Journal of Human Hypertension (2005) 19, S27–S32
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www.nature.com/jhh

ORIGINAL ARTICLE

ADVANCE: action in diabetes and vascular disease

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The burden of Type II diabetes is growing rapidly worldwide, across high-, middle- and low-income countries. This burden is associated primarily with increased risks of macrovascular and microvascular diseases, and it is agreed that multifactorial treatment regimens are required to reduce it. ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation) is a large-scale, 2 × 2 factorial, randomised clinical trial. It will investigate the potential benefits of blood pressure lowering, using a fixed low-dose combination of perindopril and indapamide *vs* placebo, and of tighter glucose control, using an intensive gliclazide-MR-based glucose control regimen *vs* a standard guidelines-based regimen, separately and together. The two primary outcomes are a composite macrovascular end point of nonfatal stroke, nonfatal myocardial infarction and cardiovascular death; and a composite microvascular end point of new or worsening nephropathy or microvascular eye disease. Following successful recruitment and randomisation of 11 140 participants by March 2003, the study is currently half way through its planned follow-up of 4.5 years. Adherence to randomised study treatment is good; and loss to follow-up is minimal. It is hoped that the study will answer a number of unresolved issues. The blood pressure lowering arm will investigate the possible reduction in major vascular disease in patients with Type II diabetes whether or not they have hypertension, and the possible benefits of blood pressure lowering in such patients already receiving background therapy with the ACE inhibitor perindopril. The glucose control arm will investigate the possible reduction in both macrovascular and microvascular disease achieved with tighter glucose control, targeting an HbA_{1c} of 6.5% and a fasting blood glucose of 6.0 mmol/l. Finally, the factorial design will enable investigation of the combined effects of more intensive glucose control and tighter control of blood pressure.
Journal of Human Hypertension (2005) **19,** S27–S32.
doi:10.1038/sj.jhh.1001890

Keywords: blood pressure lowering; glycaemic control; perindopril; indapamide; Diamicron MR; fixed dose combination

Introduction: diabetes a global health problem

Diabetes is a major health problem afflicting millions of people across high-, middle- and low-income countries.[1] Individuals with Type II diabetes have markedly increased risks of both macrovascular disease (including coronary heart disease and stroke) and microvascular disease (including nephropathy and retinopathy).[2,3] Globally, coronary disease is the commonest cause of death among subjects with diabetes[1] while in high-income countries diabetes is the leading cause of blindness and end-stage renal disease.[3] While the burden of diabetes is increasing throughout the world, it is doing so most rapidly in low- and middle-income countries.[1,3] Furthermore, the medical costs of managing diabetes and its consequences are high and rising: total medical expenditure on patients with diabetes in the USA in 1999 was four times greater than expenditure in people without diabetes.[4] The management of Type II diabetes and the prevention of its complications is a high priority for public health authorities in all nations.

Blood pressure and blood glucose levels are among the main determinants of the risk of developing both macrovascular and microvascular complications in patients with diabetes so that blood pressure control and glycaemic control are paramount in this population.

Blood pressure glucose and vascular disease in Type II diabetes

Blood pressure control and diabetes: current evidence

Observational data from the UK Prospective Diabetes Study (UKPDS)[5] demonstrated that each 10 mmHg decrement in systolic blood pressure was associated with around a 12% reduction in the risk

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of myocardial infarction in patients with diabetes. The evidence from randomised trials such as the UKPDS and HOT studies[6,7] and from meta-analyses such as that conducted by the INDANA group[8] has shown that blood pressure lowering in hypertensive patients with diabetes reduces the risk of major vascular disease, with greater benefits resulting from more intensive treatment.[6–8] More recent studies have shown reductions in the vascular complications of diabetes using an ACE inhibitor such as ramipril (the HOPE Study[9]) perindopril (the EUROPA trial[10]) or perindopril and indapamide (the PROGRESS Trial[11]). The benefits of ACE inhibitor therapy in patients with diabetes and early manifestations of nephropathy have also been confirmed in recent studies and analyses comparing ACE inhibitors with a variety of blood pressure-lowering drugs.[12–14] The potential benefits of lowering blood pressure in nonhypertensive patients with diabetes are less well documented.

Glycaemic control and diabetes: current evidence

There is only limited evidence on the effects of good glycaemic control on the risk of vascular disease in Type II diabetes. Observational data from the UKPDS[15] indicated that a reduction in the mean glycated haemoglobin Alc (HbA_{1c}) concentration of 1% was associated with a reduction in the risk of myocardial infarction of 14% and of microvascular complications of 37%. A recent meta-analysis of observational data in Type II diabetes, which included UKPDS, indicated that a 1% higher level of HbA_{1c} was associated with an 18% greater risk of cardiovascular disease.[16] More recent evidence from the Asia Pacific Cohort Studies Collaboration indicates that a 1 mmol/l lower level of plasma glucose concentration in patients with diabetes is associated with a 21% reduction in stroke and a 23% reduction in coronary events.[17]

A number of randomised clinical trials have reported that patients with Type II diabetes assigned to more intensive glucose lowering exhibited greater reductions in the incidence of microvascular events.[18–20] However, even in the largest of these trials, the effects of glycaemic control on the risk of macrovascular disease remain inconclusive.[20]

Unresolved issues

ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation) was planned in 1999 in order to address a number of these issues in the management of patients with Type II diabetes that were unresolved at the time and that remain unanswered today.[21]

1. *Are there benefits of blood pressure lowering in normotensive patients*? While the benefits of blood pressure lowering in hypertensive patients with Type II diabetes have been clearly established, there remains considerable uncertainty regarding the potential benefits in normotensive patients with diabetes.

2. *Are such benefits additional to those conferred by background ACE Inhibition?* While the reductions in vascular complications reported for patients with Type II diabetes in the HOPE study were substantial,[9] the degree to which these were due to blood pressure lowering or to specific effects of ACE inhibition remains debated and uncertain. It is therefore important to ascertain whether routine blood pressure lowering patients with Type II diabetes confers benefits that are additional to these of background treatment with an ACE inhibitor, regardless of the level of blood pressure.

3. *Will more intensive glucose control reduce the risk of macrovascular disease?* While many diabetologists fervently believe that more intensive glucose control, targeting lower levels of HbA_{1c}, will reduce the risk of major macrovascular disease, the best available evidence, from the UKPDS trial, remain inconclusive.[20] There is a clear need for fresh evidence from trials of more intensive glucose-lowering targeting lower levels of HbA_{1c} and fasting glucose.

4. *What are the combined benefits of better blood pressure control and more intensive glucose control?* Finally, while diabetes and hypertension are frequent companions and indeed have been dubbed 'The Bad Companions', there is no clear indication whether the benefits of more intensive control of blood pressure and of blood glucose will be additive. Since these two therapeutic strategies are currently foremost in the management of patients with Type II diabetes, it is clearly important to determine whether each has an independent benefit in reducing macrovascular and microvascular complications.

ADVANCE is a large-scale randomised factorial clinical trial designed to address these unresolved issues.[21]

ADVANCE: controlling blood pressure and blood glucose in Type II diabetes

Study design

ADVANCE is an investigator-initiated and -conducted trial whose study design has been described fully elsewhere[21] and is briefly presented here. The study uses a factorial 2×2 design to address separately and together, the potential benefits of blood pressure lowering and of glucose control, in reducing the risk of macrovascular and microvascular disease in patients with Type II diabetes.

Study participants
Eligible subjects were over 55 years of age at entry, had a diagnosis of Type II diabetes mellitus first made at the age of 30 years or older and had an elevated risk of vascular disease.[22] Both hypertensive

and nonhypertensive individuals were eligible for inclusion and eligibility was independent of the need for background ACE inhibitor therapy. Thus subjects for whom an ACE inhibitor was deemed to be indicated could be included unless there was a specific indication for an ACE inhibitor other than perindopril, 4 mg daily or less. Furthermore, there were no entry criteria relating to the baseline level of HbA_{1c} or fasting blood glucose or the number or type of oral hypoglycaemic agents, though patients requiring regular long-term insulin therapy were not eligible.[21,22]

Study treatment
The blood pressure lowering study regimen used is the fixed-low-dose combination of perindopril (2 mg) and indapamide (0.625 mg) for the first 3 months after randomisation, rising to perindopril (4 mg) and indapamide (1.25 mg) thereafter, or matching placebos. This regimen was chosen for a number of reasons. These included the established beneficial effects of both classes of drug in reducing the risks of cardiovascular disease in various populations including those with hypertension and diabetes.[23–25] A second reason was the broad consensus that combination therapy is necessary to achieve target blood pressures that are agreed to be lower in patients with diabetes than in those without.[23–25] The third was the increasing recognition that fixed low-dose combinations could be used either to initiate therapy or to maintain it with the potential to achieve greater tolerability and hence greater efficacy and adherence to therapy.[23–25] The use of the fixed, low-dose combination of perindopril and indapamide brought together all these advantages and avoided the contentious choice between various classes of drugs that might be used in monotherapy. For any patient for whom an ACE inhibitor is believed to be indicated, background open-label perindopril 2 or 4 mg daily is provided and can be started at any time during the trial. Other classes of blood pressure-lowering drugs can be prescribed as necessary, with the exception of thiazide-like diuretics.[21]

The modified release preparation of the sulphonylurea gliclazide MR (30–120 mg daily) forms the basis of the glucose control regimen among participants randomly assigned to the intensive glucose control group. This agent, which provides 24 - hour glucose control in a single daily dose, was the sulphonylurea used in the 'Steno-2 trial'[26] a small trial of multifactorial risk intervention among patients with Type II diabetes, that included intensive glucose control, blood pressure control, ACE inhibition and cholesterol-lowering therapy. This multifaceted regimen produced substantial reduction in both macrovascular and microvascular events, but the contribution of glucose lowering to these effects cannot be ascertained.[26] Nonpharmacological therapy, other oral agents and then insulin can be added as required in AVANCE to achieve the target of HbA_{1c} of 6.5% or less, or fasting blood glucose of 6 mmol/l or less.[21] Participants assigned to the control group received standard guidelines-based therapy for glucose control, in accord with national or institutional guidelines pertaining. If a sulphonylurea is used in participants assigned to the standard guidelines-based glucose control therapy, such agent must be other than gliclazide.[21]

Study outcomes
The study has two primary outcomes, both composite. The first is the macrovascular composite end point of nonfatal stroke, nonfatal myocardial infarction or cardiovascular death. The second is the microvascular composite end point of new or worsening nephropathy or microvascular eye disease. Secondary outcomes include cerebrovascular disease, coronary heart disease, heart failure, peripheral vascular disease, macroalbuminuria, visual deterioration, neuropathy, dementia and all-cause mortality.[21] Data are also collected on episodes of major and minor hypoglycaemia, other suspected adverse reactions, quality of life and use of health care resources.[21]

Study power and statistical consideration
The sample size estimations were based on a mean difference of 6 mmHg in systolic blood pressure and 1% in HbA_{1c} for the blood pressure-lowering and glucose control arms of the factorial study, respectively. Assuming an annual event rate of 3% or more for each of the two composite primary outcomes it was estimated that a sample size of 10 000 participants would provide 90% power to detect at least 16% reduction in the relative risk of each of the primary outcomes for each of the randomised comparisons.

Study status

Recruitment
Recruitment for ADVANCE began in June 2001 and a total of 12 878 potentially eligible patients had entered the open-label run-in phase by March 2003. These were recruited from 215 clinical centres across 20 countries in Europe, North America, Asia and Australia. Of those who entered the run-in phase, 1738 were not randomised and the final number of randomised participants was 11 140.[22] The main reasons for withdrawal during the run-in phase were patient choice (27%), patient ineligibility (25%), poor compliance (16%), cough (13%) hypotension or dizziness (5%) and other suspected intolerance to perindopril–indapamide (8%).[22]

Baseline characteristics
The baseline characteristics have been described in full elsewhere.[22] In brief, the mean age at baseline was 66 years and 43% of participants were female. At the start of the run-in phase 32% of subjects had

macrovascular and 10% had microvascular disease. Of those without a history of major vascular disease, 62% were aged over 65 years, 15% were smokers, 24% had a total cholesterol above 6.0 mmol/l, and 24% had macroalbuminuria.[22]

The mean blood pressure of randomised participants was 145/81 mmHg and the average HbA_{1c} prior to entry into the run-in phase was 7.5%. Approximately, three quarters of the study population were taking blood pressure-lowering drugs and a similar proportion were taking a sulphonylurea at the start of the trial.[22] A total of 35% were taking lipid-lowering therapy and 47% were taking antiplatelet therapy.[22]

On average, the diagnosis of diabetes had first been made 8 years before study entry, and among those without a history of macrovascular or microvascular disease, 36% of randomised participants had a diagnosis of diabetes made more than 10 years earlier.[22]

Certain characteristics of the randomised participants, such as the body mass index, the smoking rate, and the proportion taking various types of medication, varied somewhat between participating centres, and participating countries.[22]

Prior to randomisation, 40% of participants were receiving ACE inhibitor therapy and 5% were receiving an angiotensin receptor blocker.[22] At the time of randomisation, 47% of participants were prescribed background perindopril (2 or 4 mg daily) and the proportion receiving open-label perindopril has remained between 45 and 50% up to the present point in follow-up.

Follow-up

At the time of writing, approximately half of the planned average follow-up of 4.5 years has been completed. Approximately 87% of randomised participants are still adhering to the randomised treatment regimen assigned (active or control) for both the glucose control and the blood pressure control arms of the trial.

Discussion — anticipated outcomes

While the study is now only at the half-way mark in follow-up, it is anticipated that the successful recruitment of over 11 000 participants from a variety of ethnic groups and from clinical centres and countries with a broad range of treatment practices will enhance the generalisability of the study results.

Achieving the objectives of the blood pressure lowering arm of the study, detecting a 16% reduction in the two primary outcomes, requires a separation of at least 6 mmHg in the systolic blood pressure achieved by the active therapy and the control group during follow-up. This task is clearly made more difficult by the provision of background perindopril to around half of all participants to date, and by allowing all participants to receive such additional blood pressure lowering drugs as are deemed necessary by the responsible physician. On the other hand, the excellent tolerability of the fixed low-dose perindopril–indapamide combination, and the good adherence to randomised therapy observed to this point in follow-up will help achieve the separation required. So too will the known efficacy of combining a diuretic with an ACE inhibitor for lowering blood pressure, and the established value of placebo-controlled comparison in clinical trials, as demonstrated by many studies in which the effects of the active treatment regimen are tested 'on top of' all other therapies. The administration of background perindopril to around half of randomised participants will also permit assessment of the additional value of blood pressure lowering in patients already taking an ACE inhibitor. Finally, the randomisation of 11 400 patients with Type II diabetes irrespective of the initial level of blood pressure, or of a history of hypertension, will enable the study to address the hypothesis that blood pressure lowering in patients with diabetes, will reduce the burden of vascular diseases whether they are hypertensive or normotensive.

Achieving the objectives of the glucose control arm of ADVANCE, detecting a 16% reduction in the two primary outcomes, was estimated to require a 1% separation of HbA_{1c} between the intensive therapy and standard therapy groups.[21] Given that this arm of the study depends on comparison of two open treatment regimens, albeit randomised, the progressive awareness of the importance of 'tight glucose control' across the world will make it harder to achieve this separation. Thus the standard, guidelines-based regimens now recommended in many parts of the world have more stringent targets of HbA_{1c} than they did when the study was planned. On the other hand, there is some evidence that the predictions of risk based on HbA_{1c} values in the UKPDS trial,[15] used in our power calculations[21] may underestimate the strength of the association between the level of glycaemic control and cardiovascular risk.[16,17,27] Again it is hoped that the many measures adopted to enhance the achievement of the target HbA_{1c} of 6.5% and target fasting blood glucose of 6 mmol/l, will result in a sufficient separation between the intensive and standard treatment groups.

There are many ongoing trials investigating and comparing the potential benefits of a variety of glucose control and blood pressure-lowering treatment regimens. One in particular is very pertinent in relation to ADVANCE. This is the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial.[28] Like ADVANCE, ACCORD is a factorial trial, but it has three arms, with all subjects participating in the glycaemic control comparison between a target HbA_{1c} of 6% and a target of 7.5%, and subsets participating in a blood pressure-lowering arm or in a lipid lowering comparison. Since ACCORD is

planning to recruit at least 10 000 participants, and since it should be completed a little after ADVANCE, there should be ample opportunity to pool the results and conduct a meta-analysis with even greater power to address some of the key questions, than will be possible for either trial alone.

Conclusions

The ADVANCE trial has satisfactorily completed its recruitment, with 11 140 participants randomised by March 2003. It is currently approximately half way in its planned follow-up phase that will average around 4.5 years for all participants. The study is progressing well and has the potential to answer many critically important questions on the possible benefits of tighter glucose control and of blood pressure lowering in reducing the burden of major vascular disease in patients with Type II diabetes.

Acknowledgements

ADVANCE is an investigator-initiated and conducted study supported by grants from the Institut de Recherches International Servier, and the National Health and Medical Research Council of Australia.

Conflict of interest

John Chalmers has received grants from Servier as Co-Principal Investigator for the PROGRESS and ADVANCE trials, administered by the University of Sydney. All three authors have received honoraria from Servier for speaking at scientific meetings.

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