United Kingdom Prospective Diabetes Study: implications for metformin

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Abstract

One of the purposes of the United Kingdom Prospective Diabetes Study (UKPDS) was to compare the efficacy of different antidiabetic drugs in the long-term treatment of type 2 diabetes. In overweight type 2 patients, use of metformin as the initial antidiabetic drug therapy reduced overall mortality and reduced various long-term complications to a greater extent than other first-line treatments tested (sulphonylureas and insulin) whilst controlling hyperglycaemia to a similar extent. The benefit of early intervention with metformin may be due, at least in part, to its actions against insulin resistance and associated cardiovascular risk factors. Thus the UKPDS has provided evidence that early intensive glucose control with metformin in overweight type 2 diabetic patients is a particularly effective approach to reduce vascular complications and improve survival.

Key words: type 2 diabetes, metformin, survival, complications, insulin resistance.

Lessons from the UKPDS

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that sustained improvements in the control of blood glucose and blood pressure reduced the micro- and macro-vascular complications of type 2 diabetes.[1] Although intensive use of antidiabetic agents and (where required) antihypertensive drugs generally produced only modest improvements in glycaemic control and blood pressure, these gave rise to substantial long-term reductions in morbidity and mortality (table 1).[2,3] Since these benefits continued until normal levels of blood glucose and blood pressure were achieved (table 2), a mandate has been set to attain the best possible control of these parameters in type 2 patients.[3,4]

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Table 1. Benefits of improved control of blood glucose and blood pressure in type 2 diabetic patients in the UKPDS

Blood Glucose Control Study[a]	
Decreased median HbA_{1C} by 0.9%, from 7.9% to 7.0%	
	Change in risk[b]
Any diabetes-related complication	↓ 12% p=0.029
Microvascular complications	↓ 25% p=0.009
Myocardial infarction	↓ 16% p=0.052
Cataract extraction	↓ 24% p=0.046
Progression of retinopathy (at 12 years)	↓ 21% p=0.015
Microalbuminuria (at 12 years)	↓ 33% p=0.001
Blood Pressure Control Study[c]	
Decreased mean SBP by 10 mmHg from 154/87 mmHg to 144/82 mmHg	
	Change in risk[d]
Any diabetes-related complication	↓ 24% p=0.004
Diabetes-related deaths	↓ 32% p=0.019
Myocardial infarction	↓ 21% p=0.130
Stroke	↓ 44% p=0.013
Microvascular complications	↓ 37% p=0.009
Progression of retinopathy	↓ 34% p=0.003

[a]Median follow-up of 10 years except where stated
[b]Compared to diet only ([conventional therapy], median HbA_{1C} 7.9%)
[c]Median follow-up of 8.4 years
[d]Compared to less tight control (mean blood pressure 154/87 mmHg)
SBP = systolic blood pressure

Effects of different antidiabetic agents

One of the original aims of the UKPDS was to investigate whether intensive treatment with any particular oral antidiabetic therapy (sulphonylurea or metformin) or insulin offered an advantage in the long-term outcomes of type 2 diabetes.[2,5] Newly diagnosed patients first received a three-month run-in on diet therapy. Non-overweight patients were then randomised to continue diet only (conventional therapy) or receive intensive therapy with a sulphonylurea or insulin. Overweight patients were also randomised to metformin and all treatments were titrated with the aim of achieving near normal glycaemic control (fasting plasma glucose <6 mmol/L).

As illustrated with the overweight patients (figure 1), initial randomisation to any of the antidiabetic drug therapies improved glycaemic control to a similar extent.[5] However, few patients attained the glycaemic target, and all groups showed a progressive deterioration in glycaemic control after two to three years. As the study continued it became evident that the major-

Table 2. A synopsis of the UKPDS

Purpose: To study the effects of intensive management of blood glucose and blood pressure on the occurrence of long-term complications in type 2 diabetes

Design: Prospective randomised controlled study of 5,012 newly diagnosed type 2 diabetic patients at 23 UK centres between 1977 and 1997. Median follow-up was 10 years and end points were the occurrence of morbid and fatal events, particularly diabetic micro- and macrovascular complications, hyperglycaemia, hypoglycaemia and blood pressure. A parallel epidemiological analysis was undertaken to assess the benefits of risk factor management on clinical outcomes

Outcomes:

- Any improvement in glycaemic control reduced the risk of diabetic complications, with benefit continuing until glycaemic control was returned to the normal range
- There were no significant differences in glycaemic benefits achieved with sulphonylureas or insulin (or metformin used only in overweight patients)
- Glycaemic control progressively deteriorates with any of the antidiabetic therapies, and the majority of patients need multiple therapies to achieve and sustain glycaemic control
- In overweight patients initially randomised to metformin there was a lower occurrence of diabetes-related deaths and myocardial infarctions compared with randomisation to a sulphonylurea or insulin
- Any improvement in blood pressure control reduced the risk of micro- and macrovascular complications, with benefit continuing until blood pressure was returned to the normal range
- There were no significant differences in the blood pressure control achieved with captopril or atenolol as first agent, and most patients eventually required two or three antihypertensive agents

ity of patients required multiple antidiabetic therapies for long-term glycaemic control, and many eventually received combined sulphonylurea-metformin therapy.[6]

Metformin in the UKPDS

Amongst overweight patients, the group initially randomised to metformin showed several important differences to the groups initially randomised to a sulphonylurea or insulin. Although glycaemic control was similar with the various drug treatment (figure 1), there were fewer reports of hypoglycaemic symptoms amongst those assigned to metformin (4.2% annually compared with 12.1–17.5% for the sulphonylureas and 34% for insulin). Indeed, during a 10-year follow-up of those continuing to take metformin as their only antidiabetic agent there was no case of serious hypoglycaemia.

Overweight patients initially randomised to metformin showed no weight gain in comparison with the diet only (conventional therapy) group, whereas body weight increased during intensive therapy with a sulphonylurea (by 2.3 kg) and insulin (by 4.5 kg). Also, there was a small decrease in fasting plasma insulin in those assigned to metformin (about 10 pmol/L lower than those receiving diet only therapy). In contrast, fasting plasma insulin concentrations were initially raised by sulphonylurea therapy, and remained raised during insulin therapy.[5]

Figure 1. Glycated haemoglobin (HbA_{1C}) values in the UKPDS among overweight type 2 diabetic patients initially assigned to diet only (conventional therapy) or to intensive therapy with metformin or a sulphonylurea (chlorpropamide or glibenclamide) or insulin. Sourced and re-drawn from data in reference 5

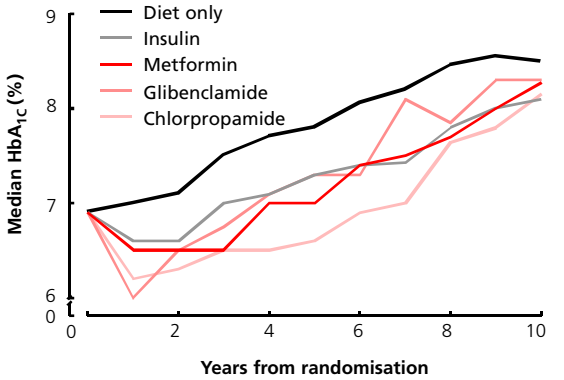
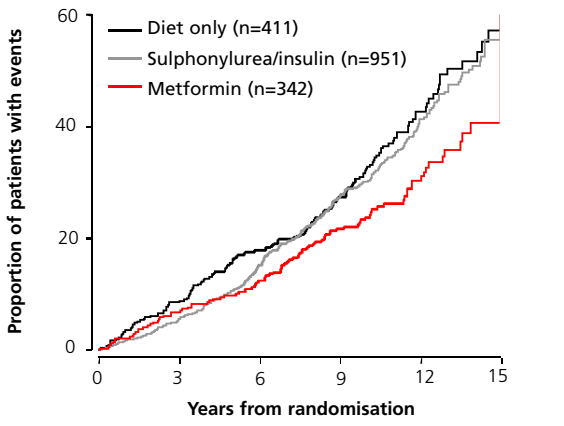


Figure 2. Kaplan-Meier plot showing the proportion of diabetes-related end points in the UKPDS among overweight type 2 diabetic patients initially assigned to diet only (conventional therapy) or to intensive therapy with metformin or a sulphonylurea or insulin. Data for the sulphonylurea and insulin groups were similar, and these data have been pooled for this figure. Sourced and re-drawn from data in reference 5



Metformin and clinical outcomes

In overweight type 2 patients, initial randomisation to metformin was associated with lower occurrence of any diabetes-related end point (microvascular and macrovascular) by 32% (p=0.002) compared with patients assigned to diet only (conventional therapy) (figure 2). The group allocated metformin also had a signif-

Table 3. End points for overweight type 2 diabetic patients allocated to intensive therapy with metformin or sulphonylurea/insulin in the UKPDS[a]

	Change in risk[b]	
	Metformin	**Sulphonylurea/ insulin**
Any diabetes-related end point	↓32% p=0.002	↓ 7% NS
Diabetes-related deaths	↓42% p=0.017	↓20% NS
All-cause mortality	↓36% p=0.011	↓ 8% NS
Myocardial infarction	↓39% p=0.010	↓21% NS
Microvascular disease	↓29% NS	↓16% NS

[a]Data sourced from reference 5
[b]Change in risk compared with group allocated to diet only (conventional therapy)
Numbers of patients at randomisation were 411 to diet only, 342 to metformin, 542 to a sulphonylurea, and 409 to insulin. Data for the sulphonylurea and insulin groups were similar, and these data have been pooled for analysis. Median follow-up was 10 years, with introduction of oral combination (sulphonylurea plus metformin) therapy or transfer to insulin if severe hyperglycaemia supervened
NS=not significant; ↓ =decreased risk

Table 4. Risk of events in overweight type 2 diabetic patients allocated to diet only (conventional therapy) or intensive therapy with metformin or sulphonylurea/insulin in the UKPDS[a]

	Absolute risk of events per 1,000 patient-years		
	Metformin	**Diet only (p *vs.* metformin)**	**Sulphonylurea/ insulin (p *vs.* metformin; p *vs.* diet only)**
Any diabetes-related complication	29.8	43.3 (p=0.002)	40.1 (p=0.003; p=0.46)
Diabetes-related mortality	7.5	12.7 (p=0.017)	10.3 (p=0.11; p=0.19)
Overall mortality	13.5	20.6 (p=0.011)	18.9 (p=0.021; p=0.49)
Myocardial infarction	11.0	18.0 (p=0.010)	14.4 (p=0.12; p=0.11)

[a]Data sourced from reference 5
Numbers of patients at randomisation were 411 to diet only, 342 to metformin, 542 to a sulphonylurea, and 409 to insulin. Data for the sulphonylurea and insulin groups were similar, and these data were pooled for analysis. Median follow-up was 10 years, with introduction of oral combination (sulphonylurea plus metformin) therapy or transfer to insulin if severe hyperglycaemia supervened

icantly lower risk of any diabetes-related end point than those assigned to intensive therapy with a sulphonylurea or insulin (p=0.003).

The overall survival of overweight type 2 patients was greater for those initially assigned metformin. There was a 42% (p=0.017) reduced risk of diabetes-related deaths and a 36% (p=0.011) reduced risk of all-cause mortality in the metformin group compared with diet only. Moreover the reduction in all-cause mortality amongst those assigned metformin was greater (p=0.021) than those assigned a sulphonylurea or insulin.

The improved survival amongst those initially randomised to metformin was accompanied by a 39% (p=0.01) lower risk of myocardial infarction and a 30% (p=0.02) lower rate of all macrovascular events (myocardial infarction, angina, stroke and peripheral vascular disease) compared with diet only. Mean percentage risk reductions in these end points for groups allocated to a sulphonylurea or insulin were not significantly different from the group allocated diet only (table 3). There were no recorded cases of lactic acidosis throughout the UKPDS.

With regard to the lower mean risk of microvascular disease (by 29%, p=0.19, not significant) there was a slower progression for retinopathy and microalbuminuria compared with diet only, similar to that observed with a sulphonylurea or insulin.

A substudy was conducted in a cohort of patients with inadequate glycaemic control on maximum dose sulphonylurea after 7.1 years. Addition of metformin, with follow-up for 6.6 years, confirmed an improvement in glycaemic control but noted a higher number of diabetes-related deaths (26 deaths in 268 patients) than in those continuing on sulphonylurea alone (14 deaths in 269 patients). It is pertinent to appreciate that each of these groups in the substudy showed a much lower death rate than in the main randomisation of the UKPDS after this period of treatment.[7] Indeed, a combined analysis of patients allocated metformin as primary treatment and in addition to sulphonylurea therapy in the UKPDS found a 19% (p=0.033) reduction in risk of any diabetes-related end point.[5]

Implications of UKPDS for metformin

The UKPDS has found that in overweight type 2 diabetic patients the initiation of oral antidiabetic therapy using metformin increased survival. The group initially assigned to metformin showed a greater reduction in the risk of any diabetes-related end point (overall macrovascular and microvascular complications) than groups assigned to the other antidiabetic drug therapies.[5] This has prompted a unique addition to the therapeutic indications for metformin which now state that "a reduction of diabetic complications has been shown in overweight type 2 diabetic patients treated with metformin as first-line therapy after diet failure".[8] Use of metformin as first-line antidiabetic drug therapy in overweight type 2 diabetic patients is supported by a further analysis of the UKPDS.This shows the absolute risk of events expressed per 1,000 patient years of treatment (table 4). The average life expectancy of overweight patients initially assigned metformin was increased by 0.4 years over 10.7 years of follow-up compared to diet only.[9]

Another interesting analysis to emerge from the UKPDS was that of cost-effectiveness.[9] The reduction in costs of complications in the metformin group was substantially greater than the cost of the therapy, which included the cost of visits to healthcare professionals to administer the therapy. The mean net saving per metformin patient was estimated to be £258 compared with the diet only group (£5,635 *vs.* £5,893), based on UK prices

Table 5. Effects of metformin to counter the insulin resistance syndrome (metabolic syndrome)[a]

Features of the insulin resistance syndrome	Effects of metformin to counter the insulin resistance syndrome
Insulin resistance	Counters insulin resistance eg. increases effects of insulin to suppress hepatic glucose output and enhance muscle glucose uptake
Hyperinsulinaemia	Reduces fasting hyperinsulinaemia
Abdominal obesity	Usually stabilises body weight; reduces weight gain and can facilitate weight loss
Impaired glucose tolerance (IGT) or type 2 diabetes	Reduces progression of IGT to type 2 diabetes; improves glycaemic control in type 2 diabetes
Dyslipidaemia (increase VLDL-TG, increase LDL-C, decrease HDL-C)	Modest improvement of lipid profile often seen in dyslipidaemic patients
Hypertension	No significant effect on blood pressure in most studies
Pro-coagulant state	Some antithrombotic activity eg. decreases in PAI-1, fibrinogen and platelet aggregation
Atherosclerosis	Evidence for anti-atherogenic activity from animal studies; no equivalent clinical studies

[a]Based on information in references 10 and 11

Key: IGT = impaired glucose tolerance; VLDL-TG = very low density lipoprotein triglyceride; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; PAI-1 = plasminogen activator inhibitor-1.

Table 6. Clinical use of metformin

Indications	As monotherapy or in combination with other antidiabetic agents in type 2 diabetic patients inadequately controlled by dietary management and exercise
Usage	Tablets 500 mg, 850 mg and 1,000 mg; take with meals; increase dose slowly; monitor glycaemic control; maximal dose 3,000 mg/day (2,550 mg/day in some countries)
Contra-indications	Renal and hepatic disease; cardiac or respiratory insufficiency; any hypoxic condition; severe infection; alcohol abuse; history of lactic acidosis; use of intravenous radiographic contrast agents; pregnancy
Side effects	Gastrointestinal symptoms and metallic taste which improve with dose reduction; may impair absorption of vitamin B_{12} and folic acid
Adverse reactions	Risk of lactic acidosis in patients with a contra-indication; hypoglycaemia if taken in combination with another antidiabetic drug or during alcohol abuse
Precautions	Check for contra-indications; check haemoglobin and plasma creatinine periodically: possible interaction with cimetidine therapy

to 1997 and a median duration of 10.7 years.

Since first-line metformin therapy produced a similar improvement in glycaemic control to other first-line antidiabetic agents included in the UKPDS, why should metformin result in several additional long-term benefits? The answer presumably resides beyond the blood glucose-lowering actions of metformin.

Metformin and insulin resistance

The actions of metformin counter insulin resistance and offer benefits against several features of the so-called insulin resistance syndrome (metabolic syndrome, syndrome X, Reaven's syndrome).[10,11] This syndrome constitutes a clustering of risk factors for coronary disease, and many of these factors are addressed by the actions of metformin (table 5). Most patients with type 2 diabetes (itself a prominent component of the syndrome) appear to manifest one or more additional features of the syndrome. Thus an agent such as metformin which acts to combat insulin resistance might be expected to offer benefits against several risk factors for coronary artery disease.

The majority (70–80%) of patients with type 2 diabetes die of premature cardiovascular disease. Since insulin resistance appears to play a role in the development of many metabolic risk factors for cardiovascular complications of type 2 diabetes,[12,13] the early use of an antidiabetic agent that targets insulin resistance is anticipated to reduce cardiovascular risk. Potentially vasoprotective effects of metformin (table 5) may thereby confer independent benefits that contribute to the reduced mortality after early intervention in patients with type 2 diabetes.

While metformin appears to benefit the prevention of cardiovascular complications in type 2 diabetes, it must be appreciated that this agent may not be appropriate if significant cardiac disease is already manifest, especially where there are hypoxaemic symptoms. Other cautions associated with the use of metformin are noted in table 6.

Conclusion

Treating type 2 diabetes is a complex issue. The best possible glycaemic control is required to optimise protection against microvascular complications, and continual vigilance is required against cardiovascular risk factors that comprise the insulin resistance syndrome.

The UKPDS has demonstrated that in overweight type 2 diabetic patients, early intervention with metformin as initial antidiabetic drug therapy substantially reduced long-term complications. As illustrated by reduced mortality, the first-line use of metformin generally resulted in greater risk reductions than with other first-line interventions (sulphonylureas and insulin) used in this study. Insulin resistance is an underlying feature of type 2 diabetes and many of its associated cardiovascular risk factors, and metformin therapy helps to counter many components of the insulin resistance syndrome. Thus there is both

Key messages

- The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that improved control of blood glucose and blood pressure reduced complications in type 2 diabetes
- Use of metformin as the initial antidiabetic drug therapy reduced overall mortality and various complications in overweight type 2 diabetic patients to a greater extent than other agents tested (sulphonylureas and insulin)
- The additional benefits of metformin in type 2 diabetes appear to reflect its actions against insulin resistance and associated cardiovascular risk factors

logic and supporting evidence for use of metformin as an early intervention to address insulin resistance in overweight type 2 diabetic patients.

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