Diabetic Retinopathy and Blockade of the Renin-Angiotensin System: So What is New?

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Wright AD, Dodson PM: **Diabetic retinopathy and blockade of the renin-angiotensin system: new data from the DIRECT study programme.** *Eye (Lond)* 2010,24(1):1–6.

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 ($P\leq 0.03$). 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.

Editor's Comment

Ordinarily we do not take information from reviews, as they rarely expand on primary data. In this case, though, there were three separate trials, which differ in design and which have important implications for treatment. What debate there is reflects the value of *post hoc* analyses.

No primary endpoints were met. The secondary endpoints showed that the beneficial effect took some years to develop—for example, 4 to 5 years of treatment in the primary prevention of diabetic retinopathy in patients with type 1 diabetes mellitus. The trial populations specified normotensive and normoalbuminuric patients, which may have resulted in a low event rate in the patients with both type 1 and type 2 diabetes. The increased regression of diabetic retinopathy in EUCLID was similar to that in the studies of the Diabetic Retinopathy Candesartan Trials (DIRECT). Nonetheless, persuasive evidence of benefit is demonstrated in all three DIRECT trials.

Taken in all, it is difficult to avoid the conclusion that candesartan, at full dosage, will benefit the patient with diabetic retinopathy.

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