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ACE Inhibitors in Heart Failure: Prospects and Limitations

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Summary. **ACE inhibitors have been shown to be effective in reducing the morbidity and mortality of patients with left ventricular systolic dysfunction, but their application to clinical practice in this situation is still limited. In part, the failure to prescribe an ACE inhibitor to a patient with left ventricular systolic dysfunction is due to perceptions regarding their side effects, such as cough and renal dysfunction. Relatively few patients with left ventricular systolic dysfunction and a serum creatinine ≥2 mg/dl receive an ACE inhibitor in clinical practice. In this situation one should consider an agent such as fosinopril, which is metabolized by the liver as well as secreted by the kidney. In patients with moderate renal dysfunction, fosinopril has been well tolerated without an increase in serum creatinine. In patients who develope cough due to an ACE inhibitor, consideration should be given to an angiotensin II type 1 receptor blocking agent, such as losartan. The relative safety and efficacy of an ACE inhibitor compared with an angiotensin II type 1 receptor blocking agent is being explored in a prospective randomized trial (Evaluation of Losartan In The Elderly [ELITE]), as well as the safety and pharmacological effectiveness of adding an angiotensin II receptor antagonist to an ACE inhibitor (Randomized Angiotensin receptor antagonists — ACE-inhibitor Study [RAAS]). There may also be a role for the combination of an aldosterone receptor antagonists and an ACE inhibitor in patients with left ventricular systolic dysfunction. Once an ACE inhibitor is administered to a patient with left ventricular systolic dysfunction it should be continued indefinitely. ACE inhibitors may be of value not only in preventing the progression of heart failure but also in reversing endothelial dysfunction and preventing the development of atherosclerosis and its consequences, such as myocardial infarction.**

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Angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective in reducing morbidity and mortality in patients with chronic left ventricular systolic dysfunction regardless of etiology, time from onset of left ventricular dysfunction, gender, or age [1–3]. They have also been shown to reduce mortality in patients with left ventricular systolic dysfunction or manifest congestive heart failure post infarction [4–9]. Recent studies suggest that patients with extensive left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%), anterior myocardial infarction, or manifest congestive heart failure should be started on an ACE inhibitor within the first 24 hours of the onset of infarction [6,7]. There is also evidence to suggest that ACE inhibitors may play an important role in patients with relatively uncomplicated small infarcts when administered orally within the first 24 hours postinfarction [6,7]. While the mechanism for the benefit in acute myocardial infarction with left ventricular systolic dysfunction has been thought to be due, in large part, prevention of left ventricular dilatation and remodeling [10,11], recent evidence suggests that administration within the first 24 hours of the onset of infarction may provide benefit related to a reduction in cardiac rupture and sudden cardiac death independent of the effect on ventricular remodeling [6,7,12].

Use of ACE Inhibitors

Although the evidence supporting the use of ACE inhibitors in patients with chronic left ventricular systolic dysfunction and postinfarction is based on randomized studies of over 100,000 patients, it is of interest that the use of these agents, at least until recently, has been suboptimal. For example, it is estimated that <50% of patients with a diagnosis of heart failure received an ACE inhibitor in the United States [13]. While clinical adaptation of results from major randomized trials has been noted to be relatively slow [14], in part because of a time lag in dissemination of information relating to these trials, a large part of the reason for not using ACE inhibitors in heart failure may relate to their perceived side effects or contraindications.

In many of the major clinical trials, ACE inhibitors were not administered if the serum creatinine was ≥2 mg/dl. It is well recognized that ACE inhibitors, by

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altering glomerular perfusion, may result in a decrease in creatinine clearance, and an increase in serum creatinine and potassium, occasionally to potentially dangerous levels. While it is reasonable to be cautious when considering the use of an ACE inhibitor in a patient with compromised renal function, it should be recognized that failure to administer them may expose the patient to an increased risk of recurrent heart failure or death. Rather than considering an elevated serum creatinine of 2–5 as an absolute contraindication, it is reasonable to administer an ACE inhibitor to these patients with careful monitoring of serum creatinine and potassium. While some of these patients will demonstrate an increase in serum creatinine and potassium, many, however, will be able to tolerate the drug. As an alternative, or in those who demonstrate an increase in serum creatinine after a trial of an ACE inhibitor, the use of fosinopril should be considered. In contrast to most ACE inhibitors, fosinopril is eliminated via a dual pathway, through the kidney and the liver [15]. In patients with moderate renal dysfunction, fosinopril has been shown to be relatively well tolerated, with little increase in serum creatinine or potassium. However, not all patients will tolerate its administration, and serum creatinine and potassium need to be carefully monitored, at least for the first several days and weeks.

Cough

Another clinical concern with the use of ACE inhibitors in patients with heart failure relates to the occurrence of cough. The incidence of cough after an ACE inhibitor appears to be greatest in the elderly and in Asian patients, occasionally reaching an incidence of 10–20% in these groups [16]. Before discontinuing an ACE inhibitor in a patient with a cough, one should consider whether the cough is due to heart failure, other causes, or the ACE inhibitor itself. In randomized trials such as the SOLVD trial [2], cough was relatively common in patients randomized to placebo. Our strategy is to discontinue the ACE inhibitor and to re-evaluate the patient after 1–2 weeks. In those in whom the cough persists despite the withdrawal of the ACE inhibitor, the cough is likely to be due to heart failure or other causes and the ACE inhibitor should be readministered. In those who become free of cough, the cough is likely to be due to the ACE inhibitor. In this situation it is often worthwhile to discuss the situation with the patient. Some patients, after reviewing the survival advantages of an ACE inhibitor, may decide that the cough, although onerous, is tolerable, while in others the cough may interfere with the quality of life and should be discontinued. In these patients consideration should be given to the use of an angiotensin II type 1 receptor blocking agent, such as losartan. While there is of yet only limited experience with the use of angiotensin II type 1 receptor-blocking agents in patients with heart failure, they have been shown to be relatively well tolerated and to improve exercise tolerance [18]. They are unlikely to provoke cough because the cough has been associated with ACE inhibitor-induced bradykinin accumulation. Angiotensin II type 1 receptor antagonists block most, if not all, of the detrimental effects of angiotensin II but do not cause an increase in bradykinin accumulation because the angiotensin-converting enzyme that is responsible for degrading bradykinin is not inhibited [18].

Angiotensin II Receptor Blockade in Heart Failure and Bradykinin

While it is reasonable to postulate that blockade of angiotensin II type 1 receptors will be beneficial in patients with heart failure, it should be emphasized that there is experimental evidence suggesting that at least part of the beneficial effects of ACE inhibitors in heart failure and postinfarction may be due to accumulation of bradykinin rather than to inhibition of angiotensin II formation. For example, in animals ACE inhibitors have been shown to reduce infarct size after experimental coronary artery occlusion [19]. This beneficial effect, however, is negated by the administration of the bradykinin antagonist HOE140 [19]. It should be pointed out, however, that there is great species differences in bradykinin accumulation and effect after ACE inhibition. Furthermore, bradykinin is an endothelial-mediated vasodilator. In patients with heart failure and in those with ischemic heart disease, endothelial dysfunction is often present [20–22] and bradykinin may lose its vasodilator effect [23]. Thus, the relative role of bradykinin accumulation in the beneficial effects of ACE inhibitors and the relatively efficacy and safety of an angiotensin II type 1 receptor antagonist in comparison with an ACE inhibitor, are uncertain. Further information in this regard should be forthcoming from the Evaluation of Losartan In The Elderly trial (ELITE), which is comparing the safety and efficacy of the angiotensin II type 1 receptor antagonist losartan with the ACE inhibitor captopril in over 700 patients with heart failure. The rationale and design of this study have been described previously [24]. An exploration of the relative efficacy and safety of an angiotensin II type 1 receptor antagonist compared with an ACE inhibitor has important implications for the therapy of patients with left ventricular dysfunction.

Residual Mortality in ACE-Inhibitor Trials and Angiotensin II Escape

Although patients on an ACE inhibitor have been shown to have a decrease in morbidity and mortality in comparison with patients maintained on digoxin, diuretics, and placebo, it should be emphasized that there

is still a relatively high incidence of morbidity and mortality despite currently recommended target doses of an ACE inhibitor, such as enalapril 10 mg bid. For example, in the SOLVD trial there was a 47.7% incidence of recurrent heart failure or death in patients randomized to 10 mg enalapril bid [2]. There are several possible explanations for this residual morbidity and mortality, including the fact that other neurohormones or factors are likely to be of pathophysiologic importance in heart failure, such as norepinephrine, endothelin, and vasopressin, and it should not be expected that even optimal blockade of the renin-angiotensin-aldosterone system would eliminate all morbidity and mortality.

It is likely, however, that while it is unreasonable to expect that optimal blockade of the RAAS would completely eliminate all morbidity and mortality in patients with left ventricular systolic dysfunction post-infarction, current strategies are not optimal and further benefit may be achieved by optimal blockade of the RAAS. For example, it has been shown that patients who show evidence of progressive heart failure despite therapy with enalapril have elevated angiotensin II levels [25]. This elevation or "escape" of angiotensin II production despite doses of enalapril that are thought to be effective in blocking serum ACE could be caused by inadequate absorption of enalapril in patients with heart failure or failure to achieve optimal dosing.

Although 10 mg bid of enalapril has been shown to be effective in reducing morbidity and mortality in the SOLVD Trial [2], it is not certain that this is the optimal dose, and others have suggested that even higher doses of enalapril are necessary to optimally suppress angiotensin II formation [26]. It is also possible that angiotensin II may be produced by non-ACE as well as ACE-dependent mechanisms [27]. While ACE inhibitors may be effective in blocking ACE-dependent angiotensin II formation, they would not be expected to block non-ACE-dependent angiotensin II formation. If non-ACE-dependent angiotensin II formation is of pathophysiologic importance in heart failure or postinfarction, it would be expected that an angiotensin II type 1 receptor blocker might in fact be more effective than an ACE inhibitor under certain circumstances. Only direct comparative studies in humans will provide the answer to the question of the relative safety and efficacy of an angiotensin II type 1 receptor antagonist versus an ACE inhibitor.

Combination of ACE Inhibitors and Angiotensin II Type I Blocking Agents

Since it is possible that at least some of the beneficial effects of ACE inhibitors are due to bradykinin accumulation and that either because of suboptimal dosing or non-ACE-dependent angiotensin II formation, angiotensin II is not optimally suppressed, we have also begun to explore the strategy of combining an ACE inhibitor and an angiotensin II type 1 receptor blocking agent. The Randomized Angiotensin receptor Antagonist — ACE-inhibitor Study (RAAS) is exploring the hypothesis that the combination of an angiotensin II type 1 receptor antagonist, losartan, and an ACE inhibitor, enalapril, is more effective than enalapril alone when used at target doses, 10 mg bid, or at even higher doses, such as 20 mg bid. Use of this combination should allow ACE-inhibitor-induced bradykinin accumulation as well as further suppression of angiotensin II, either because of receptor blockade of residual ACE-dependent angiotensin II formation and/or non-ACE-dependent angiotensin II formation. The RAAS Pilot Study is exploring the safety of this combination as well as its relative efficacy in suppressing neurohormones, including norepinephrine, aldosterone, and atrial natriuretic peptide at rest and during exercise.

ACE Inhibition and Aldosterone

Another potential problem with our current use of ACE inhibitors is that fact that aldosterone is not completely suppressed with currently used doses and may escape despite complete inhibition of plasma ACE [28]. Although aldosterone production is in large part dependent upon angiotensin II production, there are other mechanisms controlling aldosterone production, including ACTH, serum potassium, and atrial natriuretic factor. The evidence for an "escape" of aldosterone production despite ACE inhibition, and its clinical implications have been recently reviewed [29]. To explore the possibility of aldosterone escape in patients with heart failure, the Randomized ALdactone Evaluation Study (RALES) has been initiated to explore the safety and efficacy of spironolactone when administered in conjunction with an ACE inhibitor in patients with left ventricular systolic dysfunction and heart failure. The RALES Pilot Study [30] explored the safety of placebo and of spironolactone at 12.5, 25, 50, and 75 mg daily when administered in conjunction with an ACE inhibitor. This study showed spironolactone in doses of 12.5–25 mg daily to be safe and pharmacologically effective, as evidenced by a significant decrease in serum atrial natriuretic peptide levels. The results of this study were used to design the RALES Mortality Trial, which is currently exploring the effect of spironolactone 25 mg daily to reduce total mortality in patients with severe heart failure maintained on an ACE inhibitor or in patients intolerant of an ACE inhibitor.

Duration of Treatment with ACE Inhibitors

Another problem with the use of ACE inhibitors is how long they should be administered. In patients with persistent left ventricular systolic dysfunction (LVEF

≤40%), it seems reasonable to continue ACE-inhibitor therapy lifelong because withdrawal from ACE inhibitor therapy results in ventricular dilatation and recurrent signs of heart failure [31]. In patients with chronic heart failure or postinfarction with an improvement in ejection fraction to >40%, it might be reasonable to consider withdrawing ACE inhibitor therapy after 4–6 weeks because there is no evidence that patients with relatively well-preserved ventricular function (EF >40%) undergo long-term ventricular remodeling or progressive ventricular dilation. On the other hand, a case can be made for lifelong therapy, even in these patients. In the SOLVD [32] and SAVE [33] studies, ACE inhibitors were associated with a significant reduction in the incidence of ischemic events. There is increasing experimental evidence suggesting that ACE inhibitors may reverse endothelial dysfunction and prevent atherosclerosis, plaque rupture, and thrombosis [34]. Of importance in the potential benefit of ACE inhibitors in preventing myocardial infarction and ischemic events is the finding that angiotensin II can cause the oxidation of low-density lipoprotein cholesterol [35]. Oxidation of low-density lipoprotein cholesterol and free radical formation have important detrimental effects on the development of atherosclerosis and ventricular function. ACE inhibitors, by preventing angiotensin II-induced oxidation of LDL-C, oxygen free radical production, cytokine production, endothelial dysfunction, endothelin release, platelet activation, and plasminogen activator inhibitor release, could have an important effect on the prognosis of coronary and other vascular disease. The first test of this hypothesis is being explored in the QUinipril Ischemic Event Trial (QUIET), the background and design of which have been previously described [36]. The fact that ACE inhibitors prevent the oxidation of LDL-C, and reverse endothelial dysfunction and experimental atherosclerosis, suggests that they may act syngenetically or additively with cholesterol-lowering strategies, which also prevent oxidation of LDL-C, endothelial dysfunction, atherosclerosis, endothelin, and plasminogen activator inhibitor release. Should QUIET demonstrate a significant effect of the ACE inhibitor quinipril in reducing ischemic events in patients without left ventricular systolic dysfunction, ACE inhibitors might be indicated for the secondary prevention of ischemic heart disease and would likely be administered lifelong in patients with coronary artery disease, regardless of their left ventricular ejection fraction.

ACE Inhibition and Beta-Adrenoceptor Blockade

It also likely that ACE inhibitors act syngenetically or additively with beta-adrenergic receptor blocking agents. Angiotensin II causes the release of norepinephrine [37], while ACE inhibitors, at least in part, prevent norepinephrine release as well as free radical formation [38]. The recent demonstration of the effectiveness of carvedilol in patients with heart failure maintained on an ACE inhibitor [39], as well as previous studies demonstrating the effect of ACE inhibitors in patients maintained on a beta-adrenergic receptor blocking agent [4], suggest a beneficial interaction. Prevention of oxygen free radical formation by ACE inhibitors and/or an increase in antioxidant defense mechanisms may be of importance in their beneficial effect in situations in which norepinephrine release is thought to be pathophysiologically important, such as severe heart failure, because it has recently been shown that the oxidation products of catecholamines, amniochromes, are more predictive of mortality on multivariant analysis than catecholamine levels themselves [40]. The beneficial effect of carvedilol in patients with heart failure treated with an ACE inhibitor may also be explained in part by a beneficial synergistic or additive effect of carvedilol, which has antioxidant properties [41], in conjunction with the effects of ACE inhibitors on oxygen free radical formation and increasing antioxidant defense mechanisms [38,42]. Although this hypothesis requires further prospective testing, it is likely that oxygen free radical production is of critical importance in the pathophysiology of heart failure, including the tendency to develop apoptosis, progressive myocardial cell death, and sudden cardiac death.

Conclusions

Despite considerable experience with the use of ACE inhibitors in the treatment of both chronic systolic left ventricular dysfunction and postinfarction heart failure there remain many unanswered questions and opportunities for further reducing morbidity and mortality in these patients by optimizing the blockade of the RAAS and by exploring synergistic and/or complementary adjunctive strategies.

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