extend beyond the known blood pressure effects of RAS blockade, Prof. Chaturvedi said.

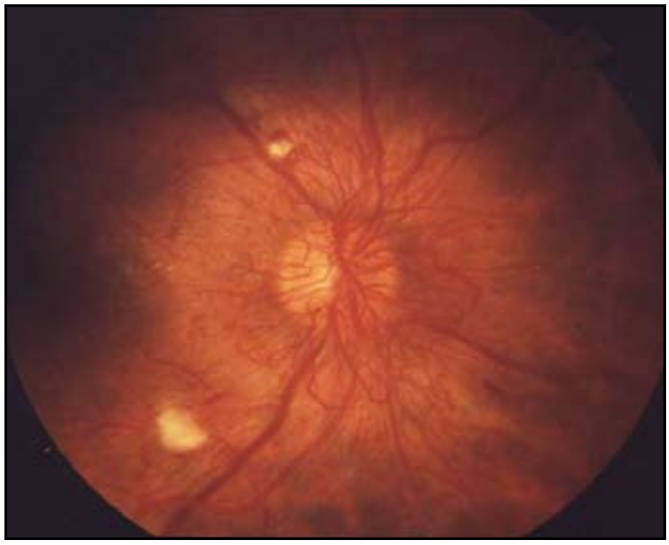
Treatment with candesartan was well tolerated in the DIRECT-Prevent 1 trial. The majority (80%) of patients in the candesartan arm received a daily dose of 32 mg for 4 to 6 years. The most common adverse events (AEs) among all patients were nasopharyngitis, hypoglycemia, hypotension, and headache. A similar proportion of patients in the candesartan and placebo groups experienced any AE (71.1% vs 72.8%) or discontinued study medication due to AEs (3.1% vs 2.5%).

"The take-home message is angiotensin inhibitors are indicated in patients with risk of progression into retinopathy," said Kristian F. Hanssen, MD, PhD, Aker University Hospital, Oslo, Norway. Data from the DIRECT Programme and other trials should be used to develop an algorithm to help clinicians identify retinopathy in patients with type 1 or type 2 diabetes.

Candesartan Reverses Retinopathy in Type 2 Diabetes

Candesartan may have a place in the treatment of retinopathy in patients with type 1 or 2 diabetes, according to findings from the Diabetic Retinopathy Candesartan Trials (DIRECT) study program. The DIRECT-Protect 1 and 2 trials are the first to show the potential benefits of angiotensin-II receptor blockers (ARBs) in patients with baseline diabetic retinopathy (Figure 1).

Figure 1. Diabetic Retinopathy.



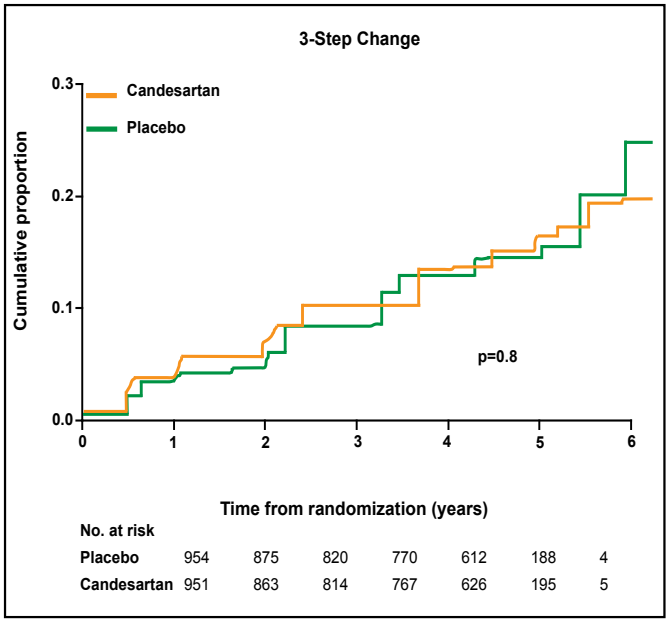
DIRECT-Protect 1 and 2 examined the effect of candesartan on the progression of retinopathy in patients with type 1 or 2 diabetes, respectively. Nishi Chaturvedi, MD, Imperial College London, UK, presented the findings from DIRECT-Protect 1 and was followed by Anne Katrin Sjølie, MD, Odense University Hospital, Denmark, who presented the findings from DIRECT-Protect 2.

No Benefits in Type 1 Diabetes

The DIRECT-Protect 1 trial included 1905 patients with type 1 diabetes and evidence of retinopathy, which was defined as ≥20/10 up to ≤47/47 on the Early Treatment of Diabetic Retinopathy Study [ETDRS] scale. At baseline, all patients had normal blood pressure (≤130/85 mm Hg) and normal albumin levels. The mean age was 32 years, and the mean duration of disease was 11 years.

Patients were randomly assigned to treatment with candesartan (n=951) or placebo (n=954) for at least 4 years. The primary endpoint was progression of retinopathy (measured by 3-step change on the 11-point ETDR Scale). By the end of the trial, candesartan appeared to have no effect on retinopathy progression (HR=1.02; p=0.8; Figure 2).

Figure 2. DIRECT-Protect 1: Change in Retinopathy Progression.



Among patients with type 1 diabetes, the most common adverse events (AEs) were nasopharyngitis, hypoglycemia, hypotension, and headache. A similar proportion of patients in the candesartan and placebo groups

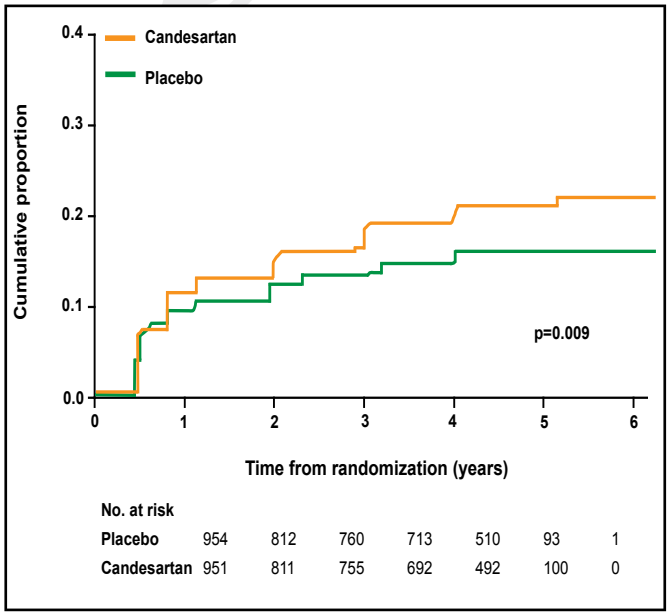
experienced any AE (77.6% vs 75.8%) or discontinued study medication due to AEs (1.8% vs 1.7%).

Reversal of Retinopathy in Type 2 Diabetes

In the DIRECT-Protect 2 trial, 1905 patients with type 2 diabetes and retinopathy were randomly assigned to treatment with candesartan (n=951) or placebo (n=954). At baseline, 62% of patients had elevated blood pressure (>130/85 mm Hg) and required antihypertensive treatment with an agent other than a RAS inhibitor.

Treatment with candesartan was associated with a nonsignificant 13% reduction in the progression of retinopathy (p=0.2). Therefore, DIRECT-Protect 2 failed to meet its primary endpoint. However, candesartan excelled in a secondary endpoint: regression of retinopathy. Patients in the candesartan group were 34% more likely to experience retinopathy regression (p=0.009) when adjusted for baseline level of retinopathy, diabetes duration, HbA1c level, urinary albumin excretion rate, antihypertensive treatment, and systolic blood pressure during the study (Figure 3). A similar proportion of patients in the candesartan and placebo groups experienced any AE (83.9% vs 82.5%) or discontinued study medication due to AEs (3.9% vs 4.4%).

Figure 3. DIRECT-Protect 2: Retinopathy Regression.



"Diabetic retinopathy is one of the most feared and common complications of diabetes, making this an important clinical finding," Prof. Sjølie said. "The reversal of this vision-threatening complication of diabetes has not been reported before in large-scale clinical trials."