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.

Po Sing Leung (ed.), Frontiers in Research of the Renin-Angiotensin System on Human Disease, 21–54.

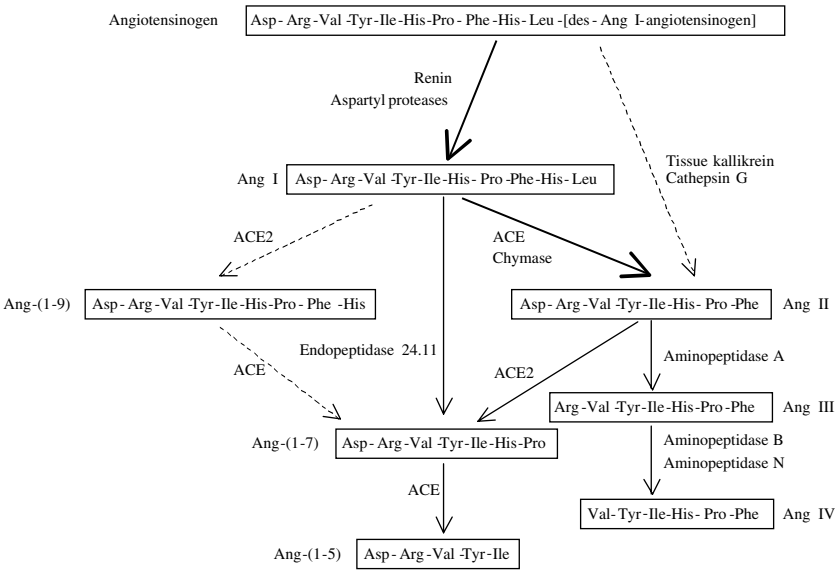

Figure 1. Pathways of Ang peptide formation and metabolism. Adapted from (Campbell 2006)

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

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)

ising 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 AT_1 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 μmol/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). By contrast, the K_m (2 μmol/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). AT_1 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). AT_1-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 (B_2) receptor antagonist icatibant (Pörsti *et al* 1994; Abbas *et al* 1997; Lima *et al* 1997; Gorelik *et al* 1998), and also by

AT_2 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 IC_{50} 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 B_2 receptor agonist by an indirect mechanism that is independent of bradykinin hydrolysis (Deddish *et al* 1998), possibly by sensitisation of the B_2 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 Pro^3 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

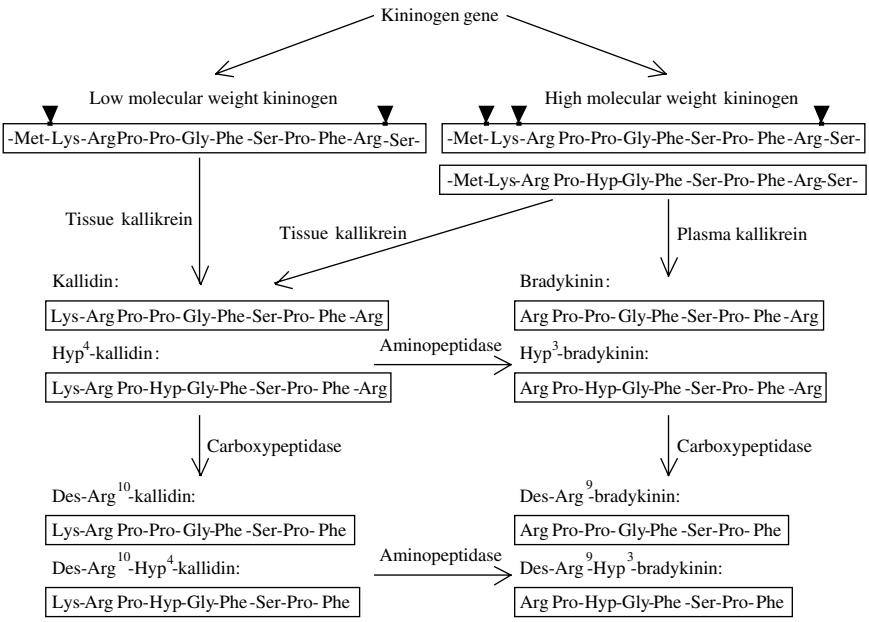

Figure 2. An outline of the formation of kallidin and bradykinin peptides in humans. A proportion of high molecular weight kininogen is hydroxylated on Pro^3 of the bradykinin sequence, giving rise to both hydroxylated and non-hydroxylated peptides. Adapted from (Campbell 2003)

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, α_2-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).

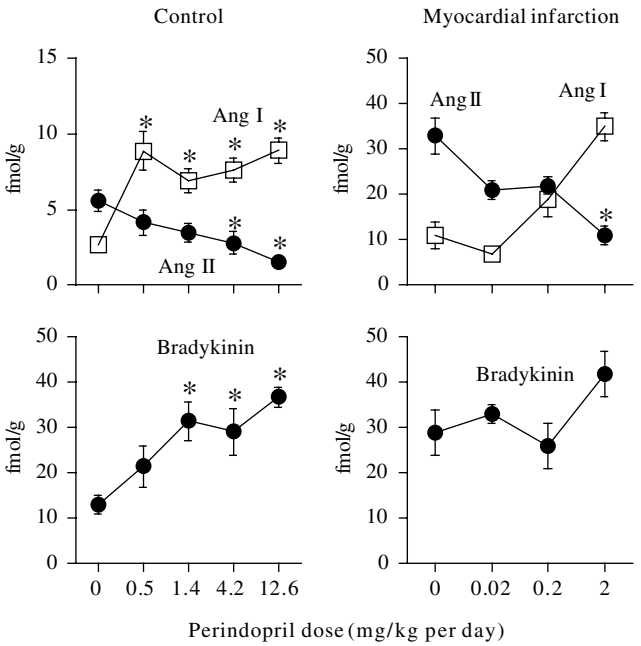

Figure 3. Dose related effects of the ACE inhibitor perindopril on Ang II, Ang I, and bradykinin levels in the cardiac ventricles of control rats and rats with myocardial infarction. *, $P < 0.05$ compared to 0 mg/kg per day perindopril. Data adapted from (Campbell et al 1994; Duncan et al 1996)

3.3. Kinin Receptors

Kinins act via two types of kinin receptor, the B_1 and the B_2 receptors. The B_2 receptor normally predominates, whereas the B_1 receptor is induced by tissue injury. The KKS generates 8 bioactive kinin peptides: bradykinin, Hyp^3-bradykinin, kallidin, and Hyp^4-kallidin act on the B_2 receptor, whereas their carboxypeptidase metabolites des-Arg^9-bradykinin, des-Arg^9-Hyp^3-bradykinin, des-Arg^{10}-kallidin, and des-Arg^{10}-Hyp^4-kallidin act on the B_1 receptor. Hydroxylated kinins have similar biological activity to non-hydroxylated kinins.

Of particular interest is the recent report that the human B_2 receptor is activated by both plasma and tissue kallikrein (Hecquet *et al* 2000). Cathepsin G and trypsin similarly activate the B_2 receptor and activation is blocked by icatibant. Thus, the B_2 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 B_2 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 B_2 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 cardio-protective 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 vasodilatation 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, B_1 receptors may have an important role in angiogenesis (Emanueli *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-ß$_4$ 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-ß$_4$ 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 veno-dilatation, 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 heat 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 trails 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 Angiotensin 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

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 ß-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 B_2 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 B_1 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 prostacylin, 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 B_1 receptor expression without modification of B_2 receptor expression (Marin-Castano *et al* 2002). Moreover, enalaprilat and other ACE inhibitors in nanomolar concentrations were shown to directly activate the human B_1 receptor, in the absence of ACE and B_1 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 B_2 receptor (Fleming 2006) and attenuation of the sequestration of the B_2 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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