CHAPTER 2

ACE INHIBITION IN HEART FAILURE AND ISCHAEMIC HEART DISEASE

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1. INTRODUCTION

Angiotensin converting enzyme (dipeptidyl carboxypeptidase I, kininase II, EC 3.4.15.1, ACE) plays a major role in the metabolism of many different peptides, including angiotensin (Ang) I, bradykinin, kallidin, and N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP). ACE inhibitors are established therapy for heart failure and ischaemic heart disease, and alterations of Ang II, bradykinin, kallidin, and AcSDKP peptide levels are implicated in the mechanisms of this therapy. This chapter briefly describes the renin angiotensin, kallikrein kinin, and AcSDKP systems, and their role in cardiovascular physiology and disease. The role of ACE inhibition in treatment and prevention of heart failure and ischaemic heart disease is summarised, and the possible mechanisms of the therapeutic benefits of ACE inhibitors are described. This is not an exhaustive review, but focuses on those aspects most relevant to the clinical application of ACE inhibitors.

2. THE CARDIAC RENIN-ANGIOTENSIN SYSTEM (RAS)

2.1. Pathways of Ang Peptide Formation and Metabolism

Figure 1 shows an outline of the pathways of Ang peptide formation and metabolism. In addition to the classical pathway involving renin and ACE, alternative pathways have been proposed (Campbell 2006). There remain many questions concerning the mechanisms of Ang peptide formation in discrete tissue compartments such as the heart. Serine proteases, for example, may form Ang II by processes independent of renin at sites of inflammation or coagulation, where kallikrein and/or cathepsin G may be active.
Figure 1. Pathways of Ang peptide formation and metabolism. Adapted from (Campbell 2006)

2.2. Renin and Angiotensinogen

Studies of nephrectomised animals show the main mechanism of Ang peptide formation in the heart involves kidney-derived renin (Campbell et al 1993; Danser et al 1994). Renin messenger RNA (mRNA) levels in the heart are very low or undetectable (De Mello et al 2000). Cardiac renin expression may, however, be induced by myocardial infarction and macrophages and myofibroblasts may express renin at the site of repair (Sun et al 2001). All Ang peptides are derived from angiotensinogen. Although angiotensinogen may be produced in low levels in the heart (Dostal et al 1999; Paul et al 2006), plasma is the main source of angiotensinogen for Ang peptide formation in the heart.

2.3. ACE

ACE is a membrane-bound zinc-containing metallopeptidase, some of which is cleaved from membranes and released as soluble ACE found in plasma and other fluids (Erdos 1990). ACE has two catalytic domains with differential substrate specificities and susceptibility to ACE inhibitors (Wei et al 1991; Wei et al 1992; Jaspard et al 1993). Table 1 lists the many substrates of ACE. Those ACE substrates most related to cardiac function are Ang I, the bradykinin and kallidin peptides, and AcSDKP. Both catalytic domains of ACE posses dipeptidyl carboxypeptidase and endopeptidase activities and can cleave Ang I, bradykinin-(1-9), bradykinin-(1-7), and substance P. However, the N-terminal catalytic domain cleaves of lutein-
Table 1. Substrates of ACE

| Substrates                                      |
|------------------------------------------------|
| Angiotensin I and angiotensin-(1-7)            |
| Bradykinin-(1-9), bradykinin-(1-8), and bradykinin-(1-7) |
| Lys\(^0\)-bradykinin-(1-9) (kallidin), Lys\(^0\)-bradykinin-(1-8), and Lys\(^0\)-bradykinin-(1-7) |
| Substance P                                    |
| N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP)  |
| Chemotactic peptide                            |
| Neurotensin                                     |
| Luteinising hormone-releasing hormone (LH-RH)   |
| Enkephalins                                     |
| Cholecystokinin                                 |
| Gastrin                                         |

Adapted from (Ehlers et al 1990; Erdos 1990; Hooper 1991; Rieger et al 1993)

isizing hormone-releasing hormone (LH-RH) and AcSDKP more efficiently than the C-terminal domain (Jaspard et al 1993; Rousseau et al 1995).

The two catalytic domains of ACE interact differently with ACE inhibitors. Captopril, enalapril, lisinopril, and trandolapril are all highly potent inhibitors of both domains. Whereas trandolapril, lisinopril and enalapril show preference for the C-terminal catalytic domain, captopril shows preference for the N-terminal catalytic domain (Wei et al 1992).

ACE has a widespread tissue distribution, including vascular endothelium and smooth muscle cells, the brush border of proximal tubule cells of the kidney, and the brain (Erdos 1990). ACE is expressed by the endothelium of the coronary vasculature, and by the endocardium and epicardium, but not by the valves in the human heart (Dostal et al 1999). ACE is also expressed by cardiac fibroblasts, and fibroblast expression of ACE is increased in the border zone of myocardial infarction (Dostal et al 1999; Burrell et al 2005). Cardiac ACE expression is up-regulated in heart failure (Hirsch et al 1991; Studer et al 1994).

2.4. Ang Receptors

Many different cell types express Ang receptors in the heart. The type 1 Ang (AT\(_1\)) receptor is expressed by coronary smooth muscle and endothelial cells, cardiomyocytes, fibroblasts, nerves, and conduction tissue (Regitz-Zagrosek et al 1998). AT\(_2\) receptors are expressed by fibroblasts and endothelial cells (Regitz-Zagrosek et al 1998). In heart failure, cardiomyocyte AT\(_1\) receptor expression may be down-regulated, whereas fibroblast expression of both AT\(_1\) and AT\(_2\) receptors is increased (Ohkubo et al 1997).

The AT\(_1\) receptor mediates most of the known actions of Ang II. There is continuing uncertainty about the role of the AT\(_2\) receptor, which may mediate actions of Ang II in the vasculature and heart that differ from those of the AT\(_1\) receptor (Carey et al 2001; Voros et al 2006). The AT\(_2\) receptor is described further by Danser in chapter 3 of this volume.
2.5. Mast Cell Chymase

Human heart chymase was initially discovered in homogenates of human heart and proposed to be the major pathway of conversion of Ang I to Ang II in the heart (Urata et al 1990). Given that chymase is not inhibited by ACE inhibitors, it represented a potential pathway of continued Ang II formation in patients taking ACE inhibitor therapy (Dell’Italia et al 2002), and thereby provided a rationale for a possible superiority of AT1 receptor blocker (ARB) therapy over ACE inhibitor therapy. However, studies of the effects of ACE inhibition in rats, mice, and humans, and of ACE gene knockout in mice, show ACE is the dominant pathway of Ang II formation in the heart (Campbell et al 1994; Campbell et al 1999; Zeitz et al 2003; Campbell et al 2004a).

2.6. ACE-related Carboxypeptidase (ACE2)

ACE-related carboxypeptidase (ACE2), like ACE, is a membrane-associated and secreted metalloprotease expressed predominantly on endothelium (Donoghue et al 2000; Tipnis et al 2000; Hamming et al 2004). ACE2 is expressed in all human tissues, with relatively high levels in renal and cardiovascular tissues, and also in the gut (Harmer et al 2002). In contrast to the dipeptidyl carboxypeptidase activity of ACE, ACE2 cleaves Ang I to Ang-(1-9) and also cleaves ANG II to Ang-(1-7). ACE2 is not inhibited by ACE inhibitors.

Kinetic considerations make it unlikely that ACE2 contributes to Ang I metabolism in vivo (Jaspard et al 1993; Vickers et al 2002). ACE and ACE2 have similar $K_m$ for Ang I (16 and 6.9 $\mu$mol/L, respectively) but the $K_{cat}$ for ACE (40 s$^{-1}$) is approximately 1000-fold higher than that for ACE2 (0.034 s$^{-1}$), such that the $K_{cat}/K_m$ ratio is approximately 500-fold higher for ACE (2.5 x 10$^6$ L/mol per s) than for ACE2 (4.9 x 10$^3$ L/mol per s$^{-1}$). By contrast, the $K_m$ (2 $\mu$mol/L), $K_{cat}$ (3.5 s$^{-1}$), and $K_{cat}/K_m$ ratio (1.8 x 10$^6$ L/mol per s) of ACE2 for Ang II (Vickers et al 2002) make it more likely to participate in Ang II metabolism.

Initial genetic studies suggested an important role for ACE2 in Ang peptide metabolism in the heart. The ACE2 gene knockout mouse was reported to have a cardiomyopathic phenotype associated with increased Ang II levels in plasma, heart, and kidney. Additionally, the cardiomyopathic phenotype was ameliorated by concomitant ACE gene knockout, suggesting that altered Ang peptide metabolism contributed to the phenotype (Crackower et al 2002). In subsequent studies the ACE2 gene knockout mouse had a normal cardiac phenotype, although it had an enhanced pressor response to Ang II administration (Gurley et al 2006).

ACE2 activity is reported to be increased in the hearts of patients with heart failure (Zisman et al 2003). However, measurement of Ang peptides in coronary venous blood of patients with heart failure or ischaemic heart disease does not support an important role for ACE2 in either Ang I or Ang II metabolism in the human heart (Campbell et al 2004b). Elucidation of the role of ACE2 in Ang II metabolism must await the development of specific ACE2 inhibitors.
2.7. Effects of the RAS on the Heart and Vasculature

2.7.1. Actions of Ang II

Both systemic and local actions of Ang II impact on the heart. Systemic actions of Ang II include its vasoconstrictor action to increase blood pressure and the stimulation of aldosterone secretion. Increased aldosterone levels may produce hypokalaemia and contribute to cardiac fibrosis (Brilla et al. 1993).

Local cardiac actions of Ang II include inotropic and hypertrophic effects, and cardiac remodelling (Paul et al. 2006). AT1 receptor stimulation induces both myocyte hypertrophy and collagen synthesis (Regitz-Zagrosek et al. 1998). Moreover, Ang II may contribute to oxidative stress, inflammation, and thrombosis (Dzau 2001; Duprez 2006). AT1-mediated NADPH oxidase activation leads to generation of reactive oxygen species, widely implicated in vascular inflammation and fibrosis (Li et al. 2004; Mehta et al. 2007). Ang II also activates gene transcription factors involved in vascular inflammation and remodelling (Oettgen 2006). Ang II and its metabolite Ang IV may promote thrombosis by stimulating plasminogen activator inhibitor type 1 (PAI-1) and PAI-2 production by the vasculature (Van Leeuwen et al. 1994; Feener et al. 1995; Kerins et al. 1995). Additionally, Ang II may promote thrombosis by activation of nuclear factor κB-dependent proinflammatory genes and accelerating vascular expression of tissue factor (Dielis et al. 2005).

Ang II stimulates endothelin release (Kohno et al. 1992; Moreau et al. 1997) and endothelin blockade prevents some of the cardiovascular actions of Ang II (Webb et al. 1992; Rajagopalan et al. 1997; Herizi et al. 1998).

2.7.2. Actions of Ang-(1-7)

Ang-(1-7) is a biologically active peptide (Ferrario et al. 1991). The main pathway of Ang-(1-7) formation is by cleavage of Ang I by neutral endopeptidase (NEP, endopeptidase 24.11) (Yamamoto et al. 1992; Duncan et al. 1999) (Fig. 1). Ang-(1-7) may also be formed by ACE2 cleavage of Ang II, but the significance of this pathway remains to be established.

Many actions of Ang-(1-7) are contrary to those of Ang II, and Ang-(1-7) is proposed to function as a counter-regulatory hormone in blood pressure control, and in other cardiovascular actions of Ang II. Ang-(1-7) reduces blood pressure and produces endothelium-dependent vasodilatation (Benter et al. 1993; Pörsti et al. 1994; Benter et al. 1995; Nakamoto et al. 1995; Brosnihan et al. 1996; Le Tran et al. 1997), actions that may be due in part to potentiation by Ang-(1-7) of the hypotensive effects of kinins (Paula et al. 1995; Lima et al. 1997) and/or to stimulation of vascular prostaglandin production (Benter et al. 1993; Paula et al. 1995). In support of a role for kinin-mediated nitric oxide production in its vasodilator effects, Ang-(1-7) induced vasodilatation and hypotension were attenuated by nitric oxide synthase (NOS) inhibition (Pörsti et al. 1994; Gorelik et al. 1998), by the type 2 bradykinin (B2) receptor antagonist icatibant (Pörsti et al. 1994; Abbas et al. 1997; Lima et al. 1997; Gorelik et al. 1998), and also by
AT₂ receptor antagonism (Lima et al 1997). Moreover, Ang-(1-7) stimulation of nitric oxide release from coronary vessels was blocked by icatibant (Brosnihan et al 1996).

High concentrations of Ang-(1-7) inhibit ACE, leading to the suggestion that Ang-(1-7) potentiates the effects of bradykinin through ACE inhibition (Li et al 1997). However, the IC₅₀ for Ang-(1-7) inhibition of ACE was 650 nmol/L and it is unlikely endogenous Ang-(1-7) levels would be sufficient to produce this effect. Ang-(1-7), like other ACE inhibitors, may potentiate the actions of a B₂ receptor agonist by an indirect mechanism that is independent of bradykinin hydrolysis (Deddish et al 1998), possibly by sensitisation of the B₂ receptor (Marcic et al 1999). This mechanism of potentiation of kinin-induced hypotension by Ang-(1-7) is unlikely to operate in vivo, however, because micromolar concentrations of Ang-(1-7) were required to produce this effect (Deddish et al 1998).

Plasma Ang-(1-7) levels are less than Ang II levels, except during ACE inhibition when Ang-(1-7) levels increase several-fold, in parallel with the increase in Ang I levels (Lawrence et al 1990; Menard et al 1997). Tissue levels of Ang-(1-7) are very low or undetectable, even with ACE inhibition (Campbell et al 1993; 1994). There is, therefore, uncertainty whether Ang-(1-7) levels are sufficient to play a role in cardiovascular physiology and disease states in humans.

3. THE CARDIAC KALLIKREIN KININ SYSTEM (KKS)

3.1. Pathways of Kinin Peptide Formation and Metabolism

Figure 2 shows an outline of the pathways of kinin peptide formation. A proportion of kininogens is hydroxylated on Pro³ of the bradykinin sequence, leading to the formation of hydroxylated kinin peptides.

3.2. Kallikreins and Kininogens

The kininogens are the sole precursors of the kinin peptides and are coded by a single gene. Differential splicing of the initial mRNA transcript produces two different mRNA coding for either high or low molecular weight kininogen. Each is a glycoprotein that contains the kinin sequence in its mid portion. Tissue kallikrein and plasma kallikrein are both serine proteases. Whereas a single gene codes for plasma kallikrein there is a large family of tissue kallikrein genes, although KLK1 is the only tissue kallikrein known to generate kinin peptides (Yousef et al 2001). Kininogens and tissue kallikrein are expressed in many different tissues. Plasma kallikrein is predominantly expressed in liver, although recent studies suggest expression of plasma kallikrein in the brain (Takano et al 1999).

In humans, plasma kallikrein forms bradykinin from high molecular weight kininogen, whereas tissue kallikrein forms kallidin from high or low molecular weight kininogens (Fig. 3). By contrast, both plasma and tissue kallikrein generate
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- Met-Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-Ser-
- Met-Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-Ser-
- Met-Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-Ser-
- Met-Lys-Arg-Pro-Hyp-Gly-Phe-Ser-Pro-Phe-Arg-Ser-
- Met-Lys-Arg-Pro-Hyp-Gly-Phe-Ser-Pro-Phe-Arg-Ser-
- Met-Lys-Arg-Pro-Hyp-Gly-Phe-Ser-Pro-Phe-Arg-Ser-

**Figure 2.** An outline of the formation of kallidin and bradykinin peptides in humans. A proportion of high molecular weight kininogen is hydroxylated on Pro of the bradykinin sequence, giving rise to both hydroxylated and non-hydroxylated peptides. Adapted from (Campbell 2003).

bradykinin in rodents (Bhoola et al 1992). Bradykinin may also be generated by aminopeptidase-mediated cleavage of kallidin.

Alternative pathways of kinin formation involving enzymes other than kallikreins may operate in disease states. Although low molecular weight kininogen is a poor substrate for plasma kallikrein, it will form bradykinin in the presence of neutrophil elastase which, by cleaving a fragment from low molecular weight kininogen, renders it much more susceptible to cleavage by plasma kallikrein (Sato et al 1988). Moreover, the combination of mast cell tryptase and neutrophil elastase releases bradykinin from oxidized kininogens that are resistant to cleavage by kallikreins (Kozik et al 1998).

Kinin production in vivo is controlled in part by endogenous inhibitors of the kallikrein enzymes. The main inhibitors of plasma kallikrein are C1 inhibitor, α2-macroglobulin and antithrombin III (Bhoola et al 1992). An important inhibitor of tissue kallikrein is kallistatin, although the function of kallistatin in vivo is uncertain (Chao et al 1996).

All components of a functional KKS are expressed in the heart (Spillmann et al 2006). The heart and vasculature express tissue kallikrein (Oza et al 1990; Xiong et al 1990; Nolly et al 1992; Nolly et al 1994). In addition, plasma kallikrein, a member of the contact system, generates bradykinin at the endothelial surface of blood vessels (Campbell 2003).
3.3. **Kinin Receptors**

Kininns act via two types of kinin receptor, the B1 and the B2 receptors. The B2 receptor normally predominates, whereas the B1 receptor is induced by tissue injury. The KKS generates 8 bioactive kinin peptides: bradykinin, Hyp3-bradykinin, kallidin, and Hyp4-kallidin act on the B2 receptor, whereas their carboxypeptidase metabolites des-Arg9-bradykinin, des-Arg9-Hyp3-bradykinin, des-Arg10-kallidin, and des-Arg10-Hyp4-kallidin act on the B1 receptor. Hydroxylated kinins have similar biological activity to non-hydroxylated kinins.

Of particular interest is the recent report that the human B2 receptor is activated by both plasma and tissue kallikrein (Hecquet et al 2000). Cathepsin G and trypsin similarly activate the B2 receptor and activation is blocked by icatibant. Thus, the B2 receptor may belong to a new group of serine-protease-activated receptors (Hecquet et al 2000).

3.4. **Kinin Metabolism**

ACE is one of many enzymes that metabolise kinin peptides (Campbell 2003) and the efficiency of metabolism is an important determinant of their levels in blood and tissues. Consequently, inhibition of any single enzyme that contributes to kinin metabolism causes only a modest increase in kinin levels.
3.5. **Effects of the KKS on the Heart and Vasculature**

Kinin peptides have a broad spectrum of activities and both systemic and local cardiac actions impact on the heart (Bhoola et al. 1992). Kinin peptides act through many different second messenger systems, in particular nitric oxide and prostaglandins (Bhoola et al. 1992). The B₂ receptor participates in an inhibitory interaction with endothelial NOS (eNOS) that is reversed by bradykinin (Ju et al. 1998). This interaction may recruit eNOS to the B₂ receptor and allow for effective coupling of bradykinin signalling to the nitric oxide pathway. Kinins are potent vasodilators and promote diuresis and natriuresis. Kinins in high concentration also participate in the cardinal features of inflammation, producing vascular permeability, neutrophil chemotaxis and pain (Bhoola et al. 1992).

Cardiac bradykinin levels are increased during the acute phase of myocardial infarction in rats (Duncan et al. 1997). By contrast, we found decreased kallidin levels in coronary sinus blood of subjects with heart failure, suggesting down-regulation of the cardiac KKS in heart failure (Duncan et al. 2000).

There is a large body of evidence demonstrating anti-hypertrophic and cardioprotective actions of the KKS (Griol-Charhbili et al. 2005; Koch et al. 2006; Park et al. 2006; Spillmann et al. 2006). The cardioprotective effects of bradykinin included the reduction of arrhythmias, reduction of lactate, lactate dehydrogenase, and creatine kinase release, and increase in myocardial contractility and myocardial levels of glycogen, adenosine triphosphate and creatine phosphate during post-ischaemic reperfusion of the isolated working rat heart (Linz et al. 1992). Moreover, bradykinin suppressed endothelin release from the post-ischaemic rat heart (Brunner et al. 1996). Kinins protect against ischaemia-reperfusion injury by decreasing endothelial adherence of leukocytes, leading to attenuation of post-ischaemic leukocyte adherence, attenuation of disruption of the microvascular barrier and reduced tissue injury (Shigematsu et al. 1999). Many of the actions of kinins counteract those of Ang II, by causing endothelium-dependent vasodilation through endothelial release of nitric oxide and prostacyclin (Pelc et al. 1991; Lamontagne et al. 1992; Gallagher et al. 1998). Kinins also counteract the hypertrophic actions of Ang II and reduce collagen formation (Gallagher et al. 1998; Ritchie et al. 1998).

Administration of kinin receptor antagonists indicates a role for endogenous kinins in the regulation of the coronary vasculature and in the myocardial response to myocardial infarction. Icatibant reduced flow-dependent vasodilatation of human coronary arteries, indicating a role for kinins in the regulation of coronary vasculature (Groves et al. 1995). Icatibant enhanced myocardial interstitial deposition of collagen following myocardial infarction in the rat, indicating a role for endogenous kinins in the modulation of collagen deposition; however, icatibant did not modify morphological and molecular markers of cardiomyocyte hypertrophy (Wollert et al. 1997). Kinins participate in the process of ischaemic preconditioning, and have also been shown to limit reperfusion injury (Baxter et al. 2002). Kinins may also protect against thrombosis by stimulating endothelial release of nitric oxide, prostacyclin, and tissue plasminogen activator (Dielis et al. 2005). New properties of kinin peptides are being discovered. For example, B₁ receptors may have an important role in angiogenesis (Emanuelli et al. 2002).
4. ACSDKP

4.1. AcSDKP Formation

AcSDKP is an inhibitor of pluripotent haemopoietic stem cell proliferation (Lenfant et al 1989; Bonnet et al 1993), and is normally present in human plasma and mononuclear cells (Pradelles et al 1990). AcSDKP is released from its precursor thymosin-β₄ by prolyl oligopeptidase (Cavasin et al 2004) and it is cleaved to an inactive form by the dipeptidyl carboxypeptidase activity of the N-terminal catalytic domain of ACE (Rousseau et al 1995). AcSDKP has a 4.5 min half-life in the circulation and is probably released continuously (Azizi et al 1997). The importance of ACE in AcSDKP metabolism is shown by the 5-fold increase in AcSDKP plasma levels that accompany ACE inhibition (Azizi et al 1997).

4.2. Functions of AcSDKP in the Heart

AcSDKP inhibits DNA and collagen synthesis by cardiac fibroblasts (Rhaleb et al 2001), and both prevents and reverses myocardial inflammation and fibrosis in rats with heart failure after myocardial infarction (Yang et al 2004). AcSDKP and thymosin-β₄ stimulate coronary vasculogenesis and angiogenesis (Wang et al 2004; Smart et al 2007), and AcSDKP increases myocardial capillary density in rats with myocardial infarction (Wang et al 2004).

5. ACE INHIBITION IN HEART FAILURE AND ISCHAEMIC HEART DISEASE

Many clinical trials demonstrate the therapeutic benefit of ACE inhibition in heart failure and ischaemic heart disease. It is of note, however, that the effects of ACE inhibitors are dose related. Large clinical trials, by necessity, use only one dose of any drug. The results of such trials are just as much a measure of the effect of the dose as they are a measure of the effect of the drug. Use of a less than optimal dose may fail to reveal a drug’s true therapeutic potential. This is of particular concern in a head-to-head comparison of two active drugs, where the result may be more due to choice of dose than to choice of drug. Clinicians should strive to achieve drug doses that have proven to be of benefit in clinical trials. At present, a large proportion of patients receiving ACE inhibitor therapy are receiving less than optimal doses (Lenzen et al 2005). Measurement of plasma Ang peptide levels is not feasible for the monitoring of ACE inhibitor therapy, but measurement of plasma AcSDKP levels may assist in this regard (Struthers et al 1999).

5.1. ACE Inhibition in Heart Failure

Heart failure is associated with neurohormonal activation that includes increased renin, Ang II, and aldosterone levels, and activation of the sympathetic nervous
system (Francis et al 1993). Increased Ang II, aldosterone, noradrenaline, and adrenaline levels predict increased mortality in heart failure patients (Swedberg et al 1990). Therapies that counteract the effects of RAS and sympathetic nervous system activation are the cornerstone of heart failure therapy (Hunt et al 2001; Swedberg et al 2005).

Acute ACE inhibition in heart failure patients promotes arterio- and venodilatation, with reduction in both afterload and preload, and an associated increase in cardiac output, stroke volume, and stroke work index, along with a decrease in pulmonary capillary wedge pressure, indicating improved left ventricular (LV) function (Gavras et al 1978; Ader et al 1980). The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) demonstrated reduced mortality and improved symptoms with enalapril therapy in patients with severe heart failure (The CONSENSUS Trial Study Group 1987). Moreover, mortality was lower with enalapril therapy than with hydralazine-isosorbide dinitrate therapy in the second Veterans Administration Cooperative Vasodilator-Heart Failure Trial (V-HeFT II) (Cohn et al 1991). The Studies of Left Ventricular Dysfunction (SOLVD) confirmed the survival benefits of enalapril therapy in patients with reduced LV ejection fraction and heart failure (The SOLVD Investigators 1991) and also demonstrated the prevention of heart failure in asymptomatic subjects with reduced LV ejection fraction (The SOLVD Investigators 1992).

ACE inhibition improves survival, symptoms, and functional capacity, and reduces hospitalisation in patients with moderate and severe heart failure and LV systolic dysfunction (Flather et al 2000; Abdulla et al 2004). ACE inhibition is recommended as first-line therapy in patients with a reduced LV ejection fraction with or without symptoms, and should be up-titrated to the doses shown to be effective in clinical trials (Hunt et al 2001; Swedberg et al 2005).

5.2. ACE Inhibition After Myocardial Infarction

Although the patients recruited to the CONSENSUS, V-HeFT II, and SOVD studies had reduced LV ejection fraction due most often to ischaemic heart disease, they were enrolled several months or more after a myocardial infarction. Studies in rats demonstrated survival advantage of ACE inhibitor therapy commenced 14 days after myocardial infarction (Pfeffer et al 1985b). Additionally, ACE inhibition reduced arterial pressure and total peripheral resistance, attenuated LV remodelling, prevented deterioration in cardiac output and stroke volume index, and prevented the increase in LV volume, LV chamber stiffness and LV end diastolic pressure in rats with myocardial infarction (Pfeffer et al 1985a).

These benefits of ACE inhibition in rats with myocardial infarction were confirmed in patients. The Survival and Ventricular Enlargement (SAVE) trial showed reduced mortality with ACE inhibitor therapy when commenced 3-16 days after myocardial infarction in patients with asymptomatic LV dysfunction (Pfeffer et al 1992). In addition, ACE inhibitor therapy reduced the incidence of both fatal and nonfatal major cardiovascular events, including the development of severe heart failure and recurrent myocardial infarction.
The benefits of ACE inhibitor therapy after myocardial infarction were confirmed in the Acute Infarction Ramipril Efficacy (AIRE) and the Trandolapril Cardiac Evaluation (TRACE) studies (The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators 1993; Kober et al 1995). The AIRE study recruited patients 2-9 days after myocardial infarction who had shown clinical evidence of heart failure at any time. The TRACE study recruited patients 3-7 days after myocardial infarction who had a LV ejection fraction $\leq 35\%$. Both the AIRE and TRACE studies showed survival advantage with ACE inhibitor therapy and the TRACE study showed less development of severe heart failure. Other large clinical trials confirmed the benefits of ACE inhibition after myocardial infarction (GISSI-3 Gruppo 1994; ISIS-4 Collaborative Group 1995).

In addition to mortality benefit and reduction of severe heart failure, ACE inhibition after myocardial infarction attenuates LV remodelling, LV enlargement and increase in LV mass, and improves LV ejection fraction after myocardial infarction (Pfeffer et al 1988; Sharpe et al 1991; Sogaard et al 1993; Johnson et al 1997).

By contrast, the CONSENSUS II trial found the commencement of ACE inhibitor therapy within 24 hours of myocardial infarction did not improve survival (Swedberg et al 1992). The failure of ACE inhibition to improve outcomes in the CONSENSUS II trial may have been due to its protocol. ACE inhibitor treatment was started with intravenous infusion of 1 mg enalaprilat within 24 hours after the onset of chest pain, followed by administration of oral enalapril. Intravascular administration of ACE inhibitor had a negative inotropic effect in several human studies (Foult et al 1988; Haber et al 1994; Zeitz et al 2003), although not in another (Friedrich et al 1994). Thus, the failure of ACE inhibitor therapy to produce benefit in the CONSENSUS II trial may have been due to the negative inotropic effect of intravenously administered enalaprilat, in addition to its administration within 24 hours of chest pain.

Current European Society of Cardiology guidelines recommend the initiation of ACE inhibitors after the acute phase of myocardial infarction in patients with signs or symptoms of heart failure, even if transient, to improve survival and to reduce re-infarctions and hospitalisations for heart failure (Swedberg et al 2005).

5.3. ACE Inhibition in Stable Vascular Disease

Two large-scale clinical trials demonstrated the benefits of ACE inhibition in patients with stable vascular disease or at high risk of vascular disease. These were the Heart Outcomes Prevention Evaluation (HOPE) study (The Heart Outcomes Prevention Evaluation Study Investigators 2000) and The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study (The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Investigators 2003).

The HOPE study was based on emerging evidence that ACE inhibition reduced the risk of myocardial infarction in patients with low ejection fraction (Pfeffer et al 1992; Yusuf et al 1992; Lonn et al 1994). It examined the effects of addition of 10 mg ramipril to standard therapy in patients aged at least 55 years with a history of
coronary artery disease, stroke, peripheral vascular disease, or diabetes, plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol level, cigarette smoking, or microalbuminuria). Patients were excluded if they had heart failure, were known to have a low ejection fraction, were taking an ACE inhibitor or vitamin E, had uncontrolled hypertension or overt nephropathy, or had had a myocardial infarction or stroke within 4 weeks before the study began. During a mean follow-up of 5 years ramipril reduced the primary outcome (composite of myocardial infarction, stroke, or death from cardiovascular causes) from 17.8% to 14.0% (relative risk 0.78, 95% confidence interval 0.70 to 0.86; P < 0.001). Treatment with ramipril reduced the rates of death from cardiovascular causes and all-cause mortality, myocardial infarction, revascularisation procedures, cardiac arrest, heart failure, and complications related to diabetes.

The EUROPA study examined the effects of addition of 8 mg perindopril to standard therapy in patients with previous myocardial infarction, angiographic evidence of coronary heart disease, coronary revascularization, or a positive stress test. Past history of heart failure was recorded in 1.3% of subjects, but none had clinical signs of heart failure, with 10% in New York Heart Association class I and none in class II or higher. During a mean follow-up of 4.2 years, perindopril reduced the primary outcome (composite of cardiovascular death, non-fatal myocardial infarction, cardiac arrest with successful resuscitation) from 9.9% to 8.0% (relative risk 0.80, 95% confidence interval 0.71 to 0.91; P < 0.001). The main contributor to this reduction in the primary outcome was the reduction in non-fatal myocardial infarction. Perindopril also reduced the incidence of heart failure requiring hospitalisation.

By contrast, the Prevention of Events with Angiotsensin Converting Enzyme Inhibition (PEACE) study failed to show an effect of ACE inhibition on its primary endpoint (The PEACE Trial Investigators 2004). The PEACE study examined the effects of addition of 4 mg trandolapril to standard therapy on cardiovascular events in patients with stable coronary heart disease and preserved LV function. During a median follow-up of 4.8 years, trandolapril produced non-statistically significant reductions in the primary endpoint (composite of cardiovascular death, myocardial infarction, and coronary revascularization) from 22.5% to 21.9%, and in cardiovascular death and non-fatal myocardial infarction from 8.5% to 8.3%, although trandolapril reduced hospitalisation or death due to heart failure from 3.7% to 2.8%. Participants in the PEACE study were at lower risk of cardiovascular events than those in the HOPE and EUROPA studies. The baseline blood pressure of PEACE participants was less than that of patients in the HOPE and EUROPA studies, and was similar to the level achieved with active therapy in the HOPE and EUROPA studies. In addition, PEACE participants received more intensive management of risk factors than did those in the HOPE and EUROPA studies, with 70% of PEACE participants receiving lipid lowering therapy (29% in HOPE, 56% in EUROPA), and 72% had undergone coronary revascularization before enrollment (40% in HOPE, 54% in EUROPA). Thus, PEACE participants had an event rate similar to that of the general population (1.6% annualised rate of death), and the
more aggressive management of their risk factors may have negated any potential benefit from ACE inhibitor therapy.

There has been debate about the reasons for the failure of the PEACE study to show an effect of trandolapril on the primary endpoint (Pitt 2004; Fox et al 2006a). Although the dose and type of ACE inhibitor may be implicated, the most likely explanation is the low event rate in its relatively low risk population (necessitating the inclusion of revascularisation as part of the primary endpoint), such that the study did not have sufficient statistical power to achieve its aim. The Ischemia Management with Accupril post bypass Graft via Inhibition of angiotensin converting enzyme (IMAGINE) study similarly showed a lack of benefit from 40 mg quinapril in optimally treated low-risk patients after coronary artery bypass grafting (Keuper et al 2005).

Pooled analysis of the HOPE, EUROPA, and PEACE trials showed ACE inhibition reduced all cause and cardiovascular mortality, non-fatal myocardial infarction, stroke, heart failure, and coronary artery bypass surgery, leading to the recommendation that ACE inhibitors be considered in all patients with atherosclerosis (Dagenais et al 2006). A meta-analysis of the HOPE, EUROPA, PEACE, and other studies came to a similar conclusion (Al-Mallah et al 2006). However, the number needed to treat for 4.4 years to prevent either one death, one non-fatal myocardial infarction, or one coronary revascularisation procedure was 100 (Al-Mallah et al 2006). Current European Society of Cardiology guidelines state: “ACE inhibition is well established in the treatment of heart failure or LV dysfunction and in the treatment of diabetic patients. Thus, it is appropriate to consider ACE inhibitors for the treatment of patients with stable angina pectoris and co-existing hypertension, diabetes, heart failure, asymptomatic LV dysfunction and post-myocardial infarction. In angina patients without co-existing indications for ACE inhibitor treatment the anticipated benefit of treatment (possible absolute risk reduction) should be weighed against costs and risks for side-effects, and the dose and agent used of proven efficacy for this indication” (Fox et al 2006b).

6. MECHANISMS OF THE THERAPEUTIC BENEFITS OF ACE INHIBITION IN HEART FAILURE AND ISCHAEMIC HEART DISEASE

ACE inhibition has many different effects, both systemic and organ-specific (Unger et al 1990). The systemic effects include the reduction of circulating Ang II and aldosterone levels and the increase in kinin and AcSDKP levels. Decreased Ang II and increased kinin levels contribute to the reduction of blood pressure by ACE inhibition.

6.1. Haemodynamic and Coronary Vascular Effects of ACE Inhibition

There is ongoing debate about the extent to which the benefits of ACE inhibition are related to blood reduction, as opposed to intrinsic benefits of ACE inhibition (Sever et al 2006). A major contributor to the benefits of ACE inhibition in heart failure
ACE inhibition in heart failure and ischaemic heart disease may be the reduction in systemic blood pressure, and consequent reduction in heart work. ACE inhibition may improve cardiac function by reducing coronary vascular resistance in patients with heart failure, thereby augmenting cardiac blood flow (Dietz et al 1993).

6.2. Effects of ACE Inhibition on Ang II Levels

ACE inhibition reduces circulating and tissue levels of Ang II in both animals and humans (Campbell et al 1994; Duncan et al 1996; Campbell et al 1999; Zeitz et al 2003). ACE inhibition produced a modest reduction in Ang II levels in EUROPA participants (Ceconi et al 2007). However, the effects of ACE inhibition on Ang II levels can be variable, and depend on the responsiveness of renin secretion (Mooser et al 1990). In situations where renin shows little increase in response to ACE inhibition, the levels of Ang II and its metabolites show a marked fall, with little change in the levels of Ang I and its metabolites. By contrast, a large increase in renin levels in response to ACE inhibition also increases the levels of Ang I and its metabolites. The increased Ang I levels promote Ang II formation by residual uninhibited ACE and by serine protease pathways of Ang I conversion, thereby buffering any fall in Ang II levels during ACE inhibition (Juillerat et al 1990).

Improved survival of heart failure patients with ACE inhibitor therapy is associated with reduction in Ang II and aldosterone levels (Swedberg et al 1990). The role of renin in determining the response of Ang II levels to ACE inhibition is most evident in heart failure, where many patients continue to have elevated Ang II levels despite ACE inhibitor therapy (Roig et al 2000; Campbell et al 2001). It is of note that maximally recommended doses of ACE inhibitor do not completely prevent ACE mediated formation of Ang II in heart failure (Jorde et al 2000). The beneficial therapeutic effects of concomitant β-blocker therapy in heart failure may be due in part to the associated reduction in renin and Ang II levels (Campbell et al 2001).

The effects of ACE inhibitors on Ang II levels are dose dependent (Fig. 3). Studies in rats showed tissue-specific differences in the dose-related effects of ACE inhibition on Ang II levels (Campbell 1996). Renal Ang II levels were reduced by lower doses of ACE inhibitor than were required to reduce Ang II levels in other tissues such as the heart (Fig. 3).

6.3. Effects of ACE Inhibition on Ang-(1-7) Levels

ACE inhibition is accompanied by increased levels of Ang-(1-7). This is due in part to the increase in Ang I levels, with subsequent conversion to Ang-(1-7). Another mechanism for the increase in Ang-(1-7) levels during ACE inhibition is the inhibition of Ang-(1-7) metabolism, given that ACE is an important pathway of Ang-(1-7) metabolism (Chappell et al 1998; Yamada et al 1998). Studies in rats led to the proposal that increased Ang-(1-7) levels mediate in part the hypotensive effects of ACE inhibition (Iyer et al 1998a; Iyer et al 1998b). However, there is as yet no evidence that these mechanisms operate in patients receiving ACE inhibitor therapy.
6.4. Effects of ACE Inhibition on Kinin Peptide Levels

There is ample evidence that kinin peptides contribute to the therapeutic effects of ACE inhibitors (Linz et al 1995; Bönner 1997). ACE inhibitors increase circulating and tissue levels of bradykinin in animals (Fig. 3) and humans (Campbell et al 1994; Duncan et al 1996; Zeitz et al 2003). The effect of ACE inhibition on kinin peptide levels in any tissue compartment depends on the contribution of ACE, relative to other kininases, to kinin peptide metabolism in that compartment. ACE inhibitor therapy did not increase either bradykinin or kallidin peptide levels in cardiac atria of patients with ischaemic heart disease, despite the reduction in Ang II levels (Campbell et al 1999).

The maintenance of low levels of kinin peptides by their efficient metabolism is relevant to the success of ACE inhibitor therapy. ACE inhibition has only a modest effect on kinin peptide levels because of the many other kininases that contribute to kinin metabolism. It is for this reason that ACE inhibitors are generally free of the side effects, such as angioneurotic oedema, that one might expect from increased kinin peptide levels (Nussberger et al 1998; Nussberger et al 2002).

Studies with kinin receptor antagonists indicate a role for kinins in the cardiovascular actions of ACE inhibitors in animals and humans (Linz et al 1995). Studies in humans indicate a role for the B₂ receptor in flow-dependent vasodilatation in normal volunteers (Hornig et al 1997) and in the hypotensive effects in patients with hypertension (Gainer et al 1998; Squire et al 2000). A role for the B₁ receptor is indicated in the systemic haemodynamic effects of ACE inhibition in patients with heart failure (Witherow et al 2001; Cruden et al 2004).

Cardioprotective effects of ACE inhibition that were attenuated by icatibant included the reduction of arrhythmias, reduction of lactate, lactate dehydrogenase, and creatine kinase release, and increase in myocardial contractility and myocardial levels of glycogen, adenosine triphosphate and creatine phosphate during reperfusion of the ischaemic isolated working rat heart (Linz et al 1992). Icatibant attenuated the ACE inhibitor-induced increase in coronary flow and nitric oxide levels in dogs with myocardial ischaemia (Kitakaze et al 2002). Icatibant also prevented the potentiation of ischaemic preconditioning by ACE inhibition in human atria (Morris et al 1997). The post-ischaemic anti-arrhythmic effect of ACE inhibition may be mediated by kinin-induced suppression of endothelin release (Brunner et al 1996).

Icatibant prevented the reduction in myocardial infarct size and the reduction in post-infarct remodelling by ACE inhibition in animal models (Linz et al 1992; Hartman et al 1993; Stauss et al 1994; McDonald et al 1995; Hu et al 1998). However, a subsequent study in an in vivo canine model of myocardial ischaemic injury did not show an effect of ACE inhibition on infarct size (Black et al 1998). Moreover, icatibant did not modify the antihypertrophic effect of ACE inhibition in rats with myocardial infarction, although it partially reversed the reduction in myocardial collagen deposition by ACE inhibitor therapy in one study (Wollert et al 1997).
Possible mechanisms by which kinin peptides mediate the therapeutic benefits of ACE inhibition include the promotion of endothelial production of nitric oxide and prostacyclin, thereby contributing to the correction of endothelial dysfunction and reduced oxidative stress (Linz et al 1995; Bönner 1997; Münzel et al 2001). ACE inhibition induced endothelial NOS (eNOS) in vasculature of control rats, and attenuated the induction of inducible NOS (iNOS) in rats administered bacterial lipopolysaccharide (Bachetti et al 2001). Icatibant prevented the increase in nitric oxide formation in the heart and reduction in myocardial oxygen consumption that accompany ACE inhibition in dogs (Zhang et al 1997). Icatibant also prevented the antiproliferative effect of ACE inhibition in neointima formation following endothelial injury to the rat carotid artery (Linz et al 1992), and the increase in capillary density induced by chronic ACE inhibitor treatment in stroke-prone spontaneously hypertensive rats (Gohlke et al 1997). Part of the benefits of ACE inhibition may be due to the enhancement of insulin-mediated muscle glucose uptake, that is also attenuated by icatibant (Henriksen et al 1996; Henriksen et al 1999).

6.5. **ACE Inhibitor Effects on the KKS Independent of Kinin Levels**

ACE inhibition also affects the KKS by mechanisms separate from prevention of kinin degradation. For example, chronic ACE inhibition in mice and rats induced both renal and vascular B₁ receptor expression without modification of B₂ receptor expression (Marin-Castano et al 2002). Moreover, enalaprilat and other ACE inhibitors in nanomolar concentrations were shown to directly activate the human B₁ receptor, in the absence of ACE and B₁ receptor ligands (Ignjatovic et al 2002).

Several studies show ACE inhibitors may potentiate the effects of bradykinin by a mechanism independent of prevention of kinin metabolism, that involves direct interaction between ACE and the B₂ receptor (Fleming 2006) and attenuation of the sequestration of the B₂ receptor (Benzing et al 1999; Chen et al 2006). Additionally, membrane ACE appears to have its own signalling cascade that is activated by binding of ACE inhibitors (Fleming 2006).

6.6. **Comparison of ACE Inhibitor and ARB Therapy**

One approach to differentiation of the respective roles of the RAS and KKS in mediating the therapeutic benefits of ACE inhibition is the comparison of ACE and ARB therapy. Comparison of ACE inhibitor and ARB therapy after myocardial infarction, or in patients with heart failure, did not show any difference in outcomes (Pitt et al 2000; Dickstein et al 2002; Pfeffer et al 2003; McMurray et al 2006). These studies suggest ACE inhibitor and ARB therapy act through blockade of the RAS, but a role for bradykinin cannot be excluded because losartan was shown to increase bradykinin levels in hypertensive humans (Campbell et al 2005).
Maximally recommended doses of ACE inhibitors do not completely prevent ACE mediated formation of Ang II in heart failure (Jorde et al 2000). Combination of ACE inhibitor and ARB therapy produces more complete blockade of the RAS that is dependent on the dose regimens of the individual therapies (Menard et al 1997; Azizi et al 2004). This combination therapy improves outcomes in heart failure patients (Cohn et al 2001; McMurray et al 2003), but not following myocardial infarction (Pfeffer et al 2003; McMurray et al 2006).

6.7. Effects of ACE Inhibition on AcSDKP Levels

ACE inhibition causes a several-fold increase in AcSDKP levels that may contribute to decreased cardiac inflammation and fibrosis, and to increased myocardial capillary density after myocardial infarction (Wang et al 2004; Yang et al 2004). Elevated AcSDKP levels during ACE inhibitor therapy may also contribute to the anaemia experienced by heart failure patients receiving ACE inhibitor therapy (van der Meer et al 2005).

6.8. Effects of ACE Inhibition on Aldosterone Levels

Heart failure patients have increased plasma aldosterone levels consequent to stimulation of aldosterone secretion by increased Ang II levels (Weber 2001). Evidence that reduced aldosterone levels may contribute to the therapeutic benefits of ACE inhibition is the reduced hypokalaemia in patients receiving ramipril therapy in the HOPE study (Mann et al 2005). In addition to promotion of sodium retention and oedema formation, aldosterone may promote cardiac fibrosis and deterioration in cardiac function (Brilla et al 1993). The possible clinical importance of this mechanism is shown by the benefits of aldosterone receptor antagonists in patients with heart failure, and in patients with LV dysfunction after myocardial infarction (Pitt et al 1999; Pitt et al 2003).

6.9. Effects of ACE Inhibition on Sympathetic Nervous System Activity

Many authors have suggested the reduction in sympathetic activity that may accompany ACE inhibition is due to a reduction in the stimulation of sympathetic activity by Ang II. However, although ACE inhibitor therapy leads to reduction in sympathetic nervous system activity in heart failure, this is thought to be mainly secondary to the improvement of cardiovascular haemodynamics, rather than the specific consequence of reduced stimulation of the sympathetic nervous system by Ang II (Esler et al 2001).

6.10. Effects of ACE Inhibition on Cardiac Remodelling

Cardiac hypertrophy is well recognised as a risk factor for death and cardiovascular events (Levy et al 1990). ACE inhibitors reduce cardiac hypertrophy in hypertensive
patients (Dahlof et al 1992) and also reduce progressive LV remodelling after myocardial infarction (Ferrari 2006). Ventricular remodelling has a dominant role in the pathogenesis of heart failure, and the prevention of remodelling is considered to be an important mechanism of the benefit of ACE inhibitor therapy in heart failure and after myocardial infarction (Cohn 1995; Abdulla et al 2007).

6.11. Effects of ACE Inhibition on Atherosclerosis

Reduction of myocardial infarction and other ischaemic events by ACE inhibition raises the possibility that these drugs inhibit atherosclerosis. ACE inhibitors correct endothelial dysfunction in patients with heart failure and ischaemic heart disease (Drexler et al 1995; Mancini et al 1996; Ceconi et al 2007). These effects of ACE inhibition may be due to the reduction of oxidative stress, vascular remodelling and inflammation by reduced Ang II levels and increased kinin levels. However, current evidence does not allow these data to be extrapolated to a reduction in atherogenesis by ACE inhibition in humans. Despite the prevention of atherosclerosis in animal models, ACE inhibitor therapy was not able to reduce atherogenesis in patients. ACE inhibition with cilazapril did not prevent restenosis after angioplasty (MERCATOR), (MERCATOR Study Group 1992; Faxon 1995). Similarly, Quinapril did not reduce restenosis after coronary stenting; in fact, late loss in minimum lumen diameter was significantly higher in the quinapril group than in controls (Meurice et al 2001). Additionally, ACE inhibition with enalapril failed to reduce progression of coronary atherosclerosis, as assessed by intravascular ultrasound, in patients with coronary artery disease (Nissen et al 2004).

A meta-analysis of randomised controlled studies of the effect of antihypertensive therapies in progression of carotid intima-media thickness showed only a weak, non-significant reduction in progression of carotid intima-media thickness by ACE inhibitor therapy, with significant heterogeneity between studies (Wang et al 2006). Some studies showed a reduction in progression of intima-media thickness by ACE inhibition and some did not. Of note, calcium channel blockers were significantly more effective than ACE inhibitors in their reduction of progression of intima-media thickness (Wang et al 2006).

6.12. Effects of ACE Inhibition on Thrombosis

Reduced rates of myocardial infarction with ACE inhibitor therapy may also be due to an effect of this therapy on the mechanisms of thrombosis and fibrinolysis. ACE inhibition reduced plasma levels of PAI-1 antigen and activity in normal subjects on low salt diet and in subjects following myocardial infarction (Wright et al 1994; Moriyama et al 1997; Oshima et al 1997; Vaughan et al 1997; Brown et al 1998; Brown et al 1999), although this effect of ACE inhibition was not confirmed in other studies of patients with previous myocardial infarction (Zehetgruber et al 1996; Pedersen et al 1997). ACE inhibition also reduced PAI-1 antigen, but not PAI-1 activity, in subjects with congestive cardiac failure (Goodfield et al 1999).
6.13. Effects of ACE Inhibition on Incidence of Type 2 Diabetes

Diabetes is well recognised to accelerate the processes of cardiovascular disease, and reduction of diabetes incidence may contribute to the therapeutic benefits of ACE inhibition. Many large clinical trials, including the HOPE, PEACE, and SOLVD studies, showed a reduced incidence of type 2 diabetes with ACE inhibitor therapy (Abuissa et al 2005). However, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study found ramipril did not reduce diabetes incidence among persons with impaired fasting glucose levels or impaired glucose tolerance, although it significantly increased regression to normoglycaemia (The DREAM Trial Investigators 2006). This improvement in insulin resistance may be due in part to the enhancement of insulin-mediated muscle glucose uptake by ACE inhibition (Henriksen et al 1996; Henriksen et al 1999).

6.14. Effects of ACE Inhibition on Arterial Stiffness

Aortic compliance is an important determinant of coronary blood flow (O’Rourke et al 1999). A recent meta-analysis showed ACE inhibitors decrease arterial stiffness (Mallareddy et al 2006). ACE inhibitors, by increasing aortic compliance, may reduce central systolic blood pressure and maintain diastolic blood pressure, thereby reducing heart work without compromising myocardial perfusion. Decrease in arterial stiffness by ACE inhibition may be due to reduced collagen deposition, as suggested by studies in spontaneously hypertensive rats (Benetos et al 1997). Reduction of aortic collagen deposition by ACE inhibition was not affected by icatibant, suggesting that this effect of ACE inhibition was not mediated by kinins (Benetos et al 1997).

6.15. Effects of ACE Inhibition on Atrial Fibrillation

Atrial fibrillation is an important contributor to poor prognosis in heart failure (Wang et al 2003), and prevention of atrial fibrillation by ACE inhibition may contribute to the therapeutic benefits of this therapy (Vermes et al 2003).

6.16. Interaction Between ACE Inhibitor and Aspirin Therapy

Given that kinin peptides mediate in part the therapeutic benefits of ACE inhibition, and that some of the actions of kinins are mediated by prostaglandins, the question arises whether a drug that inhibits prostaglandin synthesis may attenuate the effects of ACE inhibition. This question was addressed in a systematic review of the interaction between aspirin and ACE inhibitor therapy (Teo et al 2002). The SOLVD study found aspirin prevented the reduction of death by ACE inhibition, but this interaction between aspirin and ACE inhibitor therapy was not significant in the other trials examined. However, both SOLVD and the other trials showed aspirin attenuated the prevention of myocardial infarction or reinfarction by ACE inhibition.
By contrast, there was no evidence that aspirin attenuated the prevention of stroke, hospital admission for heart failure, or revascularisation by ACE inhibitor therapy. When the composite of major vascular events including death, myocardial infarction or reinfarction, hospital admission for heart failure, stroke, and revascularisation was examined, aspirin did not significantly attenuate the benefits of ACE inhibitor therapy. This analysis shows, therefore, that aspirin does interact with ACE inhibitor therapy, at least in the case of myocardial infarction. However, in the absence of clear contraindications, concomitant use of aspirin and ACE inhibitors should be considered in all patients at high risk of major vascular events (Teo et al 2002).

7. CONCLUSIONS

ACE inhibitors have a major role in the treatment and prevention of heart failure and ischaemic heart disease. Reduction in Ang II levels, and increase in kinin and AcSDKP levels, are implicated in the mechanisms of the therapeutic effects of ACE inhibitors. Much of the detail of these mechanisms, however, remains to be discovered.

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