How to ADVANCE Prevention of Cardiovascular Complications in Type 2 Diabetes

Diederick E. Grobbee

Patients suffering from type 2 diabetes are at increased risk of macrovascular and microvascular disease. This review assesses the available evidence for hypertension and hyperglycemia as risk factors for vascular disease in type 2 diabetes mellitus. Several studies showing a benefit of antihypertensive treatment and glucose-lowering therapy on the prevention of macrovascular and microvascular disease are discussed. However, questions remain concerning the overall balance of benefits and risks of intensive target-driven blood pressure and blood glucose control in type 2 diabetes. More well-powered intervention and prevention studies are therefore needed to provide the necessary reliable evidence to answer these questions. The Action in Diabetes and Vascular disease: PreterAx and DiamicroN modified release Controlled Evaluation (ADVANCE) study is discussed as a trial designed to resemble clinical practice that promises to provide answers concerning the value conferred by blood pressure–lowering therapy and intensive glucose control therapy in type 2 diabetes patients at high risk for cardiovascular disease.

TYPE 2 DIABETES is a major global health problem. According to estimations of the World Health Organization there were more than 135 million adults suffering from diabetes worldwide in 1995.[1] The prevalence of all types of diagnosed diabetes in most Western societies is between 3% and 7%. Countries with the highest absolute number of diabetics are India (19 million), China (16 million), and the United States (14 million).[1] It is projected that the total number of individuals with diabetes will rise to about 300 million in 2025, with a particularly sharp increase in the prevalence of type 2 diabetes in the developing world.

Microvascular complications contribute substantially to type 2 diabetes–associated morbidity, while cardiovascular disease is a frequent cause of death and hospitalization in this patient group. Several studies have underlined the existence of modifiable risk factors in diverse populations of type 2 diabetic patients, in particular hypertension and hyperglycemia. The value of an intensive intervention, aimed at multiple risk factors, has been recently demonstrated in the Steno-2 study, where the risk of cardiovascular and microvascular events in patients with type 2 diabetes was reduced by about 50%.[2]

TYPE 2 DIABETES AND VASCULAR COMPLICATIONS

Type 2 diabetes increases the risk of microvascular and macrovascular disease. Coronary heart disease is the most common cause of death in patients with type 2 diabetes in Western societies. For these patients, the risk of death from a cardiovascular event is increased by approximately 3-fold.[3] Similarly, the risks of nonfatal myocardial infarction, ischemic stroke, and congestive heart failure are raised.[4-6]

With regard to microvascular complications, diabetic retinopathy is the most common cause of blindness among individuals under the age of 60 years.[7] Even in patients newly diagnosed with type 2 diabetes, a high incidence of retinopathy is found. In the United Kingdom Prospective Diabetes Study (UKPDS), more than one third of patients showed signs of retinopathy at entry, with about 5% of the cases presenting with signs of advanced retinopathy.[8] Another important microvascular complication of type 2 diabetes is nephropathy, with 14% to 19% of newly diagnosed type 2 diabetes patients already with microalbuminuria.[9] Moreover, it has been demonstrated that the incidence of end-stage renal failure (eg, glomerular filtration rate < 15 mL/min) in type 2 diabetic patients 10 years after development to proteinuria ranged from 10% to 35%.[10]

Neuropathy is another example of diabetic complications involving microvascular disease and a cause of considerable morbidity among these patients. About 60% of diabetic patients suffer from some form of neuropathy, which is symptomatic in around one third of cases.[11] Lower limb amputation is a serious consequence of diabetic neuropathy and peripheral vascular complications. Diabetic patients have an approximately 15-fold increased risk of nontraumatic lower limb amputation compared with the nondiabetic population.[12]

HYPERGLYCEMIA AND THE RISKS OF VASCULAR DISEASE IN TYPE 2 DIABETES

There are several modifiable risk factors for complications in patients with type 2 diabetes. These include hyperglycemia, hypertension, and dyslipidemia.[13] Elevated blood glucose concentrations are an important determinant of microvascular and macrovascular complications in patients suffering from diabetes. A meta-analysis of several trials that assessed the effect of intensive glycemic control on vascular outcomes in type 1 diabetic patients demonstrated reductions of about 25% for microvascular complications in those patients assigned to a more intensive blood glucose control regimen.[14] With regards to type 2 diabetic patients, observational data from the UKPDS showed that each reduction of mean hemoglobin A_{1c} (HbA_{1c}) by 1% translated into a 14% lower rate of myocardial infarction and a 37% lower rate of microvascular complications.[15] The UKPDS further demonstrated that lowering HbA_{1c} by 1% using sulfonylureas or insulin therapy can reduce microvascular complications (mainly retinopathy requiring photocoagulation) by about 25% over a 10-year period.[16] In this trial a

From the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands.

Address reprint requests to Diederick E. Grobbee, MD, PhD, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands.

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borderline significant trend towards reduction in the risk of myocardial infarction was seen but no clear risk reduction was observed for stroke or diabetes-related deaths. However, relatively few macrovascular events were recorded in this study altogether, limiting the power to detect effects of glucose-lowering treatment on these outcomes.

Overwhelming clinical and pathological evidence across a wide range of populations has established that patients suffering from diabetes show higher levels of atherosclerosis-related disease compared with nondiabetics.[17,18] The role of premature and extensive atherosclerosis in the development of cardiovascular disease in type 2 diabetes patients has been mentioned previously. The management and treatment of macrovascular disease accounts for the bulk of expenditure and hospitalization. To illustrate the scale of the problem, it was, for example, shown in the US National Hospital Discharge Survey that cardiovascular disease was responsible for almost 80% of admissions for diabetic complications and accounted for almost 80% of diabetic deaths.[19]

In addition to the UKPDS, there have been studies that evaluated the effect of intensive glycemic control on macrovascular complications. The Kumamoto study showed that multiple insulin injections in type 2 diabetes patients resulted in 50% fewer macrovascular events compared with conventional insulin injection therapy.[20] However, this difference was not statistically significant, probably due to the small number of patients. Jensen-Urstad et al also reported in accordance with these results that early atherosclerosis could be delayed by improved glycemic control.[21]

HYPERTENSION AS A RISK FACTOR FOR VASCULAR DISEASE IN TYPE 2 DIABETES

Next to hyperglycemia, blood pressure has been identified as a common and important factor in determining macrovascular and microvascular complications in type 2 diabetes. In the Asia Pacific Cohort Studies Collaboration, it was demonstrated that in type 2 diabetic and nondiabetic patients there was a similar association of systolic blood pressure with stroke and coronary heart disease.[22] While the relative risks associated with a given increase in systolic or diastolic blood pressure are about the same for diabetic and nondiabetic subjects, the absolute increase in risk of blood pressure elevation is markedly higher for diabetic patients. This reflects the inherent increase in cardiovascular risk in diabetes, irrespective of blood pressure level. As a consequence, the net benefit of blood pressure reduction is much higher in diabetes than in nondiabetic hypertensive patients. “Hypertension” is not a disease but an arbitrary range of blood pressure levels for which there is consensus that the benefits of treatment are shown to be higher than the risks and costs. It has been well documented that the net benefit of blood pressure reduction is directly related to the overall cardiovascular risk, that is, the baseline risk as determined by accumulation of all known risk factors.[1] Consequently, it seems appropriate to set criteria for hypertension in diabetics lower than for nondiabetics. Reduction in blood pressure levels within the “normal” range may be worthwhile once the overall absolute cardiovascular risk is as high as it is in diabetic patients. While highly plausible, this concept requires confirmation in randomized trials. One of the first of such trials, the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS), has provided support for the benefits of lowering of blood pressure irrespective of its level in high-risk patients following a cerebrovascular event.[2] The Action in Diabetes and Vascular disease: PreterAx and DiamicroN modified release Controlled Evaluation (ADVANCE) study is exploring the tenability of this concept in diabetic patients.[23,24]

The benefit of lowering blood pressure on microvascular and macrovascular complications in diabetic patients has been demonstrated in several trials. The UKPDS showed that in newly diagnosed type 2 diabetics patients a 10–mm Hg reduction in mean systolic blood pressure translated into an 11% reduction in risk for myocardial infarction and 13% reduction in risk for microvascular complications.[25] These results have been confirmed in several randomized trials that have demonstrated the beneficial effect of lowering blood pressure among hypertensive patients with type 2 diabetes.

In the UKPDS, over an 8-year period, reductions in risk in the group assigned to tight blood pressure control (144/82 mm Hg) compared with that assigned to less tight control (154/87 mm Hg) were 44% in strokes and 32% in deaths related to diabetes. In the Hypertension Optimal Treatment (HOT) study, treatment of elevated diastolic blood pressure for an average of 3.7 years in type 2 diabetic patients resulted in a 30 % reduction in the risk for total major cardiovascular events.[26] The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that prolonged treatment with an angiotensin-converting enzyme (ACE) inhibitor and a lowered systolic blood pressure of only 3 mm Hg reduced the incidence of stroke by one third and coronary events by one fifth in high-risk diabetic patients.[27] It is of particular interest that in this study the effects of treatment were similar in diabetic and nondiabetic patients and patients suffering from hypertension as well as in nonhypertensive patients. However, no clear reduction in the risk of vascular events in the hypertensive arm of the of the Appropriate Blood pressure Control in Diabetes (ABCD) trial was shown.[28] The results of the ABCD trial might be explained by the fact that relatively few events were seen altogether.

Moreover, the HOPE study and the UKPDS-Hypertension in Diabetes Study (UKPDS-HDS)[29] provide convincing evidence about the beneficial effects of blood pressure–lowering on microvascular complications of type 2 diabetes. In the HOPE study, a reduction in microvascular complications (including nephropathy and retinopathy) was shown in hypertensive and nonhypertensive diabetic patients. Smaller ACE inhibitor–based trials have confirmed these results on renal outcomes among hypertensive and nonhypertensive patients with type 2 diabetes.[30,31] In the UKPDS-HDS, among hypertensive patients assigned to a more intensive blood pressure–lowering regimen, the incidence of microvascular complications (in most cases the need for retinal photocoagulation) was reduced by 37%.

UNRESOLVED ISSUES

It has been convincingly established that intensive glycemic control plays an important role in the prevention of microvascular disease in patients with type 2 diabetes. However, even

Table 1. Risk Factors for Vascular Disease That Determine Participant Inclusion in ADVANCE (at least one required)

History of Major Cardiovascular Disease	History of Major Microvascular Disease	Other Risk Factors
Myocardial infarction	Macroalbuminuria	Age ≥ 65 yr
Stroke	Retinal photocoagulation treatment proliferative retinopathy	Diagnosis of type 2 diabetes made ≥ 10 yr previously
Hospital admission for TIA	Macular edema	Current smoking
Hospital admission of unstable angina pectoris		
CABG	Blindness in either eye, believed to be due to diabetes	Total cholesterol > 6.0 mmol/L
PTCA with or without stent		HDL cholesterol < 1.0 mmol/L microalbuminuria
Peripheral revascularization		
Amputation secondary to vascular disease		

Abbreviations: CABG, coronary artery bypass graft; HDL, high-density lipoprotein; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.

though observational data suggest that glucose concentrations determine the risks of macrovascular events, the UKPDS results neither reliably confirm nor exclude the effects of glucose lowering on this outcomes. Moreover, there is some uncertainty as to whether a more intense glucose-lowering regimen, targeting even lower levels of HbA_{1c}, would lead to further reduction in microvascular events. The lack of conclusive results has caused some uncertainty in clinical practice about the net benefits of an intensive glucose-lowering regimen.

Furthermore, the UKPDS showed that due to the progressive nature of type 2 diabetes, most patients will eventually require a combination of oral antidiabetic agents and/or insulin to maintain glycemic control. Any hypoglycemic therapy that is to succeed in the long term will hence have to be as patient-friendly as possible, taking into account the circumstances of the individual patient.

Similarly, there is strong evidence that blood pressure–lowering drugs have the potential to reduce the risks of microvascular and macrovascular disease in patients with type 2 diabetes. Although most trials have been conducted in hypertensive patients, the results of the HOPE study suggest that lowering blood pressure with ACE inhibitors is beneficial, even in nonhypertensive individuals. As the reductions in blood pressure in the HOPE study are small, one might expect additional benefits from a more intensive effort to lower blood pressure in type 2 diabetes patients. This view is supported in an overview of several trials, suggesting that a more intensive blood pressure–lowering confers larger benefits on stroke and coronary heart disease than a less intensive approach.[32]

THE ADVANCE STUDY

The ADVANCE study has been specifically designed to address these unresolved issues and to provide definitive evidence about risks and benefits of a more aggressive blood pressure–lowering and a more intensive glucose control in individuals at high risk for cardiovascular disease.[33] Hence, the primary objective of the study was to determine the effect of blood pressure control with a fixed low-dose combination of an ACE inhibitor (perindopril) and a diuretic (indapamide) on microvascular and macrovascular events. Similarly, the effect of intensive gliclazide MR–based blood glucose control (HbA_{1c} target of ≤6.5%) on these outcomes in hypertensive and nonhypertensive type 2 diabetic patients at high risk for cardiovascular disease will be assessed, compared with guidelines-based therapy for glycemic control. The fixed low-dose ACE inhibitor–diuretic combination as baseline antihypertensive therapy in this study was chosen as the combination produces a larger effect on blood pressure than does monotherapy with either agent at the same dose.[34] The modified release formulation of gliclazide has been selected as a hypoglycemic baseline therapy as it provides 24-hour blood glucose control in a once-daily dosage and sulfonylureas are established and widely used antihyperglycemic agents in clinical practice.

The ADVANCE study includes more than 10,000 patients with type 2 diabetes at high risk for cardiovascular disease (Table 1). Patients have been enrolled in more than 200 centers in Europe, North America, and Australasia. The study consists of a 2 × 2 factorial design with participants randomly assigned to 2 treatment comparisons: a double-blind comparison of the low-dose perindopril–indapamide combination (2 mg/0.625 mg) versus placebo and an open comparison of intensive gliclazide MR–based therapy ($HbA_{1c} \leq 6.5\%$) compared with a standard guidelines–based glucose-lowering therapy (Fig 1). The primary study outcomes are a composite of macrovascular end points (nonfatal stroke, nonfatal myocardial infarction, and any cardiovascular death) and a composite of microvascular end points (new or worsening nephropathy or diabetic eye disease). Patient treatment and follow-up after randomization is scheduled to continue for an average of 4.5 years for all participants. The final results of this large morbidity-mortality trial are expected for 2007.

SUMMARY

The prevention of fatal and disabling complications of type 2 diabetes is a major challenge for clinicians and health care providers in the years to come. There is substantial evidence that improved control of blood glucose and blood pressure will delay the onset and reduce the severity of diabetic complications. However, better proof is needed about the overall balance of benefits and risks associated with intensive, target-driven

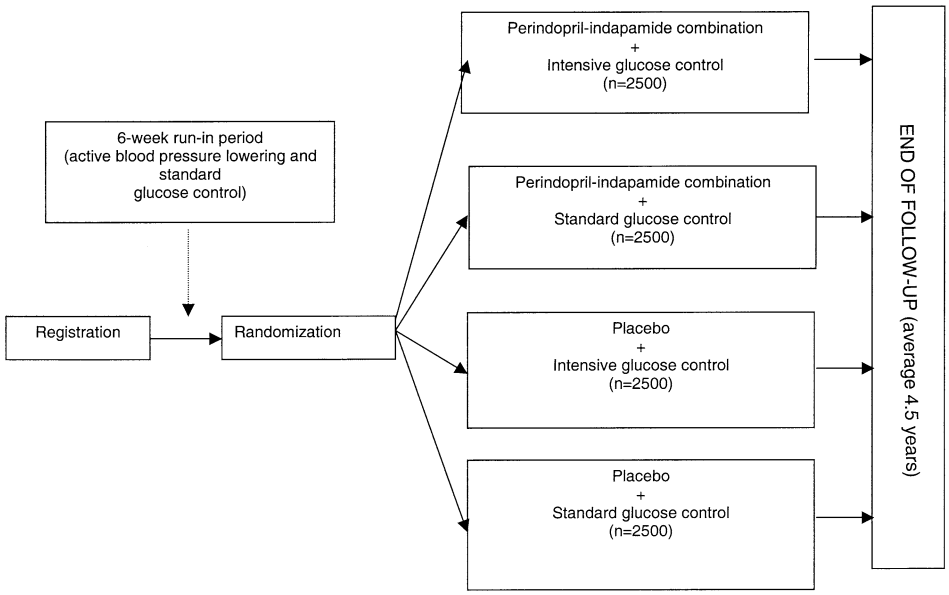

Fig 1. Study design of the ADVANCE study.

blood pressure and blood glucose control in type 2 diabetes patients at high risk for cardiovascular disease. Powerful intervention and prevention trials in type 2 diabetes are therefore needed to provide reliable evidence on these questions. The ADVANCE trial has been designed to provide these answers and as a result of its design close to clinical practice, the results will have important implications for decisions concerning the management of type 2 diabetic patients.

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