Benefits of Renin-Angiotensin Blockade on Retinopathy in Type 1 Diabetes Vary With Glycemic Control

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OBJECTIVE—Optimal glycemic control slows diabetic retinopathy (DR) development and progression and is the standard of care for type 1 diabetes. However, these glycemic goals are difficult to achieve and sustain in clinical practice. The Renin Angiotensin System Study (RASS) showed that renin-angiotensin system (RAS) blockade can slow DR progression. In the current study, we evaluate whether glycemic control influenced the benefit of RAS blockade on DR progression in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS—We used RASS data to analyze the relationships between two-steps or more DR progression and baseline glycemic levels in 223 normotensive, normoalbuminuric type 1 diabetic patients randomized to receive 5 years of enalapril or losartan compared with placebo.

RESULTS—Patients (147 of 223; 66.9%) had DR at baseline (47 of 74 patients [63.5%] in placebo and 100 of 149 patients [67.1%] in the combined treatment groups [P = 0.67]). Patients with two-steps or more DR progression had higher baseline A1C than those without progression (9.4 ± 8.2%, P < 0.001). There was no beneficial effect of RAS blockade (P = 0.92) in patients with baseline A1C ≤ 7.5%. In contrast, 30 of 112 (27%) patients on the active treatment arms with A1C > 7.5% had two-steps or more DR progression compared with 26 of 36 patients (46%) in the placebo group (P = 0.03).

CONCLUSIONS—RAS blockade reduces DR progression in normotensive, normoalbuminuric type 1 diabetic patients with A1C ≥ 7.5%. Whether this therapy could benefit patients with A1C ≤ 7.5% will require long-term studies of much larger cohorts.

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and remains the leading cause of new blindness among adults aged 20–74 years in the U.S. (1). The estimated prevalence of DR and vision-threatening DR among Americans with diabetes who are 40 years or older are 28.5 and 4.4%, respectively (2). Consequently, the ongoing increase in diabetes prevalence, the total number of people older than 40 years with DR is projected to be 16 million by year 2050 (3). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) and the UK Prospective Diabetes Study (UKPDS) clearly demonstrated the benefit of intensive glycemic control in reducing the incidence and progression of DR in type 1 and type 2 diabetes (4,5). As a consequence of these studies, guidelines to maintain glycated hemoglobin A1C (A1C) < 6.5 or 7.0% are now accepted as a standard of care in diabetes (6). However, achieving and sustaining A1C at these levels remains problematic (7). Thus additional treatment approaches to DR prevention may be helpful.

Tight blood pressure control per se has been shown to reduce progression of retinopathy in hypertensive diabetic patients (8,9). Previous studies have also suggested beneficial effects of ACE inhibitors (ACEI) on progression of DR in both normotensive and hypertensive type 1 diabetic patients (10–12). Recently, the Renin Angiotensin System Study (RASS) (13) documented a beneficial role of renin-angiotensin system (RAS) blockade on DR progression but did not slow nephropathy progression in normotensive normoalbuminuric type 1 diabetic patients. The Diabetic Retinopathy Candesartan Trial (DIRECT-Prevent) (14) also reported a reduction in the incidence of DR in type 1 diabetic patients that just failed to achieve statistical significance (P = 0.0508).

Herein we evaluated the role of glycemic control on the treatment benefit of RAS blockade on DR progression in the RASS.

RESEARCH DESIGN AND METHODS

Participants and study design
Patients were enrolled in RASS (clinicaltrials.gov, NCT00143949), a multicenter randomized, double-blinded, double dummy, placebo-controlled clinical trial comparing the effects of an ACEI; enalapril; and an angiotensin receptor blocker (ARB), losartan, with placebo on the rates of progression of diabetic nephropathy and retinopathy lesions in normotensive, normoalbuminuric type 1 diabetic patients over 5 years. RASS was conducted at the University of Minnesota (Minneapolis, MN), University of Toronto (Toronto, Canada), and McGill University (Montreal, Canada). The primary end point of RASS was a change in the fraction of glomerular volume occupied by mesangium (the mesangial fractional volume). Secondary renal end points included changes in other...
glomerular vascular, tubular, and interstitial variables and changes in albumin excretion rate (AER) and glomerular filtration rate (GFR). The retinal primary end point of two-steps or more DR progression was added shortly after RASS began. The study design and protocol (15), as well as the results of the primary end point analyses (13), have been detailed elsewhere. In brief, RASS screened 1,065 type 1 diabetic patients, and 707 declined participation and 73 were ineligible. Some (285) were randomly assigned to one of the three study groups with the use of computer-generated blocks of six, stratified according to center and sex, into the following groups: 10 mg daily enalapril, 50 mg daily losartan, or placebo daily (Supplementary Fig. A1). The original doses were doubled during the study as previously detailed (13) because of the new evidence of greater reduction in proteinuria with higher doses of these agents (16). The study patients were ≥16 years old with 2–20 years’ duration of type 1 diabetes and onset before age 45. At baseline, fulfilling the RASS entry criteria, all were normotensive (blood pressure <135/85 mmHg), normoalbuminuric (AER <20 μg/min on at least two out of three timed consecutive overnight urine collections), and had normal or increased GFR (≥90 mL/min/1.73 m²).

Retinal examination
Patients were eligible for this DR study if they had retinal exams performed both at baseline (within 1 year of randomization) and after 5 years in the trial. Patients with baseline proliferative DR (N = 4) or whose baseline fundus photographs were obtained more than 1 year after randomization (N = 28) were excluded from these analyses (Supplementary Fig. A1). Retinal fundus photographs were taken by trained photographers for seven standard fields, according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (17), and graded in a masked fashion at the University of Wisconsin Ocular Epidemiology Reading Center using the modified Airline House classification and the ETDRS retinopathy severity scale (Supplementary Table A1) (18–20). The maximal grade in any of the standard fields for each eye was used to classify retinopathy severity. If one eye was not gradable, it was assigned the score of the other eye. A concatenated scale for both eyes, with 60–85 collapsed to 60+, have severity scores from 10/10, 21/<21, 21/21, 31/<31, 31/31, 37/<37, 37/37, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60/<60+, and 60+/60+, creating 15 levels in which a person could be classified. The study end point was two-steps or more DR progression in this concatenated 15-level severity scale, which was previously shown to be clinically meaningful in predicting more severe DR lesions (21).

Other variable measurement
Blood pressure, AER, and A1C were measured before and quarterly after randomization as previously detailed (15). GFR was measured annually by plasma iohexol disappearance (22–24). The study was approved by the institutional review board at each center, and written informed consent or assent as appropriate, was obtained from all participants.

Statistical analysis
Statistical analyses were conducted using SPSS version 18.0 and SAS version 9.1. Baseline characteristics of the study cohort were compared using unpaired t test for quantitative variables and the χ² or Fisher exact test for categorical variables. Logistic regression analysis was used to estimate the odds ratio of two-steps or more of DR progression. Because the beneficial effects of enalapril and losartan on the progression of DR in RASS were nearly identical (13), odds ratios were estimated in combination for these treatment groups, relative to the placebo group, and were adjusted for mean blood pressure during the study, baseline characteristics, center, and baseline grade of DR according to the 15-level severity scale.

Table 1—Baseline characteristics of the study cohort according to fundus photography status

| Baseline and 5-year fundus photographs | Performed* | Not performed | P value |
|----------------------------------------|------------|---------------|--------|
| n                                      | 223        | 62            | NS     |
| Male                                   | 104 (47)   | 28 (45)       | NS     |
| Caucasian (%)                          | 219 (98)   | 60 (97)       | NS     |
| Age (years) (%)                        | 29.9 ± 9.7 | 28.8 ± 9.9    | NS     |
| Diabetes duration (years)              | 11.3 ± 4.7 | 10.7 ± 5.0    | NS     |
| BMI (kg/m²)                            | 25.7 ± 3.8 | 25.8 ± 3.4    | NS     |
| Systolic blood pressure (mmHg)         | 120.2 ± 11.7 | 117.7 ± 10.7 | NS     |
| Dastolic blood pressure (mmHg)         | 70.2 ± 8.2 | 70.0 ± 9.0    | NS     |
| A1C (%)                                | 8.5 ± 1.6  | 8.7 ± 1.6     | NS     |
| Serum creatinine (μmol/L)              | 71.0 ± 12.4 | 71.6 ± 12.4  | NS     |
| AER (μg/min)                           | 5.2 (3.5–7.8) | 4.7 (2.6–6.7) | NS     |
| GFR (mL/min/1.73 m²)                   | 128.9 ± 20.7 | 128.0 ± 18.2 | NS     |

*Data are number (%) or means ± SD except for AER (median [interquartile range]). NS, not significant. *n = 222 for A1C and serum creatinine.
least two-steps DR progression versus 46% in the placebo group ($P = 0.03$), this representing a 60% reduction (Table 4). These results were not altered by adjustment for the mean of all blood pressure measurements obtained during the 5-year study. Results were similar when average A1C during 5 years, instead of baseline A1C, was used (data not shown).

**CONCLUSIONS**—Although RASS found no beneficial effects of early RAS blockade on diabetic nephropathy-related structural or functional end points, there was an approximately two-thirds reduction in two-steps or more DR progression in normoalbuminuric, normotensive type 1 diabetic patients receiving either an ACEI (enalapril) or an ARB (losartan), and this was independent of blood pressure levels during the trial (13). These analyses have now been extended to demonstrate that the detectable beneficial effects of these drugs on DR are largely dependent on glycemic control. When compared with placebo, enalapril and losartan reduced at least two-steps DR progression only in the subset of patients whose baseline A1C was greater than 7.5%. This protective effect might be specially pronounced in patients with worse glycemic control.

There is little question that improving glycemic control has a major beneficial effect on DR progression and development (4,5), and glycemia was an independent predictor of DR progression in the current study. However, in type 1 diabetics, as reported by the DCCT, maintaining an A1C less than 7% required a major effort from a dedicated research staff and highly motivated volunteer participants. After an average of 6.5 years of intensive glycemic control in the DCCT, when patients returned to their usual care as reported in the EDIC component of the study, the long-term follow-up of the DCCT cohort, the A1C approached 8%, whereas in the former DCCT conventional therapy group A1C decreased from ~9 to 8% with the initiation of intensive insulin therapy (7). This illustrates the challenges of implementing and maintaining the recommended glycemic targets in patients with type 1 diabetes despite the development of newer types of insulin, insulin pumps, and better glucose monitoring systems. Thus development of alternative strategies to prevent progression of DR remains relevant. The current study demonstrated that reduction in the incidence of at least two-steps DR progression with RAS blockade was greater in patients with poorer glycemic control. The risk of at least two-steps DR progression could be reduced by 60% by RAS blockade in patients whose baseline A1C was $>7.5\%$, and this effect is independent of achieved blood pressure during the 5 years of the study and remained true if average A1C during the 5 years of the study, rather than baseline A1C, was used for the analyses.

Although our results, demonstrating protective effects of RAS blockade in patients with worse glycemic control (A1C $>7.5\%$), appear to contrast with those previously reported in the EURODIAB controlled trial of lisinopril in insulin-dependent diabetes (EUCLID) study (12), where the patients with better glycemic control (A1C $<7\%$) benefited most from ACEI treatment, the two studies are not fully comparable. Patients in EUCLID were followed for a shorter time period compared with RASS (2 vs. 5 years). Moreover, in EUCLID, A1C levels at baseline and throughout the study were significantly lower in the ACEI than in the

**Table 2—Baseline retinopathy status according to treatment group**

| Retinopathy status       | Placebo | Enalapril/losartan |
|--------------------------|---------|-------------------|
| n                        | 149     | 160               |
| None (%)                 | 27 (36.5) | 49 (32.9)        |
| Mild NPDR (%)            | 42 (56.8) | 85 (57.0)        |
| Moderate to severe NPD   | 5 (6.8)  | 15 (10.1)         |

NPDR, nonproliferative diabetic retinopathy.

**Table 3—Baseline clinical characteristics according to retinopathy progression**

|                                | No progression* | At least two-steps progression | $P$ value |
|--------------------------------|-----------------|-------------------------------|-----------|
| $n$                            | 161             | 62                            |           |
| Male (%)                       | 79 (49)         | 25 (40)                       | NS        |
| Caucasian (%)                  | 159 (99)        | 60 (97)                       | NS        |
| Age (years)                    | 30.6 ± 9.8      | 28.0 ± 9.2                    | NS        |
| Diabetes duration (years)      | 11.4 ± 4.7      | 11.1 ± 4.6                    | NS        |
| BMI (kg/m²)                    | 25.6 ± 3.6      | 26.0 ± 4.3                    | NS        |
| Systolic blood pressure (mmHg) | 120.3 ± 11.8    | 120.0 ± 11.3                  | NS        |
| Diastolic blood pressure (mmHg)| 69.7 ± 8.3      | 71.5 ± 8.0                    | NS        |
| A1C (%)                        | 8.2 ± 1.3       | 9.4 ± 1.8                     | <0.001    |
| Serum creatinine (μmol/L)      | 71.8 ± 12.5     | 68.9 ± 11.7                   | NS        |
| AER (μg/min)                   | 5.0 (3.5-7.5)   | 5.5 (3.8-8.8)                 | NS        |
| GFR (mL/min/1.73 m²)           | 127.6 ± 20.2    | 132.1 ± 21.6                  | NS        |

Data are number (%) or means ± SD except for AER (median [interquartile range]). *$n = 160$ for A1C and serum creatinine.

![Figure 1](https://www.care.diabetesjournals.org/Diabetes-Care/3/3/11762020/fig1.png)  
**Figure 1**—Incidence of at least two-steps progression of DR in the combined treatment group vs. placebo group, according to A1C categories at baseline.
placebo group, making it difficult to evaluate any association between A1C and ACEI therapy. In fact, adjusted for baseline A1C, there was no beneficial effect of ACEI therapy in the progression of retinopathy in the EUCLID study.

RASS results (13) were consistent with those of ~5 years DIRECT-Prevent 1 (14) where there was a strong trend (P = 0.0508) for a reduction in the primary end point, time to two-steps or more DR progression, in type 1 diabetic patients with DR at baseline who were randomized to candesartan. There was a preventative effect of this ARB on the secondary end point, time to three-steps or more DR progression, which remained significant after adjustment for baseline A1C; however, DIRECT found no protective effect of ARB on three-steps or more DR progression in patients with baseline DR (14). The smaller numbers of patients in RASS preclude such subanalyses.

Although enalapril and losartan showed equal benefits in slowing DR progression, the normotensive, normoalbuminuric type 1 diabetic patients whose baseline A1C was greater than 7.5%. This finding may inform clinical decisions on an appropriate therapeutic approach to slowing the progression of DR.

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