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# *Effects of Angiotensin II Antagonists in Comparison to ACE Inhibitors in Patients with Heart Failure due to Systolic Left Ventricular Dysfunction*

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***Abstract.*** **Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce morbidity and mortality in patients with heart failure due to systolic left ventricular dysfunction and are indicated in all patients unless contraindicated or not tolerated. Despite their efficacy, a relatively large percentage of patients in whom these agents are indicated do not receive them, and the patients who do are often given doses less than those shown to be effective in the major morbidity–mortality trials. The failure to use ACE inhibitors appears to be in large part due to their perceived side effects, many of which are related to bradykinin accumulation. The introduction of angiotensin II antagonists such as losartan provides an opportunity to block the effect of angiotensin II without many of the bradykinin-mediated side effects. Emerging data suggest that losartan may have an advantage compared to ACE inhibitors in reducing mortality, which appears to be due primarily to a reduction in sudden cardiac death. The potential mechanisms whereby an angiotensin II antagonist might reduce mortality in comparison to an ACE inhibitor include 1) a possible direct antiarrhythmic effect of the antagonist, 2) the fact that bradykinin, which may promote ventricular fibrillation by causing the prejunctional release of norepinephrine from sympathetic neurons, does not accumulate with use of angiotensin II antagonists as opposed to ACE inhibitors, 3) blockade of effects of angiotensin II produced in the vascular wall and myocardium by non-ACE-dependent mechanisms, and 4) the fact that angiotensin II antagonists increase angiotensin II levels, which may stimulate angiotensin II type 2 and/or other angiotensin receptors with beneficial effects. Large-scale clinical trials are currently under way comparing the effectiveness of angiotensin II antagonists alone and in combination with ACE inhibitors to ACE inhibitors alone in reducing total mortality. These trials will clearly establish whether angiotensin II antagonists are superior to ACE inhibitors in reducing mortality in patients with heart failure due to systolic left ventricular dysfunction, as has been observed with losartan versus captopril in the ELITE study.**

ACE inhibitors have been found to be effective and/or are indicated in the control of hypertension [1], in the progression of renal dysfunction in patients with type 1 diabetes mellitus and proteinuria [2], in reducing morbidity and mortality post-myocardial infarction [3], and in patients with heart failure due to systolic left ventricular dysfunction [4]. Their use, however, has been limited by side effects such as angioedema, cough, first-dose hypotension, renal dysfunction, rash, and taste disturbances [5,6]. These side effects are in part related to ACE inhibitor-induced prevention of bradykinin degradation and/or to specific properties of individual ACE inhibitors [6]. Perceptions as to a relatively high incidence of side effects, especially in the elderly, women, and Asians, have led in part to an underuse of these agents, even where the evidence for their benefit—as in heart failure due to systolic left ventricular dysfunction, where evidence is based upon prospective, double-blind, randomized trials in many thousands of patients—is overwhelming [7]. For example, in elderly patients with heart failure, it is estimated that ACE inhibitors are used in only half of the patients in whom they are indicated [8]. When used, ACE inhibitors are often used at doses considerably lower than those shown to be effective in reducing morbidity and mortality [9]. The introduction of selective angiotensin II antagonists, such as losartan, which have excellent tolerability [10] provides an opportunity to prevent the detrimental effects of angiotensin II on the cardiovascular system without many of the ACE inhibitor-related side effects. Should angiotensin II antagonists prove to be at least equally efficacious as an ACE inhibitor in some or all of the indications for which they are currently used, they would represent a major public health benefit, since they would be expected to be better tolerated and therefore used in a greater percentage of patients at effective doses, with a consequent reduction in morbidity, mortality, and long-term costs.

The most extensive evidence for a beneficial effect of angiotensin II antagonists in humans has been found in hypertension studies. Angiotensin II antagonists have been shown to be effective in reducing systolic and diastolic blood pressure but with a lower incidence of side effects commonly seen with other classes of antihypertensive agents [11,12]. Angiotensin II antagonists have also been shown to be effective in preventing myocar-

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dial hypertrophy in experimental animals [13] and in humans [14]. The prevention of myocardial hypertrophy is of particular importance, since myocardial hypertrophy has been shown to be associated with an increase in the risk of death [15]. Long-term prospective studies such as the Losartan Hypertensive Survival Study and LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) are currently under way to determine the effect of angiotensin II antagonists in patients with hypertension and left ventricular hypertrophy on cardiovascular events, including stroke, nonfatal myocardial infarction, and death [16]. The evidence for the effectiveness of angiotensin II antagonists in patients with heart failure due to systolic left ventricular dysfunction, although less extensive than the evidence for hypertension, is encouraging [17]. This article will review the emerging evidence and potential mechanisms for a beneficial effect of an angiotensin II antagonist in patients with heart failure due to systolic left ventricular dysfunction.

## *The Effect of Angiotensin II Receptor Blocking Agents on Hemodynamics and Neurohormonal Activation in Patients with Heart Failure*

In patients with New York Heart Association (NYHA) class III–IV heart failure due to systolic left ventricular dysfunction, losartan reduced mean arterial pressure and systemic vascular resistance without an increase in heart rate [18]. These changes were accomplished by a compensatory increase in angiotensin II concentration and plasma renin activity and a decrease in plasma aldosterone. Dickstein et al. [19] have studied the effect of losartan in patients with NYHA class III–IV heart failure due to systolic left ventricular dysfunction and have found a significant improvement in left ventricular ejection fraction at a dose of 50 mg qd after 8 weeks, whereas there was no significant improvement in left ventricular ejection fraction in patients randomized to enalapril 20 mg qd. Both losartan and enalapril were, however, equally effective in improving exercise performance, clinical status, and neurohormonal activation, including norepinephrine and n-terminal atrial natriuretic factor.

## *Effect of Angiotensin II Receptor Blocking Agents on Exercise Performance in Patients with Heart Failure*

The effect of angiotensin II antagonists, such as losartan, on exercise performance in patients with heart failure has been examined in placebo as well as in ACE inhibitor controlled trials [20,21]. In placebo-controlled trials of losartan, both in the United States and internationally, no significant benefit of losartan could be detected either by treadmill testing or by a 6-minute walk test after 12 weeks of therapy. Of note, however, is the finding in a meta-analysis of these two studies that patients randomized to losartan had a significant reduction in hospitalization for heart failure and death in comparison to placebo [21].

## *The Effect of an Angiotensin II Receptor Blocking Agent on Mortality in Patients with Heart Failure*

The losartan heart failure study in the elderly, ELITE (Evaluation of Losartan in the Elderly) [22], compared the effect of the angiotensin II antagonist losartan to the ACE inhibitor captopril in 722 elderly patients with symptomatic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction $\leq$ 40%) to determine the tolerability and clinical outcomes (morbidity/mortality) of these two approaches to block the renin–angiotensin–aldosterone system. Although losartan did not demonstrate a significant advantage with regard to the occurrence of persistent renal dysfunction (the primary endpoint), it was significantly better tolerated than captopril, with fewer discontinuations due to study drug intolerance. There was a similar effect in preventing the progression of hospitalization for heart failure in both losartan-and captopril-treated patients, as well as similar effects on improvement in NYHA functional class. In contrast, there was a significant reduction in all-cause mortality, mainly due to reduction in sudden cardiac death, in those randomized to losartan. These effects of losartan on all-cause mortality were relatively similar across all subgroups except for women, who composed less than one third of patients. The effects of losartan on mortality in women is essentially similar to captopril and will need to be reevaluated in a larger prospective randomized study in which total mortality is the primary endpoint.

The observed mortality benefit of losartan in symptomatic heart failure patients in ELITE has been further established in a meta-analysis of all prospective, randomized, double-blind losartan trials in patients with heart failure comprising 1894 patients of whom 740 received control therapy (274 placebo, 96 enalapril, and 370 captopril) and 1154 patients who received losartan. The incidence of death in the control group was 6.35% compared to 3.12% in losartan-treated patients; the odds of dying in the control group were 1.98-Fold greater than in the losartan group (95% confidence interval 1.24–3.17)[17].

The potential benefits of losartan on mortality in patients with systolic left ventricular dysfunction are being further studied in the Losartan Heart Failure Survival Study, ELITE II, in which patients with NYHA class II–IV heart failure and systolic left ventricular dysfunction (LVEF $\leq$ 40%) who are ACE-inhibitor naive are being randomized to a strategy of an ACE in-

hibitor (captopril 50 mg three times daily) or to losartan 50 mg once daily, and followed to a total of 406 deaths. The angiotensin II antagonist valsartan is also undergoing evaluation in a large-scale, 4000-patient mortality trial (VALHeFT) in patients with systolic left ventricular dysfunction and NYHA class II–IV heart failure [23]. In contrast to the ELITE II Losartan Heart Failure Survival Study, where losartan is being compared to an ACE inhibitor (captopril), patients in VALHeFT are being randomized to valsartan 160 mg bid or placebo on a background of ACE inhibitors. The potential mechanisms whereby an angiotensin II antagonist might exert a beneficial effect on mortality in comparison to an ACE inhibitor are of importance both for our understanding of the pathophysiology of heart failure and for the design of future clinical trials and therapeutic strategies.

## *Potential Mechanisms for the Beneficial Effects on Total Mortality and Sudden Cardiac Death of an Angiotensin II Antagonist Compared to an ACE Inhibitor in Patients with Systolic Left Ventricular Dysfunction*

### *Direct antiarrhythmic effect*

ACE inhibitors have not been shown to have a direct antiarrhythmic effect [24]. Their effect on sudden cardiac death is also uncertain. Pahor et al. [24] have reviewed the major ACE inhibitor trials in patients with heart failure. They found three studies in which ACE inhibitors were effective in reducing sudden cardiac death, while in five others there was no effect. In a recent study, Binkley et al. [25] noted that ACE inhibitors but not the angiotensin II antagonist losartan restored autonomic function as assessed by spectral analysis of heart-rate variability on 24-hour ambulatory ECG monitoring. ACE inhibitors failed, however, to restore the abnormal diurnal pattern of autonomic activity in patients with heart failure [26]. They attribute the failure of ACE inhibitors in reducing sudden cardiac death to the inability of these agents to restore the abnormal diurnal variation in autonomic balance to normal [26].

The role of angiotensin II antagonists on ventricular arrhythmias is uncertain. Thomas et al. [27] using an isolated guinea pig model with simulated ischemia and early reperfusion, have suggested that losartan has an antiarrhythmic effect by attenuating the prolongation of transmural conduction times. This antiarrhythmic effect appeared to be independent of losartan's effect as an angiotensin II antagonist. However, further studies in intact conscious animals and man, as well as comparative studies with other angiotensin II antagonists, will be required to determine the importance of this effect and the potential for losartan and/or other angiotensin II antagonists to reduce ventricular arrhythmias.

### *Effect of activation and blockade of the renin–angiotensin–aldosterone system*

Activation of the renin–angiotensin–aldosterone system, with a resultant increase in angiotensin II, has a number of potential adverse effects in patients with systolic left ventricular dysfunction. Although plasma levels of angiotensin II may not be elevated, or only moderately elevated, in patients with systolic left ventricular dysfunction, it has been shown that tissue levels, at least in animals with myocardial damage, are significantly elevated [28]. Increased plasma levels of angiotensin II cause increased vascular resistance in both the coronary and peripheral vasculature [29]. Increased plasma and/or tissue levels of angiotensin II may also activate various growth factors, cytokines, and oxidases, with a resultant release of oxygen free radicals within the vascular wall, and may lead to endothelial dysfunction, vasoconstriction, increased sensitivity of the vascular wall to angiotensin II and other endothelial-mediated vasodilators [30–32], and hence a vicious cycle leading to atherosclerosis and its consequences. Local angiotensin II production as a consequence of myocardial injury can also lead to myocardial hypertrophy and fibrosis [33], which could in itself predispose to sudden cardiac death [34]. While in the normal heart angiotensin II has been shown to have a mild positive inotropic effect, in the failing heart it exerts a negative inotropic effect that can be reversed by losartan [35]. In addition to its adverse effects on the myocardium and vascular wall, angiotensin II causes the release of norepinephrine from sympathetic nerve endings and decreases myocardial norepinephrine uptake [36], which in conjunction with decreased ventricular function and myocardial hypertrophy and/or scarring could predispose to sudden cardiac death. Many of the known physiologic and/or pathophysiologically important effects of angiotensin II have been shown to be due to stimulation of the angiotensin II type 1 ($AT_1$) receptor [37]. The $AT_1$ receptor is coupled to G proteins and involves protein lipase C. adenylate cyclase, and the release of intracellular calcium [38]. Thus, increased plasma and/or tissue levels of angiotensin II with stimulation of the $AT_1$ receptor could be expected to have an adverse effect on the morbidity and mortality of patients with heart failure due to systolic left ventricular dysfunction.

### *Bradykinin generation*

ACE inhibitors and angiotensin II antagonists block the effect of angiotensin II by inhibiting its formation or by blocking its effect on the $AT_1$ receptor. However, unlike ACE inhibitors, angiotensin II antagonists do not block the degradation of bradykinin [39], which has a number of potentially beneficial as well as adverse effects [40].

Bradykinin possess several beneficial effects and is thought to be cardioprotective [40]. By stimulating bradykinin B2 receptors, its triggers the release of nitric

oxide and prostacyclin from the vascular wall [41,42], which may account for the beneficial effects of ACE inhibitors in improving endothelial dysfunction [43]. Bradykinin has also been shown to reduce myocardial oxygen demands [44] and to have an important effect on ventricular hypertrophy and fibrosis [45]. Bradykinin also reduces the incidence of ventricular premature beats and ventricular tachycardia in dogs with myocardial ischemia [46]. Blockade of bradykinin B2 receptors by HOE-140 attenuates this antiarrhythmic effect of bradykinin [47]. Exogenous bradykinin has also been shown to reduce epinephrine-induced arrhythmias by a mechanism involving the release of NO and prostaglandin [48]. ACE inhibitors have also been shown to reduce experimental infarct size and to prevent ventricular remodeling by a bradykinin-mediated effect, since these benefits can be eliminated by the administration of the bradykinin B2 receptor antagonist HOE-140 [49,50]. The beneficial effect of ACE inhibitors at subhemodynamic doses in preventing ventricular hypertrophy and improving myocardial metabolism and infarct size in experimental animals has been attributed in part to ACE inhibitor-induced bradykinin accumulation [51]. These experiments raise the possibility that ACE inhibitors, because of their effects on preventing the degradation of bradykinin, may be more advantageous than angiotensin II antagonists in preventing progressive heart failure and death.

Considerable controversy persists, however, regarding the beneficial effects of ACE inhibitor-induced bradykinin accumulation after myocardial infarction [52–56]. In some models of experimental myocardial infarction, angiotensin II antagonists have been shown to be equal or superior to an ACE inhibitor in preventing ventricular remodeling and prolonging survival after experimental myocardial infarction. In a rat model of high-output failure, an ACE inhibitor and an angiotensin II antagonist have been equally effective in preventing ventricular hypertrophy and hemodynamic deterioration [56]. The finding that the beneficial effects of an angiotensin II antagonist may also be negated in part by the bradykinin B2 receptor antagonist HOE-140 [57] further complicates speculation concerning the differentiation of the therapeutic effects of angiotensin II receptor blockade from those of ACE inhibition. The situation may be further complicated by the suggestion that tissue levels of bradykinin may be more important than plasma levels in producing a cardioprotective effect [58]. Plasma kinins have been found to be released from the heart during myocardial ischemia in experimental animals [59–61] and in humans [62–64]. Duncan et al. [58] found, however, that although an ACE inhibitor could increase myocardial tissue and circulating bradykinin levels in normal rats, a similar increase in animals with myocardial infarction could not be demonstrated. They suggest that the failure of ACE inhibitors to increase myocardial tissue levels of bradykinin in animals with myocardial infarction may have been the result of the induction of other enzymes, such as aminopeptidase and neutral endopeptidase. They attribute the beneficial effect of an ACE inhibitor on ventricular hypertrophy and remodeling in their model to a reduction in angiotensin II formation rather than to bradykinin accumulation.

It should also be pointed out that bradykinin is an endothelial-mediated vasodilator [65]. Endothelial dysfunction is common in patients who require ACE inhibitors for disorders such as hypertension, atherosclerosis, and heart failure, especially the elderly [66]. In patients with coronary artery disease, bradykinin administered directly into a coronary artery failed to produce vasodilatation, whereas the endothelial-independent vasodilator nitroglycerin produced significant vasodilation [67]. In a study in dogs, an angiotensin II antagonist has in fact been found to be a more effective coronary vasodilator than an ACE inhibitor [68]. The beneficial effects of bradykinin, if present, may be less evident in elderly than in young patients. Experimental studies show that bradykinin has less of an effect on vasodilatation in the elderly than in the young [69,70] and may in fact cause vasoconstriction in the elderly [69].

The adverse effects of bradykinin [71] are well known and include an increase in vascular permeability that may contribute to ACE inhibitor-induced angioedema, cough, and under certain circumstances, decrease in glomerular infiltration rate [72]. Less appreciated, however, is the fact that bradykinin causes the release of norepinephrine from prejunctional sympathetic neurons [73]. Direct epicardial application of bradykinin results in a significant increase in renal sympathetic nerve activity [74]. Schwieler et al. compared the effects of norepinephrine overflow of the ACE inhibitor benazeprilat vs. losartan in a canine in situ gracilis muscle preparation [75]. Losartan significantly reduced norepinephrine overflow by 14%, whereas the ACE inhibitor significantly increased norepinephrine overflow by 12%. During ACE inhibition, the bradykinin B2 receptor antagonist HOE-140 significantly reduced norepinephrine overflow. In a model of global ischemia in isolated guinea pig hearts, Hatta et al. [76] observed an increase in norepinephrine overflow and ventricular fibrillation. Administration of the B2 receptor antagonist HOE-140 alone had no significant effect on norepinephrine release or on the duration of ventricular fibrillation in this model. The administration of enalapril, however, caused a further increase in norepinephrine overflow and a prolongation of the episodes of ventricular fibrillation. This effect could be prevented by HOE-140. Administration of an angiotensin II antagonist decreased both norepinephrine overflow and the incidence of ventricular fibrillation. There was a further decrease in norepinephrine overflow and in the incidence of ventricular fibrillation when HOE-140 was administered in addition to the angiotensin II antagonist. The authors suggest that in situations such as myocardial ischemia, angiotensin II may be locally produced in concentrations sufficient to

enhance exocytotic and carrier-mediated norepinephrine release by stimulation of $AT_1$ receptors, resulting in an increase in ventricular fibrillation. Bradykinin appears to release norepinephrine and to increase ventricular arrhythmias only when its half-life is prolonged, e.g., by an ACE-inhibitor, and/or when the effects of angiotensin II are suppressed [76]. The finding that ACE inhibitors not only prolong the half-life of bradykinin but also prevent bradykinin B2 receptor internalization and desensitization [77] could also contribute to the potentially adverse effects of ACE inhibitor-induced bradykinin accumulation under these circumstances.

Bradykinin has also been shown to have an important interaction with ouabain in causing norepinephrine release [78]. In cultured adrenal chromophil cells, the combination of ouabain plus bradykinin results in a significantly greater release of catecholamines than occurs with either agent alone. Bradykinin-induced $Ca^2$ influx into adrenal chromophil cells and the consequent activation of bradykinin B2 receptors is potentiated by a ouabain-induced $Na^+$–$K^+$ ATPase inhibition. Sodium influx into the adrenal cells as a result of bradykinin stimulation is normally balanced by $Na^+$–$K^+$ ATPase and results in increased intracellular $Na^+$ accumulation and $Ca^{2+}$ induced catecholamine secretion. In the ELITE Losartan Heart Failure Trial [22], more than 70% of patients were on digoxin, allowing the postulation that ACE inhibitor bradykinin accumulation in conjunction with digoxin could lead to increased norepinephrine release that might offset the beneficial effect of ACE inhibitor-induced reduction in angiotensin II formation. However, angiotensin II antagonists might have a greater effect in blocking norepinephrine release in patients both with or without concomitant digoxin and might thus prevent sudden cardiac death, since they are not associated with increased bradykinin formation. While this hypothesis is attractive, it should be pointed out that in the ELITE Losartan Heart Failure Trial [22], there was no significant interaction between digoxin and losartan with respect to mortality.

In addition to causing the release of norepinephrine from prejunctional sympathetic neurons, bradykinin has been shown to release interleukin (IL-1B) and tumor necrosis factor from macrophages [79]. This effect of bradykinin could also have important negative inotropic effects through cytokine stimulation of inducible nitric oxide synthase and oxygen free radical production.

Thus, the net effect of ACE inhibitor-induced bradykinin accumulation and therefore the relative effectiveness of an ACE inhibitor and an angiotensin II antagonist is difficult to predict. The relative effectiveness of an ACE-inhibitor compared to an angiotensin I antagonist may depend upon whether norepinephrine overflow is increased by endogenous bradykinin or whether bradykinin-induced nitric oxide or prostaglandin release, or both, protects against catecholamine-induced arrhythmias. These effects may vary among species and experimental conditions. The degree of sympathetic nerve activity, presence or absence of endothelial dysfunction, presence or absence of ischemia, cytokine activation, and prostaglandin synthesis is variable and may be critical in determining the net effect of an ACE inhibitor compared with that of an angiotensin II antagonist on ventricular arrhythmias and sudden cardiac death. ACE inhibitors have been shown to reduce sympathetic nerve activity [80] and metaiodobenzylgaunidine uptake [81] in patients with heart failure. The net effect of bradykinin on this effect is uncertain and may vary depending upon clinical circumstances. Clearly, only direct comparative studies in humans, such as the Losartan Heart Failure Survival Trial, ELITE II, and VALHeFT [23], will determine the relative benefits of ACE inhibitor and angiotensin II antagonists, and therefore, the potential contribution of bradykinin to the beneficial effects of ACE inhibition in patients with heart failure due to systolic left ventricular dysfunction.

### *Non-ACE-dependent angiotensin II formation*

The beneficial effects of losartan compared to captopril in reducing total mortality and, in particular, sudden cardiac death in the ELITE Trial [22] could also be related to more complete blockade of ACE and non-ACE-dependent angiotensin II formation during norepinephrine release and/or to other adverse effects of angiotensin II. Angiotensin II has been shown to be produced by both ACE and non-ACE-dependent mechanisms such as chymase [82]. ACE inhibitors block ACE-dependent angiotensin II formation, whereas angiotensin II antagonists block the effects of angiotensin II produced by both ACE- and non-ACE-dependent pathways. Plasma angiotensin II levels are increased in patients with severe heart failure whose condition deteriorate despite long-term ACE inhibitor therapy at doses shown to be effective in reducing mortality [83]. ACE inhibitors do not block all the effects of angiotensin II on human arteries, whereas losartan or the combination of a chymase inhibitor and an ACE inhibitor has been shown to be more effective, suggesting an important role for non-ACE-dependent angiotensin II formation in human vessels [84,85]. Non-ACE-dependent angiotensin II formation may also be important in the human myocardium [86]. The adverse effects of angiotensin II on myocardial hypertrophy, fibrosis, and contractility in the failing heart could therefore be blocked more effectively by an angiotensin II antagonist, which would block both ACE- and non-ACE-dependent formation of angiotensin II, than by an ACE inhibitor, which would block only ACE-dependent formation of angiotensin II. It has been noted that whereas chymase contributes relatively little to the level of angiotensin II in blood, it is prevalent in the interstitium, in the media, and in adventitial regions of

the vessel wall, where it could have important functional consequences [86]. Of particular interest is the presence of chymase in human mast cells. Schieffer et al. [87] has shown increased chymase expression in mast cells within the shoulder region of atherosclerotic coronary plaques in patients with unstable angina pectoris. There is a direct correlation between the expression of chymase in human coronary arteries and LDL cholesterol [88]. Since mast cells are thought to play an important role in plaque rupture, it can be postulated that, in patients with elevated serum cholesterol levels, an angiotensin II antagonist would be more effective than an ACE inhibitor in preventing plaque rupture. Plaque rupture with subsequent incomplete or complete thrombosis formation and distal platelet embolization has been suggested to be an important mechanism in sudden cardiac death [89]. Thus, in the presence of substantial production of angiotensin II by non-ACE-dependent mechanisms in the myocardium and vascular wall, an angiotensin II antagonist would be expected to exert a more beneficial effect than an ACE inhibitor on angiotensin II-mediated norepinephrine release as well as on plaque rupture and sudden cardiac death. Controversy exists, however, concerning the magnitude of non-ACE- dependent angiotensin II formation in the human myocardium. Further prospective studies must document the importance of this mechanism in patients with heart failure and systolic left ventricular dysfunction from both ischemic and nonischemic causes.

### *Stimulation of angiotensin II type 2 and other angiotensin receptors*

Another possibility relates to the finding that an angiotensin II antagonist may cause an increase in plasma angiotensin II levels as well as unopposed stimulation of angiotensin II type 2 ($AT_2$) and/or other angiotensin receptors [90]. Stimulation of the angiotensin IV receptor in isolated endothelial cells causes release of plasminogen activator inhibitor (PAI-I) [91] and endothelin that cannot be blocked by an angiotensin II antagonist [92]. In the intact organism, however, these effects can be blocked by an angiotensin II antagonist [93,94]. An important role has been suggested for the $AT_2$ receptor in myocardial cell growth and apoptosis [95,96]. Stimulation of the $AT_2$ receptor causes the induction of endothelial nitric oxide synthase [97] and the release of NO [98]. The production of NO by the $AT_2$ receptor could therefore have important benefits on vascular reactivity, platelet adhesion, and myocardial cell growth. In contrast, an ACE inhibitor, by blocking the conversion of angiotensin I to angiotensin II, is less likely to cause stimulation of the $AT_2$ and/or other angiotensin II receptors [90]. Accumulating data suggest that $AT_2$ receptors or the $AT_2$:$AT_1$ receptor ratio, or both, are increased in patients with myocardial hypertrophy [99] and heart failure [100]. Unopposed stimulation of these $AT_2$ receptors after blockade of the $AT_1$ receptor has been suggested to result in local release of nitric oxide directly or through kinins [101]. Myocardial fibroblasts have been shown to express $AT_1$ and $AT_2$ receptors [102,103] as well as specific receptors for angiotensin (1–7) [104]. In cardiomyopathic hamsters with heart failure, an $AT_1$ receptor antagonist decreases the extent of interstitial fibrosis by 28% after 20 weeks of therapy. An $AT_2$ receptor antagonist, in contrast, increased the extent of interstitial fibrosis by 29% [102]. Thus, it would appear that stimulation of $AT_2$ receptors inhibits collagen formation and prevents myocardial fibrosis during cardiac remodeling. This effect may be time dependent, since it was seen after 4 weeks of therapy but not at 20 weeks [102]. Unopposed stimulation of $AT_2$ receptors due to the blockade of the $AT_1$ receptor has been suggested to result in local release of nitric oxide directly or through kinins [101]. In bovine pulmonary endothelial cells, angiotensin II induces endothelial nitric oxide synthase (eNOS) [96]. Administration of an $AT_2$ blocking agent prevented the induction of eNOS, whereas losartan ingiotensin II-induced eNOS, and the combination of losartan and $AT_2$ receptor blocking agent prevented eNOS induction [96]. Liu et al. [101], in a model of chronic heart failure due to myocardial infarction in Lewis inbred rats, have shown that the beneficial effect of $AT_1$ receptor blockade in preventing ventricular remodeling could in part be blocked by the administration of the bradykinin B2 antagonist HOE-140. Administration of an $AT_2$ receptor blocking agent in conjunction with an $AT_1$ receptor blocking agent has resulted in the loss of the beneficial cardioprotective effects of an $AT_1$ receptor antagonist. Liu et al. [101] have proposed that blockade of $AT_1$ receptors results in an increase in renin: angiotensin II: other angiotensins, such as angiotensin (1–7), which stimulate $AT_2$ (1–7); and/or other receptors. Stimulation of the $AT_2$ and/or other receptors may play an important role in the beneficial effect of $AT_1$ receptor blockade by stimulating the release of NO, kinins, and/or other autocoids. Lee et al., in rats spontaneously hypertensive have shown that losartan significantly reduced infarct size, the incidence of ventricular fibrillation, and mortality [105]. They attribute this beneficial effect of losartan to $AT_2$ receptor stimulation with release of NO, and prostaglandins [105]. The beneficial effects of $AT_1$ receptor blockade on the regression of myocardial hypertrophy has also been shown to be prevented by the simultaneous administration of an $AT_2$ receptor blocking agent [108]. Stimulation of the angiotensin (1–7) receptor, in conjunction with bradykinin, causes vasodilatation as well as the release of bradykinin and NO from the endothelium [107,108], which might also contribute to the beneficial effects of an $AT_1$ blocking agent. Fernandez et al. [110] have shown that losartan increases survival in an animal model with abrupt unilateral carotid artery occlusion. The effect of losartan in this model was, however, negated by the concomitant administration of an ACE inhibitor, also suggesting the importance of unopposed

stimulation of $AT_2$ and possibly other receptors in the beneficial effects of $AT_1$ receptor blockade.

## *Combination Therapy*

The potential mechanisms by which an $AT_1$ receptor blocking agent might reduce mortality and sudden cardiac death in comparison to an ACE inhibitor in patients with heart failure due to left ventricular dysfunction are of importance in planning future therapeutic strategies. For example, if an angiotensin II antagonist reduces mortality by more complete blockade of the effects of angiotensin II (whether this blockade is produced by ACE or non-ACE-dependent mechanisms), with a resultant decrease in myocardial hypertrophy, fibrosis, coronary vasoconstriction, and possibly norepinephrine release, then the combination of an ACE inhibitor and an angiotensin II antagonist such as that being tested in VALHeFT [23] might be preferable, since it would provide the beneficial effects of bradykinin accumulation while more effectively preventing the potential adverse effects of angiotensin II (whether ACE or non-ACE dependent). The combination of the ACE inhibitor enalapril 10 mg twice daily and losartan 50 mg once daily has been compared to enalapril 10 mg twice daily in the Randomized Angiotensin Converting Enzyme Angiotensin Receptor Antagonist Study (RAAS) [111,112]. In this study, the combination of enalapril and losartan was well tolerated in patients with symptomatic heart failure and systolic left ventricular dysfunction. The combination resulted in a significant decrease in serum aldosterone levels in comparison to target-dose enalapril (10 mg twice daily) and high-dose enalapril (20 mg twice daily), as well as trend toward more effective suppression of norepinephrine in patients with an elevated level at baseline (>300 pg/mL). Other studies in patients with heart failure have shown that combination therapy with an angiotensin II antagonist, such as valsartan and an ACE inhibitor, to be more effective in reducing pulmonary capillary wedge pressure than monotherapy, with an ACE inhibitor in patients with heart failure and systolic left ventricular dysfunction [113,114]. These studies have, however, been too small and too short in duration to determine the effect of combination therapy on morbidity and/or mortality. In a canine model induced by atrial pacing [115,116] the combination of valsartan and an ACE inhibitor has been found to be significantly better than valsartan alone in preventing ventricular remodeling and some of the consequences of heart failure. The effects of angiotensin II antagonists on ventricular remodeling may, however, under certain circumstances be less important in improving survival than their effects on coronary hemodynamics, nitric oxide, and/or norepinephrine release. For example, in a rat model of myocardial infarction, the angiotensin II antagonist irbesartan improved survival in comparison to control animals without irbesartan but had relatively little effect in preventing ventricular remodeling [117]. In the ELITE Trial [22], losartan appeared equally effective as captopril in preventing progressive heart failure and ventricular remodeling [118] but was significantly better in improving survival [22]. Regardless of its effectiveness in preventing ventricular remodeling, the risk–benefit and cost–benefit effects of combination therapy will need to be prospectively investigated in comparison to monotherapy with losartan and other angiotensin II antagonists with regard to survival. One of the major benefits of angiotensin II antagonists in patients with heart failure is the tolerability of these agents in comparison to ACE inhibitors [119]. A major reason that ACE inhibitors have failed to be more widely used in patients with heart failure is the perceived side effects of these agents. In a study of patients with hypertension who were not controlled with the ACE inhibitor lisinopril, the addition of losartan resulted in better blood pressure control but also a 20% increase in the incidence of cough [120]. Thus, the benefit of combination therapy will need to be carefully investigated with regard to its tolerability and effectiveness in all patients with heart failure due to systolic left ventricular dysfunction, rather than in only the subset of patients who tolerate an ACE inhibitor. However, if losartan reduces mortality in comparison to captopril in ELITE II due to an antifibrillatory effect, independent of its effect on $AT_1$ receptor blockade, or perhaps more likely due to a lesser degree of bradykinin accumulation and norepinephrine release or a greater degree of unopposed stimulation of $AT_1$ and/or other angiotensin II receptors [90] with subsequent release of NO and/or prostaglandins, the combination of an ACE inhibitor and an angiotensin II antagonist might not be as effective as an angiotensin II antagonist alone.

## *Conclusions*

The results of the evaluation of Losartan in the Elderly (ELITE) heart failure study [22] are clearly an important stimulus for further basic and clinical investigation into the mechanisms responsible for cardiovascular death in patients with heart failure due to systolic left ventricular dysfunction. Whether these effects on sudden cardiac death are specific to losartan or to other angiotensin II antagonists as well will, however, require the results of the ELITE II Losartan Heart Failure Study and other prospective randomized trials such as VALHeFT [23] to determine their clinical role in comparison to ACE inhibitors for the therapy of patients with heart failure due to systolic left ventricular dysfunction. The suggestion that the angiotensin II antagonist candesartan alone or in combination with enalapril does not have as beneficial an effect as enalapril alone in patients with heart failure [121] suggests that we cannot extrapolate the beneficial effects of

losartan in ELITE [22] to all angiotensin II antagonists. Likewise, it may be prudent to await the results of further large-scale randomized trials such as ELITE II and VALHeFT [23] before routinely using any angiotensin II antagonist, including losartan, alone or in combination with an ACE-inhibitor in patients with heart failure in whom an ACE inhibitor is indicated and well tolerated.

It should, however, be pointed out that losartan, but not candesartan, inhibits vascular thromboxane $A_2$/prostaglandin $H_2$ receptors [123]. These receptors have been associated with arachidonic acid-induced sudden cardiac death [124]. In spontaneously hypertensive rats, Li et al. have found that losartan, but not candesartan, prevents thromboxane $A_2$/prostaglandin $H_2$-induced platelet aggregation and vasoconstriction [125]. Losartan, but not candesartan, augments acetylcholine-induced nitric oxide-dependent vasodilatation and abolishes endothelium-derived, constricting factor-mediated vasoconstriction [125]. The dose of losartan shown to be beneficial in these experiments may, however, be beyond the pharmacologic range. These experiments will need to be confirmed in humans at pharmacologic doses before we can attribute any potential difference between losartan and candesartan or other angiotensin II antagonists to this mechanism.

Perhaps the most important lesson from ELITE [22] and other studies of the renin–angiotensin–aldosterone system is that while experimental studies are of importance in determining pathophysiologically important mechanisms, the relative importance of any individual mechanism may be species and/or model dependent. Our current understanding of mechanisms, especially with regard to the renin–angiotensin–aldosterone system, is as yet incomplete. Studies of specific receptor-mediated mechanisms and/or specific receptor antagonists, while suggestive, may not be conclusive due to positive and/or negative neurohumoral feedback loops, cross-talk between receptors, internalization and desensitization of receptors, and/or uncoupling of receptors from their effector signaling pathways. While the results of large-scale clinical trials may not necessarily provide insight into pathophysiologic mechanisms, they do provide insight into the net effect of therapeutic strategies, at least under the particular circumstances of the clinical trial. Only by well-designed, large-scale, prospectively randomized clinical trials and smaller-scale preclinical and clinical studies designed to investigate specific mechanisms can we hope to increase our understanding of disease processes and to develop new and more effective therapeutic strategies.

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