Therapeutic targets for type 2 diabetes post-UKPDS

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J R Coll Physicians Lond 2000;34:254–6

The UK Prospective Diabetes Study (UKPDS), published in late 1997, finally laid to rest the few remaining doubts about whether improved glycaemic control prevents microvascular disease in type 2 diabetes. The main question asked in that study, however, was more to do with cardiovascular prevention:

Does the relationship between hyperglycaemia and coronary heart disease seen in population studies mean that improved control prevents the condition?

While the headline answer, unfortunately, came out as ‘probably’, the UKPDS did help to answer a number of other questions.

The UKPDS recruited 5,102 type 2 diabetic subjects who were randomised to either:

- conventional treatment, initially a weight reducing, low fat, low glycaemic index diet, adding additional hypoglycaemic therapy if symptoms occurred or if fasting plasma glucose (FPG) exceeded 15 mmol/l, or
- intensified treatment, using oral hypoglycaemic agents or insulin to maintain FPG below 6 mmol/l.

Despite deteriorating glycaemic control in both groups, a mean difference in glycated haemoglobin (HbA1c) of just under 1% was maintained for the median follow-up time of 10 years. Microvascular disease incidence was reduced by about 25%. For acute myocardial infarction (MI), however, the benefit of intensified control just failed to achieve significance: a 16% reduction (p = 0.052). Despite protestations that this could have occurred by chance only once in 19 such studies (because the p value did not reach 0.05), evidence-based practitioners will regard this as a negative finding.

Cardiovascular effects of improved glycaemic control

Three other questions were tackled, and answered, in the UKPDS.

- Is there evidence for adverse effects of sulphonylureas on cardiovascular risk, as suggested by the University Group Diabetes Program, perhaps related to effects on the potassium-adenosine triphosphate channel?

There was no evidence for different effects on the incidence of MI or case fatality between insulin and sulphonylureas, suggesting that this is not an important consideration.

- Is there any difference in outcome between patients treated with metformin and with other agents, perhaps related to effects on insulin resistance?

Metformin as initial treatment in overweight patients significantly reduced the risk of MI (39%), and was the only randomised therapy to reduce the incidence of diabetes-related deaths (42%) and all-cause mortality (36%). Nevertheless, the addition of metformin to sulphonylureas in poorly controlled, normal weight patients apparently had an adverse effect on coronary risk, although this finding was probably the consequence of small numbers and statistical chance. The findings strongly point to metformin being the initial therapy of choice for overweight type 2 diabetic patients.

- How do rates of macrovascular and microvascular complications of diabetes compare in type 2 diabetes?

The mean age at diagnosis of the population in this study was 52 years. In the conventional treatment group over 10 years of follow-up, 22.4% suffered an infarct or a stroke, 3.5% became blind in one eye, and fewer than 1% developed renal failure.

This last observation poses important challenges for the physician looking after diabetic patients. Even at age 52, macrovascular disease rates exceed those of clinically important microvascular disease by about 5 to 1. The incidence of microvascular disease bears little relationship to age, but that of large vessel disease is strongly age-dependent. Thus, the therapy for the typical diabetic clinic patient, in his or her mid-60s, must be aimed mainly at large vessel disease. What should these targets be?

Effects of blood pressure treatment

The UKPDS answered important questions about blood pressure treatment in these subjects. The Hypertension in Diabetes (sub)Study randomised 1,148 patients with hypertension to tight control (<150/85 mmHg) with a beta-blocker or an angiotensin-converting enzyme (ACE) inhibitor as first-line therapy, or to less tight control. The effects of reducing blood pressure by a mean of 10/5 mmHg in these hypertensive diabetic patients were much more dramatic than those of improved glycaemic control, particularly on macrovascular disease. There were significant reductions in diabetes-related deaths (32%), strokes (44%), and macrovascular end-points (37%), with less deterioration in visual acuity and less need for photocoagulation. The rate of MI was reduced by 21% (p = 0.13). The reductions in both strokes and total deaths were seen by 3–4 years. The two first-line therapies were similar in their benefits, not only on macrovascular end-points but, perhaps surprisingly, also for renal and retinal complications.

The findings of this study have been supported by results from other recent hard end-point studies of hypertension treatment which have included large numbers of diabetic patients, in
suggesting that tight blood pressure control, to levels of 140–145/80–85 mmHg, may be more important than the class of agent used in treatment. Nevertheless, other end-point studies in diabetic patients which have achieved less rigorous blood pressure control have suggested advantages for ACE inhibitors. Moreover, the results of the recently-published Heart Outcomes Prevention Evaluation (HOPE) Study are likely to have major significance for the management of the high-risk diabetic patient. In this study, 3,577 diabetic patients with cardiovascular disease or at high levels of risk were randomised to either ramipril 10 mg daily or placebo, the treatment being added to existing antihypertensive therapy. In 4.5 years of follow-up, there was a reduction of 37% in cardiovascular deaths, 22% in MI, 33% in stroke and 24% in overt nephropathy. These findings, which are likely to apply to the majority of type 2 diabetic patients, may emphasise the use of ACE inhibitors as agents for vascular protection rather than simply as antihypertensive agents.

Numbers needed to treat

The study provided figures which enabled the 'numbers needed to treat' to be calculated and compared. Intensive glycaemic control of 100 patients for 10 years prevented 2.7 MIs or 370 person-years of treatment per event. In hypertensive type 2 diabetic patients, it would take 196 person-years of treatment to prevent a stroke, 204 to prevent an MI, and 152 to prevent a diabetes-related death. Thus, in a hypertensive type 2 diabetic patient, antihypertensive therapy is of substantially greater benefit than tight glycaemia, and is easier to implement (see below).

Lipid lowering and aspirin: data from other studies

What is known about cardiovascular disease prevention from studies other than the UKPDS? As yet, there are no solid data on the benefits of aspirin and lipid lowering in primary prevention in diabetic patients. Nevertheless, an overview of antiplatelet therapy suggests similar benefit in diabetic and non-diabetic high-risk patients, while diabetic subgroup analyses of studies of hydroxymethylglutaryl coenzyme-A (HMGCoA) reductase inhibitors and fibrates in secondary prevention also imply similar benefits. Using data from studies or meta-analyses in diabetic patients, and extrapolating from others in non-diabetic subjects, an estimate of the life expectancy of a 45-year old diabetic man without or with different risk factors can be calculated, together with the effects of interventions (Fig 1). Smoking, the most influential risk factor, is the one that benefits most from intervention, while antihypertensive treatment and cholesterol lowering with an HMGCoA-reductase inhibitor provide benefits similar to aspirin in terms of gain in life expectancy (12–18 months).

Therapeutic targets post-UKPDS

Age plays a crucial role in setting therapeutic targets for diabetic patients. The exponential age-related increases in the incidence of MI and stroke

Key Points

- Blood pressure reduction, to a target of less than 145/85 mmHg, significantly prevented both micro- and macrovascular disease, with reductions in strokes, visual deterioration, and the need for photocoagulation
- Beta-blockers and angiotensin-converting enzyme inhibitors were similar in outcome benefit
- The UK Prospective Diabetes Study showed that tight glycaemic control in type 2 diabetes had major benefits in reducing microvascular disease
- In overweight subjects, metformin reduced rates of coronary heart disease and diabetes-related deaths
- In type 2 diabetes, macrovascular disease is substantially more common than microvascular disease, particularly with increasing age
- Aggressive attention to cardiovascular risk factors is therefore essential in type 2 diabetic patients
contrast with minor increases in risks to eyes and kidneys — for which glycaemic control is of crucial importance. Thus, at the age of 50, a newly diagnosed patient may have sufficient life expectancy to benefit from tight glycaemic control, whereas if he/she were diagnosed at, say, 75 years of age, it is more probable that the macrovascular event would intercede before any advantages of tight glycaemic control became apparent. Moreover, the inexorable rise in HbA1c levels seen in the UKPDS is likely to be, at least in part, a consequence of the imperfections and difficulties of administering and monitoring intensive hypoglycaemic therapies: antihypertensive therapy often needs two or three drugs, but without needles, fingerpricks or hypos.

The therapeutic targets for type 2 diabetes post-UKPDS should thus be the following:

- Strict glycaemic control, with an HbA1c target of under 7%, particularly in the younger patient.
- Aggressive attention to blood pressure, with a target of 140/80 mmHg irrespective of the agent used.
- To remember that the diabetic patient, especially with microalbuminuria\(^{16}\), is at particularly high cardiovascular risk, and needs aggressive attention to all risk factors (smoking, lipids) and consideration of aspirin in the same way as secondary prevention would be considered in a non-diabetic patient. Indeed, a diabetic patient with no cardiovascular disease history has the same level of cardiovascular risk as a non-diabetic who has sustained an infarct\(^{16}\). Increasingly, it is levels of cardiovascular risk which may need to be targeted, rather than levels of a risk factor.

### Conclusions

Type 2 diabetes is, to a great extent, a disease of arteries. The UKPDS has provided clear evidence of benefit for tight glycaemic control, particularly relevant in the younger patient. The study has also provided important evidence about the benefits of blood pressure lowering for microvascular and macrovascular disease, and quantified both levels of risk and ways to reduce them. It is, however, the clinicians, specialist nurses, and dietitians in secondary and primary care who now have to implement these strategies.

### References

1. 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.
2. BarrettConnor EM. Does hyperglycaemia really cause coronary heart disease? Diabetes Care 1997; 20:1620–3.
3. University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications of patients with adult-onset diabetes. Diabetes 1976; 25:1129–53.
4. 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.
5. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. Br Med J 1998;317:703–13.
6. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. Br Med J 1998; 317:713–20.
7. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–62.
8. Hansson L, Lindholm LH, Niskanen L, Lankje J, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611–16.
9. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–9.
10. Antplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antplatelet therapy — I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 1994;308:101–66.
11. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, et al. The Scandinavian Simvastatin Survival Study (4S). Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997;20:614–20.
12. Sacks FM, Pfeifer MA, Moye LA, Rouleau JL, et al, for the Cholesterol And Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
13. Rubins HB, Robins SJ, Collins D, Fye CL, et al, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999;341:410–8.
14. Yudkin JS. How can we best prolong life? The benefits of coronary risk factor reduction in non-diabetic and diabetic subjects. Br Med J 1993;306:1313–8.
15. Yudkin JS, Chaturvedi N. Developing risk stratification charts for non-diabetic and diabetic subjects. Diabet Med 1999;16:219–27.
16. Hoffner SM, Lehto S, Ronnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.

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