The UKPDS and *Diabetes & Primary Care:* Influencing a decade of change

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This edition of *Diabetes & Primary Care* marks the 10th anniversary of the journal. Ten years ago, the substantive results of the UKPDS (UK Prospective Diabetes Study) were also published (UKPDS Group, 1998a). To mark these two events, the editorials in this issue will reflect on a decade of developments in primary care diabetes, and the key trials that have played a role in developing best-practice guidelines that are now part of everyday clinical practice.

The impact of the UKPDS on the last 10 years

The UKPDS was a landmark study in diabetes care. It was designed to determine whether or not tight glycaemic control decreased diabetes-related complications and increased life expectancy. About 4000 people from throughout the UK newly diagnosed with type 2 diabetes were recruited from 1977 onwards. These participants were assigned to receive either conventional or more intensive treatment of glycaemic control, and were monitored for a median of 10.7 years to observe the long-term effects of the regimen.

The results of the UKPDS were reported in September 1998 (UKPDS Group, 1998a). Although tight glycaemic control reduced the risk of microvascular complications, it did not result in a significant reduction in all-cause mortality or myocardial infarction (MI) occurrence in the sulphonylurea–insulin arm (UKPDS Group, 1998a). However, regardless of their level of blood glucose control, overweight participants receiving metformin had significantly fewer diabetes-related outcomes (P=0.033) and a 39% and 36% reduction in MI risk and death, respectively (UKPDS Group, 1998b).

A sub-study within the main UKPDS investigated whether or not tighter control of blood pressure in people with hypertension decreased complications (UKPDS Group, 1998c). The effect on outcomes of tight blood pressure control (<150/<85mmHg) was more impressive than tight glycaemic control, as tight blood pressure control decreased overall mortality. Tight control of blood glucose decreased the aggregate risk of 21 different complications, although most of this benefit was due to changes in intermediate outcomes (Shaughnessy and Slawson, 2003). The considerable period between recruitment and publication of outcomes reflects the time needed for treatment with antidiabetic agents to improve microvascular outcomes.

New follow-up data

At this September's 44th annual meeting of the European Association for the Study of Diabetes (EASD) in Rome, the UKPDS lead investigator, Professor Rury Holman, and Professor David Matthews presented a 10-year follow-up of the UKPDS study. Professor Holman has written an editorial to comment on these results on page 329.

The new findings have reinforced several of the messages from the original study. The follow-up demonstrated that the use of metformin remains important, and that only persistent, intensive control will reduce the risk of cardiovascular complications. This is especially true when considering blood pressure control (Holman et al, 2008a; 2008b).

The concept of "metabolic memory" was first identified in the study carried out by the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) group, the follow-up of the landmark DCCT in people

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with type 1 diabetes (Nathan et al, 2005). The investigators reported no impact of intensive glucose lowering on cardiovascular disease in the original study (DCCT Research Group, 1995), but a 42% reduction in cardiovascular events was observed after a mean follow-up of 17 years, even when control had normalised in the interval. Tantalizingly, this suggests that there is a long-term legacy of improved cardiovascular risk from tight glycaemic control. Indeed, UKPDS investigators described the lasting effects of intensive glucose lowering as a "legacy effect" (Holman et al, 2008a). The significant risk reductions for any diabetes-related endpoint, MI, and death from any cause that were seen with metformin use in the original UKPDS trial persisted 10 years later. Moreover, significant risk reductions for MI (15%, P=0.01) and death from any cause (13%, P=0.007) emerged over time in the original sulphonylurea–insulin arm, as more events had occurred (Holman et al, 2008a).

Importance of blood pressure control

Tighter control of blood pressure, however, produced no lasting improvements in microvascular disease, MI, all-cause mortality or any diabetes-related endpoint. Indeed, the between-group differences in microvascular disease reported at the end of the original UKPDS trial had disappeared over the next 10 years (Holman et al, 2008b). Commenting on this difference, UKPDS investigator and Chairman of the Oxford Centre for Diabetes, Endocrinology and Metabolism, Professor David Matthews, said:

> *"With glucose control, it matters how well patients are treated now and how well they were treated in the past, but with blood pressure it seems to be related to just current therapy."* (University of Oxford, 2008)

The investigators speculated that the difference between the blood pressure control and the glycaemic control findings suggests different pathophysiological mechanisms.

Glucose lowering: Other analyses

Some of these findings have also been reinforced by a more recent meta-analysis, the objective of which was to systematically examine the peer-reviewed literature on the cardiovascular risks associated with oral antidiabetic agents (OADs; second-generation sulphonylureas, biguanides, thiazolidinediones, and meglitinides) for treating adults with type 2 diabetes (Selvin et al, 2008). This analysis suggested that, compared with other OADs and placebo, metformin was moderately protective, and rosiglitazone possibly harmful, but a lack of power in the rosiglitazone studies prohibited firmer conclusions (Selvin et al, 2008).

The large studies of tighter blood glucose control published recently (ACCORD [Action to Control Cardiovascular Risk in Diabetes], 2008; ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], 2008; and the VADT [Veterans Affairs Diabetes Trial], Abraira, 2008) have all been analysed in this journal, as has the fact that none of the trials revealed any significant benefit on cardiovascular events with tighter glycaemic control (O'Sullivan, 2008; Kenny, 2008a; Kenny, 2008b). A meta-analysis of these studies may shed more light on the importance of tight glycaemic control.

UKPDS and clinical practice

Reflecting on the presentation of the original UKPDS data a decade ago, it had the impact of prompting healthcare professionals working in primary care to increase their use of metformin, and use it as a first-line therapy in all people with type 2 diabetes who could tolerate it. It also reinforced the knowledge that type 2 diabetes has a significant impact on mortality from cardiovascular disease, which, in turn, reinforced the importance of optimal management of hypertension. Finally, it introduced the challenge of the iconic "J-shaped" curve (UKPDS, 1998a); an initial improvement in HbA_{1c} or fasting plasma glucose levels followed by progressive deterioration, irrespective of the glucose lowering agent employed, and confirming the need for multiple therapies to control glycaemia over time.

It is also worth noting that the statin class of medications was absent from the UKPDS, and it has taken trials such as the Collaborative Atorvastatin Diabetes Study (CARDS; Colhoun et al, 2004) and the Heart Protection Study (HPS

Collaborative Group, 2005) to act as catalysts for the dramatic increase in the use of these agents, which has also occurred within the past decade.

The UKPDS data were critical to the evidence base that underpinned the diabetes indicators in the Quality and Outcomes Framework (QOF) of the 2004 new General Medical Services contract. The annual returns from the QOF chart the geographical distribution of the prevalence of diabetes in the UK, as well as highlighting areas of regional differences in care. For a study that reflects the complex multifactorial interventions incentivised in the QOF, we need to turn to the impressive Steno-2 study carried out in people with diabetes at high-risk of cardiovascular complications (Gaede et al, 2008). There were very low numbers needed to treat in order to protect against death, cardiovascular events, and microvascular complications; the intervention was also highly cost-effective (Gaede et al, 2008). The findings of this study should be at the forefront of our minds at a time when our politicians seek to make non evidence-based changes to the diabetes QOF (see page 332 for further comment on this from Martin Hadley-Brown).

The role of *Diabetes & Primary Care*

Diabetes & Primary Care has reported and reflected on all of the important diabetes trials that have affected primary care teams in the past decade. It has also had an important role as a voice for individuals in these primary care teams throughout the UK and Ireland.

The journal gave voice to Primary Care Diabetes UK before it amalgamated with Diabetes UK, and helped nurture the Primary Care Diabetes Society (PCDS), with which it is published in association. PCDS members were provided with a forum for discussion, and have successfully engaged with the journal's publishers in a series of national and regional educational diabetes meetings, which helped to fulfil an important commitment of the Society to continuing professional development (CPD).

Looking forward to the next 10 years

There has been much to reflect on during a successful decade of diabetes care, faithfully reported in the pages of *Diabetes & Primary Care*.

The past 10 years has seen the chronic disease management of diabetes move firmly into the domain of primary care. For reasons of cost-effectiveness alone, it will remain this way, and be reinforced and extended. We will see new therapeutic agents emerge and be more specifically targeted at differing groups of people with diabetes, and the journal will reflect and report on them. Having said this, it is interesting to consider that, those who set up the UKPDS would probably not have predicted that the agents they chose to investigate – metformin, sulphonylureas and insulin – would remain the main the stalwart treatments 30 years later.

Making predictions about the next 10 years renders the individual a hostage to fortune. For example, while it is hard to imagine a life without search engines, Google is only now marking its 10th anniversary. Moving forward, this journal intends to embrace technology; its website will grow in importance, as will its commitment to CPD through electronic media.

If all of us suffered from the ancient Chinese curse of "living through interesting times" during the past decade, then we can only predict more exciting developments and changes ahead in the expanding area of primary care diabetes. ■

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