Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes

BACKGROUND
In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) factorial trial, the combination of perindopril and indapamide reduced mortality among patients with type 2 diabetes, but intensive glucose control, targeting an HbA1c level of less than 6.5 %, did not. We now report results of the 6-year post-trial follow-up.

METHODS
We invited surviving participants, who had previously been assigned to perindopril–indapamide or placebo and to intensive or standard glucose control (with the glucose-control comparison extending for an additional 6 months), to participate in a post-trial follow-up evaluation. The primary end points were death from any cause and major macrovascular events.

RESULTS
The baseline characteristics were similar among the 11,140 patients who originally underwent randomization and the 8494 patients who participated in the post-trial follow-up for a median of 5.9 years (BP-lowering comparison) or 5.4 years (glucose-control comparison). Between-group differences in blood pressure and glycated haemoglobin levels during the trial were no longer evident by the first post-trial visit. The reductions in the risk of death from any cause and of death from cardiovascular causes that had been observed in the group receiving active blood-pressure-lowering treatment during the trial were attenuated but significant at the end of the post-trial follow-up; the hazard ratios were 0.91 (95 % confidence interval [CI], 0.84 to 0.99; P=0.03) and 0.88 (95 % CI, 0.77 to 0.99; P=0.04), respectively. No differences were observed during follow-up in the risk of death from any cause or major macrovascular events between the intensive-glucose-control group and the standard-glucose-control group; the hazard ratios were 1.00 (95 % CI, 0.92 to 1.08) and 1.00 (95 % CI, 0.92 to 1.08), respectively.

CONCLUSIONS
The benefits with respect to mortality that had been observed among patients originally assigned to blood-pressure-lowering therapy were attenuated but still evident at the end of follow-up. There was no evidence that intensive glucose control during the trial led to long-term benefits with respect to mortality or macrovascular events.


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While patients with diabetes mellitus present with an increased risk of premature death, due to an increased rate of microvascular and of cardiovascular complications when compared with non-diabetic individuals, the burden seems to be higher in women than in men with diabetes. Recent meta-analyses have shed new light on this issue.

Peters et al recently published an updated meta-analysis investigating whether diabetes was associated with any sex-specific difference in risk of coronary heart disease (CHD). The meta-analysis was based upon prospective population-based cohort studies published between 1966 and 2013, reporting sex-specific relative risk (RR) for incident CHD associated with diabetes, adjusted at least for age. Meta-analysis included data from 64 cohorts, including 858 507 individuals and 28 203 incident CHD events. Compared with non-diabetic subjects, the relative risk for incident CHD was increased in men with diabetes (2.16; 95 % CI 1.82-2.56), and even more in women with diabetes (2.82; 95 % CI 2.35-3.38). In diabetes, the relative risk for CHD was thus 44 % higher in women than in men (RR 1.44; 95 % CI 1.27-1.63). No significant heterogeneity between studies was found.

Similarly, an increased risk for stroke was found by the same group in women with diabetes vs. men with diabetes compared with non-diabetic individuals. In the same manner as for CHD, systematic review and meta-analysis of 64 cohorts were performed. This included 775 385 individuals, and 12 539 incident strokes. Compared with non-diabetic individuals, the excess adjusted risk for incident stroke was higher in women with diabetes (RR 2.28; 95 % CI 1.93-2.69) than in men with diabetes (RR 1.80; 95 % CI 1.60-2.08).

No definite explanation is available yet for such a huge difference between women and men with diabetes for coronary heart disease and stroke risk. While a disparity in quality of the management and treatment of cardiovascular risk factors to the detriment of women has been pinpointed in the past, such a difference no longer exists. However, in spite of similar management, some studies indicate that control of risk factors may be less effective in women with diabetes than in men. On the other hand, differences in the level of old and new cardiovascular risk factors between individuals with and without diabetes may be more pronounced in women than in men, particularly in the pre-diabetic state. We also need to consider the results of recent study performed in the USA, searching for any differences between women and men in medication use and compliance. Significant disparities were found between women and men in intensity of medication use, adherence to medications, and likelihood of receiving guideline-based drug therapy.

These observations point to the need for more intensive and personalized management in women with diabetes, with a strong effort to reach and maintain every therapeutic goal, either in glycaemic or cardiovascular risk factor control.

Source: P.J. Guillausseau
BACKGROUND

The excess risk of death from any cause and of death from cardiovascular causes is unknown among patients with type 1 diabetes and various levels of glycaemic control. We conducted a registry-based observational study to determine the excess risk of death according to the level of glycaemic control in a Swedish population of patients with diabetes.

METHODS

We included in our study patients with type 1 diabetes registered in the Swedish National Diabetes Register after January 1, 1998. For each patient, five controls were randomly selected from the general population and matched according to age, sex, and county. Patients and controls were followed until December 31, 2011, through the Swedish Register for Cause-Specific Mortality.

RESULTS

The mean age of the patients with diabetes and the controls at baseline was 35.8 and 35.7 years, respectively. 45.1% of the participants in each group were women. The mean follow-up in the diabetes and control groups was 8.0 and 8.3 years, respectively.

Overall, 2701 of 33,915 patients with diabetes (8.0%) died, as compared with 4835 of 169,249 controls (2.9%) (adjusted hazard ratio, 3.52; 95% confidence interval [CI], 3.06 to 4.04); the corresponding rates of death from cardiovascular causes were 2.7% and 0.9% (adjusted hazard ratio, 4.60; 95% CI, 3.47 to 6.10).

The multivariable-adjusted hazard ratios for death from any cause according to the glycated haemoglobin level for patients with diabetes as compared with controls were 2.36 (95% CI, 1.97 to 2.83) for a glycated haemoglobin level of 6.9% or lower (≤52 mmol per mole), 2.38 (95% CI, 2.02 to 2.80) for a level of 7.0 to 7.8% (53 to 62 mmol per mole), 3.11 (95% CI, 2.66 to 3.62) for a level of 7.9 to 8.7% (63 to 72 mmol per mole), 3.65 (95% CI, 3.11 to 4.30) for a level of 8.8 to 9.6% (73 to 82 mmol per mole), and 8.51 (95% CI, 7.24 to 10.01) for a level of 9.7% or higher (≥83 mmol per mole).

Corresponding hazard ratios for death from cardiovascular causes were 2.92 (95% CI, 2.07 to 4.13), 3.39 (95% CI, 2.49 to 4.61), 4.44 (95% CI, 3.32 to 5.96), 5.35 (95% CI, 3.94 to 7.26), and 10.46 (95% CI, 7.62 to 14.37).

CONCLUSIONS

In our registry-based observational study, patients with type 1 diabetes and a glycated haemoglobin level of 6.9% or lower had a risk of death from any cause or from cardiovascular causes that was twice as high as the risk for matched controls.

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Impact of visit-to-visit glycaemic variability on the risks of vascular events and all-cause mortality in patients with type 2 diabetes.

A 2010 prospective study previously demonstrated that visit-to-visit variability (VVV) in systolic blood pressure (SBP) and maximum SBP were strong predictors of stroke, irrespective of mean SBP. Similar findings were reported through the blood pressure arm of the ADVANCE study where VVV in SBP was an independent risk factor for macrovascular and microvascular complications in patients with type 2 diabetes.

By contrast, the question of whether glucose variability can play a significant role in the development and/or progression of diabetic complications has no clear answer to date. Among patients with type 1 diabetes included in the DCCT, long-term fluctuation of HbA1c independently predicted the incidence of diabetic retinopathy and nephropathy, even after correction for the absolute level of HbA1c, while within-day glucose variability had little influence in the same patients followed in the EDIC study (Epidemiology of Diabetes Interventions and Complications).

A recent study from Hirakawa Y et al analyzed the effects of VVV in HbA1c and fasting glucose values on the risks of vascular outcomes among patients with type 2 diabetes included in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial. ADVANCE was a large-scale factorial randomized controlled trial of blood pressure lowering and intensive blood glucose treatment in patients with type 2 diabetes. A total of 11,140 patients aged 55 years or older were randomly assigned to a fixed combination of perindopril and indapamide (2 mg / 0.625 mg for the first 3 months and 4 mg / 1.25 mg thereafter) or matching placebo, and to either an intensive glucose control strategy (target HbA1c: 6.5 %) or standard glucose control management.

In this glycaemic VVV analysis, the patients in the intensive glucose treatment group only were included, as too few measurements were taken to accurately estimate glycaemic VVV in the standard glucose treatment group. The period of glycaemic VVV evaluation extended through the first 24 months after randomization. However, measurements during the first 2 months were not considered in order to limit the potential impact of rapid decrease in HbA1c following initiation of intensive treatment. VVV of HbA1c or fasting glucose was assessed using the standard deviation (SD) of five measurements of HbA1c and fasting glucose taken at 3, 6, 12, 18, and 24 months after randomization. Follow-up ranged from the 24-month visit until events, death, or final visit at the end of the study.

The primary outcome was a composite of major macro- and microvascular events occurring after the 24-month visit. Secondary outcomes were major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), major microvascular events (defined as new or worsening nephropathy or retinopathy), and all-cause mortality.

Among the 4,399 patients (mean age: 65.5 years, 42.6 % female) included in this glycaemic VVV analysis, 234 experienced major macrovascular events, 309 major microvascular events, and 211 deaths during a 3-year median follow-up. VVV of HbA1c was positively associated with increased risks of combined macro- and microvascular events (P=0.01), major macrovascular events (P=0.02), and all-cause mortality (P<0.001), independently of cardiovascular risk factors and mean HbA1c during the first 24 months. Nevertheless, no association between maximum HbA1c among the five measurements and these four outcomes was observed. On the other hand, SD and maximum of fasting glucose was associated with both major macrovascular (P=0.005 and P=0.01, respectively) and microvascular events (P<0.001, and P=0.007, respectively).

Therefore, in addition to the predicted value of HbA1c level, glycaemic variability seems to confer an additional risk for the development of vascular complications in type 2 diabetes. The main message to be drawn from these published data is that early, consistent, and effective control of hyperglycaemia with limited fluctuation could contribute to decreased vascular events and death in patients with type 2 diabetes.

Source: Sylvie Feldman