Effects of medical therapies on retinopathy progression in type 2 diabetes: Is blood pressure control the lower the better?

Type 2 diabetes has become an important public health challenge worldwide and, in particular, in Asian populations, which are characterized by onset at a relatively young age and low body mass index. These patients have long disease duration and thus are associated with a higher risk of long-term complications. Diabetic retinopathy is one of the major microvascular complications and is the most common cause of blindness. The Diab-care-Asia study carried out in Indonesia, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam has found that in 2001, up to 8% of type 2 diabetic patients aged 30 years or above had retinopathy, 4% has received photocoagulation and 0.7% were legally blind. For most type 2 diabetes patients, the frequency and severity of diabetic retinopathy increase over time, which substantially impacts on quality of life. Therefore, there is an urgent need for effective and safe treatment regimens against the occurrence and to slow the progression of diabetic retinopathy.

Substantial evidence has found that in addition to the degree of glycaemia, the level of blood pressure and dyslipidemia, including elevated total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides and decreased high-density lipoprotein (HDL)-cholesterol levels, were important risk factors for retinopathy in type 2 diabetes patients. A multifactorial approach optimizing all these risk factors has become the current standard in diabetes management. The concept of this multifactorial intervention to reduce the incidence and progression of diabetic retinopathy is supported by findings from the Steno type 2 randomized trial. An intensive combined treatment targeting hyperglycaemia, hypertension, dyslipidemia and microalbuminuria can reduce the risk of retinopathy progression by 55% in the follow-up period of 3.8 years. However, there are still questions that remain to be answered. First, the optimal target for blood pressure, glucose and lipid level remains unclear, in particular for different risk populations. Whether further intensification of treatments provide additional benefits needs to be evaluated. Second, it is not known whether combining blood pressure lowering, glucose control and improving lipid profile can reduce the risk of retinopathy to a greater extent than either treatment alone. There are also concerns about whether intensive treatment of one of the risk factors could modify or even negate the benefits from treatment of the other risk factors.

The recently published the Action to Control Cardiovascular Risk in Diabetes Eye study (ACCORD-EYE) sheds new light on the optimal treatment for diabetic retinopathy. The original ACCORD study was a randomized controlled trial with three components, assessing the effects of intensive glycemic control (targeted HbA1c level < 6.0%) vs standard glycemic control (targeted HbA1c 7.0–7.9%); intensive blood pressure control (targeted systolic blood pressure < 120 mmHg) vs standard blood pressure control (targeted systolic blood pressure < 140 mmHg); and using fibrates to lower triglycerides and raise HDL-cholesterol vs the placebo. Of them, 5518 with dyslipidemia were also randomly assigned, in a 2 × 2 factorial design, to receive simvastatin plus either fenofibrate or a placebo. The remaining 4733 participants, without further requirement for blood pressure level, were enrolled for evaluating the blood pressure lowering effect. The ACCORD-EYE trial is a study of a subset of the original ACCORD trial participants to evaluate the effects of the aforementioned interventions at 4 years on the progression of diabetic retinopathy by three or more steps on the Early Treatment Diabetic Retinopathy Study Severity Scale, or the development of diabetic retinopathy leading to laser photocoagulation or vitrectomy. By this complex study design, it is planned that a sample size of 4056 recruited patients would have a power of 88, 91 and 80% for the effect of glycemic control, lipid control and blood pressure control, respectively. However, only 2856 participants completed the evaluation and were included for analyses. In contrast to the original ACCORD study reporting excess mortality in intensive glucose control, results from the ACCORD-EYE glycemic trial are reassuring. The median HbA1c levels in the intensive treatment arm were 6.4%, compared with 7.5% in the standard treatment arm, and were associated with a reduced rate of progression of diabetic retinopathy by 33%. This beneficial effect was consistent across baseline levels of HbA1c, retinopathy at baseline and duration of diabetes, and was independent of effects as a result of the blood pressure and lipid intervention. This finding, in addition to previous large-scale randomized controlled trials, such as the United Kingdom Prospective Diabetes Study (UKPDS), Kumamoto study and the Action in Diabetes and Vascular Disease:
| Trial | Study population | No. participants | Mean diabetic duration | Hypertensive duration | Hypertensive control | Target blood pressure | Mean blood pressure | Medication | Mean follow-up (years) | Results |
|-------|------------------|------------------|------------------------|-----------------------|----------------------|-----------------------|---------------------|------------|-----------------------|---------|
|       | Type 2 diabetes  | 1148             | 8.3–8.9                | 11.5–119              |                      | <150/80 vs <180/105 mmHg | 144/82 vs 154/87 mmHg | Captopril, atenolol | 84                    | Retinopathy progression RR 0.66, P < 0.001 Micro-aneuysm OR 0.89, P = 0.037 Hard exudates OR 1.14, P = 0.043 Cotton wool spots OR 0.84, P = 0.29 Retinal hemorrhage OR 0.89, P = 0.31 Photocoagulation OR 1.11, P = 0.76 Macular edema OR 0.50, P = 0.002 Blindness or vision loss OR 1.27, P = 0.006 |
|       | with hypertension (BP > 160/90 mmHg) | 470                | 83–8.9                 | –                     |                      | Diastolic 75 vs 80–89 mmHg | 132/78 vs 138/86 mmHg | Nisoldipine, enalapril as initial treatment | 53                    | RR 0.88, P = 0.042 RR 0.74, P = 0.002 OR 0.78, P = 0.12 OR 0.89, P = 0.037 OR 1.14, P = 0.043 OR 0.84, P = 0.29 OR 0.89, P = 0.31 OR 1.11, P = 0.76 OR 0.50, P = 0.002 |
|       | Type 2 diabetes  | 480              | 88–92                  | –                     |                      | 10 mmHg below baseline diastolic BP | 128/75 vs 137/81 mmHg | Nisoldipine, enalapril as initial treatment | 53                    | RR 0.53, P < 0.001 RR 0.53, P < 0.001 RR 0.53, P < 0.001 RR 0.53, P < 0.001 RR 0.53, P < 0.001 RR 0.53, P < 0.001 RR 0.53, P < 0.001 RR 0.53, P < 0.001 OR 0.89, P = 0.037 OR 1.14, P = 0.043 OR 0.84, P = 0.29 OR 0.89, P = 0.31 OR 1.11, P = 0.76 OR 0.50, P = 0.002 |
|       | with hypertension (diastolic BP ≥ 90 mmHg) | 1241              |                        |                        |                      |                        |                   |                        | 41                    | OR 1.23, P = 0.029 |
|       | Type 2 diabetes  | 1263             |                        |                        |                      |                        |                   |                        |                      |                      |
|       | with diastolic BP 80–89 mmHg |                  |                        |                        |                      |                        |                   |                        |                      |                      |
|       | Type 2 diabetes  |                  |                        |                        |                      |                        |                   |                        |                      |                      |
|       | with ≥1 risk factors for cardiovascular disease |                  |                        |                        |                      |                        |                   |                        |                      |                      |
|       | Type 2 diabetes  |                  |                        |                        |                      |                        |                   |                        |                      |                      |
|       | without dyslipidemia |                  |                        |                        |                      |                        |                   |                        |                      |                      |

**Table 1 | Randomized controlled trials evaluating effect of blood pressure control on diabetic retinopathy**

- **ABCD, Appropriate Blood Pressure Control in Diabetes**
- **ACCORD-EYE, Action to Control Cardiovascular Risk in Diabetes Eye study**
- **ACE, angiotensin-converting enzyme**
- **ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation**
- **BP, blood pressure**
- **RR, relative risk**
- **UKPDS, United Kingdom Prospective Diabetes Study**
Preterax and Diamicron MR Controlled Evaluation (ADVANCE trial), confirms that tight glucose control can reduce the risk of microvascular complications. The unexpected finding comes from evaluation of blood pressure lowering. Intensive blood pressure control, instead of providing a beneficial effect, is associated with a trend of increased risk for diabetic retinopathy progression by 23% at 4 years.

As shown in Table 1, a trend of beneficial effect by intensive blood pressure control was found in four other randomized trials. Significant results were found by UKPDS, characterized by enrolling patients with short diabetic duration, substantial blood pressure lowering and long treatment duration. The Appropriate Blood Pressure Control in Diabetes (ABCD)-Normotensive study showed a favorable effect, even among patients with long diabetic duration and who had a ‘normal’ blood pressure level. Instead of targeting a specific blood pressure level, the ADVANCE Retinal Measurement Study examined the effect of the combination treatment of perindopril–indapamide vs the placebo. A favorable result was found, although not statistically significant, probably as a result of the magnitude of blood pressure lowering was modest and the follow-up duration was relatively short. In the ACCORD-EYE study, an even more intensive treatment strategy targeting systolic blood pressure below 120 mmHg was used. This raises the concern that the optimal target for blood pressure against retinopathy worsening might not be ‘the lower the better’. This argument is further substantiated by the finding from a subgroup analysis showing that the detrimental effect of intensive blood pressure lowering is greater among participants with systolic blood pressure < 133 mmHg, but not in those with >144 mmHg. The implication that the magnitude of blood pressure reduction should be individualized based on baseline blood pressure level needs to be clarified in a future study.

The ACCORD-EYE study was designed to answer the question whether a more intensive blood pressure control, rather than specific pharmacotherapy, had a beneficial effect on retinopathy improvement. All major classes of antihypertensive agents were used, although diuretics combined with either an angiotensin-converting enzyme (ACE) inhibitor or beta-blocker are recommended as initial therapy in the intensive treatment arm. Recently, there has been increasing evidence suggesting the role of the rennin-angiotensin system in diabetic retinopathy. In animal models, angiotensin has been shown to be an angiogenic growth factor. In patients with diabetic retinopathy, plasma and intravitreal prorenin levels are increased and correlate with its severity. Several randomized placebo-controlled trials have found the beneficial effect of certain ACE inhibitors or angiotensin receptor blockers on retinopathy worsening among type 1 and type 2 patients with normal blood pressure, normal microalbuminuria and mild to moderately severe retinopathy at baseline. Whether it is a class effect or specific to particular medications should be explored in properly designed studies.

Results from the ACCORD-EYE dyslipidemia control were inspiring in terms of the addition of 160 mg fenofibrate per day to statins conferring an additional 40% reduced risk among type 2 diabetic patients with a mean baseline triglycerides level of approximately 200 mg/dL, HDL-cholesterol level of approximately 40 mg/dL and LDL-cholesterol of approximately 100 mg/dL. This finding substantiates the observation from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showing the beneficial effects of fenofibrate vs the placebo in reducing laser therapy, particularly in preventing disease progression in patients with pre-existing diabetic retinopathy. In contrast to no clinically important difference in blood lipid concentrations between two treatment groups at FIELD study completion, the ACCORD-EYE study showed a medium triglyceride levels reduction from 162 to 120 mg/dL in the fenofibrate group, as compared with 147 mg/dL in the placebo group. The optimal dosage, blood lipid target and the safety of this combination therapy in the Asian population require further studies.

In conclusion, the ACCORD-EYE study has extended our knowledge of strategies to lessen diabetic retinopathy progression. Although physicians who take care of diabetic patients should continue emphasizing the importance of glycemic control, a more intensified approach for elevated plasma triglyceride levels, but judicious blood pressure lowering, might be considered based on individual patients’ risk of this condition.

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