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Antihypertensive treatment and mortality in diabetic patients

What is the evidence?

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Epidemiological evidence

In follow-up studies patients with hypertension and non-insulin-dependent diabetes mellitus (NIDDM) have a four to sevenfold increase in total mortality when compared to non-diabetic normotensive subjects. Recently, the risk of mortality associated with hypertension in diabetes was assessed in 3648 newly diagnosed NIDDM patients [1], hypertension was present in 35% of women and 46% of men. When compared to normotensive diabetic patients the mortality risk associated with hypertension was doubled over a median follow-up period of 4.6 years. Cardiac events including sudden death accounted for 58% and stroke for 13% of all causes of death.

Patients with insulin-dependent diabetes mellitus (IDDM) exhibit a dramatically reduced life expectancy when they develop diabetic nephropathy which is nearly always associated with hypertension [2]. Without antihypertensive treatment the 10-year mortality approaches 80% in these patients and the main causes of death are myocardial infarction, cardiac failure, sudden death and stroke [3, 4].

Hence, there is no doubt that hypertension adds considerably to the already increased morbidity and mortality risk in NIDDM patients and is the major determinant of the prognosis in nephropathic IDDM patients.

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; ACE, angiotensin converting enzyme; GFR, glomerular filtration rate.

Evidence from intervention studies

Patients with NIDDM

To date no prospective randomised intervention trials aiming at the relevant end points of cardiovascular morbidity and mortality have been published for hypertensive NIDDM patients. At least in Germany, the majority of these patients at diagnosis of diabetes are already above 65 years of age; until recently, there has been controversy over whether elderly patients would benefit from antihypertensive treatment. At the beginning of this decade intervention trials in older patients with essential hypertension were published including about 10% NIDDM patients [5–7]. These trials have impressively shown that antihypertensive treatment with thiazide diuretics and beta blocking agents reduces morbidity and mortality both in patients with systolic and/or diastolic hypertension and gave no indication that these beneficial effects would be different in diabetic patients.

The evidence from intervention trials in essential hypertension indicates that the overall benefit of antihypertensive treatment in the intervention group rises with an increase of the mortality risk in the control group. In a recent overview-evaluation of intervention trials in essential hypertension the mortality risk in the intervention group was correlated with the mortality risk in the control group and an equation for this linear correlation was proposed [8]. According to this equation it should be possible to estimate the benefit of antihypertensive treatment when the baseline risk of an untreated hypertensive population is known: $y = 0.47x - 2.9$ (y = reduction of mortality due to antihypertensive treatment; x = mortality risk without antihypertensive treatment). Applying this equation to the increased mortality risk in newly diagnosed hypertensive NIDDM patients of the United Kingdom Prospective Diabetes Study [1]

of 16 per 1000 patient years would predict a saving of 5 lives per 1000 patients-years (py) of antihypertensive treatment. In *high-risk* patients, such as NIDDM patients with microalbuminuria, the risk of mortality has been reported to be as high as 82 per 1000 py [9]. We have reported that this risk can be reduced to 33 deaths per 1000 py with effective antihypertensive treatment [10], resulting in a putative reduction of mortality with hypertensive treatment of NIDDM patients with increased albuminuria of 49 per 1000 py. These results are in good agreement with the above equation (theoretical mortality risk reduction of 36 per 1000 py) and the assumption is that the life-saving effect of antihypertensive treatment in NIDDM patients will be greater than that in hypertensive non-diabetic patients. However, these extrapolations are based on antihypertensive treatment with thiazide diuretics and beta blocking agents only and may not apply to newer antihypertensive agents.

There are no adequate mortality data from randomised controlled studies in essential hypertension with regard to the newer antihypertensive agents such as angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers. Recently, in several case-control trials antihypertensive treatment with calcium channel blockers was associated with an increased mortality risk [11] and in the only randomised intervention study on the effects of antihypertensive treatment with a calcium channel blocker in essential hypertension, isradipine increased the incidence of total vascular events as compared to diuretic therapy [12].

There is no doubt that ACE inhibitors reduce mortality in congestive heart failure. However, it is of note that this beneficial effect occurred only in patients with a severe reduction of ejection fraction [13]. Taking into account the total 4228 patients participating in the Studies On Left Ventricular Dysfunction (SOLVD) 37% had a history of hypertension and 15% of diabetes, at least a trend towards a reduction of mortality in patients with less severe heart failure should have occurred with ACE inhibitor treatment. In fact, in this study in the subgroup of patients with moderate heart failure (ejection fraction 0.33–0.35) a trend to even higher mortality was present in the enalapril group (12.2%) as compared to placebo (11.5%).

Hence, available evidence suggests that divergent effects of different classes of antihypertensive agents on mortality in essential hypertension are not impossible. Therefore, it seems necessary to provide data for the reduction of cardiovascular morbidity and mortality in essential hypertension for each class of drug proposed as first-line treatment for antihypertension. There is no indication that the beneficial effect of antihypertensive treatment described in studies including patients with and without diabetes will not be present in hypertensive NIDDM patients. Therefore an extrapolation of the results from these studies to hypertensive NIDDM patients should be possible and no separate evidence appears to be necessary to justify antihypertensive treatment in these patients. Because the mortality risk increases in the presence of both diabetes and hypertension, the net beneficial effect of antihypertensive treatment with beta blockers and diuretics will probably be even greater in this group when compared to non-diabetic hypertensive patients.

Patients with IDDM

In nephropathic IDDM patients treatment with ACE inhibitors was associated in two studies with a slower loss of kidney function as compared to placebo [14] or to a beta blocker [15]. However, in both studies blood pressure values were significantly lower with the ACE inhibitor treatments when compared to the respective control groups [16, 17]. It is of note, that in other randomised intervention studies, in which blood pressure control was kept comparable between the study groups, there was no difference in the decline in glomerular filtration rate (GFR) when comparing ACE inhibitors to placebo [18] or a beta blocker [19]. In meta-analyses including controlled and uncontrolled studies ACE inhibitors have been reported to be more effective than other antihypertensive agents with regard to the reduction of albuminuria and proteinuria [20] but equally effective with regard to their influence on the decline of GFR in diabetic nephropathy [21]. These results have been attributed to the effect of ACE inhibitors on the charge of glomerular basement membrane which influences glomerular albumin leakage but has no impact on the progression of glomerular histopathological changes and, hence, on the decline of GFR [22]. Thus, there is still no evidence for a specific, i.e. blood pressure independent, beneficial effect of any antihypertensive agent including ACE inhibitors on the progression of diabetic nephropathy as measured by the progression to renal replacement therapy or by the decline of GFR [22].

We have recently shown that intensification of antihypertensive treatment in IDDM patients with diabetic nephropathy is associated not only with a reduction of the progression of nephropathy and retinopathy by also with a major improvement in life expectancy [23]. In this study mortality was 56 per 1000 py in the control group as compared to 9 per 1000 py in the intervention group. The major causes of death were cardiovascular and the first-line antihypertensive treatment in the intervention group was based on cardioselective beta blockers and diuretics. Also in studies with historical control groups antihypertensive treatment based on beta blockers and diuretics resulted in a major decrease if mortality in patients with diabetic nephropathy [24, 25]. However, in a

prospective randomised study comparing captopril with placebo, mortality was not significantly decreased, despite blood pressure reduction and slowing of progression of renal failure (mortality: placebo: 23/1000 py; captopril 13/1000 py; N.S.) [14]. In addition, in a recently published randomised prospective study in patients with different causes of renal failure including diabetic nephropathy treatment with the ACE inhibitor benazapril decreased blood pressure, slowed progression of nephropathy, but increased total mortality (benazepril: 11/1000 py; placebo: 1.5/1000 py; $p = 0.04$) [26].

Patients with diabetic nephropathy die in most cases due to cardiac causes including sudden death [3, 4]. A combination of hypertension, coronary artery disease and autonomic neuropathy with increased sympathetic activity to the myocardium is very often present in these patients and is the hallmark of a very poor prognosis [4, 27]. To date a reduction of mortality in diabetic nephropathy has been documented in a controlled prospective study only for conventional antihypertensive treatment based on cardioselective beta blockers and diuretics [23]. In patients with nephropathy a relatively diminished effect on mortality during antihypertensive treatment with ACE inhibitors is possible and has been described in randomised studies [14, 26]. No mortality data are available for treatment with calcium channel blockers in diabetic nephropathy. However, these agents have been repeatedly shown to increase mortality in patients with coronary heart disease in randomised controlled trials [28–30]. Because coronary heart disease is a particularly frequent finding in patients with diabetic nephropathy [27], calcium channel blockers should be used restrictively in such patients before their safety has been convincingly demonstrated.

Available evidence strongly supports antihypertensive treatment in diabetic nephropathy. Because of the mortality results of intervention studies, the treatment should be based on cardioselective beta blockers and diuretics as the first-line agents. Until newer antihypertensive compounds, such as ACE inhibitors and calcium channel blockers, have been shown to have equally beneficial effects on mortality in diabetic nephropathy and/or be superior with regard to slowing the progression of renal failure, these classes of drugs should be used as second line or additive treatment.

Desirable blood pressure levels

On the basis of prospective controlled intervention trials, older hypertensive patients should be treated above a threshold of systolic blood pressure 160 mm Hg and/or diastolic above 90 mm Hg. In younger patients, especially those with diabetic nephropathy, the systolic threshold value is 140 mm Hg. However, it is still unclear how far the blood pressure should be lowered. The advice "the lower the better" comes from epidemiological studies in essential hypertension, in which mortality is positively associated with blood pressure levels even within the normotensive range. However, the issue of lowering blood pressure in normotensive patients, or patients with drug controlled normotension, has not been addressed in intervention trials. Administration of antihypertensive agents to such patients may be harmful especially in those with coronary artery disease and with an orthostatic decrease in blood pressure which is frequently present in older patients and patients with autonomic neuropathy [31]. Recently, a four-fold increase of ischaemic cardiac events was described in patients taking antihypertensive medication when office diastolic blood pressure levels were reduced below 90 mm Hg [32]. Also, other observational studies have described an increased risk of cardiovascular events when diastolic office blood pressure values were reduced below 85 mm Hg [33–35]. The exact mechanism by which blood pressure values below a critical point might increase the risk of cardiovascular complications is unknown. However, at very low blood pressure readings the diastolic coronary blood flow may become compromised, with less oxygen reaching the myocardium. This may be critical in some patients when occlusive coronary disease is present especially when oxygen consumption is increased in a hypertrophied ventricle. Also, with extensive lowering of blood pressure, both viscosity and platelet adhesiveness may increase, which can lead to coronary thrombus formation [36].

Because there is no evidence from intervention trials that lowering of blood pressure within the normotensive range (< 140/90 mm Hg) is beneficial for hypertensive patients with or without diabetes and because very low blood pressure values may be detrimental, it seems reasonable to set the target of antihypertensive therapy for diastolic blood pressure between 80 and 90 mm Hg and for systolic blood pressure below 140 in younger diabetic patients and below 160 in older patients. In addition to blood pressure office measurements, which often overestimate blood pressure values in hypertensive and in diabetic patients [37, 38], the use of 24-h blood pressure monitoring and blood pressure self monitoring should be encouraged. The dose of antihypertensive treatment should be frequently adapted aiming at normotensive control without very low blood pressure values. In addition, in older diabetic patients and in those with autonomic neuropathy blood pressure should be measured with the patient standing and patients with a positive "*Osler's Manoeuvre*" should be identified [39]. A positive "*Osler's Manoeuvre*" results in a substantial overestimation of systolic blood pressure values and is a consequence of excessive atheromatosis of the upper vascular tree, which is often present

particularly in NIDDM patients [40] and in IDDM patients with nephropathy [41].

In summary, the evidence available calls for the initiation or intensification of antihypertensive treatment in older diabetic patients above a threshold of 160/90 mm Hg and in younger patients above 140/90 mm Hg with conventional antihypertensive agents (cardioselective beta blockers and diuretics) as the first-line therapy.

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