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Differential Effects of Antihypertensive Treatment on the Retinal Microcirculation

An Anglo-Scandinavian Cardiac Outcomes Trial Substudy

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Abstract—Changes in the retinal microcirculation are associated with hypertension and predict cardiovascular mortality. There are few data describing the impact of antihypertensive therapy on retinal vascular changes. This substudy of the Anglo-Scandinavian Cardiac Outcomes Trial compared the effects of an amlodipine-based regimen (373 patients) with an atenolol-based regimen (347 patients) on retinal microvascular measurements made from fundus photographs. The retinal photographs were taken at a stage in the trial when treatments were stable and blood pressure was well controlled. Amlodipine-based treatment was associated with a smaller arteriolar length:diameter ratio than atenolol-based treatment (13.32 [10.75 to 16.04] versus 14.12 [11.27 to 17.81], median [interquartile range]; $P<0.01$). The association remained significant after adjustment for age, sex, cholesterol, systolic and diastolic blood pressures, body mass index, smoking, and statin treatment. This effect appeared to be largely attributable to shorter retinal arteriolar segment lengths in the amlodipine-treated group and is best explained by the vasodilator effects of amlodipine causing the visible emergence of branching side vessels. Photographic assessment of the retinal vascular network may be a useful approach to evaluating microvascular structural responses in clinical trials of antihypertensive therapy. **(*Hypertension*. 2009;54:405-408.)**

Key Words: hypertension ■ retina ■ microcirculation ■ antihypertensive treatment ■ amlodipine ■ atenolol

Hypertension is associated with many abnormalities of the retinal microvascular network, including retinopathy, generalized and focal arteriolar narrowing, arterio-venous nicking, narrowed arteriolar bifurcation angles, and arteriolar rarefaction.[1–3] Previous small studies have reported regression of some of these changes with antihypertensive treatment,[4,5] but different antihypertensive regimens have not been compared in large studies. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was a randomized, controlled multicenter clinical trial of antihypertensive therapy (amlodipine±perindopril versus atenolol±bendroflumethiazide) for 19 342 men and women ages 40 to 79 years with hypertension that demonstrated an advantageous impact on cardiovascular outcomes attributable to the newer amlodipine-based regimen as compared with the older atenolol-based regimen.[6] Retinal photography was performed after randomization in a substudy affording the opportunity to compare the effects of the 2 antihypertensive treatment regimens on the retinal microcirculation. We hypothesized that an amlodipine-based regimen would have more favorable effects on the retinal microvasculature.

Methods

The population, methods, and response rate for ASCOT are described in detail elsewhere.[7] In addition to hypertension (untreated: systolic blood pressure [BP] ≥160 mm Hg and/or diastolic BP ≥100 mm Hg at both screening and randomization; or treated: systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg at randomization), participants had ≥3 of the following cardiovascular risk factors: male sex, age >55 years, microproteinuria/macroproteinuria, smoking, dyslipidemia, family history of premature coronary heart disease, ECG abnormalities, left-ventricular hypertrophy, type 2 diabetes mellitus, peripheral arterial disease, previous stroke, or transient ischemic attack. All of the participants were randomly assigned to antihypertensive treatment with amlodipine (+perindopril added as required) or atenolol (+bendroflumethiazide-K added as required). Antihypertensive treatment was titrated to achieve target brachial BP (<140/90 mm Hg for people without diabetes mellitus and <130/80 mm Hg for people with diabetes mellitus). If necessary, additional antihypertensive agents were administered according to a prespecified algorithm to achieve the target BP. Patients were also eligible for randomization to the factorial lipid-lowering arm of ASCOT if they had a total blood cholesterol concentration ≤6.5 mmol/L and were not taking a lipid-lowering agent at the time of randomization. Patients recruited into the lipid-lowering arm of ASCOT were randomly assigned to receive 10 mg of atorvastatin daily or matching placebo.

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This trial has been registered at https://eudract.emea.europa.eu (identifier 2008-007494-20).

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Retinal photography was undertaken at 2 centers: St Mary's Hospital London and Beaumont Hospital Dublin as part of the Hypertension Associated Cardiovascular Disease Substudy.[8] The Hypertension Associated Cardiovascular Disease cohort included 1006 trial participants, and retinal photography was performed in 743 subjects who gave written, informed consent after ethical approval of the protocol by the relevant research ethics committees at both institutions. Photographs were taken at a median of 4.5 years (range: 2.7 to 6.2 years) of follow-up at a time when drug treatments and BP were stable in the 2 groups. A Zeiss FF 450 plus fundus camera (Carl Zeiss Ltd) with a 30° field of view was used after mydriasis with tropicamide (1%) eye drops. Retinal analyses were performed on digital images of superior and inferior temporal fields, as described previously.[2] A total of 720 (97%) of the 743 individuals photographed had evaluable images, and the number of nonevaluable images did not differ significantly between treatment groups (atenolol, n=13 [4%] versus amlodipine, n=10 [3%]; $P=0.4$ by χ^2 test). In brief, retinal microvascular and branching parameters were measured using a custom written program in Matlab 13 (The MathWorks). Measurements were made from an average of 6.7 vessel segments and 4.5 arterial bifurcations per subject. Measurements did not extend beyond vessel order 3 or to diameters <7.5 pixels (≈24 μm). Vessel path length was measured along the vessel center line between bifurcations. Arteriolar and venular diameters were measured at a series of intensity cross-sections at 2-pixel intervals along their lengths. At each cross-section, the vessel diameter was measured using a sliding linear regression filter technique, and an average was calculated for each vessel. To derive a measure of vessel narrowing applicable to both arterioles and venules and unaffected by the refractive properties of the eye, the length:diameter ratio (LDR) was calculated as the ratio of the length of a vessel segment between 2 branching points to its average diameter. Tortuosity was estimated as the difference between the actual path length of the vessel segment (measured by tracking) and the straight line length of the segment divided by the straight line length. Additional measurements included arteriolar bifurcation optimality ratios (the relationship between arteriolar diameters at branching points) and bifurcation angles (the internal angle between the 2 daughter vessels arising from a parent stem). Details of the methods and reproducibility have been published elsewhere.[9,10]

Data are presented as mean (SD) or median (interquartile range) for skewed data. Unadjusted comparisons were performed using a Student *t* test (with log transformation for skewed data). Multiple linear regression was also used to compare retinal parameters between treatment groups after adjustment for age, sex, cholesterol, systolic and diastolic BPs, body mass index, smoking, and randomization to atorvastatin therapy. Statistical analyses were performed using Stata 10.0 (Stata Corp).

Results

Patient characteristics at study baseline are shown in Table 1. These were comparable to the population of the main ASCOT, and there no significant differences between subjects randomized to the 2 treatment groups. Mean BPs at the time of photography in this cohort were 131±17/78±13 mm Hg in those on the atenolol-based regimen and 131±10/76±9 mm Hg in those on the amlodipine-based regimen ($P=0.8$ and $P=0.006$ for systolic and diastolic pressures, respectively). As expected, pulse rates were significantly lower in those on the atenolol-based regimen (60±11 versus 72±13 bpm; $P<0.001$). Retinal parameters according to treatment group are shown in Table 2. The main finding was a smaller arteriolar LDR associated with amlodipine treatment (13.32 [interquartile range: 10.75 to 16.04] versus 14.12 [interquartile range: 11.27 to 17.81]). There was also a significantly greater number of measurable arteriolar segments per subject in the amlodipine-treated group (6.8±2 versus 6.4±2; $P=0.012$), and arteriolar segment lengths were shorter in those on the amlodipine-based regimen (458.4 pixels [interquartile range: 389.7 to 547.0 pixels] versus 444.7 pixels [interquartile range: 377.7 to 510.5 pixels]; $P=0.02$). There was also a significant difference in arteriolar tortuosity such that this was lower in patients on the amlodipine-based regimen. There were no differences in arteriolar bifurcation angles, arteriolar bifurcation optimality, or in any venular measures between treatment groups.

Table 1. Patient Characteristics at Randomization According to Antihypertensive Treatment Allocation

Parameter	Atenolol Based (n=347)	Amlodipine Based (n=373)	*P* for Difference
Age, y	61.2±7.7	61.7±8.0	0.387
Female sex, n (%)	76 (21.9)	85 (22.8)	0.776
Ethnicity			0.220
White, n (%)	304 (87.9)	329 (88.4)	
South Asian, n (%)	10 (2.9)	17 (4.6)	
African Caribbean, n (%)	24 (6.9)	15 (4.0)	
Mixed/other, n (%)	9 (2.6)	12 (3.2)	
Current smoker, n (%)	71 (20.5)	86 (23.1)	0.399
Diabetes mellitus, n (%)	72 (20.8)	88 (23.6)	0.359
Family history of coronary artery disease, n (%)	70 (20.2)	77 (20.6)	0.876
Weight, kg	84.5±14.2	84.9±15.6	0.682
Body mass index, kg/m^2	29.2±4.6	29.3±4.7	0.721
Systolic BP, mm Hg	159.1±17.0	159.9±17.8	0.554
Diastolic BP, mm Hg	93.3±9.6	92.8±10.1	0.524
Heart rate, bpm	71.5±12.1	71.7±12.9	0.890
Biochemical			
Triglycerides, mmol/L	1.5 (1.1 to 2.0)	1.6 (1.1 to 2.2)	0.042
Total cholesterol, mmol/L	5.75±1.00	5.77±1.05	0.807
HDL cholesterol, mmol/L	1.3 (1.3 to 1.5)	1.2 (1.0 to 1.4)	0.047
LDL cholesterol, mmol/L	3.68±0.89	3.70±0.93	0.799
Glucose, mmol/L	5.3 (4.9 to 6.1)	5.3 (4.9 to 6.1)	0.927
Creatinine, μmol/L	97.0±16.6	98.4±17.1	0.341

Data are mean±SD or medians (interquartile ranges) for skewed data unless otherwise stated. *P* values were calculated by *t* tests (no normally distributed parameters were log transformed) for continuous variables and χ^2 tests for categorical data. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

The treatment difference in LDR was preserved in multivariate modeling after adjustment for age, sex, and diastolic BP (Table 2); other models, including age, sex, cholesterol, systolic and diastolic BPs, body mass index, and smoking, did not differ substantially, and a significant difference between treatments remained (LDR atenolol-treated group: 14.84 [interquartile range: 14.32 to 15.37] versus amlodipine-treated group: 13.90 [interquartile range: 13.40 to 14.41]; $P=0.012$ for all of the above variables in the model).

Discussion

This is the first large study to demonstrate differences in the retinal arteriolar microvasculature in response to different antihypertensive regimens. The principle difference between

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Table 2. Retinal Parameters According to Antihypertensive Treatment Group

Parameter	Atenolol Based (n=347)	Amlodipine Based (n=373)	*P* for Difference
Arteriolar LDR	14.12 (11.27 to 17.81)	13.32 (10.75 to 16.04)	<0.01
Arteriolar LDR (adjusted for age, sex, and diastolic BP)	14.80 (14.28 to 15.31)	13.90 (13.4 to 14.39)	0.01
Arteriolar diameter (all segments), pixels	28.4±3.2	28.7±3.1	0.2
Arteriolar diameter (symmetrical bifurcations), pixels	28.1±4.9	28.9±4.7	0.03
Arteriolar segment length, pixels	458.4 (389.7 to 547.0)	444.7 (377.7 to 510.5)	0.02
Arteriolar tortuosity ($\times 10^{-2}$)*	1.51 (0.80 to 3.08)	1.39 (0.65 to 2.52)	0.04
Arteriolar bifurcation angle, °	83.48±14.11	83.80±13.06	0.7
Arteriolar optimality ratio	0.822±0.042	0.822±0.040	>0.9
Venular LDR	10.5 (7.8 to 14.0)	10.3 (7.7 to 13.3)	0.6
Venular diameter, pixels	41.7±5.1	42.4±5.0	0.08
Venular path length, pixels	478.1 (352.6 to 610.0)	464.6 (344.4 to 571.6)	>0.9

Data are mean±SD, medians (interquartile range), or means (95% CI) for adjusted variables. *P* for difference was calculated by Student *t* test (nonnormally distributed parameters were log transformed or *square root transformed).

the 2 treatment groups is that subjects randomized to amlodipine-based therapy had lower LDR, a measure of arteriolar narrowing, than those randomized to atenolol. Amlodipine-based therapy was associated with an increased number of arterioles, and in all of the arterioles, amlodipine-based therapy appeared to be associated with shorter arteriolar segment lengths, and arteriolar diameters differed nonsignificantly. However, when only symmetrical bifurcations were examined, arteriolar diameters were significantly wider in patients randomized to amlodipine-based therapy. The most likely explanation of these observations is that amlodipine-based therapy results in vasodilation and increased counting of small side-branch arterioles. The appearance of these side branches effectively divides a stem arteriolar segment into 2 daughter segments. The resultant daughter segments are shorter and narrower, and their greater number in the amlodipine-treated group weights the overall mean values and particularly obscures the treatment difference in diameter when not normalized for length. The lower arteriolar tortuosity in the amlodipine-treated group may also be a consequence of the reduction in arteriolar segment length.

The observations of differential effects of a calcium channel blocker–based therapy versus β-blocker–based therapy are in line with previous comparisons of the effects of β-blockers and calcium antagonists on small resistance arteries reported from both in vitro and in vivo studies. Studies of human small arteries dissected from subcutaneous tissue of hypertensive subjects showed that 1 year of treatment with amlodipine resulted in outward remodeling (reduction in the media:lumen ratio), whereas treatment with atenolol had no such effect in spite of equivalent BP reduction.[11] In vivo, calcium antagonists at least preserve and may increase cerebral blood flow in the course of hypertension treatment,[12] whereas β-blockers (with the exception of those that have inherent vasodilating properties or intrinsic sympathomimetic activity) do not achieve regression of hypertensive microcirculation changes as assessed by measurements of minimum forearm vascular resistance.[13] In addition, atenolol-based antihypertensive treatment reduces carotid blood flow compared with angiotensin receptor blockade.[14] These observations are consistent with the view that small artery structure adjusts in response to vasodilatation rather than simply BP reduction during antihypertensive treatment.[15]

We have reported previously that both amlodipine-based and lisinopril-based treatments caused a reduction in arteriolar narrowing, a widening of the arteriolar bifurcation angle, and an increase in arteriolar density in a small group of hypertensive subjects.[5] In that study, comparisons of the retinal microvasculature were made between the beginning and the end of the study. The lack of retinal photography at baseline is a limitation of the current work, and, as a consequence, it is not possible to evaluate the effects of BP reduction itself on the retinal microvasculature. In addition, diastolic BP was marginally but significantly lower (≈2 mm Hg) with amlodipine-based treatment; statistical adjustment for diastolic BP did not significantly affect differences in LDR, but the possibility that treatment-related differences in microvascular pressure exist and affect arteriolar diameter cannot be excluded. Similarly, it is likely that there was a difference in central systolic BP between the 2 groups. The Conduit Artery Function Evaluation Substudy of ASCOT estimated central BP from radial tonometry using a transfer function and reported that central aortic systolic BP was 4.3 mm Hg lower in the amlodipine-treated group.[16] Unfortunately, radial tonometry measurements were not made concurrent with the retinal photography in this study, and whether central systolic BP or mean BP is the critical determinant of retinal microvascular pressure is uncertain.

The importance of retinal vascular changes associated with hypertension and cardiovascular disease is that they are predictive of cardiovascular outcomes. Graded hypertensive retinopathy has long been associated with the severity of hypertension. Emerging data indicate that a range of measures of retinal geometry and more subjective evaluations of retinopathy are independently predictive of the development of hypertension and diabetes mellitus[17] and also predictive of stroke and coronary death.[10,18] In addition, some recent studies have reported associations between retinal microvascular abnormalities and large artery (macrovascular) disease.[19–21] Clearly, if a relationship exists between microvascular and macrovascular diseases, its temporal relationship will be difficult to establish, but it is worth noting that several of the retinal vascular

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abnormalities that are described in relation to cardiovascular risk factors and outcomes are evident in youth; here they associate with low birth weight and appear to be early features of cardiovascular disease.[22,23]

Perspectives

New approaches to quantification of the retinal vascular network offer increasingly accurate noninvasive and repeatable assessment of the structure and function of the microcirculation. The pattern of retinal microvascular changes associated with hypertension is now well described. Some of these changes are predictive of subsequent cardiovascular outcomes; regression of the changes in response to BP reduction has been demonstrated previously. The data presented here indicate antihypertensive drug class–specific effects for the calcium antagonist amlodipine that are in line with vasodilatory activity and reported effects on other measures of microvascular structure.

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Disclosures

None.

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