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ORIGINAL RESEARCH

Effect of Intensive Blood Pressure Lowering Treatment on Retinal Microvasculature

Secondary Analysis From ESPRIT

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ABSTRACT

BACKGROUND Retinal microvasculature is a key affected target organ of hypertension, which can serve as a marker of systemic microcirculation. Whether intensive blood pressure–lowering treatment affects retinal microvasculature remains unknown.

OBJECTIVES The purpose of this study was to assess the effect of intensive treatment targeting systolic blood pressure <120 mm Hg on retinal microvasculature compared with standard treatment targeting systolic blood pressure <140 mm Hg.

METHODS In a multicenter randomized trial conducted at 116 sites in China, we randomly assigned adults aged 50 years or older with high cardiovascular risk to receive intensive treatment targeting systolic blood pressure <120 mm Hg or standard treatment targeting systolic blood pressure <140 mm Hg. A subgroup of participants at 17 sites was selected to undertake color fundus photography at a 3-year follow-up. Retinal microvasculature measures were derived via a standard pipeline. The main outcome was arteriole-venule ratio, a measure of retinal arteriolar caliber. Other measures of vessel complexity, density, and tortuosity were also compared. Subgroup analyses of sex, age, diabetes, coronary heart disease, stroke, systolic blood pressure level, hypertension duration, and pupil dilation status were performed for arteriole-venule ratio.

RESULTS In total, 555 participants in the intensive arm and 526 in the standard arm were included. Mean age was 62.7 ± 6.4 years, and 37.8% were women. After adjusting for age and sex, the intensive arm showed increased arteriolar caliber, as evidenced by arteriole-venule ratio ($\beta = 0.16$; 95% CI: 0.05-0.28; $P = 0.005$) compared with the standard arm, consistent with central retinal arteriole equivalent ($\beta = 0.14$; 95% CI: 0.02-0.25; $P = 0.02$). No significant results were observed for venular caliber. No heterogeneity was found across subgroups. The intensive arm also showed increased arteriolar complexity, arteriolar density, and reduced vessel tortuosity compared with the standard arm.

CONCLUSIONS Among hypertensive patients with high cardiovascular risk, lowering systolic blood pressure with a target of <120 mm Hg compared with <140 mm Hg has a favorable impact on retinal microvasculature, providing the first evidence that such intervention may improve systemic microcirculation and mitigate hypertension-mediated organ damage. (Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing RIsk of Vascular evenTs [ESPRIT] Study; NCT04030234) (JACC. 2025;86:1377-1388) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACD = peripheral anterior chamber depth

AVR = arteriole-venule ratio

CFP = color fundus photography

CRAE = central retinal arteriolar equivalent

CRVE = central retinal venular equivalent

SBP = systolic blood pressure

Retinal microvasculature offers a unique and accessible window to study the health of human microcirculation, because retina shares anatomical and physiological similarities with other critical organs, such as the brain and kidneys.[1,2] Structural changes in retinal microvasculature can reflect chronic vascular damage resulting from various cardiovascular risk factors and systemic conditions. Retinal microvasculature abnormalities, which can be precisely and objectively analyzed through color fundus photography (CFP) with artificial intelligence techniques, hold promise as biomarkers that can be routinely monitored for chronic diseases and cardiovascular health,[3] as well as exploratory surrogate outcomes for clinical trials.[4] Some microvasculature abnormalities, such as narrowed arteriolar caliber[5-7] and widened venular caliber,[8-10] are associated with an increased risk of cardiometabolic diseases.

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Hypertension significantly affects retinal microvasculature, contributing to various abnormalities, including retinopathy, generalized or focal arteriolar narrowing, and arteriolar rarefaction.[11] It is suggested that antihypertensive treatment may reverse some of these retinal microvasculature changes.[12-14] However, currently no evidence supports the additional benefit of intensive treatment targeting systolic blood pressure (SBP) <120 mm Hg on retinal microvasculature compared with standard treatment targeting SBP <140 mm Hg. Understanding these questions can provide insights into the impact of intensive blood pressure (BP)-lowering treatment on the retinal microvasculature and systemic target organ health of hypertensive patients.

ESPRIT (Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing Risk of Vascular Events; NCT04030234) is a multicenter, open-label, randomized controlled trial that demonstrated the efficacy of intensive BP-lowering treatment in reducing major vascular events in Chinese hypertensive patients with high cardiovascular risk.[15] In this prespecified secondary outcome analysis, color fundus photographs were obtained from a subgroup of participants to test the hypothesis that those randomized to intensive treatment targeting SBP <120 mm Hg would experience a favorable outcome in retinal arteriolar caliber than those in the standard treatment targeting SBP <140 mm Hg. We also performed exploratory assessments on other retinal microvasculature measures, including vessel complexity, density, and tortuosity.

METHODS

STUDY DESIGN AND POPULATION. ESPRIT is a multicenter, open-label, randomized controlled trial at 116 sites in China. The trial design and methods have been published previously.[16] The trial protocol is presented in the Supplemental Material. Participants who were at least 50 years of age and with SBP

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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130 to 180 mm Hg were considered to be eligible if they had an increased cardiovascular risk (ie, established cardiovascular disease or at least 2 major cardiovascular risk factors). The central ethics committee at Fuwai Hospital and the ethics committee of each participating site approved the trial. All participants provided written informed consent.

There were 17 sites that were capable of conducting the CFP examination and agreed to participate in this study. Exclusion criteria for the CFP examination included opacification of the refractive media, which severely affected the quality of photographs (such as severe cataract, vitreous hemorrhage, and so on) and inability to cooperate with the CFP procedure. The study population consisted of eligible participants from these 17 sites who provided additional informed consent for CFP. They undertook CFP at the 3-year follow-up.

RANDOMIZATION, BLINDING, AND PROCEDURES. Eligible participants were allocated to either intensive treatment (SBP target <120 mm Hg) or standard treatment (SBP target <140 mm Hg) in a 1:1 ratio using a minimized randomization program with site stratification. Minimization algorithm was performed based on age, sex, coronary heart disease, stroke, diabetes mellitus, smoking status, low-density lipoprotein cholesterol level, baseline SBP level, baseline statin use, and number of antihypertensive medication use. Site investigators and participants were aware of their treatment-arm assignments, but the technicians performing the CFP examination and the image analyst were blinded to the treatment allocation. At randomization, physical measurements including seated office BP, height, and weight, were collected according to standard operational procedures. Blood samples were collected for central laboratory analyses of lipid levels and creatinine. After randomization, participants in both arms were followed up at 1, 2, 3 months, and then every 3 months.

Investigators adjusted participants' antihypertensive medications based on standard office BP measurement and treatment-arm assignment, guided by unified treatment algorithms.[16] At each office visit, BP was measured by a trained investigator using an electronic BP monitor (Omron HBP-1100, Omron Corp), which was connected to a computer, so that the BP values were transferred into the electronic case report to avoid recording errors. BP was measured 3 times with an interval of 1 minute according to the standard procedure after the participant was seated and had a quiet rest for at least 5 minutes. The mean value of the 3 readings was used as the BP level.

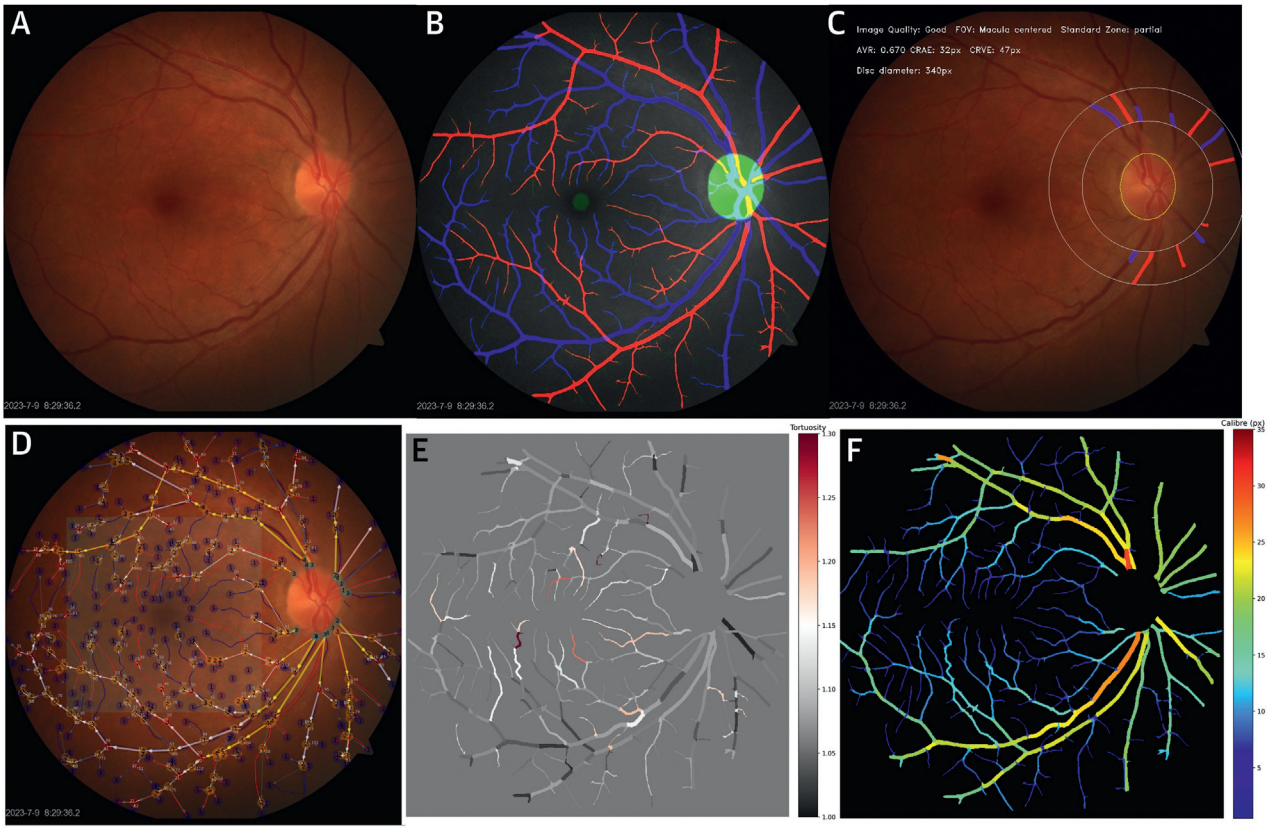
COLOR FUNDUS PHOTOGRAPHY AND MICROVASCULATURE MEASURES. We performed 45° CFP examination with the standardized Zeiss Visucam Pro NM Retinal Camera. To ensure consistency, all technicians were trained to use a standardized protocol. Before CFP examination, intraocular pressure was measured using a standard noncontact tonometer, followed by a slit-lamp examination by an ophthalmologist to assess peripheral anterior chamber depth (ACD) using the Van Herick method. Participants with an ACD greater than one-fourth corneal thickness (grade ≥2) received 1 drop of 0.5% tropicamide, with pupil dilation assessed after 20 minutes before proceeding with photography. For those with ACD less than or equal to one-fourth corneal thickness (grade ≤1), pupil dilation was avoided to prevent angle-closure glaucoma, and natural pupil dilation was performed in a dark room for 15 minutes, targeting a pupil diameter of ≥5 mm for nonmydriatic photography.

Both eyes underwent photography under standardized illumination and imaging conditions. At least 2 photographs for each eye were obtained (1 optic disc-centered and 1 macula-centered). The photographs were assessed by the designated technician for quality control to ensure consistent image quality. Qualified retinal photographs were processed and analyzed using a standard pipeline, the Retina-based Microvascular Health Assessment System.[17-20] This pipeline is an artificial intelligence system for fully automated segmentation and quantification of retinal vascular networks. It has been validated across multiple data sets for retinal artery and vein segmentation,[17] as well as in large-scale population studies from China and the United Kingdom.[18,20-23] Information on the algorithm workflow, software package, and pipeline validation is presented in the Supplemental Methods. In this study, the quality of each photograph was graded as "good," "usable," and "reject" according to the pipeline. Photographs graded as "good" or "usable" were considered as qualified and included in the analysis.

A total of 25 retinal microvasculature measures were extracted from the CFP, covering 4 key categories: caliber, complexity, density, and tortuosity. Detailed descriptions of each measure are provided in Supplemental Table 1. **Figure 1** shows an example of vessel measurements.

OUTCOMES. The retinal microvasculature outcomes were added in the protocol version 2.3 in February 2023, where arteriole-venule ratio (AVR) was prespecified as a secondary outcome, and other retinal microvasculature measures were listed as tertiary outcomes. AVR, a metric of arteriolar caliber, is defined as the ratio of the central retinal arteriolar equivalent (CRAE) to the central retinal venular

FIGURE 1 **Illustration of the Automatic Vessel Analysis of Retina-Based Microvascular Health Assessment System**



(A) Original color fundus photograph. (B) Arteries (red), veins (blue), optic disc (green), and macula (light green) segmentation. (C) Image quality shown on the plot. The standard zone is a circular region between 1 and 1.5 disc-diameters, where the central retinal arteriolar diameter equivalents (CRAE), central retinal venular diameter equivalents (CRVE), and arterio-venous ratio (AVR) are measured. (D) The topology map illustrates the hierarchy, branching pattern, and density of the retinal arteriole and venular tree network. The rectangular box indicates the macula region. The vessels are divided into segment units, with each measurement taken at the level of the segment and summarized per image. (E) Tortuosity map showing the tortuosity measured at each vessel segment using a color scale from black (smallest) to red (largest). (F) Vessel caliber map showing the diameter of retinal vessels using a color scale from blue (smallest) to red (largest).

equivalent (CRVE), measured within a circular region located 1 disc diameter from the optic disc margin. CRAE and CRVE represent the average widths of the central retinal artery and central retinal vein. We prespecified AVR as the main outcome because this measure is dimensionless with controls for magnification differences from camera lenses and refractive error.[24] CRAE and CRVE were also assessed, respectively. Length diameter ratio of arteriole and length diameter ratio of venule are the ratios of vessel length and vessel caliber, unaffected by imaging resolution and field. Larger value indicates smaller vessel caliber. Other measures on complexity, density, and tortuosity were also evaluated (Supplemental Table 1). We assessed these measures because they have been reported to correlate with multiple systemic vascular diseases.[20,25,26]

STATISTICAL ANALYSIS. Baseline characteristics were presented as mean ± SD for continuous variables or as counts (percentages) for categorical variables. We compared differences between arms with Wilcoxon rank sum tests or chi-square tests. Photographs of the right eye were primarily analyzed, with left eye photographs used for imputation if the right eye images were ungradable according to the Retina-based Microvascular Health Assessment System. For participants with >1 qualified photograph, the mean value of each retinal microvasculature measure was used. All retinal microvasculature measures were standardized, with outliers (>3 or <−3) excluded

from the analysis. The distribution of retinal microvasculature measures between arms was visualized by waterfall plots.

We fitted a linear regression model to compare retinal microvasculature measures between the 2 treatment arms, adjusting for age and sex caused by significant between-arm differences (Table 1). Several sensitivity analyses were performed to examine the robustness of our study. First, we used a mixed model with site as a random effect to account for center-specific variation, adjusting for randomization variables. We further adjusted for pupil dilation status in addition to randomization variables, given its potential impact on retinal microvascular measurements. Second, we used an inverse-probability treatment weighting method to evaluate the potential influence of excluded samples, either caused by poor image quality or participant opt-out. We fitted a logistic regression model to estimate the probability of exclusion, incorporating predictors including age, sex, cardiovascular risk factors and comorbidities. We applied inverse probability weighting based on the propensity score to weight the observed within-arm differences in microvascular measures, adjusting for randomization variables and pupil dilation status, with study site included as a random effect. Third, to evaluate whether the effect of intensive BP lowering on AVR differed between right and left eyes, we included images from both eyes and employed a mixed-effects model with participant as a random effect. An interaction term between the treatment arm and eye laterality (left or right) was included in the model. As an additional analysis, we assessed the association among SBP, diastolic BP, and mean arterial pressure at the most recent follow-up visit before CFP and retinal microvascular outcomes, adjusting for age, sex, and pupil dilation status.

Tests for heterogeneity of treatment effects on AVR were conducted in subgroups, including age, sex, diabetes mellitus, coronary heart diseases, stroke, SBP level, hypertension duration, and pupil dilation status. Additionally, because left-eye measurements were substituted for participants with ungradable right-eye images but usable left-eye images, we conducted a mirror-eye subgroup analysis to assess the consistency of treatment effects in this subset.

To assess potential antihypertensive drug-specific effects beyond BP lowering, we adjusted for regular use (self-report compliance >80%) of renin-angiotensin system inhibitors, β-blockers, calcium-channel blockers, and diuretic agents at 1-year follow-up, in addition to the randomization variables. We selected medication use at the 1-year follow-up because both treatment arms had achieved stable SBP targets by that time, and the medication pattern was considered representative of long-term use.

TABLE 1 Baseline Characteristics

	Intensive Treatment (n = 555)	Standard Treatment (n = 526)	*P* Value
Age, y	63.1 ± 6.3	62.3 ± 6.5	0.03
Women	226 (40.7)	183 (34.8)	0.04
Current smoker	237 (42.7)	235 (44.7)	0.51
Diabetes	215 (38.7)	208 (39.5)	0.79
Coronary heart disease	114 (20.5)	118 (22.4)	0.45
Stroke	109 (19.6)	100 (19.0)	0.79
Time from hypertension diagnosis to randomization visit, years	10.1 (5.4-17.0)	10.6 (5.0-19.0)	0.48
SBP at randomization, mm Hg	146.1 ± 10.5	147.2 ± 10.9	0.13
DBP at randomization, mm Hg,	83.8 ± 10.2	84.6 ± 11.1	0.19
BMI, kg/m^2	26.5 ± 3.1	26.6 ± 3.1	0.67
eGFR, mL/min/1.73 m^2	84.4 ± 13.1	84.9 ± 13.1	0.57
eGFR <60 mL/min/1.73 m^2	26 ± 4.7	17 ± 3.2	0.22
Total cholesterol, mmol/L	4.1 ± 1.1	4.0 ± 1.1	0.32
LDL cholesterol, mmol/L	2.4 ± 0.8	2.3 ± 0.8	0.58
HDL cholesterol, mmol/L	0.9 ± 0.3	0.9 ± 0.2	0.21
Statin use	220 (39.6)	231 (43.9)	0.15
Number of baseline antihypertensive medication ≥2	276 (49.7)	263 (50.0)	0.93

Values are mean ± SD, n (%), or median (Q1-Q3).
BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure.

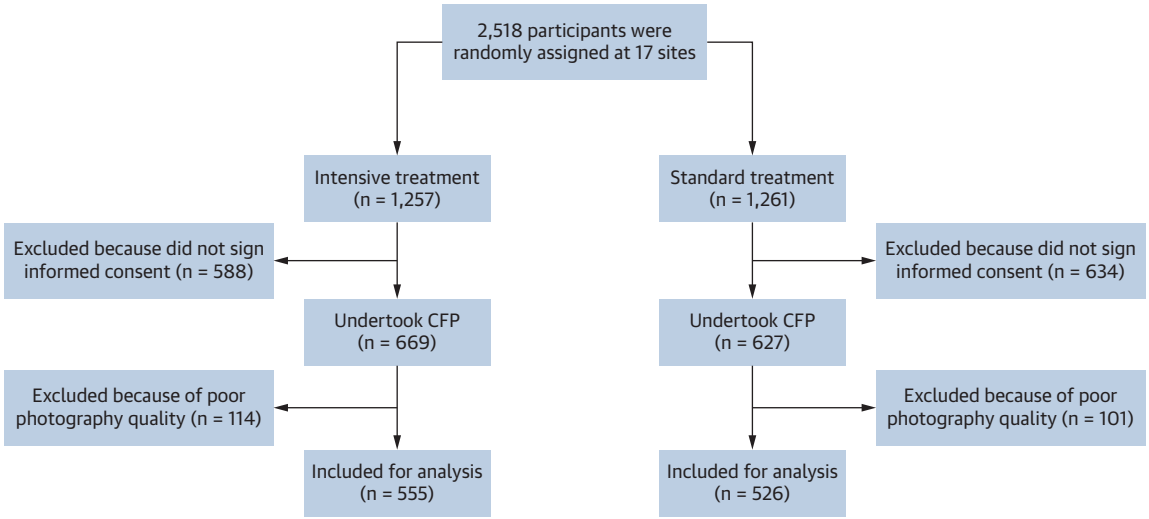
Overall, the proportion of missing values caused by outlier exclusion ranged from 0.1% for arteriolar skeleton density to 1.7% for arteriolar linear regression tortuosity. Missing values for each outcome were excluded from the respective analyses. All hypothesis tests were 2-sided at a significance level of $\alpha = 0.05$. Given the nature of exploratory analyses, we did not adjust for multiple comparisons. The quality assessment, vessel measurement, and analysis of retinal microvasculature measures were performed by Python 3.6.8. Other analyses were performed using SAS version 9.4 (SAS Institute Inc).

PATIENT AND PUBLIC INVOLVEMENT. No patients were involved in the design of the study or review of our paper. Although no patients or members of the public were directly involved in this study, the clinical investigators' informed the patients of the design and rationale of this study.

RESULTS

STUDY POPULATION. The ESPRIT trial randomized 11,255 participants across 116 sites. In 17 sites capable of conducting the CFP examination, a total of 2,518 participants were originally randomized. There were

FIGURE 2 Flowchart of Inclusion of Participants and CFP



CFP = color fundus photography.

1,267 participants who underwent CFP examinations, among whom 1,081 provided at least 1 qualified photograph, forming the study population (**Figure 2**).

For the included participants, the mean age was 62.7 ± 6.4 years, and 409 (37.8%) were women. Diabetes was reported in 423 (39.1%) participants, coronary heart disease in 232 (21.5%), and prior stroke in 209 (19.3%) (**Table 1**). The mean SBP at baseline was 146.6 ± 10.7 mm Hg. The median duration of follow-up was 3.5 years (Q1-Q3: 3.4-3.6 years). The characteristics of participants excluded because of poor image quality are presented in Supplemental Table 2. Compared with the included participants, those excluded were older, had a higher proportion of women, were more likely to have diabetes and coronary heart disease, and were less likely to have undergone pupil dilation.

BLOOD PRESSURE. At baseline, the mean SBP in the intensive and standard treatment arms for the study population was 146.1 ± 10.5 mm Hg and 147.2 ± 10.9 mm Hg, respectively. The intensive treatment arm had achieved sustained BP reduction since 9 months of randomization and maintained a stable SBP level of 120 mm Hg. The standard treatment arm had achieved sustained BP reduction since 2 months of randomization and maintained a stable SBP level of 135 mm Hg (Supplemental Figure 1). The association among SBP, diastolic BP, and mean arterial pressure at the latest follow-up visit before CFP and retinal microvasculature outcomes is shown in the Supplemental Table 3. In general, retinal microvasculature caliber, density, and complexity decreased with the increase of BP levels, whereas tortuosity showed no significant association with BP level.

RETINAL MICROVASCULATURE MEASURES. Pupil dilation was applied similarly in both treatment arms (intensive arm, 375 [67.6%], standard arm, 356 [67.7%]; $P = 0.97$). The waterfall plots of the microvasculature measures are shown in Supplemental Figures 2 to 5. The unadjusted and adjusted effects of intensive treatment on retinal microvasculature measures are shown in **Tables 2 and 3**, respectively. After adjusting for age and sex, intensive treatment significantly increased arteriolar caliber, as evidenced by an increase in AVR (β = 0.16; 95% CI: 0.05-0.28; $P = 0.005$) (Supplemental Figure 2) and CRAE (β = 0.14; 95% CI: 0.02-0.25; $P = 0.02$) compared with standard treatment. A consistent effect on AVR was observed across subgroups (**Figure 3**). No significant effect was found on venular caliber, as measured by CRVE (β = −0.05; 95% CI: −0.16 to 0.07; $P = 0.42$). Measures of arteriolar density, including area density, skeleton density, bifurcation density, and branching density, were significantly increased in the intensive treatment arm compared with the standard treatment arm, whereas corresponding venular measures did not show significant differences. Moreover, intensive treatment also significantly increased

TABLE 2 Unadjusted Analysis for Effect of Intensive vs Standard Blood Pressure–Lowering Treatment on Retinal Arteriolar and Venular Measures

	Arteriolar Measures[a]	Unadjusted Effect Size (95% CI)	*P* Value	Venular Measures[a]	Unadjusted Effect Size (95% CI)	*P* Value
Caliber	Arteriole-venule ratio	0.17 (0.06-0.28)	0.004	/	/	/
	Central retinal arteriole equivalent	0.13 (0.01-0.24)	0.03	Central retinal venule equivalent	−0.06 (−0.18 to 0.05)	0.28
	Length diameter ratio of arteriole	−0.06 (−0.17 to 0.05)	0.26	Length diameter ratio of venule	0.01 (−0.09 to 0.12)	0.83
Density	Arteriolar area density	0.15 (0.04-0.27)	0.01	Venular area density	−0.05 (−0.17 to 0.07)	0.39
	Arteriolar skeleton density	0.11 (−0.01 to 0.23)	0.08	Venular skeleton density	−0.07 (−0.19 to 0.05)	0.23
	Arteriolar bifurcation density	0.07 (−0.04 to 0.19)	0.21	Venular bifurcation density	−0.05 (−0.16 to 0.06)	0.37
	Arteriolar branching density	0.10 (−0.02 to 0.22)	0.09	Venular branching density	−0.04 (−0.15 to 0.07)	0.51
Complexity	Arteriolar fractal dimension	0.13 (0.01-0.24)	0.03	Venular fractal dimension	−0.06 (−0.17 to 0,05)	0.29
	No. of arteriolar branching point	0.12 (0-0.24)	0.03	No. of venular branching point	−0.07 (−0.19 to 0.04)	0.22
	No. of arteriolar bifurcation point	0.07 (−0.05 to 0.18)	0.28	No. of venular bifurcation point	−0.09 (−0.21 to 0.04)	0.22
	No. of arteriolar segment	0.11 (−0.01 to 0.23)	0.08	No. of venular segment	−0.09 (−0.21 to 0.03)	0.14
Tortuosity	Arteriolar turning angle	−0.14 (−0.25 to −0.02)	0.02	Venular turning angle	−0.13 (−0.25 to −0.02)	0.03
	Linear regression tortuosity	−0.05 (−0.11 to 0.01)	0.13	Linear regression tortuosity	−0.02 (−0.10 to 0.05)	0.54

[a]All the measures were standardized before modeling.

arteriolar complexity, indicated by fractal dimension, number of branching points, number of bifurcation points, and number of vessel segments, but had no significant effect on these measures of venules. Tortuosity measures, including vessel turning angle and linear regression tortuosity, showed a similar reduction tendency for both arterioles and venules in the intensive treatment arm compared with the standard treatment arm. Sensitivity analysis accounting for randomization variables and study center effect, with or without adjustment of pupil dilation status, showed consistent results with the main analysis (Supplemental Tables 4 and 5). Accounting for the participants excluded because of poor image quality or opt-out also showed similar results (Supplemental Table 6). Analysis of left-eye retinal microvasculature measures did not materially change the results, except that the between-arm difference in AVR became insignificant ($P = 0.13$) (Supplemental Table 7). Mixed model analysis showed that the effect of intensive BP-lowering treatment did not significantly differ between the left and right eyes for AVR (P for interaction = 0.21) (Supplemental Table 8). Multivariable analysis did not detect any significant effects of antihypertensive medications on AVR (Supplemental Table 9).

DISCUSSION

In this prespecified secondary outcome analysis of the ESPRIT trial, we demonstrated for the first time that intensive treatment targeting SBP <120 mm Hg in hypertensive patients with high cardiovascular risk for 3 years improved retinal microcirculation

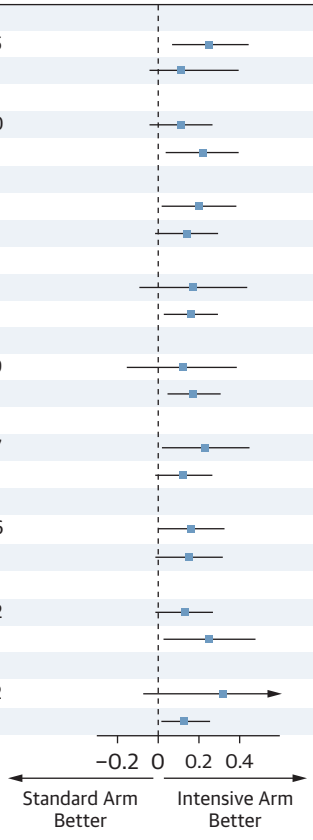
TABLE 3 Adjusted Analysis of the Effect of Intensive vs Standard Blood Pressure Lowering Treatment on Retinal Arteriolar and Venular Measures

	Arteriolar Measures[a]	Adjusted Effect Size[a] (95% CI)	*P* Value	Venular Measures[a]	Adjusted Effect Size[b] (95% CI)	*P* Value
Caliber	Arteriole-venule ratio	0.16 (0.05-0.28)	0.005	/	/	/
	Central retinal arteriole equivalent	0.14 (0.02-0.25)	0.02	Central retinal venule equivalent	−0.05 (−0.16 to 0.07)	0.42
	Length diameter ratio of arteriole	−0.09 (−0.19 to 0.01)	0.08	Length diameter ratio of venule	−0.03 (−0.13 to 0.07)	0.62
Density	Arteriolar area density	0.19 (0.08-0.30)	0.001	Venular area density	−0.01 (−0.12 to 0.10)	0.90
	Arteriolar skeleton density	0.16 (0.05-0.27)	0.003	Venular skeleton density	−0.01 (−0.11 to 0.10)	0.88
	Arteriolar bifurcation density	0.12 (0.01-0.23)	0.04	Venular bifurcation density	−0.01 (−0.12 to 0.09)	0.80
	Arteriolar branching density	0.13 (0.02-0.24)	0.02	Venular branching density	0 (−0.10 to 0.11)	0.98
Complexity	Arteriolar fractal dimension	0.17 (0.07-0.28)	0.002	Venular fractal dimension	−0.01 (−0.11 to 0.10)	0.91
	No. of arteriolar branching point	0.17 (0.06-0.28)	0.002	No. of venular branching point	−0.01 (−0.12 to 0.10)	0.86
	No. of arteriolar bifurcation point	0.11 (0-0.22)	0.05	No. of venular bifurcation point	−0.04 (−0.15 to 0.07)	0.49
	No. of arteriolar segment	0.16 (0.06-0.27)	0.003	No. of venular segment	−0.02 (−0.13 to 0.08)	0.68
Tortuosity	Arteriolar turning angle	−0.14 (−0.26 to −0.02)	0.02	Venular turning angle	−0.13 (−0.25 to −0.01)	0.03
	Linear regression tortuosity	−0.04 (−0.10 to 0.02)	0.16	Linear regression tortuosity	−0.02 (−0.09 to 0.06)	0.60

[a]All of the measures were standardized before modeling. [b]Adjusting for age and sex.

FIGURE 3 Effect of Intensive vs Standard Treatment on Arteriole-Venule Ratio by Subgroups

Subgroup	No. (%)	*P* for Interaction	Adjusted Effect Size* (95% CI)
Sex			
Women	409 (37.8)	0.25	0.25 (0.07 to 0.44)
Men	672 (62.2)		0.11 (−0.04 to 0.25)
Age			
Younger than 65 years	624 (57.7)	0.40	0.11 (−0.04 to 0.26)
65 years or older	457 (42.3)		0.22 (0.04 to 0.39)
Diabetes			
Presence	423 (39.1)	0.61	0.20 (0.02 to 0.38)
Absence	658 (60.9)		0.14 (−0.01 to 0.29)
Coronary heart disease			
Presence	232 (21.5)	0.91	0.17 (−0.09 to 0.43)
Absence	849 (78.5)		0.16 (0.03 to 0.29)
Stroke			
Presence	209 (19.3)	0.79	0.12 (−0.15 to 0.38)
Absence	872 (80.7)		0.17 (0.05 to 0.30)
Systolic blood pressure			
Lower than 140 mm Hg	324 (30.0)	0.37	0.23 (0.02 to 0.45)
140 mm Hg or higher	757 (70.0)		0.12 (−0.01 to 0.26)
Hypertension duration			
10 years or longer	586 (54.2)	0.86	0.16 (0 to 0.32)
Less than 10 years	495 (45.8)		0.15 (−0.01 to 0.31)
Pupil dilatation			
Yes	731 (67.6)	0.42	0.13 (−0.01 to 0.26)
No	350 (32.4)		0.25 (0.03 to 0.47)
Substitution of left-eye measurement			
Yes	91 (8.4)	0.32	0.37 (−0.03, 0.77)
No	990 (91.6)		0.14 (0.03, 0.26)

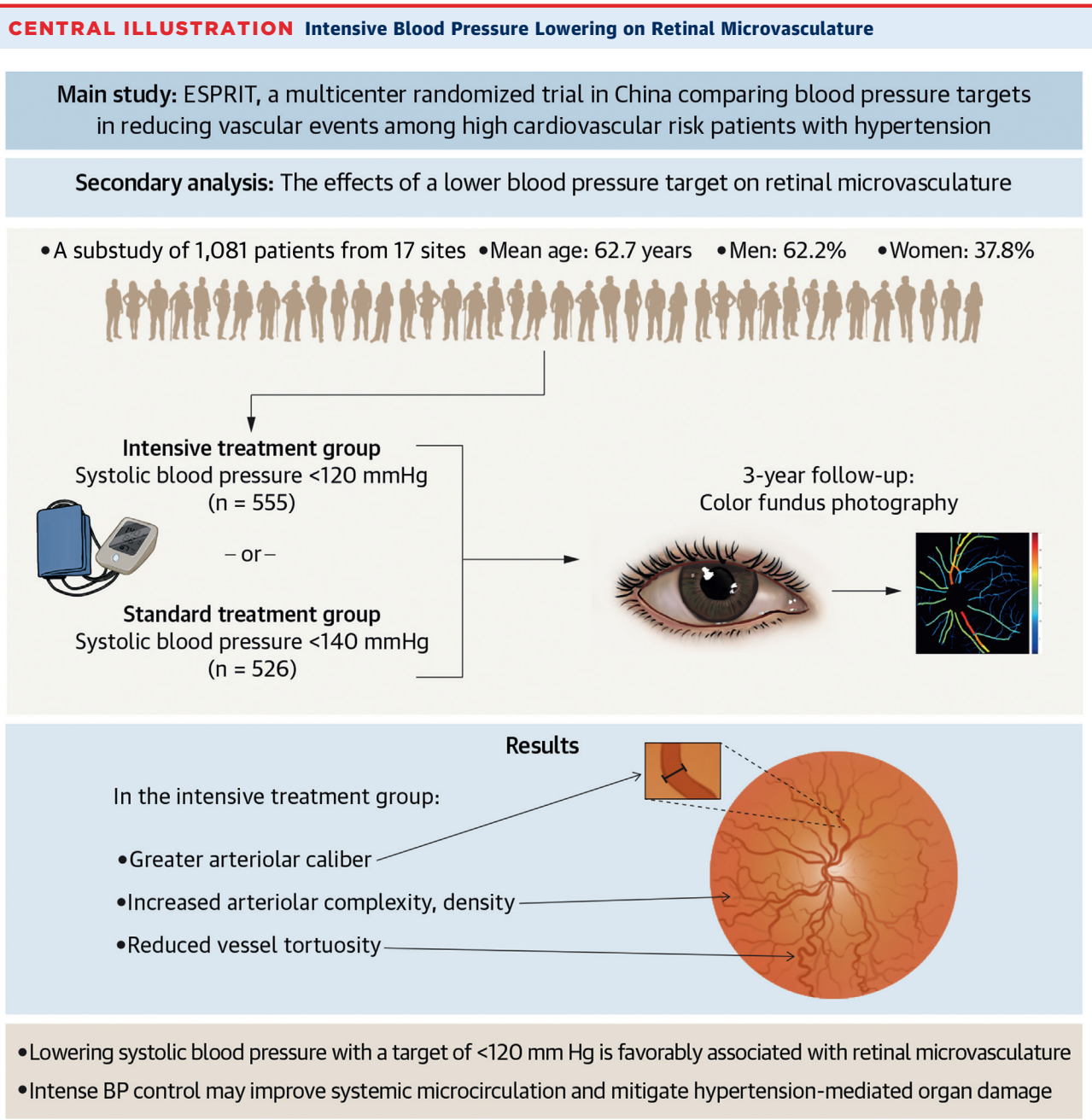


*Arteriole-venule ratio was standardized before modeling. The model adjusted for age and sex.

compared with standard treatment targeting SBP <140 mm Hg, with significant improvement in vessel caliber, density (vessel area, skeleton, bifurcation, branching), complexity (fractal dimension, number of vessel branching, bifurcation, and segment), and tortuosity (turning angle, linear regression tortuosity). No heterogenous effects on arteriolar caliber were observed across subgroups.

Our study provides new evidence that intensive BP-lowering treatment improves systemic microcirculation and mitigates hypertension-mediated organ damage among population with high cardiovascular risk. It has been previously assumed that hypertension-mediated organ damage is reversible with BP-lowering treatment at an early asymptomatic stage, but may be irreversible for long-standing hypertensive patients with increased cardiovascular risk and symptomatic manifestations, even with standard BP control,[27] such as left ventricular hypertrophy[28] and increased artery stiffness.[29] However, direct evidence for the retinal microvasculature is lacking. Although recent studies have shed light on the beneficial effect of intensive BP-lowering treatment on the heart, brain, and peripheral artery,[30-33] this is the first study to reliably assess a new major organ system: retinal microvasculature. Our study is distinguished by its randomized trial design, large sample size, and comprehensive and standardized assessment of retinal photographs through standardized protocols. Previous smaller trials comparing antihypertensive regimens found regimen-based treatment to a mean SBP of 130 mm Hg could reverse some of the retinopathy signs, including narrowed arteriolar caliber and arteriolar rarefaction.[12,13] Our study demonstrates that an SBP-lowering strategy targeting SBP <120 mm Hg could

CENTRAL ILLUSTRATION **Intensive Blood Pressure Lowering on Retinal Microvasculature**



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further benefit microcirculation compared with targeting SBP <140 mm Hg. Notably, the effect on the venular system was less evident, which may reflect the predominant effects of antihypertensive medications on the arteriolar system (Central Illustration).

The observed improvement in retinal microvasculature caliber, albeit modest in effect size in our study, mirrors the systemic and persistent beneficial changes in vascular remodeling from sustained intensive BP-lowering treatment, and reflects its potential effect on a number of underlying pathophysiological processes. The improvement in AVR in our study is mainly attributed to the reversal of narrowed arteriolar caliber, which is an indicator of microvascular damage caused by arteriolosclerosis and nitric oxide-dependent endothelial dysfunction.[34] Moreover, retinal arteriolar narrowing serves as an early marker of systemic microvascular dysfunction, and

prior work has shown an association between narrowed retinal arteriolar caliber and lower hyperemic myocardial blood flow and perfusion reserve.[35] Changes in retinal vessel caliber may also predict impairment in cardiac structure and function.[36] Population-based studies found that reduced AVR and narrowed retinal arterioles predicted long-term coronary artery disease, stroke, and heart failure, independent of traditional risk factors. For instance, the Atherosclerosis Risk In Communities Study demonstrated that each 1-SD decrease in AVR was associated with a 37% increased risk in coronary heart disease in women[37] and a 14% increased risk in ischemic stroke in the overall population.[5] These findings align with the observed reduction in the risk of major cardiovascular events from intensive BP-lowering treatment.

Moving beyond the caliber measures used in previous studies, our study leveraged fine-level quantification techniques and comprehensively assessed how intensive BP-lowering treatment affects multidimensional geometrical architecture of the microvascular system. Retinal microvasculature is a branching system that adheres to optimum design principle, and deviations from this optimal architecture are speculated to result in impaired microcirculatory transport, decreased efficiency, and an increased risk of vascular damage.[38-40] Populational studies suggested that reduction in microvascular density and branching complexity (fractal dimension) is associated with increased risk of cardiometabolic diseases, pulmonary diseases, and hematopoietic conditions.[25,26] Microvascular tortuosity is sensitive to systemic pathological damages, such as disturbed blood flow and endothelial dysfunction,[41,42] with subtle alterations potentially linked to the future development of coronary heart disease, atrial fibrillation, stroke, and renal diseases.[20,43-45] The favorable changes in the geometrical microvasculature measures suggested improvement in endothelial function, collateral microcirculation and autoregulation.[7,46]

Our study has important implications for clinical management of elevated BP and future research. The consistent benefits of intensive BP-lowering treatment in improving hypertension-mediated organ damage on retinal microvasculature across age, sex, diabetic status, SBP level, and hypertension duration should be emphasized. This evidence should be incorporated into the management of elevated BP to optimize treatment, promote patient adherence, and address clinician inertia in achieving an SBP target of <120 mm Hg. In particular, the potential of retinal microvascular imaging in visualizing hypertension-mediated organ damage could play a crucial role in motivating patients to make risk-reducing changes and in overcoming physician inertia.[47,48] Our study also lays the foundation for using retinal microvascular measures, easily obtained from CFP and automated programs, as sensitive biomarkers or endpoints in future clinical trials to assess and monitor responses to hypertension and cardiovascular risk.[49] Moreover, given that retinal microvasculature abnormalities are associated with multiple systemic diseases, such as renal diseases and cognitive impairment,[26] the effects of intensive BP-lowering treatment on them are worthy of further investigation. It remains to be determined whether intensive treatment prevents or reverses hypertensive retinopathy and other hypertension-related ocular diseases, such as diabetic retinopathy, glaucoma, optic neuropathy, and choroidal diseases.

STUDY LIMITATIONS. First, age and sex were not balanced between the treatment arms. However, given that both adjusted and unadjusted analyses yielded consistent results, it is unlikely that the observed differences substantially influenced the study findings. Second, because we did not examine CFP at baseline, we cannot evaluate the changes in retinal microvasculature measures for each participant. However, this should not affect the overall assessment of the effects of intensive BP-lowering treatment on these measures. Because the most relevant risk factors and clinical characteristics at baseline were well balanced between the 2 treatment arms, it is reasonable to assume that the 2 treatment arms had comparable retinal microvasculature measures at baseline. In addition, the consistency of results across multiple sensitivity analyses supports the robustness of our findings. Third, a proportion of participants were excluded from the analysis because of poor image quality or opt-out. The low rate of pupil dilation among these participants likely contributed to the poor image quality. However, sensitivity analyses accounting for these exclusions yielded similar results, indicating that the study findings were unlikely to have been biased by the exclusion of these individuals.

CONCLUSIONS

Among hypertensive patients with high cardiovascular risk, lowering SBP to a target of <120 mm Hg improved retinal microvasculature compared with a target of <140 mm Hg, supporting the hypothesis that such intervention may improve systemic microcirculation and mitigate hypertension-mediated organ damage.

DATA SHARING STATEMENT. Data described in the paper will not yet be made publicly available. Data collected for the study will be made available publicly upon reasonable request (ESPRIT_Data@fuwaihospital.org) after 2 years of publication.

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KEY WORDS hypertension-mediated organ damage, hypertension, intensive treatment, retinal microvasculature

APPENDIX For the trial protocol, an expanded Methods section, and supplemental figures and tables, please see the online version of this paper.