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# Meta-Analysis and Systematic Review of the Predictive Value of Carotid Plaque Hemorrhage on Cerebrovascular Events by Magnetic Resonance Imaging

Tobias Saam, MD,* Holger Hetterich, MD,* Verena Hoffmann, PhD,† Chun Yuan, MD,‡ Martin Dichgans, MD,§ Holger Poppert, MD,‖ Thomas Koeppel, MD,¶ Ulrich Hoffmann, MD,# Maximilian F. Reiser, MD,* Fabian Bamberg, MD, MPH*

*Munich, Germany; and Seattle, Washington*

**Objectives** This study sought to conduct a systematic review and meta-analysis to determine precise estimates of the predictive value of carotid intraplaque hemorrhage (IPH) as determined by magnetic resonance imaging (MRI) for cerebrovascular events.

**Background** There is emerging evidence that MR-based carotid atherosclerotic plaque assessment identifies high-risk features associated with cerebrovascular events. However, available data are based on smaller samples with heterogeneous source populations despite a promising value for noninvasive risk stratification.

**Methods** We searched PubMed, EMBASE, and the Cochrane Library through September 2012 for studies that followed >35 individuals after baseline MRI. Independent observers abstracted information on populations, MR techniques, outcomes, and study quality. Risk estimates of the presence of IPH for cerebrovascular events were derived in random effects regression analysis, and causes of heterogeneity were determined in meta-regression analysis.

**Results** We identified 8 eligible studies including 689 participants who underwent carotid MRI. The prevalence of IPH at baseline was high (49.0%). Over a median follow-up of 19.6 months, a total of 108 cerebrovascular events occurred (15.7% event rate). The presence of IPH was associated with an ~6-fold higher risk for events (hazard ratio [HR]: 5.69; 95% confidence interval [CI]: 2.98 to 10.87). The annualized event rate in subjects with detectable IPH was 17.71% compared with 2.43% in patients without IPH. Meta-regression analysis showed symptomatic subjects had higher risks as compared with asymptomatic subjects (HR: 11.71, 95% CI: 5.17 to 26.48 vs. HR: 3.50, 95% CI: 2.59 to 4.73, $p = 0.0065$), Also, differences were observed for sex and sample size (all $p < 0.01$), with moderate visual publication bias due to missing smaller sample-size studies ($p = 0.18$).

**Conclusions** Presence of IPH on MRI strongly predicts cerebrovascular events. Homogenization of future studies is warranted to allow for sufficient assessment of level of evidence for intervention trials. (J Am Coll Cardiol 2013;62:1081–91)


From the *Institute of Clinical Radiology, Ludwig-Maximilians-University Hospital Munich, Munich, Germany; †Institute of Biomedical Epidemiology, Ludwig-Maximilians-University Hospital Munich, Munich, Germany; ‡Department of Radiology, University of Washington, Seattle, Washington; §Institute for Stroke and Dementia Research, Ludwig-Maximilians-University Hospital Munich, Munich, Germany; ‖Department of Neurology, Technische Universität München, Munich, Germany; ¶Division of Vascular and Endovascular Surgery, Ludwig-Maximilians-University Hospital Munich, Munich, Germany; and the #Division of Vascular Medicine, Medical Clinic and Policlinic IV, Ludwig-Maximilians-University Hospital Munich, Munich, Germany. Dr. Saam is on the speakers' bureaus of MSD Merck, Sharp & Dohme and GlaxoSmithKline; and has received grant support from Diamed Medizintechnik. Dr. Yuan has been a consultant for ImagePace, Bristol-Myers Squibb Medical Imaging, and Boehringer Ingelheim; and has received research grants from Philips Medical and VP Diagnostics. Dr. Dichgans receives research support from BMB, NGFN-Plus, Wellcome Trust, and the Foundation for Vascular Dementia Research. Dr. Poppert has served on a scientific advisory board for Bayer Healthcare; received speaker honoraria from Bayer Healthcare, Boehringer Ingelheim, Novartis, and Roche; received funding for travel from Bayer Healthcare; and has also received research support from the government agencies Bundesministerium für Wirtschaft und Technologie, and Deutsche Stiftung Neurologie. Dr. Bamberg received speaker honoraria from Bayer Healthcare and Siemens Healthcare; and has received research grants from Bayer Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The first two authors contributed equally to this work.

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**Abbreviations and Acronyms**

CI = confidence interval

HR = hazard ratio

IPH = intraplaque hemorrhage

MRI = magnetic resonance imaging

TIA = transient ischemic attack

Recent studies suggest that intraplaque hemorrhages (IPH) are events that could play a major role in plaque progression and leukocyte infiltration, and may also serve as a measure of risk for the development of future cardiovascular events (1,2). Thus, the recent advances in our understanding of IPH as a critical factor in triggering acute clinical events might have important implications for clinical research and, possibly, future clinical practice.

Until recently, most of our knowledge of the effects of IPH was based on autopsy studies, carotid or femoral endarterectomy specimens, or animal studies (2,3). However, with the introduction of high-resolution black-blood magnetic resonance imaging (MRI), noninvasive identification of IPH in the carotid arteries is feasible with good correlation to histopathology (4–6). Thus, several studies have examined the effects of IPH on plaque progression and symptoms (7–9), suggesting a link between IPH and acute cerebrovascular events. This observation was supported by a recent MRI study in patients with symptomatic carotid stenosis, which showed that patients with IPH by MRI are more likely to have spontaneous microembolic activity and cerebral ischemic embolic lesions (10). Furthermore, American Heart Association MRI-derived type VI carotid plaque is associated with ipsilateral acute transient ischemic attack (TIA) and ischemic stroke (11).

To date, multiple longitudinal studies have shown that IPH, as assessed by MRI, is associated with the occurrence of cerebrovascular events in symptomatic and in asymptomatic subjects. However, most of these studies were relatively small, and the absolute numbers of events were therefore low. Also, there is substantial heterogeneity among published studies, and the confidence limits of the observed risk estimates remain wide despite a high relevance for future intervention trials and cost-effectiveness analyses. Thus, we pooled available evidence on the prognostic relevance of carotid MRI in a systematic review and meta-analysis.

## Methods

**Study selection.** To identify eligible studies, we searched PubMed, EMBASE, and the Cochrane Library through September 2012 using medical subject headings "magnetic resonance imaging" and "carotid artery plaque" or "atherosclerotic plaque" in combination with the text words "hemorrhage" or "thrombus" and "event" or "stroke" or "TIA" or "DWI lesion" or "amaurosis fugax" or "symptoms." In addition, we obtained expert opinions (C.Y., T.S., M.D., F.B.) on whether any potentially relevant study was missed. Eligible articles were limited to those conducted on human adults over the age of 18 years. Also, we hand searched all reference lists of all retrieved original papers and review articles to identify further relevant studies. Finally, we searched for associated publications of retrieved articles to obtain the most complete and up-to-date study results.

**Inclusion and exclusion criteria.** In our analysis, we included studies that met the following pre-specified criteria: follow-up for more than 1 month, ≥1.5-T MRI scanners, and detailed assessment of IPH in the carotid arteries at the baseline examination. IPH was defined as an area within the carotid plaque with hyperintense signal compared with the sternocleidomastoid muscle or the normal vessel wall on T1-weighted fat-suppressed images. Figure 1 shows examples of MR images of carotid atherosclerotic lesions with and without IPH. Studies were not included if they did not provide risk estimates or crude numbers of prevalence and outcome, or if the occurrence of events was not followed.

**Data abstraction and definitions.** Among 208 potentially eligible studies, we excluded 156 studies based on title and abstract review. The remaining 52 studies were retrieved for a more detailed analysis. Of those, 44 studies were excluded for various reasons, thus 8 studies were available for analysis (Fig. 2).

Two independent observers (T.S. and H.H.) abstracted information on all variables listed in Tables 1 and 2, which included the following endpoints: amaurosis fugax, TIA, and stroke. Discrepancies between the 2 investigators were resolved by discussion and re-examination of the corresponding studies with a senior investigator (F.B., M.D., or M.F.R.) or by contacting the authors of the individual studies. The total subject number was defined as the number of participants in whom the risk estimates were derived.

Study quality indicators included the presence or absence of an endpoint committee, blinded MRI results and blinded outcome assessment, clear endpoint definition, clear description of target population, clear definition of MRI findings, adjustment for potential confounders, and exclusion of subjects after enrollment.

RISK ESTIMATES. To pool the available study results, we abstracted the hazard ratios (HRs) of the included studies for the MRI finding of interest. The most extensively adjusted HR (with associated 95% confidence interval [CI] derived from multivariate regression analysis) from each original study was included to minimize the effect of confounding. For studies that did not provide multivariate-adjusted HRs, the univariate risk estimate was included in the analysis.

EVENT RATES. Estimates of absolute risks were derived from the original studies. From these, all described events were annualized by using the provided average follow-up time, which was then summarized by weighting by sample size.

ASSUMPTIONS. In order to pool available evidence, we made the following assumptions. For 1 study, we derived the pertaining HR, taking into account the prevalence of MRI findings and observed number of events in each group, assuming a consistent event rate of the mean follow-up period. We also assumed that the ipsilateral risk associated with the

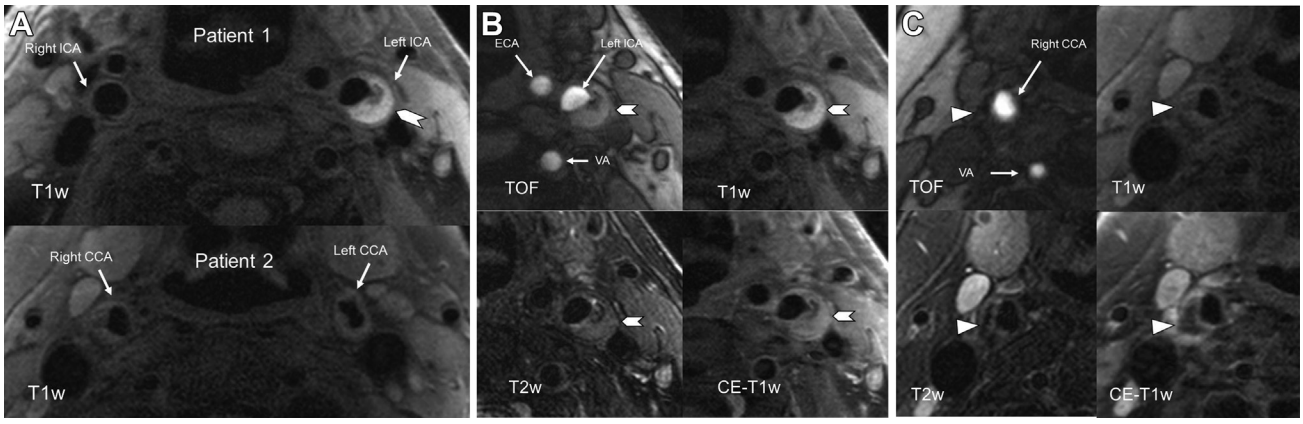


**Figure 1** **Examples of Carotid Atherosclerotic Plaque With and Without IPH as Derived by MRI**

**(A) Upper panel**: T1-weighted (T1w) fat-suppressed MR images of an 86-year-old patient with acute ischemic stroke ipsilateral to a large atherosclerotic plaque with intraplaque hemorrhage (IPH) **(chevron)** in the left ICA; **lower panel**: T1w fat-suppressed MR images of a 68-year-old asymptomatic patient with long-lasting hypercholesterolemia and large atherosclerotic plaques without intraplaque hemorrhage in both carotid arteries. **(B)** In this magnified view of the symptomatic plaque in the left ICA of patient 1, the **chevron** points to a region that is hyperintense on both TOF and fat-suppressed black-blood T1w images, consistent with intraplaque hemorrhage. The corresponding area is hypo- to isointense on black-blood T2w images, indicating acute type I hemorrhage. The contrast-enhanced T1w (CE-T1w) images demonstrate no contrast uptake in this large lesion, suggestive of a lipid-rich/necrotic core. **(C)** This magnified view of the asymptomatic plaque in the right CCA shows a large eccentric atherosclerotic plaque, which is isointense on TOF and T1w images, and hypointense on T2w images, consistent with a large lipid-rich/necrotic core without intraplaque hemorrhage **(arrowhead)**. The lipid-rich/necrotic core does not show any contrast uptake. Of note, a small contrast-enhancing band is visible on the CE-T1w images, consistent with a thick fibrous cap. CCA = common carotid artery; CE = contrast enhancement; ECA = external carotid artery; ICA = internal carotid artery; MRI = magnetic resonance imaging; TOF = time-of-flight; VA = vertebral artery.

prevalence of IPH is independent of the contralateral side, an assumption that all studies relied on. Although this approach may maximize the number of events, it does not take into account the clustered nature of the arteries per subject, which may result in skewed hazards. For the meta-regression analysis, the study by Kume et al. (12) was classified as

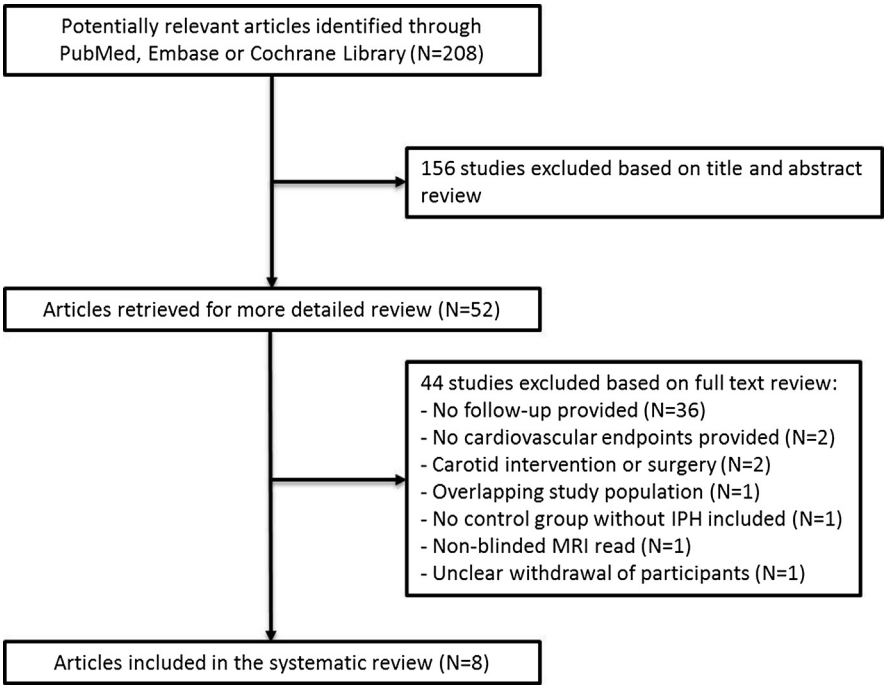


**Figure 2** **Literature Research and Selection Process of Studies Included in the Analysis**

Abbreviations as in Figure 1.

**Table 1** Prevalence of Plaque Hemorrhage and Annualized Event Rates

| First Author/Year (Ref. #) | Region | Sample Type | N | Mean Age (yrs) | Men (%) | History of CAD / Ischemic Heart Disease / Diabetes / Smoker / Hypertension / Hyperlipidemia / Statins (%) / Antiplatelets (%) | MRI Scanner (T) | Exclusion After Enrollment |
|---|---|---|---|---|---|---|---|---|
| Teng et al. 2011 (20) | Europe, U.K. | TIA, MRI scan within 72 h after symptoms | 42 | 73.4 | 60 | 16.7 / not stated / 9.5 / not stated / 73.8 / not stated / 59.5 / 36 | 1.5 | 0 |
| Kurosaki et al. 2011 (14) | Asia, Japan | TIA, stroke according to TOAST criteria | 62 | 77.8 | 81 | Not stated / 58.1 / 41.9 / not stated / 67.7 / 29.0 / 21.0 / 85.5 | 1.5 | 0 |
| Sadat et al. 2010 (21) | Europe, U.K. | TIA or minor, nondisabling stroke diagnosed by a consultant stroke physician | 61 | 74.0 | Not stated | 14.8 / 34.4 / 9.8 / not stated / 80.3 / not stated / 100 / 100 | 1.5 | 0 |
| Kume et al. 2010 (12) | Asia, Japan | Carotid plaque and >50% stenosis by US | 165 | 70.9 | 81 | Not stated / 29.7 / 46.0 / 34.0 / 67.3 / 43.0 / 14.6 / 57.0 | 1.5 | 0 |
| Singh et al. 2009 (15) | North America, Canada | Moderate asymptomatic stenosis 50%–70% | 75 | 74.9 | 100 | Not stated / not stated / 17.3 / 78.7 / 74.7 / 72.0 / 70.7 / 78.7 | 1.5 | 1 |
| Altaf et al. 2007 (22) | Europe, U.K. | Symptomatic patients with 60% to 99% stenosis | 66 | 70.0 | 70 | Not stated / 31.8 / 9.1 / 65.2 / 78.8 / not stated / 90.1 / 95.5 | 1.5 | 10 |
| Altaf et al. 2008 (13) | Europe, U.K. | Symptomatic patients with mild to moderate carotid stenosis (30%–69%) | 64 | 72.7* | 80 | Not stated / 15.6 / 20.3 / 70.3 / 78.1 / not stated / 75.0 / 98.4 | 1.5 | 9 |
| Takaya et al. 2006 (16) | North America, U.S. | Asymptomatic, 50%–79% stenosis | 154 | 71.1 | 82 | 44 / not stated / 25 / 38 / 75 / 79 / 64 / not stated | 1.5 | 29 |

*Median age.

CAD = coronary artery disease; MRI = magnetic resonance imaging; TIA = transient ischemic attack; TOAST = Trial of Org 10172 in Acute Stroke Treatment; US = ultrasound.

**Table 2** Study Characteristics—Results

| First Author/Year (Ref. #) | MRI Finding | FU (Months) | Endpoint | Events | TIA | Stroke | AmF | Multivariable Adjustment |
|---|---|---|---|---|---|---|---|---|
| Teng et al. 2011 (20) | JLH/T | 12.8 | Stroke, TIA, CEA | 11 | Not stated | Not stated | NA | No |
| Kurosaki et al. 2011 (14) | Plaque hemorrhage | 9.1 | Stroke, TIA | 7 | 4 | 3 | NA | No |
| Sadat et al. 2010 (21) | Plaque hemorrhage, FC rupture | 17.1 | Stroke, TIA | 12 | Not stated | Not stated | | No |
| Kume et al. 2010 (12) | IPH | 26 | Stroke | 29 | NA | 29 | NA | No |
| Singh et al. 2009 (15) | IPH | 24.9 | Stroke, TIA | 6 | 4 | 2 | NA | No |
| Altaf et al. 2007 (22) | IPH | 1.1 | Stroke, TIA, AmF | 17 | 9 | 3 | 5 | Yes, for age, stenosis, time between symptoms and evaluation, ischemic heart disease, CAD |
| Altaf et al. 2008 (13) | IPH | 28 | Stroke, TIA, AmF | 14 | Not stated | 5 | Not stated | No |
| Takaya et al. 2006 (16) | IPH, thin or ruptured FC | 38.2 | Stroke, TIA, AmF | 12 | 4 | 4 | 4 | No |

AmF = amaurosis fugax; CEA = carotid endarterectomy; FC = fibrous cap; FU = follow-up; IPH = intraplaque hemorrhage; JLH = juxtaluminal hemorrhage; T = thrombus; other abbreviations as in Table 1.

asymptomatic because the study population was predominantly asymptomatic (68%).

The provided median age was assumed to also provide the mean age in order to pool the age of the overall population (13). Also, in a subset, the provided mean follow-up time was assumed to be similar to the median follow-up time, allowing for pooling of the overall follow-up (12–16).

**Data analysis and statistical methods.** Data analysis was performed by an independent investigator (V.H). Descriptive statistics are provided as mean ± SD for continuous parameters, and absolute and relative frequencies for categorical variables. As a primary objective of the meta-analysis, we derived the association between the finding of IPH and the combined cerebrovascular endpoint.

We used standard statistics to summarize the individual risk estimates by using the "metafor"-package in R (version 2.10.0; the R Foundation for Statistical Computing, Vienna, Austria) to pool the natural logarithms (ln) of the HRs, using a random effects model (restricted maximum-likelihood estimator). Between-study heterogeneity was examined using the $Q$-statistic and the $I^2$ statistic (17). Publication bias was assessed using plots of study results against precision of the study (funnel plots). Symmetry of the funnel plots was tested using the methods developed by Egger et al. (18) and Begg and Mazumdar (19).

A meta-regression analysis was performed to identify sources of the detected high degree of heterogeneity of the risk estimates. The following pre-specified variables were analyzed: 1) symptomatic and asymptomatic subjects; 2) subjects older or younger than the median age (73 years); 3) enrollment of predominantly male subjects (median: 81% males); 4) higher prevalence of diabetes mellitus (median: 18% diabetic patients); 5) higher prevalence of statin therapy (median: 67% on statin therapy); 6) multisequence and single-sequence MRI; 7) subjects with high-grade stenosis versus studies that did not include subjects with high-grade stenosis; 8) symptomatic subjects and time between symptoms and MRI of <72 h versus <6 months; 9) Asian versus U.S./European studies; 10) retrospective versus prospective study design; 11) small versus large sample size (number of subjects > or ≤70); 12) studies with low versus good study quality (quality score <3.5 vs. <3.5); and 13) studies that did and did not adjust for confounders. To further investigate effect modification, for each of the subgroups, a HR was calculated. A p value of ≥0.1 was selected to indicate absence of significant heterogeneity of the estimates.

All analysis was performed using R (version 2.10.0), and a p value <0.05 was considered to indicate statistical significance.

## Results

Overall, we identified 8 studies that met the criteria and were included in the analysis (12–16,20–22); study details are provided in Tables 1 and 2. The majority of studies were conducted in the United States and Europe (2 [25%] and 4 [50%], respectively), whereas 2 (25%) studies were performed in Asia. One study (12.5%) was designed as a multicenter trial enrolling at 2 sites (12), and the majority was prospective in design, with only 2 (25%) studies of a retrospective nature (14,15).

The study population consisted of 689 subjects with 712 analyzed carotid arteries, predominantly older men (73.1 ± 2.2 years of age, and 79% men), who presented with TIA

(62.5%) or were asymptomatic with known moderate carotid stenosis as determined by sonography (12,15,16). The prevalence of diabetes, hypertension, hyperlipidemia, smoking, and prior history of cardiovascular disease was high (24%, 74%, 56%, 57%, and 30.7%, respectively). Consistently, the majority of subjects were treated medically (statin treatment, 62.0%; antiplatelet treatment, 72.0%).

All subjects were examined using a 1.5-T MR scanner. A multisequence approach was applied in 4 (50%) and electrocardiogram gating in 2 (25%) studies. The detected degree of carotid stenosis was moderate in the majority of studies (in 62.5% of studies, patients with ≥80% were not included 80% stenosis). After the MR examination, 6.3% of subjects, on average, were excluded per study (range, 0% to 15.8%) (16) for various causes, including impaired image quality in all cases (16), claustrophobia in 88.8% (13), or withdrawal from participation in 70% of excluded cases (22).

On average, the follow-up time was 19.73 months, ranging from 1.12 months (22) to 38.2 months (16). Over the follow-up period, a total of 108 outcome events were observed, consistent with a high event rate of 15.5%; details of the outcome events by study are provided in Table 2. A composite endpoint was applied in all but 1 study (87.5%) (12).

**Plaque hemorrhage and cardiovascular events.** Similar to that of the overall population, the risk associated with IPH on MRI was derived from 8 studies consisting of 689 patients. Based on a total of 108 outcome events, the combined estimated HR was 5.69 (95% CI: 2.98 to 10.87) (Figs. 3 and 4), indicating an approximately 5.7-fold higher risk among subjects with any plaque hemorrhage as detected by MRI compared with subjects without any evidence of plaque hemorrhage. The random effects estimate for impact of a positive MRI was 1.74 (95% CI: 1.09 to 2.39) with a borderline test for heterogeneity ($p = 0.072$), indicating significant between-study heterogeneity ($Q$-statistic, $p < 0.001$), and according to the $I^2$ test, 32% of the variability could be explained by between-study heterogeneity. Although the funnel plot revealed no statistical sign of asymmetry ($z = 1.34$, $p = 0.18$), there was a moderate visual publication bias due to missing studies with small sample sizes and moderate risk estimates (Fig. 5).

The prevalence of a positive MRI for IPH was high (average, 49.0%), and among subjects with a positive MRI, 30.6% experienced an event (Table 3). The weighted annualized event rate in subjects with a positive MRI was 17.7%. Conversely, 51.0% had a negative MRI associated with an average event rate of 4.1%. The weighted annualized event rate in subjects with a negative MRI was 2.4%.

**Heterogeneity analysis.** Given the detected heterogeneity of the pooled risk estimates, we identified the proportion of male subjects in the study population, symptom status (Fig. 4), and sample size as potential sources of heterogeneity (Table 4). There was no significant difference in the risk estimate for IPH by MRI according to population age, proportion of diabetes mellitus, current statin medication, MRI technology applied, degree of stenosis, time of MRI in

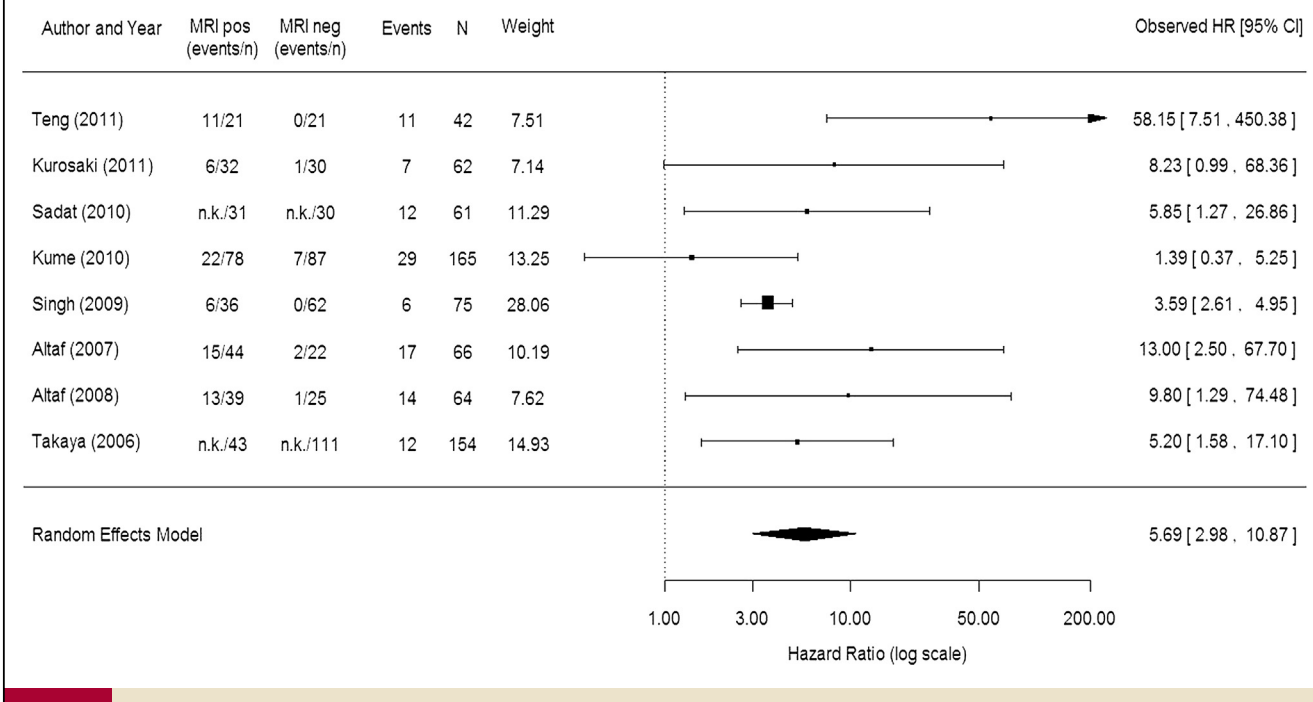


**Figure 3** Forrest Plot Showing Single Studies Included in the Analysis for the Risk Associated With the Presence of IPH

**Horizontal lines** represent 95% confidence intervals (CI). The **rectangles** represent the point estimate, and the size of the **rectangle** is proportional to the weight given to each study in the meta-analysis. The **diamond** represents the summary estimate (**size of the diamond** = 95% CI). The **dashed vertical line** represents the reference of no increased risk. HR = hazard ratio; neg = negative; pos = positive; other abbreviations as in Figure 1.

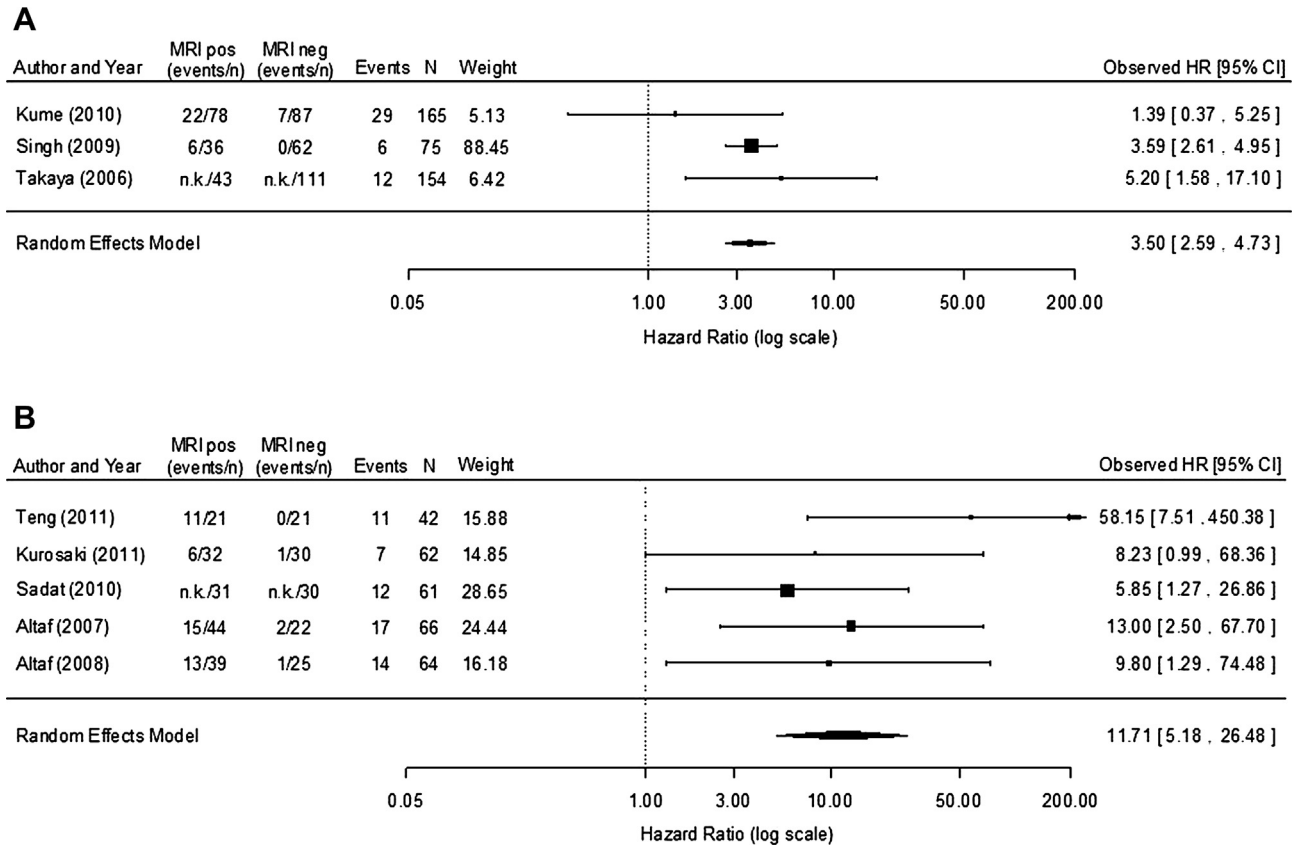


**Figure 4** **Forrest Plot Demonstrating Asymptomatic and Symptomatic Studies Included in the Analysis for the Risk Associated With the Presence of IPH**

**Horizontal lines** represent 95% confidence intervals (CI). The **rectangles** represent the point estimate, and the size of the **rectangle** is proportional to the weight given to each study in the meta-analysis. The **diamond** represents the summary estimate (**size of the diamond** = 95% CI). The **dashed vertical line** represents the reference of no increased risk. **(A)** Asymptomatic studies and **(B)** symptomatic studies. Abbreviations as in Figures 1 and 3.

relation to symptoms, region, design, included endpoints, or adjustment (all $p > 0.1$).

Studies that comprise a majority of male patients (≥81%) observed higher risk estimates for occurrence of events in patients with IPH (HR: 15.47, 95% CI: 5.89 to 40.65), whereas studies that included predominantly female patients observed a significantly lower risk (HR: 3.50, 95% CI: 2.59 to 4.73) ($p = 0.004$). We also found that the observed risk associated with IPH in studies enrolling symptomatic subjects was significantly higher as compared with studies that enrolled asymptomatic studies (HR: 11.71, 95% CI: 5.17 to 26.48 vs. HR: 3.50, 95% CI: 2.59 to 4.73, $p = 0.0065$ for symptomatic and asymptomatic subjects, respectively) (Fig. 4). Finally, we observed that studies that were characterized by a small sample size ($N < 70$) reported higher risk estimates as compared with studies with larger sample sizes ($p < 0.0065$). Specifically, although smaller studies reported a pooled hazard ratio of 11.7 (95% CI: 5.18 to 26.47), larger studies reported a risk associated with plaque hemorrhage detected by MRI of 3.5-fold (HR: 3.50, 95% CI: 2.59 to 4.73).

**Study quality.** The average study quality score was 3.5, ranging from 2 (20) to 5 (13). Although all studies provided clear definitions of the study population and MR findings, no study had an endpoint committee. In the majority of studies, a blinded analysis of MR findings was performed (12,13,15,16), whereas only 1 study explicitly stated blinded outcome assessment (13). Fifty percent of the studies provided clear definitions of endpoints (13,14,16,21). Only 1 study adjusted for potential confounders (13), and only 1 study did not exclude patients after they were enrolled (21).

## Discussion

With the present analysis, we systematically evaluated and pooled available evidence on the predictive value of IPH by MRI for the occurrence of cerebrovascular events. Although the pre-existing literature shows little controversy regarding the link between IPH and cerebrovascular events, our results indicate that the available data are very heterogeneous and limited to smaller sample-size trials of symptomatic and asymptomatic subjects. Despite these identified sources of

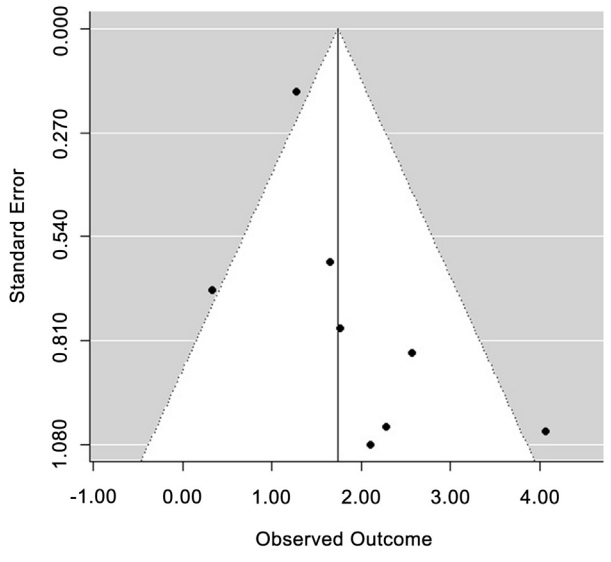


**Figure 5** Funnel Plot Assessing Publication Bias

Although there was no statistical sign of asymmetry, the funnel plot demonstrates moderate visual publication bias due to missing studies with small sample size and moderate risk estimates.

heterogeneity, the predictive value of IPH is strong, with an approximately 6-fold higher risk for events. Thus, our data are particularly relevant to harmonize reporting standards for ongoing or future studies and to provide risk estimates necessary as a baseline for prospective randomized trials applying risk modification on the basis of evaluation by MRI.

MRI has triggered the expectation that imaging features, such as IPH—defined as the presence of T1 hyperintensities—represent imaging biomarkers for high risk and thus allow the determination of who may be considered for invasive treatment strategies or who may benefit from conservative management. Findings of our meta-analysis show that symptomatic patients with carotid stenosis >50% and IPH have a particularly high risk of a recurrent event. However, our results indicate that this finding may currently not serve as a basis for clinical decision making, given the detected degree of heterogeneity of study quality and the limited level of evidence. By contrast, our data raise the need and rationale for future larger-scale trials to provide final evidence on the value of IPH evaluation by MRI.

The overall study quality we detected was moderate but ranged from low to good. Although early studies on the potential technology are highly relevant to trigger future developments, more rigorously designed and analyzed large-scale studies are warranted to provide the sufficient level of evidence for clinical decision making. This is particularly relevant with respect to the following aspects:

1. A more homogeneous definition of IPH is warranted and would allow for adequate comparison of different studies. Predominantly, in our analysis, we found IPH defined as hyperintense signal on T1-weighted fat-suppressed images as compared with the normal vessel wall or the sternocleidomastoid muscle in the literature, which should be applied to future trials.
2. Almost all of the studies failed to adjust for potential confounders. Although we did not detect any significant interaction with respect to adjustment, given the limited sample (Table 4), this certainly introduces the risk for false-positive findings. Thus, future studies are strongly advised to account for other parameters that may explain the observed effects by applying standardized advanced methods such as adjustment, matching, or stratified analysis.
3. In a number of studies, it remained unclear how many subjects were excluded after enrollment and imaging, and if excluded, for which reason. This may potentially bias the observed estimates significantly. As such, consistent with current recommendations (23), utilization of a study flowchart would demonstrate the presence of selection bias more evidently.
4. Our results indicate that the absolute and relative numbers of events by test result were inconsistently reported. For upcoming trials, it will be of critical

**Table 3** Prevalence of MRI Findings of Any Plaque Hemorrhage

| | | All | | MRI Positive | | | MRI Negative | | |
|---|---|---|---|---|---|---|---|---|---|
| First Author/Year (Ref. #) | N | Events (N) | Annualized Event Rate | Prevalence | Events | Annualized Event Rate | Prevalence | Events | Annualized Event Rate |
| Teng et al. 2011 (20) | 42 | 11 | 24.5 | 50.0 | 52.4 | 49.0 | 50.0 | 0 | 0 |
| Kurosaki et al. 2011 (14) | 62 | 7 | 14.8 | 48.4 | 18.8 | 24.7 | 51.6 | 3.3 | 4.4 |
| Sadat et al. 2010 (21) | 61 | 12 | 13.3 | 49.0 | — | — | 51.0 | — | — |
| Kume et al. 2010 (12) | 165 | 29 | 8.1 | 52.7 | 28.2 | 13.0 | 47.3 | 8.1 | 3.7 |
| Singh et al. 2009 (15) | 98 | 6 | 3.8 | 63.3 | 16.7 | 8.0 | 36.7 | 0 | 0 |
| Altaf et al. 2007 (22) | 66 | 17 | 22.9* | 33.3 | 34.1 | — | 66.7 | 9.1 | — |
| Altaf et al. 2008 (13) | 64 | 14 | 8.2 | 39.0 | 33.3 | 14.7 | 61.0 | 4.0 | 1.7 |
| Takaya et al. 2006 (16) | 154 | 12 | 2.4 | 72.0 | — | — | 28 | — | 0 |
| Weighted* | | | 9.89 | | | 17.71 | | | 2.43 |

Values are % except as noted. The prevalence of MRI findings of any plaque hemorrhage, number of events, and annualized event rates among all subjects with MRI positive and negative findings are derived from crude event numbers provided in the source publication. *Averaged annualized event rates (%) are weighted by sample size.

MRI = magnetic resonance imaging.

**Table 4 Random Effects Meta-Analysis**

| | Studies (N) | Participants (N) | Hazard Ratio (95% CI) | p Value* |
|---|---|---|---|---|
| Average age | | | | |
| >73 yrs* | 4 | 240 | 7.26 (2.58–20.45) | 0.6145 |
| ≤73 yrs | 4 | 449 | 4.95 (1.69–14.47) | |
| Proportion of males | | | | |
| ≥81%* | 4 | 456 | 15.47 (5.89–40.65) | 0.0040 |
| <81% | 3 | 172 | 3.50 (2.59–4.73) | |
| Diabetes | | | | |
| >18%* | 4 | 454 | 4.27 (1.44–12.65) | 0.4113 |
| ≤18% | 4 | 235 | 7.89 (2.95–21.11) | |
| Current statin medication | | | | |
| >67%* | 4 | 266 | 6.04 (2.24–16.31) | 0.9864 |
| ≤67% | 4 | 423 | 5.96 (1.99–17.85) | |
| Presentation | | | | |
| Asymptomatic | 3 | 394 | 3.50 (2.59–4.73) | 0.0065 |
| Symptomatic | 5 | 295 | 11.71 (5.17–26.48) | |
| MRI technology | | | | |
| Multisequence | 4 | 422 | 5.63 (1.96–16.21) | 0.8650 |
| Single sequence | 4 | 267 | 6.41 (2.27–18.05) | |
| Degree of stenosis | | | | |
| High grade included | 3 | 189 | 8.46 (2.59–27.63) | 0.4197 |
| High grade not included | 5 | 500 | 4.77 (2.29–9.94) | |
| Time MRI to symptoms | | | | |
| <72 h | 2 | 104 | 22.61 (5.19–98.48) | 0.2926 |
| <6 months | 3 | 191 | 8.75 (3.28–23.31) | |
| Region code | | | | |
| Asia | 2 | 227 | 2.59 (0.61–11.07) | 0.2304 |
| Europe, U.S. | 6 | 462 | 7.03 (3.36–14.70) | |
| Design | | | | |
| Retrospective | 2 | 137 | 4.40 (1.24–15.60) | 0.5727 |
| Prospective | 6 | 552 | 6.85 (2.87–16.36) | |
| Sample size | | | | |
| Small (N < 70) | 5 | 295 | 11.71 (5.18–26.47) | 0.0065 |
| Large (N > 70) | 3 | 394 | 3.50 (2.59–4.73) | |
| Study quality | | | | |
| Sum ≤3.5* | 4 | 344 | 4.63 (1.95–11.03) | 0.4833 |
| Sum >3.5* | 4 | 345 | 7.40 (2.78–19.65) | |
| Adjustment | | | | |
| Not adjusted | 7 | 623 | 3.83 (2.83–5.17) | 0.1532 |
| Adjusted | 1 | 66 | 13.00 (2.50–67.70) | |

The random effects meta-analysis was performed on the relationship between MRI finding of plaque hemorrhage on a combined cerebrovascular event endpoint, stratified according to potential sources of heterogeneity. *For difference.
CI = confidence interval; MRI = magnetic resonance imaging.

importance to provide a detailed reporting on the absolute numbers of events in the group of MR positive and negative patients.

5. Finally, there is inconsistency among available studies with respect to the reported number of vessels per subject. We found that these discrepancies substantially hampered the pooling of derived risk estimates because the number of control cases has an impact on the relative risks. We suggest that the risks for both carotid artery findings be reported adequately.

Notably, despite these aspects, our results also confirm the great potential of assessment of IPH by MRI, with an approximately 5.6-fold higher risk for events.

There is still an ongoing controversy over which T1-weighted sequence is best suited to detect relevant IPH. However, our analysis indicated that there was no difference in the observed risk between studies that used a multisequence strategy as compared with studies with fat-suppressed T1-weighted sequence acquisition ($p = 0.87$). Although there is a presumed improvement in visualization of plaque components in the near future with the development of new 3-dimensional sequences and higher field strengths (24), a baseline analysis with a simple fat-suppressed T1-weighted sequence analysis should be specifically reported.

Interestingly, we found that the associated risk of IPH is higher among studies including predominantly male subjects

(HR: 15.5 vs. 3.5). It is well established that women with ischemic stroke have a lower risk of ipsilateral ischemic stroke on medical treatment and a higher operative risk than do men. The same patterns were also shown in a large trial of carotid endarterectomy for asymptomatic stenosis (25). Consequently, carotid endarterectomy for asymptomatic stenosis is beneficial in men, but not in women. Similarly, a recent meta-analysis (26) showed that carotid endarterectomy is clearly beneficial in women with 70% or more symptomatic stenosis, but not in those with 50% to 69% stenosis. Therefore, identifying women with symptomatic carotid stenosis with a particularly high stroke risk might be of importance because carotid endarterectomy might prove to be beneficial for these selected individuals. Interestingly, it has been shown that women with IPH and severe stenosis have a similar risk as men have for recurrent cerebrovascular events (27). Further, sex-specific research in randomized controlled trials is required to evaluate the potential benefit of IPH detection by MRI in specific patient populations in both men and women.

We observed that smaller sample-size studies were associated with higher risk estimates as compared with larger samples. Although this finding is known from previous analysis representing publication bias, it needs to be noted that despite no statistical evidence of publication bias, visual inspection of the funnel plot demonstrated moderate publication bias due to missing studies with small sample sizes and moderate risk estimates. Thus, further smaller studies will be necessary to exclude the remaining probability of a false-positive observation.

We found an absolute annualized event rate of 17.71% in subjects with a positive MR finding for IPH, whereas subjects with a negative MR finding for IPH incurred a 2.43% annualized event rate. Therefore, similar to the relative risk, the absolute risk associated with a positive MRI finding for IPH is relatively high. That the event rate in subjects without IPH is not zero can certainly be partially attributed to the fact that there are a number of other causes of stroke, such as cardiac emboli and small vessel disease (28), but the event rate also indicates risks dependent of the presence of other high-risk plaque features well known from coronary atherosclerosis (29). The degree of carotid stenosis is a well-known risk factor for cerebrovascular events, and together with the symptomatology of the patient, forms the current basis for clinical decision making (30). In the analyzed studies, the highest event rate and shortest time to event were observed in patients with IPH and additional high-grade stenoses (22). In highly stenotic segments, even the formation of small additional thrombi, which might go unnoticed in less obstructed vessels, can lead to complete occlusion of the vessel with subsequent events. Also, several other MRI-based plaque features, such as a thin or ruptured fibrous cap, and plaques with a large lipid-rich or necrotic core, have been associated with cerebrovascular events in prospective studies (16,31). However, IPH can be easily visualized using 1 single MRI sequence, whereas multisequence protocols are needed in order to identify the status of the fibrous cap (5,32). Our included populations consisted of symptomatic and asymptomatic subjects. Findings of the meta-regression showed that symptomatic patients with carotid stenosis and IPH have a particularly high risk of a recurrent event and, as a consequence, might benefit from early interventions. We were not able to analyze the event rates of symptomatic patients with IPH and <50% stenosis, given the very limited data, although there is increasing evidence that such lesions might play a role in the pathogenesis of symptoms in patients with cryptogenic stroke (33). Several ongoing prospective MRI trials, such as the CAPIAS trial (Carotid Plaque Imaging in Acute Stroke, NCT01284933), are investigating the consequences of such lesions on the occurrence of cerebrovascular events in patients with acute ischemic stroke and without significant carotid artery stenosis.

**Study limitations.** A general limitation of this analytic technique is that the validity of the results depends on each single original study. Our meta-analytic approach relied on combining the aggregate HRs and associated 95% CIs from each trial using random effects modeling, accounting for heterogeneity among the original studies. However, besides pooling the result, it was a pre-defined objective of the present study to also identify strengths and weaknesses of current literature on IPH in a systematic review. Also, the number of potential confounders we investigated in the meta-regression was high, with the risk of false-positive findings. Importantly, our results were derived from cohorts enrolling subjects with known carotid artery disease with >30% stenosis. Thus, our results apply exclusively to patients with >30% carotid stenosis and cannot be generalized to a population with <30% stenosis. The overall HR of 5.69 needs to be interpreted with caution because it summarizes data from both symptomatic and asymptomatic patient populations. Although it may introduce bias to combine both populations, given the markedly different pretest probabilities of events in the 2 groups, we report and highlight the individual HRs of 3.50 for asymptomatic and 11.71 for symptomatic populations, which should be considered for the design of future studies. We were not able to analyze the incremental predictive value of IPH beyond other imaging markers of cardiovascular risk, such as coronary calcium scoring or intima-media thickness measurements, as none of the studies compared the prognostic value of other imaging modalities.

## Conclusions

Our results suggest that despite a large degree of detected heterogeneity of the published studies, the presence of IPH by MRI is associated with an approximately 5.6-fold higher risk for cerebrovascular events as compared with the risk for subjects without IPH. However, although this finding cannot serve as a rationale for widespread application of MRI in a clinical context in subjects referred for neurological work-up,

it forms the basis for larger-scale trials and cost-effectiveness analysis with a special emphasis on harmonized design and reporting. Thus, further work and intervention trials will be necessary to finally determine whether MR-based identification of plaque hemorrhage might consistently risk stratify patients into those who benefit from conservative versus interventional therapy.

**Reprint requests and correspondence:** Dr. Tobias Saam, Institute of Clinical Radiology, Ludwig-Maximilians-University Hospital, Munich, Pettenkoferstrasse 8a, 80336 München, Germany. E-mail: tobias.saam@med.lmu.de.

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**Key Words:** magnetic resonance imaging ■ meta-analysis ■ noninvasive imaging ■ plaque hemorrhage ■ prognostic value.