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Editorial Review

Effects of different antihypertensive drugs on human diabetic proteinuria

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In insulin-dependent (type I) diabetes mellitus, blood pressure is usually normal in the absence of nephropathy, but after the onset of incipient nephropathy, as indicated by microalbuminuria of 30–300 mg/24 h, tends to increase, and increases further when the stage of clinical nephropathy (proteinuria >300 mg/24 h) and renal failure have been reached [1,2]. In non-insulin dependent (type II) diabetes mellitus, hypertension may precede diabetes, but is further aggravated by nephropathy. Compared with the general population, relative mortality of cardiovascular disease is increased 2.5- to 7.2-fold in patients with both diabetes mellitus and hypertension [3,4] and up to 37-fold with clinical nephropathy [5,6]. Therefore, proteinuria is a prognostic index of overriding importance.

In the 35% of patients with type I diabetes mellitus who develop nephropathy, persistent microalbuminuria ('incipient nephropathy') appears 5–10 years after the clinical onset of diabetes. It will then progress within the following 5–10 years to the stage of overt nephropathy, and within a further 5–10 years to end-stage renal failure [2,7]. In patients with type II diabetes mellitus, the clinical presentation of diabetes or diabetic nephropathy and the onset of hypertension are often dissociated in time. Nevertheless, once nephropathy is present, an elevated blood pressure may also promote and accelerate the development of renal failure [8].

Antihypertensive therapy with different types of drugs will decrease microalbuminuria or overt proteinuria and retard progression of nephropathy, and usually slow the decline in glomerular filtration rate in initially non-azotaemic or mildly azotaemic nephropathy [2,6,9–13]. Antiproteinuric and renoprotective effects were initially observed with conventional antihypertensive therapy, including diuretics and β-blockers [9,10]; the exception was monotherapy with diuretics, which were suspected of accelerating diabetic nephropathy [14]. Concerning the choice of antihypertensive agents, a new argument has been introduced by experimental studies [15] in diabetic animals, which suggested disparate renoprotective effects of different antihypertensive drugs. These experiments were not confirmed by all subsequent investigations [16]. In particular, the possibility of drug-specific differences between the various classes of antihypertensive agents with respect to their antiproteinuric action in man has remained controversial.

Changes in intrarenal haemodynamics and mesangial metabolism, rather than systemic arterial pressure, are the proximate determinants of drug-induced effects on renal function. The potential of a reduction in systemic blood pressure to decrease glomerular capillary pressure may be enhanced by drugs which preferentially dilate efferent, as opposed to afferent, glomerular arterioles, such as ACE inhibitors [17]; while it may be antagonized by preferential afferent, as opposed to efferent, glomerular vasodilatation, which occurs with some calcium antagonists [18]. On the other hand, one must also consider the possibility of non-haemodynamic actions; certain calcium antagonists may inhibit renal hypertrophy associated with diabetes mellitus [19]; other calcium antagonists and ACE inhibitors may beneficially influence mesangial metabolism [19,20]; and finally, ACE inhibitors may decrease glomerular permeability for proteins [21]. Many of these studies were carried out in type I diabetes mellitus, but it is likely that the results can be extrapolated to patients with type II diabetes mellitus.

To explore further the possibility of a differential effect of antihypertensive agents on albuminuria in patients with diabetes mellitus, we carried out a meta-analysis [22] of published studies in such patients with microalbuminuria or overt proteinuria, including only studies where proteinuria had been treated for 4 or more weeks with antihypertensive drugs. This analysis showed that proteinuria decreased more in patients treated with ACE inhibitors than those treated by conventional therapy (diuretic and/or β-blocker) or calcium antagonists; while it tended to increase on nifedipine, despite a similar average reduction in blood pressure (Table 1). Based on linear regression analysis, ACE-inhibition-induced reduction in proteinuria correlated with the decrease in blood pressure ($r=0.58$, $P<0.0001$); the decrease in proteinuria averaged −30% at zero blood pressure change, and varied 1.5% for each percentage point of blood pressure change (Figure 1). On conventional therapy, proteinuria and changes in blood pressure also correlated ($r=0.62$, $P<0.02$), but proteinuria diminished only after a blood

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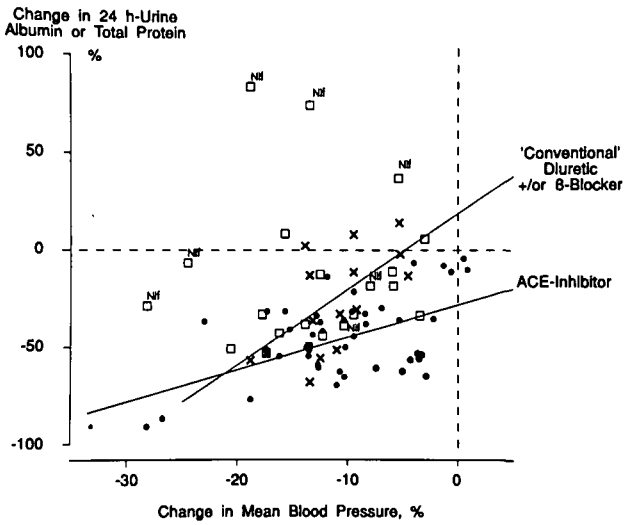
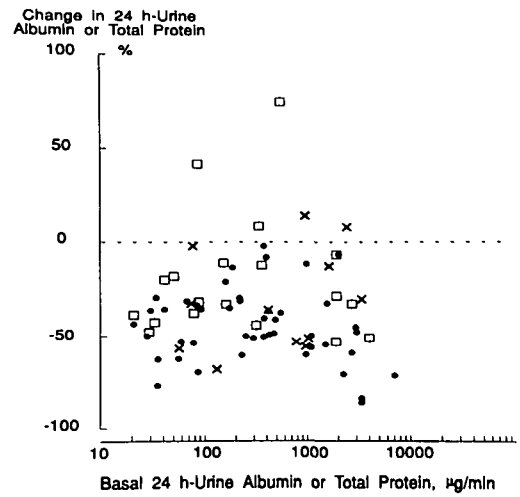
Table 1. Synthesis of reported effects of different antihypertensive treatments on albuminuria-proteinuria in diabetic patients with incipient or clinical nephropathy

Type of therapy	Number of patients	Average changes (%) in	
		Mean systemic blood pressure	Urinary albumin or protein excretion
Conventional (Diuretics and/or β-Blockers)	131	−10	−17
ACE inhibitors	589	−15	−52
Ca antagonists			
all	191	−13	−4
nifedipine	85	−13	+21
all except nifedipine	106	−12	−24
diltiazem +verapamil	52	−17	−23



Symbol	Drug	N	r	p <
•	ACE-Inhibitor	45	0.58	0.0001
×	Conventional	14	0.62	0.02
□	Ca-Antagonist	18	0.02	N.S.

Fig. 1. Percentage changes in albuminuria or total proteinuria as related to blood pressure changes in diabetic patients on different antihypertensive drug treatments. Nif, nifedipine; N, number of reported studies.



Symbol	Drug	N	r	p <
•	ACE-Inhibitor	45	-0.29	N.S.
×	Conventional	14	-0.07	N.S.
□	Ca-Antagonist	18	0.21	N.S.

Fig. 2. Percentage changes in albuminuria or total proteinuria as related to their pretreatment levels in diabetic patients on different antihypertensive drug treatments. N, number of reported studies.

pressure reduction of more than 5%. Furthermore, the slope was steeper (4% proteinuria change per percentage blood pressure change) than on ACE inhibitors. In the patients treated with calcium antagonists, changes in proteinuria were unrelated to changes in blood pressure. Changes in proteinuria on all drugs were unrelated to pretreatment proteinuria (Figure 2) or blood pressure. These findings demonstrate the predominance of drug-specific over systemic blood-pressure-dependent mechanisms in the antiproteinuric action of ACE inhibitors. In contrast, as the example of nifedipine illustrates, drug-specific intrarenal effects may antagonize a blood-pressure-dependent antiproteinuric action and sometimes even counteract the effect of lowering systemic pressure.

As ACE inhibitors exert a specific antiproteinuric effect even without a change in systemic blood pressure, they are superior to other agents in treating microalbuminuria and overt proteinuria in patients with diabetes mellitus who are normotensive or borderline hypertensive. On the other hand, when systemic blood pressure is lowered by 10–20%, as it is desirable in hypertensive patients, ACE inhibitors, conventional therapy, and several calcium antagonists all have a distinct antiproteinuric action. Based on a recent report the combination of an ACE inhibitor and a calcium antagonist in reduced doses may tend to be more effective with regard to proteinuria and protection of renal function, and may be better tolerated than the normal dose when each drug is used alone [12]. The challenge remains, however, to prove whether different antihypertensive drugs also have a disparate effect on the

long-term evolution of renal function, and most importantly, on prognosis. This remains as yet unresolved, and until such information is available, the approach to pharmacotherapy in diabetic nephropathy must remain empirical.

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