CORRESPONDENCE

The UK Prospective Diabetes Study

Sir—Robert Turner and colleagues (Sept 12, p 837[1,2]) note increased diabetes-related deaths in a subset of type 2 diabetic patients randomised to sulphonylurea-metformin combination therapy. Since this combination is widely used in patients with type 2 diabetes,[3] the subset analysis requires clarification.

In the main randomisations of the UK Prospective Diabetes Study (UKPDS), patients allocated to sulphonylurea (normal-weight and overweight patients) or metformin (overweight patients only) showed a reduction of 8% and 42%, respectively, in diabetes-related deaths.[1,2] To combat the progressive rise in hyperglycaemia, sulphonylurea-metformin combination therapy or insulin was required for 23–30% of patient-years. Why then should the subset give a different outcome to the main randomisations?

The subset consisted of 537 patients who were inadequately controlled on maximum sulphonylurea therapy. These patients were randomised to additional metformin (n=268) or continuation of sulphonylurea alone (n=269). After 6·6 years, diabetes-related deaths in those randomised to sulphonylurea-metformin (26/268) were nearly double those randomised to sulphonylurea (14/269). In the sulphonylurea group the diabetes-related deaths were 22% lower than in the main randomisation (8·6 *vs* 11·0 per 1000 patient-years of follow-up, respectively).[1,2] A combined analysis of patients allocated metformin either as primary treatment or in addition to sulphonylurea therapy presented no evidence that metformin therapy increased diabetes-related deaths.[1] Although the analyses were made on an intention-to-treat basis, an epidemiological assessment of diabetes-related deaths showed a non-significant 5% risk reduction in diabetes-related deaths on sulphonylurea-metformin combination compared with all other treatments.

Contrary to an instant interpretation of the UKPDS—that patients should not be prescribed sulphonylurea-metformin combination therapy[4]—this recommendation is not indicated by the main analyses. Since the blood glucose-lowering effects of sulphonylurea and metformin therapy are additive when used in combination,[3,5] and the UKPDS has affirmed that improved glycaemic control reduces diabetic complications,[2] we should regard cessation of one component of combination therapy as potentially hazardous, unless insulin therapy is substituted.

Clearly, the best possible glycaemic and blood pressure control will bring major reductions in morbidity and mortality from diabetic complications. The UKPDS issues a mandate to improve the morbidity and mortality of type 2 diabetes, and this should not be hijacked by any inappropriate interpretations.

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1 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352:** 854–65.
2 UK Prospective Diabetes Study (UKPDS) Group. 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* 1998; **352:** 837–53.
3 Bailey CJ, Nattrass M. Treatment-metformin. *Baillieres Clin Endocrinol Metab* 1988; **2:** 455–76.
4 British Diabetic Association. Statement on combined drug therapy, Sept 18, and Oct 6, 1998.
5 DeFronzo RA, Goodman AM. Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; **333:** 541–49.

Sir—The UKPDS results[1,2] have caused anxiety about the widespread practice of combining sulphonylureas and metformin, and some advocate a moratorium on the use of such combination therapy. For example, Barber[3] advises in *General Practitioner*, that sulphonylurea-metformin combination therapy should now never be used.

The results for combination therapy are surprising when compared with the beneficial effects of initial therapy of obese patients with metformin alone.[1] The small numbers of deaths that occurred in the combination study were highlighted by the researchers as a possible explanation for the disparity. David Nathan suggests in the accompanying commentary (Sept 12, p 832)[4] that the method of analysis may have been responsible. However, careful examination of the data reveals a third possible explanation. The diabetes-related death rate in the sulphonylurea-treated group of the combination study is unexpectedly low. The absolute diabetes-related risk of death for the 1234 patients receiving sulphonylurea treatment was 11·0 events per 1000 patient-years;[2] in the smaller combination study,[4] this was only 8·6 events per 1000 patient-years, despite patients being older, heavier, more hyperglycaemic, and having more abnormal lipid profiles at the outset that the corresponding sulphonylurea group.[2] Even a small change in the diabetes-related death rate in the sulphonylurea-treated group would have negated the statistical difference between this group and the sulphonylurea-metformin combination group.

It is ironic that the UKPDS arose from the controversy of the University Group Diabetes Programme study,[5] in which differences in small numbers of death case a shadow over sulphonylurea therapy. The UKPDS was designed and powered to show the advantages of tight blood pressure control and glycaemic management. The researchers' conclusions that combination therapy with sulphonylureas and metformin requires further study is appropriately worded. It is at the very least premature to dogmatically dismiss sulphonylurea-metformin combination therapy.

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1 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in