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DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

5 – Inhibitors of the renin-angiotensin-aldosterone system

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> *"Angiotensin-converting enzyme inhibitors have been shown to have the broadest impact of any drug in cardiovascular medicine."*
>
> *Harvey White, 2003*[1]

Since the description in 1977 of the first angiotensin-converting enzyme (ACE) inhibitor, captopril, by the Squibb group led by Ondetti and Cushman, ACE inhibitors have become the cornerstone not only of the treatment of heart failure and left ventricular (LV) dysfunction, but increasingly also play a major role in hypertension and in cardiovascular (CV) protection.[1],[2] The purpose of this chapter is to survey the pharmacologic characteristics, the use, and the limitations of these agents and their new relatives, the angiotensin receptor blockers (ARBs).

Frequent reference is made to the role of the renin-angiotensin-aldosterone system (RAAS) in CV pathologic conditions, with excess activities of angiotensin II and of aldosterone contributing to major adverse maladaptive roles. ACE inhibitors act on the crucial enzyme that generates angiotensin II and mediates the breakdown of bradykinin, whereas the ARBs act directly by blocking the major angiotensin II receptor subtype 1 (AT-1 subtype) that responds to angiotensin-II stimulation. As the result of many careful long and large trials, it is now clear that ACE inhibitors give both primary and secondary protection from cardiovascular disease (CVD), thereby interrupting the vicious circle from risk factors to LV failure at many sites (Fig. 5-1).[3] The ARBs are very well tolerated, and have been shown in several but not all outcome trials to give benefits equal to those provided by the ACE inhibitors. The final step in the RAAS, aldosterone, is increased in heart failure. Aldosterone inhibitors have additive protective effects to those of ACE inhibitors in heart failure and in high-risk postmyocardial infarction (MI) patients. The newer direct renin inhibitors are antihypertensive, but clinical outcome data are currently lacking.

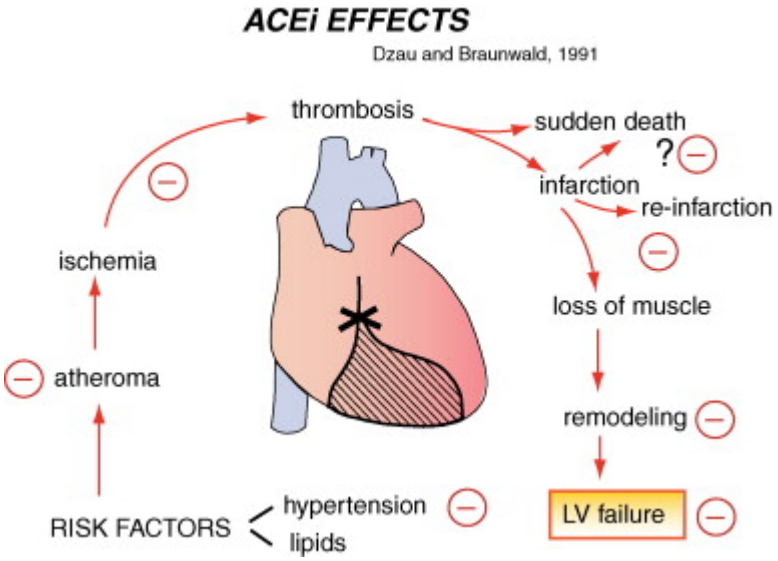

Figure 5-1 Dual role of angiotensin-converting enzyme (ACE) inhibitors, both preventing and treating cardiovascular disease. Note multiple sites of action in both primary and secondary prevention. ACE inhibitors (ACEi) have an indirect effect in primary prevention by lessening hypertension and by decreasing left ventricular (LV) hypertrophy. They protect the blood vessels

indirectly by an antihypertensive effect, and directly inhibit carotid atherogenesis and thrombogenesis. Given at the start of myocardial infarction, they improve mortality in high-risk patients. By an antiarrhythmic effect, they may act to prevent postinfarct sudden death. By lessening wall stress, they beneficially improve postinfarct remodeling and decrease the incidence of LV failure. The concept of sequential changes leading to a chain of events from risk factors to LV failure is based on concepts of Dzau and Braunwald.[3]

(Figure © L.H. Opie, 2012, and adapted from Angiotensin-Converting Enzyme Inhibitors. The Advance Continues, 3rd ed, Authors' Publishing House, New York & University of Cape Town Press, 1999.)

Mechanisms of action of ACE inhibitors

Logically, ACE inhibition should work by lessening the complex and widespread effects of angiotensin II (Table 5-1). This octapeptide is formed from its precursor, a decapeptide *angiotensin I,* by the activity of the ACE. ACE activity is found chiefly in the vascular endothelium of the lungs, but occurs in all vascular beds, including the coronary arteries. Angiotensin I originates in the liver from *angiotensinogen* under the influence of the enzyme *renin,* a protease that is formed in the renal juxtaglomerular cells. Classic stimuli to the release of renin include (1) impaired renal blood flow as in ischemia or hypotension, (2) salt depletion or sodium diuresis, and (3) β-adrenergic stimulation. The *ACE* is a protease that has two zinc groups, only one of which participates in the high-affinity binding site that interacts with angiotensin I or with the ACE inhibitors. ACE not only converts angiotensin I to angiotensin II, but also inactivates the breakdown of bradykinin. ACE inhibition is vasodilatory by decreased formation of angiotensin II and potentially by decreased degradation of bradykinin (Fig. 5-2).

Table 5-1 -- Potential Pathogenic Properties of Angiotensin II

Heart
• Myocardial hypertrophy • Interstitial fibrosis
Coronary Arteries
• Endothelial dysfunction with deceased release of nitric oxide • Coronary constriction via release of norepinephrine • Increased oxidative stress; oxygen-derived free radicals formed via NADH oxidase • Promotion of inflammatory response and atheroma • Promotion of LDL cholesterol uptake
Kidneys
• Increased intraglomerular pressure • Increased protein leak • Glomerular growth and fibrosis • Increased sodium reabsorption
Adrenals
• Increased formation of aldosterone
Coagulation System
• Increased fibrinogen • Increased PAI-1 relative to tissue plasminogen factor

LDL, Low-density lipoprotein; *NADH,* nicotine adenine dinucleotide, reduced; *PAI,* plasminogen activator inhibitor.

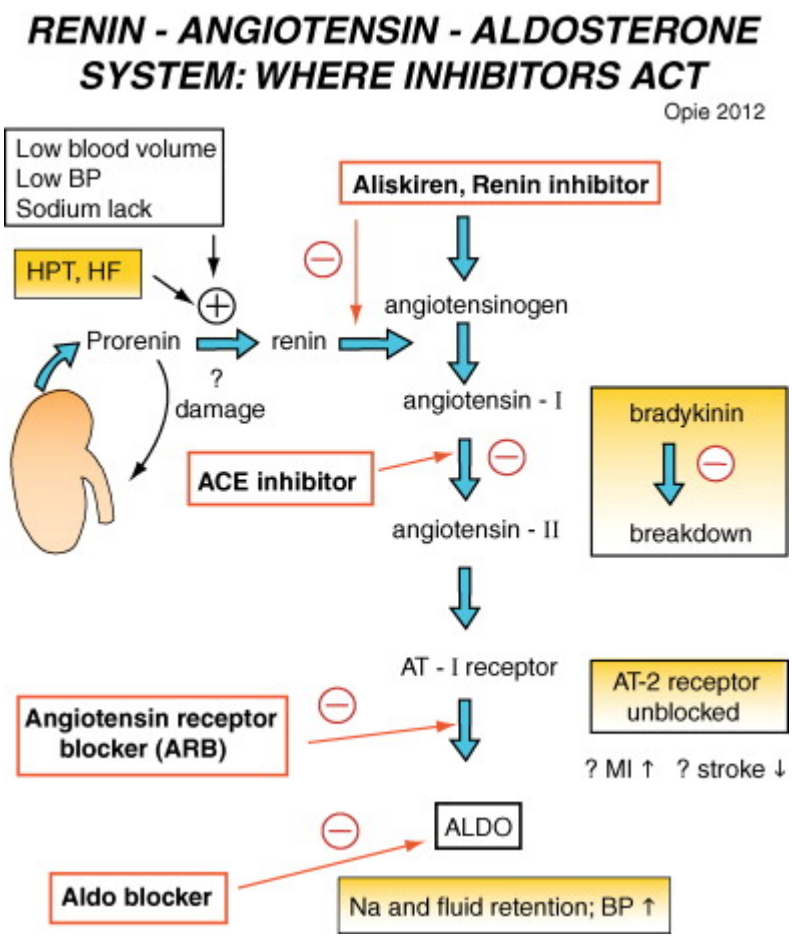

Figure 5-2 The renin-angiotensin-aldosterone system (RAAS) and where inhibitors act. Angiotensin-converting enzyme (ACE) inhibitors have dual vasodilatory actions, chiefly on the renin-angiotensin system with ancillary effects on the breakdown of vascular protective bradykinin. The angiotensin receptor blockers (ARBs) inhibit the angiotensin type 1 receptor (AT-1). The renin inhibitor aliskiren could block the whole RAAS with the theoretical downside of increased formation of prorenin. *AT-2,* Angiotensin type 2; *BP,* blood pressure; *HF,* heart failure; *HPT,* hypertension; *Na,* sodium.
(Figure © L.H. Opie, 2012.)

Alternate modes of angiotensin II generation

Not all angiotensin II is generated by ACE. Non-ACE pathways, involving chymaselike serine proteases, can also form angiotensin II, but their exact role is still the subject of controversy. One view is that more than 75% of the cardiac angiotensin II formed in severe human heart failure is formed by chymase activity, and that inhibition of chymase prevents cardiac fibrosis and limits experimental heart failure.[4] However, because ARBs are not more efficacious than ACE inhibitors in heart failure, this view is not supported by the clinical trial data.

Angiotensin II and intracellular messenger systems

There are many complex steps between occupation of the angiotensin II receptor and ultimate mobilization of calcium with a vasoconstrictor effect in vascular smooth muscle. Occupation of the angiotensin II receptor stimulates the phosphodiesterase (called *phospholipase C*) that leads to a series of signals that activate a specialized enzyme, *protein kinase C,* that in turn evokes the activity growth pathways that stimulate ventricular remodelling.[5] Phospholipase C also activates the *inositol trisphosphate signaling pathway* in blood vessels to liberate calcium from the intracellular sarcoplasmic reticulum to promote vasoconstriction as well as cardiac and vascular structural alterations.

Angiotensin II receptor subtypes: The AT-1 and AT-2 receptors

There are at least two angiotensin II receptor subtypes, the AT-1 and AT-2 receptors (Fig. 5-3). Note the potentially confusing nomenclature: both receptors respond to angiotensin II, but are subtypes 1 and 2. These link to separate internal signaling paths.[6] Clinically used ARBs should be considered as AT-1 blockers. The effects of angiotensin II acting via AT-1 receptors on the diseased heart and failing circulation are often regarded as adverse, such as stimulation of contraction, vasoconstriction, myocyte hypertrophy, fibrosis,[7] and antinatriuresis. In fetal life, these AT-1 receptors act as teratogenic growth stimulators, which explains why ACE inhibitors and ARBs are prohibited therapy in pregnancy. The physiologic role of the AT-2 receptor includes the inhibition of growth in the late fetal phase (growth can't keep on forever). In adult life, the role of the AT-2 receptors is much less well understood and controversial, but could become more relevant in pathophysiologic conditions, the receptors being upregulated in hypertrophy and in heart failure and having a postulated protective function. Again, the comparable clinical results of ACE inhibitors and ARBs (see p. 145) raise questions about the importance of unopposed AT-2 stimulation with ARBs.

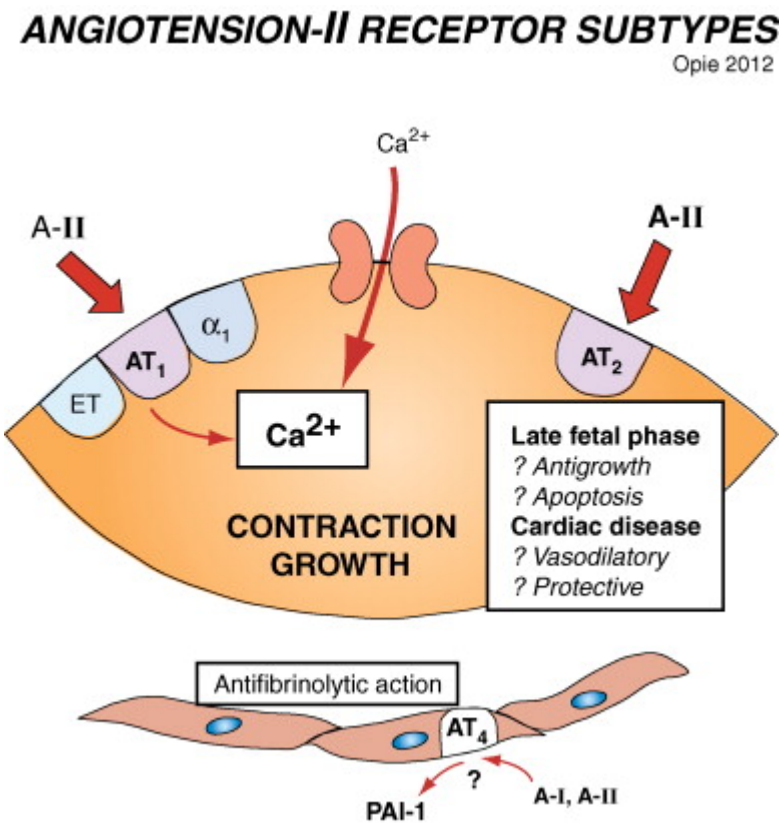

Figure 5-3 **Proposed roles of angiotensin II receptor subtypes,** which are called AT-1, AT-2, and (possibly) AT-4 subtypes. Most of the physiologic effects in adult vascular smooth muscle cells are conveyed by the AT-1 receptor subtype. The AT-2 receptor is of substantial importance in late fetal vascular growth, exerting an antigrowth effect. Hypothetically, these receptors may also play a beneficial role in various myocardial pathophysiologic conditions (see text). AT-4 receptors are postulated to have an antifibrinolytic effect.
(Figure © L.H. Opie, 2012, and adapted from Angiotensin-Converting Enzyme Inhibitors. The Advance Continues, 3rd ed, Authors' Publishing House, New York & University of Cape Town Press, 1999.)

Renin-angiotensin-aldosterone system

The major factors stimulating *renin release* from the juxtaglomerular cells of the kidney and, hence, angiotensin activation are (Fig. 5-4): (1) a low arterial blood pressure (BP); (2) decreased sodium reabsorption in the distal tubule, as when dietary sodium is low or during diuretic therapy; (3) decreased blood volume; and (4) increased $beta_1$-sympathetic activity. *Stimulation of aldosterone by angiotensin II* means that the latter stimulus releases the sodium-retaining hormone aldosterone from the adrenal cortex. Hence ACE inhibition is associated with aldosterone reduction and has potential indirect natriuretic and potassium-retaining effects. Aldosterone formation does not, however, stay fully blocked during prolonged ACE-inhibitor therapy. This late "escape" does not appear to compromise the antihypertensive effects

achieved by ACE inhibitors; nonetheless, it might detract from the prolonged benefit of these agents in heart failure. In the RALES study, *added low-dose spironolactone on top of diuretics and ACE inhibition reduced mortality* (see p. 159).

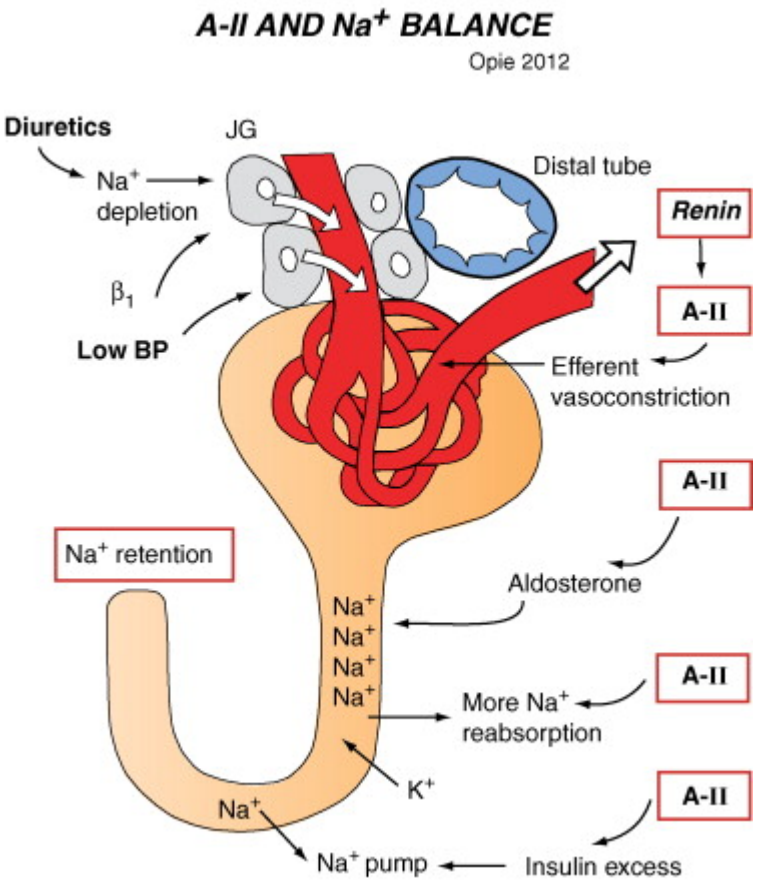

Figure 5-4 **Renal mechanisms** whereby renin-angiotensin-aldosterone system promotes sodium retention. *A-II,* angiotensin II; *JG,* juxtaglomerular cells.
(Figure © L.H. Opie, 2012.)

Adverse effects of excess aldosterone

Aldosterone, released either in response to angiotensin II or to stimulation by adrenocorticotropic hormone (ACTH) or increased potassium, has major effects on electrolyte balance. Aldosterone acts on the distal tubule to retain sodium and excrete potassium by inhibition of sodium-potassium exchange (see Fig. 5-4). Water is retained with sodium. In heart failure, plasma aldosterone rises up to 20 times normal, in response to increased angiotensin II, coupled with decreased hepatic clearance.[8] Aldosterone, some of it locally produced, may adversely alter the structure of the myocardium by promotion of cardiac fibrosis.[8] Aldosterone also promotes endothelial dysfunction.[9]

Autonomic interactions of angiotensin II

ACE inhibitors have indirect permissive antiadrenergic effects. Angiotensin II promotes the release of norepinephrine from adrenergic terminal neurons, and also enhances adrenergic tone by central activation and by facilitation of ganglionic transmission. Furthermore, angiotensin II amplifies the vasoconstriction achieved by alpha$_1$-receptor stimulation. Thus angiotensin II has facilitatory adrenergic actions leading to increased activity of vasoconstrictor norepinephrine. Vagomimetic effects could explain why tachycardia is absent despite peripheral vasodilation. The combined antiadrenergic and vagomimetic mechanisms could contribute to the *antiarrhythmic effects* of ACE inhibitors and the reduction of sudden death in several trials in congestive heart failure (CHF), especially post-MI.[10] An additional factor is probably better potassium

retention (as a result of aldosterone inhibition).

Kallikrein-kinin system and bradykinin

Besides decreased formation of angiotensin II, increased bradykinin is another alternate site of action of ACE inhibitors (see Fig. 5-2; Table 5-2). This nonapeptide, originally described as causing slow contractions in the gut (hence the *brady* in the name) is of potential CV importance. Bradykinin is inactivated by two kininases, kininase I and II. The latter is identical to ACE. ACE inhibition therefore also leads to increased local formation of bradykinin, as well as a reduction in angiotensin II production. Bradykinin acts on its receptors in the vascular endothelium to promote the release of two vasodilators (Table 5-2), nitric oxide and vasodilatory prostaglandins, such as prostacyclin and prostaglandin E_2 (PGE_2). Indomethacin, which inhibits prostaglandin synthesis, partially reduces the hypotensive effect of ACE inhibitors. The current concept is that bradykinin formation, occurring locally and thus not easily measured, can participate in the hypotensive effect of ACE inhibitors and may act via nitric oxide to protect the endothelium. These potentially favorable actions of an ACE inhibitor, mediated via bradykinin, would not occur with an ARB (but there would also be fewer adverse effects of bradykinin such as cough and angioedema).

Table 5-2 -- Indications for ACE Inhibitors Based on Trial Data

1.	Heart failure, all stages
2.	Hypertension especially in high-risk patients and in diabetics
3.	AMI, acute phase for high-risk patients, postinfarct LV dysfunction
4.	Nephropathy, nondiabetic and diabetic type 1
5.	Cardiovascular protection in specified doses (ramipril, perindopril, trandolapril)

Caution: Not all the above are licensed indications and the license for a specific ACE inhibitor may vary. Check the package insert.

ACE, Angiotensin-converting enzyme; *AMI,* acute myocardial infarction; *LV,* left ventricular.

ACE 2

A newly described enzyme, ACE 2, generates angiotensin-(1-7) (Ang-[1-7]) from angiotensin II. Ang-(1-7) acts on its vascular receptor to inhibit vasoconstriction and sodium retention[11] and metabolize angiotensin II to Ang-(1-7). Ang-(1-7) antagonizes angiotensin II actions via the G-coupled Mas receptor.[12] Genetic ablation of ACE 2 leads to heart failure in mice.[13] ACE 2 also acts on angiotensin I to form Ang-(1-9).[14] Ang-(1-9) blocks cardiomyocyte hypertrophy via the angiotensin type 2 receptor. Ang-(1-9) infusion acted on the AT-2 receptor to lessen cardiac fibrosis in stroke-prone rats, thereby supporting a direct role for Ang-(1-9) in the renin-angiotensin system (RAS).[14] Furthermore, Ang-(1-9) can be hydrolyzed to form Ang-(1-7).[12] ACE 2 agonists may soon have clinical testing because similar paths exist in human heart tissue.[15]

Tissue renin-angiotensin systems

Although the acute hypotensive effects of ACE inhibition can clearly be linked to decreased circulating levels of angiotensin II, during chronic ACE inhibition there is a reactive hyperreninemia linked to reemergence of circulating angiotensin II and aldosterone. Hence, the present proposal is that ACE inhibitors exert their sustained antihypertensive, favorable structural effects, and antiheart failure effects at least in part by acting on the tissue RASs, lessening formation of angiotensin II within the target organ. Likewise, this is the proposed site of action, in addition to BP reduction, in the regression of left ventricular hypertrophy (LVH) and vascular remodeling (Fig. 5-5).

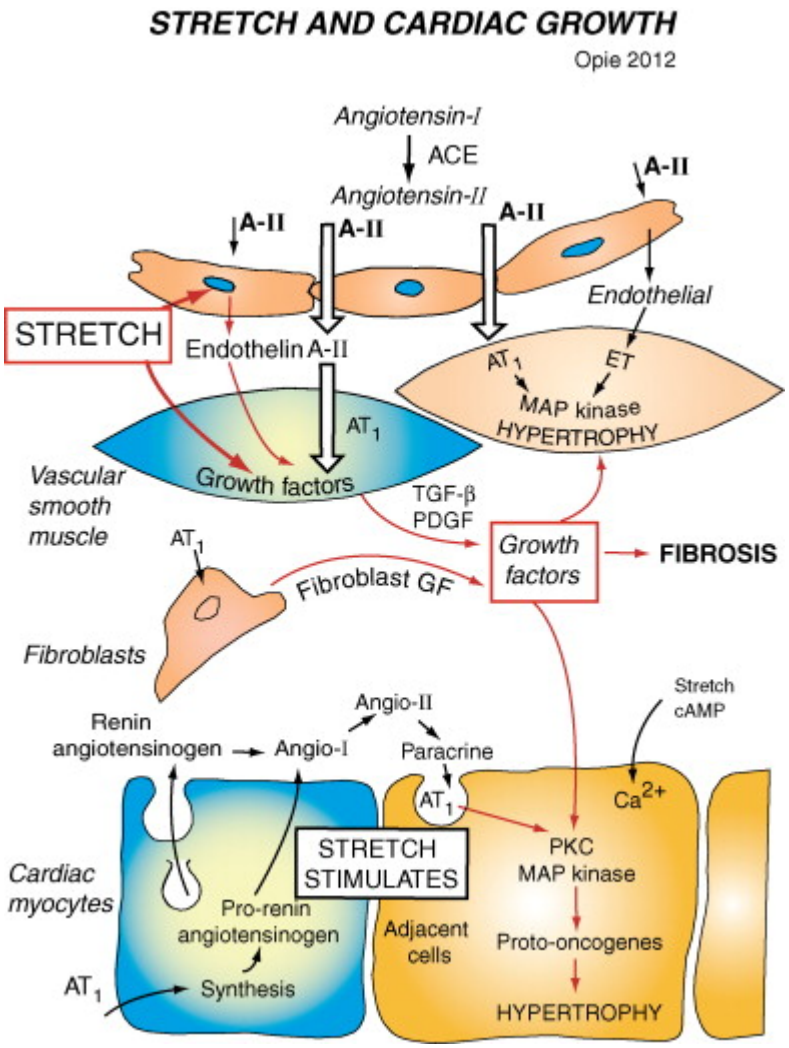

Figure 5-5 **Role of cardiac tissue renin-angiotensin system**, hypothetically as in left ventricular hypertrophy (hypertrophy), involving myocytes, fibroblasts, vascular smooth muscle and endothelium. *ACE,* Angiotensin-converting enzyme; *AT-1,* angiotensin II receptor, subtype 1; *cAMP,* cyclic adenosine monophosphate; *ET,* endothelin; *GF,* growth factor; *MAP kinase,* mitogen activated protein kinase; *PDGF,* platelet-derived growth factor; *PKC,* protein kinase C; *TGF,* transforming growth factor. Other abbreviations as in Fig. 5-2.
(Figure © L.H. Opie, 2012, and adapted from Angiotensin-Converting Enzyme Inhibitors. The Advance Continues, 3rd ed, Authors' Publishing House, New York & University of Cape Town Press, 1999.)

Cerebral effects and renin-angiotensin inhibitors

In patients with heart failure, central mechanisms play an important role in postinfarct remodelling.[5] Do brain-penetrant renin-angiotensin inhibitors improve cognition?[16],[17] If so, such agents could preferentially be used in the therapy of hypertension in older adults. However, in ONTARGET and TRANSCEND, large double-blind studies with telmisartan, ramipril, and their combination, different approaches to blocking the RAS had no clear effects on cognitive outcomes.[18] More specific prospective studies due to be presented soon are awaited.[17]

Genotypes and response to ACE inhibitors

There is no direct relevance to clinical practice at present as the phenotype does influence clinical response to pharmacologic therapy.

Pharmacologic characteristics of ACE inhibitors

Major indications and classes

Major indications are heart failure, hypertension, acute and chronic MI, renoprotection, diabetic nephropathy and hypertension, and CV protection. ACE inhibitors play a major role in secondary CVD prevention (Table 5-3 and Fig. 5-6).

Table 5-3 -- ACE Inhibitors and Other RAAS Inhibitors for Secondary Prevention in CHD and Other Atherosclerotic Diseases (AHA/ACC Foundation Recommendations)

1.	ACE inhibitors should be started and continued indefinitely in all patients with LV EF ≤40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. (Class I, *Level of Evidence: A)* It is reasonable to use ACE inhibitors in all other patients. *(*Class IIa, *Level: B)*
2.	ARBs are recommended for ACE-intolerant patients with HF or post-MI with EF ≤40%. (Class I, *Level: A)* It is reasonable to use ARBs in other ACE-intolerant patients. (Class IIa, *Level: B)*
3.	ARB use combined with an ACE inhibitor is not well established in those with systolic HF. *(*Class IIb, *Level: A)*
4.	Aldosterone blockade is recommended in post-MI patients without significant renal dysfunction or hyperkalemia and already receiving an ACE inhibitor and β-blocker with LV EF ≤40% plus either with diabetes or HF. *(*Class I, *Level: A)*

From Smith Jr SC. Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the AHA and ACC Foundation. Circulation 2011;124:2458–2473.

ACC, American College of Cardiology; *ACE,* angiotensin-converting enzyme; *AHA,* American Heart Association; *ARB,* angiotensin receptor blocker; *CHD,* coronary heart disease; *EF,* ejection fraction; *HF,* heart failure; *LV,* left ventricular; *MI,* myocardial infarction.

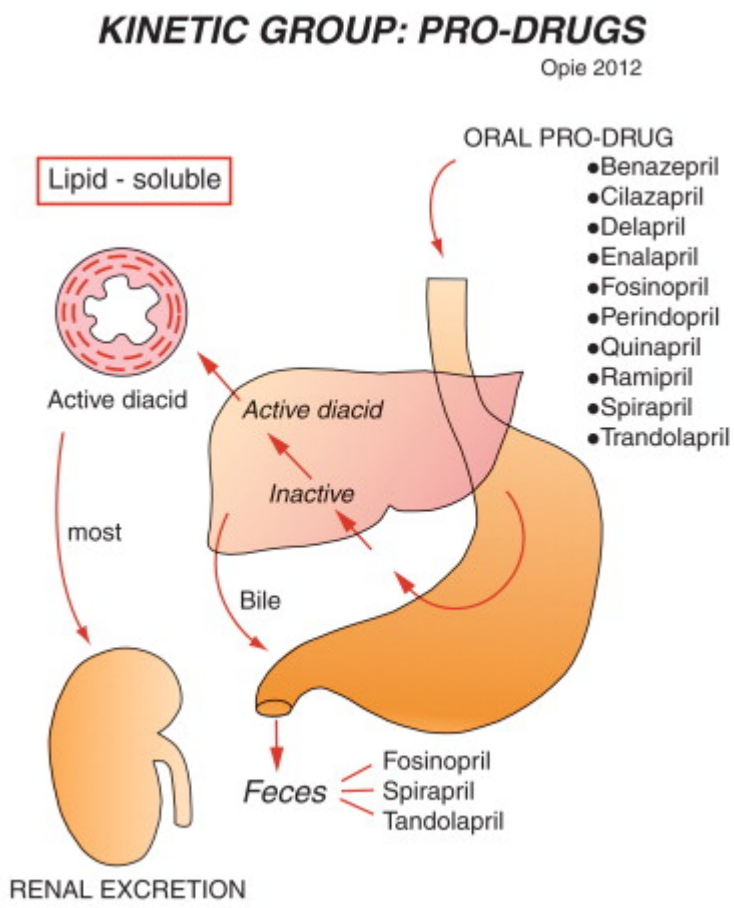

Figure 5-6 **Pharmacokinetic patterns of prodrugs** that are converted to active diacids and then excreted (Class II). The predominant pattern for most is renal excretion but with some drugs, especially fosinopril, biliary and fecal excretion may be as important.
(Figure © L.H. Opie, 2012 and adapted from Angiotensin-Converting Enzyme Inhibitors. The Advance Continues, 3rd ed, Authors' Publishing House, New York & University of Cape Town Press, 1999.)

Side effects of ACE inhibitors

Cough remains as one of the most troublesome and common of the various side-effects (Fig. 5-7; see later, Table 5-6), some serious and some not. Patients with heart failure often cough as a result of pulmonary congestion (which may need more rather than less ACE inhibitor), and in patients with hypertension such side effects are generally discovered only if volunteered. In some centers, the incidence of cough is thought to be as high as 10% to 15%, whereas others report a much lower incidence such as 5.5% in HOPE.[19] The cough is due to an increased sensitivity of the cough reflex resulting in a dry, irritating, nonproductive cough, quite different from bronchospasm. Increased formation of bradykinin and prostaglandins may play a role because ARBs have a much lower incidence of cough. Several studies suggest relief of the cough by added nonsteroidal antiinflammatory drugs (NSAIDs),[20] with the downside of diminished antihypertensive effects. Logically, and most often tried with success, a change to an angiotensin II receptor blocker consistently lessens the cough.[21]

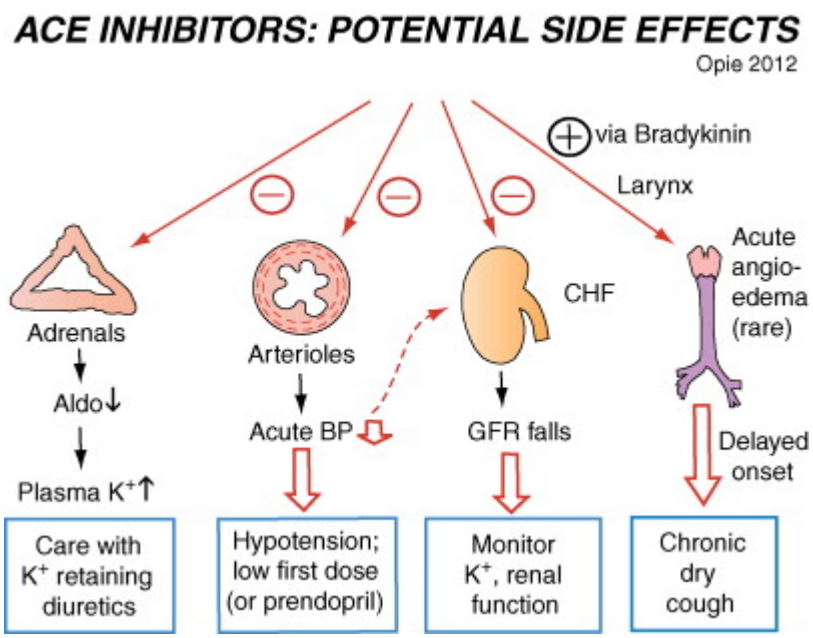

Figure 5-7 Potential side effects of angiotensin-converting enzyme (ACE) inhibitors include cough, hypotension, and renal impairment. Angioedema is rare but potentially fatal. To avoid hypotension in heart failure patients, a low first test dose is usually given. *Aldo,* Aldosterone; *BP,* blood pressure; *CHF,* congestive heart failure; *GFR,* glomerular filtration rate; *K,* potassium. *(Figure © L.H. Opie, 2012.)*

Hypotension

Particularly in CHF, orthostatic symptoms caused by excess hypotension are common and may necessitate dose reduction or even cessation of ACE-inhibitor therapy. In general, so long as orthostatic symptoms do not occur, the absolute BP is not crucial and some heart failure patients do well with systolic pressures of 80 to 90 mm Hg. *Hyponatremia* can be an indicator of heightened RAAS activity, and when present, there is an increased risk of hypotension (see later in this chapter).

Hyperkalemia is a risk, especially when ACE inhibitors are given with aldosterone antagonists, ARBs, or potassium-sparing diuretics, or in the presence of renal failure. A rough rule is that increasing RAAS block may improve the heart failure at the risk of increasing hyperkalemia. The RALES study showed the safety and efficacy of low doses of spironolactone when carefully added to β-blockers, ACE inhibitors, and diuretics in the therapy of severe systolic heart failure.[22] Careful monitoring of serum potassium is essential because hyperkalemia is potentially lethal.

Renal side effects and hyponatremia

Reversible renal failure can be precipitated by hypotension, and hyponatremia is the most reliable sign of trouble. Predisposing characteristics are a fixed low renal blood flow as in severe CHF or severe sodium and volume depletion, or underlying renal disease, including renal artery stenosis. In these conditions, efferent glomerular arterial constriction resulting from angiotensin II may be crucial in retaining the glomerular filtration rate (GFR). Rarely, irreversible renal failure has occurred in patients with bilateral renal artery stenosis, a contraindication to ACE inhibitors. In unilateral renal artery disease, with high circulating renin values, ACE inhibitors may also cause excessive hypotensive responses with oliguria or azotemia. To obviate such problems, and especially when there is unilateral renal artery stenosis or a low sodium state, a low first test dose of the ACE inhibitor should be given, although this is seldom done. An arbitrary high value of serum creatinine is often taken as a contraindication (see later in chapter). A slight stable increase in serum creatinine after the introduction of an ACE inhibitor should not limit use. A 20% rise in creatinine should make one consider renal artery stenosis.

Angioedema

Although uncommon (approximately 0.3% in ALLHAT, rising to 0.6%-1.6% in black individuals),[23],[24] this condition can very rarely be fatal, the incidence of death increasing from 0 in a large study on 12,634 patients given enalapril for 24 weeks[24] to approximately 1 in 5-10,000 patients.[23],[25] The mechanism depends on bradykinin,[26] with a further contribution from impaired breakdown of substance P.[27] The enzyme breaking down both peptides is dipeptidyl peptidase IV, which is inhibited by a group of antidiabetic drugs (see Chapter 11, page 451). Indirect evidence suggests increased angioedema in patients taking antidiabetics such as sitagliptin.[27] For urgent therapy, prompt subcutaneous epinephrine and rarely even intubation may be needed.[28] The ACE inhibitor must be stopped. Switching to an ARB may be considered,[21] yet there are isolated instances of ARB-associated angioedema.

Pregnancy risks

All ACE inhibitors (also ARBs and renin inhibitors) are embryopathic and contraindicated in pregnancy in all trimesters.[29] The Food and Drug Administration (FDA) requires a boxed warning in the package insert. *Avoid giving these drugs to women of childbearing age unless pregnancy is avoided.*

Neutropenia

Once the bane of captopril therapy, neutropenia now seems to be rare. The association with high-dose captopril, usually occurring in patients with renal failure and especially those with a collagen vascular disorder, is undoubted. In the case of all other ACE inhibitors, the American package inserts all warn that available data for all other ACE inhibitors are not sufficient to exclude agranulocytosis at similar rates to those found with captopril.

ACE inhibitors: Contraindications

Contraindications include bilateral renal artery stenosis, pregnancy, known allergy or hypersensitivity, and hyperkalemia. Often a high serum creatinine of more than 2.5-3 mg/dL (220-265 µmol/L) is taken as an arbitrary cut-off point for the use of ACE inhibitors and for ARBs, especially in heart failure. However, patients with higher creatinine values might be evaluated in the context of the renoprotection that may be achieved and nephrologists might elect to start ACE inhibition with caution. Overall benefits can be attained with lesser degrees of renal insufficiency.[30]

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ACE inhibitors for heart failure

Neurohumoral effects of overt heart failure

A crucial problem in CHF is *the inability of the left ventricle to maintain a normal BP and organ perfusion. Enhanced activity of the RAS* (Fig. 5-8) follows from (1) hypotension, which evokes baroreflexes to increase sympathetic adrenergic discharge, thereby stimulating the $beta_1$ renal receptors involved in renin release; (2) activation of chemoreflexes and ergoreflexes; (3) decreased renal perfusion resulting in renal ischemia, which enhances renin release; and (4) β-adrenergic simulation. However, even in compensated CHF, plasma renin may not be persistently elevated[31] without simultaneous diuretic therapy. Angiotensin II promotes secretion of aldosterone and the release of vasopressin. Both contribute to abnormal fluid retention and volume regulation in severe CHF. Generally, such changes are thought to be adverse because of the resultant increased vasoconstriction, fluid and sodium retention, and dilutional hyponatremia.

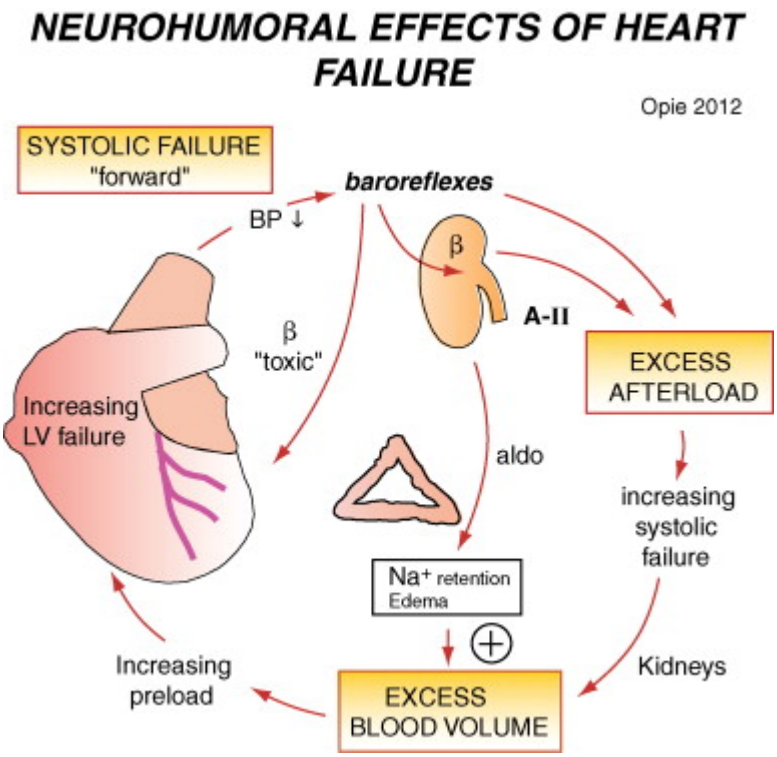

Figure 5-8 Neurohumoral adaptation in heart failure. The crucial consequence of left ventricular (LV) failure is the inability to maintain a normal blood pressure and normal organ perfusion. As a result of reflex baroreflex activation and excess adrenergic stimulation, there is alpha (α)–mediated peripheral vasoconstriction that increases the afterload and leads to increased LV failure. Excess alpha (α) adrenergic stimulation leads to peripheral vasoconstriction. Furthermore, excess beta (β)–adrenergic stimulation promotes renin release with increased vasoconstrictive angiotensin-II (A-II) and release of aldosterone. Increasing preload and afterload leads to increasing LV failure. *A-II,* Angiotensin II; *aldo,* aldosterone; *BP,* blood pressure; *Na,* sodium.
(Figure © L.H. Opie, 2012, and adapted from Angiotensin-Converting Enzyme Inhibitors. The Advance Continues, 3rd ed, Authors' Publishing House, New York & University of Cape Town Press, 1999.)

The peripheral vascular resistance is greatly increased. Thus the greater afterload against which the failing heart must work is explained by (1) increased formation of angiotensin II, (2) reflex release of

norepinephrine, (3) release of vasoconstrictor *endothelin* from the dysfunctional vascular *endothelium,* (4) reduced muscle mass, (5) thickened capillary membranes, and (6) altered endothelial cell response to muscle metabolites. Systemic and renal vascular vasoconstriction reduces renal plasma flow, which detrimentally affects salt excretion and further promotes renin formation. Vasodilator hormones of cardiac origin such as atrial and brain natriuretic peptides (BNPs), and prostaglandins of vascular origin, are also activated, but fail to achieve compensatory vasodilation for complex reasons including receptor downgrading.

The LV wall stress increases. Especially during exertion, both systolic and diastolic wall stresses become too high for the depressed contractility of the failing myocardium. The inability of the left ventricle to empty itself during systole increases the preload. The combination of increased pre- and afterload, so common in CHF, leads to progressive ventricular dilation with wall remodeling (myocyte hypertrophy and slippage with matrix changes) so that the ejection fraction progressively declines with time. Load reduction and in particular angiotensin II inhibition retards this detrimental remodeling process.[32] According to *Laplace's law,* the stress on the wall of a thin-walled sphere is proportional to the product of the intraluminal pressure and the radius, and inversely related to the wall thickness. Wall stress is one of the major determinants of myocardial oxygen uptake. Afterload and preload reduction, by decreasing the radius of the left ventricle, decreases the myocardial oxygen demand. ACE inhibition, by reducing the preload and the afterload, lessens excessive LV wall stress, limits remodeling, and enhances ventricular emptying.[33] Inhibiting these factors improves the myocardial oxygen balance and attenuates further LV chamber enlargement.

Beneficial neurohumoral effects of ACE-inhibitors are as follows: ACE inhibitors have a consistent effect in increasing plasma renin and decreasing angiotensin II and aldosterone, with a fall in norepinephrine, epinephrine, and in vasopressin. Angiotensin II production falls. Parasympathetic activity, reduced in heart failure, is improved by ACE inhibition. Although there are some exceptions to the patterns noted, most of the results are reasonably consistent. From these data it can be concluded that chronic ACE inhibition ameliorates the neurohumoral changes found in CHF.

ACE inhibitors as preventative therapy in early LV dysfunction

ACE inhibitors have earned their place as preventative therapy in early LV dysfunction, as shown for captopril in SAVE[34] and enalapril in SOLVD.[35] Longer-term 12-year follow up of such asymptomatic patients has revealed a mortality benefit of early ACE-inhibitor use.[36] This mortality benefit of ACE inhibitors can be found even in the absence of initial diuretic therapy.[37] Note the challenge posed by β-blockers to ACE inhibitors as first-line therapy in early chronic heart failure (see Chapter 6, p. 195).

How do diuretics compare with ACE inhibitors?

In postinfarct patients without clinical heart failure but with modestly depressed LV function, the ACE inhibitor captopril was better able to maintain LV function and size than the diuretic furosemide.[38] There could be many adverse effects of diuretics, including activation of the renin-angiotensin axis. Yet in overt LV failure and in CHF, diuretic therapy is still universally accepted as first-step therapy to reduce symptoms because diuretics are superior to ACE in diminishing sodium and water retention. There is no evidence that chronic diuretic therapy prolongs life, although it is clinically evident that an intravenous loop diuretic is life-saving when given to a patient with severe LV failure and pulmonary edema. Long term, it is now clear that ACE inhibitors prolong life, whereas digoxin does not, so that the automatic choice of agent to combine with a diuretic in CHF is an ACE inhibitor.

ACE inhibitors plus β-blockers for heart failure

Historically, ACE inhibitors came first in the therapy of heart failure, before β-blockers, which were better at reducing mortality. The consistently positive survival-prolonging results with bisoprolol,[39] the MERIT study with metoprolol, and several carvedilol studies[40] given in addition to ACE inhibitors were such that β-blockers are now viewed as an integral part of the standard therapy of heart failure. *Thus the combination we should strive for is that of ACE inhibitors plus β-blockers.* The β-blocker should be carefully introduced when the patient is stable, not when there is hemodynamic deterioration (see Table 1-2). Mortality reductions with β-blockers (relative risk of 0.68) was demonstrated with and without an ACE inhibitor and the combination was optimal (relative risk of 0.83).[37] *The β-blocker can be given first.*[39]

Potential problems with drug combinations in CHF

1. *Diuretics plus ACE inhibitors.* Additive effects on the preload may lead to syncope or hypotension; thus the diuretic dose is usually halved before starting ACE inhibitors. The result may be a true diuretic-sparing effect in approximately half of patients with mild CHF following the addition of the ACE-inhibitor, whereas in others the full diuretic dose must be reinstituted.
2. *ACE inhibitors plus spironolactone or eplerenone.* The major danger is hyperkalemia and the lesser is an increasing serum creatinine,[22],[41] so frequent checks are needed. Some safety guidelines to evaluate before using this combination are the prior use of potassium-retaining diuretics, a serum creatinine exceeding 2.5 mg/dL (220 µmol/L) or an estimated glomerular filtration rate (eGFR) of less than 30 (mL/min/1.73 m[2] of body-surface area) and a serum potassium exceeding 5 mm/L. Sometimes the dose of the ACE inhibitor must be adjusted downward.
3. *ACE inhibitors and aspirin or NSAIDs.* Formation of bradykinin and thereby prostaglandins may play an important role in peripheral and renal vasodilation. Hence, NSAIDs, especially indomethacin, lessen the effectiveness of ACE inhibitors in hypertension.[42] Sulindac may have less effect and ARBs seem to interact less.[42] In CHF the interaction with NSAIDs is less studied. Restrictions on renal blood flow invoked by NSAIDs are most likely to be serious in those with major renin-angiotensin inhibition receiving high-dose diuretics and with hyponatremia. If an NSAID has to be used in heart failure, frequent checks of renal function are required. In practice, low-dose (approximately 80 mg daily) aspirin is often combined with an ACE inhibitor in the therapy of ischemic heart failure.

How to start an ACE inhibitor in severe heart failure

First the patient must be fully assessed clinically, including measurements of serum creatinine, eGFR, and electrolytes. It is important to avoid first-dose hypotension and thereby lessen the risk of temporary renal failure. Patients at high *risk of hypotension* include those with serum sodium levels less than 130 mmol/L, a increased serum creatinine in the range of 1.5 to 3 mg/dL or 135 to 265 µmol/L. Hyponatremia is serious. Patients with creatinine values exceeding 3 mg/dL should be considered separately (see later in this chapter). All these patients need to have diuretic therapy stopped for 1 to 2 days and are then ideally given a test dose under supervision. Alternatively, a low initial dose of enalapril (1.25 mg) or 2 mg of perindopril (with its slow onset of action) is given. If there is no symptomatic hypotension, the chosen drug is continued, renal function is monitored, and the dose gradually is increased. Absence of first-dose hypotension suggests but does not securely establish that the subsequent course will be smooth. If the patient is fluid overloaded with an elevated jugular venous pressure, then the test dose of the ACE inhibitor can be given without first having to stop diuretic therapy.

Preexisting renal failure

In general, the serum creatinine can be expected to rise modestly and then to stabilize. In severe CHF, in which renal function is already limited by hypotension and by poor renal blood flow, it may be difficult to decide whether to introduce ACE-inhibitor therapy. For example, the serum creatinine may exceed 2.5-3 mg/dL or 220-265 µmol/L. The danger of exaggeration of renal failure must be balanced against the possible benefit from an improved cardiac output and decreased renal afferent arteriolar vasoconstriction resulting from ACE-inhibitor therapy. Problems can be expected, especially when the eGFR is low and the renin-angiotensin axis is highly stimulated. The best policy may be to improve the hemodynamic status as far as possible by the combined use of optimal doses of diuretics and other agents. Then the diuretic dose could be briefly reduced or stopped, and a very low dose of an ACE inhibitor introduced.

Hyponatremia and salt and water limitation

Patients with severe hyponatremia are 30 times more likely to develop hypotension in response to ACE-inhibitor therapy and require special care. The cause of the hyponatremia is, at least in part, release of vasopressin (antidiuretic hormone) as can result from renin-angiotensin activation following intense diuretic therapy. Vasopressin antagonists (see Fig. 4-4) may be tried to combat hyponatremia. Modest, tolerable *salt restriction* is standard practice. Patients already on strict low-sodium diets are at increased risk of first-dose hypotension. In patients who are not volume depleted, restriction of water intake is advisable because delayed water diuresis may contribute to hyponatremia in severe CHF.

Outstanding clinical problems in the therapy of heart failure

1. *Drug dose.* Whereas in hypertension the dose-response curve is flat and can be monitored from the BP response, in CHF the problem of the optimal dose does arise. Is the dose large enough to give as complete renin-angiotensin inhibition as possible? Standard medium doses were not tested. In the case of enalapril, the standard target dose is 10 mg twice daily. Increasing this to 60 mg/day did not alter death rate nor hemodynamic parameters.[43] In clinical practice lower doses than in the trials are commonly used. Although the optimal doses of ACE inhibitors in CHF have not been established by clinical studies, our opinion is that the dose should be titrated upward to the effective trial doses without going higher.
2. *Diastolic dysfunction.* Most heart failure studies have concentrated on the role of ACE inhibition in systolic failure. Diastolic failure is an early event, particularly in LVH in response to hypertension or aortic stenosis, as well as in older adults. Therapy remains challenging (see Chapter 6, p. 207).
3. *Myopathies.* The skeletal muscle myopathy found in heart failure is associated with increased proton production that stimulates the ergoreflexes that worsen the symptoms of exertional intolerance.[44] The causes of the myopathy are not clear. Increased circulating angiotensin II may play a role. Clinical studies with ACE inhibitors or ARBs geared to this problem are still lacking, yet may be very difficult to interpret because deconditioning may play a prominent role in the skeletal weakness in heart failure,[45] making exercise a more logical choice of therapy. In some patients there is a genetic link between heart failure and myopathy.[46] In a small study on Duchenne muscular dystrophy, perindopril decreased mortality at 10 years.[47]
4. *Anemia.* A low hemoglobin is a poorly understood risk factor for CVD.[48] A small decrease in hemoglobin to the order of 0.3 g/dL may occur and ACE inhibitors may be used therapeutically to treat the erythrocytosis that follows renal transplantation.[49] Attention should be paid to the possible development of anemia during ACE inhibitor therapy, especially because anemia is now recognized as an adverse risk factor in heart failure.[50] However, the development of anemia should generally not be attributed to an ACE inhibitor and other investigations should be pursued.

ACE inhibitors for hypertension

The RAAS is one of several major mechanisms that help to maintain the BP both in normal persons and in persons with essential hypertension, especially when sodium is restricted or diuretics are in use. In malignant hypertension or in renal artery stenosis, renal ischemia stimulates the release of renin from the juxtaglomerular apparatus to increase the BP. Although ACE inhibition leads to the most dramatic falls of BP in the presence of such an underlying renal mechanism, ACE inhibition is also effectively antihypertensive in mild to moderate hypertension even when plasma renin is not high. ACE inhibitors lower BP by multiple mechanisms (see Fig. 7-9). In general, ACE inhibitors are more effective in white patients who also respond to β-blockers.[51] Lesser BP efficacy in black patients, especially in older adults, can be overcome by addition of low-dose diuretics or higher doses of the ACE inhibitor. In the ALLHAT trial, the somewhat lesser efficacy of an ACE inhibitor than the diuretic[23] may be ascribed to (1) the trial design, which did not allow addition of a diuretic; and (2) the relatively high proportion of black patients, approximately one third of the study population, in whom the lack of diuretic was more serious. In the Australian study on older white subjects, enalapril gave overall better results than did the diuretic at equal BP control.[52] Because ACE inhibitors do not alter glucose tolerance, blood uric acid, or cholesterol levels with few side effects apart from cough, their use in hypertension has rapidly increased. Their ideal combination may well not be with a diuretic, as often thought, but with a calcium channel blocker (CCB), as in the ACCOMPLISH study.[53]

Less new diabetes

Rather than precipitating diabetes, as may occur with diuretic or β-blocker therapy, ACE inhibitors may lessen the development of new diabetes in hypertensives,[50],[54-57] in heart failure,[58] and in those at risk of CVD.[19] Because similar protection is found with ARBs (see Fig. 7-7), the mechanism is likely to involve AT-1 receptor blockade. Note, however, in the DREAM study, ramipril decreased fasting blood glucose but not diabetes, perhaps because the study was only 3 years in duration.[59]

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ACE inhibitors for early-phase acute myocardial infarction or postinfarct left ventricular dysfunction or failure

ACE inhibition within 24 hours of onset of acute myocardial infarction

ACE inhibitors are given for overt LV failure or LV dysfunction[60-62] starting slowly on the first day.[63] The selective policy, favored by the authors, is to give ACE inhibitors to all high-risk patients: diabetics, those with anterior infarcts,[64] or tachycardia or overt LV failure. Logically, the sicker the patients, the greater the activation of the RAAS, and the better the expected result with the use of an ACE inhibitor. The selective policy receives a class 1A (highest) recommendation from the American Heart Association and American College of Cardiology, and is based on results from several major trials. For example, in nearly 19,000 patients in GISSI-3,[65] lisinopril reduced mortality at 6 weeks from the already low value of 7.1% in controls to 6.3%. Nondiabetics can also benefit, as found in an overview of nearly 100,000 high-risk patients with acute myocardial infarction (AMI).[66] Of note, the benefit of early ACE inhibition is not annulled by early administration of aspirin.[61] Nor is the benefit explained by reduction of infarct size, which is better accomplished by β-blockade.[67]

ACE inhibitors in postinfarct left ventricular dysfunction or clinical failure

ACE-inhibitors attenuate LV remodeling and reduce the risk of subsequent MI (Fig. 5-9). If ACE inhibitors have not been started within 24 hours of the onset of AMI, then the next opportunity is a few days later. Three major trials used rather different entry criteria, one being clinical[60] and two based on LV functional measurements.[34],[62] All three showed major mortality reduction. Long-term follow-up in AIRE found that all-cause mortality was reduced by 36% with an absolute reduction of 11.4%.[68] In a 6-year follow up to the TRACE study,[69] the mean prolongation of life was 15.3 months. These impressive data strongly argue for the prolonged use of ACE inhibitors in postinfarct patients with clinical or echocardiographic LV failure, noting that the survival benefit observed was similar in those with or without pulmonary congestion, including those with asymptomatic LV dysfunction.[34],[60],[62]

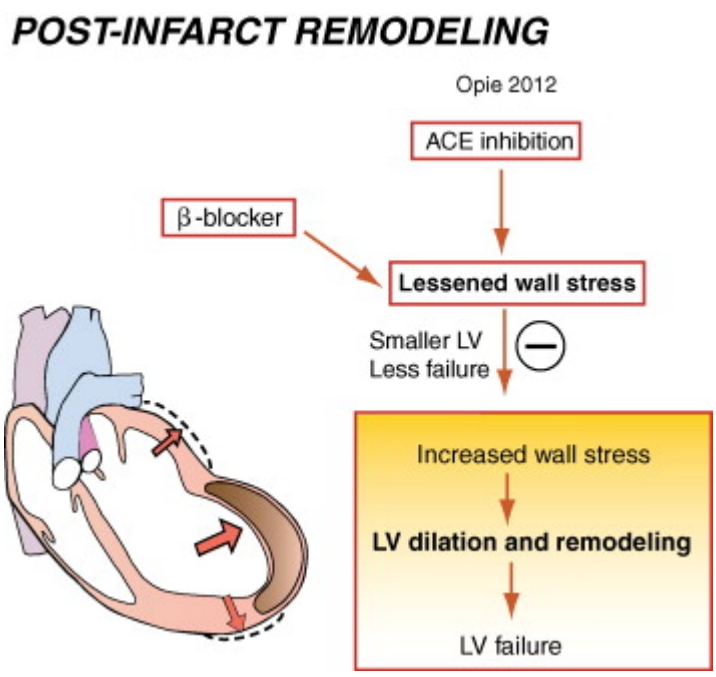
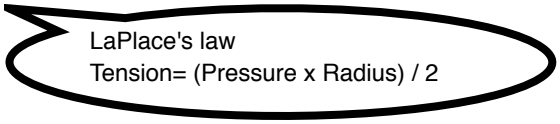


Figure 5-9 Postinfarction remodeling. Increased wall stress promotes adverse remodeling and left ventricular (LV) failure by Laplace's law (see equation). The proposal, based on substantial animal data and human studies, is that angiotensin-converting enzyme (ACE) inhibition will attenuate postinfarct LV enlargement and promote beneficial remodeling with better LV mechanical function.

(Figure © L.H. Opie, 2012.)



ACE inhibitors: Long-term cardiovascular protection

Do ACE inhibitors as a group protect against coronary heart disease? One argument is that high-risk patients are better protected.[70] Dagenais and colleagues argue that the protection extends even to low-risk groups.[71] The background to this controversy is as follows. The metaanalysis of three major ACE-inhibitor prevention trials, HOPE, EUROPA, and Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE), found an 18% reduction in the odds ratio for the combined outcomes of CV death, nonfatal MI, or stroke ($P < 0.0001$). The issue relates to the PEACE trial in which 8290 patients with stable coronary artery disease and normal or near-normal LV function were randomly assigned to 4 mg of trandolapril daily or to placebo.[72] There was a nonsignificant fall of 7% in the composite CV primary end-point, which, when merged with the larger reductions in HOPE and EUROPA, resulted in an overall decrease (odds ratio 0.82, cardiac index 0.76-0.88). These authors argue that all patients with vascular disease should receive an ACE inhibitor (in addition to other proven preventative measures such as other antihypertensives to control BP, antiplatelet agents, β-blockers, and statins). Note that in the PEACE trial trandolapril did reduce total mortality in a higher risk group with impaired renal function, supporting the alternate theory that ACE inhibitors give protection in relation to the degree of risk.[73] We believe that the overall data support use of an ACE inhibitor incrementally to lower vascular risk.

ACE-inhibitors are not direct antianginal agents. It must be emphasized that these agents only have an indirect antiischemic effect by lessening the afterload on the myocardial oxygen demand[74] by decreasing adrenergic activation, and by improving endothelial function. They are not antianginals.[75] In the long term, they reduce the need for coronary bypass grafting but not for percutaneous coronary intervention (PCI).[71] Although coronary surgery activates neurohumoral mechanisms that could be improved by ACE inhibition, when added early after surgery, quinapril unexpectedly increased rather than decreased CV events within the first 3 months.[76] However, this finding with a lesser used ACE inhibitor has never been confirmed.

Diabetes: Complications and renoprotection

In patients with diabetes, the BP goals are lower than in nondiabetics. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends a goal BP of 130/80 mm Hg. Both diabetes (type 2, maturity onset, noninsulin-dependent) and hypertension are associated with insulin resistance. Both high-dose thiazides and β-blockers can impair insulin sensitivity in nondiabetic hypertensives. Therefore there are arguments for the use of ACE inhibition or an ARB,[77] often with a CCB and diuretic.

The accord studies

The ACCORD trials examined whether ultra-intense CV risk factor reduction could improve clinical outcomes. To improve on the impressive baseline control of risk factors in the patients assigned to standard therapy in ACCORD was a formidable task, illustrating the synergistic effects of the multifactorial risk-reduction regimen. The respective intense arms achieved a more than 1% absolute difference in hemoglobin A_{1C}, a 14.2-mm Hg lower systolic pressure, and plasma triglycerides of approximately 145 mg/dL. For each of the three separate questions—further reduction of BP, glycemia, or triglycerides—the primary clinical composite was not significantly reduced despite the more intense therapies, as assessed in a Circulation editorial.[78]

Diabetes and steatosis

Impaired glucose tolerance is accompanied by cardiac lipid loading (steatosis) preceding the onset of type 2 diabetes mellitus and LV systolic dysfunction as shown in human cardiac myocytes.[79] There have been no studies with ACE inhibitors or ARBs in such patients.

Diabetics with nephropathy

In type 1 diabetic nephropathy, ACE inhibitors have repeatedly been shown to reduce proteinuria and protect against progressive glomerular sclerosis and loss of renal function.[77] In type 2 diabetic nephropathy, four trials with ARBs have shown similar renal protection.[77] Evidence-based guidelines therefore suggest ACE inhibitors for type I and ARBs for type 2 diabetic renal disease.[80] The strong likelihood is that ACE inhibitors would be as effective in type 2 patients if they had been tested, so in practice ACE inhibitors are used whenever ARBs cannot be afforded. They often have to be combined with other drugs, including diuretics, β-blockers, and CCBs to reduce the BP to less than 130/80 mm Hg.

Diabetic microalbuminuria

Microalbuminuria is one of the strongest predictors of both adverse renal and CVD outcomes in patients with type 2 diabetes mellitus. Current guideline recommendations are to screen for urinary albumin excretion (UAE) in all patients with type 2 diabetes, even in the absence of nephropathy. In a 10-year follow study, serial UAE measurements even after the initiation of antihypertensive therapy were found to have prognostic value independent of traditional CV risk factors.[81] ACE inhibition delays the onset of microalbuminuria, which is the initial step from normoalbuminuria toward potentially lethal nephropathy.[82] In MICRO-HOPE, in which ramipril reduced the development of overt nephropathy and all-cause mortality both by 24%, one entry criterion was diabetes with microalbuminuria, yet without macroalbuminuria.[83]

Diabetic albuminuria

VA NEPHRON-D is a randomized, double-blind, multicenter clinical trial in progress to evaluate whether combined ARB-ACE inhibitor therapy might benefit patients with diabetes and overt albuminuria (more than 300 mg/g creatinine). The study is assessing losartan 100 mg plus lisinopril 10-40 mg, versus losartan alone, on the progression of kidney disease in patients with diabetes and overt proteinuria.[84]

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ACE inhibition for nondiabetic renal failure

In progressive renal failure, from whatever cause, there is a steady rise in serum creatinine, a fall in glomerular function, and increasing proteinuria. Angiotensin II may play a crucial role in the progression of glomerular injury and the growth and destruction of the glomeruli (Fig. 5-10). Using the combined data of the RENAAL and IDNT trials, across all systolic blood pressure (SBP) ranges, a progressively lower CV risk was observed with a lower albuminuria level.[85] This was particularly evident in patients who reached the guideline recommended SBP target of 130 mm Hg or less. Therapies intervening in the RAAS with the aim of improving CV outcomes may therefore require a dual approach separately targeting both BP and albuminuria.

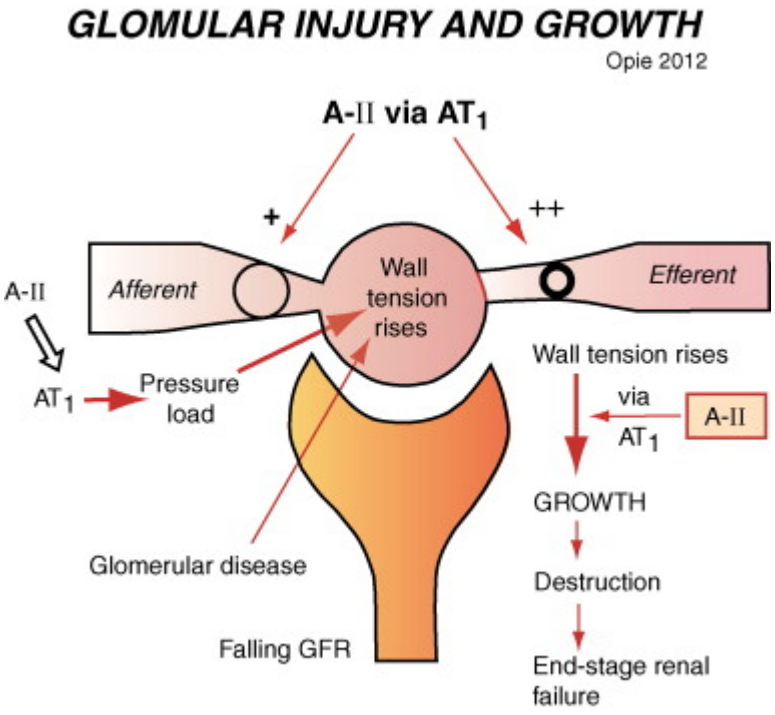

Figure 5-10 Role of angiotensin II and AT-1 receptor in glomerular injury and progressive renal failure. An increased intraglomerular pressure as from a pressure load in hypertension or primary renal disease or diabetes can evoke mesangial growth with threat of complete glomerular closure. Angiotensin II may be an important growth signal accelerating the disease process.
(Figure © L.H. Opie, 2012, and adapted from Angiotensin-Converting Enzyme Inhibitors. The Advance Continues, 3rd ed, Authors' Publishing House, New York & University of Cape Town Press, 1999.)

Ramipril in overt proteinuria

To the RENAAL and IDNT trials must be added the very impressive Ramipril Efficacy in Nephropathy (REIN) study and its long-term follow up.[86] In the initial core study, patients with proteinuria of more than 3 g per 24 hr were selected. Ramipril reduced the rate of GFR decline more than expected from the BP drop. In the follow-up study, those who were originally allocated to nonramipril therapy and then switched to ramipril at the end of the initial core study never caught up with those kept on ramipril from the start. This occurred even though the BP reduction in the switched group was greater than in those who stayed on ramipril throughout.

Studies of kidney disease and hypertension in black patients

Despite a lack of compelling evidence, numerous guidelines recommend a reduced BP target in patients with chronic kidney disease. In observational studies, the relationship between BP and end-stage renal disease (ESRD) is direct and progressive. The burden of hypertension-related chronic kidney disease and ESRD is especially high among black patients. Does intensive BP control retard the progression of chronic kidney disease among black patients? In 1094 black patients with hypertensive chronic kidney disease receiving either intensive or standard BP control, follow-up ranged from 8.8 to 12.2 years. Intensive BP control had no effect on kidney disease progression.[87] Intensive BP control had no effect on kidney disease progression. However, there was a potential benefit in patients with a protein/creatinine ratio of more than 0.22 (hazard ratio, 0.73; P = 0.01). Some earlier studies at earlier stages of renal disease were more promising. With the entry point as established hypertension with a low GFR, rather than end-stage renal failure,[88] ramipril-based therapy was more effective than amlodipine at equal BP levels in reducing the clinical endpoints, including dialysis and proteinuria. The greater renoprotection with the ACE inhibitor was independent of the BP reduction and despite the high serum creatinine. Importantly, fewer ACE inhibitor–treated black patients ended up on dialysis.[89]

Properties of specific ACE inhibitors

Captopril, the grand daddy

Captopril (Capoten, Lopril in France, Lopirin in Germany, and Captopril in Japan), the first widely available ACE inhibitor and available as a generic, was originally seen to be an agent with significant and serious side effects such as loss of taste, renal impairment, and neutropenia. Now it is recognized that these are rather rare side effects that can be avoided largely by reducing the daily dose and practicing appropriate monitoring. Captopril is widely licensed in the United States for hypertension, heart failure, postinfarct LV dysfunction, and type 1 diabetic nephropathy. It is the best-studied ACE inhibitor and has the widest range of approved indications. In the United Kingdom, it is also licensed for prevention of reinfarction and for diabetic microproteinuria. Pharmacokinetically, it belongs to a specific pattern, namely a molecule that is active as it is, but is further metabolized in the liver to active metabolites. After absorption from the stomach, captopril is largely excreted by the kidneys, approximately half as is and half as active metabolites formed in the liver and kidney. The elimination half-life is approximately 4 to 6 hours (Table 5-4). In hypertension, its biologic half-life is long enough to allow twice-daily dosage. *Of note, captopril, when optimally dosed, has never been bettered by other RAS blockers.*

Table 5-4 -- Summary of Pharmacologic Properties, Clinical Indications, and Doses of ACE-Inhibitors

Drug	Zinc Ligand	Active Drug	Elim T½ (hours)	T/P Ratio % (FDA)	Hypertension (usual daily dose)	Heart Failure or Postinfarct, Target Doses Used in Large Trials
Class I: Captopril-like						
Captopril	SH	Captopril	4-6 (total captopril)	—	25-50 mg 2× or 3×	50 mg 3×
Class II: Prodrugs						
Alacepril	Carboxyl	Captopril	8 (total captopril)	—	12.5-25 mg 2×	Not established
Benazepril	Carboxyl	Benazeprilat	11	—	10-80 mg in 1-2 doses	Not established
Cilazapril	Carboxyl	Cilazaprilat	9	—	2.5-5 mg 1×	Not established
Delapril	Carboxyl	Delaprilat 5-OH-delaprilat	1.2-1.4	—	7.5-30 mg in 1-2 doses	Not established
Enalapril	Carboxyl	Enalaprilat	6; 11 (accum)	—	5-20 mg in 1-2 doses	10 mg 2×
Fosinopril	Phosphoryl	Fosinoprilat	12	50-80	10-40 mg 1× (or 2×	Not established
Perindopril	Carboxyl	Perindoprilat	3-10	75-100	4-8 mg 1×	Not established
Quinapril	Carboxyl	Quinaprilat	1.8	50	10-40 mg in 1-2 doses	Not established
Ramipril	Carboxyl	Ramiprilat	13-17	50-60	2.5-10 mg in 1-2 doses	5 mg 2×
Spirapril	Carboxyl	Spiraprilat	<2	—	3-6 mg 1 dose*	Not established
Trandolapril	Carboxyl	Trandoprilat	10	50-90	0.5-4 mg 1× then 4 mg 2×	4 mg 1×
Class III: Water-soluble						

Drug	Zinc Ligand	Active Drug	Elim T½ (hours)	T/P Ratio % (FDA)	Hypertension (usual daily dose)	Heart Failure or Postinfarct, Target Doses Used in Large Trials
Lisinopril	Carboxyl	Lisinopril	7; 12 (accum)	—	10-40 mg 1× (may need high dose if given 1×)	10-35 mg 1×

Data based on FDA-approved information if available.

accum, Accumulation half-life; *Elim T½,* elimination half-life; *FDA,* Food and Drug Administration; *T/P ratio,* trough/peak ratios, FDA-approved values.

* Thurmann PA, *Hypertension,* 1996;28:450.

Dose and indications

In *hypertension,* captopril has an average daily dose of 25 to 50 mg orally given twice or three times daily (instead of much higher previous doses). The risk of excess hypotension is highest in patients with high renin states (renal artery stenosis, preexisting vigorous diuretic therapy, severe sodium restriction, or hyponatremia) when the initial dose should be low (6.25 to 12.5 mg). In *CHF,* during initiation captopril may cause excessive hypotension, especially in vigorously diuresed patients so that a test dose of 6.25 mg may be required, followed by 12.5 mg three times daily, and working up to 50 mg three times daily as tolerated. The diuretic may have to be stopped prior to captopril to avoid an excess renin state. In *postinfarct patients with LV dysfunction* (ejection fraction 40% or less), captopril is licensed to improve survival and prevent overt heart failure and, in the United Kingdom, to reduce recurrent MI and coronary revascularization procedures. In VALIANT, valsartan was noninferior to captopril.[90] In *diabetic nephropathy,* captopril improves proteinuria and decreases hard end-points, such as death, transplantation, or dialysis. However, captopril is largely renal excreted, so doses should be reduced as in *renal disease*.

Contraindications

Contraindications include bilateral renal artery stenosis; renal artery stenosis in a single kidney; immune-based renal disease, especially collagen vascular disease; severe renal failure (serum creatinine >3 mg/dL or >265 µmol/L [see p.128 for renal side-effects of ACE-inhibitors); preexisting neutropenia; and systemic hypotension. Pregnancy is an absolute contraindication for all ACE inhibitors for all trimesters.[29]

Side effects

In general, the serious side effects initially described are seldom found today when the total daily dose is 150 mg daily or less. Cough is the most common side effect with all ACE inhibitors. Other class side effects include transient renal failure, angioedema, and hyperkalemia. Immune-based side effects are probably specific to captopril and found especially with high doses. These are taste disturbances, immune-based skin rashes, and neutropenia (<1000/mm[3]). The latter is extremely rare in hypertensive patients with normal renal function (1/8600 according to the package insert), more common (1/500) with preexisting impaired renal function with a serum creatinine of 1.6 mg/dL or more, and is a grave risk (1/25) in patients with both collagen vascular disease and renal impairment. When captopril is discontinued, recovery from neutropenia is usual except when there is associated serious disease, such as severe renal or heart failure or collagen vascular disease. *Proteinuria* occurs in approximately 1% of patients receiving captopril, especially in the presence of preexisting renal disease or with high doses of captopril (>150 mg/day). Paradoxically, captopril is used in the therapy of diabetic type 1 nephropathy with proteinuria. *Other side-effects* include hypotension (frequent in the treatment of CHF), impaired taste (2% to 7%), skin rashes (4% to 10%) sometimes with eosinophilia, and rarely, as with all ACE inhibitors, serious angioedema (1/100 to 1/1000).

Pretreatment precautions

Bilateral renal artery stenosis and pregnancy must be excluded as far as possible. Patients with renal impairment caused by collagen disease, or patients receiving immunosuppressives or immune system

modifiers such as steroids. Pretreatment hypotension excludes therapy.

Precautions during treatment

Regular monitoring of neutrophil counts is required in patients with preexisting serious renal impairment, especially on the basis of collagen vascular disease (pretreatment count, then twice-weekly counts for 3 months). The risk of renal damage from captopril is much reduced by limiting total daily doses to 150 mg/day, as is now standard practice.

Enalapril

Enalapril (Vasotec in the United States; Innovace in the United Kingdom; Xanef, Renitec, or Pres in Europe; Renivace in Japan) is the standard prodrug, and is also available as a generic. The major trials showing clinical benefit have been in heart failure and in hypertension for which it was at least as good as and in some ways better than, a diuretic.[52] The chief differences from captopril are (1) a longer half-life; (2) a slower onset of effect because of the requirement of hydrolysis in the liver of the pro-drug to the active form, enalaprilat, so that the therapeutic effect depends on hepatic metabolism (see Table 5-4); and (3) the absence of the sulfhydryl (SH) group from the structure, thus theoretically lessening or removing the risk of immune-based side effects. Enalapril is approved for hypertension, heart failure, and to decrease the development of overt heart failure in asymptomatic patients with LV dysfunction (ejection fraction equal to or less than 35%). In the latter group of patients, enalapril is also licensed in the United Kingdom to prevent coronary ischemic events.

Pharmacokinetics

Approximately 60% of the oral dose is absorbed with no influence by meals. Enalapril is deesterified in the liver and kidney to the active form, enalaprilat (see Table 5-4). Time to peak serum concentration is approximately 2 hours for enalapril, and approximately 5 hours for enalaprilat, with some delay in CHF. Excretion is 95% renal as enalapril or enalaprilat (hence the lower doses in renal failure). The elimination half-life of enalaprilat is approximately 4 to 5 hours in hypertension and 7 to 8 hours in CHF. Following multiple doses, the effective elimination half-life of enalaprilat is 11 hours (package insert). One oral 10-mg dose of enalapril yields sufficient enalaprilat to cause significant ACE inhibition for 19 hours. In hypertension and in CHF, the peak hypotensive response to enalapril occurs approximately 4 to 6 hours after the oral dose.

Dose and indications

In hypertension, the dose is 2.5 to 20 mg as one or two daily doses. In some patients the effect wanes over 24 hours so that twice-daily dosing may be better. Doses higher than 10 to 20 mg daily give little added benefit. A low initial dose (2.5 mg) is a wise precaution, especially when enalapril is added to a diuretic or the patient is salt-depleted, in older adults, or when high-renin hypertension is suspected. *In asymptomatic LV dysfunction and in CHF,* in the SOLVD trials,[35],[50],[91] enalapril was started with an initial dose of 2.5 mg twice daily and worked up to 10 mg twice daily (mean daily dose 17 mg). *In renal failure* (GFR less than 30 mL/min), the dose of enalapril must be reduced. In severe liver disease, the dose may have to be increased (impaired conversion of enalapril to enalaprilat). In early-phase AMI, within 24 hours of symptoms, an initial dose of only 1.25 mg at 2-hour intervals for three doses was followed by 5 mg three times daily with long-term benefits.

Contraindications, precautions, and side effects

Pregnancy is a clear contraindication to all ACE inhibitors (and ARBs) (see previous discussion of captopril). In hypertensives, bilateral renal artery stenosis or stenosis in a single kidney must be excluded.

Precautions

To avoid the major risks of excess hypotension, use a low initial dose and evaluate pretreatment renal function and drug co-therapy, including diuretic dose. It is presumed that enalapril, without the SH group found in captopril, does not produce the same immune-based toxic effects. Thus monitoring of the neutrophil count is not essential.

Side effects

Cough is most common, as for all ACE inhibitors. Enalapril may be safer when captopril has induced a skin rash. As for all ACE inhibitors, angioedema is a rare but serious risk,[24] as highlighted in the package insert.

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Other prodrugs

Benazepril (*Lotensin* in the United States) is rapidly converted to an active metabolite, benazeprilat, with an elimination half-life of 22 hours (see Table 5-4). However, the trough/peak ratio is only 0.4, less than the ideal ratio of 0.5 that the FDA recommends for once-daily antihypertensive agents. The optimal dose in hypertension is 10 mg twice daily. In the influential ACCOMPLISH trial in hypertension, benazepril once daily combined with the long acting CCB amlodipine gave better CV protection than when combined with a diuretic (see Chapter 7, p. 244).

Fosinopril (*Monopril* in the United States, *Staril* in the United Kingdom) differs from other ACE inhibitors in that it uses phosphinic acid as the zinc ligand. In common with most ACE inhibitors, it is a prodrug (see Table 5-4), yet has unique pharmacokinetic features in that there are dual routes of excretion, hepatic and renal. In chronic renal failure the active fosinoprilat form accumulates less in the blood than would enalaprilat or lisinopril. In older adults, the major reason for decreasing doses of other ACE inhibitors is renal impairment. In the case of fosinopril, no dosage adjustment is required. It has not been widely tested. In one large clinical trial, 40 to 80 mg fosinopril once daily was antihypertensive, and an additional diuretic was required in approximately half the patients. Compared with amlodipine, it was less antihypertensive but reduced plasminogen activator inhibitor-1 antigen, which amlodipine did not.[92]

Perindopril (*Coversyl* in the United Kingdom, *Aceon* in the United States; 4 to 8 mg once daily for hypertension) is converted to perindoprilat, which is moderately long acting (see Table 5-4) with a good peak/trough ratio. Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA) compared the effects on major hypertension outcomes of amlodipine versus atenolol.[93] The trial was prematurely stopped because of an 11% reduction in all-cause mortality in the amlodipine-perindopril arm compared with the atenolol-diuretic arm. (For overall benefits, see Chapter 7, p. 243.) In CHF, the effect of a first dose of 2 mg is well documented and appears to cause little or no hypotension, in contrast to low-dose enalapril or captopril.[94] This interesting property warrants further study. Perindopril was used in PROGRESS, a large trial aimed at prevention of repeat stroke. Unexpectedly, despite BP reduction the ACE inhibitor did not reduce stroke unless combined with a diuretic.[95] In EUROPA, a large prophylactic trial in those with stable coronary artery disease, perindopril 8 mg daily resulted in a 20% lowering of major CV effects. In the HYVET trial on older persons with hypertension (see Chapter 4, p. 103 and Chapter 7, p. 241) the initial mean BP was 173/91 mm Hg. The addition of perindopril 2 mg to the diuretic indapamide roughly doubled the percentage with a controlled BP (SBP <150 mm Hg) with a further doubling by increasing the perindopril dose from 2 to 4 mg daily.[96] In the large ADVANCE trial on more than 11,000 persons, combined BP lowering based on perindopril-indapamide plus intensive glucose control reduced macrovascular and microvascular outcomes and mortality in patients with type 2 diabetes.[97] Perindopril is licensed by the FDA “to reduce the risk of cardiovascular mortality or nonfatal MI in patients with stable coronary heart disease.”

Quinapril (*Accupril* in the United States; *Accupro* in the United Kingdom) works through conversion to active but short-acting quinaprilat, which activates the parent molecule (see Table 5-4). In *hypertension*, the dose recommended in the package insert is initially 10 mg/day given once or twice daily up to a maximum of 80 mg/day. Dosage should be adjusted by measuring both the peak response (2-6 hr after the dose) and the trough (before the next dose). When combined with a diuretic, the initial dose may be reduced to 5 mg/day (package insert). In *CHF,* the initial dose of 5 mg twice daily is titrated upward to the usual maintenance dose of 10 to 20 mg twice daily (package insert). Mortality data are not available. *Impaired endothelial function* in normotensive patients with coronary artery disease could be reversed by 6 months of therapy with quinapril, 40 mg once daily.[98] However, the study was not large enough to provide clinical outcome data.

Ramipril (*Altace* in the United States, *Ramace, Tritace* elsewhere) is a very well-studied agent, active via transformation to ramiprilat, is a long-acting (see Table 5-4) antihypertensive in a dose of 2.5 to 20 mg in one or two daily doses. It is also licensed for post-MI heart failure (dose 12.5 to 5 mg twice daily) and for CV

protection (see later in this chapter). It is proposed as a relatively tissue-specific ACE inhibitor. *In anterior AMI,* the ramipril dose in the HEART study was 1.25 mg on the first day, then 2.5 mg at 12 hr, then uptitrated at 24-hr intervals to a full dose of 10 mg/day.[63] In early postinfarct heart failure in the AIRE study,[60] ramipril 2.5 mg twice daily and then 5 mg twice daily, as tolerated, was used to show a major reduction (27%) in mortality of patients with diagnosed clinically. The mortality benefit was maintained over a 5-year follow-up.[68] It is also the drug used in the REIN nephropathy study to show an excellent long-term benefit (see previous section on renal failure). In the landmark prophylactic HOPE trial,[19] ramipril given to high-risk patients, starting with 2.5 mg daily and working up to 10 mg once daily at night, gave markedly positive results, including reduction in all-cause mortality. As a result of this study, the extensive cardioprotective license given to ramipril in the United States is to reduce the risk of MI, stroke and death from CV causes in those at high risk, which is defined as age 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other risk factor (hypertension, high total cholesterol or low high-density lipoprotein cholesterol, cigarette smoking, or microalbuminuria). The dose is 2.5 mg, 5 mg, and then 10 mg once daily (for prophylaxis, given at night).

In the ONTARGET studies, which included more than 25,000 persons, the ARB telmisartan was not palpably superior to this proven dose of ramipril and had equivalent effects on major CV outcomes in patients judged to be at high CV risk.[99],[100]

Trandolapril (Mavik), after conversion to trandolaprilat, has one of the longer durations of action (see Table 5-4). It has been studied in one positive postinfarct trial[62] and in a large prophylactic trial (PEACE) in those with stable coronary artery disease in which it did not reduce the primary mortality end-point.[101] These patients had predominantly preserved ejection fractions (pEFs) (mean 58%) and trandolapril decreased the risk of new heart failure.[102]

In hypertension, the initial dose is 1 mg daily in nonblack patients and 2 mg daily in black patients (packet insert). Most patients require 2-4 mg once daily. If once-daily dosing at 4 mg is inadequate, twice-daily divided dosing may be tried, or the agent combined with a diuretic (trandolapril-verapamil [Tarka]). *In postinfarct heart failure or LV dysfunction* (US license) the package insert recommends an initial dose of 1 mg going up to 4 mg. *In older adults* with normal renal function, dose adjustment is not needed. *In chronic renal failure*, despite the predominant biliary excretion, there is some accumulation of trandolaprilat. The initial dose should be reduced to 0.5 mg daily when the creatinine clearance falls to less than 30 mL/min or in hepatic cirrhosis (US package insert). In *type 2 diabetes* with hypertension and normoalbuminuria, trandolapril decreased the rate of development of new microalbuminuria in the BENEDICT study.[82]

Zofenopril contains an SH group and is metabolized to zofenoprilat, a powerful antioxidant.[103] The dose in the SMILE study on severe AMI was 7.5 mg initially, repeated after 12 hours, then doubled to a target of 30 mg twice daily.[64] During 48 weeks of follow up there was a 29% reduction in the risk of mortality.

Lisinopril: Not metabolized

Lisinopril *(Zestril, Prinivil)* is approved for hypertension, CHF, and AMI in the United States and United Kingdom, and also for diabetic nephropathy in the United Kingdom. It differs from all the others in its unusual pharmacokinetic properties (see Table 5-4). It is not a prodrug, it is not metabolized by the liver, it is water-soluble, and it is excreted unchanged by the kidneys (reminiscent of the kinetic patterns of water-soluble β-blockers). Therefore it can be given a class of its own, Class III. The half-life is sufficiently long to give a duration of action exceeding 24 hours. Once-daily dosing for *CHF* is licensed in the United States. The initial dose is 2.5 to 5 mg in heart failure, and the maintenance dose is 5 to 20 mg per day. *In hypertension,* the initial dose is 10 mg once daily and the usual dose range is 20 to 40 mg per day. In *renal impairment* and in *older adults*, the dose should be reduced. Lisinopril was the drug used in the GISSI-3 mega-study in acute-phase AMI[65] and in the Assessment of Treatment with Lisinopril and Survival (ATLAS) study. The latter study in CHF showed modest benefits for even higher doses of lisinopril (35 mg daily or more) than those usually used.[104] In the ALLHAT antihypertensive study, lisinopril was compared with a diuretic and a CCB and, unexpectedly, failed to reduce the development of heart failure when compared with the diuretic[23] (for reasons, see this chapter, p.134).

Choice of ACE inhibitor

In general, we see little advantage for any one agent compared with others. But when a specific ACE inhibitor is very well tested in a major outcome trial, we are more sure of the dosage of that drug for that indication. All those tested work in hypertension and heart failure. However, some drugs are much better for specific situations than others. *Captopril*, the first agent available, is now much less used than before despite its wide range of approved indications, probably in part because it requires three daily doses. In postinfarct heart failure or LV dysfunction, it gave protection from death equal to the ARB valsartan,[90] and is much cheaper. Not being a prodrug, it has a rapid onset of action, thus creating the risk of hypotension especially in heart failure. Note that captopril in high doses may incur the risk of certain side effects specific to the SH group, including ageusia and neutropenia. *Enalapril* is very well tested for all stages of heart failure in several landmark studies including the CONSENSUS study, V-HeFT II, and the SOLVD studies (prevention and treatment arms), including the remarkable 12-year follow-up.[36] It is the drug with the best data on reduction of mortality in CHF. Yet (and this point is often forgotten) it is clearly not a once-a-day drug and was used twice daily (total dose 20 mg) in all these studies. *Ramipril* is especially well tested in (1) early postinfarct clinical heart failure, in which it reduced mortality substantially; (2) renoprotection; and (3) CV prophylaxis, for which it gave such striking results in the HOPE trial at a dose of 10 mg daily given in the evening. However, its BP reduction is not sustained over 24 hr.[105] *Perindopril* was the agent used in another important prophylactic study, EUROPA, on stable coronary artery disease, at a dose of 8 mg, higher than usual. Perindopril was also the partner to amlodipine in the highly successful hypertension trial, ASCOT (see Chapter 7, p. 243) and the partner to indapamide in the mortality-saving HYVET study. *Lisinopril* has simple pharmacokinetics, being water soluble with no liver transformation and renal excretion, making it an easy drug to use and understand. It is very widely used, especially in the Veteran's Administration system. There is no risk of hepatic pharmacokinetic interactions. Lisinopril has also been studied in several major postinfarct and heart failure trials.

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ACE inhibitors versus ARBs

Before we delve into ARBs, we may pause to reflect on the outstanding common mechanisms and benefits, with some differences in side-effects, of these two major groups of CV agents that both act on the RAS. They both inhibit the adverse pathogenic properties of angiotensin II (see Table 5-1).They both have a clear role in secondary prevention (see Table 5-3). They both have an impressive series of major outcome trials (Table 5-5). Furthermore, they have similar contraindications, with the major side-effect differences being the lower rate of cough and the virtual absence of angioedema with ARBs (Table 5-6). They both have impressive studies to their credit, many in the New England Journal of Medicine or The Lancet, the doyens of clinical journals (Tables 5-7 and 5-8). Their comparative properties are summarized in table format in Table 5-9. Between them, they have considerably expanded our vistas in cardiology, moving from therapy of established disease to prevention of disease development to management of CV risk factors (see Table 5-9). At the beginning of this chapter, we quoted Harvey White. That quotation can now be modified: "Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been shown to have the broadest impact of any drug in cardiovascular medicine."1

The story does not end there. The rapid expansion of interest in aldosterone blockers and now in the renin-blocker, aliskiren, means that the concept of RAS blockers has now turned to RAAS blockade, thereby providing an even more rigorous control of the RAAS system, which is essential for life, but far too often overactive.

Table 5-5 -- Major Outcome Trials with Renin-Angiotensin-Aldosterone Inhibitors

Renin-Angiotensin-Aldosterone Blocker	Risk Prevention	HPT (Stroke*)	Chronic Heart Failure	Heart Failure, Post-MI	AMI, Early Phase	Diabetic Nephropathy	Chronic Renal Disease
ACE Inhibitor							
Captopril		3 CAPP		33 SAVE		33 Type 1	3
Enalapril		33 ANBP2	33 SOLVD, V-HeFT, CONSEN-SUS				3
Lisinopril		3 ALLHAT	3 ATLAS		33 GISSI		
Perindopril	33 EUROPA	3 ASCOT					
Ramipril	33 HOPE			33 AIRE		33 MICRO-HOPE	33 REIN, AASK
Trandolapril	3 PEACE	3 INVEST		33 TRACE			
ARBs							
Candesartan			33 CHARM				
Eprosartan		33 MOSES*					
Irbesartan						33 IDNT, IRMA	

Renin-Angiotensin-Aldosterone Blocker	Risk Prevention	HPT (Stroke*)	Chronic Heart Failure	Heart Failure, Post-MI	AMI, Early Phase	Diabetic Nephropathy	Chronic Renal Disease
Losartan		33 with LVH, LIFE	?No ? 3 ELITE 1 & 2 (?dose too low)	No, OPTI-MAAL (?dose too low)		33 RENAAL	
Valsartan		33 VALUE3 JIKEI-heart	33 VAL-HeFT	33 VALIANT			
Aldosterone Antagonist							
Spironolactone			33 RALES				
Eplerenone				33 EPHE-SUS			

33 = Strongly indicated in opinion of authors; 3 = indicated; No = not indicated.

ACE, Angiotensin-converting enzyme; *AMI,* acute myocardial infarction; *ARB,* angiotensin receptor blocker; *HPT,* hypertension; *MI,* myocardial infarction.

* Recurrent stroke.

Table 5-6 -- ACE Inhibitors and ARBs: Side Effects and Contraindications

ACE Inhibitors: Side Effects, Class
• Cough—common • Hypotension—variable (care with renal artery stenosis; severe heart failure) • Deterioration of renal function (related in part to hypotension) • Angioedema (rare, but potentially fatal) • Renal failure (rare, risk with bilateral renal artery stenosis) • Hyperkalemia (in renal failure, especially with K-retaining diuretics) • Skin reactions (especially with captopril)
ACE Inhibitors: Side Effects First Described for High-Dose Captopril
• Loss of taste • Neutropenia especially with collagen vascular renal disease • Proteinuria • Oral lesions; scalded-mouth syndrome (rare)
ACE Inhibitors and ARBs: Shared Contraindications and Cautions
• Pregnancy all trimesters (NB: prominent FDA warning) • Severe renal failure (caution if creatinine > 2.5-3 mg/dL, 220-265 µmol/L) • Hyperkalemia requires caution or cessation • Bilateral renal artery stenosis or equivalent lesions • Preexisting hypotension • Severe aortic stenosis or obstructive cardiomyopathy • Often less effective in black subjects without added diuretic

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *FDA,* Food and Drug Administration; *K,* potassium.

Table 5-7 -- Cardiovascular Trials with ACE Inhibitors

Category	Acronym	Reference	Major Benefit
Hypertension	CAPPP	*Lancet* 1999;353:611–616[54]	Captopril vs usual BP drugs result in similar CV outcomes.
	ALLHAT	*JAMA* 2002;288:2981-2997[23]	Lisinopril vs diuretic vs amlodipine result in same primary CV outcomes and all-cause mortality.
	ANBP2	*N Engl J Med* 2003;348:583-592.[52]	ACE inhibitors in older hypertensive men result in better outcomes than diuretics.
Coronary Artery Disease and Vascular	HOPE	*N Engl J Med* 2000;342:145-153.[19]	
	EUROPA	*Lancet* 2003;362: 782-788.	Perindopril 8 mg daily reduced CV death, MI.
	PEACE	*N Engl J Med* 2004;351:2058-2068.[72]	Trandolapril did not alter major outcomes in stable CHD and preserved LV function with low rates of CV events.
	IMAGINE	*Circulation* 2008;117:24-31.[76]	In low-risk patients after CABG, early quinapril increased adverse events.
Myocardial Infarction	SAVE	*N Engl J Med* 1992;327:669-677.[34]	In asymptomatic LV dysfunction post-MI, captopril improved survival and reduced CV morbidity and mortality.
	CONSENSUS II	*N Engl J Med* 1992;327:678-684.	Enalapril within 24 hours of onset of AMI does not improve survival over 180 days.
	AIRE	*Lancet* 1993;342:821-828.[60]	Ramipril started 2nd-9th day in post-AMI patients with HF reduced all-cause premature deaths.
	GISSI-3	*Lancet* 1994;343:1115-1122.[65]	Lisinopril 5 mg initially, then 10 mg daily started within 24 hr from AMI symptoms, reduced mortality.
	SMILE	*N Engl J Med* 1995;332:80-85.[64]	Zofenopril for severe AMI initially 7.5 mg up to 30 mg twice daily reduced mortality risk by 29%.
	ISIS-4	*Lancet* 1995;345:669-685.	Captopril 6.25 mg initially titrated to 50 mg twice daily within 24 hr of the onset of suspected AMI reduced mortality by 7% in large study.
	TRACE	*N Engl J Med* 1995;333:1670-1676.[62]	Trandolapril long-term for systolic dysfunction after AMI reduced mortality by 22% and severe HF by 29%.
Heart Failure	CONSENSUS	*N Engl J Med* 1987;316:1429-1435.[182]	Enalapril added to conventional therapy for severe CHF reduced mortality by 31%.
	V-HeFT II	*N Engl J Med* 1991;325:303-310.[183]	Enalapril in HF vs hydralazine-isosorbide dinitrate resulted in 25% lower 2-year mortality.
	SOLVD	*N Engl J Med* 1992;327:685-691.[35]	Enalapril for asymptomatic LV dysfunction reduced heart failure and hospitalizations.
	PEP-CHF	*Eur Heart J* 2006;27:2338-2345.	Perindopril in older adults with HF improved symptoms and exercise capacity. Decreased HF hospitalizations.
			Study underpowered.

Cerebrovascular	PROGRESS	*Lancet* 2001;358:1033–1041[95]	In recurrent stroke study, perindopril plus indapamide reduced BP by 12.5 mm Hg and stroke risk by 43%.
Diabetes Prevention	DREAM	*N Engl J Med* 2006;355:1551-1562.[59]	Ramipril for 3 years given to persons with impaired fasting glucose levels or impaired glucose tolerance did not reduce the incidence of diabetes or death but increased regression to normoglycemia.
Diabetic Nephropathy	Collaborative Study Group	*N Engl J Med* 1993;329:1456-1462.[110]	Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is more effective than BP control alone.
	REIN	*Lancet* 1997;349:1857-1863.	Ramipril safely reduces proteinuria and the rate of GFR decline in chronic nephropathies with proteinuria of 3 g or more per 24 hr.
	ABCD	*N Engl J Med* 1998:338:645-652.	Enalapril for diabetes with hypertension gave a lower incidence of MI than nisoldipine over 5 years of follow-up, a secondary end point needing confirmation.
	AASK	*JAMA* 2001;285:2719-2728.[88]	Ramipril, compared with amlodipine in African Americans with hypertensive renal disease, retards progression of renal disease and proteinuria.

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ACE, Angiotensin-converting enzyme; *AMI,* acute myocardial infarction; *BP,* blood pressure; *CABG,* coronary artery bypass surgery; *CHD,* coronary heart disease; *CHF,* congestive heart failure; *CV,* cardiovascular; *GFR,* glomerular filtration rate; *HF,* heart failure; *LV,* left ventricular; *MI,* myocardial infarction.

Table 5-8 -- Cardiovascular Trials with ARBs

Category	Acronym	Reference	Major Benefit
Hypertension	SCOPE	*J Am Coll Cardiol* 2004 15;44:1175-1180.	Candesartan, 42% RR reduction in stroke in older adults.
	VALUE	*Lancet* 2004;363:2022-2031.[57]	Valsartan = amlodipine on composite cardiac mortality and morbidity.
Vascular	JIKEI	*Lancet* 2007;369:1431-1439.[184]	Valsartan added to conventional therapy reduced CV events.
	ONTARGET	*N Engl J Med* 2008;358:1547-1559.[100]	Telmisartan = ramipril for vascular events.
	TRANSCEND	*Lancet* 2008;372:1174-1183.	Telmisartan: less hospitalization for CV events.
	HIJ-CREATE	*Eur Heart J* 2009;30:1203-1212.	Although candesartan = non-ARBs, also less new-onset diabetes.
Myocardial Infarction	OPTIMAAL	*Lancet* 2002;360:752-760.	Losartan (50 mg daily) = captopril (50 mg thrice daily).
	VALIANT	*N Engl J Med* 2003;349:1893-1906.[90]	Valsartan = captopril in high risk for CV post-MI.

Category	Acronym	Reference	Major Benefit
Heart Failure	ELITE-II	*Lancet* 2000;355:1582-1587.	Survival in hypertensive older adults with HF. Losartan (50 mg daily) = captopril (50 mg thrice daily).
	Val-HeFT	*N Engl J Med* 2001;345:1667-1675.[116]	Valsartan added. Fewer hospitalized for HF.
	CHARM	*Lancet* 2003;362:759-766.	Chronic HF. Candesartan 32 mg daily: less CV deaths
	I-PRESERVE	*N Engl J Med* 2008;359:2456-2467.	HF preserved ejection fraction. Irbesartan 300 mg shows no benefit.
Cerebrovascular	PRoFESS	*N Engl J Med* 2008;359:1225-1237.	Telmisartan after ischemic stroke, no benefit.
Prediabetes	NAVIGATOR	*N Engl J Med* 2010;362:1477-1490.	Prediabetes with CV disease or risk factors. Valsartan: less new diabetes, unchanged CV events.
Diabetic Retinopathy	DIRECT	*Lancet* 2008;372:1394-1402.	Type 1 diabetes. Candesartan 16 mg daily: retinopathy incidence lower but progression not delayed.
Diabetic Nephropathy	RENAAL	*N Engl J Med* 2001;345:861-869.[147]	Losartan 50-100 daily. Reduced end-stage renal disease. Mortality unchanged.
	IDNT	*N Engl J Med* 2001;345:870-878.[141]	Irbesartan 300 mg daily reduced onset of diabetic nephropathy.
	ROADMAP	*N Engl J Med* 2011;364:907-917.	Olmesartan 40 mg daily delayed onset of microalbuminuria. Subgroup with preexisting coronary heart disease, higher CV deaths.
	VA-NEPHRON-D	*Clin J Am Soc Nephrol* 2009;4:361-368.[84]	Ongoing—results not yet reported.
Atrial Fibrillation	GISSI-AF	*N Engl J Med* 2009;360:1606-1617.	Valsartan did not reduce incidence of recurrent atrial fibrillation.
	ACTIVE-I	*N Engl J Med* 2011;364:928-938.	Irbesartan did not reduce CV events in patients with atrial fibrillation.

Created by Deepak K. Gupta and Marc Pfeffer.

ARB, Angiotensin receptor blocker; *CV,* cardiovascular; *HF,* heart failure; *MI,* myocardial infarction; *RR,* relative risk.

Table 5-9 -- Comparison of Some Properties of ARBs Versus ACE Inhibitors Relevant to Use in Hypertension

Property	ARB	ACE Inhibitor
Major site of block	AT-1 receptor	Converting enzyme
Major claims, basic science	More complete AT-1 block, AT-2 activity increased; latter may be beneficial (not certain)	Block of two receptors: AT-1, AT-2. Inhibition of breakdown of protective bradykinin
Side effects	Generally similar to placebo; cough unusual; angioedema very rare but reported (CHARM)[21]	Dry cough; angioedema higher in black (1.6%) than nonblack patients (0.6%), enalapril data from OCTAVE[24]
Licensed for hypertension?	Yes	Yes

Property	ARB	ACE Inhibitor
Compelling indications, modified from JNC 7[185]	Heart failure, diabetes, chronic renal disease, recurrent stroke (eprosartan)	As for ARB plus post-MI, high coronary risk, recurrent stroke (with diuretic)
Favored therapy in hypertension, European Guidelines[80]	ACE inhibitor—cough, HF, LVH, diabetes, renal disease or microalbuminuria, post-MI, metabolic syndrome	HF, LVH, diabetes, renal disease or microalbuminuria, post-MI, metabolic syndrome, asymptomatic atherosclerosis
Major clinical claims in hypertension	Equal BP reduction to ACE-inhibitors, little or no cough, excellent tolerability, well tested in LVH and in diabetic nephropathy	Well tolerated, years of experience especially in CHF, good quality of life; used in coronary prevention trials (HOPE, EUROPA, PEACE)
Effect on LVH vs β-blockers	Better (losartan, valsartan) Major outcome trial, LIFE[106]	Better (lisinopril, ramipril)
Effect on sex life vs β-blockers	Better	Better
Less new diabetes	Losartan, candesartan, valsartan	CAPPP,[54]STOP-2[56]
Outcome trials (death, stroke, coronary events, etc.)	LIFE (losartan better than atenolol, stroke less, deaths less in diabetics)[106]; VALUE (valsartan vs amlodipine; about equal); JIKEI-heart (valsartan)[185]	Enalapril > diuretic,[52] Diuretic > lisinopril in ALLHAT[23]

>, better than; *ACE,* angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *AT-1,* angiotensin II receptor, subtype 1; *BP,* blood pressure; *CHF,* congestive heart failure; *HF,* heart failure; *JNC,* Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; *LVH,* left ventricular hypertrophy; *MI,* myocardial infarction.

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ARBs

Because ACE inhibitors exert their major effects by inhibiting the formation of angiotensin II, it follows that direct antagonism of the receptors for angiotensin II should duplicate many or most of the effects of ACE inhibition. ARBs should largely avoid the bradykinin-related side effects of ACE inhibitors such as cough and angioedema. Hence the ARBs, the prototype of which is losartan, are being evaluated and used more and more in hypertension, heart failure, stroke prevention, and proteinuric renal disease, including diabetic nephropathy (Tables 5-8 and 5-9).

Use in hypertension

ARBs have the capacity to reduce BP with “an astonishing lack” of side effects, and in particular the absence or much lower incidence of cough and angioedema. In recent trials with hard end points such as end-stage renal failure in diabetic nephropathy and stroke in LVH, they have been better than comparators,[106],[107] with better reduction of stroke and heart failure (Table 5-8). They are already regarded as possible first-line therapy by the European guidelines, but not by the American JNC 7 committee, which nonetheless recognizes the following compelling indications for ARBs: heart failure, diabetes, and chronic kidney disease (see Chapter 7, p. 235). These are also recognized as compelling indications for ACE inhibitors, so that patient tolerability and price (higher for the ARBs than generic ACE inhibitors) are likely to be the deciding factors. Furthermore, systemic review of 50 studies comparing ACE inhibitors with ARBs revealed similar BP control and outcomes, yet with less cough and angioedema.[108] However, despite several comparisons, ARBs have not been superior to ACE inhibitors. Note that the established contraindications to ACE inhibitor therapy such as pregnancy and bilateral renal artery stenosis are the same for the ARBs.

Use in chronic renal disease, including diabetic nephropathy

ARBs have better supporting documentation for benefits in type 2 diabetes.[109] On the other hand, in type 1 diabetes, the ACE inhibitors have better evidence of benefit.[110] In neither situation are there direct comparisons between ARBs and ACE inhibitors. In proteinuric renal disease, with or without diabetes, ARBs and ACE inhibitors similarly reduced proteinuria.[111] A dual approach, targeting both BP and albuminuria, is required.[85]

Fewer cases of new diabetes

In hypertension, losartan was associated with fewer cases of new diabetes than atenolol,[112] candesartan was associated with fewer cases than hydrochlorothiazide (HCTZ),[113] and valsartan was associated with fewer cases than amlodipine.[57] In heart failure, there were fewer cases of new diabetes with candesartan than with placebo.[114] However, it must be cautioned that all these observations were secondary analyses. In the NAVIGATOR study of patients with impaired glucose tolerance and CVD or risk factors, administration of valsartan up to 160 mg daily for 5 years, plus lifestyle modification, reduced the incidence of diabetes by 14% without reducing the rate of CV events.[115]

Use in heart failure

Both ACE inhibitors and ARBs inhibit the RAAS and are now well tested in heart failure (see Table 5-9). The overall data from two major trials, Val-HeFT[116] and VALIANT,[114] show that ARBs give outcome results as good as ACE inhibitors (see Table 5-9). Therefore ARBs become a reasonable alternative for use in heart failure, not only in ACE inhibitor–intolerant patients for which the case for their use is very strong.[21] Major mechanistic arguments for using ARBs are the following: (1) Benefits of ARBs are bought almost without any costly side–effects, in particular a consistently lower incidence of cough and angioedema; (2) The adverse effects of major renin-angiotensin activation in heart failure are mediated by the stimulation by angiotensin II of the receptor subtype, AT-1, which the ARBs specifically block (Fig. 5-11); (3) Non-ACE paths may be of substantial importance in the generation of pathogenic angiotensin II;[4] (4) The AT-2

receptor is not blocked and can still respond to the increased concentrations of angiotensin II as result of the AT-1 receptor block. Unopposed AT-2 receptor activity may have benefits[117],[118] and harm.[119] However, the lack of clinical superiority of ARBs places in doubt the relevance of the experimental observations.

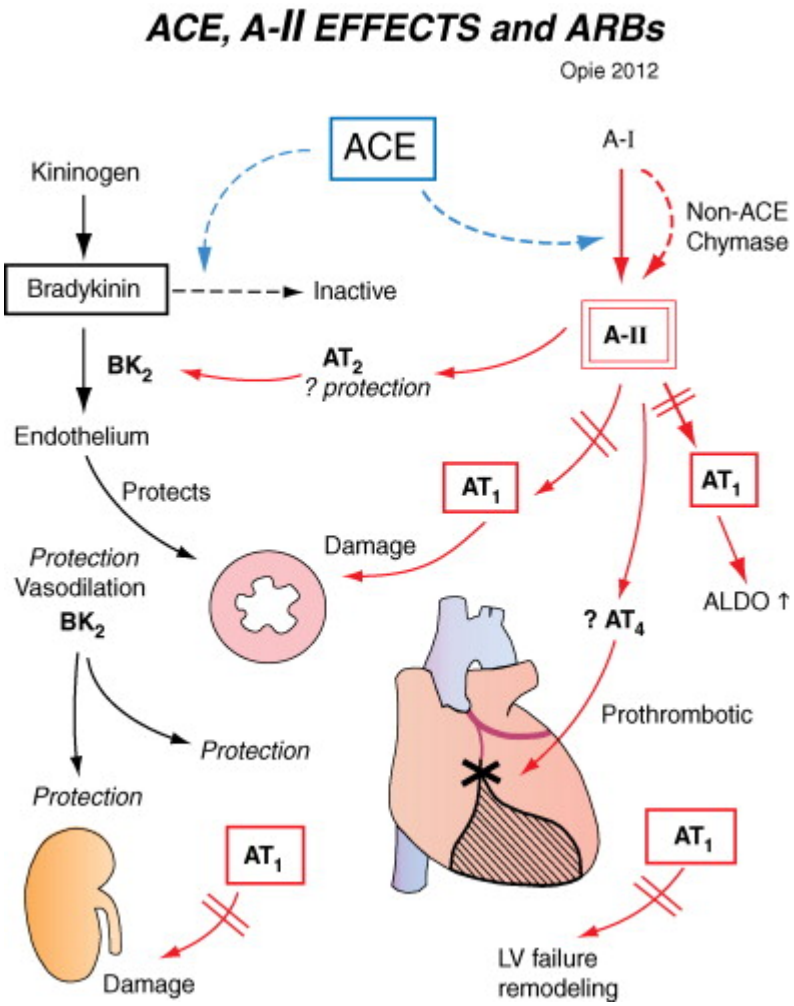

Figure 5-11 Mechanisms whereby angiotensin II (A-II) exerts adverse effects on the cardiovascular system. Most of the damaging effects are via the AT-1 receptor, with possible protection via the unopposed AT-2 receptor (see Fig. 5-3) that may unexpectedly lead to relatively small amounts of bradykinin (BK) formation. The putative AT-4 receptor may mediate prothrombotic effects. BK, formed especially during inhibition of angiotensin-converting enzyme (ACE) mediates protection by activation of the BK-2 receptor. *Double-slashed red lines* indicate effects of AT-1 receptor blockade. *Aldo,* Aldosterone.
(Figure © L.H. Opie, 2012, and adapted from Angiotensin-Converting Enzyme Inhibitors. The Advance Continues, 3rd ed, Authors' Publishing House, New York & University of Cape Town Press, 1999.)

Thus although ACE inhibitors remain the logical first-line therapy because of the vast experience with these agents in heart failure, including postinfarction LV dysfunction, this prime position is gradually being eroded by the better-tolerated ARBs.

Use in stroke

More than 25 years ago Brown hypothesized that angiotensin II could protect against strokes to explain the early trial observations that a diuretic better protected against stroke than a β-blocker.[120] Three recent trials support the Brown hypothesis. First, in PROGRESS an ACE inhibitor reduced BP but not repeat stroke unless combined with a diuretic.[95] Second, an ARB, eprosartan, reduced repeat stroke better than a CCB,[121] although CCBs are among the best medications for stroke prevention.[122] Third, losartan gave better protection from stroke in patients with LVH than did atenolol in the LIFE study.[106] Nonetheless, in an

overview of 12 trials on 94,338 patients, amlodipine was better at reduction of stroke and MI by 16% to 17% versus ARBs, possibly in part because of small differences in SBP or in aortic pressure.[122]

Nonissues with ARBs: Myocardial infarction and cancer

The *ARB-MI paradox* refers to the theoretical and unexpected proposal that ARBs may increase the risk of MI.[119] Because angiotensin II can be produced by non-ACE pathways (see Fig. 5-2), blocking at the receptor level by ARBs might be supposed to result in even greater reductions in the adverse actions of angiotensin II. Nonetheless, there was controversy about the effects on MI of ARBs versus ACE inhibitors, which was the subject of two articles with opposing views in *Circulation*.[119],[123],[124]

The controversy has been settled by the large and comprehensive analysis based on 37 randomized clinical trials including 147,020 participants with a total follow-up of 485,166 patient years.[125] This study firmly refutes the claim that ARBs increase the risk of MI (ruling out even a 0.3% absolute increase). ARBs reduce the risk of stroke, heart failure, and new-onset diabetes.

Another nonissue is the proposal that ARBs are associated with an increased incidence of cancer. Again, this stems from an inadequate assessment of all the data, and can be fully dismissed.[126]

Combinations of ACE inhibitor–ARB therapy

In heart failure, the outcome benefits of adding the ARB candesartan to an ACE inhibitor are recognized by the FDA-approved license. Some principles are as follows:[127]

1. Addition of a proven ARB such as candesartan or valsartan to established ACE-inhibitor therapy is associated with improved outcomes in CHF, perhaps by treating RAS escape from ACE inhibition.
2. Candesartan benefits can be found even in patients who are on higher-than-average ACE-inhibitor doses.[128] Candesartan can benefit when added to prior β-blockade,[127] whereas valsartan lacks such data.[116]
3. In patients with LV systolic dysfunction who remain symptomatic on ACE inhibitors and β-blockers, ARBs can give added benefit as an alternative to the addition of third-line aldosterone blockers.[127]
4. In those with an LV ejection fraction of 40% or more, retrospective analyses suggest that candesartan added to prior ACE inhibition, β-blockade, and aldosterone blockade could improve all-cause mortality.[129]

Such "quadruple therapy" may be offset by a marked increase in adverse effects, especially worsening renal function and hyperkalemia[130] and needs prospective trial testing. Additionally, note that the combination of an ARB with β-blockade has only been trial-supported with positive outcomes for candesartan.[114]

In chronic renal disease with proteinuria, the combination of an ARB with an ACE inhibitor reduces progression of proteinuria better than either drug alone according to an exhaustive review.[111] The accompanying editorial proposes that monotherapy with either an ACE inhibitor or an ARB is appropriate for early-stage renal disease, reserving the combination for use when monotherapy fails to decrease proteinuria to less than 0.5 g.[131] However, safety concerns remain, with hyperkalemia the major danger.[131] A more recent large observational analysis shows that the ACE inhibitor with ARB combination can be disappointing even for renal disease,[132] although the study confirms that, in addition to BP, an effect on albuminuria is a good marker for renal protection.[133] Overall, the arguments for dual therapy are much weakened by the ONTARGET and TRANSCEND investigators,[132] despite the criticisms of the study.[133]

Combined ACE inhibitor–ARB therapy provides **CV protection in high-risk persons.** The ONTARGET study tested the effects on high-risk persons of ramipril 10 mg daily compared with telmisartan 80 mg daily and with the combination.[100],[134] Telmisartan was not superior to ramipril, despite telmisartan 80 mg reducing BP better over 24 hr than ramipril 10 mg.[105] The combination produced unchanged CV outcomes, although it resulted in increased hypotension, syncope, and renal dysfunction. Thus this combination is not the gold standard for RAS inhibition, whereas renin blockade needs consideration.[135]

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Specific ARBs

Candesartan (atacand)

Pharmacologically, candesartan differs from other ARBs in that active candesartan is formed during the process of gastrointestinal absorption, with a somewhat longer half-life than losartan (Table 5-10). In *hypertension,* the usual starting dose is 16 mg once daily, lower in volume depletion, with a top dose of 32 mg daily, given in one or two doses according to the package insert. However, when given once daily (dose 16 mg) there is still at 48 hr about two thirds of the effect seen at 24 hr.[136] Note that full hypotensive effect may take several weeks.

Table 5-10 -- Comparison of ARBs and ACE Inhibitors in Heart Failure, CV Prevention, and Stroke

Property	ARB	ACE Inhibitor
HF: Licensed in United States	Valsartan for HF to reduce hospitalization; candesartan for class 2-4 HF with LV EF ≤40% to reduce CV deaths and hospitalization; may be added to ACEi.	Yes, several but not all.
Major clinical claims in heart failure	Use in ACEi-intolerant patients (CHARM-alternative); also when added to ACEi (CHARM-added).	Many studies with large database, at least 12,000 patients, definite mortality reduction of 20%, prevents reinfarction.
Post-MI: Major studies	VALIANT, valsartan noninferior to captopril in postinfarct heart failure.[90]	Several large studies, definite protection including LV dysfunction.
Diabetic nephropathy: Major claims	Renoprotective in type 2 diabetes independently of hypertension;[142],[147] slows progress of microalbuminuria.[141]	Renoprotective in type 1 diabetes independently of hypertension; slows development of microalbuminuria in diabetics.
Nondiabetic renal disease	Decreases proteinuria.	Better outcome, REIN, AASK.
Prevention of CV complications (MI, heart failure, stroke, or CV death)	ONTARGET evaluates telmisartan vs ramipril vs combination in HOPE-like study. TRANSCEND compares telmisartan with placebo.	HOPE, reduction of this primary end-point by 22%;EUROPA, reduction of MI and combined endpoints.
Prevention of stroke	LIFE, less stroke in LVH treated by losartan usually with diuretic versus atenolol; less repeat stroke with eprosartan in MOSES.	PROGRESS, less repeat stroke with perindopril only if with diuretic.
Major warnings	Pregnancy, all trimesters.	Pregnancy, all trimesters.
Additional warnings	Hypotension, hyperkalemia, renal function.	Angioedema, hypotension, hyperkalemia, renal function.

ACE, Angiotensin converting enzyme; *ACEi,* ACE inhibitor; *ARB,* angiotensin receptor blocker; *CV,* cardiovascular; *EF,* ejection fraction; *HF,* heart failure; *LV,* left ventricular; *LVH,* left ventricular hypertrophy; *MI,* myocardial infarction.

Candesartan was chosen in three large *heart failure* trials, the CHARM studies, at a target dose of 32 mg. In the CHARM-alternative trial, in patients with ACE inhibitor intolerance, candesartan significantly reduced the

combined endpoint of CV death or hospitalization for CHF by 23%, with less cough and angioedema than anticipated.[21] In CHARM-added,[137] candesartan added to prior ACE inhibitor therapy reduced CV death at the cost of an increase in creatinine (3.7% more than placebo) and hyperkalemia (2.7% more than placebo). Of note, the effects of candesartan were as effective in those receiving both an ACE inhibitor and a β-blocker. Thus in these studies, the triple neurohumoral inhibitor therapy (ARB plus ACE inhibitor plus β-blocker) was successful. This hypothesis was also supported by CandHeart, a much smaller study on 514 patients (73% New York Heart Association [NYHA] II).[138] Candesartan (aim 32 mg daily) added to ACE inhibitors (92%) and β-blockers (85%) did not reduce circulating BNP but improved LV function and decreased aldosterone levels.

Compared with losartan in the therapy of heart failure, high doses (candesartan 16-32 mg; losartan 100 mg daily) were equal,[139] as found in the nationwide Danish National Patient Registry cohort. Note that in the CHARM studies candesartan 32 mg was the target dose.

In *acute stroke* candesartan was not successful, and was possibly harmful.[140]

Candesartan is registered in the United States for both hypertension and heart failure, class 2-4, with an LV ejection fraction of 40% or less, to reduce CV deaths and heart failure hospitalization. It is also licensed for added benefit if combined with an ACE inhibitor. It may also be added to prior therapy by β- and aldosterone-blockade, as in the CHARM studies,[129] but these combinations are not part of the licensed indications.[127] The starting dose is 4 mg daily, working up to 32 mg daily depending on the tolerance of the patient. BP, serum creatinine, and potassium must be monitored. Potassium level monitoring is especially important if combined with an ACE inhibitor or aldosterone blocker.

Irbesartan (avapro)

Irbesartan has no active metabolite, a terminal half-life of 11-15 hr, and for hypertension there is a single daily dose of 150-300 mg (see Table 5-10). There are the usual caveats: use a lower dose for volume depletion; beware of the initial rapid hypotensive effect, then a full effect in weeks; and a better response is obtained to added diuretic than to an increased dose. The diuretic combination, Avalide, contains irbesartan 150 or 300 mg combined with 12.5 mg HCTZ. In important studies on type 2 diabetic nephropathy, IRMA2 and others, irbesartan reduced the rate of progression of microalbuminuria to overt proteinuria.[141] In established diabetic nephropathy, it lessened the primary renal endpoint, which included the rate of rise of serum creatinine and ESRD.[142] These benefits were found both in comparison with placebo and with amlodipine therapy, and were not explained by BP changes. Irbesartan is licensed in the United States for hypertension and for nephropathy in patients with type 2 diabetes with hypertension. In the ACTIVE I study on 9000 high-risk patients with atrial fibrillation, irbesartan was added to prior therapy, including an ACE inhibitor in 60%. Irbesartan did not reduce CV events, yet hospitalization was reduced (first hospitalization for heart failure, $P < 0.003$; fewer total hospital stays for CV events, $P < 0.001$).[143]

In diastolic heart failure with pEF, irbesartan had no effect on the primary outcome, yet showed unexpected benefit in lower-risk patients.[144] Irbesartan was started at 75 mg and up titrated to 300 mg daily. These patients were in the lower range of plasma natriuretic peptides, suggesting benefits early on, but not later, high-risk stages of diastolic heart failure. As this was a post-hoc analysis, prospective studies are now required.

Losartan (cozaar)

This is the prototype ARB, historically the first, with numerous clinical studies to support its efficacy in BP reduction, and now in diabetic nephropathy and LVH (see Table 5-10). For hypertension, the standard start-up dose is 50 mg once daily, with an increase to 100 mg if needed. The package insert allows for twice daily dosing, the half-life being 6-9 hr. As with all the ARBs, a dose increase is usually less effective than the addition of a low-dose diuretic in achieving greater BP control.[145] When there is volume depletion or liver disease (risk of decreased plasma clearance), the starting dose should be only 25 mg. The combination with HCTZ is Hyzaar (losartan 50, thiazide 12.5 mg; or losartan 100, thiazide 25 mg). As for all the ARBs, the major antihypertensive effect is present within 1 week. The full effect may take up to 3-6 weeks, and is potentiated by diuretic action or low-salt diet more than by dose increase. In *hypertensive patients with LVH,* in the LIFE study, losartan (mean dose 82 mg daily) protected from stroke when compared with equivalent BP reduction by atenolol, both agents mostly with a diuretic.[106] In addition, in LIFE substudies, mortality was reduced in diabetics[112] and in older adults with isolated systolic

hypertension.[146] In *diabetic nephropathy,* in the RENAAL study, losartan (50-100 mg daily) reduced ESRD and proteinuria.[147] In *heart failure,* losartan 50 mg daily was disappointing, whereas a higher dose (150 mg daily) gave positive results.[148] The higher dose reduced the rate of death or admission for heart failure, reduced LV ejection fraction, and intolerance to ACE inhibitors compared with losartan 50 mg daily.[149] Observational data support the view that losartan 50 mg is ineffective although suggesting that 100 mg could be effective in lessening mortality in heart failure.[139] In the United States losartan is registered for hypertension, including the subgroup with LVH, in the latter only for stroke reduction, and for diabetic nephropathy with a history of hypertension.

Telmisartan (micardis)

With no active metabolite, and a very long half life of 24 hr, this drug is attractive at 40 to 80 mg once daily (see Table 5-10). However, the formulation is such that the dose cannot be reduced to less than 40 mg even when there is hypovolemia. There is a small increase in hypotensive effect going from 40 to 80 mg daily, with the expected response to added thiazide (Micardis HCT tablets 40/12.5 mg, 80/12.5 mg). Other caveats are much the same as for all the ARBs. The US license is for hypertension, with the proviso that the fixed dose combination is not indicated for initial therapy.

In the main ONTARGET study, 25,620 participants were randomly assigned to ramipril 10 mg a day (n = 8576), telmisartan 80 mg a day (n = 8542), or the combination of both drugs. Telmisartan and ramipril had equal outcomes in patients judged to be at high CV risk.[100] In the ONTARGET renal study, telmisartan gave equal renoprotection to ramipril, but the combination of these two agents increased major adverse renal outcomes despite decreasing proteinuria.[99] In the combined TRANSCEND and ONTARGET populations, in patients at high vascular risk, telmisartan reduced new-onset electrocardiographic LVH by 37%.[150] The combination with ramipril gave no additional benefit. However, these results with telmisartan must be cautiously extrapolated to other ARBs because telmisartan has dual AT-1 blocker/PPARγ-agonist activity; the latter might account for superior reduction of microalbuminuria versus valsartan at equivalent BP levels.[151]

Valsartan (diovan)

Valsartan also has no active metabolite (see Table 5-10). Despite the food effect of up to 50%, the package insert indicates that the drug may be given with or without food. The half-life is shorter than that of irbesartan, yet the dose is also only once daily (80-320 mg). Like the others, added diuretic is more effective in lowering BP. *Diovan HCT* has a fixed dose of 12.5 mg HCTZ with valsartan 80 or 160 mg. There are the usual caveats about volume depletion and the length of time for a full response. In the VALIANT trial, valsartan up to 160 mg twice daily was as effective as captopril up to 50 mg thrice daily in patients at high risk for fatal and nonfatal CV events after MI.[90] Combining valsartan with captopril increased the rate of adverse events without improving survival.

Besides the standard license for hypertension, FDA approval is for heart failure (NYHA class II-IV) to reduce hospitalization, with the caveat that there is no evidence that valsartan confers benefits if used with an adequate dose of an ACE inhibitor. Thus it is not approved as an add-on to ACE inhibition. It is, however, now also approved for reduction of CV mortality in clinically stable patients with LV failure or LV dysfunction.

VALUE is the largest ARB trial on 15,254 high-risk hypertensives.[57] VALUE compared valsartan 160 mg daily with the CCB, amlodipine 10 mg daily, both arms with added thiazide if needed. Despite the theoretical advantages of RAS blockade, final outcomes were similar after an initial period of accelerated BP drop with amlodipine, reflected in early decreases in all-cause mortality and in primary CV endpoints. This result supports those who argue that BP reduction by any means is what matters most, not the agent used to get it down. These conclusions are fortified by the retrospective head-to-head comparison of patients given monotherapy in whom the BP reduction patterns were virtually identical.[152] The advantage of the ARB over the CCB were less new heart failure[152] and less new diabetes.[57],[152]

Unexpectedly, in the NAVIGATOR study, valsartan (up to 160 mg daily) given prophylactically to persons with impaired glucose tolerance and established CVD or CV risk factors in addition to lifestyle modification did not prevent new CVD.[115] In the accompanying editorial, the following are noted: the high rates of loss to follow-up (13%), the use of off-study ACE inhibitors or ARBs among participants assigned to placebo (24%), and nonadherence to valsartan (34% by study end), besides poor lifestyle adherence.[153]

Regarding heart failure, valsartan was compared with amlodipine in Japanese hypertensive persons with type 2 diabetes or impaired glucose tolerance. All major CV outcomes were similar with these two drugs except that new heart failure (in only 18 of a total of 1150 patients) was less common in the valsartan group.[154]

Other agents

Eprosartan *(Teveten)* is registered for hypertension, the usual dose being 600 mg once daily, but varying from 400 to 800 mg and given once or twice daily. In the MOSES trial it was superior to the CCB nitrendipine in secondary prevention of stroke.[121]

Olmesartan *(Benicar)* is likewise licensed for hypertension, with a half-life of 13 hr, the dose being 20-40 mg once daily. This dose range decreases BP as much as equal doses of nitrendipine in isolated systolic hypertension of older adults.[155] It improves endothelial-dependent coronary dilation in hypertensives.[156] In a review of 36 studies in which the effect of various ARBs on BP was measured over 24 hr, olmesartan was one of the best taking into account a variety of modes of judging the 24-hr response, including the last 4 hr of the interdose period.[157] Olmesartan (40 mg daily) delayed the onset of microalbuminuria in patients with type 2 diabetes and normoalbuminuria. It acted beyond BP control, which was excellent.[158] Haller and colleagues state, “The higher rate of fatal cardiovascular events with olmesartan among patients with preexisting coronary heart disease is of concern.”[158]

Caveats for use of ARBs in hypertension

There are a number of caveats common to ACE inhibitors and ARBs: reduce the dose in volume depletion, watch out for renal complications, check for hyperkalemia, and don’t use in pregnancy or bilateral renal artery stenosis. In general, care is required in liver or renal disease (most ARBs are either metabolized by the liver or directly excreted by the bile or the kidneys). A good antihypertensive effect can be expected in 1 week with a full effect over 3-6 weeks, and if needed a diuretic is added rather than increasing the ARB dose. As in the case of ACE inhibitors, and in the absence of diuretic cotherapy, there is relative resistance to the antihypertensive effects of ARBs in black patients.[159]

ARBs: The future

In view of the large number of careful trials now completed with various ARBs (see Table 5-10), the true place of these more specific inhibitors of the RAAS has emerged as follows. In hypertension, there is no question of the excellent tolerability of the ARBs, which makes them an especially attractive early option for hypertension therapy. ARBs have outcome benefit versus several other different modes of BP reduction in specialized situations such as diabetic type 2 nephropathy or LVH. In high-risk vascular patients, the ONTARGET studies showed the equivalence of telmisartan and ramipril. In heart failure, they are excellent in ACE-intolerant patients, yet also increasingly used instead of ACE inhibitors on the grounds of better tolerance and extrapolation of the benefit of candesartan in ACE-intolerant patients to the overall population of those with heart failure.

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Aldosterone, spironolactone, and eplerenone

The RALES and EPHESUS studies have focused on the fact that aldosterone is the final link in the overactive RAAS, which underlies the lethality of heart failure.[22],[160] Aldosterone production increases in response to increased stimulation by angiotensin II, and hepatic clearance decreases. Initially increased aldosterone values fall with ACE-inhibitor therapy, but later may "escape" during prolonged therapy. Because there is a correlation between aldosterone production and mortality in heart failure, the addition of the aldosterone antagonists spironolactone or eplerenone is logical (see Table 5-5).

Mechanism of benefit: Diuresis or tissue effects?

Aldosterone, by sodium and water retention, tends to worsen edema (Fig. 5-12). Nonetheless, the benefits of spironolactone-eplerenone are not only the result of diuresis. Rather, there are several other beneficial mechanisms that oppose the harmful effects of aldosterone excess, including increased myocardial fibrosis, more severe heart failure, and some fatal arrhythmias.[161] Aldosterone levels are associated with adverse clinical outcomes, including mortality in ST-elevation MI.[162] Specifically, aldosterone has adverse vascular effects, including inhibition of release of nitric oxide and an increased response to vasoconstrictor doses of angiotensin I in human heart failure.[9] Aldosterone is the critical mediator of early A II–induced experimental myocardial injury.[163] Spironolactone therapy can decrease extracellular markers of fibrosis in heart failure patients.[164] Additionally, spironolactone decreases the release of cardiac norepinephrine, which should reduce ventricular arrhythmias and sudden death. Furthermore, spironolactone also has vasodilator properties.[9]

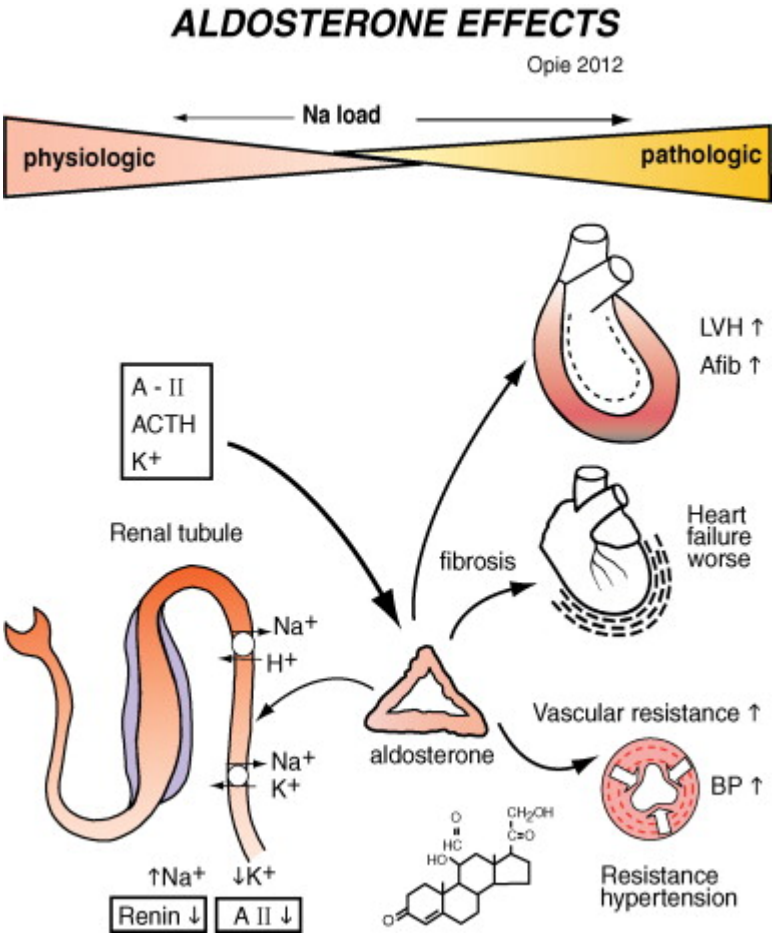

Figure 5-12 Factors promoting release of aldosterone from the adrenal cortex. During a physiologic body sodium load (left side) aldosterone exerts beneficial effects such as maintaining sodium and potassium balance and countering excess renin-angiotensin system (RAS) activation by decreasing plasma renin and thus angiotensin II. During pathologic sodium loading as in heart failure, aldosterone exerts negative effects such as increased left ventricular hypertrophy (LVH) and atrial fibrillation (Afib), worsening heart failure, and greater peripheral vascular resistance. For concepts see Dluhy R, et al. *N Engl J Med* 2004;351:8-10. *ACTH,* Adrenocorticotropic hormone; *BP,* blood pressure; *H,* hydrogen; *K,* potassium; *Na,* sodium.
(Figure © L.H. Opie, 2012.)

All these effects together may explain the therapeutic benefit of even the low dose of spironolactone used in the treatment of severe heart failure in RALES and why sudden cardiac death was less. It should be stressed that the patients selected did not have renal impairment, a risk factor for serious hyperkalemia. Serum potassium was carefully monitored, and there was provision for reduction of the dose of the ACE inhibitor or the aldosterone-blocker in case of hyperkalemia.

Eplerenone (inspra)

Eplerenone is a derivative mineralocorticoid blocker with less antiandrogenic (gynecomastia, impotence) and antiprogestational (oligomenorrhea) side-effects than with spironolactone. *In hypertension,* the dose is 50-100 mg once daily, and it is equally effective in white and black patients.[165] LVH is reduced and better achieved by combination with an ACE inhibitor (enalapril) in the 4E-study.[160]

In post-infarct heart failure, in EPHESUS,[160] eplerenone was added to optimal medical treatment, usually including an ACE inhibitor (86%), a β-blocker (75%), and a diuretic (60%). Morbidity and mortality were reduced. The US license is for (1) hypertension, and (2) to improve survival of stable patients with LV systolic dysfunction (ejection fraction ≤40%) and clinical evidence of CHF after an AMI. The major danger is hyperkalemia, so that in heart failure the dose is based on the serum potassium level. The starting dose of 25 mg daily is increased to 50 mg if the potassium level is less than 5 mEq/L, aiming for 5 to 5.4 mEq/L. If the serum potassium level is more than 5.5 mEq/L, the dose must be decreased or discontinued (package insert). However, one opinion is that the reduced risk of hypokalemia “more than offsets” the lesser associated risk of serious hyperkalemia. Nonetheless, there is a specific warning in the package insert against the use of eplerenone in type 2 diabetes with hypertension and microalbuminuria, because of the risk of hyperkalemia.

In the EMPHASIS-HF trial, eplerenone was compared with placebo in patients with post-MI systolic heart failure (mean ejection fraction 26%) and mild symptoms.[166] Base-line therapy included diuretics in 85%; ACE inhibitor, ARB, or both in 94%; and β-blocker in 87%. Eplerenone reduced both the risk of all-cause death (HR 0.76, CI 0.62-0.93; P = 0.008) and the risk of hospitalization (HR 0.77; CI 0.76-0.88; P < 0.001). Eplerenone was started at 25 mg once daily and increased after 4 weeks to 50 mg once daily, provided the serum potassium level was no more than 5 mmol/L. If the eGFR was 30 to 49 mL/min /1.73 sq m, the starting dose was 25 mg on alternate days, and cautiously increased to 25 mg daily. Doses were decreased if the serum potassium was 5.5-5.9 mmol/L and withheld if the serum potassium level was 6 mmol/L or more. As might be expected, hypokalemia was less common in the eplerenone group (38.8%) versus 48.4% in the placebo group (P < 0.001).

Recent studies in heart failure

In EMPHASIS-HF, presented at the European Society of Cardiology in 2011 and not yet published, eplerenone was given to patients with mild systolic heart failure (NYHA class II) on top of traditional heart failure therapy, including ACE inhibitors, β-blockers, and diuretics.[167] The study was stopped prematurely after 21 months. All-cause death was reduced by 24% (p = 0.008) and hospitalization by 23%. The reviewers suggested that all systolic heart failure patients should be treated with an aldosterone antagonist irrespective of the disease severity.[167]

Does eplerenone impair renal function in HF? An early decline in eGFR by more than 20% in EPHESUS should have been associated with worse CV outcomes independent of baseline eGFR. Nonetheless, eplerenone retained its prognostic benefits even under these circumstances.[168] The benefits exceeded the harm of the decrease in GFR. The proposed postulated mechanisms are pleiotropic actions on nonepithelial tissues, thereby preventing CV remodeling.

Heart failure: Role of aldosterone blockade

Does aldosterone inhibition by spironolactone or eplerenone become a new imperative for heart failure therapy? As already outlined in both RALES and EPHESUS, both aldosterone blockers reduced mortality in heart failure.[22],[169] In EPHESUS eplerenone reduced death even in the subgroup already receiving both ACE inhibitors and β-blockers for postinfarct heart failure.[169] In both studies the rise in serum potassium was limited and the outcome positive. However, serum potassium *must be* carefully monitored, with reduction of the dose of the ACE inhibitor or the aldosterone blocker in case of hyperkalemia. Note that an initial serum potassium value exceeding 5 mmol/L was an exclusion criterion in both RALES and EPHESUS. Note the new analyses listed previously suggesting that aldosterone blockade should be more widely used in heart failure of all severities, including early-stage systolic heart failure.[167] Most recent studies have been with eplerenone. Extrapolation to spironolactone (much cheaper) may be justified if costs are a dominant consideration.

Is addition of an ARB an alternate third-line therapy to aldosterone blockade? Increasingly, the optimal therapy of advanced heart failure is seen as a combination of the three neurohumoral blockers. Besides ACE inhibitors and β-blockers, third line includes aldosterone blockade.[169] The CHARM studies raise the issue of adding a proven ARB, candesartan, as third-line therapy,[129] thus being an alternate to an aldosterone blocker.[127] However, there are no such studies with other ARBs, and the general lesson from ONTARGET is to avoid double blockade of the RAAS system in patients with renal problems. Thus the standard triple therapy is ACE inhibition, β-blockade, and aldosterone blockade. For choice between the two proven third-line therapies, there are no head-to-head comparisons between a proven ARB and an aldosterone blocker.

Regarding trials in progress, TOPCAT, supported by the National Heart and Lung Institute, is designed to evaluate the effect of spironolactone on morbidity, mortality, and quality of life in patients with heart failure with pEF.[170] The trial is fully recruited and underway.

The Aldo-DHF trial tests whether spironolactone 25 mg daily added to prior therapy will improve exercise capacity and diastolic function in patients with preserved LV ejection fraction (> or = 50%), and echocardiographic diastolic dysfunction.[171]

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Renin inhibition by aliskiren

Aliskiren is the first in the class of renin blockers, which should be a one-stop shop to equal ACE inhibition or ARB, or, if there is known benefit to combining an ACE inhibitor and an ARB, as may be the case in renal disease, then aliskiren potentially could be better than either of the agents singly. Furthermore, renin inhibition decreases all the downstream messengers leading to the receptors. By contrast, as outlined by O'Brien and colleagues,[123] ACE inhibitors, ARBs, and diuretics all increase renin and plasma renin activity (PRA). Renin and its precursor, prorenin, both bind to the same newly discovered receptor to stimulate a novel path that may have adverse renal effects independently of generation of angiotensin II.[172] Furthermore, in human renin receptor transgenic rats, plasma aldosterone and BP increase.[173] ACE inhibitors increase PRA and angiotensin I, which can form angiotensin II both by ACE that is not fully blocked and by chymase, whereas ARBs and diuretics increase PRA, angiotensin I, and angiotensin II. By contrast, aliskiren neutralizes any compensatory increase in PRA even during combined therapy with a thiazide diuretic, an ACE inhibitor, or ARB and prevents the formation of both angiotensin I and angiotensin II.[123]

Despite this attractive theoretical framework, others are more skeptical because of the potentially adverse effects of excess renin secretion from the kidneys.[174] Evidence favoring the view that renin inhibition blocks RAS better than an ARB is that aliskiren 300 mg daily added to maximal antihypertensive doses of the ARB valsartan (320 mg daily) reduced PRA and further decreased BP.[175] Dual inhibition of the renin system limits the escape from chronic inhibition at any single step. Of direct relevance to aliskiren, renin inhibitors on top of ACE inhibitors or ARBs inhibit PRA despite any reactive rise in renin. In line with this concept, Oparil and colleagues found that the combination of aliskiren with valsartan reduced PRA by 44%, despite a ninefold increase in the plasma renin concentration. Dangerous hyperkalemia (≥6.0 mmL/L) was no more common than with placebo.[175] Moderate hyperkalemia (5.5-6 mmL/L) is relatively common and should warn of more serious potassium rises.[176] These studies have set the stage for the ALTITUDE, ATMOSPHERE, and ACCLERATE studies.

ALTITUDE was a large outcome study in which aliskiren was given on top of ACE inhibitor or ARB therapy in patients with type 2 diabetes and renal impairment. The study was prematurely stopped because the active treatment group experienced an increased incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension over 18 to 24 months of follow-up. In December 2011 Novartis announced termination of the ALTITUDE study with Rasilez and Tekturna. Thereafter, the European Medicines Agency declared that aliskiren-containing drugs are contraindicated in patients with diabetes or moderate to severe renal impairment who are taking ACE inhibitors or ARBs. The Agency stated, "For all other patients receiving aliskiren-containing medicines in combination with an ACE inhibitor or an ARB, the balance of benefits and risks of continuing treatment should be considered carefully." Despite this abrupt stop, final events must still be evaluated. This adverse experience with aliskiren on top of one other RAAS inhibitor is in keeping with the principle uncovered by ONTARGET, in which dual ACE inhibitor plus ARB therapy given to patients at high CV risk, including diabetics, increased serious renal outcomes when compared with monotherapy with either agent.[177]

The Aliskiren Trial of Minimizing Outcomes for Patients with Heart Failure (ATMOSPHERE) is an ongoing study of patients with systolic heart failure and an elevated BNP or N-terminal pro BNP concentration in which patients are randomized in equal proportions to receive either enalapril 10 mg twice daily, aliskiren 300 mg once daily, or the combination of both drugs.[178] The aim is to improve systolic heart failure, testing a different population from that in ALTITUDE. Furthermore, there will be an open-label run in and postrandomization checks by the Data Monitoring and Safety Committee.

ACCELERATE was a small study in which hypertensive persons were given either aliskiren (150-300 mg) or amlodipine (5-10 mg) or the combination; the BP drop, not surprisingly, was greater in the combination-therapy group. The major point of this study is that it opens the way to the further testing of the potential use of aliskiren as the theoretically ideal partner to amlodipine.[179]

Aliskiren has been tested as part of a dual or triple fixed dose combination. High-risk US minority patients with stage 2 hypertension were given aliskiren and amlodipine (300 and 10 mg) or aliskiren, amlodipine, and HCTZ (300, 10, and 25 mg).The SBP, initially at 167 mm Hg, dropped over 8 weeks to 138 mm Hg and 131 mm Hg, respectively.[180] Adverse events were experienced by 34% and 40%, but there was no placebo comparator. The concept under test is that aliskiren could become one component of a two- or three-drug combination tablet with amlodipine.

ASTRONAUT is an outcome study that will test Aliskiren on patients with chronic heart failure and acute deterioration (acute heart failure), a LV ejection fraction of 40% or less, and an eGFR of 40 mL/min/1.73 m[2] or more. Concurrent therapy with an ACE inhibitor or ARB is a contraindication.[181]

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Summary

1. ***Inhibition of the RAAS*** is established for the treatment and prevention of a wide range of CVDs. The basic concept hinges on the adverse effects of excess angiotensin II and aldosterone. ACE inhibitors both decrease the formation of angiotensin II and increase protective bradykinin. ARBs directly block the AT-1 receptor, thereby largely avoiding the side effects of excess bradykinin such as cough and angioedema. Aldosterone blockers oppose the cellular effects of aldosterone, including sodium retention and myocardial fibrosis.
2. ***In CHF,*** thousands of patients have been studied in many large trials that have focused attention on the important therapeutic and potential prophylactic role of the ACE inhibitors. Reduction of "hard" end-points, such as mortality, hospitalization, and prevention of disease progression, can be achieved in certain patient populations. In a minority of patients, ACE inhibitors fail to benefit. Careful use is needed to avoid potential harm (hypotension, renal dysfunction, hyperkalemia). The strong argument is to start therapy with ACE inhibition as early as possible in the course of heart failure, even when only mild to moderate, and whether symptomatic or asymptomatic. Whenever possible, ACE inhibitors are used with β-blockers, which are also life conserving (death delaying). The next step is either the addition of aldosterone blockers (spironolactone or eplerenone) or a trial-supported ARB (candesartan). Although first-line experience with ACE inhibitors is very robust, ARBs are increasingly selected because of greater tolerability. The greater the degree of RAAS inhibition by multiple inhibitors, the greater the care necessary to avoid the risk of potentially fatal hyperkalemia.
3. ***In hypertension,*** ACE inhibitors are effective as monotherapy in BP reduction in most patient groups except blacks, in whom higher doses may be needed. There are few side effects and contraindications. A particularly attractive combination is with diuretics because diuretics increase circulating renin activity and angiotensin II levels, which ACE inhibitors counterregulate by inhibiting the conversion of angiotensin I to angiotensin II. Another attractive combination is with a CCB, as in ACCOMPLISH (see Chapter 7, p. 244).
4. ***In early-phase AMI,*** ACE inhibitors achieve a modest but statistically significant reduction in mortality (6% to 11%). Best results are obtained in higher-risk patients treated long term, such as those with large infarcts or with diabetes in whom ACE inhibitors give a striking reduction of 26% in mortality.[90]
5. ***In asymptomatic LV dysfunction,*** whether postinfarct or otherwise, ACE inhibitors can prevent the development of overt CHF, as shown by two large trials, SAVE and SOLVD, the latter having a 12-year follow-up.
6. ***In juvenile diabetic nephropathy,*** ACE inhibition added to other antihypertensives has achieved reduction of hard end-points, such as death, dialysis, and renal transplantation. Indirect evidence suggests similar protection in type 2 diabetics; RAS blockade delays the onset of microalbuminuria and the increases of proteinuria, as well as improving outcomes in advanced renal failure. Specific evidence is for ACE inhibitors for the former and for ARBs for the latter.
7. ***In non-diabetic nephropathy,*** renoprotection occurred independently of any BP reduction with ramipril in the REIN and AASK studies.
8. ***CV prophylaxis in high- and moderate-risk patients*** was studied in two large-scale preventative trials on patients at high risk of CV events, HOPE and EUROPA. The studies found reduced hard end-points, including myocardial infarction, stroke, and all-cause mortality.
9. ***ARBs act at a different site from ACE-inhibitors to block the effects of angiotensin II at the AT-1 receptor.*** Substantial experimental evidence shows that angiotensin II promotes vascular and myocardial hypertrophy. Theoretically, AT-1 receptor blockade gives all the benefits of ACE inhibition, except for formation of protective bradykinin. Hence, ARBs are virtually without bradykinin-attributed adverse side effects such as cough and angioedema; the latter is rare but potentially fatal. The ARBs are increasingly seen as having similar efficacy with fewer side effects. They are now used not only

for ACE-intolerant patients, but when avoidance of symptomatic side effects is crucial and when these drugs can be afforded. They have the same contraindications as the ACE inhibitors, and there is also relative resistance to their BP-lowering effects in blacks.

10. ***ARBs have been successful in treating heart failure.*** ARBs have been tested in an era when ACE inhibitors were already the established therapy of choice for heart failure. Had the ARBs come earlier, they would probably have been the first choice. Candesartan is exceptionally well tested in heart failure in the CHARM studies. Losartan has been underdosed. Taking together the results of several large trials such as Val-HeFT, CHARM, and VALIANT, the ARBs in the specific doses used are not inferior to ACE inhibitors, whether the basic problem is heart failure or postinfarct protection.
11. ***In studies of ARBs and post-MI heart failure,*** valsartan was equivalent to captopril in reducing death and adverse CV outcomes, with decreased cough, rash, and taste disturbances (VALIANT trial). The downside was increased hypotension and renal problems.
12. ***Combination therapy of systolic heart failure with ACE inhibitors,*** *β-blockers, and aldosterone blockade is favored.* The benefits of three separate modes of RAAS blockade appear to be additive. Eplerenone was given to patients with mild systolic HF (NYHA class II) on top of standard current heart failure therapy, including diuretics.
13. ***ARBs have been well-studied in those with LVH and type 2 diabetic nephropathy,*** with outcome benefits. When compared with control antihypertensive regimes, ARBs were better at reducing stroke and heart failure, but not coronary heart disease.[107]
14. ***ARBs and reduction of CV risk*** needs to be studied. CV protection, achieved by ramipril in the HOPE trial and perindopril in EUROPA, needs to be repeated with an ARB. In 2008 the results of a large prevention trial, ONTARGET, have remedied this defect by comparing telmisartan with ramipril and with the combination. The results of this huge landmark trial set new standards for CV risk prevention.
15. ***Fewer cases of new diabetes occur.*** An important finding with ACE inhibitors and ARBs, especially when compared with β-blockers or diuretics, is the decreased development of new diabetes.
16. ***Cautions must be taken in treatment of black patients.*** Monotherapy for hypertension often requires either the addition of a diuretic or a higher dose of the ACE inhibitor or ARBs. Angioedema with ACE inhibitors occurs more commonly in black patients. In heart failure, diuretic co-therapy may explain why ACE inhibitors seem to be as effective in black patients as in others.
17. ***Contraindications to ACE inhibitors and to the ARBs are few.*** Bilateral renal artery stenosis and pregnancy (a boxed warning for both groups of agents) preclude use. Hypotension and a substantially increased serum creatinine require thorough evaluation before use and careful monitoring after starting the drug. Hyperkalemia is also a risk with both ACE inhibitors and the ARBs and increases with their combination.
18. ***Combination ACE inhibitor–ARB therapy*** can have adverse renal outcomes in patients at high CV risk, as shown in ONTARGET and ALTITUDE. In severe heart failure, however, the candesartan–ACE inhibitor combination is approved for use. Current trials are evaluating combined ACE inhibitor–ARB therapy in overt diabetic proteinuria.
19. ***Aldosterone,*** the final effector of the RAAS, is increased in heart failure, both systemically and locally in the heart, with adverse effects including sodium retention. Inhibition by *spironolactone or eplerenone* improves the outcome beyond that of prior standard proven therapy for heart failure, usually an ACE inhibitor or ARB, β-blocker, and diuretic. The downside is the increased risk of hyperkalemia. Trials with added spironolactone or eplerenone are in progress.
20. ***Aliskiren*** is the newly developed renin blocker, still under full evaluation, with promising early results in hypertension. Currently a major trial focuses on the therapy of heart failure with due consideration of relevant safety issues.

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