Angiotensin II antagonists in systolic blood pressure control

Gordon T McInnes

Control of systolic blood pressure should be the primary goal of treatment as it is increasingly recognized as a major determinant of cardiovascular risk. Better control offers enormous potential benefits. Effective treatment is desirable but difficult to achieve. All antagonists, particularly eprosartan, are likely to have an increasingly important role in management strategies.

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Each time the heart beats, oxygenated blood is discharged from the left ventricle into the large arteries. In health, during systole, about 60% of the stroke volume is taken up by these compliant elastic vessels with only about 40% passing to the periphery. During diastole, the volume stored in the compliant vessels runs off into the peripheral circulation, ensuring constant delivery of oxygen and nutrients to vital organs.

As part of the ageing process in westernised societies there is gradual increase in large artery stiffness (loss of elasticity or compliance). Consequently, these vessels become less distensible, the storage volume and diastolic run off declines, and the shape of the pulse wave changes. In summary, diastolic blood pressure falls while systolic blood pressure and pulse pressure rise.

In North America and Europe, systolic blood pressure rises throughout life, while diastolic blood pressure reaches the highest level in the sixth decade and thereafter tends to fall (Burt et al, 1995; Colhoun et al, 1998). This is not an inevitable consequence of the ageing process as it is not seen in certain cultures (e.g. Kenyans living in the country but not in cities or Bushmen of the Kalahari), or in Italian women who enter convents. Blood pressure changes over a lifetime probably reflect vascular damage mediated by diet, lifestyle and the influences of blood pressure itself. Whatever the mechanism, the main blood pressure problem in middle-aged or older individuals is systolic hypertension (Burt et al, 1995; Colhoun et al, 1998).

SYSTOLIC BLOOD PRESSURE AND RISK

There is evidence that systolic blood pressure is a powerful predictor of all-cause mortality, coronary heart disease and stroke (Neaton and Wentworth, 1992; Stamler et al, 1993). Across the range of blood pressure for each of these complications systolic blood pressure is a stronger risk factor than diastolic. In black Americans, a similar relationship between systolic blood pressure and end-stage renal disease has been reported (Klag et al, 1996). However, it is uncertain whether non-malignant essential hypertension predisposes to renal damage in Caucasians.

In over 300 000 screenees for the Multiple Risk Factor Intervention Trial (MRFIT), coronary heart disease mortality during follow-up was greater in those with the highest systolic pressure and lowest diastolic pressure (Neaton and Wentworth, 1992). Such observations suggest that pulse pressure may be the key predictor of cardiovascular risk (Black et al, 1999). A vicious cycle (*Figure 1*) is proposed. Thus, vascular damage predisposes to atherosclerosis, hence to increased aortic stiffness, increased central vein reflection and increased pulse pressure which causes further vascular damage.

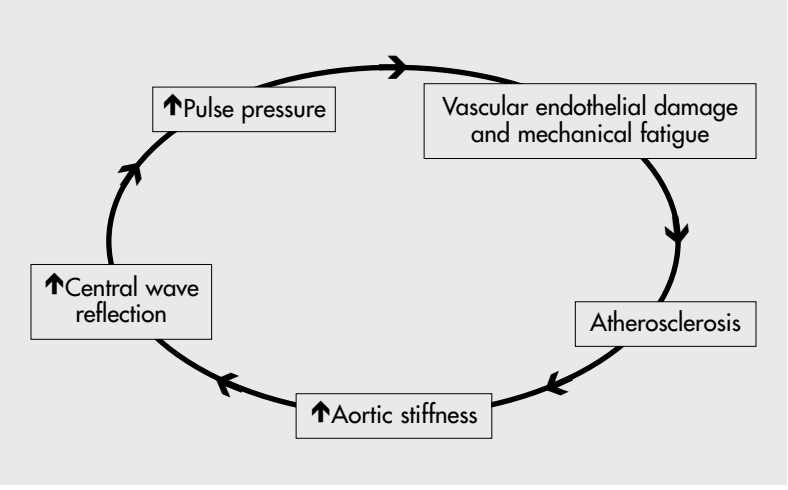


Figure 1. Vicious cycle of vascular damage provoked by high systolic and pulse pressure.

TREATMENT OF SYSTOLIC HYPERTENSION

The decisive information necessary to determine the practical significance of systolic hypertension is the value of its treatment. Two seminal studies provided conclusive evidence of benefit – Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Hypertension-Europe (SYST-EUR) Study (SHEP Cooperative Research Group, 1991; Staessen et al, 1997). Diuretic-based therapy (SHEP) and calcium channel blocker-based therapy (SYST-EUR) produced similar reduction in systolic blood pressure and was associated with similar reduction in the risk of stroke, myocardial infarction, cardiovascular events and all-cause mortality (*Table 1*). The number of patients needed to be treated (NNT) for 5 years to prevent a cardiovascular event was low – similar to that for treatment of hyperlipidaemia with a statin in patients with prior coronary heart disease (Scandinavian Simvastatin Survival Study Group, 1994). Thus, the treatment of systolic hypertension should be considered a major national health priority.

The clinical benefits of treating systolic hypertension have been confirmed in other trials (He and Whelton, 1999). A meta-analysis of these trials (He and Whelton, 1999) has indicated that a 12–13 mmHg reduction in systolic pressure provides cardiovascular benefits at least as great as a 5–6 mmHg fall in diastolic pressure (Collins and MacMahon, 1994); reductions in coronary heart disease events appear to be numerically greater than those for changes in diastolic pressure (*Table 2*). Cardiovascular risk reduction is greatest at an achieved systolic pressure less than 140 mmHg (Hansson et al, 1998).

DELIVERY OF CARE

Systolic blood pressure is now given prominence in guidelines for diagnosis and management of hypertension. The most recent British Hypertension Society guidelines (Ramsay et al, 1999) recommend that treatment should be considered in high-risk patients with systolic blood pressure over 140 mmHg and that all treated patients should aim for systolic pressure under 140 mmHg.

TABLE 1.
Studies of isolated systolic hypertension the elderly

			SYST-EUR	SHEP
Drug	First line		Nitrendipine (84%)	Chlorthalidone (69%)
	Second line		Enalapril (33%)	Atenolol (23%)
	Third line		Hydrochlorothiazide (16%)	Reserpine (23%)
Blood pressure response			10/5 mmHg	12/4 mmHg
Relative risk reduction	Stroke		42% (P<0.01)	36% (P<0.01)
	Myocardial infarction		30%	27% (P<0.05)
	Cardiovascular events		31% (P<0.001)	32% (P<0.001)
	All-cause deaths		14%	13%
Absolute risk reduction	NNT	Stroke	34	33
		Any cardiovascular event	19	17

NNT = number needed to treat for 5 years to prevent one event. Systolic Hypertension in the Elderly Program = SHEP (SHEP Cooperative Research Group, 1991); Systolic Hypertension-Europe Study = SYST-EUR (Staessen et al, 1997).

TABLE 2.
Meta-analysis of trials of systolic hypertension: results from ten randomized trials with 9278 active treatment and 9264 control participants

	Events			
	Active	Control	% risk reduction (95% CI)	P-value
Total coronary heart disease	412	520	21 (10, 31)	<0.001
Fatal coronary heart disease	250	341	27 (13, 38)	<0.001
Total stoke	385	596	37 (28, 45)	<0.001
Fatal stroke	101	158	36 (18, 50)	<0.001
Cardiovascular deaths	467	617	25 (15, 34)	<0.001
All-cause mortality	906	1028	13 (4, 21)	0.005

CI = confidence interval. From He and Whelton (1999)

This emphasis on systolic pressure reflects a marked change in attitude. Until recently, only diastolic blood pressure was considered important and many practitioners have yet to accept the new paradigm. In fact, actuarial data from the early years of the 20th century show a clear association between rising levels of systolic pressure and mortality (May, 1925). Why this knowledge has been so slow to be incorporated into practice is unclear.

Community data indicate that hypertension is underdiagnosed, undertreated and that control in those treated is suboptimal (Burt et al, 1995; Colhoun et al, 1998). Evidence from across the world (Swales, 1999) reveals that control of systolic pressure falls dramatically behind that for diastolic pressure. Most treated patients with uncontrolled blood pressure fail to reach acceptable targets because of high systolic pressure (Swales, 1999). Thus, the time is ripe to focus attention on systolic hypertension.

NEW APPROACH TO TREATMENT OF SYSTOLIC HYPERTENSION

The haemodynamic changes (increased peripheral resistance, reduced arterial compliance and increased reflected waves) which underlie systolic hypertension are provoked by factors which include activation of the renin–angiotensin system (RAS) and sympathetic nervous system (SNS). Thus, drugs which inhibit these neurohumeral pathways might be expected to be particularly useful in the treatment of systolic hypertension.

Although beta-blockers might be considered candidates on theoretical grounds, in practice these drugs are rather poor at reducing systolic pressure (Medical Research Council Working Party, 1992), possibly because their main antihypertensive action is prolongation of diastole. Angiotensin-converting enzyme (ACE) inhibitors and the newly introduced angiotensin II (AII) antagonists appear more promising.

Blockade of the RAS

Both ACE inhibitors and AII antagonists block the RAS but there are differences in modes of action (McInnes, 1998).

- AII antagonists provide more complete blockade since these drugs act at the receptor to inhibit the agonist however it is produced. Thus AII antagonists inhibit the classical circulating RAS and also alternative tissue systems where AII is generated by enzymes other than ACE. Tissue systems may be particularly important in mediating vascular damage.
- ACE inhibitors are not specific for the RAS since ACE is an ubiquitous enzyme with other actions, e.g. breakdown of kinins (as kininase II). Thus, ACE inhibition is associated not only with reduced levels of AII but also accumulation of bradykinin. Whether this action adds to the beneficial effect of ACE inhibition is uncertain but it is very likely to be responsible for the main side effects of the class – angioedema and cough. In contrast, AII antagonists have actions specific for the RAS and do not cause cough or angioedema.
- By reducing circulating AII, ACE inhibitors block all angiotensin receptors while AII antagonists act highly selectively at angiotensin 1 (AT_1) receptors which mediate all the potential adverse effects of AII, including release of catecholamines from sympathetic nerve endings and the adrenal medulla.

The properties of AII antagonists (complete, specific and highly selective AT_1 receptor blockade) are desirable to interrupt the interaction between the RAS and SNS that contributes to systolic hypertension. In addition, AT_1 blockade interferes with the negative feedback loop controlling renin release and AII levels. Increased AII stimulates unblocked AT_2 receptors increasing intracellular bradykinin and nitric oxide levels. This ancillary property may facilitate vasodilatation and vascular repair.

AII antagonists

Six AII antagonists are available in the UK (*Figure 2*). All are highly selective for the AT_1 receptor and all have prolonged duration of action (McInnes, 1998). Most are biphenyl tetrazoles but eprosartan and telmisartan do not share this chemical structure. The ‘sartans’ are competitive antagonists of AII but eprosartan is unique in exhibiting classical surmountable antagonism. Eprosartan forms a dynamic interaction with the AT_1 receptor rather than prolonged insurmountable binding as seen with the other AII antagonists or their metabolites. Eprosartan undergoes no significant metabolism and the parent drug is the active moiety.

Eprosartan

The clinical properties of eprosartan have been reviewed by Hedner (1999). In hypertensive patients, reductions in blood pressure are dose-related. Antihypertensive efficacy is similar in young and elderly subjects. Response rate is greater in patients treated with eprosartan than those treated with enalapril; the advantage over the ACE inhibitor is seen in Caucasian and black patients.

Eprosartan appears particularly effective in reducing systolic blood pressure. In comparison with enalapril (Hedner, 1999) eprosartan is at least as effective in reducing diastolic pressure but statistically superior for systolic pressure (*Figure 3*). This advantage may reflect a particular effect of eprosartan at AT_1 receptors mediating catecholomine release (*Figure 4*). Eprosartan inhibits the sympathetically stimulated increase in blood pressure in the pithed rat model (Ohlstein et al, 1997). The action does not appear to be shared by other AII antagonists.

Eprosartan is extremely well tolerated (Hedner, 1999). The side-effect profile is indistinguishable from that of placebo and adverse effects are no more frequent at higher doses. This favourable pattern is attractive since the currently recommended rigorous targets for systolic blood pressure demand the use of drugs at high doses and in combination (Hansson et al, 1998; Ramsay et al, 1999). A very well-tolerated and effective agent, such as eprosartan, should facilitate the task of reaching these targets.

Figure 2. Chemical structures of angiotensin II receptor antagonists.

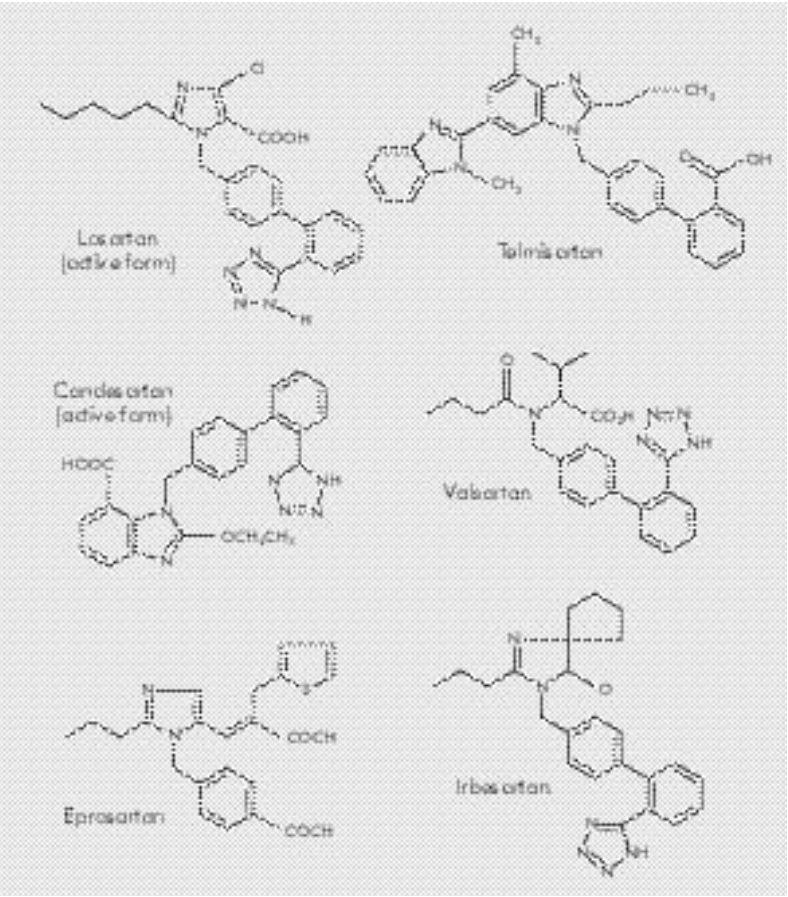
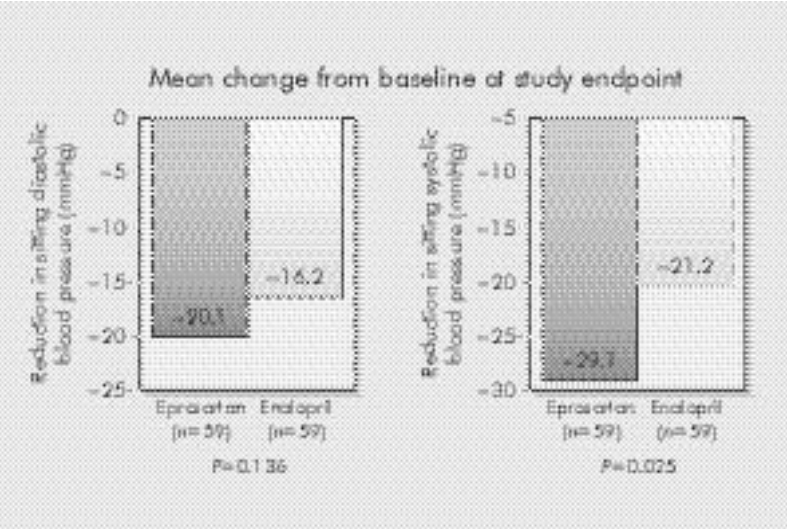


Figure 3. Eprosartan vs enalapril in severe hypertension. From Hedner (1999).



Beyond blood pressure

Recent outcome trials indicate that AII antagonists have an advantage beyond that attributable to blood pressure reduction in diabetic patients with nephropathy (Lewis et al, 2001). Eprosartan reduces proteinuria in type II diabetes and therefore might be expected to share this benefit.

Eprosartan prolongs survival in stroke-prone spontaneous hypertensive rats. This raises the prospect of particular benefit in stroke. A major outcome study (MOSES) with eprosartan is underway in patients with cerebrovascular disease.

CONCLUSIONS

Systolic blood pressure is increasingly recognized as a major determinant of cardiovascular risk. Control of systolic blood pressure should therefore be the primary goal of treatment. The significance of systolic hypertension is still often overlooked in practice. Better control offers enormous potential benefits. Effective treatment is desirable but difficult to achieve. AII antagonists, and particularly eprosartan, are likely to have an increasingly important role in management strategies. **HM**

Conflict of interest: The author is an investigator in trials of AII antagonists. He has advised several manufacturers of AII antagonists and has received honoraria for presentations at meetings.

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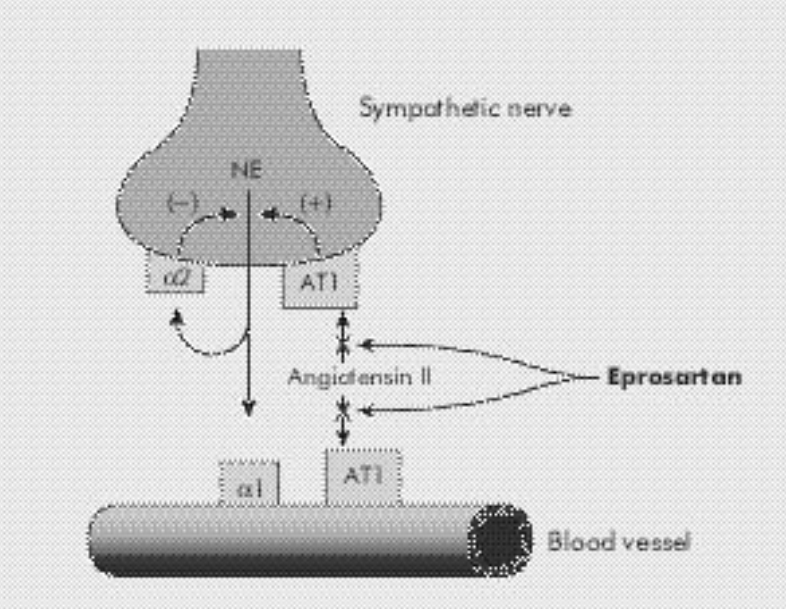

Figure 4. Eprosartan inhibition of sympathetic nerve stimulation mediated at angiotensin (AT) 1 receptors. NE = norepinephrine.

KEY POINTS

- Systolic blood pressure is a major determinant of cardiovascular risk.
- Control of systolic blood pressure should be the primary goal of antihypertensive treatment.
- The significance of systolic hypertension is often overlooked.
- Better control of systolic hypertension offers enormous potential benefit.
- Effective control of systolic blood pressure is difficult to achieve.
- Angiotensin II antagonists, and particularly eprosartan, have considerable potential for management of systolic hypertension.