Retinopathy

Candesartan: What effects on diabetic retinopathy?

Deborah Broadbent, Director of Diabetic Eye Screening, Royal Liverpool University Hospital

There has been clear evidence that good glycaemic control is important for minimising the development and progression of diabetic retinopathy, but recent interest has centred on the role of blood pressure in the pathophysiology of the disease. Unfortunately, most interventions for diabetic retinopathy are introduced when sight-threatening changes have developed, long after the pathological changes in the capillary are seen.

The United Kingdom Prospective Diabetes Study (1998) showed that good control of blood pressure was as, if not more, important than good glycaemic control in people with type 2 diabetes. This study, however, did not identify a difference between specific antihypertensive agents.

There is a theoretical benefit from the use of inhibitors of the renin–angiotensin system, thought to be independent of their hypertensive action. The European Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Study (EUCLID Study Group, 1997) suggested that blockade using an angiotensin-converting enzyme inhibitor might be protective against the progression of retinopathy. However, the study was not designed to specifically address this question and was under-powered.

The DIRECT (Diabetic Retinopathy Candesartan Trials) programme assessed the effect of candesartan on prevention and progression of retinopathy in type 1 diabetes (Chaturvedi et al, summarised alongside), and the progression and regression of retinopathy in type 2 diabetes (Sjølie et al, summarised below). Individuals were randomised to candesartan or placebo, and 1421 patients with type 1 and 1905 people with type 2 diabetes were recruited.

In those with type 1 diabetes there was a reduction in the incidence of retinopathy, but no effect on progression. In people with type 2 diabetes, there was a reduction in the progression of retinopathy (not quite reaching statistical significance) and a significant increase in regression of retinopathy. Effects were most evident in those with mild retinopathy at baseline.

These two papers provide compelling evidence of the beneficial effect of treatment with candesartan, particularly in people with type 2 diabetes and early disease.

EUCLID Study Group (1997) Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* **349**: 1787–92

UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317**: 703–13

LANCET

Candesartan reduces retinopathy progression in type 2 diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓

1 Blockade of the renin–angiotensin system has not been studied in people with type 2 diabetes and retinopathy.

2 As part of the DIRECT (Diabetic Retinopathy Candesartan Trials) programme, DIRECT-Protect 2 examined the progression of retinopathy in people with type 2 diabetes.

3 In this study, 1905 people with type 2 diabetes and mild-to-moderately severe retinopathy were randomised to candesartan (n=951) or placebo (n=954).

4 Progression of retinopathy was seen in 17% (n=161) of people in the candesartan group and in 19% (n=182) of people in the placebo group.

5 Candesartan reduced the progression of retinopathy by 13% compared with the placebo group.

6 In people in the candesartan group, there was a significant trend towards a change to less severe retinopathy compared with those in the placebo group (P=0.003).

Sjølie AK, Klein R, Porta M et al (2008) Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised, placebo-controlled trial. *Lancet* **372**: 1385–93

LANCET

Candesartan reduces the incidence of retinopathy in type 1 diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓

1 A major complication of diabetes is loss of vision as a result of retinopathy.

2 Previous studies have suggested that diabetic retinopathy could be prevented or slowed by blockade of the renin–angiotensin system.

3 The DIRECT (Diabetic Retinopathy Candesartan Trials) programme was set up to determine whether the angiotensin-receptor antagonist, candesartan, could reduce the incidence of retinopathy in people with type 1 diabetes (DIRECT-Prevent 1) or the progression of retinopathy in people with type 1 diabetes (DIRECT-Protect 1).

4 Participants with type 1 diabetes and no retinopathy entered DIRECT-Prevent 1 (candesartan group n=711; placebo group n=710), and people with type 1 diabetes and present retinopathy entered DIRECT-Protect 1 (candesartan group n=951; placebo group n=954).

5 In DIRECT-Prevent 1, the incidence of retinopathy was 31% (n=217) in the placebo group and 25% (n=178) in the candesartan group, with candesartan causing a relative risk reduction of 18%. This beneficial effect increased to 35% after data adjustments, but did not reach statistical significance.

6 In DIRECT-Protect 1, progression of retinopathy continued in 13% of both the placebo group (n=124) and the candesartan group (n=127), which suggests no beneficial effects but warrants further investigation.

Chaturvedi N, Porta M, Klein R et al (2008) Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. *Lancet* **372**: 1394–402

OPHTHALMOLOGY

Focal/grid photocoagulation is best treatment for DMO

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓

1 Treatments for diabetic macular oedema (DMO) include focal/grid photocoagulation, vitrectomy, pharmacological therapy, intravitreal injection of targeted antibodies and intravitreal injection of corticosteroids (for example triamcinolone acetonide).

2 Although the popularity of using intravitreal triamcinolone for the treatment of DMO has increased, there are no long-term clinical trial results to evaluate the most efficacious dose.

3 The study compared the safety and efficacy of intravitreal triamcinolone at 1 mg and 4 mg doses compared with focal/grid photocoagulation.

4 Of 693 people with DMO, 330 eyes were randomised to focal/grid photocoagulation, 256 eyes to intravitreal triamcinolone 1 mg and 254 eyes to intravitreal triamcinolone 4 mg; outcome was determined at 2 years.

5 Best outcome for visual acuity at 4 months was for the intravitreal triamcinolone 4 mg group, although at 1 year there were no significant differences between treatments.

6 From 16 months to the 2-year follow-up, mean visual acuity was better in the focal/grid photocoagulation group compared with both intravitreal triamcinolone groups (1 mg and 4 mg).

7 Focal/grid photocoagulation was determined as the most effective treatment for DMO, with better visual acuity over 2 years and fewer side effects than comparators.

Diabetic Retinopathy Clinical Research Network (2008) A randomised trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular oedema. *Ophthalmology* **115**: 1447–59

DIABETES CARE

At-risk people avoid retinal screening

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓

1 Digital retinal photography is effective at detecting sight-threatening lesions in people with diabetes.

2 It is unknown what determines screening uptake in this at-risk population.

3 People with diabetes in Tayside, Scotland (n=16 258), underwent digital retinal photography as part of a national retinal screening programme.

4 In total, 12% of retinal screening appointments were missed; risk factors for non-attendance included young age, longer duration of diabetes, poor glycaemic control, high blood pressure, smoking and living in a deprived area.

5 People who were least likely to attend screening were at most risk of developing sight-threatening complications.

Leese GP, Boyle P, Feng Z et al (2008) Screening uptake in a well-established diabetic retinopathy screening program. *Diabetes Care* **31**: 2131–5

OPHTHALMOLOGY

Diabetic retinopathy improves with good glycaemic control

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓

1 This study observed the progression and regression of diabetic retinopathy in 955 people with type 1 diabetes (onset <30 years old) over 25 years.

2 The 25-year cumulative rate of progression of diabetic retinopathy was 83%; progression was significantly associated with male gender, high HbA_{1c} and greater body mass index (BMI) at baseline.

3 The 25-year cumulative incidence of proliferative diabetic retinopathy was 42%; incidence was associated with more severe diabetic retinopathy, high HbA_{1c}, gross proteinuria, systolic blood pressure and greater BMI at baseline.

4 The 25-year cumulative rate of improvement in diabetic retinopathy was 18%; less improvement was associated with being male, high HbA_{1c} and current smoking.

5 Improved management of diabetes, with better glycaemic control, may have reduced the incidence of proliferative diabetic retinopathy and increased the improvement of diabetic retinopathy.

Klein R, Knudtson MD, Lee KE et al (2008) The Wisconsin epidemiologic study of diabetic retinopathy. *Ophthalmology* **115**: 1859–68

AMERICAN JOURNAL OF OPHTHALMOLOGY

Better definitions needed for focal and diffuse DMO

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓

1 The terms "focal" and "diffuse" diabetic macular oedema (DMO) are inconsistently used in the literature, with unclear definitions causing confusion regarding classification.

2 Definitions of focal and diffuse DMO were examined in a literature review to evaluate their effectiveness in classifying DMO.

3 As definitions vary, a new vocabulary would enable better descriptions of the extent and location of macular thickening, with its regional variation, quantity and pattern of lipid exudates and source of fluorescein leakage.

4 New definitions would enable better prediction of treatment outcomes and consistency between studies.

Browning DJ, Altaweel MM, Bressler NM et al (2008) Diabetic macular oedema: what is focal and what is diffuse? *Am J Ophthalmol* **146**: 649–55

"In total, 12% of retinal screening appointments were missed; risk factors for non-attendance included young age, longer duration of diabetes, poor glycaemic control, high blood pressure, smoking and living in a deprived area."