Major journals

The long-term effects of early glycaemic control and blood pressure lowering in type 2 diabetes

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Data from interventional studies involving both patients with type 1 diabetes (e.g. the DCCT–EDIC [Diabetes Control and Complications Trial–Epidemiologic Diabetes Intervention and Complications Trial]) and those with type 2 diabetes (e.g. the UKPDS [UK Prospective Diabetes Study]) have previously shown that earlier periods of intensive glucose control, but not blood pressure (BP) lowering, have long-term beneficial effects on a range of outcomes, including mortality and macrovascular events (Nathan et al, 2005; Holman et al, 2008a; 2008b). In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, the investigators assessed the effects of routine BP lowering and intensive glucose control on outcomes in people with type 2 diabetes. BP lowering was associated with a reduction in the risk of the primary composite endpoint of major macrovascular and microvascular events, along with reductions in the risk of death from any cause, death from cardiovascular (CV) causes and nephropathy. Intensive glucose control was also associated with a reduction in the risk of the primary endpoint, owing primarily to a reduction in the incidence of new or worsening nephropathy. The latter benefit included a reduction in the incidence of end-stage renal disease but not of death from renal disease. No clear protective or harmful effects of intensive glucose control in terms of all-cause death or major macrovascular events were identified.

In the current study, surviving ADVANCE participants took part in a 6-year post-trial follow-up evaluation, with the comparison of glucose control versus placebo extending for an additional 6 months. The baseline characteristics were similar between the original 11 140 participants and the 8494 who participated in the follow-up extension. The between-group differences in BP and HbA_{1c} observed in the original trial follow-up were no longer significant in the post-trial assessments. The reductions in all-cause and CV death in the group receiving active BP control remained significant but were weakened in the post-trial follow-up, with hazard ratios (HRs) of 0.91 (95% confidence interval [CI], 0.84–0.99; $P=0.03$) and 0.88 (95% CI, 0.77–0.99; $P=0.04$), respectively. There were no differences in the risk of all-cause death or major macrovascular events between the standard and intensive glucose control groups (HR, 1.00; 95% CI, 0.92–1.08 for both endpoints).

The difference in outcomes between this and previous studies of glucose control in people with diabetes may be explained by the differences in response to blood glucose lowering across the different trial populations. The younger people with type 1 diabetes in DCCT–EDIC and those with newly diagnosed type 2 diabetes in the UKPDS were more likely to have long-term benefits from blood glucose control than the older patients with established diabetes who were included in ADVANCE. Furthermore, there were differences between the studies in the levels of glucose control achieved. The between-group difference in HbA_{1c} during the 5-year treatment period in ADVANCE was only 0.67% (7.4 mmol/mol), whereas it was 0.90% (9.8 mmol/mol) in the UKPDS and 2.0% (21.9 mmol/mol) in the DCCT.

The results of the current study, therefore, support the importance of achieving and maintaining good glycaemic control early within the natural history of type 2 diabetes and further highlight the outcome utility of lowering BP in people with this condition. ■

Holman RR, Paul SK, Bethel MA et al (2008a) Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* **359**: 1565–76

Holman RR, Paul SK, Bethel MA et al (2008b) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

Nathan DM, Cleary PA, Backlund JY et al (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* **353**: 2643–53

N Engl J Med

ADVANCE-ON study: Long-term follow-up of earlier glycaemic and blood pressure control in T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In ADVANCE-ON (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation–Observational Study), the authors observed the long-term effects of glycaemic control and blood pressure (BP) lowering in surviving participants from the original ADVANCE trial.

2 In a 2×2 factorial design, the ADVANCE cohort received either a fixed-dose combination of perindopril and indapamide or placebo for a median of 4.4 years, and were also randomised to receive intensive glycaemic control or standard local care for 5.0 years; after these periods finished, they returned to standard local care.

3 Around 3 years after discontinuing therapy, 8494 of the original 11 140 participants were recruited to ADVANCE-ON and followed up for a further 6 years.

4 There was no difference in the primary outcomes (all-cause death and a composite of non-fatal myocardial infarction, non-fatal stroke, or death from any cardiovascular cause) either during ADVANCE or the extended follow-up between the intensive and standard glycaemic control groups.

5 However, the difference in the primary outcomes between the BP control and placebo groups remained significant, although attenuated, in the ADVANCE-ON follow-up (hazard ratios, 0.91 for all-cause death and 0.88 for the composite of major macrovascular events).

Zoungas S, Chalmers J, Neal B et al (2014) Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* **371**: 1392–406

Lancet

The effects of blood pressure-lowering drugs at different BMIs

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this meta-analysis of 135 715 people from 22 trials, the authors compared the effects of different antihypertensive regimens on cardiovascular (CV) risk (stroke, coronary heart disease, heart failure and CV death) in people of differing BMIs.

2 BMI status (normal weight, overweight or obese) did not appear to alter the cardioprotective effects of any of the drug regimens.

3 When BMI was analysed as a continuous variable, angiotensin-converting enzyme inhibitors were slightly more effective than calcium channel blockers (hazard ratio [HR], 0.93; $P=0.004$) and diuretics (HR, 0.93; $P=0.002$); however, the authors caution that this could be a chance finding given the large number of comparisons made in the analysis.

4 They conclude that it is probably unnecessary to select antihypertensive drug classes on the basis of BMI.

Blood Pressure Lowering Treatment Trialists' Collaboration (2014) Effects of blood pressure lowering on cardiovascular risk according to baseline body-mass index: a meta-analysis of randomised trials. *Lancet* 4 Nov [Epub ahead of print]

PLoS One

Cardiovascular risk in people with T2D and MCA stenosis

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 In this prospective cohort study, 2144 Chinese people with T2D and no history of stroke or atrial fibrillation were assessed to determine the association between asymptomatic middle cerebral artery (MCA) stenosis and the risk of cardiovascular disease (CVD; a composite of ischaemic stroke, acute coronary syndrome [ACS] or death from CV causes).

2 MCA stenosis was detected in 264 participants (12.3%) at baseline. Over a median follow-up of 14.5 years, the 10-year cumulative incidence of stroke (20% vs 11%), ACS (24% vs 13%) and CV death (10% vs 4%) was significantly higher in participants with MCA stenosis than those without stenosis, with adjusted hazard ratios of 1.40, 1.35 and 1.56, respectively.

3 The authors conclude that asymptomatic MCA stenosis, as detected with Doppler ultrasonography, increases the risk of CVD in Chinese people with T2D, and that it may be used to guide decisions on starting primary prevention therapy.

Duan JG, Chen XY, Lau A et al (2014) Long-term risk of cardiovascular disease among type 2 diabetic patients with asymptomatic intracranial atherosclerosis: a prospective cohort study. *PLoS One* **9**: e106623

PLoS One

Efficacy of standard and intensive statin regimens in people with diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 In this study, the authors performed two meta-analyses, one comparing standard-dose statins with placebo and the other comparing intensive and standard statin regimens, in terms of efficacy in preventing major cardiovascular (CV) and cerebrovascular events in people with diabetes.

2 Only high-quality, double-blinded randomised controlled trials between 1990 and 2013 were reviewed. This yielded five studies of statins versus placebo ($n=4351$) and four of standard- versus intensive-dose placebo ($n=4805$).

3 Compared with placebo, standard statin regimens resulted in a significantly lower risk of a major CV event over approximately 5 years' mean follow-up (relative risk [RR], 0.85; 95% confidence interval [CI], 0.79–0.91).

4 Compared with standard-dose statins, intensive regimens further reduced this risk (RR, 0.91; 95% CI, 0.84–0.98).

de Vries FM, Kolthof J, Postma MJ et al (2014) Efficacy of standard and intensive statin treatment for the secondary prevention of cardiovascular and cerebrovascular events in diabetes patients: a meta-analysis. *PLoS One* **9**: e111247

> *"The authors conclude that it is probably unnecessary to select antihypertensive drug classes on the basis of BMI."*

PLoS One

Optimal HbA_{1c}, SBP and LDL-cholesterol levels in T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this retrospective cohort study from a single large centre in Taiwan, the authors evaluated the HbA_{1c}, systolic blood pressure (SBP) and LDL-cholesterol levels associated with the lowest all-cause mortality risk in 12 643 adults with T2D.

2 The mean age of the participants was 57.2 years and 50.4% were male. There were 1278 deaths over a mean follow-up of 5.6 years.

3 Mortality risk had a U-shaped association with the three variables, with the lowest hazard ratios (HRs) at an HbA_{1c} of 53–64 mmol/mol (7–8%; HR compared with overall cohort, 0.69), an SBP of 130–140 mmHg (HR, 0.80) and an LDL-cholesterol of 100–130 mg/dL (HR, 0.68).

4 Mortality risk increased significantly at HbA_{1c} levels <42 mmol/mol (6%) and ≥86 mmol/mol (10%); at SBP <120 mmHg and ≥160 mmHg; and at LDL-cholesterol levels <70 mg/dL and ≥160 mg/dL.

Chiang HH, Tseng FY, Wang CY et al (2014) All-cause mortality in patients with type 2 diabetes in association with achieved hemoglobin A(1c), systolic blood pressure, and low-density lipoprotein cholesterol levels. *PLoS One* **9**: e109501