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Application of mask images of contrast-enhanced MR angiography to detect carotid intraplaque hemorrhage in *patients with moderate to severe symptomatic and asymptomatic carotid stenosis*

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ABSTRACT

Purpose: Carotid intraplaque hemorrhage (IPH) on MRI predicts stroke. Magnetization-prepared rapid acquisition gradient (MP-RAGE) is widely used to detect IPH. CE-MRA is used routinely to assess stenosis. Initial studies indicated that IPH can be identified on mask images of CE-MRA, while Time-of-Flight (TOF) images were reported to have high specificity but lower sensitivity. We investigated the diagnostic accuracy of detecting IPH on mask images of CE-MRA and TOF.

Methods: Thirty-six patients with ≥ 50% stenosis enrolled in the ongoing 2nd European Carotid Surgery Trial underwent carotid MRI. A 5-point quality score was used. Inter-observer agreement between two independent readers was determined. The sensitivity and specificity of IPH detection on mask MRA and TOF were calculated with MP-RAGE as a reference standard.

Results: Of the 36 patients included in the current analysis, 66/72 carotid arteries could be scored. The inter-observer agreements for identifying IPH on MP-RAGE, mask, and TOF were outstanding (κ: 0.93, 0.96, and 0.85). The image quality of mask (1.42 ± 0.66) and TOF (2.42 ± 0.66) was significantly lower than MP-RAGE (3.47 ± 0.61). When T1w images were used to delineate the outer carotid wall, very high specificities (>95%) of IPH detection on mask and TOF images were found, while the sensitivity was high for mask images (>81%) and poor for TOF (50–60%). Without these images, the specificity was still high (>97%), while the sensitivity reduced to 62–71%.

Conclusion: Despite the lower image quality, routinely acquired mask images from CE-MRA, but not TOF, can be used as an alternative to MP-RAGE images to visualize IPH.

Abbreviations: 3D FFE, Three-dimensional fast field echo; CAR, Carotid Artery Risk score; CI, Confidence interval; CE-MRA, Contrast-enhanced MR angiography; DIR/QIR, Double/quadruple inversion recovery; ECST-2, 2nd European Carotid Surgery Trial; HR, Hazard ratio; IPH, intraplaque hemorrhage; NASCET, North American Symptomatic Carotid Endarterectomy Trial ; TR-TFE, Inversion recovery turbo-field echo; MRI, Magnetic Resonance Imaging; MP-RAGE, Magnetization-prepared rapid acquisition gradient; T1w, T1 weighted; TOF, Time-of-flight; TSE, Turbo spin echo.

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1. Introduction

It has been estimated that about 15% of TIAs or ischemic strokes are related to carotid atherosclerotic plaques [1]. Currently, clinical decisions concerning managing patients with carotid artery plaques are still mainly based on degree of internal carotid artery stenosis [2].

Recently, it has been recognized that plaque composition and specifically intraplaque hemorrhage (IPH) detected using Magnetic Resonance Imaging (MRI) are important predictors of patients at high risk of stroke [3–7]. Schindler et al showed that IPH has a strong predictive value for ipsilateral ischemic stroke in symptomatic patients (hazard ratio: 10.2, 95% confidence interval (CI): 4.6–22.5) and asymptomatic patients (hazard ratio: 7.9, 95% CI: 1.3–47.6) [3]. However, additional specialized advanced MR sequences are used to identify IPH. Most commonly a magnetization-prepared rapid acquisition gradient (MP-RAGE) sequence, also known as T1w "inversion recovery turbo-field echo" (IR-TFE) is used for this purpose. MP-RAGE is well validated to visualize IPH with high sensitivity and specificity (80% and 97%, respectively) [8] and high inter-observer agreement ($\kappa = 0.73$, 95% CI $= 0.53–0.92$) [9]. However, in most centers, additional MR sequences beyond the contrast-enhanced MR angiography (CE-MRA) to measure degree of stenosis are not acquired during a routine carotid MRA examination, mostly because of time constraints and because they are currently not included in imaging guidelines.

CE-MRA is a standard element of a carotid MRI examination [10]. A Time-of-flight (TOF) MRA is also acquired in most centers during carotid MRI examination. Due to the magnetic properties of blood products, IPH can be recognized as an area of high signal intensity within the bulk of the plaque on CE-MRA and TOF [11]. The usefulness of pre-contrast source images of CE-MRA (mask images) to identify high signal intensity in the vessel wall, to determine IPH was shown in a case report [12]. Later, the sensitivity and specificity to detect IPH on mask images was shown to be 87% and 99% and on TOF images it was 79% and 87% in a single center study of 15 patients [11].

The objective of the present study is to determine the diagnostic accuracy of identifying IPH using mask images from CE-MRA and TOF images in patients with $\geq$ 50% carotid stenosis by using MP-RAGE as reference standard in a multi-center study.

2. Material and methods

2.1. Study population

This study involved patients enrolled at participating centers in the ongoing 2nd European Carotid Surgery Trial (ECST-2; ISRCTN 97744893). Eligible patients were adult (>18 years) with symptomatic or asymptomatic atherosclerotic carotid artery stenosis (>50%, NASCET criteria), a 5-year risk of ipsilateral stroke < 20% estimated by the Carotid Artery Risk score. The score predicts the 5-year risk of ipsilateral stroke on the side of the stenotic carotid artery in patients treated with optimized medical therapy alone. The model was derived from the results of a Cox regression model in ECST-1 and validated in the NASCET trial [13]. In the current analysis, we included only patients that underwent a baseline carotid MRI examination including an MP-RAGE, TOF and CE-MRA (with mask images available) sequences. Ethical and NHS approval from the National Research Ethics Service in the UK after review by the NRES Committee East of England, Cambridge Central was obtained. Outside of UK, approval was obtained from the local medical ethical committees. Written informed consent was obtained from all subjects. The study protocol conforms to the ethical guidelines of Declaration of Helsinki.

2.2. Carotid MRI acquisition and image analysis

The carotid MR imaging examinations were carried out on 3T MRI systems (Achieva; Philips Healthcare, The Netherlands or Prisma; Siemens Healthineers, Erlangen, Germany) using a neurovascular or dedicated carotid radio-frequency coil. The parameters of the carotid MR sequences are presented in Table 1.

For the CE-MRA series, a 3D fast field echo fast field echo sequence was acquired before (i.e., the mask images) and after intravenous injection of 0.1 mmol/kg body weight of gadobutrol (Gadovist, Bayer Schering, Leverkusen, Germany).

Axial reconstructed images of the mask, MP-RAGE, and TOF images were anonymized and scored by the two trained observers (MK and SdK) independently of each other and blinded to their scores of the other sequences. A minimal one-month period between scoring IPH on each MRI weighting was set to minimize prior knowledge. Dedicated software (Vesselmass) was used for MR image analysis. The presence of IPH was defined as high signal intensity within the bulk of the plaque compared with the adjacent muscle tissue. The presence of IPH on mask images was scored two times independently with and without the help of black blood T1 weighted images with a minimal two-months period between these two sessions. In the first session the mask images of the CE-MRA and the TOF and MP-RAGE images were co-registered with pre-contrast/post-contrast 2D T1 weighted (T1w) double/quadruple inversion recovery turbo spin echo (TSE) images or any other black blood sequence such as blade. If the automated co-registration was not perfect, then the images were manually aligned. The luminal and outer vessel wall were defined on T1w images in this first session. In a second session IPH was scored without the help of T1w images. In this case, the lumen of the carotid artery was delineated on the post-contrast MRA. However, the outer vessel wall is difficult to observe only on CE-MRA. Therefore, any hyperintense signal surrounding the lumen at the side of the bifurcation compared with the adjacent sternocleidomastoid was considered to be IPH. A 4-poinst certainty score was used (4: very certain and 1: uncertain). In addition, a 5–point image quality score was used (5 high, 1 low) [14]. For an exploratory analysis, IPH volume was quantified on MP-RAGE images by delineating the region with hyperintense signal in the bulk of the plaque on each IPH-positive slice.

3. Statistical analysis

All analyses were performed with a dedicated statistical package (IBM SPSS statistics version 26). The Cohen κ coefficient was calculated to evaluate the inter-observer agreement on scoring IPH on MP-RAGE, mask and TOF images. $\kappa < 0.4$ is considered poor agreement, 0.4 to 0.75 is fair to good and $\kappa > 0.75$ is excellent [15]. The sensitivity and specificity of IPH detection on mask MRA and TOF were calculated with MP-RAGE as reference standard and were expressed in percentages with 95% confidence intervals. The Mann-Whitney test was used to compare the median volume of IPH between the true positive and false negative cases.

4. Results

217 patients out of 455 patients underwent baseline carotid MRI within 2nd European Carotid Surgery Trial (ECST-2). CE-MRA with mask images available, MP-RAGE (IR-TFE) and TOF have been acquired in 36 patients (72 carotid arteries). Six arteries were excluded due to motion artifacts on MP-RAGE (two arteries) or location of the plaque was located outside the field of view (four arteries). Finally, the data of 66 arteries were eligible for final analysis. The image quality of mask (1.42 ± 0.66) and TOF (2.42 ± 0.66) was significantly lower ($p < 0.05$) than MP-RAGE (3.47 ± 0.61).

4.1. Scoring IPH on mask images of CE-MRA with the aid of high resolution black blood T1w images

The inter-observer agreements for identifying IPH on MP-RAGE, mask and TOF with the aid of black blood high resolution T1w images were excellent (κ: 0.93, 0.96 and 0.85, respectively). There were two,

one and three disagreement cases of IPH scores on MP-RAGE, mask and TOF, respectively (Table 2).

CE-MRA mask showed very high specificities (97.8% [95%CI: 88.2 to 99.9%] and 97.9% [85%CI 88.7 to 99.9%]) and high sensitivity (81.0% [95%CI: 58.1 to 94.5%] and 84.2% [95%CI: 60.4% to 96.6]) of identifying IPH using MP-RAGE as reference standard by reader 1 and reader 2, respectively. However, TOF demonstrated high specificity (95.6% [95%CI: 84.8% to 99.5] and 97.9% [95%CI: 88.7 to 99.9%]) and poor sensitivity (50.0% [95%CI: 27.2 to 72.8%] and 57.9% [95%CI: 33.5 to 79.7%]) by reader 1 and 2, respectively. False positive and negative results for both readers are presented in Table 3. Examples of true and false negative findings are shown in Figs. 1 and 2.

The exploratory analysis demonstrated that the median IPH volume of the true positive cases (tended) to be significantly larger than the false negative cases (0.18 ml [interquartile range (IQR) 0.10–0.27] vs. 0.02 ml [0.003–0.05], p = 0.001 for reader 1; 0.18 ml [0.09–0.27] vs. 0.05 ml [0.003–0.16], p = 0.06 for reader 2).

4.2. Scoring IPH on mask images of CE-MRA without the aid of black blood T1w images

The intra-observer agreement of IPH detection on mask images when black blood T1w was not used was lower (κ = 0.88 and κ = 0.87) for reader 1 and 2, respectively. When we excluded cases with a low certainty score (≤2), the intra-observer agreement increased (κ = 0.92 and κ = 0.91) for reader 1 and 2, respectively. The inter-observer agreement between two readers of scoring IPH on mask images without using T1w TSE images was still excellent (κ = 0.87). The specificities of scoring IPH on mask images without the black blood T1w images using MP-RAGE as reference standard were 100% [95%CI: 92.1 to 100%] and 97.8% [95% CI: 88.4 to 99.9%], while the sensitivities were 71.4% [47.8 to 88.7%] and 61.9% [95%CI: 38.4 to 81.9%] for reader 1 and reader 2, respectively (Table 4). When cases with certainty scores ≤ 2 were excluded, the specificity and sensitivity became 100 [95%CI: 92.3 to 100%] % and 72.2% [95%CI: 46.5 to 90%] for reader 2, while the results of reader 1 remained unchanged.

Table 2
Level of Agreement on IPH detection between two observers for the three different sequences. CE_MRA, contrast-enhanced MR angiography; IPH, intraplaque hemorrhage, MP-RAGE, magnetization-prepared rapid acquisition gradient; TOF, time-of-flight.

CE-MRA mask	Reader 1		Total
Reader 2	IPH −	IPH +	
IPH −	48	1	49
IPH +	0	17	17
Total	48	18	66
MP-RAGE	**Reader 1**		**Total**
Reader 2	IPH −	IPH +	
IPH −	45	2	47
IPH +	0	19	19
Total	45	21	66
TOF	**Reader 1**		**Total**
Reader 2	IPH −	IPH +	
IPH −	52	2	54
IPH +	1	11	12
Total	53	13	66

5. Discussion

We demonstrated that there is an excellent inter-observer agreement for identification of IPH on mask MRA and TOF images. Moreover, we showed very high specificities of IPH detection on mask and TOF images, while the sensitivity was high for mask but poor for TOF when

Table 1
Scan parameters of the carotid MRI examination.

Pulse sequence	CE-MRA				MP-RAGE				TOF				T1w TSE			T1w BLADE
Center	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Vendor	Philips			Siemens	Philips			Siemens	Philips			Siemens	Philips			Siemens
Scanner type	Achieva			Prisma	Achieva			Prisma	Achieva							Prisma
Acquisition format	3D				3D				3D				2D			2D
Acquisition plane	Coronal				Coronal				Transversal				Transversal			
Sequence name	T1-FFE	T1-FFE	T1-FFE	FLASH	T1-FFE	T1-FFE	T1-FFE	MP-RAGE	T1-FFE	T1-FFE	T1-FFE	T1-TFE	TSE			BLADE
TR (ms)	4.6	5.1	4.6	3.0	15	9.1	15	12	224	24	24	24	800			1500
TE (ms)	1.6	1.6	1.7	1.1	4.8	5.5	4.8	5.3	4.6	4.6	4.6	4.6	10			53
TI (ms)	NA	NA	NA	NA	500	304	NA	500	NA	NA	NA	NA	282, 61			659
Flip angle (°)	27	30	27	22	15	15	15	15	20	20	20	20	90			60
No. of slices	150	150	150	88	75	80	82	128	75	30	75	22	15			18
Slice thickness (mm)	1.0	0.8	1.0	0.9	0.6	0.6	0.6	0.6	2.0	2.0	2.0	1.0	2.0			2.0
FOV (mm)	320 × 320	360 × 360	320 × 320	297 × 340	160 × 160	160 × 160	160 × 160	160 × 160	180 × 180	160 × 160	180 × 180	160 × 145	160 × 160			160 × 160
Acquisition matrix	508 × 508	348 × 346	508 × 508	210 × 320	228 × 228	268 × 266	268 × 2.68	256 × 256	300 × 300	268 × 266	300 × 300	256 × 243	260 × 256			320 × 320
Acquired voxel size	0.6 × 0.6	1.0 × 1.0	0.6 × 0.6	1.1 × 1.4	0.7 × 0.7	0.6 × 0.6	0.6 × 0.6	0.6 × 0.6	0.6 × 0.6	0.6 × 0.6	0.6 × 0.6	0.6 × 0.6	0.6 × 0.6			0.5 × 0.5
Reconstruction matrix	640 × 640	768 × 768	640 × 640	512 × 512	288 × 288	560 × 560	288 × 288	256 × 256	320 × 320	528 × 528	320 × 320	256 × 243	528 × 528			320 × 320
Reconstructed voxel size	0.5 × 0.5	0.5 × 0.5	0.5 × 0.5	0.6 × 0.7	0.5 × 0.5	0.3 × 0.3	0.5 × 0.5	0.6 × 0.6	0.6 × 0.6	0.3 × 0.3	0.6 × 0.6	0.6 × 0.6	0.3 × 0.3			0.5 × 0.5
Echo train length	NA	NA	NA	NA	26	30	27	64	NA	NA	NA	NA	10			9
Parallel imaging	Yes	Yes	Yes	Yes	2	No	2	No	2	No	2	Yes	No			Yes
No. of signal averages	1	1	1	1	1	1	1	1	1	1	1	1	1			1
Fat suppression	No	No	No	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes			Yes

1: UCL, 2: Maastricht, 3: Verona, 4: Basel. CE-MRA, contrast-enhanced MR angiography; MP-RAGE magnetization-prepared rapid acquisition gradient; TOF, time of flight; FFE, fast field echo; FLASH, fast low angle shot; IR-TFE, inversion recovery turbo field echo; TSE, turbo spin echo; TR, repetition time; TE, echo time; TI, inversion time; NA, not applicable; FOV, field of view.

Table 3
Sensitivity and specificity of identification of IPH on the mask images of CE-MRA and on the TOF images using MP-RAGE as reference standard and using black blood T1w images to define the outer vessel wall. CE_MRA, contrast-enhanced MR angiography; IPH, intraplaque hemorrhage, MP-RAGE, magnetization-prepared rapid acquisition gradient; TOF, time-of-flight.

CE-MRA mask	MP-RAGE		
	Reader 1	IPH −	IPH +
	IPH −	44 (97.8%)	4
	IPH +	1	17 (81.0%)
TOF	**MP-RAGE**		
	Reader 1	IPH −	IPH +
	IPH −	43 (95.6%)	10
	IPH +	2	10 (50.0%)
CE-MRA mask	**MP-RAGE**		
	Reader 2	IPH −	IPH +
	IPH −	46 (97.9%)	3
	IPH +	1	16 (84.2%)
TOF	**MP-RAGE**		
	Reader 2	IPH −	IPH +
	IPH −	46 (97.9%)	8
	IPH +	1	11 (57.9%)

observers were allowed to use black blood T1w TSE MR images to detect the outer vessel wall. The specificity and sensitivity of scoring IPH on mask images without the aid of these black blood T1w images was high and moderate, respectively.

Numerous studies have established that IPH on MRI is a strong predictor of stroke and is therefore of high relevance for the identification of a subgroup of patients with an increased risk for stroke[3,7]. Therefore, during the past decades, there has been an increasing interest in MRI sequences to visualize IPH [16]. In 2003, Moody discovered that MP-RAGE was capable of detecting IPH [17]. Compared to two-dimensional T_1-weighted fast spin echo and 3D TOF, Ota et al demonstrated that MP-RAGE is the optimal T1w sequence to detect the presence of IPH as it has the highest specificity and sensitivity (97% and 80%, respectively) [8]. In line, Cappendijk *et al* showed a high detection rate (81–93%) for IPH on MP-RAGE images and less (72–91%) on T1w TSE images using histology as reference standard [9]. Recently, expert consensus recommendations on vessel wall MR imaging protocol stated that MP-RAGE is well suited to detect IPH [6,18].

Our results are in line with earlier findings by Qiao *et al* [11]. They showed in 15 patients a specificity of 99% and sensitivity of 87% when IPH was identified on mask images using histology as a reference standard. Also, the inter-observer agreement for IPH detection on mask images ($\kappa = 0.91$) was comparable to the present study. On TOF images, these authors showed a high specificity and sensitivity of detecting IPH (87% and 79%) using histology as reference standard. However, in our study we confirmed the high specificity but found a lower sensitivity of scoring IPH on TOF when MP-RAGE was used as reference standard.

We showed that the sensitivity of detecting IPH on mask images became lower when the black blood sequence was not used to visualize the outer vessel wall, while the specificity remained very high. Distinction of the outer wall could be challenging on mask images since no fat suppression was applied. Therefore, small high signal intensity regions on mask images can be erroneously identified as perivascular tissue.

We also observed a few false negative cases. Since the false negative cases showed a smaller median IPH volume than the true positive ones, this was probably due to the lower spatial resolution of mask images compared to the MP-RAGE images which can limit the ability to visualize small regions of IPH. Two false positive cases on TOF images were associated with ulceration that also appears as a high signal intensity region on TOF images.

More recently, Simultaneous Non-contrast Angiography and intraplaque hemorrhage (SNAP) MR imaging was proposed to detect both luminal stenosis and hemorrhage in patients with carotid plaques with a single sequence [19]. Strong agreement ($\kappa = 0.82$, $p < 0.001$) was identified between SNAP and MP-RAGE images for detecting IPH. Also, fast simultaneous non-contrast angiography and intraplaque hemorrhage (fSNAP) performs similar to SNAP but with 37.5% less scan time [20]. In addition, simultaneous T_1 and T_2 mapping of carotid plaque (SIMPLE) [21] and golden angle radial k-space sampling (GOAL-SNAP) were proposed to score IPH [22]. Moreover, MATCH was developed to image IPH and other vulnerable plaque components using a single multi-contrast sequence [23]. However, most of these sequences are not available in the standard MR system configuration. Software patches or work in progress (WIP) packages are required to use these sequences on clinical MR systems.

In general, high-resolution MRI is sensitive to patient motion. Therefore, we recommend to fixate the head of the patient by using cushions and soft belts. Swallowing artefacts can be reduced by positioning a regional saturation slab over the pharynx. In addition, the MP-RAGE sequence contains a non-selective inversion pre-pulse. However, this non-selective inversion pre-pulse is limited to the field-of-view of the body coil. Therefore, incomplete blood suppression can occur especially in tall patients due to inflow of incompletely suppressed blood. This can be prevented by positioning the patient slightly off-center towards the feet direction.

A limitation of our study is the lack of histological validation. Patients were randomized for optimized medical treatment or revascularization in ECST-2. Storage of the surgery specimen and histological

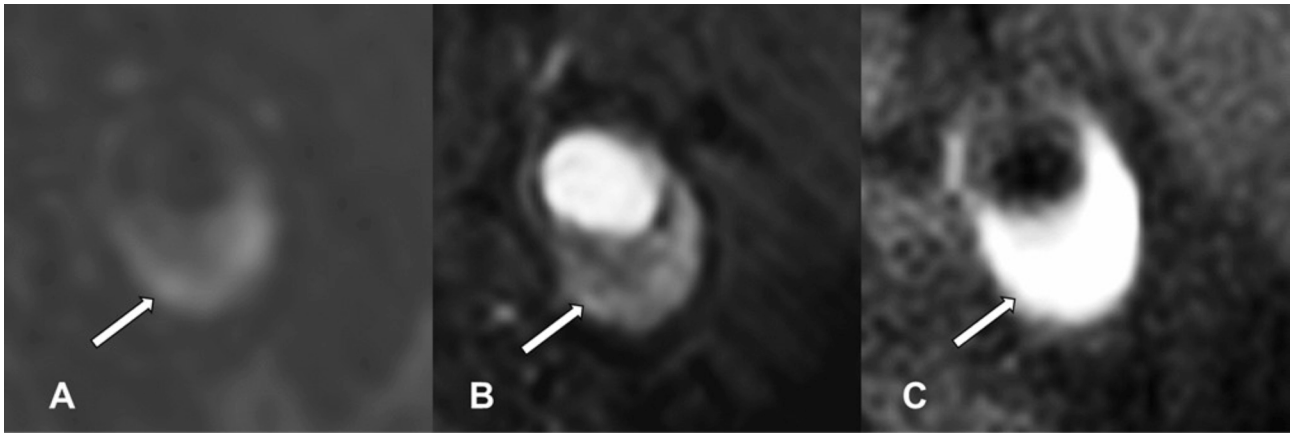

Fig. 1. An example of a true positive finding. IPH is shown as a region within the bulk of the plaque with high signal intensity (arrow) on all three MRI weightings: A) contrast-enhanced MR angiography (CE-MRA) mask image, and B) Time-Of-Flight (TOF) and C) Magnetization Prepared-Rapid Acquisition Gradient Echo (MP-RAGE) image.

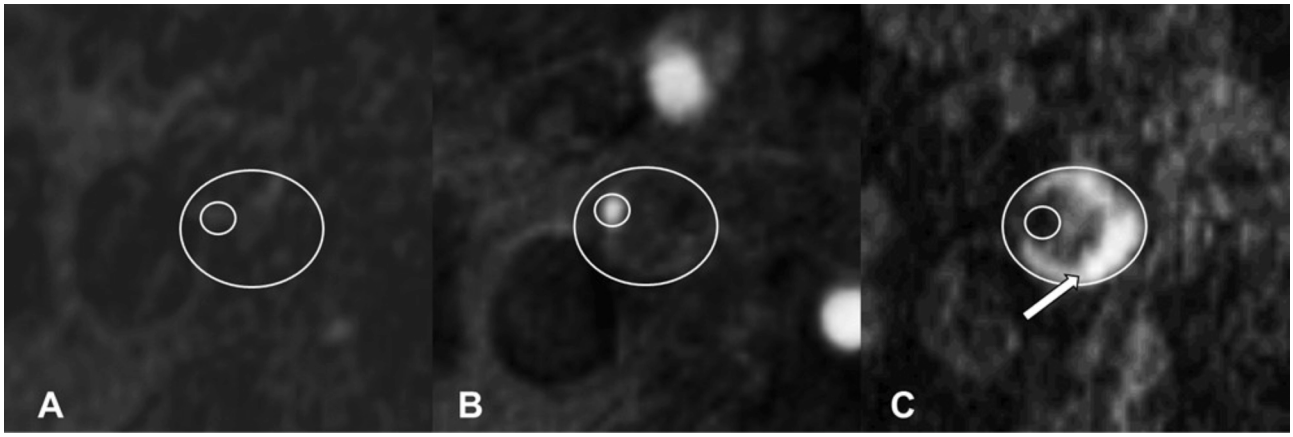

Fig. 2. An example of a false negative finding. IPH is not shown on the A) contrast-enhanced MR angiography (CE-MRA) mask image and B) time-of-flight (TOF) image, while IPH is clearly seen as region within the bulk of the plaque with high signal intensity (arrow) on the C) Magnetization-Prepared Rapid Acquisition Gradient Echo (MP-RAGE) image. White boundaries indicate inner (lumen) and outer carotid wall.

Table 4
Sensitivity and specificity of identification of IPH on the mask images of CE-MRA using MP-RAGE as reference standard without using black blood T1w images to define the outer wall. CE_MRA, contrast-enhanced MR angiography; IPH, intraplaque hemorrhage, MP-RAGE, magnetization-prepared rapid acquisition gradient.

CE-MRA mask without T1w	MP-RAGE		
	Reader 1	IPH −	IPH +
	IPH −	45 (100%)	6
	IPH +	0	15 (71.4%)
	MP-RAGE		
	Reader 2	IPH −	IPH +
	IPH −	44 (97.8%)	8
	IPH +	1	13 (61.9%)

analysis was not part of the study design. Alternatively, we have used MP-RAGE as a reference standard, which has been validated with histology in numerous previous studies [9,17]. Another limitation is that we validated the use of the mask images in asymptomatic and symptomatic patients with moderate to severe stenosis with a 5-year risk of ipsilateral stroke $< 20\%$ estimated by the Carotid Artery Risk score. Future studies need to investigate whether intraplaque hemorrhage on mask images can also be detected in patients with mild carotid stenosis or a non-stenotic carotid plaque. The strength of the present study is the larger sample size compared to that of the previous study [11].

6. Conclusion

In addition to measuring the degree of stenosis using only the contrast-enhanced images, our results showed that the mask images of CE-MRA can also be used to score the presence of IPH. Using an additional black blood sequence to visualize the outer vessel wall can further improve the accuracy. Scoring IPH during the routine assessment of CE-MRA can provide additional information about the risk of stroke and could contribute to treatment decisions.

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Trial registration

This study involved patients enrolled at centers in the 2nd European Carotid Surgery Trial (ECST-2; ISRCTN 97744893) participating in the plaque-imaging substudy.

9. Consent for publication

A written-informed consent form has been signed by all patients that were included in this study agreeing to take part in 2nd European Carotid Surgery Trial (ECST-2).

Availability of data and materials

For ethical reasons the raw data that we collected cannot be made publicly available. The access to the data is granted only to 1) members of the research team, 2) the Medical Ethics Committee members that approved this study, and 3) authorized personnel of the Health Care Inspectorate. Hence, participants did not consent to publicly archiving their data. However, requests for anonymous data can be sent to prof. dr. Leo Bonati at leo.bonati@usb.ch.

Authors' contributions

All authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, and have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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