

## Retinal vascular lesions in patients with type 2 diabetes mellitus of Caucasian and Asian origin - baseline results from the AdRem study

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**Running title:** AdRem: retinal lesions in type 2 diabetes

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## ABSTRACT

*Objective:* To describe prevalent vascular retinal lesions among patients with type 2 diabetes enrolled in the ADVANCE Retinal measurement study (AdRem), a sub-study of the Action in Diabetes and Vascular disease – Preterax and Diamicon Controlled Evaluation (ADVANCE) trial.

*Research Design and Methods:* Seven field stereoscopic photographs of both eyes were obtained at the baseline assessment of ADVANCE. All photographs were graded in a central reading center. Gradable retinal images were received from 1605 patients.

*Results:* The number of patients with any retinopathy (ETDRS score  $\geq 20$ ) was 645 (40.2%, 95%CI 37.8-42.6), of these 35 (2.2%, 1.6-3.0) had severe diabetic retinopathy (ETDRS  $\geq 50$ ). Focal arterial narrowing, venous beading and arteriovenous (AV) 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 (49.4%, 46.0%, 31.3%;  $p < 0.001$  adjusted for age, gender, HbA1c, systolic blood pressure and duration of diabetes) and specific vascular lesions (e.g. AV nicking 12.3%, 8.5%, 7.5%; adjusted  $p < 0.005$ ). HbA1c, 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 AdRem had retinal lesions at baseline. Despite differences in prevalence and severity of retinopathy between Chinese, South-Asian and Caucasian patients included in this study, the cross-sectional associations between established risk factors for retinopathy and retinal lesions were similar across ethnic groups.

## ABBREVIATIONS.

AdRem: ADVANCE Retinal measurement study

ADVANCE: Action in Diabetes and Vascular disease – Preterax and Diamicon MR Controlled Evaluation

AV nicking: arteriovenous nicking

DIRECT: Diabetic Retinopathy Candesartan Trial

ETDRS: Early Treatment of Diabetic Retinopathy Study

MESA: Multi-Ethnic Study of Atherosclerosis

UKPDS: United Kingdom Prospective Diabetes Study

**D**iabetic retinopathy is a progressive disorder of the microcirculation in the retina.(1) It is the commonest cause of blindness in people aged 30-69 years.(2,3) Moreover, the prevalence of blindness due to diabetic retinopathy has increased considerably during the last decades and has doubled in older people since the nineties.(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 (AV) nicking are associated with increased risk of stroke, atherosclerosis and renal dysfunction(9,10) This suggests that retinal vascular lesions may be important markers of subclinical vascular diseases. At present there is limited information regarding the relationship of microvascular abnormality to diabetic retinopathy and whether this differs by ethnicity.

ADVANCE (Action in Diabetes and Vascular disease – Preterax and Diamicon MR Controlled Evaluation) 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 AdRem substudy (ADVANCE Retinopathy Measurements), detailed fundus photographs in a subgroup of ADVANCE participants were obtained. In this paper we present the prevalence of retinal vascular lesions of the multi-ethnic 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.

**Participants.** AdRem was conducted in patients that have been randomized in the ADVANCE trial in a selected number of study centers with access to retinal cameras. Patients were eligible for ADVANCE if they had their first diagnosis of type 2 diabetes mellitus at age 30 years or older, were aged 55 or older at entry, and were at a high risk of vascular disease indicated by a diagnosis of diabetes made 10 or more years before entry, or age 65 years or older at entry, or a history of cardiovascular disease or diabetes complications, or elevated levels of cardiovascular risk factors.(11) In addition to these inclusion criteria of ADVANCE, patients who had a previous ophthalmologic 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 AdRem.

Assessments of HbA1c, blood pressure, smoking, and duration of diabetes mellitus 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/South-East Asian, and “other” which included mainly Arabic, African and mixed.

**Photography.** Photographs were taken with 35mm 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, two superior and two inferior fields. In patients with non-gradable images according to strict criteria(12) the centers were asked to obtain repeat photographs.

**Retinopathy grading.** The ETDRS classification was slightly modified in the 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 between both readers and an experienced ophthalmologist.

**Statistical analyses.** Differences in characteristics between patients with and without retinopathy were assessed by analyses of covariance, adjusting for age, gender, HbA1c, 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 where a significant association with retinal disease was demonstrated in the overall population, these relationships were also examined in subgroups defined by ethnicity. SAS version 9.1 was used for all analyses.

## RESULTS

Retinal images were received from 1984 patients. In the final analysis, 1605 (81%) patients had images of sufficient quality for

evaluation. Patients with non-gradable images were slightly, though significantly, more likely to be female, more likely to be of South Asian ethnicity, less likely to be a smoker, and were on average older, with a longer duration of diabetes, higher levels of HbA1c, and higher blood pressure (data not shown).

Table 1 shows clinical characteristics of the participants in the AdRem substudy. A total of 645 patients (40.2%, 95% CI 37.8-42.6) had any retinopathy (ETDRS score  $\geq$  20). The number of patients with mild or moderate retinopathy (ETDRS score between 20 and 50) was 610 (38.0%, 95%CI 35.6-40.4), whereas 35 (2.2%,1.6-3.0) patients had severe diabetic retinopathy (ETDRS  $\geq$  50). The prevalence of retinopathy was not associated with age or gender (data not shown). Macular oedema was present in 4.1% of men and 3.1% of women (difference  $p>0.2$ ). The prevalence of specific vascular lesions in this population were: focal arterial narrowing 3.8%, venous beading 5.1%, arteriovenous (AV) nicking 9.8%. The presence of each vascular lesion was strongly associated with the presence of retinopathy (ETDRS  $\geq$  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 to 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. Mean HbA1c level in patients with focal arterial narrowing was 0.3% higher than in patients without focal arterial narrowing ( $p<0.05$ ), whereas current HbA1c levels did not differ significantly in patients with or without macular oedema, venous beading and AV nicking (data not shown). Systolic and diastolic blood pressure were higher in patients with venous beading and macular edema ( $p<0.05$ , adjusted for age, gender and duration of diabetes). Patients with retinal vascular lesions had about one year longer

duration of diabetes, compared to those without ( $p < 0.01$ ). Current smoking was not associated with prevalent vascular retinal lesions (data not shown).

Almost half of the AdRem population was of Asian (Chinese, South Asian) ethnicity (Table 1). Compared to Caucasians, these patients had more retinopathy (defined by ETDRS score) and increased prevalence of vascular lesions (except focal arterial narrowing, Table 3). This was true for both specific white and red colored lesions (cottonwool 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, had longer diabetes duration, higher HbA1c and lower blood pressure levels compared to Caucasians: 64.9 (SD 5.5) vs 66.5 (6.0) years, 8.3 (6.4) vs 6.3 (5.6) years, 7.6% (1.6) vs 7.2% (1.3), 135/76 (21/11) vs 138/78 (21/10) mmHg, respectively, all  $p < 0.01$ . Chinese and South Asian patients also used on average 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%,  $p < 0.01$ ) compared to Caucasians. However, the differences in prevalence of retinopathy or vascular lesions between ethnic groups remained statistically significant after adjustment for these variables. The results were essentially similar by excluding the minority of patients not living in their country of origin or by including study center as an explanatory variable.

The associations between HbA1c, duration of diabetes, and systolic blood pressure with retinopathy did not differ significantly by ethnicity (Table 4). After adjustment for age, gender and ethnic group, the odds ratios for mild/moderate retinopathy were 1.24 per %HbA1c (95% confidence interval 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. Due to small numbers, separately 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 odds ratio of diabetes duration for mild/moderate retinopathy, which was slightly lower in patients from China and South Asia compared to Caucasians (Table 4).

## CONCLUSIONS

In this international study that included a broad range of patients with type 2 diabetes, more than a third of patients had retinal vascular lesions at baseline diagnosed by a sensitive procedure. Differences in prevalence of these lesions between ethnic groups were unexplained by differences in known risk factors for retinopathy. However, the associations between HbA1c, duration of diabetes, and blood pressure on retinal lesions did not differ significantly between 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 to studies using single and/or non-mydratic cameras. Indeed, the prevalence of retinopathy in AdRem (40.2%) is higher than that reported in the Multi-Ethnic Study of Atherosclerosis (MESA), which reported a prevalence of 33.2%, which is similar to previous population based studies.(16-19) However, the Diabetic RETinopathy Candesartan Trial (DIRECT), which also used seven fields photography, reported an even higher prevalence of retinopathy than AdRem.(20)

It has been shown that small vascular retinal lesions are easily overlooked by

direct fundoscopy and routine ophthalmological examination.(21) Until now vascular measurements have been limited to 45° photographs centered on the macula.(22) An additional asset of the protocol used in AdRem is the central film processing and central duplicate grading of the images. This prevents potential differences in classification between centers, which is especially relevant when comparing ethnic groups.(12)

There are some limitations to the interpretation of these data. ADVANCE 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. Since 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 between ethnic groups. Another limitation of the present study is its cross-sectional nature, which limits etiologic inferences from the results. Therefore, while the cross-sectional associations described here are likely to be generalizable, it must be emphasized that the AdRem data are not population-based and hence the prevalence estimates may not be representative.

While several studies have compared the prevalence between ethnic groups within the United States, the AdRem study provides the opportunity to directly compare the prevalence of retinopathy and vascular retinal lesions between different ethnic groups within their country of origin. A pooled analysis of studies on diabetic retinopathy in the US demonstrated lower prevalence in Caucasians compared to Hispanics and Blacks.(23) The recent MESA Study showed that the prevalence of retinopathy was lower in White and Chinese diabetes patients compared to Hispanic and Black patients.(16) The lower prevalence in Caucasians is in agreement with our results.

The difference between these results and the AdRem 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 to our patients from mainland China. Differences in recruitment for clinical studies between the United States and China may also play a role. The differences in risk factors for retinopathy between ethnic groups are too small to explain the differences in prevalence of retinopathy in AdRem. Multi-ethnic studies from both the US, New Zealand, China and Hong Kong also show that the ethnic differences cannot be explained by differences in risk factors like 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 ARIC study a lower prevalence of vascular lesions in Caucasian participants was found compared to Blacks.(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 if these subtle vascular lesions are clinically relevant. It is well known that both increased blood glucose (or HbA1c) levels and increased blood pressure 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 HbA1c and systolic blood pressure was of similar magnitude to that observed in the UKPDS.(14)

In the multi-ethnic studies conducted in the US 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) AdRem extends these findings to other ethnic groups predominantly living in their country of origin.

In conclusion, 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 if these subtle and peripheral vascular lesions are clinically relevant. Despite differences in prevalence and severity of retinopathy between 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 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 study did not demonstrate clear effects of routine blood pressure lowering with the perindopril-indapamide combination on new or worsening retinopathy.(29) However, AdRem provides an opportunity to evaluate the treatment effects using much more sensitive indicators of retinal vascular disease progression.

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**TABLE 1.** Clinical characteristics of the AdRem study population and the main ADVANCE study.

	<b>AdRem</b>	<b>ADVANCE</b>
Number	1605	11140
Female	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)
HbA1c, %	7.4 (1.5)	7.5 ( 1.6)
Diabetes treatment:		
- Dietician	36%	35%
- Oral glucose lowering medication	89%	91%
o 1 drug	43%	43%
o 2 drugs	39%	42%
o $\geq 3$ drugs	7%	6%
- Insulin	1%	1%
Blood pressure, mmHg	136/77 (21/11)	145/81 (22/11)
Blood pressure lowering medication	70%	75%

Values are means with standard deviation between parentheses or percentage.

**TABLE 2.** HbA1c, duration of diabetes, and blood pressure in patients with and without retinopathy.**2a: Any retinopathy**

	<b>No retinopathy</b> (n=960)	<b>Retinopathy present</b> (ETDRS $\geq$ 20) (n=645)	<b>p-value,</b> adjusted for age and gender
HbA1c, %	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

**2b: Severe retinopathy**

	<b>No or mild/ moderate retinopathy</b> (n=1570)	<b>Severe retinopathy present</b> (ETDRS $\geq$ 50) (n=35)	<b>p-value,</b> adjusted for age and gender
HbA1c, %	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

Values are means with standard deviation between parentheses.

**TABLE 3.** Prevalence of retinal lesions by ethnicity.

	<b>Caucasian (n=770)</b>	<b>Chinese (n=609)</b>	<b>South Asian (n=176)</b>	<b>Other (n=50)</b>	<b>p-value*</b>
Retinopathy (ETDRS $\geq$ 20)	31.3%	49.4%	46.0%	44.0%	<0.001
Severe retinopathy (ETDRS $\geq$ 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
AV nicking	7.5%	12.3%	8.5%	18.0%	<0.005

\* adjusted for age, gender, HbA1c, systolic blood pressure, duration of diabetes, number of glucose lowering drugs and insulin use

**TABLE 4.** Risk factors for mild/moderate retinopathy by ethnicity.

	<b>Caucasian (n=770)</b>	<b>Chinese (n=609)</b>	<b>South Asian (n=176)</b>	<b>Other (n=50)</b>
HbA1c (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)

Odds ratios, adjusted for age and gender, with 95% confidence intervals

## **Appendix 1** AdRem staff

### ***AdRem Investigators (project team)***

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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.

Mrs. Karin M. Nijssen (*head Vascular Imaging Center*)

### ***ADVANCE Management Committee***

John Chalmers (Chairman) (Australia), Stephen MacMahon (Vice-Chairman) (Australia), Mark Cooper (Australia), Eleuterio Ferrannini (Italy), Paul Glasziou (Australia), Diederick Grobbee (Netherlands), Pavel Hamet (Canada), Stephen Harrap (Australia), Simon Heller (United Kingdom), Liu Lisheng (China), Giuseppe Mancina (Italy), Michel Marre (France), Carl Mogensen (Denmark), Bruce Neal (Australia), Chang Yu Pan (China), Anushka Patel (Australia), Neil Poulter (United Kingdom), Anthony Rodgers (New Zealand), Bryan Williams (United Kingdom), and Mark Woodward (Australia).