

REVIEW

RAS inhibition in hypertension

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Drugs that inhibit the renin–angiotensin system (RAS), namely angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor antagonists (ARA) are gaining increasing popularity as initial medications for the management of hypertensive patients. In the year 2002, ACE-I were the most commonly prescribed drugs for the treatment of hypertension in USA. Although their antihypertensive efficacy as monotherapy is similar to other antihypertensive agents, they have the advantage of better tolerability, limited side effects and a favorable metabolic profile. When compared to other antihypertensive agents (diuretics, beta-adrenergic blockers and calcium antagonists) in large clinical trials, ACE-I and ARA provided no additional advantages regarding improvement in cardiovascular and total mortality. With the exception of the superiority of ARA in prevention of stroke, RAS inhibitors have no advantage over other agents in prevention of other cardiovascular morbid events, namely, heart failure (though ACE-I are superior to calcium antagonists), coronary heart disease and total

cardiovascular events. However, there is the possibility that these agents have other benefits beyond blood pressure lowering. At equal degrees of blood pressure reduction, RAS inhibitors prevent or delay the development of diabetes mellitus and provide better end-organ protection, kidneys, blood vessels and the heart when compared with other antihypertensive agents. The combined use of ACE-I and ARA is particularly useful in organ protection. RAS inhibitors are specifically indicated in the treatment of hypertension in patients with impaired left ventricular systolic function, diabetes, proteinuria, impaired kidney function, myocardial infarction, multiple cardiovascular risk factors and possibly elderly patients. The main limitation of the ACE-I is cough and rarely angioedema. Elderly patients or those who are volume depleted or receiving large doses of diuretics or in heart failure are liable to develop hypotensive reaction and/or deterioration in kidney function.

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Introduction

Activation of renin–angiotensin system (RAS) results in the elevation of blood pressure through a number of mechanisms. Angiotensin II (A-II), besides its very potent direct vasoconstrictor action, increases systemic vascular resistance through sympathetic nervous system stimulation. A-II increases extracellular blood volume through salt and water retention secondary to aldosterone production and antidiuretic hormone stimulation and through direct renal mechanisms. Both expansion of blood volume and increase in vascular resistance produce a rise in blood pressure.

In addition to its blood pressure regulatory function, inappropriate activation of RAS, on the other hand, has many deleterious effects. A-II has a proatherogenic potential,^{1–3} it causes vascular endothelial injury, it increases oxidative stress, stimu-

lates vascular smooth muscle cell and monocyte proliferation and activation. A-II has prothrombotic effects;^{4,5} it activates blood platelets and inhibits fibrinolysis. A-II increases insulin resistance by acting directly on insulin receptors at the cellular level.⁶

Inhibition of RAS results in lowering of blood pressure owing to reduction in systemic vascular resistance. Vasodilatation occurs through direct action, attenuation of sympathetic nervous system activity and in case of angiotensin-converting enzyme inhibitors (ACE-I) through excess bradykinin generation. Vasodilatation following RAS inhibition occurs preferentially in the vital organs (heart, kidney, brain) whose vasculature is more sensitive to the pressor effect of A-II than the vasculature of abdominal viscera and musculoskeletal tissues.⁷ This leads to redistribution of blood flow with enhanced perfusion of vital organs in the face of falling systemic blood pressure. RAS blockade in the kidney increases effective renal blood flow and alters intrarenal hemodynamics by dilating the efferent more than the afferent arterioles, thus causing a fall in intraglomerular pressure, which accounts for the antiproteinuria and nephroprotective effects of RAS blockade,^{7,8} beyond those

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attributable to blood pressure lowering *per se*. The vasodilatation and reduction of blood pressure following RAS blockade is not accompanied by reflex tachycardia owing to sympathetic nervous system attenuation and possible increased vagal activity.

The fact that hypertension is not simply a disease of numbers, but, in the majority of patients, it is a syndrome where high blood pressure is associated with metabolic and other proathrogenic, procoagulant and other risk factors, makes agents such as RAS inhibitors particularly advantageous because of their antiatherosclerotic and antithrombotic potentials.

Antihypertensive response

ACE-Is and angiotensin receptor antagonists (ARAs) when given as monotherapy to patients with mild to moderate hypertension achieve a satisfactory hypotensive response in 40–60% of patients, similar to other antihypertensive drugs.^{7,9–14} The antihypertensive response to RAS blockade is more obvious in high renin forms of hypertension whether renal or essential.¹¹ When combined with diuretics, RAS inhibitors can achieve an effective antihypertensive response in up to 85% of patients with mild hypertension.⁹

Limited effects of RAS inhibition is present in black patients,¹² some low-renin forms of hypertension, intake of diet rich in sodium chloride and after NSAIDs intake.¹³

The duration of hypotensive action varies among different ACE-Is (Table 1). Short-acting preparations such as captopril require two to three times daily administration, whereas long-acting ACE-Is such as ramipril, perindopril and lisinopril are administered once daily.

Measurement of blood pressure at the peak of hypotensive effect (2–3 h after drug administration and at the trough effect (24 h after administration)) can provide an index of trough to peak ratio (T/P). A T/P greater than 50% is required for once daily administration.^{15,16} A high T/P indicates a long duration of action and a better achievement of 24 h blood pressure control. A sustained antihypertensive action has the advantage of attenuating blood pressure variability. Increased fluctuations of blood pressure level are associated with increased risk of target organ damage,¹⁷ for example, left ventricular hypertrophy. Agents with high T/P are perindopril, lisinopril and trandolapril.¹⁸ While the significance of the T/P of ACE-Is have not been evaluated in clinical outcome studies, consistent effective control over the entire 24 h period is desirable.

Comparison of antihypertensive efficacy

Efficacy depends, among other factors, upon the dose given, state of salt intake, patients ethnicity,

Table 1 Duration of action of various ARAs and ACE-Is

Active ingredient	Dosage (mg)	T _{1/2} (h)	T _{max} (h)	Duration (h)
Valsartan	40–320	9	2–4	24
Losartan	50–100	6–9	3–4	24
Candesartan	4–32	9	3–4	36
Telmisartan	40–80	24	3–4	48
Irbesartan	150–300	11–15	2	24
Ramipril	1.25–20	13–17	3–6	18–24
Captopril	6.25–150	<2	1	Dose related
Perindopril	4–8	20–30	3–4	24
Lisinopril	2.5–40	12	4–6	24
Fosinopril	10–40	12	2–6	24

T_{max}: time to peak therapeutic effect.

T_{1/2}: time of elimination half-life.

age, which if not accounted for will lead to difficulties in comparing antihypertensive effects of different RAS inhibitors. Among ACE-Is, perindopril achieved a better 24 h blood pressure control than enalapril.¹⁹ Ramipril, captopril and enalapril are approximately equieffective. Among ARAs, candesartan, in a single trial, was more effective than losartan in lowering blood pressure (CANDLE trial, 1999) (Tables 2 and 3).²⁰

When comparing ACE-Is vs ARAs, a similar blood pressure reduction is achieved by appropriate doses of both types of agents.

Combination of ACE-Is with calcium antagonists can increase the antihypertensive response rate to 90%.²¹

Potential advantages of RAS inhibitors

1. **Better tolerability:** ARAs are possibly the best well-tolerated antihypertensive drugs. They have a placebo-like side-effect profile.
2. **Neutral and sometimes favorable metabolic effects:** When combined with thiazide diuretics, they correct concomitant electrolyte (K) and metabolic (uric acid, glucose) disturbances.
3. Sudden discontinuation of RAS inhibitors is not followed by rebound hypertension.

Benefits of RAS inhibitors beyond blood pressure lowering

Owing to their wide spectrum of pharmacologic activities, it is possible that RAS inhibitors might have additional benefits beyond blood pressure lowering. They proved to be superior to other antihypertensive agents in providing end-organ protection and in delaying or preventing new onset diabetes mellitus.

End-organ protection

Renal protection. At equal levels of blood pressure lowering, RAS inhibitors proved more effective than

other antihypertensive agents in retarding progression of renal damage in hypertensive patients with albuminuria.^{22–26} This advantage was present in both diabetic and non-diabetic patients. Furthermore, RAS inhibitors can prevent or delay the development of microalbuminuria. Treatment with ACE-I (trandolapril) significantly reduced the incidence of microalbuminuria in patients with type II diabetes and normal urinary albumin excretion, as compared with placebo (BENEDICT trial, 2004).²⁷ Recent clinical trials suggested that inhibition of RAS may actually prevent nephropathy.²⁸ They decrease glomerular capillary pressure and prevent progression of microalbuminuria to overt proteinuria. ACE-I reduce loss of kidney function in patients with diabetic nephropathy, above and beyond any such effect attributable to a reduction in blood pressure. At similar blood pressures, ACE-Is resulted in 24% greater decrease in the rate of progression to overt nephropathy than did placebo in patients with type II diabetes and normo- or microalbuminuria (HOPE trial, 2001).²⁹ Comparing ACE-I with conventional antihypertensive drugs in patients with proteinuric non-diabetic nephropathy or in black patients with renal impairment, ACE-I improved kidney survival beyond blood pressure reduction (REIN Study, 1997³⁰ and AASK Trial, 2001).³¹ Compared to dihydropyridine calcium antagonists, ACE-I (fosinopril) administered to patients with renal failure and hypertension owing to primary renal disorder slowed the decay in renal function (ESPIRAL Trial, 2001).³² ARAs reduced the number of patients who had progression to end-stage renal failure or a doubling of serum creatinine level, independently of a reduction in blood pressure. Compared with conventional treatment alone, ARA (losartan), combined with the conventional treatment, reduced the risk of end-stage renal disease by 28% and decreased the level of urinary protein excretion by 35% in type II diabetes and nephropathy (RENAAL Study, 2001).³³ In another study in patients with diabetic nephropathy, ARA (irbesartan) reduced the risk of doubling serum creatinine, the onset of end-stage renal disease or death by 20% compared with conventional treatment (IDNT Trial, 2001).²³

Most of the nephroprotective effect of RAS inhibitors is observed in proteinuric nephropathy and is related to their major efficacy in reducing proteinuria. The antiproteinuric response to treatment is the strongest predictor of long-term nephroprotective efficacy.³⁴

The antiproteinuric effects of RAS inhibitors are increased by sodium restriction and by the concomitant administration of diuretics.³⁵

Vascular protection: vessel wall and vascular endothelium. RAS inhibitors are more effective than other antihypertensive agents in vascular protection. Clinical evaluation of vascular damage is performed through study of changes in: (1) intimal

medial thickness (IMT) of carotid arteries during carotid duplex ultrasound examination; (2) vascular endothelial function and (3) arterial compliance. At equal degrees of reduction in blood pressure, RAS inhibitors produced a greater reduction in carotid IMT,^{36,37} greater improvement in vascular endothelial function assessed non-invasively by flow mediated dilatation in brachial artery^{18,38} and in arterial compliance^{18,39} when compared with other antihypertensive agents.

Comparing the effects of beta-adrenergic blocker (atenolol) vs ACE-I (perindopril) produced an increase in small artery diameter and a reduction in the arterial media/lumen ratio.⁴⁰ Changes in small artery morphology reflect normalization of vascular remodeling by ACE-I therapy.

Cardiac protection: regression of left ventricular hypertrophy. ACE-Is and ARAs are more effective than other antihypertensive medications in inducing regression of left ventricular hypertrophy. In a meta-analysis of 80 trials (2003)⁴¹ comparing the effects of antihypertensive drugs on left ventricular mass, ARAs were shown to induce the greatest reduction in left ventricular mass index. Comparing ARA (losartan) with beta-adrenergic blocker (atenolol), in hypertensive patients with left ventricular hypertrophy, while achieving the same degree of blood pressure lowering, ARA induced a greater decrease in ECG voltage criteria of left ventricular hypertrophy (LIFE Study, 2002).³⁶ In another study, ACE-I (ramipril) produced a greater reduction in LVMI assessed by echocardiography than dihydropyridine calcium antagonist (nifedipine) in spite of achieving same levels of blood pressure (1999).⁴²

Prevention of diabetes mellitus

Diabetes is more common in hypertensive than normotensive individuals. The incidence of new cases of diabetes mellitus is about 2.5 times greater among hypertensives aged 45–64 years than normotensives of similar age (2.9 vs 1.2/100 patient year).⁴³ Furthermore, hypertension in diabetics increases mortality up to fivefolds.⁴³ Whether tested against placebo or against other antihypertensive agents, RAS inhibitors proved effective in delaying or preventing development of diabetes in both normotensive and hypertensive individuals. A number of studies investigated the effects of RAS blockade on the onset of new cases of diabetes. Both ACE-Is (captopril (CAPP),⁴⁴ ramipril (HOPE),⁴⁵ perindopril (EUROPA),⁴⁶ lisinopril (ALLHAT),⁴⁷ and enalapril (SOLVD)⁴⁸) and ARAs (losartan (LIFE),³⁶ candisartan (SCOPE)⁴⁹ and valsartan (VALUE)⁵⁰) decreased the incidence of new onset diabetes. Incidence of new onset diabetes was reduced on the average by about 25% by RAS inhibiting agents. On the other hand, RAS inhibitors were found to improve insulin sensitivity.⁶

Prevention of cardiovascular events and mortality

The following is a summary of meta-analysis of 29 randomized trials from Blood Pressure Lowering Treatment Trialists' Collaboration (2003):⁵¹

Cardiovascular events

Stroke. ARAs reduced the risk of stroke by an average of 21% when compared with other anti-hypertensive regimens. At equal degrees of reductions in blood pressure, ARA (losartan) reduced the risk of stroke by 25% in comparison to beta-adrenergic blocker (atenolol) in hypertensive patients with left ventricular hypertrophy (LIFE Trial, 2002).³⁶ On the other hand, ACE-Is were either inferior or comparable to beta-blockers, diuretics and calcium antagonists regarding prevention of stroke.

Coronary heart disease. ACE-I-based regimens reduced the risk of coronary heart disease (20%) compared with placebo. However, in treated hypertensive patients, there was no clear difference between either ACE-I- or ARA-based regimens and other antihypertensive regimens (diuretics, beta-blockers, calcium antagonists).

Heart failure. ARA-based treatment reduced the risk of heart failure (16%) compared with control regimens. Effects of regimens based on ACE-Is did not differ significantly from effects of those based on diuretics or beta-blockers. However, compared with regimens based on calcium antagonists, those based

on ACE-Is produced greater reductions in risk (18%) of heart failure.

Major cardiovascular events. Comparison of regimens based on ACE-Is with placebo indicated significant reduction in the composite of all major cardiovascular events with active treatment (22%). ARA-based regimens reduced major cardiovascular events more than did control regimens (10%). However, there were no significant differences between regimens based on ACE-Is and other antihypertensive medications.

Cardiovascular death and total mortality

Compared with placebo, ACE-I-based regimens reduced the risk of cardiovascular death (20%), but no clear evidence of difference in risk reduction between ARA-based regimens and control regimens. ACE-I regimens have effects on cardiovascular mortality similar to other antihypertensive regimens. Total mortality did not differ between ARA-based regimens and control regimens or between treatment regimens based on ACE-Is, calcium antagonists, beta-blockers or diuretics. However, comparing ACE-Is with diuretics in elderly hypertensives showed that ACE-Is were superior regarding prevention of all cardiovascular events or death from any cause, particularly in male subjects (ANB₂ trial, 2003).⁵²

At this stage, it seems that blood pressure control is the key issue in reducing cardiovascular risk in hypertension. Since atherosclerotic cardiovascular disease is a chronic multifactorial disorder with

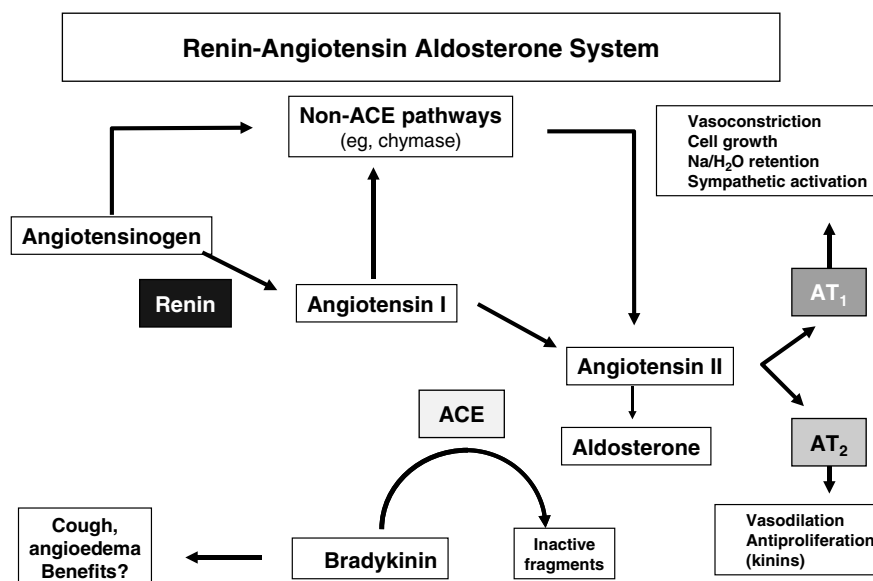


Figure 1 The different components of the renin–angiotensin system are outlined. Angiotensinogen under the effect of renin is broken to the decapeptide angiotensin I, which is changed through angiotensin-converting enzymes (ACE) to an octapeptide angiotensin II. Also, angiotensin II can be generated directly from angiotensinogen through non-ACE pathways. ACE is the same as kinase II that breaks bradykinin into inactive fragments. Angiotensin II produces its effects through activating a number of receptors, mainly angiotensin I and angiotensin II receptors. Angiotensin II stimulates the production of aldosterone in the zona glomerulosa of the adrenal cortex.

Table 2 Major clinical trials on ACE inhibitors in hypertension

Trial name	Public. year	Drug	Comparator	No. of patients	Population	End points	Results
REIN	1999	Ramipril (R)	Placebo	325	Non-diabetic proteinuria	Mean rate of GFR decline	GFR decline slower with R
CAPPP	1999	Captopril (C)	Atenolol ± HCZ	10 985	DBP ≥ 100 mmHg	MI+stroke+CV death	No difference in EP. More stroke with C
HOPE	2000	Ramipril	Placebo	9297	High risk with DM or CVD	MI+stroke+CV death	RRR 26% for CV death, 32% for stroke, 20% for MI
PROGRESS ⁶⁶	2001	Perindopril (± indapamide)	Placebo	6105	Previous stroke or TIA	Total stroke	RRR 28%
ESPIRAL	2001	Fosinopril	Nifedipine LA	241	HTN+creatinine 1.5–4 mg/Dl	Doubling creatinine or ESRD	RRR 53%
AASK	2002	Ramipril (R)	Amlodipine (A) Metoprolol (M)	1094	HTN with moderate CKD	Decline of GFR	Less GFR in R than M, not different from A
ALLHAT	2002	Lisinopril (L)	Amlodipine (A) Chlorthalidone (C)	33 357	HTN+≥ 1 CV risk factor	Fatal and non-fatal CAD	No significant difference between L, A and C
FACET	2002	Fosinopril (F)	Amlodipine (A)	380	DM and HTN	Effect on PAI-1	PAI-1 reduced by F, rise with A
ANB ₂	2003	Enalapril ± other drugs	HCZ ± other drugs	6803	HTN in old age	All CV events, all-cause mortality	RRR 11% (17% in males, none in females)
EUROPA	2003	Perindopril	Placebo	12 218	Stable CAD	CV death+MI+cardiac arrest	20% RRR of the composite EP

EP = end point; ESRD = end-stage renal disease; DM = diabetes mellitus; GFR = glomerular filtration rate; HTN = hypertension; MI = myocardial infarction; TIA = transient ischemic attack.

Table 3 Major clinical trials on ARA in hypertension

Trial name	Public. year	Drug	Comparator	No. of patients	Population	End points	Results
RENAAL	2000	Losartan	Placebo	1513	HTN+type II DM+nephropathy	Doubling serum creatinine, ESRD	RRR 25% for doubling creatinine and 28% for ESRD
IDNT	2001	Irbesartan	Amlodipine (A), placebo (P)	1715	HTN+type II DM+nephropathy	All-cause death, doubling serum creatinine, ESRD	RRR 32% vs P, 37% for doubling creatinine vs A, 23% for ESRD vs A
LIFE	2002	Losartan	Atenolol	9193	HTN+LVH	CV death+MI+stroke	RRR 25% for stroke
SCOPE	2003	Candesartan	Placebo	4937	HTN in old age	CV death+MI+stroke	RRR 28% for non-fatal stroke
ALPINE	2003	Candesartan ± felodipine	HCZ ± atenolol	392	HTN	Incident DM	RRR 88%
VALUE	2004	Valsartan	Amlodipine	15 245	HTN at high CV risk	HF, MI, cardiac death, incident DM	RRR 20% for HF, 23% for incident DM, equal in MI and stroke
ASCOT	2005	Perindopril+amlodipine	Atenolol+bendrofluazide	19 000	HTN at high CV risk	All-cause death, CV death, stroke	RRR 25% for stroke and CV death, 15% for total mortality

unpredictable course, clinical studies of longer duration or addressing a hypertensive population at particularly greater risk of future cardiovascular events might be needed in order to show a potential advantage of RAS blockade over other antihypertensive agents.

Dual (combined) RAS blockade

ACE-I decrease the generation of A-II through the blockade of ACE. However, A-II can still be generated through other enzymatic pathways (Figure 1).⁵³ Furthermore, a decrease in A-II generation will suppress the A-II-negative feedback on renin release, resulting in rise in plasma renin activity and increased angiotensin I (A-I) generation. A-I is the substrate for the ACE. These two mechanisms explain attenuation of blood pressure response to ACE-I 24–48 h after last drug intake in spite of persistent plasma ACE inhibition. The combination of two pharmacological agents that inhibit both ACE and angiotensin receptors can minimize or even overcome the scope observed with single-site RAS blockade.

Effects on blood pressure. Dual RAS blockade was shown to be more effective than doubling the usual dose of ARA. Combination of ACE-I and ARA induces a greater reduction in blood pressure at trough than single-site blockade. This was demonstrated in white patients with low-renin hypertension, type II diabetes or in patients with progressive renal failure. This combination may have the same blood pressure lowering effect as a combination of a single-site RAS blockade with a diuretic.³⁵

Nephroprotection. A single study (COOPERATE Trial, 2003)⁵⁴ showed the superiority of combined RAS blockade on single-site RAS blockade in non-diabetic chronic nephropathy and persistent proteinuria. In spite of the same reductions in blood pressure, the combination group (ACE-I + ARA) had a greater proteinuria-reducing effect than either agent alone (losartan or trandolapril).

Risks. There is increased risk of combined RAS blockade in elderly or salt-depleted patients, and in patients receiving COX inhibitors, patients with renal artery stenosis and during anesthesia induction. Significant hypotension and creatinine increase are more likely in these patients.

Recommendations: specific indications of RAS inhibitors

(1) *Heart failure owing to systolic dysfunction:* ACE-Is slow the rate of progression of cardiac dysfunction and improvement in survival.^{55–60}

- (2) *Chronic renal failure, both diabetic and non-diabetic:* RAS inhibitors slow the rate of loss of renal function.^{23,24,59,61–63} Caution with renovascular hypertension might be advisable.
- (3) *Renal proteinuria both diabetic and non-diabetic:* RAS inhibitors decrease urinary albumin and delay or prevent development of renal failure.^{8,23,24,63}
- (4) After a myocardial infarction, with or without impairment in left ventricular systolic function, in which survival is improved.^{42,48,56,64,65,67}
- (5) High-risk patients, that is, patients with associated atherosclerotic cardiovascular disease or diabetic patients with one additional risk factor (age, dyslipidemia, cigarette smoking).^{45,56,62,63}
- (6) *Elderly patients:* RAS inhibitors may be superior to other antihypertensive agents regarding prevention of cardiovascular events and mortality.⁵² ARAs are particularly effective in prevention of stroke. RAS inhibitors may slow physical decline in muscle strength.^{36,49}

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