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Cardiac Imaging

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

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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)

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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