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REVIEW

Diabetic retinopathy and blockade of the renin–angiotensin system: new data from the DIRECT study programme

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Abstract

The pathogenesis and medical management of diabetic retinopathy is reviewed. The importance of good control of blood glucose and blood pressure remain key elements in the prevention and treatment of diabetic retinopathy, and a number of specific metabolic pathways have been identified that may be useful additional targets for therapeutic intervention. Trial data, however, aimed specifically to answer the questions of optimum medical management are limited, so the DIRECT study of renin–angiotensin blockade using oral candesartan 32 mg daily is a welcome addition to our knowledge. This arose from the promising improvement of retinopathy outcomes in the EUCLID study of lisinopril in type I diabetes. In DIRECT, 5 years of candesartan treatment in type I diabetes reduced the incidence of retinopathy by two or more steps (EDTRS) in severity by 18% ($P = 0.0508$) and, in a *post hoc* analysis, reduced the incidence of retinopathy by three-step progression by 35% ($P = 0.034$). In type I diabetes patients there was no effect on progression of established retinopathy. In contrast, in type II diabetes, 5 years of candesartan treatment resulted in 34% regression of retinopathy ($P = 0.009$). Importantly, an overall significant change towards less-severe retinopathy was noted in both type I and II diabetes ($P \leqslant 0.03$). Although there is still no absolute proof that these effects were specific to RAS blockade, or just an effect of lower blood pressure, it is reasonable to conclude that candesartan has earned a place in the medical management of diabetic retinopathy, to prevent the problem in type I diabetes and to treat the early stages in type II diabetes.

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Introduction

Retinopathy is the commonest and the most feared long-term complication of diabetes mellitus, occurring with increasing frequency and severity in the majority of patients over time. Retinopathy confers substantial burden on quality of life and is not always arrested by laser treatment. Diabetic retinopathy is a complex disease process and understanding the metabolic pathways involved in its development offers promises of future therapies for both prevention and management of established disease.[1]

Pathogenesis of diabetic retinopathy

Microangiopathy and capillary occlusion underlie the pathogenesis of diabetic retinopathy.[2,3] Diabetic macular oedema results from breakdown of the blood–retinal barrier and cotton-wool spots, intra-retinal haemorrhages, and intra-retinal microvascular abnormalities arise with increasing capillary closure. With further retinal ischaemia, proliferative retinopathy develops, which is characterised by the growth of new blood vessels on the surface of the retina and/or on the optic disc.

A key initiating factor in diabetic retinopathy is impaired autoregulation in the micro-vasculature, arising from high intracellular glucose concentrations.[4] A number of other

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biochemical pathways have been identified that modulate the disease process through effects on cellular metabolism, signalling, and growth factors, and these have been reviewed[5] and include oxidative stress, the formation of advanced glycation end products, increased aldose reductase activity, activation of protein kinase C isoforms, and pro-inflammatory gene expression. An increase in vascular endothelial growth factor, a key angiogenic factor implicated in the pathogenesis of diabetic retinopathy,[6] and increased flux through the hexosamine pathway resulting in modulation of transcription factors and pathological changes in gene expression may also be important.

Another potential angiogenic mechanism is the renin–angiotensin system (RAS), which is active both systemically and locally in the eye. Renin, angiotensin-converting enzyme (ACE), and angiotensin II receptors are distributed throughout the retinal and choroidal vessels, and angiotensin has been shown to be an angiogenic growth factor in animal experiments.[7] Plasma and intravitreal concentrations of prorenin are increased in patients with diabetic retinopathy and correlate with its severity.[8] The role of RAS in diabetic retinopathy has been reviewed in detail.[9]

Medical treatment of diabetic retinopathy

Duration of diabetes, the degree of glycaemia, and level of blood pressure, which are the main risk factors for diabetic retinopathy, have been studied extensively. Data from large therapeutic trials monitored with retinal photography are limited, but published results show clear benefits of glucose lowering and blood pressure control,[10–12] and possible benefits of fenofibrate.[13] Despite these current management strategies, an unmet clinical need for preventive therapy and better treatment of established retinal disease remains. Indeed, the strategy of very tight glycaemic and blood pressure control has been questioned by recent data. In the ACCORD study,[14] increased mortality occurred in the tight glucose-control group, and in the ADVANCE study, the incidence of retinopathy was the same in the intensively controlled groups, both for glycaemia and blood pressure.[15,16] In this context, the ACCORD Eye study results will be of particular interest.

An earlier study of the ACE inhibitor, lisinopril, using 10–20 mg daily for 2 years compared with placebo in type 1 diabetes (EUCLID)[17] showed a non-significant reduction in incidence of retinopathy, a significant reduction in the progression of diabetic retinopathy and a trend to regression (Table 1). The exact significance of these findings was weakened by differences in initial and final HbA1c levels in favour of the lisinopril-treated patients.

Table 1 EUCLID study

	Placebo	*Lisinopril*	*Odds ratio*	
			Unadjusted	*Adjusted*[a]
Number of patients	179	175		
Retinopathy				
Baseline[b]	65%	59%		
Progression by at least one step	23.4%	13.2%	0.5 ($P=0.02$)	0.55 ($P=0.07$)
Regression	14%	18%	1.48 ($P=0.2$)	1.41 ($P=0.3$)
Incidence	25%	16%	0.69 ($P=0.4$)	

[a]Adjusted for centre, glycaemic control, and baseline characteristics.
[b]Mostly nonproliferative (<10% photocoagulated or proliferative).

Results from studies of blockade of RAS in retinopathy in patients with type II diabetes, however, have not shown any convincing specific benefits of ACE inhibition—enalapril compared with nisoldipine,[18] captopril compared with atenolol,[12] and perindopril compared with placebo,[16] although ramipril had a non-significant relative risk reduction in requirement for laser treatment in the HOPE study.[19] However, there are difficulties in interpreting the results of many of these trials of medical management of diabetic retinopathy because of the changes in blood pressure and glycaemic control occurring concurrently, which particularly applied to the EUCLID study. An additional difficulty with modern studies arises from the widespread current use of both ACE inhibitors and angiotensin II receptor antagonists for the management of diabetic nephropathy and cardiovascular disease, as well as the general reductions in endpoints due to better overall care of diabetes. Although ACE inhibition will have an effect on both angiotensin-1 and angiotensin-2 concentrations, there is little evidence so far to suggest that the more selective effect of angiotensin-1 receptor blockade has any specific advantages apart from a different side effect profile. A large randomised trial of enalapril and telmisartan showed similar efficacy in renoprotection.[20]

DIRECT trial

The most recent publication on the use of an angiotensin II receptor antagonist in DIRECT (DIabetic REtinopathy Candesartan Trials)[21,22]—the largest trial that has been conducted in diabetic retinopathy—is therefore an important addition to our knowledge. To what extent does this new information merit the conclusions that candesartan may prevent retinopathy in type I diabetes and improve outcome of retinopathy in type II diabetes?

Table 2 DIRECT trial

	Type I diabetes		*Type II diabetes*
	Prevent 1	*Protect 1*	*Protect 2*
Number randomised	1421	1905	1905
Retinopathy in worst eye			
EDTRS scale 20	—	49%	28–20%
35	—	41–43%	53–56%
>35	—	8–10%	15–19%
% of control group starting RAS inhibition during trial	3%	6%	28%
Mean reduction of BP (mm Hg)	2.6/2.7	3.6/2.5	2.9/1.3[a] 4.3/2.5[b]
Reduction incidence of DR			
Two step unadjusted	HR 0.82 ($P=0.0508$)	—	—
Adjusted[c]	HR 0.92 ($P=0.413$)	—	—
Three step unadjusted	HR 0.65 ($P=0.0034$)	—	—
Adjusted[c]	HR 0.74 ($P=0.046$)	—	—
Progression of DR			
Unadjusted	—	HR 1.02 (NS)	0.87 (NS)
Adjusted[c]	—	HR 1.01 (NS)	Not altered
Final EDTRS grade improvement odds ratio	1.16 ($P=0.0048$)	1.12 ($P=0.0264$)	1.17 ($P=0.003$)

DR, diabetic retinopathy; HR, hazard ratio; NS, not significant.
[a]Not on hypotensive drugs.
[b]On hypotensive drugs.
[c]Adjusted for baseline characteristics and changes in blood pressure.

The basic premise of the DIRECT studies was that inhibition of the RAS has additional benefits on diabetic retinopathy specific to this drug group that are independent of effects on blood pressure.

DIRECT was a specific study with diabetic retinopathy as a primary endpoint using photographs graded by standard ETDRS scales. An impressive number of 3326 type I and 1905 type II patients with diabetes were enrolled with a median follow-up of 4.7–4.8 years in the three trials (Table 2). The maximum dose of candesartan 32 mg daily was used and was well tolerated. The terminology describing the three component trials is confusing. Prevention was studied in type I patients only (DIRECT-Prevent 1), whereas progression of established retinopathy was studied in both type I patients (DIRECT-Protect 1) and (DIRECT-Protect 2). Overall glycaemic control as measured by HbA1c did not change in type I patients but, although similar data for type II patients has not been formally published, glycaemic control was reassuringly the same in the actively treated group compared with placebo ($P=0.48$). Candesartan was associated with a small persistent reduction in blood pressure (Table 2). These relatively small changes in blood pressure are important and adjustment for blood pressure attenuated the results in type I, but not in type II patients. The proportion of patients starting ACE inhibitors or angiotensin II receptor antagonists in the placebo group during the trial was small in type I diabetes but significant in type II diabetes (Table 2).

Prevent 1 showed an encouraging effect of candesartan in reducing the incidence of retinopathy (defined as at least two-step deterioration on the EDTRS scale) after 4 years from 31 to 25% (HR 0.82 $P=0.0508$) and remained just nonsignificant after adjusting for changes in baseline characteristics and changes in blood pressure during the trial. A *post hoc* analysis showed that a three-step deterioration of diabetic retinopathy was reduced from 16 to 10.5% (HR 0.65, $P=0.034$) in favour of candesartan, which remained significant after adjustments for the small blood pressure changes (HR 0.74, $P=0.046$).

Protect-1 failed to show any significant difference in progression of established retinopathy by candesartan. However, in Prevent-1 and in Protect-1 studies, final ETDRS levels were better in those on candesartan treatment (odds ratio 1.16, $P=0.0048$ and 1.12 $P=0.0264$, respectively) see Figure 1.

Protect-2 showed a non-significant change in the primary endpoint of progression of diabetic retinopathy (HR 0.87, $P=0.2$) but a significantly greater regression of established diabetic retinopathy (HR 1.34 $P<0.009$), which was a secondary endpoint. Regression was similar when adjusted for baseline characteristics and for changes in blood pressure in the trial. Regression was noted in patients with mild, but not in those with

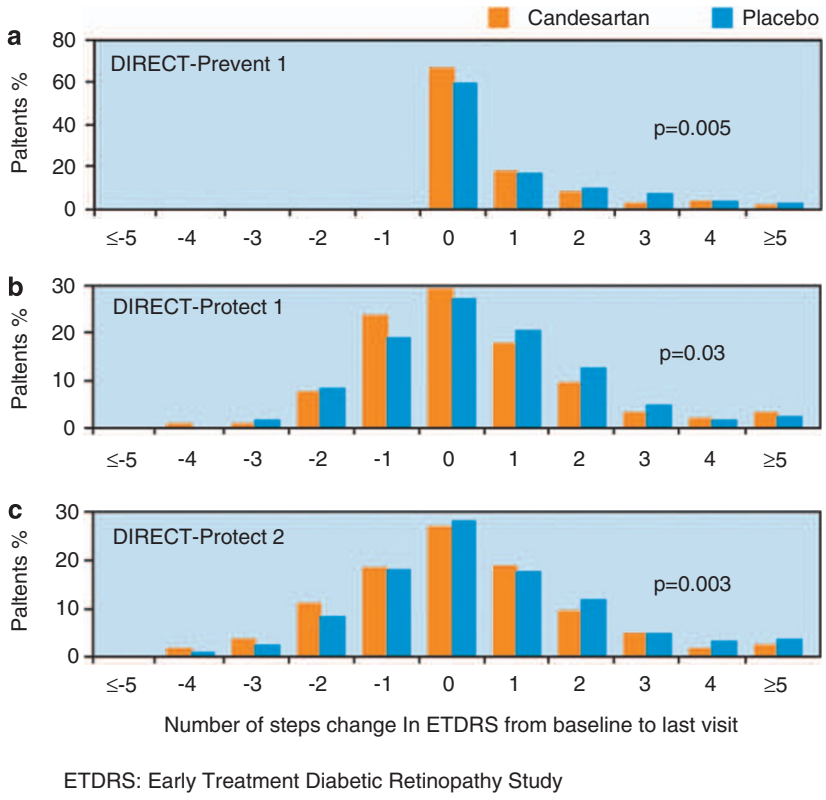

Figure 1 Changes in diabetic retinopathy on completion of DIRECT study. Changes in EDTRS level in the candesartan-treated patients *vs* placebo in the three DIRECT studies, (**a**) Prevent 1 (prevention in type I diabetes), (**b**) Protect 1 (treatment of existing retinopathy in type I diabetes), and (**c**) Protect 2 (treatment of existing retinopathy in type II diabetes). Reprinted with permission from Sjølie *et al*[22].

moderate to moderately severe diabetic retinopathy, and candesartan had no effect on the incidence of proliferative retinopathy or macular oedema. This supports the concept that once capillary closure and ischaemia is extensive, medical therapies may have less impact on the progression of diabetic retinopathy.

Clinical implications of DIRECT

Although there will be debate over the implications for clinical practice of the DIRECT study for both diabetes and ophthalmology, it is clear that DIRECT offers the largest and the most reliable data in this field, which is unlikely to be repeated in the coming years. The debate stems from the interpretation of conventional statistics, and the value of *post-hoc* analyses rather than clear statistically significant results in the primary endpoints.

The DIRECT study was well conducted in a large number of patients and results corrected for small, confounding changes in blood pressure. The dose of candesartan used was high at 32 mg daily and showed impressive safety and tolerability with only 2–4% discontinuation, which was similar to placebo. Clearly there are concerns about the use of RAS-blocking drugs in women of child-bearing age, but these could be met by appropriate counselling, and discontinuation of the drug before planned pregnancy, or as soon as pregnancy is confirmed. Identifying 'at risk patients' is also difficult, but the DIRECT study suggests that this should include duration of diabetes more than 6 years, and those with poor glycaemic control, especially with poor control in the first few years of diabetes, and those with hypertension, dyslipidaemia, and nephropathy.

No primary endpoints were met, and secondary endpoints and *post-hoc* analyses showed that the beneficial effects took some years to develop—for example, 4–5 years of treatment in the primary prevention of diabetic retinopathy in patients with type I diabetes. A longer period of treatment may have shown more significant results. The trial population studied specified normotensive ($\leqslant$130/80 mm Hg) and normoalbuminuric (urine albumin <20 μg/min) patients. This may have resulted in low event rates in both type I and type II patients, as retinopathy is commonly associated with nephropathy, particularly with type II diabetes. Thus, the trial may have been underpowered for detection of differences in endpoints as the event rate in the placebo arm was only about half of that was predicted. Other issues include the lack of

Table 3 Evidence-based clinical therapeutic implications of DIRECT and EUCLID studies of diabetic retinopathy

Type I diabetes—primary prevention of retinopathy

RAS blockade[a] (candesartan or lisinopril) should be considered in patients who are at risk with:

1. HbA1c >8% and no retinopathy after a 6 year-duration of diabetes and even when normotensive (⩽130/85)
2. if hypertensive (>130/80)
3. in the presence of diabetic nephropathy

Type II diabetes

RAS blockade[a] (candesartan) should be considered in patients with:

1. early stages of diabetic retinopathy (background R1 and early pre-proliferative R2), even when normotensive (⩽130/85)
2. if hypertensive (>130/85)
3. in the presence of diabetic nephropathy

[a]Provided no contra-indications to RAS blockade, and caution and counselling in all women of child-bearing age. These drugs should be discontinued if planning for pregnancy or on the first notification of pregnancy. At present, these drugs are not licensed for prevention or treatment of diabetic retinopathy.

differentiation of the nature of differing lesions, such as haemorrhages, micro-aneurysms, and cotton wool spots, which are present in background diabetic retinopathy. The EDTRS classification used in DIRECT may not have been the most sensitive method for the detection of early treatment effects. Interestingly, despite the limitations of the conclusion of the original EUCLID study owing to changes in blood pressure and glycaemic control in favour of patients on lisinopril, reduction of diabetic retinopathy incidence and an increased regression of diabetic retinopathy in EUCLID was similar to that in the DIRECT study. Nevertheless, persuasive evidence of benefit on diabetic retinopathy parameters is demonstrated in all three DIRECT trials with a shift to lower retinopathy levels with candesartan treatment (see Figure 1).

Diabetes physicians and ophthalmologists are well aware of the unmet clinical need of prevention and effective treatment of diabetic retinopathy, and must therefore give careful consideration in their clinical interpretation, particularly as the DIRECT results are broadly similar to those in EUCLID. Candesartan is widely prescribed, relatively inexpensive, effective in blood pressure lowering, and well tolerated. We have therefore drawn up an algorithm of our interpretation of these studies (Table 3) with a note of caution in women of child-bearing age.

The Renin-Angiotensin System Study (RASS)

A smaller, group of 223 patients with type 1 diabetes and no albuminuria were randomised to an ACE inhibitor (enalapril), or an angiotensin II receptor antagonist (losartan) or placebo and followed for five years.[23] A progression in diabetic retinopathy of two steps or more was significantly less on enalapril (25%) and losartan (21%) compared with placebo (38%). Results were similar for progression of three steps or more. These effects remained significant when adjusted for mean reduction in blood pressures on enalapril 4/2 mm Hg and on losartan 2/2 mm Hg compared with placebo, and there were no changes or differences in glycaemic control between the groups.

In summary, we suggest that candesartan should be considered for all 'at risk patients' with type I diabetes, that is, those of more than 6-year duration of diabetes, especially if there is an indication for RAS blockade such as the presence of albuminuria or hypertension. In type II diabetes, candesartan should be considered for patients with early stages of diabetic retinopathy, particularly if there is an indication for RAS blockade. Many diabetic patients will already be established on a RAS-blocking drug, and whether the DIRECT study suggests a specific effect strong enough to warrant switching to candesartan is a matter for debate. We suspect that diabetes care clinicians will interpret the results of DIRECT as supporting a beneficial role for RAS blockade in the long-term care of patients with diabetes.

The DIRECT and RASS studies have added to our knowledge of RAS blockade in relation to diabetic retinopathy, and we hope this review and our views will result in evidence-based use of this class of drug in both diabetic and ophthalmological practice.

Key points

Implications for ophthalmology in preventing and managing diabetic retinopathy

- Vascular risk factors must be addressed
- Blood glucose, blood pressure control, and lipid lowering are important
- The RAS system has a role
- ACE inhibitors and angiotensin II receptor antagonists are valuable drugs in preventing and managing long-term complications of diabetes and may be equally efficacious (DIRECT and EUCLID studies)
- RAS inhibitors should be considered in adults with type I diabetes without established complications[a]
- RAS inhibitors should be considered in adults with type II diabetes and mild/moderate background retinopathy[a]

[a]Caution and counselling in women of child-bearing age, and this drug should be discontinued if planning for pregnancy or on the first notification of pregnancy.

Conflict of interest

The authors declare no conflict of interest.

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