Retinal Vascular Lesions in Patients of Caucasian and Asian Origin With Type 2 Diabetes

Baseline results from the ADVANCE Retinal Measurements (AdRem) study

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OBJECTIVE — The objective of this study was to describe prevalent vascular retinal lesions among patients with type 2 diabetes enrolled in the ADVANCE Retinal Measurements (AdRem) study, a substudy of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial.

RESEARCH DESIGN AND METHODS — Seven-field stereoscopic photographs of both eyes were obtained at the baseline assessment of the ADVANCE trial. All photographs were graded in a central reading center. Gradable retinal images were received from 1,605 patients.

RESULTS — The number of patients with any retinopathy (Early Treatment of Diabetic Retinopathy Study [ETDRS] score ≥20) was 645 (40.2% [95% CI 37.8–42.6]); of these, 35 (2.2% [1.6–3.0]) had severe diabetic retinopathy (ETDRS score ≥50). Focal arterial narrowing, venous beading, and arteriovenous nicking were present in 3.8, 5.1, and 9.8% of participants, respectively. Among participants included in this study, Chinese and South-Asian patients had more retinopathy than Caucasians, as defined both by ETDRS score (49.4, 46.0, and 31.3%, respectively; $P < 0.001$, adjusted for age, sex, A1C, systolic blood pressure, and duration of diabetes) and specific vascular lesions (e.g., arteriovenous nicking 12.3, 8.5, and 7.5%, respectively; adjusted $P < 0.005$). A1C, duration of diabetes, and systolic blood pressure were similarly associated with increased retinal lesions in Chinese, South-Asian, and Caucasian patients.

CONCLUSIONS — Using a sensitive diagnostic procedure, more than one-third of patients with type 2 diabetes enrolled in the AdRem study had retinal lesions at baseline. Despite differences in prevalence and severity of retinopathy among Chinese, South-Asian, and Caucasian patients included in this study, the cross-sectional associations among established risk factors for retinopathy and retinal lesions were similar across ethnic groups.

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Diabetic retinopathy is a progressive disorder of the microcirculation in the retina (1). It is the most common cause of blindness in people aged 30–69 years (2,3). Moreover, the prevalence of blindness attributable to diabetic retinopathy has increased considerably during recent decades and has doubled in older people since the 1990s (4). When not identified and treated early, the disease is usually progressive, and laser treatment is rarely effective in restoring vision (5).

From clinical practice it is known that diabetic retinopathy is the most common microvascular complication in diabetes, but most reliable epidemiological data using fundus photography (including peripheral retinal fields) cited to support this notion were obtained from studies conducted more than a decade ago (6–8). The management of diabetes and its complications has evolved considerably over recent years, and these data may no longer reflect contemporary experience. Moreover, most population-based studies using fundus photography did not include patients from Asian countries, where the prevalence of type 2 diabetes is rising sharply.

In addition to diabetic retinopathy, changes in the retinal microcirculation, such as focal arterial narrowing and arteriovenous nicking, are associated with increased risks of stroke, atherosclerosis, and renal dysfunction (9,10). This finding suggests that retinal vascular lesions may be important markers of subclinical vascular diseases. At present there is limited information on the relationship of microvascular abnormalities to diabetic retinopathy and whether this relationship differs by ethnicity.

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Abbreviations: AdRem, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Retinal Measurements; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ETDRS, Early Treatment of Diabetic Retinopathy Study; UKPDS, United Kingdom Prospective Diabetes Study.

ease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) is an ongoing factorial randomized trial of blood pressure lowering with a fixed low-dose perindopril-indapamide combination (versus placebo) and intensive glucose control with a modified-release gliclazide-based regimen (versus standard care) among 11,140 high-risk individuals with type 2 diabetes from 20 countries in Australasia, Asia, Europe, and North America (11). As part of the ADVANCE Retinal Measurements (AdRem) study, detailed fundus photographs in a subgroup of ADVANCE participants were obtained. In this article we present the prevalence of retinal vascular lesions in the multiethnic AdRem study population at baseline.

RESEARCH DESIGN AND METHODS

— The design of the AdRem study has been published previously (12). The main objectives are to determine the effects of blood pressure lowering and intensive glucose lowering on the incidence and progression of retinal vascular disorders in patients with type 2 diabetes.

The AdRem study was conducted in patients that have been randomly assigned in the ADVANCE trial in a selected number of study centers with access to retinal cameras. Patients were eligible for the ADVANCE trial if they had their first diagnosis of type 2 diabetes at age ≥30 years, were aged ≥55 years at entry, and had a high risk of vascular disease as indicated by a diagnosis of diabetes made ≥10 years before entry, age ≥65 years at entry, a history of cardiovascular disease or diabetes complications, or elevated levels of cardiovascular risk factors (11). In addition to these criteria for inclusion in the ADVANCE trial, patients who had a previous ophthalmological intervention procedure in one or both eyes that might interfere with retinal circulation (such as laser coagulation treatment and vitrectomy) were excluded from participation in the AdRem study.

Assessments of A1C, blood pressure, smoking, and duration of diabetes were conducted as part of the ADVANCE Study (11). Ethnicity was based on self-categorization derived from questionnaire data. Participants' ethnicity was classified as Caucasian/European, Chinese, South Asian/Southeast Asian, and "other," which included mainly Arab, African, and mixed.

Table 1—*Clinical characteristics of the AdRem study population and the main ADVANCE study*

	AdRem	ADVANCE
n	1,605	11,140
Female sex (%)	38.6	42.5
Age (years)	65.6 ± 5.8	65.8 ± 6.4
Current smoking (%)	15.8	15.1
Ethnicity (%)		
Caucasian	48	60.0
Chinese	38	30.1
South Asian	11	7.9
Other	3	2
Duration diabetes (years)	7.3 ± 6.1	7.9 ± 6.4
A1C (%)	7.4 ± 1.5	7.5 ± 1.6
Diabetes treatment (%)		
Dietician	36	35
Oral glucose-lowering medication	89	91
1 drug	43	43
2 drugs	39	42
≥3 drugs	7	6
Insulin	1	1
Blood pressure (mmHg)	136/77 ± 21/11	145/81 ± 22/11
Blood pressure lowering medication	70	75

Data are means ± SD or %.

Photography

Photographs were taken with 35-mm high-quality color films (Kodak EPR64 135-36). Stereoscopic photographs were made of both left and right eyes, according to the seven standard fields Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol (13). The seven fields include one centered on the optic disc, one centered on the macula, one temporal to the macula, and two superior and two inferior fields. In patients with nongradable images according to strict criteria (12), the centers were asked to obtain repeat photographs.

Retinopathy grading

The ETDRS classification was slightly modified in the United Kingdom Prospective Diabetes Study (UKPDS), and this modified classification is used in the AdRem study (14). Detected lesions were graded in comparison with the ETDRS final scale standard photographs. Vascular lesions were also assessed in each field using standard photographs (12).

All images were graded by two independent readers. If scores differed a consensus score was assigned by a meeting with both readers and an experienced ophthalmologist.

Statistical analyses

Differences in characteristics between patients with and without retinopathy were assessed by ANCOVA, with adjustments for age, sex, A1C, systolic blood pressure, and duration of diabetes. Use of log-transformed data did not change the reported associations. Cross-sectional associations between established risk factors or ethnicity and the presence of retinal lesions were estimated by multiple logistic regression analyses. For those risk factors that showed a significant association with retinal disease in the overall population, these relationships were also examined in subgroups defined by ethnicity. SAS (version 9.1; SAS Institute, Cary, NC) was used for all analyses.

RESULTS

— Retinal images were received from 1,984 patients. In the final analysis, 1,605 (81%) patients had images of sufficient quality for evaluation. Patients with nongradable images were slightly, although significantly, more likely to be female, more likely to be of South-Asian ethnicity, were less likely to be smokers, and were on average older, with a longer duration of diabetes, higher levels of A1C, and higher blood pressure (data not shown).

Table 1 shows clinical characteristics of the participants in the AdRem study. A total of 645 patients (40.2% [95% CI 37.8–42.6]) had any retinopathy (ETDRS score ≥20). The number of patients with mild or moderate retinopathy (ETDRS score between 20 and

Table 2—*A1C, duration of diabetes, and blood pressure in patients with and without retinopathy.*

Any retinopathy	No retinopathy	Retinopathy present (ETDRS score ≥20)	*P* value*
n	960	645	
A1C (%)	7.2 ± 1.4	7.6 ± 1.6	<0.001
Duration of diabetes (years)	6.5 ± 5.7	8.6 ± 6.4	<0.001
Systolic blood pressure (mmHg)	135 ± 20	138 ± 21	<0.01
Diastolic blood pressure (mmHg)	77 ± 11	77 ± 11	NS

Severe retinopathy	No or mild/ moderate retinopathy	Severe retinopathy present (ETDRS score ≥50)	*P* value*
n	1,570	35	
A1C (%)	7.4 ± 1.5	7.8 ± 1.9	0.06
Duration of diabetes (years)	7.3 ± 6.1	8.7 ± 6.4	0.2
Systolic blood pressure (mmHg)	136 ± 21	144 ± 22	<0.05
Diastolic blood pressure (mmHg)	77 ± 10	81 ± 13	0.01

Data are means ± SD. *Adjusted for age and sex.

50) was 610 (38.0% [35.6–40.4]), whereas 35 (2.2% [1.6–3.0]) patients had severe diabetic retinopathy (ETDRS score ≥50). The prevalence of retinopathy was not associated with age or sex (data not shown). Macular edema was present in 4.1% of men and 3.1% of women (difference $P > 0.2$). The prevalences of specific vascular lesions in this population were 3.8% with focal arterial narrowing, 5.1% with venous beading, and 9.8% with arteriovenous nicking. The presence of each vascular lesion was strongly associated with the presence of retinopathy (ETDRS score ≥20, $P < 0.001$). There were no differences in the prevalence of any of the vascular lesions between men and women.

Table 2 shows that established risk factors were increased in patients with diabetic retinopathy compared with those without retinopathy. Results were similar for men and women (data not shown). The use of oral glucose-lowering drugs or insulin was not associated with retinopathy. The mean A1C level in patients with focal arterial narrowing was 0.3% higher than in patients without focal arterial narrowing ($P < 0.05$), whereas current A1C levels did not differ significantly in patients with or without macular edema, venous beading, and arteriovenous nicking (data not shown). Systolic and diastolic blood pressures were higher in patients with venous beading and macular edema ($P < 0.05$, adjusted for age, sex, and duration of diabetes). Patients with retinal vascular lesions had ~1 year longer duration of diabetes compared with those without ($P < 0.01$). Current smoking was not associated with vascular retinal lesions (data not shown).

Almost half of the AdRem population was of Asian (Chinese or South-Asian) ethnicity (Table 1). Compared with Caucasians, these patients had more retinopathy (defined by ETDRS score) and increased prevalence of vascular lesions (except focal arterial narrowing) (Table 3). This finding was true for both specific white- and red-colored lesions (cotton-wool spots and microaneurysms), which suggests that misclassification due to their darker retina is an unlikely explanation. Patients with Chinese or South-Asian ethnicity (mainly Philippine and Malaysian) were on average younger and had a longer duration of diabetes, higher A1C levels, and lower blood pressure levels than Caucasians (mean ± SD): 64.9 ± 5.5 versus 66.5 ± 6.0 years, 8.3 ± 6.4 versus 6.3 ± 5.6 years, 7.6 ± 1.6 versus 7.2 ± 1.3%, and 135/76 ± 21/11 versus 138/78 ± 21/10 mmHg, respectively (all $P < 0.01$). Chinese and South-Asian patients also, on average, used more glucose-lowering drugs (53 vs. 38% used two or more drugs, $P < 0.01$) and more often received insulin treatment (1.3 vs. 0.5%, $P < 0.01$) than Caucasians. However, the differences in prevalence of retinopathy or vascular lesions among ethnic groups remained statistically significant after adjustment for these variables. The results were essentially similar after excluding the minority of patients not living in their country of origin or including study center as an explanatory variable.

The associations among A1C, duration of diabetes, and systolic blood pres-

Table 3—*Prevalence of retinal lesions by ethnicity*

	Caucasian	Chinese	South Asian	Other	*P* value*
n	770	609	176	50	
Retinopathy (ETDRS score ≥20)	31.3	49.4	46.0	44.0	<0.001
Severe retinopathy (ETDRS score ≥50)	1.2	3.5	1.7	4.0	<0.05
Macular edema	2.3	5.4	2.3	10.0	0.001
Focal arterial narrowing	4.2	3.0	4.6	6.0	NS
Venous beading	2.1	8.7	6.3	4.0	<0.001
Arteriovenous nicking	7.5	12.3	8.5	18.0	<0.005

Data are %. *Adjusted for age, sex, A1C, systolic blood pressure, duration of diabetes, number of glucose-lowering drugs, and insulin use.

Table 4—*Risk factors for mild/moderate retinopathy by ethnicity*

	Caucasian	Chinese	South Asian	Other
n	770	609	176	50
A1C (per %)	1.23 (1.09–1.38)	1.23 (1.11–1.37)	1.26 (1.03–1.53)	1.18 (0.78–1.79)
Diabetes duration (per year)	1.08 (1.05–1.12)	1.03 (1.01–1.06)	1.02 (0.98–1.07)	1.11 (1.00–1.23)
Systolic blood pressure (per 10 mmHg)	1.05 (0.98–1.13)	1.12 (1.04–1.21)	1.09 (0.92–1.28)	1.20 (0.80–1.80)

Data are ORs, adjusted for age and sex (95% CI).

sure with retinopathy did not differ significantly by ethnicity (Table 4). After adjustment for age, sex, and ethnic group, the odd ratios (ORs) for mild/moderate retinopathy were 1.24 per percent A1C (95% CI 1.15–1.33), 1.06 per year of diabetes duration (1.04–1.08), and 1.09 per 10 mmHg of systolic blood pressure (1.03–1.14), respectively (all $P < 0.001$). Similar associations with severe diabetic retinopathy and vascular lesions were also independent of ethnic group. Because of the small sample size, separate significant associations within each ethnic group could not be clearly demonstrated. In all analyses, interaction terms with ethnic group were not statistically significant ($P > 0.2$) except for the OR of diabetes duration for mild/moderate retinopathy, which was slightly lower in patients from China and South Asia compared with Caucasians (Table 4).

CONCLUSIONS — In this international study that included a broad range of patients with type 2 diabetes, more than one-third of patients had retinal vascular lesions at baseline diagnosed by a sensitive procedure. Differences in the prevalence of these lesions among ethnic groups were unexplained by differences in known risk factors for retinopathy. However, the associations between A1C, duration of diabetes, and blood pressure and retinal lesions did not differ significantly among ethnic groups.

One of the strengths of the AdRem study is the use of seven-field stereoscopic photography of both eyes, allowing the detection of subtle lesions. This procedure is considered the reference standard for diagnosing diabetic retinopathy in randomized clinical trials (15). If smaller lesions are diagnosed with this approach, one would expect reporting of a higher prevalence of retinopathy compared with studies using single and/or nonmydriatic cameras. Indeed, the prevalence of retinopathy in the AdRem Study (40.2%) is higher than that reported in the Multi-Ethnic Study of Atherosclerosis (MESA) (33.2%), which is similar to the prevalence in previous population-based studies (16–19). However, the Diabetic Retinopathy Candesartan Trial (DIRECT), which also used seven-field photography, reported an even higher prevalence of retinopathy than the AdRem study (20).

It has been shown that small vascular retinal lesions are easily overlooked by direct funduscopy and routine ophthalmological examination (21). Until now, vascular measurements have been limited to 45° photographs centered on the macula (22). Additional assets of the protocol used in the AdRem study are the central film processing and central duplicate grading of the images. These prevent potential differences in classification among centers, which is especially relevant when one is comparing ethnic groups (12).

There are some limitations to the interpretation of these data. The ADVANCE trial included patients at high risk of vascular disease, which will result in overestimation of retinopathy. On the other hand, exclusion of individuals with previous laser coagulation treatment would have resulted in an underestimation of the prevalence of retinopathy in this population. Because we are looking mainly at mild/moderate retinopathy and vascular lesions that do not require laser treatment, potential differences in access to these facilities are unlikely to explain the differences in prevalence among ethnic groups. Another limitation of the present study is its cross-sectional nature, which limits etiologic inferences from the results. Therefore, although the cross-sectional associations described here are likely to be generalizable, it must be emphasized that the AdRem study data are not population-based and hence the prevalence estimates may not be representative.

Whereas several studies have compared the prevalence among ethnic groups within the U.S., the AdRem study provides the opportunity to directly compare the prevalence of retinopathy and vascular retinal lesions among different ethnic groups within their country of origin. A pooled analysis of studies on diabetic retinopathy in the U.S. demonstrated lower prevalence in Caucasians compared with Hispanics and blacks (23). The recent MESA showed that the prevalence of retinopathy was lower in white and Chinese diabetic patients compared with Hispanic and black patients (16). The lower prevalence in Caucasians is in agreement with our results. The difference between these results and the AdRem study findings with respect to retinopathy prevalence in Chinese patients may be explained by changes in lifestyle associated with migrant populations and, possibly, earlier diagnosis of diabetes in the American Chinese population compared with our patients from mainland China. Differences in recruitment for clinical studies between the U.S. and China may also play a role. The differences in risk factors for retinopathy among ethnic groups are too small to explain the differences in prevalence of retinopathy in the AdRem study. Multiethnic studies from both the U.S., New Zealand, China, and Hong Kong also show that the ethnic differences cannot be explained by differences in risk factors such as duration of diabetes, glycemic control, blood pressure, or body weight (16,18,24–26).

Retinal vascular lesions have not been compared between Asian and Caucasian populations. However, since vascular lesions mirror retinopathy, it is unlikely that the patterns differ from those reported for retinopathy. Indeed, in the Atherosclerosis Risk in Communities (ARIC) study a lower prevalence of vascular lesions was found in Caucasian than in black participants (22).

Vascular retinal lesions are common in patients with diabetes, who also experience an increased burden of atherosclerotic disease. Follow-up of these patients will show whether these subtle vascular lesions are clinically relevant. It is well known that both increased blood glucose (or A1C) levels and increased blood pres-

sure are risk factors for the incidence and progression of retinopathy (2,6,27). In the current cross-sectional study these associations were confirmed. The differences in A1C and systolic blood pressure was of a magnitude similar to that observed in the UKPDS (14).

In the multiethnic studies conducted in the U.S., the associations between glucose level, diabetes duration, or blood pressure and the presence of retinopathy have been reported to be similar across ethnic groups (16,28). The AdRem study extends these findings to other ethnic groups predominantly living in their country of origin.

In summary, the AdRem study has shown a high prevalence of retinopathy as measured by the current "gold standard" in subjects with diabetes and differing ethnicity. Follow-up of these patients will show whether these subtle and peripheral vascular lesions are clinically relevant. Despite differences in prevalence and severity of retinopathy among Chinese, South-Asian, and Caucasian patients, the cross-sectional associations between retinal lesions and established risk factors for retinopathy were similar across ethnic groups. This result suggests that the potential benefits of glucose and blood pressure lowering on diabetic retinopathy will apply to all people irrespective of ethnicity. The main ADVANCE trial did not demonstrate clear effects of routine blood pressure lowering with the perindopril-indapamide combination on new or worsening retinopathy (29). However, the AdRem study provides an opportunity to evaluate the treatment effects using much more sensitive indicators of retinal vascular disease progression.

APPENDIX

Members of the AdRem study staff are as follows:

AdRem Investigators (project team): Prof. Ronald P. Stolk, Groningen/Utrecht, the Netherlands (principal investigator); Dr. J. Kennedy Cruickshank, Manchester, U.K. (co-principal investigator); Stephen J. Aldington, London, U.K.; Prof. Diederick E. Grobbee, Utrecht, The Netherlands (chair project team); Prof. Alun D. Hughes, London, U.K.; Prof. Juming Lu, Beijing, China; Dr. Alice A. Stanton, Dublin, Ireland; Dr. Simon A.McG. Thom, London, U.K.; and Dr. Johannes R. Vingerling, Rotterdam, the Netherlands.

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AdRem Coordination Center: Dr. Ronald P. Stolk (director AdRem Coordination Center); Truus Meijers (coordinator); Frank R. Leus (data manager); Dr. Mary J. van Schooneveld (advisor photo grading). The AdRem Substudy Coordination Center is part of the Vascular Imaging Center of the Julius Center, University Medical Center Utrecht, the Netherlands: Karin M. Nijssen (head Vascular Imaging Center).

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