Effect of AT₁-receptor blockade on cardiovascular structure and function

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Surrogate endpoints such as left-ventricular hypertrophy and arterial function are increasingly accepted as prognostically relevant, and appropriate targets for therapeutic intervention. Emerging evidence shows that AT₁-receptor blockade with candesartan has beneficial effects on a number of such endpoints. In the Candesartan Assessment in the Treatment of Cardiac Hypertrophy (CATCH) Study, candesartan 8–16 mg/day was as effective as enalapril 10–20 mg/day in reducing blood pressure and left-ventricular mass index in hypertensive patients with left-ventricular hypertrophy. In the Candesartan Atenolol Carotid Haemodynamics Endpoint Trial (CACHET), candesartan and atenolol produced significant regression of carotid intima-medial thickness, compared with baseline; however, carotid blood flow remained unchanged in candesartan-treated patients, but decreased by approximately 40% in those receiving atenolol, suggesting that unlike atenolol candesartan is associated with relative outward remodelling of the common carotid. Vascular remodelling of small resistance arteries is a characteristic feature of type-2 diabetes, and is associated with impaired endothelial function due to hypercholesterolaemia.

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Introduction

Large clinical endpoint studies have repeatedly shown that effective control of elevated blood pressure reduces the risk of cardiovascular and cerebrovascular events. Studies such as the Hypertension Optimal Treatment (HOT) Study have suggested that the benefits are proportional to the level of blood pressure achieved, suggesting that the aim of antihypertensive therapy should be to lower blood pressure as far as possible. Recently, other studies have suggested that blockade of the renin-angiotensin system by angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II type-1 (AT₁) receptor blockers may provide additional benefits that are independent of blood pressure. This hypothesis, however, has been controversial. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study showed that AT₁-receptor blockade was associated with greater reductions in cardiovascular mortality and morbidity than atenolol; however, the blood-pressure reductions achieved were slightly greater with losartan than with atenolol (mean reductions 31/17 mmHg and 28/17 mmHg, respectively), raising the possibility that the additional benefit might have been related to blood pressure per se.

An alternative means of assessing the potential benefits of antihypertensive therapy is provided by surrogate endpoint studies of cardiovascular structure and function. It is increasingly accepted that such markers are prognostically important and hence warrant therapeutic intervention. This paper reviews recent studies with the AT₁-receptor blocker candesartan on cardiovascular structure and function.

Left-ventricular hypertrophy

Left-ventricular hypertrophy (LVH) is a recognized risk factor for cardiovascular events and stroke in hypertensive patients. Antihypertensive therapy has
been shown to reverse LVH 8, resulting in improved cardiac function and coronary reserve 9,10 and a reduced risk of cardiovascular events 11,12. Such treatment should therefore be considered mandatory in all patients with raised blood pressure and a diagnosis of LVH.

Meta-analyses have consistently shown that all classes of antihypertensive drugs can produce regression of LVH, but to differing extents (Fig. 1) 13,14. Such findings must be interpreted with caution, however, since many of the studies included in these analyses were non-comparative or non-randomized, or of too small a size or too short a duration to provide adequate statistical power. The lack of central assessment of echocardiograms has also been a concern in some studies.

The Candesartan Assessment in the Treatment of Cardiac Hypertrophy (CATCH) Study was a multicentre, randomized, prospective trial that compared the effects of candesartan cilexetil 8–16 mg once daily and enalapril 10–20 mg once daily on LVH 15. A total of 239 hypertensive patients with documented LVH (left-ventricular mass index \(>120 \text{g/m}^2\) in men or \(>100 \text{g/m}^2\) in women) were recruited, of whom 182 completed the study. Two-dimensional M-mode echocardiograms were obtained at the beginning and end of treatment. All echocardiograms were read at the end of the study at central laboratories by assessors who were blinded to the treatment allocation and scan timing.

Both candesartan and enalapril significantly \((P<0.001)\) reduced systolic and diastolic blood pressures, compared with baseline, and there was no significant difference between the two treatments in the blood-pressure reductions achieved or the proportion of patients achieving a diastolic blood pressure of less than 140/90 mmHg (candesartan: 60.4%; enalapril: 60.0%). Similarly both treatments significantly reduced the left-ventricular mass index (LVMI), compared with baseline: the mean decrease in LVMI was 15.0±22.6 (SD) g/m² (10.9±15.5%) with candesartan and 13.2±23.4 g/m² (8.4±17.4%) with enalapril. The difference between the effects of the two treatments was not statistically significant (mean ± 2.0 g/m² candesartan minus enalapril; 95% confidence interval –8.3, +4.2). The proportion of patients showing regression of LVH was slightly higher in the candesartan group than in the enalapril group at both 24 and 48 weeks, but the differences did not reach statistical significance (Fig. 2). This study showed, therefore, that AT(1)-receptor blockade with candesartan was as effective in reducing blood pressure and left-ventricular mass as ACE inhibition with enalapril.

### Large-artery structure and function

Hypertension results in a number of structural and functional changes in large arteries. Early endothelial dysfunction contributes to the development of atherosclerosis and an increase in the intima-medial thickness (IMT). Subsequent pressure-related remodelling results in an increase in lumen size, collagen deposition and thickening of the media, and decreased arterial compliance, leading to an increased pulse pressure 16. Epidemiological and clinical studies have shown that both increased IMT and increased pulse pressure are important cardiovascular risk factors 5,17.

Assessment of these structural changes in large arteries requires ultrasonic investigation of the radial artery or determination of the carotid IMT, neither of which are practicable in routine clinical practice. Notwithstanding the technically demanding nature of these techniques, however, the recent hypertension management guidelines of the European Society of Hypertension recommend that measurement of carotid IMT should be included in the assessment of global cardiovascular risk 5.

The impact of AT(1)-receptor blockade on vascular remodelling in large arteries has recently been studied in the Candesartan Atenolol Carotid Haemodynamics Endpoint Trial (CACHET) 18–20. This study involved 80 hypertensive patients who were treated for 52 weeks with candesartan cilexetil 8–16 mg or atenolol 50–100 mg; doses were titrated according to the blood-pressure response, and hydrochlorothiazide, felodipine and doxazosin added as necessary to achieve a target blood pressure of below 140/90 mmHg. IMT was measured in the distal common carotid and carotid bulb by B-mode ultrasound at the beginning and end of treatment.

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**Fig. 1.** Meta-analysis of changes in left ventricular mass during antihypertensive therapy. Results are presented as means and 95% confidence intervals, adjusted for change in diastolic blood pressure and treatment duration. *P<0.05 vs. \(\beta\)-blockers; †P<0.01 vs. \(\beta\)-blockers. Reproduced from Klingbeil et al. 2003 14. Copyright (2003), with permission from Excerpta Medica.

**Fig. 2.** Proportion of patients showing regression of LVH following treatment with candesartan cilexetil 8–16 mg or enalapril 10–20 mg in the CATCH Study 15.
Candesartan and atenolol produced significant regression of carotid IMT, compared with baseline, and there was no significant difference between the effects of the two treatments. By contrast, carotid blood flow remained unchanged in candesartan-treated patients, but decreased by approximately 40% in those receiving atenolol. Blood pressure was reduced to a similar extent in both groups. These findings suggest that, in contrast to atenolol, candesartan is associated with relative outward remodelling of the common carotid, and hence preserves cerebral blood flow.

Small-artery structure and function

Changes in the structure of small resistance arteries (relaxed diameter <300 μm) are difficult to assess, but can be measured by in vitro myography in blood vessels dissected from biopsies of subcutaneous fat (usually taken from the gluteus). Hypertension has been shown to be associated with structural changes in such vessels, resulting in a decrease in lumen size and an increase in the media : lumen ratio. Recent studies have shown that such changes are associated with an increased risk of cardiovascular events.

Remodelling of small resistance vessels is also seen in type-2 diabetes. In a recent study, the wall : lumen ratio and cross-sectional area of the vessel wall were measured in patients with essential hypertension and normotensive or hypertensive patients with type-2 diabetes. Compared with control subjects, the diabetic patients showed an increase in wall : lumen ratio irrespective of their blood-pressure level, while the patients with essential hypertension showed the highest ratios. By contrast, the cross-sectional area of the vessel wall was significantly increased, compared with controls, in diabetic patients but not in patients with essential hypertension. This suggests that vascular remodelling of small resistance arteries, with wall hypertrophy, is characteristic of type-2 diabetes: this may represent an important therapeutic challenge since a recent study suggests that such remodelling may be difficult to reverse. In this study, the media : lumen ratio in patients with type-2 diabetes and hypertension remained significantly higher than that in hypertensive patients or control subjects, despite antihypertensive therapy (with ACE inhibitors in 70% of patients) that was effective in controlling diastolic blood pressure. By contrast, there is extensive evidence that in hypertensive patients without diabetes small-artery diameter can be reduced by a variety of antihypertensive agents, including ACE inhibitors, AT₁-receptor blockers, and long-acting calcium channel blockers.

Small-artery function is also impaired in diabetes. In the study described above, the vasodilator response to acetylcholine in resistance arteries preconstricted with noradrenaline was significantly reduced in patients with type-2 diabetes, but not in those with essential hypertension. The addition of l-N-monomethyl arginine (l-NMMA), an inhibitor of nitric oxide synthase, prior to preconstriction significantly reduced the maximal response to acetylcholine in vessels from control subjects and patients with essential hypertension, but not in vessels from diabetic patients. There was a significant negative correlation (r = -0.65, P = 0.007) between total serum cholesterol concentrations in diabetic patients and the responsiveness to acetylcholine, suggesting that...
substantial proportion of the endothelial dysfunction in these patients was related to dyslipidaemia.

**AT1-receptor blockers and endothelial dysfunction in diabetes**

Activation of the renin-angiotensin system is a key factor in this association between dyslipidaemia and endothelial dysfunction in diabetic patients. Expression of AT1 receptors is increased in the presence of hypercholesterolaemia 26, and AT1-receptor activation leads to increased production of free radicals, thereby inducing oxidative stress and endothelial dysfunction 27. Blockade of the AT1 receptor might therefore be expected to have beneficial effects on endothelial function, and this is supported by a number of recent studies.

In one study, 20 patients with CHD received intrabrachial infusions of candesartan 800 μg/minute, with and without icatibant (a bradykinin B2-receptor antagonist) or L-NMMA 28. Candesartan treatment significantly improved flow-dependent dilatation: this effect was blocked by both icatibant and L-NMMA, indicating that bradykinin and nitric oxide each contribute to the vascular effects of AT1-receptor blockers. In a second study, involving 47 hypercholesterolaemic patients, treatment with candesartan cilexetil 16 mg/day for 6 weeks significantly improved forearm blood flow, whereas placebo or the calcium-channel blocker felodipine had no effect 29. Similarly, candesartan cilexetil has also been shown to improve endothelial function in the retinal vasculature of hypertensive patients 30.

**Conclusions**

Surrogate measures of cardiovascular structure and function are now recognized to be prognostically important, and hence such endpoints warrant therapeutic intervention. Emerging evidence suggests that AT1-receptor blockade with candesartan has beneficial effects on a number of surrogate endpoints, resulting in regression of LVH, outward remodelling of the common carotid, and improvements in endothelial function in small resistance vessels. These effects appear to be independent of the antihypertensive effects of candesartan, and create a strong rationale for the use of AT1-receptor blockade in patients at high cardiovascular risk.

**References**


