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Diab Vasc Dis Res 2008; 5; 216
DOI: 10.3132/dvdr.2008.036

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Four decades of uncertainty: landmark trials in glycaemic control and cardiovascular outcome in type 2 diabetes

Controversy has dogged trials of glycaemia in type 2 diabetes. The first substantial trial was the University Group Diabetes Programme (UGDP), which was published in 1970.¹ In a group which comprised patients on tolbutamide compared to those on placebo, there were 26 cardiovascular deaths, compared to 10 such deaths in a placebo group of 205 patients, during an eight-year study period. This difference was highly significant but the results were announced fully six months before the final report was issued and there were strange aspects of the trial which raised concerns: diabetes was diagnosed in a non-standard way with a sum of blood glucose values at 0, one, two and three hours after a glucose load, and more importantly the randomisation was significantly skewed – for example, there were 30% more baseline ECG abnormalities in the tolbutamide group and 40% more patients with angina in the tolbutamide group.²

The United Kingdom Prospective Diabetes Study (UKPDS) was initiated to address the uncertainty. The recruitment began in 1977 and the trial ended 20 years later, after recruiting 5,012 patients, with data published in 1998.^{3,4} This also led to controversy. On this occasion it appeared that good glycaemic control was generally beneficial in the overweight group using metformin³ but there was no clear answer in the main randomisation group where cardiovascular disease was less in the intensively treated group but with a borderline significant value of $p=0.052$.⁴ Statistical fundamentalists regarded this as a negative result, so the question remained open. With new agents and new enthusiasm to demonstrate how diabetes should best be treated, a variety of trials were begun. The PROspective pioglitAZone Clinical Trial In macrovascular Events trial (PROactive) examined the effect of pioglitazone and a Diabetes Outcome Prospective Trial (ADOPT) examined whether beta-cell failure could be slowed using rosiglitazone.

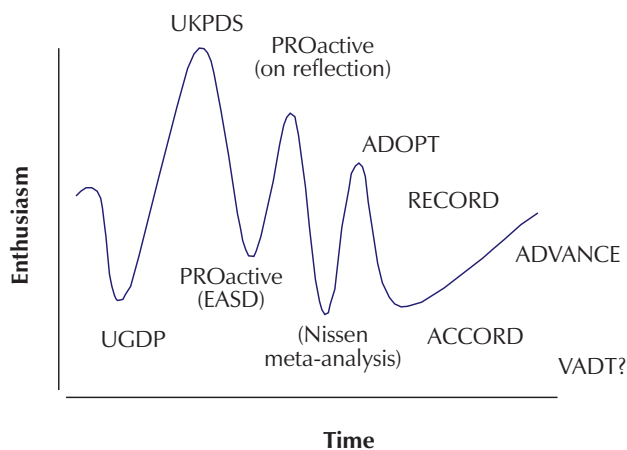
PROactive⁵ reported at the European Association for the Study of Diabetes (EASD) in 2005, to some howls of protest over the linguistic contortions of a 'positive' result only relating to the 'primary secondary outcome'. The trial was bedevilled by the classic problem of selecting a primary combined outcome which involved not only onset of new pathology but interventions relating to pathology. Interventions, of course, are health-service specific and whether or not you have an intervention is clearly not the same as whether a pathological process has occurred to trigger an 'event'. As the howls of protest declined, PROactive has gradually been regarded as probably having a positive outcome in terms of the cardiovascular protection of pioglitazone. But the trial highlighted the problem

of combining outcomes – this increases the event rate but can do so at the expense of specificity.

Then Nissen *et al.*⁶ produced a meta-analysis which seemed to demonstrate that rosiglitazone might have an adverse effect on cardiovascular outcome. That meta-analysis was also heavily criticised,⁷ especially on the basis that the meta-analysis was not based on a comprehensive search for all studies that might yield evidence about rosiglitazone's cardiovascular effects, and that studies were combined on the basis of a lack of statistical heterogeneity, despite variability in study design and outcome assessment. Diamond *et al.*⁷ concluded that the risk for myocardial infarction and death from cardiovascular disease for diabetic patients taking rosiglitazone was uncertain, and concluded that 'neither increased nor decreased risk is established'. There has been a distrust of meta-analytical methodology in that the result of such combinatorial analysis is not as robust as that from a randomised trial. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD), an intervention trial using rosiglitazone, produced an early interim analysis⁸ reporting that in a total of 217 patients in the rosiglitazone group and 202 patients in a control group the hazard ratio for hospitalisation or death from cardiovascular causes was 1.11 (95% confidence intervals [CI] 0.93 to 1.32) and there were more patients with heart failure in the rosiglitazone group than in the control group (hazard ratio 2.15; 95% CI 1.30 to 3.57). So the jury is out: it remains to be demonstrated that the use of rosiglitazone is not associated with a cardiovascular risk.

In the summer of 2008, three cardiovascular disease (CVD) trials reported at the American Diabetes Association (ADA). These were Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE),⁹ Action to Control Cardiovascular Risk in Diabetes trial (ACCORD)¹⁰ and the Veterans Affairs Diabetes Trial (VADT),¹¹ though the full publication of the results of VADT is still awaited. ACCORD produced a startling headline result that mortality was worse in the group that was intensively treated to lower the glycosylated haemoglobin (HbA_{1c}) toward 6%. At one year, stable median glycosylated haemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio 0.90; 95% CI 0.78 to 1.04; $p=0.16$). During the same period, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio 1.22;

Figure 1. Fluctuating enthusiasm for glycaemic control in type 2 diabetes: the effects of trials



Key: UKPDS = United Kingdom Prospective Diabetes Study; PROactive = PROspective pioglitAzone Clinical Trial In macrovascular Events; ADOPT = A Diabetes Outcome Prospective Trial; RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes; ADVANCE = Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; EASD = European Association for the Study of Diabetes; UGDP = University Group Diabetes Programme; ACCORD = Action to Control CardiOvascular Risk Diabetes trial; VADT = Veterans Affairs Diabetes Trial

95% CI 1.01 to 1.46; $p=0.04$).¹⁰ But these patients were very dissimilar from those in the UKPDS in that they were 10 years into established diabetes and had pre-existing cardiovascular disease or specific risk factors. Making sudden changes in glycaemia in such patients may not be an intelligent therapeutic idea. In fact, in this trial, the reports show that the majority of the glucose-lowering effect was already achieved within the first four months, by which time the median HbA_{1c} was 6.6%. Although there was no explicit evidence that hypoglycaemia was the precipitating cause of death, it remains the highest suspect for the increased death rate. Hypoglycaemia rates were three times higher in the intensively treated group, and unfortunately death precludes a contemporaneous measurement of blood glucose. Many of the patients were receiving rosiglitazone (91% in the intensive and 57% in the standard therapy arm).

ADVANCE is the largest trial of cardiovascular disease in type 2 diabetes to date.⁹ This trial used gliclazide (mainly gliclazide modified release) to achieve a lower level of glycaemia in the intensive group. In this trial the target was an HbA_{1c} below 6.5% and this median was achieved over a period of four years – a much slower rate than that of the ACCORD patients. Interestingly, the duration of diabetes was similar (eight years). But by contrast with ACCORD, the total major macrovascular event rate was not different in the intensive vs. the standard control group ($p=0.32$). The differences between the two trials are a marked contrast in rate of achievement of target glycaemia, a very high hypoglycaemia rate in ACCORD (nearly four times greater

rates than in ADVANCE), and a clear variation in the choice of agents for the two trials.

The VADT trial also presented its results at the ADA meeting, though they were not then available in print. The trial again ran for about four years but the numbers of patients were so small that it was scarcely surprising that there was no differential in the cardiovascular outcome. The trial essentially was grossly under-powered – 1,792 subjects¹² followed for five to seven years.¹¹ This was a strange error to make in view of the large number of patient-years required to produce a meaningful answer, as shown by the UKPDS. A subgroup analysis of calcification in the VADT¹³ suggested that this was a clear marker of CVD risk – though these data do not help us decide on the generality of CVD risk reduction.

We can conclude that finding significant answers to cardiovascular disease in glycaemia trials is going to require large numbers of patients over long periods of time. We cannot afford to abandon common sense in trial objectives.¹⁴ We cannot afford to make mistakes in the statistics or the randomisation or the end points or the longevity of the trials or the numbers of patients that are recruited. Getting informative results from trials is hard and complex work!

Acknowledgements

We would like to acknowledge the funding by NIHR Biomedical Research Centre Program for the support of this work.

Conflicts of interest statement

DRM is an additional investigator in the UKPDS and has received honoraria for advisory boards and lectures from Servier, GSK and Takeda. AT: none declared.

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Diabetes Vasc Dis Res 2008;**5**:216–18

doi:10.3132/dvdr.2008.036

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