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Blockade of the renin-angiotensin system

腎素－血管緊縮素系統的阻塞

The renin-angiotensin-aldosterone system plays a key role in the regulation of fluid and electrolyte balance. Angiotensin-converting enzyme inhibitors inhibit angiotensin-converting enzyme and have been shown to be effective in many cardiovascular diseases. They should be considered for the treatment of hypertension in patients with heart failure, previous myocardial infarction, diabetes, or proteinuria. There are a number of side-effects associated with angiotensin-converting enzyme inhibitors, especially persistent dry cough. Angiotensin II receptor antagonists (sartans) provide a more specific blockade of the renin-angiotensin-aldosterone system and are associated with fewer side-effects, including cough. Their long-term efficacy and tolerability in the treatment of patients with hypertension has, however, yet to be established. Periodic monitoring of renal function and electrolytes is required in patients treated with an angiotensin-converting enzyme inhibitor or a sartan.

腎素－血管緊縮素－醛甾酮系統在調節流體和電解平衡中扮演著一個關鍵角色。血管緊縮素轉換酶抑製劑能抑制血管緊縮素轉換酶，並在許多心血管病治療中顯示出其有效性。應考慮在患心力衰竭、早期心肌梗塞、糖尿病或蛋白尿的患者中使用這種抑製劑來治療高血壓。血管緊縮素轉換酶抑製劑有許多相關的副作用，尤其是持續乾咳。血管緊縮素II受體對抗劑(sartans)提供腎素－血管緊縮素－醛甾酮系統更特定的阻塞，且包括咳嗽在內的副作用小。然而，在治療高血壓患者中這種抑製劑的長期影響和可接受性還未確定。在對患者中使用血管緊縮素轉換酶抑製劑或sartans治療時，需要對腎功能和電解物進行週期性監測。

Introduction

The renin-angiotensin-aldosterone system (RAAS) has a central role in regulating fluid and electrolyte balance (Fig). Renin is released in response to a decrease in renal perfusion pressure, which can be due to hypotension. Renin is
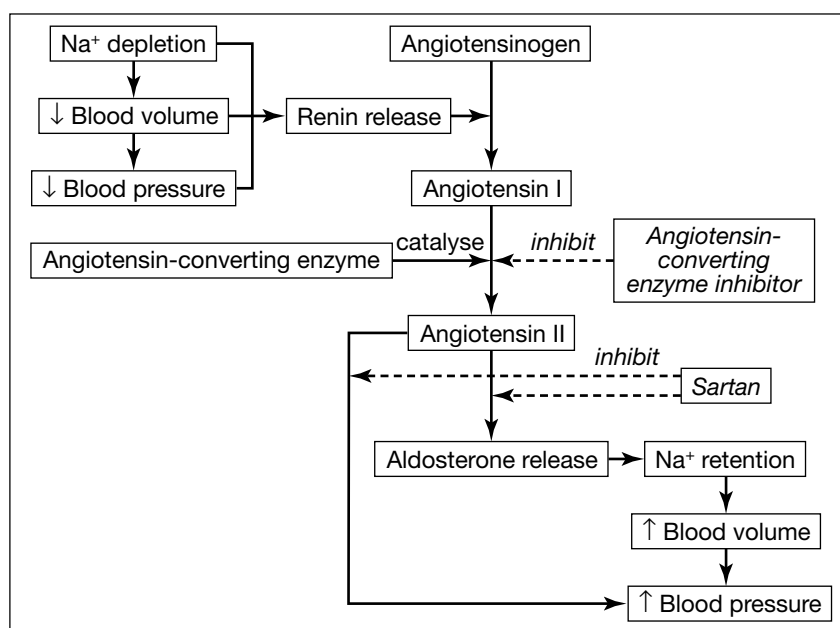
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Fig. A simplified diagram illustrating the role of the renin-angiotensin-aldosterone system in sodium and volume homeostasis

an enzyme present in the plasma that cleaves angiotensinogen to form angiotensin I. Angiotensin I is relatively inactive; its activity is increased 100-fold when it is converted to angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II is a potent stimulant for the contraction of vascular smooth muscle. It also stimulates the synthesis and release of aldosterone from the adrenal cortex. Aldosterone increases the absorption of sodium and excretion of potassium in the distal tubules and collecting ducts of nephrons in the kidney.

Angiotensin-converting enzyme inhibitors (ACEIs) belong to a class of drugs which are increasingly used in the management of a variety of diseases, including hypertension, heart failure, myocardial infarction (MI), and diabetic and other forms of nephropathy. Angiotensin-converting enzyme inhibitors inhibit the formation of angiotensin II, which is a powerful vasoconstrictor. They also indirectly reduce aldosterone secretion and so suppress the reabsorption of sodium and excretion of potassium in the distal tubule. Angiotensin-converting enzyme inhibitors have other effects in addition to the ones on the RAAS. Indeed, ACE has been described as a promiscuous enzyme. In addition to converting angiotensin I to angiotensin II, it has other substrates such as kinins.[1,2] Whereas angiotensin I is converted to the more active angiotensin II by ACE, bradykinin is inactivated by ACE. Angiotensin-converting enzyme inhibitors inhibit ACE and may increase the level of bradykinin. More studies are needed to determine whether the latter accounts for part of the side-effects profile of ACEIs and whether or not the potentiation of bradykinin is beneficial.

Angiotensin-converting enzyme inhibitor for the treatment of hypertension

Angiotensin-converting enzyme inhibitors lower blood pressure effectively and are one of the first-line drugs in the treatment of hypertension.[3,4] The latest results from the STOP-hypertension-2 (Swedish Trial in Old Patients with Hypertension-2) showed that there was no difference in terms of all-cause mortality, cardiovascular mortality, and the risk of a major cardiovascular event between an antihypertensive regimen based on older drugs, ie diuretics and β-blockers, and newer drugs, ie ACEIs and calcium channel blockers.[5] This trial, along with the CAPP (CAptopril Prevention Project) study,[6] provide the scientific evidence for using ACEIs as an alternative first-line treatment for hypertension.

Angiotensin-converting enzyme inhibitors may also have additional beneficial effects. These include regression of left ventricular hypertrophy (LVH) and remodelling of blood vessels. In a meta-analysis of trials investigating agents which regress LVH, ACEIs have been shown to be superior to other classes of antihypertensive drugs.[7] Left ventricular hypertrophy is now recognised to be a potent risk factor for cardiovascular events and mortality. Angiotensin-converting enzyme inhibitors may also improve endothelial dysfunction. The TREND (Trial on Reversing ENdothelial Dysfunction) study showed that quinapril restores the reactivity of vascular muscle to vasodilating agents in coronary arteries.[8] Angiotensin-converting enzyme inhibitors may also reduce the thickness of arterial walls and restore arterial compliance.[9,10]

If one chooses an ACEI for hypertension, one should use a once-daily agent to minimise the peaks and troughs in blood pressure and to improve compliance. Angiotensin-converting enzyme inhibitors are not uniformly effective in all individuals. The response to ACEI may have a genetic component and may also be dependent on the degree of activation of the RAAS.[11,12] Younger hypertensive patients may have a better blood pressure response to ACEIs than elderly patients.[13] If the blood pressure response to an ACEI is unsatisfactory despite adequate dosage and compliance, another class of antihypertensive drugs should be considered.

There are now a large number of ACEIs (Table 1). They are largely similar in terms of their effects, but differ in some

Table 1. Angiotensin-converting enzyme inhibitors and sartans currently available in Hong Kong

Drug name	Trade name	Dosage	Comments	Major trials
Angiotensin-converting enzyme inhibitor				
Captopril	Capoten	12.5 mg bd*-50 mg td†	Short-acting	SAVE,[22] ISIS-4,[26] CAPP[6]
Cilazapril	Inhibace	1 mg od‡-5 mg od	-	-
Enalapril	Renitec	5-20 mg od	-	CONSENSUS,[17,18] V-HeFT II,[19] SOLVD[20]
Fosinopril	Monopril	10-40 mg od	Hepatic and renal route of elimination	FACET[32]
Lisinopril	Zestril	2.5-20 mg od	-	GISSI-3,[25] ATLAS[21]
Perindopril	Acertil	2-8 mg od	First-dose hypotension less likely	-
Quinapril	Accupril	2.5-20 mg od-bd	-	QUIET[27]
Ramipril	Tritace	1.25-10 mg od	-	AIRE,[23] AIREX,[24] HOPE[28]
Sartan				
Candesartan	Blopress	2-16 mg od	-	RESOLVD[49]
Irbesartan	Aprovel	75-300 mg od	-	-
Losartan	Cozaar	25-100 mg od	-	ELITE,[47] ELITE II[48]
Valsartan	Diovan	40-160 mg od	-	-

* bd   twice a day
† td   three times a day
‡ od   once daily

Table 2. Summary of the major clinical trials investigating the effect of treatment with angiotensin-converting enzyme inhibitors or sartans on mortality

Trial	Condition	Drug	Relative risk reduction (% deaths prevented)
CONSENSUS[17,18]	CHF* (NYHA[†] Class IV)	Enalapril	40%
SOLVD[20]	CHF (EF[‡] ≤35%)	Enalapril	13%
SAVE[22]	MI[§] (EF ≤40%)	Captopril	19%
AIRE[23]	MI with HF[‖]	Ramipril	27%
AIREX[24]	MI with HF	Ramipril	36%
GISSI-3[25]	MI	Lisinopril	11%
ISIS-4[26]	MI	Captopril	9%
HOPE[28]	CHD[¶]	Ramipril	16%
CAPP[6]	HT**	Captopril	Equivalent to treatment with a β-blocker
STOP-hypertension-2[5]	HT	Angiotensin-converting enzyme inhibitor	Equivalent to treatment with a diuretic/β-blocker; equivalent to treatment with a calcium channel blocker
ELITE[47]	CHF	Losartan	Superior to treatment with captopril
ELITE II[48]	CHF	Losartan	Equivalent to treatment with captopril
RESOLVD[49]	CHF	Candesartan	Equivalent to treatment with enalapril

* CHF	congestive heart failure	‖ HF	heart failure
† NYHA	New York Heart Association	¶ CHD	coronary heart disease
‡ EF	ejection fraction	** HT	hypertension
§ MI	myocardial infarction		

respects, particularly pharmacokinetics. Captopril was the first ACEI developed and has a relatively short half-life, necessitating two or three times a day dosages. Newer ACEIs tend to have longer half-lives allowing once-daily dosage. Some of the new ACEIs, such as fosinopril, are metabolised by the liver as well as excreted by the kidneys. This dual route of excretion may be an advantage in patients who have impaired renal function or in the elderly who may have declining renal function but a normal plasma creatinine level. Angiotensin-converting enzyme inhibitors also differ in the extent of tissue binding. It is now known that in addition to circulating angiotensin II, angiotensin II is also present in tissue. The latter is generated by tissue ACE. It is possible that the harmful effects of angiotensin II in tissue may be reduced by treatment with ACEIs which achieve higher tissue concentrations. Some ACEIs are claimed to cause fewer side-effects. For example, first-dose hypotension is rare with perindopril while fosinopril is associated with a lower incidence of cough.[14,15] These claims are interesting; however, their scientific basis has not been elucidated.

As there are now numerous ACEIs to choose from, choice will depend on prior experience of a particular drug, availability, and price. Captopril has been used as a test drug when ACEI therapy is started for the first time because it is short-acting. For long-term use, a long-acting drug has the theoretical advantage of once-daily dosage to achieve improved compliance and smoother plasma levels. If first-dose hypotension or renal impairment is a concern, then perindopril or fosinopril, respectively, may be preferred. When using some of the newer ACEIs, one is extrapolating from clinical trials in which a different ACEI might have been used, but the evidence so far suggests that the benefits are class effects.

Concomitant medical conditions

Angiotensin-converting enzyme inhibitor therapy is indicated in patients with hypertension who have concomitant conditions such as heart failure, a history of MI, or diabetes.

Heart failure
In heart failure, there is activation of the RAAS, resulting in sodium and fluid retention. This may initially be a response to low cardiac output but can be deleterious over time. It is believed that such neurohormonal activation in heart failure is harmful and should be counteracted with therapy.[16] Angiotensin-converting enzyme inhibitors are effective in suppressing the RAAS. Successive clinical trials such as the CONSENSUS (COoperative North Scandinavian ENalapril SUrvival Study),[17,18] V-HeFT II (Vasodilator Heart Failure Trial II),[19] and SOLVD (Studies Of Left Ventricular Dysfunction[20]) have shown that ACEIs reduce morbidity and decrease hospitalisation due to heart failure (Table 2). Furthermore, SOLVD showed that patients with a left ventricular ejection fraction of 35% or less benefited from treatment with an ACEI even if they were asymptomatic. The initiation of treatment with ACEIs in patients with heart failure should be closely monitored. The starting dose should be low and increased gradually. Diuretics should be reduced or stopped for a few days before introducing an ACEI so as to avoid hypovolaemia, which exacerbates the effect of first-dose hypotension. The optimal dose of an ACEI in heart failure remains unresolved. In SOLVD, the target dose of enalapril (20 mg daily) was quite high. In practice, most physicians tend to use lower doses. The ATLAS (Assessment of Treatment with Lisinopril And Survival) study showed that high-dose ACEI therapy is more effective in reducing cardiovascular events and preventing hospital admissions compared with low-dose therapy.[21] Ideally, one should therefore aim at using high doses.

Previous myocardial infarction
Large-scale studies such as the SAVE (Survival And Ventricular Enlargement study),[22] AIRE (Acute Infarction Ramipril Efficacy study),[23,24] GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico),[25] and the ISIS-4 (International Study of Infarct Survival[26])

all testified to the efficacy of ACEIs in reducing long-term mortality and improving cardiac function of patients after MI (Table 2). By influencing cardiac remodelling following MI, ACEIs help to prevent deterioration in ventricular function and development of heart failure. Acute MI patients with overt heart failure[23] or poor ejection fractions[22] appear to benefit most from these drugs, but all MI patients might benefit to some extent.[25,26] Early initiation of ACEIs in the first day after acute MI has been shown to incur greater benefit.

Coronary heart disease

The survival benefit seen in patients with heart failure or MI treated with ACEIs led to the hypothesis that ACEIs may be beneficial for all patients at risk of dying from coronary heart disease. The QUIET (QUinapril Ischemic Event Trial) study was unable to show any significant coronary angiographic improvements,[27] but the HOPE (Heart Outcomes Prevention Evaluation) study demonstrated an across-the-board reduction in mortality regardless of age-group, sex, previous MI, presence of hypertension, heart failure, diabetes, or microalbuminuria.[28] Angiotensin-converting enzyme inhibitors therefore rank alongside statins as useful therapy for primary and secondary prevention of coronary heart disease.

Diabetes

The pioneering study by Lewis et al[29] showed that captopril prevented the progression of diabetic nephropathy. The outcome measures were doubling of serum creatinine or progression to dialysis or transplantation. Other studies showed that ACEIs prevent the progression from micro-albuminuria to albuminuria.[30] Microalbuminuria (albumin excretion 30-300 mg/24 hr) is an early marker for deterioration in renal function, and is often present 10 years after the onset of diabetes. Currently, it is thought that patients with diabetes with microalbuminuria or albuminuria should receive an ACEI. For hypertensive patients with diabetes, ACEI may well be the first choice treatment. Diuretics and β-blockers, the first-line drugs in non-diabetic, hypertensive patients, are viewed by some as less suitable for treating hypertension in patients with diabetes because of their metabolic effects. Calcium channel blockers have been widely used in hypertensive patients with diabetes, but recent data, especially from the ABCD (Appropriate Blood pressure Control in Diabetes trial) and FACET (Fosinopril versus Amlodipine Cardiovascular Events randomized Trial) studies, suggested that such patients treated with an ACEI had fewer cardiovascular events than those treated with a calcium channel blocker.[31,32] The UKPDS 39 (UK Prospective Diabetes Study 39),[33] however, suggested that ACEIs and β-blockers are equivalent in their effect on microvascular and macrovascular complications. It appears that tight control of blood pressure in diabetics is as important, if not more so, as the choice of drug.[34] On the other hand, in CAPP and HOPE, there was a lower incidence of diabetes in patients treated with an ACEI.[6,28]

Adverse effects of angiotensin-converting enzyme inhibitors

Since ACEIs inhibit the release of aldosterone, the sodium/potassium exchange in the distal renal tubules is decreased and potassium retention and hyperkalaemia may occur. Hyperkalaemia is a common side-effect of ACEIs (Box) and is especially likely in patients with poor baseline renal function. Most physicians should be very cautious about prescribing potassium supplements or potassium-sparing diuretics, such as amiloride or spironolactone, in patients treated concurrently with an ACEI.

When a person is volume or salt depleted, the RAAS is activated. In these patients ACEIs may induce postural hypotension, especially when it is the first dose. This phenomenon has been termed 'first-dose hypotension' and is a well-recognised side-effect. In patients at risk of first-dose hypotension, such as those with severe heart failure already receiving high-dose diuretics, those whose blood pressure is already low, and elderly patients, ACEI therapy should be initiated very carefully. In such patients, the dosage of diuretics should be reduced, at least temporarily, and any hypovolaemia corrected. The lowest dose of an ACEI should be used as the starting dose. The patient is advised to remain recumbent for a few hours after the first dose. Usually, this may mean taking the drug before going to bed. In patients who require large doses of diuretics for the treatment of heart failure, hospital admission may be necessary for the initiation of ACEI therapy and the titration of drugs. Perindopril is reported to have a lower incidence of first-dose hypotension than other agents.[14]

In patients with renal impairment, ACEIs should be used cautiously. Most ACEIs are excreted by the kidneys, thus plasma drug levels will be higher in patients with pre-existing renal disease. Moreover, ACEIs often reduce the glomerular filtration rate and may markedly worsen renal function, particularly in patients with bilateral renal artery stenosis or stenosis in the renal artery of a single

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Adverse effects associated with angiotensin-converting enzyme inhibitor and sartan therapy

Adverse effects of angiotensin-converting enzyme inhibitor
Hypotension (especially following the first dose)
Persistent dry cough
Taste alteration
Renal impairment
Hyperkalaemia
Urticaria
Rashes
Angioedema
Hypersensitivity reactions
Blood disorders (anaemia, thrombocytopenia, neutropenia, agranulocytosis)
Jaundice

Adverse effects of sartan
Symptomatic hypotension
Hyperkalaemia
Rash
Angioedema

functioning kidney. Some young patients with hypertension have bilateral renal artery stenosis due to fibromuscular hyperplasia. In the elderly, the renal arteries may be narrowed by atherosclerosis. Hence, it is customary to be cautious when prescribing an ACEI in patients with peripheral vascular disease as they may have silent renovascular disease. A sudden change in renal function after the initiation of an ACEI in such patients should alert the clinician to this possibility. The renal toxicity of ACEIs is exacerbated when other nephrotoxic drugs are prescribed concurrently. For example, non-steroidal anti-inflammatory drugs should be prescribed with caution in a patient already taking an ACEI. Angiotensin-converting enzyme inhibitors tend to reduce the renal excretion of lithium and toxic plasma levels of lithium may occur. Although ACEIs may reduce glomerular filtration rate or cause dangerous hyperkalaemia in patients with renal failure, ACEIs are used in early renal failure to retard disease progression.[35] They have been shown to slow down the deterioration of renal function in diabetic and non-diabetic nephropathy.[29,36,37] Angiotensin-converting enzyme inhibition should be used with special care in these patients, with their renal function closely monitored.

None of the ACEIs have been tested in pregnant patients, and this class of drugs should not be used in pregnancy. Methyldopa (Aldomet), nifedipine, and in the third trimester, β-blockers are drugs that can be used for the treatment of hypertension during pregnancy.

Captopril used at high doses has been associated with rare cases of thrombocytopenia, neutropenia, and agranulocytosis. These effects are thought to be related to the sulphhydryl group in captopril. Other ACEIs lacking the sulphhydryl group have not been associated with these problems. Angiotensin-converting enzyme inhibition may depress erythropoiesis, which may pose a problem in patients with chronic renal failure. Occasionally ACEIs cause hypersensitivity reactions, rash, urticaria, and angioneurotic oedema. In such patients, use of ACEIs is contraindicated.

A common problem with ACEIs is that a proportion of patients suffer from a persistent dry cough. This side-effect may be caused by potentiation of kinins and substance P. The cough tends to occur at night. It responds poorly to cough mixtures and antihistamines, and may require a reduction in dosage or withdrawal of the drug. The incidence of dry cough is particularly high in Hong Kong Chinese,[38] and may be related to the high level of environmental pollution.[39] It is worth checking that the cough is truly related to ACE inhibition. Sometimes, a careful history may reveal that the cough is due to other reasons such as common cold, chest infection, or worsening heart failure. There is little evidence that cough mixtures commonly prescribed are effective. If cough persists the indications for an ACEI should be reviewed to see if another class of drugs can be used instead. In those patients who require an ACEI despite cough, it is worth trying inhaled

sodium cromoglycate, which is normally used for asthma. There is some evidence from small trials that sodium cromoglycate is effective and well tolerated.[40] If there are no budgetary restraints, an angiotensin II receptor antagonist such as losartan, may be used instead of an ACEI, as the former does not cause cough.

Sartans

The remarkable success of ACEIs in the treatment of cardiovascular diseases has prompted the search for better alternative drugs to block the renin-angiotensin system. The ACE is a non-specific enzyme and blocking the ACE may increase the levels of kinins. Moreover, the effectiveness of ACE inhibition may reduce over time because of non-ACE enzymatic pathways, eg chymases, and increased levels of angiotensin I. Hence, angiotensin II receptor antagonists (sartans) have been developed. This new class of antihypertensive drugs has been launched in recent years.[41] Unlike the ACEIs, the sartans block the binding of angiotensin II to one of its receptors (angiotensin II type 1 [AT_1] receptors). This G-protein-coupled AT_1 receptor is believed to mediate the physiological effects of angiotensin on the circulatory system, such as vasoconstriction, aldosterone stimulation, and sodium and water balance. Angiotensin II receptor antagonists are expected to block the cardiovascular effects of angiotensin II more completely, specifically, and durably than ACEIs. The incidence of side-effects should also be lower because of the specificity of the blockade. For instance, angiotensin II receptor antagonists do not cause cough which is commonly associated with ACEI therapy.[42] The long-acting nature of the sartans also leads to a lower incidence of first-dose hypotension. Evidence from controlled clinical trials suggests that the sartans are very well tolerated and generally have a side-effect profile similar to placebo. The most frequently reported side-effect is dizziness. This is not unexpected for a blood pressure–lowering drug and is more likely to occur in patients who are volume-depleted. Many of the cautions and contraindications to ACEIs also apply. For instance, the concurrent use of potassium supplements and potassium-sparing diuretics must be carefully judged. Plasma potassium and creatinine should be measured before and after initiation of therapy. As with ACEIs, sartans should not be used in pregnancy or in women of reproductive age who may become pregnant. Nor should sartans be used in patients with bilateral renal artery stenosis and advanced renal failure. There have also been rare incidents of angioedema in patients treated with sartans. On the other hand, both ACEIs and sartans can be safely given to hypertensive patients with concomitant conditions such as diabetes, hyperlipidaemia, gout, asthma, or heart failure.

Further knowledge of the pharmacology of angiotensin II receptors has been gained from clinical use of sartans. Sartans block the AT_1 but not the AT_2 receptor. At the same time, angiotensin II levels increase. The unprotected stimulation of AT_2 receptors is of concern. Preliminary evidence

suggests that stimulating the AT_2 receptors enhances the vasodilatory effects of sartans.[43] The AT_2 receptor is expressed in human tissues but not to the same extent in rat tissues, so extrapolating the effects of sartans in rat models to man may be difficult or even misleading. The functions of the AT_2 receptor and the consequences of its long-term stimulation require further clarification.

A large number of sartans are now approved for use in the treatment of patients with hypertension, and this class of antihypertensive drugs is endorsed in the WHO-ISH Guidelines for the Management of Hypertension as one of the first-line treatment agents.[44] Nevertheless, there are reasons why sartans should currently be used with reservation for the treatment of hypertension. Firstly, they are new drugs and long-term studies investigating their effect on the reduction of mortality in hypertension, such as the LIFE (Losartan Intervention For Endpoint reduction in hypertension study[45]) and the VALUE (Valsartan Antihypertensive Long-term Use Evaluation trial[46]) studies are not yet completed. Post-hoc analyses of the ELITE (Evaluation of Losartan In The Elderly study) trial in heart failure patients suggested a reduction in all-cause mortality and sudden death in the losartan-treated group compared with the captopril-treated one,[47] but this was not confirmed in the larger well-powered study, ELITE II.[48] Indeed, the captopril-treated group were found to have a lower all-cause mortality (odds ratio=0.88; 95% confidence interval, 0.75-1.05), although this did not reach statistical significance. Another trial comparing a sartan with an ACEI in patients with heart failure, RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction), was terminated prematurely because the results were negative.[49] Secondly, ACEIs block not only the RAAS but also enhance the formation of kinins. There are animal data to suggest that some of the beneficial effects of ACEI are brought about by changes in the kinin system.[2] Sartans have no direct effect on the kinin system and, therefore, may not reproduce all the benefits of ACEIs.[50] Finally, the cost-effectiveness of antihypertensive drugs vary enormously. The sartans are all recently developed, patented drugs, and thus, are considerably more expensive than diuretics and β-blockers. At the present time, it cannot be said that they are superior in terms of outcome, but they do appear to be superior in terms of tolerability and incidence of side-effects.

Conclusions

Angiotensin-converting enzyme inhibitors have established an enviable reputation, especially in the treatment of heart failure and MI. There are many potential problems and side-effects associated with ACEIs, and patients taking ACEIs require periodic monitoring of renal function and electrolytes. However, large clinical trials have established the usefulness of ACEIs in hypertension, heart failure, MI, and diabetic nephropathy, ensuring these agents an important place in the formulary. The role of sartans is less clear at this time. Sartans lower blood pressure and are well tolerated. However, they are more expensive than ACEIs. Results of large clinical trials are needed before they can be promoted widely as first-line treatment for hypertension. For patients in whom ACEIs are indicated, but who are unable to tolerate side-effects such as cough, a sartan should certainly be considered.

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