The FOTO-TIA Study
Retinal Microvascular Changes Differentiate Mild Stroke and Transient Ischemic Attack (TIA) from Mimics among Patients Presenting to the Emergency Department (ED) with Suspected TIA

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Disclosures

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Retinal microvascular changes are associated with the risk of long-term cardiovascular mortality

Blue Mountains Eye Study

Heart 2006;92:1583
Retinal microvascular changes are associated with the long-term risk of stroke.

The Atherosclerosis Risk in Communities (ARIC) Study found a 6-year risk of stroke of 1.8-3.1 times higher for individuals with retinal microvascular changes compared to those without.
Do retinal microvascular changes have short-term value?

**Hypothesis**: Retinal microvascular changes will have value in the risk stratification of patients presenting with possible transient ischemic attack or stroke.
ABCD² Clinical Prediction Rule

- Widely used as a TIA risk stratification tool in the emergency department
- Assigns points based on
  - Age,
  - Blood pressure,
  - Clinical symptoms,
  - Duration of symptoms, and
  - Diabetes

Lancet 2007;369:283.
Preliminary Data:
Focal Neurological Symptoms from the FOTO-ED study (n=257)

- 144 (56%) had retinal microvascular findings
- ARIC study grid
- Retrospective study
Arteriolar narrowing

- ≥2 sectors of focal narrowing
  - 18% of stroke patients
  - 10% of TIA patients
  - 3% of other patients
- ≥4 sectors of generalized narrowing
  - 41% of stroke patients
  - 22% of TIA patients
  - 12% of other patients
Retinal Findings in Stroke or TIA vs non-cerebrovascular disease: FOTO-ED Study

- Presence of retinal microvascular findings were significantly associated with stroke or TIA diagnosis (vs non-cerebrovascular disease)*:
  - ≥2 sectors of focal narrowing
    • OR 8.11 (1.82-36.1; p=0.006)
  - ≥4 sectors of general narrowing
    • OR 2.39 (1.01-5.68; p=0.049)
  - Non-microvascular
    • OR 0.10 (0.01-0.77; p=0.03)

*Controlled for age, blood pressure, diabetes, clinical presentation, duration of symptoms, diffusion weighted imaging positivity
FOTO-ED TIA Study: Methods

**Prospective** cohort study

- ≥ 18 years old
- Suspected TIA or minor stroke based on ED physician assessment (NIHSS 3 or less)
- Admitted to clinical decision unit on TIA accelerated diagnostic protocol (ADP)
- 3 hospitals: university, public, community
- Non-mydriatic fundus photography taken during ADP
FOTO-ED TIA: Methods

TIA Accelerated Diagnostic Protocol

- Serial clinical examinations
- MRI Brain, MRA Head/Neck w/ and w/o contrast
- Transthoracic echocardiogram
- Cardiac telemetry
- Neurology consultation
Non-mydriatic fundus photography

- Can be done by non-ophthalmic experts
- No pupillary dilation required
- Able to take quality photographs of the posterior pole
Non-mydriatic Direct ophthalmoscopy fundus photography
Retinal Microvascular Findings

- Retinal hemorrhages
- Cotton wool spots
- Retinal emboli or occlusions
- Hard exudates
- Microaneurysms
- Focal arterial narrowing
- Arteriovenous nicking
Primary Outcomes

• New stroke, CV event, or death within 90 days

• Neurologist opinion about whether the event represented a cerebrovascular event
  – Blinded to fundus photography findings
Cerebrovascular event?

- Probability each patient’s presentation represented a cerebrovascular event on a 10 cm visual analogue scale
Results: 395 patients enrolled

- Median age: 57 years (IQR: 50–66)
- 219 (55%) women
- 253 (64%) black
- 34 (9%) patients with ≥1 retinal microvascular findings
- Median cerebrovascular event probability assessment: 22% (IQR: 5–100)
- 4 (1.0%) primary endpoint events (strokes) within 90 days
• 34 patients with retinal findings
• 22 CVE / 12 no CVE at baseline

- Retinal embolisms (RE) 4%
- Retinal occlusions (RO) 6%
- Focal arteriolar narrowing (FN) 9%
- Optic disc pallor (ODP) 10%
- Hard exudates (HE) 10%
- Arteriovenous nicking (AVN) 16%
- Microaneurysms (MA) 13%
- Cotton wool spots (CWS) 32%
- Retinal hemorrhages (RH) 40%
Any retinal microvascular finding increased the cerebrovascular event probability assessment by 15.6%.

- 95%CI: 4.2–27.1%, p=0.008
- Controlled for
  - Each individual component of the ABCD² score
  - Presence of a MRI-DWI positive lesion
Excluding patients with MRI DWI+ lesions, any retinal microvascular finding increased the cerebrovascular event probability assessment by 21.8%.

- 95%CI: 6.1–37.5%, p=0.007
- Controlled for each individual component of the ABCD² score
Conclusion

• Retinal microvascular findings assessed by nonmydriatic ocular fundus photographs during the evaluation of suspected TIAs are an independent factor differentiating TIA and stroke from mimics.

• Retinal microvascular findings provide a “diagnostic test” for TIA, the diagnosis of which is currently based on expert opinion.
Conclusion

• Promising developments in the automatic reading of fundus photographs using artificial intelligence will facilitate the routine incorporation of fundus photography findings into ED workflows.

Overall quality
1: inadequate for any diagnostic purpose
2: unable to exclude all emergent findings
3: able to exclude emergent findings only
4: suboptimal quality, but able to exclude subtle findings
5: optimal quality
Regional quality
(optic disc and 0.5 DD around; macula; superotemporal and superonasal vessels; inferotemporal and inferonasal vessel)
A. grader can say with certainty whether the area is normal
B. grader cannot say with certainty whether the area is normal
C. the area is unable to see the relevant area
**Focal arteriolar narrowing**

Evaluated on the full fundus picture.
Arteriole estimated to be 50 µm diameter or greater (approximately \( \frac{1}{5} \) of the diameter of a major vein at the disc margin) with a constricted area of \( \frac{2}{3} \) or less the width of proximal and distal vessel segments.
Based on the length of the narrowing, it is graded as:
- 0. absent
- 11. questionable
- 2. \(<0.5\) disc diameter (DD)
- 3. 0.5-2DD
- 4. >2DD
- 88. cannot grade

Focal arteriolar narrowing is considered absent if at least the ST and IT areas are gradable and no abnormalities were seen.

**Findings**

Binary evaluation (absent=0, present=2): occlusion, embolus, hard exudate, optic disk edema, optic disk pallor.
11 for questionable, 88 for non-gradable

Quantitative evaluation (0 to \( \geq 10 \)): hemorrhage, cotton wool spot, microaneurysms/dot microhemorrhages.
11 for questionable, 88 for non-gradable

**AV nicking**

Excluding zone A of the ARIC grid.
Vein tapered on both sides of its crossing under an arteriole:
- 0. absent
- 11. questionable
- 2. mild/moderate (less than that in the Early Treatment Diabetic Retinopathy Study (ETDRS) standard photograph 9 (with narrowing of the blood column by approximately \( \frac{1}{2} \))
- 3. Severe (greater than ETDRS) standard photograph 9
- 88. cannot grade
Central vessel equivalent (CVE) calculation on zone B of the ARIC grid

Central vessel equivalent (central retinal artery equivalent [CRAE] and central retinal vein equivalent [CRVE]) is calculated to determine the arteriovenous (AV) ratio equivalent and the generalized arteriolar narrowing using the 6 larger arterioles and the 6 larger veins. Generalized arteriolar narrowing is defined as the smallest quintile (20%).

Calibration of the image is performed on the basis of the standard disc diameter (1850 µm).

For the 6 largest arterioles and the 6 largest veins passing through zone B:

Three measures of the width (that are averaged) are performed.

Calculate the vessel equivalent for each vessel according to the modified Knudtson formula using iterative procedures to obtain a single CVE.

Arterioles: \( W_a = 0.88 \sqrt{(w_1^2 + w_2^2)} \)

Venules: \( W_v = 0.95 \sqrt{(w_1^2 + w_2^2)} \)

With \( w_1, w_2, \) and \( W \) the width of the narrower branch, the wider branch, and the estimated parent trunk.
Figure: ARIC grid centered by the optic disc. Examples of measurement of the width of one of the venules yielding a width of 24 pixels in this example (versus 327 pixels for the height of the optic disc), thus a width of \((24\text{px} \times 1850\mu\text{m})/327\text{px} = 135\mu\text{m}\).