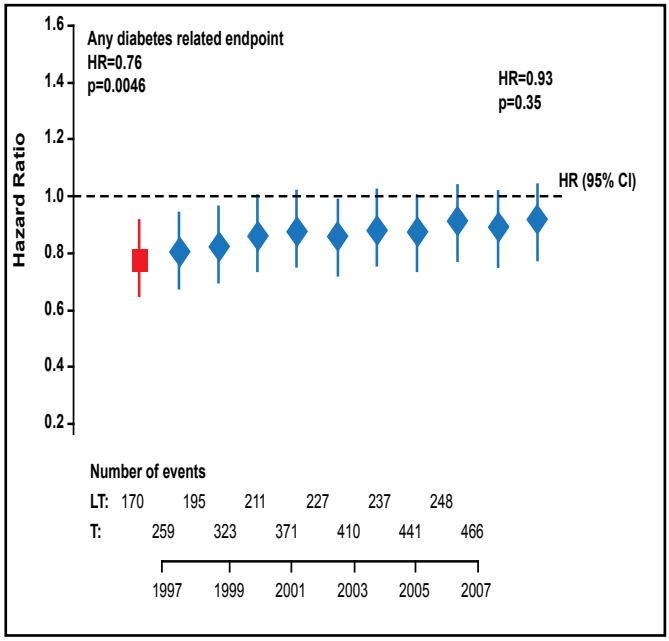
Two additional benefits that are related to intensive glucose control have emerged with longer follow-up. Regarding MI, the relative risk reduction (RRR) that was observed in 1997 (RRR=16%; p=0.052) became statistically significant by 2007 (RRR=15%; p=0.01). In addition, although no effect on all-cause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

Interestingly, the VADT investigators found that patients with a shorter duration of T2DM were more likely to benefit from intensive therapy (p<0.0001). This suggests that the damage inflicted by many years of T2DM is too great for even intensive therapy to overcome, Dr. Duckworth said. However, if verified, these data support the use of intensive therapy early in the treatment of T2DM, he concluded.

Candesartan Slows the Onset of Retinopathy in Patients with Type 1 Diabetes

Treatment with an angiotensin-II receptor blocker (ARB) may slow the development of retinopathy among patients with type 1 diabetes, according to findings from the Diabetic Retinopathy Candesartan Trials (DIRECT) Study Programme. Although the primary endpoint was not met, secondary findings suggest that inhibition of the renin-angiotensin system (RAS) may lessen the risk of microvascular complications in this patient population.

The DIRECT Programme involves 3 randomized controlled studies that enrolled a total of 5231 patients with type 1 or type 2 diabetes mellitus. The DIRECT-Protect 1 and DIRECT-Protect 2 trials were designed to evaluate the effect of candesartan on the progression of retinopathy in patients with type 1 and type 2 diabetes mellitus, respectively.

Nishi Chaturvedi, MD, Imperial College, London, UK, presented findings from the DIRECT-Prevent 1 trial, which was designed to evaluate the effect of candesartan on the incidence of new-onset retinopathy in type 1 diabetes. In DIRECT-Prevent 1, patients with type 1 diabetes who had no existing eye disease were randomly assigned to treatment with candesartan (n=710) or placebo (n=710) for at least 4 years.

Patients (mean age, 30 years) had an average duration of diabetes of 6.7 years at study entry. All patients had normal blood pressure (mean, 116/72 mm Hg) and kidney function (mean urinary albumin excretion rate, 4.5 µg/min).

The primary endpoint was incidence of new retinopathy, as measured by 2-step change on the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale. Candesartan reduced the incidence of diabetic retinopathy by 18% compared with placebo (p=0.0508; Figure 1). In a post hoc analysis that used more stringent criteria for the onset of eye disease (a 3-step change on the ETDRS scale), candesartan reduced the risk of retinopathy by 35% compared with placebo (p=0.003; Figure 2).

Figure 1. 2-Step Change in Retinopathy Incidence.

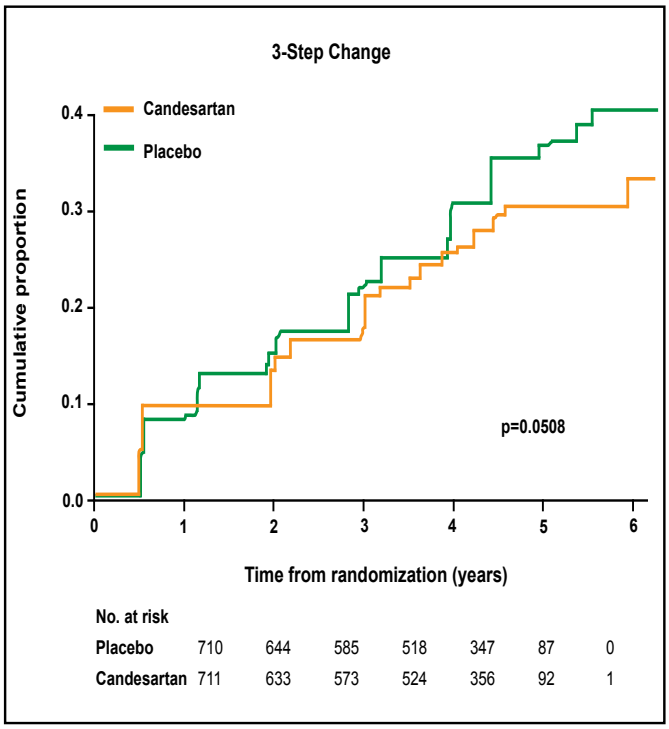
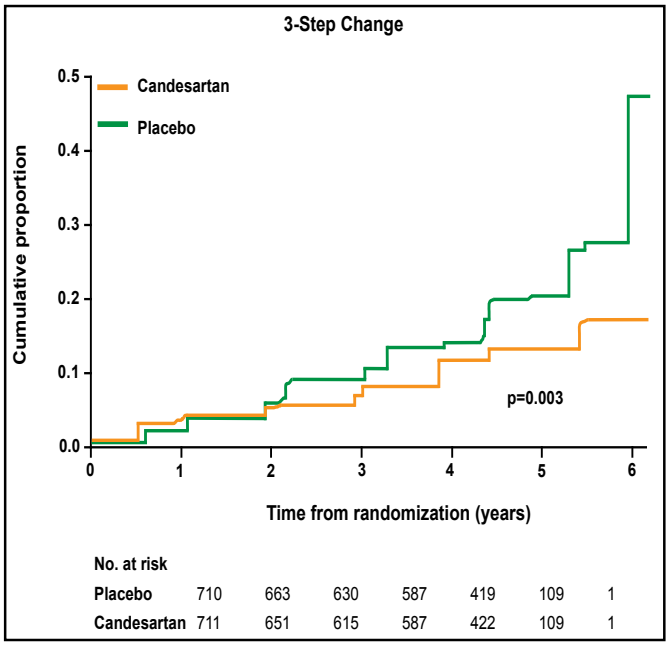


Figure 2. 3-Step Change in Retinopathy Incidence.



Adjustments for baseline blood pressure levels slightly lessened the magnitude of the treatment effect but did not change the overall findings. This suggests that the effects of candesartan on the development of diabetic retinopathy