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de Vries, J.H.

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Intensified glucose lowering in type 2 diabetes: don’t throw the baby out with the bathwater

J. H. DeVries

Keywords Cardiovascular disease · Glycaemic control · Guidelines · Risk factors · Risk reduction · Type 2 diabetes

Abbreviations

ACCORD Action to Control Cardiovascular Risk in Diabetes
ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
NNT Number needed to treat
UKPDS UK Prospective Diabetes Study
VADT Veterans Affairs Diabetes Trial

To the Editor: In their Editorial, Yudkin, Richter and Gale argue that ‘Hyperglycaemia is a substantially weaker risk factor for CVD than cholesterol or blood pressure, and glucose-lowering interventions are correspondingly less effective’ [1]. They come to this conclusion on the basis of number needed to treat (NNT) derived from epidemiological studies, the UK Prospective Diabetes Study [2] and three recent megatrials (Action to Control Cardiovascular Risk in Diabetes [ACCORD] [3], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE] [4] and Veterans Affairs Diabetes Trial [VADT] [5]), which were subsequently meta-analysed. Of course, the results of any meta-analysis are dependent on the validity of the individual trials analysed. The external validity of ACCORD and VADT is severely compromised with the recent decision of the European Medicines Agency to retract the market authorisation of rosiglitazone. In VADT, all patients in the intensively treated group were started on rosiglitazone by trial design. In ACCORD, 91.2% of patients were on rosiglitazone in the intensively treated group. It seems impossible to draw any conclusion on possible cardiovascular benefits of glucose lowering if such glucose lowering was attained using a drug which has now been concluded to increase the risk of myocardial infarction by its very nature. So we are left with UKPDS and ADVANCE as the relevant studies. The key differentiators between these two studies are duration of disease at enrolment and the treatment targets in the intensively and conventionally treated groups. In UKPDS, patients were randomised soon after the diagnosis of type 2 diabetes was made, and ADVANCE enrolled patients with a diabetes duration of 8 years. Using the UKPDS follow-up data [6], Yudkin et al. calculated the NNT for 10 years to prevent one myocardial infarction or stroke to be 29.4 [1]. This number relates to the sulfonylurea–insulin group. In the metformin group, the corresponding NNT is 14. Moreover, the 10 year NNT to prevent one death was 29 in the sulfonylurea–insulin and 14 in the metformin group. I think most diabetologists would agree that patients with newly diagnosed diabetes are entitled to treatment aiming to achieve an HbA1c value of <7.0% for at least 10 years. There is no reason to believe that the UKPDS results would have been different if the trial had been of longer duration, so it seems reasonable to keep this as the HbA1c target. After the first 10 years of diabetes, ADVANCE becomes a relevant study. This study showed only minimal beneficial effects of intensive treatment of glucose as compared with conventional treatment, but it should be noted that mean HbA1c in the conventionally
treated group was maintained at 7.3% throughout the trial. There is no trial evidence to indicate that HbA1c levels above this are safe. Therefore, treatment guidelines will probably continue to advise a target HbA1c of 7.0% for people with diabetes, with the possibility of a slightly higher target of 7.3% after a diabetes duration of 8–10 years. Of course, considerations relating to hypoglycaemia, weight gain, diminished life-expectancy or adherence may well justify higher targets in selected individuals.

**Duality of interest** The author declares that there is no duality of interest associated with this manuscript.

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