Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2012;34:343–350
DOI: 10.1159/000343227

Received: June 25, 2012
Accepted: September 4, 2012
Published online: November 14, 2012

Plaque Characteristics of Asymptomatic Carotid Stenosis and Risk of Stroke

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Key Words
Asymptomatic carotid stenosis · Plaque components · Vulnerable plaque · Predictive factors · Future cerebrovascular events

Abstract
Background: The optimal treatment of asymptomatic carotid stenosis (ACS) is controversial. To optimize the risk-benefit ratio of carotid artery revascularization, it is crucial to identify ACS patients who are at increased stroke risk. Recent data suggest that plaque vulnerability depends on its composition. Therefore, we assessed plaque composition in ACS to determine predictors for ipsilateral cerebrovascular events. ***Methods:*** 62 patients with 65 ACS ≥50% underwent 3-T MRI of the carotid bifurcation (TOF, special dark-blood weighted noncontrast and contrast-enhanced T_1 and T_2 images) and of the brain. The different plaque components (lipid core, intraplaque hemorrhage, calcification and the status of the fibrous cap) were assessed. Furthermore, the plaque volume and the volume of clinically silent cortical and subcortical infarcts in the territory of the stenosed carotid artery as seen on FLAIR images were determined by using a semi-automated software. Carotid stenosis was considered asymptomatic if there had not been any clinically apparent ischemic events in the corresponding vascular territory within the previous 6 months. During follow-up, information on the occurrence of cerebrovascular events, medical treatment and sonographic changes of the stenosis was collected. ***Results:*** At baseline, 24 ACS (37%) were classified as high grade. A lipid-rich necrotic core was the dominant plaque component in 16 ACS (25%). The plaque volume was higher in ACS with a lipid-rich necrotic core as dominant plaque component ($p = 0.002$) and in patients with prior stroke/TIA ($p = 0.010$). After a median follow-up of 18.9 months (interquartile range 3.5–30.1) there were 2 ipsilateral strokes and 3 ipsilateral TIAs. The average annual event rate was 7.7%. A lipid-rich necrotic core (HR 7.21; 95% CI 1.12–46.28; $p = 0.037$), sonographic progression of the stenosis (HR 7.00; 95% CI 1.13–41.34; $p = 0.036$), history of stroke (HR 11.03; 95% CI 1.23–99.36; $p = 0.032$), and the volume of clinically asymptomatic ischemic brain lesions (HR 1.14/cm^3; 95% CI 1.03–1.25; $p = 0.008$) predicted cerebrovascular events. Patients on statin therapy at follow-up were at lower risk of events (HR 0.17; 95% CI 0.03–1.00; $p = 0.05$). ***Conclusions:*** In addition to medical history and sonographic

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findings, a lipid-rich necrotic core within the plaque turned out as a predictor of cerebrovascular events. Therefore, MR imaging of carotid plaques deserves further attention and might be helpful to improve risk stratification of asymptomatic carotid disease. The identified predictors could be combined in a risk model and tested in larger prospective studies.

Introduction

The optimal treatment of asymptomatic carotid stenosis (ACS) is controversial. Two large randomized trials have demonstrated a benefit from carotid end arterectomy (CEA) in patients with ACS. However, the absolute benefit was small, mostly because the risk of ipsilateral stroke did not exceed 2% per year in medically treated patients [1, 2]. More recent data suggest an even lower annual stroke risk around 1% with best medical treatment [3–5]. To optimize the risk-benefit ratio of carotid artery revascularization (CEA or carotid artery stenting, CAS), it appears crucial to identify ACS patients who are at increased stroke risk.

Recent data suggest that plaque composition influences plaque vulnerability [6, 7].

Plaques with a thin or disrupted fibrous cap, a large lipid-rich necrotic core, inflammatory infiltrates, neovasculature growth and intraplaque hemorrhage (IPH) are considered 'vulnerable' [8, 9]. Some of these plaque components (e.g. disrupted fibrous cap, intraplaque hemorrhages or large lipid core) can accurately be depicted by multisequence MRI [10, 11]. Furthermore, they have frequently been observed on MRI of symptomatic carotid plaques [12–15]. However, the predictive value of carotid plaque components in ACS has been assessed in only two prospective studies [16, 17].

In this study, we depicted the plaque composition in ACS ≥50% by 3-T MRI and followed the patients clinically and with ultrasound. The goal was to identify imaging predictors for ipsilateral cerebrovascular events.

Methods

Study Population

From December 2007 to August 2009, 68 patients with 71 ACS ≥50% as determined by carotid duplex ultrasound [18–20] gave their informed consent to undergo 3-T MRI of the carotid bifurcation and the brain. Carotid stenosis was considered asymptomatic if there were no clinically apparent ischemic events within the previous 6 months in the corresponding carotid territory. Six patients (9%) were excluded due to poor image quality. Sixty-two patients with 65 carotid stenoses ≥50% were included in the present analysis.

The medical treatment at baseline and the following risk factors were assessed: history of coronary artery disease, atrial fibrillation, stroke or transient ischemic attack (TIA) outside the territory of the ACS, stroke or TIA within the territory of the stenosed carotid artery if they had occurred more than 6 months ago, hypertension (treated hypertension or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg measured on two different occasions), diabetes mellitus (symptoms of diabetes plus random blood glucose concentrations >11 mmol/l or fasting glucose >7 mmol/l), current cigarette smoking, and hypercholesterolemia (treated or total venous plasma cholesterol concentration >5 mmol/l).

Carotid stenosis was categorized into high- (>70%) or moderate-grade (50–69%) stenosis according to widely used sonographic criteria [18–20]. The ethics committee of the canton of Bern approved the study protocol and all patients gave written informed consent to participate.

Imaging Protocol of the Carotid Bifurcation, Image Analysis and Volumetry of the Carotid Plaque

The carotid artery was imaged using a 3-T MRI system (Magnetom TrioTim syngo, VB15, Siemens, Erlangen, Germany) with a four-channel phased array surface coil (Machnet BV, Eelde, The Netherlands). A coronal sequence was used to localize the carotid bifurcation and its plaque distribution and was followed by an axial 3D multislab time of flight (TOF) angiography (TR/TE 22/3.86 ms, FOV read 200 mm, FOV phase 83.3%, slice thickness 0.65 mm, averages 1). This was followed by three pulse-triggered, double inversion recovery, turbo spin echo dark-blood sequences in order to avoid artifacts from the inflowing blood: (1) nonfat saturated T_1-weighted images (WI) (TR/TE 400/ 8.6 ms, 10 slices, slice thickness 3 mm, FOV read 150 mm, FOV phase 100%, averages 2); (2) fat-saturated sequence T_2WI (TR/TE 700/52.0 ms, 10 slices, slice thickness 3 mm, FOV read 150 mm, FOV phase 100%, averages 3), and (3) contrast-enhanced (CE) fat-saturated T_1WI after intravenous gadolinium (TR/TE 400/8.6 ms, 10 slices, slice thickness 3 mm, FOV read 150 mm, FOV phase 100%, averages 2). With a zero-filled Fourier transform applied to all sequences, a voxel size of $0.5 \times 0.5 \times 3.0$ mm was achieved. All images were reviewed by 3 readers (M.-L.M., A.K., M.El-K.) in consensus in a randomized order. The readers were blinded to clinical details. The carotid bifurcation was used as a landmark for matching the 4 different sequences at each slice location. Plaque components were characterized according to previously published criteria based on relative tissue signal intensities in comparison to the adjacent sternocleidomastoid muscle [10, 11, 21–24]. Details of the criteria were as follows: calcifications were of hypointense signal intensity in all sequences; the signal intensity of the lipid-rich necrotic core with IPH depended on the age of the hemorrhage: IPH type I (fresh) was hyperintense in TOF and T_1WI and hypo-/isointense in T_2WI and CE-T_1WI, whereas IPH type II (recent) was hyperintense in all sequences (fig. 1a); the lipid-rich necrotic core without IPH was isointense in TOF, hyperintense in T_1WI, of variable intensity on T_2WI and hypointense in CE-T_1WI (fig. 1b). The dominant component of the plaque was determined by visual assessment. The status of the fibrous cap was dichotomized into two groups: the group with thick and intact caps and

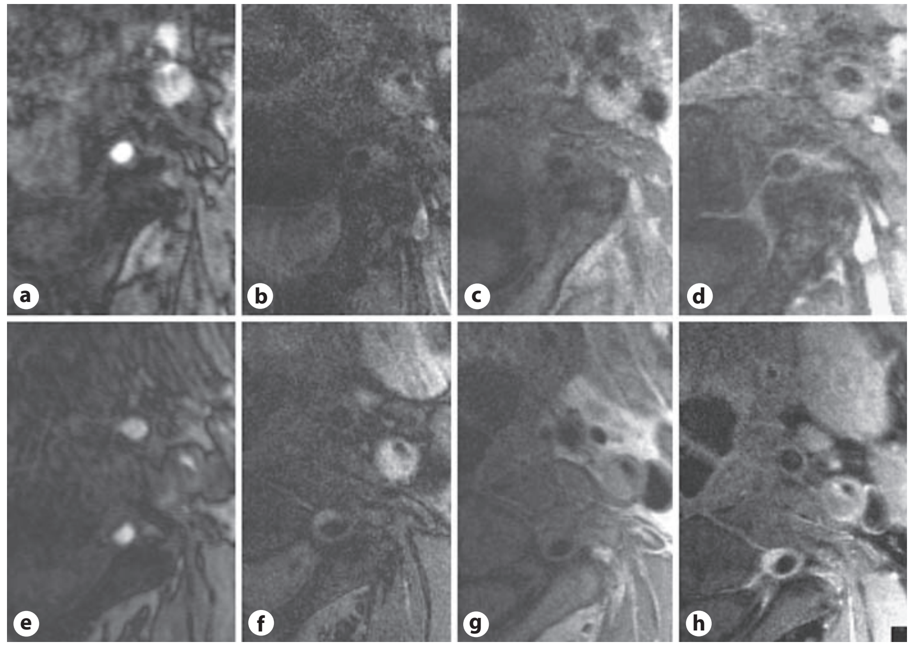


Fig. 1. MRI appearance of a lipid-rich necrotic core with (**a**) or without (**b**) intraplaque hemorrhage on TOF, T_2-weighted and pre- and postcontrast T_1-weighted images. The lipid-rich necrotic core with subacute intraplaque hemorrhage appears hyperintense in all sequences: TOF images (**a**); T_2-weighted images (**b**), T_1-weighted precontrast images (**c**); T_1-weighted postcontrast images (**d**). The lipid-rich necrotic core without hemorrhages appears isointense in TOF images (**e**), hyperintense in T_2-weighted images (**f**), hyperintense in T_1-weighted precontrast images (**g**) and hypointense in T_1-weighted postcontrast images (**h**).

the group with thin or disrupted caps. A thick fibrous cap was characterized by a uniform dark band adjacent to the lumen on TOF images that showed strong enhancement on CE-T_1WI and a smooth luminal surface on all images. In thin fibrous caps, the dark band adjacent to the lumen on TOF was missing and there was no enhancement adjacent to the lumen on CE-T_1WI, but a smooth luminal surface on all images. The fibrous cap was considered ruptured when the dark band adjacent to the lumen was missing or discontinuous on TOF images, the signal at the site of the presumed rupture was hyperintense on TOF images and the surface was irregular on the images of all sequences.

For the volumetric measurement of the carotid plaque, the sequence with the most detailed appearance of the plaque shape on visual assessment was used. The luminal and adventitial boundary of the vessel was detected and outlined using custom-designed software for image processing written in JAVA [25]. The software allowed quantification of the cross-sectional areas as well as the volumes of the imaged plaques. Each slice was assessed separately and any visualized plaque was measured with the software semi-automatically.

MRI Imaging Protocol of the Brain, Image Analysis and Volumetry of the Cerebral Ischemic Lesion Load

Diffusion-weighted echo planar images, fluid attenuated inversion recovery (FLAIR) and T_2-weighted turbo spin echo images and TOF MR angiograms of the intracranial arteries were obtained. Using the same software and principle as for the volumetry of the carotid plaque, the volume of cortical/subcortical infarcts in the territory of the corresponding carotid stenosis was quantified on FLAIR images. Cortical infarcts were defined as focal atrophy of the cortex and the underlying white matter with signal intensity similar to cerebrospinal fluid surrounded by a hyperintense rim. Subcortical infarcts were defined as hypointense lesion with signal intensity of cerebrospinal fluid with or without a hyperintense rim [26]. The reviewer was blinded to the patient's history.

Follow-Up

Follow-up information was complete for 60 patients (97%). Only 2 patients (3%) who moved abroad were lost. Forty-nine patients (79%) were routinely followed-up at our neurovascular ultrasound unit every 6 months with clinical and ultrasound examination and were surveyed on the occurrence of cerebrovascular events and the current medical treatment. Ultrasound progression of the carotid stenosis was defined as an increase of the degree of the stenosis from moderate to high grade. To gather information on occurrence of cerebrovascular events and the current medical treatment in the 11 patients without ultrasound follow-up examination, a structured telephone interview was used.

According to a scientific statement of the American Heart Association and American Stroke Association stroke council, a TIA was defined as a transient episode of focal neurologic dysfunction without evidence of acute infarction on brain imaging. Ischemic stroke was defined as a focal neurological deficit with evidence of acute infarction on CT or MRI [27]. If a cerebrovascular event was suspected, all available medical records related to the event were collected.

During follow-up, 21 patients (34%) underwent carotid intervention (CEA in 28% and CAS in 6%). Patients who underwent carotid intervention were more likely to have a high-grade stenosis at baseline ($p = 0.008$) or to show a progression of the carotid stenosis during follow-up ($p = 0.031$). These patients were included in our analysis for the time they were treated medically.

Statistical Analysis

Continuous variables were expressed as mean ± 1 SD or median/interquartile ranges depending on the skew of the distribution. The χ^2 test for contingency tables was used to compare nominal variables and the Mann-Whitney test to compare continuous variables. Statistical significance was assumed at $p < 0.05$. Actuarial analysis of freedom from cerebrovascular events was calculated according to the Kaplan-Meier method. Average annual event rates were determined by using the formula $1-(1-P)^{1/n}$, where P equals the cumulative event rate at n years of follow-up. The log-rank test was used for univariate analyses of independent risk factors for the occurrence of cerebrovascular events. Meaningful multivariate analyses could not be performed because of the limited number of cerebrovascular events during follow-up.

Results

Demographic and Baseline Characteristics

Demographic and baseline characteristics of 62 patients with 65 asymptomatic ≥50% carotid stenoses are summarized in tables 1 and 2. Twenty patients (32%) had experienced a prior stroke outside the territory of the ACS or within its territory more than 6 months ago. At baseline, 58 patients (94%) were taking antithrombotics and 48 patients (77%) statins. Twenty-four ACS (37%) were classified as high grade. The fibrous cap was thin or disrupted in 42 ACS (65%). A lipid-rich necrotic core was the dominant plaque component in 16 ACS (25%). The plaque volume was higher in ACS with a lipid-rich necrotic core as dominant plaque component (p = 0.002) and in patients with prior stroke/TIA (p = 0.010). Neither the degree of the ACS nor other baseline characteristics were associated with the volume of the carotid plaque or the volume of cortical/subcortical ischemic lesions on FLAIR images in the ACS territory.

Follow-Up

Median time of follow-up was 18.9 months (interquartile range 3.53–30.10). At the end of follow-up, all patients were on antithrombotic treatment and 51 patients (82%) on statins. A follow-up sonographic examination of the ACS was performed in 49 patients (79%). The carotid stenosis was unchanged in 43 patients (66%), showed regression in 1 (2%) and progression in 7 (11%). Carotid plaques with a lipid-rich necrotic core as dominant plaque component showed more frequently a progressive stenosis compared to plaques without a lipid-rich necrotic core (p = 0.033). Neither the presence of IPH within the lipid-rich necrotic core nor the state of the fibrous cap were significantly associated with ipsilateral cerebrovascular events during follow-up. Patients without statins at follow-up were at higher risk for progression of their carotid disease (p = 0.009).

Table 1. Demographic and baseline clinical characteristics of 62 patients with 65 asymptomatic carotid stenoses of ≥50%

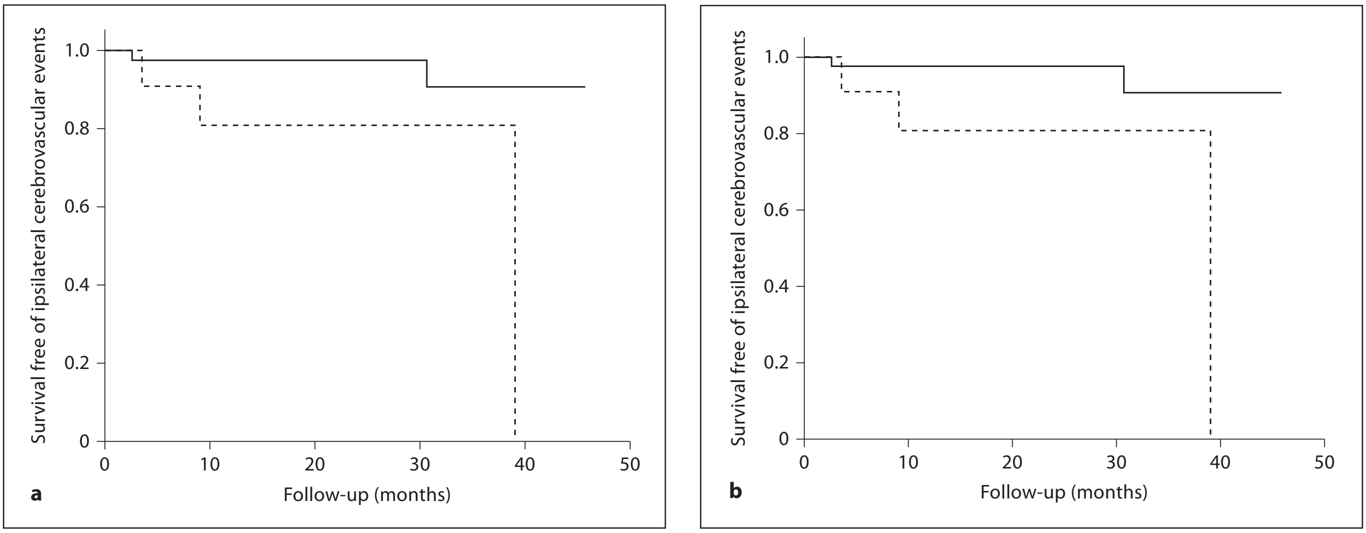
Characteristics	n (%)
Mean age ± SD, years	68.7 ± 8.6
Women	16 (26)
Vascular risk factors	
Arterial hypertension	52 (84)
Smoking	10 (16)
Diabetes mellitus	15 (24)
Hypercholesterolemia	54 (87)
Coronary artery disease	16 (26)
Atrial fibrillation	4 (7)
Current medical treatment	
Antithrombotic treatment	58 (94)
Antihypertensive treatment	52 (84)
Statin therapy	48 (77)
Prior stroke/TIA	20 (32)
Contralateral stenosis/occlusion	
50–70%	2 (3)
>70%	1 (2)
Occlusion	7 (11)

Table 2. Baseline characteristics of 65 asymptomatic carotid stenoses of ≥50%

Characteristics	
High-grade carotid stenosis (≥ 70%), n (%)	24 (37)
Lipid-rich necrotic core as dominant plaque component, n (%)	16 (25)
Lipid-rich necrotic core without intraplaque hemorrhage	7 (11)
Lipid-rich necrotic core with intraplaque hemorrhage	9 (14)
Thick fibrous cap, n (%)	23 (35)
Thin or disrupted fibrous cap, n (%)	42 (65)
Plaque volume, cm^3	
Median (interquartile range)	0.39 (0.23-0.56)
Volume of cortical/subcortical ischemic lesions on FLAIR images, cm^3	
Median (interquartile range)	0.23 (0.05-0.72)

Cerebrovascular Events during Follow-Up

Five cerebrovascular events (3 TIAs and 2 strokes) occurred during a median follow-up of 18.9 months, all of them ipsilaterally to the carotid artery stenosis. The average annual rate of stroke and TIA was 7.7% and that of stroke 2.6%. Among all baseline characteristics listed in tables 1 and 2, a lipid-rich necrotic core as dominant plaque component (HR 7.21; 95% CI 1.12–46.28; p =



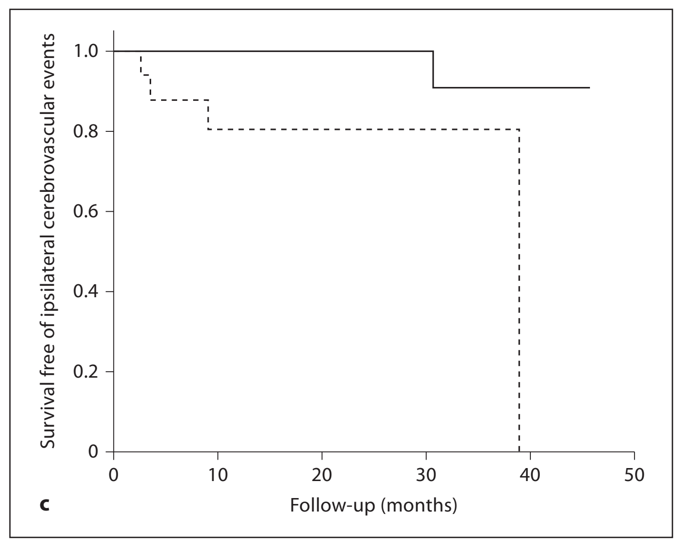


Fig. 2. Kaplan-Meier curves of survival free of cerebrovascular events during follow-up. The x-axis indicates time in months since inclusion in the study. The y-axis indicates the proportion of patients surviving free of cerebrovascular events. **a** The continuous line shows carotid stenoses without a dominant lipid-rich necrotic and the dotted line carotid stenoses with a lipid-rich necrotic core as dominant plaque component. **b** The continuous line represents carotid stenoses without progression and the dotted line carotid stenoses with progression at follow-up with ultrasound examination. **c** The continuous line represents patients without a history of stroke and the dotted line patients with a history of stroke.

0.037), the progression of the carotid stenosis (HR 7.00; 95% CI 1.13–41.34; p = 0.036), history of stroke (HR 11.03; 95% CI 1.23–99.36; p = 0.032) and the volume of cortical/subcortical ischemic lesions (HR 1.14/cm^3; 95% CI 1.03–1.25; p = 0.008) on FLAIR images were risk factors for ipsilateral cerebrovascular events during follow-up (table 3; fig. 2). Patients on statins at follow-up were at lower risk of clinical events (HR 0.17; 95% CI 0.03–1.00; p = 0.05).

Discussion

The main findings of our study are that medical history, baseline MR characteristics and sonographic follow-up have a predictive value for TIA and stroke in patients with ACS. A history of stroke, progression of stenosis as assessed by ultrasound, a large lipid-rich necrotic core within the plaque as dominant plaque component as seen on MRI, and the volume of clinically silent ischemic brain lesions in the territory of the ACS turned out to be predictors of TIA and stroke, while statins decreased this risk.

The degree of carotid stenosis is probably the most important predictor of stroke risk [28, 29]. However, in ACS the overall incidence of TIA and stroke is generally low and in clinical medicine it would be desirable to know additional factors in an individual patient to assess his risk more accurately. Accumulating evidence demonstrates that plaque composition determines its vulnerability and therefore also the risk for stroke. With the ad-

Table 3. Risk factors for ipsilateral cerebrovascular events during follow-up

Variable	HR	95% CI	p
Dominant lipid-rich necrotic core	7.20	1.12–46.28	0.037
Progression of carotid stenosis	7.00	1.13–43.38	0.036
Volume of cortical/subcortical ischemic lesions on FLAIR images per cm^3	1.14	1.03–1.25	0.008
Prior stroke/TIA	11.03	1.23–99.36	0.032
Statin therapy at follow-up	0.17	0.03–1.00	0.05

vent of high-resolution MRI of the carotid plaques a new promising diagnostic approach opens up [10, 11].

To date, only two MRI studies have assessed the plaque components and their predictive value for ipsilateral TIA and stroke in ACS. One study enrolled 98 male with 50–70% ACS. The presence of fresh or recent IPH within the plaque was associated with subsequent cerebrovascular events. Six of 36 patients with IPH suffered cerebrovascular events during follow-up of 24.9 months compared to none of 62 patients without IPH [16]. Another study reported on 154 subjects with 50–79% ACS. During a mean follow-up of 38.2 months 12 cerebrovascular events were observed. Subjects with MRI evidence of fresh or recent IPH, a thin or disrupted fibrous cap and a large lipid-rich necrotic core within the plaque were at increased risk for cerebrovascular events [17]. These findings are largely similar to the results of our series. Plaques with a lipid-rich necrotic core (lipid core with or without IPH) as dominant plaque component had a sevenfold increased TIA or stroke risk in our ACS patients. Both IPH and a lipid core are features of a so-called 'vulnerable plaque', and its relevance has been consistently demonstrated in symptomatic carotid stenosis [8, 9, 12, 14, 15]. In contrast to the results of Takaya et al. [17], a thin or disrupted fibrous cap was not associated with future cerebrovascular events in our study. As atherosclerosis is a dynamic process, changes of plaque composition over time may lead to regression from a vulnerable to a stable or progression from a stable to a vulnerable plaque [30–32]. This dynamism affects also, and perhaps in particular, the fibrous cap as an important marker of plaque vulnerability. However, MRI of the carotid plaque only offers a snapshot of the status of the fibrous cap at the time of investigation, which may explain the missing correlation of plaques with thin/disrupted fibrous cap and future cerebrovascular events in our study. Serial MRI examinations would be helpful to overcome this limitation and to improve prediction of cerebrovascular event in asymptomatic carotid stenosis.

The progression of the carotid stenosis as assessed by ultrasound at follow-up examinations was an additional strong predictor for ischemic events in our study. This was also the case in a prospective study of 1,065 patients with ACS: stenosis progression was associated with a twofold risk of ipsilateral stroke during a 3-year follow-up [33].

Among baseline clinical characteristics, a history of stroke was associated with an eleven-fold increased TIA and stroke risk. A history of stroke was found to increase this risk also in other studies, i.e. approximately 3-fold in two large registries [29, 34].

Furthermore, the volume of clinically silent ischemic brain lesions on FLAIR images also predicted the risk of clinically apparent events, albeit less strongly than other factors. In the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study, the subgroup of patients with >60% ACS and CT scan evidence of silent infarction had a twofold increased risk of cerebrovascular events compared to patients with no silent infarcts on CT ($p = 0.032$) [35].

Statins at follow-up had a small but significant effect in preventing cerebrovascular events. In addition, patients without statins were more likely to show progression of their ACS. The beneficial effect of statins on size and composition of carotid plaques has been demonstrated in many previous studies [36]. Accordingly, the 10-year results of the ACST-1 trial showed that patients on statin therapy were at lower risk of stroke, independent of randomization to CEA or best medial treatment [4].

The annual stroke rate of 2.6% in our study was somewhat higher than the usually reported 1 to 2% in ACS. The high prevalence of cardiovascular risk factors might explain this slightly elevated rate, especially the high rate of history of stroke. It might also be a chance finding due to the relatively small sample size. Both, the small sample size and the high prevalence of cardiovascular risk factors in our study render comparisons with other studies difficult [1, 2, 5]. Furthermore, the sample size of our study was too small to allow a meaningful multivariate analysis. However, the results of the univariate analysis were highly significant for the presence of a lipid-rich necrotic core, history of stroke/TIA and progression of the carotid stenosis, so that a multivariate analysis would probably not have changed these results.

Conclusions

Clinical, sonographic and MR characteristics were identified as predictors of cerebrovascular events in our study. A lipid-rich necrotic core as dominant plaque component, history of stroke/TIA and progression of the carotid stenosis in sonographic follow-up examinations were strong predictors of cerebrovascular events in patients with ≥50% ACS. Determination of plaque components by 3-T MRI deserves further attention and might be helpful to improve risk stratification of asymptomatic carotid disease. The identified predictors could be combined in a risk model and tested in a larger prospective study. The identification of reliable predictors for clinically apparent cerebrovascular events would considerably improve the management of patients with ACS.

Acknowledgement

We thank Pietro Ballinari for statistical advice.

The study was funded by a grant of the Swiss Heart Foundation.

Dr. Marwan El Koussy is funded by the Swiss National Science Foundation, grant number SPUM 33CM30-124114 *Impact of qualitative MR perfusion imaging of patients with carotid artery disease.*

Disclosure Statement

None declared.

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