

CHAPTER

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Effects of Tight BP Control on Vascular Complications in Type 2 Diabetes

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Background

The prevalence of hypertension in T2DM is significantly higher than that in the general population, especially in younger patients. At the age of 45 around 40% of patients with type 2 diabetes are hypertensive, with the proportion increasing to 60% by the age of 75. Hypertension increases the already high risk of cardiovascular disease (CVD) associated with T2DM and is also a risk factor for the development of microalbuminuria and retinopathy

Elevated blood pressure is an important determinant of the risks of macrovascular and microvascular complications in type 2 diabetes, and guidelines recommend intensive lowering of blood pressure for diabetic patients with hypertension. However, globally only about one quarter of all hypertensive patients achieve long-term blood pressure control targets. In India, the proportion of subjects meeting target is even lower.

The traditional strategy based on arbitrary blood pressure levels at which treatment is initiated and arbitrary goals against which it is titrated, needs multiple patient visits, careful monitoring of both blood pressure and side-effects, and the coordination of complex drug regimens. This may discourage long-term compliance with treatment. Additionally, it neglects normotensive patients for

whom blood pressure remains an important risk of vascular disease.

An alternative approach that is less resource-intensive and more inclusive is to add a fixed-dose combination of blood pressure lowering drugs irrespective of initial blood pressure level or the use of other antihypertensive drugs. Although this approach might not produce the largest blood pressure reductions possible, it will shift the entire distribution of blood pressure values down in patients with diabetes, with minimum requirements for titration and, potentially, with fewer side-effects.

The ADVANCE study assessed the effects of routine administration of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs.

Methods

The study was done by 215 collaborating centres in 20 countries, and included 471 patients from India. After a 6-week active run-in period on a fixed combination tablet consisting of perindopril (2 mg) and indapamide (0.625 mg) in addition to all other existing treatments, 11140 patients with type 2 diabetes were randomised to continue the

run in treatment or receive a matching placebo for 3 months. Thereafter, the doses of randomised therapy were doubled to 4 mg for perindopril and 1.25 mg for indapamide, or matching placebo, and patients followed up at 6 monthly intervals. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease. Analysis was by intention-to-treat.

Results

After a mean 4.3 years of follow-up, 73% of those assigned active treatment and 74% of those assigned control remained on randomised treatment. Compared with patient's assigned placebo, those assigned active therapy had a mean reduction in systolic blood pressure of 5.6 mm Hg and diastolic blood pressure of 2.2 mm Hg. The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%] active vs 938 [16.8%] placebo; hazard ratio 0.91, 95% CI 0.83–1.00, $p=0.04$). The relative risk of death from cardiovascular disease was reduced by 18% (211 [3.8%] active vs 257 [4.6%] placebo; 0.82, 0.68–0.98,

$p=0.03$) and death from any cause was reduced by 14% (408 [7.3%] active vs 471 [8.5%] placebo; 0.86, 0.75–0.98, $p=0.03$). There was no evidence that the effects of the study treatment differed by initial blood pressure level or concomitant use of other treatments at baseline.

Conclusion

Routine administration of a fixed dose combination of perindopril and indapamide, irrespective of blood pressure level, and in addition to existing treatments in patients with type 2 diabetes was well tolerated. The treatment reduced the risks of major vascular events, including death. The results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy, placebo; 0.82, 0.68–0.98, $p=0.03$) and death from any cause was reduced by 14% (408 [7.3%] active vs 471 [8.5%] placebo; 0.86, 0.75–0.98, $p=0.03$). There was no evidence that the effects of the study treatment differed by initial blood pressure level or concomitant use of other treatments at baseline, implying that this therapy can be considered in normotensive patients with type 2 diabetes.