



ADVANCE Study Design and Methodology – Media Backgrounder –

ADVANCE (Action in Diabetes and Vascular Disease) is the largest clinical trial ever performed in patients with type 2 diabetes.

Study rationale and topline findings¹⁻⁷

The ADVANCE study was set up to provide new evidence on the effects of more intensive blood pressure (BP) lowering and tighter glucose control on the risk of major vascular complications in adults with type 2 diabetes. The size of the trial and patient population involved is such that the results will have direct clinical implications for the management of BP and glucose in a large proportion of all patients with type 2 diabetes. The results of the blood pressure lowering arm of the study were published in the *Lancet* in 2007 and those of the blood glucose lowering arm in the *New England Journal of Medicine* in 2008.^{6,7}

The results of the blood pressure lowering arm of the study showed that a treatment regimen based on the fixed combination of the ACE inhibitor perindopril and the diuretic indapamide (Preterax[®]) significantly reduced mortality in patients with diabetes. The risk of death from any cause was reduced by 14% and the risk of death from cardiovascular disease by 18%.

The findings of the blood glucose lowering arm of the study showed that intensive treatment with modified release gliclazide (Diamicon MR[®]), in combination with other drugs as required, lowered blood glucose levels progressively and safely to 6.5% haemoglobin A1c and protects patients against the serious complications of diabetes. In particular, this strategy reduced the risk of kidney disease by one-fifth and reduced the risk of proteinuria, a potent predictor of increased cardiovascular risk, by nearly one third (30%).

ADVANCE - intensive glucose-lowering rationale in context

As few studies have been carried out (or are currently underway) assessing the benefits of tighter glucose control in preventing diabetic complications, important questions remain unanswered. The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated the impact of glucose lowering on microvascular complications in diabetes, but with less evident benefits in reducing risk of macrovascular complications, especially heart attack or stroke. ADVANCE was specifically designed to extend UKPDS findings, to demonstrate whether tighter glucose control ($\leq 6.5\%$ HbA1c vs 7% in the UKPDS intensive arm), based on a gliclazide-MR regimen, is able to reduce major micro and macrovascular complications.

Study objectives and design^{1,2}

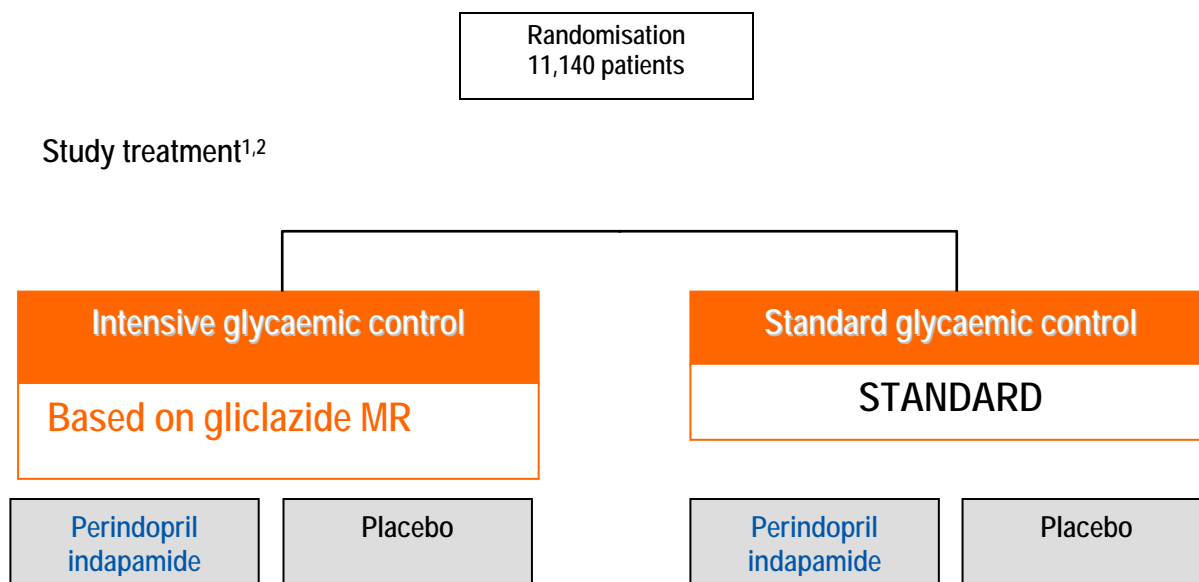
ADVANCE is an investigator-initiated and conducted, multicentre, randomised, placebo-controlled and 2x2 factorial study in type 2 diabetes. It was set up to determine the effects of routine blood pressure lowering and tighter glucose control on major microvascular (new or worsening eye or kidney damage) and macrovascular (stroke, myocardial infarction, cardiovascular death) complications. In the intensive glucose lowering arm of the study, patients received 1 – 4 tablets of modified release gliclazide (30 – 120 mg) daily as the treatment basis, together with other glucose control medications at the discretion of the treating physician. The aim of this regimen was to achieve a haemoglobin A1c (HbA1c) a measure of glucose control of $\leq 6.5\%$.

Study participants^{1,2}

11,140 patients from 215 centres in 20 participating countries in Asia, Australasia, Europe and North America were recruited into ADVANCE. Approximately one third of patients came from Asian countries, with the remainder deriving predominately from Caucasian populations. Countries taking part in ADVANCE were reflective of the global type 2 diabetes problem. India, China, Russia and Germany all feature in the top 10 countries in the world in terms of the number of people with diabetes – with China, the largest participating country in ADVANCE, at position two on the global list.

ADVANCE participants were subject to key inclusion and exclusion criteria to ensure the recruitment of a wide cross-section of individuals with type 2 diabetes. Broadly speaking, any diabetic patient aged over 55 was eligible if at risk of vascular disease. In terms of baseline patient characteristics, 43% of participants were female, patients' mean age was 65.8 years,

mean blood pressure was 145/81 mm Hg and average body mass index (BMI) was 28 kg/m². A total of 69% of study subjects had a history of hypertension, 75% were on concurrent BP-lowering therapy (most commonly an ACE inhibitor), 91% were receiving oral hypoglycaemic agents, 40% had a history of micro or macro vascular disease and 14% were smokers.



Patients were randomised to:

- Intensive glucose control based on gliclazide MR or standard glycaemic control, and
- Fixed combination of perindopril and indapamide or matching placebo

Randomisation followed ADVANCE's 2x2 factorial design and was stratified by study centre, history of macrovascular or serious microvascular disease.

For the glucose control arm of ADVANCE, patients were assigned to either intensive glucose-lowering therapy (aiming for HbA1c ≤ 6.5%), or to standard guidelines-based therapy. The intensive regimen targeted an HbA1c of 6.5% or less and so relied on maximisation of both drug therapy and non-drug interventions to achieve and maintain this tight control. Standard control simply involved the usual practice of the responsible physician following any relevant local, regional or national guidelines. The relevant glucose control measures used in each study arm were maintained until the end of the ADVANCE follow-up period.

Rationale for choice of gliclazide modified release

Gliclazide MR was included as a standard component of the intensive control regimen in ADVANCE because of its known effectiveness and safety in lowering blood glucose with the convenience of once-daily administration (as a result of the modified-release formulation).

Study follow-up^{1,2}

Patients in the ADVANCE glucose lowering arm were followed-up for an average of five years. During follow-up, blood pressure and HbA1c were measured in all patients. Patients were also assessed for the occurrence of study outcomes at every visit, with quantitative assessment of urinary protein and a formal eye examination at the 2nd and 4th years.

Study outcomes^{1,2}

The primary endpoint was a composite of:

- *Major macrovascular complications* – non-fatal stroke, non-fatal acute coronary syndrome and death from any cardiovascular cause
- *Major microvascular complications* – new or worsening nephropathy (defined as development of macroalbuminuria, doubling of serum creatinine to $\geq 200 \mu\text{mol/L}$, the need for dialysis, transplantation or death from renal disease) or micro vascular eye disease (defined as the need for retinal photocoagulation therapy, development of proliferative retinopathy, macular oedema or diabetes-related blindness)

It was pre-specified that these primary outcomes would be assessed both jointly and separately.

Secondary outcomes included a broad range of cause-specific vascular and non-vascular events, cognitive function and dementia, health-related quality of life and cost-effectiveness.

ADVANCE substudies^{1,2}

In addition to its primary aim, ADVANCE also included four major substudies looking at heart and eye function after intervention, cost-effectiveness and quality of life and genetic factors.

- *The ADVANCE Echocardiography Study* was set up to examine the effects of study treatments on heart function in around 500 patients.
- *The ADVANCE Retinopathy Measurements (AdRem) Study* was performed to examine the effects of study treatments on eye disease in around 2000 patients.

- *The ADVANCE Cost Effectiveness and Quality of Life Substudy Objectives (CEQoL)* was designed to investigate the cost effectiveness of the treatment regimens employed in ADVANCE and their impact on quality of life.
- *Prognomix* was designed to identify the genotypic predictors of vascular complications, specifically heart attack, stroke and nephropathy, in type 2 diabetics.

ADVANCE-ON: a new follow-up study

The primary aim of ADVANCE-ON is to define the long-term effects of intensive glucose control with gliclazide MR-based therapy (targeting an HbA1c $\leq 6.5\%$) compared to standard glucose control, on death and major macrovascular events in the patients with type 2 diabetes who took part in ADVANCE. The secondary aims are to determine the long-term effects of routine blood pressure lowering with a fixed combination of perindopril-indapamide on the same 2 outcomes.

All surviving patients who took part in ADVANCE (11,140 high-risk patients from 213 active clinical centres in Australasia, Asia, Europe and North America) will be observed for five years after their final ADVANCE study visit, in the setting of their usual care. Vital status and major clinical events will be documented at annual follow-up. The two primary outcomes will be death from any cause and major macrovascular events (non-fatal myocardial infarction, non-fatal stroke and cardiovascular death). The evidence provided by the ADVANCE-ON study, representing a contemporary cohort of patients with long standing diabetes from around the world, will play a pivotal role in defining future clinical management for tens of millions of individuals with type 2 diabetes worldwide.

References

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