10: 1417–1427.
24. Wood JM *et al*. Aliskiren, a novel, orally effective renin inhibitor, lowers blood pressure in marmosets and spontaneously hypertensive rats. *J Hypertens* 2005; 23: 417–426.
25. Cada DJ *et al*. Aliskiren. *Hosp Pharm* 2007; 42: 737–749.
26. Cheng JWM. Aliskiren: renin inhibitor for hypertension management. *Clin Ther* 2008; 30: 31–47.
27. Azizi M *et al*. Renin inhibition with aliskiren: where are we now and where are we going? *J Hypertens* 2006; 24: 243–256.
28. Sica D *et al*. Aliskiren, an oral renin inhibitor, provides long-term antihypertensive efficacy and safety in patients with hypertension. *Eur Heart J* 2006; 27: P797.
29. Vaidyanathan S *et al*. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract* 2006; 60: 1343–1356.
30. Ferro A *et al*. Importance of renin in blood pressure regulation and therapeutic potential of renin inhibition. *Int J Clin Pract* 2006; 60: 577–581.

31. Meredith PA. Role of trough to peak efficacy in the evaluation of antihypertensive therapy. *J Hypertens Suppl* 1998; 16: S59–S64.
32. Nussberger J *et al.* Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (SPP100): comparison with enalapril. *Hypertension* 2002; 39: E1–E8.
33. Shagdarsuren E *et al.* Complement activation in Angiotensin II–induced organ damage. *Circ Res* 2005; 97: 716–724.
34. Westermann D *et al.* Renin inhibition improves cardiac function and remodeling after myocardial infarction independent of blood pressure. *Hypertension* 2008; 52: 1068–1075.
35. Stegbauera J *et al.* Role of the renin-angiotensin system in autoimmune inflammation of the central nervous system. *Proc Natl Acad Sci USA* 2009; 106: 14942–14947.
36. Lu H *et al.* Renin inhibition reduces hypercholesterolemia-induced atherosclerosis in mice. *J Clin Invest* 2008; 118: 984–993.
37. Feldman DL *et al.* Effects of aliskiren on blood pressure, albuminuria, and (Pro)renin receptor expression in diabetic TG(mRen-2)27 rats. *Hypertension* 2008; 52: 130–136.
38. Singh VP *et al.* Intracellular angiotensin II production in diabetic rats. Is correlated with cardiomyocyte apoptosis, oxidative stress, and cardiac fibrosis. *Diabetes* 2008; 57: 3297–3306.
39. Nussberger J *et al.* Renin inhibition by aliskiren prevents atherosclerosis progression comparison with irbesartan, atenolol and amlodipine. *Hypertension* 2008; 51: 1306–1311.
40. Gratze P *et al.* Energy metabolism in human renin-gene transgenic rats. Does renin contribute to obesity? *Hypertension* 2009; 53: 516–523.
41. Imanishi T *et al.* Renin inhibitor aliskiren improves impaired nitric oxide bioavailability and protects against atherosclerotic changes. *Hypertension* 2008; 52: 563–572.
42. Pilz B *et al.* Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. *Hypertension* 2005; 46: 569–576.
43. Yamamoto E *et al.* Aliskiren enhances the protective effects of valsartan against cardiovascular and renal injury in endothelial nitric oxide synthase-deficient mice. *Hypertension* 2009; 54: 633–638.
44. Dong YF *et al.* Aliskiren prevents cardiovascular complications and pancreatic injury in a mouse model of obesity and type 2 diabetes. *Curr Diab Rep* 2009; 9: 447–452.
45. Dong YF *et al.* Aliskiren enhances protective effects of valsartan against type 2 diabetic nephropathy in mice. *J Hypertens* 2010; 28: 1554–1565.
46. Fischer R *et al.* Dietary n-3 polyunsaturated fatty acids and direct renin inhibition improve electrical remodeling in a model of high human renin hypertension. *Hypertension* 2008; 51: 540–546.
47. Feldt S *et al.* The putative (Pro)renin receptor blocker HRP fails to prevent (Pro)renin signaling. *J Am Soc Nephrol* 2008; 19: 743–748.
48. Dechend R *et al.* Low-dose renin inhibitor and low-dose AT1-receptor blocker therapy ameliorate target-organ damage in rats harbouring human renin and angiotensinogen genes. *JRAAS*. 2007; 8: 81–84.
49. Whaley-Connell A *et al.* Comparative effect of direct renin inhibition and AT1R blockade on glomerular filtration barrier injury in the transgenic Ren2 rat. *Am J Physiol Renal Physiol* 2010; 298: F655–F661.
50. Batenburg WW *et al.* Aliskiren-binding increases the half life of renin and prorenin in rat aortic vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 2008; 28: 1151–1157.
51. Habibi J *et al.* Renin inhibition attenuates insulin resistance, oxidative stress, and pancreatic remodeling in the transgenic Ren2 Rat. *Endocrinology* 2008; 149: 5643–5653.
52. Vanourkova Z *et al.* Despite similar reduction of blood pressure and renal ANG II and ET-1 levels aliskiren but not losartan normalizes albuminuria in hypertensive Ren-2 rats. *Physiol Res* 2010; 59: 339–345.
53. Iwai M *et al.* Direct renin inhibition improved insulin resistance and adipose tissue dysfunction in type 2 diabetic KK-A(y) mice. *J Hypertens* 2010; 28: 1471–1481.
54. Ke CY *et al.* Aliskiren ameliorates chlorhexidine digluconate-induced peritoneal fibrosis in rats. *Eur J Clin Invest* 2010; 40: 301–309.
55. Rakusan D *et al.* Persistent antihypertensive effect of aliskiren is accompanied by reduced proteinuria and normalization of glomerular area in Ren-2 transgenic rats. *Am J Physiol Renal Physiol* 2010; 299: F758–F766.
56. Wu WP *et al.* A reduction of unilateral ureteral obstruction-induced renal fibrosis by a therapy combining valsartan with aliskiren. *Am J Physiol Renal Physiol* 2010; 299: F929–F941.
57. Ino J *et al.* Dynamic observation of mechanically-injured mouse femoral artery reveals an antiinflammatory effect of renin inhibitor. *Arterioscler Thromb Vasc Biol* 2009; 29: 1858–1863.
58. Rashikh A *et al.* Protective effects of aliskiren in doxorubicin-induced acute cardiomyopathy in rats. *Hum Exp Toxicol* 2011; 30: 102–109.
59. Dieterle W *et al.* Effect of the oral renin inhibitor aliskiren on the pharmacokinetics and pharmacodynamics of a single dose of warfarin in healthy subjects. *Br J Clin Pharmacol* 2004; 58: 433–436.
60. Dieterle W *et al.* Pharmacokinetic interactions of the oral renin inhibitor aliskiren with lovastatin, atenolol, celecoxib and cimetidine. *Int J Clin Pharmacol Ther* 2005; 43: 527–535.
61. Gradman AH, Kad R. Renin inhibition in hypertension. *J Am Coll Cardiol* 2008; 51: 519–528.
62. Zhao C *et al.* Aliskiren exhibits similar pharmacokinetics in healthy volunteers and patients with type 2 diabetes mellitus. *Clin Pharmacokinet* 2006; 45: 1125–1134.
63. Verdecchia P *et al.* The renin angiotensin system in the development of cardiovascular disease: role of aliskiren in risk reduction. *Vasc Health Risk Manag* 2008; 4: 971–981.

64. Uresin Y *et al*. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. *J Renin Angiotensin Aldosterone Syst* 2007; 8: 190–200.
65. Jordan J *et al*. Direct renin inhibition with aliskiren in obese patients with arterial hypertension. *Hypertension* 2007; 49: 1047–1055.
66. Oh BH *et al*. Aliskiren, an oral rennin inhibitor, provides dose-dependent efficacy and sustained 24-h blood pressure control in patients with hypertension. *J Am Coll Cardiol* 2007; 49: 1157–1163.
67. Villamil A *et al*. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with HCTZ. *J Hypertens* 2007; 25: 217–226.
68. Azizi M *et al*. Hormonal and hemodynamic effects of aliskiren and valsartan and their combination in sodium-replete normotensive individuals. *Clin J Am Soc Nephrol* 2007; 2: 947–955.
69. Nickenig G *et al*. Efficacy of aliskiren/hydrochlorothiazide single-pill combinations in aliskiren nonresponders. *Blood Press Suppl* 2008; 2: 31–40.
70. Dietz R *et al*. Effects of the direct renin inhibitor aliskiren and atenolol alone or in combination in patients with hypertension. *J Renin Angiotensin Aldosterone Syst* 2008; 9: 163–175.
71. Andersen K *et al*. Comparative efficacy and safety of aliskiren, and ramipril in hypertension: a 6-month, randomized, double-blind trial. *J Hypertens* 2008; 26: 589–599.
72. Parving HH *et al*. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008; 358: 2433–2446.
73. McMurray JJV *et al*. Effects of the oral direct renin inhibitor Aliskiren in patients with symptomatic heart failure for the Aliskiren Observation of Heart Failure Treatment (ALOFT) investigators. *Circ Heart Fail* 2008; 1: 17–24.
74. Solomon SD *et al*. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* 2009; 119: 530–537.
75. Schmieder RE *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.
76. Yarows SA *et al*. Aliskiren and valsartan in stage 2 hypertension: subgroup analysis of a randomized, double-blind study. *Adv Ther* 2008; 25: 1288–1302.
77. Duprez DA *et al*. The AGELESS Study: the effect of aliskiren vs ramipril alone or in combination with hydrochlorothiazide and amlodipine in patients >65 years of age with systolic hypertension. *Circulation* 2008; 118: S886–S887.
78. Persson F *et al*. Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. *Diabetes Care* 2009; 32: 1873–1879.
79. Cherney DZI *et al*. Effect of direct renin inhibition on renal hemodynamic function, arterial stiffness, and endothelial function in humans with uncomplicated type 1 diabetes. *Diabetes Care* 2010; 33: 361–365.
80. Kushiro T *et al*. Aliskiren, provides dose-dependent efficacy and placebo-like tolerability in Japanese patients with hypertension. *Hypertens Res* 2006; 29: 997–1005.
81. O'Brien E *et al*. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. *Hypertension* 2007; 49: 276–284.
82. Nussberger J *et al*. Plasma renin and the antihypertensive effect of the orally active renin inhibitor aliskiren in clinical hypertension. *Int J Clin Pract* 2007; 61: 1461–1468.
83. Ayalasomayajula S *et al*. A study of the pharmacokinetic interactions of the direct renin inhibitor aliskiren with allopurinol, celecoxib and cimetidine in healthy subjects. *Curr Med Res Opin* 2008; 24: 717–726.
84. Vaidyanathan S *et al*. Pharmacokinetic interaction of the direct renin inhibitor aliskiren with furosemide and extended-release isosorbide-5-mononitrate in healthy subjects. *Cardiovasc Ther* 2008; 26: 238–246.
85. Vaidyanathan S *et al*. Pharmacokinetics of the oral direct renin inhibitor aliskiren in combination with digoxin, atorvastatin, and ketoconazole in healthy subjects: the role of P-glycoprotein in the disposition of aliskiren. *J Clin Pharmacol* 2008; 48: 1323–1338.
86. Persson F *et al*. Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. *Kidney Int* 2008; 73: 1419–1425.
87. Limoges D *et al*. A study of dose-proportionality in the pharmacokinetics of the oral direct renin inhibitor aliskiren in healthy subjects. *Int J Clin Pharmacol Ther* 2008; 46: 252–258.
88. Freel EM *et al*. Aldosterone status associated with insulin resistance in patients with heart failure-data from the ALOFT study. *Heart* 2009; 95: 1920–1924.
89. Palatini P *et al*. Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irbesartan or ramipril: results of a randomized, double-blind study. *J Hum Hypertens* 2010; 24: 93–103.
90. Scirica BM *et al*. Patients with acute coronary syndromes and elevated levels of natriuretic peptides: the results of the AVANT GARDE-TIMI 43 Trial. *Eur Heart J* 2010; 31: 1993–2005.
91. Tapaninen T *et al*. Rifampicin reduces the plasma concentrations and the renin-inhibiting effect of aliskiren. *Eur J Clin Pharmacol* 2010; 66: 497–502.
92. López V *et al*. Renin-angiotensin system dual blockade using angiotensin receptor plus aliskiren decreases severe proteinuria in kidney transplant recipients. *Transplant Proc* 2010; 42: 2883–2885.

93. Persson F *et al.* Optimal antiproteinuric dose of aliskiren in type 2 diabetes mellitus: a randomised crossover trial. *Diabetologia* 2010; 53: 1576–1580.
94. Fogari R *et al.* Different effects of aliskiren and losartan on fibrinolysis and insulin sensitivity in hypertensive patients with metabolic syndrome. *Horm Metab Res* 2010; 42: 892–896.
95. Gheorghiade M *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.
96. Rebello S *et al.* Effect of verapamil on the pharmacokinetics of aliskiren in healthy participants. *Clin Pharmacol* 2011; 51: 218–228.
97. Phillips LM *et al.* The renin inhibitor aliskiren attenuates high-glucose induced extracellular matrix synthesis and prevents apoptosis in cultured podocytes. *Nephron Exp Nephrol* 2011; 118: e49–e59.
98. Schweizer J *et al.* Efficacy and tolerability of aliskiren 300 mg/hydrochlorothiazide 25 mg (± amlodipine 5 mg) in hypertensive patients not controlled by candesartan 32 mg plus HCT 25 mg. *Curr Med Res Opin* 2011; 27: 131–140.
99. Rahuel J *et al.* Structure-based drug design: the discovery of novel nonpeptide orally active inhibitors of human renin. *Chem Biol* 2000; 7: 493–504.
100. Sanoski CA. Aliskiren: an oral direct renin inhibitor for the treatment of hypertension. *Pharmacotherapy* 2009; 29: 193–212.
101. Buczko W, Hermanowicz JM. Pharmacokinetics and pharmacodynamics of aliskiren, an oral direct renin inhibitor. *Pharmacol Rep* 2008; 60: 623–631.
102. Tassell BWV, Munger MA. Aliskiren for renin inhibition: a new class of antihypertensives. *Ann Pharmacother* 2007; 41: 456–464.
103. Weir MR *et al.* Antihypertensive efficacy, safety and tolerability of the oral renin inhibitor aliskiren in patients with hypertension: a pooled analysis. *J Am Soc Hypertens* 2007; 1: 264–277.
104. Malmqvist K *et al.* Relationships between left ventricular mass and the renin-angiotensin system, catecholamines, insulin and leptin. *J Intern Med* 2002; 252: 430–439.
105. Maggioni AP. Efficacy of angiotensin receptor blockers in cardiovascular disease. *Cardiovasc Drugs Ther* 2006; 20: 295–308.
106. Greenberg B *et al.* Role of aldosterone blockade for treatment of heart failure and post-acute myocardial infarction. *Am J Cardiol* 2006; 97: 34F–40F.
107. Parving HH *et al.* Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant* 2009; 24: 1663–1671.