

Management of Hypertension and Heart Failure with AT1 Receptor Blockade

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Hypertension and the Systemic Renin-Angiotensin System

The First Report of the National Task Force on hypertension by the Pakistan Hypertension League estimated that 12 million people in Pakistan have hypertension, of which 60% are undiagnosed and therefore untreated¹. Chronic hypertension is a risk factor for stroke, ischaemic heart disease, progressive renal damage, peripheral vascular disease and heart failure. The benefits of treating even mild hypertension have been documented.

The systemic renin-angiotensin system (RAS) has been implicated in the pathogenesis of hypertension, primarily due to the actions of its major effector peptide, angiotensin II (AngII)^{2,3}. AngII is a potent vasoconstrictor and is formed by proteolytic cleavage of AngI by angiotensin converting enzyme (ACE). The biological effects of AngII are predominantly mediated through the AT I and AT2 angiotensin receptor subtypes. AngII acting through the AT I receptor causes vasoconstriction that may sustain the elevation of blood pressure in hypertension. AngII-coupled AT1 receptor stimulation also causes volume expansion through aldosterone release and decreased sodium excretion, positive inotropy in the heart and at the cellular level, promotes proliferation and cellular hypertrophy. Less well understood are the effects and signalling of AngII coupling to the AT2 receptor, but actions of AngII through the AT2 receptor have been shown to have effects opposing those of the AT1 receptor on cell growth and blood pressure regulation with AT2 receptor stimulation causing vasodilation and an inhibition of cellular growth and proliferation^{4,5} (Figure 1).

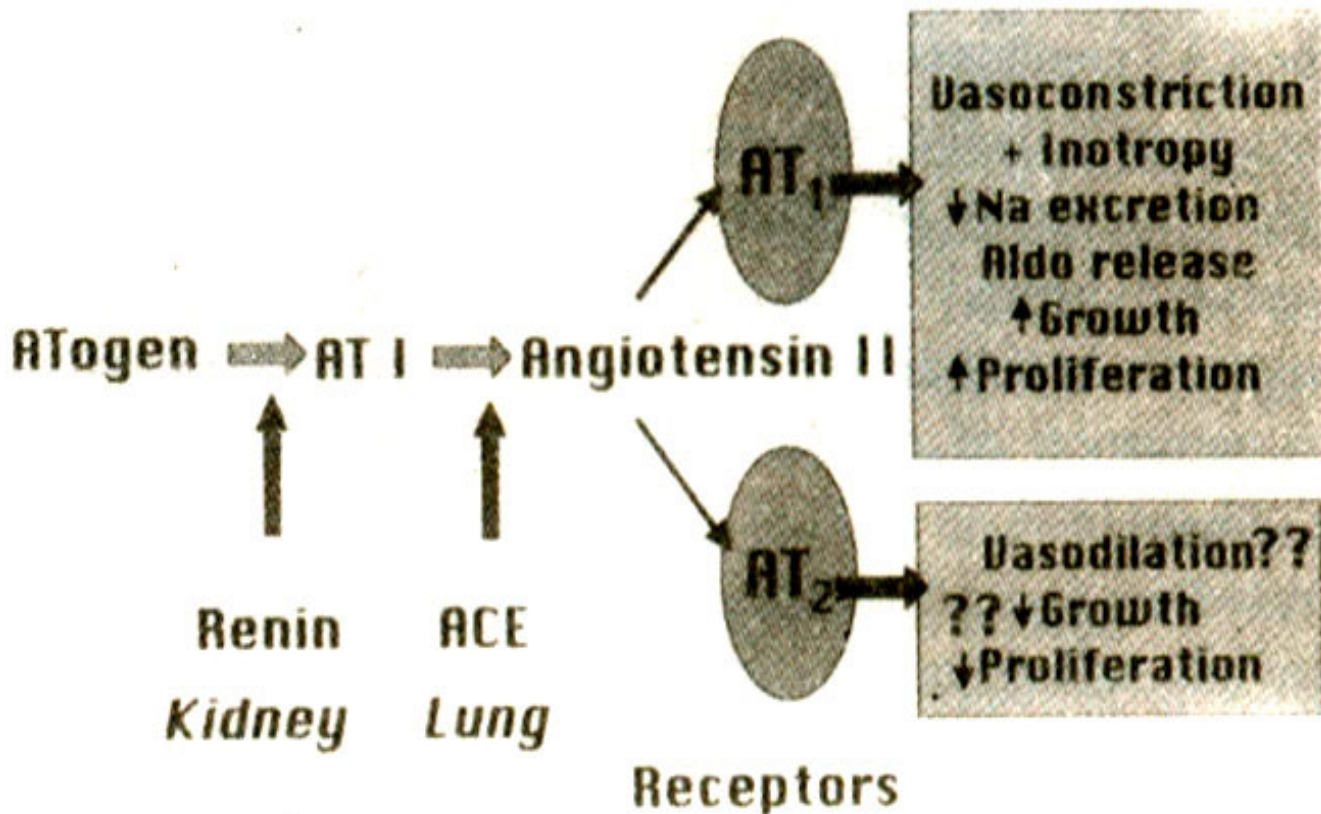


Figure 1

Blocking the effects of AngII at the AT₁ receptor has important clinical implications for the treatment of hypertension and prevention of its potential later cardiovascular complications.

Selective AT₁ Receptor Blockade

Recently, selective AT₁ receptor blockers have been developed and approved for use in hypertension. They have been shown to have dose-related efficacy in the treatment of hypertension⁶ and to be effective over 24 hours⁶. AT₁ receptor blockers can be clinically combined with - atenolol, amlodipine, indomethacin or glibenclamide⁷⁻¹⁰. They are equally efficacious in the treatment of hypertension as the beta-blocker, atenolol¹¹, the calcium-channel antagonist, amlodipine¹², and the ACE inhibitors, enalapril and lisinopril^{13,14}. All receptor blockers have lesser incidence of cough¹⁴.

Involvement of the Cardiac Renin-Angiotensin System in Left Ventricular Hypertrophy

Cardiac hypertrophy is a clinically significant consequence of chronic hypertension. Normalization of blood pressure usually results in regression of left ventricular (LV) hypertrophy, indicating that systolic load is a stimulus for cardiac growth. Although cardiac hypertrophy is initially a beneficial adaptation to an increase in haemodynamic load such as produced by hypertension, this adaptation cannot be maintained and eventually heart failure ensues¹⁵. While the systemic renin-angiotensin system is involved in the pathogenesis of hypertension through Ang II-AT₁ receptor mediated vasoconstriction, the local cardiac renin-angiotensin system is involved in the development of left ventricular hypertrophy through direct AngII-AT₁ receptor signalling on hypertrophic growth of cardiac

myocytes¹⁶. Evidence for a local cardiac autocrine/paracrine renin-angiotensin system includes i) the detection of mRNA and protein of the RAS components angiotensinogen, ACE, ATI and AT2 receptors¹⁶, ii) the demonstration of cardiac ACE activity (the conversion of AngI to AngII in isolated buffer-perfused hearts¹⁷, iii) release of AngII from cardiac myocytes in culture in response to stretch which is coupled to activation of cardiac hypertrophic growth signalling pathways^{18,19}. Several studies have shown that the local cardiac RAS is activated in patients with heart failure and in experimental animal models of cardiac hypertrophy and failure¹⁶. As shown by Schunkert et al., RNA expression and activity of left ventricular tissue ACE is increased in hearts with pressure overload LV hypertrophy, which is accompanied by increased intracardiac conversion of angiotensin I to angiotensin II¹⁷. Using competition binding assays, Lopez et al. demonstrated that the ATI receptor is down-regulated with AT2 receptor subtype predominance in LV tissue from rats with pressure overload LV hypertrophy²⁰. The early growth response is decreased in hearts with pre-existing LV hypertrophy, measured by new protein synthesis in isolated buffer-perfused hearts²¹. Whether this is the result of decreased ATI receptor levels and signalling in hearts with LV hypertrophy remains to be elucidated. Weinberg et al. showed that chronic treatment with an ACE inhibitor of normotensive rats with pressure overload LV hypertrophy due to ascending aortic stenosis was associated with regression of LV hypertrophy at both the whole heart and myocyte levels as well as improved survival²². It was recently demonstrated that the geometric and molecular LV adaptation to pressure overload is dependent on gender^{23,24}. LV ATI receptor expression is higher in females compared to males in the absence of LV hypertrophy, but the decrease in ATI receptor expression with LV hypertrophy is similar between female and male rats with pressure overload due to ascending aortic stenosis. Further work in the area of gender and the influence of the oestrogen status on expression of RAS components in cardiovascular disease states is needed, and could impact therapy aimed at interference with this system.

Aetiology and Pathophysiology of Heart Failure

Heart failure is a syndrome characterized by reduced cardiac output that results in the activation of compensatory neurohormonal mechanisms. While the data is unavailable for the Pakistani population, between 1-2% of the United States population suffer from heart failure, with 400,000 new cases being diagnosed each year. Heart failure is a progressive disease with a poor prognosis, with 60-70% of patients dying within 6 years of first diagnosis²⁵⁻²⁷.

The incidence of heart failure is increasing, due to the aging of the population, a decrease in mortality from infectious diseases and malnutrition, and advances in delaying death from other cardiovascular diseases^{25,28,29}. In the past, rheumatic and congenital heart disease were the primary causes of heart failure but presently cardiac surgery can alleviate most of these structural abnormalities. The most common cause of heart failure today is coronary artery disease, resulting in either myocardial infarction and loss of functioning myocytes, or hibernating myocardium in which LV function is depressed due to insufficient perfusion of large regions of the LV^{25,27}. A preventable, treatable cause of heart failure is hypertension. When untreated, the chronic haemodynamic pressure overload causes LV hypertrophy which later progresses to heart failure as discussed above. Other causes of heart failure include hypertrophic cardiomyopathy, which is often genetic, and dilated cardiomyopathy due to infections and toxic metabolites²⁷.

Irrespective of whether the initiating stimulus leading to heart failure is an acute event such as a myocardial infarction, or a chronic situation such as prolonged untreated hypertension, ejection fraction decreases with time and the patient progresses from being asymptomatic to symptomatic in conjunction with progressive LV remodelling and deterioration of LV performance, LV chamber dilatation and wall thinning (Figure 2).

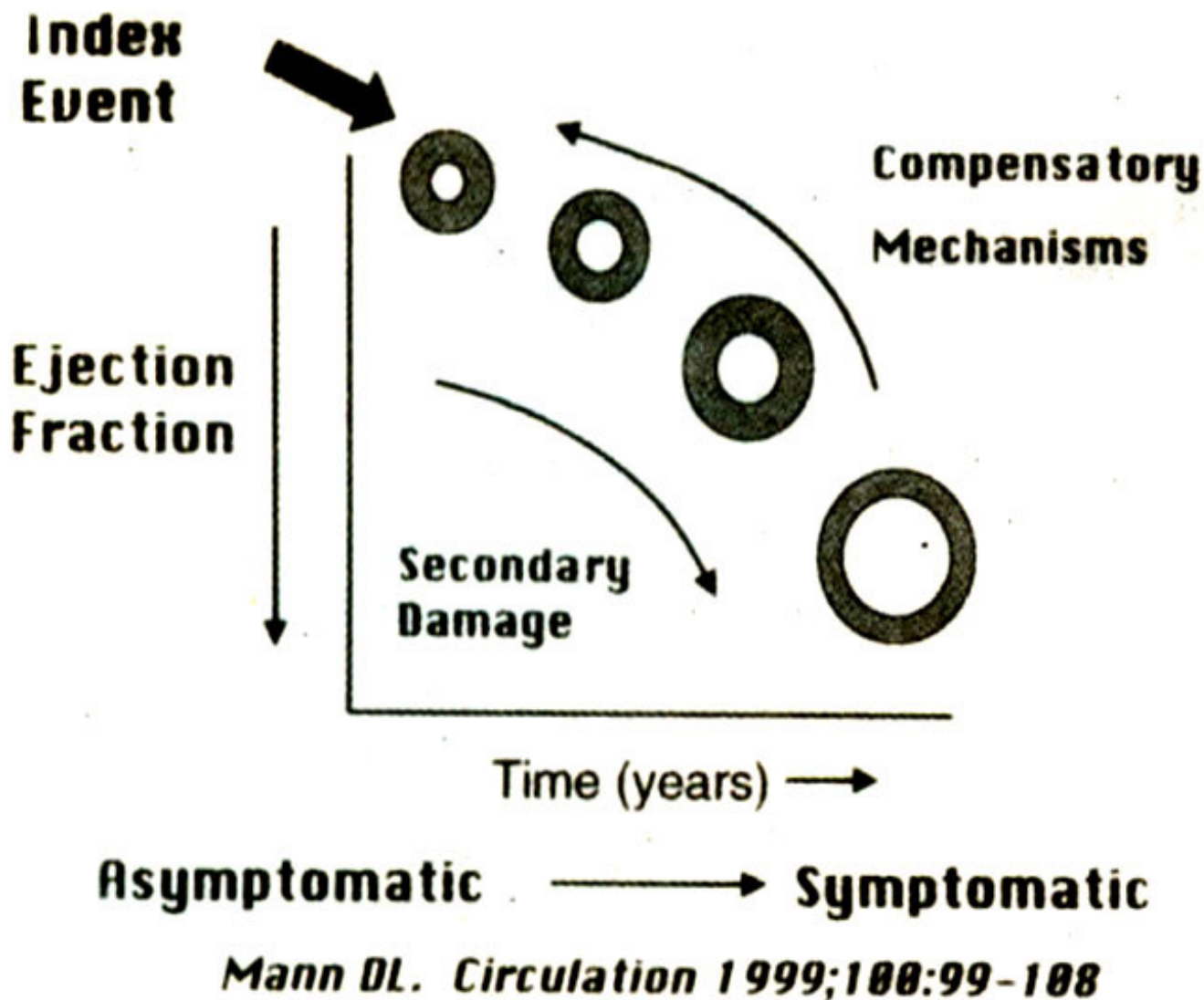
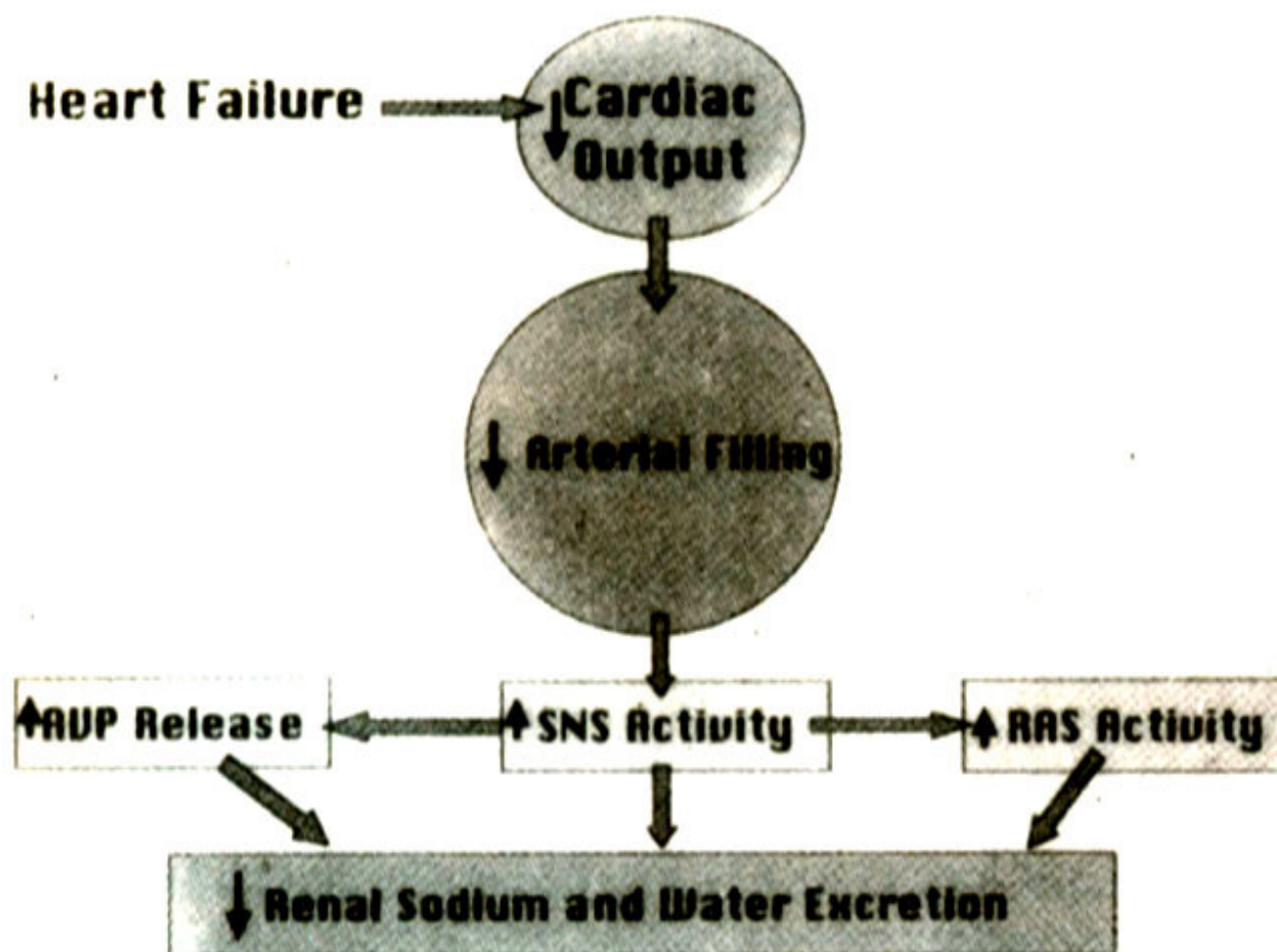


Figure 2

Several neurohormonal compensatory mechanisms are activated that attempt to restore LV function during the progressive decline in ejection fraction. While initially beneficial, prolonged activation of these compensatory mechanisms can cause direct end-organ damage, and hence heart failure treatment strategies have been developed targeted to these systems.

Recalling to mind the physiological relationship between the integrity of arterial circulation and renal sodium and water excretion aids in the understanding of the pathophysiology of heart failure. The integrity of the arterial circulation, determined by cardiac output and peripheral vascular resistance, is the primary determinant of renal sodium and water excretion. In heart failure patients in which cardiac output is decreased, arterial filling is consequently decreased. This leads to an increase in sympathetic outflow, activation of the renin-angiotensin-aldosterone system, and central arginine vasopressin release (Figure 3).



Schrier RW and Abraham WT. New Eng J Med. 1999; 341:577-584

Figure 3

Activation of these three neurohormonal systems causes a decrease in renal sodium and water excretion in an attempt to restore the integrity of the arterial circulation³⁰.

Heart Failure

There has been a shift in our conceptualization of heart failure which is reflected in the changing therapies used to treat this syndrome^{26,27}.

Initially, heart failure was viewed as a problem of excessive salt and water retention, the so-called “cardiorenal” model, in which diuretics were used to alleviate the excessive fluid retention, congestion and peripheral oedema. The thiazide diuretics were developed in the 1950s. The volume depletion they achieved initially relieved the pulmonary congestion and peripheral edema, but also had the effect of reducing preload which reduced ejection and cardiac output, which then led to compensatory neurohormonal activation., and a vicious cycle of further worsening LV failure and fluid retention. Importantly, the thiazide diuretics when used alone did not prolong survival.

When the ability to perform haemodynamic measurements became available, heart failure was viewed as a problem of reduced cardiac output and excessive peripheral vasoconstriction, the so-called “cardiocirculatory-haemodynamic” model. In the 1970s, peripheral vasodilators were developed and utilized. The decrease in afterload brought about by vasodilator treatment increased cardiac output and temporarily improved heart failure. However, their effect to decrease blood pressure activated compensatory haemodynamic and neurohormonal mechanisms which resulted in LV hypertrophy and increased myocardial oxygen consumption. Similar to the diuretics, with the exception of nitrates,

vasodilators such as calcium channel blockers, alpha-adrenergic blockers or phosphodiesterase inhibitors, when used alone for the treatment of heart failure, did not prolong survival, nor did they prevent disease progression. These clinical observations in parallel with numerous basic molecular research efforts have led to the most current revisionary model, the “neurohormonal” model of heart failure.

Neurohormonal Activation in Heart Failure -

Treatment Strategies Aimed at Blocking the Renin-Angiotensin System

Compensatory neurohormonal systems are activated in heart failure that cause the release and chronic signalling of biologically active molecules that, independent of their haemodynamic effects, cause direct end-organ damage due to prolonged exposure²⁶. These molecules include the renin-angiotensin-aldosterone system effector molecules, angiotensin II and aldosterone, the sympathetic nervous system effector molecule, norepinephrine, as well as endothelin, and cytokines such as TNF, and interleukins. The most successful treatment for heart failure has thus far been achieved by interference with renin-angiotensin system signalling. Angiotensin converting enzyme (ACE) inhibitors, which block the conversion of angiotensin I to angiotensin II, have been shown in large clinical trials to prolong survival in patients with heart failure. Based on the successful outcome on mortality of the clinical trials on ACE inhibitors, SOLVD and CONSENSUS, treatment guidelines in heart failure have been published in 1994-1995 by the United States and Europe. under the auspices of the Federal Government/Agency for Health Care Policy and Research, US Department of Health and Human Services, and The American College of Cardiology/American Heart Association Task Force on Practice Guidelines³¹. These guidelines encourage the use of ACE inhibitors in all patients with symptomatic heart failure and in asymptomatic patients with moderate to severe LV dysfunction. Diuretics are advised to be added when fluid retention is present.

More recently, the AT₁ receptor blockers, already approved for use in hypertension, (described above) have been and are currently being evaluated for their efficacy in the treatment of heart failure^{32,33}.

ELITE (Evaluation of

Losartan in the Elderly) was the first trial to determine whether AT₁ receptor blockade with losartan offered safety and efficacy advantages (primary end-point: tolerability of persisting increase in serum creatinine) over ACE

inhibition with captopril in patients with heart failure³⁴. Safety and efficacy were similar between losartan and captopril. but treatment with losartan was associated with an unexpected lower mortality in comparison to captopril. In addition, the AT₁ receptor blocker was better tolerated than the ACE inhibitor. As the primary end-point of ELITE was not mortality and the patient size was not statistically empowered to evaluate mortality, the ELITE II trial was designed and executed with similar patient inclusion criteria in a much larger sampling population. ELITE II showed that mortality was similar between the losartan vs. captopril groups (16%/year, both groups, NS) and the conclusion was reached that the mortality results of the first ELITE trial could be attributed to chance³⁵. In ELITE II, as with ELITE, the AT₁ receptor blocker was better tolerated with better patient compliance than the ACE inhibitor. Since mortality was similar and not improved with AT₁ receptor blockade vs. ACE inhibition, the official treatment guidelines for heart failure as outlined above could not be changed to recommend that AT₁ blockers be preferred over ACE inhibitors (unless the patient is intolerant to ACE inhibitors), because a mortality benefit with ACE inhibitors vs. placebo had already been established.

The concept is emerging that AT₁ receptor blockade combined with ACE inhibition may more adequately suppress the deleterious neurohormonal effects

of AngII in patients with heart failure³⁶. An important and well-executed study in support of this demonstrated that additional haemodynamic benefit (decrease in systolic blood pressure, pulmonary capillary wedge pressure and diastolic pressure) and neurohormonal benefit (decrease in plasma aldosterone and a trend for decrease in plasma norepinephrine) was achieved when the AT₁ receptor,

valsartan, was added to standard ACE inhibitor treatment for 4 weeks in patients with heart failure³⁷. This study suggested that indeed, haemodynamically and hormonally active levels of AngII persist during long term treatment with standard doses of ACE inhibitors in patients with heart failure. A large, multi-centre clinical trial designed to rigorously evaluate mortality in heart failure patients receiving ATE receptor blockade combined with ACE inhibition is now currently underway. The Valsartan Heart Failure Trial (Val-HeFT) will test the hypothesis that the ATI receptor blocker, valsartan, by exerting a more complete inhibition of the renin-angiotensin system, will lead to further clinical benefit in patients with heart failure receiving standard therapy alone³⁸. Recruitment began in March 1997 and has been completed³⁹ and the results are eagerly anticipated. Proof of the Val-HeFT hypothesis will provide a major advance in the treatment of heart failure.

References

1. Guidelines for detection, control and management of hypertension (high blood pressure) in Pakistan. First Report of National Task Force (NTF-I) on Hypertension. Pakistan Hypertension League. 1998.
2. Stroth U. and Unger T. The renin-angiotensin system and its receptors. *J. Cardiovasc. Pharmacol.*, 1999;33 Suppl I S2 1-8.
3. Allikmets K., Parik T. and Viigimaa M. The renin-angiotensin system in essential hypertension: associations with cardiovascular risk. *Blood Press*, 1999;8(2): 70-8.
4. Horiuchi M., Akishita M. and Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system Hypertension. 1999;33:613-21.
5. Cares R.M., Wang Z-Q. and Siragy H.M. Role of the angiotensin type 2 receptor in the regulation of blood pressure and renal function. *Hypertension*. 2000;(35Part) 2:155-63.
6. Neutel J., Weber M., Pool J. et al. Valsartan, A new angiotensin II antagonist: antihypertensive effects over 24 hours *Clin. Ther.* 1997;19:447-58.
7. Flesch, G., Mueller, P., Hell, F. et al. Absolute oral bioavailability of valsartan in healthy volunteers *Eur J. Drug Metab. Pharmacokinet.*, 1996;21 :Abstract 163.
8. Mueller, P., Flesch, G., de Gasparo, M. et al. Single- and multiple-dose phase I trials with the angiotensin II antagonist valsartan *J. Hypertension*, 1993;11 Suppl 5, S459-60.
9. Waldmeier, F., Flesch, G., Mueller, P. et al. Pharmacokinetics, disposition and biotransformation of ¹⁴C-radiolabelled valsartan in healthy male volunteers after a single oral dose *Xenobiotica*, 1997;27:59-71.
10. Colussi, D.M., Parisot, C., Rossolino, M.L. et al. Protein binding in plasma of valsartan, a new angiotensin II receptor antagonist. *J. Clin. Pharmacol.*, 1997;37:214-21.
11. Cifkova R, Peleska J, Hradec J. et al. Valsartan and atenolol in patients with severe essential hypertension. *J. Hum. Hypertension*. 1998;12:563-7.
12. Cores L, Cardoni O, Rogari R, et al. Valsartan, A new angiotensin II antagonist for the treatment of essential hypertension: a comparative study of the efficacy and safety against amlodipine. *Clin Pharmacol. Ther.* 1996;60:341-6.
13. Hoiwerda NJ, Fogari R, Angeli P. Valsartan, A new angiotensin II antagonists for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. *J. Hypertension*, 1996;14:1147-51.
14. Benz J, Oshrain C, Henry D, et al. Valsartan. A new angiotensin II receptor antagonist: a double-blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. *Am. J. Clin. Pharmacol.* 1997; 37:101-7.
15. Wollert KC, Drexler H. The renin-angiotensin system and experimental heart failure. *Cardiovasc. Res.*, 1999;43:838-49.
16. Dosil DE, Baker KM. The cardiac renin-angiotensin system. Conceptual, or a regulator of cardiac

function? *Circ. Res.*, 1999;85:643-50.

17.Schunkert H, Dzau VJ, Tang SS, et al. Increased rat cardiac angiotensin converting enzyme activity and RNA expression in pressure overload left ventricular hypertrophy *J. Clin Invest.*, 1990;86:1913-20.

18.Sadoshima Y, Xu Y, Slayter IIS et al. Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. *Cell*, 1993;75:977-84.

19.Yamazaki T, Kommiro I, Kudoh S. et al. Angiotensin II partly mediates mechanical stress-induced cardiac hypertrophy *Circ. Res.*, 1995;77:258-65.

20.Lopez JJ, Lorell BH, Ingelfinger JR. et al. Distribution and function of cardiac angiotensin ATI- and AT2 receptor subtypes in hypertrophied rat hearts. *Am. J. Physiol.*, 1999 :267:H844-H852.

21.Schunkert H, Weinberg EO, Bruckschlegel G, et al. Alteration of growth responses in established cardiac pressure overload hypertrophy. *J. Clin Invest*, 1995;96:2768-74.

22.Weinberg EU, Schoen FJ, George D. et al. Angiotensin-converting enzyme inhibition prolongs survival and modifies the transition to heart failure in rats with pressure overload hypertrophy due to ascending aortic stenosis. *Circulation*, 1994;90:1410-22.

23.Douglas PS, Katz SE, Weinberg EU, et al. Hypertrophic remodeling: gender differences in the early response to left ventricular pressure overload. *J. Am. Coll. Cardiol.*, 1998;32:1118-25.

24.Weinberg EU, Tlihenelt CD, Katz SE, et al. Gender differences in molecular remodeling in pressure overload hypertrophy. *J. Am. Coll. Cardiol.*, 1999;34:264-73.

25.Gheorghe M, Bonow RO. Chronic heart failure in the United States. A manifestation of coronary artery disease. *Circulation*. 1998;97:282-9.

26.Mann DL. Mechanisms and models in heart failure. A combinatorial approach. *Circulation*, 1999;100:999-1008.

27.Katz AM. Heart failure. Pathophysiology molecular biology and clinical management. Lippincott. Williams and Wilkins, 1999.

28.Sorlie R. Global epidemic of cardiovascular disease expected by the year 2050 *Circulation*, 1999;100:e101.

29.Fox R. New risk factors in primary prevention. *Circulation*. 1999;100:e100

30.Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *New Engl. J. Med.*, 1999;341:577-85.

31.Konstantinides S, Yusuf S. Treatment guidelines in heart failure. *Prog. Cardiovasc. Dis.*, 1998;41 (Suppl) 1:65-72.

32.Spina FG, Lannini JP, Mukherjee R. et al. Angiotensin II receptor inhibition, an angiotensin-converting enzyme inhibition, and combination therapy with developing heart failure: cellular mechanisms of action. *J. Cardiac. Failure*. 1998;1:325-32.

33.De-Gasparo M, Levens N. Does blockade of angiotensin II receptors offer clinical benefits over inhibition of angiotensin-converting enzyme?. *Pharmacol. Toxicol.*, 1998;82:257-71.

34.Pitt B, Segal R, Martinez FA, et al. On behalf of ELITE Study Investigators. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of losartan in the elderly study, ELITE) *Lancet*, 1997;349:747-52.

35.Pitt B, Presented at the American Heart Association Scientific Sessions, Atlanta, GA, November 1999.

36.Remme WJ. Neurohormonal modulation in heart failure, ACE inhibition and beyond. *Eur. Heart J.*, 1995;16(Suppl N):73-8.

37.Baruch L, Anand I, Cohen IS, et al. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. *Circulation*, 1999;99:2658-64.

38.Cohn JN, Tognoni G, Glazer RD. et al. Rationale and design of the valsartan heart failure trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure. *J. Cardiac Failure*. 1999;5: 155-60.

39. Cohn IN. Val-HeFT Trial. International newsletter. Val-HeFT Study Chairnan, Minneapolis, MN. December. 1999.