

**Keywords:**  
diabetes,  
diabetic  
retinopathy,  
diabetic  
nephropathy,  
angiotensin II  
type 1 receptor  
blocker,  
candesartan

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Accepted for  
publication  
11th March 2005

JRAAS 2005;6:25–32

## The Diabetic REtinopathy Candesartan Trials (DIRECT) Programme: baseline characteristics

*The DIRECT Programme Study Group*

### Abstract

Renin-angiotensin system blockade has been shown to be superior to other antihypertensive therapy in slowing progression of renal disease in diabetic patients, but questions remain regarding diabetic retinopathy. The primary objective of the Diabetic REtinopathy Candesartan Trials (DIRECT) Programme is to examine primary (incidence) and secondary (progression) prevention of diabetic retinopathy when blocking angiotensin II type 1-receptors with candesartan in normoalbuminuric, normotensive Type 1 diabetic patients, and secondary prevention only in normoalbuminuric, normotensive or treated hypertensive Type 2 diabetic patients. The secondary objectives include examining the effect of candesartan treatment on urinary albumin excretion rate (UAER) in each of the three studies and to examine the incidence of proliferative retinopathy in all three populations combined.

Standardised investigations for patients at enrolment include blood pressure measurement, analysis of HbA<sub>1c</sub> and serum lipids, and a detailed ophthalmological examination. Retinopathy and UAER outcomes are assessed yearly. Retinopathy is graded centrally, based on seven-field stereo photographs using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Randomisation was performed when the results of retinal gradings were available, and treatment with 16 mg candesartan cilexetil or matching placebo was initiated; the dose was increased to 32 mg after one month. Calculations of UAER are based on two timed overnight urine collections.

A sample size re-assessment was carried out when approximately 70% of the patients had been randomised in the DIRECT Programme to ensure the results to be conclusive.

In total, 5,231 patients were randomised in the DIRECT Programme in 30 countries. One thousand, four hundred and twenty one and 1,905 patients are evaluated in the primary and secondary prevention studies in Type 1 diabetes, respectively and 1,905 patients in the secondary prevention study in Type 2 diabetes.

HbA<sub>1c</sub> showed mean values of 8.1, 8.5 and 8.2% for the Type 1 primary, Type 1 secondary and Type 2 secondary prevention studies, respectively. In the Type 1 secondary prevention study, 49% of the patients had mild nonproliferative retinopathy (level 20) in at least one eye, and 9% had moderate-moderately severe non-proliferative retinopathy (level 43–47). In Type 2 patients, 17% had level 43–47 and the remainder less severe retinopathy.

### Introduction

Retinopathy and nephropathy are common and feared complications of diabetes.<sup>1,6</sup> Although laser-photocoagulation for retinopathy and medical treatment for microalbuminuria have delayed or dramatically reduced the impact of complications, not all patients manage to avoid developing blindness and renal failure.<sup>7,8</sup>

Strict glycaemic regulation and blood pressure (BP) control have been shown to reduce the development and progression of retinopathy and nephropathy in Type 1 and Type 2 diabetes.<sup>9–12</sup> In the UK Prospective Diabetes Study (UKPDS), both a  $\beta$ -blocker (atenolol) and an angiotensin-converting enzyme (ACE) inhibitor (captopril) -based therapy used to achieve tight BP control showed a reduction in the need for photocoagulation for sight-threatening retinopathy, mainly diabetic maculopathy, in hypertensive Type 2 diabetic patients.<sup>13</sup>

In the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID) study, a 50% reduction in progression of retinopathy and a significant reduction in the development of proliferative retinopathy were observed,<sup>14</sup> comparing treatment with the ACE-inhibitor (ACE-I) lisinopril versus placebo in 354 out of the 530 normotensive Type 1 diabetic patients. A reduction in the progression of urinary albumin excretion rate (UAER) was also demonstrated. The results from EUCLID were promising, but in this relatively small study retinopathy was not the primary endpoint, and its findings need to be confirmed before changes to clinical practice can be advocated.

The Diabetic REtinopathy Candesartan Trials (DIRECT) Programme was initiated to explore whether blockade of the renin-angiotensin-system (RAS) with the angiotensin II receptor blocker (ARB) candesartan would answer some of the questions that remain from EUCLID and UKPDS, most importantly, whether a reduction in the risk of retinopathy and nephropathy can be obtained by effective RAS blockade. Optimal blood glucose and BP control is not possible in every patient and, even when achieved, retinopathy may still develop.<sup>15</sup> There remains a need for therapeutic interventions in people with diabetes to further reduce these devastating complications.

### Programme design

The DIRECT Programme design and objectives

**Journal of  
the Renin-  
Angiotensin-  
Aldosterone  
System**  
(Including other  
peptidergic systems)

March 2005  
Volume 6  
Number 1













