

# The continuing legacy of the United Kingdom Prospective Diabetes Study

*Five years after the completion of the study, some of its benefits have been maintained*

THE UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS) provided definitive evidence for the benefit of intensive management of blood glucose level and blood pressure in people with type 2 diabetes.<sup>1,2</sup> When the main findings of the UKPDS were published in 1998, a year after the study had closed, several questions arose. How much would the UKPDS findings influence usual care? Would the vascular benefits of intensive therapy be sustained? Would the status of borderline or unexpected results change with longer observation?

To answer these questions, post-study monitoring was initiated after completion of the UKPDS. All patients stopped protocol-driven management but were asked to participate in further regular assessment. The 5-year post-study monitoring period ran from September 1997 to September 2002. Some early results were presented at the International Diabetes Federation Scientific Meeting in Paris in August 2003. The Chief Investigator, Professor Rury Holman, stressed the preliminary nature of the data, and foreshadowed full peer-reviewed publication in 2004. Nevertheless, given the impact of the UKPDS since 1998, the data were of great interest to many delegates present.

In the UKPDS, 3867 patients newly diagnosed with type 2 diabetes were randomly allocated to receive either conventional diet-based blood glucose control therapy or intensive pharmacotherapy, primarily with sulfonylurea or insulin (with a target fasting plasma glucose level of < 6.0 mmol/L). Of the original cohort, 489 died during the study period and 76 were lost to follow-up. Thus, 3302 patients (85.4%) entered post-study monitoring. Endpoint data were collected for all of these patients. More detailed results were available for the 1696 (51.4%) patients who were followed up in UKPDS clinics. Regardless of whether or not the patients elected to continue attending UKPDS clinics after the study had finished, management was left to the discretion of the treating physician.

The median haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) values in the two therapy groups were close to 7% at the start of the UKPDS; they diverged during the first year of the study, then rose in parallel, with a separation approaching 1%.<sup>1</sup> After the end of the UKPDS, the median HbA<sub>1c</sub> levels in the conventional therapy group plateaued at about 8.5%, while those in the intensive therapy group continued to rise. By the end of 3 years of post-study monitoring, the curves had converged.

## Key findings of 5-year post-study monitoring after the United Kingdom Prospective Diabetes Study<sup>1,2</sup>

- Diabetes control (assessed by haemoglobin A<sub>1c</sub> levels) in patients treated either conventionally or with intensive pharmacotherapy converged
- The effect of intensive blood glucose control on diabetes endpoints was maintained
- The reduced risk of a fatal or non-fatal myocardial infarction became statistically significant
- The benefit of metformin treatment in overweight people was maintained
- The increased risk of all-cause and diabetes-related mortality with combination sulfonylurea and metformin therapy was no longer evident
- Blood pressure levels converged in the conventionally and intensively treated groups, but the beneficial effects of aggressive antihypertensive therapy were only maintained for microvascular complications

Over the next 2 years, the median HbA<sub>1c</sub> level fell progressively in both groups by about 1%. Only a quarter of patients had achieved the target HbA<sub>1c</sub> level of < 7.0% by the end of post-study monitoring, even though most were receiving insulin treatment at the time.

The post-UKPDS changes in median HbA<sub>1c</sub> level mirror those found after the end of the equivalent type 1 diabetes study, the Diabetes Control and Complications Trial.<sup>3</sup> The convergence during the first 3 years of post-study monitoring probably reflects a combination of patient reluctance to maintain intensive therapy (in view of the risks of hypoglycaemia and weight gain), set against increasing acceptance of lower glycaemic targets by patients and their doctors in the conventionally managed group. The subsequent downward trend suggests that incorporation of UKPDS-based recommendations into usual care was increasing, but the availability of new therapies, including thiazolidinediones, may have contributed.

When analysed on an intention-to-treat basis, post-study monitoring data confirmed that participation in the intensive blood glucose lowering policy group was associated with a significantly lower rate of any diabetes-related endpoint (eg, myocardial infarction, stroke, renal failure, retinopathy, death from hyper- or hypoglycaemia) and of microvascular complications 5 years after the UKPDS had finished. This

sustained effect has been termed “metabolic imprinting”.<sup>3</sup> Although there were no group-specific differences in all-cause mortality and diabetes-related deaths during the UKPDS, intensive therapy during the study period was associated with a lower risk of diabetes-related death during post-study monitoring. The benefit of intensive therapy on fatal or non-fatal myocardial infarction — borderline in the UKPDS — was still weak by the end of post-study monitoring, but had become statistically significant.

During the UKPDS, metformin therapy in overweight patients substantially reduced the risk of any diabetes-related endpoint, all-cause mortality, diabetes-related deaths and myocardial infarction compared with conventional therapy.<sup>4</sup> During post-study monitoring, these risk reductions were attenuated but remained significant. There were unexpected increases in all-cause mortality (relative risk, 1.60; 95% CI, 1.02–2.52) and diabetes-related deaths (relative risk, 1.96; 95% CI, 1.02–3.75) in patients taking combination sulfonylurea plus metformin compared with sulfonylurea monotherapy in the UKPDS.<sup>4</sup> This was considered a chance finding resulting from the low number of deaths in the latter group. These differences were no longer evident at the end of post-study monitoring.

In the UKPDS, a subset of 1148 hypertensive patients were randomly allocated to tight blood pressure control (target, < 150/85 mmHg) or less tight control (target, < 180/105 mmHg).<sup>2</sup> Of these, 884 were available for post-study monitoring, of whom 522 continued to attend UKPDS clinics. The pattern of change in systolic and diastolic blood pressure was similar to the pattern of change in HbA<sub>1c</sub> levels during post-study monitoring, with convergence between groups during the first 3 years and progressive reduction over the next 2 years. Despite a doubling of the percentage of patients taking three or more antihypertensive medications during the post-study period, only one in six patients had achieved a systolic blood pressure of < 130 mmHg and a diastolic blood pressure of < 80 mmHg at the end of this time.

Compared with event rates in the less tightly controlled patients at the end of the UKPDS, there were impressive reductions in any diabetes-related endpoint, diabetes-

related deaths, stroke and microvascular disease among patients subject to tight blood pressure control.<sup>2</sup> By the end of post-study monitoring, the relative risk reductions in the first three of these categories were no longer statistically significant. For microvascular disease, a significant but attenuated risk reduction remained in the tight-control group.

The UKPDS design was complex, and analysis of post-study monitoring data will be further complicated by the fact that clinical management was non-uniform after completion of the UKPDS. Nevertheless, it appears that the microvascular benefit of tight glycaemic control is maintained after resumption of usual care. This was also seen in the Diabetes Control and Complications Trial,<sup>3</sup> and argues for early and aggressive blood glucose management strategies. Concerns about the safety of combination metformin–sulfonylurea therapy appear to have been allayed, and the macrovascular benefits of metformin in overweight patients are supported by the data presented in Paris. Disappointingly, it appears that the effects of aggressive antihypertensive therapy may wane relatively quickly. Formal analysis of post-study monitoring data is eagerly awaited, but, until then, there is reason to believe that the legacy of the UKPDS continues.

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