ACE inhibitors or AT₁ receptor blockers in heart failure?

See European Heart Journal Supplements Suppl. Q which accompanies this issue

Angiotensin II is a peptide produced from angiotensin I by the action of angiotensin converting enzyme (ACE). It has a number of potentially adverse effects which may contribute to the development and progression of heart failure, including vasoconstriction, salt and water retention, and activation of the sympathetic nervous system[1,2]. In addition, angiotensin II is associated with collagen deposition, fibrosis, and myocardial and vascular hypertrophy, which contribute to cardiac remodelling after myocardial infarction[1].

The effects of angiotensin II are mediated via two receptor subtypes, designated AT₁ and AT₂. The AT₁ receptor has been extensively characterized, and has been shown to be widely distributed in the vasculature, heart, kidney, adrenal gland, and brain. This receptor subtype is responsible for most of the physiological effects of angiotensin II on blood pressure, salt and water homeostasis and cell growth[1], and thus play a central role in the pathogenesis of heart failure. By contrast, until recently the role of the AT₂ receptor has remained unclear. It is now believed, however, that these receptors are involved in the inhibition of cell proliferation and the regulation of cell differentiation and programmed cell death (apoptosis)[3–5]. Hence, the AT₂ receptor may have beneficial effects that counteract the effects on cardiac remodelling mediated by the AT₁ receptors.

In view of the potential adverse effects of angiotensin II on the cardiovascular system, inhibition of angiotensin production or activity represents a rational therapeutic approach in heart failure. This can be achieved by ACE inhibition or blockade of the AT₁ receptor with AT₁ receptor blockers (Fig. 1). ACE inhibitors block the conversion of angiotensin I to angiotensin II, thereby reducing circulating concentrations of the active peptide. Blockade is not complete, however, because angiotensin II can also be produced by enzymes such as chymase[6]. Furthermore, ACE inhibitors also block the conversion of bradykinin to inactive peptides, resulting in accumulation of bradykinin. This peptide is believed to be responsible for the cough that sometimes occurs in patients treated with ACE inhibitors[2], but it may also have beneficial effects on ventricular function and cardiac remodelling, since there is evidence from animal models that kinins reduce collagen deposition and improve coronary flow reserve after myocardial infarction[7]. AT₁ receptor blockers directly oppose the actions of angiotensin II at the AT₁ receptor without inhibiting ACE activity and hence bradykinin degradation. In addition, AT₁ receptor blockade leads to a feedback increase in renin secretion by the kidney, and hence to a rise in circulating angiotensin II concentration[8,9]. As a result, angiotensin binding to AT₂ receptors may be enhanced, resulting in the increased expression of the beneficial effects of these receptors on cell proliferation and tissue repair[11].

The benefits of ACE inhibitor therapy in heart failure have been clearly established. A number of large controlled trials have shown that ACE inhibitors reduce mortality and morbidity in heart failure, and that these agents can delay the onset of overt heart failure in asymptomatic patients with left ventricular dysfunction[10–13]. Similarly, these agents have been shown to reduce mortality and limit cardiovascular remodelling after acute myocardial infarction[14]. As a result, current guidelines recommend the use of ACE inhibitors in all patients with heart failure due to left ventricular dysfunction, unless such treatment is contra-indicated[15].

The evidence for the benefits of AT₁ receptor blockers in heart failure is, so far, less convincing. In the Evaluation of Losartan in the Elderly (ELITE) Study, mortality was significantly lower among heart failure patients treated with losartan than in captopril-treated patients[16]. However, the total number of deaths in this study was small (49 of 722 patients), and the difference between the groups did not reach significance when adjusted for different endpoints[15]. Furthermore, there was no significant difference between the groups in hospitalizations for heart failure or the combined risk of mortality and morbidity. In the Randomized Evaluation of Strategies for Left Ventricular Function (RESOLVD) Study[17], treatment with candesartan was associated with a significant increase in mortality, compared with ACE inhibitor treatment, and hence the trial was
stopped prematurely. The study, however, was not designed to demonstrate mortality benefits and only a small number of patients were enrolled. Hence, the study was not powered to demonstrate any clear conclusions regarding mortality. At present, therefore, evidence for possible benefits with AT₁ receptor blockers in heart failure is limited. It seems reasonable therefore, to reserve AT₁ receptor blockers for patients who are unable to tolerate ACE inhibitors because of angioedema or intractable cough, as recommended in current guidelines[15]. The role of AT₁ receptor blockers in heart failure is currently being investigated in trials such as ELITE II, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM), and ValHeFT. The results of these trials are eagerly awaited, since they are powered to give a firm answer to the question of whether inhibition of the renin-angiotensin system in heart failure patients is best performed with ACE inhibitors or AT₁ receptor blockers.

In conclusion, there is strong and convincing evidence that ACE inhibitors prolong life in heart failure, whereas the role of AT₁ receptor blockers remains to be established. The principles of evidence-based medicine would therefore suggest that ACE inhibitor therapy should remain the cornerstone of heart failure therapy. Nevertheless, there is evidence that ACE inhibitors are currently under-prescribed, particularly in general practice[18,19]. An under-use of ACE inhibitors may cause unnecessary costs to society due to increased numbers of hospitalizations. Compared to the cost of drug treatment, hospitalizing heart failure patients incurs considerable expenditure for health care providers, as recently surveyed by Andersson et al.[20]. This may be at least partly due to concern about possible adverse effects of high-dose ACE inhibitor therapy[19]. However, the results of the recent ATLAS Study[21], in which high-dose lisinopril was associated with a significantly reduced risk of mortality and hospitalizations compared with low-dose treatment, and demonstrated similar tolerability to low-dose, suggest that such concern is inappropriate. Hence, a change in physician behaviour may be required to promote greater use of ACE inhibitors. It
seems likely that continuing medical education programmes, and initiatives aimed at empowering patients to become actively involved in the management of their condition, will prove to be useful in generating such a change.

This was the rationale for holding a roundtable discussion on the use of ACE inhibitors and AT$_1$ receptor blockers in the treatment of congestive heart failure, held during the 48th Scientific Session of the American College of Cardiology in March 1999 in New Orleans, U.S.A. A group of international experts on heart failure treatment and the implementation of best practice in cardiovascular medicine, addressed the use of these compounds in light of recent achievements regarding suppression of neuroendocrine stimulation in heart failure patients by the use of beta-blockers$^{[22,23]}$ and aldosterone antagonists$^{[24]}$. Following a review of existing data, the group debated the barriers to, and possibilities for, accomplishing relevant and evidence-based treatment of heart failure patients. The proceedings and recommendations from the roundtable discussion are now available in the Supplement accompanying this issue. For those with an interest in this field of medicine, this Supplement is recommended as a comprehensive overview and update of the latest evidence for best practice management of heart failure.

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**References**