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Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75)

Abstract *Aims/hypothesis:* The relative importance of glucose and blood pressure control in type 2 diabetes remains uncertain. We assessed interactive effects of glycaemia and systolic blood pressure (SBP) exposure on the risk of diabetic complications over time. *Subjects, materials and methods:* HbA_{1c} and SBP, measured annually for a median of 10.4 years in 4,320 newly diagnosed type 2 diabetic patients from the UK Prospective Diabetes Study (UKPDS), were categorised as updated mean values <6.0, 6.0–6.9, 7.0–7.9 or ≥8.0%, and <130, 130–139, 140–149 or ≥150 mmHg, respectively. Clinical outcomes were UKPDS predefined composite endpoints. *Results:* The incidence of the 'any diabetes-related endpoint' in the lowest (HbA_{1c} <6.0%, SBP <130 mmHg) and highest (HbA_{1c} ≥8%, SBP ≥150 mmHg) category combinations was 15 and 82 per 1,000 person-years, respectively, and 24 and 120 per 1,000 person-years in a Poisson model adjusted to white Caucasian male sex, age 50 to 54 years and diabetes duration of 7.5 to 12.5 years. Updated mean HbA_{1c} and SBP effects were additive in an adjusted proportional hazards model with risk reductions of 21% per 1% HbA_{1c} decrement and 11% per 10 mmHg SBP decrement. Endpoint rates obtained in the 887 patients randomised in both the glycaemia and hypertension intervention trial arms were consistent with the observational data. Those allocated to both intensive glucose and tight blood pressure control policies had fewer events than those allocated to either policy alone or to neither (*p* for trend 0.024). *Conclusions/interpretation:* Risk of complications in type 2 diabetes is associated independently and additively with hyperglycaemia and hypertension. Intensive treatment of both these risk factors is required to minimise the incidence of complications.

Keywords Blood pressure · Complications · Glycaemia · Risk · Type 2 diabetes · UKPDS

Abbreviations BP: blood pressure · SBP: systolic blood pressure · UKPDS: UK Prospective Diabetes Study

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Introduction

In patients with newly diagnosed type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) showed that an intensive compared with a conventional blood glucose control policy reduced the risk of developing any diabetic complications [1]. Microvascular complications were reduced significantly with a borderline significantly reduced risk of myocardial infarction (*p*=0.052). In a subset of UKPDS patients who also were hypertensive, tight compared with less tight blood pressure (BP) control reduced the risk of developing macrovascular and microvascular complications of diabetes [2]. Observational analyses of UKPDS data have confirmed independent associations of HbA_{1c} and systolic BP (SBP) levels over time with diabetic complications [3, 4] with no evidence of any apparent threshold of risk across the range of HbA_{1c} and SBP values studied. Although it is now known that therapies to lower HbA_{1c} and SBP can reduce the risk of diabetic complications [1, 5, 6], it remains uncertain whether treatment of either alone is sufficient, or whether, to obtain maximum benefit, both of these risk factors need to be treated simultaneously [7]. A multiple risk factor

intervention trial in type 2 diabetes has shown that increased benefit can be obtained by targeting several risk factors simultaneously [8].

To determine whether the associations observed between the risk of developing diabetes-related complications and different combinations of HbA_{1c} and SBP levels over time are additive, we undertook further observational analyses in 4,320 UKPDS patients with the requisite data available. To investigate the extent to which a combined therapeutic approach of simultaneously improving both blood glucose and BP might confer greater benefit than by treating either alone, we examined the clinical outcomes that occurred in the 887 hypertensive UKPDS patients who were randomised in both the glycaemia and hypertension intervention arms of the study.

Subjects, materials and methods

Patients

The UKPDS recruitment and selection process has been reported previously [9]. The study received ethical committee approval in each of the 23 clinical centres and conformed to the guidelines of the Declarations of Helsinki (1975 and 1983). Briefly, 5,102 of the 7,616 patients referred were recruited. The patients, all of whom gave informed consent, were aged 25 to 65 years with newly diagnosed type 2 diabetes and fasting plasma glucose levels >6.0 mmol/l on two mornings after referral. Of the 5,102, 81% were white Caucasian, 10% Asian-Indian and 9% Afro-Caribbean. Exclusion criteria included severe vascular disease, a myocardial infarction or stroke within the previous year or a major systemic illness.

The 3,867 of the 5,102 patients who continued to have fasting plasma glucose levels in the range 6.0 to 15.0 mmol/l after a dietary run-in period were allocated randomly either to a conventional glucose control policy treated primarily with diet alone or to an intensive glucose control policy treated primarily with sulphonylurea or insulin [1]. In a factorial manner, 1,148 of the 5,102 patients, who also were hypertensive, were randomised in addition either to a tight or to a less tight BP control policy. Of these 1,148 patients, 758 were randomised to a tight BP control arm and allocated to therapy primarily with an ACE-inhibitor (captopril) or a beta-blocker (atenolol), whereas these therapies were avoided in the remaining 390 patients allocated to a less tight BP control arm [9–11].

Glycaemic and BP exposure

Of the 5,102 patients recruited into the UKPDS, 4,320 had HbA_{1c} and SBP measurements available at baseline, following the dietary run-in period, and annually thereafter. HbA_{1c} was measured by HPLC using an automated glycosylated haemoglobin analyser (Diamat; Bio-Rad Laboratories, Hemel Hempstead, UK), (non-diabetic range 4.5–6.2%) [12, 13]. HbA_{1c} measurements were certified comparable with those of the DCCT by the US National Glycohemoglobin Standardization Program. Glycaemic exposure over time was assessed as the updated mean of the annual HbA_{1c} measurements, calculated for each individual from baseline to the last year of follow-up or to the last value before the occurrence of a predefined UKPDS endpoint. BP was measured by a trained nurse using an electronic sphygmomanometer (Copal UA-251 or Takeda UA-751; Andrew Stephens Co., Brighouse, West Yorkshire, UK) or a random zero sphygmomanometer (Hawksley & Sons, Lancing, Sussex, UK) [11]. The first reading was discarded and the mean of the next three readings with a CV <15% used. SBP exposure over time was calculated as for the updated mean HbA_{1c}.

Only 887 UKPDS patients were randomised both to one of the two blood glucose control policies and also to one of the two BP control policies. Although this was done in a factorial manner, the randomisation ratios of 3:7 for conventional to intensive glucose control policies and 1:2 for less tight to tight BP control policies meant that unequal numbers of patients were allocated to the four possible randomisation combinations. Of the 887 patients, 87 were allocated to conventional glucose/less tight BP, 155 to conventional glucose/tight BP, 231 to intensive glucose/less tight BP and 414 to intensive glucose/tight BP intervention policies.

Clinical outcomes

Patients were followed for a median of 10.4 years. UKPDS predefined endpoints were assessed independently by two clinicians who were masked to therapy allocations [9]. The three primary composite endpoints were: (1) any diabetes-related endpoint (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); (2) diabetes-related death (myocardial infarction, sudden death, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia); and (3) all-cause mortality. The three secondary composite endpoints were: (1) myocardial infarction (fatal myocardial infarction, non-fatal myocardial infarction or sudden death); (2) stroke (fatal and non-fatal); or (3) microvascular disease (retinal photocoagulation, vitreous haemorrhage and fatal or non-fatal renal failure). The time to the first event within each composite was used for analyses.

Statistical analyses

Overview

Observational analyses were undertaken to determine the unadjusted and adjusted composite endpoint rates for different combinations of blood glucose and BP levels over time and to examine the degree to which these associations

might be synergistic or antagonistic. In addition, we present the composite endpoint rates for the subset of patients who were randomised in both the blood glucose and BP control arms. All analyses were carried out using SAS v8.2 and 9.1.3 (SAS Institute, Cary, NC, USA). Data are presented as mean (SD), median (interquartile range) or geometric mean (1 SD interval), apart from incidence data, which are presented as mean (95% CI). A 1% level of statistical significance was chosen to minimise potential Type 1 errors.

Unadjusted incidence rates

Updated mean HbA_{1c} and SBP values for each patient were categorised into four levels of glycaemia (<6%, 6–6.9%, 7.0–7.9% and ≥8%) and four levels of SBP (<130, 130–139, 140–149 and ≥150 mmHg). Composite endpoint crude incidence rates were calculated, as events per 1,000 person-years, for each of the 16 category combinations.

Adjusted incidence rates

Adjusted composite endpoint incidence rates for a norm-adjusted population were calculated for each of the 16 category combinations as events per 1,000 person-years using a Poisson regression model adjusted to white Caucasian male sex, age 50- to 54 years and diabetes duration of 7.5–12.5 years. The relative risk of the highest (HbA_{1c} ≥8%, SBP ≥150 mmHg) to the lowest (HbA_{1c} <6.0%, SBP <130 mmHg) category combination was determined.

Potential additive effects of glycaemia and BP

A proportional hazards regression model was used to determine the association between time to event, updated mean HbA_{1c} and updated mean SBP, and also to estimate separately the risk reductions for a 1% absolute decrement in updated mean HbA_{1c} and for a 10 mmHg decrement in updated mean SBP. At each event time the updated mean HbA_{1c} and SBP values for individuals with an event were compared with the updated values for those who had not had an event by that time. Updated mean HbA_{1c} and SBP values were included as time-dependent covariates to evaluate glycaemic and BP exposure during follow-up. Risk decrease was defined as 1 minus the reciprocal of the hazard ratio. Potential confounding risk factors included in the models were: sex, age, ethnicity, smoking status (current/ever/never) at time of diagnosis of diabetes and HDL-cholesterol, LDL-cholesterol, triglycerides and albuminuria (>50 mg/l measured in a single morning urine sample) immediately after the dietary run-in period. Patients were included irrespective of their randomisation to different blood glucose or BP control policies.

In addition to fitting HbA_{1c} and SBP as continuous variables for each of the composite endpoints under consideration in the proportional hazard model, a product term for these two factors was also included to test for possible interactions.

Randomised glycaemia and BP intervention trial

The small number of patients randomised into both the glycaemia and BP intervention arms of the UKPDS meant that there was insufficient statistical power to undertake specific analyses of the composite endpoints obtained in the four combinations of allocated glucose and BP control policies. To estimate the extent to which the factorial intervention trial might be in accord with the observational analyses presented here, we have examined, on an intention-to-treat basis, the composite endpoint incidence

Table 1 Clinical characteristics of the UKPDS patients included in the observational analyses and of the subset who were randomised in both the glycaemia and hypertension intervention arms of the trial

	Observational study	Randomised intervention trial of blood glucose and BP
n	4,320	887
Age (years)	53 (9)	57 (8)
Duration of diagnosed diabetes (years)	0	2.6 (0.5)
Sex (male)	60%	58%
Ethnic group		
White Caucasian	82%	87%
Afro-Caribbean	8%	7%
Asian-Indian	10%	6%
Smoking		
Never	35%	35%
Ex-smoker	34%	44%
Current smoker	31%	21%
BMI (kg/m^2)	27.7 (5.3)	29.5 (5.5)
HbA_{1c} (%), median (interquartile range)	6.9 (6.0–8.0)	6.5 (5.8–7.6)
SBP (mmHg)	135 (20)	154 (16)
Diastolic BP (mmHg)	83 (10)	90 (8)
Total cholesterol (mmol/l)	5.4 (1.0)	5.6 (1.0)
HDL-cholesterol (mmol/l)	1.07 (0.24)	1.08 (0.25)
LDL-cholesterol (mmol/l)	3.5 (1.0)	3.6 (1.0)
Triglycerides (mmol/l), geometric mean (1 SD range)	1.5 (0.9–2.5)	1.9 (0.9–4.1)
Albuminuria (>50 mg/l)	13.4%	17.3%

Measurements were made following the dietary run-in period and data are shown as mean (SD) except where indicated

Fig. 1 Incidence of UKPDS composite endpoints in 4,320 patients, as rate per 1,000 person-years. **a** Any diabetes-related endpoint, **b** diabetes-related deaths, **c** all-cause mortality, **d** myocardial infarction, **e** microvascular disease, **f** stroke. Values are for 16 different combinations of updated mean HbA$_{1c}$ and updated mean SBP. Unadjusted rates are shown for the three primary and three secondary composite endpoints
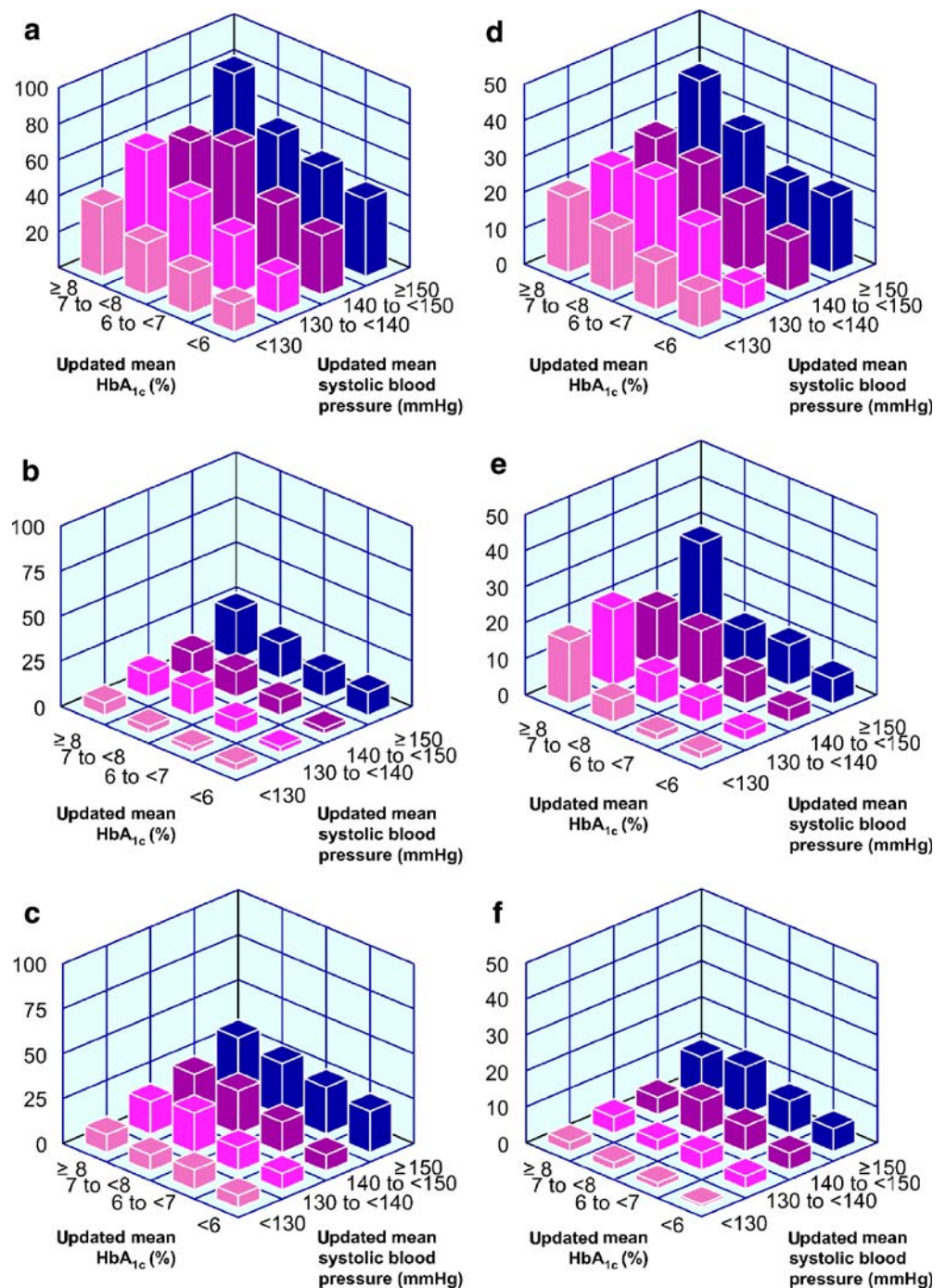
rates per 1,000 person-years using a life-table approach with log-rank tests. Only composite endpoints that occurred following a patient's randomisation into the BP control study were included. A trend test was used to compare the composite endpoint incidence rates according to whether patients had been allocated to both an intensive glucose and tight BP control policy, either of these alone or neither.

Results

Patients

Patient characteristics, following their dietary run-in period, are shown in Table 1. Updated mean HbA$_{1c}$ and SBP 1st to 99th percentiles were 4.6–11.2% and 85–230 mmHg, respectively, in the 4,320 patients included in the observational analyses. Median HbA$_{1c}$ and SBP values for their respective four categories were 5.5, 6.5, 7.5 and 9.0% and 119, 135, 144 and 162 mmHg with

Table 2 Median HbA_{1c} and SBP values for the four highest and lowest category combinations of updated mean HbA_{1c} and updated mean SBP

	Updated mean HbA_{1c}				Relative risk (95% CI) highest: lowest category combination
	<6.0%		≥8%		
	SBP <130 mmHg	SBP ≥150 mmHg	SBP <130 mmHg	SBP ≥150 mmHg	
HbA_{1c} (%)	5.4%	5.5%	9.1%	8.9%	N/a
SBP (mmHg)	118	162	119	162	N/a
Composite endpoints					
Any diabetes-related endpoint					
Risk rate (95% CI)	24 (17–32)	56 (43–72)	67 (54–83)	120 (96–150)	5.2 (3.9–7.5)
No. of events/no. of patient years	54/3,550	44/891	147/3,771	61/677	
Diabetes-related death					
Risk rate (95% CI)	7 (4–12)	15 (9–23)	16 (10–24)	40 (27–58)	6.7 (3.8–12.0)
No. of events/no. of patient years	15/3,746	16/1,075	31/4,275	30/878	
All-cause mortality					
Risk rate (95% CI)	13 (8–20)	27 (19–38)	22 (16–32)	46 (34–64)	4.1 (2.6–6.5)
No. of events/no. of patient years	27/3,746	29/1,075	44/4,276	38/878	
Myocardial infarction					
Risk rate (95% CI)	10 (7–16)	21 (15–31)	21 (15–30)	38 (27–54)	4.1 (2.6–6.6)
No. of events/no. of patient years	27/3,688	22/1,031	52/4,188	27/832	
Stroke					
Risk rate (95% CI)	1 (0–4)	6 (3–11)	4 (2–8)	12 (7–22)	12.8 (3.8–43.2)
No. of events/no. of patient years	3/3,726	8/1,014	11/4,210	11/834	
Microvascular disease					
Risk rate (95% CI)	3 (1–6)	11 (6–19)	26 (18–37)	46 (32–68)	16.3 (7.3–36.1)
No. of events/no. of patient years	7/3,700	10/1,016	69/4,049	27/771	

The left-hand section shows the composite endpoint absolute risk rates per 1,000 person-years adjusted in a Poisson model to white Caucasian male sex, age 50–54 years and diabetes duration 7.5–12.5 years, and the number of events and number of person-years for each category. On the right: the relative risk of the highest (HbA_{1c} ≥8%, SBP ≥150 mmHg) to the lowest (HbA_{1c} <6.0%, SBP <130 mmHg) category combination

corresponding person-years of observation being 9,785, 13,589, 9,538 and 10,646 and 15,881, 9,428, 7,938 and 10,311. The 887 patients included in both the blood glucose and BP intervention arms of the trial had been diabetic for a mean of 2.6 years, tended to be older at diagnosis of diabetes, to have a greater BMI and to have a higher BP than those included in the observational analyses.

Unadjusted incidence rates

The crude composite endpoint incidence rates in the 16 category combinations of updated HbA_{1c} and updated SBP for the three primary and the three secondary composite endpoints are shown in Fig. 1. The incidence of the 'any diabetes-related endpoint' in the lowest (HbA_{1c} <6.0%, SBP <130 mmHg) and highest (HbA_{1c} ≥8%, SBP ≥150 mmHg) category combinations was 15 and 82 per 1,000 person-years, respectively. The incidence in the other two extreme category combinations (HbA_{1c} <6.0%, SBP ≥150 mmHg and HbA_{1c} ≥8%, SBP <130 mmHg) was 43 and 39 per 1,000 person-years, respectively. A gradation of increasing incidence of composite endpoints as exposure to HbA_{1c} and SBP increased was observed. A similar pattern

was seen for each of the other primary and secondary composite endpoints.

Adjusted incidence rates

Table 2 shows Poisson model adjusted composite endpoint rates for the four extreme HbA_{1c} and SBP category combinations. As for the unadjusted rates, the incidence of composite endpoints increased with increasing updated mean HbA_{1c} and SBP exposure. Comparing the highest with the lowest HbA_{1c} and SBP category combination, there was an approximately four-fold increase in the rate of myocardial infarction, whereas for microvascular disease the increase was approximately 16-fold.

Potential additive effect of glycaemia and BP

Table 3 shows the risk reductions calculated for a 1% decrement in updated mean HbA_{1c} and for a 10 mmHg decrement in updated mean SBP. For the 'any diabetes-related endpoint' these were 21% (95% CI 19–24%) and 11% (95% CI 9–13%), respectively. The interaction test

indicated that the effects of updated mean HbA_{1c} and updated mean SBP on composite endpoints were additive, apart from the microvascular disease endpoint, where their effects were sub-additive ($p<0.0001$).

Patients randomised to both the glycaemic and BP intervention arms of the trial

Table 4 shows data for the 887 hypertensive UKPDS patients who were randomised in both the glycaemic and the BP arms of the trial. The proportions allocated to each of the four possible blood glucose and BP control policy combinations who developed any of the three primary composite endpoints are shown and their relative risks compared with those randomised to a conventional glucose control policy and to less tight BP control policy. Figure 2 shows these data as the incidence per 1,000 person-years. For the 'any diabetes-related endpoint' those allocated to the intensive glucose and to the tight BP control policies had fewer events than those allocated to either policy alone or neither (p for trend 0.024). Similar trends were seen for the diabetes-related deaths and all-cause mortality composite endpoints. To examine the potential confounding effect of randomised therapies with updated mean HbA_{1c} and SBP the model was re-run for the 589 patients with the requisite data available. No significant differences were seen in any of the results obtained.

Discussion

This study shows that the risk of developing type 2 diabetic complications is independently and additively associated with previous exposure to hyperglycaemia and hypertension. Patients with higher levels of both HbA_{1c} and SBP were at greater risk than those with just one of these risk factors raised and at much greater risk than those with neither of them raised. For example, those patients with an updated mean HbA_{1c} ≥8.0% and an updated mean SBP ≥150 mmHg had an approximately four-fold increased risk of myocardial infarction and 16-fold risk of developing microvascular disease compared with those with updated mean values of HbA_{1c} <6.0% and SBP <130 mmHg. The effects of updated mean HbA_{1c} and SBP on incidence rates of composite endpoints were shown to be additive in an adjusted proportional hazards model, suggesting strongly that to minimise the risk of diabetic complications it is necessary to treat both blood glucose and BP aggressively. The results obtained in the intervention trial were consistent with the observational data showing that those patients allocated to both intensive glucose and tight BP control policies tended to have fewer events than those allocated to either policy alone or neither (p for trend 0.024).

The adjusted absolute risk rates for composite endpoints seen with exposure to differing levels of updated mean HbA_{1c} and updated mean SBP confirm our previously published observational analyses for the associations seen with HbA_{1c} and SBP values measured shortly after diagnosis of diabetes [3, 4]. The analyses presented here differ in that simultaneous adjustments have been made for both updated mean HbA_{1c} and updated mean SBP values. The unadjusted incidence rates for the composite endpoints show a gradation of increasing risk with increasing HbA_{1c} and SBP values, with no evidence of a threshold effect for any of the composite endpoints with differing combinations of updated mean HbA_{1c} and SBP categories.

A combination of diabetes and hypertension is known to give an increased risk of cardiovascular mortality [14–17], but these studies were too small in duration or size to allocate risks by categories. Our data confirm the increasing risk of cardiovascular disease with hyperglycaemia and hypertension as well as showing that the risk is additive when they co-exist. The Framingham study reported that the incidence of cardiovascular disease was substantially increased in diabetic compared with non-diabetic subjects

Table 3 Risk reductions in 3,418 UKPDS patients

	Number of endpoints	Risk decrease per 1% decrement in updated mean HbA_{1c} (95% CI)	p	Risk decrease per 10 mmHg decrement in updated mean SBP (95% CI)	p	p for interaction
Primary composite endpoints						
Any diabetes-related endpoint	1,172	21% (17–24)	<0.0001	11% (9–13)	<0.0001	0.028
Diabetes-related death	325	22% (16–28)	<0.0001	16% (12–20)	<0.0001	0.11
All-cause mortality	556	14% (11–19)	<0.0001	12% (9–16)	<0.0001	0.74
Secondary composite endpoints						
Myocardial infarction	461	14% (8–19)	<0.0001	11% (7–15)	<0.0001	0.68
Stroke	153	11% (0–21)	0.045	18% (13–23)	<0.0001	0.075
Microvascular disease	298	37% (33–41)	<0.0001	10% (7–14)	<0.0001	<0.0001

Risks reductions were calculated for a 1% decrement in updated mean HbA_{1c} and a 10-mmHg decrement in updated mean SBP using a proportional hazards model adjusted for sex, age at diagnosis, ethnicity, smoking, HDL-cholesterol, LDL-cholesterol, triglycerides and albuminuria. A product term for HbA_{1c} and SBP was included in the model to test for possible interactions with a 1% level of significance chosen to avoid potential Type 1 errors. Non-statistically significant product terms are indicative of additive effects

Table 4 Incidence of composite endpoints in the 887 patients who were randomised in both the glycaemia and hypertension intervention arms of the UKPDS

	p for trend for neither, either or both intensive interventions	No. of patients	Patients with composite endpoints	Absolute event risk per 1,000 person-years	p for log-rank	Relative risk compared with neither intensive intervention policy	95% CI
Any diabetes-related endpoint	0.024						
Neither intervention							
Conventional glucose and less tight BP		87	37	65.5	–	1.00	–
Either intervention							
Conventional glucose and tight BP		155	59	57.9	0.55	0.88	0.59–1.33
Intensive glucose and less tight BP		231	100	66.8	0.97	1.02	0.70–1.47
Both interventions							
Intensive glucose and tight BP		414	134	48.8	0.11	0.74	0.52–1.07
Diabetes-related deaths	0.058						
Neither intervention							
Conventional glucose and less tight BP		87	15	21.8	–	1.00	–
Either intervention							
Conventional glucose and tight BP		155	19	15.7	0.33	0.72	0.37–1.41
Intensive glucose and less tight BP		231	32	18.0	0.54	0.83	0.45–1.53
Both interventions							
Intensive glucose and tight BP		414	42	12.9	0.077	0.59	0.33–1.06
All-cause mortality	0.26						
Neither intervention							
Conventional glucose and less tight BP		87	20	29.1	–	1.00	–
Either intervention							
Conventional glucose and tight BP		155	27	22.3	0.35	0.77	0.43–1.36
Intensive glucose and less tight BP		231	45	25.4	0.62	0.87	0.52–1.48
Both interventions							
Intensive glucose and tight BP		414	71	21.8	0.26	0.75	0.46–1.23

The comparator group comprises those patients who were randomised to both the conventional blood glucose policy and the less tight BP control policy (neither)

[18]. Dyslipidaemia and smoking, which have been shown to be major risk factors for coronary artery disease [19, 20], were included as covariates in the analyses presented here. Moreover, we estimated the absolute and relative risks at several different levels of glycaemic and BP exposure, rather than by the broader classes used by some previous studies [21–23] and examined the effects on both the macrovascular and microvascular complications of diabetes.

For all composite endpoints, the risk associated with the combination of elevated blood glucose and BP is as least as great as the sum of the individual exposures. For diabetes-related deaths, all-cause mortality, myocardial infarction and stroke, the combined glycaemia and BP effects were additive. This finding is in accord with other studies [7]. For microvascular endpoints, however, this relationship was sub-additive, suggesting that the deleterious effects of hyperglycaemia and hypertension are not as great at elevated levels of each other as they are at lower levels of the other risk factor. This may be due to pre-existing tissue damage that cannot deteriorate further.

The risk reduction trends seen with the HbA_{1c} and SBP decreases obtained in the clinical trial are consistent with the observational data presented here. Direct comparisons between the trial and observational data should be undertaken cautiously as only hypertensive individuals were included in the BP-lowering arm of the UKPDS. The median HbA_{1c} and SBP differences between randomised policy groups reflect the central tendencies of the HbA_{1c} and SBP distributions obtained, whereas the observational analyses were based on selection of patients between limits of exposure defined by 1% HbA_{1c} and 10 mmHg SBP intervals. The observational analyses also contain considerably more data (43,558 person-years) than the combined trial analysis of randomised BP and glycaemic control policies (9,184 person-years). The UKPDS was designed to address separately the degree to which clinical outcomes in type 2 diabetes might be improved by more intensive treatment of blood glucose or BP, and was not powered to evaluate whether simultaneous improvement of these two risk factors might be additive. The small number of patients included in both the blood glucose and BP interventions means that there is insufficient statistical power to provide definitive answers with respect to an approach that improves blood glucose and BP simultaneously. We await with interest the results of the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) (http://www.accordtrial.org/public/index.cfm) and Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) [24] studies, both of which are examining in a factorial design the impact of improved blood glucose and BP control on macrovascular outcomes in people with type 2 diabetes.

The results of the observational analyses presented here are likely to be generalisable to patients with newly diagnosed type 2 diabetes. Whilst the UKPDS excluded people with a recent myocardial infarction, there is no reason to believe that the associations shown here with glycaemia and BP would be any different in these individuals. The commonest reason for not entering the study was lack of interest, with only 28% being excluded for other reasons [9]. It is not clear whether these results would be applicable to the elderly, e.g. over 70 years, as the upper age limit for entry to the UKPDS was 65 years. Although hypertension has been assessed here using SBP, similar results were obtained using diastolic BP (data not shown). The absolute event rates reported here are lower than might be expected for people with type 2 diabetes, possibly because UKPDS patients were newly diagnosed, aged 65 or below, did not have a history of a recent myocardial infarction or life-threatening disease at entry and received additional health care as participants in a clinical trial [9].

Our data have major clinical relevance, since more than half of patients with type 2 diabetes have HbA_{1c} values >8.0% [25], and almost as many may have SBP values >150 mmHg [25]. Since therapy of each of the risk factors is known to reduce the risk of complications [1, 5, 6, 26], and the presence of both risk factors markedly increases the risk over the presence of just one, there is potential for achieving a major reduction in the incidence of the complications of diabetes by treating both blood glucose and BP. The data presented here are further evidence for taking a view of prevention based on assessment of overall risk of complications rather than on that assessed from individual risk factors [7], particularly now that the coronary heart disease risks can be calculated specifically for people with type 2 diabetes [27, 28]. The concordance of the intervention trial data with the observational analyses indicates that optimal therapy of both elevated blood glucose and elevated BP is essential to help minimise the risk of diabetic complications in type 2 diabetes.
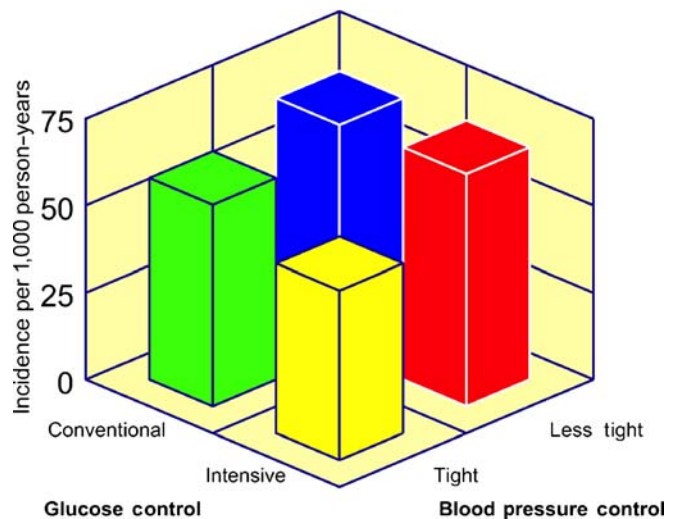

Fig. 2 Incidence of the UKPDS primary composite 'any diabetes-related endpoint' by intention-to-treat, as rate per 1,000 person-years, in the 887 patients randomised in a factorial design between the four different interventions: a conventional or intensive glucose control policy and a less tight or tight BP control policy. Only endpoints that occurred following each patient's randomisation into the BP control study are included. Those allocated to both the intensive glucose and the tight BP control policies had fewer events than those allocated to either policy alone or to neither (p for trend 0.024)

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