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Magnetic Resonance Imaging Identified Brain Ischaemia in Symptomatic Patients Undergoing Carotid Endarterectomy Is Related to Histologically Apparent Intraplaque Haemorrhage

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WHAT THIS PAPER ADDS

This study investigated the relation between histologically apparent intraplaque haemorrhage (IPH) and the presence of recent brain lesions on diffusion weighted imaging prior to carotid endarterectomy. It was demonstrated that patients with IPH have an increased risk of developing silent brain ischaemia in the waiting period between index event and surgery. These results qualify IPH as a potential marker for identifying patients at risk of recurrent events.

Objective: Intraplaque haemorrhage (IPH) has been independently associated with a higher risk of future ipsilateral stroke in patients with carotid artery stenosis. Evaluation of plaque characteristics may contribute to risk assessment of recurrent (silent) cerebrovascular events in order to prioritise patients for timing of treatment. It is unknown if patients showing histologically apparent IPH also have increased risk of silent ischaemic brain lesions in the waiting period between index event and revascularisation.

Methods: A retrospective analysis was performed based on prospectively collected data of patients included simultaneously in the magnetic resonance imaging (MRI) substudy of the International Carotid Stenting Study and Athero-Express biobank. Patients randomised for carotid endarterectomy (CEA) underwent surgery between 2003 and 2008. Brain MRI was performed one to seven days prior to CEA. Plaques were histologically examined for presence of IPH. The primary outcome parameter was presence of silent ipsilateral brain ischaemia on magnetic resonance diffusion weighted imaging (MR-DWI) appearing hypo or isointense on apparent diffusion coefficient.

Results: Fifty-three patients with symptomatic carotid stenosis meeting the study criteria were identified, of which 13 showed one or more recent ipsilateral DWI lesion on pre-operative scan. The median time between latest ipsilateral neurological event and revascularisation was 45 days (range 6—200) in DWI negative patients *vs.* 34 days (range 6—74, $p = .16$) in DWI positive patients. IPH was present in 24/40 (60.0%) DWI negative patients *vs.* 12/13 (92.3%) DWI positive patients (OR 8.00; 95% CI 0.95—67.7, $p = .06$). Multivariable logistic regression analysis correcting for age and type of index event revealed that IPH was independently associated with DWI lesions in the waiting period till surgery (OR 10.8; 95% CI 1.17—99.9, $p = .04$).

Conclusion: Symptomatic patients with ipsilateral carotid stenosis and silent brain ischaemia on pre-operative MR-DWI, more often showed pathological evidence of IPH compared with those without ischaemic lesions. This identifies carotid IPH as a marker for patients at risk of silent brain ischaemia and possibly for future stroke and other arterial disease complications. Such patients may be more likely to benefit from CEA than those without evidence of ipsilateral carotid IPH.

Keywords: Carotid stenosis, Intraplaque haemorrhage, Silent brain ischaemia, Magnetic resonance diffusion weighted imaging
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INTRODUCTION

The presence of carotid artery intraplaque haemorrhage (IPH) is considered an important maker of plaque instability and associated with a high risk of clinically relevant events such as transient ischaemic attack (TIA) or stroke due to the

tendency to rupture.[1] Signs of presence of carotid artery IPH on magnetic resonance imaging (MRI) or duplex ultrasound have been associated with an increased risk of future cerebrovascular events and IPH is more common in symptomatic patients than in asymptomatic patients.[2,3] Moreover, IPH is associated with an increased risk of any type of secondary cardiovascular event in male patients such as (fatal) myocardial infarction (MI) (fatal) stroke, coronary and peripheral interventions, and cardiovascular death.[4]

Risk assessment of recurrent cerebrovascular events based on plaque characteristics may be helpful for prioritising patients for the timing of carotid revascularisation. Current guidelines recommend that symptomatic patients with carotid stenosis should be considered (in case of 50%—69% stenosis) or recommended (in case of 70%—99% stenosis) for treatment within 14 days of the index event.[5] Nonetheless, these recommendations have been based on *post hoc* analyses of outdated randomised controlled trials (RCTs) and additionally may not always be feasible due to pre-hospital or in hospital delay.[6] Identification of IPH may help to select patients that are most at risk of recurrent events and may help to select those in whom urgent revascularisation may be appropriate.

Ischaemic brain lesions on magnetic resonance diffusion weighted imaging (MR-DWI) are being used increasingly as a surrogate marker of ischaemic events for post-operative outcome after revascularisation as they are associated with an increased risk of future cerebrovascular events.[7] To date, no studies investigating the role of DWI lesions specifically in the pre-operative period have been performed. One of the major advantages of assessing the presence of new DWI lesions is that they may appear within a few hours after a thrombo-embolic event and DWI is therefore sensitive to recent changes. By assessing diffusion restricted brain areas with MR-DWI in combination with apparent diffusion coefficient (ADC), recent infarction can be identified. ADC maps may show darkening within minutes of stroke onset and distinguish stroke from "T2 shine through", which can be seen later after infarction and appears bright on DWI. Low signal intensity on ADC persists for about 7—10 days.[8] Up to now, it has been unclear if carotid plaque characteristics are associated with these silent brain lesions, identifying them as their potential source. For this, patients with characteristics of plaque instability were investigated to see whether they have an increased risk of silent pre-procedural ischaemic brain lesions during their waiting period for carotid intervention.

Since thrombo-embolic events are the most common underlying cause of ischaemic brain lesions in carotid patients, it is hypothesised that patients showing histologically apparent signs of IPH in the atherosclerotic plaque (excised during carotid endarterectomy) are more likely to show (recurrent) silent ischaemic brain lesions in the waiting period between index event and revascularisation.

METHODS

A retrospective analysis was performed based on prospectively collected data of patients included simultaneously in the MRI substudy of the International carotid stenting study (ICSS)[9] and the Athero-Express (AE) biobank study of the University Medical Centre (UMC) Utrecht.[10] Patients that underwent carotid endarterectomy (CEA) between October 2003 and October 2008 were included with a median waiting time (defined as the number of days between the most recent event and surgery) of 44 days. Patients included in the ICSS were symptomatic (symptoms attributable to the randomised artery within 12 months before randomisation) carotid stenosis patients with a stenosis $>$50% deemed to require treatment. Symptomatic patients included those with previous stroke (acute disturbance of focal neurological function attributed to vascular disease and of ischaemic origin, lasting more than 24 h), TIA (acute disturbance of focal neurological function attributed to vascular disease with recovery within 24 h), or amaurosis fugax (transient monocular blindness attributed to vascular disease with recovery within 24 h). The following were exclusion criteria: previous revascularisation in the randomised artery, contraindications for either treatment and planned major surgery.[11] In the course of the study protocol of the ICSS MRI substudy, all patients underwent an additional MRI scan one to seven days before surgery for assessment of silent brain ischaemia. Carotid plaques were collected within the AE biobank. There were no additional exclusion criteria for the AE biobank study other than that the patient had to be randomised for CEA.

MRI

Primary outcome parameters included ipsilateral ischaemic lesions on MR-DWI appearing hypo or isointense on apparent diffusion coefficient (ADC), and its correlation with intraplaque haemorrhage (see Fig. 1 for an illustrative timeline). Secondary outcome parameters included presence of white matter lesions (WMLs) semi-quantitatively assessed on fluid attenuation inversion recovery sequences by use of the age related white matter changes (ARWMC) score. White matter lesions and basal ganglia lesions were both assessed on a 0 to 3 point scale for the ipsilateral hemisphere and a sum score was used for further data analyses (see Table SI for exact definitions).[12]

Atherosclerotic plaque assessment

After CEA, all atherosclerotic plaques were immediately processed. The carotid plaque was cut into segments of 5 mm thickness along the longitudinal axis. The segment with the largest plaque burden was chosen as a culprit lesion and subjected to histological examination. A more detailed description can be found in the Supplementary information. The investigated plaque characteristics resulting from immunochemical staining were presence of IPH, presence of lipid core ($\geq$40%), moderate/heavy calcifications, moderate/heavy collagen, mean number of microvessels per hotspot, percentage of positive macrophage staining per plaque, and percentage of positive smooth muscle cell (SMC) staining per plaque.[13] IPH was defined as the composite of plaque bleeding at the luminal side of the

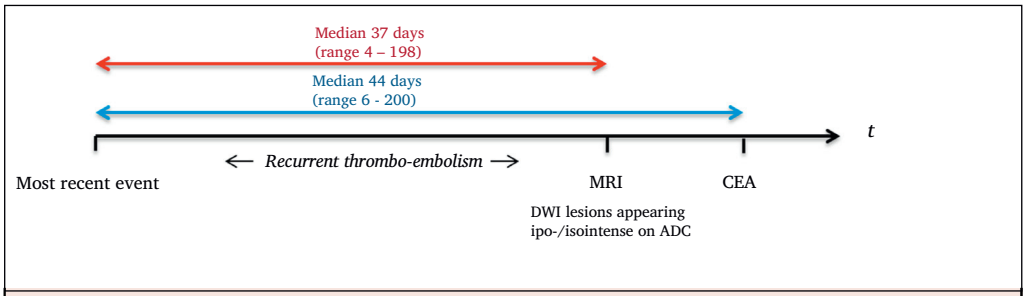

Figure 1. Timeline illustrating waiting time to revascularisation. Waiting time (indicated by blue arrow) was defined as the number of days between the most recent event (hemispheric/retinal stroke, transient ischaemic attack, or amaurosis fugax) and CEA. The red arrow represents the time between latest symptom and pre-operative MRI. ADC = apparent diffusion coefficient; CEA = carotid endarterectomy; DWI = diffusion weighted imaging; MRI = magnetic resonance imaging.

plaque as a result of plaque disruption and haemorrhage within the tissue of the plaque.[14]

Clinical outcome

Major cardiovascular events during three years of follow up were reported, consisting of non-fatal MI, non-fatal stroke, and cardiovascular death. MI was reported when at least two of the following criteria were present: (i) chest pain for $\geq$ 20 min, not disappearing after administration of nitrates; (ii) ST elevation $>$1 mm in two following leads or a left bundle branch block on the electrocardiogram; (iii) creatine kinase (CK) elevation of at least two times the normal value of CK and a muscle/brain (MB) fraction $>$ 5% of the total CK.

Statistics

A sample size of at least of 48 patients was required on the basis of detecting a difference in the proportion of patients with IPH in the DWI positive group of two times that in the DWI negative group at a statistically significant level of .05, 80% power, assuming 25% of patients having pre-operative DWI lesions and 80% of DWI positive patients having IPH. Data were inspected for patterns of missing values. The proportion of randomly missing values for baseline characteristics did not exceed 2%. Differences in binary characteristics were analysed with Pearson's chi square test. Differences in continuous parameters were calculated with the Student *t* test when data were normally distributed and otherwise using a Mann—Whitney U test. For the ARWMC score a binary outcome parameter was used based on median ipsilateral ARWMC score (sum score $\leq$ 2 compared with sum score $>$2). To investigate independent associations between histological plaque characteristics and presence of fresh DWI lesions as well as ARWMC score, a multivariable logistic regression analysis was conducting correcting for any baseline characteristics with $p < .1$ in univariable analysis. Age and type of qualifying event were also added to the multivariable models since these are considered as potential confounders based on earlier described associations with IPH.[3,15] In case of ARWMC score, estimated pack years was identified as an additional potential confounder from univariable analysis and therefore included in multivariable analysis. Non-normally distributed quantitative histological parameters, including number of microvessels and percentages of macrophage and SMC staining, required logarithmic transformation before entering into regression models. SPSS 25.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analysis.

RESULTS

Patient characteristics

53 patients met the inclusion criteria of the ICSS-MRI substudy and were simultaneously included in the AE biobank study. Qualifying events were major stroke ($n = 7$), minor stroke ($n = 11$), cerebral TIA ($n = 28$), and amaurosis fugax ($n = 7$). Mean waiting time between the latest symptom (stroke/TIA) and CEA was 51 days (median 44, range 6—200 days)

DWI/ADC lesions

Thirteen (25%) of 53 patients had pre-operative ipsilateral DWI lesions that appeared hypo or isointense on ADC. Baseline characteristics of patients with and without recent DWI lesions are presented in Table 1. No statistical differences in baseline features were found between the two groups. In patients with pre-operative ipsilateral DWI lesions, the mean number of DWI lesions was 2 (median 1, range 1—6). The mean time between the latest symptom and revascularisation was 56 days (median 45, range 6—200 days) in the DWI negative group and 36 days (median 34, range 6—74 days, $p = .16$) in the DWI positive group. The mean time between latest symptom and MRI was 52 days (median 40, range 5—198) in DWI negative patients *vs.* 34 (median 33, range 4—73, $p = .218$) in DWI negative patients.

The investigated histological plaque characteristics are shown in Table 2 for DWI negative and DWI positive patients. Twenty-four of 40 (60.0%) DWI negative patients showed IPH on histological assessment, *vs.* 12 of 13 (92.3%) in DWI positive patients (see example in Fig. 2). A lipid core of $\geq$40% of the total plaque area was present more often in the DWI negative group (23/40; 57.7%) than in the DWI positive group (3/13; 23.1%). For other plaque characteristics results were similar between DWI positive and DWI negative patients. Of the 36 patients with IPH 12 (33.3%) had pre-operative DWI lesions. Of the 17 patients without IPH one (6%) showed DWI lesions.

Table 1. Baseline characteristics of ipsilateral diffusion weighted imaging (DWI) negative *vs.* DWI positive patients

Characteristic[a]	DWI negative (n = 40)	DWI positive (n = 13)	p value
Mean age ± SD − years	68.2 ± 8.6	69.3 ± 8.4	.67
Male gender − n (%)	28 (70.0)	11 (84.6)	.30
Hypertension − n (%)	26 (65.0)	11 (84.6)	.18
Mean systolic blood pressure ± SD − mmHg	163 ± 29	158 ± 21	.72
Mean diastolic blood pressure ± SD − mmHg	86 ± 15	80 ± 13	.26
Blood pressure medication use − n (%)	29 (72.5)	12 (92.3)	.14
Diabetes mellitus − n (%)	9 (22.5)	3 (23.1)	.97
Hypercholesterolaemia − n (%)	26 (65.0)	8 (61.5)	.82
Median LDL (range) − mmol/L	2.50 (0.91−5.80)	1.84 (0.57−4.50)	.19
Statin use − n (%)	35 (87.5)	13 (100)	.18
Antiplatelet use − n (%)	36 (90.0)	13 (100)	.24
Oral anticoagulants − n (%)	6 (15.0)	1 (7.7)	.50
Currently smoking − n (%)	15 (37.5)	3 (23.1)	.34
Median estimated pack years (range)	15.0 (0−86)	12.5 (0−65)	.46
Mean BMI ± SD − kg/m^2	25.8 ± 3.7	25.0 ± 2.9	.52
History of PAOD − n (%)	8 (20.0)	2 (15.4)	.71
History of CAD − n (%)	12 (30.0)	5 (38.5)	.57
Qualifying symptom = hemispheric stroke − n (%)	13 (32.5)	5 (38.5)	.69
Major stroke − n (%)	3 (7.5)	4 (30.8)	
Minor stroke − n (%)	10 (25.0)	1 (7.7)	
Cerebral TIA − n (%)	21 (52.5)	7 (53.8)	
Amaurosis fugax − n (%)	6 (15.0)	1 (7.7)	
Stenosis grade ≥70% − n (%)	38 (95.0)	11 (84.6)	.22
Median waiting time (range) − days	45 (6−200)	34 (6−74)	.16
Median time between event and MRI (range) − days	40 (5−198)	33 (4−73)	.22

Data are given as proportion of the group (%), as mean with standard deviation in case of normally distributed data, or as median with range in case of not normally distributed data. BMI = body mass index; CAD = carotid artery disease; CEA = carotid endarterectomy; DWI = diffusion weighted imaging; LDL = low density lipoprotein; MRI = magnetic resonance imaging; PAOD = peripheral arterial occlusive disease; SD = standard deviation; TIA = transient ischaemic attack.

[a] Hypertension: previously diagnosed by a doctor or use of antihypertensive drugs. Systolic and diastolic blood pressure were measured on hospital admission. Blood pressure medication use: use of one or more antihypertensive drugs. Diabetes mellitus: previously diagnosed by a doctor or use of antidiabetic medication. LDL: mmol/L measured within 1 month prior to surgery. Antiplatelet use: dipyridamole, acetylsalicylic, carbasalate calcium, or clopidogrel; anticoagulation: coumarone or direct acting oral anticoagulant. PAOD: defined as a history of peripheral interventions or intermittent claudication or ankle brachial index <0.7. History of CAD: defined as a composite of angina pectoris, myocardial infarction, percutaneous coronary intervention, or coronary bypass surgery. Stenosis grade ≥70%; ipsilateral stenosis grade ≥70% as measured by NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria. Waiting time: number of days between the most recent event and CEA. Time between most recent event and MRI: number of days between the most recent pre-operative cerebrovascular event and pre-operative MRI.

Table 2. Odds ratios represent the risk of each of the plaque characteristics for presence of pre-procedural ipsilateral diffusion weighted imaging (DWI) lesions appearing hypo or isointense on apparent diffusion coefficient (ADC)

Plaque characteristic	DWI negative (n = 40)	DWI positive (n = 13)	OR (95% CI) unadjusted	p value univariable	OR (95% CI) adjusted	p value multivariable
Intraplaque haemorrhage − n (%)	24 (60.0)	12 (92.3)	8.00 (0.95−67.7)	.06	10.8 (1.17−99.9)	.04
Lipid core ≥40% − n (%)	23 (57.5)	3 (23.1)	0.22 (0.05−0.93)	.04	0.18 (0.04−0.83)	.03
Mod/heavy calcifications − n (%)	17 (42.5)	5 (38.5)	0.85 (0.24−3.05)	.80	0.82 (0.22−3.04)	.77
Mod/heavy collagen − n (%)	31 (77.5)	7 (53.8)	0.34 (0.09−1.27)	.11	0.34 (0.09−1.27)	.11
Median mean number of microvessels (range)	9.15 (0−25)	9.00 (0−18)	1.01 (0.93−1.09)	.90	1.01 (0.92−1.10)	.89
Median possible macrophage staining (range) − %	0.63 (0.01−4.93)	0.74 (0.01−3.74)	1.00 (0.88−1.13)	.98	1.01 (0.89−1.15)	.89
Median possible SMC staining (range) − %	1.16 (0.00−5.35)	0.91 (0.01−5.73)	0.97 (0.86−1.08)	.55	0.97 (0.86−1.09)	.63

ORs are given per 10% increase in case of continuous independent variables. Multivariable analysis was corrected for age and qualifying event. ADC = apparent diffusion coefficient; CI = confidence interval; CEA = carotid endarterectomy; DWI = diffusion weighted imaging; OR = odds ratio; SMC = smooth muscle cell.

Univariable logistic regression showed an odds ratio (OR) of 8.0 (95% CI 0.95—67.7, $p = .06$) for presence of DWI lesions in IPH positive patients compared with IPH negative patients. Multivariable logistic regression analysis with correction for age and type of index event revealed that IPH was independently associated with the presence of DWI lesions in the waiting period till surgery (OR 10.8; 95% CI 1.17—99.90, $p = .04$). Univariable analysis showed decreased odds for presence of DWI lesions in patients with a large (>40%) lipid core (OR 0.22; 95% CI 0.05—0.93, $p = .04$) which remained statistically significant after correction for age and type of index event (OR 0.18; 95% CI 0.04—0.84, $p = .03$). Other plaque characteristics did not show any significant association with development of DWI lesions in either univariable or multivariable analysis.

In 53 patients a total of 28 DWI lesions were detected of which 26 were ipsilateral and two were contralateral. Of the total cohort the mean number of DWI lesions was 0.5 (median 0, range 0—6 lesions). Mean number of ipsilateral DWI lesions in IPH positive patients was 0.7 (median 0, range 0—6) *vs.* 0.1 (median 0, range 0—1) DWI lesions in IPH negative patients *($p = .03$)*. Of the two patients that had a (single) contralateral DWI lesion, one was IPH positive and one was IPH negative.

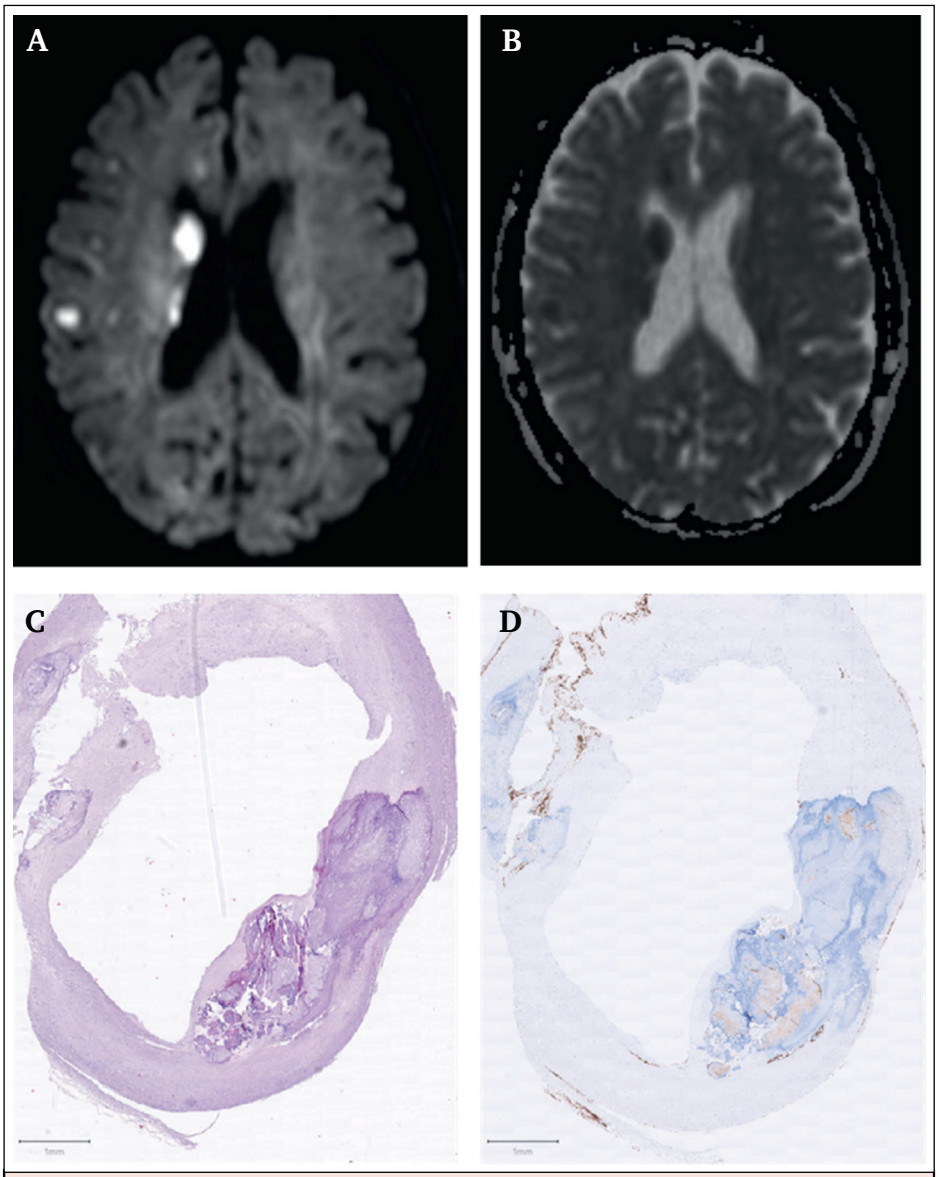

Figure 2. Typical example of patient presenting with minor stroke in right hemisphere and right sided carotid stenosis. Magnetic resonance imaging just prior to carotid endarterectomy showed ipsilateral diffusion weighted imaging lesions (A) appearing hypo-intense with apparent diffusion coefficient (B). On histological examination the culprit lesion showed intraplaque haemorrhage quantified using haematoxylin and eosin staining (C; bar, 1 mm) and glycophorine staining (D; bar, 1 mm).

ARWMC score

The median ipsilateral ARMWC sum score was 2. Patients with an ipsilateral ARWMC sum score of ≤ 2 ($n = 30$) were compared with those with a score > 2 ($n = 23$). Patients with a high ARWMC sum score were significantly older (72.5 ± 6.5) than patients with a low score (65.3 ± 8.6, $p = .002$). Other baseline characteristics did not differ between the two groups, although estimated pack years was identified as a potential confounder ($p = 0.06$, see Table SII). Univariable analysis showed less macrophage staining in the high ARWMC group (OR 0.19; 95% CI 0.05—0.75, $p = .02$), which was no longer significant after adjustment for confounders in multivariable logistic regression (OR 0.23 95% CI 0.05—10.0 $p = .05$), see Table SIII.

Post-operative course

The median follow up period was 3.0 years (IQR 2.9—3.2). Of the 53 patients, two developed peri-operative (<30 days) stroke, one ischaemic and one haemorrhagic; both were IPH positive. No additional major peri-operative events (MI or death) occurred in either IPH positive or IPH negative patients. In six additional patients a major post-operative arterial disease complication (non-fatal stroke, non-fatal MI, vascular death) occurred during follow up: two developed stroke (one ischaemic and one haemorrhagic); three suffered from MI and one additional patient died of another cardiovascular cause (sudden cardiac death). All but one of these patients were IPH positive; of the IPH negative patients one patient had MI. No IPH negative patients suffered from stroke or died of arterial disease complication during follow up.

DISCUSSION

This study investigated the presence of recent silent ischaemic lesions in patients with IPH compared with those without IPH. It was demonstrated that carotid IPH is associated with presence of MR-DWI ischaemic brain lesions in the waiting period between symptom onset and revascularisation, identifying IPH as the potential pathological substrate for such lesions.

This finding is in agreement with imaging studies on carotid plaque characteristics that show that intraplaque haemorrhage is an independent risk factor for future stroke or TIA in patients with carotid artery atherosclerosis.[16,17] This study, relating histological data to the development of silent ischaemic lesions, provides unique insight into the natural course and pathology in the time leading up to revascularisation. The results suggest that revascularisation procedures of patients with IPH should be prioritised over patients without IPH in order to avert the risk of recurrent ischaemia. It should be noted that this also applies in case of a pre- or in hospital delay of >14 days after the index event. Moreover, a broad consensus on early *vs.* expedited treatment is still lacking.[6,18—20] This study contributes to the ongoing discussion on this matter by stressing the importance of eliminating an unstable plaque prior to any (clinical or subclinical) recurrent event. Although IPH cannot specifically identify all patients at risk of recurrent ischaemic events (silent or symptomatic) as the IPH rate is higher than the DWI rate, it can help to prioritise those that may benefit more from a rapid revascularisation procedure. A more tailored therapy for symptomatic patients based on, amongst others, plaque imaging may be a solution for risk reduction of individual patients.

One other clinical study has shown that patients with symptomatic carotid stenosis with IPH are more likely to develop recurrent cerebrovascular events in the waiting period until revascularisation.[21] This study did not use histological data but MR T1 weighted three dimensional gradient echo sequence to demonstrate IPH. Reliable methods for pre-operative assessment of IPH on imaging are essential for clinical applicability. Over the years, several studies investigating IPH imaging on MR have been performed using various sequences and protocols.[22,23] More recent articles propose magnetisation prepared rapid acquisition gradient echo (MPRAGE) as one of the most promising for sequence identification of IPH, with high sensitivity, specificity and κ values when validated with histological data.[24] However, the reliability of MR imaging of IPH in the plaque remains limited in the case of smaller haemorrhages or coexisting calcifications.[24]

The presence of a large lipid core was found to be negatively associated with DWI lesions whereas hypercholesterolaemia, statin use, and low density lipoprotein levels did not differ between groups. One might expect a lipid rich necrotic core to be positively associated with plaque instability and therefore recurrent events. Nonetheless, the results are in agreement with earlier research showing that large lipid core and macrophages are not associated with any vascular event, although no subanalyses specifically for cerebrovascular events were performed in this study.[14] Another study comparing symptomatic with asymptomatic arteries within patients with unilateral symptomatic carotid stenosis found that IPH, but not a large lipid core, was more often seen on the symptomatic side.[25] Perhaps the presence of a large lipid core shows that plaque rupture has not yet occurred and therefore at this time does not characterise an acute risk of thrombo-embolism.

The study used MR-DWI in combination with ADC imaging as the primary outcome parameter. Presence of DWI lesions as a surrogate marker for cerebral ischaemia may become increasingly important, especially considering the evidence that DWI lesions are associated with a higher risk of recurrent cerebrovascular events.[7] In light of the continuously decreasing stroke rate under improvements in procedural timing and medical therapy, stroke rate alone is no longer sufficient for determination of therapeutic strategies. A surrogate marker for stroke is warranted and use of DWI as surrogate marker is both biologically plausible and clinically relevant.[26] As the rate of recurrent cerebrovascular events in the period up to revascularisation is as low as 1.6%,[27] use of DWI lesions (seen in 25% of this population) provides the opportunity to detect statistically significant differences in relatively small patient cohorts.

No difference was found in ARWMC score between IPH positive and IPH negative patients. Although one might hypothesise that plaque instability can contribute to development of age related white matter lesions via embolic events,[21] convincing evidence of a causal relation between the two was not demonstrated in earlier studies either.[28,29] A shared aetiology for atherosclerosis and white matter lesions may be more likely.[29]

Limitations

Intraplaque haemorrhage was determined histologically after the plaque was excided during CEA. Considering the long time interval between symptom onset and surgery, IPH was not necessarily already present at the moment of the index event. Relation to signs of IPH on pre-operative imaging (MRI/duplex) may have improved the clinical applicability of the data. Additionally, analyses to differentiate older (healed) IPH from acute IPH were not performed, although identification of healed IPH on histology is technically possible as shown in studies of coronary arteries.[30] Furthermore, DWI cannot be used to reliably estimate the age of an ischaemic lesion. Although ADC values can help to differentiate from older lesions by excluding T2 shine through, exact determination of the moment of onset of these lesions is impossible[31] and it cannot be ruled out that the detected lesions were already present at the time of hospital presentation.

In the context of clinical relevance, the impact of DWI lesions on future cerebrovascular events would have been of interest. However, MR-DWI performed within a few days after revascularisation revealed that several patients developed (new) peri-procedural DWI lesions. Hence, any correlation between presence of DWI lesions on pre-operative imaging and future events is clouded by the carotid intervention shortly after and thus no statements can be made on the clinical impact of pre-procedural silent ischaemic lesions.

No information was available on the presence or lack of IPH in other sites of the arterial tree, such as the aortic arch and the contralateral carotid artery. IPH in the carotid artery may be a sign of general inflammation and although an ipsilateral carotid revascularisation procedure contributes to averting the risk of ipsilateral stroke it does not necessarily reduce the risk of any stroke. Additionally, non-arterial sources of embolism could not be excluded and any differences between patients in quality of medical intervention prior to baseline is lacking.

There is a chance of type II statistical error or over fitting of the statistical model as a result of the small patient cohort. Patients of this study were included between 2004 and 2007 when, under current standards, substantial delay between hospital presentation and intervention was common practice. The obtained knowledge is still of surplus value as prioritising patients may be challenging when multiple patients qualify for treatment at the same time. Also, patients with a late hospital presentation sometimes may be postponed in favour of patients with more recent events. This study emphasises the relevance of prompt action even after more than 14 days since the index event. This small patient cohort also limits statistical comparison of the clinical course of IPH positive *vs.* IPH negative as well as DWI positive *vs.* DWI negative patients. Future research should focus on validation of the results in a large cohort using both histological data as well as MRI plaque data to compare development of future cerebrovascular events.

Future perspectives

Symptomatic patients with a low risk of future events based on several clinical and radiological features are currently under investigation in the ECST-2 trial randomising between best medical therapy alone or an additional revascularisation procedure.[32] Assessment of IPH on plaque imaging can potentially help in stratification of these low risk patients. Identification of histological IPH as a potential source of ischaemic brain lesions also suggests that assessment of plaque characteristics may be useful in decision making on optimal treatment strategy in asymptomatic carotid stenosis patients. Studies on imaging of carotid plaque IPH and follow up in asymptomatic patients are needed to confirm this.

A meta-analysis including studies that performed MR plaque imaging on both symptomatic and asymptomatic patients demonstrated that patients with IPH have an annualised cerebrovascular event rate of 18% compared with 2% in those without IPH.[16] On the other hand, earlier research demonstrated that IPH is a common phenomenon in both symptomatic and asymptomatic patients[33] suggesting that plaque complications such as IPH often heal without giving rise to symptoms and IPH alone may not be sufficient for risk stratification. Imminent clinical decision making algorithms should include multiple risk factors as it has already been demonstrated that such models can reliably predict major cardiovascular events in patients with carotid artery disease.[34] These algorithms should take into account not only IPH but also other promising diagnostic tools such as brain imaging for detection of silent infarction and embolus detection. Prospective observational studies are running that assess amongst others, baseline MRI characteristics (both plaque and brain) to develop such a clinically applicable tool for risk stratification.[35]

CONCLUSION

In this study, it was demonstrated that MR-DWI identified silent brain ischaemia in symptomatic patients undergoing CEA is associated with histologically apparent carotid plaque IPH. This qualifies IPH as a potential marker for identifying patients at risk of these ischaemic brain lesions.

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.07.017.

REFERENCES

1 Michel JB, Virmani R, Arbustini E, Pasterkamp G. Intraplaque haemorrhages as the trigger of plaque vulnerability. *Eur Heart J* 2011;**32**:1977–85.

2 Takaya N, Yuan C, Chu B, Saam T, Underbill H, Cai J, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI - initial results. *Stroke* 2006;**37**:818–23.

3 Turc G, Oppenheim C, Naggara O, Eker OF, Calvet D, Lacour JC, et al. Relationships between recent intraplaque hemorrhage and stroke risk factors in patients with carotid stenosis: the HIRISC study. *Arterioscler Thromb Vasc Biol* 2012;**32**:492–9.

4 Vrijenhoek JEP, Den Ruijter HM, De Borst GJ, De Kleijn DPV, De Vries JPPM, Bots ML, et al. Sex is associated with the presence of atherosclerotic plaque hemorrhage and modifies the relation between plaque hemorrhage and cardiovascular outcome. *Stroke* 2013;**44**:3318–23.

5 Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, et al. Management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the european society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:3–81.

6 Meershoek AJA, de Borst GJ. Timing of carotid intervention. *Br J Surg* 2018;**105**:1231–3.

7 Gensicke H, van der Worp HB, Nederkoorn PJ, Macdonald S, Gaines PA, Van Der Lugt A, et al. Ischemic brain lesions after carotid artery stenting increase future cerebrovascular risk. *J Am Coll Cardiol* 2015;**65**:521–9.

8 Allen LM, Hasso AN, Handwerker J, Farid H. Sequence-specific MR imaging findings that are useful in dating ischemic stroke. *RadioGraphics* 2012;**32**:1285–97.

9 Bonati LHLH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol* 2010;**9**:353–62.

10 Verhoeven BAN, Velema E, Schoneveld AH, De Vries JPPM, De Bruin P, Seldenrijk CA, et al. Athero-express: differential atherosclerotic plaque expression of mRNA and protein in relation to cardiovascular events and patient characteristics. Rationale and design. *Eur J Epidemiol* 2004;**19**:1127–33.

11 Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 2010;**375**:985–97.

12 Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, et al. A new rating scale for age-related white matter changes. *Stroke* 2001;**32**:1318–22.

13 Wesseling M, van Koeverden ID, van Lammeren GW, van der Laan SW, Haitjema S, de Vries JPPM, et al. Impaired kidney function is associated with intraplaque hemorrhage in patients undergoing carotid endarterectomy. *Atherosclerosis* 2017;**266**:128–35.

14 Hellings WE, Peeters W, Moll FL, Piers S, Van Setten J, Van Der Spek PJ, et al. Composition of carotid atherosclerotic plaque is associated with cardiovascular outcome: a prognostic study. *Circulation* 2010;**121**:1941–50.

15 Singh N, Moody AR, Zhang B, Kaminski I, Kapur K, Chiu S, et al. Age-Specific sex differences in magnetic resonance imaging-depicted carotid intraplaque hemorrhage. *Stroke* 2017;**48**:2129–35.

16 Saam T, Hetterich H, Hoffmann V, Yuan C, Dichgans M, Poppert H, et al. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *J Am Coll Cardiol* 2013;**62**:1081–91.

17 Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke* 2013;**44**:3071–7.

18 Tsantilas P, Kuehnl A, König T, Breitkreuz T, Kallmayer M, Knappich C, et al. *Short time interval between neurologic event and carotid surgery is not associated with an increased procedural risk*. 2016. p. 2783–90.

19 Sharpe R, Sayers RD, London NJM, Bown MJ, Mccarthy MJ, Nasim A, et al. Procedural risk following carotid endarterectomy in the hyperacute period after onset of symptoms. *Eur J Vasc Endovasc Surg* 2013;**46**:519–24.

20 Strömberg S, Gelin J, Österberg T, Bergström GML, Karlström L, Österberg K. Very urgent carotid endarterectomy confers increased procedural risk. *Stroke* 2012;**43**:1331–5.

21 Altaf N, MacSweeney ST, Gladman J, Auer DP. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke* 2007;**38**:1633–5.

22 Kerwin WS, Miller Z, Yuan C. Imaging of the high-risk carotid plaque : magnetic resonance imaging. *Semin Vasc Surg* 2017;**30**:54–61.

23 McNally JS, Kim S, Mendes J, Hadley JR, Sakata A, De Havenon AH, et al. Magnetic resonance imaging detection of intraplaque hemorrhage. *Magn Reson Insights* 2017;**10**. 1178623X1769415.

24 Ota H, Yarnykh VL, Ferguson MS, Underhill HR, DeMarco JK, Zhu DC, et al. Carotid intraplaque hemorrhage imaging at 3.0-T MR imaging: comparison of the diagnostic performance of three T1-weighted sequences. *Radiology* 2010;**254**:551–63.

25 Saam T, Cai J, Ma L, Cai Y-Q, Ferguson MS, Polissar NL, et al. Comparison of symptomatic and asymptomatic atherosclerotic carotid plaque features with in vivo MR imaging. *Radiol* 2006 Aug;**240**:464–72.

26 Traenka C, Engelter ST, Brown MM, Dobson J, Frost C, Bonati LH. Silent brain infarcts on diffusion-weighted imaging after carotid revascularisation: a surrogate outcome measure for procedural stroke? A systematic review and meta-analysis. *Eur Stroke J* 2019;**4**:127–43.

27 Shahidi S, Owen-Falkenberg A, Gottschalksen B, Ellemann K. Risk of early recurrent stroke in symptomatic carotid stenosis after best medical therapy and before endarterectomy. *Int J Stroke* 2016;**11**:41–51.

28 Potter GM, Doubal FN, Jackson CA, Sudlow CLM, Dennis MS, Wardlaw JM. Lack of association of white matter lesions with ipsilateral carotid artery stenosis. *Cerebrovasc Dis* 2012;**33**:378–84.

29 van den Bouwhuijsen QJA, Vernooij MW, Verhaaren BFJ, Vrooman HA, Niessen WJ, Krestin GP, et al. Carotid plaque morphology and ischemic vascular brain disease on MRI. *AJNR Am J Neuroradiol* 2017;**38**:1776–82.

30 Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, et al. Healed plaque ruptures and sudden coronary death. *Circulation* 2001;**103**:934–40.

31 Abbott AL, Silvestrini M, Topakian R, Golledge J, Brunser AM, de Borst GJ, et al. Optimizing the definitions of stroke, transient ischemic attack, and infarction for research and application in clinical practice. *Front Neurol* 2017;**8**:1–14.

32 Featherstone RL, Brown MM. The second European carotid surgery trial. *Endovasc today* 2012;**October**:75–7.

33 Bassiouny HS, Davis H, Massawa N, Gewertz BL, Glagov S, Zarins CK. Critical carotid stenoses: morphologic and chemical similarity between symptomatic and asymptomatic plaques. *J Vasc Surg* 1989;**9**:202–12.

34 Khanna NN, Jamthikar AD, Araki T, Gupta D, Piga M, Saba L, et al. Nonlinear model for the carotid artery disease 10-year risk prediction by fusing conventional cardiovascular factors to carotid ultrasound image phenotypes: a Japanese diabetes cohort study. *Echocardiography* 2019;**36**:345–61.
35 *TAXINOMISIS Project*. 2018 https://taxinomisis-project.eu/.

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COUP D'OEIL

Do Not Forget to Pull the Graft!

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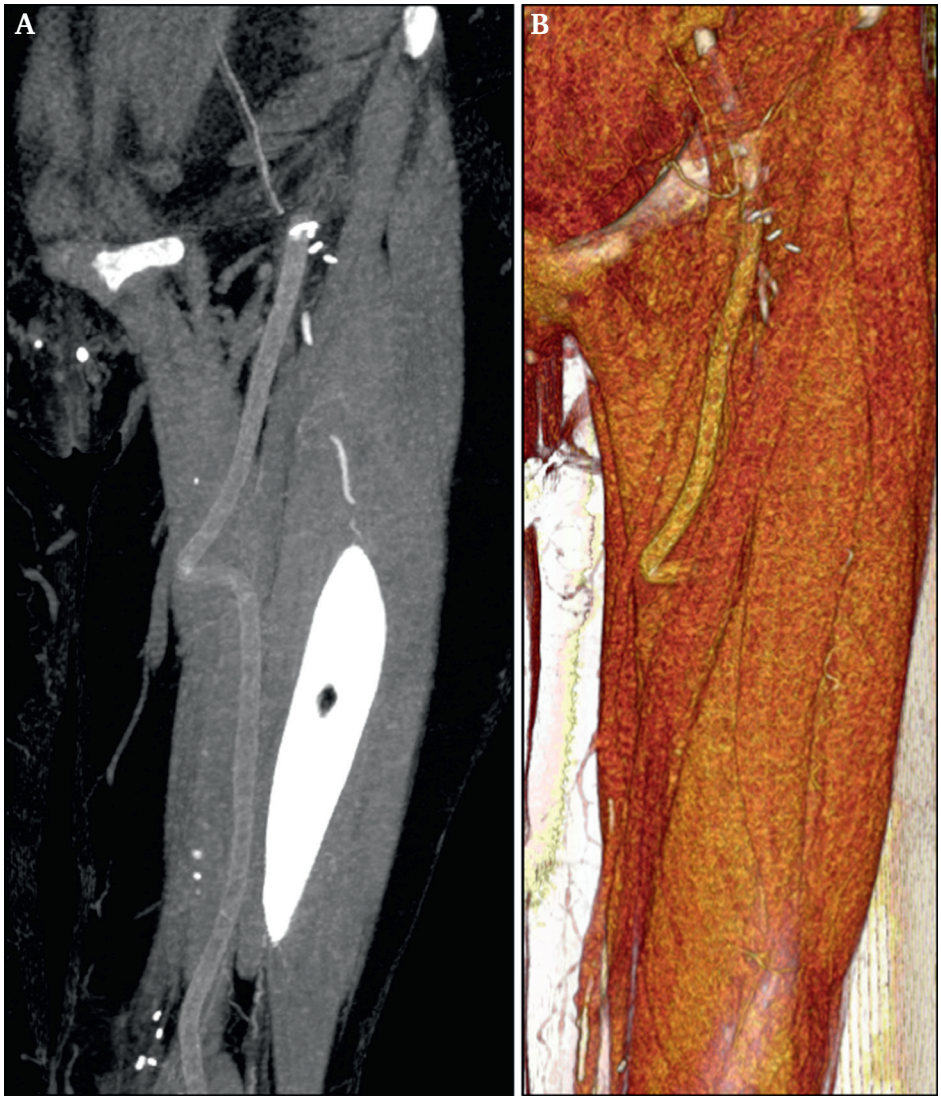

A 71 year old woman presented with a two month history of left lower limb claudication. Her history included an above knee femoropopliteal bypass using a 7 mm heparin bonded expanded polytetrafluoroethylene graft (Propaten, WL Gore & Associates, Flagstaff, USA) six months previously for critical limb ischaemia (rest pain). Computed tomography angiography revealed a thrombosed graft, severely kinked where it lay beneath sartorius (A and B). Lack of appropriate intra-operative graft pulling and straightening probably caused the problem. This case illustrates the importance of intraoperative quality control after bypass surgery to prevent kinks or other problems that might hinder flow and predispose to occlusion.

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