Cardiovascular Risk in Type 2 Diabetes – Reflecting on the ADVANCE Study

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Abstract

The world is facing an unprecedented increase in type 2 diabetes. Most disability and premature mortality experienced by patients with diabetes is related to vascular disease and, in particular, macrovascular disease (such as coronary heart disease and stroke) and microvascular disease (such as retinopathy, nephropathy and neuropathy). Indeed, around 1.9 million cardiovascular deaths worldwide are attributable to high blood glucose levels and diabetes, as well as to their associated dangerous companions of high blood pressure and abnormal lipid levels. The global economic costs of diabetes, including foregone economic growth and increasing healthcare expenditure, are substantial and are anticipated to grow. Therefore, strategies to reduce disease burden have continued to focus on reducing cardiovascular risk. Recently, a number of large-scale clinical trials have evaluated approaches for managing cardiovascular risk in patients with type 2 diabetes. Among them the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) trial has reported the effects of blood pressure lowering and intensive glucose control on major vascular events in patients with established type 2 diabetes. In this article we summarise the findings of the ADVANCE trial and discuss its relevance to the management of cardiovascular risk in patients with type 2 diabetes worldwide.

Keywords

Type 2 diabetes, cardiovascular risk, mortality, complications, blood pressure treatment, glycaemic control, clinical trials

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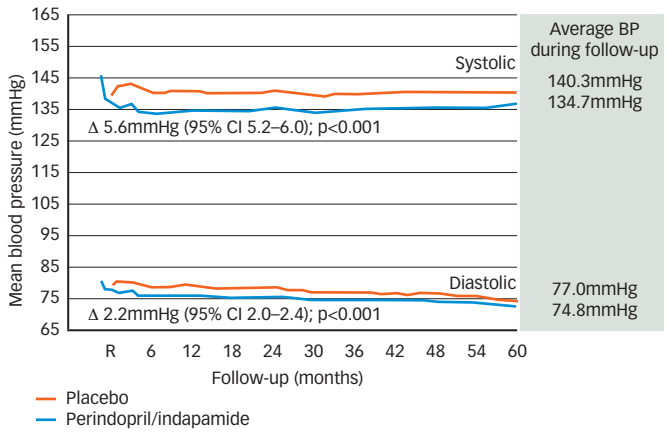
Summary of the ADVANCE Trial Findings

The ADVANCE trial was a factorial, randomised study of 11,140 individuals with type 2 diabetes from over 200 collaborating centres in 20 countries from Asia, Australasia, Europe and North America. Participants with either a history of macrovascular or microvascular disease or at least one major risk factor for cardiovascular disease and any initial level of blood pressure (BP) and blood glucose were randomly assigned to the fixed combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril and the thiazide diuretic indapamide (4/1.25mg) or matching placebo and to intensive glucose control or standard guideline-based glucose control.[1,2] The glucose-lowering regimen for those randomised to intensive glucose control was based on the modified-release sulphonylurea gliclazide-MR 30–120mg daily. However, non-pharmacological approaches, other oral agents and insulin were recommended to be added as required to achieve the target glycated haemoglobin (HbA_{1c}) level of ≤6.5%.[2] The choice of additional treatments was left to the discretion of the responsible physician. Participants randomised to standard guidelines-based glucose control were permitted to use sulphonylureas (other than gliclazide) and any other available glucose-lowering therapy, including insulin. The primary outcomes were composites of major macrovascular (non-fatal acute myocardial infarction, non-fatal stroke and cardiovascular death) and major microvascular events (new or worsening nephropathy and microvascular eye disease), analysed jointly and separately. The average duration of follow-up was 4.3 years for the BP-lowering intervention and five years for the glucose control intervention.[1,2]

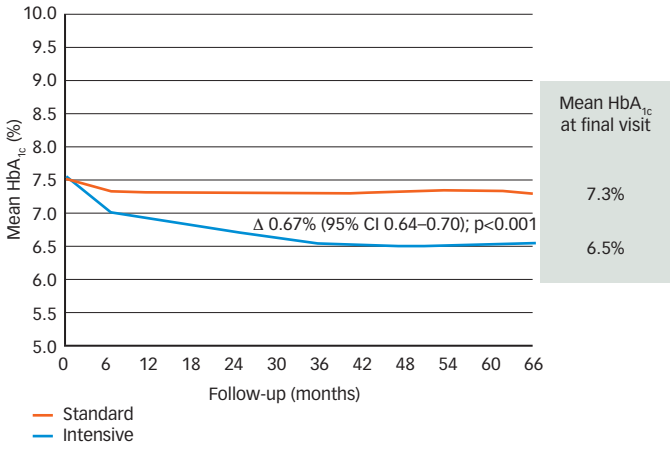
In the BP-lowering arm of the study, the mean entry BP of participants was 145/81mmHg, with over 40% recording a BP below 140/90mmHg.[1] Over the duration of active treatment, BP was reduced by a mean of 5.6/2.2mmHg compared with placebo. At the end of follow-up the mean BP achieved was 134.7/74.8mmHg in the active treatment group and 140.3/77.0mmHg in the placebo group (see *Figure 1*).[1] Active treatment reduced the risk of the combined composite primary outcome of macrovascular and microvascular events by 9% (95% confidence interval [CI] 0–17; p=0.043). The effects on major macrovascular events considered separately were of similar magnitude but not statistically significant (see *Figure 2*).[1] Among those on active treatment, there was a 14% (95% CI 2–25; p=0.025) reduction in all-cause mortality, driven by an 18% (95% CI 2–32; p=0.027) reduction in cardiovascular mortality, as well as reductions in coronary events (14%; p=0.02) and renal events (21%; p=0.0001). No statistically significant reductions were observed in cerebrovascular events or microvascular eye disease. There was no

Figure 1: Blood Pressure



Mean systolic and diastolic blood pressure during run-in on active treatment and after randomisation to active treatment or placebo in the blood pressure lowering arm of the ADVANCE trial.[1]

Figure 3: Glycaemic Control



Glycaemic control at baseline and during follow-up, according to glucose control strategy, in the ADVANCE trial.[2]

Figure 2: Key Results from the ADVANCE Trial

Effects of Blood Pressure Lowering (ΔBP = 5.6/2.2mmHg)

	Number of Events				
	Per/Ind (n=5,569)	Placebo (n=5,571)	Favours Per/Ind	Favours Placebo	Relative Risk Reduction (95% CI)
Primary End-points					
Combined macro + micro	861	938			9% (0 to 17)
Macrovascular events	480	520			8% (-4 to 19)
Microvascular events	439	477			9% (-4 to 20)
Mortality					
All-cause death	408	471			14% (2 to 25)
Cardiovascular death	211	257			18% (2 to 32)
Renal End-points					
New/worsening nephropathy	181	216			18% (-1 to 32)
New microalbuminuria	1,094	1,317			21% (14 to 27)
New macroalbuminuria	114	163			31% (12 to 46)

0.5 1.0 2.0
Hazard ratio

Effects of Blood Glucose Lowering (ΔHbA$_{1c}$ = 0.7%)

	Number of Events				
	Intensive (n=5,569)	Standard (n=5,571)	Favours Intensive	Favours Standard	Relative Risk Reduction (95% CI)
Primary End-points					
Combined macro + micro	1,009	1,116			10% (2 to 18)
Macrovascular events	557	590			6% (-6 to 16)
Microvascular events	526	605			14% (3 to 23)
Mortality					
All-cause death	498	533			7% (-6 to 17)
Cardiovascular death	253	289			12% (-4 to 26)
Renal End-points					
New/worsening nephropathy	230	292			21% (7 to 34)
New microalbuminuria	1,318	1,434			9% (2 to 15)
New macroalbuminuria	114	163			31% (13 to 45)

0.5 1.0 2.0
Hazard ratio

Per/Ind = perindopril/indapamide.

evidence of heterogeneity in treatment effect in subgroups of participants defined by key baseline characteristics. In particular, the effects of the treatment were similar across a range of initial BP levels and regardless of use of concomitant therapies (including ACE inhibitors, statins and aspirin).[1]

In the glucose-lowering arm, the mean entry HbA$_{1c}$ of participants was 7.5%, with 91% already receiving oral hypoglycaemic agents.[2] By the end of follow-up of those in the intensive control group and standard care group, respectively, 92 and 59% were receiving sulphonylurea, 74 and 67% metformin, 40 and 24% insulin and 17 and

11% thiazolidinediones. Intensive glucose control resulted in a mean HbA_{1c} of 6.5%, compared with 7.3% in the standard arm, to produce an average difference during follow-up of 0.7% between the groups (see *Figure 3*).[2] In addition, the target HbA_{1c} of 6.5% or less was achieved by 65% of those assigned intensive glucose control, compared with 29% of those assigned standard care. Intensive glucose control reduced the incidence of combined major macrovascular and microvascular events by 10% (95% CI 2–18; p=0.01). This was primarily due to a significant 21% reduction in the incidence of new or worsening nephropathy. There were no significant effects of intensive glucose control on major macrovascular events (relative risk reduction [RRR)] 6%, 95% CI -6 to 16; p=0.32) (see *Figure 2*), cardiovascular mortality (RRR 12%, 95% CI -4 to 26; p=0.12) or all-cause mortality (RRR 7%, 95% CI -6 to 17; p=0.28).[2] The treatment effects were consistent across a range of participant subgroups defined by key baseline characteristics, including duration of diabetes and prior history of macrovascular or microvascular disease (p>0.1 for heterogeneity for all comparisons).[2]

As expected, in the glucose control arm severe hypoglycaemia was more frequent with intensive glucose control (0.7 cases per 100 patient-years) than with standard care (0.4 cases per 100 patient-years).

Safety and Tolerability of the ADVANCE Trial Interventions

The fixed combination of perindopril and indapamide was well tolerated. At the end of follow-up, 73 and 74% of patients in the active treatment and placebo groups, respectively, remained adherent to their randomised treatment.[1] Serious suspected adverse drug reactions leading to discontinuation were reported in 47 (0.8%) of patients on active treatment and 31 (0.6%) of patients on placebo. These included 14 cases of hyperkalaemia (six active, eight placebo), two cases of hypokalaemia (two active) and five cases of hyponatraemia (four active, one placebo). There were also five non-fatal cases of angioedema (three active, two placebo).[1]

As expected, in the glucose control arm severe hypoglycaemia was more frequent with intensive glucose control (0.7 cases per 100 patient-years) than with standard care (0.4 cases per 100 patient-years).[2] However, the overall incidence of severe hypoglycaemia in ADVANCE was much less than that reported by other studies of more intensive glucose lowering.[3–5] In addition, there was no increase in mean bodyweight among patients randomised to intensive glucose control, but a small reduction in mean bodyweight among those allocated to standard glucose control, so the mean bodyweight of the participants in the intensive arm was 0.7kg higher than in the standard care arm at the end of follow-up (p<0.001).[2] No increase in death was observed with intensive glucose control compared with standard glucose control.[2]

Treatment of Blood Pressure in Type 2 Diabetes

BP is a particularly important determinant of the risk of macrovascular and microvascular complications in patients with type 2 diabetes.[6,7] In observational analyses, systolic BP levels have been shown to be linearly associated with the risks of myocardial infarction and microvascular events.[8] Although the strength of the association appears to attenuate somewhat with age, BP remains a leading determinant of risk in both older and younger individuals.[9] The effectiveness of BP lowering in patients with type 2 diabetes has been consistently observed in trials of individuals with hypertension.[10–15] Current treatment guidelines recommend aiming for a target BP level of 130/80mmHg or lower, with initial therapy including an ACE inhibitor or an angiotensin receptor blocker.[16] However, observational data demonstrating a continuous association between BP and cardiovascular risk have been largely ignored despite suggesting potential benefits of BP lowering for a broader range of people with diabetes. In addition, the relative benefits of specific therapeutic regimens continue to be debated. The recently published results of the ADVANCE trial are therefore highly relevant to these important clinical questions.

The BP-lowering arm of the trial indicated that, regardless of initial BP level, the presence or absence of hypertension and any other treatment being taken, routine administration of the fixed combination of perindopril and indapamide to individuals with type 2 diabetes was well tolerated and reduced the risk of death and major vascular events.[1] In addition, the results suggested that treatment with a single tablet of perindopril–indapamide once daily would prevent one major vascular event among every 66 patients, one death among every 79 patients, one coronary event among every 75 patients and one renal event among every 20 patients treated for five years.[1] From a global perspective, if only half of all patients with type 2 diabetes were to be treated with the fixed combination of perindopril and indapamide over five years, over 1.5 million deaths would be prevented. The trial thus highlighted the potential benefits of an alternative effective strategy for delivering a BP-lowering treatment to patients with a broader range of BPs, including those with 'normal' BP, and a strategy that would also be applicable to the vast majority of patients who fail to reach recommended BP targets.

Treatment of Glucose Levels in Type 2 Diabetes

Epidemiological studies have also demonstrated a strong relationship between the level of glycaemic control (HbA_{1c}) and risks of macrovascular and microvascular complications in people with type 2 diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS) of newly diagnosed individuals with type 2 diabetes, for example, each 1% higher level of mean HbA_{1c} level was associated with an approximate 14% greater risk of all-cause death, 14% greater risk of myocardial infarction and 37% greater risk of microvascular disease.[17] Tight glucose control in the UKPDS was also

The overall incidence of severe hypoglycaemia in ADVANCE was much less than that reported by other studies of more intensive glucose lowering.

shown to produce significant reductions in the risk of microvascular events but only a non-significant trend towards a reduction in myocardial infarction.[3,18] In combination, the observational data and the randomised evidence provided by the UKPDS provided support for the notion that strategies that lowered glucose levels to below those achieved in the UKPDS should further reduce the risks of macrovascular and microvascular outcomes. As such, clinical guidelines universally recommend target HbA_{1c} values of 7 or 6.5% for the prevention of both microvascular and macrovascular disease complications. However, the effects of strategies achieving target HbA_{1c} levels below 6.5%, or indeed below 7%, on macrovascular events in patients with type 2 diabetes, have not been examined, and the generalisability of the UKPDS results to a broader population of patients with type 2 diabetes, including patients with long-standing disease, remain untested. In this context, the ADVANCE findings were important and timely.

The results of the blood-glucose-lowering arm of the ADVANCE trial indicated that HbA_{1c} values at or below levels currently recommended by most guidelines could be safely achieved in patients with long-standing type 2 diabetes using the regimen employed in ADVANCE.[2] In the short term, this approach did not reduce the risks of major cardiovascular events, but it did reduce the risk of new or worsening nephropathy.[2] As worsening albuminuria and progressive renal dysfunction are strongly associated with increased risk of major cardiovascular events, end-stage renal disease and death in patients with type 2 diabetes, the renal effects may yet prove beneficial for long-term cardiovascular risk. As expected, an increased incidence of hypoglycaemia was observed among patients in the intensive glucose control compared with standard control arms.[2] Overall, the incidence of severe hypoglycaemia was much lower than that reported in other trials of intensive glucose lowering. Using this approach, intensive glucose control was not associated with increased mortality, rather a small, non-significant reduction of 7% in all-cause death.[2]

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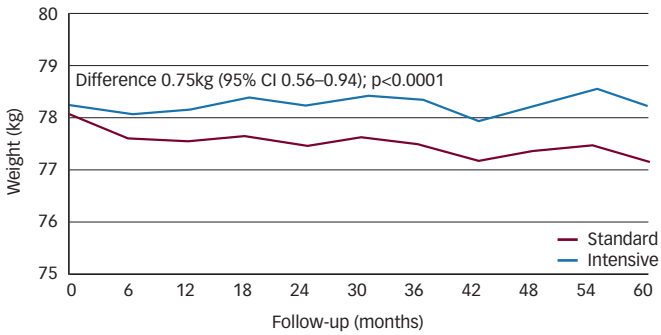
In contrast, two other recent large-scale clinical trials of intensive glucose lowering (achieved HbA_{1c} range 6.4–6.9%) in patients with type 2 diabetes (the Action to Control Cardiovascular Risk in Diabetes [ACCORD] and VA Trial of Glycemic Control and Complications in Diabetes Mellitus Type 2 [VADT]) have reported no significant effects of intensive versus standard glucose control on all combined major macrovascular events (ACCORD and VADT) or microvascular events (VADT).[4,5] In fact, the ACCORD trial, targeting an HbA_{1c} level of less than 6% and conducted in a different population in North America, was terminated prematurely due to a 22% increase in the risk of all-cause mortality with intensive compared with standard glucose control, and questioned the safety of intensive glucose lowering in older patients with diabetes of longer duration and existing cardiovascular complications.[4] However, the ACCORD trial also demonstrated a 24% decrease in the risk of non-fatal myocardial infarction with intensive compared with standard glucose control and significant heterogeneity in treatment effects across patient subgroups, with macrovascular benefits suggested for those with HbA_{1c} levels less than 8% or those without prevalent cardiovascular disease.[4]

Table 1: Comparison of Key Baseline Characteristics of Patients in the ADVANCE, ACCORD and VADT Trials

	ADVANCE (n=11,140)	ACCORD (n=10,251)	VADT (n=1,791)
Mean age (years)	66	62	60
Mean duration of diabetes (years)	8	10	11.5
Mean baseline HbA_{1c} (%)	7.5	8.3	9.4
Prior vascular disease (%)	32	35	40
Insulin use at study entry (%)	1.4	35	52

Figure 4: Effects of Glucose Control Strategy on Bodyweight in the ADVANCE Trial



ACCORD, like ADVANCE, was a large, well-designed and rigorously conducted factorial clinical trial of patients with established type 2 diabetes, whereas VADT was a much smaller study of mainly male patients with longer disease duration and inadequate glycaemic control on maximum oral or insulin therapy.

Assuming the adverse mortality effects in ACCORD were not due to chance, there are a number of explanations for the different findings in the three trials. One is that ACCORD, VADT and ADVANCE studied different types of patients (see *Table 1*), and another is that the different approaches taken to intensive glucose control in the three trials led to the differing results. However, *post hoc* analyses of patient subgroups defined by duration of diabetes and previous history of cardiovascular disease in ADVANCE did not reveal any significant heterogeneity in the treatment effects on-all cause mortality. Another explanation is that ACCORD and VADT used an aggressive strategy with early implementation of a regimen using multiple oral hypoglycaemic agents, as well as insulin, whereas ADVANCE used a more incremental approach with progressive intensification over a much longer time-frame. This is reflected in the high proportion of patients in the intensive glucose control arm of ACCORD who eventually took insulin (77%) and thiazolidinediones (92%), whereas ADVANCE had a slower rate of decline of HbA_{1c} in the intensive arm, with more than 90% on a sulphonylurea (gliclazide-modified release) but only 40% on insulin and 17% on thiazolidinediones by the end of follow-up. As a consequence, most of the reduction in HbA_{1c} achieved in the intensive group in ACCORD

and VADT was observed within six to eight months, whereas the decline in ADVANCE occurred over three years. Almost certainly as a consequence of the different strategies for intensive glucose control utilised, the rate of severe hypoglycaemia (using comparable definitions) in ACCORD and VADT was more than six times that observed in ADVANCE (approximately 16.1% over 3.5 years in ACCORD and 15.1% over 5.6 years in VADT compared with 2.7% over five years in ADVANCE).[2,4,5] There were also significant differences in the mean weight gain in these three studies. In the ACCORD and VADT trials, the mean weight gain from baseline was 3.5 and 4kg in those on intensive glucose lowering, respectively, whereas in the ADVANCE trial there was no weight gain among patients in the intensive glucose lowering arm (see *Figure 4*).[2,4,5]

A recent report from the UKPDS[19] has also provided a strong indication that the reason for the apparent lack of effect on macrovascular outcomes in ADVANCE, ACCORD and VADT could be because the full effects of glucose lowering do not evolve until many years after the intervention has commenced. The post-trial follow-up study demonstrated that the differences in HbA_{1c} between the two originally assigned intervention groups (intensive treatment with sulfonylurea and insulin versus conventional treatment) were lost within one year of the study ending, yet relative risk reductions were maintained at 10 years for diabetes-related outcomes (9%; p=0.004) and microvascular disease (24%; p=0.001), and new significant benefits on cardiovascular outcomes and all-cause mortality emerged.[19] These positive findings of a 'legacy' effect of intensive glucose control urgently require confirmation in other larger studies of more diverse populations with long-standing diabetes. If the effects observed in the post-UKPDS trial are indeed confirmed, this will have enormous implications for the management of type 2 diabetes.

Conclusions

The results of ADVANCE provide additional guidance to help prevent many of the devastating vascular complications of type 2 diabetes. The findings of the BP-lowering arm of the study provide a strong basis for clinicians to recommend routine BP lowering for the vast majority of patients with type 2 diabetes. The evidence from the glucose control arm suggests that clinicians should consider a pragmatic and progressive glucose control strategy to improve microvascular renal disease and long-term cardiovascular risk. These findings add to the compelling evidence for a multifactorial approach that includes statin therapy, smoking cessation, BP lowering and glucose control. Widespread implementation of a comprehensive management strategy addressing all cardiovascular risk factors is essential for combating the global epidemic of diabetes with its ever-increasing burden of cardiovascular disease. ■

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John Chalmers is Emeritus Professor of Medicine at the University of Sydney and Senior Director of the George Institute for International Health in Sydney. His research has focused on the prevention of cardiovascular diseases in high-risk groups, including those with diabetes, elevated blood pressure and previous stroke. Professor Chalmers was the principal investigator for the ADVANCE and PROGRESS trials and one of the founders of the Blood Pressure Lowering Treatment Trialists' Collaboration.

Anushka Patel is Director of the Cardiovascular Division at the George Institute, a consultant cardiologist at Royal Prince Alfred Hospital and an Associate Professor of Medicine at the University of Sydney. She was Study Director and a member of the Steering Committee of the ADVANCE study. Dr Patel has an MSc in epidemiology from Harvard University and a PhD in medicine from the University of Sydney.

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