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Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study

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Abstract

Objective To determine the relation between systolic blood pressure over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes.

Design Prospective observational study.

Setting 23 hospital based clinics in England, Scotland, and Northern Ireland.

Participants 4801 white, Asian Indian, and Afro-Caribbean UKPDS patients, whether randomised or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk.

Outcome measures Primary predefined aggregate clinical outcomes: any complications or deaths related to diabetes and all cause mortality. Secondary aggregate outcomes: myocardial infarction, stroke, lower extremity amputation (including death from peripheral vascular disease), and microvascular disease (predominantly retinal photocoagulation). Single end points: non-fatal heart failure and cataract extraction. Risk reduction associated with a 10 mm Hg decrease in updated mean systolic blood pressure adjusted for specific confounders

Results The incidence of clinical complications was significantly associated with systolic blood pressure, except for cataract extraction. Each 10 mm Hg decrease in updated mean systolic blood pressure was associated with reductions in risk of 12% for any complication related to diabetes (95% confidence interval 10% to 14%, $P < 0.0001$), 15% for deaths related to diabetes (12% to 18%, $P < 0.0001$), 11% for myocardial infarction (7% to 14%, $P < 0.0001$), and 13% for microvascular complications (10% to 16%, $P < 0.0001$). No threshold of risk was observed for any end point.

Conclusions In patients with type 2 diabetes the risk of diabetic complications was strongly associated with raised blood pressure. Any reduction in blood pressure is likely to reduce the risk of complications, with the lowest risk being in those with systolic blood pressure less than 120 mm Hg.

Introduction

The UK prospective diabetes study (UKPDS) has shown that a policy of tight control of blood pressure, which achieved a median blood pressure of 144/82 mm Hg compared with 154/87 mm Hg over median 8.4 years of follow up, substantially reduced the risk of microvascular disease, stroke, and deaths related to diabetes,¹ but not myocardial infarction. Complementary information for estimates of the risk of complications including myocardial infarction at different levels of blood pressure can be obtained from observational analysis of the UKPDS data. This information can help to estimate the expected reduction in the risk of diabetic complications from a given change in blood pressure. It can also help to assess whether or not thresholds in blood pressure exist below which the risk of complications is substantially reduced. Such thresholds would have substantial influence on the establishment of guidelines on clinical care.

People with type 2 diabetes have a greater incidence of cardiovascular disease, cerebrovascular disease, and renal disease than the general population. Epidemiological studies suggest that relative hyperglycaemia accounts for part but not all of the increased risk.²⁻⁷ Raised blood pressure is more common in people with type 2 diabetes than in the general population,⁸⁻¹² and in people without diabetes it is a major risk factor for myocardial infarction and stroke.^{13 14} Epidemiological studies of the role of blood

pressure on the development of cardiovascular disease have categorised people as either hypertensive or normotensive or have measured blood pressure on a single occasion,^{5,6,15-17} whereas repeated measurements of blood pressure over several years should be more informative.

In these analyses, we evaluated the relation between systolic blood pressure over time and the development of macrovascular and microvascular complications using data from the UKPDS and looked for possible thresholds. We compared these results to those of the UKPDS trial of a policy of tight control of blood pressure.¹ When the achieved reduction in risk notably exceeded that expected from observational data, analyses were performed to evaluate the presence of a treatment effect beyond that of blood pressure alone.¹

Methods

Participants recruited to the UKPDS

We enrolled 5102 of 7416 patients with newly diagnosed type 2 diabetes (defined as fasting plasma glucose concentrations over 6.0 mmol/l on two separate mornings) who were referred to the UKPDS and were aged 25 to 65 years. Recruitment occurred between 1977 and 1991 at 23 clinical centres in England, Scotland, and Northern Ireland. Exclusion criteria are presented elsewhere¹⁸; the main reasons were severe vascular disease, myocardial infarction or stroke within the year before recruitment, or major systemic illness.

Participants in epidemiological analyses

We studied the incidence of complications of diabetes in the 4801 white, Asian Indian, and Afro-Caribbean patients who had blood pressure measured at two and nine months after the diagnosis of diabetes. Of these, 3642 with complete data for potential confounders were evaluated in proportional hazards models. Their characteristics are presented in table 1.

Participants in UKPDS blood pressure control study

The UKPDS clinical trials of blood glucose and blood pressure control are described elsewhere.^{19, 20} In summary, 1148 patients with hypertension, defined as previously receiving antihypertensive treatment and with a blood pressure $\geq 150/85$ mm Hg or not previously receiving antihypertensive treatment and a blood pressure $\geq 160/90$ mm Hg, were randomised to a policy of tight control of blood pressure with a β blocker or an angiotensin converting enzyme inhibitor or to a policy of less tight control. At entry, the mean duration of known diabetes was 2.6 years, and the patients were older and heavier than in the whole cohort (table 1). The aim in the group allocated to tight control was to achieve blood pressure values $< 150/< 85$ mm Hg. If this target was not met with maximal doses of a β blocker or angiotensin converting enzyme inhibitor, additional agents were prescribed, including a loop diuretic, a calcium channel blocker, and a vasodilator. The aim in the group allocated to less tight control was to achieve blood pressure values $< 180/< 105$ mm Hg without the use of a β blocker or an angiotensin converting enzyme inhibitor but using the same stepwise addition of other treatments.

Blood pressure measurement

Blood pressure was measured with the person in a seated position after a five minute rest with a Copal UA-251 or a Takeda UA-751 electronic, auscultatory blood pressure reading machine (Andrew Stephens, Brighouse, West Yorkshire). The first reading was discarded, and the mean of the next three consecutive readings with a coefficient of variation below 15% was used. In participants with atrial fibrillation, examiners used a Hawksley random zero sphygmomanometer.

Blood pressure exposure

Blood pressure was measured firstly at baseline (mean of measures taken at two and nine months after diagnosis) and secondly as an updated mean of annual measurement of systolic blood pressure, calculated for each participant from baseline to each year of follow up. For example, at one year the updated mean is the average of the baseline and one year values and at three years it is the average of baseline, one year, two year, and three year values.

Biochemical methods

The biochemical methods used have been reported previously.²¹ Biochemical variables are quoted for measurements after the initial dietary run-in period.

Clinical complications

The clinical end points studied¹⁸ and their definitions¹⁹ were separated into aggregate and single end points (see box).

Statistical analysis

Incidence rates by category of systolic blood pressure

The unadjusted incidence rates were calculated by dividing the number of people with a given complication by the person years of follow up for the given complication within each category of updated mean systolic blood pressure and reported as events per 1000 person years of follow up. The categories were defined (median values in parentheses) as: < 120 (114), 120-129 (125), 130-139 (135), 140-149 (144), 150-159 (154), and ≥ 160 (168) mm Hg over the range of updated mean systolic blood pressures 85-230 mm Hg.

Table 1 Characteristics of patients included in proportional hazards models measured after three month dietary run-in after diagnosis of diabetes and those included in UKPDS blood pressure control study.¹ Figures are means (SD) unless stated otherwise

	Proportional hazards model of observational analyses (n=3642)	Clinical trial of tight v less tight blood pressure control policy (n=1148)
Age (years)	53 (8)	56 (8)
Proportion of men (%)	60	55
Ethnicity (% white/Asian Indian/Afro-Caribbean/other)	82/10/8/0	87/8/5/1
Body mass index (kg/m ²)	27.7 (5.3)	29.6 (19.2)
Fasting plasma glucose (mmol/l)*	7.9 (6.6-10.0)	7.4 (6.2-9.5)
Haemoglobin A _{1c} (%)	7.1 (1.8)	7.0 (1.7)
Systolic blood pressure (mm Hg)	135 (19)	159 (19)
Low density lipoprotein cholesterol (mmol/l)	3.5 (1.0)	3.6 (1.1)
High density lipoprotein cholesterol (mmol/l)	1.06 (0.24)	1.10 (0.27)
Triglyceride (mmol/l)†	1.5 (0.9-2.5)	1.6 (0.9-2.7)
Albuminuria (%)‡	13.3	17.7

*Median (interquartile range).

†Geometric mean (1 SD range).

‡ > 50 mg/l in single morning sample.

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Professor Turner died unexpectedly after completing work on this paper

Aggregate end points

- Complications related to diabetes (myocardial infarction, sudden death, angina, stroke, renal failure, lower extremity amputation or death from peripheral vascular disease, death from hyperglycaemia or hypoglycaemia, heart failure, vitreous haemorrhage, retinal photocoagulation, and cataract extraction)
- Death related to diabetes (myocardial infarction, sudden death, stroke, lower extremity amputation or fatal peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia)
- All cause mortality
- Myocardial infarction (fatal myocardial infarction, non-fatal myocardial infarction, and sudden death)
- Stroke (fatal and non-fatal stroke)
- Lower extremity amputation or death from peripheral vascular disease
- Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure)

Single end points

- Heart failure (non-fatal, without a precipitating myocardial infarction)
- Cataract extraction

Time of follow up was calculated from the end of the initial period of dietary treatment to the first occurrence of that complication or loss to follow up, death from another cause, or the end of the study on 30 September 1997 for those who did not have that complication. The median follow up time for all cause mortality was 10.5 years. For myocardial infarction and stroke, for participants who had a non-fatal event before a fatal event, the time to the first event was used.

We calculated adjusted incidence rates for each category of updated mean systolic blood pressure using a Poisson regression model adjusted for male sex, white ethnic group, age at diagnosis 50-54 years, and duration of diabetes 7.5-12.5 years, and expressed as events per 1000 person years of follow up. These parameters were chosen to reflect the cohort's median age and duration of diabetes and modal ethnic group and sex.

Hazard ratios and risk reduction

To assess potential associations between updated mean systolic blood pressure and complications we used proportional hazards (Cox) models. The hazard ratio was used to estimate the relative risk. Potential confounding risk factors included in all Cox models were sex, ethnic group, age, and smoking (current/ever/never) at diagnosis of diabetes and baseline concentrations of high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride, albuminuria (> 50 mg/l measured on a single morning urine sample), and haemoglobin A_{1c}. At each event time, the updated mean systolic blood pressure for a person with an event was compared with the updated mean systolic blood pressure of those who had not had an event by that time. The updated mean systolic blood pressure was included as a time dependent covariate to evaluate systolic blood pressure during follow up. It was included as a categorical variable in the categories of blood pressure listed above, with the lowest category (< 120 mm Hg) as the reference category assigned a hazard ratio of 1.0. (This is reflected in the point estimates shown below in figures 3 and 4.) In the analyses for stroke, heart failure, and lower extremity amputation or deaths from peripheral vascular disease, the two lowest categories were

combined—that is, < 130 mm Hg (median 120 mm Hg)—to increase the reliability of the results as there were few of these end points in this range. A separate model with updated mean systolic blood pressure as a continuous variable was used to determine risk reduction associated with a 10 mm Hg reduction in blood pressure. (This is reflected in the regression line in figures 3 and 4.) The 95% confidence intervals were calculated on the basis of absolute floating risk.²² Log linear relations are reported by convention.^{1 18} The risk reduction associated with a reduction of 10 mm Hg in updated mean systolic blood pressure was calculated as 100% minus the reciprocal of the hazard ratio expressed as a percentage.

The regression lines were fitted with updated mean systolic blood pressure as a continuous variable centred on the mean of the risk estimates for the categories 130-139 mm Hg and 140-149 mm Hg. The P value reported is that associated with systolic blood pressure as a continuous variable. Evaluation of a threshold level of systolic blood pressure for each complication was assessed by visual inspection. The risk reduction from the continuous variable model associated with a 10 mm Hg reduction in observed systolic blood pressure was compared with the risk reduction seen in the UKPDS intervention trial of a tight versus a less tight policy of blood pressure control, for which no adjustment for potential confounders was required as they were balanced by the randomisation.¹ The main exposure of interest for the observational analyses was updated mean systolic blood pressure regardless of the control policy or the antihypertensive treatments used.

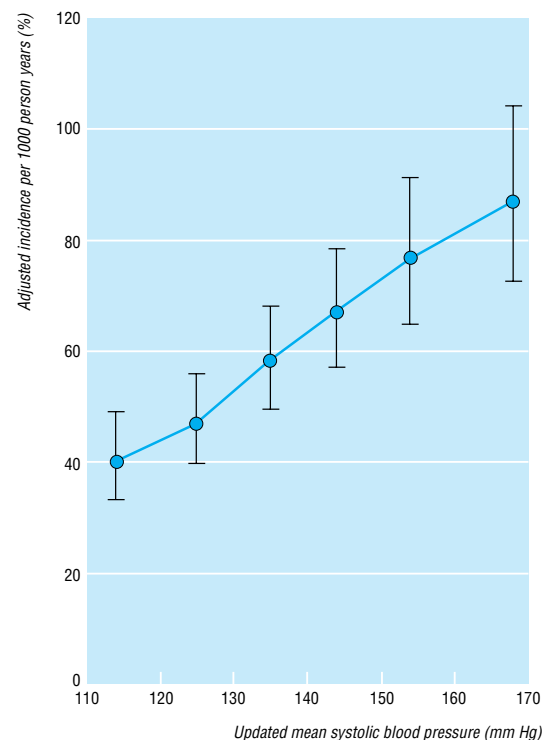


Fig 1 Incidence rate (95% confidence interval) of any aggregate end point related to diabetes by category of updated mean systolic blood pressure, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and mean duration of diabetes of 10 years

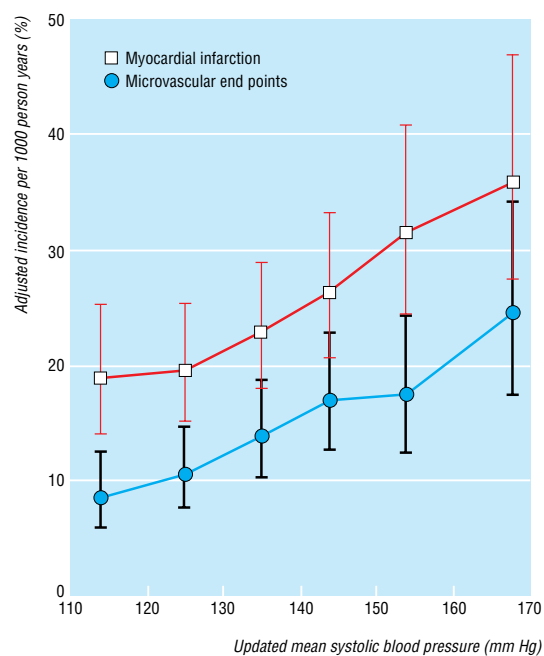


Fig 2 Incidence rates (95% confidence interval) of myocardial infarction and microvascular end points by category of updated mean systolic blood pressure, adjusted for age, sex, and ethnic group expressed for white men aged 50-54 years at diagnosis and mean duration of diabetes of 10 years

To assess whether treatment with drugs to lower blood pressure reduced the complications independently of the reduction in blood pressure, a proportional hazards model was fitted that included allocation to tight versus less tight blood pressure policies, updated mean systolic blood pressure, age, sex, ethnic group, smoking, and concentrations of high and low density lipoprotein cholesterol, triglyceride, and albuminuria. An interaction term between blood pressure treatment and mean updated blood pressure was included.

Statistical analyses were performed with SAS version 6.12.²³

Results

The risk of each of the macrovascular and microvascular complications of type 2 diabetes evaluated was strongly associated with blood pressure, as measured by updated mean systolic blood pressure. The incidence of cataract extraction was not associated with blood pressure. Figure 1 shows the incidence rated by category of updated mean systolic blood pressure for any end point related to diabetes adjusted for age, sex, ethnic group, and duration of diabetes. The increase in risk was monotonic, showing no evidence of a threshold, and showed a twofold increase over the range of systolic blood pressure from <120 mm Hg (median 114 mm Hg) to ≥ 160 mm Hg (168 mm Hg). The unadjusted and adjusted rates are shown in table 2. Figure 2 shows the adjusted incidence rates for myocardial infarction and microvascular end points, both being strongly associated to a similar degree with increasing blood pressure. Myocardial infarction, however, occurred about twice as frequently as microvascular end points at each level of blood pressure. Thus the incidence of myocardial infar-

tion increased from 18 per 1000 patient years in the group with the lowest systolic blood pressure to 33 per 1000 patient years in the group with blood pressure >160 mm Hg, with the comparable data for microvascular disease being 7 to 21 per 1000 patient years.

The estimated hazard ratios associated with each category of updated mean systolic blood pressure, relative to the lowest category, are shown as log linear plots in figures 3 and 4. Mortality related to diabetes and all cause mortality were both strongly associated with blood pressure ($P < 0.001$). The risk of each of the complications evaluated, except cataract extraction, rose with increasing updated mean systolic blood pressure with and without adjustment for baseline variables including age, sex, ethnic group, lipid concentrations, HbA_{1c}, smoking, and albuminuria. The decrease in risk for each 10 mm Hg reduction of updated mean systolic blood pressure was between 12% and 19% for both macrovascular and microvascular complications (table 3 and figures 3 and 4).

There was no indication of a threshold for any of the complications examined below which risk no longer decreased nor a level above which risk no longer increased. The updated mean systolic blood pressure showed similar risk relations to baseline systolic blood pressure (table 3).

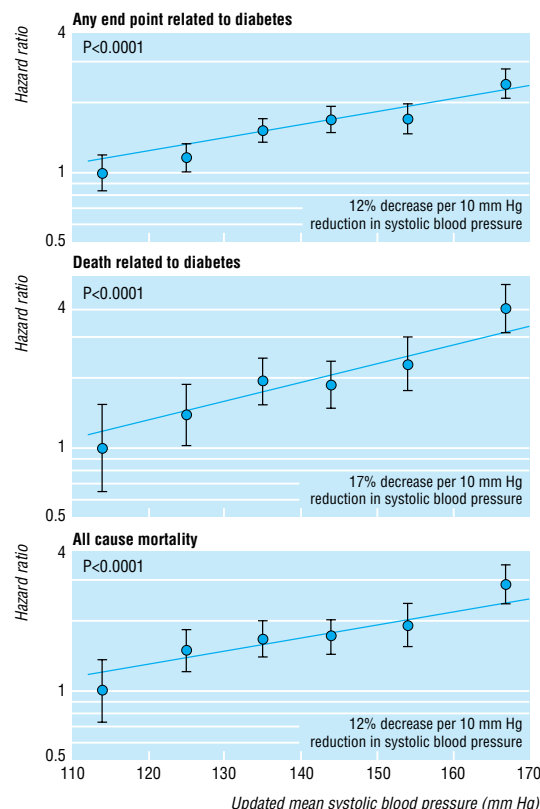


Fig 3 Hazard rates (95% confidence intervals as floating absolute risks) as estimate of association between category of updated mean systolic blood pressure and any end point related to diabetes, death related to diabetes, and all cause mortality with log linear scales. Reference category (hazard ratio 1.0) is systolic blood pressure <120 mm Hg; P value reflects contribution of systolic blood pressure to multivariate model. Data adjusted for age at diagnosis, ethnic group, smoking status, presence of microalbuminuria, haemoglobin A_{1c}, high and low density lipoprotein cholesterol, and triglyceride

Table 2 Incidence of complications in patients with type 2 diabetes by category of updated mean systolic blood pressure. Rates per 1000 person years' follow up adjusted in Poisson regression model to white men aged 50 to 54 years at diagnosis and followed up for 7.5 to <12.5 years, termed "10 years" (n=4801)

	<120 mm Hg	120-129 mm Hg	130-139 mm Hg	140-149 mm Hg	150-159 mm Hg	≥160 mm Hg
Aggregate end points						
Complications related to diabetes:						
Events/person years	198/8662	366/9327	375/9946	365/8044	272/5107	262/4493
Unadjusted rate	22.9	28.5	37.7	45.4	53.3	58.3
Adjusted rate (95% CI)	36.0 (29.7 to 43.6)	40.4 (34.0 to 47.9)	51.3 (43.9 to 60.0)	58.3 (49.7 to 68.3)	67.1 (56.4 to 79.8)	76.2 (63.6 to 91.3)
Deaths related to diabetes:						
Events/person years	40/9353	59/10 406	115/11 540	104/9589	96/6207	110/5537
Unadjusted rate	4.3	5.7	10.0	10.8	15.5	19.9
Adjusted rate (95% CI)	9.6 (6.5 to 14.1)	10.0 (7.2 to 13.9)	15.7 (11.9 to 20.7)	15.4 (11.6 to 20.5)	21.3 (15.9 to 28.7)	28.7 (21.3 to 38.7)
All cause mortality:						
Events/person years	65/9353	133/10 406	183/11 540	184/9589	152/6207	163/5537
Unadjusted rate	6.9	12.8	15.9	19.2	24.5	29.4
Adjusted rate (95% CI)	14.4 (10.7 to 19.5)	20.3 (16.0 to 25.8)	22.2 (17.8 to 27.7)	23.8 (19.1 to 29.7)	29.1 (23.0 to 36.9)	36.2 (28.4 to 46.1)
Fatal or non-fatal myocardial infarction:						
Events/person years	85/9083	104/10 064	152/11 048	149/9198	114/5912	115/5326
Unadjusted rate	9.4	10.3	13.8	16.2	19.3	21.6
Adjusted rate (95% CI)	18.4 (13.8 to 24.6)	17.6 (13.5 to 22.9)	21.9 (17.3 to 27.8)	24.2 (19.1 to 30.7)	28.7 (22.2 to 37.3)	33.1 (25.3 to 43.3)
Stroke:						
Events/person years*		36/19 523	41/11 334	56/9359	50/6008	58/5271
Unadjusted rate		1.8	3.6	6.0	8.3	11.0
Adjusted rate (95% CI)		2.8 (1.7 to 4.4)	4.4 (2.8 to 6.9)	6.5 (4.3 to 9.9)	8.7 (5.6 to 13.5)	11.9 (7.6 to 18.6)
Lower extremity amputation or death from peripheral vascular disease:						
Events/person years*		11/19 573	17/11 393	13/9432	11/6081	15/5409
Unadjusted rate		0.6	1.5	1.4	1.8	2.8
Adjusted rate (95% CI)		1.0 (0.4 to 2.4)	2.4 (1.1 to 5.2)	2.1 (0.9 to 4.8)	2.8 (1.2 to 6.6)	4.8 (2.1 to 11.1)
Fatal or non-fatal microvascular disease:						
Events/person years	52/9150	72/10 059	102/10 971	100/9026	67/5769	74/5084
Unadjusted rate	5.7	7.2	9.3	11.1	11.6	14.6
Adjusted rate (95% CI)	7.3 (5.0 to 10.6)	8.9 (6.4 to 12.4)	11.9 (8.8 to 16.1)	14.2 (10.5 to 19.3)	15.2 (10.8 to 21.4)	20.8 (14.8 to 29.2)
Single end point						
Heart failure:						
Events/person years		26/19 534	34/11 326	33/9356	31/6036	34/5331
Unadjusted rate*		1.3	3.0	3.5	5.1	6.4
Adjusted rate (95% CI)		2.4 (1.4 to 4.2)	4.2 (2.5 to 6.9)	4.1 (2.5 to 6.9)	5.6 (3.3 to 9.6)	7.0 (4.0 to 12.0)
Cataract extraction:						
Events/person years	37/9173	53/10 136	55/11 113	62/9190	37/5993	35/5296
Unadjusted rate	4.0	5.2	4.9	6.7	6.2	6.6
Adjusted rate (95% CI)	4.7 (3.0 to 7.5)	5.1 (3.4 to 7.7)	4.4 (2.9 to 6.6)	5.2 (3.5 to 7.8)	4.4 (2.8 to 7.0)	4.4 (2.7 to 7.2)

Person years, events, and unadjusted rates are for all patients.

*For these three end points lowest category was <130 mm Hg.

Table 3 also shows the risk reductions associated with a 10 mm Hg reduction in blood pressure in the observational analysis compared with the risk reduction associated with a 10 mm Hg median difference in blood pressure from the clinical trial of blood pressure control.¹ After exclusion of cataract extractions, the relation with blood pressure tended to be stronger in the clinical trial than in the observational analysis, although in the clinical trial the confidence intervals were wider (table 3), reflecting the smaller number of people at risk and of events.¹ With adjustment for updated mean systolic blood pressure in the trial, allocation to tight blood pressure control had a greater effect on reducing the risk of heart failure ($P=0.0054$; 17 events in 749 patients allocated to tight control and 20 events in 384 patients allocated to less tight control) than expected from the blood pressure reduction per se. This was also true for stroke ($P=0.027$), with 29 events in 752 patients allocated to tight control and 26 events in 386 patients allocated to less tight control, and for all deaths related to diabetes ($P=0.038$), with 63 events in 752 patients allocated to tight control and 49 events in 386 patients allocated to less tight control.

There was no interaction between treatment and updated mean blood pressure.

Discussion

This observational analysis shows an important association between the occurrence of each of the diabetic complications evaluated (except cataract extraction), including all cause mortality, and systolic blood pressure exposure across the range observed in patients with type 2 diabetes. This association persisted after adjustment for other characteristics that are associated with risk of complications (age, sex, ethnic group, glycaemia, lipid concentrations, smoking, and albuminuria). On average, each 10 mm Hg reduction in systolic blood pressure was associated with a 12% decrease in the risk of any end point related to diabetes and a 15% reduction in the risk of death related to diabetes. Myocardial infarction occurred more commonly than microvascular complications, but the relative risk reduction for a 10 mm Hg reduction in systolic blood pressure was similar at 11% and 13%, respectively.

This observational analysis provides an estimate of the reduction in risk that might be achieved by the therapeutic lowering of blood pressure. While it is important to realise that epidemiological associations cannot necessarily be transferred to clinical practice, the results are consistent with those achieved by the policy of tight control of blood pressure in the clinical trial.¹ Whereas tight control did not significantly reduce the risk of myocardial infarction in the clinical trial, the effect size was commensurate with the observational analysis. The risk reductions in the clinical trial of tight control seemed to be greater than those anticipated from the epidemiological analyses for any complications or deaths related to diabetes, stroke, microvascular disease, and heart failure.¹ After allowance for differences in blood pressure between the tight and less tight policies in the clinical trial, this apparent treatment effect, per se, was significant only for deaths related to diabetes, stroke, and heart failure. The absence of significant interaction suggests that treatment effect does not differ by level of blood pressure. The heart outcomes prevention evaluation studies (HOPE and MICRO-HOPE) that used ramipril can also be interpreted to have effects beyond those anticipated by changes in blood pressure alone.^{24 25} This suggests the possibility that treatment with angiotensin converting enzyme inhibitors^{26 27} and β blockers^{28 29} may have cardioprotective effects separate from blood pressure reduction. For example, both are beneficial in heart failure.^{1 28 30 31} The diminished risk of heart failure may have reduced the risk of embolic stroke, but no direct data are available. Effects greater than anticipated have also been shown in studies in the general population, where the risk reduction in odds of stroke from pooled trials of antihypertensive drug treatment exceeded the 35-40% expected from epidemiological studies.³² It is possible that the association between blood pressure and cardiovascular disease differs in magnitude in diabetic and non-diabetic populations, which could not be tested in this study. In support of this possibility, the multiple risk factor intervention trial (MRFIT) observed that the association of

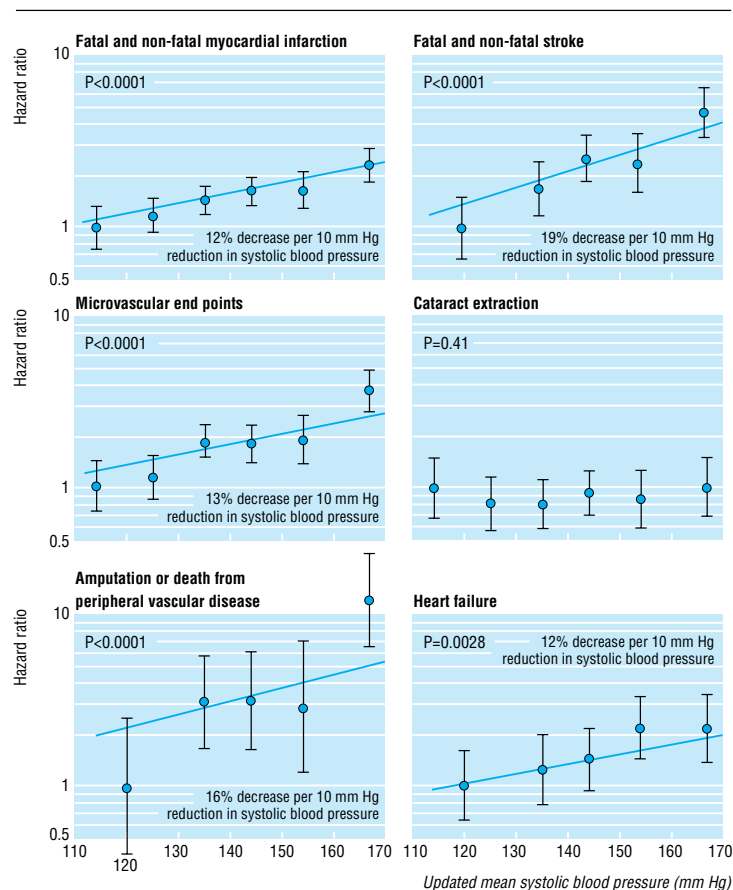


Fig 4 Hazard rates (95% confidence intervals as floating absolute risks) as estimate of association between category of updated mean systolic blood pressure and myocardial infarction, stroke, microvascular end points, cataract extraction, lower extremity amputation, or fatal peripheral vascular disease and heart failure, with log linear scales. Reference category (hazard ratio 1.0) is systolic blood pressure <120 mm Hg for myocardial infarction, microvascular disease, and cataract extraction and <130 mm Hg for stroke, lower extremity amputation or fatal peripheral vascular disease, and heart failure; P value reflects contribution of systolic blood pressure to multivariate model. Data adjusted for age at diagnosis of diabetes, ethnic group, smoking status, presence of albuminuria, haemoglobin A_{1c}, high and low density lipoprotein cholesterol, and triglyceride

Table 3 Observational data analysis of relation between systolic blood pressure exposure and complications of diabetes as estimated by risk reduction for 10 mm Hg reduction in systolic blood pressure, measured at baseline and as updated mean, controlled for age at diagnosis of diabetes, sex, ethnic group, smoking, microalbuminuria, haemoglobin A_{1c} concentration, high and low density lipoprotein cholesterol, and triglycerides (n=3642) compared with results of clinical trial of tight v less tight blood pressure control policy (n=1148)¹

	Observational analyses				Clinical trial (less tight v tight policy) ¹			
	No of events	Baseline SBP		Updated mean SBP		No of events	Decrease in risk (%)/10 mm Hg difference in SBP (95% CI)	P value
		Decrease in risk (%)/10 mm Hg reduction (95% CI)	P value	Decrease in risk (%)/10 mm Hg reduction (95% CI)	P value			
Aggregate end points								
Any end point related to diabetes	1255	9 (7 to 12)	<0.0001	12 (9 to 14)	<0.0001	429	24 (8 to 38)	0.0046
Deaths related to diabetes	346	19 (15 to 23)	<0.0001	17 (13 to 21)	<0.0001	144	32 (6 to 51)	0.0019
All cause mortality	597	13 (10 to 17)	<0.0001	12 (9 to 16)	<0.0001	217	18 (-8 to 37)	>0.05
Myocardial infarction	496	13 (9 to 16)	<0.0001	12 (7 to 16)	<0.0001	176	21 (-7 to 41)	>0.05
Stroke	162	13 (7 to 19)	0.0002	19 (14 to 24)	<0.0001	72	44 (11 to 65)	0.013
Peripheral vascular disease*	41	30 (20 to 39)	<0.0001	16 (9 to 23)	<0.0001	16	49 (-37 to 81)	>0.05
Microvascular disease	323	10 (4 to 15)	0.0007	13 (9 to 26)	<0.0001	122	37 (11 to 56)	0.0092
Single end points								
Heart failure	104	14 (5 to 21)	0.0016	15 (4 to 19)	<0.0001	45	56 (6 to 80)	0.0043
Cataract extraction	195	7 (0 to 14)	0.043	-3 (-11 to 5)	0.41	42	-34 (40 to -202)	>0.05

SBP=systolic blood pressure.

*Lower extremity amputation or fatal peripheral vascular disease.

systolic blood pressure and death from cardiovascular disease was of a lower magnitude in diabetic compared with non-diabetic men.¹⁵ Stroke and heart failure were the complications least strongly associated with glycaemia,² suggesting that for these complications, by comparison, raised blood pressure is of greater pathogenetic importance.

Lack of thresholds

We observed no thresholds of systolic blood pressure for any complication of diabetes. This suggests that there is no specific target blood pressure to aim for but that the nearer to normal systolic blood pressure the lower the risk of complications, in accord with recommendations to reduce systolic blood pressure to less than 130 mm Hg³³⁻³⁵ or less than 125 mm Hg in the presence of microalbuminuria.³⁶ Whether these target values can realistically be achieved depends on an individual's initial blood pressure and willingness to modify life style or to take several drugs that may have side effects. Neither our study nor the hypertension optimal treatment (HOT) study³⁷ found a J or U shaped association between systolic blood pressure and complications, which is now thought to reflect coexisting morbidity with low blood pressures rather than the effect of treatment.³⁸ Unlike the HOT study the UKPDS did not observe a flattening of the relation at low levels of blood pressure. There was no indication of a level above which systolic blood pressure was no longer associated with an increased risk of complications. Thus any reduction of raised blood pressure is likely to have benefit.

As in this analysis, a large study of diabetic applicants for life insurance in the United States showed that hypertension was strongly associated with all cause mortality.³⁹ Our finding of a 15% risk reduction for deaths related to diabetes associated with 10 mm Hg systolic change is similar to the 15% risk reduction observed for cardiovascular death in a global study⁴⁰ and to that calculated from the data in the multiple risk factor intervention trial (MRFIT)¹⁵ in people with diabetes. Other studies have observed an association between blood pressure and cardiovascular mortality.^{14 39 41-42} The increasing risk of stroke with raised systolic blood pressure has also been shown.⁴³⁻⁴⁵

These observational analyses show that people at high risk for diabetic complications can be identified on the basis of as few as two blood pressure readings within the year after diagnosis as these measurements were associated with a risk of complications of similar magnitude to the updated mean systolic blood pressure measured over many years. Regression dilution bias from the baseline measurement was probably minimised as two readings taken six months apart, rather than a single measurement, were used in the model. The similarity of the risk probably reflects tracking of blood pressure in populations over years.⁴⁶ The choice of systolic rather than diastolic pressure reflects convention and the knowledge that both are associated with heart disease.^{32 40 47}

This analysis indicates the importance of early assessment of blood pressure in the course of diabetes. Improved control of blood pressure in diabetic patients has been shown to be effective in reducing the risk of cardiovascular complications^{37 48 49} and nephropathy,⁵⁰ as well as providing considerable savings in healthcare costs.^{51 52} Whereas treatment of glycaemia in patients

What is already known on this topic

People with diabetes who also have hypertension are more likely to develop complications

Treatment of blood pressure in these individuals reduces the risk of complications

What this study adds

There is a direct relation between the risk of complications of diabetes and systolic blood pressure over time

No threshold of systolic blood pressure was observed for a substantive change in risk for any of the clinical outcomes examined

The lower the systolic blood pressure the lower the risk of complications

There may be additional risk reduction with angiotensin converting enzyme inhibitors and β blockers over and above that associated with lowering of blood pressure

with type 2 diabetes is difficult because of the progressive hyperglycaemia,⁵³ it is easier to maintain improved blood pressure control, although with time additional blood pressure lowering agents are required.¹ As the risk of diabetic complications rises across the range of blood pressures studied, lifestyle interventions that also reduce blood pressure in people without hypertension⁵⁴ or not at high risk for diabetes⁵⁵ should also be beneficial in diabetic patients. Targeting and treating patients with the highest blood pressure will reduce individual risk the most, but targeting and treating people with moderately raised blood pressure will reduce the risk in greater numbers of people.⁵⁶ The UKPDS provides an evidence base for the management of raised blood pressure and hyperglycaemia to reduce the complications of type 2 diabetes.

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