SVN Stroke & Vascular Neurology

Retinal microvascular signs and recurrent vascular events in patients with TIA or minor stroke

Philipp Klyscz ,[1] Thomas Ihl,[1] Inga Laumeier,[1] Maureen Steinicke,[1] Matthias Endres,[1,2,3,4,5,6] Georg Michelson,[7,8] Heinrich J Audebert[1,2]

To cite: Klyscz P, Ihl T, Laumeier I, *et al*. Retinal microvascular signs and recurrent vascular events in patients with TIA or minor stroke. *Stroke & Vascular Neurology* 2023;**8**: e001784. doi:10.1136/svn-2022-001784

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2022-001784).

GM and HJA are joint senior authors.

Received 15 June 2022
Accepted 5 February 2023
Published Online First 1 March 2023

For numbered affiliations see end of article.

Correspondence to
Philipp Klyscz;
philipp.klyscz@charite.de

ABSTRACT

Background and purpose Retinal pathologies are an independent risk factor for ischaemic stroke, but research on the predictive value of retinal abnormalities for recurrent vascular events in patients with prior stroke is inconclusive. We investigated the association of retinal pathologies with subsequent vascular events.

Methods In a substudy of the Intensified secondary prevention intending a reduction of recurrent events in TIA and minor stroke patients (INSPiRE-TMS) trial, we enrolled patients with recent transient ischaemic attack (TIA) or minor stroke with at least one modifiable risk factor. Primary outcome was the composite of subsequent vascular events. Retinal photographs were taken at baseline and categorised into three different fundus groups by a telemedically linked ophthalmologist.

Results 722 patients participated in the current study and 109 major vascular events occurred. After multivariable adjustments, we did not find a significant association between fundus categories and risk for subsequent vascular events (HRs for moderate vascular retinopathy and vascular retinopathy with vessel rarefaction in comparison to no vascular retinopathy 1.03 (95% CI 0.64 to 1.67), p=0.905 and 1.17 (95% CI 0.62 to 2.20), p=0.626). In a selective post hoc analysis in patients with diabetes mellitus and hypertension, patients with vascular retinopathy with vessel rarefaction had a higher risk for recurrent stroke (HR 24.14 (95% CI 2.74 to 212.50), p=0.004).

Conclusions Retinal changes did not predict major subsequent vascular events in patients with recent TIA or minor stroke. Further studies are needed to examine the utility of fundus photography in assessing the risk of stroke recurrence in patients with diabetes mellitus and hypertension.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Microvascular pathologies are an independent risk factor for incidental ischaemic strokes, but data regarding subsequent vascular events are sparse.

WHAT THIS STUDY ADDS

⇒ In patients with recent transient ischaemic attacks (TIA) or minor stroke, the burden of retinal abnormalities was not associated with recurrent vascular events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Although we did not show a general association between fundus changes and subsequent vascular events, retinal imaging might be useful in a subset of patients with diabetes and hypertension for identifiying those at risk for recurrent ischaemic stroke.

INTRODUCTION

Microvascular changes of the retina have been linked to a higher risk of incidental ischaemic stroke as well as cardiovascular and all-cause mortality independent of long-established risk factors such as arterial hypertension and diabetes mellitus.[1–3]

In particular, associations between retinal changes and cerebrovascular diseases were extensively investigated as the retina embryologically developed from the neural plate and therefore may act as a surrogate for the cerebral microvasculature.[4] Furthermore, alterations in retinal vessels might reflect pathologies in the systemic microcirculation of other organs especially in the heart[5] and kidneys.[6] These relationships have been shown predominantly in individuals free of any vascular event.

Patients with recent transient ischaemic attack (TIA) or minor stroke are at particular risk for developing subsequent strokes.[7] In addition, these patients have an increased risk for other cardiovascular events such as myocardial infarction or vascular death.[8] Even though prediction scores, such as the ABCD2 (acronym for age, blood pressure, clinical findings, duration of symptoms and presence or absence of diabetes) score, have shown good predictive value for short-time prognosis after TIA, there remain uncertainties regarding the long-term risk for recurrent adverse events. Fundus photography might offer an additional tool for stratifying those patients, as assessment of the retinal microvasculature might help in predicting future cardiovascular events.[9]

Prior studies mainly focused on predicting major vascular events through fundus

photography in individuals without history of cerebrovascular events.

In this study, we examined the association between certain fundus pathologies and risk for subsequent vascular events after TIA or minor stroke. For a more practical approach, we classified the retinal images using a telemedical grading system in different fundus groups.

The current report is a substudy of the multicentre, secondary stroke prevention Intensified secondary prevention intending a reduction of recurrent events in TIA and minor stroke patients (INSPiRE-TMS) study.[10]

METHODS

Study population and design

The INSPiRE-TMS trial was a multicentre two-armed, secondary prevention study examining the effectiveness of a multifaceted support programme for reducing recurrent major vascular events, described in detail elsewhere.[10] In this substudy, patients were included if they were recruited for the trial at the Charité-Universitätsmedizin Berlin—Campus Benjamin Franklin study centre.

In short, patients were recruited between 2011 and 2017 if they had a TIA or minor stroke within 14 days before study inclusion, were independent according the modified Rankin Scale (mRS) of 2 or below and had an ABCD2 score of 3 or above or an acute ischaemic or haemorrhagic stroke in cerebral imaging. Additionally, eligible patients had to have one modifiable cardiovascular risk factor (ie, arterial hypertension, diabetes mellitus, atrial fibrillation or current tobacco smoking). Participants were randomised to either the standard care group or the intensified secondary prevention group, which provided standard care plus a support programme with eight outpatient visits over the first 2 years. During these appointments, risk factor targets were assessed by trained study nurses and stroke physicians. The support programme was based on motivational interviewing.[11] Study data were collected and managed using REDCap electronic data capture tools.[12]

Patients with severe cognitive disability, malignant disease with life expectancy of <3 years, a current substance abuse (except for nicotine) and ischaemic stroke or TIA of an aetiology without evidence-based secondary prevention options (eg, dissection or vasculitis) were excluded from the study.

Assessment of stroke, risk factors and vascular outcomes

Eligible patients were evaluated by a stroke physician. Stroke subgroups were classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST). The National Institute of Health Stroke Scale (NIHSS) and mRS were used to determine the extent of neurological deficits. Secondary prevention targets for modifiable risk factors were adopted from the guidelines for secondary prevention after stroke of the German Society of Neurology[13] and European Stroke Organisation.[14] Patients with a symptomatic carotid stenosis or unstable symptomatic plaque were treated according the aggressive treatment targets from the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial.[15]

Primary outcome was the composite of major vascular events consisting of subsequent stroke (either ischaemic or haemorrhagic), acute coronary syndrome (including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and unstable angina pectoris) or vascular death. Data about vascular events were obtained during annual appointments and, if available, confirmed by medical reports. In case of death, death certificates were obtained from local authorities.

Retinal imaging

Fundus photographs of both eyes were taken after randomisation with a 45-degree non-mydriatic colour fundus camera (KOWA NM-45, non-mydriatic-alpha) centred at the optic nerve head. Because we refrained from using a mydriatic agent to dilate patients' pupils, participants were placed in a darkened room for 5 min prior to the photograph in order to widen pupils through dark adaptation. The images were uploaded to the cloud-based software MedStage (Siemens, Medical Product, class IIa, Talkingeyes & More, Erlangen)[16 17] and saved in the MedStage-patient chart. An experienced senior ophthalmologist (GM from Department of Ophthalmology Friedrich-Alexander University Erlangen-Nürnberg) classified—using a standardised protocol through the Tele-Ophthalmic Consultation Service Talkingeyes (Talkingeyes & More)—the pictures into three different fundus categories: no or mild vascular retinopathy, moderate vascular retinopathy and vascular retinopathy with vessel rarefaction. The fundus groups were defined by the presence and severity of focal and general arteriolar narrowing, arteriovenous nicking and rarefaction of

Table 1 Fundus groups specifications

	No or mild vascular retinopathy	Moderate vascular retinopathy	Vascular retinopathy with vessel rarefaction
Arteriolar narrowing	Absent or age-related	Mild to moderate narrowing	Severe narrowing
Arteriovenous nicking	Absent or age-related	Sporadically	Various nickings
Rarefaction of arterioles and venules	Absent	Absent	Significant rarefaction

arterioles and venules (table 1). Prior works of the examiner on the reliability of assessing different retinal pathologies revealed a Cronbach's alpha coefficient of 0.77.[17] Because the left and right eye were examined distinctively, we excluded patients from the analysis if classification for each eye yielded different fundus groups.

Statistical analysis

SPSS (IBM, V.27) was used for all statistical procedures. Prevalences of risk factors, baseline characteristics and past vascular events were compared between fundus groups. We used Cox regression models to analyse the predictive value of fundus pathologies on risk of vascular events for the primary composite outcome and separated for stroke, acute coronary syndrome and vascular death. We selected the no or mild vascular retinopathy group as the reference category. The model was adjusted for sex, age (years), body mass index (BMI), ABCD2, index event type, study arm, hypertension, diabetes mellitus, atrial fibrillation, current smoking, stroke aetiology according to TOAST and carotid surgery to minimise a bias through possible confounders. HRs and 95% CIs are reported.

Following the main analysis, we carried out a selective subgroup analysis in patients with diabetes mellitus and hypertension. Those cardiovascular diseases are well-established risk factors for incidental vascular events and act synergistically for recurrent ischaemic stroke as expressed in the ABCD2 score[7] and in the CHA2DS2-VASc score.[18] Also, diabetes mellitus and hypertension are frequent causes for retinal pathologies.[19] An interaction analysis revealed a significant interaction between diabetes mellitus and hypertension and vascular retinopathy with vessel rarefaction on the risk for recurrent ischaemic stroke (p=0.006) but not for composite vascular events (p=0.342). No statistically significant interaction was shown when testing for the other outcome events. HRs were only computed for composite vascular events, recurrent stroke and vascular deaths because no acute coronary syndromes occurred in the fundus category vascular retinopathy with vessel rarefaction. P values <0.05 were defined as statistically significant.

RESULTS

Study population

In total, we enrolled 954 patients at the Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin study site, of which 841 participants received a fundus photograph. We excluded 119 patients due to ungradable pictures, missing data and study protocol violations at study inclusion (ie, stroke not being most probable diagnosis and missing option for evidence-based secondary prevention). Hence, we included 722 patients in the final analysis (figure 1). Among the 722 subjects included in the final analysis, mean age was 69 years (SD 10 years), 34.8% were female, median ABCD2 was 4 (IQR 4–5) and median NIHSS was 1 (IQR 0–2). Incidental stroke aetiologies according to TOAST were distributed as followed:

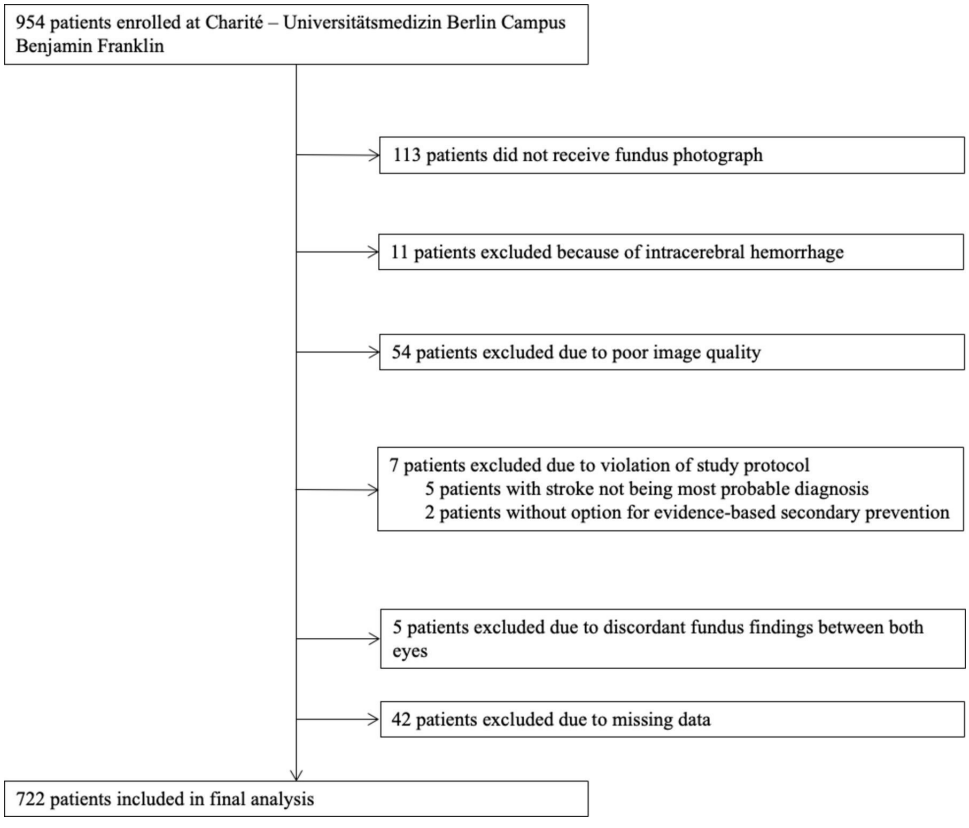

Figure 1 Flow chart.

Table 2 Baseline characteristics for study cohort by composite outcome and vascular events

		Composite events		Recurrent stroke	Acute coronary syndrome	Vascular death
	Total (n=722)	Yes (n=109)	No (n=613)	Yes (n=74)	Yes (n=20)	Yes (n=15)
Age (years), mean (±SD)	69 (±10)	70 (±10)	68 (±10)	70 (±10)	70 (±7)	70 (±10)
Sex, n (%)						
Female	251 (34.8)	36 (33.0)	215 (35.1)	25 (33.8)	5 (25.0)	6 (40.0)
Male	471 (65.2)	73 (67.0)	398 (64.9)	49 (66.2)	15 (75.0)	9 (60.0)
Study arm, n (%)						
Conventional care	352 (48.8)	57 (52.3)	295 (48.1)	38 (51.4)	12 (60.0)	7 (46.7)
Intensified care	370 (51.2)	52 (47.7)	318 (51.9)	36 (48.6)	8 (40.0)	8 (53.3)
BMI (kg/m^2), mean (±SD)	28 (±4)	28 (±4)	28 (±4)	28 (±4)	28 (±5)	29 (±4)
ABCD2, median (IQR)	4 (4–5)	5 (4–6)	4 (4–5)	5 (4–6)	5 (4–5)	4 (4–5)
NIHSS, median (IQR)*	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	2 (0–2)
Carotid surgery, n (%)	22 (3.0)	7 (6.4)	15 (2.4)	3 (4.1)	3 (15.0)	1 (6.7)
Vascular risk factors, n (%)						
Hypertension	640 (88.6)	99 (90.8)	541 (88.3)	67 (90.5)	19 (95.0)	13 (86.7)
Diabetes mellitus	174 (24.1)	37 (33.9)	137 (22.3)	24 (32.4)	7 (35.0)	6 (40.0)
Atrial fibrillation	127 (17.6)	16 (14.7)	111 (18.1)	13 (17.6)	2 (10.0)	1 (6.7)
Smoking	127 (17.6)	23 (21.1)	104 (17.0)	12 (16.2)	6 (30.0)	5 (33.3)
Index event, n (%)						
TIA	326 (45.2)	39 (35.8)	287 (46.8)	30 (40.5)	5 (25.0)	4 (26.7)
Minor stroke	396 (54.8)	70 (64.2)	326 (53.2)	44 (59.5)	15 (75.0)	11 (73.3)
Stroke aetiology, n (%)						
Large vessel atherosclerosis	67 (9.3)	13 (11.9)	54 (8.8)	8 (10.8)	4 (20.0)	1 (6.7)
Cardioembolism	133 (18.4)	17 (15.6)	116 (18.9)	11 (14.9)	4 (20.0)	2 (13.3)
Small vessel disease	59 (8.2)	11 (10.1)	48 (7.8)	4 (5.4)	6 (30.0)	1 (6.7)
Other aetiology	11 (1.5)	3 (2.8)	8 (1.3)	3 (4.1)	0 (0)	0 (0)
Undetermined cause	452 (62.6)	65 (59.6)	385 (63.1)	48 (64.9)	6 (30.0)	11 (73.3)
Previous vascular event, n (%)						
TIA†	40 (5.7)	11 (10.8)	29 (4.9)	9 (12.9)	0 (0)	2 (14.3)
Stroke‡	117 (16.5)	26 (24.8)	91 (15.0)	16 (22.2)	9 (47.4)	1 (7.1)
Myocardial infarction§	57 (8.0)	15 (14.0)	42 (6.9)	7 (9.6)	5 (26.3)	3 (20.0)
Fundus groups, n (%)						
No or mild vascular retinopathy	155 (21.5)	27 (24.8)	128 (20.9)	16 (21.6)	7 (35.0)	4 (26.7)
Moderate vascular retinopathy	473 (65.5)	60 (55.0)	413 (67.4)	43 (58.1)	7 (35.0)	10 (66.7)
Vascular retinopathy with vessel rarefaction	94 (13.0)	22 (20.2)	72 (11.7)	15 (20.3)	6 (30.0)	1 (6.7)

*Data available for 720 patients.
†Data available for 696 patients.
‡Data available for 710 patients.
§Data available for 714 patients.
ABCD2, age, blood pressure, clinical findings, duration of symptoms and presence or absence of diabetes; BMI, body mass index; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischaemic attack.

9.3% large vessel atherosclerosis, 18.4% cardioembolic, 8.2% small vessel disease, 1.5% other causes and 62.6% undetermined aetiology (6.5% competing causes, 24.3% no potential cause, 31.1% incomplete diagnostics, 38.1% unknown reasons).

The baseline characteristics and distribution of cardiovascular risk factors separated for the different outcome events are shown in table 2. In total, 109 vascular events occurred during the course of the trial. Most of these events were subsequent strokes (n=74, 65.4%), followed

by acute coronary syndromes (n=20, 18.3%) and vascular deaths (n=15, 13.1%). The majority of the examined retinas were classified as moderate vascular retinopathy (65.5%), followed by no or mild vascular retinopathy (21.5%) and vascular retinopathy with vessel rarefaction (13.0%).

Vascular risk factors between fundus groups were distributed as follows (online supplemental table 1). Patients classified as vascular retinopathy with vessel rarefaction had the highest rates of hypertension. Furthermore, these patients were older and their index event was classified more often as small vessel disease compared with the rest of the cohort. On the other hand, patients with no or mild vascular retinopathy were more often affected by diabetes mellitus and were more frequently tobacco smokers.

Subsequent vascular events in all patients

Bivariate Cox regression analysis did not yield a significant predictive value between fundus groups and any subsequent vascular event (HR for moderate vascular retinopathy and vascular retinopathy with vessel rarefaction in comparison with no fundus changes 1.19 (95% CI 0.75 to 1.88), p=0.469 and 1.40 (95% CI 0.79 to 2.47), p=0.248, respectively). HRs for different outcomes are shown in the online supplemental table 2.

After adjusting the model for age, sex, BMI, ABCD2, index event type, study arm, hypertension, diabetes mellitus, atrial fibrillation, current smoking, stroke aetiology and carotid surgery, there was no independent association between fundus categories and the composite of vascular events or any subcategory of recurrent vascular events (table 3). HR for subsequent composite vascular events in patients with moderate vascular retinopathy was 1.03 ((95% CI 0.64 to 1.67), p=0.905) compared with patients that lacked retinal lesions (ie, no or mild vascular retinopathy). In patients with vascular retinopathy with vessel rarefaction, HR was 1.17 ((95% CI 0.62 to 2.20), p=0.626) compared with patients classified as no or mild vascular retinopathy.

Subsequent vascular events in patients with diabetes mellitus and hypertension

In a post hoc analysis, we investigated the association between fundus pathologies and recurrent vascular events in patients diagnosed with diabetes mellitus and hypertension (table 4 and online supplemental table 3).

In total, 154 patients had a diagnosis of both arterial hypertension and diabetes mellitus. Most of these patients were classified as moderate vascular retinopathy (66.9%), followed by no or mild vascular retinopathy (22.1%), and vascular retinopathy with vessel rarefaction (11.0%), respectively. Subsequent vascular events in this subgroup were distributed as follows: 20 (62.5%) recurrent strokes, 7 (21.9%) acute coronary syndromes and 5 (15.6%) vascular deaths.

In line with our main findings, in patients with diabetes mellitus and hypertension the Cox proportional hazards

Table 3 Cox proportional hazards with multivariable adjustments* in all patients

	Composite events (n=109)		Recurrent stroke (n=74)		Acute coronary syndrome (n=20)		Vascular death (n=15)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
No or mild vascular retinopathy	Reference		Reference		Reference		Reference	
Moderate vascular retinopathy	1.03 (0.64 to 1.67)	0.905	1.40 (0.76 to 2.57)	0.284	0.32 (0.10 to 1.03)	0.056	1.05 (0.31 to 3.54)	0.941
Vascular retinopathy with vessel rarefaction	1.17 (0.62 to 2.20)	0.626	1.47 (0.66 to 3.24)	0.346	0.84 (0.22 to 3.24)	0.802	0.51 (0.05 to 4.94)	0.558

*Model adjusted for age, sex, BMI, ABCD2, index event type, randomisation arm, hypertension, diabetes mellitus, atrial fibrillation, current smoking, stroke aetiology and carotid surgery.
ABCD2, age, blood pressure, clinical findings, duration of symptoms and presence or absence of diabetes; BMI, body mass index.

Table 4 Post hoc analysis: Cox proportional hazards with multivariable adjustments in patients with diabetes mellitus and hypertension

	Composite events (n=32)*		Recurrent stroke (n=20)*		Acute coronary syndrome (n=7)		Vascular death (n=5)†	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
No or mild vascular retinopathy	Reference		Reference		Reference		Reference	
Moderate vascular retinopathy	0.82 (0.32 to 2.13)	0.685	2.56 (0.51 to 12.91)	0.254	0	0	2.13 (0.17 to 26.14)	0.554
Vascular retinopathy with vessel rarefaction	2.11 (0.47 to 9.54)	0.333	24.14 (2.74 to 212.50)	0.004	0	0	8.15 (0.25 to 262.14)	0.236

*Model adjusted for age, sex, BMI, ABCD2, index event type, randomisation arm, atrial fibrillation, current smoking, stroke aetiology and carotid surgery.
†Model adjusted for age, sex, BMI, ABCD2, index event type, randomisation arm, current smoking and carotid surgery.
ABCD2, age, blood pressure, clinical findings, duration of symptoms and presence or absence of diabetes; BMI, body mass index.

after multivariable adjustments (ie, age, sex, BMI, ABCD2, index event type, study arm, atrial fibrillation, current smoking, stroke aetiology and carotid surgery) did not show a statistically significant association between fundus changes and the composite of vascular events (HR for vascular retinopathy with vessel rarefaction compared with no or mild vascular retinopathy 2.11 (95% CI 0.47 to 9.54), p=0.333). When examining the possible relationship between fundus groups and different outcome events, we found a statistically significant association between vascular retinopathy with vessel rarefaction and an elevated risk for recurrent stroke compared with patients with no or mild vascular retinopathy (HR 24.14 (95% CI 2.74 to 212.50), p=0.004) but not for vascular death (HR 8.15 (95% CI 0.25 to 262.14), p=0.236).

DISCUSSION

In this substudy of the INSPiRE-TMS trial of patients with TIA or minor stroke, no independent association was found between retinal pathologies categorised into different severity levels and the risk for subsequent vascular events. Retinal pathologies were also not correlated with single major vascular events, that is, recurrent stroke, acute coronary syndrome and vascular death.

Different retinal parameters and their association with the risk of major vascular events have already been studied in several aspects. In our study, we focused on fundus parameters which are relatively easy to assess by a telemedical approach: arteriolar narrowing, arteriovenous nicking and vessel rarefaction. Arteriolar narrowing describes a tapering of arterioles width compared with venules. Arteriovenous nicking is characterised by a reduction of vessel diameters before and after arteriovenous junctions. Vessel rarefaction represents an overall reduction of vessel density in the retina. These pathologies of the retinal microvasculature can be observed in patients with hypertension and diabetes mellitus.

Our goal was to establish an easy and quick-to-learn classification system of the retina in order to standardise fundus photographs. Therefore, we only used a limited set of parameters to keep the grading as simple as possible. We hypothesised that patients with no or mild vascular retinopathy, who only had marginally changes of the retina, would have a low risk for recurrent vascular events. Contrarily, we speculated that patients with a decent load of retinal pathologies as in the moderate vascular retinopathy group or a high burden of retinal changes as in the vascular retinopathy with vessel rarefaction group would be more likely to be affected by subsequent vascular events.

Data regarding the usefulness of retinal imaging in predicting recurrent vascular events are sparse because most of the studies on predictive value of retinal pathologies were conducted in patients who had not experienced a cerebrovascular event. The most relevant study examining a possible association between fundus changes and recurrent events was published by De Silva *et al*. In a

prospective cohort study with 652 patients with ischaemic stroke, arteriovenous nicking and severe focal arteriolar narrowing were associated with an elevated risk for recurrent cerebrovascular event.[9] These findings were confirmed by Zhuo *et al*.[20] Furthermore, Yuanyuan *et al* identified retinal haemorrhages and exsudates as additional predictors for subsequent strokes.[21] On the other hand, a Swedish retrospective cohort study found no association between the presence of diabetic retinopathy and stroke recurrence in patients with type 2 diabetes mellitus.[22]

In contrast to previous studies, we did not find an independent predictive value of arteriolar narrowing, arteriovenous nicking or vessel rarefaction stratified in different severity categories for the risk of recurrent events. Because all our patients had a TIA or minor stroke as an index event and presence of a cardiovascular risk factor (ie, hypertension, diabetes mellitus, atrial fibrillation or smoking) was obligatory for study inclusion, our patient cohort had a higher vascular risk than patients in prior reports. Therefore, we also observed higher prevalence of fundus changes. Hence, a possible explanation for our findings might be that the predictive value of retinal parameters depends on the burden of cardiovascular comorbidities as proposed by De Silva *et al*.[9]

Even though we did not assess parameters of diabetic retinopathy, a post hoc analysis in patients with diabetes mellitus and hypertension revealed a significant association between retinal changes and risk for subsequent ischaemic stroke. Non-proliferative diabetic retinopathy is defined by the presence of microaneurysms, cotton wool spots (nerve fibre layer infarcts), haemorrhages, hard exudates and intraretinal microvascular abnormalities (ie, shunt-vessels or neovascularisations within the retina). Neovascularisations mark the transition to proliferative diabetic retinopathy and therefore a progressive disease status. Previous research showed that both mild[23] and severe[24] diabetic retinopathy predict incident ischaemic stroke, but recent results regarding patients with diabetic retinopathy and stroke recurrence were inconclusive.[22 25] Furthermore, patients with hypertension have an elevated risk for incidental vascular events if retinopathy signs were present.[26] The results of the post hoc analysis might implicate that retinal changes (ie, arteriolar narrowing, arteriovenous nicking, vessel rarefaction), which are not directly linked to diabetic retinopathy, are an independent predictor for subsequent stroke in patients with diabetes with hypertension. The synergistic effect of hypertension and diabetes mellitus on the risk for recurrent ischaemic stroke[7] (as expressed in the ABCD2 and CHA2D2S-VASc scores) and on the progression on retinopathy[27] has been widely accepted. It therefore seems plausible that these patients have an additional risk for subsequent vascular events when severe fundus changes are present.

The strengths of the present study are its prospective design as part of a randomised trial, standardised evaluation of stroke through trained stroke physicians and the standardised and independent evaluation of fundus images by an experienced senior ophthalmologist using a telemedical approach. This study is the largest investigation, in terms of number of patients, to examine the association between retinal changes and recurrent vascular events.

Our study has some limitations that need to be discussed. For the definitions of the fundus groups, we only used qualitative parameters. Qualitative parameters might have a lower inter-rater reliability than quantitative parameters. We tried to minimise a potential bias by focusing on just three essential parameters and applying a standardised protocol. In order to increase concordance, only one experienced ophthalmologist graded the images. Also, as the results from the subgroup analysis were derived from a post hoc analysis, these associations need to be treated with caution. We therefore cannot rule out that the reported associations are due to chance. Larger prospective cohort studies are needed to confirm these results. At last, because an uneven distribution of risk factor control between fundus groups might bias the results, we assessed the achievement of secondary prevention targets (online supplemental tables 4-6). Overall, there were no major differences in secondary prevention targets through all examined follow-ups apart from achievements of blood pressure targets and proportion of smokers.

In this prospective study in patients with recent TIA or minor stroke, we did not find an independent correlation between retinal pathologies stratified into different severity categories and risk for vascular events. A post hoc analysis in patients with type 2 diabetes mellitus and hypertension hints towards an increased risk for recurrent ischaemic stroke in these patients with severe fundus changes. Further studies are needed to examine the predictive value of non-diabetic retinopathy signs for future vascular events.

Author affiliations
[1]Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany
[2]Center for Stroke Research Berlin, Charité-Universitätsmedizin Berlin, Berlin, Germany
[3]Berlin Institute of Health, Berlin, Germany
[4]Excellence Cluster NeuroCure, Charité-Universitätsmedizin Berlin, Berlin, Germany
[5]German Center for Neurodegenerative Diseases, partner site Berlin, Germany
[6]German Center for Cardiovascular Research, partner site Berlin, Germany
[7]Ophthalmology, Friedrich-Alexander-Universität Erlangen-Nürnberg Medizinische Fakultät, Erlangen, Germany
[8]Talkingeyes & More GmbH, Erlangen, Germany

Contributors GM and HJA contributed equally to the manuscript as last author. PK was responsible for analysing and interpreting the data, as well as writing and drafting the manuscript. TI participated in trial management, analysing the data, revising the manuscript and gave important intellectual input. IL participated in trial design and management. MS participated in trial management. ME participated in funding acquisition, trial conduct and gave critical input to the manuscript. GM and HJA were the principal investigators of the study and participated in drafting and editing the manuscript. GM conceptualised and designed the study, was responsible for analysing the data and interpreted the results. HJA was responsible for study design, funding acquisition, trial conduct, quality management and analysing and interpreting the result. HJA was the guarantor of the study.

Funding The INSPIRE-TMS trial was funded by the German Federal Ministry of Education and Research, Pfizer and German Stroke Foundation.

Competing interests PK, TI, IL, MS declare no disclosures or competing interest. ME reports grants from Bayer and fees paid to the Charité from AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, Novartis, Pfizer, all outside the submitted work. GM reports grants from Bayer, outside the submitted work. HJA has received funding from the Deutsche Forschungsgemeinschaft (DFG), the Federal Ministry of Research and Education (BMBF) and the German Innovation Fund for other projects. He reports personal fees from AstraZeneca, Bayer Vital, Boehringer Ingelheim, Bristol Myers Squibb, Novo Nordisk, Pfizer and Sanofi.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by Charité Berlin ethics committee (EA2/084/11). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data supporting the findings in the present study are available from the principal investigator (heinrich.audebert@charite.de) on reasonable request.

ORCID iD

Philipp Klyscz http://orcid.org/0000-0003-0058-2365

REFERENCES

1 Wong TY, Klein R, Couper DJ, *et al*. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis risk in Communities study. *The Lancet* 2001;358:1134–40.
2 Wong TY, Klein R, Nieto FJ, *et al*. Retinal microvascular abnormalities and 10-year cardiovascular mortality: A population-based case-control study. *Ophthalmology* 2003;110:933–40.
3 Fisher DE, Jonasson F, Klein R, *et al*. Mortality in older persons with retinopathy and concomitant health conditions: the age, gene/environment susceptibility-reykjavik study. *Ophthalmology* 2016;123:1570–80.
4 Goto I, Katsuki S, Ikui H, *et al*. Pathological studies on the intracerebral and retinal arteries in cerebrovascular and noncerebrovascular diseases. *Stroke* 1975;6:263–9.
5 Witt N, Wong TY, Hughes AD, *et al*. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. *Hypertension* 2006;47:975–81.
6 Sabanayagam C, Tai ES, Shankar A, *et al*. Retinal arteriolar narrowing increases the likelihood of chronic kidney disease in hypertension. *J Hypertens* 2009;27:2209–17.
7 Amarenco P, Lavallée PC, Monteiro Tavares L, *et al*. Five-Year risk of stroke after TIA or minor ischemic stroke. *N Engl J Med* 2018;378:2182–90.
8 van Wijk I, Kappelle LJ, van Gijn J, *et al*. Long-Term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. *Lancet* 2005;365:2098–104.
9 De Silva DA, Manzano JJF, Liu EY, *et al*. Retinal microvascular changes and subsequent vascular events after ischemic stroke. *Neurology* 2011;77:896–903.
10 Ahmadi M, Laumeier I, Ihl T, *et al*. A support programme for secondary prevention in patients with transient ischaemic attack and minor stroke (inspire-tms): an open-label, randomised controlled trial. *Lancet Neurol* 2020;19:49–60.
11 Irewall A-L, Ögren J, Bergström L, *et al*. n.d. Nurse-Led, telephone-based, secondary preventive follow-up after stroke or transient ischemic attack improves blood pressure and LDL cholesterol: results from the first 12 months of the randomized, controlled nailed stroke risk factor trial. *PLoS ONE*;10:e0139997.
12 Harris PA, Taylor R, Minor BL, *et al*. The redcap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
13 Endres MD, Rother J, Behnke M. Leitlinien der dgn: sekundärprophylaxe ischämischer schlaganfall und transitorische ischämische attacke. 2015.
14 Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;25:457–507.
15 Chimowitz MI, Lynn MJ, Derdeyn CP, *et al*. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365:993–1003.
16 Michelson G, Groh M, Groh MJ, *et al*. Telemedical-supported screening of retinal vessels (“ talking eyes ”) [telemedical-supported screening of retinal vessels ("talking eyes]. *Klin Monbl Augenheilkd* 2005;222:319–25.
17 Michelson G, Laser M, Müller S, *et al*. Validation of telemedical fundus images from patients with retinopathy. *Klin Monbl Augenheilkd* 2011;228:234–8.
18 Lip GYH, Halperin JL. Improving stroke risk stratification in atrial fibrillation. *Am J Med* 2010;123:484–8.
19 van Leiden HA, Dekker JM, Moll AC, *et al*. Risk factors for incident retinopathy in a diabetic and nondiabetic population: the hoorn study. *Arch Ophthalmol* 2003;121:245–51.
20 Zhuo Y, Yu H, Yang Z, *et al*. Prediction factors of recurrent stroke among chinese adults using retinal vasculature characteristics. *J Stroke Cerebrovasc Dis* 2017;26:679–85.
21 Yuanyuan Z, Jiaman W, Yimin Q, *et al*. Comparison of prediction models based on risk factors and retinal characteristics associated with recurrence one year after ischemic stroke. *J Stroke Cerebrovasc Dis* 2020;29:104581.
22 Hjelmgren O, Strömberg U, Gellerman K, *et al*. Does retinopathy predict stroke recurrence in type 2 diabetes patients: a retrospective study? *PLoS ONE* 2019;14:e0210832.
23 Kawasaki R, Tanaka S, Tanaka S, *et al*. Risk of cardiovascular diseases is increased even with mild diabetic retinopathy: the japan diabetes complications study. *Ophthalmology* 2013;120:574–82.
24 Cheung N, Rogers S, Couper DJ, *et al*. Is diabetic retinopathy an independent risk factor for ischemic stroke? *Stroke* 2007;38:398–401.
25 Seferovic JP, Bentley-Lewis R, Claggett B, *et al*. Retinopathy, neuropathy, and subsequent cardiovascular events in patients with type 2 diabetes and acute coronary syndrome in the elixa: the importance of disease duration. *J Diabetes Res* 2018;2018:1631263.
26 Cheung CY, Biousse V, Keane PA, *et al*. Hypertensive eye disease. *Nat Rev Dis Primers* 2022;8:14.
27 Flaxel CJ, Adelman RA, Bailey ST, *et al*. Diabetic retinopathy preferred practice pattern®. *Ophthalmology* 2020;127:66–145.