The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes

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The burden of type 2 diabetes

Diabetes was first recognized 3500 years ago by the Ancient Egyptians. One of the first clinical descriptions was by Aretaeus, who practised in Cappadocia around 120 AD. He wrote that the condition was 'fortunately rare', but 'short will be the life of the man in whom the disease is fully developed' [1].

In modern society, the first statement is far from true. The incidence of diabetes has doubled every 20 years since 1945 [2]. In 1994 the world wide prevalence of type 2 (non-insulin dependent) diabetes was 99 million (1.8% of the population); by 2010 it is estimated that this figure will rise to 215 million (3.8%) [3].

The second statement is as true today as it was almost 2000 years ago. In the West, 44% of patients with type 2 diabetes die within 10 years of diagnosis [4], mostly from macrovascular disease; the incidence of and mortality from cardiovascular disease are 2–3 times greater than in the general population [5]. As the majority of patients develop complications, which are present in up to 50% even at the time of diagnosis [6], type 2 diabetes imposes a significant burden on health services, as well as on the individuals who suffer from this progressive and incurable disease. Currently the 2% of the UK population with diabetes consume 5% of the health service budget; by comparison the 12% with arthritis consume just 1.9% [7]. With the increasing prevalence of the condition, these figures will escalate. Prevention would be the ideal solution, but is currently a remote prospect. In the meantime any way of significantly reducing the burden of diabetes-related complications will have a major impact on patient well-being and on cost effectiveness of management.

The benefits of treatment?

Until the early 1990s, there was no evidence that our management of diabetes had any beneficial impact on the incidence of vascular complications. On the contrary, the pioneering study of the 1960s, the University Group Diabetes Program (UGDP) [8], suggested that treatment with tolbutamide might be harmful. The study was designed to assess the impact of blood glucose lowering therapies on complications, with patients being randomly allocated to placebo, tolbutamide, phenformin, or insulin. The study was stopped after 8 years because of an increase in cardiovascular deaths in those receiving tolbutamide. However, for many years the design and conduct of the UGDP were subject to fierce debate which was never satisfactorily resolved; uncertainty continued about treatment and glycaemic targets for type 2 diabetes.

The Diabetes Control and Complications Trial (DCCT), published in 1993 [9], showed that intensive glycaemic control (i.e. keeping blood glucose as near to normal as possible) reduces the incidence and progression of microvascular complications (retinopathy, nephropathy and neuropathy) in type 1 diabetes. Whether the same holds true in type 2 diabetes remained uncertain. Intensive treatment often results in hyperinsulinaemia, with weight gain and an increase in hypoglycaemia [9], both of which have theoretical adverse effects on macrovascular disease, the major life threatening complication of type 2 diabetes. Patients with type 2 diabetes frequently have other risk factors for macrovascular disease, such as hypertension and hyperlipidaemia, the former having a prevalence of 40%-60% [10, 11]. Antihypertensive therapy reduces the risk of both cardiovascular and cerebrovascular disease in the general population [12], but to what extent these findings apply to type 2 diabetes was again not clear.

The United Kingdom Prospective Diabetes Study (UKPDS) was conceived to explore these uncertainties and provide clearer guidelines for the management of type 2 diabetes.

Design of the UKPDS (Figures 1–3)

The UKPDS was set up in the late 1970s, by Dr Robert Turner and colleagues in Oxford. Over 7600 subjects at 23 centres across the UK were considered for inclusion; 5102 took part. It was the largest and longest study ever

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- does improved blood glucose control reduce the incidence of complications?
- do different treatments have specific advantages or disadvantages?

Figure 1 UKPDS–the principal questions.

- Hypertension in Diabetes Study
  - does tight control of blood pressure have an impact on complications?
  - do atenolol or captopril have specific advantages or disadvantages?
- glycaemic control using combination treatment (Glucose study 2)
- acarbose
- quality of life
- cost-effectiveness
- many incidental scientific, epidemiological and clinical studies

Figure 2 UKPDS–embedded studies.

undertaken in diabetes; median follow-up was 10 years. As well as attempting to resolve unanswered clinical issues, the study generated a huge epidemiological database, comprising over 20 million data items.

The primary aim was to determine the effect of intensive glycaemic control on the incidence of complications; the secondary aim was to assess whether there were differences between treatments (Figure 1). Protocol amendments were made to add topics not originally included. These strengthened the study by broadening its scope, but at the cost of complicating the treatment allocation, conduct and analysis of the study. Numerous substudies were embedded (Figure 2), the most notable being the Hypertension in Diabetes Study. Over 30 papers have been published from the UKPDS database, and many more are in preparation or planned.

Key points (Figure 4)

Glucose control studies [13, 14]

Subjects were randomized to receive 'conventional' or 'intensive' therapy. In the former, the intention was to keep patients aymptomatic, with a fasting plasma glucose less than 15 mmol l^{-1}; in the latter, the target fasting glucose was 6 mmol l^{-1}. When diet failed to achieve these targets, subjects were randomized to sulphonylureas, insulin or metformin, the latter in obese patients only. When single treatments failed, combinations were used.

The results were primarily expressed in terms of aggregate end points: 'any diabetes related end point', which included both microvascular and macrovascular events, and 'diabetes related death'. Twenty-one single end points were also defined. The emphasis on aggregate end-points allowed the study outcomes to be presented in a clinically meaningful way, i.e. overall risk. Their use also reduced the number of treatment comparisons, thus minimizing the chances of false-positive results, but had the disadvantage of concealing the magnitude of effects on individual end points.

Intensive glucose control significantly reduced any diabetes-related end point, but had no effect on mortality. The predominant effect of tighter control was a reduction of microvascular disease by a quarter, largely due to a reduction in laser photocoagulation. There was also a trend, just short of statistical significance, towards a reduction in macrovascular disease. No threshold was seen, i.e. any improvement in glycaemic control is beneficial. These findings are similar to those of the DCCT and a more recent study in Japanese patients with type 2 diabetes, in whom 6 years' intensive therapy with insulin reduced the incidence of microvascular complications [15]. That the reduced occurrence of myocardial infarction was not significant may be due to type 2 statistical error. The study was set up to detect a 15% difference in events over the 10 years' study period, and a larger number of macrovascular than microvascular events occurred, but the separation of HbA_{1c} between intensive and conventionally treated groups was disappointingly low: 0.9% (half that in the DCCT). Had the separation of HbA_{1c} between groups been greater, a significant effect of intensive control on macrovascular disease might have been demonstrated.

The secondary aim of the study was to compare the effects of different treatments for diabetes, since some have theoretical advantages and disadvantages. For example, sulphonylureas close myocardial ATP-sensitive potassium channels, which could impair ischaemia induced vasodilatation [16], perhaps explaining the results of the UGDP. In addition, some studies have suggested that hyperinsulinaemic states are atherogenic [17], and the increased incidence of hypoglycaemia with intensive control with insulin could theoretically precipitate a cerebrovascular or cardiovascular event. The UKPDS showed no difference in outcome between treatments, which is at first sight reassuring, but the study was powered to assess the effects of intensive therapy in general and it is unclear whether there is adequate power in this subgroup analysis. In addition, actual therapy often differed from allocated treatment, especially as patients required additional treatment over time. The results of this aspect of the study should therefore be interpreted with caution.

The results of metformin treatment are the most controversial [14]. Metformin use was associated with fewer aggregate end-points (including overall mortality)

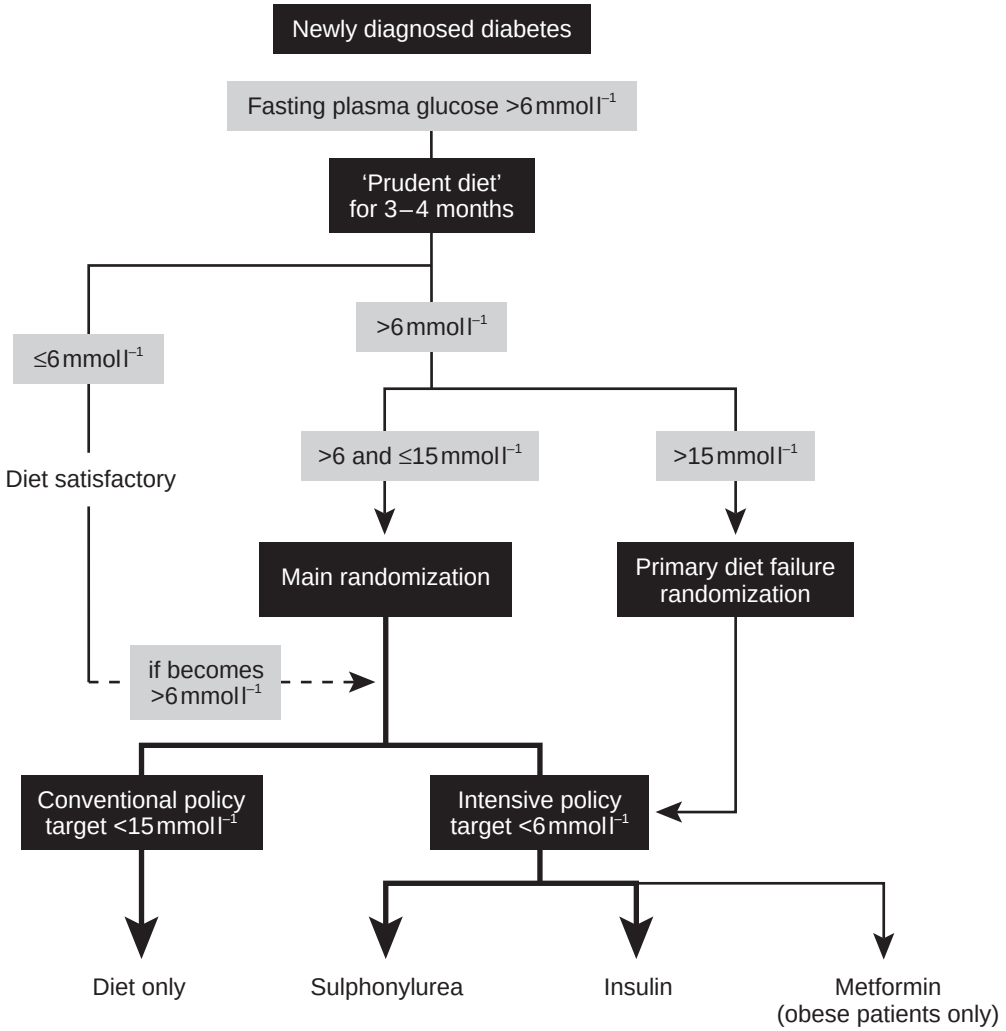

Figure 3 Design of UKPDS.

- intensive glucose control, using existing treatments, improved microvascular morbidity, but not mortality
- insulin and sulphonylureas were similarly effective
- metformin was advantageous in the obese
- intensive **blood pressure control was more beneficial**, improving morbidity (both micro- and macrovascular), and mortality
- ideal targets: HbAlc < 7%, BP < 140/80 mm Hg
- any reduction was beneficial

Figure 4 Key points.

in obese patients. However the number of patients allocated to metformin was less than 10% of all those randomised. The findings could also be interpreted as indicating that insulin and sulphonylureas are equally harmful in the obese, possibly as a consequence of hyperinsulinaemia.

An unexpected finding was that the addition of metformin to sulphonylureas (in both obese and nonobese patients) was associated with increased mortality. The numbers involved in this subgroup analysis were very small, with few deaths (26 *vs* 14 in the group treated with sulphonylureas alone) and no difference in the incidence of heart attacks or strokes between the groups, only in the proportion who died. Furthermore, the mortality in the group treated by sulphonylureas alone was unexpectedly low. The authors therefore concluded that this anomalous result was likely to be have been due to chance.

Hypertension in Diabetes Study [18, 19]

One thousand one hundred and forty-eight patients took part. Half the participants were allocated to 'tight control' (target blood pressure less than 150/85 mm Hg) and were randomised to either atenolol or captopril, with other agents added as necessary. The remainder were allocated to 'less tight control' (target blood pressure less

than 180/105 mm Hg); in these patients, drugs other than β-adrenoceptor blockers and ACE inhibitors were used. Mean blood pressure was 144/82 mm Hg in the tight control group, compared with 154/87 mm Hg in the less tight control group. One-third of patients allocated to tight control required three more drugs in the attempt to achieve the target blood pressure.

Tight control of blood pressure reduced both diabetes-related morbidity *and* mortality. Unlike glycaemic control, there was a significant effect on *macrovascular* as well as microvascular complications, with strokes and heart failure reduced by a half. Myocardial infarction was reduced by a fifth, but this was not statistically significant. As in the glucose control study, no threshold for risk was seen in the hypertension study. These are very impressive results, establishing that blood pressure control is at least as important as glycaemic control, if not more so, in the prevention of complications in type 2 diabetes.

In the last 2 years, the results of several other studies of hypertension which have included patients with diabetes have been published. These also demonstrated a reduction in macrovascular risk, including myocardial infarction [20, 21]. A variety of agents was used, but blood pressure differences between treatment and control groups were comparable with the UKPDS, and protective effects were observed despite shorter periods of follow up (2–5 years). Thus there is no doubt of the significance of blood pressure control in type 2 diabetes, but there remains the question whether particular drugs have advantages or disadvantages.

The UKPDS compared captopril and atenolol, both drugs having theoretical benefits. In the general population with hypertension, β-adrenoceptor blockers reduce macrovascular events and are specifically cardioprotective, reducing sudden death and further myocardial events in those with prior myocardial infarction[22]. ACE inhibitors improve survival in patients with heart failure [23, 24]; in type 1 diabetes, they reduce the progression of nephropathy [25, 26] and possibly retinopathy [27], but whether ACE inhibitors have specific advantages over other antihypertensive agents in type 2 diabetes is not yet agreed. Recently the ABCD trial showed a reduction in myocardial infarction in diabetic hypertensive subjects treated with an ACE inhibitor compared with a calcium channel blocker [28], but it was not clear whether the ACE inhibitor was especially beneficial or the calcium channel blocker relatively harmful, particularly as the groups were inadequately matched for concomitant medication. The UKPDS found that captopril and atenolol were equally effective as antihypertensive agents, in preventing macrovascular complications and in reducing the progression of retinopathy and albuminuria. The ACE inhibitor was however, better tolerated. These results are again reassuring at first sight, but, as with the glucose control study, type 2 errors cannot be excluded; there was a trend in favour of the atenolol treated group.

Therapeutic implications, study limitations and outstanding questions (Figures 5–7)

The UKPDS demonstrated that any improvement in glycaemic control and blood pressure reduces diabetes-related complications. In trials such as this, patients are selected both by investigators and by themselves. The observation that UKPDS patients had a lower mortality than the general population with type 2 diabetes may be a reflection of this. What was achievable and acceptable to a trial population cannot be necessarily translated to everyone with type 2 diabetes. This must be remembered when applying the results of the study to clinical practice.

There is no doubt that aggressive management of blood pressure is important, particularly in reducing macrovascular disease, the main cause of morbidity and mortality in these patients. A target blood pressure of less than 140/80 is suggested by the authors. The fact that benefits are achieved within 2 or 3 years means that all patients should be treated irrespective of age. Clearly, achieving this goal will require aggressive follow up (patients in the UKPDS were seen 3 monthly), and this may not be acceptable to all patients. With one third requiring 3 or more agents to maintain target blood pressures, compliance will certainly be a problem in some.

Whether intensive glycaemic control should be routinely introduced in type 2 diabetes is more controversial.

- limited separation between conventional and intensive glucose groups (patient compliance?)
- insufficient statistical power for subgroup analyses

Figure 5 Limitations of the study.

- how worthwhile are the benefits achieved?
- can targets be achieved in routine practice?
- benefit of increasing insulin dose?
- benefit of insulin/tablet combinations
- place of aspirin, statins, anti-oxidants, etc.

Figure 6 Outstanding questions.

- treatment with several drugs will often be necessary
- increased resources will be needed to realize benefits of better control
- treatment is cost effective, when benefits are taken into account
- screening programmes should be considered

Figure 7 Therapeutic implications.

Despite achieving statistical significance, the absolute risk reduction from intensive glycaemic control is small, with a reduction of 5 events over 10 years compared with 16 for blood pressure (Table 1). Furthermore, the benefits of glucose reduction did not accrue for several years, unlike intensive blood pressure control. Intensive glycaemic control, particularly with insulin, also leads to morbidity from hypoglycaemia and weight gain. Thus, unlike blood pressure control, intensive glycaemic control is not suitable for all patients, particularly the elderly, or those with existing severe complications. The small absolute risk reduction also needs to be compared with the possible effects of other risk factor interventions, e.g. treatment with aspirin, lipid lowering drugs or anti-oxidants. Despite these limitations, the UKPDS provides evidence and quantitative guidelines for those in whom intensive control is achievable.

The study also assessed effects of intensive treatment on quality of life; no adverse effect was apparent. One scale demonstrated that poor quality of life is related to complications rather than the treatments given [unpublished]. This is reassuring in implementing the results of the study, though the results may not apply equally to an unselected population.

One aspect of management inadequately addressed by the study is the optimal combination of drugs to be used either for glucose or blood pressure control. Different agents seemed equally effective, but the possibility of type 2 errors in these subgroup analyses cannot be excluded, as already discussed. To date, the effectiveness of insulin and oral hypoglycaemic agent combinations is not known, although there are unpublished data from the study on the combination of insulin and sulphonylureas. Data on possible dose-dependent effects of insulin, and the combination of insulin and metformin are lacking. For now, until further information is available, clinical practice should be based on achieving glucose and blood pressure reduction by whatever means best suits an individual patient.

In the study, patients were reviewed 3 monthly, rather than 6–12 monthly as in routine clinical practice, which has considerable resource implications. The reduction in blood pressure [29] and glucose [unpublished] achieved were relatively cheap, £48 and £22 per patient per year, respectively, when the benefits were discounted. These figures are valuable ammunition in the battle to improve services for patients. With 50% of patients presenting with complications, the issue of screening should also be addressed.

Table 1 Absolute risk.

	Number of events		
	Intensive	*Conventional*	**NNT*
Glucose control	41	46	20 (95% CI 10–500)
Blood pressure control	51	67	6 (3–10)

*number needed to treat for 10 years to prevent 1 event.

The UKPDS provides management guidelines for selected patients, but leaves many questions unanswered. The advantages of good care have been more clearly defined than ever before, but the huge gulf between the benefits achieved in the study and the many frustrations of everyday practice remains. In most centres, there are large numbers of patients with poor control of both blood glucose and blood pressure. Type 2 diabetes must at least be taken more seriously.

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Note added in proof

We wish to pay tribute to Robert Turner whose recent untimely death is such a tragedy.

