

Vascular and renal benefits are additive using intensive blood pressure control and incremental glucose control in type 2 diabetic patients

The results of the ADVANCE trial studying the effect of the interaction between the two interventions (intensive glucose lowering with modified-release gliclazide and fixed combination of perindopril and indapamide) were released at the EASD on Monday, 8 September.

The effects of this incremental strategy of intensively lowering blood pressure and glucose in type 2 diabetic patients with the fixed combination of perinopril and indapamide, together with modified-release gliclazide plus other glucose-lowering drugs, were additive and independent of one another (figures 1, 2).

Joint treatment resulted in a significantly reduced risk of cardiovascular death (24%) and a

highly significant reduction in the risk of kidney complications (33%). Kidney protection was evident in a 20% risk reduction of kidney disease and a 30% risk reduction in the development of proteinuria (figures 3, 4).

'It is very reassuring that this patient-friendly and easy-to-implement strategy has confirmed the independent and fully additive benefits of blood pressure control and incremental glucose lowering in patients with established type 2 diabetes who were at cardiac risk', noted Prof John Chalmers of the George Institute for International Health, Australia and chairman of the ADVANCE investigator group.

'The main findings of the glucose-lowering arm of ADVANCE were highly ben-

eficial, with major macro- or microvascular complications reduced by 10% (significant), very low rates of both minor and severe hypoglycaemic events in the intensive arm of the study, and no significant weight gain from baseline to the end of the study in patients receiving the intensive therapy', he pointed out.¹

'These results are also significant in the light of the ACCORD study, which used a very rapid and aggressive strategy to lower glucose levels, showing increased cardiovascular risk and generally casting doubt on the macrovascular benefits of intensive glucose lowering', Prof Chalmers added.²

The glucose-lowering arm of the ADVANCE study was based on, firstly, systematically



Prof Chalmers

prescribing the sulfonylurea gliclazide as modified-release tablets, up to a maximum dose of four tablets per day, and then progressively adding other conventional drugs, followed by insulin if necessary to reach haemoglobin A_{1c} levels of 6.5%.

Figure 1. Blood pressure reduction.

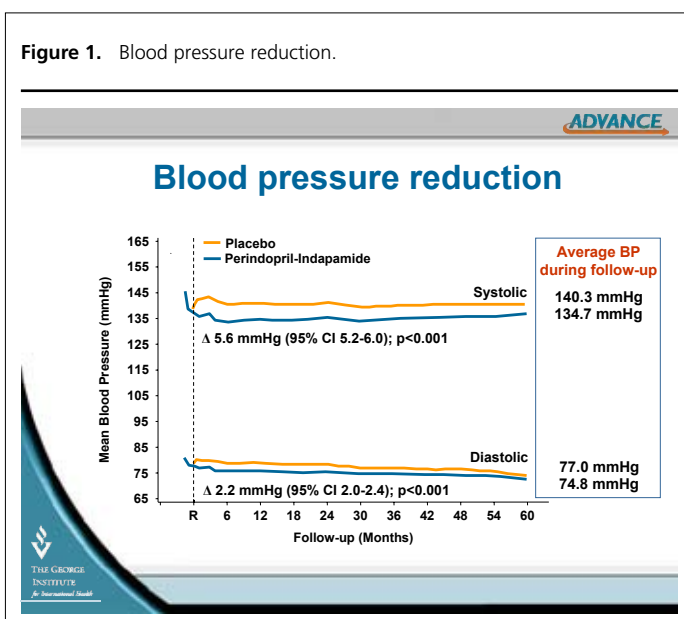


Figure 2. Haemoglobin A_{1c}.

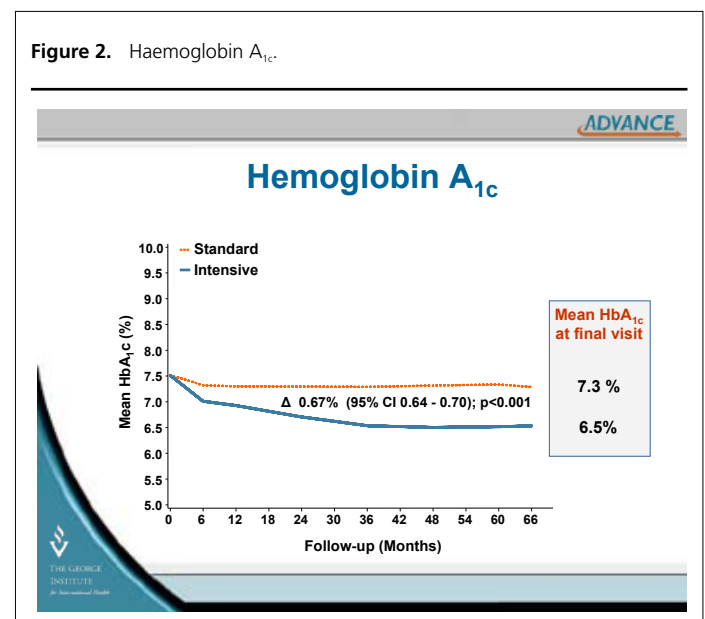


Figure 3. Renal events from glucose-lowering arm.

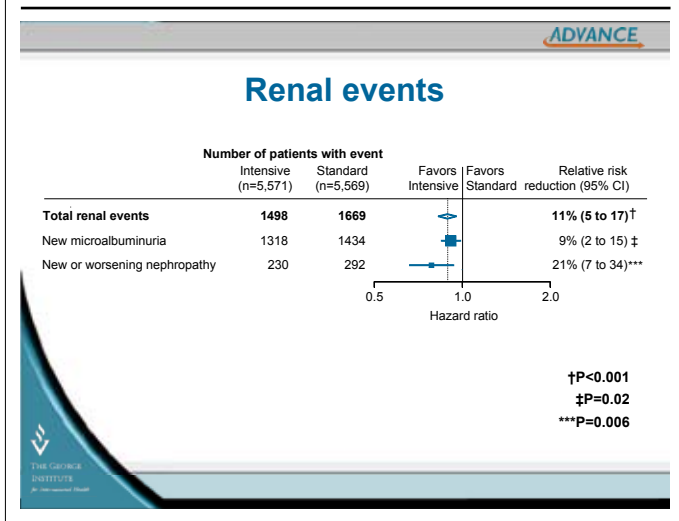
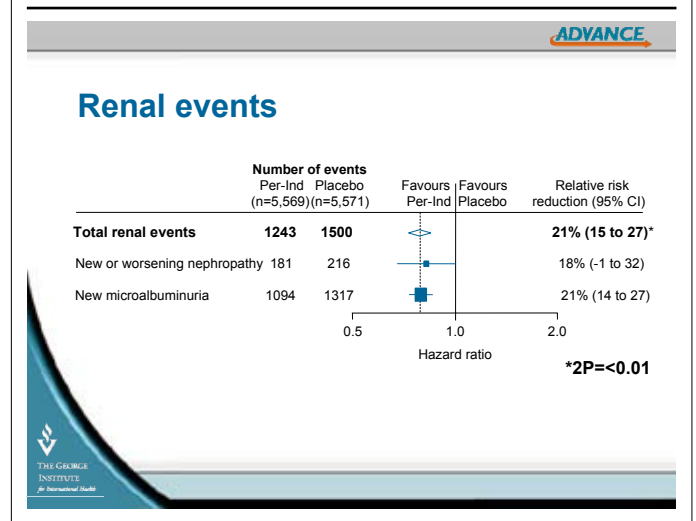


Figure 4. Renal events from blood pressure-lowering arm.



Comment from attending South African experts

Dr Larry Distiller, specialist diabetologist, Centre for Diabetes and Endocrinology, Houghton, Johannesburg

ADVANCE as a large, long-term, prospective study has confirmed what we had suspected and expected for a long time from other smaller studies; that the more cardiovascular risks you can bring under control, the better the overall outcome for the patient.

The fact that the benefits of intensive blood pressure control plus staged and intensive glucose lowering were additive was therefore expected. Mind you, if these benefits had not been additive, we would have been extremely disappointed and this could have led to the notion that glucose control is less important.

This finding from ADVANCE has dispelled any thought that

glucose lowering is unimportant and more difficult to achieve in type 2 diabetic patients with established disease (mean duration of diabetes was eight years).

For the current South African environment in which neither blood pressure nor glucose levels are adequately controlled, this is a wake-up call for physicians to be more aggressive in the management of cardiovascular risk factors.

Dr Aslam Amod, specialist physician, private practice, Durban

In my view, the key messages of this study for clinical practice are, firstly, the need to individualise patient care with clinical acumen and insight regarding the control of glucose levels in patients when the HbA_{1c} is greater than 7%, as this

approach accrues key benefits: microvascular in the medium term and probably macrovascular in the long term.

Secondly, we should place an even greater emphasis on effectively lowering blood pressure (BP) to levels below 130 mmHg as demonstrated with a Coversyl Plus-based regimen in ADVANCE. This is very important as the magnitude of benefit from tighter BP control is greater and occurs earlier than with tight glucose control. This can be achieved at a lower cost: UK £368 compared to £6 000 in the UKPDS 72 study.³

One of the reasons why ADVANCE was successful was that it fully incorporated the discretion of the responsible clinician with regard to a graded approach to glucose lowering and the attainment of target glycated haemoglobin levels.

In ACCORD, aggressive lowering of HbA_{1c} with multiple daily injections of insulin plus three oral antidiabetic agents without careful consideration of potential drug interactions and risk of hypoglycaemia resulted in patient deaths.

Therefore, in clinical practice today, we need a rational, common-sense approach, using clinical judgement based on the individual patient profile (for example, diabetes duration, age, longevity, severity of any underlying macrovascular disease, presence of autonomic neuropathy, availability of external assistance in the event of hypoglycaemia).

In the ADVANCE study, medication was given and individualised to each patient, with the exception that modified-release (MR) gliclazide was given in the intensive-treat-

ment arm, achieving better results than with other patients non-intensively treated with other sulphonylureas. Basal insulin was given, if needed, following the use of oral anti-diabetic medication, and then short-acting insulin was added for those patients who had not reached desired levels of

HbA_{1c}.

At the end of the study, 90% of patients in the intensive-treatment arm were on gliclazide with 70% receiving the 120-mg dose. This approach showed that a gliclazide MR-based strategy is safe when dose adjustments and the use of additional medications are

left to the discretion of the physician.

Compiled by J Aalbers, A Amod, L Distiller and W Mollentze.

1. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560–2572.
2. The ACCORD study group. Effects of glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–2559.
3. Clarke PN, Gray AM, Briggs A, et al. Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). *Diabetologia* 2005; **48**(5): 868–877.