*Intensive Glucose Control*

Patients who were treated with intensive glucose control had a lower mean HbA1c (6.5%) at the final visit in the ADVANCE trial than those who were treated with standard therapy (7.3%; p<0.001). In addition, compared with guideline-based strategy, intensive glucose-lowering therapy prevented major microvascular events (HR=0.86; p=0.01) and diabetic nephropathy (HR=0.79; p=0.006).

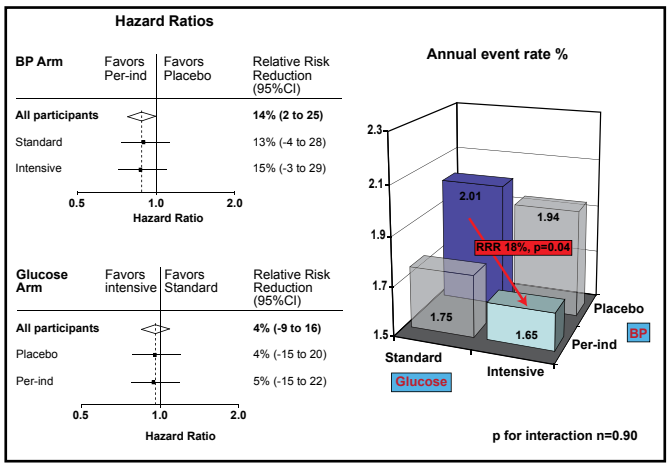
"Treatment with a pragmatic and progressive glucose control regimen, as used in ADVANCE, can help patients to achieve an HbA1c of ≤6.5% and reduce serious complications, especially renal events," Prof. Chalmers said. Intensive therapy was associated with acceptable rates of hypoglycemia and no evidence of weight gain.

*Joint Effects*

Further analysis of ADVANCE outcomes showed that the effects of blood pressure-lowering and intensive glucose control are independent, with no interaction between treatment approaches. In addition, the benefits of these treatment approaches are additive, leading to a greater reduction together than either strategy alone.

Compared with standard glucose control only, the combination of intensive glucose-lowering and blood pressure control reduced the annual risk of new or worsening nephropathy by 33% (p=0.005), reduced the risk of all-cause mortality by 18% (p=0.04; Figure 2), and reduced the risk of cardiovascular death by 24% (p=0.04). Given these clear benefits, the combined strategy of routine blood pressure-lowering and intensive glucose control is indicated for all patients with T2DM, Prof. Chalmers concluded.

**Figure 2. Joint Effects of Blood Pressure Control and Intensive Glucose-Lowering on All-Cause Mortality.**




# Benefits of Early Glucose Control Maintained After 10 Years in UKPDS

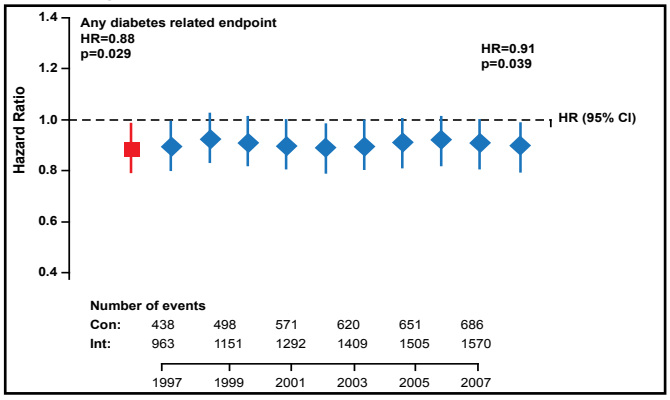
Early intensive glucose-lowering provides long-term protection against major diabetes outcomes as well as myocardial infarction (MI) and all-cause mortality, according to new 10-year follow-up data from the United Kingdom Prospective Diabetes Study (UKPDS). However, the benefits of tighter blood pressure control that were observed in 1997 were not maintained in the 2007 analysis of UKPDS.

The newest UKPDS (ISRCTN75451837) findings represent 30 years of data, including 20 years of active intervention and 10 years of post-trial follow-up data. UKPDS researchers Rury R. Holman, FRCP, and David R. Matthews, DPhil, Oxford Centre for Diabetes, Endocrinology, and Metabolism, Oxford, UK, presented the follow-up findings exactly 10 years to the day after the initial UKPDS findings were reported at the 1998 EASD meeting in Barcelona, Spain. Results also were published online in the *New England Journal of Medicine* (www.nejm.org; DOI: 10.1056/NEJMoa0806359; DOI: 10.1056/NEJMoa0806470).

*Glucose Control*

Between 1977 and 1991, UKPDS randomly assigned patients with newly diagnosed type 2 diabetes mellitus (T2DM) to intensive glucose-lowering with sulfonylurea or insulin treatment (n=2729) or conventional glucose control through diet (n=1138). Compared with conventional treatment, intensive glucose control reduced the risk of major diabetes outcomes by 12% in the 1997 analysis (p=0.029) and by 9% in 2007 (p=0.040; Figure 1). Intensive glucose control also reduced the risk of microvascular disease by 25% in 1997 (p=0.0099) and by 24% in 2007 (p=0.001).

**Figure 1. Long-Term Effects of Early Intensive Glucose-Lowering.**



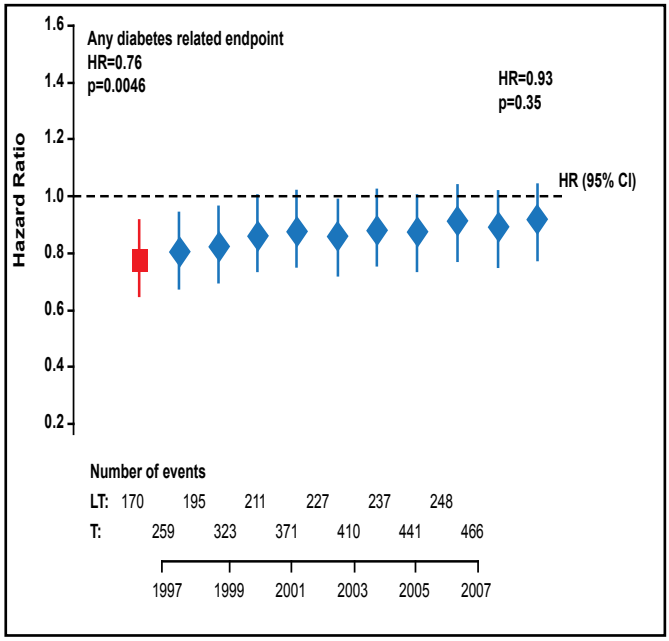
Two additional benefits that are related to intensive glucose control have emerged with longer follow-up. Regarding MI, the relative risk reduction (RRR) that was observed in 1997 (RRR=16%; p=0.052) became statistically significant by 2007 (RRR=15%; p=0.01). In addition, although no effect on all-cause mortality was observed in 1997 (p=0.44), a statistically significant mortality benefit in favor of intensive therapy emerged by 2007 (RRR=13%; p=0.007).

*Blood Pressure Control*

In the UKPDS blood pressure factorial study, 1448 patients with T2DM and hypertension were randomly assigned to tight blood pressure control with an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker, or to less aggressive blood pressure control with any pharmacologic intervention except ACE inhibitor or beta-blocker therapy. Of these patients, 884 continued with post-trial monitoring.

In the 1997 analysis of UKPDS data, tight blood pressure control reduced the risk of any diabetes-related endpoint by 24% versus less aggressive control (p=0.005); this benefit was lost by 2007 (Figure 2). Similarly, the protection against microvascular disease that was shown in 1997 (HR=0.63; p=0.0092) faded in the 2007 analysis (HR=0.84; p=0.020). Blood pressure control did not appear to affect the risk of MI or all-cause mortality at any time point.

**Figure 2. Tight Blood Pressure Control and Diabetes-Related Outcomes.**




## Intensive Therapy Fails to Improve Cardiovascular Outcomes in High-Risk Patients

Intensive glucose-lowering therapy, defined as aiming for HbA1c levels below 7%, improves glycemic control among high-risk patients with type 2 diabetes mellitus (T2DM). However, it has no long-term effect on cardiovascular outcomes in this patient population, according to findings from the Veterans Administration Diabetes Trial (VADT).

VADT (NCT00032487) was designed to evaluate whether intensive control of blood glucose levels would reduce the risk of cardiovascular events compared with standard therapy among 1,791 patients with T2DM who were at high risk for cardiovascular disease (CVD). The primary outcome was a composite of cardiovascular events, including cardiovascular death, myocardial infarction (MI), congestive heart failure, and severe coronary artery disease (CAD); amputation for ischemia; and interventions for CAD and peripheral vascular disease.

Compared with other recent trials of standard versus intensive glycemic control such as ADVANCE and ACCORD, VADT enrolled patients with a longer duration of T2DM and more severe cardiovascular risk, said VADT Co-Chair William Duckworth, MD, Veterans Administration Medical Center, Phoenix, AZ. The VADT study population included mostly male (97%), older patients (mean age, 60 years) with high background cardiovascular risk. At baseline, the mean HbA1c was 9.5%. Patients tended to be obese (mean body mass index, 31 kg/m$^2$), 72% of patients had high blood pressure (mean, 132/76 mm Hg), 50% had an abnormal lipid profile, and 40% had a history of MI, angina, bypass surgery, stroke, or transient ischemic events. In addition, 43% had diabetic neuropathy at baseline, and 62% had retinopathy.

After a median of 6 years, patients in the intensive-treatment arm had a lower HbA1c (6.9%) than those in the standard-treatment arm (8.4%). As expected, compared with standard therapy, intensive glucose control was more likely to lead to episodes of mild hypoglycemia (77.1% vs 93.4%; p=0.01) and severe hypoglycemia (9.7% vs 21.1%; p=0.01).

Despite differences in glucose control, there was no difference in the time to primary outcome between the two treatment groups (p=0.12). Moreover, compared with standard therapy, intensive glucose control had no affect on the risk of all-cause mortality (HR=1.065; p=0.67).