Risks of Progression of Retinopathy and Vision Loss Related to Tight Blood Pressure Control in Type 2 Diabetes Mellitus

UKPDS 69

*UK Prospective Diabetes Study (UKPDS) Group**

Objective: To determine the relationship between tight blood pressure (BP) control and the different aspects of diabetic retinopathy in patients with type 2 diabetes mellitus (DM).

Setting: Nineteen hospital-based clinics in England, Scotland, and Northern Ireland.

Design: Outcome of retinopathy status assessed by 4-field retinal photography related to allocation within a randomized controlled trial comparing a tight BP control policy aiming for a BP less than 150/85 mm Hg with a less tight BP control policy aiming for a BP less than 180/105 mm Hg.

Subjects: One thousand one hundred forty-eight hypertensive patients with type 2 DM were studied. These patients had type 2 DM for a mean duration of 2.6 years at the inception of the Hypertension in Diabetes Study, had a mean age of 56 years; and had a mean BP of 160/94 mm Hg. Seven hundred fifty-eight patients were allocated to a tight BP control policy with angiotensin-converting enzyme inhibitor or β-blockers as the main therapy; 390 were allocated to a less tight BP control policy.

Main Outcome Measures: Deterioration of retinopathy (≥2-step change on a modified Early Treatment Diabetic Retinopathy Study [ETDRS] final scale), together with end points (photocoagulation, vitreous hemorrhage, and cataract extraction) and analysis of specific lesions (microaneurysms, hard exudates, and cotton-wool spots). Visual acuity was assessed at 3-year intervals using ETDRS logarithm of the minimum angle of resolution charts. Blindness was monitored as an end point with the criterion of Snellen chart assessment at 6/60 or worse.

Results: By 4.5 years after randomization, there was a highly significant difference in microaneurysm count with 23.3% in the tight BP control group and 33.5% in the less tight BP control group having 5 or more microaneurysms (relative risk [RR], 0.70; $P=.003$). The effect continued to 7.5 years (RR, 0.66; $P<.001$). Hard exudates increased from a prevalence of 11.2% to 18.3% at 7.5 years after randomization with fewer lesions found in the tight BP control group (RR, 0.53; $P<.001$). Cotton-wool spots increased in both groups but less so in the tight BP control group which had fewer cotton-wool spots at 7.5 years (RR, 0.53; $P<.001$). A 2-step or more deterioration on the ETDRS scale was significantly different at 4.5 years with fewer people in the tight BP control group progressing 2 steps or more (RR, 0.75; $P=.02$). Patients allocated to tight BP control were less likely to undergo photocoagulation (RR, 0.65; $P=.03$). This difference was driven by a difference in photocoagulation due to maculopathy (RR, 0.58; $P=.02$). The cumulative incidence of the end point of blindness (Snellen visual acuity, ≥6/60) in 1 eye was 18/758 for the tight BP control group compared with 12/390 for less tight BP control group. These equate to absolute risks of 3.1 to 4.1 per 1000 patient-years, respectively ($P=.046$; RR, 0.76; 99% confidence interval, 0.29-1.99). There was no detectable difference in outcome between the 2 randomized therapies of angiotensin-converting enzyme inhibition and β-blockade.

Conclusions: High BP is detrimental to each aspect of diabetic retinopathy; a tight BP control policy reduces the risk of clinical complications from diabetic eye disease.

Arch Ophthalmol. 2004;122:1631-1640

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Group Information: A list of the UKPDS Group as of September 17, 2004, was published in *Lancet*. 1998;352:837-853.
Financial Disclosure: None.

TYPE 2 DIABETES MELLITUS (DM) and hypertension are frequently associated, often within the context of the metabolic syndrome, where obesity and dyslipidemia are prominent. The prevalence of hypertension in type 2 DM may be higher than in the general population. At age 40 years, approximately 32% of the patients with type 2 DM are hypertensive, the proportion increasing to 47% by age 60 years.[1] Hypertension increases risk for the development of

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microvascular disease and the UK Prospective Diabetes Study (UKPDS) Group has documented both the prevalence and the extent to which intervention to reduce blood pressure (BP) reduced the in-

cidence of microvascular end points.[2] The reduction of systolic BP (SBP) by a median 10 mm Hg with diastolic BP (DBP) reduction of 5 mm Hg resulted in a 37% decrease in microvascular disease, and an observational analysis has demonstrated the absence of any threshold of hypertension effect between the SBP limits of 120 and 180 mm Hg.[3] Microvascular disease, for the previous analyses, was a composite of predefined conditions that included photocoagulation, vitreous hemorrhage, and renal disease (plasma creatinine level, >2.8 mg/dL [>250 µmol/L]). We present the specific retinopathy data (distinct from the wider-defined microvascular disease) as assessed by 4-field fundal photography, eye-related end points, and visual acuity.

METHODS

Seven thousand six hundred sixteen patients with newly diagnosed type 2 DM were referred to the 23 hospital recruiting clinics within the United Kingdom between December 8, 1977, and December 31, 1991. Exclusion criteria have previously been published.[4] Of the patients referred, 5102, who had fasting plasma glucose values greater than 108 mg/dL (>6.0 mmol/L) on 2 separate mornings and who fulfilled all other inclusion criteria, were recruited. Those with malignant hypertension and those with preexisting retinopathy needing laser treatment were excluded. The study conformed to the guidelines of the Declarations of Helsinki (1975 and 1983). All patients gave informed consent. The study received institutional review board approval from the Central Oxford Ethics Committee, Oxford, England.

In 1987, a BP control study was introduced in a factorial manner with the glucose control study.[4] One thousand one hundred forty-eight hypertensive patients with type 2 DM were studied. These patients had type 2 DM for a mean duration of 2.6 years and an SBP greater than 160 mm Hg and/or a DBP greater than 90 mm Hg (if not receiving treatment for hypertension) or an SBP greater than 150 mm Hg and/or a DBP greater than 85 mm Hg (if already receiving treatment for hypertension) were randomly allocated between a less tight BP control policy, aiming for an SBP less than 180 mm Hg and a DBP less than 105 mm Hg, and a tight BP control policy, with a random allocation to either an angiotensin-converting enzyme (ACE) inhibitor or a β-blocker, aiming for an SBP less than 150 and a DBP less than 85 mm Hg.

Within the UKPDS glucose control study, patients were treated by diet alone for 3 months. Patients who remained hyperglycemic (fasting plasma glucose level, 110-270 mg/dL [6.1-15.0 mmol/L]) in the absence of diabetic symptoms were randomized to a conventional blood glucose control policy, primarily with diet or to an intensive policy (aiming for a fasting plasma glucose level <108 mg/dL [<6.0 mmol/L]) with either additional sulfonylurea, insulin, or metformin therapy.

Of 20 UKPDS centers included in the Hypertension in Diabetes Study, 19 took retinal photographs. Of the 4297 patients recruited, 243 had either died or were lost to follow-up prior to its start in 1987. Of the remaining 4054 patients, 1544 (38%) had hypertension, defined in patients not receiving antihypertensive therapy who had an SBP of 160 mm Hg or higher and/or a DBP of 90 mm Hg or higher or in patients receiving antihypertensive therapy as an SBP of 150 mm Hg or higher and/or a DBP of 85 mm Hg or higher. Patients were enrolled on the basis of the mean of 3 BP measurements taken at consecutive clinic visits. Of the 1544 hypertensive patients, 252 were excluded and 144 patients did not enroll in the study. A total of 1148 patients (54% male), mean (SD) age of 56.4 (8.1) years were randomized; 727 had no previous therapy and 421 were previously treated for hypertension.

TREATMENT PROTOCOL

Two thirds of the patients (n=758) were randomized to a tight BP control policy, aiming for BP less than 150/85 mm Hg (with 400 patients allocated to an ACE inhibitor, captopril, and 358 to a β-blocker, atenolol, as the main therapy) and one third of the patients (n=390) were randomized to a less tight BP control policy, aiming for BP of 180/105 mm Hg or less but avoiding therapy with ACE inhibitors or β-blockers. The randomization was stratified for those with or without previous therapy for hypertension. The original allowable upper limit of 200/105 mm Hg in the less tight BP control group was reduced to 185/105 mm Hg in 1992 by the steering committee following publication of the results of studies of elderly, nondiabetic subjects in the years 1991-1992.[5-7]

Captopril therapy was usually started at a dose of 25 mg twice daily increasing to 50 mg twice daily. Atenolol therapy was usually started at a daily dose of 50 mg increasing to 100 mg, if required. If control criteria were not met in the tight BP control group despite maximum allocated therapy or, in the less tight BP control group without drug therapy, other 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) thrice daily. Patients were seen at 3- to 4-monthly clinic visits.

BP MEASUREMENTS

Sitting BP (diastolic phase 5) was measured by a trained nurse, after at least 5-minutes rest, with an electronic, auscultatory blood pressure reading machine (Copal UA-251 or a Takeda UA-751; Andrew Stephens Co, Brighouse, England) or with a random zero sphygmomanometer (Hawksley & Sons Ltd, Sussex, England) in patients with atrial fibrillation. The first reading was discarded and the mean of the next 3 consecutive readings with a coefficient of variation below 15% was used in the study, with additional readings, if required. Monthly quality assurance measurements showed the mean (SD) difference between the Takeda and Hawksley machines to be 1(4) mm Hg or less. Doppler BP readings were taken every 3 years.

RETINOPATHY ASSESSMENT

At enrollment to the UKPDS and subsequently every 3 years thereafter, patients underwent a clinical examination that included retinal color photography, ophthalmoscopy by a diabetologist clinician or an ophthalmologist, and recording of visual acuity. Annual direct ophthalmoscopy was also carried out and a checklist for clinical events completed. Visual acuity was measured using Snellen charts until 1989 and subsequently with ETDRS logarithm of the minimum angle of resolution (logMAR) charts with best-corrected vision, current refraction, or through a pinhole. Retinal color photographs of 4 standard 30° fields per eye (temporal to macular, macular, disc, and nasal fields) were taken in duplicate or with stereopsis, with additional stereophotographs of the macula. A second photograph was taken if the quality of the photograph was unsatisfactory. Retinal photographs were masked to avoid any patient identification prior to being assessed at a central grading center. Assessment involved an initial review by 2 independent assessors for image quality, adherence to proto-

Table 1. Grading System

Level	Severity	Definition
10	DR absent	All diabetic retinopathy features absent
20	MA only	MA(s) only, other lesions absent
35	Mild NPDR	MA plus retinal hemorrhage(s) and/or HEs and/or CWSs
43	Moderate NPDR	Lesions as above and either extensive or severe HMAs or IRMAs present
47	Moderately severe NPDR	Lesions of 35 and either extensive or severe HMAs with IRMAs or venous beading
53	Severe NPDR	Extensive and severe HMAs, IRMAs, and/or venous beading
61, 65, 71, 75, 81	Proliferative DR	NVD and/or NVE without or with complications

Abbreviations: CWSs, cotton-wool spots; DR, diabetic retinopathy; HEs, hard exudates; HMAs, hemorrhages and microaneurysms; IRMAs, intraretinal microvascular abnormalities; MA, microaneurysm; NPDR, nonproliferative diabetic retinopathy; NVD, new vessels on the optic disc; NVE, new vessels elsewhere.

col, and the presence or absence of diabetic retinopathy. Any eyes with retinopathy were then graded by 2 independent senior assessors (one of whom was S.J.A.). Retinopathy lesions were assessed against corresponding Early Treatment Diabetic Retinopathy Study (ETDRS) standard photographs or measurements,[8] following which a computerized algorithm allocated a retinopathy severity score to the eye using a modified version of the ETDRS final scale. The ETDRS final scale, together with a description of their clinical features, is given in **Table 1**. Differences in opinion between assessors at any stage were managed by independent adjudication. The numeric scale was then used to derive a worse eye/better eye score.[8] Microaneurysms (MAs) were counted in each eye, avoiding overlapping fields, and summated.

Randomization into the hypertension study was not tied to annual or triennial visits of the UKPDS. To form the baseline data set, we used the retinal photograph taken up to 3 years prior to hypertension randomization. We then report intervals of 1.5, 4.5, and 7.5 years—the median interval from randomization for the subsequent photographs.

CLINICAL END POINTS AND PHOTOGRAPHS

Retinopathy requiring photocoagulation or vitreous hemorrhage were independently assessed and recorded throughout the study. These data were used to augment the photographic evidence. The reasons for visual loss were not prospectively collected in the UKPDS data set and were assessed from ophthalmic notes, where available, retrospectively.

STATISTICAL ANALYSIS

All analyses were calculated on an intention-to-treat basis, comparing patients allocated to tight or less tight BP control policy. Change in diabetic retinopathy was defined in the protocol as a 2-step or greater change in ETDRS grading (both eyes 1 step or 1 eye ≥2 steps) with a worse eye/better eye scale including retinal photocoagulation or vitreous hemorrhage as the most serious grade.[9] We present a 3-step change for purposes of comparability with the Diabetes Control and Complications Trial.[10]

Table 2. Comparison of Snellen and ETDRS LogMAR Scales

Visual Acuity (Snellen, Corrected, Pinhole, or Own Eyeglasses)	ETDRS LogMAR Equivalent
6/5	–0.1
6/6	0.0
6/9	0.2
6/12	0.3
6/18	0.5
6/24	0.6
6/36	0.8
6/60	1.0
>6/60 or blind	1.1

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; LogMAR, logarithm of the minimum angle of resolution.

Visual loss was defined as the best vision in either eye, deteriorating by 3 lines on the ETDRS chart (**Table 2**).

Survival function estimates were calculated using the product-limit (Kaplan-Meier) method with log rank tests and hazard ratios (relative risks [RRs]) were obtained from Cox proportional hazards models. All statistically significance tests were 2-sided; 99% confidence intervals (CIs) are used for assessment of surrogate end points that were measured at triennial visits. Since these visits were synchronized with the fasting plasma glucose control study and not the BP study, the results were grouped in 3-year intervals and expressed as 1.5, 4.5, and 7.5 years from randomization. Mean (SD), geometric mean (1-SD interval), or median (IQ range) have been quoted for the biometric and biochemical variables, with Wilcoxon, t, or χ^2 tests for comparison tests. The overall values for BP during a period were assessed for each patient as the mean during that period and for each allocation as the mean of patients with data in the allocation. Blood pressure control was assessed in the cohort of patients allocated to tight and less tight BP control policies who had data at 9 years' follow-up.

RESULTS

FOLLOW-UP

The median time from randomization date to the end of the trial was 9.3 years. The median follow-up to death, the last known date at which vital status was known, or to the end of the trial was 8.4 years. The vital status was known at the end of the trial in all patients except 14 patients (1%) who had emigrated and a further 33 patients (3%) who could not be contacted in the last year of the study for assessment of clinical end point status.

BP CONTROL

The mean (SD) BP in the 1148 patients at randomization to tight and less tight BP control groups was similar.[2] The mean (SD) cohort BP during the study over 9 years follow-up was 144 (14)/82 (7) mm Hg (n=297) for the tight BP control group and 154 (16)/87 (7) mm Hg (n=156) for the less tight BP group (each $P<.001$). The mean (98% CI) SBP and DBP differences were 10 (9-12) mm Hg for the tight BP control group and 5 (4-6) mm Hg for the less tight BP group.

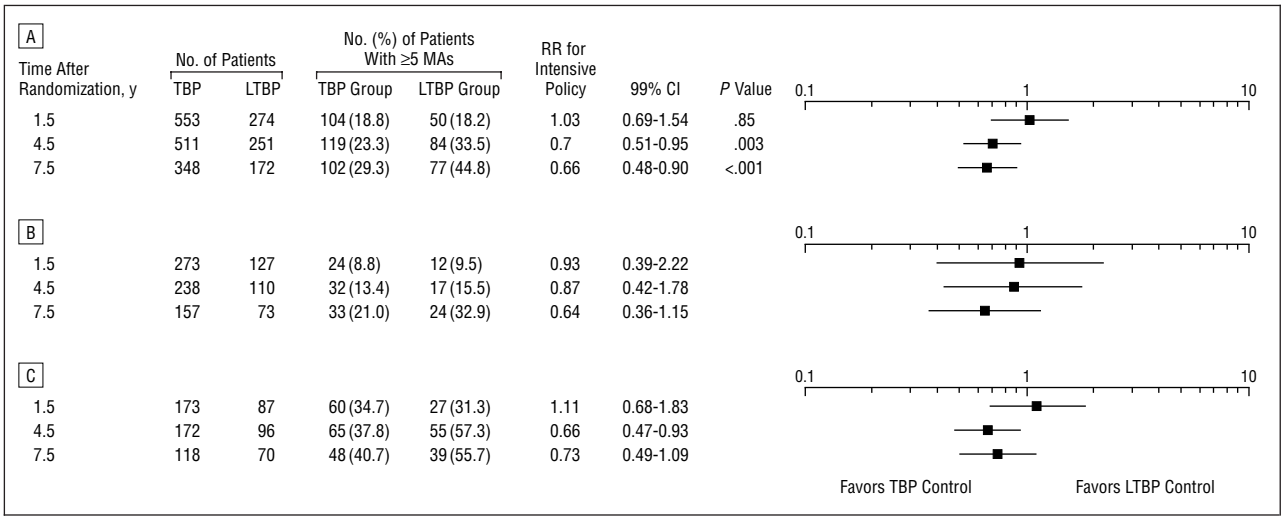

Figure 1. Relative risk (RR) of 5 or more microaneurysms (MAs) in those randomized to the tight (TBP) and less tight blood pressure (LTBP) control groups. A, Overall randomization. B, Those with no retinopathy at randomization. C, Those with any type of retinopathy at randomization. CI indicates confidence interval.

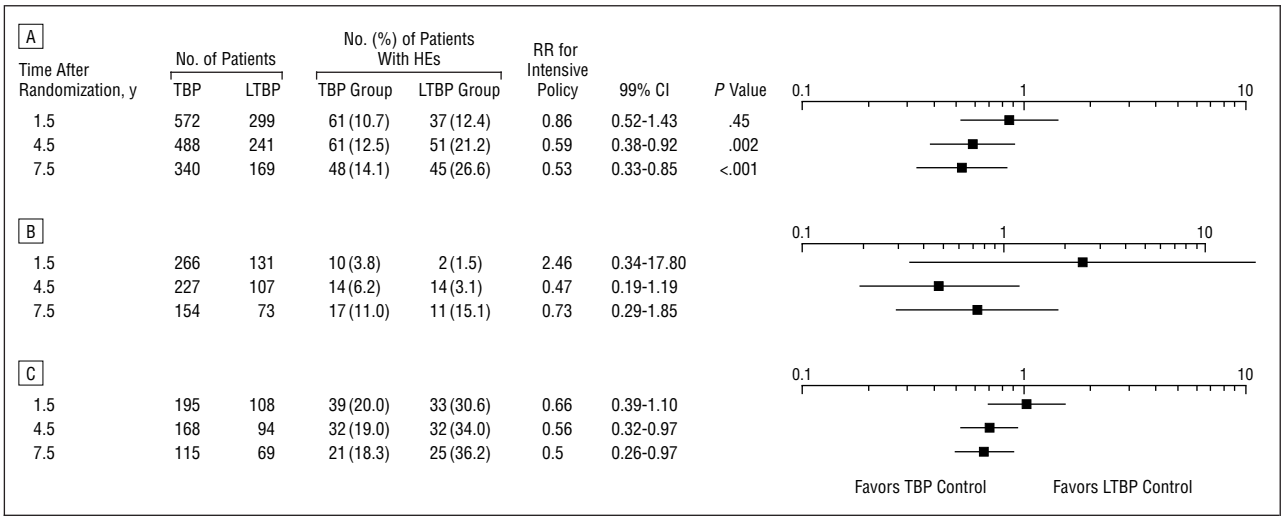

Figure 2. Relative risk (RR) of hard exudates (HEs) in those randomized to the tight (TBP) and less tight blood pressure (LTBP) control groups. A, Overall randomization. B, Those with no retinopathy at randomization. C, Those with any type of retinopathy at randomization. CI indicates confidence interval.

BLOOD GLUCOSE LEVEL CONTROL

The mean glycosylated hemoglobin level A_{1c} over years 1 through 4 was 7.2% in both groups and over years 5 through 8 was 8.3% and 8.2% in the tight and less tight BP groups, respectively.

PROGRESS OF RETINOPATHY ASSESSED BY SPECIFIC LESIONS

Microaneurysms

The RRs of 5 or more MAs in total (counting lesions in both eyes) in the tight vs less tight BP control groups are shown in **Figure 1**. By 4.5 years after randomization there was a highly significant effect with 23.3% in the tight control BP group and 33.5% in the less tight BP group having met this criterion (RR, 0.70; $P=.003$). The effect persisted to 7.5 years (RR, 0.66; $P<.001$). When the data were divided into those with no lesions at randomization (primary prevention, **Figure 2**B) and those with some detectable lesions (secondary prevention, Figure 2C), the effects were still seen at 7.5 years for both groups (RR, 0.64; $P=.053$, and RR, 0.73; $P=.046$), respectively. Comparing captopril with atenolol therapy, there was no difference in the effect observed within the tightly controlled BP group. Nor was there a detectable difference in the trend with time between the agents at 4.5 or 7.5 years.

Hard Exudates

Hard exudates increased with time in the study, from a prevalence of 11.2% to 18.3% at 7.5 years after randomization. There were significant differences between the tight and less tight BP control groups, with fewer lesions found in the tight control BP group (RR, 0.59; $P<.002$ and RR, 0.53; $P<.001$ at 4.5 and 7.5 years, respectively) Figure 2A.

When data from these patients were divided into those having no lesions at randomization (primary prevention,

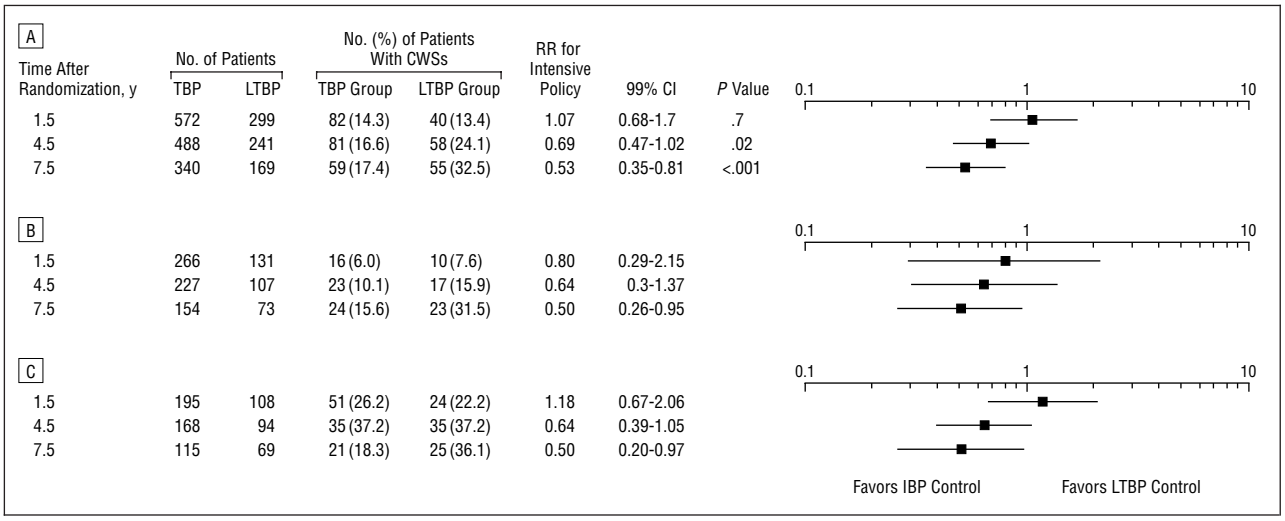

Figure 3. Relative risk (RR) of at least 1 cotton-wool spot (CWS) in those randomized to the tight (TBP) and less tight blood pressure (LTBP) control groups. A, Overall randomization. B, Those with no retinopathy at randomization. C, Those with any type of retinopathy at randomization. CI indicates confidence interval.

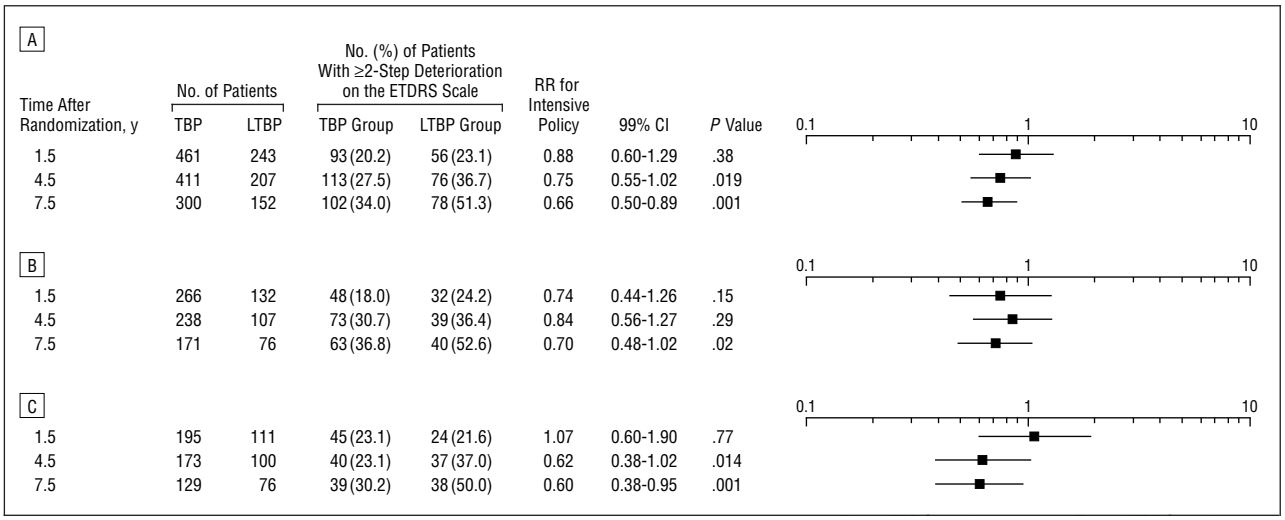

Figure 4. Relative risk (RR) of 2-step or worse deterioration on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale in those randomized to the tight (TBP) and less tight blood pressure (LTBP) control groups. A, Overall randomization. B, Those with no retinopathy at randomization. C, Those with any type of retinopathy at randomization. CI indicates confidence interval.

Figure 2B) and those having some detectable lesions (secondary prevention, Figure 2C), the effects were still seen at 7.5 years for both groups. There was no difference in the observed effect within the tightly controlled BP group between captopril and atenolol therapy for hard exudates.

Cotton-wool Spots

Cotton-wool spots increased throughout the trial, from an overall prevalence of 14.0% at 1.5 years to 22.4% at 7.5 years. There was a highly significant difference between the groups with the tight control BP group having fewer CWSs at 4.5 and 7.5 years (RR, 0.69, $P=.02$ and RR, 0.53; $P<.001$, respectively) (**Figure 3**). These differences between the tight and less tight BP control groups were demonstrable for both primary and secondary prevention (**Figure 4**B and C). An examination of those in the tight control BP group alone, allocated to atenolol or captopril therapy, revealed no differences between these therapies overall, nor were any detectable in either primary or secondary prevention groups.

RETINOPATHY PROGRESSION BY ETDRS GRADING

Two-step or more deterioration on the ETDRS scale was significantly different at 4.5 years with fewer people in the tight control BP group progressing 2 steps or more (RR, 0.75; $P=.02$) to retinopathy and was more marked at 7.5 years (RR, 0.66; $P<.001$, Figure 4). The effects were similar irrespective of the retinopathy status (no retinopathy or any) at enrollment in the study (Figure 4B and C). Three-step deterioration was concordant with the 2-step changes (at 4.5 years RR, 0.76; $P=.06$; at 7.5 years RR, 0.61; $P<.001$). More than one third of those in the tight BP control group did not change, whereas only one fifth in the less tight BP control group remained at the same level, the differences being attributable to worsening retinopathy.

Retinal Photocoagulation	No. of Patients TBP (n=758)	No. of Patients LTBP (n=390)	Absolute Risk, Events per 1000 Patient-years TBP Group	Absolute Risk, Events per 1000 Patient-years LTBP Group	RR for Intensive Policy	99% CI	*P* Value
Overall	61	47	11.0	17.0	0.63	0.39-1.07	.03
Due to retinopathy	7	3	1.3	1.1	1.17	0.20-6.90	.82
Due to maculopathy	42	36	7.6	13.0	0.58	0.32-1.04	.02
Due to both	5	3	0.9	1.1	0.83	0.13-5.43	.80
Unknown	7	5	1.3	1.8	0.70	0.16-3.17	.54

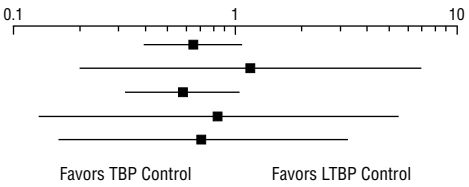

Figure 5. Relative risk (RR) of retinal photocoagulation in those randomized to the tight (TBP) and less tight blood pressure (LTBP) control groups. CI indicates confidence interval.

Table 3. Prevalence of Blindness and Assessed Causes in Those Randomized to Tight and Less Tight Blood Pressure Control Groups

Cause of Blindness	No. of Events TBP Group (n = 18)	No. of Events LTBP Group (n = 12)	Absolute Risk, Events per 1000 Patient-years TBP Group	Absolute Risk, Events per 1000 Patient-years LTBP Group	RR for Intensive Policy	99% CI	*P* Value
Total No.	**758**	**390**	3.1	4.1	0.76	0.29-1.99	.46
Cataract	2	2	0	0	0	0	0
Diabetic maculopathy	6	1	0	0	0	0	0
Laser therapy	0	1	0	0	0	0	0
Vitreous hemorrhage	0	1	0	0	0	0	0
Retinal traction or detachment	1	2	0	0	0	0	0
Nondiabetic maculopathy	0	1	0	0	0	0	0
Accident or amblyopia	0	0	0	0	0	0	0
Retinal vein occlusion	2	1	0	0	0	0	0
Unknown	7	3	0	0	0	0	0

Abbreviations: CI, confidence interval; LTBP, less tight blood pressure control; RR, relative risk; TBP, tight blood pressure control.

In particular, twice as many subjects in the less tight BP control group changed by 10 steps or more.

OCULAR END POINTS IN THE TRIAL

Photocoagulation

The effect of the tight BP control group with antihypertensive treatment compared with less tight control BP group on the occurrence of photocoagulation is shown in **Figure 5**. There were many more events relating to the occurrence of photocoagulation with maculopathy than with the development of proliferative retinopathy (78 vs 10, respectively; 12 unknown).

Patients allocated to the tight BP control group were less likely to undergo photocoagulation (RR, 0.65; $P=.03$) (Figure 5). This difference was driven by a difference in photocoagulation due to maculopathy (RR, 0.58; $P=.02$). There were no statistically significant treatment differences between ACE inhibitor and β-blockade.

Vitreous Hemorrhage

Five patients had a vitreous hemorrhage: 3 in the tight BP control group and 2 in the less tight BP control group. Clearly these were too few events to analyze.

Cataract Extraction

Thirty-six patients in the tight BP control group and 14 patients in the less tight BP control group had cataract extractions. There was no difference in the event rates or in the incidence rate in the captopril- and atenolol-treated groups.

VISION LOSS

Blindness in 1 Eye

The cumulative incidence of the end point of blindness (Snellen visual acuity, ≥6/60) in 1 eye was 18/758 for the tight BP control group compared with 12/390 for less tight BP control group (**Table 3**). These equate to absolute risks of 3.1 to 4.1 per 1000 patient-years, respectively ($P=.046$; RR, 0.76; 98% CI, 0.29-1.99). Of the recorded blindness 4 events were due to cataract, 7 by diabetic maculopathy, 9 by other causes, and for 10 the reason was unknown. No patient became blind in both eyes. There was no detectable effect of therapy allocation between ACE inhibitor and β-blocker.

LogMAR Score Changes

The incidence, in either eye, of a deterioration of 0.3 on the logMAR chart (approximately equivalent to 3 lines on a Snellen visual acuity chart) is shown in **Figure 6** for 3, 6, and 9 years (**Table 4**). The cumulative risk for such a change over 9 years was RR, 0.63; (98% CI, 042-0.92, $P=.002$). The tight BP control group compared with the less tight BP control group had a 47% lower

Retinopathy Status at Baseline	Cohort	No. of Patients in TBP Group	>0.3 Deterioration in LogMAR, No. (%) of Patients		No. of Patients in LTBP Group	RR for Intensive Policy	99% CI	*P* Value
			TBP	LTBP				
Unknown	0-3 y	116	15 (12.9)	8 (13.1)	61			
Unknown	0-6 y	103	16 (15.5)	11 (20.8)	53			
Unknown	0-9 y	73	13 (17.8)	9 (23.7)	38			
None	0-3 y	269	29 (10.8)	18 (14.1)	128	0.77	0.37-1.58	.34
None	0-6 y	238	34 (14.3)	19 (16.7)	114	0.86	0.37-1.86	.56
None	0-9 y	144	32 (22.2)	22 (29.7)	74	0.75	0.41-1.38	.22
Some	0-3 y	190	28 (14.7)	19 (18.3)	104	0.81	0.40-1.62	.43
Some	0-6 y	182	35 (19.2)	20 (22.2)	90	0.87	0.46-1.64	.56
Some	0-9 y	115	23 (20.0)	28 (41.2)	68	0.49	0.26-0.89	.002
Total	0-3 y	575	72 (12.5)	45 (15.4)	293	0.82	0.52-1.28	.25
Total	0-6 y	523	85 (16.3)	50 (19.5)	257	0.84	0.55-1.27	.27
Total	0-9 y	332	68 (20.5)	59 (32.8)	180	0.63	0.42-0.92	.002

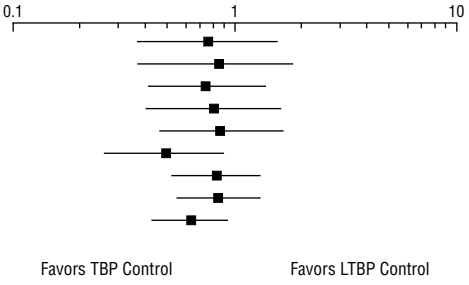

Figure 6. Relative risk (RR) of 3 lines or more of deterioration in either eye in those randomized to the tight (TBP) and less tight blood pressure (LTBP) control groups. CI indicates confidence interval.

Table 4. Proportion of Patients With Reduced Vision Assessed by Better Eye in Those Randomized to Tight and Less Tight Blood Pressure Control Groups

Cohort	TBP Group			LTBP Group				*P* Value
	No. of Patients	No. With LogMAR >0.3	%	No. of Patients	No. With LogMAR >0.3	%	RR for Intensive Policy (99% CI)	
At enrollment	664	11	1.7	339	6	1.8	0.94 (0.26-3.42)	.90
At 3 y	623	27	4.3	319	7	2.2	1.98 (0.67-5.80)	.10
At 6 y	577	37	6.4	287	17	5.9	1.08 (0.52-2.25)	.78
At 9 y	369	31	8.4	199	23	11.6	0.73 (0.37-1.42)	.22

Abbreviations: CI, confidence interval; logMAR, logarithm of the minimum angle of resolution; LTBP, less tight blood pressure control; RR, relative risk; TBP, tight blood pressure control.

risk of a deterioration in visual acuity by 3 or more lines ($P=.004$) on a Snellen visual acuity chart. For 2-line deterioration we found no significant changes.

Considering visual loss (visual acuity worse than logMAR 0.3 assessed in the better eye), the proportion of patients in the tight BP control group was 1.7% at enrollment increasing to 8.4% at 9 years. This compared with a proportion in the less tight BP control group of 1.8% at enrollment increasing to 11.6% at 9 years.

COMMENT

The UKPDS groups have previously reported that intensive treatment of the fasting plasma glucose level and tight control of BP reduces the progression of microvascular complications in DM.[2,11-13] The overall median difference in BP between the 2 intervention arms was 10 mm Hg SBP and 5 mm Hg DBP. Photocoagulation used for sight-threatening retinopathy, diabetic macular edema, and proliferative retinopathy was reduced by 37% in the tightly controlled BP group.[2] The UKPDS was the longest and most detailed clinical trial of newly diagnosed type 2 DM to date. This cohort can be regarded as being representative of the United Kingdom as a whole, but there are caveats that apply. These include the fact that there were few nonwhites in the study, and that the eldest subjects were 65 years of age at recruitment. The subjects were cared for in a routine way with 3-month follow-up visits with physicians and nurses, and this may not always reflect the care package elsewhere.

In this article we analyze the specific features and changes in retinopathy and ocular complications in those patients who participated in the hypertension control study. Each feature and end point of diabetic retinopathy was favorably affected by tight control of BP and this was further demonstrated by the aggregate measurement of reduction of 2- and 3-step changes in retinopathy severity, using the ETDRS grading system.

The overall magnitude of the favorable effect of BP control on retinopathy progression is greater than has previously been described. For example in the Wisconsin Epidemiologic Study of Diabetic Retinopathy cross-sectional study, Klein et al[14] found that while high BP was important, it had no effect on the incidence and progression of retinopathy over a 4-year follow-up, although DBP was higher after 10 years in those in whom macular edema developed.[15] However, the study by Klein et al was a cohort study rather than a clinical trial and had no specified intervention; there was no systematic attempt to optimize BP control. Furthermore, in the Klein et al study, mortality was high, so the results are only those of the survivor population; patients who died had higher BPs than those who survived.[16] In our study, we have censored data to avoid bias by survival.

Two other clinical trials have looked at BP control in subjects with type 2 DM. In the Appropriate Blood

Pressure Control in Diabetes (ABCD) Trial the subjects were stratified on the basis of their DBP at baseline, into a trial of hypertensive subjects with a DBP of 90 mm Hg or higher (n=470)[17] and a trial of normotensive subjects (n=480).[18] Within each study subjects were randomized to either intensive or moderate control. In the hypertensive trial the mean BP achieved was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate group. Over the follow-up period in the hypertensive trial, there was no difference observed in the progression of diabetic retinopathy between the intensive and moderate control groups. However, in the normotensive trial, where the mean BP in the intensive group over the follow-up period was 128/75 mm Hg in the intensive group and 137/81 in the moderate group, there was less progression in the intensive group (34 vs 46%, $P=.02$). This differential effect may have been seen because hypertension seems to be more important in initiating diabetic retinopathy than in influencing progression,[19] and a higher proportion of those in the normotensive ABCD trial had no retinopathy at baseline than those in the hypertensive study. Within the Steno-2 Study[20] 160 subjects with type 2 DM and microalbuminuria were randomly assigned to either conventional treatment in accord with national guidelines or to intensive treatment with stepwise implementation of behavior modification and pharmacologic therapy that included targets for hypertension. The intensive group achieved a significant greater decline in SBP and DBP, and a lower risk of progression of retinopathy (hazard ratio, 0.42; 95%CI, 0.17-0.87).

RETINOPATHY FEATURES

Microaneurysms

The earliest clinically recognizable lesions in diabetic retinopathy are MAs, and the significance of MA counts in the risk for progression has been previously reported .[21] Herein we report that at randomization 18.8% and 18.2% of the tight BP and less tight BP control groups, respectively, had 5 or more MAs. By 7.5 years this increased to 29.3% and 44.8%, respectively, representing a 34% risk reduction. This is likely to be of real clinical importance. At 7.5 years median follow-up from randomization to tight BP control, 44% of patients had no retinopathy—that is, not even a single MA—compared with 27% retinopathy free in the less tightly controlled BP group. Thus, tight BP control was delaying the onset of tissue damage in this group, and this is concordant with the epidemiological analysis reported previously.[19]

Hard Exudates

In DM hard exudates often appear early in the natural history of the disease. Hard exudates have been reported in grade 3 and grade 4 hypertensive retinopathy, when a macular star indicates receding edema in treated hypertension.[22] The proportion of patients with hard exudate 7.5 years after randomization in the tight control BP group was almost half that observed in the less tight control BP group (14.1% vs 26.6%, respectively). Hard exudates, as a consequence of capillary leakage, would be increased by the higher intravascular pressure in those with less tight BP control. In this analysis we did not specify the location of the hard exudates but their importance in the vicinity of the center of the macula was emphasized by the ETDRS definition of clinically significant macular edema.[23] Eighty-six (80%) of 108 photocoagulation episodes were undertaken because of maculopathy alone or in combination with proliferative retinopathy. There was no difference between the risk reduction shown in those with no or those with any retinopathy at study enrollment.

CWSs (Soft Exudates)

Cotton-wool spots (soft exudates) usually indicate occlusion of small arterioles and are a well-known feature of hypertensive retinopathy. In DM, vascular occlusion occurs even in the absence of hypertension, and multiple CWSs have been found to indicate rapidly advancing retinopathy.[24] The importance of CWSs as a feature of severe nonproliferative retinopathy and their use as a predictor of proliferative lesions was questioned by the ETDRS.[7] In our study a higher proportion of the less tightly controlled BP patients had CWSs at 4.5 and 7.5 years than the tightly controlled BP group, suggesting that these lesions were related to the level of BP.

Comparison of Captopril and Atenolol Therapy

There was no evidence of differences in rates of progression of those retinal lesions that we have analyzed between those allocated to captopril or to atenolol therapy. Some have claimed that slowing of retinopathy progression would be optimized by the use of ACE inhibitors,[25] but these data suggest that it is reduction in BP per se that is the crucial intervention.

END POINTS

Photocoagulation

As expected, in type 2 DM, maculopathy was the most common reason for photocoagulation. Although macular edema has sometimes been thought not to be preventable, we, nevertheless, have demonstrated herein that there was a 42% reduction in those in the tight control BP group. Concordant with these data on ETDRS step changes and individual features, we did not find any difference between the 2 policies of BP control, emphasizing that it is tight BP control that is more important than the pharmacological agent.

Visual Loss

No patient became blind in both eyes. Blindness in 1 eye only occurred in 30 eyes—a small number that might be expected in a group of patients even under close clinical monitoring. However, other visual loss is also important. Losing 3 lines in visual acuity is an important event and would mean that one with initially normal vision

would have difficulty with small print or figures, and someone with even slightly reduced vision initially would have significant problems. The proportion of patients who lost this degree of visual acuity was significantly higher in the less tight BP control group compared with the tightly controlled BP group.

WHY IS HIGH BP DETRIMENTAL TO DIABETIC RETINOPATHY?

The question arises as to why high BP is so detrimental to the progression of diabetic retinopathy. The retina has no functioning sympathetic nerve fibers, so that the control of blood flow is entirely by autoregulation. The normal autoregulatory response to high BP is vasoconstriction, tending to keep blood flow constant. However, in patients with poorly controlled DM and retinopathy, blood flow is increased[26] and this counteracts the normal vasoconstrictive effect of raised BP. Furthermore, in long-standing DM, autoregulation is impaired.[27] High BP, therefore, increases blood flow and, thus, by increasing shear stress will damage vessel walls and will precipitate and worsen retinopathy. Rassam et al[28] found that to normalize autoregulatory function of the retinal vessels, both BP and blood glucose level had to be controlled. This is also apparent in the observational studies within the UKPDS relating to microvascular disease generally.[3] We have also demonstrated that tight control of BP is important for both primary and secondary prevention of diabetic retinopathy.

CONCLUSION

High BP is detrimental to each aspect of diabetic retinopathy and a tight BP control policy reduces the risk of clinical complications from diabetic eye disease.

Submitted for Publication: July 1, 2003; final revision received July 22, 2004; accepted July 22, 2004.
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Funding/Support: This study was supported in part by major grants from the United Kingdom (UK) Medical Research Council, London, England; British Diabetic Association; the UK Department of Health, London; National Eye Institute, National Institute of Digestive, Diabetes, and Kidney Disease in the National Institutes of Health, Bethesda, Md; the British Heart Foundation, London; Novo-Nordisk A/S, Copenhagen, Denmark; Bayer (Schweiz) AG, Zurich, Switzerland; Bristol-Myers Squibb, New York, NY; Hoechst AG, Kehl, Germany; Eli Lilly & Co, Indianapolis, Ind; Lipha and Farmitalia Carlo Erba, Milan, Italy. Other funding companies and agencies, the supervising committees and all participating staff are acknowledged in an earlier paper.[13]
Acknowledgment: We acknowledge the help of Hung Cheng, FRCS, and Carol Hill in the preparation of this manuscript. The cooperation of the patients and many National Health System and non-National Health System staff at the centers is much appreciated.

The Participating UK Centers are: Radcliffe Infirmary, Oxford, England; Royal Infirmary, Aberdeen, Scotland; University Hospital, Birmingham, England; St George's Hospital, ; Hammersmith Hospital, Hammersmith, England; and Whittington Hospital, London, England; City Hospital and Royal Victoria Hospital, Belfast, Northern Ireland; North Staffordshire Royal Infirmary, Stoke-on-Trent, England; St Helier Hospital, Carshalton, England; Norfolk and Norwich Hospital, Norwich, England; Lister Hospital, Stevenage, England; Ipswich Hospital, Ipswich, England; Ninewells Hospital, Dundee, Scotland; Northampton General Hospital, Northampton, England; Torbay Hospital, Torbay, England; Peterborough General Hospital, Peterborough England; Scarborough Hospital, Scarborough, England; Derbyshire Royal Infirmary, Derby, England; Manchester Royal Infirmary, Manchester, England; Hope Hospital, Salford, England; Leicester General Hospital, Leicester, England; Royal Exeter and Devon Hospital, Exeter, England.

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