ONLINE SUPPLEMENT

Cortical gray matter lesions are associated with no persistent infarction after transient ischemic attack

Havsteen et al. 2017

Supplemental methodology:

Clinical risk factors:

Symptoms, symptom duration, vascular risk factors and ABCD2 were recorded including prior stroke, TIA or myocardial infarction (MI), angina pectoris, peripheral arterial disease, diabetes or depression. Hypertension was defined as pre-admission use of antihypertensive medication or hypertension diagnosis in our out-patient clinic. Atrial fibrillation was diagnosed by medical history, admission 12-lead ECG, in-hospital telemetry (24 - 48 hours) or subsequent out-patient cardiac follow-up. We defined hypercholestrolemia as total plasma cholesterol above 5.0 mmol/L or statin treatment. Diabetes was defined by medical history or HbA1c >6.5%. We defined smoking as present or prior smoking, and alcohol overuse as weekly alcohol consumption above 252 g for males and 168 g for females. Recorded hereditary factors were first degree relative with stroke or MI. Clinical data were collected from electronic patient files. Subsequently, clinical and radiological data were compared for consistency under supervision of a senior neurological consultant (HC).

CT-angiography or transcranial Doppler was not included in the protocol; standard carotid examination was performed by ultrasound in the department.

Definition of post-hoc vascular findings

Standard work-up was extracranial carotid Doppler ultrasound. Some patients were investigated with TCD or CTA for clinical suspicion of large vessel disease. For ultrasound we defined carotid stenosis as peak systolic velocity >230 cm/s. For CTA we defined extracranial carotid stenosis as lumen reduction >70%, posterior circulation and intracranial arteries were stenotic with lumen reduction >50%. Atherosclerosis was defined as visible plaque (ultrasound) or calcification (CTA).

Supplemental tables:

Supplemental table I: Acute lesion areas [cm^2].

	DWI	ADC	Initial FLAIR
N with visible lesion, all	84 (54%)	76 (49%)	67 (43%)
Area, range	0.03-5.88	0.03-5.07	0.04-6.03
Area, median (IQR)	0.28 (0.11-0.56)	0.25 (0.14-0.60)	0.32 (0.16-0.80)
N, scar	54 (65%)	53 (71%)	53 (80%)
Area range, persistent infarction	0.05-5.88	0.03-5.07	0.05-6.03
Area range, no persistent infarction	0.03-1.10	0.03-2.17	0.04-1.56
Area median (IQR), persistent infarction	0.40 (0.13-0.86)	0.34 (0.16-0.90)	0.37 (0.18-0.89)
Area median (IQR), no persistent infarction	0.16 (0.08-0.22)	0.17 (0.07-0.23)	0.20 (0.08-0.28)
[a]P	<0.0001	0.002	0.019
cGM area range, persistent infarction (n=21)	0.20-5.88	0.09-5.07	0.12-6.03
cGM area range, no persistent infarction (n=26)	0.03-0.38	0-0.42	0-0.91
cGM area median (IQR), persistent infarction	0.53 (0.37-1.35)	0.34 (0.22-1.22)	0.51 (0.33-1.18)
cGM area median (IQR), no persistent infarction	0.15 (0.08-0.20)	0.09 (0.04-0.22)	0 (0-0.17)
[a]P	<0.0001	<0.0001	<0.0001

122 patients with 155 events completed 8-week (8w) MRI. [a]Initial areas of lesions with and without persistent infarction development, Mann-Whitney U test.

Supplemental table II: Characterization of 122 included patients with and without recurrence

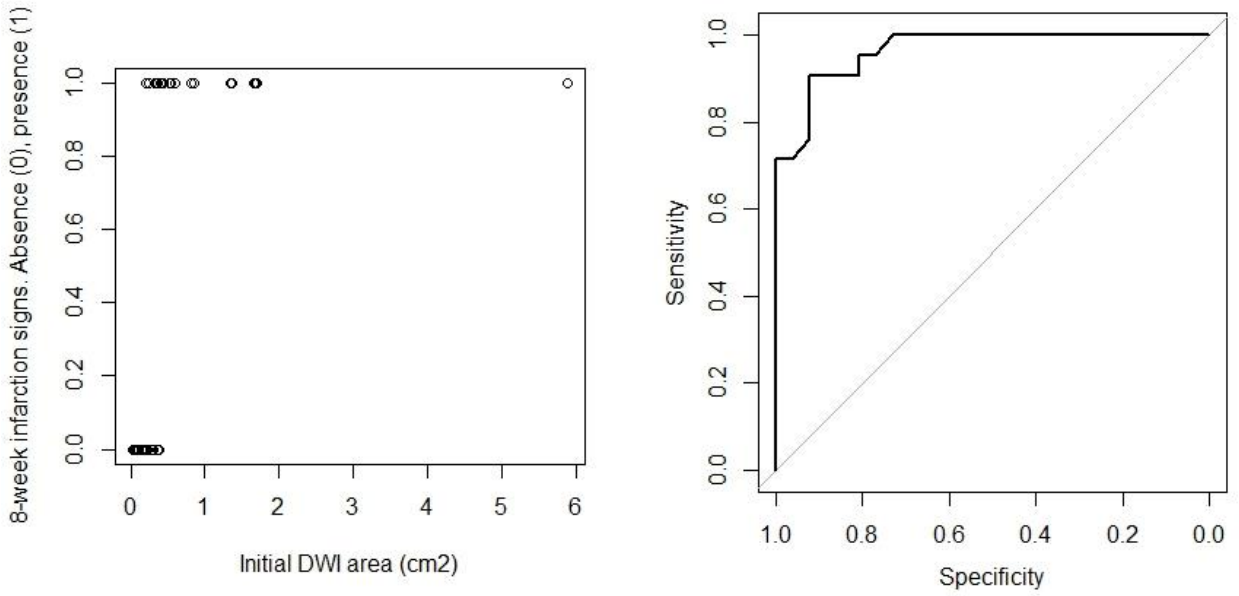
	Recurrent event	No recurrent event	P	OR (95%CI)
	n=14	n=108		-
Female sex, n(%)	5 (36%)	47 (44%)	[a]0.775	-
Median (IQR) age, y	64 (56-76))	65 (53-70)	[b]0.612	-
Microbleeds	3 (21%)	30 (28%)	[a]0.756	0.70 (0.18-2.69)
Old infarctions	8 (57%)	44 (41%)	[a]0.264	1.94 (0.63-5.98)
Small vessel disease (R)	11 (79%)	62 (57%)	[a]0.156	2.72 (0.72-10.31)
Large vessel disease (R)	8 (57%)	37 (34%)	[a]0.139	2.56 (0.83-7.93)
Cardioembolic pattern (R)	1 (7%)	13 (12%)	[a]0.703	0.56 (0.07-4.66)
DWI positive (qualifying event)	3 (21%)	47 (44%)	[a]0.152	0.35 (0.09-1.43)
Symptom duration <60 min			1.000	
<60 min	7 (50%)	51 (47%)		1.00
>60 min	7 (50%)	57 (53%)		0.90 (0.29-2.73)
Atrial fibrillation	0	12 (11%)	[a]0.356	….
Hypertension	8 (57%)	52 (48%)	[a]0.580	1.44 (0.47-4.42)
Diabetes	2 (14%)	14 (13%)	[a]1.000	1.12 (0.23-5.54)
Active smoking	8 (57%)	35 (33%)	[a]**0.083**	**2.74 (0.88-8.52)**
Alcohol overuse	1 (7%)	11 (10%)	[a]1.000	0.66 (0.08-5.58)
Ipsilateral carotid stenosis >70%	3 (21%)	2 (2%)	[a]**0.011**	**14.46 (2.18-96.0)**
Non-ipsilateral extracranial stenosis	2 (14%)	4 (4%)	[a]0.141	4.33 (0.72-26.2)
TOAST etiology (qualifying event):			0.013	
Small vessel (C+R)	4 (29%)	45 (42%)		1.00
Large vessel (C+R)	2 (14%)	26 (24%)		0.86 (0.15-5.05)
Cardiogenic (C+R)	0	18 (17%)		….

Several possible etiologies (C+R)	8 (57%)	19 (18%)		**4.74 (1.27-17.64)**
Infarction-yielding patient	3 (21%)	40 (37%)	[a]0.37	0.46 (0.12-1.76)

[a]Fisher's exact test. [b]Mann-Whitney-U test. RR=relative risk. Y=years. R=radiological. C=clinical

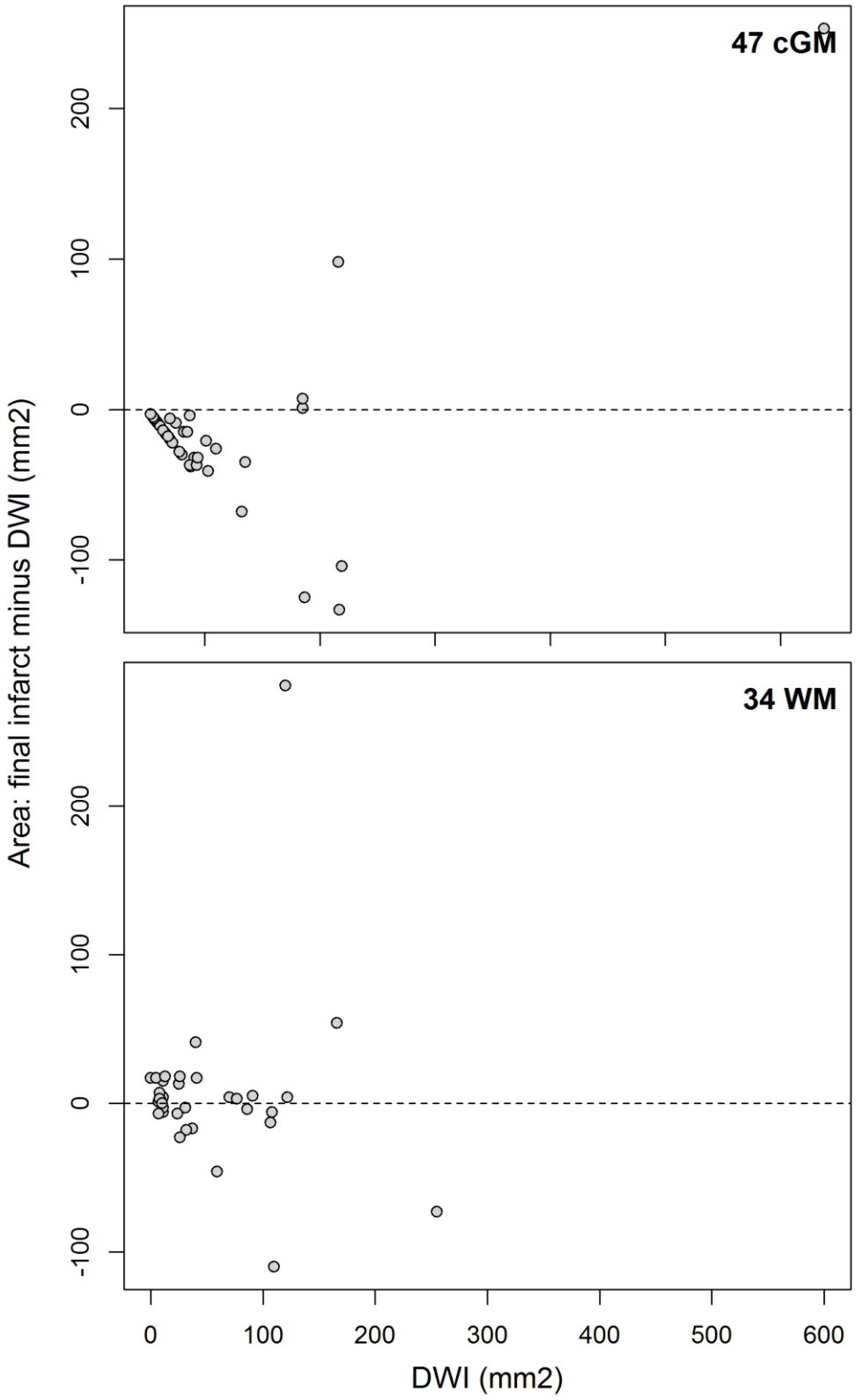
Supplemental figures:

Supplemental figure I: Association between 8-week infarction signs and cortical gray matter (cGM) lesion area.

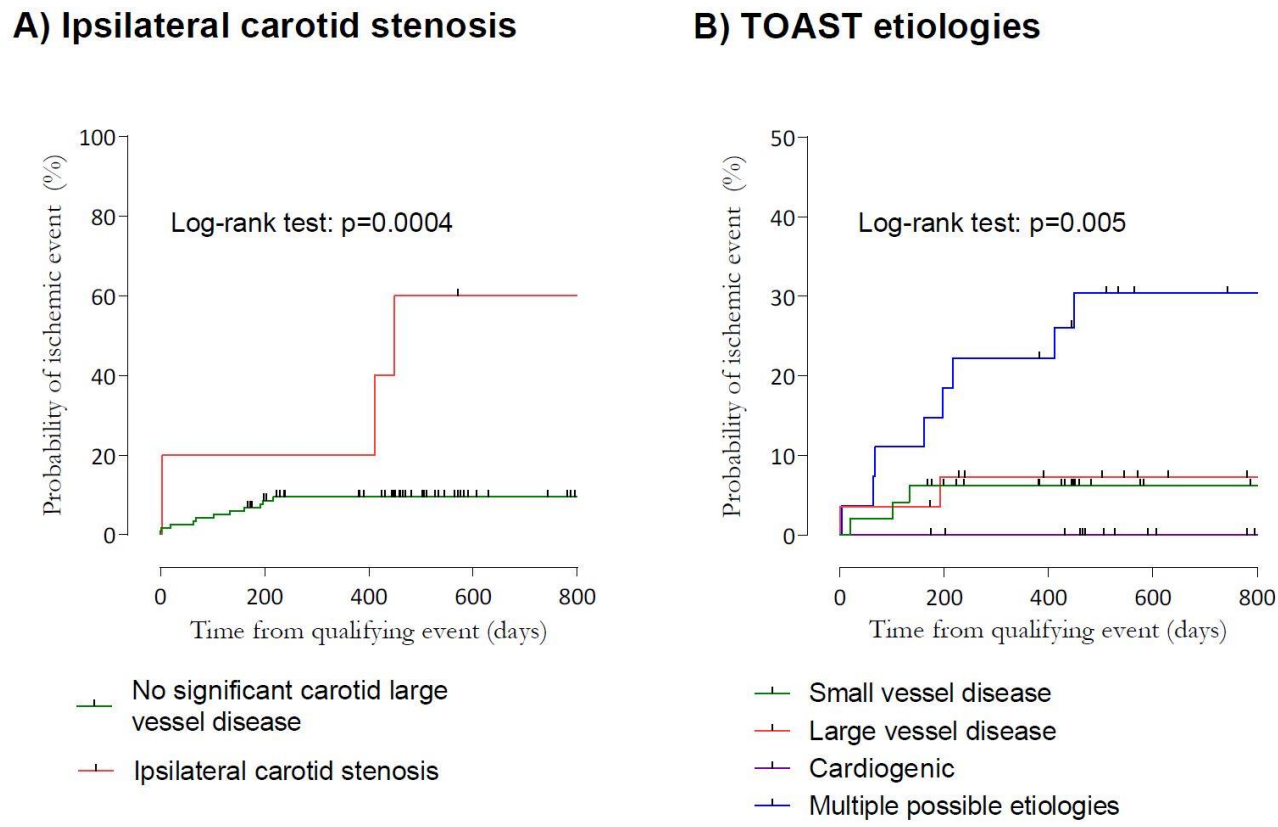


Left panel shows 47 cGM lesions' initial DWI area and presence or absence of 8-week infarction signs. Right panel shows ROC curve illustrating cGM DWI size as binary classifier for 8-week infarction with optimal threshold 0.31 cm^2, AUC 0.97.

Supplemental figure II: Lesion area decrease or increase between ictus and 8-week follow-up for 47 cortical gray matter (cGM) lesions (upper panel) and 34 white matter lesions (lower panel).



Supplemental figure III: Kaplan-Meier curves for patients with significant risk factors of recurrent cerebrovascular event.



Patients with ipsilateral carotid stenosis (panel A) and clinically and radiologically multiple possible etiologies (panel B) have significantly higher probability of recurrent ischemic event.