

ADVANCE Study Milestones -Media Backgrounder-

- ADVANCE stands for **A**ction in **D**iabetes and **V**ascular disease: PreterAx and DiamicroN MR Controlled Evaluation.
- ADVANCE is the largest clinical trial ever performed in patients with type 2 diabetes, with the inclusion of 11,140 randomised patients.
- ADVANCE is a landmark trial which has been set up to answer some of the key unresolved issues related to glucose control and blood pressure lowering in type 2 diabetes – specifically, the influence which these interventions have on the risk of major vascular complications.
- The ADVANCE study consists of two parts:
 - o The **glucose lowering arm** of the study investigated the effect of intensive blood glucose control on both macrovascular complications (stroke, myocardial infarction and cardiovascular death) and microvascular complications (new or worsening nephropathy and retinopathy) in adults with type 2 diabetes. The main results were published in the NEJM in 2008 (*NEJM* 2008; 358: 2560-2572). These demonstrated that intensive control reduced the combined major macrovascular and microvascular end point (18.1% vs. 20.0%; hazard ratio (HR) 0.90; 95% confidence interval 0.82 to 0.98; $P=0.013$). Major microvascular events were reduced (9.4% vs. 10.9%; HR 0.86 [0.77 to 0.97]; $P=0.014$), primarily because of a reduction in nephropathy (4.1% vs. 5.2%; HR 0.79 [0.66 to 0.93], $P=0.006$), with no significant effect on retinopathy ($P>0.1$).
 - o The other arm of the ADVANCE study, the **blood pressure (BP) lowering arm**, reported its results in 2007.2 The BP arm evaluated the effect of routine BP lowering, regardless of initial blood pressure level, on micro and macrovascular complications in type 2 diabetes. The results were published in the *Lancet* in 2007 (*Lancet*. 2007;370:829-840)
- 11,140 patients with type 2 diabetes took part in the ADVANCE study. A total of 20 countries across Asia, Australasia, Europe and North America were involved in ADVANCE, with patients drawn from 215 collaborating centres.
- The study had broad inclusion criteria and included patients without restrictions on the level of blood glucose control on study entry. Patients were eligible to participate in the study if they were over 55 years of age and at a high risk of cardiovascular disease.
- The ADVANCE study is investigator-initiated and led. It is a multicentre, randomised, placebo-controlled trial and has a 2x2 factorial design.
- The intensive glucose lowering therapy used for ADVANCE, was based on Diamicon MR (modified-release gliclazide), but allowed the addition of any other glucose lowering drug to help achieve the HbA1c target of 6.5% or below.
- The blood pressure lowering treatment used for ADVANCE was Preterax – a fixed-dose combination of perindopril (an ACE inhibitor) and indapamide (a diuretic).

- Both drugs were selected for the ADVANCE study based on their proven efficacy and safety, as well as the substantial body of evidence which exists demonstrating the advantages of these two drugs in the treatment of vascular disease in diabetes.
- Also included in ADVANCE were four key sub studies looking at left ventricular function (echocardiography) and incidence and progression of retinopathy (retinal imaging) after intervention, cost effectiveness and quality of life, and genetic predictors of cardiovascular and renal complications.
- ADVANCE started in 2001 and patient recruitment ended in March 2003. The blood pressure lowering arm completed in June 2007 and the study itself was completed in January 2008 with the end of the follow up of the glucose lowering arm of the study.
- ADVANCE showed a positive trend toward a reduction of major cardiovascular events in diabetes patients who received intensive glucose control. This finding was confirmed in a recent collaborative meta-analysis performed by the main investigators of the four main trials in type 2 diabetes. This analysis, that included the original data from ADVANCE, ACCORD, VADT and UKPD, demonstrated the benefits of intensive glucose lowering with a significant 9% reduction in major cardiovascular events, primarily reflecting a 15% reduction in myocardial infarction. Among the different studies, only ADVANCE showed to reduce both total and cardiovascular death (6% and 12% respectively).
- On the basis of observational data, several national registers (including more than 70,000 patients with type 2 diabetes: 8.000 patients from Denmark and 64.000 from Ukraine), have recently reported that glucose lowering regimens that included gliclazide in monotherapy were associated with lower risks of mortality compared to other therapeutic strategies.
- New analyses from ADVANCE presented at the IDF congress in 2009 show that the efficacy and safety of intensive blood glucose control using gliclazide MR-based regimen is maintained across a broad range of patients in different clinical settings, irrespective of age, duration of diabetes, sex, body mass index, or HbA_{1c} at study entry, and also irrespective of initial glucose lowering treatment.
- A follow-up study – ADVANCE-ON -- was started in 2009. 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. 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 will play a pivotal role in defining future clinical management for tens of millions of individuals with type 2 diabetes worldwide.
- The ADVANCE study has also provided important insights into factors predicting cardiovascular risk in type 2 diabetics. Age at diagnosis, known duration of diabetes, sex, pulse pressure, treated hypertension, atrial fibrillation, retinopathy, HbA_{1c}, albumin/creatinine ratio, and non-HDL cholesterol level at baseline were all found to be significant predictors of cardiovascular events. A new risk prediction tool has been developed by ADVANCE investigators using these variables, paving the way for a new 'risk engine' that may be more relevant for contemporary populations of treated patients with diabetes compared to older risk prediction tools such as the Framingham and UKPDS (United Kingdom Prospective Diabetes Study) models.