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Hypertension in Diabetes Study IV. Therapeutic requirements to maintain tight blood pressure control

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Summary We report the efficacy of therapy over 5 years follow-up in 758 non-insulin-dependent diabetic patients in a prospective, randomised controlled study of therapy of mild hypertension. Patients were recruited who on antihypertensive therapy had systolic blood pressure over 150 mmHg or diastolic over 85 mmHg, or if not on therapy had systolic blood pressure over 160 mmHg or diastolic over 90 mmHg. Their mean blood pressure at entry to the study was 160/94 mmHg at a mean age of 57 years. They were allocated to tight control (aiming for systolic < 150/diastolic < 85 mmHg) or to less tight control (aiming for systolic < 180/ diastolic < 105 mmHg). The tight control group were allocated to primary therapy either with a beta blocker (atenolol) or with an antiotensin converting enzyme inhibitor (captopril), with addition of other agents as required. Over 5 years, the mean blood pressure in the tight control group was significantly lower (143/82 vs 154/88 mmHg, $p < 0.001$). No difference was seen between those allocated to atenolol or captopril. The proportion of patients requiring three or more antihypertensive therapies to maintain tight control in those allocated to atenolol or captopril increased from 16 and 15 %, respectively at 2 years to 25 and 26 %, respectively at 5 years, whereas in the less tight control group at 2 and 5 years only 5 and 7 %, respectively required three or more therapies. There was no difference in the incidence of side effects or hypoglycaemic episodes between those allocated to atenolol or captopril, but those allocated to atenolol increased their body weight by a mean of 2.3 kg compared with 0.5 kg in those allocated to captopril ($p < 0.01$). Allocation to atenolol was also associated with small increases in triglyceride, and decreases in LDL and HDL cholesterol, which are of uncertain clinical relevance. The study is continuing to determine whether the improved blood pressure control, which was obtained, will be beneficial in maintaining the health of patients by decreasing the incidence of major clinical complications, principally myocardial infarction and strokes, and microvascular complications, such as severe retinopathy requiring photocoagulation and deterioration of renal function. [Diabetologia (1996) 39: 1554–1561]

Keywords Non-insulin-dependent diabetes mellitus, hypertension therapy, angiotensin converting enzyme, beta blocker.

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Abbreviations: IDDM, Inslin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; ACE, angiotensin converting enzyme inhibitor; HDS, Hypertension in Diabetes Study; UKPDS, United Kingdom Prospective Diabetes Study.

In the general population, therapy for moderate or severe hypertension is known to reduce the incidence of strokes and myocardial infarction [1]. Recent studies have shown that the absolute benefit is more marked in the elderly, since their risk of cardiovascular events is greater than in the general population [2–4].

Improved therapy for hypertension in insulin-dependent diabetic (IDDM) patients with reduced glomerular filtration rate reduces the deterioration of renal function [5, 6]. However, no studies have evaluated whether therapy of mild hypertension in non-insulin-dependent diabetic (NIDDM) patients will be clinically advantageous. While this might be assumed, since hypertensive NIDDM patients have an increased incidence of cardiovascular events, patients with hypertension often have other associated risk factors for heart disease including obesity, and raised triglyceride and insulin levels [7, 8]. Thus, the effect of blood pressure reduction might be less than anticipated, particularly since some therapies have an adverse effect on lipid levels [9, 10]. As patients with raised urine albumin excretion, termed 'microalbuminuria', have an increased risk of myocardial infarction [11, 12], it is often suggested that they would particularly benefit from reduction of blood pressure, since this reduces albumin excretion [13]. However, this may reflect solely renal haemodynamic changes [14] and may not make any difference to the subsequent progression of renal disease or to the associated increased mortality from cardiac disease. In addition, potential side effects of therapy might arise, including an increased risk of hypoglycaemic attacks, since beta blockers can mask the adrenergic symptoms of hypoglycaemia and angiotensin converting enzyme (ACE) inhibitors can increase insulin sensitivity. Other unsuspected long-term side effects cannot be excluded, as exemplified by recent caution concerning the safety of calcium channel blocking agents [15] and the previously unexpected side-effect of retroperitoneal fibrosis arising from practolol therapy [16].

There is uncertainty as to whether any specific class of antihypertensive therapy may be particularly beneficial. Both beta blockers and ACE inhibitors potentially have specific advantages. Beta blockers are given routinely after myocardial infarction to decrease cardiac mortality [17]. In view of the high incidence of myocardial infarction in hypertensive NIDDM patients, treatment with beta blockers before, rather than after, heart attacks develop might be advantageous. Similarly, ACE inhibitors are a specific therapy for heart failure [18] and produce some reduction in mortality following myocardial infarction [19]. In addition, it has been suggested that ACE inhibitors may have a specific beneficial effect on improving microvascular blood flow as shown by reduction of microalbuminuria in IDDM patients without defined hypertension [20], although such patients still have blood pressure levels slightly higher than control subjects without microalbuminuria. Whether the reduction in urine albumin is a specific effect or is secondary to reduced blood pressure is uncertain, although a study in hypertensive IDDM subjects with renal failure has suggested benefit from ACE inhibitors [21].

The Hypertension in Diabetes Study (HDS) is a prospective, multicentre study designed to determine whether more intensive therapy of mild hypertension, routinely aiming for blood pressure under 150/85 mmHg, will be clinically beneficial in patients with NIDDM [22, 23]. The study includes patients with albuminuria, so it will determine whether patients with increased urine albumin excretion might gain specific benefit or whether treatment of hypertension per se is important.

We report the efficacy of ACE inhibitor and beta blocker therapies and associated side effects over 5 years of follow-up, including the degree to which additional antihypertensive agents are required to maintain improved blood pressure at under 150 mmHg systolic and under 80 mmHg diastolic.

Patients and methods

Patients recruited into HDS. Eligible hypertensive NIDDM patients in the UK Prospective Diabetes Study (UKPDS) [23] were invited to enter the study between 1987 and 1991. Patients were excluded if they required strict blood pressure control (due to a previous stroke, accelerated hypertension, cardiac or renal failure) or beta blockade (for myocardial infarction in the previous year or current angina), had severe vascular disease (more than one major vascular episode), had a severe concurrent illness or if beta blockade was contraindicated (asthma, intermittent claudication, foot ulcers or amputations). Pregnant women were also excluded.

We recruited 1148 patients on the basis of the mean of blood pressure measurements at three separate clinic visits. We report on the 758 patients who attended the 5 years' follow-up (Table 1). At randomisation 296 had previously been taking therapy for hypertension, but still had mean blood pressure from three visits above the entry criteria of over 150 mmHg systolic and/or over 85 mmHg diastolic, whereas 462 had previously not been on therapy and had mean blood pressure from three visits above the entry criterion of over 160 mmHg systolic and/or over 90 mmHg diastolic. The two groups had similar blood pressure at entry to the study, 166/93 and 160/95 mmHg respectively. Of those previously on therapy 34 % had been taking a beta blocker and 7 % an ACE inhibitor.

Blood pressure measurements. Blood pressure was measured by a trained nurse, with the patient sitting, resting for at least 5 minutes, with the forearm semi-flexed supported on a pillow with the palm facing upwards. Measurements were made with a Copal UA-251 or a Takeda electronic, auscultatory blood pressure reading machine (Andrew Stephens Co., Brighouse, West Yorkshire, UK), except for those with obese arms (circumference > 33 cm), when a large cuff was used, and in patients with atrial fibrillation, when the blood pressure was measured with a Hawksley random zero sphygmomanometer (Hawksley & Sons Ltd, Lancing, Sussex, UK). Diastolic blood pressure was taken as the Korotkoff phase 5. In each patient, four consecutive readings were taken with at least 2-min intervals between readings and the first reading was discarded, while the mean of the last three readings was used in the study if the coefficient of variation was less than 15 %. If the coefficient of variation was greater, additional readings were taken until it became less than 15 %. For quality assurance, every

Table 1. Characteristics of patients at entry to the HDS

	Previous antihypertension therapy			
	All patients	No	Yes	*p* value
n	758	462	296	
Age (years)	57.0 ± 7.9	56.4 ± 8.1	57.9 ± 7.4	< 0.01
Gender (% male)	53	57	47	< 0.01
Ethnic Group Caucasian/Asian/Afro-Carribean	87/5/8	89/5/6	86/5/9	NS
Systolic BP (mm Hg)	160 ± 20	160 ± 18	160 ± 21	NS
Diastolic BP (mm Hg)	94 ± 10	95 ± 10	93 ± 10	< 0.01
Body mass index (kg m^{-2})	29.4 ± 5.4	29.1 ± 5.3	29.9 ± 5.4	< 0.05
Duration of diabetes (years)	3.2 ± 2.1	3.1 ± 2.1	3.3 ± 2.1	NS
HbA_{1c} (%)	6.8 ± 1.6	6.8 ± 1.6	6.8 ± 1.7	NS
Fasting plasma glucose (mmol l^{-1})	7.9 ± 2.6	7.8 ± 2.6	8.0 ± 2.5	NS
Triglyceride (mmol l^{-1})[a]	1.6 (0.9–2.7)	1.5 (0.9–2.6)	1.7 (1.1–2.8)	< 0.01
Cholesterol (mmol l^{-1})	5.5 ± 1.1	5.5 ± 1.1	5.5 ± 1.1	NS
LDL cholesterol (mmol l^{-1})	3.58 ± 1.11	3.57 ± 1.12	3.60 ± 1.10	NS
HDL cholesterol (mmol l^{-1})	1.10 ± 0.26	1.13 ± 0.27	1.06 ± 0.24	< 0.001
Smoking (never/ex/current)	38/40/22	38/38/24/	39/41/20	NS
Urine albumin (mg l^{-1})[a]	15 (4–54)	13 (4–50)	16 (4–60)	NS

Values are mean ± SD or geometric mean (SD interval)

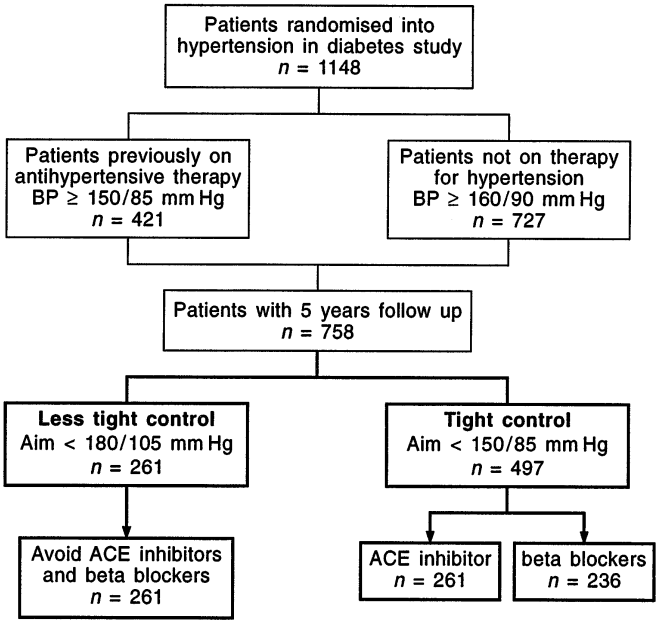

Fig. 1. Flow chart of entry into study and of subjects studied

month blood pressure readings from each automatic machine were compared with a simultaneous random zero sphygmomanometer (Hawksley) reading. If an absolute systolic or diastolic difference was over 10 mmHg, or a coefficient of variance 10 % or more, additional blood pressure measurements were made. Apparently faulty machines are returned to the central administrative centre for checking repair. The mean difference between Takeda and Hawksley machines has been 1 mmHg or less, SD 4 mmHg.

Randomisation and therapeutic regimens. Patients were allocated at random to one of three therapeutic groups (Fig. 1). Two thirds of the 1148 patients recruited, 758 patients, were randomised to a tight blood pressure control policy, aiming for blood pressure less than 150 mmHg systolic and 85 mmHg diastolic. We randomly allocated 400 patients to primary treatment with an ACE inhibitor (captopril) and 358 to primary treatment with a beta blocker (atenolol). One third of the patients (390) were allocated to a less tight control group. HDS is in a factorial design with UKPDS and, as would be expected, the allocation to the three HDS therapy groups was statistically independent from eight therapeutic allocations of the UKPDS ($\chi^2$18.0 on 14 *df*, NS).

In the 758 patients studied for 5 years, 497 were allocated to tight blood pressure control, 261 to ACE inhibitor and 236 to beta blockers, and 261 to less tight blood pressure control. Initially the aim in the less tight control group was for blood pressure less than 200/105 mmHg, but this was modified in 1992 to less than 180/105 mmHg by the Data Monitoring and Ethics Committee following publication of results of studies of elderly, non-diabetic subjects in the years 1991–1992 [2–4].

In the tight control group captopril was usually started at a dose of 25 mg twice daily, increasing to 50 mg twice daily if required. Diuretic therapy was stopped at least 24 h before captopril was introduced at a lower dose of 6.25 mg twice daily with observation for 6 h after the first dose. Atenolol was usually started at a daily dose of 50 mg increasing to a maximum of 100 mg if required.

If control criteria (blood pressure less than 150 mmHg/85 mmHg), were not met in the tight control group despite maximum allocated therapy, additional agents were added, the suggested sequence being frusemide 20 mg daily (maximum 40 mg twice daily), slow release nifedipine 10 mg (maximum 40 mg) twice daily, methyldopa 250 mg (maximum 500 mg) twice daily and prazosin 1 mg (maximum 5 mg) three times daily. Drugs could be stopped if patients experienced side-effects. Physicians were asked not to treat patients allocated to atenolol with ACE inhibitors, and in those allocated to captopril with beta blockers, unless this was required as a last resort in order to reduce the blood pressure to less than 150/ < 85 mmHg. In the less tight control group, the same sequence of agents was used if the blood pressure was over 180 mmHg/105 mmHg, avoiding ACE inhibitors and beta blockers if feasible, i. e. therapy initially with frusemide, with additions of slow release nifedipine, methyldopa or prazosin.

Follow-up. Patients were seen every 3 or 4 months at the routine UKPDS clinic visits when blood pressure and fasting plasma glucose were measured and therapies, presence of side effects and history of hypoglycaemic episodes noted. The number of patients who had a minor hypoglycaemic episode (did

not require medical assistance) or major episodes (required medical assistance or admission to hospital) was assessed each year. The average of five annual assessments was calculated for these patients who remained on their allocated therapy throughout the 5 years. Each year haemoglobin A_{1c}, fasting plasma triglyceride, HDL- and LDL-cholesterol and urine albumin [24] were measured and every 3 years plasma creatinine, urea, urate and electrolytes.

Statistical analysis

The data are provided for all subjects who attained 5 years' follow-up with an intention-to-treat analysis irrespective of their current therapies. The exception for side-effects including hypoglycaemic reactions, was an analysis according to those who were taking the appropriate allocated therapy. Data are expressed as mean and standard deviation, with log transformation of plasma triglyceride. Two tailed *t*-tests, two-way analysis of variance and Mantel-Haenzel chi-square tests for trend were used and analyses were performed using the Statistical Analysis System [25]. Responses over 5 years were assessed by repeat measures analysis of variance, providing mean values from annual visits at 1–5 years, with differences between therapies and changes from baseline data being assessed using the mean of these 5-year values.

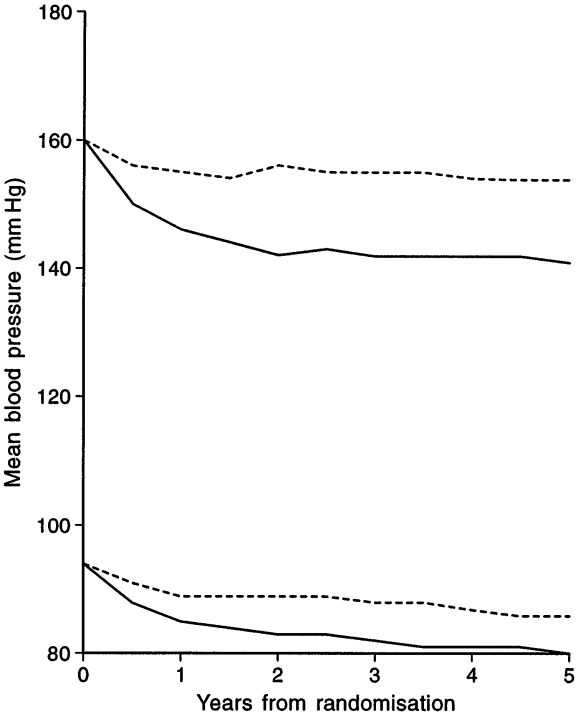

Fig. 2. Mean systolic and diastolic blood pressure in cohort of patients studied over 5 years, 497 allocated to tight control (——) and 261 to less tight control (----)

Results

Table 1 shows the characteristics of the 758 patients followed for 5 years and Figure 1 shows the flow chart of the study. The patients already on antihypertensive therapy at entry into the HDS were slightly older than the untreated patients, with a greater proportion of females. Of the patients at entry 48 % had both raised systolic and diastolic blood pressures, 16 % had only a raised systolic blood pressure and 36 % only a raised diastolic blood pressure. A greater proportion of previously treated patients had both systolic and diastolic raised than in those previously on no therapy, 58 vs 41 % with 15 vs 17 %, respectively having only systolic hypertension.

Blood pressure control. The blood pressure responses over 5 years are shown in Figure 2 with baseline and 5-year data in Table 2. In the tight control group the blood pressure fell from the baseline level of 160/94 mmHg to 142/83 mmHg at 2 years with no subsequent significant change to 141/80 mmHg at 5 years. In the less tight control group the blood pressure fell from 160/94 mmHg at entry to 156/89 mmHg at 2 years with no subsequent significant change to 154/86 mmHg at 5 years. Over 5 years, the mean blood pressures in those allocated to tight and less tight groups were 143/82 and 154/88 mmHg, respectively ($p < 0.0001$). At 5 years, a significant blood pressure difference (13 mmHg systolic and 6 mmHg diastolic) between the tight and less tight control group was obtained. The blood pressure values achieved in the atenolol group and in the captopril-treated group over 5 years were similar.

Table 2. Blood pressure (mm Hg) at entry and mean values over 5 years post randomisation according to allocated therapy

	Pre-treatment	Mean over 5 years
Less tight control	160 ± 19/94 ± 10	154 ± 15/88 ± 18
Tight control	160 ± 20/94 ± 10	143 ± 13/82 ± 7
Difference (95 % Cl)	–	11 (9 to 13) [a]/6 (5 to 7)[a]
Captopril	159 ± 20/94 ± 10	142 ± 13/82 ± 7
Atenolol	161 ± 20/94 ± 10	143 ± 13/83 ± 7
Difference (95 % Cl)	–	1 (0 to 4)/1 (0 to 2)

Data are mean ± SD unless stated otherwise
[a] $p < 0.0001$, tight vs less tight control

Therapies. Table 3 shows that at 5 years' follow-up of patients not previously taking blood pressure therapy, 69 % of those allocated beta blockers and 80 % allocated to ACE inhibitors were taking the allocated therapy ($p < 0.02$), whereas in those previously on therapy the relevant proportions were similar being 84 and 77 %, respectively. Figure 3 shows the increasing proportion of patients that required additional therapies each year with, as expected significantly more subjects allocated to tight control requiring one, two, three or more therapies for less tight control at 5 years ($p < 0.0001$). By 2 and 5 years 16 and 25 %,

Table 3. Actual therapies at 5 years and percentage of subjects with blood pressure 150/85 mm Hg according to randomisation group and treatment status before entry into HDS

	Tight control				Less tight control	
	Captopril		Atenolol			
Previous antihypertensive treatment	No	Yes	No	Yes	No	Yes
Blood pressure under 150/85 mm Hg at 5 years (%)	50	46	60	58	25	19
Beta blocker (%)	3	13	69	84	8	10
ACE inhibitor	80	77	3	10	11	16
On maximum dose of allocated therapy (%) (% of those on allocated therapy)	70	78	75	89	NA	NA
On allocated therapy alone (%)	29	13	26	4	52[a]	25[a]
plus one other	33	29	28	44	34[b]	40[b]
plus two others	16	28	14	32	10[c]	24[c]
plus three others	2	7	1	4	4[d]	11[d]
Not on antihypertensive therapy	7	0	12	2	52	25
On diuretics (%)	43	61	36	52	21	35

[a] On no antihypertensive agents; [b] on one agent; [c] on two agents; [d] on three agents or more

Results as percentage of patients allocated
NA, Not allocated

respectively, of those allocated to atenolol were taking three or more drugs and similarly 15 and 26 %, respectively, of those allocated to an ACE inhibitor were taking three or more drugs, compared with 5 and 7 %, respectively, in those allocated to less tight control. Over the first 2 years the increased number of therapies was associated with slightly better blood pressure control, but from 2 years onwards there was no significant change in the blood pressure control. Fewer patients allocated to less tight control required additional therapies, but the same trend for an increasing proportion requiring more therapies was apparent (Fig. 3).

The blood pressure control at 5 years was similar in those who required the allocated therapy or an additional one or two other agents. For those allocated to captopril and atenolol, the mean blood pressures in those taking only the allocated therapy were 138/79 and 137/78 mmHg, respectively; with one additional agent 142/80 and 141/80 mmHg, respectively; and on two or more additional agents 140/80 and 140/80 mmHg, respectively. This indicates that the physicians were heeding the study's control criteria viz, they were aiming for under 150/85 mmHg and adding additional therapies to achieve that aim, irrespective of how many agents the patients were taking.

Side effects. Table 4 shows that those allocated to atenolol had a mean increase in body weight of 2.3 kg compared with 0.5 kg in those allocated to captopril ($p < 0.0001$) and 1.2 kg in those allocated to less tight control. A mean increase in fasting plasma glucose of 1.0 mmol · l^{-1} in those allocated to atenolol, was greater than an increase of 0.7 mmol · l^{-1} with captopril ($p < 0.01$), although a similar trend in haemoglobin A_{1c} was not significantly different. Those allocated to atenolol had a marginally greater increase

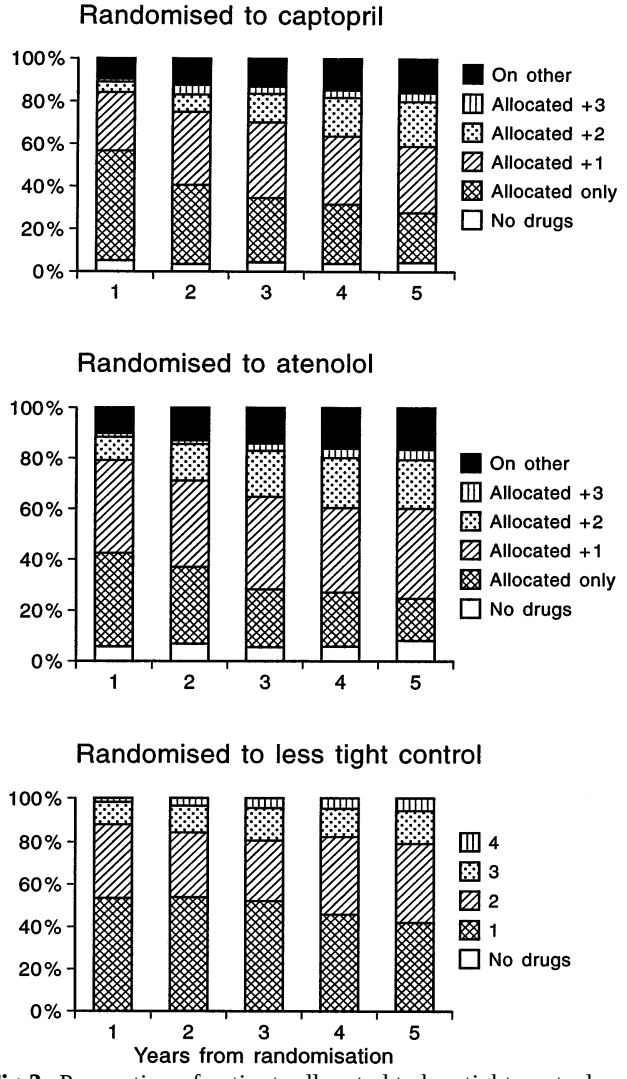

Fig. 3. Proportion of patients allocated to less tight control and tight control with atenolol or captopril taking different numbers of drugs

Table 4. Changes from baseline to mean values over 5 years for body mass index, fasting plasma glucose, triglyceride, LDL and HDL cholesterol in subjects by allocated therapy

	Baseline values			Change from baseline to mean values over 5 years			Repeated measures *p* values adjusting for baseline data	
	Tight control		Less tight control	Tight control		Less tight control		
	Captopril	Atenolol		Captopril	Atenolol		Captopril vs Atenolol	Tight vs less tight
Body weight (kg)	81 ± 16	84 ± 17	81 ± 16	0.5 ± 4.7	2.3 ± 4.8	1.2 ± 4.2	< 0.0001	NS
Fasting plasma glucose (mmol l^{-1})	7.7 ± 2.4	8.0 ± 2.6	8.1 ± 2.7	0.70 ± 2.09	1.02 ± 2.40	0.53 ± 2.41	0.0091	NS
HbA_{1c} (%)	6.7 ± 1.5	6.9 ± 1.6	6.7 ± 1.5	0.69 ± 1.48	0.81 ± 1.28	0.68 ± 1.45	NS (0.066)	NS
Triglyceride (mmol l^{-1})[a]	1.65 (0.98–2.77)	1.67 (0.98–2.83)	1.64 (0.96–2.81)	0.48 ± 0.52	0.51 ± 0.48	0.50 ± 0.51	0.044	NS
HDL cholesterol (mmol l^{-1})	1.11 ± 0.26	1.11 ± 0.28	1.09 ± 0.25	– 0.20 ± 0.29	– 0.24 ± 0.29	– 0.18 ± 0.27	0.028	NS
LDL cholesterol (mmol l^{-1})	3.62 ± 1.37	3.54 ± 1.64	3.58 ± 1.42	– 0.17 ± 0.86	– 0.24 ± 0.75	– 0.16 ± 0.80	NS	NS

Values are mean ± SD or geometric mean (SD interval)

Table 5. Annual rates of hypoglycaemic episodes over 5 years in subjects who took allocated therapy

Time post randomisation	Any hypoglycaemic episode			Major hypoglycaemic episode		
	Tight control		Less tight control	Tight control		Less tight control
	Captopril	Atenolol		Captropril	Atenolol	
n	247	223	258	247	223	228
1st year	16 %	14 %	17 %	2.5 %	0.5 %	0.8 %
2nd year	19 %	20 %	16 %	0.9 %	1.0 %	0.4 %
3rd year	20 %	23 %	18 %	0	1.0 %	0.8 %
4th year	22 %	25 %	18 %	1.0 %	3.1 %	0.9 %
5th year	24 %	22 %	21 %	0.5 %	1.6 %	1.8 %
Ever over 5 years	38 %	40 %	40 %	4.0 %	4.9 %	3.1 %

No significant differences were found between the randomisation groups either by chi-squared test or Fisher's exact test

in triglyceride and reduction of HDL cholesterol than those allocated to captopril (Table 4).

Table 5 shows there was no significant difference between allocations in the proportion of patients having hypoglycaemic episodes, when analysing those who remained on their allocated therapy. The data analysed on an intention-to-treat basis were similar.

At each visit, patients were asked to report any symptoms. The only difference between tight control and less tight control was 41 and 31 % ($p < 0.01$), respectively who said they had nausea or dyspepsia, with no significant difference between those allocated to captopril and atenolol. No difference was observed for other symptoms including tiredness, depression, or being peripherally cold.

Plasma electrolytes. At 5 years there were no significant differences in plasma electrolytes between therapy allocation (Table 6). Those taking diuretic therapy had lower mean potassium values, with a greater proportion having potassium values under 3.5 mmol · l^{-1}. Those taking captopril had similar potassium values to those taking atenolol, with both therapies being associated with a greater proportion with potassium values over 5.0 mmol · l^{-1}.

Discussion

The study has shown that in NIDDM patients with mild hypertension, improved blood pressure control can be maintained over 5 years. The patients, mean age 62 years, had a mean blood pressure over 5 years of 143/82 mmHg in those allocated to tight control, compared with 154/88 mmHg in those allocated to less tight control. In practice, physicians often accept blood pressure control similar to that observed in the less tight control group. If the study finds that aiming for blood pressure under 150/85 mmHg is clinically advantageous, greater emphasis on improving blood pressure control would be required.

Therapy with atenolol or captopril induced similar blood pressure lowering efficacy, with a similar proportion of patients attaining the required blood pressure control with atenolol or captopril alone, and a similar proportion requiring additional therapies. In those allocated to tight control by 5 years' follow-up, 25 % were requiring three or more different agents. In addition, there was a continuing trend for an increasing proportion of patients requiring additional agents. Thus, as for blood glucose therapy, if improved blood pressure control is shown to be

Table 6. Plasma electrolytes, by allocation and in those taking ACE inhibitor, beta blockers, or diuretics

	n	Sodium (μmol/l)	Potassium (mEq/l)	$K^+ < 3.5$ (%)	$K^+ > 5.0$ (%)	Bicarbonate (mEq/l)
By allocation						
Less tight control	235	140.3 ± 2.8	4.20 ± 0.46	3 %	6 %	26.2 ± 3.7
Captopril	233	140.4 ± 3.2	4.27 ± 0.46	3 %	6 %	26.3 ± 3.4
Atenolol	215	140.3 ± 2.6	4.30 ± 0.42	1 %	6 %	26.2 ± 3.5
By therapy						
Allocated to less tight control	142	140.3 ± 2.9	4.24 ± 0.38	2 %	3 %	26.1 ± 3.3
and taking diuretic	46	140.5 ± 2.4	4.23 ± 0.45	4 %	4 %	26.5 ± 3.6
		NS	NS			
Allocated to captopril						
taking captopril	89	140.1 ± 3.2	4.35 ± 0.45	1 %	8 %	26.1 ± 3.3
and taking diuretic	93	140.7 ± 3.0	4.20 ± 0.44	3 %	4 %	26.7 ± 3.6
		NS	$p < 0.05$			
Allocated to atenolol						
taking atenolol	85	139.5 ± 2.7	4.41 ± 0.41	0 %	8 %	26.2 ± 3.4
and taking diuretic	75	141.0 ± 2.4	4.20 ± 0.43	3 %	4 %	26.3 ± 3.7
		$p < 0.001$	$p < 0.01$			

Data are mean ± SD

beneficial, continued review of whether additional therapy is required will be necessary. The blood pressure control was similar in those allocated to tight control who were taking monotherapy, and one or more additional therapies. This indicates that when the control criteria of aiming for under 150/85 mmHg was set, it was generally feasible for physicians to add additional therapies to meet these criteria.

The proportion of patients experiencing symptoms over 5 years was similar in those allocated to captopril and atenolol. By this time, patients with recognised specific side effects such as cough or cold legs, had been changed to other therapies [22]. The symptom questionnaire showed no continuing unexpected symptoms between allocation to atenolol and captopril, although 41 % of those allocated to tight control reported nausea/dyspepsia compared with 31 % in the less tight control group with no difference between atenolol and captopril therapies. Those allocated to atenolol had a mean 1.8 kg greater increase in weight compared with those allocated to captopril, in keeping with other studies [26]. They also had a greater increase of 0.3 mmol/l plasma triglyceride compared with captopril, confirming the analysis after 2 years' therapy. Whether these aspects of therapy with atenolol will have any associated disadvantages is not known, but prospective studies of therapy of hypertension and angina have shown benefit from beta blocker therapy. These were predominantly with non-selective beta blockers, and it is not known whether similar benefit would be obtained from selective beta blockers [27].

Therapy with ACE inhibitors is known to be associated with increased plasma potassium levels, but there was no difference between those treated with captopril or atenolol. Diuretics are known to decrease the potassium concentrations and this occurred irrespective of other therapies. It is not known whether the minor differences are of clinical significance.

If HDS shows that improved blood pressure control is advantageous, it would mean that more than 50 % of diabetic patients in their sixth decade would require therapy for hypertension and that approximately 25 % of these would use three or more drugs. The study will evaluate whether beta blockers (which are relatively inexpensive) or ACE inhibitor therapy have any specific advantages or disadvantages, both in terms of prevention of major clinical complications and in the progress of subclinical variables assessing the progress of macrovascular or microvascular disease.

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