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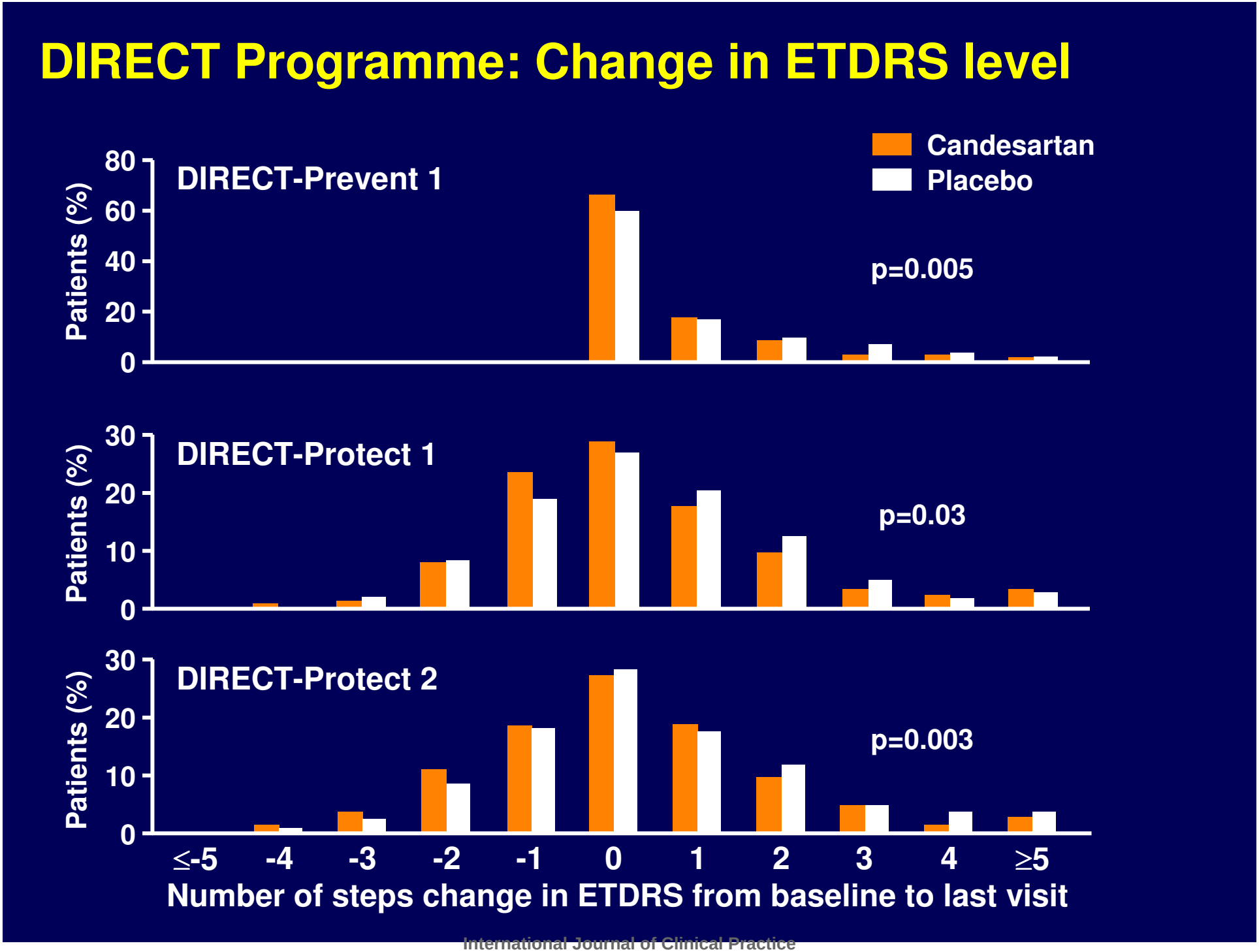
DIRECT Programme: Change in ETDRS level
Candesartan
Placebo
DIRECT-Prevent 1
p=0.005
DIRECT-Protect 1
p=0.03
DIRECT-Protect 2
p=0.003
Patients (%)
80
60
40
20
0
30
20
10
0
≤-5
-4
-3
-2
-1
0
1
2
3
4
≥5
Number of steps change in ETDRS from baseline to last visit

Does renin-angiotensin system blockade have a role in preventing diabetic retinopathy? A clinical review

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AK Sjølie received honoraria as a member of the DIRECT Programme Steering Committee. P Dodson and FDR Hobbs have been on advisory boards for the DIRECT Programme.

Summary

Diabetes management has increasingly focused on the prevention of macrovascular disease, in particular for type 2 diabetes. Diabetic retinopathy, one of the main microvascular complications of diabetes, is also an important public health problem. Much of the care invested in retinopathy relates to treatment rather than prevention of disease. Tight glycaemic and blood pressure control helps to reduce the risk of retinopathy but this is not easy to achieve in practice and additional treatments are needed for both primary and secondary prevention of retinopathy. A renin angiotensin system (RAS) has been identified in the eye and found to be upregulated in retinopathy. This has led to specific interest in the role of RAS blockade in retinopathy prevention. The recent DIRECT programme assessed use of the angiotensin receptor blocker (ARB) candesartan in type 1 and type 2 diabetes. Although the primary trial endpoints were not met, there was a clear trend to less severe retinopathy with RAS blockade. A smaller trial, RASS, reported reduced retinopathy progression in type 1 diabetes from RAS blockade with both the ARB losartan and the angiotensin converting enzyme (ACE) inhibitor enalapril. The clinical implications of these new data are discussed.

How did you gather, select and analyze the information you considered in your review?

The information for this review was gathered at an advisory meeting held to discuss diabetic retinopathy and its prevention in the light of new clinical trial data on renin angiotensin system blockade

What is the take home message for the clinician?

- Good control of glycaemia and blood pressure is central to reducing risk of diabetic retinopathy but is not easy to achieve.
- There is a need for additional therapy for prevention of retinopathy development and progression and new clinical trial evidence suggests that drugs that block the renin angiotensin system may be effective.
- It is not clear whether this effect is specific to RAS blockade or is largely explained by blood pressure lowering.

Introduction

Diabetic retinopathy is the most common long-term complication of diabetes and the most common cause of blindness in working age people in developed countries. It is one of the most feared complications in people with diabetes (1) and has marked effects on patients' quality of life (2). Quality of life can be affected in people with diabetic retinopathy before they have visual loss, because of anxiety about the future (3).

At the time of the diagnosis of diabetes, up to 40% of patients with type 2 disease already have some degree of diabetic retinopathy (4). In data from the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) collected about 30 years ago, more than 60% of patients with type 2 diabetes and almost all those with type 1 diabetes had some retinopathy after 20 years (5).

There is evidence from the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) and other studies that recent improvements in the treatment of diabetes have led to lower incidence of retinopathy; however this is offset by the current increase in prevalence of diabetes (6). In the UK, diabetes prevalence increased from 2.8% in 1996 to 4.3% in 2005. The marked increase in type 2 diabetes is probably related to changes in lifestyle, including increased obesity prevalence (7).

If untreated, a large proportion of people who develop proliferative diabetic retinopathy will experience severe loss of vision within five years (8). Panretinal laser photocoagulation (PRP) is the only proven treatment with long-term beneficial effect in preventing severe visual loss once proliferative diabetic retinopathy (PDR) is present. It can induce regression of retinal new vessels, but PRP is not always effective and can itself produce side effects on visual function such as loss of visual field and, in rare cases, accidental scars in the macula (9). This treatment is usually used for patients in whom sight-threatening retinopathy has developed.

By the time visual symptoms occur, severe and irreversible damage to the retina has already occurred, and laser treatment is less effective. Therefore regular screening for retinal new vessels is recommended, the aim being to detect retinopathy at an asymptomatic stage when treatment is more likely to be successful.

Specific drug treatments for retinopathy are being investigated but these are mostly used in advanced disease when damage to the retina and visual function has already occurred. The aim of this review was to evaluate the data on prevention of diabetic retinopathy development and progression, specifically considering new clinical trial data on the possible effect of drugs that inhibit the renin angiotensin system.

Causes of visual problems

There are two main causes of visual problems in diabetic retinopathy: proliferative retinopathy and maculopathy (macular oedema).

Diabetic retinopathy is characterised by capillary dilatation and leakage of lipoproteins and blood, capillary occlusion and subsequent new vessel formation. In type 1 diabetes, the most common cause of visual loss is proliferative retinopathy, which may lead to severe haemorrhage into the vitreous; in type 2 diabetes, the most common cause is macular oedema, caused by breakdown of the blood retinal barrier. However, both types of sight threatening manifestations may occur in all diabetic patients, and may also occur together (10).

Proliferative retinopathy can lead to profound global sight loss while macular oedema can cause gradual and largely irreversible loss of central vision, and these two sight threatening manifestations often occur together in the same eye.

Chronic hyperglycemia is an initiating factor for the retinal changes in diabetes, but the exact mechanism by which retinopathy develops is not clearly established. A number of biochemical pathways have been identified that modulate the disease process through

effects on cellular metabolism, signalling and growth factors (11) and these have led to investigation of new treatment targets.

Modifiable risk factors

The major modifiable risk factors for diabetic retinopathy are high blood sugar and blood pressure. The UKPDS and DCCT showed that intensive glycaemic control (12, 13) can reduce risk of developing diabetic retinopathy and slow progression of existing retinopathy. The UKPDS also showed that tight blood pressure control (14) reduced visual loss in people with type 2 diabetes.

DCCT and UKPDS indicated that the lower the glycaemia, the lower the risk of retinopathy. Two recent studies, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Eye study (15) and the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) Retinal Measurements (AdRem) study, (16) assessed the effect of intensive glucose lowering in type 2 diabetes, aiming for greater HbA1c reduction than achieved in UKPDS. In the ACCORD Eye study, intensive glycaemic control reduced progression of retinopathy (15). In AdRem, intensive glycaemic control did not significantly reduce incidence and progression of retinopathy although a trend to benefit was seen (16).

Lowering blood pressure in hypertensive diabetes patients reduces both macrovascular and microvascular risk. Blood pressure targets in diabetes get ever lower: the British Hypertension Society and the European Society of Cardiology both recommend a target of <130/80mm Hg (17, 18).

In the ACCORD Eye study, intensive blood pressure control (target <120 mmHg) did not have a significant effect on retinopathy progression when compared with standard treatment (target <140mm Hg) (15). However, both treatment groups in ACCORD had

lower blood pressure than in the UKPDS tight control arm, indicating that there may be a threshold below which benefits cannot be obtained for retinopathy progression.

There is conflicting evidence on whether elevated lipids levels are a risk factor for retinopathy, but many patients with diabetes will already be taking statins for cardiovascular disease prevention. In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial in type 2 diabetes, fenofibrate reduced the need for laser treatment for retinopathy (19). The beneficial effect was not related to plasma lipid levels, suggesting that the drug might have some other, as yet unknown, effect. These data are interesting but require confirmation, particularly as need for laser treatment was only a tertiary endpoint, and was performed at the discretion of the treating physician. Some further data on this come from the ACCORD Eye study which compared two treatments of dyslipidaemia (simvastatin alone or a combination of simvastatin and fenofibrate) and reported that the combination treatment, which was associated with reduced triglyceride levels, reduced progression of retinopathy (15).

Medical management of diabetic retinopathy

Tight control of blood glucose and blood pressure is key to primary and secondary prevention of diabetic retinopathy, but is difficult to achieve in practice. Tight glucose control can be limited by risk of hypoglycaemia, particularly in type 1 diabetes, and fear of hypoglycaemia can be a barrier to adherence (20).

In the UK, control of glycaemia and blood pressure in patients with diabetes has been steadily improving, but less than 80% of patients have blood pressure ≤145/85mmHg (the Quality and Outcomes Framework standard) and less than 70% have HbA1c ≤7.4% (21). A recent US study reported that for patients with diabetes treated in primary care clinics only 34% met an HbA1c target of <7% and only 30% met a blood pressure target of <130/80mm Hg (22).

Even with good control, retinopathy remains an important clinical problem and there is a need for additional treatments to reduce risk.

RAS and diabetic retinopathy

Among new approaches to retinopathy prevention there has been considerable interest in whether drugs that block the renin angiotensin system (RAS) might have a preventive effect, over and above their blood pressure lowering effect. RAS blockade can slow the progression of diabetic nephropathy (23) and there is growing evidence that the RAS may also play an important role in the pathogenesis of diabetic retinopathy

A local renin-angiotensin system has been shown to operate in the eye and there is evidence from clinical and experimental models that this system is upregulated in active retinopathy. Angiotensin II has been shown to increase exudation from retinal vessels (24), as well as stimulate formation of new retinal blood vessels, via upregulation of vascular endothelial growth factor (VEGF) activity and other growth factors, and studies in animal models suggest that RAS blockade might be associated with protective effects on the retina (10, 25).

Small short-term clinical studies have also demonstrated beneficial effect of RAS blockade on retinal permeability (26, 27). These findings could indicate a long-term beneficial effect on diabetic retinopathy.

In the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID), treatment with the angiotensin converting enzyme (ACE) inhibitor was associated with a non-significant reduction in incidence of retinopathy and a significant reduction in retinopathy progression in normotensive patients with type 1 diabetes (28). However, these data were not conclusive because retinopathy was not a primary trial endpoint; also, patients randomised to lisinopril had lower HbA1c levels at baseline than placebo patients.

DIRECT programme

Following the positive results from EUCLID, the DIRECT (Diabetic Retinopathy Candesartan Trials) programme was set up to assess further the effects of RAS blockade on diabetic retinopathy. The programme involved three placebo-controlled trials evaluating the effect of the angiotensin receptor blocker (ARB) candesartan 32mg daily on the incidence of new retinopathy and the progression of retinopathy in type 1 (29) and type 2 (30) diabetes.

DIRECT involved 5231 patients, making it the largest trial that has been carried out with diabetic retinopathy as the primary endpoint. Prevention of retinopathy and progression of established retinopathy was assessed in type 1 diabetes and progression of retinopathy in type 2 diabetes, with follow-up for at least four years.

The three components of the DIRECT programme were: DIRECT-Prevent 1 —1421 patients with type 1 diabetes (mean age 30) who were normotensive and had no retinopathy at baseline; DIRECT-Protect 1 — 1905 patients with type 1 diabetes (mean age 32) who were normotensive and had mild-moderate non-proliferative retinopathy at baseline; and DIRECT-Protect 2 — 1905 patients with type 2 diabetes (mean age 57) who were normotensive (BP < 130/85) or mildly hypertensive (BP < 160/90) and being treated, and had mild-moderate non-proliferative retinopathy at baseline.

Retinopathy was assessed on the ETDRS (Early Treatment Diabetic Retinopathy Study) severity scale. This is the gold standard for evaluating diabetic retinopathy in clinical trials and is based on grading seven-field stereo photographs of the eyes. The primary trial endpoint was at least a two-step increase on the ETDRS scale for incidence and at least a three-step increase for progression. A secondary endpoint was regression of retinopathy, defined as either reduction of at least three steps from baseline on any follow-up visit, or two or more steps sustained on two visits one year apart.

In DIRECT-Prevent 1 (29), candesartan reduced the incidence of retinopathy by 18% (HR 0.82, P=0.0508). Although this primary endpoint just missed conventional levels of statistical significance, in a post hoc analysis of three-step increase — a more stringent criteria for development of retinopathy — there was significant benefit in favour of active treatment (HR 0.65, P=0.0034), which was reduced but still significant (HR 0.74, P=0.046) when the results were adjusted for baseline characteristics and small changes in blood pressure during the trial.

In DIRECT-Protect 1 (29), there was no significant difference between candesartan and placebo in retinopathy progression in patients with type I diabetes (P=0.85).

In DIRECT-Protect 2 (30), retinopathy progression was reduced by 13% in the candesartan group, which was not statistically significant (HR 0.87, P=0.20). However, the secondary endpoint of retinopathy regression was increased by 34% with candesartan treatment (HR 1.34. P=0.009), and this was still significant (P=0.015) after adjustment for baseline variables and blood pressure during the course of the trial. Regression was only seen in patients with mild retinopathy, supporting the hypothesis that retinopathy might reach a "point of no return".

Adverse event were similar in active and placebo groups in the three trials.

Although DIRECT did not meet its primary endpoints, there was an overall change towards less severe retinopathy in both type 1 and 2 diabetes. For all three trials, the final ETDRS level – also a predefined endpoint — was more likely to have improved in candesartan patients than in placebo patients (Figure 1), suggesting that the active treatment has a biological effect on the disease process.

The mechanism for candesartan's apparent beneficial effect has not been examined in the DIRECT Programme. It may be partially related to blood pressure lowering with a possible additional specific effect of RAS blockade on the eye, as the effects shown in the

primary analyses remained significant after adjustment for blood pressure. Further analysis may help to clarify these mechanisms.

RASS trial

Further support for a beneficial effect on diabetic retinopathy from RAS blockade comes from the RASS (Renin-Angiotensin System Study) which evaluated whether RAS blockade can slow retinopathy progression in type 1 diabetes (31). In this study nephropathy was the primary endpoint, and retinopathy was another prespecified endpoint.

RASS compared the ACE inhibitor enalapril 20mg daily, the ARB losartan 100mg daily, and placebo in 223 normotensive patients, with mean age 30 years. At baseline, over 90% of patients had either no diabetic retinopathy (34%) or minimal / early non-proliferative retinopathy (58%). Only 9% had moderate to severe non-proliferative retinopathy. There was no significant difference in baseline retinopathy levels in the three groups.

The study retinopathy endpoints were progression of two steps or more or three steps or more on the ETDRS severity scale. After five years, retinopathy progression occurred in 38% of patients receiving placebo compared with 25% of patients on enalapril (P=0.02) and 21% of patients on losartan (P=0.008).

The effects of the active treatments remained after adjustment for mean blood pressure measurements during the study, although the study authors report that effects of blood pressure on the retinopathy outcomes cannot be ruled out.

In both DIRECT and RASS, patients were normoalbuminuric at baseline. Unexpectedly, given the known beneficial effect of RAS inhibition in patients with more advanced nephropathy, neither trial showed any statistically significant effect of RAS blockade on development of microalbuminuria (31, 32).

Clinical implications of the RAS studies

Prevention of diabetic retinopathy and its progression is highly relevant to general practitioners as nearly all type 2 diabetes and the majority of type 1 diabetes in an increasing number of European countries is now managed in primary care.

It is perhaps not surprising that the DIRECT trials did not meet their primary endpoints. Retinopathy incidence and progression was lower than expected, and this is probably because the trial population was younger and better controlled than most patients seen in everyday practice. With this "healthier" population, four years may have been too short a period to show benefit.

Nonetheless, the DIRECT trials do show a strong trend to shifting the risk of retinopathy in the diabetic population (Figure 1). We believe that some suggestions can be made regarding clinical implications of the data.

For secondary prevention in patients with type 2 diabetes, RAS blockade fits well into the current multifactorial intervention strategies. Most patients with diabetes will become hypertensive at some point and standard practice is to prescribe an RAS inhibitor as a key component of the antihypertensive therapy for reno-protection.

The recent data further suggest that RAS blockade in earlier stages of retinopathy may be effective, and that those that benefit the most are people whose retinopathy progresses rapidly. The problem is that these population phenotypes are not identifiable in routine practice. Therefore, if a prescriber has any reason to consider using a drug that modifies the RAS in patients with diabetes, such as hypertension, the new data offer a compelling argument to think about prescribing this treatment earlier, in patients with early retinopathy. More intensive treatment might also be considered, bearing in mind the relatively high candesartan dose of 32mg used in DIRECT.

For preventing retinopathy in type 1 diabetes, further research is needed to identify high-risk patients, for example those who are unable to obtain good glycaemic control, who might benefit from RAS blockade. But at present the evidence does not justify routine use of an RAS blocker in a metabolically well-controlled normotensive, normoalbuminuric patient with type I diabetes.

Conclusion

Microvascular complications remain important causes of morbidity. They also contribute significantly to the cost of treating diabetes in the long-term, and will become more common as the incidence of the disease increases and more people with diabetes survive macrovascular complications.

There is an unmet need in retinopathy prevention and the new data on RAS blockade are encouraging. It is not yet clear whether RAS blockade has direct effects on the eye or whether the effect on retinopathy is largely explained by blood pressure lowering, but this is of little consequence for day-to-day clinical practice. Blood pressure targets in diabetes are getting lower and the DIRECT data add weight to existing evidence to consider use of an RAS blocker as antihypertensive agent in patients with diabetes.

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Author contributions

All authors contributed to discussion on the content of the paper and critical revision of the paper

Figure 1

Overall change in Early Treatment Diabetic Retinopathy Study (ETDRS) level from baseline to final visit in the DIRECT programme (adapted, with permission, from references 29 and 30)

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