Blood Pressure Lowering with Perindopril and Indapamide - an ADVANCE in Improving Diabetic Mortality

Dr. Godwin TC Leung

FKHAM (Medicine), FRCP
Specialist in Cardiology, CardioMed Heart Centre

Original article:

Summary

The effects of the routine administration of an angiotensin converting enzyme inhibitor (ACEI)-diuretic combination on serious vascular events in patients with diabetes were assessed, irrespective of initial BP levels or the use of other BP lowering drugs. A total of 11,140 patients with type 2 diabetes were randomised to treatment with a fixed combination of perindopril and indapamide or matching placebo in addition to existing therapy. The use of concomitant treatments during follow-up remained at the discretion of the responsible physician, with two exceptions - the use of thiazide diuretics was not allowed, and open-label perindopril, to a maximum of 4 mg a day, was the only angiotensin-converting enzyme (ACE) inhibitor allowed, thus ensuring that the maximum recommended dose of 8 mg for perindopril could not be exceeded by patients randomly assigned to active treatment. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from cardiovascular (CV) disease, non-fatal stroke or non-fatal myocardial infarction (MI), and new or worsening renal or diabetic eye disease.

The results showed that after a mean duration of 4.3 years, compared with patients assigned placebo, those assigned active therapy had a mean reduction in systolic BP of 5.6 mm Hg and diastolic BP of 2.2 mm Hg. The relative risk of a major macrovascular or microvascular event was significantly reduced by 9%. There was a 14% reduction in total mortality which was mainly due to an 18% reduction in CV deaths in the active treatment group. There was no evidence that the effects of the study treatment differed by initial BP level or concomitant use of other treatments at baseline. By the end of follow-up, antihypertensive drugs were being used by more than three-quarters of participants. The results suggest that for every 66 patients commencing long-term treatment with perindopril and indapamide, one patient would avoid at least one major vascular event in five years. Over five years, one death would be averted in every 79 patients commencing treatment with the study drug. In summary, the results of ADVANCE indicate that the routine administration of a fixed combination of perindopril and indapamide to a broad range of patients with diabetes reduces the risks of death and major macrovascular or microvascular complications, irrespective of initial BP level or ancillary treatment with many other preventive treatments typically provided to diabetic patients today. The authors concluded that if the benefits seen in ADVANCE were applied to just half the population with diabetes worldwide, more than a million deaths would be avoided over five years.

Comment

ADVANCE, the largest-ever randomised trial of the prevention of diabetes complications, is a very important study that supports the idea that lower mortality rates could be achieved with lower blood pressures in diabetic patients. ADVANCE confirmed that more aggressive BP reduction in type 2 diabetics provides greater protection against both micro- and macrovascular events.

In the past, the United Kingdom Prospective Diabetes Study (UKPDS)\(^2\) established that reducing BP produced benefits in diabetics. It demonstrated that each 10 mmHg decrease in systolic BP was associated with average reductions in rates of diabetes-related mortality (15 percent), myocardial infarction (11 percent), and the microvascular complications of retinopathy or nephropathy (13 percent). Mean systolic BP was lowered from 155 mmHg to 145 mmHg in UKPDS, and the ADVANCE study extended these findings to patients with lower pressures. In ADVANCE, the average BP at baseline was 145/81 mm Hg, and this was reduced to 135/75 mm Hg in the active-treatment group vs 140/77 in the placebo group over 4.3 years. This greater reduction in BP in the active-treatment arm was associated with significant improvement in outcomes. These benefits were achieved on top of aggressive ancillary drug therapy, with the majority of patients in both arms also taking other blood-pressure-lowering agents. Most guidelines\(^3,4\) recommend lower blood-pressure targets for diabetics (130/80 mmHg) than the normal population (140/90 mmHg), and this study reinforces this recommendation. There was no direct evidence in the past because the recommendation was mainly based on data largely generated from subgroup analyses within the more general hypertensive populations\(^5\). ADVANCE provides new and more solid evidence to support the recommendations already in the guidelines for lower target blood pressures in diabetic patients. An important message from this trial is that diabetic patients should be treated aggressively to lower their BP below 130/80 mmHg.
It is generally believed that the link between reducing BP and improving mortality shown in this study may be generalisable to other antihypertensive medications. However, the tolerability and benefits of ACEI-diuretic combination were well shown in this trial, with only 3.6% of patients withdrawn because of suspected side effects during the pre-randomisation run-in period. At the end of the study, adherence to active treatment was 73%, only 1% less than adherence to placebo. Whether this excellent tolerability will apply in Chinese patients remains to be seen because Chinese patients may be more susceptible to ACEI-related cough.

This finding also indicates that a short course of active treatment is able to identify the small proportion of patients who are intolerant. This result has important implications for health service delivery, since only one follow-up visit is needed to establish patient’s suitability for long-term treatment with this regimen. Thereafter, follow-up visits can be maintained at 3 to 6-month intervals with minimum requirement for titration. This simple strategy may prove more practical and affordable in most clinical circumstances.

This trial also supports the recommendation that in treatment-naive high-risk diabetic patients, initiation of combination treatment immediately to reduce BP is beneficial and well tolerated. The rationale of commencing combination treatment right at the beginning is that even short periods of uncontrolled hypertension can translate into additional risks of cardiovascular events and more than one anti-hypertensive agents will often be required to lower BP to the target in majority of diabetic patients. The use of fixed-dose combination treatment is more convenient and simplify the treatment regimen and may cost less than the individual components prescribed separately. Greater BP reduction can usually be achieved at lower doses of the component agents, resulting in fewer side effects.

Lastly, optimal care for diabetic patients should include global risk reduction. In this cohort of patients, only about half of them were on aspirin or statin. Hence optimising anti-platelet and lipid lowering therapies may achieve even greater cardiovascular risk reduction in addition to intensive BP control.

### References


### Dermatological Quiz

**Dr. Lai-yin Chong**

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)

Yaumatei Dermatology Clinic, Social Hygiene Service

**Questions:**

1. What is your preliminary diagnosis or differential diagnosis?
2. What are the main clues in the diagnosis?
3. How do you confirm your diagnosis if necessary?
4. What is the mainstay of treatment?

*(See P. 31 for answers)*

**Fig 1:** Dusky erythematous and edematous plaque at dorsum of right forearm