

Diffusion-Weighted Imaging (DWI) hyperintensities in subtypes of acute intracerebral hemorrhage: meta-analysis

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ABSTRACT

Background and Purpose: Diffusion-Weighted Imaging (DWI) hyperintensities in intracerebral hemorrhage (ICH) are associated with increased risk of recurrent ICH, cognitive impairment and death, but whether these lesions are specific to a subtype of ICH remains uncertain. We investigated the association between DWI lesions and ICH subtype and explored the risk factors for DWI lesions.

Methods: In a systematic review of ICH studies, we identified those reporting prevalence of DWI lesions. Two reviewers independently assessed study eligibility and risk of bias and collected data. We determined the pooled prevalence of DWI lesions within 90 days after ICH onset for cerebral amyloid angiopathy(CAA)- and hypertensive angiopathy-related ICH using random effects meta-analysis. We calculated odds ratios (ORs) to compare prevalence of DWI lesions by ICH subtype and to assess risk factors for DWI lesions.

Results: 11 studies (1910 patients) were included. The pooled prevalence of DWI lesions was 18.9% (95%CI 11.1-26.7) in CAA- and 21.0% (95%CI 15.3-26.6) in hypertensive angiopathy-related ICH. There was no difference in the prevalence of DWI lesions between CAA- (64/292 [21.9%]) and hypertensive angiopathy-related ICH (79/370 [21.4%]), OR=1.25, 95%CI 0.73-2.15) in the 5 studies reporting data on both ICH etiologies. In all ICH, presence of DWI lesions was associated with neuroimaging features of microangiopathy (leukoaraiosis extension, previous ICH, presence and number of microbleeds) but not with vascular risk factors or the use of antithrombotic therapies.

Conclusions: Prevalence of DWI lesions in acute ICH averages 20%, with no difference between CAA- and hypertensive angiopathy-related ICH. Detection of DWI lesions may add valuable information to assess the progression of the underlying microangiopathy.

Small Diffusion-Weighted Imaging (DWI) hyperintensities in patients with acute intracerebral hemorrhage (ICH) are reported to be associated with an increased risk of recurrent (ischemic and hemorrhagic) stroke, cognitive impairment and death¹⁻³ and to evolve into chronic lesions⁴ and cause local microstructural injury.⁵ However, data on presence of DWI lesions in ICH patients come from small cohorts, mainly of cerebral amyloid angiopathy (CAA) patients, and whether DWI lesions are specific to a subtype of ICH remains uncertain. Also, no previous study has compared the presence of DWI lesions by ICH location or etiology and risk factors for DWI lesions remain unclear. We therefore undertook a systematic review and meta-analysis to assess the association between DWI lesions and ICH subtype and to explore risk factors for DWI lesions.

MATERIALS AND METHODS

The data, analytic methods, and study materials used have been made available to other researchers for purposes of reproducing the results or replicating the procedure. We declare that all supporting data are available within the article and its online supplementary file.

We report our study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.⁶ We sought studies of adults with acute ICH quantifying the number with DWI lesions by ICH location (lobar or non-lobar ICH) or presumed etiology (CAA- or hypertensive angiopathy-related ICH) or those with data available on risk factors for DWI lesions. Studies were eligible if they reported confirmation of spontaneous (non-traumatic) primary (not secondary to an underlying cause, such as intracranial tumor or vascular malformation) ICH diagnosis by brain MRI within 90 days of ICH onset. Where appropriate, we also excluded patients in the presence of excessive anticoagulation (e.g. INR >3) at the time of ICH, as a secondary cause of ICH cannot be ruled out.

DWI lesions had to be defined as focal hyperintensities, remote from the site of the ICH or the perihematoma region. Lobar ICH was defined as ICH occurring in the cortical or juxtacortical cerebral hemisphere and non-lobar ICH as those occurring in deep hemispheric regions (i.e. basal ganglia and thalamus), brainstem or cerebellum. We relied on authors' likelihood for the diagnosis of CAA-related ICH, using Boston criteria,⁷ and of hypertensive angiopathy, which definition includes the combination of a history of hypertension or high blood pressure measurements and a haemorrhage located in the territory of small perforating arteries. The sole presence of a history of hypertension was considered insufficient for the diagnosis of hypertensive angiopathy-related ICH. We did not restrict inclusion by language of publication or sample size.

We used electronic search strategies (Appendix in the online-only Data Supplement) to identify studies indexed in Medline and Embase until April 30, 2017 and we screened the bibliographies of relevant studies. Two reviewers (MB and RS) screened all titles and abstracts to determine potentially eligible studies, any uncertainties or disagreements between reviewers were resolved by one reviewer (ET). Two reviewers (MB, RS) independently screened these studies, assessed eligibility and collected data using a prespecified data extraction file. To obtain unpublished data on the prevalence of DWI lesions by ICH etiology we contacted authors of the eligible studies that did not report this information but described the frequency of CAA- or hypertensive angiopathy-related ICH in the entire cohort. When unspecified in the study, we contacted authors to request information on imaging characteristics (type of DWI, DWI slices thickness), burden of microbleeds, leukoaraiosis extent, and traditional vascular risk factors in patients with and without DWI lesions.

We also extracted data on study design (retrospective, prospective, hospital-, population-based), baseline ICH volume, DWI lesions location, traditional vascular risk factors (age, sex, history of hypertension, diabetes, smoking, hypercholesterolemia, ischemic stroke), history of previous ICH, dementia and atrial fibrillation, use of antiplatelet or anticoagulant therapy prior to ICH, arterial pressure level at hospital admission, change in mean arterial pressure levels between hospital admission and the lowest within 24 hours and radiological markers of microangiopathy (presence of moderate to severe leukoaraiosis [defined as Fazekas score 2-3 evaluated on fluid-attenuated inversion-recovery [FLAIR] images], lacunar infarct, enlarged perivascular space, brain atrophy and presence and numbers of microbleeds). We also collected information on the proportion of all ICH patients who were explored by MRI within 90 days of ICH onset.

Critical appraisal for assessing quality of observational (nonrandomized) studies was based on RoBANS tool.⁸ Additionally, assessment of risk of bias was undertaken at the study level based on study design, imaging characteristics (timing of MRI from ICH onset, field strength, type of DWI and DWI slices thickness), proportion of ICH patients explored by MRI and on whether authors reported a definition of lobar and non-lobar ICH or of CAA- and hypertensive angiopathy-related ICH. Funnel plots were used to assess the risk of bias across studies.

Statistical analyses

We determined the pooled prevalence of DWI lesions in ICH patients using random effect meta-analysis.⁹ We assessed any difference by timing of MRI (\leq or >7 days of ICH onset) using interaction tests (p_{int}). To investigate any difference based on the proportion of ICH patients explored by MRI, we used interaction tests and reported funnel plots, stratified by ICH subtype (i.e. ICH location and etiology).

We also compared the pooled prevalence of DWI lesions by ICH etiology (CAA vs. hypertensive angiopathy-related ICH) and by ICH location (lobar vs. non-lobar ICH) using the Mantel-Haenszel random-effect method¹⁰ and reported the unadjusted Odds Ratios (ORs). Any difference by study design, timing of MRI and slice-thickness was assessed using interaction tests.

Unadjusted ORs using similar methods were calculated for categorical risk factors for DWI lesions while mean difference in continuous risk factors were meta-analyzed using inverse-variance random-effects method.⁹ As only the median and range of the number of microbleeds were reported, we contacted studies' authors to request the mean and standard deviation to be able to meta-analyze this variable. Data were skewed, we therefore performed log transformation to calculate the number of microbleeds in patients with and without DWI

lesions. Statistical heterogeneity between studies was quantified with the χ^2 test and the p-value (P_{het}) of the test was reported. Statistical analyses were performed in R version 3.1.3 and Review Manager version 5.3.

RESULTS

9055 titles and 294 abstracts were screened leading to the assessment of 37 full texts. 26 of these 37 full texts were finally excluded leaving 11 studies¹¹⁻²⁰ (1910 patients) for inclusion (figure I in the online-only Supplemental Data). Prevalence of DWI lesions was reported by ICH location in 8 studies^{11-15, 17, 18, 21} and by ICH etiology in 2^{15, 17} and we obtained unpublished data on prevalence of DWI lesions in CAA- and hypertensive angiopathy-related ICH from two studies.^{18, 20} One study¹⁹ reported data on patients with acute and non-acute ICH, and we obtained unpublished information on characteristics (ICH subtype and potential risk factors for DWI lesions) of acute ICH patients (i.e. those undergoing MRI within 7 days of ICH onset). We obtained the number of patients with moderate to severe leukoariosis in those with and without DWI lesions in two studies,^{18, 20} and the mean and standard deviation of the number of microbleeds in 3.^{13, 18, 20}

Risk of bias within studies

Low risk of bias was found in the RoBANS assessment tool (table I in the online-only Supplemental Data). All studies were hospital-based and 4 were prospective (table 1). Presence of DWI lesions was assessed on b1000 sequences with 5mm slice thickness on 1.5T scanners within 7 days from ICH onset in the majority of the studies (table 1). Assessing the association between prevalence of DWI lesions and ICH subtype was the primary aim of one study.¹⁹ Definitions of lobar and non-lobar ICH were reported in one study.¹⁸ Two studies were only included in the calculation of prevalence of DWI lesions in lobar ICH because of the exclusion of cerebellar ICH in one study¹⁹ and because definition for other locations than lobar ICH did not meet our criteria for either non-lobar or deep hemispheric ICH in the other study.¹⁷ Data from another study²⁰ were not included in the analysis by ICH location because of the inclusion of intracerebellar location in lobar ICH. Among the 6 studies with information

available on DWI lesions for CAA-related ICH, one¹⁸ included patients with possible or probable CAA; two^{14, 19} included those with probable or definite CAA; two included^{17, 20} those with probable CAA, and one did not specify the degree of certainty of CAA diagnosis.¹⁵ 6 studies^{13, 15, 17-20} reported information in patients with hypertensive angiopathy-related ICH, with an explicit definition being described in one¹³ (table 1). Among the 9 studies with information available on the proportion of all ICH patients explored by MRI, 100% of ICH patients underwent MRI in 5 studies and <50% in 4, but information on the use of MRI was not reported by ICH subtype (table 1).

Prevalence of DWI lesions

Prevalence of DWI lesions in individual studies is reported in Table II in the online-only Data Supplement. The pooled prevalence of DWI lesions was 25.6% (95%CI 19.7-31.5, $P_{\text{het}} < 0.001$, 9 studies¹¹⁻¹⁹) in lobar ICH, ranging from 16.0%¹⁸ to 51.6%;¹⁶ 20.5% (95%CI 12.3-28.8, $P_{\text{het}} < 0.001$, 5 studies^{12-15, 18}) in non-lobar ICH, ranging from 6.3%¹² to 27.5%;¹⁴ and 26.4% (95%CI 22.7-30.2, $P_{\text{het}} = 0.28$, 5 studies^{11, 13-15, 17}) in deep hemispheric ICH, ranging from 24.0%¹³ to 42.8%.¹¹ In the sensitivity analyses restricted to studies in which MRI was performed within 7 days of ICH onset, the pooled prevalence of DWI lesions was 25.5% (95%CI 18.2-32.7, $P_{\text{het}} = 0.06$, 8 studies^{11-16, 18, 19}) in lobar ICH and 26.5% (95%CI 22.5-30.5, $P_{\text{het}} = 0.21$, 4 studies^{11, 13-15}) in deep hemispheric ICH. All patients with non-lobar ICH underwent MRI within 7 days of ICH onset. There was no difference in the prevalence of DWI lesions by timing of MRI ($p_{\text{int}} = 0.74$ for lobar and $p_{\text{int}} = 0.96$ for deep hemispheric ICH) and by the proportion of ICH patients explored by MRI ($p_{\text{int}} = 0.40$ for lobar ICH, $p_{\text{int}} = 0.85$ for non-lobar ICH, $p_{\text{int}} = 0.54$ for deep hemispheric ICH). Funnel plots were symmetrical for each ICH location, suggesting no publication bias (figures II in the online-only Data Supplement).

The pooled prevalence of DWI lesions was 18.9% (95%CI 11.1-26.7, $P_{\text{het}}=0.003$, 6 studies^{14, 15, 17-19}) in CAA-related ICH, ranging from 0%¹⁵ to 32.8%;¹⁷ and 21.0% (95%CI 15.3-26.6, $P_{\text{het}}=0.03$, 6 studies^{13, 15, 17-20}) in hypertensive angiopathy-related ICH, ranging from 10.0%²⁰ to 27.7%¹⁵. In the sensitivity analysis restricted to studies with MRI performed within 7 days of ICH onset, the prevalence of DWI lesions was 14.8% (95%CI 7.1-22.6, $P_{\text{het}}=0.06$, 4 studies^{14, 15, 18, 19}) in CAA- and 22.9% (95%CI 17.8-28.0, $P_{\text{het}}=0.31$, 5 studies^{13, 15, 18-20}) in hypertensive angiopathy-related ICH. We found no difference in the pooled prevalence of DWI lesions by timing of MRI ($p_{\text{int}}=0.06$ for CAA- and $p_{\text{int}}=0.41$ for hypertensive angiopathy-related ICH) and by the proportion of ICH patients explored by MRI ($p_{\text{int}}=0.31$ for CAA-related ICH and $p_{\text{int}}=0.87$ for hypertensive angiopathy-related ICH). Funnel plots were symmetrical for each ICH subtype, suggesting no publication bias (figures III in the online-only Data Supplement).

Number of patients with more than one DWI lesion was reported in 5 studies, being 2/15 (13%),¹⁸ 6/26 (23%),²⁰ 6/17 (35%),²² 15/40 (37.5%)¹⁹ and 8/15 (53%),²¹ but information stratified by ICH subtype was not available.

There was no difference in the pooled prevalence of DWI lesions between lobar (22.8% [79/347]) and non-lobar ICH (24.2% [160/661]) in the 5 studies providing data on both ICH locations (unadjusted OR=1.03, 95%CI 0.65-1.64, $P_{\text{het}}=0.24$, figure 1). MRI was performed within 7 days in all studies. The sensitivity analysis restricted to the 4 studies using b1000 with a 5-mm slices thickness did not alter the result (OR=1.25, 95%CI 0.60-2.61, $P_{\text{het}}=0.20$, figure 1). Findings did not differ between the 2 prospective^{13, 14} and the 3 retrospective studies^{12, 15, 18} ($p_{\text{int}}=0.52$).

There was no difference in the pooled prevalence of DWI lesions between lobar (118/444 [26.6%]) and deep hemispheric ICH (142/531 [26.7%]) in the 5 studies^{11, 13-15, 17} reporting these data (OR=0.96, 95% CI 0.71-1.30, $P_{\text{het}}=0.89$, figure 2). The sensitivity analysis restricted to the 4 studies with MRI undertaken within 7 days after ICH onset did not alter the result (OR=0.92, 95% CI 0.66-1.29, 774 patients, $P_{\text{het}}=0.85$). Findings did not differ between the 3 studies^{13, 15, 17} using b1000 with a 5-mm slices thickness and the two^{11, 14} with unspecified slice thickness ($p_{\text{int}}=0.69$) or between the 2 prospective^{15, 17} and the 3^{11, 13, 14} retrospective studies ($p_{\text{int}}=0.91$).

There was no difference in the pooled prevalence of DWI lesions between CAA- and hypertensive angiopathy-related ICH in the 5 studies, which were all retrospective, reporting these data, (21.9% [64/292] vs.21.4% [79/370], OR=1.25, 95% CI 0.73-2.15, $P_{\text{het}}=0.23$, figure 3). b1000 with 5mm-slice thickness was used in all studies. There was no difference in the association between the three studies with MRI performed within 7 days^{15, 18, 19} and the other 2^{17, 20} ($p_{\text{int}}=0.20$).

Location of DWI lesions was more likely to be cortical than deep in all ICH (table 1). No study reported data on the location of DWI lesions stratified by ICH location. In the only study reporting the information, DWI lesions in hypertensive angiopathy-related ICH were more frequently located in the brainstem or subcortical white matter than in the cortical grey matter.¹³ We could not adjust our analyses for other risk factors because data were not presented by ICH subtype.

Risk factors for DWI lesions

Information on potential risk factors for DWI lesions was rarely reported by ICH subtype, we therefore reported findings in all ICH (figure 4). Pooled analyses for each variable are presented in figures IV-XV in the online-only Data Supplement.

5^{13, 14, 17, 18, 20} out of the 7 studies^{13, 14, 16-20} reporting information on leukoaraiosis extension identified a significant positive association with DWI lesions. Due to difference in methodology of leukoaraiosis measurement, we were able to meta-analyse the association in four studies^{13, 18-20} and found a significant higher risk of DWI lesions in patients with moderate to severe leukoaraiosis than those without (figure 4). Presence of microbleeds was a significant risk factor for DWI lesions in 7 studies^{13, 14, 17, 18, 20-22} but not in two.^{12, 19} Due to difference in measurement, we could meta-analyse data for 6 studies^{13, 14, 17, 20-22} and identified a significant positive association (figure 4). Also, the number of microbleeds was significantly higher in patients with DWI lesions than in those without ($p=0.005$, 3 studies,^{13, 18, 20} 297 patients). Microbleeds were assessed on T2* sequence in two studies^{13, 20} and on T2* or susceptibility-weighted imaging (SWI) in one.¹⁸ Information on location (lobar versus deep) of microbleeds by presence of DWI lesions was available in 4 studies,^{12, 17, 19, 22} with 2 studies^{17, 22} reporting a significant association. Previous ICH was associated with a higher risk of DWI lesions (figure 4). Enlarged perivascular space was an independent risk factor for DWI lesions whereas lacunar infarct was not in the only study reporting these data.¹⁷ No study reported information on brain atrophy.

History of hypertension, diabetes, smoking, hypercholesterolemia, atrial fibrillation, ischemic stroke, use of pre-ICH antiplatelets or anticoagulants did not significantly predict the presence of DWI lesions (figure 4). Information on history of dementia was available in only one study,¹⁷ with no association with presence of DWI lesions. Authors identified inconsistent findings on the association between baseline ICH volume and presence of DWI lesions^{12, 13, 15-}

¹⁷ and we were unable to meta-analyse the data as mean and standard deviation of ICH volume were not reported by presence of DWI lesions.

Patients with DWI lesions had a greater decrease in systolic pressure in the acute phase of the ICH than those without DWI lesions ($p < 0.001$, figure 5). Findings on the association between initial systolic arterial pressure and presence of DWI lesions showed discrepancies. Compared with patients without DWI lesions, systolic arterial pressure at ICH admission in those with DWI lesions was significantly lower in one study,¹¹ higher in three^{14, 18, 22} and no statistically different in three studies.^{12, 13, 20}

DISCUSSION

In this meta-analysis, the prevalence of DWI lesions in patients with acute ICH averages 20%, with no difference between lobar and non-lobar ICH, or between CAA- and hypertensive angiopathy-related ICH. The severity of the microangiopathy seems to be the main determinant of DWI lesions.

DWI lesions have mainly been reported in patients with CAA-related ICH, however, their prevalence appears to be as frequent as in hypertensive angiopathy-related ICH, which may be expected. CAA and chronic hypertensive microangiopathies both lead to a range of characteristic ischemic (leukoaraiosis, microinfarct, ischemic stroke) and hemorrhagic complications (microbleed, ICH), although the distribution of bleeds may differ between the two diseases. Although we were unable to control the association for potential confounders, previous ICH and microangiopathy burden (leukoaraiosis extension and number of microbleeds) significantly predicted the presence of DWI lesions while conventional vascular risk factors and use of pre-ICH antithrombotic therapy did not. This suggests a similar underlying pathophysiological mechanism for DWI lesions and markers of microangiopathy, and presence of DWI lesions might be correlated with the progression of microangiopathy.

The pathophysiology of DWI lesions in ICH patients, although not well established, is estimated to be mediated by an ischemic mechanism.⁴ Despite conflicting findings on initial systolic arterial pressure in patients with and without DWI lesions, we found a significant association between mean arterial pressure reduction and DWI lesions. Microangiopathy is characterized by a dysregulation of cerebral pressure autoregulation, the ability of small arteries' vasoreactivity in response of cerebral perfusion pressure changes being impaired, reducing the capacity to ensure a constant cerebral blood flow.²³⁻²⁵ It is therefore possible that,

in the presence of an existing microangiopathy, acute variations of arterial pressure exceed the regulatory process, leading to a prompt modification of the cerebral blood flow that favors ischemia. In case of acute arterial pressure levels change, patients with severe microangiopathy might be at risk of DWI lesions and aggressive management of high arterial pressure levels should maybe be avoided.

Several clinicopathological studies have reported presence of microinfarcts in microangiopathies, including CAA and hypertensive angiopathy²⁶⁻²⁹ and hereditary syndromes such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)³⁰ and the cumulative number of microinfarcts is thought to be a strong contributor to vascular cognitive impairment.² A mathematical model has been developed to estimate the total cerebral microinfarct burden based on the presence of DWI lesions in ICH patients, with the presence of a single DWI lesion predicting an annual incidence of hundreds of microinfarcts.³¹ Despite their small size limiting their identification on conventional MRI, we found a high prevalence of DWI lesions in patients with acute ICH. DWI lesions were estimated to be present in up to 26% of non-acute ICH patients,^{16, 19} with no difference between the acute and the non-acute phase in ICH patients undergoing MRI in both time periods.¹⁹ This suggests that DWI sequences might be a convenient noninvasive method for detecting some microinfarcts during life time and could help identifying patients with progressive microangiopathy.

Although we consider our findings to be valid, our study has limitations. First, definitions of CAA- and hypertensive angiopathy-related ICH were not systematically described and there are potential for selection bias. Second, all studies were hospital-based, which tend to include more severe ICH than population-based studies, however severe ICH is often fatal and less

likely to be investigated by MRI. Third, all ICH patients were not systematically explored by MRI in the acute phase. It is possible that MRI was less commonly used in patients with severe hypertensive angiopathy-related ICH than in those with CAA-related ICH. This could have underestimated the prevalence of DWI lesions in hypertensive angiopathy-related ICH patients as the severity of microangiopathy was found to significantly predict the presence of DWI lesions. However, we found no difference in the prevalence of DWI lesions by the proportion of ICH patients explored by MRI. Also, eligible studies were centers interested in DWI lesions in ICH, with probably a more systematic use of MRI in ICH patients than centers that did not publish data on this. Fourth, prevalence of DWI lesions is likely to be influenced by MRI timing and DWI technique and random misclassification biases cannot be excluded. However, sensitivity analyses restricted to studies with MRI undertaken within 7 days of ICH onset and to those using b1000 with a 5-mm slices thickness did not alter the results. Fifth, we were unable to determine risk factors for DWI lesions by ICH subtype as data were scarce. However, we found no difference in the prevalence of DWI lesions by ICH subtype and we believe that risk factors are likely to be similar in ICH due to any microangiopathy. Moreover, markers of microangiopathy, but not conventional vascular risk factors, were also reported to predict DWI lesions among CAA patients¹ and among hypertensive angiopathy-related ICH patients,¹³ supporting that determinants of DWI lesions are probably not related to ICH etiology. Because data were rarely reported by ICH subtype, we were also unable to control for potential confounders of the associations between DWI lesions and ICH. Antithrombotic therapies and history of hypertension and ischemic stroke are expected to be the main potential confounders but none of these factors were significantly associated with the presence of DWI lesions, it is therefore unlikely that they altered the association.

In conclusion, prevalence of DWI hyperintensities in acute ICH averages 20%, with no difference by ICH subtype. Detection of DWI lesions may add valuable information to assess the progression of the underlying microangiopathy, although further research is needed to determine the mechanisms by which these lesions might lead to cognitive impairment and stroke recurrence.

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FIGURE LEGENDS

Figure 1: Association between lobar and non-lobar intracerebral hemorrhage (ICH) and presence of DWI lesions, stratified by slices thickness

CI: confidence interval; events: number of patients with DWI lesions; M-H: Mantel-Haenszel

Figure 2: Association between lobar and deep hemispheric intracerebral hemorrhage (ICH) and presence of DWI lesions, stratified by slices thickness

CI: confidence interval; events: number of patients with DWI lesions; M-H: Mantel-Haenszel

Figure 3: Association between cerebral amyloid angiopathy (CAA)- and hypertensive angiopathy-related intracerebral hemorrhage (ICH) and presence of DWI lesions, stratified by MRI timing

CI: confidence interval; events: number of patients with DWI lesions; M-H: Mantel-Haenszel

Figure 4: Forest plots of the meta-analyses of risk factors for DWI lesions in intracerebral hemorrhage (ICH)

CI: confidence interval, M-H: Mantel-Haenszel, P_{het} : p value for heterogeneity, N: number of studies, n: number of patients. The size of the square is proportional to the sample size of the study. History of hypercholesterolemia was based on the use of statin in 5 studies.

Figure 5: Difference in systolic blood pressure reduction in the acute phase of the intracerebral hemorrhage between patients with DWI lesions and those without

CI: confidence interval; SD: standard deviation; IV: inverse variance, total: number of patients with and without DWI lesions

Table: Characteristics of the 11 studies included

Study	Study location	Study design	Proportion of all ICH patients explored by MRI (%)	CAA definition (Boston criteria)	DWI technique, Field strength, thickness (mm)	MRI median time from ICH onset (range if specified) (days)	Lobar/ non-lobar ICH (%)	CAA-/hypertensive angiopathy-related ICH (%)	History of hypertension (%)	Mean or median age (years)	Men (%)	Median ICH volume (mL)	DWI lesions location (%)
Arsava ¹⁸ 2013	Turkey	R	36	possible or probable CAA	b1000, 1.5T, 5	3 (1-4)	29 /71	30 /65	78	64	59	DWI+: 23 /DWI-: 10	Cortical (47), subcortical (47), deep (7)
Auriel ¹⁹ 2012	USA	R	41	probable or definite CAA	b1000, 1.5T, 5	≤7*	70 /NS	44 /25	72	73‡	51	DWI+: 25 /DWI-: 22	Cortical (87), deep (7)
Garg ¹¹ 2012	USA	P	100	NS	b1000, 1.5T, NS	2 (0-7)	39 /44	15/62	79	64‡	49	DWI+: 9 /DWI-: 12	NS
Gioia ¹² 2015	Canada	R	NS	possible or probable CAA	b1000, 1.5T, 5	2	45 /55	9/46	65	66‡	52	DWI+: 16 /DWI-: 9	Cortical (50), subcortical (48)
Gregoire ²⁰ 2011	UK and Belgium	R	100	probable CAA	b1000, 1.5T, 5	≤90	114/ 0	34 /44	77	72	61	DWI+: 12 /DWI-: 10	Cortical and subcortical (75)
Kang ¹³ 2012	South Korea	P	100	probable or definite CAA	b1000, 1.5T, 5	≤5*	9 /91	0 /100	85	59‡	61	DWI+: 7 /DWI-: 6	Cortical (24), subcortical or deep (75)
Kidwell ¹⁴ 2017	USA	P	33	possible or probable CAA	NS, 1.5T, NS	2	9 /63	16 /NS	80	61‡	55	DWI+: 9 /DWI-: 9	NS

Study	Study location	Study design	Proportion of all ICH patients explored by MRI (%)	CAA definition (Boston criteria)	DWI technique, Field strength, thickness (mm)	MRI median time from ICH onset (range if specified) (days)	Lobar ICH / non-lobar ICH (%)	CAA-/hypertensive angiopathy-related ICH (%)	History of hypertension (%)	Mean or median age (years)	Men (%)	Median ICH volume (mL)	DWI lesions location (%)
Menon ¹⁶ 2012	USA	P	NS	NA	NS, 1.5 or 3T, NS	2	NA /NA	2 /62	84	59‡	54	25	Lobar (44)
Prabhakaran ¹⁵ 2010	USA	R	100	NS	b1000, 1.5T, 5	1 (1-3)	39 /60	12 /70	77	60‡	48	DWI+:18 /DWI-: 41	Subcortical (70), purely cortical (26)
Tsai ²² 2014	Taiwan	P	100	NA	b1000, 3T, 4	4 (1-14)	NS /NS	NS /NS	91	64‡	61	NS	Cortical and subcortical (80), deep (16), cerebellar (4)
Wu ¹⁷ 2015	USA	R	48	Probable CAA	b1000, 1.5T, 5	2 (0-31)	NS /65†	35 /55	72	71	60	DWI+: 31 /DWI-: 12	Cortical (46), subcortical (37), deep (14), cerebellar (2)

R: retrospective. P: prospective. CAA: cerebral amyloid angiopathy. NA: not appropriate, NS: Not specified, DWI+/-: Patients with and without DWI lesions, T: Tesla, *MRI was performed within 7 days of ICH onset in Auriel's study and within 5 days in Kang's study, †: deep hemispheric ICH, ‡:mean age. Proportions of lobar and non-lobar ICH and of CAA-and hypertensive angiopathy-related ICH may not add up as some patients could remain uncategorized.