Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)

UK Prospective Diabetes Study (UKPDS) Group*

Summary

Background In patients with type 2 diabetes, intensive blood-glucose control with insulin or sulphonylurea therapy decreases progression of microvascular disease and may also reduce the risk of heart attacks. This study investigated whether intensive glucose control with metformin has any specific advantage or disadvantage.

Methods Of 4075 patients recruited to UKPDS in 15 centres, 1704 overweight (>120% ideal bodyweight) patients with newly diagnosed type 2 diabetes, mean age 53 years, had raised fasting plasma glucose (FPG; 6·1–15·0 mmol/L) without hyperglycaemic symptoms after 3 months' initial diet. 753 were included in a randomised controlled trial, median duration 10·7 years, of conventional policy, primarily with diet alone (n=411) versus intensive blood-glucose control policy with metformin, aiming for FPG below 6 mmol/L (n=342). A secondary analysis compared the 342 patients allocated metformin with 951 overweight patients allocated intensive blood-glucose control with chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409). The primary outcome measures were aggregates of any diabetes-related clinical endpoint, diabetes-related death, and all-cause mortality. In a supplementary randomised controlled trial, 537 non-overweight and overweight patients, mean age 59 years, who were already on maximum sulphonylurea therapy but had raised FPG (6·1–15·0 mmol/L) were allocated continuing sulphonylurea therapy alone (n=269) or addition of metformin (n=268).

Findings Median glycated haemoglobin (HbA$_{1c}$) was 7·4% in the metformin group compared with 8·0% in the conventional group. Patients allocated metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13–47, p=0·002) for any diabetes-related endpoint, 42% for diabetes-related death (9–63, p=0·017), and 36% for all-cause mortality (9–55, p=0·011). Among patients allocated intensive blood-glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint (p=0·0034), all-cause mortality (p=0·021), and stroke (p=0·032). Early addition of metformin in sulphonylurea-treated patients was associated with an increased risk of diabetes-related death (96% increased risk [95% CI 2–275], p=0·039) compared with continued sulphonylurea alone. A combined analysis of the main and supplementary studies showed fewer metformin-allocated patients having diabetes-related endpoints (risk reduction 19% [2–33], p=0·033). Epidemiological assessment of the possible association of death from diabetes-related causes with the concurrent therapy of diabetes in 4416 patients did not show an increased risk in diabetes-related death in patients treated with a combination of sulphonylurea and metformin (risk reduction 5% [−33 to 32], p=0·78).

Interpretation Since intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints in overweight diabetic patients, and is associated with less weight gain and fewer hypoglycaemic attacks than are insulin and sulphonylureas, it may be the first-line pharmacological therapy of choice in these patients.

Introduction

The UK Prospective Diabetes Study reported that intensive blood-glucose control with sulphonylureas or insulin substantially reduced the risk of complications but not macrovascular disease.[1]

Metformin is a biguanide that decreases blood glucose concentration by mechanisms different from those of sulphonylurea or insulin. It lowers, rather than increases, fasting plasma insulin concentrations[2] and acts by enhancing insulin sensitivity, inducing greater peripheral uptake of glucose, and decreasing hepatic glucose output.[3] The improved glucose control is achieved without weight gain.[4] Biguanides also decrease concentrations of plasminogen-activator inhibitor type 1 (PAI-1)[5] and may thus increase fibrinolytic activity. This effect may be secondary either to enhanced insulin sensitivity or to lower insulin concentrations, because therapy with troglitazone (a thiazolidinedione) also decreases production of PAI-1 and increases insulin sensitivity.[6]

The only long-term outcome data on biguanides available were from the University Group Diabetes Program (UGDP) study of phenformin. An unexpected outcome was higher mortality from cardiovascular causes with phenformin than with placebo, and for total mortality for phenformin than with a combination of

*Study organisation given at end of paper

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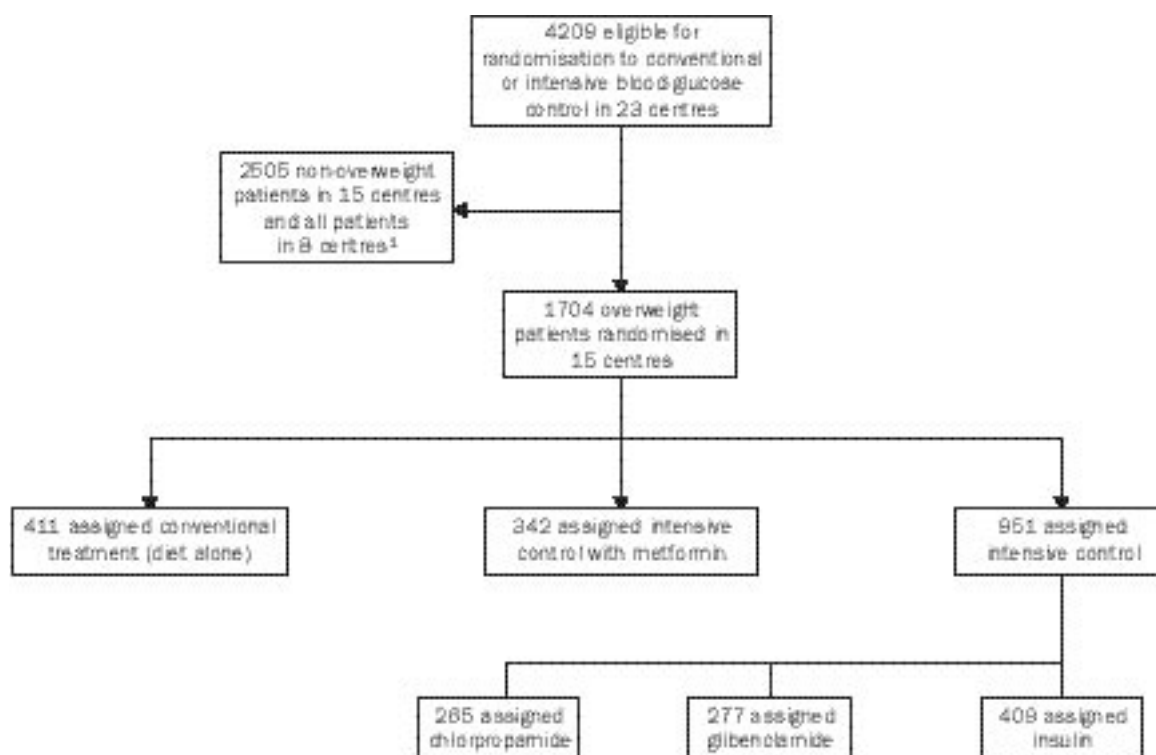
Figure 1: **Trial profile for diet/metformin study in overweight diet-treated patients**

insulin and placebo allocations.[7] The study design did not allow comparison of phenformin with the sulphonylurea used in the UGDP (tolbutamide). One death from lactic acidosis occurred in the phenformin group. Phenformin was withdrawn from clinical use in many countries, partly because of the UGDP data and partly because of the association with lactic acidosis.[8]

Metformin is now the only biguanide in general use, since it has a 10–20-fold lower risk of lactic acidosis than phenformin, and is regarded as a safe drug provided it is not used in at-risk patients, such as those in renal failure.[9]

Metformin was included as a randomisation option in overweight patients in the UK Prospective Diabetes Study (UKPDS) from 1977 as part of the original protocol in the first 15 centres. The primary aim was to compare conventional treatment (primarily with diet alone) with intensive treatment with metformin,[10–12] with a secondary aim of comparing the group allocated metformin with overweight patients allocated sulphonylurea or insulin therapies.

In 1990, increasing glycaemia despite maximum sulphonylurea therapy was noted. Following a UKPDS protocol amendment, normal-weight and overweight patients allocated sulphonylurea treatment, who had fasting plasma glucose (FPG) concentrations of 6·1–15·0 mmol/L but no symptoms on maximum doses, were then assigned either continuing treatment with sulphonylurea alone or addition of metformin to sulphonylurea.

We report here on whether addition of metformin reduces the risk of clinical complications of diabetes.

Methods
Patients
UKPDS has been described in the accompanying paper.[1,10] In brief, between 1977 and 1991, general practitioners in 23 centres in the UK referred patients with newly diagnosed type 2 diabetes, aged 25–65 years, for possible inclusion in UKPDS. 5102 diabetic patients with FPG above 6·0 mmol/L on two mornings were recruited. The patients were advised to follow a diet high in carbohydrates and fibre and low in saturated fats, with energy restriction in overweight patients. After 3 months on diet, 4209 eligible patients with FPG above 6·0 mmol/L were randomised by a stratified design: 2022 (48%) were non-overweight patients (<120% ideal bodyweight[13]) and 2187 (52%) were overweight. Patients were allocated conventional treatment with diet or intensive treatment with sulphonylurea or insulin with metformin as an additional intensive therapy option in overweight patients in the first 15 centres. We report here results for the overweight participants who had FPG between 6·1 and 15·0 mmol/L (n=1704) without symptoms of hyperglycaemia, after diet treatment.

This paper reports on two randomised controlled trials in patients in the first 15 centres, in which metformin was a therapeutic option.

Trial in overweight, diet-treated patients of intensive blood-glucose control with metformin versus conventional treatment
The 1704 overweight patients were randomly assigned conventional treatment, primarily with diet (24%), or intensive treatment with chlorpropamide (16%), glibenclamide (16%), insulin (24%), or metformin (20%). This report primarily compares the 411 overweight patients assigned conventional treatment and 342 overweight patients assigned intensive treatment with metformin, as designated in the protocol[10] (figure 1). The paper also reports the secondary analysis comparing the outcomes between overweight patients allocated metformin (n=342) with the 951 patients allocated intensive therapy with chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409).

Conventional treatment policy
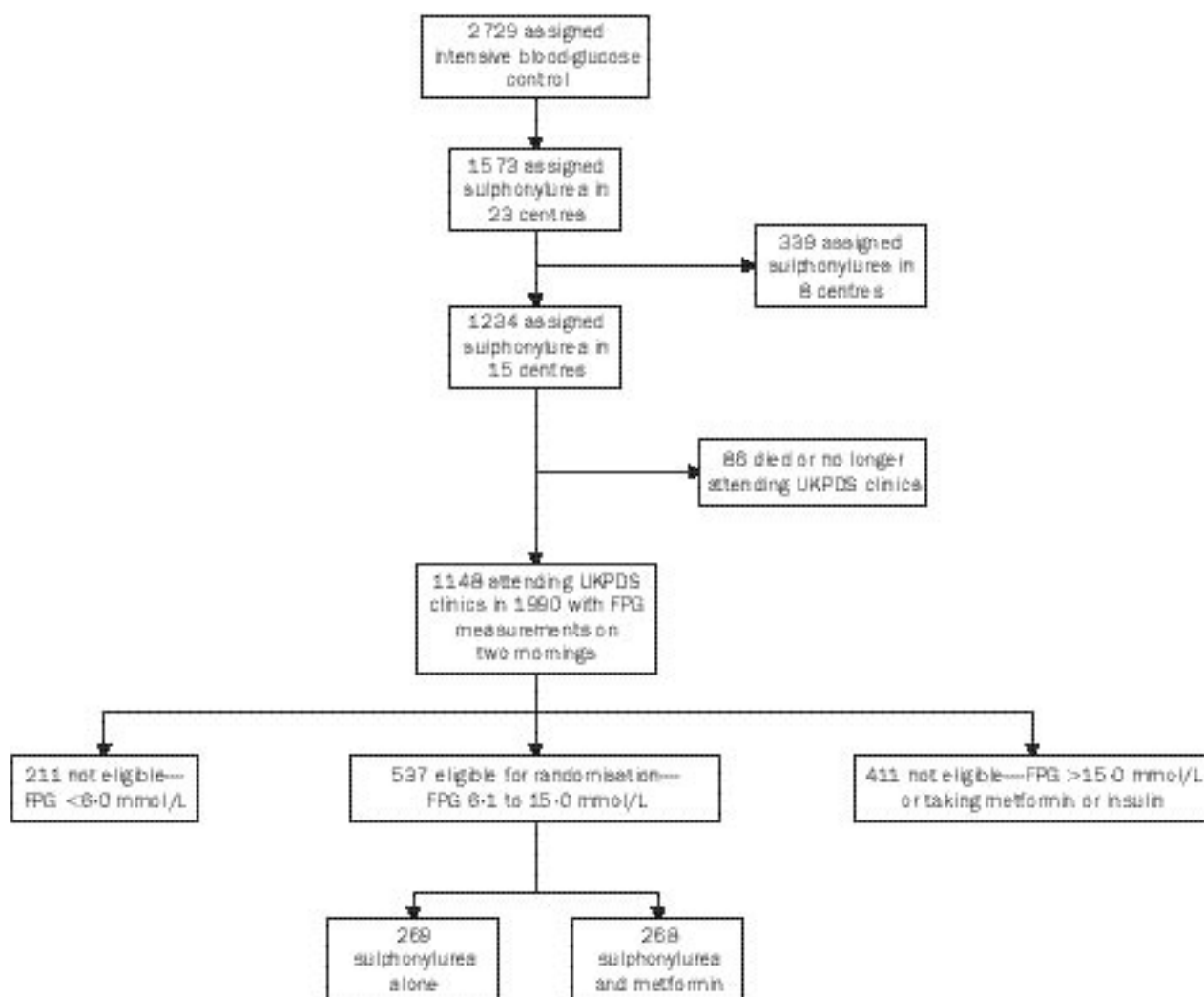The 411 overweight patients assigned the conventional approach continued to receive dietary advice at 3-monthly

Figure 2: **Trial profile for sulphonylurea-treated patients with randomisation to metformin**

clinical visits with the aim of attaining normal bodyweight and FPG to the extent that is feasible in clinical practice. If marked hyperglycaemia developed (defined by the protocol as FPG above 15 mmol/L or symptoms of hyperglycaemia[1]) patients were secondarily randomised to additional non-intensive pharmacological therapy with the other four treatments (metformin, chlorpropamide, glibenclamide, and insulin) in the same proportions as in the primary randomisations, with the aim of avoiding symptoms and maintaining FPG below 15 mmol/L.[1] If patients assigned sulphonylurea therapy developed marked hyperglycaemia, metformin was added to their regimen; if marked hyperglycaemia recurred, the allocation was changed to insulin therapy.

Intensive treatment policy with metformin

The aim of the intensive approach for glucose control with metformin, sulphonylurea, or insulin therapies, in addition to dietary advice, was to obtain near-normal FPG (ie, <6·0 mmol/L). If FPG increased, patients were kept on the allocated monotherapy alone until marked hyperglycaemia developed, so that the clinical effects of each therapy could be assessed.

342 overweight patients were assigned intensive control with metformin. Treatment started with one 850 mg tablet per day, then 850 mg twice daily, and then 1700 mg in the morning and 850 mg with the evening meal (maximum dose=2550 mg). If on any dose, symptoms of diarrhoea or nausea occurred, patients were asked to reduce the dose to that which previously did not cause symptoms.

When marked hyperglycaemia developed in those allocated metformin, glibenclamide was added with the aim of

maintaining FPG below 6·0 mmol/L. If marked hyperglycaemia again developed, treatment was changed to insulin, initially ultralente (Ultratard HM, Novo, or Humulin Zn, Lilly) or isophane (NPH) insulin, with the addition of short-acting (regular) insulin, usually soluble insulin before meals when premeal or bedtime blood-glucose concentrations were above 7·0 mmol/L. If the glucose control was not satisfactory, other regimens could be introduced (eg, soluble/isophane regimens).

Trial in non-overweight and overweight sulphonylurea-treated patients of addition of metformin versus continued sulphonylurea alone

1234 patients, both non-overweight and overweight, were assigned to intensive treatment with sulphonylurea in the first 15 centres. Of these, 537 who were treated with maximum doses of sulphonylurea and had FPG of 6·1–15·0 mmol/L without symptoms of hyperglycaemia, were randomly assigned in equal proportions early addition of metformin to the sulphonylurea (n=269) or continued sulphonylurea alone (n=268; figure 2). If those allocated sulphonylurea alone later developed protocol-defined marked hyperglycaemia, metformin was added. If patients with early or later addition of metformin developed protocol-defined marked hyperglycaemia, oral therapy was stopped and changed to insulin therapy.

Combined analysis of two randomised controlled trials

The unexpected finding of an increased risk of mortality in

	Conventional (n=411)	Metformin (n=342)	Insulin (n=409)	Chlorpropamide (n=265)	Glibenclamide (n=277)	All patients (n=1704)
Demographic						
Age (years)*	53 (9)	53 (8)	53 (8)	53 (9)	53 (9)	53 (8)
M/F	193 (47%)/218	157 (46%)/185	192 (47%)/217	119 (45%)/146	127 (46%)/150	784 (46%)/920
Ethnicity (%) Caucasian/Indian Asian/ Afro-Caribbean/other	86/6/7/1	85/4/10/1	88/4/8/0	86/6/8/0	87/4/8/1	86/5/8/1
Clinical						
Weight (kg)*	87 (15)	87 (17)	85 (14)	85 (15)	86 (14)	86 (15)
Body-mass index (kg/m²)	31·8 (4·9)	31·6 (4·8)	31·0 (4·2)	31·2 (4·5)	31·5 (4·4)	31·4 (4·6)
Systolic blood pressure (mm Hg)*	140 (18)	140 (18)	139 (19)	141 (18)	139 (19)	140 (18)
Diastolic blood pressure (mm Hg)*	86 (10)	85 (9)	85 (10)	86 (9)	85 (9)	86 (10)
Smoking (%) never/ex/current	39/36/25	43/32/25	37/34/39	38/30/32	34/35/31	38/34/28
Alcohol (%) none/social/regular/ dependent	30/56/14/0·5	27/58/14/1·5	27/57/15/1·2	28/54/17/1·1	25/56/19/1·1	27/56/15/1·1
Exercise (%) sedentary/moderately active/active/fit	24/40/34/3	29/34/35/3	24/37/36/4	21/38/38/3	21/34/40/5	24/36/36/4
Biochemical						
FPG (mmol/L)†	8·0 (7·1–9·3)	8·1 (7·2–9·8)	8·2 (7·2–10·0)	8·0 (7·2–9·6)	8·2 (7·3–9·6)	8·1 (7·1–9·7)
HBA₁c (%)*	7·1 (1·5)	7·3 (1·5)	7·2 (1·5)	7·2 (1·7)	7·2 (1·5)	7·2 (1·5)
Plasma insulin (pmol/L)‡	114 (71–183)	116 (66–203)	116 (71–186)	111 (65–189)	114 (68–189)	114 (69–190)
Triglyceride (mmol/L)‡	2·96 (1·03–8·47)	2·79 (1·01–7·74)	2·89 (1·02–8·19)	2·85 (1·03–7·86)	2·65 (0·99–7·10)	2·84 (1·02–7·92)
Total cholesterol (mmol/L)*	5·5 (1·0)	5·6 (1·3)	5·6 (1·1)	5·6 (1·2)	5·6 (1·2)	5·6 (1·2)
LDL cholesterol (mmol/L)*	3·66 (1·04)	3·67 (1·16)	3·69 (1·04)	3·59 (1·10)	3·59 (1·07)	3·65 (1·08)
HDL cholesterol (mmol/L)*	1·04 (0·22)	1·06 (0·23)	1·05 (0·23)	1·05 (0·23)	1·07 (0·26)	1·05 (0·23)
Medications						
More than one aspirin daily (%)	1·5	1·5	2·9	1·9	1·1	1·8
Diuretic (%)	20	17	20	20	19	19
Others (%) digoxin/antihypertensives/ lipid lowering/HRT or OC	0·5/16/0·4/0·4	0·9/15/0/0·3	1·7/12/0/0·3	1·9/15/0·7/0·4	0·4/16/0/0·7	0·9/15/0·1/0·4
Surrogate clinical endpoints						
Retinopathy (%)	33	38	39	37	29	36
Proteinuria (%)	3·1	2·0	1·1	2·2	2·6	2·2
Plasma creatinine (μmol/L)‡	78 (64–96)	77 (63–95)	77 (63–94)	79 (65–96)	79 (65–97)	79 (66–96)
Biothesiometer more than 25 V (%)	13·6	13·7	15·4	19·9	14·3	15·2

Data are % of group, *mean (SD),†median (IQR), or ‡geometric mean (1 SD).
HRT=hormone replacement therapy; OC=oral contraceptive therapy.

Table 1: **Baseline characteristics of patients in conventional group and in individual intensive-treatment groups**

sulphonylurea-treated patients allocated addition of metformin led us to undertake a further statistical analysis. Following a test for heterogeneity between the two trials described above,[15] a combined analysis of addition of metformin in patients on diet therapy and in those on sulphonylurea therapy was done. The datasets were merged by taking time from randomisation to metformin or not, to an event, or to a censor date. A formal meta-analysis[16] was also done.

Epidemiological assessment

We excluded 623 of the patients (537 in randomised controlled trial in patients on maximum sulphonylurea treatment of early or late addition of metformin, and 86 patients who had insufficient baseline data or were not in the main three ethnic groups). The aim of the epidemiological assessment in 4416 participants was to find out whether the combination of sulphonylurea and metformin was associated with an increase in mortality from diabetes-related causes. 457 patients were treated by sulphonylurea and metformin: 107 patients assigned conventional therapy in the main randomisation who received the combination after recurrent episodes of protocol-defined marked hyperglycaemia; 257 patients assigned sulphonylurea or metformin in the main randomisation, or those with marked hyperglycaemia after the initial 3 months' period, who had the other therapy added when marked hyperglycaemia developed; and 93 who refused allocated insulin. All these patients were treated by combined therapy because of the progressive hyperglycaemia of type 2 diabetes,[11] but if marked hyperglycaemia recurred, the treatment of these patients was changed to insulin. The combination of sulphonylurea and metformin was compared with all other therapies in terms of diabetes-related deaths by means of a Cox proportional-hazards model, with the actual therapy as a time-dependent covariate, and allowance for age, sex, ethnic group, and FPG after 3 months' diet.

Clinic visits

Patients were seen every month for the first 3 months and then every 3 months or more frequently if required to attain control criteria. Patients attended fasting for plasma glucose and other biochemical measurements, blood pressure and bodyweight were measured, and therapy was adjusted if necessary. Details were recorded of actual therapies, hypoglycaemic episodes, and home blood-glucose monitoring. At each visit, patients were asked whether they had experienced hypoglycaemic symptoms. Physicians recorded hypoglycaemic episodes as minor when the patient was able to treat the symptoms unaided, or major if third-party help or medical intervention was necessary. The number of patients, in an allocation and taking the allocated therapy, who had one or more minor or major hypoglycaemic episodes in a year was recorded, and the mean over 10 years calculated. Hypoglycaemic episodes in each year were analysed both by intention to treat and by actual therapy.

Clinical endpoint analyses

The closing date for the study was Sept 30, 1997. Endpoints were aggregated for analysis to keep to a minimum the numbers of statistical tests.[12] The three predefined primary outcome analyses were the time to the first occurrence of: any diabetes-related clinical endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hypoglycaemia, or hyperglycaemia, and sudden death); and all-cause mortality. Four additional clinical endpoint aggregates were used to assess the effect of therapies on different types of vascular disease in secondary outcome analyses: myocardial infarction (fatal and non-fatal
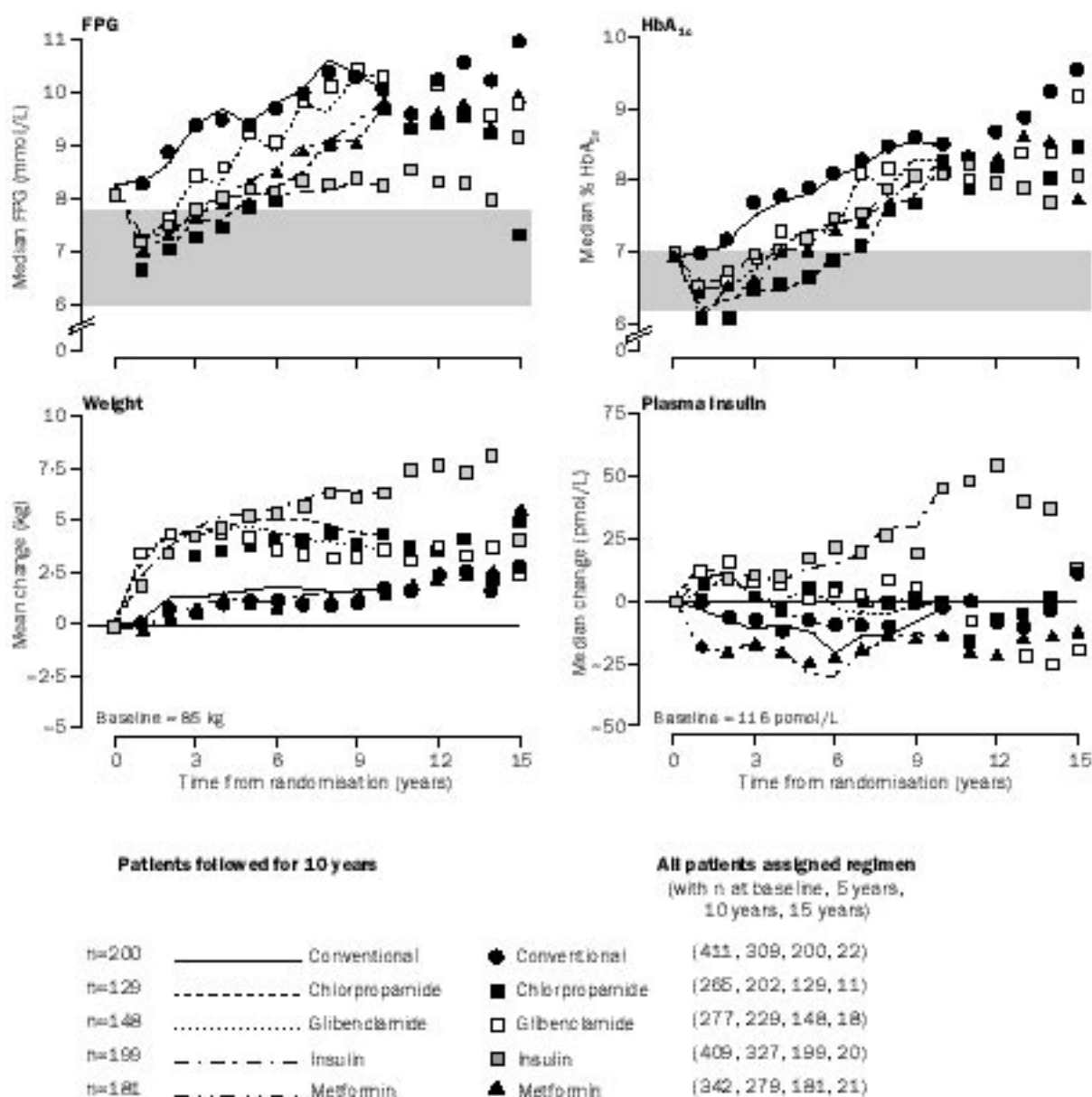
Figure 3: Median FPG, median HbA$_{1c}$, mean change in bodyweight, and median change in fasting plasma insulin in cohorts of patients followed up to 10 years by assigned treatment (shown by continuous lines)
Cross-sectional data at each year are shown by individual symbols for all patients assigned regimen.

and sudden death); stroke (fatal and non-fatal); amputation (of at least one digit) or death due to peripheral vascular disease (including death from gangrene); and microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure). Subclinical, surrogate variables[1] were assessed every 3 years.

Biochemistry
Methods have been previously reported.[1,17] The normal range for glycated haemoglobin (HbA$_{1c}$) was 4·5–6·2%. Microalbuminuria has been defined for this study as urinary albumin concentration above 50 mg/L and clinical grade proteinuria as more than 300 mg/L.

Assignment
All randomisations were done at the level of the individual patient, by means of therapy allocations in sealed opaque envelopes, which were opened in sequence. The numerical

sequence of envelopes used, the dates they were opened, and the therapies stipulated were monitored. No placebo was given.

Statistical analysis
Analyses were by intention to treat. Life-table analyses were done with log-rank tests and hazard ratios, used to estimate relative risks, were obtained from Cox proportional-hazards models. For the primary and secondary outcome analyses of clinical endpoint aggregates, 95% CIs are quoted. For single endpoints 99% CIs are quoted, to make allowance for potential type 1 errors.[1] Further details are given in the accompanying paper.[1]

Results
Intensive blood-glucose control with metformin versus conventional treatment in overweight patients
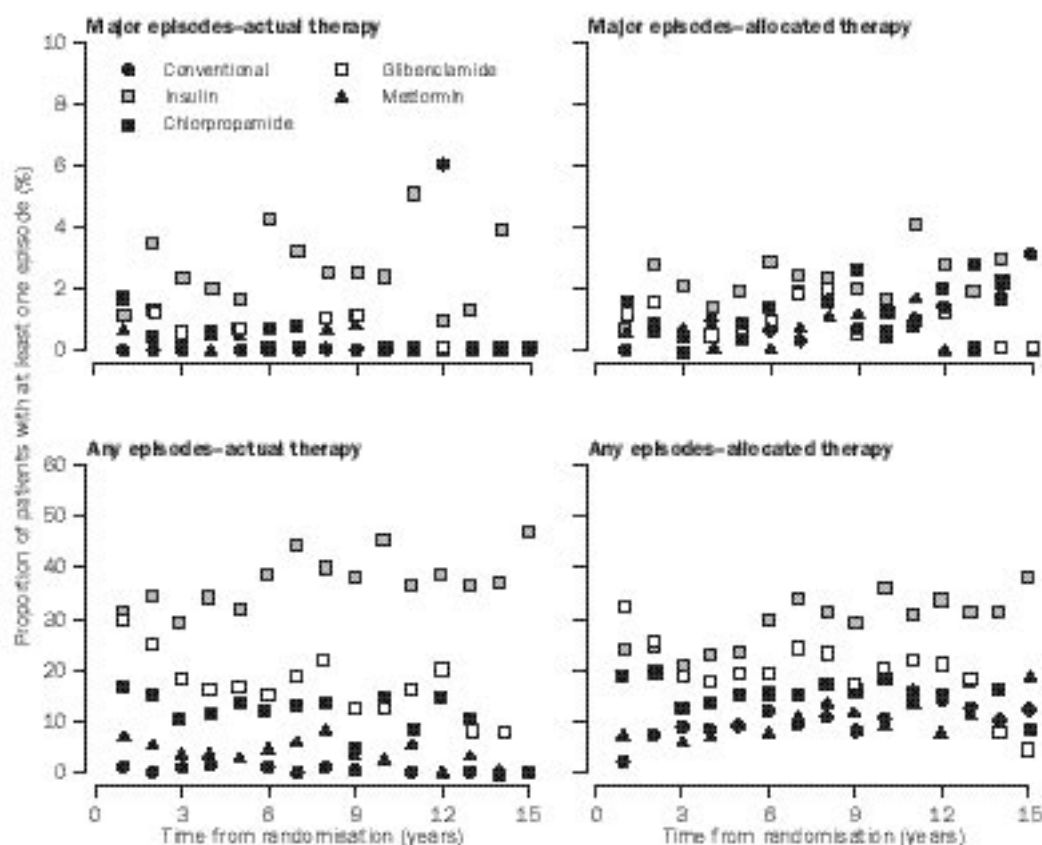Table 1 shows the baseline data for overweight patients

Figure 4: Proportion of patients who reported one or more episodes of major hypoglycaemia or any hypoglycaemia per year, assessed by actual therapy and by allocation (intention to treat)

Numbers of patients studied at 5 years, 10 years, and 15 years in actual therapy analysis=168, 60, and 6 for conventional group; 220, 101, and 6 for metformin group; 235, 166, and 26 for insulin group; 148, 60, and 5 for chlorpropamide group; and 161, 71, and 6 for glibenclamide group.

at the time of randomisation to conventional treatment or intensive treatment with chlorpropamide, glibenclamide, insulin, or metformin. The mean body-mass index for overweight patients with type 2 diabetes was 31·4 kg/m² (SD 4·6); 99·5% of patients had body-mass index greater than 25 kg/m², and 54·0% had body-mass index greater than 30 kg/m².

The median follow-up (to the last known date at which vital status was known or to the end of the trial) was 10·7 years. Vital status was not known at the end of the trial for 13 (1·8%) patients who had emigrated. A further 43 (2·5%) patients could not be contacted in the last year of the study for assessment of clinical endpoints.

Figure 3 shows the median FPG and HbA$_{1c}$ in the cohort of 482 patients with data available studied over 10 years and cross-sectional data for all those assigned each therapy. In the metformin group there was a decrease in FPG and HbA$_{1c}$ in the first year, with a subsequent gradual rise in both variables. From 10 years, FPG in the metformin group approached that of the conventional treatment group. The median HbA$_{1c}$ during the 10 years of follow-up was 7·4% in the metformin group and 8·0% in the conventional treatment group. The patients assigned intensive control with sulphonylurea or insulin had similar HbA$_{1c}$ to the metformin group. The median HbA$_{1c}$ values in the metformin group and conventional control group were 6·7% and 7·5%, respectively, in the first 5 years of follow-up, 7·9% and 8·5% in the second 5 years, and 8·3% and 8·8% in the last 5 years. The cross-sectional

data, of all patients at each year, were similar to the cohort data.

For the cohorts followed up for 10 years, the change in bodyweight was similar in the metformin and conventional control groups, and less than the increase in bodyweight observed in patients assigned intensive control with sulphonylureas or insulin. There was a decrease in fasting plasma insulin in the patients assigned metformin, which persisted throughout follow-up (figure 3).

Of the 4292 person-years of follow-up among patients assigned conventional control, 2395 (56%) were treated by diet. The remaining 44% of person-years required, as per protocol, additional non-intensive pharmacological therapies. Of the 3682 person-years of follow-up among the overweight patients assigned metformin, 3035 (82%) were treated with metformin alone or in combination. The median dose of metformin was 2550 mg/day (IQR 1700–2550). For the conventional control group, there were 3557 (83%) of person-years with crossover to metformin therapy.

Figure 4 shows the proportion of patients per year who had a major hypoglycaemic episode according to actual therapy and intention to treat. The rate of any hypoglycaemic episodes was higher in patients taking metformin as allocated than in those on diet alone but lower than the rates in those taking sulphonylureas as allocated. The rate of hypoglycaemic episodes increased over time among patients treated with insulin, as higher insulin doses were required, and decreased among those on sulphonylurea therapy, as glucose concentrations
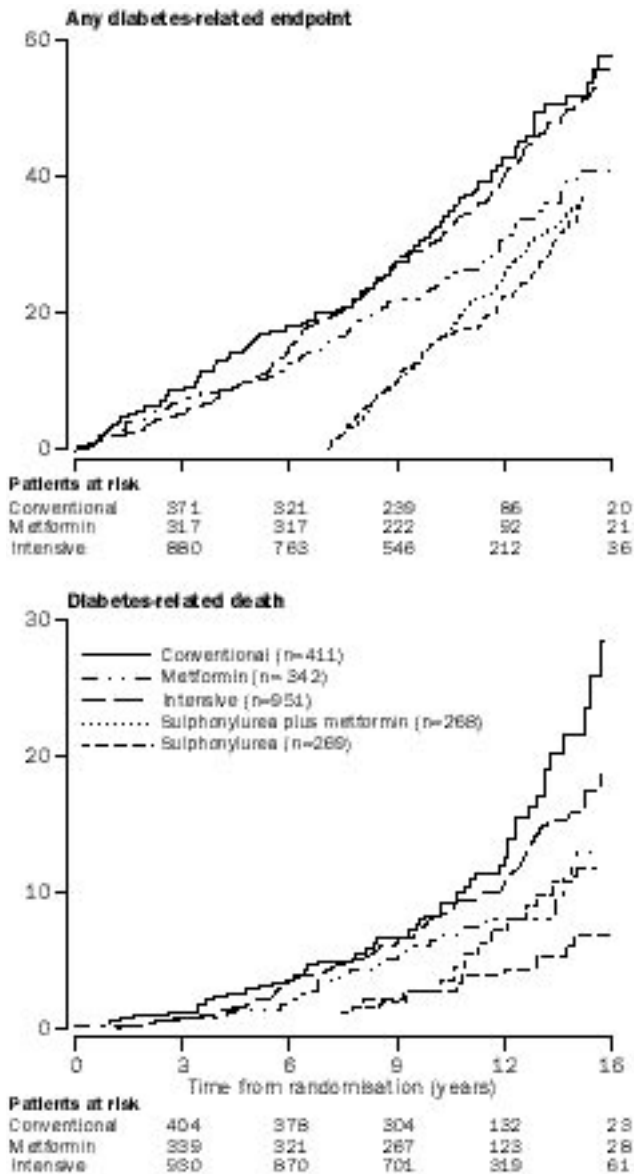
Figure 5: **Kaplan-Meier plots in diet/metformin study for any diabetes-related clinical endpoint and diabetes-related death**
Intensive, in this figure, indicates chlorpropamide, glibenclamide, and insulin groups. Similar plots of data for sulphonylurea/metformin study are superimposed showing relative time of commencement.

increased. Over 10 years of follow-up among patients taking therapy as allocated, the proportions of patients per year who had one or more major hypoglycaemic attacks in the conventional, chlorpropamide, glibenclamide, insulin, and metformin groups were 0·7%, 0·6%, 2·5%, 0·3%, and 0% respectively; for any hypoglycaemic episode the corresponding proportions were 0·9%, 12·1%, 17·5%, 34·0%, and 4·2%.

Among all patients assigned treatments (intention-to-treat analyses), major hypoglycaemic episodes occurred in 0·7%, 1·2%, 1·0%, 2·0%, and 0·6%, respectively, of the conventional, chlorpropamide, glibenclamide, insulin, and metformin groups, and any hypoglycaemic episodes in 7·9%, 15·2%, 20·5%, 25·5%, and 8·3%, respectively. Hypoglycaemic episodes in patients on diet therapy were reactive hypoglycaemic attacks, either after meals or, in some patients, after termination of glucose infusions while in hospital (eg, postoperatively).

Aggregate and single endpoints (diet vs metformin study)

Patients assigned intensive blood-glucose control with metformin had a 32% lower risk (p=0·0023) of developing any diabetes-related endpoint than those allocated conventional blood-glucose control (figures 5 and 6). These endpoints included macrovascular and microvascular complications and represented the effect of intensive policy with metformin on complication-free survival. The group assigned metformin had a significantly greater risk reduction than those assigned intensive therapy with sulphonylurea or insulin (p=0·0034).

The metformin group had a lower risk of diabetes-related death than the conventional treatment group (figures 5 and 6), with no significant difference between the metformin group and those assigned therapy with sulphonylurea or insulin. There were no deaths from lactic acidosis.

Cardiovascular disease accounted for 62% of the total mortality in the overweight patients in the conventional treatment group. The metformin group had a 36% lower risk (p=0·011) of all-cause mortality than the conventional group (figure 6). There was a greater risk reduction than in the groups assigned intensive therapy with sulphonylurea or insulin (p=0·021). The metformin group had a 39% lower risk (p=0·010) of myocardial infarction than the conventional treatment group, but did not differ from the other intensive treatment group (figure 6). There were no significant differences between the metformin group and the conventional group in the other aggregate endpoints. For all macrovascular diseases together (myocardial infarction, sudden death, angina, stroke, and peripheral disease), the metformin group had a 30% (5–48, p=0·020) lower risk than the conventional treatment group but did not differ significantly from the other intensive groups.

Data for the single endpoints are shown in figures 7 and 8. There was no difference in the rate of death due to non-diabetes-related endpoints (accidents, cancer, other specified causes, or unknown causes).

Surrogate endpoints—The metformin group had a lower rate of progression to retinopathy than the conventional group, of borderline significance (p=0·044), at 9 years; there was no difference at 12 years. The result was similar to that in the other intensive therapy group. The proportion of patients with urine albumin above 50 mg/L did not differ significantly between the intensive treatment, metformin, and conventional groups (24%, 23%, and 23% respectively). There was no difference between the treatment groups in any of the surrogate indices of macrovascular disease.

Addition of metformin in patients receiving sulphonylurea

Table 2 shows the demographic data for the patients whose response to maximum sulphonylurea treatment was not adequate (FPG 6·1–15·0 mmol/L) and who were assigned continuing intensive policy with sulphonylurea alone or with early addition of metformin. The mean body-mass index of normal and overweight patients in this study was 29·6 kg/m² (SD 5·5); 17% had body-mass index below 25 kg/m² and 39% had values above 30 kg/m².

AGGREGATE ENDPOINT	p for metformin vs other intensive	Patients with aggregate endpoints		Absolute risk (events per 1000 patient-years)		Log-rank 2p	RR (95% CI) vs conventional	Favours metformin or intensive	Favours conventional
		Metformin or intensive	Conventional	Metformin or intensive	Conventional				
Any diabetes-related endpoint	p=0·0034								
Metformin		96	160	29·8	43·3	0·0023	0·68 (0·53–0·87)		
Intensive		350	160	40·1	43·3	0·46	0·93 (0·77–1·12)		
Diabetes-related death	p=0·11								
Metformin		28	55	7·5	12·7	0·017	0·58 (0·37–0·91)		
Intensive		103	55	10·3	12·7	0·19	0·80 (0·58–1·11)		
All-cause mortality	p=0·021								
Metformin		50	89	13·5	20·6	0·011	0·64 (0·45–0·91)		
Intensive		150	89	18·9	20·6	0·49	0·92 (0·71–1·18)		
Myocardial infarction	p=0·12								
Metformin		39	73	11·0	18·0	0·01	0·61 (0·41–0·89)		
Intensive		139	73	14·4	18·0	0·11	0·79 (0·60–1·05)		
Stroke	p=0·032								
Metformin		12	23	3·3	5·5	0·13	0·59 (0·29–1·18)		
Intensive		60	23	6·2	5·5	0·60	1·14 (0·70–1·84)		
Peripheral vascular disease	p=0·62								
Metformin		6	9	1·6	2·1	0·57	0·74 (0·26–2·09)		
Intensive		12	9	1·2	2·1	0·18	0·56 (0·24–1·33)		
Microvascular	p=0·39								
Metformin		24	38	6·7	9·2	0·19	0·71 (0·43–1·19)		
Intensive		74	38	7·7	9·2	0·38	0·84 (0·57–1·24)		

Figure 6: **Incidence of clinical endpoints among patients assigned intensive control with metformin (n=342), intensive control with chlorpropamide, glibenclamide, or insulin (intensive; n=951), or conventional control (n=411)**
Relative risk (RR) is for metformin or intensive group compared with conventional group.

The median duration from the initial randomisation to subsequent randomisation of addition or no addition of metformin was 7·1 years. The median follow-up after randomisation was 6·6 years. Vital status was not known in ten (2%) patients who had emigrated and a further five (1%) who could not be contacted.

Figure 9 shows the median FPG and HbA_{1c} in the cohorts studied for 4 years after second randomisation to addition or no addition of metformin therapy compared with data for all the overweight patients in the comparison of intensive control with metformin and conventional control. There was a decrease in FPG in patients on sulphonylurea therapy who were assigned addition of metformin, whereas FPG concentrations in those on sulphonylurea therapy alone approached those of overweight patients in the conventional treatment group. HbA_{1c} values in patients with addition of metformin decreased initially but approached those of the patients remaining on sulphonylurea alone after 3

years. The median HbA_{1c} over 4 years in the cohort with addition of metformin was 7·7% compared with 8·2% in those on sulphonylurea alone. There were no significant differences in bodyweight or plasma insulin between the groups allocated addition of metformin or continued sulphonylurea therapy alone.

The patients assigned addition of metformin took this drug for 62% of their person-years of follow-up. For those randomly assigned continuing sulphonylurea alone, there were 75% of person-years without metformin therapy.

Aggregate and single endpoints (addition of metformin study)
Figure 10 shows the aggregates of endpoint data and figure 11 the single endpoint data.

The addition of metformin to sulphonylurea was associated with a 96% increased (p=0·039) risk of diabetes-related death. Addition of metformin to

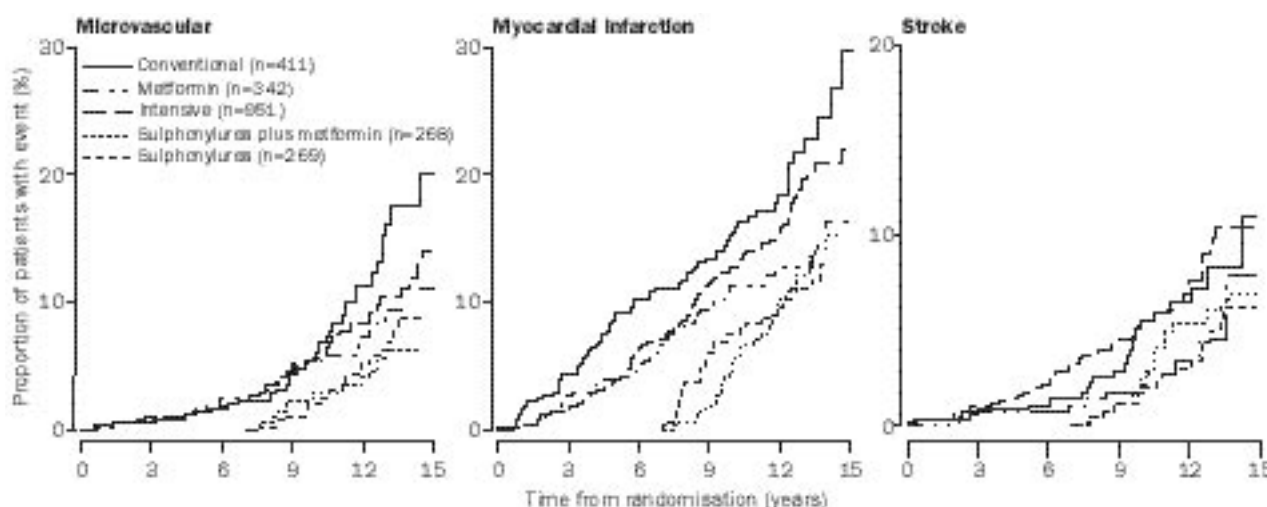Figure 7: **Kaplan-Meier plots in diet/metformin study for microvascular disease (renal failure or death from renal failure, retinopathy requiring photocoagulation, or vitreous haemorrhage), myocardial infarction (non-fatal and fatal, including sudden death), stroke (non-fatal and fatal) and cataract extraction**
Similar plots of data for sulphonylurea/metformin study are superimposed showing relative time of commencement.

CLINICAL ENDPOINT	Patients with clinical endpoint		Absolute risk (events per 1000 patient-years)		Log-rank 2p	RR (95%CI) metformin vs conventional	Favours metformin	Favours conventional
	Metformin	Conventional	Metformin	Conventional				
Fatal myocardial infarction	16	36	4·3	8·3	0·02	0·50 (0·23–1·09)		
Non-fatal myocardial infarction	24	40	6·8	9·9	0·15	0·69 (0·35–1·34)		
Sudden death	3	6	0·8	1·4	0·44	0·58 (0·09–3·61)		
Heart failure	11	17	3·0	4·0	0·41	0·73 (0·27–1·97)		
Angina	21	22	5·9	5·3	0·71	1·12 (0·51–2·46)		
Fatal stroke	6	9	1·6	2·1	0·59	0·75 (0·19–2·93)		
Non-fatal stroke	6	16	1·6	3·8	0·06	0·42 (0·12–1·45)		
Death from peripheral vascular disease	0	2	0	0·5				
Amputation	6	9	1·6	2·1	0·57	0·74 (0·19–2·89)		
Death from renal disease	2	1	0·5	0·2	0·45	2·44 (0·10–57·46)		
Renal failure	2	2	0·5	0·5	0·90	1·14 (0·09–14·94)		
Retinal photocoagulation	22	36	6·1	8·7	0·17	0·69 (0·34–1·39)		
Vitreous haemorrhage	2	3	0·5	0·7	0·75	0·75 (0·07–7·82)		
Blind in one eye	12	13	3·3	3·1	0·87	1·07 (0·38–2·99)		
Cataract extraction	14	25	3·9	6·0	0·20	0·65 (0·28–1·56)		
Death from hyperglycaemia	0	1	0	0·2				
Death from hypoglycaemia	1	0	0·3	0				
Fatal accident	0	0	0	0				
Death from cancer	13	21	3·5	4·9	0·33	0·71 (0·29–1·76)		
Death from any other specified cause	7	12	1·9	2·8	0·41	0·68 (0·20–2·30)		
Death from unknown cause	2	1	0·5	0·2	0·49	2·29 (0·10–53·8)		

Figure 8: Incidence of single endpoints in diet vs metformin study
Relative risk (RR) is for comparison with conventional control.

sulphonylurea therapy also increased the risk of death from any cause (60% increase, p=0·041). There were no significant differences between the groups for the other aggregate endpoints. In a subgroup analysis, there was no significant difference between patients allocated metformin in addition to chlorpropamide or glibenclamide (data not shown).

The data for the single endpoints are shown in figure 11.

Combined analysis of both trials
Heterogeneity tests confirmed the different outcomes between the two trials for any diabetes-related endpoint (p=0·034), diabetes-related death (p=0·00256), and all-cause mortality (p=0·0173), with a non-significant trend for myocardial infarction (p=0·068). Figure 10 shows the results for the two trials combined, with a 12% reduced risk for any diabetes-related endpoint (p=0·033). A formal meta-analysis gave similar results for diabetes-related endpoints (observed minus expected 22·7, variance 104·9, p=0·026) and for myocardial infarction (observed minus expected 12·2, variance 43·9, p=0·065).

Epidemiological analysis
The 4417 patients had 45 527 person-years of follow-up; 5181 (11%) of these person-years were treated with sulphonylurea plus metformin therapy. 39 (8%) of the 490 diabetes-related deaths occurred while patients were receiving sulphonylurea plus metformin therapy. A Cox proportional-hazards model, with adjustment for age, sex, ethnic group, and FPG after 3 months' diet,

	Sulphonylurea alone (n=269)	Sulphonylurea plus metformin (n=268)	All patients (n=537)
Demographic			
Age (years)*	58 (9)	59 (8)	59 (9)
M/F	164 (61%)/108	158 (59%)/118	322 (60%)/226
Ethnicity (%) Caucasian/Indian Asian/Afro-Caribbean/other	77/13/10/0	77/11/12/0	77/11/11/1
Clinical			
Weight (kg)*	82 (16)	83 (16)	83 (16)
Body-mass index (kg/m²)	29·4 (5·7)	29·7 (5·3)	29·6 (5·5)
Systolic blood pressure (mm Hg)*	138 (21)	140 (20)	139 (21)
Diastolic blood pressure (mm Hg)*	81 (11)	83 (11)	82 (11)
Smoking (%) never/ex/current	31/40/29	35/40/24	33/40/27
Alcohol (%) none/social/regular/dependent	37/44/18/0·4	32/51/16/1·1	34/52/13/0·8
Exercise (%) sedentary/moderately active/active/fit	14/38/45/3	22/35/39/4	18/37/42/3
Biochemical			
FPG (mmol/L)†	9·2 (7·8–10·9)	9·0 (7·6–11·3)	9·1 (7·7–11·1)
HBA$_{1c}$ (%)*	7·6 (1·8)	7·5 (1·7)	7·5 (1·7)
Plasma insulin (pmol/L)‡	102 (58–180)	102 (58–181)	102 (58–181)
Triglyceride (mmol/L)‡	1·61 (0·91–2·86)	1·64 (0·89–3·04)	1·63 (0·90–2·95)
Total cholesterol (mmol/L)*	5·9 (1·0)	5·6 (1·1)	5·6 (1·1)
LDL cholesterol (mmol/L)*	3·67 (0·96)	3·53 (0·93)	3·60 (0·95)
HDL cholesterol (mmol/L)*	1·08 (0·28)	1·10 (0·30)	1·09 (0·29)
Medications			
More than one aspirin daily (%)	6·4	4·5	5·5
Diuretic (%)	13	16	15
Others (%) digoxin/antihypertensives/lipid lowering/HRT or OC	1·9/24/0·4/0·8	1·5/25/0/0·4	1·7/25/0·4/0·8

Data are % of group, *mean (SD), †median (IQR), or ‡geometric mean (1 SD).
HRT=hormone replacement therapy; OC=oral contraceptive therapy.

Table 2: Baseline characteristics of patients assigned sulphonylurea treatment and subsequently randomised to continuing sulphonylurea treatment alone or with early addition of metformin
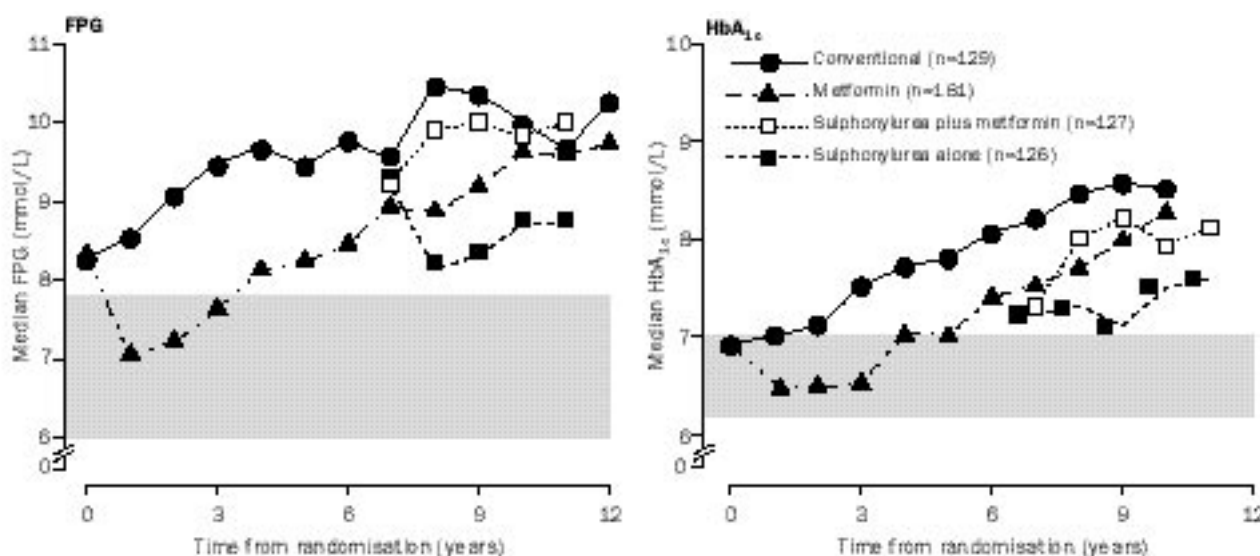
Figure 9: Median FPG and median HbA₁c in cohorts of patients followed to 10 years from primary randomisation in diet *vs* metformin study, and cohorts of patients followed to 4 years from second randomisation to sulphonylurea alone or sulphonylurea plus metformin in sulphonylurea *vs* metformin study

with current therapies as a time-dependent variable, showed a non-significant risk reduction in diabetes-related death for sulphonylurea plus metformin compared with all other treatments of 5% (95%CI -33 to 32, p=0·78).

Discussion

The main trial reported in this paper evaluated the effect of metformin in diet-treated overweight patients with type 2 diabetes. The study design parallels that in the accompanying paper,[1] comparing conventional blood-glucose control primarily with diet alone and intensive treatment with sulphonylurea or insulin. The data shown here suggest that metformin therapy in diet-treated overweight patients reduced the risk for any diabetes-related endpoint, diabetes-related death, and

all-cause mortality. These possible benefits were not seen in the second trial reported here, which suggests an increased risk for diabetes-related deaths and all-cause mortality when metformin is given in addition to sulphonylurea therapy in non-overweight and overweight patients. Because the difference in the effect of metformin between diet-treated and sulphonylurea-treated patients could be extremes of the play of chance, a combined analysis of all the data was undertaken. This showed that addition of metformin had a comparable effect to that seen with intensive therapy with sulphonylurea or insulin reported in the accompanying paper[1] with a net reduction of 19% in any diabetes-related endpoint (p=0·033).

The trend to a reduced risk for microvascular endpoints with metformin therapy was comparable to

AGGREGATE ENDPOINT	Patients with aggregate endpoint/total		Absolute risk (events per 1000 patient-years)		Log-rank 2p	RR (95%CI) for conventional/ metformin	Favours added metformin	Favours no additional metformin
	Added metformin	Conventional/ sulphonylurea	Added metformin	Conventional/ sulphonylurea				
Any diabetes-related endpoint								
Metformin	98/342	160/411	29·8	43·3	0·0023	0·68 (0·53–0·87)		
Sulphonylurea plus metformin	81/268	82/269	60·5	58·4	0·78	1·04 (0·77–1·42)		
Combined groups	179/610	242/680	38·7	47·5	0·033	0·81 (0·67–0·98)		
Diabetes-related death								
Metformin	28/342	55/411	7·5	12·7	0·017	0·58 (0·37–0·91)		
Sulphonylurea plus metformin	26/268	14/269	16·8	8·6	0·039	1·96 (1·02–3·75)		
Combined groups	54/610	69/680	10·3	11·6	0·47	0·88 (0·61–1·25)		
All-cause mortality								
Metformin	50/342	89/411	13·5	20·6	0·011	0·64 (0·45–0·91)		
Sulphonylurea plus metformin	47/268	31/269	30·3	19·1	0·041	1·60 (1·02–2·52)		
Combined groups	97/610	120/680	18·4	20·2	0·49	0·91 (0·70–1·19)		
Myocardial infarction								
Metformin	39/342	73/411	11·0	18·0	0·010	0·61 (0·41–0·89)		
Sulphonylurea plus metformin	33/268	31/269	22·0	20·2	0·73	1·09 (0·67–1·78)		
Combined groups	72/610	104/680	14·2	18·6	0·077	0·76 (0·56–1·03)		
Stroke								
Metformin	12/342	23/411	3·3	5·5	0·13	0·59 (0·29–1·18)		
Sulphonylurea plus metformin	15/268	13/269	9·9	8·2	0·61	1·21 (0·58–2·65)		
Combined groups	27/610	36/680	5·2	6·2	0·49	0·84 (0·51–1·38)		
Peripheral vascular disease								
Metformin	6/342	9/411	1·6	2·1	0·57	0·74 (0·26–2·09)		
Sulphonylurea plus metformin	2/268	1/269	1·3	0·6	0·53	2·12 (0·19–23·3)		
Combined groups	8/610	10/680	1·7	1·7	0·82	0·90 (0·35–2·27)		
Microvascular disease								
Metformin	24/342	38/411	6·7	9·2	0·19	0·71 (0·43–1·19)		
Sulphonylurea plus metformin	15/268	19/269	10·1	12·1	0·62	0·84 (0·43–1·66)		
Combined groups	39/610	57/680	7·7	10·0	0·20	0·77 (0·51–1·15)		

Figure 10: Incidence of clinical endpoints in sulphonylurea *vs* metformin study and diet *vs* metformin study
Relative risk (RR) is for comparison with conventional or sulphonylurea alone. Results of a combined analysis of these two studies shown also.
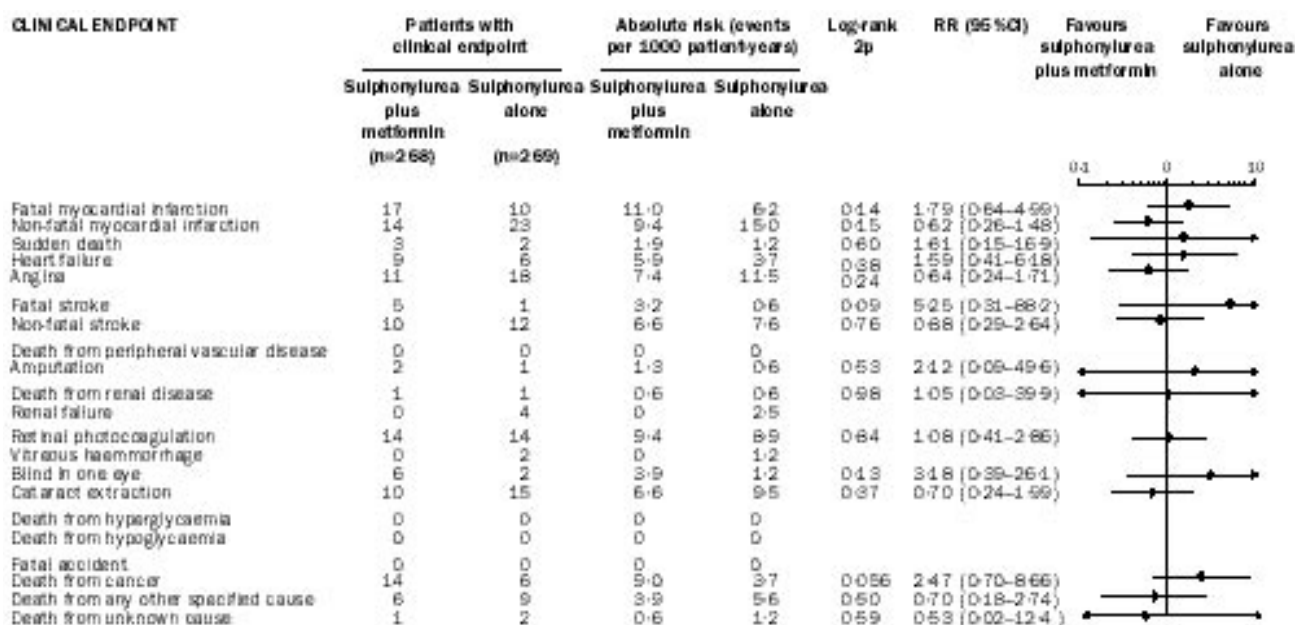
CLINICAL ENDPOINT	Patients with clinical endpoint		Absolute risk (events per 1000 patient·years)		Log·rank 2p	RR (95 %CI)	Favours sulphonylurea plus metformin	Favours sulphonylurea alone
	Sulphonylurea plus metformin (n=268)	Sulphonylurea alone (n=269)	Sulphonylurea plus metformin	Sulphonylurea alone				
Fatal myocardial infarction	17	10	11·0	6·2	0·14	1·79 (0·64–4·99)		
Non-fatal myocardial infarction	14	23	9·4	15·0	0·15	0·62 (0·26–1·48)		
Sudden death	3	2	1·9	1·2	0·60	1·61 (0·15–169)		
Heart failure	9	6	5·9	3·7	0·38	1·59 (0·41–618)		
Angina	11	18	7·4	11·5	0·24	0·64 (0·24–1·71)		
Fatal stroke	5	1	3·2	0·6	0·09	5·25 (0·31–882)		
Non-fatal stroke	10	12	6·6	7·6	0·76	0·88 (0·29–2·64)		
Death from peripheral vascular disease	0	0	0	0				
Amputation	2	1	1·3	0·6	0·53	2·12 (0·09–49·6)		
Death from renal disease	1	1	0·6	0·6	0·98	1·05 (0·03–39·9)		
Renal failure	0	4	0	2·5				
Retinal photocoagulation	14	14	9·4	8·9	0·84	1·08 (0·41–2·86)		
Vitreous haemorrhage	0	2	0	1·2				
Blind in one eye	6	2	3·9	1·2	0·13	3·18 (0·39–264)		
Cataract extraction	10	15	6·6	9·5	0·37	0·70 (0·24–1·99)		
Death from hyperglycaemia	0	0	0	0				
Death from hypoglycaemia	0	0	0	0				
Fatal accident	0	0	0	0				
Death from cancer	14	6	9·0	3·7	0·056	2·47 (0·70–8·66)		
Death from any other specified cause	6	9	3·9	5·6	0·50	0·70 (0·18–2·74)		
Death from unknown cause	1	2	0·6	1·2	0·59	0·53 (0·02–12·4)		

Figure 11: Incidence of single endpoints in sulphonylurea *vs* metformin study
Relative risk (RR) is for sulphonylurea plus metformin *vs* sulphonylurea alone.

that reported in the accompanying paper for intensive glucose control[1] but did not achieve statistical significance.

Clinical use of metformin in overweight patients
In diet-treated overweight patients metformin similarly improved HbA_{1c} levels as with sulphonylurea and insulin therapy but did not induce weight gain and was associated with fewer episodes of hypoglycaemia. Given the equivalent HbA_{1c} levels obtained, the possible additional benefit of metformin observed in overweight diet-treated patients, of a reduced risk for any diabetes-related endpoint, all mortality, and stroke is not explicable on the basis of glycaemic control. The improvements in the predominantly cardiovascular outcomes seen with metformin may be due to the decrease in PAI-1 that accompanies the metformin-induced increase in insulin sensitivity.[3] PAI-1 can inhibit fibrinolysis; thus decrease in PAI-1 could lessen the likelihood of extension of a thrombolysis. In addition, metformin lowers systemic methylglyoxal concentrations in patients with type 2 diabetes,[18] which suggests that it may have an aminoguanidine-like action. However, these postulated mechanisms may not be relevant since, in the combined analysis, the effect of metformin on cardiovascular outcomes was not substantiated.

Clinical use of metformin in patients already treated with sulphonylurea
When metformin was prescribed in the trial in both non-overweight and overweight patients already treated with sulphonylurea there was a significant increase in risk of diabetes-related death and all-cause mortality rather than a beneficial effect on the primary outcome. The different outcomes seen in these two trials may be explained by differences in the patients studied. The sulphonylurea-treated patients were on average 5 years older; more hyperglycaemic (baseline median FPG 9·1 *vs* 8·1 mmol/L); less overweight; and followed up on

average for 5 years less. Secondly, it is important to note that the differences in outcome relate to a relatively small number of endpoints. The epidemiological analysis did not corroborate an association of diabetes-related deaths with combined sulphonylurea and metformin therapy although the CIs were wide.

The UKPDS studied metformin primarily in obese patients, since when the study started (1970s), metformin was generally prescribed only in such patients. Obesity is common among patients with type 2 diabetes.[19] At entry to UKPDS, body-mass index was above 25 kg/m² in 75% of patients and above 30 kg/m² in 35%.

Since metformin seems to give risk reduction of diabetes-related endpoints in overweight patients with type 2 diabetes, does not induce weight gain, and is associated with fewer hypoglycaemic attacks than sulphonylurea or insulin therapy,[10] it could be chosen as the first-line pharmacological therapy in such patients. Although these findings may not apply to non-overweight patients, metformin seems to lower glycaemia in patients with type 2 diabetes, irrespective of the degree of obesity.[1]

Conclusion
The addition of metformin in patients already treated with sulphonylureas requires further study. On balance, metformin treatment appears to be advantageous as a first-line pharmacological therapy in diet-treated overweight patients with type 2 diabetes.

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