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1. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study, *The Lancet* 2001; 358:1134-1140;

Wong TY, Klein R, Couper DJ, Cooper LS, Shahar E, Hubbard LD, Wofford MR, Sharrett AR

BACKGROUND: Retinal microvascular abnormalities reflect damage from hypertension and other vascular processes. We examined the relation of such abnormalities to incident stroke. **METHODS:** A cohort of 10358 men and women (aged 51 to 72 years) living in four US communities underwent retinal photography and standard grading for retinal microvascular abnormalities. The calibres of all retinal arterioles and venules were measured after digital conversion of the photographs, and a summary arteriole-to-venule ratio (AVR) was calculated as an index of arteriolar narrowing (smaller AVR indicates greater narrowing). Cases of incident stroke admitted to hospital were identified and validated by case record reviews. **FINDINGS:** Over an average of 3.5 years, 110 participants had incident strokes. After adjustment for age, sex, race, 6-year mean arterial blood pressure, diabetes, and other stroke risk factors, most retinal microvascular characteristics were predictive of incident stroke, with adjusted relative risks of 2.58 (1.59-4.20) for any retinopathy, 3.11 (1.71-5.65) for microaneurysms, 3.08 (1.42-6.68) for soft exudates, 2.55 (1.27-5.14) for blot haemorrhages, 2.26 (1.00-5.12) for flame-shaped haemorrhages, and 1.60 (1.03-2.47) for arteriovenous nicking. The relative risk of stroke increased with decreasing AVR ($p=0.03$). The associations were similar for ischaemic strokes specifically, and for strokes in individuals with hypertension, either with or without diabetes. **INTERPRETATION:** Retinal microvascular abnormalities are related to incident stroke. The findings support a microvascular role in the pathogenesis of stroke. They suggest that retinal photography may be useful for cerebrovascular-risk stratification in appropriate populations.

2. Retinal microvascular abnormalities and 10-year cardiovascular mortality, *Ophthalmology* May 2003, Pages 933-940;

Wong TY, Klein R, Nieto FJ, Klein BE, Sharrett AR, Meuer SM, Hubbard LD, Tielsch JM

PURPOSE: Retinal microvascular abnormalities reflect persistent arteriolar damage from hypertension and independently predict stroke. We examined their associations with long-term cardiovascular mortality. **DESIGN:** Population-based, nested, case-control study. **POPULATION:** Cases were Beaver Dam Eye Study participants (age range, 43-84 years) who died of coronary heart disease or stroke between the baseline examination in 1988 to 1990 and 1999 ($n = 413$). Nearly 3 controls per case were selected from the baseline cohort, frequency-matched on 5-year age intervals and gender ($n = 1198$).

METHODS: Retinal photographs of cases and controls at baseline were evaluated for retinopathy, focal arteriolar narrowing, and arteriovenous nicking by graders masked to case-control status using standardized protocols. To obtain an estimate of generalized arteriolar narrowing, photographs were digitized and diameters of individual retinal vessels were measured and summarized by a computer program. **MAIN OUTCOME MEASURE:** Ten-year cardiovascular mortality. **RESULTS:** After controlling for systolic blood pressure, diabetes, glycosylated hemoglobin levels, and other risk factors, retinopathy was associated with increased cardiovascular mortality, with odds ratios of 1.8 (95% confidence interval [CI], 1.2, 2.7). For other retinal abnormalities, associations with cardiovascular mortality were present only in younger people, with odds ratios of 2.7 (95% CI, 1.0, 7.4) for focal arteriolar narrowing, 1.8 (95% CI, 0.8, 4.5) for arteriovenous nicking, and 1.9 (95% CI, 1.2, 2.9) for generalized arteriolar narrowing in persons 43 to 74 years of age but odds ratios of 1.1, 0.4, and 1.0 for the corresponding retinal abnormalities in persons 75 years and older. **CONCLUSIONS:** Retinopathy is independently associated with cardiovascular mortality. Associations for other retinal abnormalities were only observed in middle-aged persons. These data support recent studies that suggest retinal microvascular abnormalities provide independent information regarding cardiovascular risk.

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3. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study, *Ophthalmology* 1999 Dec; 106(12):2269-80;

Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, Cooper LS, Sharrett AR, Davis MD, Cai J.

OBJECTIVE: To develop protocols to photograph and evaluate retinal vascular abnormalities in the Atherosclerosis Risk in Communities (ARIC) Study; to test reproducibility of the grading system; and to explore the relationship of these microvascular changes with blood pressure. **DESIGN:** Population-based, cross-sectional study.

PARTICIPANTS: Among 4 examination centers, 11,114 participants (48-73 years of age) at their third triennial examination, after excluding persons with diabetes from this analysis.

METHODS: One eye of each participant was photographed by technicians with nonmydriatic fundus cameras. Reading center graders evaluated focal arteriolar narrowing, arteriovenous (AV) nicking, and retinopathy by examining slides on a light box and measured diameters of all vessels in a zone surrounding the optic disc on enhanced digitized images. To gauge generalized narrowing, vessel diameters were combined into central arteriolar and venular equivalents with formulas adjusting for branching, and the ratio of equivalents (A/V ratio) was calculated. **MAIN OUTCOME MEASURES:** Retinal vascular abnormalities, mean arteriolar blood pressure (MABP). **RESULTS:** Among 11,114 participants, photographs were obtained of 99%, with quality sufficient to perform retinal evaluations in 81%. In the 9040 subjects with usable photographs, A/V ratio (lower values indicate generalized arteriolar narrowing) ranged from 0.57 to 1.22 (median = 0.84, interquartile range = 0.10), focal arteriolar narrowing was found in 7%, AV nicking in 6%, and retinopathy in 4%. Because of attrition of subjects and limitation of methods, prevalence of abnormality was likely underestimated. Controlling for gender, race, age, and smoking status, these retinal changes were associated with higher blood pressure. For every 10-mmHg increase in MABP, A/V ratio decreased by 0.02 unit ($P < 0.0001$), focal arteriolar narrowing had an odds ratio (OR) of 2.00 (95% confidence interval [CI] = 1.87-2.14), AV nicking had an OR of 1.25 (95% CI = 1.16-1.34), and retinopathy had an OR of 1.25 (95% CI = 1.15-1.37). For any degree of generalized narrowing, individuals with focal narrowing had MABP approximately 8 mmHg higher than those without ($P < 0.0001$). Masked replicate assessment of a sample found the following reproducibility: for A/V ratio, correlation coefficient = 0.79 and median absolute difference = 0.03; for focal arteriolar narrowing, kappa = 0.45; for AV nicking, kappa = 0.61; and for retinopathy, kappa = 0.89. **CONCLUSION:** Protocols have been developed for nonmydriatic fundus photography and for evaluation of retinal vascular abnormalities. Several microvascular changes were significantly associated with higher blood pressure; follow-up will show whether these are predictive of later cerebrovascular or cardiovascular disease independently of other known risk factors.

4. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke.;

Witt N, Wong TY, Hughes AD, Chaturvedi N, Klein BE, Evans R, McNamara M, Thom SA, Klein R. Hypertension. 2006 May;47(5):975-81. Epub 2006 Apr 3.

Abnormalities of the retinal microcirculation are found in hypertension and diabetes and predict cardiovascular mortality. This study examined the relationship between abnormalities of the retinal microvasculature and death from ischemic heart disease (IHD) and stroke. A population-based, nested case-control study was undertaken within the Beaver Dam Eye Study. Subjects (43 to 74 years) who died of IHD (n=126) or stroke (n=28) over a 10-year period were age and gender matched with controls subjects (n=528; case:control matching, approximately 1:4). Retinal photographs of cases and controls were digitized and analyzed using a computer-based technique. Increased risk of IHD death was associated with a suboptimal relationship of arteriolar diameters at bifurcation ($P=0.02$ unadjusted) and decreased retinal arteriolar tortuosity ($P=0.011$ unadjusted). These associations remained significant after adjustment for age, sex, past history of cardiovascular disease, and other known cardiovascular risk factors. Increased arteriolar length:diameter ratio, a measure of generalized arteriolar narrowing, was associated with increased stroke mortality ($P=0.02$ unadjusted). This association was independent of age and gender but was attenuated by adjustment for systolic blood pressure ($P=0.15$). Other quantitative measures of the retinal microvascular network (eg, venular tortuosity and arteriolar and venular bifurcation angle) were not associated with death from IHD or stroke. Retinal

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microvascular abnormalities are predictive of death from IHD and stroke. A detailed assessment of the retinal microvascular network from digitized photographs may be useful in the noninvasive assessment of target organ damage and cardiovascular risk.

5. Telemedizinisch unterstütztes Screening der retinalen Gefäße („Talking Eyes“), *Klinische Monatsblätter für Augenheilkunde*; 04, 2005;

Michelson, G.; Groh, M.; Groh, M. J. M.; Baleanu, D.; Harazny, J.; Horstmann, R.; Kolominsky-Rabas, P.

Hintergrund: Zerebrale und retinale Gefäße verhalten sich ähnlich unter dem Einfluss von vaskulären Risiko-faktoren. Mehrere Arbeitsgruppen konnten zeigen, dass retinale mikrovaskuläre Abnormalitäten einen unab-hängigen Risikofaktor hinsichtlich Schlaganfall und Herzinfarkt darstellen. Absicht: Durchführung einer pro-spektiven Screening-Untersuchung hinsichtlich retinaler mikrovaskulärer Abnormalitäten und einer erweiterten Gefäßdiagnostik bei einer Untergruppe daraus mit erniedrigten arteriovenösen Ratiowerten. Methode: Im Rahmen einer prospektiven Querschnittstudie („Talking Eyes“) erfolgte von 1.9.2001 bis 1.8.2002 bei 7163 Personen eine telemedizinisch unterstützte Screening-Untersuchung der Netzhautgefäße (Studie I). Die Patientenauswahl erfolgte ohne Ein- und Ausschlusskriterien. Das mittlere Alter war $48,2 \pm 8$ J. (18 - 83 J.) mit einer Geschlechtsverteilung von 39,2 % Frauen und 60,8 % Männern. Bei allen Personen wurde ein digitales Fundusfoto vom rechten und linken Auge erstellt. Die Aufnahmen wurden ohne Pupillenerweiterung mit einer CANON-NM-Kamera durchgeführt. Die Bilder und die Anamnese wurden mit einer webbasierten Software (MedStage, Siemens) auf einem zentralen Server abgelegt. In einem zentralen Reading-Zentrum wurde telemedizinisch mittels der Parr-Hubbard-Formel die arteriovenöse Ratio von beiden Augen bestimmt und die Netzhaut von einem Facharzt für Augenheilkunde standardisiert befundet. Unter Verwendung der Daten des arteriovenösen Ratio, dem augenärztlichen Befund hinsichtlich mikrovaskulärer Abnormalitäten und anamnestischer Daten erfolgte die Berechnung eines retinalen Risikoindex. Die Reproduzierbarkeit (Alpha-Kronbach-Koeffizient) der Messung der arteriovenösen Ratio wurde durch Doppeluntersuchungen von 1332 Bildern bewertet. Bei einer Untergruppe aus Studie I mit arteriovenösen Ratiowerten $< 0,76$ ($n = 107$) wurde eine erweiterte Gefäßdiagnostik mit Messung des 24-h-Blutdrucks und gefäßrelevanter Blutwerte (Homocystein, Cholesterin, LDL, HDL, CRP, TG, HbA1c) durchgeführt (Studie II). Ergebnisse: Studie I: Der Alpha-Kronbach-Koeffizient als Index für die Reproduzierbarkeit betrug 0,77. Die mittlere arteriovenöse Ratio der retinalen Gefäße war $0,83 \pm 0,09$ und zeigte eine ausgeprägte Altersabhängigkeit ($R = 0,9$, $p < 0,0001$). Bei multivariater Testung korrelierte die arteriovenöse Ratio signifikant ($R = 0,33$, $p < 0,001$) mit den Faktoren Alter, systolischer Blutdruck, diastolischer Blutdruck und Bodymass-Index. Den stärksten Einfluss hatte der diastolische Blutdruck gefolgt vom Alter. Die Prävalenzen der mikrovaskulären Abnormalitäten am rechten Auge (RA) bzw. am linken Auge (LA) waren: Cotton-Wool-Herde RA 0,0015 %, LA 0,003 %, retinale Blutungen RA 0,1 %, LA 0,1 %, fokale Stenosen RA 3,4 %, LA 3,4 %, Tortuositas vasorum RA 4,1 %, LA 4,0 %, arteriovenöse Kreuzungszeichen RA 11,2 %, LA 11,2 %. Das Vorliegen von retinalen mikrovaskulären Abnormalitäten korrelierte bei multivariater Testung signifikant ($R = 0,38$, $p < 0,001$) mit den Faktoren anamnestisch bekannter Hypertonus, Alter, diastolischer Blutdruck, Bodymass-Index und dem Geschlecht. Den stärksten Einfluss hatte das Vorliegen einer arteriellen Hypertonie gefolgt vom diastolischen Blutdruck. Der berechnete retinale Risikoindex korrelierte mit der Prävalenz von Angina pectoris. Studie II: 2/3 der Untersuchten mit arteriovenösen Ratiowerten $< 0,76$ wiesen pathologisch erhöhte 24-h-Blutdruckwerte auf. Bei diesen Patienten zeigten sich signifikante Korrelationen zwischen der arteriovenösen Ratio und der Low-Density-Lipoprotein-Konzentration bzw. dem Framingham-Risikoscore. Schlussfolgerung: Im Rahmen einer prospektiven, telemedizinisch unterstützten Screening-Untersuchung der retinalen Gefäße bei mehr als 7000 Personen zeigte die arteriovenöse Ratio eine starke Alters- und Blutdruckabhängigkeit. Bei Personen mit erniedrigten arteriovenösen Ratiowerten zeigten 2/3 eine arterielle Hypertonie bei der 24-h-Blutdruckmessung.