*For debates***ACE inhibitors, diabetes and cardiovascular disease****A. Gazis, S. R. Page, J. R. Cockcroft**

Treatment of hypertension with beta blockers or thiazide diuretics reduces the risk of stroke more than that of myocardial infarction [1, 2]. This may be due in part to adverse effects of these drugs on serum lipids and insulin resistance – both independent risk factors for cardiovascular disease. Newer antihypertensive agents with neutral or beneficial effects on these parameters may offer greater protection against atheromatous vascular disease, particularly in high-risk groups such as patients with non-insulin-dependent diabetes mellitus (NIDDM) where hypertension, dyslipidaemia and insulin resistance often coexist. Interest has focused on angiotensin converting enzyme inhibitors (ACEI) because of mounting evidence that they may improve impaired vascular endothelial function, an early surrogate marker of atheroma.

The vascular endothelium and atheromatous disease

The vascular endothelium is a cellular monolayer which lines all blood vessels and is essential for normal arterial smooth muscle relaxation [3]. This relaxation is mediated in part by nitric oxide (NO) which is synthesised from the amino acid L-arginine in endothelial cells and then diffuses to subjacent vascular smooth muscle cells. Tonic NO release maintains the vasculature in a state of relaxation [4, 5] and in addition has powerful anti-atherogenic activity [6]. NO release and vascular relaxation is physiologically stimulated *in vivo* by shear stress or, experimen-

tally, by exogenous administration of endothelium-dependent agonists such as acetylcholine, carbachol, substance P and bradykinin. Integrity of the L-arginine/NO pathway may be important in protecting the blood vessel from atheromatous disease. Indeed blunting of responses to endothelium-dependent agonists is an early finding in a number of conditions associated with high cardiovascular risk including NIDDM [7], hypercholesterolaemia [8] and smoking [9]. Drugs may improve endothelial function indirectly via effects on cardiovascular risk factors or directly via endothelial actions. There is accumulating evidence that ACEI improve endothelial function independently of any effects on blood pressure.

The vascular endothelium and ACEI

ACEI reverse abnormalities of endothelium-dependent vascular relaxation in animal models of hypertension [10] and hypercholesterolaemia [11] and in humans with hypertension and atheromatous disease [12, 13]. In spontaneously hypertensive rats, acute and chronic treatment with an ACEI improved vascular endothelial dysfunction, whereas hydralazine did not despite a similar antihypertensive effect [10]. Similarly, abnormal endothelium-dependent relaxation, seen in the aorta of cholesterol fed rabbits, is reversed by ACE inhibition, but not by isradipine, a calcium channel blocker [14].

In humans with hypertension, treatment with captopril or nifedipine produced similar reductions in blood pressure but only ACE inhibition was associated with improved endothelium-dependent vasodilatation [12]. Finally, improved endothelium-dependent vasodilatation has been demonstrated in the human coronary circulation following ACE inhibition [13]. The Trial on Reversing ENdothelial Dysfunction (TREND) examined the effect of ACE inhibi-

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Abbreviations: ACEI, Angiotensin converting enzyme inhibitors; NIDDM, non-insulin-dependent diabetes mellitus; NO, nitric oxide; GTN, glyceryl trinitrate.

tion on endothelial function in patients with several risk factors for cardiovascular disease and angiographically proven coronary atherosclerosis. At baseline, acetylcholine, an endothelium-dependent vasodilator, infused directly into the coronary arteries produced paradoxical constriction whereas responses to the endothelium-independent vasodilator glyceryl trinitrate (GTN) were unaffected. Patients were then randomised to receive 6 months' treatment with the ACEI quinapril or placebo. This caused significant reversal of the constrictor response to acetylcholine (from 14.3% at baseline to 2.3% at follow up) in those patients treated with quinapril with no change in those treated with placebo (9.4–10.5%). Responses to GTN were unaffected. Interestingly, the beneficial effect of ACE inhibition on endothelial function was similar in magnitude to that of cholesterol reduction seen in similar studies [15]. Few subjects with diabetes have been studied, so the effects of ACE inhibition on endothelial dysfunction in diabetes are uncertain and require further investigation.

Possible mechanisms of endothelial protection in diabetes

ACEI have a number of properties that may increase the bioavailability of endothelium-derived NO and so improve endothelial function. Bradykinin is produced by endothelial cells [16] and stimulates NO release [17]. Systemic ACE inhibition elevates circulating levels of bradykinin [18] and enhances the vasodilator response to exogenous bradykinin in the human forearm vascular bed [19]. Preserved vasodilator responses to bradykinin have been demonstrated in vessels from insulin-dependent diabetic animals and man (for review see [20]) despite blunted responses to acetylcholine. In hypercholesterolaemia, the endothelial defect is more generalised [21]. Such studies suggest that acetylcholine and bradykinin stimulate NO release via different signal transduction mechanisms [22] and provide a possible mechanism by which ACEI may improve endothelial dysfunction in diabetes.

Angiotensin II increases superoxide production from vascular smooth muscle cells in culture by up-regulating the actions of NADH and NADPH oxidases [23]. Superoxide, a free radical, reacts with NO to form peroxynitrite [24] and so reduces NO bioavailability. Removal of NO from the constrictor/dilator equilibrium in vessels may cause excess constrictor influence and an inability of the vasculature to respond to physiologic stimuli to NO production. In diabetes, superoxide mediated NO destruction may occur more rapidly since diabetes is associated with an increase in circulating oxygen derived free radicals [25]. Angiotensin II also upregulates production of the vasoconstrictor endothelin-1 [26] further exacerbating the problem of reduced NO availability by enhancing constrictor influences. ACE inhibition reduces local angiotensin II levels and so may increase NO availability and decrease vasoconstrictor tone.

Free radicals also enhance the production of oxidised low density lipoprotein cholesterol (ox-LDL) which acutely inhibits endothelium-dependent vascular relaxation [27]. ACEI may preserve vascular endothelial function by acting directly as antioxidants to protect lipids from peroxidation [28, 29].

To date, three studies have examined the effect of ACE inhibition on endothelial function in patients with diabetes [30, 31]. All the studies used small numbers of subjects. Chronic ACE inhibition for 6 months had no effect on methacholine-induced vasodilation in the forearm vascular bed of individuals with the insulin resistance syndrome [30], though researchers have questioned whether methacholine releases NO directly from the endothelium [32]. The same technique was used to investigate the effects of the endothelium-dependent vasodilator acetylcholine in nine patients with IDDM and eight matched patients without diabetes. Blunted vasodilator responses to acetylcholine in the diabetes group were reversed acutely by intra-arterial infusion of the ACEI enalaprilat and further improved after one month of oral enalapril [33]. In contrast, flow-mediated increase in brachial artery diameter in patients with uncomplicated IDDM was unchanged after 5 weeks' chronic ACE inhibition [31].

ACEI, microalbuminuria and macrovascular disease

Diabetes complicated by proteinuria is associated with vascular endothelial dysfunction [34, 35], increased cardiovascular risk and progression to renal failure. In IDDM, ACEI reduce the rate of progression of microalbuminuria [36] and nephropathy [37], and are widely used as first-line therapy. In patients with NIDDM and proteinuria, cardiovascular death normally precedes end-stage renal failure [38]. ACEI mediated improvement in endothelial function may be of particular benefit in reducing cardiovascular risk in these high-risk populations.

Conclusions

Hypercholesterolaemia and hypertension are prevalent in subjects with NIDDM and may act synergistically to impair endothelial function. ACEI by improving vascular endothelial function, may reduce cardiovascular risk below that achieved by blood pressure lowering alone. The Hypertension in Diabetes Trial, part of the United Kingdom Prospective Diabetes Study (UKPDS) will provide clinical endpoints for hypertensive diabetic subjects, but further

studies will be needed to determine how ACEI affect vascular endothelial function. This class of drugs has major therapeutic potential to improve the clinical outcome in a population at high risk of cardiovascular disease.

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