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Renal Protection and Antihypertensive Drugs
Current Status

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Abstract

The renal protective effect of antihypertensive drugs is linked to 2 mechanisms. First, reduction in blood pressure (BP) is a fundamental prerequisite common to all antihypertensive drugs. The exact definition of the level to which BP should be reduced remains to be established, although there is some evidence that BP should be reduced below 130/85mm Hg in patients with diabetic and nondiabetic nephropathies and below 125/75mm Hg in patients with nondiabetic nephropathies and proteinuria >1 g/day. However, available data suggest that tight BP control (BP < 140/80mm Hg) can reduce the risk of cardiovascular complications in hypertensive patients with type 2 diabetes mellitus (non–insulin-dependent diabetes mellitus; NIDDM). Secondly, intrarenal actions on mecha-

nisms such as glomerular hypertension and hypertrophy, proteinuria, mesangial cell proliferation, mesangial matrix production and probably endothelial dysfunction, which can cause and/or worsen renal failure, are relevant for the renal protective action of some drug classes. ACE inhibitors possess such properties and also seem to lower proteinuria more than other antihypertensive drugs, despite a similar BP lowering effect. Calcium antagonists likewise exert beneficial intrarenal effects, but with some differences among subclasses. It remains to be evaluated whether angiotensin II-receptor antagonists can exert intrarenal effects and antiproteinuric actions similar to those of ACE inhibitors.

While primary prevention of diabetic nephropathy is still an unsolved problem, there is convincing evidence that in patients with type 1 (insulin-dependent diabetes mellitus; IDDM) or 2 diabetes mellitus and incipient nephropathy ACE inhibitors reduce urinary albumin excretion and slow the progression to overt nephropathy. Similar effects have been reported with some long-acting dihydropyridine calcium antagonists, although less consistently than with ACE inhibitors. In patients with diabetic overt nephropathy, ACE inhibitors and nondihydropyridine calcium antagonists are particularly effective in reducing proteinuria and both drugs can slow the decline in glomerular filtration rate more successfully than other antihypertensive treatment.

Available data in patients with nondiabetic nephropathies indicate that ACE inhibitors can be beneficial, principally in patients with significant proteinuria, in slowing the progression of renal failure. However, it is still unclear whether this beneficial effect of ACE inhibitors is particularly evident in patients with mild and/or more advanced renal failure and whether calcium antagonists possess a similar nephroprotective effect.

Overall, data from clinical trials thus seem to indicate that ACE inhibitors and possibly calcium antagonists should be preferred in the treatment of patients with diabetic and nondiabetic nephropathies. However, further information is needed to understand renal protection.

Available data indicate that the occurrence of end-stage renal failure (ESRF) is increasing both in the US[1] and in Europe[2] with 2 main adverse consequences. First, ESRF has a negative impact on the prognosis of patients both in terms of survival and quality of life. Secondly, it increases the economic costs for healthcare systems.[3] Thus prevention of ESRF is an important target of medical therapy. Such therapy is based on two strategies, namely primary prevention of renal damage and slowing or halting the progression of renal failure. Since antihypertensive drugs are frequently used in order to achieve these therapeutic targets[4-7] we will review both the mechanisms through which these drugs can exert a renal protective action and the clinical evidence of their renal protection in diabetic and nondiabetic nephropathies.

1. Mechanisms of Renal Protection

Antihypertensive drugs may exert a renal protective action through 2 main mechanisms. First, the reduction of blood pressure (BP), which is a mechanism common to all available antihypertensive drugs, and secondly, intrarenal effects, which can differ according to different classes of antihypertensive drugs.

1.1 Antihypertensive Effects

Available data clearly indicate that hypertension is one of the main mechanisms causing kidney damage.[8-12] In the presence of renal damage hypertension quickens the progression toward ESRF.[13-18] Therefore, BP reduction can be viewed as an efficient means of preventing renal damage and halting or slowing the progression toward ESRF.[19-23]

However, both the definition of normal BP and the level that high BP should be reduced by are still to be defined (see sections 2.1 and 2.2).

1.2 Intrarenal Mechanisms

Renal vasoconstriction is considered a typical feature of patients with hypertension since it can occur at an early stage in the development of hypertension. Furthermore, renal vasoconstriction may precede and/or contribute to renal vascular lesions.[24] Thus, it is tempting to speculate that reduction in renovascular resistances induced by different antihypertensive drugs, such as angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, angiotensin II-receptor (AT_1) antagonists, nonselective and third generation β-blockers, loop diuretics and thiazide diuretics when given over the long term, could contribute to renal protection.[20,21,25-29]

A second intrarenal mechanism for the protection of renal function is the effect on glomerular hypertension and glomerular hypertrophy. Experimental and clinical data have shown that in the presence of diabetes mellitus[15,30] and in diseased kidney remnant nephrons[31,32] glomerular filtration rate (GFR) autoregulation is impaired, with the consequence that systemic BP is transmitted downstream to the glomeruli, resulting in glomerular hypertension. This latter phenomenon can be amplified by constriction of the efferent glomerular arteriole induced by intrarenal production of angiotensin II.[33-35] Moreover diabetes mellitus and nephron adaptation in remnant nephrons is characterised by glomerular hypertrophy with an increase in capillary radius.[31,36] Both these processes increase capillary wall tension, a mechanism that causes glomerular damage (glomerulosclerosis).[31,36]

Glomerular hypertension can be reduced by antihypertensive drugs that cause a predominant vasodilation of the efferent glomerular arteriole. ACE inhibitors seem to have such an effect[20,30,37-42] not only through inhibition of intrarenal angiotensin II generation but also through a bradykinin-mediated action.[43,44] The latter effect is not exerted by AT_1-antagonists.[43,44] However, it is unclear whether this bradykinin-mediated effect of ACE inhibitors on the glomerular efferent arteriole results in a greater reduction in glomerular BP compared with AT_1-antagonists. Some experimental data suggest that AT_1-antagonists are less effective in reducing glomerular hypertension than ACE inhibitors,[43,44] while other experimental data indicate that these 2 classes of drugs reduce glomerular capillary pressure to a similar extent.[28,45-47] Moreover in patients with nondiabetic chronic renal failure, both the ACE inhibitor enalapril and the AT_1-antagonist losartan potassium caused a similar increase in renal blood flow (RBF) with no change in GFR and a similar significant decrease in filtration fraction (FF).[48] Thus these data suggest that ACE inhibitors and AT_1-antagonists can exert a similar intrarenal haemodynamic action in patients with renal disease, a suggestion that needs to be confirmed.

The reduction in intraglomerular pressure induced by ACE inhibitors can account for the initial, albeit modest, decrease in GFR.[49-53] This effect is a functional phenomenon since it is reversible even after long term treatment in patients with either diabetic[50] or nondiabetic[52] nephropathies and appears to be a prerequisite for the subsequent attenuation of the decline in GFR.[50-53]

It is still unclear whether nondihydropyridine calcium antagonists, such as verapamil and diltiazem, can reduce glomerular hypertension through mechanisms independent of systemic BP reduction. Possible mechanisms include inhibition of the calcium-dependent vasoconstricting effect of angiotensin II on the efferent glomerular arteriole[26] and preservation of renal autoregulation.[54-57] With the possible exception of manidipine,[58] dihydropyridine calcium antagonists act predominantly by relaxing the afferent glomerular arteriole.[59] Therefore, they do not reduce, or may even increase glomerular capillary pressure[39] and impair renal autoregulation.[32] However, these drugs can reduce glomerular hypertrophy,[26,39,55,59] an effect which can also be exerted by ACE inhibitors through interference with the direct or indirect trophic effects of

angiotensin II.[60] Conventional treatment with diuretics, β-blockers, vasodilators, α_1-antagonists and their combinations seem to be devoid of any specific effect on glomerular hypertension beside that induced by BP reduction.[10]

A third intrarenal mechanism is the effect on urinary protein excretion. Proteinuria is caused by alterations in glomerular membrane permeability and selectivity due to several mechanisms including mechanical injury induced by glomerular hypertension, incomplete covering of the glomerular surface area by podocytes in the presence of glomerular hypertrophy or lesions caused by toxins or immunoreactants.[61] Moreover, intrarenal angiotensin II can contribute to proteinuria either by inducing glomerular hypertension and hypertrophy or by causing contraction of mesangial cells and therefore altering intraglomerular circulation and glomerular membrane permselectivity.[33,62]

Although proteinuria can be an indicator of the degree of renal damage[63,64] experimental data suggest that it can play a causative role in the development of glomerulosclerosis through various mechanisms, including mesangial cell and tubular protein overload and epithelial cell damage.[61] This hypothesis is consistent with the finding that, both in diabetic and nondiabetic nephropathies, proteinuria is a predictor of the rate of renal function deterioration;[5,53,65-72] furthermore a reduction in proteinuria was found to correlate with better renal function outcome.[5,53,71,73-78] Therefore, the antiproteinuric effect of antihypertensive drugs should be an additional mechanism through which these drugs can protect the kidney.

Available data indicate that the long term beneficial effects of antihypertensive drugs in reducing urinary protein excretion are proportional to BP reduction both in diabetic and nondiabetic nephropathy.[4-6,53,79-84] However, ACE inhibitors seem to lower urinary protein excretion more than other antihypertensive agents despite a similar BP lowering effect.[79-84] This additional antiproteinuric effect of ACE inhibitors can be tentatively explained by an improvement in glomerular membrane permselectivity to macromolecules induced by a reduction in glomerular capillary pressure or by other mechanisms.[49,85,86] Interestingly, the antiproteinuric effect of ACE inhibitors seems to be a functional phenomenon since it is readily detectable[41,49,87-89] and reversible after withdrawing drug therapy even following long term treatment.[50]

As reviewed by Burnier and Brunner,[28] in some experimental models[45,62,90-92] but not in others[92,93] AT_1-antagonists were shown to exert an antiproteinuric effect that was similar to that of ACE inhibitors,[45,90-92] while in patients with nondiabetic nephropathy, losartan potassium and enalapril exerted a similar antiproteinuric effect.[48] Recent preliminary data indicate that the addition of losartan potassium to patients with various renal diseases who were receiving ACE inhibitors further reduced proteinuria.[94] This finding is in agreement with experimental data showing that the combination of lisinopril and losartan potassium was more effective than single drug treatment in reducing proteinuria in rats with passive Heymann nephritis.[95] Taken together these data suggest that the antiproteinuric effect of ACE inhibitors seems in some way linked to inhibition of intrarenal generation of angiotensin II, and that a more complete blockade of intrarenal angiotensin II can exert a greater antiproteinuric effect.

It has been reported that nondihydropyridine calcium antagonists, such as verapamil and diltiazem, exert an antiproteinuric effect similar to ACE inhibitors[82,96] owing to their capacity to preserve renal autoregulation and improve glomerular membrane permselectivity.[97] In contrast, dihydropyridine calcium antagonists exert a modest or no apparent antiproteinuric effect.[82] They have been shown to worsen glomerular autoregulation,[32] not improve glomerular membrane permeability and selectivity[97] and reduce tubular protein reabsorption.[98] However, the perceived lack of antiproteinuric effect seems to be due to the inclusion in the meta-analyses of data concerning nifedipine, which has been claimed not to reduce proteinuria in diabetic nephropathy[81-83] or to reduce proteinuria less than other calcium antagonists in diabetic and nondiabetic nephropathies.[84]

Since these meta-analyses were based on studies in which mainly short-acting nifedipine formulations were used, it is tempting to speculate that pressure oscillations and reflex activation of the sympathetic nervous system (SNS) and therefore of the renin angiotensin system[99] may have blunted and/or counteracted the antiproteinuric effect linked to BP reduction. This hypothesis seems to be supported by the following data. First, chronic SNS activation induced proteinuria in rats.[100] Furthermore, sympathovagal imbalance with a relative sympathetic dominance is present in patients with diabetes mellitus at high risk of progression to microalbuminuria,[101] with incipient and overt nephropathy[102] and associated with a greater progression of diabetic nephropathy.[103] Secondly, some long-acting dihydropyridine calcium antagonists significantly reduced microalbuminuria in patients with incipient diabetic nephropathy, with an effect similar to ACE inhibitors (see section 3.2.1). Moreover there is some evidence that while the antiproteinuric effect of ACE inhibitors is detectable early, that of dihydropyridine calcium antagonists can be observed only after prolonged treatment.[104,105] Finally, it is possible that the combination of an ACE inhibitor with a nondihydropyridine or a dihydropyridine calcium antagonist could exert an additional antiproteinuric effect.[106-108]

1.3 Other Mechanisms

Mesangial cells play a key role in controlling glomerular microcirculation. Proliferation of these cells as well as increased deposition of mesangial extracellular matrix, which is triggered by haemodynamic factors and/or inflammatory changes, seems to play a pivotal pathogenetic role in most forms of glomerular injury.[40,109] Since ACE inhibitors[109] and calcium antagonists[59,109] can counteract these processes it is reasonable to assume that such processes might be additional mechanisms through which these drugs exert renal protection.

Endothelium is a paracrine and autocrine organ that plays an important role in the control of vascular tone and structure in various organs including the kidney. The endothelium produces its effects through production of vasodilating substances, mainly nitric oxide (NO), and vasoconstrictor substances such as endothelium derived constricting factors (EDCFs), tentatively identified as prostanoids, thromboxane A_2 and prostaglandin H_2, and superoxide anions, and endothelin-1 (ET_1).[110] As reviewed elsewhere,[111-114] endothelial dysfunction as a result of reduced bioavailability of NO and increased production of EDCFs and ET_1 could cause both acute and chronic kidney damage.

Available data in humans indicate that both ACE inhibitors[115-118] and dihydropyridine calcium antagonists[119-121] can improve endothelial function. Moreover, experimental data suggest that ACE inhibitors can reduce ET_1-production[114] and both experimental[122-123] and clinical data[124] indicate that calcium antagonists counteract the vascular action of ET_1. However, whether these endothelial effects of ACE inhibitors and calcium antagonists are additional mechanisms of renoprotection is still to be evaluated in humans.

2. Definition of Hypertension and How Far Blood Pressure Should be Reduced

2.1 Patients With Diabetes Mellitus

As reviewed elsewhere,[6,15,125] there are several proposals but no definite agreement on the definition of hypertension or on how far BP should be reduced in patients with diabetes mellitus. According to World Health Organization/International Society of Hypertension (WHO-ISH),[126] WHO[127] and US[128] guidelines, hypertension is defined in the overall population as BP values > 140/90mm Hg. However, these guidelines recommend that BP should be reduced to below 130/85mm Hg in patients with diabetes mellitus. Thus, it is tempting to speculate that in patients with diabetes mellitus hypertension can be defined as BP ≥ 130/85mm Hg.

There is even greater uncertainty concerning how far BP should be reduced in patients with diabetic nephropathy.[6,129] Two ongoing trials have been designed to answer this question. The first trial[130] has been designed in a subset of patients

with type 1 diabetes and nephropathy, who were enrolled in a previous trial.[131] The aim of the study was to determine whether the level of BP control obtained using an ACE inhibitor, ramipril, as the primary therapeutic agent, is associated with improved prognosis in the rate of decline in renal function, the rate of ESRF, proteinuria, morbidity and mortality. The primary end-point of this study was comparison of the rate of loss of renal function between 2 groups randomised to moderate [mean arterial pressure (MAP); ≥ 100 ≤ 107mm Hg] and more intensive (MAP ≤ 92mm Hg) BP control on a 2-year follow-up.

The second study,[132] the Appropriate BP Control in Diabetes (ABCD) trial, is a randomised, prospective, blinded trial designed to determine the effects of moderate versus intensive reduction in diastolic BP (DBP) on the outcome of diabetic nephropathy. The primary end-point is creatinine clearance, and secondary end-points are albuminuria, retinopathy, neuropathy and cardiovascular diseases. The study population is 480 patients with normotension and type 2 diabetes (DBP 89-80mm Hg) and 470 patients with hypertension and type 2 diabetes (DBP ≥ 90mm Hg). The normotensive cohort has been randomised to have a reduction in DBP of either 10mm Hg below baseline or to maintain DBP between 89 to 80mm Hg. The hypertensive cohort has been randomised to DBP reduction to 75mm Hg or to 89mm Hg. The secondary objective of this study is to determine if a calcium antagonist (nisoldipine) and an ACE inhibitor (enalapril), used as first line medications, have an equivalent beneficial effect on diabetic complications. Baseline characteristics of these patients, recently reported,[133] show that both systolic and diatolic hypertension are significantly associated with diabetic nephropathy as well as with its macrovascular complications. It is expected that these trials will offer important information on the target BP values to be reached with regard not only to diabetic nephropathy but also to other vascular diabetic complications.

2.2 Patients Without Diabetes Mellitus

How far BP should be reduced was evaluated in the Hypertension Optimal Treatment (HOT) Study, in which 19,196 patients with hypertension (of whom 7% had diabetes mellitus) were randomised to reach 3 different levels of DBP (<90, <85, <80mm Hg).[134] This study ended in August 1997 and ongoing analyses of data will include the outcome of renal function, as reflected by creatinine clearance (Cockcroft's formula). Moreover a renal substudy of this trial will evaluate GFR in a sample of patients.[135] Analyses of previous studies[20,21,136] have suggested that BP should be reduced well below 140/90mm Hg, but more precise information was derived from the Modification of Diet in Renal Disease (MDRD) study[137] and additional analyses.[53,138-140] The data from this study prompted the authors to suggest that BP should be reduced to ≤ 130/80mm Hg in patients with proteinuria of 0.25 to 1.0 g/day and to ≤ 125 to 75mm Hg in those with proteinuria > 1.0 g/day.

Moreover, very recent guidelines by the Joint National Committee indicate that in patients with nondiabetic nephropathy, BP should be reduced to 130/85mm Hg or lower (125/75mm Hg) in those with proteinuria in excess of 1 g/day.[128] Finally, a subanalysis of MDRD data suggests that similar target BP values are appropriate in Black patients and that controlling BP to lower values may be even more important in African Americans than in Caucasians in slowing the progression of renal disease.[141] An ongoing trial, the African American Study of Kidney (AASK) Disease and Hypertension, should help to define the optimal target BP in this population.[142]

3. Effects of Antihypertensive Drugs on Diabetic Nephropathy

3.1 Primary Prevention

Prevention of microalbuminuria (30 to 300 mg/dl or 20 to 200 μg/min), which is a well accepted marker of incipient nephropathy, is a rational therapeutic target. ACE inhibitors are regarded as first choice drugs owing to their intraglomerular action

(see sections 1.2 and 1.3). A recent multicentre, double-blind, randomised, parallel-design placebo-controlled study, the Eurodiab Control Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID) trial,[143] addressed this issue in 440 normotensive, normoalbuminuric patients with type 1 diabetes, 213 treated with lisinopril (10 to 20 mg/day) and 227 with placebo. At the 2-year follow-up microalbuminuria was nonsignificantly reduced by 12.7% in the group treated with lisinopril. Progression to microalbuminuria was 8% (18 of 227 patients) and 6% (13 of 213 patients) in the placebo and lisinopril groups, respectively, a difference which was not statistically significant. Although the authors concluded that a 15% reduction in normoalbuminuria 'may be of clinical importance in limiting the progression of renal disease', it seems from the above report that 2 year treatment with an ACE inhibitor does not exert an apparent primary preventive effect in normotensive-normoalbuminuric type 1 diabetes patients. Therefore, to date there is no clear evidence supporting the concept of preventive treatment with ACE inhibitors in normoalbuminuric and normotensive patients with diabetes mellitus.[15]

Three double blind, randomised, parallel-group, prospective studies have been performed in hypertensive normoalbuminuric patients with type 2 diabetes, comparing the effect of enalapril and nifedipine modified release,[144] of captopril and conventional treatment[145] and of cilazapril and amlodipine.[146] In a mean follow-up ranging from 1[144] to 3[145,146] years, BP was reduced similarly and the urinary albumin excretion (UAE) rate was unchanged by all treatments. Taken together, these 3 studies suggest that in hypertensive normoalbuminuric type 2 diabetes patients ACE inhibitors, dihydropyridine calcium antagonists and conventional therapy exert a similar effect on UAE. However, since these studies lacked a placebo control group, it is unclear whether these treatments truly prevent progression toward incipient nephropathy.

The relevance of antihypertensive therapy in primary prevention of diabetic nephropathy is the subject of an ongoing randomised, double-blind, placebo-controlled study, the BErgamo NEphrologic DIabetes Complications Trial (BENEDICT) (G. Remuzzi, personal communication). In this study, 2400 normoalbuminuric hypertensive patients with type 2 diabetes will be randomised to receive an ACE inhibitor, trandolapril (2 g/day), a nondihydropyridine calcium antagonist, verapamil SR (240 mg/day), their fixed combination (verapamil SR/trandolapril 180/2 mg/day) or placebo. These patients will be followed for at least 3 years in order to evaluate the effect of these treatments on the onset of microalbuminuria (UAE > 20 μg/min). Patients progressing to microalbuminuria will be randomised to receive trandolapril (2 mg/day) or the fixed combination of verapamil SR + trandolapril (180/2 mg/day) with the objective of evaluating the effect of these treatments on progression of microalbuminuria to macroalbuminuria.

3.2 Secondary Prevention: Incipient Nephropathy

The effect of antihypertensive drugs on the progression of incipient nephropathy is generally evaluated by taking into account changes in UAE rate and/or the rate of progression to macroalbuminuria, a marker of overt diabetic nephropathy. Changes in GFR did not appear to provide useful information in normotensive patients with type 1 diabetes, since these patients showed no change in GFR over a follow-up period of 4 to 8 years irrespective of antihypertensive treatment.[147-149] In contrast, in hypertensive patients with type 2 diabetes and incipient nephropathy GFR measurement is a rational parameter since it shows an early decline in untreated patients.[150]

3.2.1 Patients With Type 1 Diabetes

As shown in table I, 8 controlled studies evaluated the effect of antihypertensive drugs on microalbuminuria in normotensive patients with type 1 diabetes. In all studies, the ACE inhibitor significantly reduced UAE, with one exception[151] in which captopril did not significantly change this parameter. In 2 studies,[149,155] changes in UAE

were significantly related to changes in mean BP, while in other studies[42,152,154] there was no correlation between these parameters. The efficacy of ACE inhibitors in reducing UAE was confirmed in another 2 studies, an open randomised, long term trial in which captopril significantly reduced UAE[147] and a double-blind, randomised trial without placebo control group in which enalapril significantly reduced UAE while hydrochlorothiazide did not reduce UAE.[156] Studies with nifedipine showed divergent results. Nifedipine retard, a pharmaceutical formulation with a favourable trough to peak (T/P) effect on BP when given twice daily,[157] increased UAE in 1 short term study[42] in which captopril reduced UAE. In another long term study[151] nifedipine retard given once daily also increased UAE while captopril did not.

In 2 studies,[149,153] nifedipine gastro intestinal therapeutic system (GITS), a long-acting pharmaceutical formulation with a favourable T/P effect on BP when given once daily,[157] significantly reduced UAE, an effect which was unrelated to changes in BP. In the trial of the Italian Microalbuminuria Study Group in IDDM,[149] the UAE reduction induced by nifedipine GITS was around 17.1% compared with a 46.3% reduction in UAE

Table I. Effect of antihypertensive drugs on mean blood pressure (MBP) and microalbuminuria in patients with normotension and type 1 diabetes mellitus (insulin-dependent diabetes mellitus; IDDM)

Reference	Drugs (dosage)	No. of patients	Treatment duration	MBP	Microalbuminuria
Double-blind, randomised, placebo-controlled studies					
Mimran et al.[42]	Nifedipine retard (20mg bid)	7	6 weeks	=	↑*
	Captopril (25mg bid)	8		=	↓*
	Placebo	7		=	=
Bilo et al.[151]	Nifedipine retard (20mg od)	7	1 year	=	↑*
	Captopril (50mg od)	6		=	=
	Placebo	5		=	=
Viberti et al.[152]	Captopril (50mg bid)	46	2 years	↓*	↓#
	Placebo	46		=	↑*
Schnack et al.[153]	Nifedipine GITS (30mg od)	8	1 year	=	↓#
	Placebo	7		=	=
Laffel et al.[154]	Captopril (50mg bid)	70	2 years	↓#	↓*#
	Placebo	73		↑*	=
Microalbuminuria Captopril Study Group[155]	Captopril (50mg bid)	111	2 years	↓#	↓*#
	Placebo	114		=	=
Eurodiab Control Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID) study[143]	Lisinopril (20mg od)	45	2 years	↓#	↓#
	Placebo	34		=	=
Crepaldi et al.[149]	Lisinopril (20mg od)	32	3 years	↓#	↓#
	Nifedipine GITS (30-60mg od)	26		=	↓#
	Placebo	34		=	=
Open randomised study					
Mathiesen et al.[147]	Captopril (25-100mg od)	21 treated	4 years	=	↓*†
	+ thiazide	23 untreated		=	↑*
Double-blind, randomised, without placebo-controlled study					
Hallab et al.[156]	Enalapril (20mg od)	11	1 year	=	↓‡
	Hydrochlorothiazide (25mg od)	10		=	=

bid = twice daily; **GITS** = gastro intestinal therapeutic system; **od** = once daily; **=** no significant change; ↓ = reduced; ↑ = increased; ***** = $p < 0.05$ *vs* basal; **#** = $p < 0.05$ *vs* placebo; **†** = $p < 0.05$ *vs* untreated; **‡** = $p < 0.05$ *vs* hydrochlorothiazide.

induced by lisinopril. However, in this study only lisinopril significantly reduced BP, an effect which can at least partially explain the greater reduction in UAE induced by this drug. In a sequential study without a placebo control, Fioretto et al.[158] found that in patients with type 1 diabetes and hypertension cilazapril was more effective than verapamil sustained release in reducing UAE and that their combination at a reduced dose induced a more marked reduction in UAE than single drug treatment. In the same study, these authors found that verapamil was more effective than nifedipine in decreasing UAE.

Taken together, the above reported studies in normotensive patients with type 1 diabetes suggest the following conclusions. First, ACE inihibitors are effective in reducing microalbuminuria and this effect is at least partially independent of BP reduction (see section 1.2). Secondly, a long-acting nifedipine formulation can significantly reduce microalbuminuria, while a less long-acting formulation can increase UAE, a finding that suggests the smoothness and duration of action of this drug may be relevant in its intrarenal effect (see section 1.2). Thirdly, there are no data concerning the effect of nondihydropyridine calcium antagonists on microalbuminuria in normotensive patients with type 1 diabetes. However, in hypertensive patients with type 1 diabetes verapamil seems to be more effective than nifedipine sustained release, but less effective than ACE inhibitors in reducing microalbuminuria. Furthermore, the combination of verapamil with an ACE inhibitor seems to exert an additive effect in lowering UAE.

3.2.2 Patients with Type 2 Diabetes

The effect of antihypertensive drugs on UAE and GFR of patients with type 2 diabetes has been evaluated in several controlled studies with different designs (table II). In normotensive patients with type 2 diabetes 5-year treatment with enalapril stabilised UAE and renal function, evaluated as mean reciprocal creatinine, which significantly increased in the placebo group.[159] In a double-blind, randomised, cross-over study without a placebo group conducted on a small group of hypertensive patients with type 2 diabetes, Baba et al.[160] found that enalapril and nicardipine, a dihydropyridine calcium antagonist, similarly reduced BP and UAE and increased GFR after treatment for 1 month.

Seven double-blind, randomised studies further compared long term renal effects of different antihypertensive drugs (table II). In these studies BP was reduced similarly with all drugs, and in 4 of 7 studies ACE inhibitors were more effective in reducing UAE than conventional treatment,[145] nifedipine retard[144,162] and nitrendipine.[164] However, calcium antagonists did not change[162,164] or significantly reduce[144] UAE and, similarly to ACE inhibitors, did not significantly change GFR. In 2 other studies, in which patients received cilazapril or amlodipine[146] and enalapril or nitrendipine,[163] the ACE inhibitor and the dihydropyridine calcium antagonist similarly and significantly reduced UAE, and similarly tended to reduce[146] or significantly increased[163] GFR. There is as yet no clear explanation of the different GFR outcome in these 2 studies. Finally, Ruggenenti et al.[161] found that after 14 weeks enalapril tended to reduce UAE, while nitrendipine tended to increase UAE, while after 1 year neither drug changed UAE and both significantly increased GFR.

Taken together, the above data from hypertensive patients with type 2 diabetes indicate that ACE inhibitors and some dihydropyridine calcium antagonists reduced UAE and either improved or did not worsen GFR.

3.2.3 Patients with Type 1 and Type 2 Diabetes

Studies have been performed in a mixed group of patients with type 1 and type 2 diabetes, who were either normotensive[165,166] or hypertensive,[167] and in groups who had a mixture of hypertension and normotension.[168] In patients with normotension long term treatment with enalapril[165] and lisinopril[166] significantly reduced UAE as compared with placebo without significantly changing GFR, while in a 12-month, prospective, non-controlled trial nitrendipine significantly reduced UAE and increased GFR.[157] In the Melbourne Study,[168] normotensive and hypertensive patients with type 1 and type 2 diabetes were

randomised to receive perindopril or nifedipine retard for 1 year. Both the ACE inhibitor and the dihydropyridine calcium antagonist significantly reduced BP and did not change UAE, while in patients with hyperfiltration both drugs decreased GFR. Taken together, these studies confirm the efficacy of ACE inhibitors in reducing UAE and again indicate that a similar effect can be exerted by dihydropyridine calcium antagonists in a mixed group of patients with microalbuminurea and type 1 and 2 diabetes. Moreover, both drugs either ameliorated or did not worsen GFR.

Table II. Effect of antihypertensive drugs on mean blood pressure (MBP), microalbuminuria and renal function in patients with type 2 diabetes mellitus (non–insulin-dependent diabetes mellitus; NIDDM)

Reference	Drugs (dosage)	No. of patients	Treatment duration	MBP	Microalbuminuria	Renal function (GFR)
Normotensive patients: double-blind, randomised, placebo-controlled study						
Ravid et al.[159]	Enalapril (10mg/day)	49	5 years	=	=	=
	Placebo	45		=	↑*	↓*[a]
Hypertensive patients double-blind, randomised, crossover study						
Baba et al.[160]	Enalapril (5-10mg bid)	7	4 weeks	↓*	↓*	=
	Nicardipine (20-40mg bid)			↓*	↓*	=
Double-blind, randomised, without placebo control group studies						
Chan et al.[144]	Enalapril (20mg od)	21	1 year	↓*	↓*	=
	Nifedipine retard (20-40mg bid)	15		↓*	↓*	=[b]
Lacourcière et al.[145]	Captopril [C] (25-50mg bid)	- Capt C alone or combined with H n = 9	3 years	↓*	↓†	=
	Metoprolol [M] (50-100mg bid) Hydrochlorothiazide [H] (12.5-25mg bid)	- Conv Treat (H/M/M+H) n = 12		Conv Treat[c] ↓*	Conv Treat[c] =	Conv Treat[c] =
Ruggenenti et al.[161]	Enalapril (5-20mg od)	8	Short term 14 weeks, long term 1 year	↓*	↓†	=
	Nitrendipine (10-40mg od)	8		↓*	=	=
				↓*	=	↑*
				↓*	=	↑*
Agardh et al.[162]	Lisinopril (10-20mg od)	168	1 year	↓*	↓†	=
	Nifedipine retard (20-40mg bid)	167		↓*	=	=[b]
Velussi et al.[146]	Cilazapril (2.5-5mg od)	9	3 years	↓*	↓*	=
	Amlodipine (5-10mg od)	9		↓*	↓*	=
Mosconi et al.[163]	Enalapril (5mg od-10mg bid)	6	27 months	=	↓*	↑*
	Nitrendipine (10mg od-10mg bid)	7		↓*	↓*	↑*
Piñol et al.[164]	Enalapril (10-20mg od)	15	6 months	↓*	↓†	=
	Nitrendipine (20-40mg od)	13		↓*	=	=

a 1/creatinine (reciprocal creatinine).

b Creatinine clearance.

c Conventional treatment indicates treatment with hydrochlorothiazide, metoprolol or their combination.

bid = twice daily; **GFR** = glomular filtration rate; **od** = once daily; **=** = no significant change; ↓ = reduced; ↑ = increased; ***** = $p < 0.05$ *vs* baseline; † = $p < 0.05$ *vs* control drug/drugs.

3.2.4 Progression to Overt Nephropathy

The effect of antihypertensive drugs on progression from incipient to overt nephropathy, i.e the progression from micro- to macroalbuminuria, has been evaluated in several controlled studies with different designs both in normotensive patients with type 1 and 2 diabetes, and in hypertensive patients with type 2 diabetes and incipient nephropathy (table III). Overall, these studies indicate that ACE inhibitors are more effective in preventing the progression to overt nephropathy compared with no antihypertensive treatment in normotensive patients with type 1 diabetes,[147] and with placebo in normotensive patients with type 1 diabetes,[152,154,155] type 2 diabetes[159] and type 1 and 2 diabetes.[165,166] ACE inhibitors have also been shown to be more effective compared with a thiazide diuretic, hydrochlorothiazide, in normotensive patients with type 1 diabetes[156] and with conventional treatment in hypertensive patients with type 2 diabetes.[145,169]

In 2 studies the effect of an ACE inhibitor was compared with that of a dihydropyridine calcium antagonist, demonstrating a slight but nonsignificant greater efficacy of lisinopril compared with nifedipine retard in hypertensive patients with type 2 diabetes,[162] and similar efficacy of lisinopril and nifedipine GITS in normotensive patients with type 1 diabetes.[149] Thus, these data indicate that ACE inhibitors exert a significant protective action in preventing progression to overt nephropathy in normotensive patients with microalbuminuria and type 1 and type 2 diabetes. This effect is also true for patients with microalbuminuria, hypertension and type 2 diabetes. Moreover, 1 study showed that a similar renal protective action is exerted by a long-acting nifedipine formulation.[149]

3.3 Secondary Prevention: Overt Nephropathy

The renal protective action of antihypertensive drugs has been evaluated by taking into account the effect on proteinuria and GFR, as well as that on creatininaemia doubling and on hard end-points such as incidence of ESRF and mortality.

3.3.1 Effect on Proteinuria and Glomerular Filtration Rate

This topic has recently been reviewed[5,6] and the antiproteinuric effect of antihypertensive drugs was previously discussed (see section 1.2). Early sequential studies indicated that captopril exerted a significant antiproteinuric effect in patients with type 1 diabetes and severe diabetic nephropathy[87] and in patients with type 2 diabetes.[170] However, another study[171] showed no significant effect of captopril on severe proteinuria in patients with type 2 diabetes and renal insufficiency. Subsequent short and long term studies with different protocols have documented the antiproteinuric action of ACE inhibitors both in patients with type 1 and type 2 diabetes (tables IV and V). In patients with type 1[98,173,177] and in those with type 2[144,181,183] diabetes various dihydropyridine calcium antagonists did not significantly change urinary protein excretion with the exception of 2 short term studies, in which urinary protein excretion was significantly reduced[106] or increased.[180] On the other hand, nondihydropyridine calcium antagonists diltiazem[97,107,180] and verapamil[97,188] significantly reduced urinary protein excretion.

With selective β-blockers urinary protein excretion was either not changed in patients with type 1 diabetes[174] and with type 2 diabetes[97,184,187] or significantly reduced in type 1[176] and type 2,[178] whereas it remained unchanged when thiazide diuretics were given alone[179] or combined with guanfacine.[107] Furthermore, in 1 study the combination of lisinopril with verapamil[107] further reduced protein excretion as compared with each drug alone (tables IV and V). In 3 additional studies in patients with type 1 and 2 diabetes who received ACE inhibitors, urinary protein excretion was significantly reduced in normotensive patients,[189] remained unchanged in normotensive and hypertensive patients,[190,191] while no modification was induced by a dihydropyridine calcium antagonist.[191]

The different effect on proteinuria of various antihypertensive drugs cannot be explained by different effects on BP, the only exception being 1

Table III. Studies on progression to overt nephropathy

Reference	Drugs (dosage)	Treatment duration	Progression to overt nephropathy [no. of patients (%)]
Patients with normotension and type 1 diabetes mellitus (insulin-dependent diabetes mellitus; IDDM)			
Mathiesen et al.[147]	Captopril (25-100mg od) + bendroflumethiazide (bendrofluazide), dosage unknown	4 years	7/23 (30) untreated
			0/21 (0) treated
Hallab et al.[156]	Enalapril (20mg od)	1 years	1/11 (9)#
	Hydrochlorothiazide (25mg od)		6/10 (60)
Viberti et al.[152]	Captopril (50mg bid)	2 years	4/46 (9)*
	Placebo		12/46 (26)
Laffel et al.[154]	Captopril (50mg bid)	2 years	4/67 (6)*
	Placebo		13/70 (19)
Microalbuminuria Captopril Study Group, 1996[155]	Captopril (50mg bid)	2 years	8/111 (7.2)*
	Placebo		25/114 (21.2)
Crepaldi et al.[149]	Lisinopril (20mg od)	3 years	2/32 (6.3)*
	Nifedipine GITS (30-60mg od)		2/26 (7.7)*
	Placebo		7/34 (20.6)
Patients with normotension and type 2 diabetes mellitus (non–insulin-dependent diabets mellitus; NIDDM)			
Ravid et al.[159]	Enalapril (10mg)	5 years	6/49 (12)* 19/45 (42)
Patients with type 1 or type 2 diabetes mellitus			
Marre et al.[165]	Enalapril (20mg od)	1 year	0/10
	Placebo		3/10 (30)
O'Donnel et al.[166]	Lisinopril (10mg od)	1 year	0/12
	Placebo		3/15 (20)
Patients with hypertension and type 2 diabetes mellitus			
Lebovitz et al.[169]	Antihypertensive treatment including: enalapril (20mg od/bid) or placebo	3 years	2/30 (7)†
	Conventional treatment		8/38 (21)
Lacourcière et al.[145]	Captopril (25mg bid)	3 years	2/30 (7)†
	Conventional treatment: metoprolol (50mg bid) ± hydrochlorothiazide (12.5mg bid)		8/38 (21)
Agardh et al.[162]	Lisinopril (10-20mg od)	1 year	(3.8)
	Nifedipine retard (20-40mg bid)		(6.9)
Patients with normotension or hypertension and type 1 or 2 diabetes mellitus			
Melbourne Diabetic Nephropathy Study Group, 1991[168]	Perindopril (2-8mg od)	1 year	0/20
	Nifedipine retard (20-80mg od)		0/23

bid = twice daily; **GITS** = gastro intestinal therapeutic system; **od** = once daily; ***** = $p < 0.05$ *vs* placebo; **#** = *vs* hydrochlorothiazide; † = *vs* conventional treatment.

study in hypertensive patients with type 1 diabetes and renal insufficiency[174] (tables IV and V).

As far as GFR is concerned, 3 longitudinal before-versus-after therapy within group comparison trials[192-194] and 3 comparative (treated *vs* untreated) studies[195-197] have shown that conventional antihypertensive therapy slows the decline in GFR in hypertensive patients with type 1 diabetes. In a retrospective study the decline in GFR in patients with type 2 diabetes was significantly

smaller in hypertensive patients with well controlled BP than in patients with uncontrolled BP.[198] Therefore, as also shown by meta-analyses[79,82] BP control is a clear determinant of slowing the decline in GFR in hypertensive patients with overt nephropathy.

Studies of patients with type 1 diabetes, in which treatment was ≥ 6 months, indicate that ACE inhibitors did not change,[172,174,177] increased[175] or reduced[176,98] GFR, whereas dihydropyridine calcium antagonists did not change GFR.[177] Lisinopril reduced GFR to a significantly greater extent than nisoldipine.[98] Moreover, β-blockers did not change[174] or reduced[175,176] GFR (table IV).

In studies of patients with type 2 diabetes and normal or reduced GFR (table V) receiving treatment for ≥ 6 months, there does not seem to be any significant difference in effect on GFR between the various antihypertensive drugs. The exception has been 4 randomised studies. In these studies nondihydropyridine calcium antagonists did not change[107] or slowed the decline in GFR as compared with a β-blocker.[97] ACE inhibitors similarly slowed the decline in GFR,[97] reduced GFR,[107] or did not change GFR, which was reduced by a dihydropyridine calcium antagonist[183] and by a vasodilator.[185] Taken together, these data indicate, in agreement with previous meta-analyses performed on studies published until the beginning of 1994,[82-84] that ACE inhibitors and nondihydropyridine calcium antagonists are particularly effective in reducing proteinuria in patients with type 1 and 2 diabetes and overt nephropathy. However, there is not so clear evidence that these drugs offer additional advantages in ameliorating or slowing the decline in GFR in type 2 diabetes patients when the BP lowering effect is taken into account.[82]

Table IV. Effect of antihypertensive drugs on mean blood pressure (MBP), proteinuria and renal function in patients with type 1 diabetes mellitus (insulin-dependent diabetes mellitus; IDDM)

Reference	Drugs (dosage)	No. of patients	Treatment duration	MBP (mm Hg)	Proteinuria	Renal function (GFR)
Patients with normotension in an open randomised study						
Parving et al.[172]	Captopril (25-100mg od)	Treated: 15	1 year	↓#	↓#	=
		Untreated: 17		=	=	=
Patients with hypertension in an open randomised crossover study						
Holdaas et al.[173]	Lisinopril (20mg od)	12	3 weeks	↓*	↓*†	=
	Nifedipine retard (20mg bid)			↓*	=	=
Open randomised parallel-group study						
Björck et al.[174]	Enalapril (20mg od) + furosemide (50 mg/day)	22	2-3 years	↓*	↓*‡	=
	Metoprolol (100mg od) + furosemide (120 mg/day)	18		=	=	=
Double-blind, randomised parallel-group study						
De Cesaris et al.[175]	Enalapril (20mg od)	10	8 months	↓*	↓*	↑*
	Atenolol (100mg od)	10		↓*	↓*	↓*
Elving et al.[176]	Captopril (25-50mg tid)	15	2 years	↓*	↓*	↓*
	Atenolol (50-100mg od)	14		↓*	↓*	↓*
Norgaard et al.[177]	Spirapril (6mg od)	7	6 months	↓*	↓*†	=
	Isradipine sustained release (5mg od)	8		↓*		=
Rossing et al.[98]	Lisinopril (10-20mg od)	24	1 year	↓*	↓*†	↓*†
	Nisoldipine (20-40mg od)	25		↓*	=	↓*

bid = twice daily; **GFR** = glomular filtration rate; **od** = once daily; **tid** = three times daily; ***** = $p < 0.05$ *vs* baseline; **=** = no significant change; ↓ = decreased; ↑ = increased; **#** = $p < 0.05$ *vs* untreated; † = $p < 0.05$ *vs* dihydropyridine calcium-antagonist; ‡ = $p < 0.05$ *vs* metoprolol.

Table V. Effect of antihypertensive drugs on mean blood pressure (MBP), proteinuria and renal function in patients with type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus; NIDDM)

Reference	Drugs (dosage)	No. of patients	Treatment duration	MBP (mm Hg)	Proteinuria	Renal function (GFR)
Double-blind, randomised crossover studies of patients with normotension						
Stornello et al.[178]	Enalapril (5mg od)	12	6 months	=	↓*	=
	Atenolol (50mg od)			=	↓*	=
Patients with hypertension						
Stornello et al.[106]	Captopril (50mg bid)	12	4 weeks	↓*	↓*	↓
	Nicardipine (20mg tid)			↓	↓*	=
	Nicardipine + captopril			↓*	↓*	=
Stornello et al.[179]	Enalapril (20mg od)	12	6 weeks	↓	↓*	↓
	Chlortalidon (12.5mg od)			↓	↑	↓
	Atenolol (50mg od)			↓*	↓*	=
DeMarie et al.[180]	Diltiazem LA (100mg bid)	14	6 weeks	↓*	↓*	=
	Nifedipine SR (30-60mg od)			↓*	↑*	↓*
Randomised crossover study						
Bakris et al.[181]	Diltiazem (392mg od)	15	1 month	↓*	↓*†	=
	Nifedipine SR (84mg od) in patients treated with clonidine			↓*	=	=
Patients with hypertension in parallel-group, double-blind, randomised placebo-controlled study						
Lebovitz et al.[169]	Antihypertensive treatment including: enalapril (20mg od/bid)	28	3 years	=	↓*	=
	Placebo	18		=	=	=
Bauer et al.[182]	Enalapril (5-40mg od)	18	18 months	↓*#	↓*#	↓*
	Placebo	15		=	=	↓*
Open-label randomised, without placebo control group studies						
Bakris et al.[107]	Lisinopril (10-40mg od)	8	13 months	↓*	↓*	↓*
	Verapamil (240-480mg od)	8		↓*	↓*	=
	Hydrochlorothiazide (12.5-25mg od) + guanfacine (1-3mg od)	6		↓*	=	↓
	Lisinopril (10-25mg od) + verapamil (180-240mg od)	8		↓*	↓*	=
Bakris et al.[97]	Lisinopril (dosage unknown)	18	8 years	↓*	↓*	=[a]
	Diltiazem (dosage unknown)	8		↓*	↓*	=[a]
	Verapamil (dosage unknown)	10		↓*	↓*	=[a]
	Atenolol (dosage unknown)	16		↓*	=	↓*
Double-blind randomised, without placebo control group studies						
Chan et al.[144]	Enalapril (20mg od)	21	1 year	↓*	=	=[a]
	Nifedipine retard (20-40mg bid)	15		↓*	=	=[a]
Ferder et al.[183]	Enalapril (20mg bid)	18	1 year	↓*	↓*‡	=
	Nifedipine retard (10mg qid)	12		↓*	=	↓*
Nielsen et al.[184]	Lisinopril (10-20mg od)	16	1 year	↓*	↓*†	↓*
	Atenolol (50-100mg od)	19		↓*	=	↓*
Liou et al.[185]	Captopril (25-75mg od)	24	18 months	↓*	↓*	=
	Hydralazine (40-200mg od)	18		↓*	=	↓*
Fogari et al.[186]	Ramipril (5mg od)	20	6 months	↓*	↓*	=[a]
	Nitrendipine (20mg od)	20		↓*	=	=[a]
Nielsen et al.[187]	Lisinopril (10mg od)	17	3.5 years	↓*	↓*†	=
	Atenolol (50mg od)	19		↓*	=	=

a Creatinine clearance.

bid = twice daily; **GFR** = glomular filtration rate; **LA** = long-acting; **od** = once daily; **qid** = four times daily; **SR** = sustained release; **tid** = three times daily; * = $p < 0.05$ *vs* baseline; = = no significant change; ↓ = decreased; ↑ = increased; # = $p < 0.05$ *vs* placebo; ‡ = $p < 0.05$ *vs* nifedipine; † = $p < 0.05$ *vs* atenolol.

3.3.2 Effect on Creatininaemia Doubling and on Hard End-Points

The best way to assess the renal protective action of antihypertensive drugs is to evaluate their effect on creatininaemia doubling and on so-called hard end-points, such as incidence of ESRF and mortality.[199] In 1993, Lewis et al.[200] reported the data of a prospective, double-blind randomised clinical trial. This trial involved 409 patients with type 1 diabetes, proteinuria ≥500 mg/day and creatininaemia ≤2.5 mg/dl, most (approximately 75%) of whom were hypertensive and were being treated with antihypertensive drugs other than ACE inhibitors and calcium antagonists, principally diuretic agents. These patients were randomised to receive captopril 25mg 3 times daily (n = 207) or placebo (n = 202). At 3-year follow-up the risk, adjusted for mean BP, creatininaemia doubling was significantly reduced by 43%, and the risk of secondary combined end-points of death, dialysis and transplantation by 46% in the group treated with captopril. Subgroup analysis showed that captopril reduced the risk of creatininaemia doubling by 4, 40 and 74% in the subgroups with baseline creatininaemia of 1.0, 1.5 and 2.0 mg/dl, respectively. Moreover, captopril significantly reduced proteinuria compared with placebo. Thus, this study clearly indicates that captopril has protective effects on the kidneys in patients with type 1 diabetes and overt nephropathy. In addition, this effect was independent of its antihypertensive action at least in patients with baseline creatininaemia of 1.5 to 2.5 mg/dl. A subsequent analysis of this study showed that captopril caused a greater reduction in systolic BP and a greater remission of nephrotic range proteinuria than placebo (16.7 *vs* 1.5%). The study also showed that GFR remained stable in the remission group but declined significantly in the no-remission group.[201]

In a recent open study[188] 34 African Americans with hypertension, type 2 diabetes, proteinuria ≥1.5 g/day and creatinine clearance <80 ml/min were randomised to receive verapamil sustained release (n = 18) or atenolol (n = 16), titrated to maximum dosages of 480 mg/day and 100 mg/day, respectively. The addition of furosemide [frusemide] (100% of patients) or other antihypertensive drugs such as α-blockers, hydralazine and minoxidil (76% of patients) was permitted. Mean BP on an average 4.5 year follow-up was 99 ± 4 and 101 ± 3mm Hg in the groups treated with verapamil and atenolol, respectively, and proteinuria was reduced to a significantly greater extent in the group treated with verapamil. Data obtained so far show that the rate of decline in creatinine clearance and the incidence of a 50% or more increase in creatininaemia were significantly lower in the group treated with verapamil than in the group treated with atenolol. Thus, this open study in a small number of patients suggests that a nondihydropyridine calcium antagonist can slow the progression of overt nephropathy in African Americans with type 2 diabetes to a greater extent than a β-blocker.

To our knowledge, there are no ongoing trials in patients with type 1 diabetes and overt nephropathy aimed at evaluating the renal protective action of other antihypertensive drugs, such as calcium antagonists or AT_1-antagonists, or the combination of a calcium antagonist with either an ACE inhibitor or an AT_1-antagonist. In contrast, 2 ongoing trials in patients with type 2 diabetes and proteinuria will evaluate the renal protective action of two AT_1-antagonists, losartan potassium and irbesartan. The RENAAL study is a double-blind, randomised, prospective trial in 1520 patients with hypertension, type 2 diabetes, albuminuria >300 mg/g and creatininaemia 1.5 to 3.0 mg/dl. Patients will be randomised to receive Losartan potassium (100 mg/day) or placebo in addition to background antihypertensive therapy not including ACE inhibitors. A 4-year follow-up will evaluate creatininaemia doubling, ESRF and total mortality as primary end-points, and proteinuria and cardiovascular morbidity and mortality as secondary end-points.

The Collaborative Group Study Trial on Effect of Irbesartan (CGSTEI) is a prospective, double-blind, randomised, parallel group trial involving 1650 patients with hypertension, type 2 diabetes, proteinuria ≥1 g/day and creatininaemia 1 to 3 mg/dl in women and 1.2 to 3.0 mg/dl in men. Patients will be randomised to receive irbesartan (75

to 150 mg/day), amlodipine (2.5 to 10 mg/day) or placebo. A 2- to 4-year follow-up will assess creatininaemia doubling, ESRF and total mortality as primary end-points, and cardiovascular morbidity and mortality as secondary end-points.

3.4 Total Mortality and Cardiovascular Morbidity and Mortality

It is beyond the scope of this review to examine this topic extensively. However, it should be kept in mind that coronary and cerebrovascular diseases are the main cause of morbidity and mortality principally in patients with type 2 diabetes[202-204] but also in patients with type 1 diabetes.[15,205]

There is some evidence that total and cardiovascular mortality is reduced in patients with diabetic nephropathy receiving antihypertensive treatment versus no treatment[206] and in patients receiving intensified therapy compared with routine treatment.[207] Recently the study in the hypertensive cohort of the ABCD trial was suspended since the incidence of fatal and nonfatal myocardial infarction was significantly lower in the group treated with enalapril compared with those receiving nisoldipine.[208] However, these findings were based on a secondary end-point of the study and the rate of myocardial infarction among patients assigned to nisoldipine therapy was not significantly different from that in other studies of patients with type 2 diabetes.[208]

In another recent open label, randomised study, the FACET trial,[209] 380 patients with hypertension, type 2 diabetes and microalbuminuria <40 μg/min, although randomised to receive fosinopril or amlodipine, were in effect treated with fosinopril (n = 131), amlodipine (n = 141) or the combination (n = 108). Although the intention-to-treat analysis showed that the cumulative incidence of myocardial infarction, stroke and hospitalised angina was significantly lower in patients receiving fosinopril (7.4%) than in those treated with amlodipine (14.1%), analysis of post-randomisation data indicates that the incidence of cardiovascular events was even lower in patients receiving the combination therapy (3.7%). Thus, these 2 studies suggest that ACE inhibitors could be particularly beneficial in prevention of cardiovascular complications of hypertensive type 2 diabetes patients. This hypothesis is in agreement with recent data from the Captopril Prevention Project (CAPP) trial, which indicates that the incidence of cardiovascular events in a subgroup of patients with diabetes mellitus treated with captopril was lower than that of patients treated with conventional therapy.[210]

Dihydropyridine calcium antagonists also seem to have cardioprotective effects, or at least are not deleterious, considering in particular the striking cardiac protection seen in the HOT study among 1501 patients with diabetes mellitus receiving a dihydropyridine calcium antagonist.[211,212] In the context of the United Kingdom Prospective Diabetes Study (UKPDS), 1148 hypertensive type 2 diabetic patients were randomised either to tight control of blood pressure (758 patients), aiming for BP <150 to 85mm Hg, or to a less tight control of BP (390 patients), aiming for a BP <180 to 105mm Hg. In the former group patients were further randomised to receive an ACE inhibitor, captopril (400 patients) of a β-blocker, atenolol (358 patients) with the possible addition of other drugs, such as furosemide, slow release nifedipine, methyldopa and prazosin. In the latter group, treatment with ACE inhibitors or β-blockers was not included. In a median follow-up of 8.4 years the group assigned to tight BP control showed a significant reduction in the risk of fatal and nonfatal diabetic macrovascular complications, principally fatal and nonfatal strokes. Microvascular disease outcomes, principally retinopathy, were also reduced as compared with the group assigned to less tight control.[213] Data concerning the outcome of renal microvascular disease showed that the group under tight BP control exhibited a significant reduction in risk of microalbuminuria (≥50 mg/L) and a nonsignificant reduction in risk of proteinuria (≥300 mg/L), while plasma creatinine levels and the proportion of patients who had a two-fold increase in plasma creatinine did not significantly differ between the 2 groups.[213] Moreover, captopril and

atenolol were equally effective in reducing the risk of fatal and nonfatal macrovascular and microvascular complications.[214] Thus this study indicates that tight BP control is the most successful therapeutic approach aimed at reducing fatal and nonfatal complications in diabetic patients irrespective of treatment used. The relevance of tight BP control designed to reduce BP < 130/85mm Hg is further supported by the HOT study data in a subset of 1501 diabetic patients[211] and by recent WHO-ISH guidelines.[215] Ongoing trials in patients with type 1[130] and type 2[132,216] diabetes (BENEDICT, RENAAL, CGSTEI) will offer additional information on the potential benefit of different treatments in reducing total mortality and cardiovascular morbidity and mortality.

4. Nondiabetic Nephropathy

The renal protective action of different antihypertensive drugs must be evaluated by taking into account those factors which are known to influence the progression of renal insufficiency. These factors include baseline proteinuria, the antiproteinuric effect (see section 1.2) as well as the degree of BP reduction (see section 1.1). Other confounding factors are include intrinsic renal lesions, which are a well known determinant of the rate of progression of renal insufficiency[69,71,217] as well as the degree of renal insufficiency.[71,217] Data on short term studies are reviewed elsewhere[59,218] and therefore we will examine only long term studies.

4.1 Hypertensive Nephrosclerosis

Hypertensive nephrosclerosis is considered to be one of the most common causes of ESRF in the US and Europe, with a greater prevalence in African Americans.[1,2] The increasing incidence of ESRF as a result of this disease is a paradox considering the improvement in the treatment of hypertension.[17,23,219] However, it may be overestimated because of failure to recognise other causes, such as ischaemic nephropathy,[219-221] atheroembolic renal disease (cholesterol embolisation),[219-221] episodes of accelerated hypertension[220] or other renal lesions.[220] However, in a recent pilot study of the AASK Trial, data of renal biopsies in African Americans without diabetes or marked proteinuria but with hypertension and mild to moderate renal insufficiency are consistent with the clinical diagnosis of hypertensive nephrosclerosis.[222]

Microalbuminuria, which is found in about 10 to 40% of patients with uncomplicated essential hypertension,[223] is considered a marker of cardiovascular risk since it represents the renal expression of generalised disorder characterised by increased endothelial permeability.[223-225] It has been reported that in patients with mild to moderate essential hypertension microalbuminuria is associated with impaired functional reserve,[226] blunted renal vasodilation response to ACE inhibition,[115] salt sensitivity[227] and renal vasoconstriction.[228] However, there is no evidence that microalbuminuria could predict the development and/or represent a marker of nephrosclerosis. Therefore, the effect of various antihypertensive drugs on this parameter[229-233] cannot be taken as evidence of renal protection.

Uncontrolled long term studies have suggested that in patients with essential hypertension conventional treatment might[234] or might not[235] prevent renal deterioration, and that ACE inhibitors can preserve[236-238] or improve[239] renal function in patients with normal or moderately impaired renal function. Controlled studies in patients with essential hypertension and normal renal function suggest that ACE inhibitors can preserve renal function better than[240] or similarly to[241] β-blockers. Uncontrolled long term studies[59] suggest that in patients with essential hypertension and renal insufficiency calcium antagonists improve or do not change renal function.

In patients with nephrosclerosis, mostly (89%) African Americans, reduction in DBP to between 86 and 83mm Hg induced by various drug combinations improved renal function.[242] An extension of this study showed that similar DBP values were associated with a slowing of decline in GFR both in African Americans and Caucasians.[243] However, it has been reported that in some of these

patients ACE inhibitors can cause a marked and reversible increase in creatininaemia.[244] A subgroup analysis of the Angiotensin-converting-enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) Trial showed that in patients with nephrosclerosis the incidence of creatininaemia doubling was low, precluding any evaluation of the possible benefit of benazepril treatment.[245] Thus, both prevention and treatment of nephrosclerosis remain an unsolved problem and additional controlled studies with a long term follow-up and an appropriate sample size of patients with hypertensive nephrosclerosis are needed.

The AASK study has been planned to evaluate the effects of 2 levels of BP control (mean blood pressure [MBP] = 92 and between 107 to 102mm Hg) and of 3 drug regimens (amlodipine, atenolol and enalapril) in slowing the rate of GFR decline in African Americans with hypertensive nephrosclerosis and with mild to moderate renal insufficiency.[222] Recent data from the AASK pilot study[246] indicated that at 3 months GFR tended to increase in the atenolol recipients and even more in the group treated with amlodipine, while decreasing in the group treated with enalapril.

4.2 IgA Nephropathy

Two nonrandomised, comparative, retrospective studies[247,248] and one before-versus-after study[249] have indicated that in patients with hypertension and IgA nephropathy, ACE inhibitors can slow the decline in renal function without changing[249] or with significantly reducing[247,248] proteinuria. The effect of the ACE inhibitor was greater than that of conventional treatment,[249] of various drug combinations[247] and of β-blockers[248] with a greater[249] or similar[247,248] reduction in BP.

An open nonrandomised study reported that creatinine clearance was unchanged in a small number of patients with hypertension and IgA nephropathy treated with nifedipine or nicardipine or with captopril or enalapril, while proteinuria was reduced only in the patients treated with an ACE inhibitor.[250]

A prospective, randomised, parallel group study in a small number of patients with hypertension and IgA nephropathy showed that enalapril and nifedipine at 1-year follow-up similarly reduced BP and did not change GFR, while only enalapril tended to reduce proteinuria.[251]

In conclusion, there is some evidence, but no conclusive proof, that ACE inhibitors can exert greater renal protection than conventional treatment. Furthermore, calcium antagonists can exert a similar renal protective action to ACE inhibitors despite their lack of effect on proteinuria.

4.3 Diverse Nephropathies

Long term uncontrolled studies[73,252-254] and one controlled study[185] have indicated that ACE inhibitors are effective in reducing BP and proteinuria and that these drugs may preserve renal function or reduce the rate of decline in renal function in patients with various nondiabetic nephropathies. Moreover a single-blind, randomised study in 70 patients with severe renal insufficiency showed that enalapril as compared with conventional treatment slowed the decline in GFR and reduced proteinuria. A similar number of patients (10 of 35 on enalapril *vs* 13 of 35 on conventional therapy) had ESRF, while the interval time (17 *vs* 18 months, respectively) to ESRF was also similar in the 2 groups.[255]

Two long term uncontrolled studies[256,257] and one controlled long term study[258] have indicated that calcium antagonists are effective in reducing BP and in slowing the progression of renal failure. In a single-blind randomised study in a small number of patients with stable renal function enalapril and nicardipine similarly reduced BP and did not change creatinine clearance, while only enalapril significantly reduced proteinuria.[259] Overall, these long term studies, also reviewed elsewhere,[59,82,218] suggest a similar beneficial effect of ACE inhibitors and calcium antagonists in reducing the rate of decline in GFR, despite a possible divergent effect on proteinuria, in patients with nondiabetic nephropathies.

More relevant information derives from recent controlled long term studies, which evaluated the renal protective effect of 2 different drug classes, i.e comparative studies, or of one drug class versus placebo added to existing antihypertensive drugs (table VI). One study[260] showed that captopril and nifedipine retard similarly reduced BP and slowed the decline in renal function as compared with 1 year of conventional treatment. Moreover at 3-year follow-up proteinuria was similar and non significantly reduced in both groups. The percentage of patients reaching the end-point of the study, i.e ESRF, was nonsignificantly higher in the nifedipine group compared with the captopril group. However, this study has 2 main caveats. First, BP was greatly and significantly reduced by both drugs and this can explain the beneficial effect of captopril and nifedipine as compared with conventional treatment. Secondly, the relatively small number (37 patients in each group) of patients who completed the follow-up might have obscured a significant difference in the occurrence of ESRF between the 2 groups.

A recent open, randomised Italian study, the LEOPARD (Lisinopril Effects On Pressure And Renal Damage) trial, has evaluated 121 patients with mild proteinuria (0.5 g/day), hypertension and chronic renal failure (creatinine clearance 20 to 50 ml/min), whose BP was well controlled by lisinopril or other drugs (79% were receiving calcium antagonists) in a 3-month titration phase.[265] On 20 month follow-up BP reduction in the lisinopril group was similar to results in patients treated with the other drugs, and proteinuria tended to be greatly reduced in the group treated with lisinopril, in which the rate of decline of creatinine clearance was significantly lower than in the control group. GFR, measured by inulin clearance, did not change in the group treated with lisinopril but declined in the control group. Furthermore, in the lisinopril and control groups, respectively, 3 and 6 patients had creatininaemia doubling and/or halving of GFR, with 2 and 5 patients reaching ESRF. These data suggest that ACE inhibitors may have a greater renoprotective action compared with control treatment based mainly on calcium antagonists in patients with mild proteinuric hypertension and diverse nondiabetic nephropathies.

Two studies comparing ACE inhibitors and β-blockers offered quite divergent results. Hannedouche et al.[261] reported that enalapril slowed the rate of progression of renal failure more than atenolol or acebutolol, with a significantly lower number of patients reaching ESRF in the group treated with enalapril. In contrast, van Essen et al.[262] recently reported that enalapril and atenolol similarly slowed the rate of progression of renal failure, with a slightly greater number of patients reaching ESRF in the group treated with enalapril. However, there are relevant differences between these 2 studies. In the latter trial patients had relatively well preserved renal function, only mildly elevated BP and modest proteinuria. In addition, a greater number of patients had polycystic kidney disease, a nephropathy whose evolution is poorly influenced both by BP reduction[137] and treatment with one ACE inhibitor.[245] Finally, there was a significant reduction in proteinuria even during atenolol treatment compared with the former study.

Three placebo-controlled studies evaluated the effect of ACE inhibitors on different outcomes of renal function. In a small number of patients with proteinuria and markedly depressed renal function, enalapril significantly reduced proteinuria, which increased in the placebo group, greatly reduced BP and slowed the rate of decline in renal function.[263] In the largest trial published so far, the AIPRI study,[245] benazepril significantly reduced the occurrence of a primary end-point, creatininaemia doubling, but it also reduced BP and proteinuria, which tended to increase in the placebo group. Only 2 patients reached the other primary endpoint, i.e. ESRF. After adjustment for differences in BP the difference in primary end-points between the 2 groups was less marked but still significantly lower in the group treated with benazepril.

Subanalyses of this study offered interesting suggestions. First, the benefit of benazepril was detectable in patients with glomerular disease (n = 192), diabetic nephropathy (n = 21) or miscellaneous or

Table VI. Controlled long term studies in miscellaneous of nondiabetic nephropathies

Reference	Trial plan	Drug (dosage)	No. of patients	Basal GFR (ml/min•1.73m^2)	Treatment duration	BP	Proteinuria	Renal function	No. of patients with ESRF (%)
Comparative study: ACE inhibitors and calcium antagonists *vs* conventional treatment (CT)									
Zucchelli et al.[260]	DB, R	Captopril (12.5-50mg bid)	60	NR	3 years	↓*†	=	Δ GFR, Cl creat, 1/SCr captopril = nifedipine retard better than CT	7/60 (11.6%)
		Nifedipine retard (10-20mg bid)	61			↓*†	=		14/61 (23%)
Comparative studies: ACE inhibitors *vs* β-blockers									
Hannedouche et al.[261]	O, R	Enalapril (5-10mg od)	52	24.8	3 years	↓*	↓*	Δ GFR enalapril = β-blocker	10/52 (19%)#
		Acebutolol (400mg od) or atenolol (100mg od)	48	26.6		↓*	=	1/SCr enalapril better than β-blocker	17/48 (35%)
van Essen et al.[262]	DB, R	Enalapril (10-40mg od)	43	55.5	3.9 years	↓*	↓*#	Δ GFR enalapril = atenolol	5/43 (11.6%)
		Atenolol (50-100mg od)	46	50.9		↓*	↓*		2/46 (4.3%)
Placebo-controlled studies									
Ihle et al.[263]	DB, R, PC	Enalapril (5mg od)	36	14.3	2 years	↓*#	↓*#	Δ GFR, Cl creat, 1/SCr enalapril better than placebo	7/36 (19%)
		Placebo	34	15.1		=	↑*		9/34 (26%)
Maschio et al.[245]	DB, R, PC	Benazepril (10mg od)	300	42.9	3 years	↓*#	↓*#	DCr 31/300 (10.3%)#	
		Placebo	283	42.3 (Cl creat)		=	=	57/283 (20.1%)	
Remuzzi et al.[264]	DB, R, PC	Ramipril (2.5-5mg od)	78	40	2 years	=	↓*#	DCr 18/78 (23%)#	17/78 (21.8%)
		Placebo	88	37		=	=	40/88 (45%)	29/88 (32.9%)

bid = twice daily; **BP** = blood pressure; **Cl creat** = creatinine clearance; **DB** = double blind; **DCr** = doubling creatininaemia; **GFR** = glomerular filtration rate; **NR** = not reported; **O** = open; **od** = once daily; **PC** = placebo-controlled; **R** = randomised; **1/SCr** = reciprocal serum creatinine; **=** = no significant change; ***** = $p < 0.05$ *vs* baseline; ↓ = decreased; ↑ = increased; **#** $p < 0.05$ *vs* control drug(s) or *vs* placebo; † = $p < 0.05$ *vs* 1 year of conventional treatment.

unknown renal disorders (n = 104), but not in those with polycystic kidney disease (n = 64). The number of primary end-points was too small in patients with nephrosclerosis (n = 97) and interstitial nephritis (n = 105) to allow any conclusion. Secondly, the benefit was greater in patients with mild than in those with moderate renal insufficiency and most obvious in patients with proteinuria >1 g/day. Finally, an unexpected excess of cardiovascular mortality was found in the group treated with benazepril. However, the intention-to-treat data of the extension of this study on a mean 6.6 year follow-up indicated that patients randomised to take benazepril in the core study showed a significant reduction in hard end-points, such as need for dialysis, transplantation or renal-related death, without any increase in total mortality.[266]

The relevance of proteinuria and of the antiproteinuric effect of ACE inhibitors in slowing the progression of renal failure was further reinforced by a recent trial, the Ramipril Efficacy in Nephropathy (REIN) study. The objective of this study was to evaluate the effect of ramipril versus conventional treatment on the rate of decline in GFR in relation to the drug's antiproteinuric effect, as primary end-point, and on other secondary end-points including creatininaemia doubling or progression to ESRF. The patients had mainly unknown glomerular renal disease prestratified for 2 values of proteinuria (stratum 1: 1.0 to 2.9 g/day and stratum 2: 3.0 g/day).[264] The study was interrupted in 166 patients in stratum 2, since in the group treated with ramipril there was a significantly lower decline in creatinine clearance and a lower number of patients reaching the combined end-points of creatinine doubling and ESRF, despite similar BP values in the 2 groups. Moreover, in this study proteinuria was greatly and significantly reduced in the group treated with ramipril (*vs* conventional treatment) and the percentage reduction in proteinuria was inversely related to the decline in GFR. In the REIN follow-up trial[267] a small number of patients ending the core study[264] continued to receive ramipril and those originally treated with placebo plus conventional therapy were switched to ramipril. During follow-up, BP control, proteinuria and the rate of GFR decline was similar in both groups, but the incidence of ESRF was greater in patients switched to ramipril, a finding explainable by the fact that these patients showed lower GFR values at the end of core study. Thus this follow-up study suggests that the earlier the treatment is started in patients with nondiabetic nephropathy and severe proteinuria (>3 g/24 hours), the higher the ability of an ACE inhibitor to provide protection from ESRF.

Finally, a recent meta-analysis, including some of the already reported studies and unpublished data, indicated that the pooled relative risk for ESRF was reduced by about 30% in patients receiving ACE inhibitors without significant increase in mortality.[268]

Overall, these studies provide the following information. First, although there is no doubt that ACE inhibitors can be beneficial in slowing the progression of renal failure, it is still unclear whether this benefit is particularly evident in patients with mild renal insufficiency[245] or, more controversially, in patients with more advanced renal failure.[255,261,263,269] Secondly, it is still unclear whether ACE inhibitors and calcium antagonists possess a similar nephroprotective effect[261,265] and whether ACE inhibitors exert a greater renal protection than β-blockers only in patients with a higher degree of hypertension, proteinuria and renal insufficiency.[261,262] Finally, the beneficial effect of ACE inhibitors seems to be restricted to patients with significant proteinuria.

Does the latter finding indicate that renal protection is linked to the antiproteinuric effect of these drugs, as indicated by the REIN study? Alternatively, the beneficial effects can be readily detected since the progression of renal failure is faster in the presence of proteinuria?[270] Another important question is whether the renal protective effect can differ according to the underlying nephropathy.[245] Finally, in all these studies ACE inhibitors and placebo were superimposed on various background antihypertensive therapies in order to achieve optimal BP control. Thus, it is appropriate

to suggest controlled trials comparing the effect of different rational combinations of antihypertensive drugs on progression of renal failure.

5. Conclusions

The renal protective effect of antihypertensive drugs is linked to 2 mechanisms. First, reduction in BP is a fundamental prerequisite common to all antihypertensive drugs. However, although there is some evidence that BP should be reduced to 130/85mm Hg in patients with diabetes mellitus and to 125/75mm Hg in patients with nondiabetic nephropathy and proteinuria >1 g/day, the exact definition both of BP normality and of the level to which BP should be reduced remain to be established. Ongoing controlled trials will probably help to answer these questions. Secondly, intrarenal actions on mechanisms such as glomerular hypertension and hypertrophy, proteinuria and probably mesangial cell proliferation and endothelial dysfunction, which can cause and/or worsen renal failure, seem to be relevant for the renal protective action of some drug classes. ACE inhibitors possess such properties, which seem to be a class effect, in agreement with the finding that renal penetration of different subclasses of these drugs is similar.[271]

Calcium antagonists, also exert beneficial intrarenal effects with possible differences among subclasses and pharmaceutical preparations. It remains to be evaluated whether AT_1-antagonists exert intrarenal actions similar to ACE inhibitors as well playing a role in slowing the progression of diabetic and nondiabetic nephropathies, an issue which is under evaluation in patients with type 2 diabetes and overt nephropathy.

Overall data from clinical trials indicate that ACE inhibitors and possibly calcium antagonists should be preferred in the treatment of patients with diabetic and nondiabetic nephropathies, given also the neutral effect of these drugs on glucose and lipid profiles.[272,273] Although this proposal has been challenged on the hypothesis that conventional treatment could be more effective in reducing cardiovascular morbidity and mortality in patients with diabetic nephropathy,[204] recent data suggest that ACE inhibitors can be particularly beneficial in reducing cardiovascular events in patients with hypertension and diabetes mellitus and that dihydropyridine calcium antagonists do not worsen or possibly improve the prognosis in these patients. Ongoing trials (see section 3.4) are likely to offer additional information. Moreover there is no evidence that treatment with an ACE inhibitor increases total mortality in patients with nondiabetic nephropathies.

Further information is needed in order to understand renal protection. First, information is required on the role of antihypertensive drugs in the primary prevention of diabetic nephropathy, a topic which is under investigation in patients with hypertension and type 2 diabetes. Secondly, the possibility that rational combinations of antihypertensive drugs may be more effective than single drugs superimposed on previous treatments in slowing the progression of renal disease needs to be ascertained. This topic is under investigation, to our knowledge, only in patients with incipient diabetic nephropathy. Thirdly, information is needed on the renal protective action of different drug classes in nephrosclerosis, a topic which is under investigation in hypertensive African Americans.

Finally, in nondiabetic nephropathies the comparative renal protective action of various drugs, including AT_1 antagonists, still remains to be evaluated, as does their potential beneficial effects in patients with mild proteinuria and with different degrees and causes of renal failure.

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