

A brief history of the UK Prospective Diabetes Study

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Abstract

The UK Prospective Diabetes Study (UKPDS) epidemiological findings confirmed that T2DM is not a “mild” disease, with roughly 50% of patients having clinically evident complications at diagnosis, emphasising the need for its early detection and treatment. Hyperglycaemia was identified as an independent coronary heart disease risk factor, with progressive hyperglycaemia shown to be a major pathophysiological feature of T2DM, driven by declining beta-cell function. People with T2DM and hypertension were found to be at double jeopardy for any diabetes endpoint, and worsening kidney function was shown to increase the risk of death substantially.

The UKPDS 20-year trial results were the first to demonstrate that diabetic complications are not inevitable but can be prevented by more intensive blood glucose control and by metformin therapy, changing T2DM management guidelines worldwide. The UKPDS also showed that tighter blood pressure control prevents diabetic complications; the benefits of the glucose and blood pressure interventions are additive.

The UKPDS 10-year post-trial monitoring study was the first to identify the T2DM glycaemic and metformin legacy effects, with early more intensive therapy having continuing benefits long after the trial terminated. The trial demonstrated the need to achieve good glycaemic control as early as possible to minimise the risk of future complications.

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Background

The UK Prospective Diabetes Study (UKPDS) was conceived in the years of uncertainty following the premature termination of the University Group Diabetes Program (UGDP) study in the late 1960s, which appeared to demonstrate excess cardiovascular mortality with tolbutamide and excess all-cause mortality with phenformin. I joined Robert Turner as his first research fellow in Oxford in 1975 and undertook a series of studies examining 24-hour plasma glucose profiles in people with and without type 2 diabetes (T2DM). Contrary to the prevailing view that plasma glucose values in T2DM rose progressively during the day and returned to normal with fasting overnight, these studies demonstrated that subjects had highly

repeatable elevated early morning glucose values, the magnitude of the elevation reflecting their individual degree of insulin deficiency. We concluded that T2DM is an endocrine disease of relative insulin deficiency and that a logical treatment for it would be hormone replacement therapy.¹

My further studies showed that fasting normoglycaemia could be achieved in people with diet-treated T2DM, either by increasing endogenous insulin concentrations with a long-acting sulfonylurea (chlorpropamide) or by providing exogenous insulin supplementation in the form of subcutaneous long-acting insulin injections (ultratard).² When I presented these findings at the International Diabetes Federation Congress in Delhi in November 1976 the audience were sceptical about the value of achieving normoglycaemia, and in particular the suggestion that insulin might become a first-line therapy. Given this feedback, and the results of the UGDP, Robert and I concluded that a major clinical trial was needed to demonstrate the potential benefits of good glycaemic control on clinical outcomes and the possible utility of early insulin treatment. By the time we returned to the UK we had agreed the protocol for what was to become the United Kingdom Diabetes Prospective Study (UKPDS), which commenced just one year later in December 1977 with the aid of a small grant from the Clothworkers' Foundation.

Study design

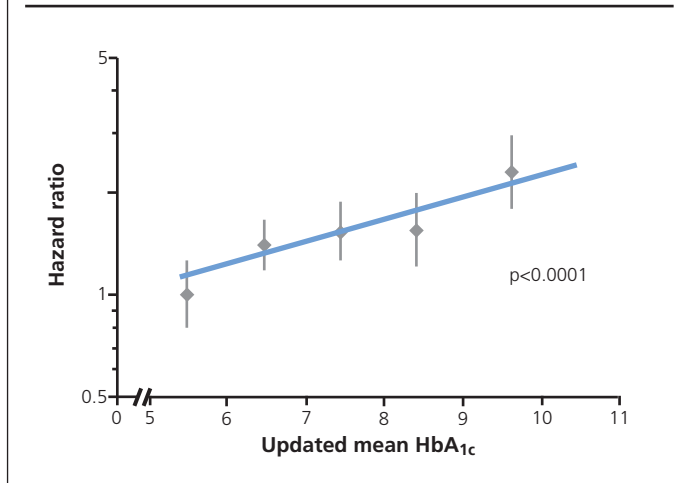
The UKPDS was a 20-year randomised, controlled, clinical outcome trial of 5,102 people with newly-diagnosed T2DM that ran in 23 English, Scottish and Northern Ireland hospital centres from 1977 to 1997. Participants were allocated to an intensive blood glucose control strategy with sulfonylureas or insulin or (if overweight) metformin, or to a conventional blood glucose control strategy, primarily with diet. Those who also had hypertension were randomised to tight or less-tight blood pressure control in a factorial design.³ The trial closed out on September 30th 1997, with the results presented the following year at the 1998 EASD meeting in Barcelona.

Following termination of the trial, all 3,277 surviving participants entered a 10-year post-trial monitoring study and returned to their usual care provider. No attempt was made to maintain randomised therapies; mean HbA_{1c} and blood pressure values rapidly became similar between groups, as did their glucose-lowering and antihypertensive therapies with the new more stringent post-UKPDS management guidelines for T2DM that were being rolled out. Post-trial monitoring closed out on September 30th 2007, with the results presented the following year at the 2008 EASD meeting in Rome.

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Figure 1. Log-linear relationship between coronary heart disease risk and glycaemic exposure, expressed as updated mean HbA_{1c} values.⁷



Epidemiological findings

Observational analyses conducted during the trial identified a number of key epidemiological findings that transformed our understanding of T2DM. These included: 1) at diagnosis there was an unanticipated high rate of complications, with approximately half of all patients having clinically evident tissue damage such as retinopathy or an abnormal ECG;³ 2) the identification of progressive hyperglycaemia as a major pathophysiological T2DM feature, with mean HbA_{1c} values rising inexorably over 10 years irrespective of treatment modality;⁴ 3) the driver for progressive hyperglycaemia was shown to be a concomitant decline in HOMA-derived measure of beta cell function, with an average annual reduction of 4% over four years irrespective of allocated therapy;⁵ 4) hyperglycaemia was shown to be a major independent modifiable risk factor for coronary heart disease, with Robert Turner renaming the “deadly quartet” (high LDL-cholesterol, low HDL-cholesterol, hypertension and smoking) as the “deadly quintet”;⁶ the relationship between the log hazard ratio for coronary heart disease and the updated mean HbA_{1c} was shown to be a straight line (Figure 1), suggesting that a 14% relative risk reduction for coronary heart disease might be achieved for each one percentile decrement in HbA_{1c};⁷ 5) the UKPDS was the first study to identify that participants who were hypertensive in addition to having T2DM were at double jeopardy, with a 45% greater risk of experiencing the UKPDS aggregate outcome of any diabetes-related endpoint compared with those who had T2DM alone.⁸ This double jeopardy finding led to the factorial-design addition of the Hypertension in Diabetes Study (HDS); 6) the major impact of worsening nephropathy increasing the risk of death. Although the annual rate of progression from no nephropathy to microalbuminuria, to macroalbuminuria, and to end stage renal disease was only 2.0–2.8%, the corresponding annual risks of death were 1%, 3%, 5% and 19%, respectively.⁹ This finding led to a much greater focus on renal impairment in T2DM and methods to prevent it.

Table 1 Relative risk reductions (RRR) and P values for the 20-year interventional trial (1997) and the subsequent 10-year post-trial monitoring study (2007). P values <0.05 shown in bold.

		1997	2007
Glucose Study (Intensive vs. Conventional)			
Any diabetes-related endpoint	RRR:	12%	9%
	P:	0.029	0.040
Microvascular disease	RRR:	25%	24%
	P:	0.0099	0.001
Myocardial infarction	RRR:	16%	15%
	P:	0.052	0.014
All-cause mortality	RRR:	6%	13%
	P:	0.44	0.007
Metformin Study (Intensive vs. Conventional)			
Any diabetes-related endpoint	RRR:	32%	21%
	P:	0.0023	0.013
Microvascular disease	RRR:	29%	16%
	P:	0.19	0.31
Myocardial infarction	RRR:	39%	33%
	P:	0.010	0.005
All-cause mortality	RRR:	36%	27%
	P:	0.011	0.002
Blood Pressure Study (Tight vs. Less tight)			
Any diabetes-related endpoint	RRR:	24%	7%
	P:	0.0023	0.31
Microvascular disease	RRR:	37%	16%
	P:	0.0092	0.17
Myocardial infarction	RRR:	21%	10%
	P:	0.13	0.35
All-cause mortality	RRR:	18%	11%
	P:	0.17	0.18

Results

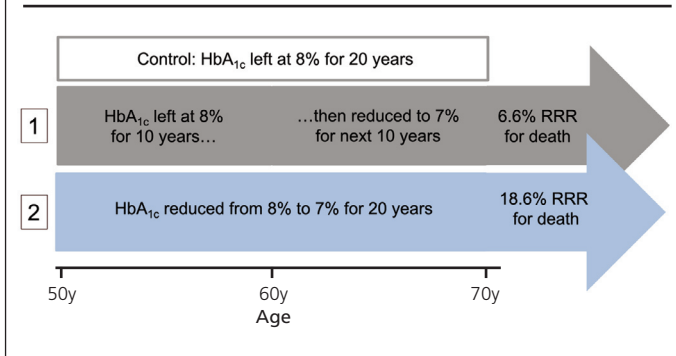
Glucose study

A median HbA_{1c} difference of 0.9% (7.0% vs. 7.9%) was achieved in 3,867 participants with sulfonylurea/insulin therapy, compared with conventional therapy, during a median follow-up of 10.0 years. This resulted in a 12% relative risk reduction in any diabetes-related endpoint and a 25% relative risk reduction in microvascular disease, but no significant reductions in the risk of myocardial infarction or death (Table 1).¹⁰ Following the further post-trial median follow-up of 8.2 years, significant relative risk reductions remained for any diabetes-related endpoint (9%) and microvascular disease (24%), with emerging benefits for myocardial infarction (15%) and all-cause mortality (13%).¹¹ We dubbed these continuing and emerging benefits of prior more intensive glucose control a glycaemic “legacy effect”.

Metformin study

A median HbA_{1c} difference of 0.6% (7.4% vs. 8.0%) was achieved in 753 overweight participants with metformin therapy, compared with conventional therapy, during a median follow-up of 10.7 years. This resulted in a 32% relative risk reduction in any diabetes-related endpoint, a 39% relative risk reduction in myocardial

Figure 2. Two simulated treatment scenarios for a 50-year-old male with newly-diagnosed T2DM and an HbA_{1c} of 8%.¹⁸



infarction and a 36% relative risk reduction in all-cause mortality (Table 1).¹² Following the further post-trial median follow-up of 8.8 years, significant relative risk reductions remained for any diabetes-related endpoint (21%), myocardial infarction (33%) and all-cause mortality (27%).¹¹ We dubbed these continuing benefits a metformin “legacy effect”.

Blood pressure study

A median systolic blood pressure difference of 10/5 mmHg (144/82 vs. 154/87 mmHg) was achieved in 1,148 participants with tight, compared with less tight, blood pressure control during a median follow-up of 8.4 years. This resulted in a 24% relative risk reduction in any diabetes-related endpoint and a 37% relative risk reduction in microvascular disease, but no significant reductions in the risk of myocardial infarction or death (Table 1).¹³ The benefits of intensive blood glucose control and tight blood pressure control were shown to be additive (p for trend = 0.024).¹⁴ Following the further post-trial median follow-up of 8.0 years, no significant relative risk reductions were seen for any diabetes-related endpoint, microvascular disease, myocardial infarction or all-cause mortality, demonstrating that there was no “legacy effect” for prior tight blood pressure control.¹⁵

First-line insulin therapy

Concerns about the possible adverse effects of insulin therapy on cardiovascular disease in T2DM were raised whilst the UKPDS was underway, with the Veterans Affairs Diabetes Feasibility Trial reporting an apparent excess of non-fatal cardiovascular events in a study of 153 men randomly assigned to a standard insulin treatment group or to an intensive therapy group.¹⁶ A subgroup analysis of the UKPDS glucose study, comparing participants randomised to first-line insulin therapy with those allocated to conventional therapy, allayed these fears, at least in people with newly-diagnosed T2DM. Numerical relative risk reductions were seen with insulin therapy for any diabetes-related endpoint (13%), myocardial infarction (13%) and all-cause mortality (7%), with a statistically significant 30% relative risk reduction for microvascular disease ($p=0.015$).¹⁰ The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, which randomly assigned 12,537 people



Key messages

- Diabetic complications are not inevitable and can be prevented by improved blood glucose control and by improved blood pressure control
- The benefits of improved blood glucose and improved blood pressure control are additive
- The glycaemic “legacy effect” in type 2 diabetes highlights the need to achieve good glycaemic control as early as possible to maximise potential benefits
- The metformin “legacy effect” shows enduring risk reductions for myocardial infarction and all-cause mortality
- First-line therapy with insulin does not increase the risk of cardiovascular disease in type 2 diabetes

with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance or T2DM to receive insulin glargine or standard care, demonstrated a neutral effect on cardiovascular outcomes, confirming that insulin therapy did not increase cardiovascular risk in this population.¹⁷

Glycaemic legacy effect

The glycaemic legacy effect is likely driven by the lifetime impact of early exposure to hyperglycaemia, possibly mediated by oxidative stress, generation of AGE proteins or epigenetic changes leading to enhanced expression of proinflammatory genes. Lind *et al.* have shown that historical HbA_{1c} values appear to explain the glycaemic legacy effect, with older values having a substantially greater impact on the risk of all-cause mortality than more recent values.¹⁸ Using modelled UKPDS data, they performed a simulation exercise for two hypothetical treatment scenarios for a 50-year-old male with newly-diagnosed T2DM and an HbA_{1c} of 8%. In scenario one, the modelled impact on the risk of all-cause mortality of leaving the HbA_{1c} at 8% for 10 years and then reducing it to 7% for the subsequent 10 years, compared with leaving the HbA_{1c} at 8% for 20 years, was a 6.6% relative risk reduction (Figure 2). In scenario two, where the HbA_{1c} was reduced to 7% for 20 years from the time of diagnosis, the modelled impact on the risk of all-cause mortality was a relative risk reduction of 18.6%, an effect almost three times greater. These HbA_{1c} analyses and simulations emphasise the crucial importance of establishing and maintaining near-normoglycaemia from the time T2DM is diagnosed in order to minimise the risk of complications and to prolong life.

Summary

Starting in 1977, the UKPDS randomly allocated people with newly-diagnosed type 2 diabetes to an intensive blood glucose control strategy with sulfonylureas, insulin or metformin, or to a conventional blood glucose control strategy, primarily with diet. The 20-year trial results, published in 1998, showed that diabetic com-

plications are not inevitable and that the risk of problems experienced by people with T2DM, including heart attacks, kidney failure and vision loss, can be reduced by good glycaemic control. UKPDS was a landmark trial that changed guidelines worldwide to recommend intensive blood glucose control for everyone with T2DM. This meant that the therapies and blood glucose levels in the two UKPDS groups rapidly became similar. Despite this convergence, the 10-year post-study follow-up analysis (published in 2008) showed that the reduction in the risk of diabetic complications continued for up to 30 years, identifying legacy effects of early intensive blood glucose control with insulin or sulfonylurea therapy, and with metformin therapy.

Conflict of interest The author reports research support from AstraZeneca, Bayer and Merck Sharp & Dohme, and personal fees from Anji Pharmaceuticals, AstraZeneca, Novartis and Novo Nordisk.

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