Therapy for type 2 diabetes: where do we stand after the UK Prospective Diabetes Study?

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The Diabetes Control and Complications Trial (DCCT) in type 1 diabetes, published in 1993, demonstrated the beneficial effects of intensive insulin therapy on the onset and progression of diabetic retinopathy, nephropathy and neuropathy (1). Although many clinicians assumed that these results were also applicable to type 2 diabetic patients, this has not been demonstrated so far. In fact, a previous clinical trial in 1970, the University Group Diabetes Program (UGDP), compared five different treatments (diet and placebo, standard insulin doses according to body weight, variable insulin doses according to glycemia, and tolbutamide or phenformin) in type 2 diabetics (2). During the 5.5 years (range 3–8 years) that the 1000 patients were followed, the UGDP revealed no statistically significant differences in cardiovascular mortality or microvascular disease between the different treatment groups, except for the phenformin- and tolbutamide-treated patients whose cardiovascular mortality was significantly higher compared with the placebo group. These results generated great controversy about the use of oral hypoglycemic agents, which was fueled by potential methodological deficiencies. For example, 46% of the patients included in the study already had signs of pre-existing cardiovascular disease and potentially due to non-homogeneous randomization, the phenformine and tolbutamide group had a higher incidence of myocardial infarctions. Despite a reassessment by an international committee of the Biometric Society in 1976 the controversy over these results remains. Since then, in vitro studies have added to the fear that sulfonylureas may aggravate cardiovascular disease (3).

In the study from Kumamoto, Japan in 1995 the effects of intensive and conventional insulin therapy on microvascular complications were compared in 100 lean (body mass index <22 kg/m²) type 2 diabetic patients over a 6-year period (4). This treatment achieved a >2% difference in mean HbA1c levels (7% versus 9%) over the whole study period. Intensive glycemic control delayed the onset and the progression of diabetic retinopathy, nephropathy, and neuropathy. No major effect on macrovascular disease was seen. Despite the data showing a reduction in microvascular complications by insulin therapy, the effect of oral antidiabetic therapy on these complications remained to be elucidated.

In the mid 1970s, the prospective and randomized United Kingdom Prospective Diabetes Study (UKPDS) was designed to try to clarify whether intensive therapy as compared with dietary therapy had a better long-term outcome in type 2 diabetes. An additional aim was to compare the advantages and disadvantages of insulin and sulfonylureas among patients in the intensive therapy group. In obese patients, an additional group was assigned to metformin. Later on, a hypertension study was added to examine the effects of tight blood pressure control on the risk of macro- and microvascular complications. Three aggregate endpoints were used to assess differences between the conventional and intensive treatments: (i) diabetes-related endpoints (sudden death, death from hyperglycemia or hypoglycemia, myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); (ii) diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, and sudden death); and (iii) all-cause mortality. The most important results of the UKPDS have now been published in four different papers in September 1998 (5–8).

Before examining the results of the UKPDS, it should be noted that, unavoidably, considerable therapeutic overlap among the different treatment groups occurred (9). If in the control or intensive therapy groups fasting plasma glucose (FPG) levels were above predefined limits (FPG>15 mmol/l or FPG>6 mmol/l respectively), a sulfonylurea was added. This therapy could be further supplemented with metformin, and eventually replaced by insulin if necessary. Thus, in each treatment group at least 30% of patients took at least one additional drug than they were initially assigned to.

In the UKPDS 33 publication (5), intensive therapy with a sulfonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin aimed at obtaining a FPG of less than 6 mmol/l was compared with conventional therapy (diet only with drugs added only if hyperglycemia was symptomatic or if FPG>15 mmol/l) by randomizing patients with a FPG>6 mmol/l to either treatment group. On recruitment 93% of the patients had a FPG>7.0 mmol/l (novel American Diabetes Association (ADA) criteria for the diagnosis of diabetes)
and 86% had a FPG > 7.8 mmol/l (WHO criteria). After 10 years, the median HbA1c values were 7.0% (95% confidence intervals (CI) 6.2–8.2%) and 7.9% (CI 6.9–8.8%) (<0.0001) in the intensive and conventional groups respectively, as compared with the DCCT and Kumamoto studies (HbA1c reductions by 1.8% and 2% respectively). The mean weight gain in the intensive as compared with the conventional group was 3.1 kg (insulin: 4.0 kg, sulfonylureas: 1.7–2.6 kg). Intensive therapy reduced the risk of any diabetes-related endpoint by 12% (CI 1–21%), but did not reduce diabetes-related mortality or all-cause mortality significantly (5). A 23% (CI 7–40%) risk reduction in microvascular endpoints and retinopathy in particular, was responsible for most of the risk reduction in the any diabetes-related endpoint aggregate. There was no difference between the three intensive therapies (chlorpropamide, glibenclamide, or insulin) for any of the aggregate endpoints. Nevertheless, the risk for a myocardial infarction was reduced by 16%, although this did not quite reach statistical significance (P = 0.052). However, for several reasons it would be imprudent to draw a definite conclusion that the efficacy of sulfonylureas and insulin in preventing microvascular disease is identical: (i) as stated previously, there is therapeutic overlap between the three intensive therapy groups resulting in patients from the sulfonylurea groups receiving insulin; (ii) the size of the subgroups also limits the statistical power and hence the conclusions that can be drawn on the absence of statistically significant differences. However, there was very clearly no evidence of a higher mortality rate in patients treated with sulfonylureas, contrary to what was suggested by the UGDP. An additional concern are the potentially adverse effects of hyperinsulinemia per se. In the UKPDS, the median insulin doses at 3, 6, 9, and 12 years were 22 U, respectively, as compared with the DCCT and Kumamoto studies (HbA1c reductions by 1.8% and 2% respectively). The mean weight gain in the intensive as compared with the conventional group was 3.1 kg (insulin: 4.0 kg, sulfonylureas: 1.7–2.6 kg). Intensive therapy reduced the risk of any diabetes-related endpoint by 12% (CI 1–21%), but did not reduce diabetes-related mortality or all-cause mortality significantly (5). A 23% (CI 7–40%) risk reduction in microvascular endpoints and retinopathy in particular, was responsible for most of the risk reduction in the any diabetes-related endpoint aggregate. There was no difference between the three intensive therapies (chlorpropamide, glibenclamide, or insulin) for any of the aggregate endpoints. Nevertheless, the risk for a myocardial infarction was reduced by 16%, although this did not quite reach statistical significance (P = 0.052). However, for several reasons it would be imprudent to draw a definite conclusion that the efficacy of sulfonylureas and insulin in preventing microvascular disease is identical: (i) as stated previously, there is therapeutic overlap between the three intensive therapy groups resulting in patients from the sulfonylurea groups receiving insulin; (ii) the size of the subgroups also limits the statistical power and hence the conclusions that can be drawn on the absence of statistically significant differences. However, there was very clearly no evidence of a higher mortality rate in patients treated with sulfonylureas, contrary to what was suggested by the UGDP. An additional concern are the potentially adverse effects of hyperinsulinemia per se. In the UKPDS, the median insulin doses at 3, 6, 9, and 12 years were 22 U, 28 U, 34 U, and 36 U respectively. For obese patients (>35 kg/m²), the corresponding median daily insulin doses were 36 U at 3 years and 60 U after 12 years. Nevertheless, these doses were apparently not associated with an increase in cardiovascular complications (see also the accompanying Highlight by U Vischer (10)).

In the UKPD34 paper (6), the effect of intensive blood-glucose control (target FPG < 6 mmol/l) with metformin on complications in 1704 overweight (>120% ideal body weight) type 2 diabetics was compared with conventional (diet only, target FPG < 15 mmol/l) and intensive (chlorpropamide, glibenclamide, or insulin) therapy with a follow-up over nearly 11 years. Inclusion criteria and therapeutical modifications were according to the same protocol as in UKPDS 33 and the treatments were allocated randomly. Baseline FPG was superior or equal to 8 mmol/l (CI 7.1–9.8 mmol/l) in every group. Metformin produced better diabetes-related outcomes, diabetes mortality, and all-cause mortality than did conventional therapy with risk reductions of 32% (CI 13–47%), 42% (CI 9–63%), and 36% (CI 9–55%) respectively. In the intensive blood-glucose control group, metformin significantly reduced the incidence of any diabetes-related endpoint, all-cause mortality, and stroke compared with insulin and sulfonylureas (Figs., 5 and 7 in reference 6). Metformin therapy was also associated with less weight gain and fewer hypoglycemic episodes. Median HbA1c during the follow-up was 7.4% in the metformin group and 8.0% in the conventional treatment group. While intensive control with sulfonylureas and insulin resulted in HbA1c values close to those of the metformin group (Fig. 3 in reference 6), metformin had more substantial effects on any diabetes-related endpoint, all-cause mortality, and stroke, suggesting that the beneficial effects of metformin in obese patients might be due to pharmacological effects beyond the reduction of hyperglycemia per se. These may include a decrease in insulin levels, plasminogen-activator inhibitor levels, enhanced insulin sensitivity, inhibition of hepatic gluconeogenesis, less weight gain, as well as the documented decrease in the number of hypoglycemic events (11). In a subgroup of 268 patients treated with sulfonylureas the early addition of metformin increased the risk of diabetes-related death by 96% (CI 2–275%) compared with sulfonylureas alone. However, patients in the sulfonylurea group were on average 5 years older, had higher baseline fasting plasma glucose, and were less overweight than the patients treated with metformin alone. In addition, supplementary epidemiological and meta-analyses failed to corroborate this finding in other studies examining combined sulfonylurea and metformin therapy.

The two other papers (UKPDS 38 and 39) looked at the effect of tight blood pressure control on macrovascular and microvascular complications in type 2 diabetes and compared the efficacy of a β-blocker (atenolol) with an angiotensin converting enzyme inhibitor (captopril) (7). Over an 8.4 year median follow-up period, the mean blood pressure was reduced in the tight control group to 144/82 mmHg (target blood pressure < 150/85 mmHg on atenolol or captopril therapy) compared with the less tight control group with a blood pressure of 157/87 mmHg (target blood pressure < 180/105 mmHg) where the use of an angiotensin converting enzyme inhibitor and β-blocker were avoided. The reduction in risks in the tight control group compared with that of the less tight control group was 24% (CI 8–38%) in diabetes-related endpoints, 32% (CI 6–51%) in diabetes-related deaths, and 44% (CI 11–65%) in strokes. Strikingly, a 37% (CI 11–56%) reduction in microvascular end points (retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or non fatal renal failure) was also demonstrated. The risk of heart failure was reduced by 56% (8). However, the reduction in all-cause mortality was not significant.

Both atenolol and captopril controlled blood pressure with similar efficacy and reduced the risk of
macrovascular and microvascular complications to the same extent. Over the first 4 years compliance was similar but subsequently more patients discontinued atenolol due to side effects. The authors hypothesize that the reduction in blood pressure is responsible for the reduction in complications, rather than the treatment used to achieve it, questioning whether angiotensin converting enzyme inhibitors indeed have a specific renal effect in type 2 diabetes. Long term follow-up and more studies will be necessary to elucidate this point.

The UKPDS did not give quite as clear answers as were expected, despite the long follow-up period. This is mainly due to the therapeutic overlap among the various study groups which reflects the clinical realities of diabetes management, and which cannot be avoided when the best medical care should be given. What has been shown by the UKPDS is that intensive therapy, as in the DCCT, is beneficial to patients with type 2 diabetes (1, 5). Neither insulin nor sulfonylureas cause an increase in macrovascular complications and sulfonylureas do not increase mortality as compared with insulin. In obese patients, metformin proved to be as safe and perhaps even more efficacious than insulin and sulfonylureas, with less weight gain and fewer hypoglycemic episodes, and it may be an attractive initial therapy for type 2 diabetes, since it may have beneficial effects beyond its hypoglycemic action. Taken together, it seems reasonable therefore to attempt to achieve good glycemic control (e.g. HbA1c<7%) and, even more importantly, treat hypertension aggressively (target: <140/85 mmHg) in type 2 diabetics. However, potential adverse effects of combined sulfonylurea and metformin therapy and the relative benefits of these two drugs still remain to be clarified.

References
9 UK Prospective Diabetes Study (UKPDS) Group. UK Prospective Diabetes Study (UKPDS) VIII. Study design, progress and performance. Diabetologia 1991 34 877–890.