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Drug Treatment of Hypertension Complicating Diabetes Mellitus

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Abstract

Hypertension and diabetes mellitus are both common conditions associated with a high morbidity and mortality. When the two conditions occur together, as they do in 50% of diabetic individuals, the result is a 7.2-fold increase in mortality. If hypertension occurs in association with diabetes mellitus and diabetic nephropathy, mortality rises to 37-fold above that of a healthy population.

Despite the increase in incidence of nephropathy, cardiovascular disease remains the major cause of death in diabetic individuals. Therapy should therefore take into consideration the results of large, placebo-controlled trials which have shown reduction in cardiovascular morbidity and mortality as a result of active treatment. Although studies with the newer antihypertensive agents such as calcium antagonists and angiotensin converting enzyme (ACE) inhibitors are ongoing, only diuretics and β-adrenoceptor antagonists have been clearly shown to reduce cardiovascular risk.

Despite concerns regarding adverse metabolic effects and loss of hypoglycaemic awareness, β-blockers and diuretics do have a role in the management of diabetic patients. While it is clear that ACE inhibitors reduce the progression of diabetic nephropathy, evidence suggests that diuretics may be just as effective. However, unlike diuretics or β-blockers, ACE inhibitors have no proven benefit

in the prevention of stroke or myocardial infarction. Despite the claims of metabolic neutrality made for many antihypertensive agents there appears to be no advantage in their use in the majority of hypertensive diabetic patients, except where there exist specific contraindications to established therapies.

1. Overview

Hypertension is a common comorbid condition occurring at least twice as frequently in patients with type 1 (insulin-dependent) and type 2 (non–insulin-dependent) diabetes mellitus as in the non-diabetic population. Of the 25 million diabetic individuals worldwide, approximately 50% are also hypertensive (25% in the young, 75% in the elderly).[1,2]

Although the exact relationship between diabetes mellitus and hypertension differs between type 1 and type 2 diabetic patients, in both populations the presence of hypertension is associated with a significant multiplication of cardiovascular risk, particularly for stroke and ischaemic heart disease and renal disease. A recent review by Sowers and Epstein[3] assessing the cardiac complications of diabetes mellitus in the presence of hypertension has confirmed that diabetic patients have a higher incidence of coronary artery disease, systolic and diastolic ventricular dysfunction and left ventricular hypertrophy than individuals with either diabetes mellitus or hypertension alone. It is now recognised that approximately 80% of diabetic mortality is secondary to macrovascular complications.[4]

Within the type 2 population the association between hypertension, diabetes mellitus and increased cardiovascular risk may be on the basis of a shared aetiology, with endothelial dysfunction, insulin resistance, alterations in platelet aggregation and dyslipidaemia contributing to the underlying pathophysiology.[5] In comparison with the general population, relative mortality due to cardiovascular disease is increased about 2.5- to 7.2-fold in patients with both diabetes mellitus and hypertension, and up to 37-fold with the addition of established nephropathy.[6] It has also been estimated that hypertension is associated with 35 to 75% of diabetic complications.[7]

In addition to poor glycaemic control or frank nephropathy, the development of microalbuminuria in the diabetic population has also been shown to predict an increased risk of cardiovascular mortality.[8] Microalbuminuria (defined as 30 to 300mg urinary albumin/24 hours) results from an alteration in glomerular shunting of albumin, increased intraglomerular pressure and increased levels of growth factors which alter cell permeability.[9] The features which predispose to microalbuminuria include poor diabetic control as assessed by glycosylated haemoglobin (HbA1) duration of diabetes and also inherited factors.[9] Persisting microalbuminuria is a strong predictor of progression to more severe renal disease and also of future macrovascular episodes. Diabetic nephropathy is now the leading cause of end-stage renal disease in the Western world,[10] and affects one-fifth of patients who are on renal replacement therapy worldwide. Evidently, hypertension and microalbuminuria are closely related, either directly or indirectly, and the ideal treatment for hypertension in diabetic patients should also take into account diabetic renal disease.

Type 1 diabetes mellitus is associated with hypertension in approximately 30% of patients.[2] The presence of hypertension in this population is thought to be a consequence rather than a cause of renal disease, as hypertension tends to closely follow the onset of microalbuminuria.[11] In type 1 diabetes mellitus, the natural history following development of microalbuminuria is a progression to proteinuria, reduced glomerular filtration rate (GFR) and eventually end-stage renal disease.[9] About 40 to 45% of type 1 and about 25% of type II diabetic patients develop a degree of nephropathy.[12] Although the major cause of death in diabetic patients is cardiovascular disease, the incidence of nephropathy is increasing, with obvious economic consequences.[13] This is reflected in the

growing interest in preventing or slowing the progression of renal disease by drug intervention.

The time from onset of proteinuria to onset of terminal renal failure is 6 to 8 years in both type 1 and 2 diabetes mellitus. It has been established that GFR declines linearly in diabetic patients with untreated hypertension (by between 4 and 18 ml/min/year).[14] Treatment of elevated blood pressure has been shown to reduce and in some cases reverse the progress of renal damage. In type 1 patients included in the UK Microalbuminuria Study, blood pressure control rather than glycaemic control was the main predictor of nephropathy.[15]

Type 2 diabetes mellitus is preceded by the presence of hypertension in up to 50% of patients. Approximately 40% of newly diagnosed type 2 patients recruited to the United Kingdom Prospective Diabetes Study (UKPDS) study were hypertensive at entry.[16] Evidence from this trial confirms that morbidity and mortality due to cardiovascular complications often intervene before the consequences of end-stage renal failure.[17]

Both systolic and diastolic hypertension alike appear to be associated with diabetic nephropathy in type 2 diabetes mellitus (and produce an 86% increase in the risk of diabetic nephropathy, macrovascular complications such as peripheral vascular disease and left ventricular hypertrophy).[18] The high prevalence of hypertension in this population presents an obvious target for intervention to reduce morbidity and mortality. Unfortunately, no long term data exist to definitively demonstrate a beneficial effect of antihypertensive therapy on the progression of renal disease in patients with type 2 diabetes mellitus, although such trials are under way.[18]

1.1 Definition of Hypertension

The threshold for the definition of hypertension has fallen over the past decade, with a value of 140/90mm Hg now being accepted by the American Diabetes Association as the upper limit of normal blood pressure. As a consequence of this reduction in threshold, the number of diabetic patients classified as hypertensive and thus requiring therapy has risen considerably.[2]

Even among patients with normal clinic blood pressure (<140/90mm Hg), values may not entirely reflect normotension. The use of ambulatory blood pressure monitoring (ABPM) has revealed a group of individuals who do not display the normal diurnal variation in blood pressure with evidence of a nocturnal fall (usually >10%):[19] these are classified as 'nondippers'. The prevalence of nondippers rises in patients who are diabetic, and is even higher in those with microalbuminuria and diabetic nephropathy. In a long term study, ABPM has shown a 4-fold higher rate of increase in mean 24-hour blood pressure in patients who progress to microalbuminuria, compared with persistently normoalbuminuric patients (approximately 4 *vs* 1mm Hg per year).[20] This may be in part due to fluid retention or a reduction in parasympathetic activity.

1.2 Targets for Blood Pressure Reduction

Further studies are required to clarify the exact targets for blood pressure reduction such that a satisfactory reduction in cardiovascular and renal risk can be obtained. The synergistic effect of blood pressure reduction and improved glycaemic control also remains to be fully characterised. Some have suggested that in diabetic patients with nephropathy the principle of blood pressure reduction should be 'the lower the better'. An acceptable compromise of <130/80mm Hg has been suggested by the US National Institutes of Health, while a pressure of 130/85mm Hg should be aimed for in non-nephropathic diabetic patients.[21] The concept of risk stratification, where targets for therapy are determined by the overall risk profile of the individual, is also becoming a focus of attention.[22]

2. Antihypertensive Therapy and the Diabetic Patient

2.1 Nonpharmacological Measures

2.1.1 Bodyweight Reduction

Obesity is a very strong correlate with both hypertension and type 2 diabetes mellitus. There is

now indisputable evidence that bodyweight loss improves insulin sensitivity and lowers blood pressure.[1] Reducing bodyweight has been shown to achieve blood pressure reduction equivalent to that obtained with a low dose diuretic.[23] Thus, bodyweight reduction should be a key target in obese hypertensive diabetics. The Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure (JNC VI)[24] suggests that all hypertensive patients above their desirable bodyweight should be placed on a bodyweight reduction programme involving caloric restriction and increased physical activity.

2.1.2 Dietary Modification

Low Salt Diet

Sodium is thought to play a more important pathogenic role in the hypertension associated with diabetes mellitus, partly due to an increase in extravascular fluid. Excess sodium retention is already present in the uncomplicated stages of diabetes mellitus and differentiates diabetic from nondiabetic essential hypertensive individuals. Thus, diabetic hypertension appears to represent a pathogenetically distinct form of hypertension. Hypertensive diabetic patients may also have an enhanced sensitivity of blood pressure to sodium.[25] Thus, all hypertensive diabetic individuals should be encouraged to follow a low sodium diet.

Lipid-Lowering Diet

Although not related to blood pressure reduction *per se*, reduction in dietary saturated fat may be recommended as part of an overall strategy to lower cardiovascular risk.

2.2 Drug Therapy

The treatment of hypertension in diabetic patients must take into account the presence of a cluster of metabolic abnormalities such as insulin resistance and dyslipidaemia.[26] The aim of therapy should therefore be to lower blood pressure satisfactorily without adversely affecting metabolic control or adding to the burden of compromised end organs such as the heart and kidney.

Apart from blood pressure reduction *per se*, reduction in long term cardiovascular complications and mortality, along with prevention or slowed progression of renal disease, are important considerations. Clearly, studies which look at primary endpoints such as mortality and time to dialysis are time-consuming and thus less frequently pursued. Consequently, most studies use surrogate endpoints such as blood pressure reduction, regression of left ventricular hypertrophy or reduction in albuminuria/proteinuria. Until more long term studies are available, debate regarding the optimal management of hypertension in diabetes mellitus will continue. Despite this, subgroup analyses of large mortality/morbidity studies of hypertension and cardiovascular disease have demonstrated that diabetic patients benefit considerably from appropriate antihypertensive therapy.

We consider below the various classes of agents used to achieve blood pressure control, with special reference to their use in diabetes mellitus. Diabetic patients are a heterogeneous group with many individuals demonstrating multiple pathologies which will clearly influence the pharmacokinetics and pharmacodynamics of drug therapy.

A summary of the effects of various antihypertensive agents in diabetes mellitus is given in table I. The effects of therapy on renal function and morphology are summarised in table II.

2.2.1 Diuretics

In the nondiabetic population, diuretics, along with β-adrenoceptor antagonists, are well established as first-line therapy in hypertension. Both classes of drugs are associated with a proven reduction in cardiovascular morbidity and mortality as demonstrated by long term controlled clinical trials.[24]

Diuretics would be expected to be beneficial in diabetic patients, given that diabetic individuals have lower renin levels and more marked salt sensitivity.[25] Hypertension in diabetes mellitus results from an increase in peripheral vascular resistance, and hence the vasodilatory action of diuretics is beneficial.

Table I. Summary of effects of antihypertensive drugs in patients with diabetes mellitus

Drug	Insulin resistance	Lipid metabolism			Potassium	Peripheral blood flow	Microalbuminuria	LVH	Disturbances of sexual function
		cholesterol	triglycerides	HDL					
Diuretics	–	–	–	–	–	(–)	0, +	0, +	–
β-Blockers									
nonselective	–	(–)	–	–	0	–	0, +	+	–
selective	(–)	0	(–)	0	0	(–)	0, +	+	(–)
Calcium antagonists	0	0	0	0	0	(+)	0[a], +	+	+
ACE inhibitors	(+)	0	0	0	0	0	++	+	0
Angiotensin II antagonists	–	0	0	0	0	0	(+)[b]	+	0
α-Blockers	+	+	+	+	0	0	0	+	(–)

a Applies only to dihydropyridine calcium antagonists such as nifedipine.

b Results awaited.

ACE = angiotensin converting enzyme; **HDL** = high density lipoprotein cholesterol; **LVH** = left ventricular hypertrophy; **–** = adverse effect; + = beneficial effect; **0** = no effect; **(–)** = possible adverse effect; **(+)** = possible beneficial effect.

Early studies showed an adverse effect of diuretics on glycaemic control, reflected in a rise in serum glucose and HbA1c levels. Most of these studies, however, were performed in patients who were on very high doses of diuretics.[27,28]

Various mechanisms have been proposed by which diuretics may adversely affect glucose metabolism. Serum potassium depletion has been associated with a marked reduction in glucose-stimulated insulin release, and may also predispose individuals to the occurrence of arrhythmias.[29] Conversely, the effects on insulin release are completely abolished if potassium supplements are given along with thiazide diuretics.[30] Increased peripheral insulin resistance may also contribute to the effect of thiazides on glycaemic control. Studies using the euglycaemic hyperinsulinaemic clamp have demonstrated that hydrochlorothiazide therapy results in a decrease in insulin-stimulated glucose uptake.[31] It has also been suggested that increased hepatic glucagon release by thiazides may also contribute to hyperglycaemia. However, this has not been demonstrated in diabetic patients.[32]

Diuretics may also potentiate orthostatic hypotensive changes in patients with diabetic autonomic neuropathy.[1] Concerns regarding the use of thiazides in individuals with diabetes mellitus have been compounded by 2 studies which reported excessive mortality in diabetic patients receiving relatively high doses of thiazides.[33,34] In one study,[33] a 4-fold excess mortality was reported in patients receiving diuretics compared with those who were not. It has been postulated that this excess mortality may have been related to hypokalaemia and perhaps volume depletion induced by high diuretic doses.[1]

As current clinical practice recognises the useful role of low doses of thiazides in blood pressure control, the adverse effects seen with higher doses are less relevant. Indeed, lower doses are not associated with adverse effects on lipid and carbohydrate metabolism and their use is acceptable in diabetic patients who do not have contraindications. Subgroup analysis of the Systolic Hypertension in the Elderly Program (SHEP)[35] confirms that low dose thiazide therapy in diabetic patients is well tolerated and has a negligible effect on glucose, lipid and uric acid levels. More importantly, SHEP reported a comparable reduction in the incidence of cardiovascular events in the diabetic cohort.

Although the diuretic indapamide has yielded promising results with regard to glycaemic control,[36] benefits from its use in reducing morbidity and mortality have not yet been proven.

Diuretics and Renal Disease

Although early studies suggested that diuretic use might accelerate renal disease, a more recent

Table II. Summary of the effects of antihypertensive therapies on renal morphology, function and proteinuria (after Bakris et al[1])

Drug class	Mesangial volume	Albuminuria	Glomerulosclerosis	Time to dialysis	Cardiovascular mortality
Diuretics	?	→, ↓	↓	?	↓
β-Blockers	→	→, ↓	↓	↓	↓
Calcium antagonists	→[a], ↓	→[a], ↓	→[a], ↓	→[a], ↓	→[a], ↓
ACE inhibitors	↓↓↓	↓↓	↓↓↓	↓↓↓	↓
Angiotensin II antagonists	?	?	?	?	?
α-Blockers	→	→	→	?	?

a Applies only to short-acting dihydropyridine calcium antagonists such as nifedipine.

ACE = angiotensin converting enzyme; ↑ = increased; → = no significant effect; ↓ = reduced; **?** = effect unknown.

double-blind, placebo-controlled study with low doses of hydrochlorothiazide (12.5 to 25 mg/day) has demonstrated a slowed progression of nephropathy comparable with that obtained with angiotensin converting enzyme (ACE) inhibitors.[37]

2.2.2 β-Adrenoceptor Antagonists

Despite being preferred first-line agents in the management of essential hypertension,[38] β-blockers are used with a greater degree of caution in diabetic patients. These drugs are believed to adversely affect glucose and lipid metabolism, to reduce awareness of and prolong recovery from hypoglycaemia and also to result in peripheral vasoconstriction.[2]

Many of the studies on which this evidence is based involved the use of nonselective β-blockers, which are recognised to detrimentally affect glucose tolerance in diabetic patients.[39,40] On the other hand, cardioselective β-blockers appear to have less of an effect on glycaemic control.[40]

It has also been suggested that β-blockers may precipitate diabetes mellitus among hypertensive obese patients, due to an increase in insulin resistance.[1] The mechanisms responsible are not well established, but could reflect a change in pancreatic insulin secretion through inhibition of β_2-receptors.[39] Nonselective β-blockers have been associated with decreased glucose-stimulated insulin release[40] while a switch to selective β-blockers has been reported to increase insulin levels and reduce blood glucose.[41] Hepatic glucose production does not appear to be altered by β-blockers, suggesting that this is an unlikely mechanism.[42] Reports of β-blocker–induced alterations in peripheral insulin sensitivity still remain difficult to interpret.[43,44]

One study which reported a 4-fold increase in the incidence of diabetes in patients receiving β-blockers or a diuretic for treatment, compared with those on no treatment, neither took into consideration the effect of severity of hypertension, nor made comparisons with other therapies.[45]

As the antihypertensive effects of β-blockers are mediated by blockade of the β_1-adrenoceptor while impaired glycaemic control is mediated via the β_2-adrenoceptor, the use of β_1-selective agents is clearly preferable in diabetic patients.

Hypoglycaemia

One of the main areas of concern regarding the use of β-blockers in diabetic patients is the loss of hypoglycaemic awareness, and potential interference with the metabolic response.

Serious hypoglycaemia is usually averted by the presence of neuroglycopenic and autonomic symptoms which accompany low blood glucose, triggering an increase in counter-regulatory hormones such as adrenaline (epinephrine) and glucagon. While there is some evidence in patients with diabetes mellitus that the use of nonselective β-blockers may increase blood pressure and impair glucose recovery rate following hypoglycaemia,[46] low dose β_1-selective blockade does not appear to have this effect.[47] In any case, lack of hypoglycaemic awareness due to β-blockade has not been unequivocally proven. One study examining the effect of propranolol on insulin-induced

hypoglycaemia did not find any reduction in hypoglycaemic awareness.[48] Similar findings have also been reported for atenolol[49] and metoprolol,[49] which appears to enhance the peak response to adrenaline and growth hormone following the onset of hypoglycaemia. Further evidence also suggests that hypoglycaemia-induced sweating is enhanced by both selective and nonselective β-blockers, which may counteract the effect on heart rate and blood pressure.[46]

A recent retrospective cohort study in 13 559 elderly diabetic patients (mean age 78 ± 7 years) receiving either insulin or sulphonylureas has reported no differences in hospitalisation, emergency room admissions or death associated with hypoglycaemic symptoms between those who were receiving antihypertensive therapy and those who were not. Nonselective β-blockers, however, were associated with a 2-fold increase in the risk of serious hypoglycaemic episodes in patients receiving insulin therapy.[50]

Both selective and nonselective β-blockers increase plasma triglyceride levels, and may also lower high density lipoprotein (HDL) cholesterol levels.[41] When prescribing these drugs, the practitioner must balance these effects against their potential cardioprotective role.

After myocardial infarction (MI), cardioselective β-blockers have been shown to reduce mortality in the general population.[51] Diabetic patients are particularly vulnerable to sudden death following MI.[52] A meta-analysis of studies of β-blocker therapy after MI indicate a 37% reduction in acute mortality in diabetic patients compared with 13% in nondiabetic individuals during the immediate *post*-MI period. Following discharge, the differences in mortality between the 2 groups are similar: 48 and 33%, respectively.[53] The observed improvement in mortality in diabetic patients is probably due to a combination of antiarrhythmic and anti-ischaemic effects.

β-Blockers also adversely affect the lipid profile, resulting in an increase in triglycerides and a reduction in HDL cholesterol levels.[1] Despite this, β-blockers have been proven to reduce acute and chronic morbidity and mortality *post* MI in diabetic patients.[54]

Studies examining diabetic renal function have suggested that β-blockers provide no renoprotective effect other than that of blood pressure reduction. When enalapril was compared with metoprolol, the latter was associated with a faster decline in renal function over a 2.2-year period despite similar blood pressure reduction in both groups.[55] Comparison with nondihydropyridines in an African-American population has reported a 55% slower decline in renal function in patients randomised to verapamil or diltiazem compared with β-blockers.[56]

In summary, β_1-selective β-blockers are indicated in diabetic patients with ischaemic heart disease who have no contraindications, but they do not offer any benefits in terms of improved glycaemic control or renoprotection.

2.2.3 Angiotensin Converting Emzyme Inhibitors

The original introduction of ACE inhibitors in the diabetic population concentrated on their neutral effects on lipid and carbohydrate metabolism. Early studies suggested that ACE inhibitors in fact increased insulin sensitivity, such that some patients required a reduction in insulin dose or oral hypoglycaemic therapy.[57] Subsequent studies have demonstrated no significant improvement in blood glucose with these agents, possibly due to the fact that while increasing insulin sensitivity they also appear to reduce insulin levels.[58]

These agents were then demonstrated to reduce proteinuria in type 1 diabetic patients with overt nephropathy. A study examining 409 patients with type 1 diabetes mellitus over almost 3 years showed that captopril reduced the risk of the combined end-points of death, dialysis and transplantation by 52% compared with the rates in individuals who had equivalent blood pressure reduction with other agents. This study also suggested that the renoprotective effects of captopril were independent of blood pressure reduction alone. The mechanism was thought to be a reduction in both intraglomerular pressure and volume.[59] This results in reduction of glomerulosclerosis, suggest-

ing that ACE inhibitors may protect the injured kidney from haemodynamically mediated glomerular damage.[60]

In patients with incipient nephropathy, the benefits of ACE inhibitors do not appear to be limited to the hypertensive population. Hallab et al.[61] demonstrated that enalapril therapy for 1 year retarded the development of albuminuria in a group of normotensive type 1 diabetic patients, while equivalent blood pressure reduction with a thiazide did not produce this effect.[61] Lisinopril has also been shown to reduce microalbuminuria in normotensive patients with type 1 diabetes mellitus. After 18 months of therapy, patients treated with lisinopril showed a reduction in renal size and GFR compared with patients treated with placebo.[62]

Captopril has been shown to have a similar effect on albuminuria within a population of normotensive diabetic individuals.[63] A study which now has 8 years of follow-up has confirmed that captopril not only reduces urinary albumin excretion but also postpones the development of overt proteinuria over the period studied (40% in the placebo group, compared with 10% in the captopril group, developed overt nephropathy).[64]

In contrast, the Collaborative Study Group has shown that although captopril retarded the development of renal impairment in type 1 diabetes mellitus with overt proteinuria, a significant proportion of patients progressed despite ACE inhibitor therapy.[65] Studies remain inconsistent, however: indapamide 3 mg/day has been shown to be as effective as captopril 12.5mg 3 times daily in lowering blood pressure and albuminuria over a 12-week period.[66] A short follow-up may explain some of the discrepancy between studies.

In type 2 diabetes mellitus, hypertension is present in up to 40% of patients at diagnosis, and often precedes the development of microalbuminuria.[14] Lacourciere et al.[67] have reported that captopril prevented the development of albuminuria in a group of hypertensive microalbuminuric type 2 diabetic patients over a 3-year study period. A separate arm of the study in which patients obtained corresponding reductions in blood pressure with a thiazide and metoprolol failed to show any beneficial effect on albuminuria.

Longer term studies are clearly required to assess the long term effects of ACE inhibitor therapy on renal parameters in hypertensive and normotensive microalbuminuric individuals. It also remains to be clarified at what stage ACE inhibitor therapy should be introduced in order to give the best renoprotection.

Comparison with Other Antihypertensive Therapies

Two meta-analyses of ACE inhibitors in diabetic renal disease have confirmed that they are superior to other antihypertensives with respect to attenuation of albuminuria.[68,69] One criticism is that confounding factors such as blood pressure levels and the degree of nephropathy have not been fully taken into account. It has been suggested that, if these factors are included, at maximal antihypertensive doses there may be no significant difference between the antiproteinuric effects of ACE inhibitors and those of other antihypertensive drugs.[70]

On the evidence currently available, it is generally accepted that ACE inhibitors should be considered for both type 1 and type 2 diabetic patients with microalbuminuria, irrespective of the presence of hypertension.[71] This policy has economic consequences for prescribers, with the cost of therapy offset by savings in hospital care due to progressive nephropathy. The cost effectiveness of this prescribing policy has been assessed by Hendry et al.,[10] modelling on data from the Diabetic Nephropathy Collaborative Study Group (DNCSG) trial.[59] Comparing 2 cohorts of diabetic patients with proteinuria, one treated with an ACE inhibitor and one not treated, there was a cost benefit of almost £1 million sterling over 4 years in the treated group. This is equivalent to a cost benefit of almost £1000 per patient, and to 195 life-years saved.

There is naturally some concern regarding the widespread use of ACE inhibitors, particularly in the type 2 diabetes mellitus population, because of the possibility of coexisting renal artery stenosis.

Renal artery stenosis does appear to be more common in the diabetic population, with some epidemiological studies suggesting that at least 20% of patients with this disease have type 2 diabetes mellitus.[72] The use of ACE inhibitors in patients with refractory hypertension and diffuse atherosclerotic disease should be preceded by investigations to exclude significant renal artery stenosis. In the remainder of the hypertensive diabetic population, ACE inhibitors can be introduced cautiously with monitoring of the serum creatinine within 7 to 10 days of starting therapy.

Silent MI is particularly common in patients with diabetes mellitus, and the presence of left ventricular hypertrophy is known to be a significant risk factor for MI and arrhythmias. ACE inhibitors (along with calcium antagonists) are effective at reducing left ventricular hypertrophy, thus improving the overall risk factor profile.[73]

Combined Therapy with ACE Inhibitors and Thiazides

The synergistic action of thiazides with ACE inhibitors remains to be fully characterised in diabetic patients, but it is likely that combined therapy will have a beneficial effect on both blood pressure and progression of renal disease.[1]

2.2.4 Angiotensin II Antagonists

The angiotensin II antagonists have been shown to be as efficacious as ACE inhibitors at lowering blood pressure.[74] Studies in diabetic rats have shown a beneficial effect on diabetic renal disease, and studies in human diabetic individuals are awaited with interest.[75] A recent study has compared the effect of losartan or metoprolol on insulin sensitivity, insulin secretion, glucose tolerance, lipids and lipoproteins in 20 hyperinsulinaemic hypertensive patients. While losartan achieved a greater fall in blood pressure, neither drug resulted in any alteration of the measured parameters, suggesting that losartan, like metoprolol, is metabolically neutral.[76]

2.2.5 Calcium Antagonists

The role of calcium antagonists in patients with ischaemic heart disease is currently under scrutiny. In particular, short-acting dihydropyridines such as nifedipine have been associated with an increased morbidity and mortality in selected patient groups. Long term trials assessing the cardiovascular effects of longer acting formulations are under way.[77] The Appropriate Blood Pressure Control in NIDDM (ABCD) Trial recently reported a higher incidence of fatal and nonfatal MI in hypertensive patients with type 2 diabetes mellitus taking nisoldipine (a long-acting dihydropyridine) compared with those treated with enalapril. Equivalent blood pressure control was obtained in both populations. Although a subgroup analysis, these results are undergoing further scrutiny.[78]

As a class, calcium antagonists have been demonstrated to have a neutral effect on both carbohydrate and lipid metabolism,[79] while verapamil has been reported to improve glucose tolerance.[80] Thus, calcium antagonists are of potential benefit in hypertensive diabetic patients. Along with ACE inhibitors, calcium antagonists are effective at reducing left ventricular hypertrophy, a significant risk factor for myocardial infarction.[73]

Although dihydropyridines are efficacious antihypertensive agents, they appear to have distinct effects on the diabetic kidney compared with nondihydropyridines. While some studies demonstrated a short term reduction in proteinuria with dihydropyridines, longer term follow-up failed to confirm a sustained effect.[67]

By comparison, nondihydropyridines have been shown to reduce proteinuria: a 2-year randomised, prospective study of patients with type 2 diabetes mellitus and proteinuria demonstrated a clear reduction in proteinuria with diltiazem compared with nifedipine. This difference persisted at 2 years.[1] Further studies have confirmed a difference between dihydropyridines and nondihydropyridines,[81] although it appears that some of the longer-acting dihydropyridines may also have a renoprotective effect.[82] As with ACE inhibitor therapy, further long term studies are awaited with interest.

Both verapamil and diltiazem have been shown to reduce proteinuria to a similar extent to ACE

inhibitors (Bakris et al.,[1] and see table I), and also to markedly slow development of glomerulosclerosis in animal models of type 1 diabetes mellitus.[1] In diabetic individuals, nondihydropyridines have been associated with a reduction in proteinuria and slowed progression of microalbuminuria.[83]

Despite the clear advantages of long-acting nondihydropyridines over the short-acting dihydropyridines, there are very few studies looking at the long term effects of the longer-acting dihydropyridines. A recent 1-year, randomised, double-blind study in hypertensive type 1 diabetic patients with diabetic nephropathy showed a better attenuation of the rate of decline in GFR in patients treated with nisoldipine (a long-acting dihydropyridine) than with an ACE inhibitor, although albuminuria was reduced (by 47%) in the ACE inhibitor group, and increased (by 11%) in the dihydropyridine group.[80] The mean 24-hour arterial blood pressure during this study was almost identical in both treatment groups, at 103 (SD ± 9) and 101 (SD ± 11) mm Hg, respectively. These results appear to suggest that both drugs may be working by different renoprotective mechanisms. Further long term follow-up to assess the progression of disease in both patient groups is clearly indicated.

In contrast to results with nondihydropyridines, in patients with type 2 diabetes mellitus, proteinuria, hypertension and renal impairment, comparison of 2 different dihydropyridine calcium antagonists [isradipine and nifedipine sustained-release (XL)] with achievement of equivalent blood pressure reduction (<140/90mm Hg) over 6 months showed no reduction in albuminuria with either drug.[84]

Why should there be a difference in the effect of nondihydropyridines and dihydropyridines on the kidney? It has been demonstrated that increased renal vascular resistance is an underlying renal haemodynamic abnormality in diabetic nephropathy. Dihydropyridines act on both afferent and efferent arterioles, and thus do not alter glomerular membrane permeability. By contrast, nondihydropyridines may reduce permeability.[84] Both groups may also retard renal growth, and may also attenuate mesangial entrapment of macromolecules and attenuate the mitogenic effect of diverse growth factors.[84] Thus, dihydropyridines may have a beneficial effect related to reduction of mesangial proliferation which is independent of their lack of antiproteinuric effect.[81] Studies in animal models have confirmed that nondihydropyridines have a beneficial effect on renal morphology which is independent of blood pressure reduction. Spontaneously hypertensive rats given either nonhypotensive doses of verapamil or ACE inhibitor, or a combination of the 2 drugs, showed an attenuation of mesangial matrix expansion and prevention of glomerulosclerosis. This was true for both preparations and was independent of blood pressure reduction.[85] Similar findings have been noted with diltiazem in diabetic dogs.[86]

There is still a paucity of long term, randomised, controlled trials assessing the long term effects of nondihydropyridines on microalbuminuria and established diabetic nephropathy. The use of hard endpoints other than microalbuminuria will also need to be considered (e.g. time to dialysis/renal transplant, mortality or progression of renal structural lesions).[82]

Despite the concerns expressed regarding dihydropyridines, immediate release preparations of nondihydropyridines do not appear to have the adverse proischaemic effects reported with the other preparations.[77] A meta-analysis of the large clinical trials in postmyocardial infarction patients has shown that these agents moderately reduce the risk of reinfarction and that the mortality effect is largely neutral. However, patients with left ventricular dysfunction randomised to either verapamilor diltiazem experienced an increased risk of mortality, reinfarction or new or worsening congestive heart failure.[87] In elderly hypertensive individuals, both verapamil and diltiazem have been associated with a 2- to 3-fold increase in the risk of hospitalisation due to congestive heart failure, and a doubling in the risk of gastrointestinal bleeding.[88] Thus, these agents should be used with cau-

tion in diabetic individuals who have impaired left ventricular function.

Additive Effects of ACE Inhibitors and Calcium Antagonists

Both calcium antagonists and ACE inhibitors have a similar effect on mean arterial blood pressure, while ACE inhibitors have a greater beneficial effect on albuminuria.[1] The beneficial effect on GFR is the same for both classes of drugs. A recent 5-year, randomised, open study in hypertensive type 2 patients with diabetic nephropathy has revealed the same beneficial effects of nondihydropyridine calcium antagonists and ACE inhibition on the progression of diabetic nephropathy. By comparison, use of a sympatholytic drug such as guanfacine resulted in a doubling of serum creatinine level in more than 50% of patients, compared less than 10% in the other group.[82]

Most studies comparing the 2 preparations have been of short duration, and have looked at surrogate end-points rather than principal end-points such as development of dialysis/renal transplant, all-cause mortality or progression of renal structural lesions.

There is as yet no definite answer as to whether ACE inhibitors and calcium antagonists have an additive effect on proteinuria. However, preliminary data from both animal and clinical studies suggest that combined nondihydropyridine and ACE inhibitor therapy produces an additional fall in proteinuria and has a more favourable adverse effect profile than observed with either drug alone.[89] Long term studies of combined therapy with ACE inhibitors and calcium antagonists are still awaited, but combination therapy may be useful in diabetic patients with renal insufficiency and blood pressure which is difficult to control.

2.2.6 Centrally Acting α_2-Receptor Agonists

Moxonidine and Methyldopa

While α-blockers are metabolically neutral, they have not been widely investigated in diabetic patients. There is a paucity of studies assessing their effect on the progression of renal disease. The relatively high frequency of adverse effects means that their role has been reserved for patients with blood pressure which is very difficult to control.[1]

2.2.7 α-Adrenoceptor Antagonists

α-Blockers are recognised to improve insulin sensitivity and have a neutral or mildly beneficial effect on the lipid profile. This is recognised to result in improved glycaemic control in insulin-resistant hypertensive patients.[90] These drugs have also been noted to have a favourable effect on lipid profiles, reducing total cholesterol level by 5 to 8% and triglyceride level by 3 to 5%, and increasing levels of HDL cholesterol.[91] α-Antagonists therefore attenuate the effect of HMGCoA reductase inhibitors, which may result in a reduction of dose of the latter.[92]

The effect of α-blockers on the diabetic kidney has not been fully elucidated. A number of small, short term studies failed to show any reduction in either proteinuria or microalbuminuria, despite a satisfactory reduction in blood pressure.[93] Animal studies have also failed to demonstrate any slowing of early nephropathic changes with doxazosin,[94] in contrast to studies with ACE inhibitors.[85] Long term studies are still awaited.

Thus, although α-blockers do not appear to have a beneficial effect on diabetic renal disease, they have a useful role in patients who have hypertension which is difficult to control with other therapies.[95]

3. The Future: Tailoring Individual Drug Therapy

It was hoped that the development of antidiabetic drugs such as troglitazone, which improve insulin sensitivity and also appear to have a favourable effect on blood pressure, would have a beneficial long term effect on morbidity and mortality within the diabetic population.[96] The subsequent withdrawal of troglitazone from several markets due to adverse hepatic reactions has obviously been disappointing.[97]

As thresholds for definition of hypertension change, more patients will be required to be commenced on antihypertensive therapy. Targets for treatment are also changing as more evidence from

studies examining morbidity and mortality become available. Increased awareness and prevention of cardiovascular sequelae of diabetes mellitus are resulting in reduction in morbidity and mortality from ischaemic heart disease. Thus, patients are surviving long enough to develop significant nephropathy, and therapy has to bear this in mind. The proven benefits of β-blockade an diuretics in prevention of stroke and reduction in myocardial infarction in hypertensive diabetic patients will have to be weighed against the evidence from studies suggesting a beneficial role for ACE inhibitors and calcium antagonists in slowing progression of nephropathy. Whether these agents are of more benefit than diuretics in type II diabetes mellitus remains to be clarified.

As more information from long term trials for calcium antagonists, ACE inhibitors and angiotensin II antagonists becomes available, and as we gain further insight into the genetic and pathophysiological processes determining the development of diabetes mellitus and its micro- and macrovascular complications, it is likely that antihypertensive therapy will become increasingly tailored to the risk profile of an individual patient. The point at which ACE inhibitor therapy should be introduced in patients with incipient nephropathy needs to be fully clarified, as does the exact role of calcium antagonists in a population at high risk of ischaemic heart disease. It is hoped that studies underway will address these issues.

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