BLOOD PRESSURE, DIABETES AND DIABETIC NEPHROPATHY

F. CHANTREL, B. MOULIN, T. HANNEDOUCHE

SUMMARY - Despite multiple evidence-based data that diabetic nephropathy is largely preventable and its progression slowed by currently available interventions diabetic patients are often undertreated, especially for the lowering of blood pressure. Recent studies, (HOT Syst-Eur, SHEP, UKPDS, CAPP, ABCD, HOPE) have confirmed the efficiency of intensively treated blood pressure in reducing morbidity-mortality in this group of patients at high risk. Low blood pressure targets are mandatory, but may not be that easy to achieve, especially in the presence of renal failure. Early prescription of a combination of antihypertensive drugs is often necessary. Thus, the clinical question relates to the best combination of drugs. Most studies in hypertensive diabetic patients have dealt with 3 classes of antihypertensive drugs: diuretics, beta-blockers and ACE-inhibitors. Diuretics are one of the most efficient hypotensive drugs available for treatment of hypertension in diabetic patients. Their use must be encouraged early in the stepped approach since diabetes is usually associated with mid-volume expansion due to hyperinsulinism and hyperadrenergic state. In spite of the proven benefit of beta-blockers in diabetic patients, these drugs are largely underused. The indications for selective beta-blockers should probably be broadened for most diabetic patients in primary prevention. Beta-blockers are essential in secondary prevention for patients with coronary artery disease and hypertension. ACE-inhibitors are now more and more widely prescribed in diabetic patients at all stages of hypertension and nephropathy, but paradoxically their use has not been validated in Type 2 diabetic nephropathy. When the desired blood pressure target is obtained, cardiovascular outcome and probably also progression of diabetic nephropathy are significantly improved independently of a specific drug. Early combination therapy, including ACE-inhibitors, diuretics and beta-blockers, should be promptly proposed to all hypertensive diabetic patients to achieve low blood pressure and prevent high cardiovascular burden and progression of nephropathy.

Key-words: diabetes, hypertension, diuretics, beta-blockers, ACE-inhibitors.

RÉSUMÉ - Pression sanguine, diabète et néphropathie diabétique. Il est maintenant établi que l’évolution du patient diabétique vers l’insuffisance rénale secondaire à la néphropathie diabétique n’est pas inéluctable et peut être prévenue ou au moins ralentie par un traitement adapté particulièrement de la pression artérielle. Malgré cela un grand nombre de patients reste sous-traité. Les études récentes, (Syst-Eur, SHEP, UKPDS, CAPP, ABCD, HOT, HOPE) ont confirmé les cibles tensionnelles basses et la nécessité d’un traitement intensif pour obtenir une réduction significative de la morbi-mortalité de ces patients diabétiques à haut risque vasculaire. Cet objectif tensionnel bas nécessaire est souvent difficile à obtenir, particulièrement en présence d’une insuffisance rénale. La prescription précoce d’une combinaison d’antihypertenseur est souvent nécessaire. Si bien que en pratique il importe de déterminer quelle association thérapeutique est la plus judicieuse chez ces patients diabétiques. La plupart des études chez les patients diabétiques hypertendus ont évalué 3 classes d’antihypertenseurs, c.-à-d., diurétique, bêta-bloquant et inhibiteurs de l’enzyme de conversion. Les diurétiques sont les médicaments les plus constamment efficaces et indispensables au traitement de l’hypertension chez les patients diabétiques. Leur utilisation doit être encouragée tôt dans l’approche thérapeutique, le diabète étant habituellement associé à une expansion volémique favorisée par l’hyperinsulinisme et la stimulation adrénergique. Malgré le bénéfice largement prouvé des bêta-bloquants chez les diabétiques ceux-ci restent largement sous-utilisés en pratique clinique. Les bêta-bloquants sont essentiels pour la prévention secondaire des patients coronariens et hypertendus. Les inhibiteurs de l’enzyme de conversion sont actuellement largement utilisés à tous les stades évolutifs du diabète, paradoxalement leur bénéfice n’est pas bien établi au stade de néphropathie avancée dans le diabète de type 2. Lorsque le contrôle tensionnel est obtenu, la prévention de la morbidité cardiovasculaire et la prévention de l’évolution de la néphropathie est très significative, ceci indépendamment du traitement anti-hypertenseur utilisé. Le recours à une tri-thérapie rapide, sur quelques mois, incluant inhibiteur de l’enzyme de conversion, diurétique et bêta-bloquant pourrait être proposé à une grande majorité des patients diabétiques afin d’obtenir les cibles tensionnelles nécessaires à la prévention de la morbidité cardio-vasculaire et à la prévention de la progression de la néphropathie.

Mots-clés : diabète, hypertension, diurétique, bêta-bloquant, inhibiteur de l’enzyme de conversion.

SYSTEMIC HYPERTENSION OR AN ABNORMAL CIRCADIAN BLOOD PRESSURE PROFILE HAS BEEN FOUND IN AT LEAST 80% OF PATIENTS AT THE TIME OF DIAGNOSIS OF TYPE 2 DIABETES [1]. IN MANY COUNTRIES, TYPE 2 DIABETES IS NOW THE MOST FREQUENT CAUSE OF END-STAGE RENAL DISEASE (ESRD) [2-4]. DESPITE THE EVIDENCE-BASED ARGUMENT THAT ESRD IN DIABETIC PATIENTS IS LARGELY PREVENTABLE BY CURRENTLY AVAILABLE INTERVENTIONS, DIABETIC PATIENTS ARE OFTEN UNDERTREATED, ESPECIALLY FOR LOWERING OF BLOOD PRESSURE. THIS PAPER WILL FOCUS ON RECENT DATA FAVOURING THE USE OF AN EARLY COMBINATION OF HYPOTENSIVE DRUGS IN DIABETIC PATIENTS.

BLOOD PRESSURE LOWERING TARGETS

IT IS NOW WELL-ESTABLISHED THAT HIGH BLOOD PRESSURE IS A PROMOTING FACTOR FOR THE PROGRESSION OF DIABETIC NEPHROPATHY AND CARDIOVASCULAR MORTALITY [5, 6]. CONVERSELY, AGGRESSIVE TREATMENT OF BLOOD PRESSURE LEADS TO DRAMATIC IMPROVEMENT OF CARDIOVASCULAR OUTCOME (IRRESPECTIVE OF RENAL DISEASE) AND PROGRESSION OF RENAL FAILURE IN THOSE PATIENTS WITH ESTABLISHED NEPHROPATHY.

IN THE HOT STUDY [7], NO J CURVE RELATIONSHIP WAS FOUND BETWEEN CARDIOVASCULAR MORTALITY AND BLOOD PRESSURE LEVEL IN NON-DIABETIC SUBJECTS UNDER TREATMENT, BUT NO ADDITIONAL BENEFIT WAS DEMONSTRATED WHEN BLOOD PRESSURE WAS BELOW 134/82 MMHG. CONVERSELY, IN TYPE 2 DIABETIC PATIENTS, A LINEAR RELATIONSHIP WAS FOUND BETWEEN CARDIOVASCULAR MORTALITY AND BLOOD PRESSURE LEVELS, SUGGESTING AN ADDITIONAL BENEFIT FOR LOW OR VERY LOW BLOOD PRESSURE LEVELS.

SYSTOLIC HYPERTENSION HAS BEEN LARGELY NEGLECTED IN THE PAST. HOWEVER, POST-HOC ANALYSIS OF THE DIABETIC SUBGROUP OF SYST-EUR (492 PATIENTS FOLLOWED UP FOR 2 YEARS, WITH AN ISOLATED SYSTOLIC BLOOD PRESSURE OF 160-219 MMHG AND DBP < 95 MMHG) SHOWED THAT ACTIVE TREATMENT REDUCED CARDIOVASCULAR MORTALITY BY 76%, CEREBRAL VASCULAR ACCIDENTS BY 73%, AND TOTAL MORTALITY BY 55%. THE ABSOLUTE REDUCTION OF RISK IN DIABETIC PATIENTS WAS TWICE THAT OF NON-DIABETICS PATIENTS BECAUSE OF HIGHER INITIAL ABSOLUTE RISK [8].

IN A RETROSPECTIVE OBSERVATIONAL ANALYSIS OF 94 TYPE 1 DIABETIC PATIENTS, MOGENSEN ET AL. [9] FOUND A CORRELATION BETWEEN AVERAGE BLOOD PRESSURE AND INCREASE IN URINARY ALBUMIN EXCRETION IN PATIENTS WITH INCIPiens NEPHROPATHY, AND A VARIATION OF GFR IN PATIENTS WITH OVERT PROTEINURIA. HOWEVER, THERE WAS NO PROGRESSION WHEN MEAN BLOOD PRESSURE WAS BELOW 90-95 MMHG IN PATIENTS WITH MICROALBUMINURIA OR BELOW 100 MMHG IN THOSE WITH PROTEINURIA. THIS STUDY SUGGESTS A THRESHOLD EFFECT AT A BLOOD PRESSURE OF 95 MMHG FOR MICROALBUMINURIC PATIENTS AND AT 105 MMHG FOR PROTEINURIC PATIENTS.

IN TYPE 1 DIABETICS WITH OVERT NEPHROPATHY, INTENSIFICATION OF ANTI-HYPERTENSIVE TREATMENT WAS FOUND TO DECREASE THE RATE OF PROGRESSION TEN-FOLD [10] WHEN BLOOD PRESSURE DROPPED FROM 160/95-100 MMHG TO ABOUT 140-130/85 MMHG.


IN TYPE 2 DIABETES, HYPERTENSION USUALLY PRECEDES ONSET, AND ITS SIGNIFICANCE IS NOT UNIVOCAL SINCE OTHER CAUSES COULD ACCOUNT FOR HIGH BLOOD PRESSURE (ESSENTIAL HYPERTENSION, OBESITY, RENOVASCULAR DISEASE). HYPERTENSION HAS BEEN CONSISTENTLY FOUND AS AN INDEPENDENT RISK FACTOR FOR PROTEINURIA IN TYPE 2 DIABETIC PATIENTS [12]. BIESENBACH ET AL. ALSO SHOWED A FASTER DECLINE OF THE GLOMERULAR FILTRATION RATE IN HYPERTENSIVE DIABETIC SUBJECTS (SBP > 160 MMHG) [13].

THE HYPERTENSION SUB-STUDY OF UKPDS (UKPDS 38) [14] INCLUDED 1,148 HYPERTENSIVE PATIENTS, WHO WERE DIVIDED INTO 2 GROUPS AND TREATED TO OBTAIN EITHER A “TIGHT” BLOOD PRESSURE TARGET < 150/85 MMHG, (N = 758) OR A “LESS TIGHT” < 180/105 MMHG (N = 390). DURING THE 8.4 YEARS OF FOLLOW-UP, MEAN BLOOD PRESSURE WAS 144/82 MMHG IN THE “TIGHT” GROUP AND 154/87 MMHG IN THE “LESS TIGHT” GROUP. COMPLICATIONS WERE SIGNIFICANTLY REDUCED IN THE “TIGHT” GROUP, WITH THE FOLLOWING RISK REDUCTION: 32% (6-51%) FOR DEATH RELATED TO DIABETES, 44% (11-65%) FOR CEREBRAL VASCULAR DISEASE, 37% (11-56%) FOR MICROVASCULAR COMPLICATIONS (ESPECIALLY RETINOPATHY), 56% (6-40%) FOR CARDIAC HEART FAILURE, 29% (1-49%) FOR THE INCIDENCE OF MICROALBUMINURIA (UAE > 50 MG/L), AND 39% (21-69%) FOR THE INCIDENCE OF PROTEINURIA (UAE > 300 MG/L). THESE LAST NON-SIGNIFICANT VALUES WERE RELATED TO THE SMALL NUMBER OF PATIENTS (53 IN TOTAL).

IN THE ABCD STUDY [15] OF 950 TYPE 2 DIABETIC PATIENTS, A CORRELATION WAS NOTED BETWEEN SYSTOLIC AND DIASTOLIC PRESSURES AND THE OCCURRENCE OF DIABETIC NEPHROPATHY. HYPERTENSION (> 140/90 MMHG) INCREASED THE RISK OF DIABETIC NEPHROPATHY BY 86% [ODDS RATIO (OR) 1.86]. THESE OBSERVATIONS SUGGEST THAT NEPHROPATHY IN TYPE 2 DIABETES CAN ACTUALLY BE PREVENTED BY OPTIMISATION OF ANTIHYPERTENSIVE TREATMENT. THIS HYPOTHESIS IS CURRENTLY BEING EXAMINED IN THE BERGAMO NEPHROLOGIC DIABETES COMPLICATION TRIAL IN A COHORT OF 2,400 TYPE 2 MICROALBUMINURIC HYPERTENSIVE DIABETIC PATIENTS [16].
In the Steno study [17], “intensified” versus “standard” treatments were compared in 160 Type 2 diabetic patients. All patients, irrespective of blood pressure, received an ACE-inhibitor initially (equivalent to 100 mg/d captopril) or an AT1 antagonist when ACE-inhibitors were poorly tolerated. In the “intensified” group, the blood pressure target was < 140/85 mmHg. Thiazides, calcium antagonists and beta-blockers were added in a stepwise approach when necessary. “Intensified” treatment was associated with a significantly lower rate of progression of nephropathy, retinopathy and autonomic neuropathy.

The benefit of blood pressure control on progression is less firmly established in the advanced stage of diabetic nephropathy. In these patients, the loss of GFR is estimated at approximately 1 ml/min/month, so that for a patient with a GFR of 30 ml/min renal replacement therapy will be required 15 to 20 months later. A 30% reduction in the rate of progression would correspond to 4-6 months of dialysis in this case. However, the risk of worsening GFR acutely when blood pressure is lowered too rapidly should also be considered.

Drug combination

Blood pressure control is one of the major ways of preventing cardiovascular mortality and the progression of diabetic nephropathy. Most available data suggest that the blood pressure target may be more important than a specific drug. However, most studies showing the benefit of lowering blood pressure have used a stepped care approach combining 2 or 3 antihypertensive drugs in order to achieve the desired blood pressure target.

The Hypertension sub-study of the UKPDS study (UKPDS 38) [14] included 1,148 hypertensive patients randomised into 2 groups and treated to obtain either a “tight” blood pressure target < 150/85 mmHg, (N = 758) or a “less tight” one < 180/105 mmHg (N = 390). The blood pressure target was not easy to achieve in these patients without renal failure, and a drug combination was frequently required: at least 2 antihypertensive drugs in 62% of patients and 3 drugs in 29%. For high blood pressure resistant to a single drug, furosemide 20 to 40 mg/d was added as a second step.

In another study, Bakris et al. [18] compared the effect of verapamil vs. the beta-blocker atenolol on the progression of diabetic nephropathy in 34 Type 2 diabetic Afro-Americans followed up for 54 months. In the verapamil group, the variation of GFR was weaker and the decrease of proteinuria greater. In this study, the normotensive target (< 140/90 mm Hg) was obtained with a combination of 2 drugs in 20-30% of patients (including furosemide in second line). Three drugs were necessary in 40-50% of patients, and even 4 drugs in 20-30%.

In the study of Nielsen et al. [19], three-fourths of patients were treated by 2 antihypertensive drugs, including a diuretic, which confirms the need for combined treatment to achieve optimal blood pressure in patients with nearly normal renal function (GFR ~75 ml/min/1.73m²).

Recently Fogari et al. [20] conducted a prospective 2-year study in 107 Type 2 diabetics patients with nephropathy, proteinuria, impaired renal function (creatinine 1.6-3 mg/d) and baseline high diastolic blood pressure (≥95 and ≤ 105mmHg). This study compared two single anti-hypertensive therapies (ni- tendipine 20 mg and ramipril 5 mg). After three and six months of treatment, patients who did not reach the blood pressure goal were withdrawn. Almost 20% dropped out for inadequate lowering of blood pressure in both the nifedipine and ramipril groups.

The results of various studies show the benefit of aggressive blood pressure control in Type 2 diabetic patients, regardless of the stage of nephropathy (without renal insufficiency: UKPDS [14] and HOT; with renal insufficiency: [7] and [21]). However, blood pressure control is still largely reported to be suboptimal in these patients, and antihypertensive drugs are largely underused. In the inclusion cohort of the IDNT study, 44% of Type 2 diabetic patients with hypertension and nephropathy received no treatment, 40% received only one antihypertensive drug, 12% two, and only 4% three (E.J. Lewis, personal communication).

Most, if not all, studies reporting some benefit of lowering blood pressure have used a “stepped” approach combining successively 2 or 3 antihypertensive drugs to achieve the desired blood pressure target. This requirement of combined therapy has been largely overlooked in routine practice. Some practitioners suppose that the prognosis of these patients can be improved merely by administering pills without achieving a marked lowering of blood pressure. Others wait for months before considering combined therapy, leaving patients under suboptimal treatment during many years despite evidence of end organ damage. A more “aggressive” strategy based on “early” combined therapy would seem to be more effective in diabetic patients, especially those with nephropathy: bi- or even tritherapy should be instituted rapidly within 2 or 3 months, as soon as blood pressure does not decrease significantly.

- WHICH DRUGS SHOULD BE USED?

As shown in the preceding paragraph, most patients will ultimately need combined therapy to achieve the blood pressure target. In a pragmatic approach, the question arises as to which is the best combination of drugs for achieving a good blood pressure target in such diabetic patients.

Most studies of hypertension in diabetic patients have dealt with 3 classes of antihypertensive drugs:
diuretics, beta-blockers and ACE-inhibitors. The potential benefits and dangers of these drugs will be reviewed here, especially for diabetic patients. The potential advantage of combining these drugs (especially diuretics and ACE-inhibitors) for efficacy and tolerability will also be considered.

Diuretics

Diabetes is usually associated with mild sodium retention and volume expansion, which are related to the hyperadrenergic state and the effect of hyperinsulinism on sodium tubular reabsorption. The UKPDS study of Type 2 diabetic patients confirms the large requirement of diuretics to lower blood pressure. Twenty-nine percent of patients required three or more hypotensive drugs (including diuretics, a suggested second line drug) [14].

Thiazide diuretics have been discredited in diabetic patients following the retrospective observational study of Warram et al. [22], which showed excess mortality in the group treated by thiazide as compared to patients not receiving diuretics. These noxious effects were attributed to the role of hypokalaemia, insulin resistance and the increased prevalence of dyslipidaemia. However, careful examination of the data reveals a higher pulse pressure in the diuretic-treated group as well as a significantly higher proportion of patients with renal insufficiency (a significant risk factor for cardiovascular mortality per se).

Insulin resistance and increased prevalence of hyperlipidaemia are usually considered as secondary to the potassium depletion induced by these drugs in patients with normal renal function (which was especially the case in the past when thiazides were used at a high dosage). The risk of hypokalaemia has decreased dramatically since the use of thiazides at a lower dosage (less than 12.5-25 mg/d of hydrochlorothiazide or equivalent), and these drugs can now correct hyperkalaemia induced by ACE-inhibitors and increase their hypotensive effects. The risk of hyperkalaemia is lower in patients with renal impairment, whereas diabetic patients are usually more prone to hyperkalaemia since hyporeninism-hypoaldosteronism is partly induced by volume expansion.

A major concern is the risk of functional acute renal failure through overzealous use of diuretic therapy. The rise in creatinine is partly explained by volume contraction and interference with tubular secretion. Isolated systolic hypertension is a frequent complication of Type 2 diabetes. Analysis of the sub-group of diabetic patients of SHEP (SBP > 160 mmHg and DBP < 90 mmHg) (n = 583) showed that antihypertensive treatment, including a thiazide diuretic (chlorothalidone 12.5-25 mg ± beta-blockers ± reserpine when needed) was well-tolerated and markedly more effective than a placebo. The incidence of major cardiovascular events was reduced by 35% (similarly to non-diabetic patients), but the absolute reduction of risk was even more impressive: 101 at over 5 years, corresponding to 12 patients needed to treat (NNT) [23].

In the HOT study [7], diuretics were required in 19 to 24% of all patients, depending on the target of diastolic blood pressure (80-85-90 mmHg). This relative underuse of diuretics in the HOT study [24] was mainly due to the increment procedure of the study design. Diuretics were initiated as third-line antihypertensive treatment after the use of calcium blockers and ACE-inhibitors or beta blockers, all given at full dosage. However, to achieve good target blood pressure in a population of nearly normal renal function, including a few diabetic patients (8%: 1,501 patients), up to 20% of patients needed a combination of three antihypertensive drugs, including a diuretic.

Walker et al. [25] studied 84 macroalbuminuric hypertensive Type 2 diabetic patients receiving either enalapril or hydrochlorothiazide and found similar effective blood pressure control and a decline in GFR (99 Tc-DTPA) (−3 ± 1.4 vs −4.1 ± 1.3 ml/min/year in diuretic and ACE-inhibitor groups respectively).

More recently, Trocha et al. [11], in a prospective study of 91 Type 1 diabetic patients, confirmed the great need for diuretics in 76% and 63% of patients with “intensive” and “routine” antihypertensive therapy respectively after 10 years of follow-up. However, blood pressure control was not impressive (151/87 vs 150/89 mmHg) despite only mild renal failure in both groups (1.34 vs 1.17 ml/s/l.73 m²).

The nephropathy of Type 2 diabetes, particularly at the stage of advanced renal insufficiency, is characterised by overhydration, which is partly responsible for high blood pressure. This latent volume expansion is indicative of the loss of a fall in night blood pressure (non-dipping), which is now recognised as a potent inducer of left ventricular hypertrophy, eventually leading to diastolic dysfunction and pulmonary oedema. Volume expansion and hyperhydration are often overlooked in diabetic patients, especially those with advanced renal failure. Surprisingly, in a cohort of Type 2 diabetic patients starting dialysis therapy, a loss of 6 to 7 kg during the first month was required on average to achieve dry weight [26].

Prevention of hyperhydration in these patients requires strict control of sodium intake, which is often either not recommended or not followed. As a result, diuretics are usually necessary [27]. When renal function is impaired, thiazide diuretics are ineffective and potassium-sparing diuretics are dangerous because of the potentially lethal risk of hyperkalaemia metabolic acidosis. Loop diuretics such as furosemide or bumetamide are the only effective ones in this setting and thus the mainstay of therapy. Because of their pharmacodynamic characteristics, the dosage of loop diuretics must be increased proportionally to the decrease of GFR. Efficacy can also be considerably
enhanced when the dosage is fractionated (several administrations a day).

In summary, diuretics are one of the more efficient hypotensive drugs available for treatment of hypertension in Type 1 and Type 2 diabetic patients. Their use must be strongly encouraged early in the stepped approach since a single drug is generally unable to achieve the required blood pressure goals. In the case of progressive renal failure, diuretics deserve special consideration since they achieve the same efficiency on blood pressure.

**Beta-blockers**

In a sub-study of UKPDS (UKPDS 39) [14, 28], 758 patients included in the “tight” blood pressure target <150/85 mmHg group were randomised to receive either captopril or atenolol as the first drug step, with the exclusion of any other ACE-inhibitor or beta-blocker. A comparison of captopril and atenolol showed no differences in the prevention of microvascular and macrovascular complications. Furthermore, there were no differences in the incidence of progression to nephropathy. The proportion of patients with a EUA > 50 mg/l at 9 years was 31% and 26% in the captopril and atenolol groups respectively, and 5% and 10% for proteinuria > 300 mg/l. Final plasma creatinine was similar, and the proportion of patients with doubled creatinine was not significantly different in the two groups.

In the study of Sawiki et al. [29] in Type 1 diabetic patients with nephropathy, very good blood pressure control was achieved with a beta-blocker-diuretic combination as well as a very significant reduction of cardiovascular morbi-mortality. A more recent extension of this study [11] also suggests a benefit in terms of limiting the progression of renal insufficiency.

Beta-blockers have proven their effectiveness not only for the treatment of hypertension but also in primary prevention of cardiovascular complications (MRC, HAPPHY) [30, 31]. In secondary prevention of post-myocardial infarction, 73 randomised studies vs placebo (51,563 patients) gathered in the Soriano meta-analysis [32] showed a relative risk (RR) of death of 0.89 for patients treated by beta-blockers. The reduction of risk was greater with selective, lipophilic beta-blockers, those without membrane stabilising activity and those lacking intrinsic sympathetic activity.

Despite their well-proven effectiveness, beta blockers for diabetic patients have never gained wide acceptance, as recently noted by Majumdar [33] in a review. Beta blockers have few clinically important effects on hypoglycaemic awareness and recovery, insulin resistance and hyperglycaemia or lipid profiles.

The underuse of beta-blockers in diabetic patients is mainly related to concern for their interference with glucose and lipid metabolism and the common belief that peripheral arterial ischaemia may be exacerbated by these drugs.

The risk of masking adrenergic symptoms of hypoglycaemia in Type 1 diabetic patients is negligible with B1 cardio-selective beta-blockers, which do not blunt the increase in plasma glucose following hypoglycaemia induced by insulin. The impairment of insulin resistance and dyslipidaemia have not been well-documented in long-term treatment with beta-blockers, and the actual impact of these metabolic abnormalities on cardiovascular risk therefore remains speculative. Beta-blocker treatment may require modification of other therapeutics (insulin, hypolipaemic drugs), but this should not lead to the rejection of this effective class of antihypertensive drugs.

With respect to the risk of worsening arteriopathy, several studies have shown no significant aggravation of claudication, especially with B1-selective beta-blockers or beta-blockers with combined alpha-blocker properties.

In spite of the proven benefit of beta-blockers in diabetic patients, these drugs are largely underused. Beta-blockers such as carvedilol, bisoprolol (Cibis 2), or metoprolol have recently been found effective in the treatment of congestive heart failure when added to conventional therapy including ACE-inhibitors and diuretics. There is no reason that this benefit could not apply to patients with renal failure, including those with ESRD on dialysis [34]. The indication of selective beta-blockers should probably be broadened in most diabetic patients in primary prevention. Beta-blockers are essential in secondary prevention for patients with coronary artery disease and hypertension.

**ACE-inhibitors**

ACE-inhibitors are now more and more frequently prescribed for diabetic patients at all stages of hypertension and nephropathy.

In the diabetic sub-group of the CAPPP study, which compared treatment based on ACE-inhibitors (captopril 50-100 mg/d) with beta-blockers or diuretics, 574 patients were followed up for an average of 6.1 years [24]. For a similar decrease in blood pressure (−11 mmHg SBP), the treatment by ACE-inhibitors reduced the relative risk of myocardial infarction significantly (66%) as well as that of global mortality (48%). There was no difference in effectiveness between the two types of treatment in the non-diabetic population. It is noteworthy that a lower incidence of new diabetes cases was observed in the captopril group (OR: 0.86; confidence interval (CI): 95% (0.74-0.99)), which suggests a clinical benefit of ACE-inhibitors for metabolic balance (insulin resistance).

The results of the HOPE trial [35] have been recently published. This double-blind, two-by-two factorial, randomised “Heart Outcomes Prevention” study evaluated ramipril and vitamin E in 9,541 patients at high risk for cardiovascular events over a 5-year follow-up period. A total of 4,355 patients had...
hypertension, and 3.578 had diabetes. Mean blood pressure at baseline was 139/79 mmHg in both groups, and treatment with ramipril reduced the rates of death from cardiovascular events significantly (3.1% vs 9.1%; RR = 0.75; p < 0.001). The beneficial effect of treatment on the composite outcome of death from cardiovascular events persisted in some predefined groups such as diabetic, normotensive and microalbuminuric patients. Among these “fairly hypertensive patients”, almost 40% received beta-blockers, 46% calcium channel blockers, and 15% diuretics in addition to ramipril, confirming the need for an anti-hypertensive drug combination in most patients in order to achieve the pressure goal.

Although ACE-inhibitor therapy (ramipril) had a positive effect on mortality from cardiovascular disease in a high-risk population, specific results for diabetic patients are still awaited in this study. Nonetheless, these preliminary results suggest that such drugs should be used more often in high-risk patients, including diabetic patients.

The optimal pressure goal and the effect of specific antihypertensive classes were evaluated in the ABCD trial in 950 normotensive or hypertensive Type 2 diabetic patients (29% with microalbuminuria). This study was constructed according to a bifactorial design: two blood pressure targets (diastolic blood pressure 75 vs 80-89 mmHg) and two types of antihypertensive drugs (the dihydropyridine nisoldipine vs. the ACE-inhibitor enalapril) [15]. The results of this study are partially available for the sub-group of 470 hypertensive patients. For a similar blood pressure drop, nisoldipine was associated with a higher risk of fatal or near-fatal myocardial infarction (OR 9.5; CI 95% (2.3-21.4) than enalapril [36]. These unexpected results suggest that the different antihypertensive drugs do not afford the same degree of cardio-protection in diabetic patients.

The use of ACE-inhibitors has been largely validated in Type 1 diabetes with nephropathy at the stages of isolated microalbuminuria and normotensive retinopathy.

The North-American collaborative study coordinated by Lewis et al. [37] showed a benefit for the treatment of hypertension by ACE-inhibitors in 409 Type 1 diabetic patients with diabetic nephropathy and a mean follow-up of 3 years. These patients were randomised to receive either captopril (25 mg x 3/d) or placebo. Blood pressure control was similar in the two groups (median 130/80 mmHg), with a slightly lower mean diastolic blood pressure (3-4 mmHg) in the captopril group. This difference was largely accounted for by the 25% of patients who were normotensive at the beginning of the study and whose blood pressure decreased on captopril (~3.5 mm Hg), whereas blood pressure increased slightly in the placebo group (~1.5 mm Hg). The group of normotensive patients had a lower number of final events, so that the significance of the differences in blood pressure for the two groups was probably negligible.

The combined criteria of ESRD and death were reached in 23 patients (11%) in the captopril group as compared with 42 (21%) in the placebo group. This represents a reduction of risk of approximately 50% for captopril treatment (p < 0.006).

A non-significant reduction of the risk of doubling time of plasma creatinine [33%, CI 95% (44%-69%), P = 0.31] was observed among 307 patients with plasma creatinine < 133 µmol/l. In patients with initial plasma creatinine > 133 µmol/l, the reduction of risk in the captopril group was significant [68%, CI 95% (39-63%)]. This benefit, confined to patients with an initial plasma creatinine > 133 µmol/l, may be explained by the higher rate of progression. No improvement was found in patients with lower initial plasma creatinine, probably because the rate of progression was very slow in this group (plasma creatinine increasing only from 9 to 18 µmol/l per year). The beneficial effect of captopril remained after adjustment for achieved blood pressure levels, suggesting that this effect was largely independent of blood pressure control.

ACE-inhibitors have not been so firmly validated in Type 2 diabetic patients with nephropathy, but several studies are currently ongoing.

The study of Ravid et al. [38] in normotensive Type 2 diabetic patients suggests that enalapril reduces urinary albumin excretion, the incidence of macroalbuminuria, and the slope of decrease of 1/Screatinine. In 94 patients randomised (enalapril vs. placebo) during the first 5 years (RCT) and then followed up in an open study for 2 years [39], plasma creatinine and urinary albumin excretion remained stable on enalapril 10 mg/d for 7 years. Patients receiving a placebo had an increase of 16% of plasma creatinine and proteinuria (from 123 to 393 mg/d). At 7 years, the benefit of enalapril was still evident, with a decrease of 42% of progression to macroalbuminuria [39].

However, several lines of evidence suggest that these drugs afford a renal benefit in Type 2 diabetic patients since they can slow the progression of renal insufficiency in non-diabetic glomerular disease with proteinuria, probably through a non-specific mechanism (i.e. reduction of glomerular hypertension and proteinuria) [40-42]. Several studies in Type 2 diabetic patients with nephropathy showed that ACE-inhibitors reduced proteinuria [43, 44], an effect related to the decrease of the progression of nephropathy [37, 45]. The benefit of ACE-inhibitors in this situation seems more related to the inhibition of the renin system (i.e. a class effect) than to a specific drug.

Several general guidelines should be emphasised regarding the use of ACE-inhibitors in diabetic patients with nephropathy. It is recommended to start with a low dosage and increase the dose very gradu-
ally, depending on renal tolerance and pressure goals. Functional renal failure is frequent, especially if ACE-inhibitors are associated with high doses of diuretics. This decrease of renal function is probably related to the collapse of glomerular capillaries and is usually reversible. For 42 hypertensive Type 1 diabetic patients, withdrawal of ACE-inhibitors increased both blood pressure and GFR (from 76 to 81 ml/min) [46].

It should be kept in mind that the prevalence of renal artery stenosis is 15-30% in Type 2 diabetic patients. Renovascular disease should be evaluated routinely by Doppler ultrasonography in this population, especially before starting ACE-inhibitor therapy [47].

Hyperkalaemic metabolic acidosis is a common complication associated with the use of ACE-inhibitors, especially in patients with renal failure and/or diabetes. Hyperkalaemic metabolic acidosis is favoured by hyporeninaemic hypaldosteronism and also by the decrease of sodium delivery in the distal tubule. An increase of diuretic dosage is a simple and effective way of preventing or correcting this hyperkalaemic state. When diuretic dosage is too high and likely to worsen renal failure, hyperkalaemia can be effectively corrected by prescribing an ion-exchange resin (polystyrene sulphonate) and taking the sodium load into account. Non-steroid anti-inflammatory drugs can worsen renal function, leading sometimes to irreversible renal failure and/or risk of hyperkalaemic metabolic acidosis. These drugs are formally contraindicated in patients with renal failure, especially in combination with other hyperkalaemic drugs such as ACE-inhibitors.

The concern over increased risk of hypoglycaemia with ACE-inhibitors has not been confirmed. In the North-American study of Lewis et al. [37], HbA1c did not change significantly during the study in either group, and there was no increase in sensitivity to insulin in the captopril group.

There are no specific data concerning the use of AT1 blockers in diabetic patients with nephropathy. Two large studies (RENAAL, IDNT) are currently underway to validate these drugs in Type 2 diabetic nephropathy for prevention of ESRD and cardiovascular complications, but the results are not likely to be available before 2003. Preliminary data for non-diabetic patients suggest a similar antiproteinuric effect for AT1RA and ACE-inhibitors [48].

## Conclusion

Most of the published literature on the treatment of high blood pressure in diabetic patients confirms the need for achieving low target blood pressure. However, this target is frequently difficult to reach with single drug therapy. When the desired target is obtained, cardiovascular outcome and probably the progression of diabetic nephropathy as well are significantly improved independently of a specific drug. The vast majority of studies show that diuretics and beta-blockers are underused in this specific population with high cardiovascular morbidity. ACE-inhibitors seem to be efficient drugs, especially in regard to progression of renal failure in patients with nephropathy. Early combination therapy, including ACE-inhibitors, diuretics and beta-blockers, should be promptly proposed to all hypertensive diabetic patients to achieve low blood pressure and prevent a high cardiovascular burden and progression of nephropathy.

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### References


