

TABLES AND FIGURES

| | DWI - N=40 | DWI + N=13 | P= |
|---|------------------|------------------|----------|
| Age mean (std) | 68.15 (8.59) | 69.31 (8.42) | P = .673 |
| Male gender n (%) | 28 (70.0) | 11 (84.6) | P=.299 |
| Hypertension n (%) | 26 (65.0) | 11 (84.6) | P=.181 |
| Diabetes Mellitus n (%) | 9 (22.5) | 3 (23.1) | P=.966 |
| Hypercholesterolemia n (%) | 26 (65) | 8 (61.5) | P=.821 |
| Statin use n (%) | 35 (87.5) | 13 (100) | P=.180 |
| Currently smoking n (%) | 15 (37.5) | 3 (23.1) | P=.340 |
| Estimated pack-years median (IQR) | 15.0 (10-24) | 12.5 (2-33.3) | P=.461 |
| BMI mean (std) | 25.8 (3.7) | 25.0 (2.91) | P=.520 |
| History of PAOD n (%) | 8 (20.0) | 2 (15.4) | P=.712 |
| History of CAD n (%) | 12 (30.0) | 5 (38.5) | P=.570 |
| Qualifying symptom = hemispheric stroke n (%) | 12 (32.5) | 5 (38.5) | P =.693 |
| Stenosis grade \geq 70% n (%) | 38 (95.0) | 11 (84.6) | P=.218 |
| Waiting time (days) median (IQR) | 45.0 (29.5-70.0) | 34.0 (20.5-53.0) | P=.160 |

Table 1 Baseline characteristics of ipsilateral DWI-negative versus DWI-positive patients. Data are given as proportion of the group (%), as mean with standard deviation in case of normally distributed data, or as median with interquartile range in case of not normally distributed data.

| | DWI – (n=40) | DWI + (n=13) | OR unadjusted | P-value uni- variate | OR adjusted | P-value multi- variate |
|---|------------------------|--------------------|--------------------|-------------------------|--------------------|---------------------------|
| IPH <i>n (%)</i> | 24 (60.0) | 12 (92.3) | 8.00 (0.95 – 67.7) | 0.056 | 10.8 (1.17 – 99.9) | .036 |
| Lipid core≥40% <i>n (%)</i> | 23 (57.5) | 3 (23.1) | 0.22 (0.05 – 0.93) | 0.040 | 0.18 (0.04 – 0.83) | .028 |
| Mod/heavy calcifications <i>n (%)</i> | 17 (42.5) | 5 (38.5) | 0.85 (0.24 – 3.05) | 0.798 | 0.82 (0.22 – 3.04) | .770 |
| Mod/heavy collagen <i>n (%)</i> | 31 (77.5) | 7 (53.8) | 0.34 (0.09 – 1.27) | 0.108 | 0.34 (0.09 – 1.27) | .107 |
| Mean number of microvessels <i>Median (IQR)</i> | 9.15 (6.08 – 11.23) | 9.00 (4.72-13.2) | 1.01 (0.93 – 1.09) | 0.895 | 1.01 (0.92 – 1.10) | .890 |
| % pos macrophage staining <i>Median (IQR)</i> | 0.63 (0.24 – 1.75) | 0.74 (0.26 – 1.93) | 1.00 (0.88 – 1.13) | 0.981 | 1.01 (0.89 – 1.15) | .886 |
| % pos SMC staining <i>Median (IQR)</i> | 1.156 (0.39 – 2.79) | 0.91 (0.32 – 1.89) | 0.97 (0.86 – 1.08) | 0.548 | 0.97 (0.86 – 1.09) | .630 |

Table 2 Odds ratios represent the risk for each of the plaque characteristics for presence of preprocedural ipsilateral DWI lesions appearing hypo-/isointense on ADC. In case of continuous independent variables, odds ratios are given per 10% increase. Multivariate analysis was corrected for age and qualifying event. CI, confidence interval; IQR, interquartile range; SMC, smooth muscle cell. Bold values were considered statistically significant with a $p < 0.05$.

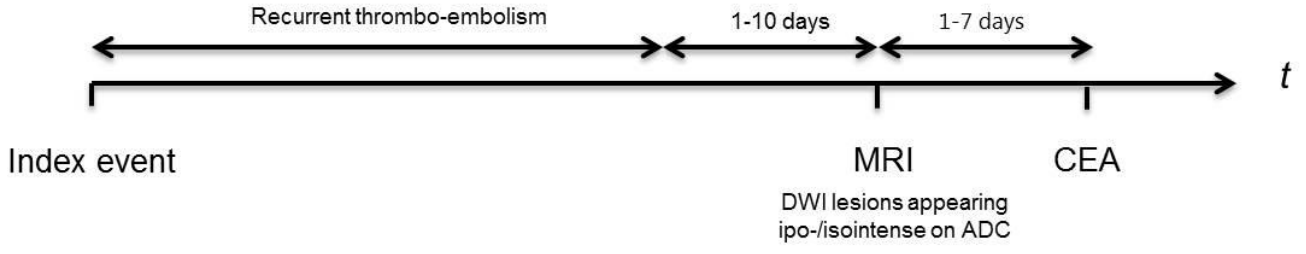


Figure 1: Timeline representing time between index event and revascularization.

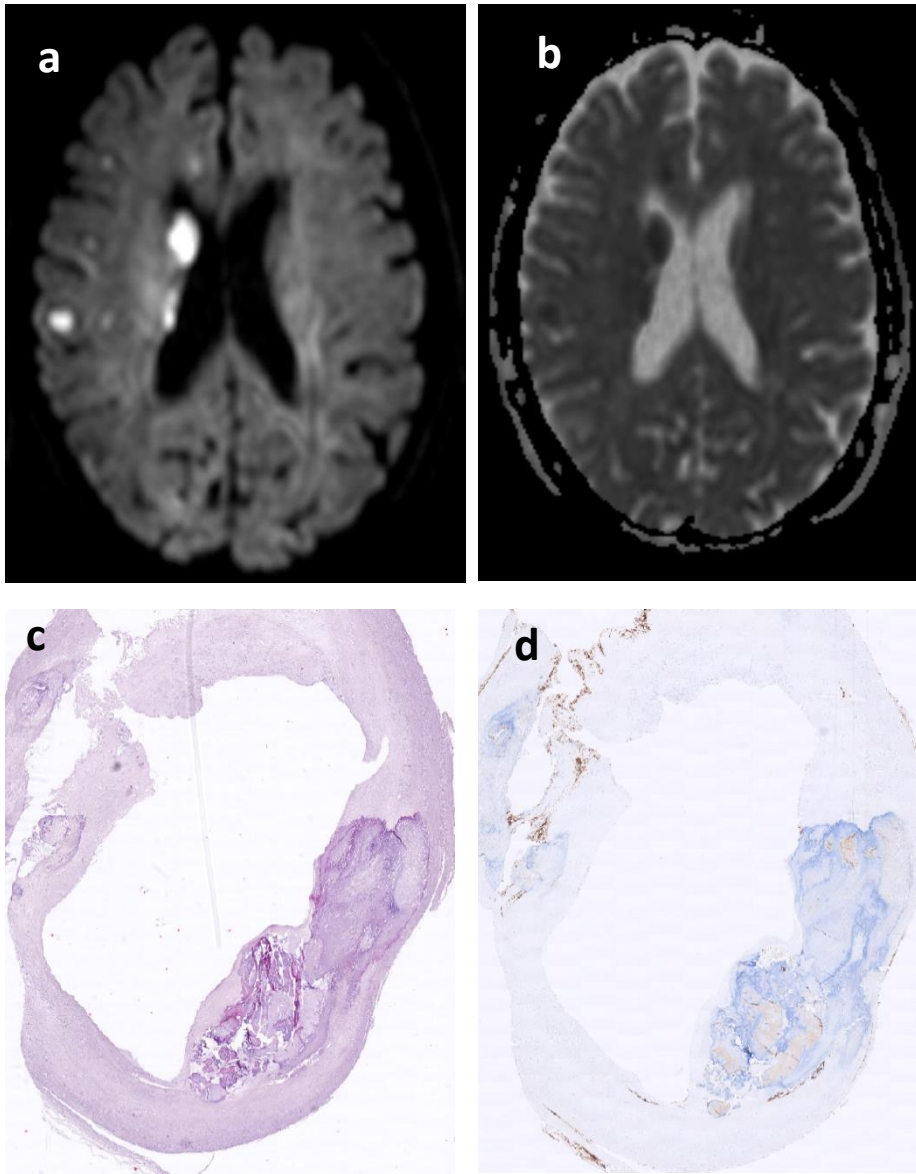


Figure 2: Typical example of patient presenting with minor stroke in right hemisphere and right-sided carotid stenosis. MRI just prior to CEA showed ipsilateral DWI lesions (a) appearing hypointense on ADC (b). Upon histological examination the culprit lesion showed intraplaque hemorrhage quantified using Hematoxylin and eosin staining (c, bar 1 mm.) and glycoporphine staining (d, bar 1 mm.)

SUPPLEMENTAL DATA

Supplemental methods

Specimens were stained with CD68 for macrophages, alpha-actin for smooth muscle cells (SMC), picro-sirius Red (PSR) for collagen, hematoxylin eosin (HE) for general overview including calcifications, CD34 for microvessels and HE and fibrin for plaque hemorrhages. Macrophage content and SMC content were measured quantitatively using computerized analyses using AnalySIS 3.2 software (Soft Imaging Systems GmbH, Münster, Germany), and reported as percentage positive staining per plaque area. Microvessels in the plaque were scored quantitatively in three hotspots and reported as an average number of vessels per hot spot(20). In addition, presence of collagen and calcification was scored semiquantitatively as no/minor or moderate/heavy staining, according to the following criteria: 1. no or minor staining along part of the luminal border of the plaque, or a few scattered spots within the lesion; 2. moderate or heavy staining along the entire luminal border or evident parts within the lesion. Size of the lipid core was visually estimated as a percentage of total plaque area using HE and PSR staining. A carotid plaque with a lipid core covering >40% of the plaque surface was considered as an atheromatous plaque, a carotid plaque with a lipid core covering >10% and <40% was considered a fibrous-atheromatous plaque and a lipid core covering <10% of the plaque surface was considered a fibrous plaque(18). Intraplaque hemorrhage was defined as a hemorrhage within the plaque without signs of cap rupture and no continuum to a luminal thrombus, and was scored as present or absent(24). Intraobserver and interobserver variability were examined previously and showed good reproducibility (κ 0.6-0.9)(17).

Supplemental tables

| White matter lesions | |
|-----------------------|---|
| 0 | No lesions (including symmetrical, well-defined caps or bands) |
| 1 | Focal lesions |
| 2 | Beginning confluence of lesions |
| 3 | Diffuse involvement of the entire region, with or without involvement of U fibers |
| Basal ganglia lesions | |
| 0 | No lesions |
| 1 | 1 Focal lesion (≥ 5 mm) |
| 2 | >1 Focal lesions |
| 3 | Confluent lesions |

Supplemental table S1 ARWMC score. For this study a sum score was used for assessment of the severity of the age related white matter changes.

| | ARWMC ≤ 2 N = 30 | ARWMC > 2 N = 23 | P= |
|--|------------------------|------------------------|-----------------|
| Age mean (std) | 65.33 (8.63) | 72.48 (6.46) | p = .002 |
| Male gender n (%) | 22 (73.3) | 17 (73.9) | p = .962 |
| Hypertension n (%) | 20 (66.7) | 17 (73.9) | p = .569 |
| Diabetes Mellitus n (%) | 5 (16.7) | & (30.4) | p = .235 |
| Hypercholesterolemia n (%) | 18 (60.0) | 17 (69.6) | p = .472 |
| Statin use n (%) | 28 (93.3) | 20 (87.0) | p = .431 |
| Currently smoking n (%) | 12 (40.0) | 6 (26.1) | p = .289 |
| Estimated pack-years median (IQR) | 19.5 (IQR 13.3 – 40.0) | 13.8 (IQR 6.00 – 20.6) | p = .057 |
| BMI mean (std) | 25.6 (3.84) | 25.5 (3.09) | p = .917 |
| History of PAOD n (%) | 7 (23.3) | 3 (13.0) | p = .343 |
| History of CAD n (%) | 8 (26.7) | 9 (39.1) | P = .335 |
| Qualifying symptom = hemispheric stroke n (%) | 12 (40.0) | 6 (26.1) | p = .298 |
| Stenosis grade ≥ 70% n (%) | 29 (96.7) | 20 (87.0) | p = .185 |
| Waiting time (days) median (IQR) | 45.0 (IQR 24.0 – 64.0) | 36.0 (IQR 29.0 – 61.0) | p = .680 |

Supplemental SII Data given as proportion of the group (%), as mean with standard deviation in case of normally distributed data, or as median with interquartile range in case of not normally distributed data. Std, standard deviation; IQR, interquartile range

Supplemental table (III)

| | ARWMC \leq 2 | ARWMC $>$ 2 | OR unadjusted | P-value uni-variate | OR adjusted | P-value multi-variate |
|---|--------------------|--------------------|---------------------|---------------------|--------------------|-----------------------|
| IPH <i>n</i> (%) | 19 (63.3) | 17 (73.9) | 1.640 (0.50 – 5.40) | P=0.415 | 4.61 (0.95 – 22.5) | .059 |
| Lipid core \geq 40% <i>n</i> (%) | 15 (50.0) | 11 (47.8) | 0.917 (0.31 – 2.72) | P=0.875 | 0.63 (0.17 – 2.42) | .502 |
| Mod/heavy calcifications <i>n</i> (%) | 11 (36.7) | 11 (47.8) | 1.58 (0.52 – 4.78) | P=0.415 | 0.95 (0.27 – 3.43) | .941 |
| Mod/heavy collagen <i>n</i> (%) | 22 (73.3) | 16 (69.6) | 0.83 (0.25 – 2.76) | P=0.763 | 1.50 (0.48 – 4.71) | .485 |
| Mean number of microvessels <i>Median</i> (<i>IQR</i>) | 9.72 (6.59 – 11.4) | 8.13 (1.70 – 12.7) | 0.47 (0.21 – 1.07) | P=0.070 | 0.62 (0.25 – 1.55) | .308 |
| % pos macrophage staining <i>Median</i> (<i>IQR</i>) | 1.03 (0.54 – 2.30) | 0.40 (0.08 – 0.96) | 0.19 (0.05 – 0.75) | P=0.017 | 0.23 (0.05 – 10.0) | .053 |
| % pos SMC staining <i>Median</i> (<i>IQR</i>) | 1.24 (0.46 – 2.90) | 0.85 (0.27 – 1.93) | 0.657 (0.24 – 1.83) | P=0.421 | 1.01 (0.31 – 3.29) | .994 |

Supplemental table SIII. Odds ratios represent the risk for each of the plaque characteristics for preprocedural ipsilateral ARWMC score expressed binary as a sum-score of \leq 2 vs a sum-score of $>$ 2. In case of continuous independent variables, odds ratios are given per 10% increase. Multivariate analysis corrected for age, qualifying event and packyears. CI, confidence interval; IQR, interquartile range; SMC, smooth muscle cell. Bold values were considered statistically significant with a $p < 0.05$.