UKPDS at 44 years

Up to 24 years of follow-up of nearly 1500 participants who completed the UKPDS (UK Prospective Diabetes Study) demonstrates persisting, significant reductions in all-cause mortality and microvascular complications in those achieving tight glycaemic control with sulfonylurea or insulin treatment shortly after diagnosis. Those in the overweight group who received intensive glycaemic control with metformin had reductions in all-cause mortality and myocardial infarction risk compared to the original controls managed less intensively with diet. This is despite all cohorts equalising to similar HbA$_{1c}$ levels by 1 year after completion of the original 10-year randomised controlled trial. These findings remind us of the importance of supporting people to avoid hyperglycaemia and achieve tight glycaemic control as soon as possible after diabetes diagnosis, and to maintain this for as long as is achievable.

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The UKPDS (UK Prospective Diabetes Study) was a 10-year randomised controlled trial undertaken from 1977 to 1997 in people newly diagnosed with type 2 diabetes (UKPDS Study Group, 1998a; 1998b):

- 1138 were assigned to a conventional glycaemic control strategy based on dietary modification.
- 2729 were treated with intensive sulfonylurea or insulin therapy, and achieved 10 mmol/mol (0.9%) tighter glycaemic control than the conventional group.
- 342 overweight (>120% ideal body weight) participants were assigned to intensive treatment with metformin, achieving 6 mmol/mol (0.6%) tighter control than the conventional group.

The initial outcomes of this study changed the standard of type 2 diabetes care, due to recognition of the benefits of tight glycaemic control and the value of metformin treatment, which became the first-line therapy of choice not just for those who were overweight (as in the trial) but to everyone with a new diagnosis. This has persisted in most guidelines to this day.

In 1997, 3277 surviving participants of UKPDS entered a 10-year, observational, post-trial monitoring study, during which glycaemic control in all groups rapidly equalised. The results of this follow-up demonstrated the significant "legacy effect" of the original tight glycaemic control and of metformin treatment, further confirming the benefit of tight initial control even if this is allowed to lapse after 10 years (Holman et al, 2008a). A legacy effect is defined as the impact that previous conditions have on current processes or properties, in this case the impact that previous hyperglycaemia has on the risk of complications of type 2 diabetes. UKPDS also examined the effects of tight blood pressure control, but found that benefits of this only occurred while the control was maintained, with no legacy effect demonstrated (Holman et al, 2008b).

In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, people with type 2 diabetes for 10+ years were treated with multiple glucose-lowering drugs, aiming to demonstrate benefits of achieving normoglycaemia (HbA$_{1c}$ <6.5%) with intensive glycaemic control. However, the study was stopped early due to increased mortality in the intervention group, and the publicity surrounding this resulted in widespread concern amongst clinicians and patients about tight glycaemic control. This has had a negative impact on practice for many years, and resulted from a failure to differentiate between the "legacy" benefits of tight glycaemic control in the **newly diagnosed** population in UKPDS, versus the risks in those with **long-standing** type 2 diabetes, often with significant pre-existing complications, in ACCORD, many of whom suffered severe hypoglycaemia from the multiple drugs prescribed.

The present study: UKPDS at 44 years

From 2007 until 2021, 1489 surviving participants (10–12% of the original participants) in UKPDS were able to be followed up for an additional

References

ACCORD Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**: 2545–59

Adler AI, Coleman RL, Leal J et al (2024) Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). *Lancet* 17 May [Epub ahead of print]. https://doi.org/10.1016/S0140-6736(24)00537-3

Holman RR, Paul SK, Bethel MA et al (2008a) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

Holman RR, Paul SK, Bethel MA et al (2008b) Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* **359**: 1565–76

UK Prospective Diabetes Study Group (1998a) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**: 837–53

UK Prospective Diabetes Study Group (1998b) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**: 854–65

14 years, via linkage with their NHS notes (Adler et al, 2024). Seven prespecified clinical endpoints were explored based on the original randomisation, including any diabetes-related endpoint, diabetes-related death, death from any cause, myocardial infarction, stroke, peripheral arterial disease and microvascular disease.

Results

Up to 24 years after the UKPDS study end, the legacy effects of early glycaemic control and metformin persist.

Compared with conventional dietary control, early intensive treatment with sulfonylureas or insulin had the following benefits:

- 10% relative risk reduction (RRR) in death from any cause (absolute risk reduction [ARR] 2.7%).
- 17% RRR in myocardial infarction (ARR 3.3%) – not significant during original study; emerged by end of monitoring period.
- 26% RRR in microvascular disease (ARR 3.5%).

Compared with conventional dietary control, early intensive glycaemic control with metformin had the following benefits:

- 20% RRR in death from any cause (ARR 4.9%).
- 31% RRR in myocardial infarction (ARR 6.2%).
- No significant RRR for microvascular disease.

There were no differences in risk of stroke or peripheral arterial disease in either of the interventions groups throughout the study.

The legacy effect appears to be linked to avoidance of hyperglycaemia, with poor glycaemic control inducing irreversible changes that permanently increase the risk of diabetes complications and mortality. Furthermore, the hyperglycaemia appears to have a greater impact the longer ago it occurred; for example, each 11 mmol/mol higher HbA_{1c} value from 20 years prior to death confers a 36% increased risk of mortality, whereas that same 11 mmol/mol increase occurring 5 years prior to death only increases the relative risk of death by 8%. Delaying a reduction in HbA_{1c} by 10 years compared to immediate reduction attenuates the estimated mortality relative risk reduction from 18.6% to only 6.6%.

This glycaemic legacy effect is similar to the "metabolic memory" demonstrated in people with type 1 diabetes in the EDIC (Epidemiology of Diabetes Interventions and Complications) follow-up of the DCCT (Diabetes Control and Complications Trial). Multiple contributing mechanisms have been proposed, including oxidative stress, increased formation of advanced glycation end-products and epigenetic changes enhancing expression of pro-inflammatory genes.

Implications for practice

This paper is a potent reminder of the "legacy effect" – a near life-long reduced risk of death and myocardial infarction – achievable with tight glycaemic control using sulfonylurea, insulin or metformin therapy beginning immediately after type 2 diabetes diagnosis. The benefits of avoiding hyperglycaemia early after diagnosis persisted after more than 80 000 person-years of follow-up, despite loss of glycaemic difference between groups shortly after the original UKPDS trial ended.

Aiming for diabetes remission as the first stage of type 2 diabetes management after diagnosis fits nicely with this legacy effect, taking it one step further with the achievement of normoglycaemia whilst off all glucose-lowering therapies.

Modern diabetes drugs provide additional cardiorenal benefits, throughout the course of type 2 diabetes, some of which are independent of glucose lowering. This extension to UKPDS once again flags up the benefits of ensuring tight, early glycaemic control, whichever drugs are used to achieve this. It also reminds us of the greater legacy effect of early metformin therapy, despite smaller effects on HbA_{1c}, than in the sulfonylurea/insulin group, suggesting that metformin may have drug-specific protective benefits. This is important as some guidelines no longer include first-line metformin use for everyone.

It is a salutary exercise to run a search for people with type 2 diabetes diagnosed within the last 2 years in our practice or service, and to identify how many have not achieved either remission or tight glycaemic control. This paper should encourage us to share the long-term benefits of early tight glycaemic control with the people we support, and reinvigorate our efforts to help them optimise their control as early as possible after diagnosis. ∎