UKPDS: United Kingdom Prospective Diabetes Study

In 1988 at the European Association for the Study of Diabetes (EASD) Conference in Barcelona, 10-year data on the UKPDS (United Kingdom Prospective Diabetes Study) were presented. The results greatly influenced the approach to the management of type 2 diabetes, being quoted worldwide and supporting national and international guidelines on diabetes and cardiovascular health, but what is the UKPDS and what did it tell us?

Glucose Control Study

The aims of the Glucose Control Study were:

- To determine whether intensive glucose control of type 2 diabetes (sulfonylurea therapy with or without insulin) would reduce the incidence of complications compared to conventional treatment (diet).
- To determine whether there were any differences in health outcomes between metformin, sulfonylurea (first or second generation) or insulin.

Blood Pressure Control Study

In addition to the Glucose Control Study, a large subgroup of participants who had hypertension were randomised as part of the Blood Pressure Control Study to either a tight blood pressure target (<150/85 mmHg) or a conventional target (<180/105 mmHg). The aims of the Blood Pressure Control Study were:

- To determine whether tight blood pressure control reduced morbidity and mortality in people with type 2 diabetes.
- To determine if angiotensin-converting enzyme (ACE) inhibitors (captopril) or beta-blockers (atenolol) were advantageous in reducing the risk of developing clinical complications.

Conclusions from the UKPDS that continue to shape clinical practice

- Intensive glucose control leads to a reduction in risk for diabetes-related complications compared to diet therapy alone. There was a significant 25% risk reduction for microvascular disease and 12% risk reduction for any diabetes-related endpoint compared to conventional diet therapy, and a 16% reduction in risk of myocardial infarction which just failed to reach significance.
- The UKPDS provided evidence-based targets for the treatment of type 2 diabetes (Barnett, 2004). The intensive control group maintained a lower HbA_{1c} level by a mean value of 0.9% over a median follow-up of 10 years from diagnosis of type 2 diabetes. Mean HbA_{1c} in the intensive group was 53 mmol/mol (44–66 mmol/mol; 7.0% [6.2–8.2%]) compared to 63 mmol/mol (52–73 mmol/mol; 7.9% [6.9–8.8%]) with conventional therapy (UKPDS 33, 1998a).
- Intensive glucose control with metformin decreased the risk of diabetes-related complications in obese people with type 2 diabetes (UKPDS 34, 1998b). It was associated with fewer hypoglycaemic events and less weight gain than insulin and sulfonylureas. Insulin and sulfonylurea did not increase the risk of cardiovascular deaths, myocardial infarction or sudden death (UKPDS 33, 1998a).
- Tight blood pressure control in people with hypertension and type 2 diabetes resulted in reductions in diabetes-related deaths, complications related to diabetes, progression of diabetic retinopathy and deterioration in visual acuity. A target blood pressure of 135/85 mmHg or less was recommended for people with type 2 diabetes (UKPDS 38, 1998d).
- ACE inhibitors and beta-blockers were equally effective in lowering mean blood pressure in people with type 2 diabetes who had hypertension. They were also equally effective in reducing the risk of any diabetes-related endpoint, diabetes-related deaths and microvascular endpoints (UKPDS 39, 1998c).

UKPDS key statistics

- Multi-centre randomised, controlled, open-label trial.
- 23 UK clinical sites.
- 5102 patients with newly diagnosed type 2 diabetes.
- 20-year study started in 1977.
- In September 1997, all surviving UKPDS participants entered into 10-year, post-trial monitoring programme. Completed December 2007.

Post-trial monitoring programme results and the legacy effect

From 1997 to 2007, a 10-year post-trial monitoring programme continued to follow participants of the UKPDS and collect and analyse data. The main findings included:

- Even though the differences between the intensive and conventional treatment groups for blood glucose control disappeared after the main trial, participants who had been randomised to tight glycaemic control lived longer and healthier lives than those who were in the comparison groups (Brett, 2008). This is called legacy effect (Holman et al, 2008a).
- Within 2 years of the trial's end, blood pressure differences between tight and conventional target groups had disappeared. During post-trial follow-up, the differences in clinical endpoints also diminished and lost statistical significance, and as such, there was no legacy effect for tighter blood pressure control (Holman et al, 2008b).

Take-home message

- UKPDS showed that the complications of type 2 diabetes, previously regarded as inevitable, could be reduced by improving blood glucose and/or blood pressure control.
- People were newly diagnosed with type 2 diabetes at entry to the study, so it highlighted the importance of early, intensive therapy.
- Intensive monitoring and the use of therapies available at the time (metformin, sulfonylureas and insulin) were effective at reducing glycaemia and risk of complications.
- Metformin decreased the risk of diabetes-related endpoints in obese people with diabetes, and is now the recommended first-line therapy for type 2 diabetes (NICE, 2015).
- Early tight control results in long-term benefits (the "legacy effect").
- A legacy effect for blood pressure control was not observed; however, maintaining target blood pressure does reduce the risk of any diabetes-related endpoint, diabetes-related deaths and microvascular endpoints. ■

Clinical perspective – UKPDS results

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Speakers at diabetes meetings often refer to *the* UKPDS study. However, as this summary demonstrates, the study produced several publications, which have had a varying impact on clinical practice. The study took 20 years from recruitment to publication because it took a long time for the significant reduction in microvascular complications with blood glucose reduction to become apparent.

UKPDS 34 (1998b) showed metformin use in the intensive blood-glucose control group with metformin was associated with fewer aggregate end-points (including overall mortality) in obese people. In UKPDS 33 (1998a), insulin and sulfonylureas did not increase the risk of cardiovascular deaths, but did not show the mortality reduction demonstrated with metformin. Metformin's impact on mortality propelled it to the drug of first choice for people newly diagnosed with type 2 diabetes, and into first-line treatment in most contemporary evidence-based guidelines. UKPDS 38 (1998d) showed a reduction in deaths with tight blood pressure control, and encouraged us to focus on cardiovascular risk in our patients with type 2 diabetes, and subsequently more modern ACE inhibitors proved more effective than captopril.

Finally, the 10-year follow up of the UKPDS, published in 2008, produced the unexplained "legacy" effect from early and intensive intervention. Although the science is clear, this has never been incentivised, and evidence suggests newly diagnosed people with type 2 diabetes in our care often experience considerable treatment inertia. The observed "legacy" effect suggests we should encourage tight control early after diagnosis to foster better long-term outcomes.

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United Kingdom Prospective Diabetes Study (UKPDS) Group (1998c) Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* **317**: 713–20

United Kingdom Prospective Diabetes Study Group (1998d) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317**: 703–13