Recent Insight Into Therapy of Congestive Heart Failure: Focus on ACE Inhibition and Angiotensin-II Antagonism

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One possible intervention to interrupt the deleterious effects of the renin-angiotensin system is suppression of angiotensin II (Ang II) formation by inhibition of angiotensin-converting enzyme (ACE). However, ACE inhibition incompletely suppresses Ang II formation and also leads to accumulation of bradykinin. Angiotensin II type 1 (AT1) receptors are believed to promote the known deleterious effects of Ang II. Therefore, AT1 receptor antagonists have been recently introduced into therapy for hypertension and congestive heart failure (CHF). Although there are significant differences between the effects of AT1 receptor antagonists and ACE inhibitors including the unopposed stimulation of angiotensin II type 2 (AT2) receptors by AT1 receptor antagonists, the discussion of whether ACE inhibitors, AT1 receptor antagonists or the combination of both are superior in the pharmacotherapy of CHF is still largely theoretical. Accordingly, AT1 receptor antagonists are still investigational. Angiotensin-converting enzyme inhibitors remain first line therapy in patients with CHF due to systolic dysfunction. However, in patients not able to tolerate ACE inhibitor induced side effects, in particular cough, AT1 receptor antagonism is a good alternative. In clinical practice, emphasis should be placed on increasing the utilization of ACE inhibitors, as more than 50% of patients with CHF do not receive ACE inhibitors. In addition, the majority of those on ACE inhibitors receive doses lower than the dosage used in the large clinical trials. Although not yet completely proved, it is likely that high doses of ACE inhibition are superior to low doses with respect to prognosis and symptoms. (J Am Coll Cardiol 1999;33:1163–73) © 1999 by the American College of Cardiology

One of the major consequences of reduced cardiac performance in chronic congestive heart failure (CHF) is activation of the sympathetic nervous system and the renin angiotensin system (RAS) (1,2). Angiotensin (Ang) II is believed to mediate the deleterious effects of RAS activation. Apart from other effects, Ang II induces vasoconstriction, aldosterone secretion and possibly activation of the sympathetic nervous system and norepinephrine release (3). Vasoconstriction and volume overload lead to augmented wall stress which increases myocardial oxygen consumption (4). Together with other mechanisms (5,6), this promotes myocardial dysfunction, which further stimulates the RAS as well as the sympathetic nervous system.

One possible intervention to interrupt this vicious cycle may be suppression of Ang II formation by inhibition of ACE. Several large clinical trials have shown that ACE inhibitors reduce mortality and morbidity in patients with CHF (7–11). However, ACE inhibition incompletely suppresses ACE activity and thus Ang II formation (12,13). Further, Ang II production may occur independently of ACE via other pathways (14,15). This may explain why plasma aldosterone concentrations tend to rise on ACE inhibitors after an initial fall (16).

Angiotensin II type 1 (AT1) receptors are believed to promote the known deleterious effects of Ang II. Therefore, AT1 receptor antagonists have been recently introduced into therapy for hypertension and CHF (17). Angiotensin II type 2 (AT2) receptor mediated effects in CHF are largely unknown but may be involved in antihypertrophic, pro-apoptotic effects on the myocardium (18). These effects could be important since AT1 receptor antagonism leads to an increase in Ang II levels (19). In addition, Ang II is cleaved to Ang III and IV (20). These degraded peptides have been claimed to have important biologic actions (21) not inhibited by AT1 receptor antagonists.

Furthermore, in contrast to AT1 receptor antagonists, ACE inhibition leads to accumulation of bradykinin, which is responsible for some of the side effects of ACE inhibitors but may also have a therapeutic benefit in CHF (22,23).

It is apparent from these observations that there are significant differences between the AT1 receptor antagonists and ACE inhibitors, beyond issues of tolerability and selective blockade of the AT1 receptor. Thus, AT1 receptor antagonists are not just “better ACE inhibitors.” Figure 1 depicts the site of action of ACE-inhibitors and AT1...
receptor antagonists and the theoretical differences between these two classes of drugs.

This article will focus on properties of ACE inhibitors and AT1 receptor antagonists and theoretical differences between them. The significance of these differences with respect to morbidity and mortality in CHF are largely unknown. Nevertheless, a clearer understanding may be helpful in planning new clinical studies and individualizing therapy for patients. This review will also endeavor to summarize the clinical data comparing these two drug classes with an emphasis on underutilization and suboptimal dosage of ACE inhibitors in therapy for CHF and the possible impact of AT1 receptor antagonists on these issues.

THEORETICAL ISSUES OF ACE INHIBITORS VERSUS AT1 RECEPTOR ANTAGONISTS

Differences that may exist between the two classes of drugs are as follows (Fig. 1):

1) Angiotensin-converting enzyme inhibition decreases activity at all Ang receptors. Angiotensin II type 1 receptor antagonists are selective, therefore Ang may act unopposed on other receptors. Angiotensin II type 1 receptor mediated effects may be suppressed more completely by AT1 receptor antagonists,

2) angiotensin converting enzyme inhibition causes significant bradykinin accumulation, and

3) the sympathetic nervous system may be differentially influenced by the two classes of drugs.

Angiotensin receptors. There are believed to be four Ang receptors—AT1 through AT4. The AT1 receptor is believed to mediate the classic actions of Ang II such as vasoconstriction and sodium and water retention and also seems to play a role in cardiovascular remodeling (Fig. 1) (5,24–27). The AT2 receptor appears to have a role in cellular growth and remodeling; however, other functions are less well defined. The role of the other Ang receptors is less well characterized.

Suppression of AT1 receptor mediated effects. Angiotensin II type 1 receptor antagonists may suppress the AT1

Figure 1. Cascades of RAS and kinins and mechanisms of action of ACE inhibitors and AT1 receptor antagonists. Conversion from Ang I to Ang II promoted by ACE and non-ACE pathways. Accordingly, ACE inhibitors cannot completely inhibit Ang II formation. Angiotensin II effects are mediated by AT1- and AT2-receptors. While AT1-receptor mediated effects are well defined, AT2-receptor mediated effects are less clear. Angiotensin II type 1 receptor effects can be inhibited by AT1 receptor antagonists while AT2 receptor mediated effects and the formation of Ang III and IV are unconstrained by them. Angiotensin II type 2 receptor stimulation might increase bradykinin levels. Thus, it is possible that increased bradykinin levels may be caused not only by ACE inhibition, but also by AT1 receptor antagonism to a lesser extent. AT = Ang II receptors; t-PA = tissue plasminogen activator; SNS = sympathetic nervous system; GFR = growth factors; PAI = plasminogen activator inhibitor. White arrows indicate enzymatic activation, black arrows formation of substances, double arrows receptor or substance mediated effects.
receptor mediated effects more completely than ACE inhibitors (28). Angiotensin II type 1 receptor antagonists block these effects directly at the receptor site while ACE inhibitors act only indirectly by inhibition of Ang II formation. However, this inhibition of Ang II formation is incomplete only. Plasma levels of Ang II after chronic ACE inhibition tend to return towards initial values (29), probably due to a reactive rise in renin and Ang I levels as well as Ang II formation by alternative pathways such as cardiac chymase (30). Nevertheless, dosage of ACE inhibitors may affect Ang II levels since only high doses have been shown to suppress plasma ACE activity almost completely throughout 24 h in chronic therapy (31). Low to moderately high doses suppress it only partially (13,32). This finding concurs with the findings that high ACE inhibitor doses lower aldosterone concentration (33) and suppress Ang II formation in plasma more effectively (12).

**Cellular growth and remodeling.** Fibrosis and remodeling, now well recognized processes in various cardiac diseases, may impair cardiac function (34,35). Decompensated cardiac failure is associated with increased mRNA expression of extracellular matrix proteins which manifests as cardiac fibrosis (36). Angiotensin II type 1 receptors appear to be involved in this process (37–39) while AT2 receptors may counteract the AT1 mediated effects (37,40).

The differential distribution of AT1 and AT2 receptors in normal and failing human hearts has recently been shown (41). Focal areas of very high AT2 receptor density were localized to areas of fibroblast activity and collagen deposition in the failing human heart. The infarct/noninfarct border zone also showed high AT2 and ACE levels (41). This suggests that the RAS is involved in fibrotic repair after cardiac insults. In response to Ang II, rat cardiac fibroblasts and myofibroblasts produce transforming growth factor β which may stimulate cardiac fibrosis. This effect can be attenuated by losartan and to a lesser extent AT2 antagonists (38). Angiotensin II type 1 receptor antagonists used in the rat infarct model of CHF have been shown to derive part of their beneficial effect from high Ang II levels on unopposed AT2 receptors (40). In addition, AT2 blockade in rats following myocardial infarction showed significant reductions in interstitial cell DNA synthesis and a decrease in cardiac output, not observed when an AT1 antagonist was used (42), supporting the role of AT2 receptors in myocardial repair. However, results in models of acute ischemia using AT2 receptor antagonism are contradictory. These studies showed improved recovery after ischemia-reperfusion in isolated working rat hearts (43). In addition, AT2 receptors may stimulate apoptosis (18), which may be related to myocardial cell loss in CHF (44). Thus, it is not yet clear whether stimulation of AT2 receptors is beneficial in CHF. Although the inhibitory effects on remodeling and cardiac fibrosis as well as vasodilatation are believed to be beneficial, it is conceivable that the net effect is dependent on the stage and the underlying cause of CHF. This may be supported in that Ang receptors appear to have different functions in animal models of CHF (40), myocardial infarction (42,43) and hypertension (39), suggesting different roles in different pathological processes. Confounding the interpretation of results further is the cross species difference in receptors, exemplified by the differential chromosomal distribution of receptors between humans and animals (45).

Angiotensin II may also play a role in vascular pathology which seems to be mediated by AT1 receptors. The application of Ang II to the rat carotid artery has been shown to induce adventitial thickening in vivo (46). Moreover, monocyte infiltration into vessel walls partially mediated by monocyte chemotactic protein-1 (MCP-1) is believed to play a role in atherogenesis. Angiotensin II increases MCP-1 levels, while losartan attenuates this effect (47). In addition, the platelet derived growth factors α and β, implicated in the pathogenesis of atherosclerosis (48), are markedly diminished by AT1 receptor antagonists in balloon injured rat carotid arteries (49). Results from the TREND study indicate that inhibition of Ang II formation improves vascular function (50). However, it remains to be determined whether this effect is primarily AT1 receptor mediated.

**Angiotensin type IV receptor and fibrinolytic system.** Plasminogen activator inhibitor C-1 (PAI-1) plays a critical role in the balance of the fibrinolytic system. It is synthesized locally in endothelium and smooth muscle cells and is therefore important in local thrombosis. In fact, PAI-1 levels have been shown to be elevated in human atherosclerotic plaques, and younger survivors of myocardial infarction have significantly elevated PAI-1 levels (51). Angiotensin IV stimulates endothelial release of PAI-1 through its action on the specific AT4 receptor (52). In the HEART study, the effect of ramipril on plasma fibrinolytic balance in patients with acute anterior myocardial infarction demonstrated that the ACE inhibitor treated group had a significant decrease in PAI-1 levels compared with the placebo group (53). However, it remains to be seen whether the increase in Ang IV formation by AT1 receptor antagonists is of therapeutic importance.

**Effects of bradykinin accumulation caused by ACE inhibition.** Angiotensin converting enzyme is a ubiquitous enzyme, predominantly synthesized in endothelium, particularly in the lung. It is responsible for converting Ang I to Ang II and for degrading bradykinin to inactive peptides and amino acids (Fig. 1).

**Hemodynamics.** Angiotensin converting enzyme inhibitors have significant hemodynamic effects which may be partially mediated by bradykinin. Smooth muscle and endothelial cells of muscular arteries and arterioles possess bradykinin type 1 (B1) and bradykinin type 2 (B2) receptors (54). There is evidence that bradykinin induced arterial dilation is largely endothelial dependent (55). Quinaprilat
induces arterial vasodilatation in humans, partly by increasing release of nitric oxide (56), and ACE inhibition has also been shown to enhance flow dependent endothelial dilation in humans through a bradykinin mediated effect (57). Additionally, bradykinin induces dilation of epicardial and resistance coronary arteries in humans, which is NO-dependent and enhanced by prior ACE inhibition (58). Angiotensin converting enzyme inhibitors further promote NO production in coronary microvessels from failing explanted human hearts (59). In a study on the rat infarct model of CHF, beneficial effects on cardiac function and remodeling obtained by an ACE inhibitor were partially mediated by B2 receptors (40). Dogs with CHF have high levels of endogenous bradykinin, which has significant positive effects on cardiac function (60). These results together with the natriuretic effects of bradykinin (61) suggest that the kinin system may be an important mediator through which ACE inhibitors achieve their therapeutic effect (62). Nevertheless, clinical studies do not support significant hemodynamic differences between ACE inhibitors and AT1 receptor antagonists (63). A possible explanation may be that AT1 receptor antagonists more effectively suppress AT1 receptor mediated vasoconstriction (28), while ACE inhibitor induced hemodynamic effects are a result of partial suppression of Ang II formation and accumulation of bradykinin.

Ischemic cardiac events. It is believed that the pathogenesis of ischemic cardiac events may involve an imbalance in the local coagulatory system. Fibrinolytic dysfunction is thought to play a critical role in the pathogenesis of acute ischemic events (64). Bradykinin is a potent stimulator of tissue plasminogen activator (t-PA) release and may therefore have an important role in the balance of the fibrinolytic system. Infusions of bradykinin in humans markedly elevated t-PA in subjects pretreated with the ACE inhibitor captopril or quinapril (65). However, in the HEART study, despite a reduction of PAI-1 levels by 44%, ramipril showed no effect on t-PA (53). Bradykinin appears to inhibit the alpha-thrombin induced activation of platelets and therefore may inhibit their aggregation (66). There is also suggestive evidence that bradykinin, by acting on B1 receptors on the surface of platelets, may influence the arachidonic acid cascade, hence having a role in the regulation of platelet function (67).

Angiotensin converting enzyme inhibition may augment ischemic preconditioning, which is considered an important cardioprotective mechanism in acute myocardial ischemia. It has been suggested that this effect is mediated by bradykinin, as HOE-140, a specific B2 receptor antagonist, abolished this cardioprotective effect in human atrial trabeculae (68).

Specific lipid abnormalities are established causal factors in the pathogenesis of coronary vascular disease. Oxidized LDL is a powerful atherogenic agent. In a study on rat aorta incubated in human oxidized LDL, ramipril prevented the development of endothelial dysfunction probably via a B2 receptor mediated effect, while losartan (AT1 receptor antagonist) did not (69).

These potentially beneficial effects of bradykinin on ischemic cardiac events might explain the decrease in ischemic events by ACE inhibition as shown in the SAVE-trial (11). However, the effect of bradykinin on ischemia may be diminished in patients with endothelial dysfunction and the effect may differ between species (62).

Adverse effects. Angiotensin converting enzyme inhibitor induced cough may be a result of bradykinin accumulation; inhaled bradykinin has been shown to significantly increase airway hyperresponsiveness to allergenic stimuli in sheep (70). In patients with ACE inhibitor induced cough, a significant correlation between intradermal inflammatory response to bradykinin and incidence of cough has been shown (71). Thromboxane A2 may play an important role in kinin-mediated cough. Angiotensin-converting enzyme inhibitor cough has been shown to be significantly reduced in humans by the use of thromboxane synthetase antagonists (72,73).

Angioedema is a potentially life-threatening complication of ACE inhibitor therapy with an incidence of 0.1% to 0.2% (74). The pathophysiology is poorly understood; however, a recent human study showed significant elevations in plasma bradykinin during acute attacks of captopril induced angioedema (75). There may be racial differences in susceptibility to ACE inhibitor induced angioedema; African-Americans have a greater sensitivity to accumulation of bradykinin and an increased incidence of angioedema (76).

Renal dysfunction is a well-recognized complication of ACE inhibitor therapy, particularly in cardiac failure, which may be partially mediated by bradykinin accumulation. Since bradykinin causes a NO-dependent renal vasodilation (77), it may lead to a drop in renal perfusion pressure in situations where systemic and renal pressure are borderline. Nevertheless, there was no difference in renal dysfunction in the ELITE trial comparing captopril and losartan (78).

Angiotensin and the sympathetic nervous system. Activation of the sympathetic nervous system is believed to be of importance in the progressive nature of cardiac failure and the high incidence of sudden death (79,80). Chronic ACE inhibition in CHF may reduce sympathetic activity (81,82) and augment baroreflex control of sympathetic activity in CHF (83). Baroreflex control of sympathetic outflow in rabbits is also improved by losartan (84). Angiotensin II type 1 blockade and ACE inhibition produce similar decreases in cardiac beta-adrenergic signal transduction in transgenic rats with cardiac failure (85). Angiotensin-converting enzyme inhibition enhances cardiac responsiveness to adrenergic stimuli which is depressed by beta-receptor down-regulation in individuals with left ventricular dysfunction (86). Whether these effects are due to direct inhibition of the sympathetic nervous system or as a
consequence of hemodynamic improvement is unknown. However, Ang II increases noradrenaline release from atria by acting on AT1 receptors in isolated guinea pig hearts (87). Given the more complete blockade of AT1 receptor mediated effects, AT1 receptor blockade may result in a more complete suppression of the sympathetic nervous system. In addition, bradykinin releases noradrenaline as a reflex response (88). Angiotensin II type 1 receptor antagonists may also directly decrease central sympathetic tone since there is a high concentration of AT1 receptors in the rostral ventrolateral medulla, a region involved in modulation of sympathetic vasomotor tone (89), and AT1 receptor antagonists may pass the blood-brain barrier more easily than ACE inhibitors (45). However, unopposed AT2 receptors in the adrenal gland may elicit the local release of catecholamines (90).

The maintenance of sodium balance by the kidney is regulated in part by sympathetic activity, and renal sympathetic tone is high in human CHF (91). In rats with experimental CHF, losartan improved cardiac baroreflex regulation of renal sympathetic nerve activity. This was associated with improved ability to excrete acute and chronic sodium loads (92). Renal sympathetic inhibition may underlie the ability of both AT1 antagonists and ACE inhibitors to prevent cardiac decompensation by counteracting volume overload.

The available data suggests that ACE inhibitors and AT1 antagonists may have differing effects on sympathetic activity in CHF; however, it is likely that both drug classes act favorably in this regard.

CLINICAL COMPARISON OF ACE INHIBITION AND AT1-RECEPTOR ANTAGONISM IN HEART FAILURE

There have recently been reported several small, short term studies investigating the effects of AT1 receptor antagonists as compared with those of ACE inhibitors on symptoms, hemodynamics, neurohormones and exercise capacity in patients with CHF. They suggest that both classes of drugs are equally effective with respect to these endpoints. The first reports comprised a comparison of losartan with enalapril in two parallel, randomized studies including 166 and 112 patients with symptomatic CHF (93,94). Both drugs had comparable effects on symptoms, exercise capacity and neurohormones over a period of 8 to 12 weeks. More recent studies investigating losartan (95), irbesartan (96) and valsartan (63) as compared with ACE inhibition, confirmed these results. No study as yet has directly compared the different AT1 receptor antagonists. It is therefore impossible to say at this stage whether there will be clinically relevant differences between the various AT1 receptor antagonists in patients with CHF.

ELITE was the first study of sufficient size (n = 722) and duration (follow-up, 48 weeks) to allow comment on relative survival benefits (78). The AT1 receptor antagonist losartan was compared with the ACE inhibitor captopril in patients with a left ventricular ejection fraction ≤40%. Perhaps surprisingly, survival was significantly better with losartan, largely attributable to lower sudden cardiac death rate. In addition, losartan was better tolerated, although the primary end-point — renal dysfunction — was similar in both groups. The authors concluded that losartan has an apparent mortality advantage over captopril. However, the difference in sudden cardiac death between the two groups in absolute numbers was only nine (5 vs. 14) (78). It is also important to note that this study was not designed to have significant statistical power to show any difference in mortality (62).

RESOLVD, a study similar in size to ELITE, included 769 patients with symptomatic systolic left-ventricular dysfunction followed for a period of ten months. The AT1 receptor antagonist candesartan at three different doses (4 mg, 8 mg and 16 mg daily) was compared with the ACE inhibitor enalapril alone and the combination of both drugs (97). Although this study was also not designed to show any effects on mortality, it is remarkable that the trend was the opposite of the ELITE study, showing a better outcome with the ACE inhibitor (p = 0.15). A direct comparison between the RESOLVD and ELITE studies is not possible, in part because the data from the RESOLVD study has been published only in abstract form. However, given the similar effects of captopril and enalapril on survival in a broad range of patients (7), the decrease in mortality of 46% by losartan (ELITE) and the increase in mortality by candesartan of 60% (RESOLVD), the results might translate in a cross-study comparison into a mortality rate approximately three times higher on candesartan than on losartan. Such a huge difference is improbable and emphasizes the randomness of trial results which can be achieved with statistically underpowered studies. Accordingly, whether AT1 antagonists are beneficial in CHF remains to be elucidated. Until larger mortality trials comparing ACE inhibitors with AT1 receptor antagonists are available, the use of AT1 antagonists in CHF will remain investigational and ACE inhibitors remain first line treatment in CHF.

Combined therapy of ACE inhibition and AT1 receptor antagonism. As discussed in detail above, it is possible that bradykinin accumulation contributes to the beneficial effects of ACE inhibitors. In addition, AT1 receptors mediate most of the harmful effects of Ang II. Thus, the incomplete suppression of AT1 receptor mediated effects and the accumulation of bradykinin by ACE inhibitors provide rationale for the combination of ACE inhibitors and AT1 receptor antagonists in the therapy of CHF. However, the role and effectiveness of such a combination remains to be better defined. In the RESOLVD study, remodeling of the left ventricle, plasma levels of natriuretic peptides and suppression of aldosterone production were beneficially influenced by the combination of candesartan and enalapril, as compared to either drug alone which led to similar results. There was no significant difference in tolerability between the different groups (97). In addition, hemody-
namic benefits have been observed after administration of valsartan in combination with an ACE inhibitor (98) and adding losartan to conventional therapy improved left ventricular ejection fraction and volumes (99). Despite the further reduction in blood pressure observed on adding losartan, no symptomatic hypotension or renal dysfunction was observed (100). Whether the combination of ACE inhibition and AT1 receptor antagonism will achieve greater benefits on morbidity and mortality than either of these agents alone remains to be determined in large multicenter trials which are being conducted.

**UNDERUTILIZATION AND SUBOPTIMAL DOSAGE OF ACE INHIBITORS IN CLINICAL PRACTICE: ARE AT1-RECEPTOR ANTAGONISTS THE SOLUTION?**

Despite the clear evidence that ACE inhibitors improve survival, only about 30 to 50% of CHF patients actually receive ACE inhibitors (101,102). Some are not on ACE inhibitors secondary to tolerability problems, but the proportion that falls into this category is largely unknown. However, even in the setting of tertiary medical care with a much higher use of ACE inhibition (103,104) than in general patient populations (101), many of those not taking ACE inhibitors could probably tolerate them (104). Accordingly, the underuse of this evidence-based therapy in the general population seems to be only infrequently caused by intolerability.

Additionally, the majority of patients on ACE inhibitors receive doses lower than the dosages used in the large clinical trials (105). However, high doses of ACE inhibition are superior to low doses with respect to symptoms (106), exercise performance (107,108) and suppression of neurohumoral stimulation (12,33,108). The recently completed ATLAS study (109) reported at the 1998 meeting of the American College of Cardiology included 3,164 CHF patients (follow-up, 46 months). It demonstrated a trend that the introduction of AT1 receptor antagonists, better tolerated than ACE inhibitors, will considerably increase the appropriate prescription of drugs influencing the RAS in CHF patients (62).

**Tolerability of ACE inhibitors and AT1 receptor antagonists.** Hypotension is probably the most important reason for concern regarding the use of ACE inhibitors in CHF. Early reports of severe hypotensive reactions using high initial doses (114–116) may still support these concerns. However, hypotensive response is dependent on initial dose and concomitant therapy, particularly diuretics (10,117–119). Accordingly, patients often tolerate even maximal doses of ACE inhibitors (110) if the initial dose is kept low, uptitration is slow and diuretic dosage is stable (120). Available reports in CHF patients do not support the premise that hypotensive responses occur less often with AT1 receptor antagonists than with ACE inhibitors (78,93,94), even if the hypotensive effect of ACE inhibitors is partly mediated by bradykinin accumulation (121,122).

Renal dysfunction, principally due to diminished renal perfusion, is common in CHF patients and signals caution when utilizing ACE inhibitors. However, despite a significant worsening of renal function in up to one-third of these patients after initiation of ACE inhibition, most patients show only a mild increase in serum creatinine, and ACE inhibitor therapy does not have to be discontinued (123). In fact, a recent, randomized, placebo-controlled study showed that over the course of three years renal function was significantly improved by ACE inhibition in patients with renal dysfunction, despite an initial rise in serum creatinine of 10% to 15% (124). Again, AT1 receptor antagonists do not seem to be substantially superior to ACE inhibitors with respect to renal function despite experimental evidence for better renal tolerability of AT1 receptor antagonists (125). The incidence of persistent renal dysfunction was not different between losartan and captopril in the ELITE study (78).

It is well-documented that up to one-third of patients develop dry cough during therapy with ACE inhibitors (126,127). Although differences between individual ACE inhibitors have not been fully excluded (128), cough secondary to ACE inhibition is probably related to accumulation of kinins and therefore a class effect (129,130). However, cough may be aggravated by pulmonary congestion. Indeed, in a recent trial, a decrease in dry cough was found in some patients when increasing enalapril dosage was accompanied by an improvement in clinical symptoms and neurohumoral stimulation (113).

In patients not able to tolerate cough, AT1 receptor antagonism is a good alternative (131,132). However, only 3.8% of the patients enrolled in ELITE discontinued captopril because of cough (78). Furthermore, discontinuation rate was not different in the various groups in the RESOLVD study (97).
Finally, underutilization of evidence-based medicine is a general problem not limited to the use of ACE inhibitors (133–135). Even the good tolerability accorded to AT1 antagonists may not be enough to “avoid” underutilization.

**Conclusions.** The discussion of whether ACE inhibitors, AT1 receptor antagonists or the combination of both are superior in the pharmacotherapy of CHF is largely theoretical. Accordingly, AT1 receptor antagonists remain investigational at present and are reserved for patients with intolerance to ACE inhibition. Angiotensin-converting enzyme inhibitors remain first line therapy in patients with CHF due to systolic dysfunction unless contraindicated. An emphasis should be placed on increasing the utilization of ACE inhibitors, as more than 50 percent of patients with CHF do not receive ACE inhibitors. In addition, the majority of those on ACE inhibitors receive doses lower than the dosage used in the large clinical trials. Although not yet completely proved, it is likely that high doses of ACE inhibition are superior to low doses with respect to prognosis and symptoms.

Apart from establishing the place, if any, of AT1 receptor antagonists in the primary therapy of CHF, it remains to be seen whether all AT1 receptor antagonists will confer similar benefits. In addition, the value of combined therapy with ACE inhibitors and AT1 receptor antagonists needs to be determined. Finally, equivalent doses of ACE inhibitors and AT1 receptor antagonists remain to be defined.

An increasingly important consideration will be the value of RAS antagonism in combination with a variety of other medication such as beta-adrenergic blocking agents, central inhibitors of the sympathetic nervous system (e.g., imidazolone type 1 receptor agonists), endothelin antagonists, endopeptidase inhibitors and new generation calcium channel blockers. The predominant challenge in the future management of CHF will be to tailor medical therapy individually by selecting from a range of drugs proven beneficial for each patient. Hypotension is likely to be a key limiting factor with multiple drug use. Therefore, a more individualized therapeutic approach will likely be necessary, as opposed to a standardized therapeutic regime for all patients with CHF. Criteria for such an individualized approach, however, are largely unknown and remain to be defined.

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