Plaque At RISK (PARISK): prospective multicenter study to improve diagnosis of high-risk carotid plaques

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Background **Patients with symptomatic carotid artery stenosis are at high risk for recurrent stroke. To date, the decision to perform carotid endarterectomy in patients with a recent cerebrovascular event is mainly based on degree of stenosis of the ipsilateral carotid artery. However, additional atherosclerotic plaque characteristics might be better predictors of stroke, allowing for more precise selection of patients for carotid endarterectomy.**

Aims and hypothesis **We investigate the hypothesis that the assessment of carotid plaque characteristics with magnetic resonance imaging, multidetector-row computed tomography angiography, ultrasonography, and transcranial Doppler, either alone or in combination, may improve identification of a subgroup of patients with < 70% carotid artery stenosis with an increased risk of recurrent stroke.**

Methods **The Plaque At RISK (PARISK) study is a prospective multicenter cohort study of patients with recent (<3 months) neurological symptoms due to ischemia in the territory of the carotid artery and < 70% ipsilateral carotid artery stenosis who are not scheduled for carotid endarterectomy or stenting. At baseline, 300 patients will undergo magnetic resonance imaging, multidetector-row computed tomography angiography, and ultrasonography examination of the carotid arteries. In addition, magnetic resonance imaging of the brain, ambulatory transcranial Doppler recording of the middle cerebral artery and blood withdrawal will be performed. After two-years, imaging will be repeated in 150 patients. All patients undergo a follow-up brain magnetic resonance imaging, and there will be regular clinical follow-up until the end of the study.**

Study outcomes **The combined primary end-point contains ipsilateral recurrent ischemic stroke or transient ischemic attack or new ipsilateral ischemic brain lesions on follow-up brain magnetic resonance imaging.**

Key words: atherosclerosis, CT, stroke, MRI, prospective, ultrasound

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Introduction and rationale

Ischemic stroke is the second most common cause of death in Europe, accounting for almost 1·1 million deaths each year (1). Atherosclerosis is an important cause of clinical cerebrovascular events. The pathophysiology can be ascribed to cerebral embolism from an atherosclerotic carotid plaque or hypoperfusion due to carotid luminal stenosis.

Currently, the decision to perform carotid endarterectomy (CEA) in patients with a recent cerebrovascular event is based on the degree of luminal stenosis. CEA is highly beneficial for symptomatic patients with an ipsilateral carotid artery stenosis of 70–99% (2–4). However, the beneficial effect of surgery for symptomatic patients with an ipsilateral stenosis between 30% and 69% is only marginal. Several studies show that vulnerable plaque features are related to cerebral embolization (5–7). Features of a vulnerable atherosclerotic plaque are a large lipid-rich necrotic core (LRNC), a thin or ruptured fibrous cap (FC), the presence of inflammatory cells, ulcerations, and intraplaque haemorrhage (IPH). Recent studies in symptomatic patients did show that IPH (8–10), LRNC, and a thin or ruptured FC (8,10) as assessed with magnetic resonance imaging (MRI) are associated with cerebrovascular events. For multidetector-row computed tomography (MDCT), it is known that ulcerations and large calcifications and LRNC are significantly more present in symptomatic patients with an atherosclerotic cause of ischemic stroke (11). Prospective studies for MDCT have not been conducted yet. Several prospective studies have investigated the predictive value of ultrasonography (US) in the occurrence of recurrent ischemic stroke, with conflicting results (12–14). Microemboli detected with

transcranial Doppler (TCD) predict short-term ipsilateral ischemic stroke (15). However, all these studies were single modality studies (8–11,15) or had a relative small population size (9). Therefore, we hypothesize that the assessment of markers of plaque vulnerability with MRI, MDCT angiography (MDCTA), US, TCD, either alone or in combination, improves the identification of a subgroup of patients in the < 70% carotid artery stenosis group with an increased risk of recurrent ischemic stroke.

Methods

Study design

The Plaque At RISK (PARISK) study (clinical trials.gov NCT01208025) is a prospective multicenter cohort study (Table 1), which investigates whether (a combination of) non- or minimally invasive imaging techniques enable us to identify patients with symptomatic carotid artery stenosis < 70%, who have an increased risk of recurrent stroke. All patients undergo multi-sequence 3·0 Tesla (T) MRI, MDCTA and US imaging of the carotid arteries, MRI of the brain and TCD recordings of the middle cerebral artery (MCA). Also blood will be drawn for the determination of different biomarkers. Imaging will be repeated two-years after inclusion.

Table 1 Participating centers in the Netherlands. In bold, the academic hospitals

No. of center	Name	Abbreviation
1.	**Academic Medical Center Amsterdam (PJ Nederkoorn, MD, PhD)** Flevoziekenhuis, Almere (M Limburg, MD, PhD) Kennemer Gasthuis, Haarlem (M Weisfelt, MD, PhD) Slotervaartziekenhuis, Amsterdam (ND Kruyt, MD, PhD)	AMC
2.	**Erasmus Medical Center Rotterdam (A van der Lugt, MD, PhD; PJ Koudstaal, MD, PhD)** Maasstad Hospital, Rotterdam (R Saxena, MD, PhD) Sint Franciscus Gasthuis, Rotterdam (SLM Bakker, MD, PhD) Vlietland Hospital, Schiedam (JCB Verhey, MD) IJsselland Hospital, Capelle a/day IJsel (AD Wijnhoud, MD, PhD)	EMC
3.	**Maastricht University Medical Center (ME Kooi, PhD; WH Mess, MD, PhD; RJ van Oostenbrugge, MD, PhD)** Atrium Medical Center, Heerlen (T Schreuder, MD) Laurentius, Roermond (AG Korten, MD, PhD) Orbis Medical Center, Sittard (NP van Orshoven, MD, PhD) Viecuri Medical Center, Venlo (BJ Meems, MD, PhD)	MUMC
4.	**University Medical Center Utrecht (J Hendrikse, MD, PhD; LJ Kappelle, MD, PhD)** Diakonessenhuis, Utrecht (R Donders, MD, PhD) Sint Antonius ziekenhuis, Nieuwegein (S Tromp, MD, PhD) Ter Gooi ziekenhuizen, Hilversum Blaricum (J de Kruijk, MD, PhD)	UMCU

Study objectives

The primary objective of the PARISK study is to identify whether high-resolution MRI, MDCTA, US, and/or TCD enable us to predict future ischemic events in recent symptomatic patients with < 70% carotid stenosis.

The secondary objectives are to study (1) determinants for plaque progression; (2) the relationship between plaque characteristics, microemboli, and vascular damage on brain MRI; and (3) the association between blood biomarkers and plaque parameters.

Patient population

Eligible for the study are patients with a transient ischemic attack (TIA), amaurosis fugax or minor stroke (modified Rankin scale ≤3) of the carotid artery territory and an atherosclerotic plaque with a < 70% stenosis of the ipsilateral internal carotid artery (ICA) who are not scheduled for a revascularization procedure. Patients need to be eligible for imaging and blood withdrawal within three-months after initial ischemic event. Exclusion criteria are a probable cardiac source of embolism, a clotting disorder, severe comorbidity, standard contraindications for MRI, a documented allergy for MRI or CT contrast agent or a renal clearance of <30 ml/min. Written informed consent will be obtained from all patients before enrolment.

Study protocol

Degree of stenosis will be determined with clinically obtained Doppler US or CT angiography (CTA). The upper cutoff value of 70% is based on the North American Symptomatic Carotid Endarterectomy Trial criteria (16). The lower cutoff value is an atherosclerotic plaque with a thickness of at least 2–3 mm, which corresponds to an European Carotid Surgery Trial stenosis of 30% (3). A total of 300 patients will be included.

At baseline, clinical data such as age, sex, occurrence of last symptoms, medication use and cardiovascular risk factors are collected. Blood samples will be drawn. All noninvasive imaging examinations will be performed within a five-day time window.

Follow-up by telephone will be done after three-months, one-year, and yearly until the end of the study in December 2014 (Fig. 1). During follow-up, clinical data such as daily functioning (modified Rankin scale), changes in medication use, cardiovascular risk factors, cardiovascular and cerebrovascular events and hospital admissions are collected. Two-years after inclusion, non-invasive imaging of the carotid artery will be repeated in the first 150 patients. Follow-up brain MRI will be performed in all patients after two-years.

MRI

Magnetic resonance imaging will be performed on 3·0-T whole body scanners. A dedicated eight-channel phased-array coil (Shanghai Chenguang Medical Technologies Co., Shanghai,

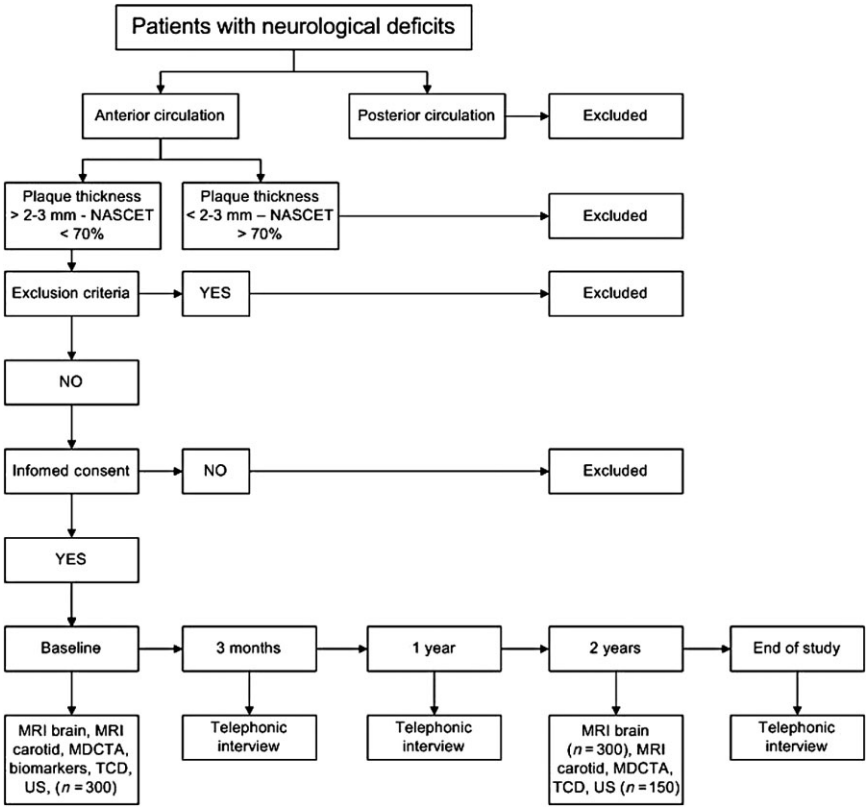

Fig. 1 Flowchart of study protocol.

Table 2 Scan parameters: MR brain

Pulse sequence	T2w FSE	T2w TSE	FLAIR		T2*w SPGR	T2*w FFE	DWI	
Center	2	1,3,4	2	1,3,4	2	1,3,4	2†	1,3,4†
Acquisition format	2D		2D		3D	2D	2D	
TR (ms)	6900	3198	8800	11 000	25	1653	5100	3835
TE (ms)	80	19/140	140	125	16	20	72	90
Ti (ms)	–		2250	2 800	–		–	
Flip angle (°)	90		90		12	20	90	
No. of slices	48		48		94*	48	48	30
Slice thickness (mm)	3		3		1·6	3	3	5
Slice gap (mm)	0		0		0		0	0·1
FOV (mm)	230 × 190	230 × 190	230 × 230	230 × 190	230 × 190	230 × 190	230 × 230	208 × 153
Acquisition matrix	256 × 192	232 × 179	256 × 160	232 × 148	224 × 192	232 × 190	116 × 130	128 × 102
Acquired voxel size	0·89 × 0·99	0·99 × 1·06	0·90 × 1·44	0·99 × 1·28	1·03 × 0·99	0·99 × 1·00	1·98 × 1·77	1·63 × 1·5
Reconstruction matrix	256 × 256	240 × 240	256 × 256	240 × 240	256 × 256	240 × 240	256 × 256	128 × 128
Reconstructed voxel size	0·90 × 0·74	0·96 × 0·79	0·90 × 0·90	0·96 × 0·79	0·90 × 0·74	0·96 × 0·79	0·90 × 0·90	1·63 × 1·20
Echo train length	15	26	42	31	1		Single-shot	
Parallel imaging	Yes		No	Yes	Yes		Yes	
No. of signal averages	1	2	1		1		2	1

*180 reconstructed slices of 0·8 mm. †No of B-factors 3. FSE, fast spin echo; TSE, turbo spin echo; FLAIR, fluid attenuated inversion recovery; SPGR, spoiled gradient echo; FFE, fast field echo; DWI, diffusion weighted imaging; TR, repetition time; TE, echo time; TI, inversion time; FOV, field of view.

China) is used for imaging of the carotid artery in three centers; a dedicated four-channel carotid phased-array coil with an angulated setup (Machnet B.V., Roden, the Netherlands) is used in one center. For brain imaging, dedicated head coils are used. First, brain MR images will be acquired using the sequences as listed in Table 2. Second, the carotid bifurcation will be identified by means of MR angiography without contrast enhancement. The atherosclerotic plaque will be imaged with a multi-sequence MR protocol as listed in Table 3. Fifteen transverse adjoining slices of 2 mm each, covering the entire plaque or a 3D volume of the extracranial carotid artery is used. Six-minutes after injection of 0·1 mmol/kg body weight of a gadolinium-based contrast agent

Table 3 Scan parameters: MR carotid arteries

Pulse sequence	FSPGR	TOF FFE	SPGR	IR-TFE*	T2w DIR FSE	T2w TSE	T1w DIR FSE	T1wQIR TSE
Center	2	1,3,4	2	1,3,4	2	1,3,4	2	1,3,4
Acquisition format	3D		3D		2D		2D	
Acquisition plane	coronal	transversal	coronal	transversal	transversal		transversal	
TR (ms)	3·3	20	9	9·1	2 RR	4800	1 RR	800
TE (ms)	2·1	5	1·3	5·5	50	49	5·2	10
TI (ms)	n/a		n/a	304	Auto†	n/a	Auto†	282, 61
Flip angle (°)	5	20	30	15	–		–	
No. of slices	120	15	248	15	15		15	
Slice thickness (mm)	0·8	2	0·8	2	2		2	
FOV (mm)	160 × 160	160 × 160	160 × 160	160 × 128	140 × 160	160 × 160	140 × 160	160 × 160
Acquisition matrix	160 × 128	260 × 258	160 × 123	260 × 204	256 × 224	260 × 252	256 × 224	260 × 240
Acquired voxel size	1·00 × 1·25	0·62 × 0·62	1·00 × 1·25	0·62 × 0·63	0·55 × 0·71	0·62 × 0·63	0·55 × 0·71	0·62 × 0·67
Reconstruction matrix	256 × 256	528 × 528	256 × 256	528 × 528	256 × 256	528 × 528	256 × 256	528 × 528
Reconstructed voxel size	0·63 × 0·63	0·30 × 0·30	0·63 × 0·63	0·30 × 0·24	0·55 × 0·63	0·30 × 0·30	0·55 × 0·63	0·30 × 0·30
Echo train length	1		1	51	24	12	12	10
Parallel imaging	No		No		No		No	
No. of signal averages	7	1	1	6	1		1	
ECG triggered	No		No		Yes	No	Yes	No
Fat suppression	No	Yes	Yes		Yes		Yes	

*Shot interval time: 550 ms. †Approximately TI adjusted to T_1 relaxation time of blood by scanner. FSPGR, fast spoiled gradient echo; TOF, time of flight; FFE, fast field echo; SPGR, spoiled gradient echo; TFE, turbo field echo; DIR, double inversion recovery; FSE, fast spin echo; QIR, quadruple inversion recovery; TSE, turbo spin echo; TR, repetition time; TE, echo time; TI, inversion time; n/a, not applicable; FOV, field of view; NSA, number of signal averages.

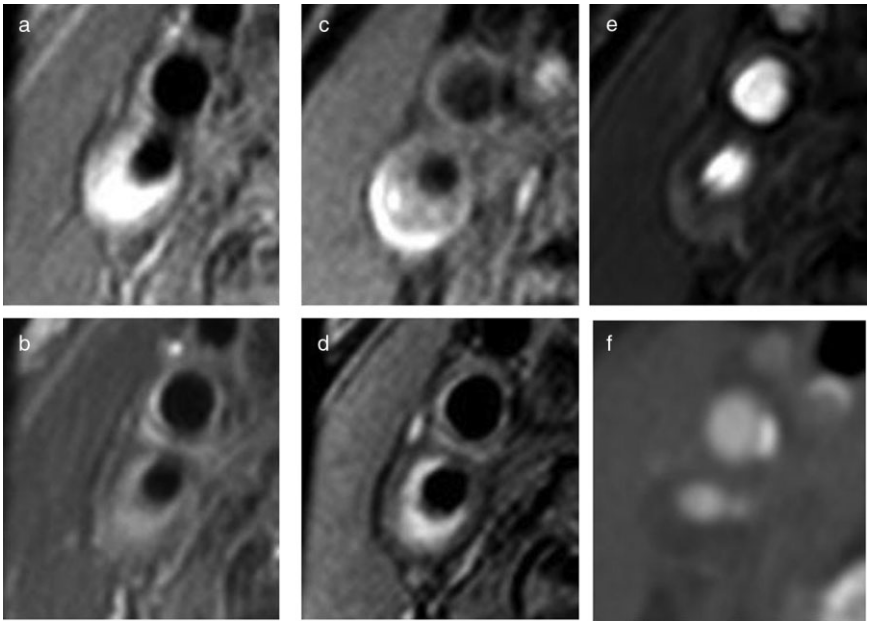

Fig. 2 Coregistered pre- (a) and postcontrast (b) T1-w TSE, T1-w TFE (c), T2-w TSE (d) TOF (e) and MDCTA (f) of the internal carotid artery from a 66-year-old male patient with transient dysarthria.

the T1w DIR FSE (center 2) or T1w QIR TSE (center 1, 3, 4) are repeated to obtain postcontrast images (Fig. 2).

MDCTA

Image acquisition will be performed using a 16, 64, or 128 slice multi-detector row CT system using a standardized optimized contrast-enhanced MDCTA protocol (120 kVp, 150–180 mAs, collimation 16 × 0·75 mm or 64 × 2 × 0·6 mm, pitch <1). One center reconstructs 120 kVp images from the 100 kVp and 140 kVp images obtained with dual-energy MDCTA. The scan range extends from the ascending aorta to the intracranial circulation (3 cm above the sella turcica). All patients receive 80–85 ml of an iodinated contrast agent (300–320 mg/ml) followed by a 45 ml saline bolus chaser, both at an injection rate of 4 or 5 ml/s. Real-time bolus tracking at the level of the ascending aorta is used. Image reconstructions are made with a FOV of 120–

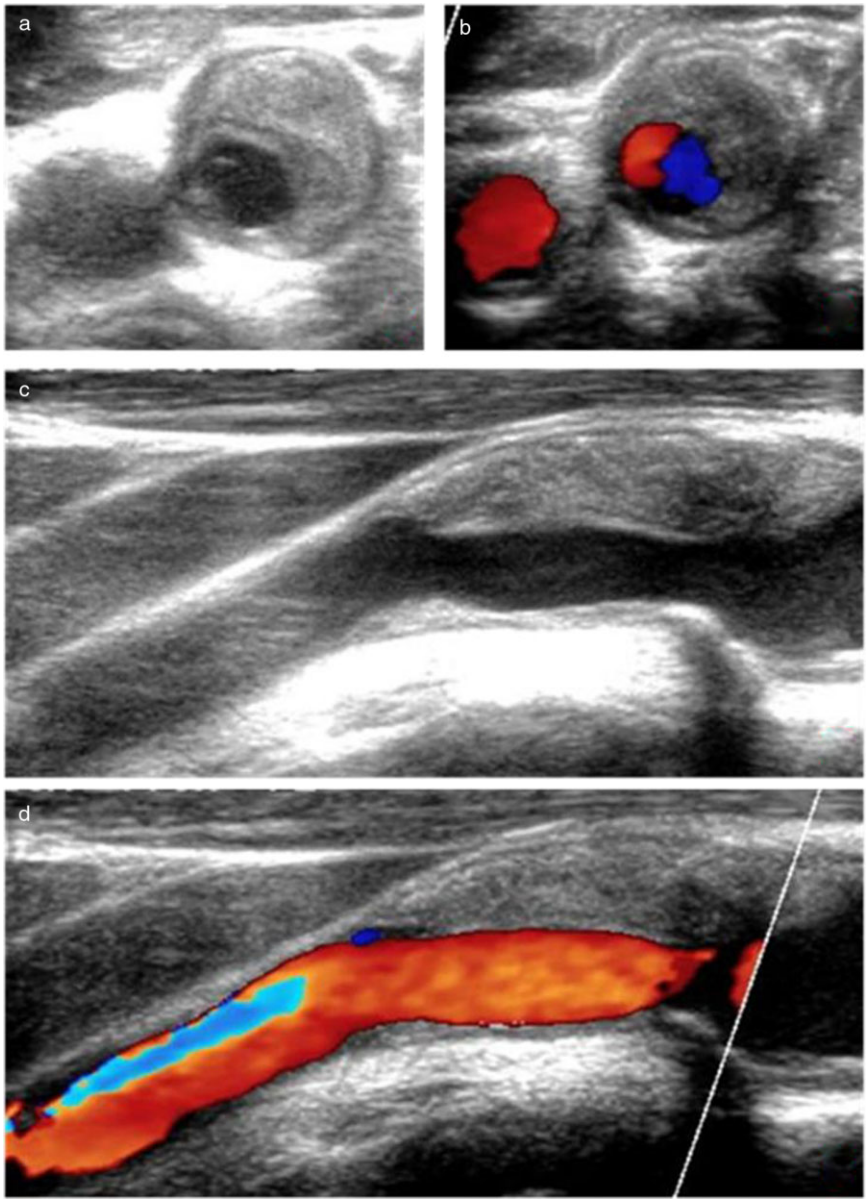

Fig. 3 Transverse (a, b) and longitudinal (c, d) ultrasound images of the internal carotid artery in B-mode (a, c) and color-coded (b, d). Images are from the same patient as Fig. 2.

160 mm, matrix size 512 × 512, slice thickness 1·0 mm, increment 0·6–0·7 mm and with intermediate reconstruction algorithms.

Ultrasound

After 10 min of rest in supine position, duplex ultrasound examination (Fig. 3) will be performed by a well-trained US technician. The extracranial arteries are visualized with a 17-5 MHz linear array transducer. If the artery is located too deep, a 12-5 or a 9-3 MHz transducer will be used. The protocol consists of (1) longitudinal images of the common carotid artery (CCA), the carotid bulb, and the ICA in B-mode and color Doppler mode, (2) pulsed Doppler recordings of the CCA and the ICA with a sample volume of 1 mm, and (3) transversal recording from the CCA to the ICA in B-mode and color Doppler covering a total length of 8 cm. All images will be recorded from anterolateral and posterolateral views at a frame rate >40 Hz and with a cine loop of five seconds.

TCD

Transcranial Doppler measurements will be performed on the symptomatic side only. With conventional Doppler, the transtemporal window is investigated, as well as the depth of the main stem of the MCA. In case of a sufficient window, an ambulatory TCD system (TCD-X, Hemodynamics AG, Bern, Switzerland) is positioned at the location of the transtemporal bone window. When the signal of the MCA is detected, settings such as sample volume, gain, power, and depth are optimized by means of dedicated software on a laptop connected to the TCD-X. Afterward, the device is disconnected from the laptop and the four-hour recording will start.

Biomarkers

Nine milliliters (ml) of citrated plasma for platelet-rich plasma, 9 ml citrated plasma for platelet-poor plasma, 8·5 ml of serum, 10 ml of ethylenediaminetetraacetic acid plasma, and 4·5 ml acidified citrated plasma (Stabilyte) will be taken for the determination of different biomarkers. All samples will be processed within one-hour and stored in 0·5 ml tubes at −80 °C until analysis. Markers for thrombus generation and formation, fibrinolysis, endothelial function, and vascular inflammation will be assessed. Blood samples will be stored for 15 years. The informed consent form includes an additional question on the use of blood samples for extra testing (e.g. genetic testing) for research related to the main hypothesis.

Image data analysis

All data will be evaluated by trained readers blinded to the results of other image modalities, clinical data, and baseline/follow-up data. Each reader performs training on test sets and interobserver reproducibility will be assessed beforehand.

MRI evaluation of the carotid artery will be done using dedicated vessel wall analysis software (VesselMass, department of Radiology, Leiden University Medical Center, the Netherlands) as described previously (17). MR images will be assessed for vessel wall and luminal area, LRNC area, calcification area, presence of IPH and FC status using previously published criteria (18–20). MRI of the brain will be scored for cortical and lacunar infarcts, microbleeds, and the severity of white matter lesions according to Fazekas *et al.* (21).

All MDCTA data will be evaluated for the most severe stenosis in the carotid bifurcations and internal carotid arteries. Calcifications at extracranial carotid arteries within 3 cm proximal and distal of the bifurcation will be measures and expressed as calcification volume in mm3. A threshold of 600 Hounsfield units will be used to differentiate calcifications from contrast material in the lumen. Plaque ulceration is defined as extension of contrast material of >1 mm into the atherosclerotic plaque on at least two orthogonal planes. Plaque volumes will be assessed with custom-made software (22). Plaques will be subdivided into fatty plaques, mixed or calcified plaques based on attenuation values (23).

Ultrasound data will be analyzed on software developed in-house, based on previously published algorithms (24–26). The anatomical course of the carotid artery, the presence of plaques, and the degree of stenosis will be scored. Second, images will be quantified on appearance by using dedicated gray scale analysis software. The morphology of the plaque will be determined by manually contouring plaques to quantify its area, thickness, length, and echogenicity. In addition, the morphology of the artery will be characterized by end diastolic diameter and vessel wall thickness, and their inhomogeneities along the artery section. Finally, dynamic vessel wall characteristics will be quantified by distension, i.e. the change in diameter over a cardiac cycle, and its spatial inhomogeneity.

The four-hour transcranial Doppler recordings will be analyzed using semiautomatic software (Hemodynamics AG, Bern, Switzerland). All high-intensity transient signals will be verified by a trained reader. Based upon predefined criteria (27) they will be identified as either microembolic signals (Fig. 4) or artifacts.

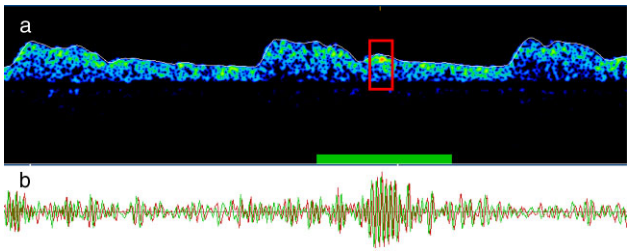

Fig. 4 The red box indicates a typical example of a microembolic signal, both in the frequency (a) and time (b) domain.

Outcome measures

The primary end-point is an ipsilateral recurrent ischemic stroke, or TIA and/or new ipsilateral ischemic brain lesions on follow-up brain MRI. Clinical events are verified by a neurologist. Secondary end-point is new ipsilateral ischemic brain lesions on MRI.

Statistical analysis

Cox proportional hazard models will be used to compute hazard ratios with 95% confidence intervals for the association of plaque parameters with the primary and secondary end-points. In the primary analysis we will focus on four plaque parameters: (1) presence of IPH as assessed on ipsilateral MRI of carotid plaque, (2) ipsilateral carotid plaque ulceration as assessed on MDCTA, (3) ipsilateral carotid plaque volume as assessed on MRI, and (4) the proportion of calcifications with respect to the ipsilateral carotid plaque volume as assessed with MDCTA. First, we will analyze the data univariately, then we will adjust for age, sex, and major cardiovascular risk factors. Subsequently, we will adjust for the other plaque parameters.

Additionally, we will investigate the association between number of microemboli, ultrasound gray scale values and vessel wall motion, volume of plaque components on MRI (calcifications, LRNC, fibrous tissue), FC status on MRI, plaque volume on MDCTA, and the end-points.

Sample size

The expected incidence of ischemic stroke is 2·5% per year based on the standard medical treatment of antiplatelet therapy, a statin and antihypertensive agents to obtain strict blood pressure control. This means in a group of 300 patients, with a follow-up of two-years, we expect an incidence rate of 15 ischemic strokes. In a recent study in one of our participating centers 14/72 (19%) symptomatic patients with 30–69% carotid stenosis had a new silent infarct on brain MRI after one-year. Assuming that this number will not increase with a follow-up of two-years, we expect that 57 of the 300 patients will demonstrate a new infarct on brain MRI. Based on this number we will be able to evaluate 6–11 imaging parameters for the primary analysis.

Data storage

All clinical information from the different centers will be stored in a sophisticated web-based database system (OpenClinica version 3·1.2, Community Edition, Boston, MA, USA). All image data from different centers are anonymized and centrally stored on a

DICOM server (based on open source DCM4CHEE software) hosted by one of the participating centers. Image data are accessible for all partners.

Ethical and regulatory considerations

The PARISK study will be performed in the Netherlands and has been approved by the Medical Ethical Committees of the participating academic centers. All participants will provide written informed consent.

Discussion

We present the protocol of a prospective multicenter cohort study, PARISK, to identify imaging parameters that can improve risk prediction for stroke recurrence in recently symptomatic patients with < 70% carotid artery stenosis and help in the selection of patients for CEA. These imaging parameters will be determined using detailed imaging of the carotid arteries using 3T MRI, MDCTA, and US as well as TCD of the MCA.

Atherosclerotic plaques in carotid arteries have been studied intensively over the last decades. However, the PARISK study has a different approach, as compared with previously published studies. To our knowledge, it is the first prospective multicenter cohort study with multimodality imaging of the carotid artery. Patients referred to academic hospitals as well as to regional hospitals will be included and centrally imaged in the academic centers. This setting enables us to include a large number of patients in a relative short period of time. In the various academic hospitals different MRI and MDCT scanners are used, which reflects variation in clinical practice.

The multimodality approach allows us not only to study morphological parameters, such as the size of LRNC or FC status, but also biological and biomechanical parameters such as blood biomarkers and vessel wall motion. The ability to define which (combination of) parameters predicts a recurrent stroke makes this a highly clinical relevant prognostic cohort study. The event rate of stroke has significantly decreased in the last decade. Based on studies from Rothwell *et al.* (2) we originally expected 30 clinical end-points in 36 months of follow-up in our study population. However, this number will probably be much lower due to widespread use of statins (28), antiplatelet therapy, and blood pressure optimization. For this reason, the PARISK trial uses a primary composite end-point that combines clinical events and silent brain infarcts on MRI.

Imaging studies have revealed that 30–50% of the TIAs are accompanied by ischemic lesions on diffusion weighted imaging MRI in the acute phase (29) and that most of these lesions lead to permanent brain damage (30). Vernooij *et al.* (31) showed in healthy participants that silent brain infarcts are much more prevalent than previously expected. These silent infarcts have the same risk factors as infarcts with neurological deficits as result and are considered to have the same pathophysiological mechanism.

Conclusion

The PARISK study represents a prospective multicenter study of symptomatic patients with recent (<3 months) neurological symptoms due to ischemia in the territory of the carotid artery and a < 70% ipsilateral carotid artery stenosis who are not scheduled for CEA or stenting. The primary objective of this study is to identify whether MRI, MDCTA, US, or TCD or a combination of these techniques enable us to identify patients with an increased stroke risk. This would highly influence clinical decision making.

References

1 Nichols M, Townsend N, Luengo-Fernandez R *et al.* European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis 2012.
2 Rothwell PM, Eliasziw M, Gutnikov SA *et al.* Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003; **361:**107–16.
3 European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998; **351:**1379–87.
4 Mayberg MR, Wilson SE, Yatsu F *et al.* Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA* 1991; **266:**3289–94.
5 Sitzer M, Muller W, Siebler M *et al.* Plaque ulceration and lumen thrombus are the main sources of cerebral microemboli in high-grade internal carotid artery stenosis. *Stroke* 1995; **26:**1231–3.
6 Spagnoli LG, Mauriello A, Sangiorgi G *et al.* Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. *JAMA* 2004; **292:**1845–52.
7 Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. *Circulation* 2006; **113:**2320–8.
8 Takaya N, Yuan C, Chu B *et al.* Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI – initial results. *Stroke* 2006; **37:**818–23.
9 Altaf N, Daniels L, Morgan PS *et al.* Detection of intraplaque hemorrhage by magnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. *J Vasc Surg* 2008; **47:**337–42.
10 Kwee RM, van Oostenbrugge RJ, Mess WH *et al.* MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. *J Magn Reson Imaging* 2013; **37:**1189–1194.
11 Wintermark M, Arora S, Tong E *et al.* Carotid plaque computed tomography imaging in stroke and nonstroke patients. *Ann Neurol* 2008; **64:**149–57.
12 Polak JF, Shemanski L, O'Leary DH *et al.* Hypoechoic plaque at US of the carotid artery: an independent risk factor for incident stroke in adults aged 65 years or older. Cardiovascular Health Study. *Radiology* 1998; **208:**649–54.
13 Gronholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation* 2001; **104:**68–73.
14 Halliday A, Mansfield A, Marro J *et al.* Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004; **363:**1491–502.
15 Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke* 2005; **36:**971–5.
16 North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke* 1991; **22:**711–20.
17 Kwee RM, Teule GJ, van Oostenbrugge RJ *et al.* Multimodality imaging of carotid artery plaques: 18F-fluoro-2-deoxyglucose positron emission tomography, computed tomography, and magnetic resonance imaging. *Stroke* 2009; **40:**3718–24.

18 Cappendijk VC, Heeneman S, Kessels AG *et al*. Comparison of single-sequence T1w TFE MRI with multisequence MRI for the quantification of lipid-rich necrotic core in atherosclerotic plaque. *J Magn Reson Imaging* 2008; **27:**1347–55.
19 Cai J, Hatsukami TS, Ferguson MS *et al*. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. *Circulation* 2005; **112:**3437–44.
20 Kwee RM, van Engelshoven JM, Mess WH *et al*. Reproducibility of fibrous cap status assessment of carotid artery plaques by contrast-enhanced MRI. *Stroke* 2009; **40:**3017–21.
21 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987; **149:**351–6.
22 van Gils MJ, Vukadinovic D, van Dijk AC, Dippel DW, Niessen WJ, van der Lugt A. Carotid atherosclerotic plaque progression and change in plaque composition over time: a 5-year follow-up study using serial CT angiography. *AJNR Am J Neuroradiol* 2012; **33:**1267–73.
23 Schroeder S, Kopp AF, Baumbach A *et al*. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. *J Am Coll Cardiol* 2001; **37:**1430–5.
24 Meinders JM, Brands PJ, Willigers JM, Kornet L, Hoeks AP. Assessment of the spatial homogeneity of artery dimension parameters with high frame rate 2-D B-mode. *Ultrasound Med Biol* 2001; **27:**785–94.
25 Meinders JM, Kornet L, Hoeks AP. Assessment of spatial inhomogeneities in intima media thickness along an arterial segment using its dynamic behavior. *Am J Physiol Heart Circ Physiol* 2003; **285:**H384–91.
26 Kakkos SK, Stevens JM, Nicolaides AN *et al*. Texture analysis of ultrasonic images of symptomatic carotid plaques can identify those plaques associated with ipsilateral embolic brain infarction. *Eur J Vasc Endovasc Surg* 2007; **33:**422–9.
27 Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. Basic identification criteria of Doppler microembolic signals. *Stroke* 1995; **26:**1123.
28 Milionis HJ, Giannopoulos S, Kosmidou M *et al*. Statin therapy after first stroke reduces 10-year stroke recurrence and improves survival. *Neurology* 2009; **72:**1816–22.
29 Easton JD, Saver JL, Albers GW *et al*. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals. *Stroke* 2009; **40:**2276–93.
30 Oppenheim C, Lamy C, Touze E *et al*. Do transient ischemic attacks with diffusion-weighted imaging abnormalities correspond to brain infarctions? *AJNR Am J Neuroradiol* 2006; **27:**1782–7.
31 Vernooij MW, Ikram MA, Tanghe HL *et al*. Incidental findings on brain MRI in the general population. *N Engl J Med* 2007; **357:** 1821–8.