Patients with type 2 diabetes mellitus without a history of myocardial infarction have the same risk of a coronary event as patients without diabetes who do have a history of myocardial infarction. This observation was part of the basis for the recommendation by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program that diabetes should be considered a “coronary heart disease risk equivalent” and a target for aggressive reduction of risk factors. It has also contributed to the rationale for randomized clinical trials to evaluate the effects of risk-factor reduction in such high-risk patients.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (ClinicalTrials.gov number, NCT00000620) was one of the landmark trials to evaluate the overall effects of drug intervention in patients with type 2 diabetes. In comparison with two other, related trials, the United Kingdom Prospective Diabetes Study (UKPDS; Current Controlled Trials number, ISRCTN75451837) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (NCT00145925), the ACCORD study included not only intervention groups aiming for control of hyperglycemia and hypertension but also one for control of hyperlipidemia.

A previous study by the ACCORD investigators concluded that a strategy of intensified glycemic control was associated with an increased risk of death. However, a recent meta-analysis did not confirm such an increase in risk, and the role of intensified glycemic control has been a subject of debate. In this issue of the Journal, the joint publication of the ACCORD blood pressure trial (ACCORD BP) and the ACCORD lipid trial (ACCORD Lipid), although not resolving this issue, makes the picture of diabetes management more complete.

In the ACCORD BP study, investigators evaluated the potential benefits of targeting a systolic blood-pressure level below 120 mm Hg versus a level below 140 mm Hg in patients with type 2 diabetes (34% of whom had cardiovascular disease). After 4.7 years, there was no significant between-group difference in the annual rate of the primary outcome, a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Serious adverse events that were attributed to blood-pressure medication were more frequent in the intensive-therapy group.

Owing to the factorial design of the overall ACCORD study and the inclusion and exclusion criteria that were applied, the study’s statistical power was reduced, and the event rate was lower than expected. It thus remains a possibility that a larger trial or one in a higher-risk population might have shown a significant benefit. A beneficial effect was shown for the secondary end point of total stroke. However, the number of major coronary disease events was far higher than the number of total strokes (253 vs. 36 in the intensive-therapy group and 270 vs. 62 in the standard-therapy group). Thus, the main conclusion to draw from this study must be that a systolic blood-pressure target below 120 mm Hg in patients with type 2 diabetes is not justified by the evidence.

Unfortunately, the design and results of the ACCORD BP study leave unresolved the issue of the optimal blood-pressure target in patients with diabetes. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation,
and Treatment of High Blood Pressure,\textsuperscript{10} published after the ACCORD BP study had started to enroll patients, recommended a blood-pressure goal below 130/80 mm Hg in patients with diabetes, but this recommendation was not based on evidence from randomized, controlled trials. The ACCORD BP investigators may be able to shed further light on this question in subsequent post hoc analyses of their data.

The findings of the ACCORD BP study are also of importance in determining whether it will be useful to proceed with the Systolic Blood Pressure Intervention Trial (SPRINT),\textsuperscript{11} sponsored by the National Institutes of Health. The design of SPRINT is essentially the same as that of the ACCORD BP study but involves patients without diabetes. It is worth considering whether the funds would be better used for other studies or even for implementation programs to address the fact that hypertension control is still inadequate for so many patients.

In the ACCORD Lipid study, patients were randomly assigned to receive either simvastatin plus fenofibrate or simvastatin alone. The goal of fenofibrate therapy was to reduce plasma triglyceride levels and increase plasma high-density lipoprotein (HDL) cholesterol levels in patients who were already taking a statin to reduce plasma low-density lipoprotein (LDL) cholesterol. The addition of fenofibrate to simvastatin did not result in a significant improvement in the primary composite outcome.\textsuperscript{9} There was even a trend toward an increased risk in women as compared with men.

In a prespecified subgroup analysis, there was a trend toward benefit of fenofibrate in patients with signs of dyslipidemia, which was defined as a triglyceride level of 204 mg per deciliter (2.30 mmol per liter) or more and an HDL cholesterol level of 34 mg per deciliter (0.88 mmol per liter) or less. This finding is of potential importance, since the ATP III guidelines define a high triglyceride level as 200 mg per deciliter (2.3 mmol per liter) or more and a low HDL cholesterol level as below 40 mg per deciliter (1.0 mmol per liter).\textsuperscript{2} Since many of the patients in this subgroup analysis did not meet these criteria, the role of fibrates for correcting dyslipidemia in high-risk patients with diabetes is still not settled.

The standards of diabetes care have improved considerably during the past decade. This is at least partially a consequence of the publication of the UKPDS in 1998.\textsuperscript{4} Reports from the UKPDS helped to establish that optimal treatment of diabetes requires not only attention to glucose control but also appropriate evaluation and management of cardiovascular risk. The control of cardiovascular risk factors has gradually improved during this period, as is evident, for example, in register-based data from Sweden,\textsuperscript{12} with similar trends also recorded in other countries. Such progress is reassuring, but now we learn from the completed ACCORD study that flexible goals should probably be applied to the control of hyperglycemia, blood pressure, and dyslipidemia in patients with type 2 diabetes, taking into account individual clinical factors of importance. A period of three landmark studies (UKPDS, ADVANCE, and ACCORD) has now come to an end. New trials should be designed on the basis of our new understanding.


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