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ADVANCE to ADVANCE on: The First Evidence of Legacy Effect in the Management of Hypertensive Diabetic Patients

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INTRODUCTION

Diabetes mellitus is associated with chronic macro and micro-vascular complications, which impair duration as well as quality of life. One of the main goals of diabetes care is to prevent and delay these complications. A comprehensive approach, focusing on control of glycaemia, blood pressure, lipids and weight is followed to achieve this aim.

VASCULAR HEALTH

Advances in understanding of the pathology and natural history of non-enhanced communicable disease have contributed to enhanced importance of non-glycemic parameters in diabetes management. The INTERHEART study, for example, revealed that dyslipidemia (odds ratio [3.25]), hypertension (1.91), and obesity (1.62) are as important determinants of the risk of myocardial infarction as diabetes (2.37) is. Similarly, in INTERSTROKE, hypertension (3.89), dyslipidemia (1.89), and obesity (1.65) were found to be more important than diabetes (1.36) in increasing the risk of stroke.

VASCULAR LEGACY

The beneficial impact of glucose-lowering and lipid-lowering on diabetes- related outcomes has been known for long. UKPDS and FIELD have shown reduction in cardiovascular outcomes with intensive glucose-lowering strategies. The legacy effect of these strategies, i.e., persistence in cardiovascular benefit has also been reported recently.

While the phenomenon of glycemic legacy is well-known, the concept of 'vascular legacy 'or blood pressure lowering legacy' has not been discussed adequately. Though preclinical and clinical studies have suggested the feasibility of such a legacy, clinical data to prove this has been lacking till recently. This chapter reviews and analyses the findings of the ADVANCE and ADVANCE ON trials. Based upon this evidence, it proposes a pragmatic approach to utilize the vascular legacy of perindopril + indapamide combination.

THE ADVANCE STUDY

The ADVANCE study assessed the effects of the routine administration of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination (perindopril + indapamide) on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs. A multinational trial, ADVANCE was conducted in 215 collaborating centers in 20 countries. After a 6-week active run-in period, 11 140 patients with type 2 diabetes were randomized to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy. The primary endpoints were composites of major macro vascular 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.

After a mean of 4.3 years of follow-up, 73% of those assigned active treatment and 74% of those assigned control remained on randomized treatment. Compared with patients assigned placebo, those assigned active therapy had a mean reduction in blood pressure of 5.6 / 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 separate reductions in macrovascular and microvascular events were similar but were not independently significant (macro vascular 0.92; 0.81-1.04, p=0.16; microvascular 0.91; 0.80-1.04, p=0.16). 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).

The ADVANCE study therefore proved the cardiovascular and the renal benefit of a perindopril + indapamide combination, administrated as routine therapy, irrespective of baseline blood pressure, to all patients with type-2 diabetes. This study demonstrated that both primary prevention and secondary prevention of cardiovascular and renal events could be achieved with perindopril + indapamide combination. In this regard, the ADVANCE results were an improvement over the results of MICRO HOPE, which included only high risk patients.

THE ADVANCE ON STUDY

The ADVANCE researchers assessed the long term outcomes of intensive intervention in ADVANCE. They 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. 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 (blood pressure lowering comparison) or 5.4 years (glucose-control comparison). Between group differences in blood pressure and glycated hemoglobin 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 macro vascular 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.

The ADVANCE ON trial showed that 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. Thus, it proved a vascular legacy effect in diabetes care, provided appropriate therapy is instituted early on in the course of the disease. This legacy is effective in both macro and micro-vascular beds.

DISCUSSION

ADVANCE was a landmark trial in diabetes care, as it established the cardiovascular benefit of perindopril + indapamide in all persons with type-2 diabetes, irrespective of blood pressure status. The ADVANCE and ADVANCE ON trial reveal better effects on cardiac, as compared to the cerebrovascular, and on renal, as opposed to the retinal vasculature. This discordance is similar to that seen with ramipril, empagliflozin and liraglutide in their studies. In spite of this limitation, the results of ADVANCE and ADVANCE ON support the universal use of perindopril + indapamide, as a preventive and therapeutic strategy, in type-2 diabetes.

Based upon their data, a target blood pressure of approximately 144/80mm Hg appears safe in the long run. A perindopril+indapamide combination can be used in any type-2 diabetes person in conjunction with all commonly used cardiovascular drugs, including other blood pressure lowering drugs, statins and anti-platelet drugs, irrespective of age, gender, history of hypertension / microvascular disease / macro vascular disease, or degree of glycemic control. Thus, ADVANCE supports the use of this combination as standard of care in not only hypertensive, but normotensive persons with type-2 diabetes as well. It must be noted that the incidence of cough is much lower with perindopril as compared to other ACE inhibitor.

ADVANCE ON adds strength to this contention, as it proves the long term advantages of perindopril + indapamide on cardiovascular and renal outcomes, even after the extra initial blood pressure lowering effect as compared to placebo has been lost. However, the drugs should not be used along with other ACE inhibitors or thiazide diuretics. The robust results of these randomized controlled trials support the use of the active study drug, as opposed to angiotensin receptor blockers (ARBs) and other ACE inhibitors, which do not enjoy such evidence-based backing.

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